Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

5.01
1,2,3-Triazoles

S. Rachwal
Cortex Pharmaceuticals, Inc., Irvine, CA, USA
A. R. Katritzky
University of Florida, Gainesville, FL, USA

5.01.1 Introduction

The present chapter is devoted to 1,2,3-triazole and benzotriazole and their various derivatives. Triazolines (4,5-dihydro-1*H*-1,2,3-triazoles) are discussed in Section 5.01.6. Tautomeric forms of the parent molecules and atom numbering are given in **Figure 1**.

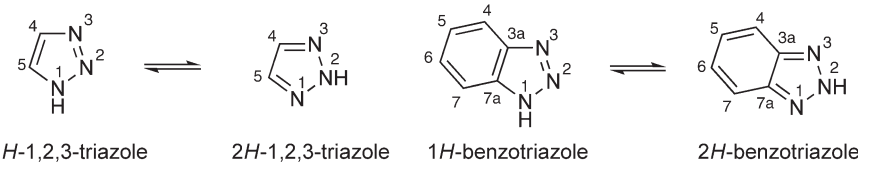


Figure 1 Tautomeric forms and atom numbering for 1,2,3-triazole and benzotriazole.

In CHEC(1984) <1984CHEC(5)669>, Chapter 4.11 on 'Triazoles and their Benzo Derivatives' (64 pages) covered the literature through 1982 and was strongly aligned to the monocyclic 1,2,3-triazoles with the considerable emphasis on ring-reduced derivatives. In CHEC-II(1996) <1996CHEC-II(4)1>, the corresponding 126-page chapter covered the literature from 1982–94, when the position had already changed significantly with the realization of the utility of benzotriazole as a synthetic auxiliary.

The present chapter is heavily biased toward benzotriazole as a consequence of numerous synthetic methods developed with the help of this molecule. It has been impossible to cover the field in a comprehensive manner in the pages available. We refer readers to the following reviews that have appeared during the last ten years:

(1) 'Properties and Synthetic Utility of Substituted Benzotriazoles' <1998CRV409> – this review covers the literature in a comprehensive manner through 1996;
(2) 'Benzotriazole-Based Reagents for Efficient Organic Synthesis' <1998ALD33> – another review of some of the synthetic applications;
(3) 'Benzannulations' <1999T8263> – specifically deals with benzotriazole mediated benzannulations;
(4) 'Michael Additions of Benzotriazole-Stabilized Carbanions' <1998CCC599>;
(5) 'The Generation and Reactions of Non-stabilized α-Aminocarbanions' <1998T2647> – includes significant amount of benzotriazole chemistry;
(6) 'Designing Efficient Routes to Poly-functionality' <2000PAC1597> – deals with benzotriazole derivatives;
(7) 'The Preparation of Mono-, 1,1-Di-, *trans*-1,2-Di- and Tri-Substituted Ethylenes by Benzotriazole Methodology' <2001SL458>;
(8) 'Benzotriazole an Ideal Synthetic Auxiliary' <2003CEJ4587> – gives some highlights,
(9) 'Benzotriazole-Mediated Amino-, Amido-, and Alkylthio-Alkylation' <2005T2555>; and
(10) 'Benzotriazoles as Advantages N-, C-, S-, and O-Acylating Agents' <2005SL1656>.

5.01.2 Theoretical methods

Experimental dipole moments and acidities of azoles, including 1,2,3-triazole, show linear correlations with their π-electron excess calculated by the semiempirical AM1 method <2003CHE71>. Experimental dipole moments of azoles agree well with those calculated by the DFT program ALLCHEM <2003PCA4172>. Calculated dipole moments μ (in units of Debye,D) of a few selected azoles are listed below:

Pyrrole	1.93
Pyrazole	2.33
Imidazole	3.84
1*H*-1,2,3-triazole	4.55
2*H*-1,2,3-triazole	0.12
1*H*-1,2,4-triazole	2.93
4*H*-1,2,4-triazole	5.81

Ab initio optimized geometries at B3LYP/6-311+G levels suggest that aromatic stabilization of 2*H*-1,2,3-triazole is the highest of all azoles <2003T1657>. Some values (in units of kcal mol^{-1}) are given below for comparison:

Pyrrole	18.04
Pyrazole	20.46
Imidazole	16.18
1*H*-1,2,3-triazole	20.21
2*H*-1,2,3-triazole	22.21
4*H*-1,2,4-triazole	12.19
1*H*-tetrazole	14.13

Bond dissociation energies for several heterocyclic systems calculated by two *ab initio* methods, CBS-Q, G3 and G3B3, show similar values <2003JPO883>. The G3B3 data for three selected azoles are as follows:

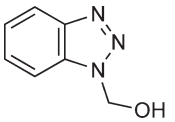
Pyrrole	N(1)-H	95.2 (kcal mol^{-1})
	C(2)-H	119.7
	C(3)-H	119.2
Pyrazole	N(1)-H	109.2
	C(3)-H	117.8
	C(4)-H	121.0
	C(5)-H	119.9
1*H*-1,2,3-triazole	N(1)-H	109.5
	C(4)-H	121.5
	C(5)-H	122.7

Potassium cation affinities of several azoles and other compounds in the gas phase were calculated by hybrid density functional theory [B3-LYP with 6-311 + G(3df , 2p) basis set] <2003CEJ3383>. There is a striking difference in binding energies of 1*H*- and 2*H*-1,2,3-triazoles. Some of the collected data are as follows:

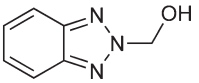
Pyrrole	77.1 (kJ mol^{-1})
Pyrazole	90.5
1-methylpyrazole	94.5
3-methylpyrazole	92.8
1,4-dimethylpyrazole	100.0
1,3,5-trimethylpyrazole	103.4
Imidazole	111.1
1*H*-1,2,3-triazole	118.6
2*H*-1,2,3-triazole	64.5
1*H*-tetrazole	109.7
2*H*-tetrazole	88.5

Monte Carlo calculations of interactions of 1*H*-benzotriazole with water reveal significant electronic polarization of the heterocycle. The dipole moment is increased by 2.89 D for the ground state and 2.75 D for the excited state to the total values of 6.89 and 6.40 D, respectively. Direct measurements of dipole moments in water are not possible, but these numerical results are supported by experimental solvatochromic blue shift of the $\pi \rightarrow \pi^*$ transition <2003IJQ572>.

Theoretical calculations at the B3LYP/6-31G* and B3LYP/6-311++G** levels concluded that 2-(hydroxymethyl)-benzotriazole **2** is slightly more stable than 1-(hydroxymethyl)benzotriazole **1**. The energy difference of 0.22 kcal mol^{-1} suggests that both isomers should be almost equally abundant; however, in solid state and in solutions, only isomer **1** is observed. One of the possible explanations of this phenomenon is formation of strong intermolecular hydrogen bonding between the OH group and N-3 in condensed phase of derivative **1**. Less basic nitrogen atoms in derivative **2** do not provide such stabilization <2004JHC285>.



1

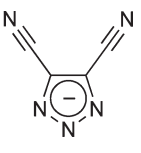


2

Atomic charges of anions **3** and **4** have been evaluated at the HF/6-31G* level using several partitioning schemes. The data obtained from the natural population analysis (NPA) method are listed below. The electron-withdrawing power of the CN groups is clearly demonstrated by the total charge of the ring change from −1.34 to −0.84 <2003SSI129>.

	3	**4**
N-1	−0.41	−0.31
N-2	−0.18	−0.12
C-4	−0.17	−0.05
Σ_{ring}	−1.34	−0.84

3

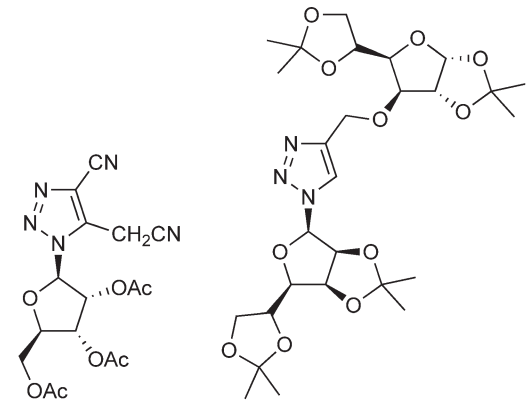


4

5.01.3 Experimental Structural Methods

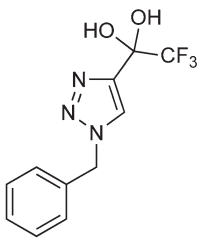
5.01.3.1 X-Ray Crystal Structure

X-Ray crystallographic data for several basic derivatives of 1*H*-1,2,3-triazole and benzotriazole are included in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)669, 1996CHEC-II(4)1>. Hundreds of new 1*H*-1,2,3-triazole structures have been analyzed since; some crystallographic data for representative examples (structures **5–12**) are collected in **Table 1**.

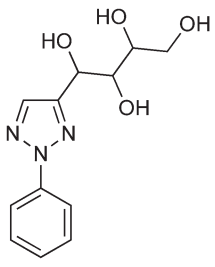


5

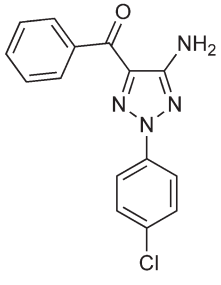
6



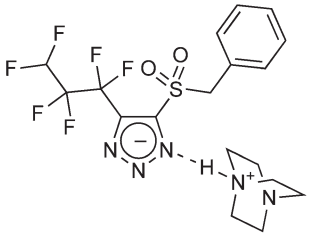
7



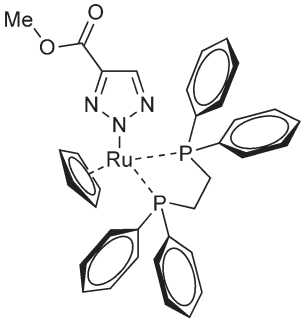
8



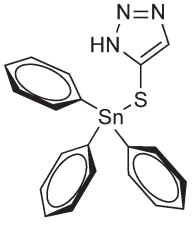
9



10



11



12

Table 1 Selected bond lengths (in Å) for 1,2,3-triazole derivatives **5–12**

Compound	*N(1)–N(2)*	*N(2)–N(3)*	*N(3)–C(4)*	*N(1)–C(5)*	*C(4)–C(5)*	*Other*	*Reference*
5	1.359	1.293	1.359	1.351	1.373	1.486:N(1)–Cα	2004NN521
6	1.354	1.303	1.361	1.351	1.372	1.442: N(1)–Cα, 1.493: C(4)–Cα	2005H(65)1035
7	1.342	1.309	1.365	1.344	1.342	1.484: N(1)–Cα, 1.503: C(4)–Cα'	2002JFC(116)81
8	1.341	1.333	1.329	1.339	1.399	1.422: N(2)–Cα, 1.490: C(4)–Cα'	2002BMC963
9	1.324	1.358	1.338	1.340	1.417	1.416: N(2)–Cα, 1.356: C(4)–Nα	2006ARK(xv)53
10	1.334	1.321	1.351	1.334	1.368	1.477: C(4)–Cα, 1.749: C(5)–S	2001CHE470
11	1.332	1.331	1.352	1.351	1.400	2.090: N(2)–Ru	2003OM3107
12	1.316	1.329	1.317	1.348		0.858: N(1)–H, 1.746: C(5)–S	2004POL1981

As can be seen in Table 1, for N-1 substituted triazoles (structures 5–7), the N(1)–N(2) bonds (1.342–1.359 Å) are significantly longer than the N(2)–N(3) bonds (1.293–1.309 Å), reflecting more single- and more double-bond character, respectively. An electron-withdrawing substituent at C-4 (compound 5 vs. 6) shortens slightly the N(2)–N(3) bond and stretches the N(1)–Cα bond indicating that such derivatives should dissociate more easily. In 2-substituted triazole 8, both N–N bonds are approximately equal. However, when two substituents of different electronic properties are attached, as in compound 9, the N–N bonds differ substantially, with that closer to an electron-withdrawing substituent being shortened and that closer to an electron donor being elongated. This observation can be rationalized by contribution of resonance forms involving the amino and carbonyl groups at C-4 and C-5, respectively. For the same reason, the C(4)–C(5) bond in derivative 9 is the longest one in the series suggesting diminished aromatic character for this molecule.

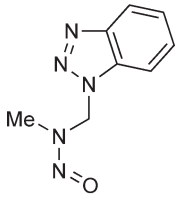
Because substituents of the ring may have different effects on the individual bonds, it is informative to compare averages of the five ring bond lengths. In this aspect, the average bond of the triazole system in compound 9 (1.355 Å) is the longest in the series 5–12 supporting the low aromatic character of this molecule. For comparison, the average bond length in molecule 8 is 1.348 Å. Triazole anion structure 10 reveals relatively short bonds with an average bond length of 1.341 Å. The triazole ring in ruthenium complex 11, with average bond length of 1.353 Å, exhibits similar character to that of molecule 9 due in part to its resonance involving the carbonyl group at C-4. In the relatively simple and electron-rich molecule 12, the average N–N bond (1.322 Å) and N–C bonds (1.332 Å) are the shortest in the whole series.

Table 2 lists bond lengths for the heterocyclic ring of the benzotriazole systems in derivatives 13–21. In comparison with 1,2,3-triazoles, N-1 substituted benzotriazoles have significantly longer N(1)–N(2) bonds (average 1.364 Å vs. 1.352 Å) and somewhat longer N(2)–N(3) bonds (average 1.307 Å vs. 1301 Å). In general, the C–N bonds and C–C bonds in the heterocyclic ring of benzotriazole derivatives are also slightly longer than the corresponding bonds in 1,2,3-triazoles. This causes the average heterocyclic ring bond in the whole series of benzotriazole derivatives 13–21 (1.361 Å) to be significantly longer than that in 1,2,3-triazole derivatives 5–12 (1.346 Å), reflecting the diminished aromatic character and therefore the higher reactivity of the benzotriazole system.

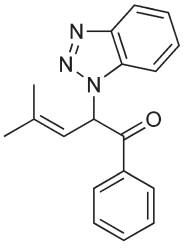
Table 2 Selected bond lengths (in Å) for benzotriazole derivatives 13–21

Compound	*N(1)–N(2)*	*N(2)–N(3)*	*N(3)–C(3a)*	*N(1)–C(7a)*	*C(3a)–C(7a)*	*Other*	*Reference*
13	1.368	1.296	1.367	1.361	1.391	1.440[a]	2001RCB1630
14	1.349	1.309	1.373	1.365	1.404	1.468[a]	2001JOC6787
15	1.377	1.310	1.383	1.371	1.410	1.434[a]	2001JOC6787
16	1.373	1.307	1.380	1.367	1.407	1.471[a]	2001JOC6787
17	1.369	1.299	1.374	1.367	1.388		2003ANS973
18	1.344	1.326	1.381	1.343	1.376	1.457[a]	2003JOC5713
19	1.368	1.302	1.380	1.377	1.391	1.431[a]	2003JOC407
20	1.336	1.353	1.354	1.356	1.381	1.413[b]	2001JCX217
21	1.351	1.296	1.374	1.363	1.411	1.477[a]	2006OM416
						1.455[c]	

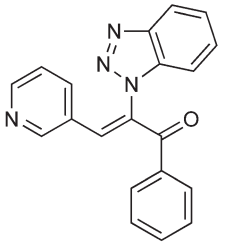
[a]N(1)–Cα.
[b]N(2)–Nα.
[c]N(2)–Cα'.



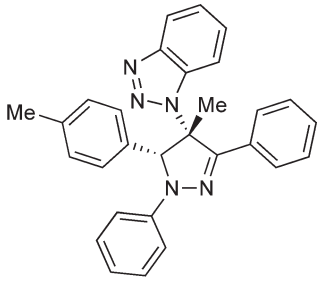
13



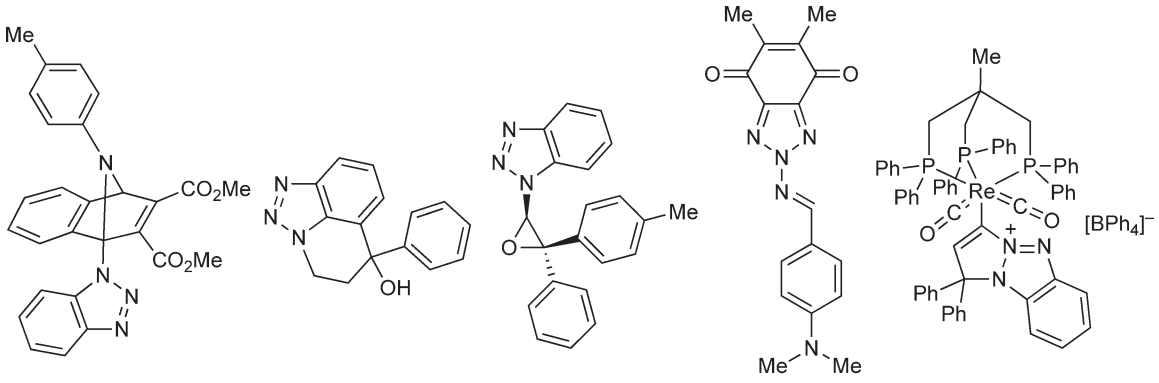
14



15



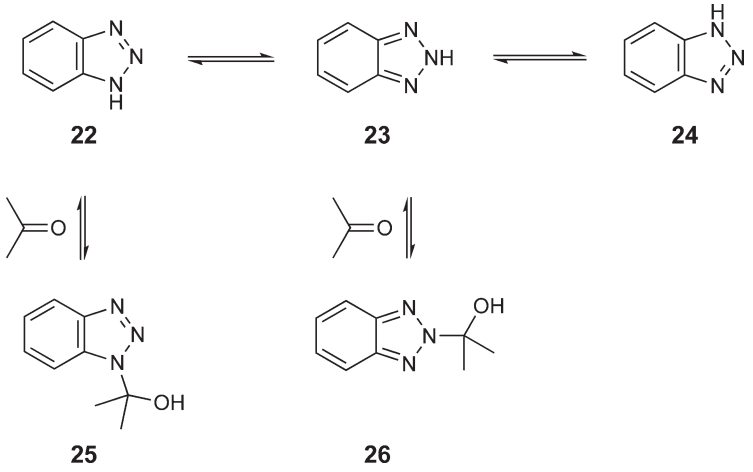
16



17 18 19 20 21

5.01.3.2 ^{1}H NMR Spectroscopy

Due to rapid proton exchange between forms **22**, **23**, and **24** (**Scheme 1**), benzotriazole exhibits at room temperature just two C–H signals, each for two protons, in its ^{1}H NMR spectra. However, when the temperature is lowered, the signals broaden and finally split into four separate resonances of the four individual C–H protons. The results of such study for an acetone solution of benzotriazole are given in **Table 3** <2002T9089>. The situation is additionally complicated by formation of adducts **25** and **26**, which at −90 °C contribute 25% and 5%, respectively, to the total molecular population.

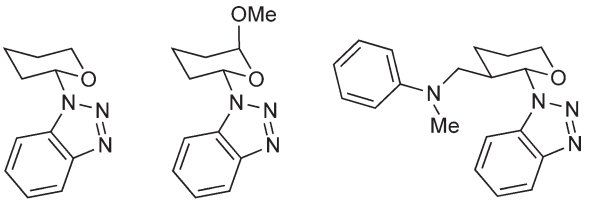


Scheme 1

Table 3 ^{1}H NMR chemical shifts in ppm for acetone-d_6 solutions of benzotriazole

Compound	*Temperature*	*H-4*	*H-5*	*H-6*	*H-7*
22–24	21 °C	8.00	7.44	7.44	8.00
22–24	−85 °C	8.11	7.48	7.48	8.05
25	21 °C	8.20	7.36	7.47	8.06
25	−85 °C	8.28	7.45	7.56	8.11

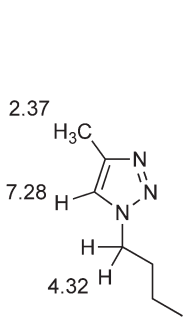
To illustrate the ^{1}H NMR assignment of benzotriazole derivatives, spectral data for three benzotriazol-1-yl derivatives of tetrahydropyran, **27–29**, are presented in **Table 4** <2001CJC1655>. Chemical shifts (in ppm) for the ring protons as well as the α-hydrogen atoms of the attached substituents in triazole derivatives **30** <2004TL6129>, **31** <2002BMC947>, **32** <2005JCO490>, **33** <2006T8115>, **34** <2006SC951>, **35** <2006OL3227>, **36** <2006OL3227>, **36** <2005JA15998>, and **38** <2005JA15998> are also shown below together with the structures.



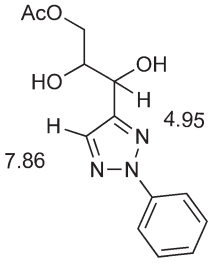
27 **28** **29**

Table 4 ^{1}H NMR chemical shifts (ppm), multiplicity and coupling constants (Hz) for benzotriazol-1-yl derivatives **27–29**

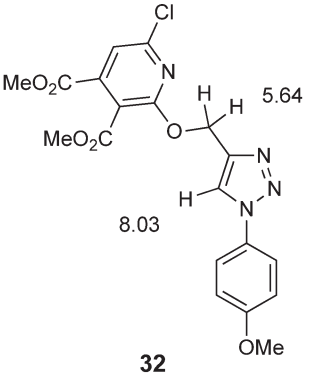
Compound	*H-4*	*H-5*	*H-6*	*H-7*	*H-α*
27	8.05 dt (8.2, 0.9)	7.37 ddd (8.2, 6.9, 0.9)	7.48 ddd (8.4, 6.9, 0.9)	7.74 dt (8.4, 0.9)	6.02 dd (8.3, 3.0)
28	8.07 dt (8.2, 0.9)	7.38 ddd (8.2, 6.9, 0.9)	7.50 ddd (8.2, 6.9, 0.9)	7.73 dt (8.2, 0.9)	6.41 dd (10.7, 2.7)
29	8.08 dt (8.3, 0.9)	7.39 ddd (8.2, 7.0, 0.9)	7.48 ddd (8.2, 7.0, 0.9)	7.67 dt (8.3, 0.9)	5.87 d (7.5)



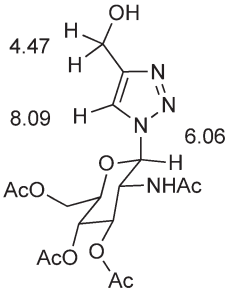
30



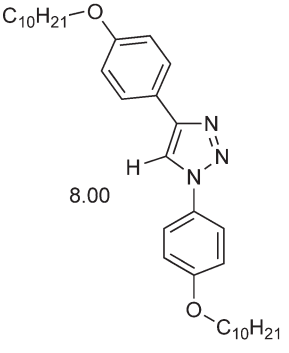
31



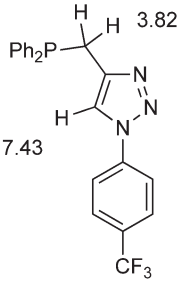
32



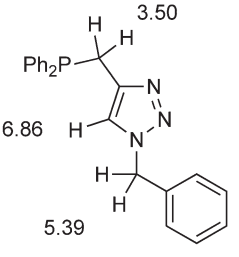
33



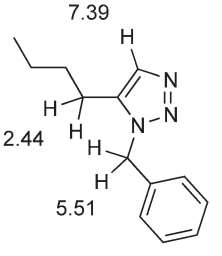
34



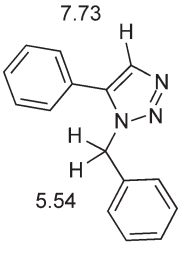
35



36



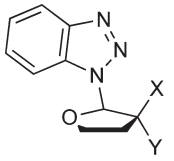
37



38

5.01.3.3 ^{13}C NMR Spectroscopy

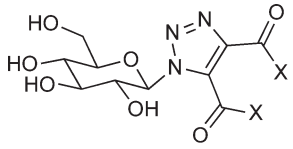
To illustrate signal assignments in ^{13}C NMR spectra of the benzotriazol-1-yl system, chemical shifts for five α-(benzotriazol-1-yl)tetrahydrofurans (structures **39–43**) <2003JPO158> and three corresponding tetrahydropyrans (structures **27–29**) <2001CJC1655> are listed in **Table 5**. Selected ^{13}C NMR spectral data for triazolyl nucleoside analogs **44–50** <2003SPL461> are collected in **Table 6**.



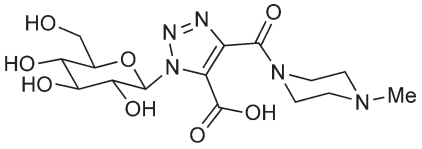
39: X = Y = H
40: X = Cl, Y = H
41: X = H, Y = Cl
42: X = CH_2NEt_2, Y = H
43: X = H, Y = CH_2NEt_2

Table 5 ^{13}C NMR chemical shifts (in ppm) for the benzotriazol-1-yl and α-carbon atoms in the spectra of derivatives **27–29** and **39–43** taken in $CDCl_3$

Compound	*C-α*	*C-4*	*C-5*	*C-6*	*C-7*	*C-7a*	*C-3a*
27	85.5	119.6	124.0	127.1	110.7	132.1	146.3
28	80.2	120.0	124.1	127.5	110.6	132.2	146.1
29	87.9	120.2	124.3	127.9	110.1	132.2	146.6
39	87.9	119.8	124.1	127.4	110.4	132.8	146.2
40	88.8	119.8	124.0	127.6	110.3	133.4	145.4
41	93.6	119.9	124.4	128.1	109.9	132.7	145.9
42	88.3	119.5	123.8	126.9	110.1	133.2	145.1
43	90.6	119.7	124.1	127.4	110.6	132.9	146.2



44: X = OH
45: X = NH_2
46: X = NHMe
47: X = NHBu
48: X = $NHCH_2Ph$
49: X = $NHCH_2CH_2OH$



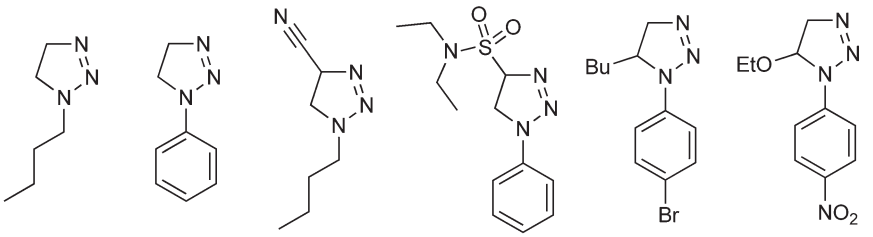
50

Table 6 Chemical shifts (ppm) for selected carbon atoms of derivatives **44–50** in their ^{13}C NMR spectra taken in DMSO-d_6

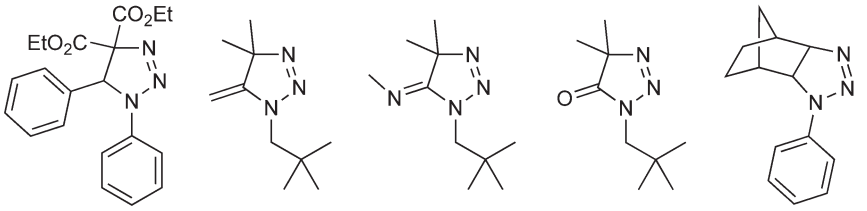
Compound	*C-4*	*C-5*	*C-1α*	*C-4α*	*C-5α*
44	143.1	140.0	87.9	180.0	180.0
45	138.9	132.2	86.2	163.1	158.0
46	138.5	133.0	86.4	161.2	156.9
47	138.7	132.0	86.4	160.7	156.2
48	138.7	132.3	86.5	160.7	156.5
49	138.7	132.1	86.2	160.8	156.4
50	144.3	135.3	85.2	163.5	176.7

5.01.3.4 ^{15}N NMR Spectroscopy

In the previous issue of *Comprehensive Heterocyclic Chemistry* <1996CHEC-II(4)1>, the ^{15}NMR spectra of 1,2,3-triazoles and benzotriazoles are extensively discussed, but 1,2,3-triazolines are only briefly mentioned. To clarify the picture, data for typical 4,5-dihydro-1*H*-1,2,3-triazoles (**51–61**) <2002J(P2)126> are collected in **Table 7**. For the ring nitrogen atoms, the highest field resonance is always assigned to N-1. To distinguish positions of N-2 and N-3 resonances, which sometimes come close to each other, isotopic labeling at N-1 and N-2 is used.



51 52 53 54 55 56



57 58 59 60 61

Table 7 ^{15}N Chemical shifts in ppm for 4,5-dihydro-1*H*-1,2,3-triazoles **51–61** taken in $CDCl_3$ with nitromethane as external reference ($\delta = 0$ ppm)

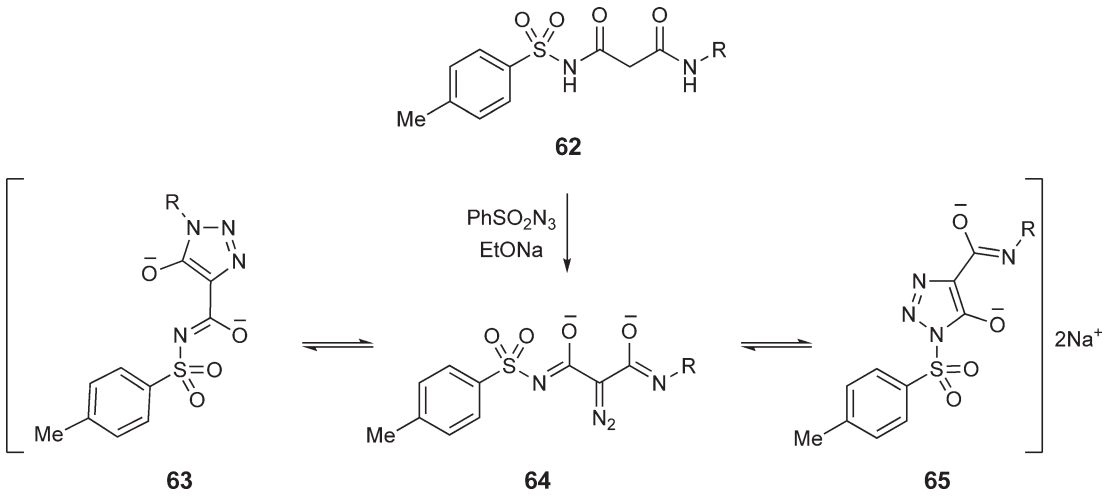
Compound	*N-1*	*N-2*	*N-3*	*Other nitrogens*
51	−195.5	54.6	−31.4	
52	−182.8	35.0	−29.3	
53	−195.5	52.8	−56.2	−127.1 (CN)
54	−182.5	37.6	−50.7	−286.4 (NEt_2)
55	−175.4	34.6	−30.4	
56	−168.3	32.7	−17.6	−12.7 (NO_2)
57	−176.9	35.8	−46.8	
58	−179.7	32.4	−6.9	
59	−172.9	36.4	3.5	−160.4 (NMe)
60	−163.1	44.0	32.8	
61	−173.9	33.5	−27.5	

The data presented indicate that change of a N-1 substituent from aliphatic to aromatic causes moderate downfield shifts of the N-1 and N-3 resonances and a strong upfield shift of the N-2 resonance. This feature can be explained by the resonance effect of the aromatic ring. Electron-withdrawing substituents at C-4 shift strongly upfield the N-3 signals but do not significantly change the N-1 and N-2 resonances. Substituents at C-5 shift significantly upfield the N-1 resonances. An sp^2 C-5 atom shifts the N-3 resonance dramatically downfield, especially when a heteroatom is attached (structures **58–60**).

5.01.4 Thermodynamic Aspects

5.01.4.1 Ring-Chain Equilibriums

Mixed malondiamide **62** on reaction with benzenesulfonyl azide and sodium ethoxide in ethanol is converted into open-chain diazo-derivative **64**, which readily cyclizes to triazoles **63** and **65** (**Scheme 2**). Rapid equilibration in solution prevents separation of individual components of the reaction mixture. NMR studies of the equilibrium between products **63**, **64**, and **65**, carried out in DMSO-d_6 are summarized in **Table 8**. It is evident from the collected data that the equilibrium depends strongly on the substituent R. Electron-withdrawing substituents on the phenyl ring destabilize structure **63** but stabilize form **65**. *Ortho*-substituents on the aromatic ring, both electron-donating and electron-withdrawing, strongly destabilize triazoles **63**, but they stabilize open-chain form **64**. The benzyl derivative exists almost exclusively in the triazole form **63** <2003CHE168>.



62 63 64 65

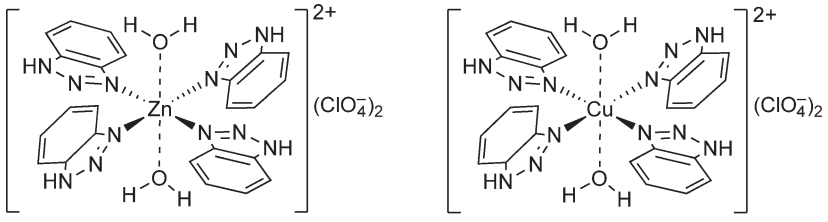
Scheme 2

Table 8 Ratio between compounds **63–65** in DMSO-d_6 solutions

Substituent R	**63** (%)	**64** (%)	**65** (%)
Ph	35	35	30
4-$MeOC_6H_4$	42	42	16
4-BrC_6H_4	25	40	35
3-$(NO_2)C_6H_4$	0.8	0.2	99
2-$MeOC_6H_4$	<0.1	58	42
2,4,6-$Cl_3C_6H_2$	<0.1	90	10
$PhCH_2$	99.6	0.2	0.2

5.01.4.2 Mononuclear Complexes

The strong coordination of benzotriazole and its derivatives to metal ions makes them attractive ligands. Thus, slow concentration of an aqueous solution of benzotriazole and zinc perchlorate results in formation of colorless prism crystals of composition $Zn[(BtH)_4(H_2O)_2](ClO_4)_2$, where BtH = benzotriazole. X-Ray crystal structure analysis shows that the crystals belong to monoclinic *C2/c* space group, with lattice parameters $a = 13.838$ Å, $b = 13.374$ Å, and $c = 16.944$ Å, $\beta = 103.206°$, $V = 3053.1$ Å^3, $Z = 4$, $R_1 = 0.0411$. The zinc ion is coordinated by four nitrogen atoms from four benzotriazole molecules and two oxygen atoms from water molecules to form an octahedral coordination polyhedron of complex **66**. Detailed analysis of the X-ray data indicates that the complex consists of two pairs of identically bonded benzotriazolyl systems located on the opposite sides of the central atom with the Zn–N bond lengths of 2.119 and 2.223 Å, respectively. The Zn–O bond length is 2.157 Å. The difference in Zn–N bond lengths is attributed to strong hydrogen bonding of two of the benzotriazolyl substituents with the perchlorate anions that decreases electron density on the N-3 atoms and weakens their bonding with the Zn ion. A similar complex, structure **67**, is obtained from copper (II) perchlorate with the Cu–N bond lengths of 2.009 and 2.090 Å, and the Cu–O bond length of 2.393 Å. The much longer Cu–O bond of complex **67** in comparison with the Zn–O bond in complex **66** is attributed to strong Jahn–Teller effect in the copper complex <2002ICC453>.

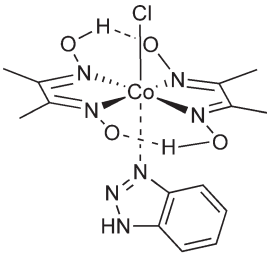


66 67

Concentration of an ethanolic solution of dimethylglyoxime, cobalt(II) chloride and benzotriazole results in deposition of crystalline complex **68**. The product is stable at room temperature; however, it slowly decomposes upon heating. Thermal analysis reveals that the compound releases first the chlorine atom and 50% of the benzotriazole content to form a new complex that is stable to 225 °C. Probably in this new form, the benzotriazole moiety coordinates two cobalt ions simultaneously. Further heating to 350 °C removes the benzotriazolyl moieties completely <2003JPY699>. The first step of decomposition can be summarized as follows:

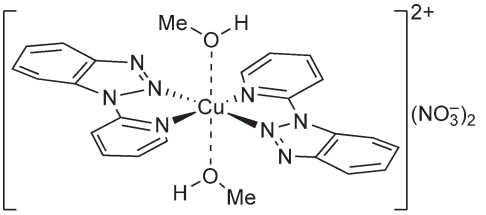
$$[Co(dmgH)_2(BtH)Cl] \rightarrow [Co(dmgH)_2(Bt)_{0.5}]$$

where dmgH = dimethylglyoxime anion, BtH = benzotriazole.



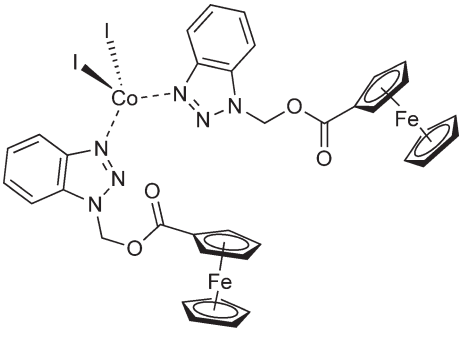
68

A reaction of 2-(benzotriazol-1-yl)pyridine with copper(II) nitrate, carried out in methanol, provides complex **69**. The product crystallizes in monoclinic space group $P2_1/n$. The copper atom lies in the crystallographic center of inversion, and it is coordinated to two chelating ligands and two methanol molecules. In structures **66–68** discussed above, the benzotriazolyl N-3 atom is involved in bonding. By contrast, in structure **69**, the benzotriazolyl N-2 atom is used to coordinate to the copper ion, with the bond length of 2.047 Å. The bond length of pyridyl-N-Cu is 2.034 Å. In analogy to structure **67**, the axial Cu–O bonds in complex **69** are elongated (2.298 Å) <2003JCD992>.



69

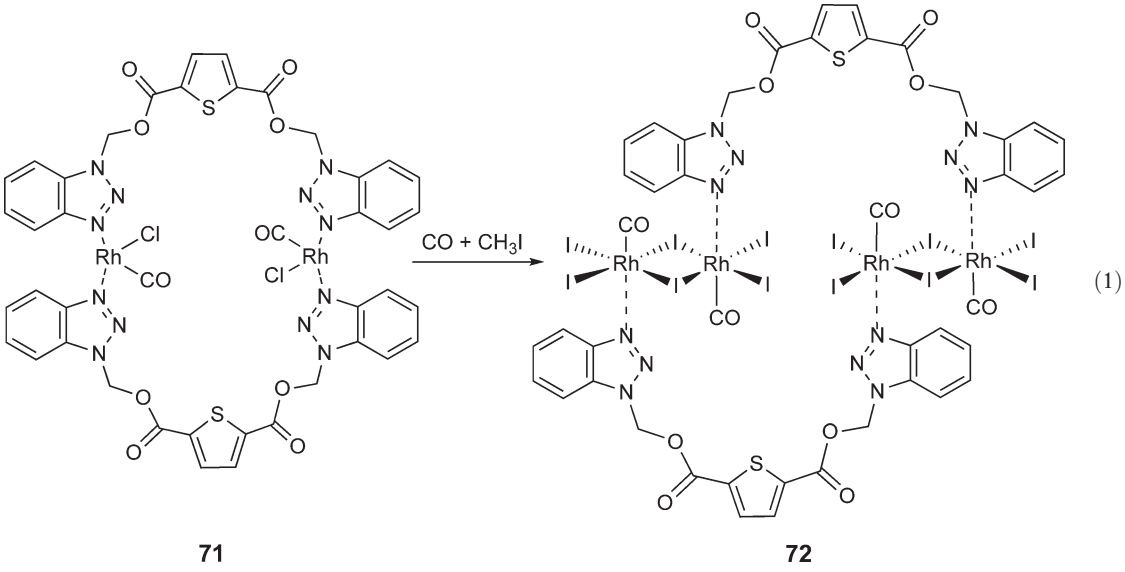
The ester derived from (benzotriazol-1-yl)methanol and ferrocenecarboxylic acid reacts in dichloromethane with cobalt(II) iodide to provide complex **70** in quantitative yield, which recrystallizes from dichloromethane/hexane to give green air-stable crystals. The X-ray structure analysis reveals that the cobalt center is coordinated to two iodine atoms and the N-3 atoms of two benzotriazole ligands. The angles N–Co–N, N–Co–I, and I–Co–I of 103.5°, 109.0° (average), and 116.2°, respectively, are close to the ideal tetrahedral angle. Some deviation from the tetrahedral geometry is indicated by the relatively large I–Co–I and relatively small N–Co–N angles; this is presumably caused by strong repulsion between the iodide anions. The bond lengths, Co–N 2.033 and 2.044 Å and Co–I 2.551 and 2.569 Å, are typical for this type of complexes <2002JOM(658)251>.



70

5.01.4.3 Di-, Tri-, and Polynuclear Complexes

(Benzotriazol-1-yl)methyl 2,5-thiophenedicarboxylate reacts with $[RhCl(CO)_2]_2$ in toluene at room temperature to give quantitatively rhodium(I) complex **71** as an air-stable yellow solid. The dimeric nature of the molecule is clearly indicated by its ESI molecular peak at $m/z = 1220$. Complex **71** catalyzes methyl iodide promoted carbonylation of methanol to give acetic acid and methyl acetate with much higher catalytic activities than the classical rhodium catalysts. Treatment with carbon monoxide and methyl iodide converts compound **71** into complex **72** in high yield (Equation 1). In a single-crystal X-ray analysis, complex **72** turns out to be a macrocycle containing two dinuclear iodo-bridged Rh(III) units. The four rhodium atoms have distorted octahedral geometries. The four Rh–N bonds are almost equal in length (2.091, 2.102, 2.128, and 2.139 Å). The Rh–C bond lengths are 1.840–1.867 Å. The bond lengths for each of the Rh_2I_6 units (2.605–2.692 Å) are typical for that type of structures. In contrast to Rh(I) macrocycle **71**, Rh(III) complex **72** does not catalyze the carbonylation of methanol <2001EJI3005>.

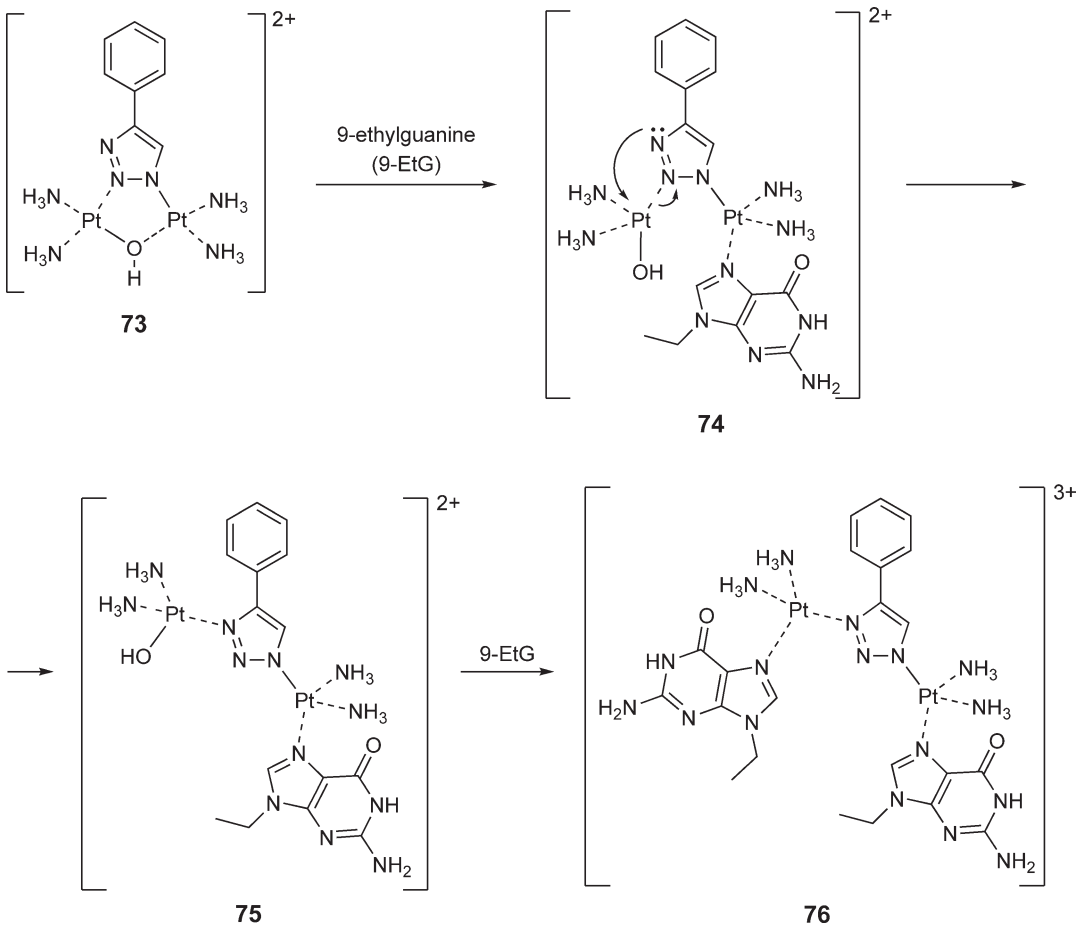


(1)

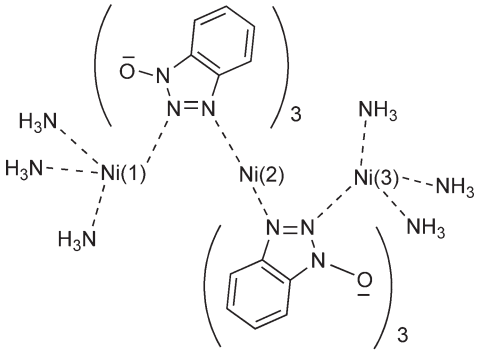
Cisplatin is one of the most frequently used anticancer agents despite several drawbacks including acquired drug resistance and serious side effects. To overcome these problems, an intensive search is going on to find safer alternatives. In one such approach, dinuclear Pt(II) complex **73** is obtained as dinitrate salt from a reaction of [*cis*-$Pt(NH_3)_2(\mu\text{-}OH)_2](NO_2)_2$ with 4-phenyl-1,2,3-triazole. According to X-ray structure determination, the coordination of the Pt atoms is square planar with the Pt–N(ammine) distances slightly longer (2.015–2.044 Å) than the Pt–N(triazole) distances (1.985–1,996 Å). The Pt–O bond lengths are 2.027 and 2.028 Å. A weak intramolecular hydrogen bond is observed between one of the ammine groups as donor and the triazole N-3 atom as acceptor <2002JA4738>.

Compound **73** and its simpler analog without any substituent on the triazole ring exhibit higher cytotoxicity to L1210 murine leukemia cells than cisplatin. To explain the effect of its action on DNA, a reaction of complex **73** with 9-ethylguanine, as a model nucleobase, was studied using NMR. In the first step, the hydroxyl bridge is broken and 9-ethylguanine is attached to one of the platinum centers to give intermediate **74**. In the following step, the freed diamminohydroxyplatinum group migrates to N-3 of the triazole ring to provide thermodynamically more stable intermediate **75**. Finally, a reaction with another molecule of 9-ethylguanine provides final adduct **76** (**Scheme 3**) <2002JA4738>.

Reaction of $Ni(NO_3)_2{\cdot}6H_2O$ with 1-hydroxybenzotriazole (BtOH) and NH_3 in DMF provides trinuclear complex $[Ni_3(BtO)_6(NH_3)_6]$ **77**. Variation of the solvent and the BtOH/Ni(II) ratio afford the same complex, in various solvated forms, as the only product isolated. According to the X-ray analysis, the central Ni atom, Ni-2, in the trinuclear molecule is joined to each of the other two Ni atoms, Ni-1 and Ni-3, by three bridging BtO^- ligands. Each BtO^- ion is coordinated to Ni-2 via the N-3 atom of the benzotriazole ring and to one of the terminal Ni atoms via N-2. The ammonia ligands complete the six-coordination pattern at each of the terminal Ni atoms. The metal centers have slightly distorted octahedral geometries. The molecule is almost linear, with the Ni(1)–Ni(2)–Ni(3) bond angle of 177.9°. The Ni–N(ammine) bond distances (2.074–2.123 Å) are very close to the Ni–N(Bt) bond lengths (2.087–2.160 Å) <2002TMC377>.

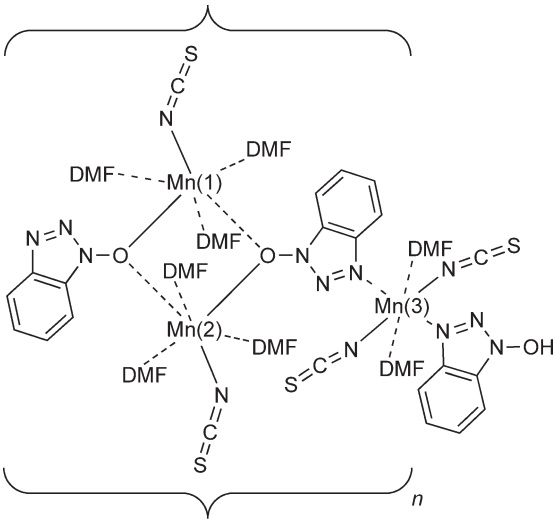


Scheme 3



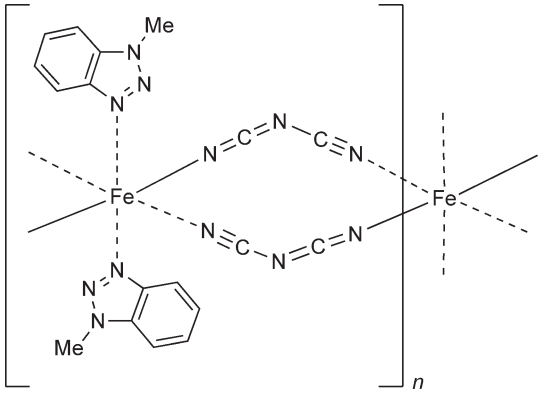
Heating of a suspension of powdered manganese in a DMF solution of 1-hydroxybenzotriazole and ammonium thiocyanate in air results in formation of a polymeric complex 78 of general formula $[Mn_3(BtO)_2(NCS)_4(DMF)_8]_n$. In this reaction zero-valent manganese is oxidized by oxygen from the air to Mn(II). Composition of this complex does not depend on the reagent ratio indicating that complex 78 is a thermodynamic product. According to X-ray analysis, complex 78 consists of dinuclear subunits of two Mn(II) atoms bridged by two oxygen atoms from BtO^- ligands, forming a planar four-membered ring [–Mn(1)-O-Mn(2)-O–]. The octahedral coordination of each of these manganese atoms is completed by three oxygen atoms from DMF molecules and one nitrogen atom from the NCS^- anion.

The dinuclear subunits in polymer **78** are connected via mononuclear subunits containing atoms Mn(3) coordinated by N-3 atoms of two anions derived from 1-hydroxybenzotriazole. The octahedral coordination of the Mn(3) atom is completed by two oxygen atoms from DMF molecules and two nitrogen atoms from NCS^- anions. The Mn(1)-O(BtO) bond lengths are 2.186 and 2.206 Å, which is a little more than the Mn(1)-O(DMF) bond lengths of 2.176 Å. The Mn(3)-N(BtO) bonds (2,262 and 2.277 Å) are also longer than the Mn(3)-N(NCS) bonds (2.199 and 2.218 Å) <2002EJI2488>.



78

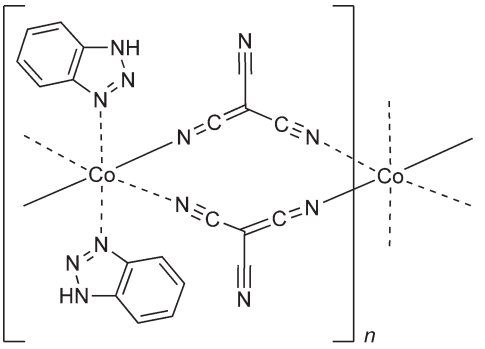
Addition of a methanolic solution of 1-methylbenzotriazole (BtMe) to an aqueous solution of $Fe(II)(ClO_4)_2 \cdot xH_2O$ and sodium dicyanamide (Nadca) results in slow deposition of crystalline complex $[Fe(BtMe)_2(dca)_2]$. X-Ray analysis reveals that the obtained complex (structure **79**) consists of one-dimensional linear chains, in which the Fe(II) centers are bridged by the dicyanamide anions. The coordination sphere at each Fe(II) center is completed by two 1-methylbenzotriazole ligands occupying the axial positions. Coordination geometry around the Fe(II) atom is distorted octahedral with the Fe-N(dca) bond length of 2.136 Å and the Fe–N(BtMe) bond length of 2.208 Å. Similar linear polymeric complexes are obtained from Mn(II) and Cu(II) salts <2006POL360>.



79

A similar complex **80** is also produced in a reaction of cobalt(II) nitrate with potassium tricyanomethanide (Ktcm) and benzotriazole (BtH). According to the X-ray data for this complex, the CoN_6 octahedron is only slightly distorted, having the N–Co–N′ angles in the range of 88.37–91.16°. The equatorial Co–N(tcm) distances (2.106 and 2.110 Å) are

slightly shorter than the axial Co–N(Bt) bonds (2.149 Å). The polymeric one-dimensional chains are cross-linked by hydrogen bonding between the benzotriazole NH atoms and the uncoordinated CN groups of the bridging ligands in the adjacent chains <2004AXC250>.

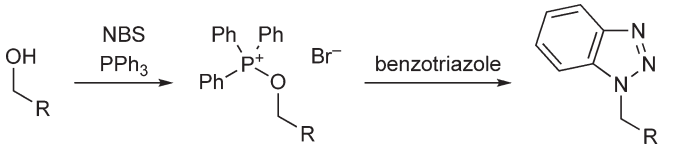


80

5.01.5 Reactivity of Fully Conjugated Rings

5.01.5.1 Nucleophilic Aliphatic Substitution

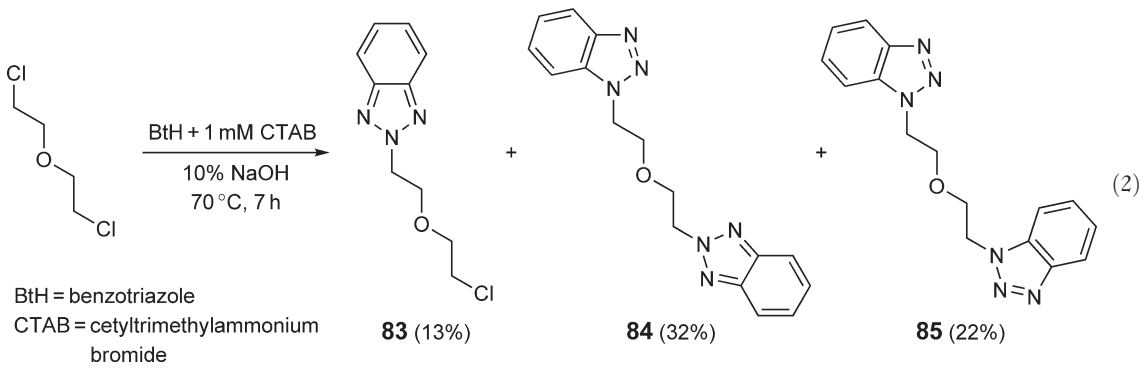
Alkylation reactions of 1,2,3-triazole and benzotriazole are exhaustively discussed in CHEC(1984) and CHEC-II(1996). The electrophilic reagents, usually alkyl halides, sulfates or sulfonates, attack N-1 or N-2 atoms of the ring producing mixtures of the corresponding 1-alkyl- and 2-alkyl triazoles <1984CHEC(5)669, 1996CHEC-II(4)1>. Some progress in this field provides finding of direct alkylation of benzotriazole with alcohols in the presence of triphenylphosphine and NBS <1997SC1613>. Presumably, the first step is formation of a reactive intermediate **81** that is attacked later by benzotriazole in the S_N2 fashion to give derivative **82** (**Scheme 4**). The reaction is regioselective and provides exclusively 1-alkyl-, 1-(arylmethyl)-, 1-(2-alken-1-yl)-, and 1-(2-alkyn-1-yl)benzotriazoles, respectively. Secondary alcohols give the corresponding alkyl derivatives in low yields, while tertiary alcohols do not alkylate benzotriazole under these conditions.



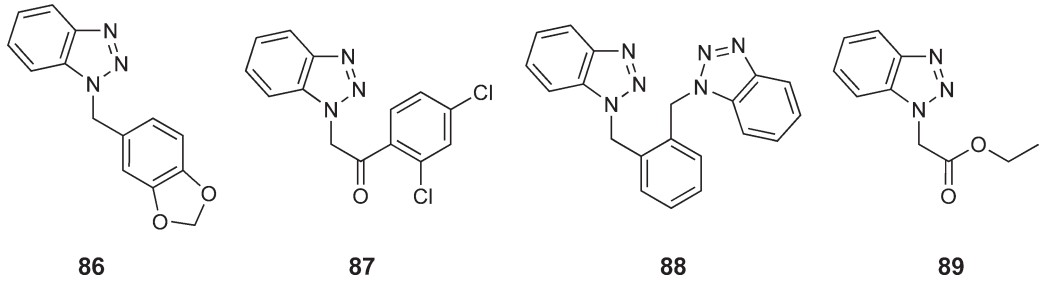
81 **82**

Scheme 4

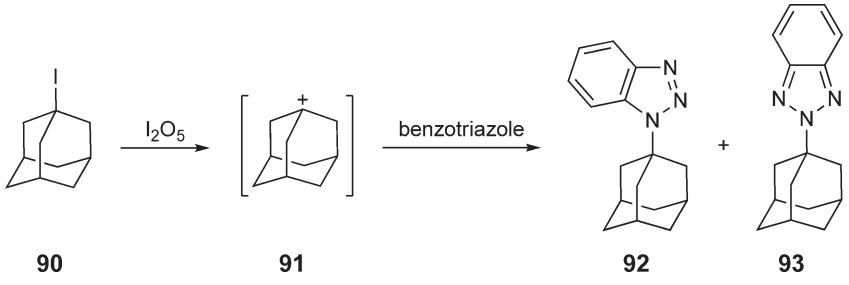
In aqueous micellar medium using cetyltrimethylammonium bromide as a surfactant, benzotriazole is alkylated regioselectively at N-1 with *n*-propyl and *n*-butyl bromides, but activated alkylating agents (benzyl chloride, allyl bromide, phenacyl chloride, etc.) produce mixtures of benzotrizol-1-yl and -2-yl isomers in ratios varying from 55:45 to 80:20, respectively <2001BCJ2133>. Alkylation of benzotriazole with bis(2-chloroethyl) ether under these conditions provides a mixture of derivatives **83–85** with isolated yields of 13%, 32% and 22%, respectively (Equation 2). Use of ionic liquids as media for alkylation of benzotriazole provides generally higher regioselectivity; however, the trend is opposite to that under micellar conditions with phenacyl bromide and similar compounds providing exclusively benzotriazol-1-yl derivatives and *n*-alkyl halides giving mixtures of benzotriazol-1-yl and -2-yl derivatives in a ratio of 15:1 <2004H(63)1077>.



Microwave irradiation can facilitate alkylation of benzotriazole. Thus, compound **86** is cleanly prepared in 95% yield upon irradiation of a solution of benzotriazole and the corresponding benzyl bromide in DMF for 40 s <2006BML999>. Very often microwave-assisted alkylation of benzotriazole works best when no solvent is used; for example, derivative **87** is prepared this way in 94% yield <2003T865>. Phase-transfer catalysis can also be used to increase the yield and improve regioselectivity of the alkylation process as it is illustrated by preparation of compound **88** in 72% yield in the presence of a pyridinophane <2006S654>. In another example, a reaction of benzotriazole with ethyl chloroacetate and K_2CO_3 in ethyl acetate is catalyzed by polyethylene glycol (PEG 400) to give a mixture of ethyl (benzotriazol-1-yl)acetate **89** (56%) and its benzotriazol-2-yl isomer (15%) <2002SRI265>.



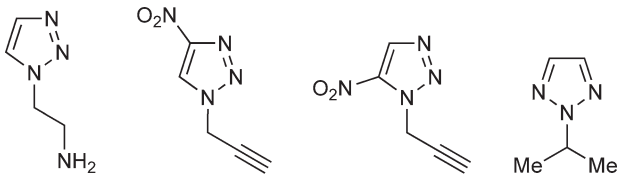
Adamantylation of benzotriazole represents a special case because direct substitution in adamantanyl halides by an S_N2 mechanism is impossible, and an S_N1 mechanism is improbable. In this case, reactive cation **91** is generated by oxidative cleavage of the C-I bond in 1-iodoadamantane **90**. Benzotriazole added to the reaction mixture binds cations **91** to afford a mixture of benzotriazol-1-yl **92** and -2-yl **93** derivatives in a ratio of 26:74 and the total yield of 67% (**Scheme 5**) <2001RJO1762>.



Scheme 5

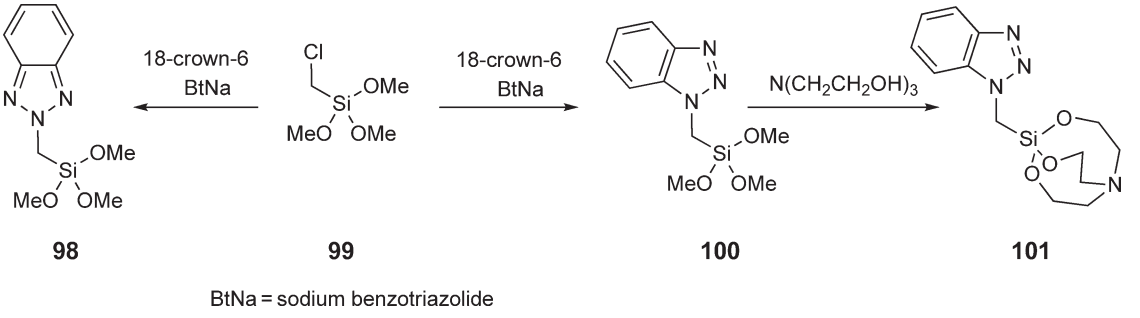
Alkylation of 1,2,3-triazole with *N*-(2-bromoethyl)phthalimide in the presence of Cs_2CO_3 followed by cleavage of the phthalyl moiety with hydrazine provides 1-(2-aminoethyl)-1,2,3-triazole **94** in 51% yield <2003JME1116>. A reaction of 4-nitro-1,2,3-triazole with propargyl bromide in the presence of KOH gives a mixture of isomeric 1-propargyl-1,2,3-triazoles **95** and **96** in the equimolar ratio <2003RJO1792>. However, in acidic media, when N-1

and N-3 positions are protonated, 2-substituted derivatives of 1,2,3-triazole are formed regioselectively. Thus, isopropyl alcohol reacts with 1,2,3-triazole in 95% sulfuric acid to provide 2-isopropyl-1,2,3-triazole **97** in 80% yield <2002JHC1111>.



94 **95** **96** **97**

Alkylation of benzotriazole with (chloromethyl)trimethoxysilane **99** provides a mixture of its derivatives **98** and **100** in a ratio of 1:3. In a reaction with tris-(2-hydroxyethyl)amine, compound **100** is converted to derivative **101** in nearly quantitative yield. Compound **98** reacts with tris-(2-hydroxyethyl)amine similarly (**Scheme 6**) <2003ARK(xiii)125, 2003CHE1639>.



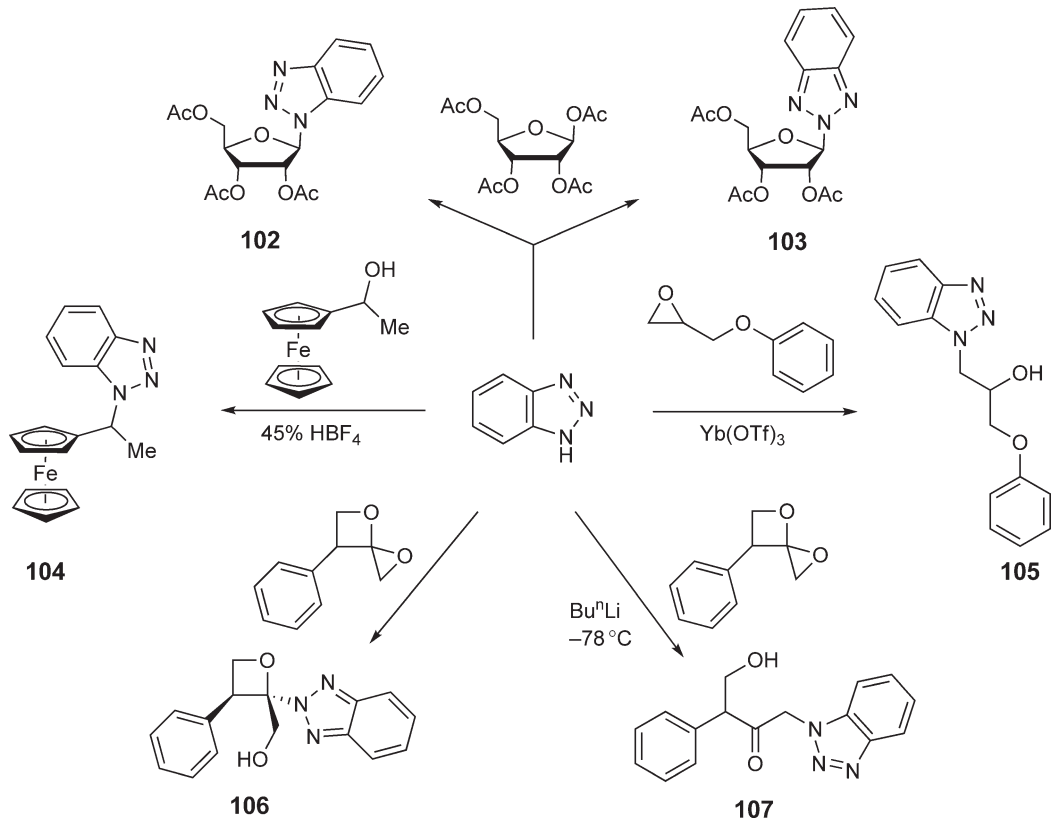
98 **99** **100** **101**

Scheme 6

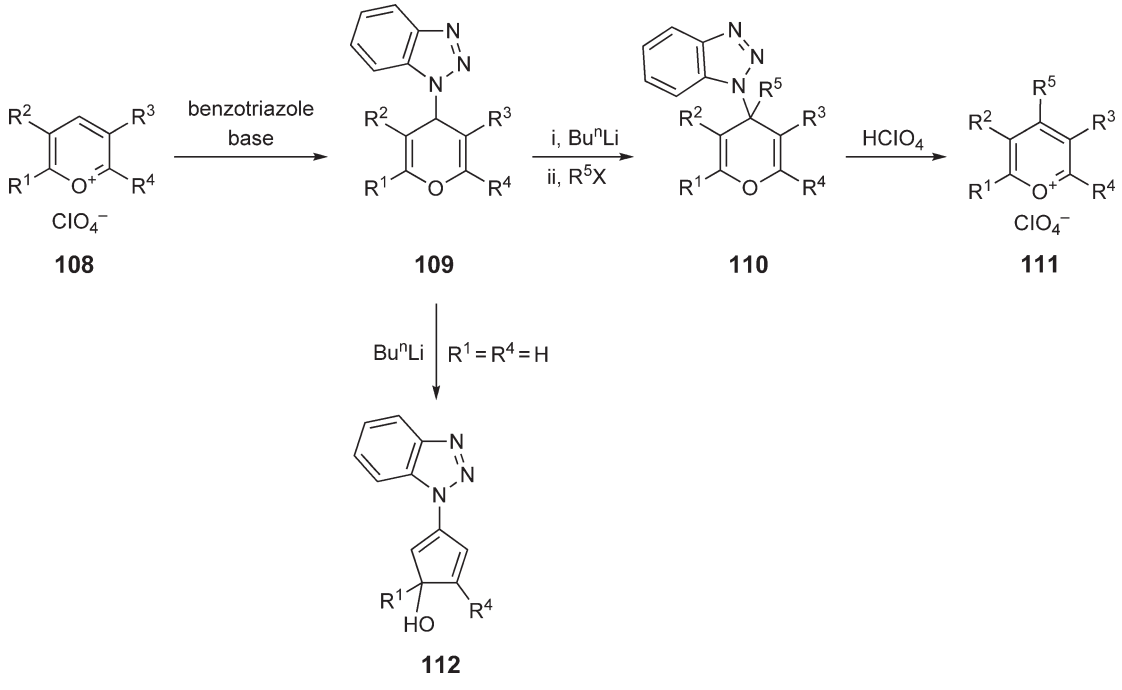
When positive charge of the reaction center is stabilized by an adjacent atom, even the acetoxy anion can be a good leaving group. Such a situation is typical in derivatives of sugars. Thus, heating of an equimolar mixture of benzotriazole and tetraacetylribose at 150 °C for 15 min results in formation of products **102** (63%) and **103** (3%) <2002NN73>. Due to strong electron-donating abilities of the ferrocene system, ferrocenyl methyl carbinol reacts eagerly with benzotriazole in the presence of 45% fluoroboric acid to give 1-(α-ferrocenylethyl)benzotriazole **104** in 93% yield (**Scheme 7**) <2004JOM(689)2473>. Catalyzed by ytterbium triflate, (phenoxymethyl)oxirane reacts with benzotriazole to afford derivative **105** in 71% yield <2003SC2989>. 1,5-Dioxaspiro[3,2]hexane with remarkably strained molecules reacts directly with benzotriazole without any catalyst to give oxetane derivative **106** as the main product in 41% isolated yield. The preference for N-2 substitution in product **106** seems to result from steric hindrance at the reaction center. However, under basic conditions, the same reagent gives product **107** (isolated yield 27%) as a result of a regular S_N2 attack on the oxirane methylene carbon atom <2003JOC1480>.

5.01.5.2 Nucleophilic Attack on Aromatic Rings

The anion derived from benzotriazole attacks electron-deficient aromatic rings of pyrylium salts **108** in position *para* to oxygen to give *4H*-pyrans **109** in high yields. Positions *ortho* in salts **108** are blocked by aryl groups ($R^1 = R^4 = Ar$) to avoid reactions there <1999JPR152>. Derivatives **109** have been found to be very useful in the synthesis of corresponding 4-alkyl pyrylium salts **111**, via 4-alkyl-4-(benzotriazole-1-yl)-*4H*-pyrans **110** (**Scheme 8**). Benzo[*b*]pyrylium <1997JOC8198, 1998EJO2623> and xanthylium <1997JOC8198> salts react similarly. Derivatives similar to adducts **109** were also obtained from nitrogen (*N*-methylacridinium) and sulfur (thioxanthylium) cationic heterocyclic systems <1999JHC927>. When $R^1 = R^4 = H$, the anions derived from pyrans **109** may also rearrange to 1,2-diaryl-2,4-cyclopentadien-1-ols **112** <1999JPR152>.

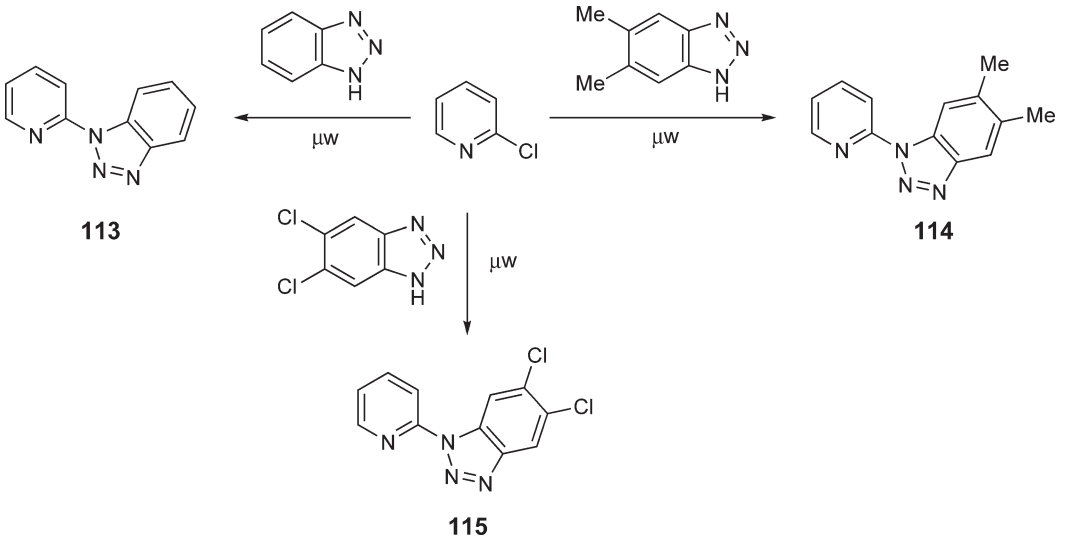


Scheme 7



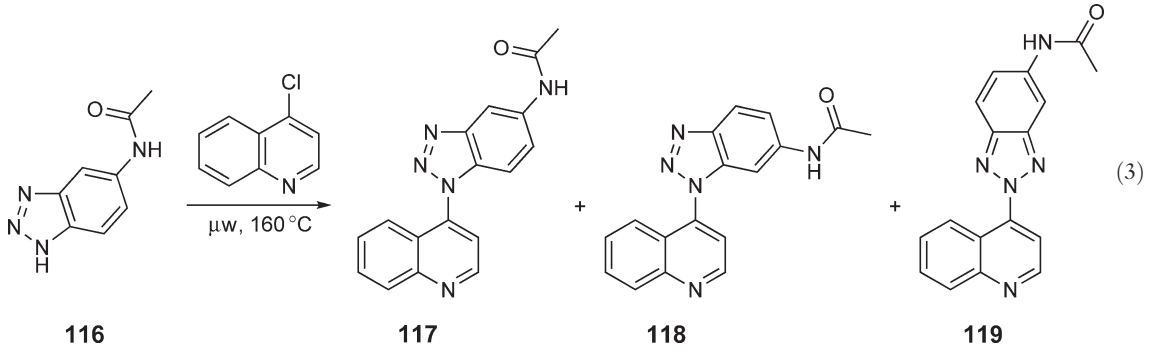
Scheme 8

Upon microwave (μw) irradiation, benzotriazole and its derivatives react readily with 2-chloropyridine to afford products **113-115** in 87%, 72%, and 70% yield, respectively (**Scheme 9**). 2-Chloroquinoline reacts similarly. 2-Bromopyridine and 2-bromoquinoline give generally lower yields in these reactions <2006OL415>.



Scheme 9

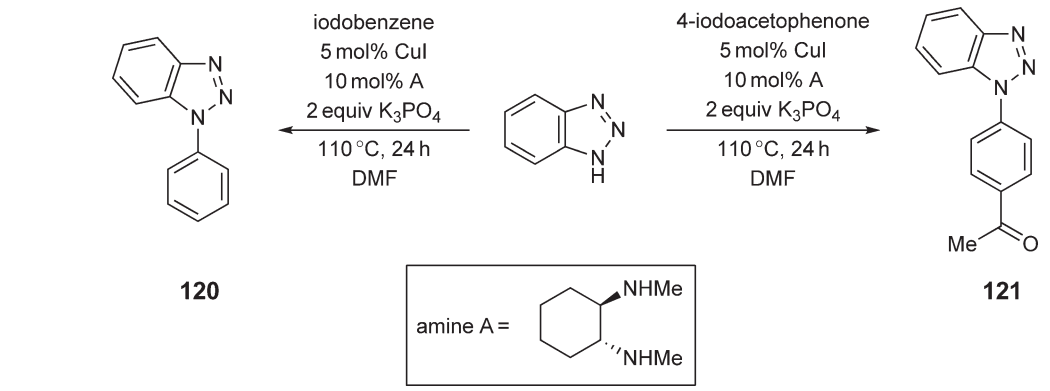
Microwave-induced reaction of 5-acetamidobenzotriazole **116** with 4-chloroquinoline gives a mixture of products **117** (43%), **118** (30%), and **119** (10%) (Equation 3). Interestingly, the product ratio does not depend on the solvent used (toluene, DMF, NMP) <2006T1895>.



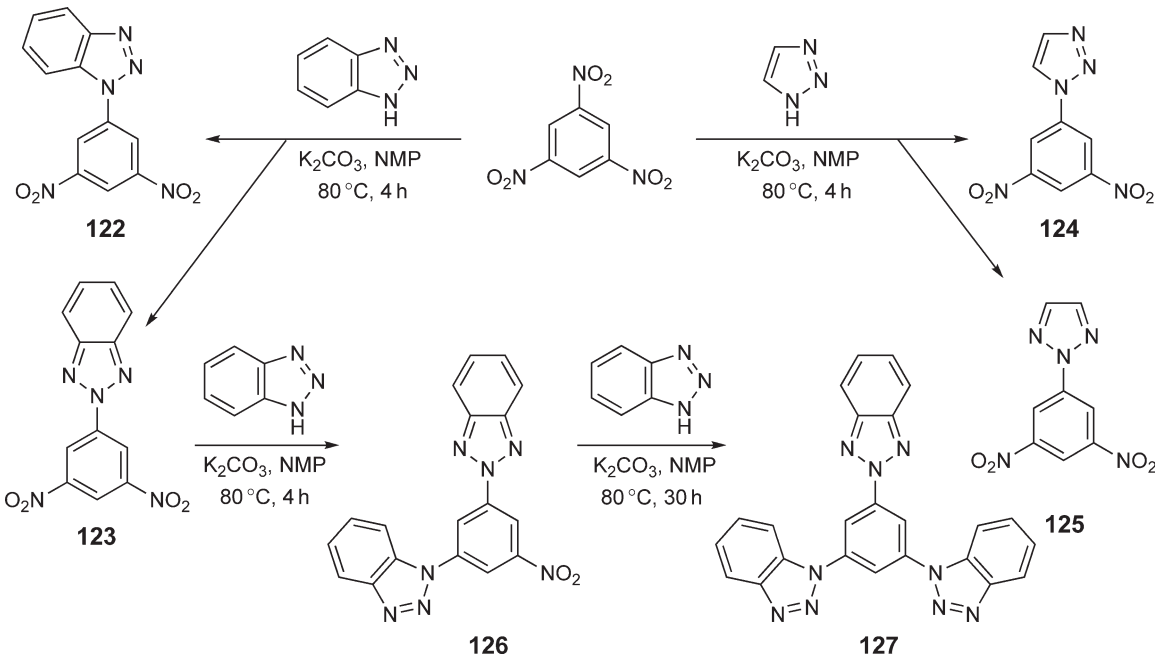
(3)

Catalyzed by a copper–diamine complex, benzotriazole reacts well even with nonactivated aromatic iodides. The case is illustrated in **Scheme 10** by formation of 1-phenylbenzotriazole **120** in 90% yield. The acetyl group as an electron-withdrawing substituent in *para* position has surprisingly negative effect on the product yield as derivative **121** is isolated in only 63% yield. Potassium phosphate is used as a base. The reactions are highly regioselective with the benzotriazol-1-yl to benzotriazol-2-yl isomer ratio higher than 25: 1 <2004JOC5578>.

Nucleophilic substitution of a nitro group by benzotriazole or triazole in strongly electron-deficient aromatic systems can also be easily achieved. Thus, heating of an equivalent mixture of 1,3,5-trinitrobenzene with benzotriazole and K_2CO_3 in NMP at 80 °C for 4 h affords products **122** and **123** in a ratio of 2:3 with 96% total yield. A similar reaction of 1,3,5-trinitrobenzene with 1,2,3-triazole gives a mixture of derivatives **124** and **125** in a molar ratio of 1:9. Surprisingly, only N-2 substitution is observed when 2-(3,5-dinitrophenyl)benzotriazole **123** is heated with benzotriazole and K_2CO_3 to give product **126** in 92% yield. Substitution of the last nitro group is also possible, but the reaction is much slower. Insoluble in most common solvents, 1,3,5-tribenzotriazolylbenzene **127** is isolated in analytically pure form in 62% yield. It can be concluded that electron-withdrawing abilities of benzotriazolyl substituents are comparable to those of a nitro group to activate aromatic rings for nucleophilic substitution (**Scheme 11**) <2004RCB588>.



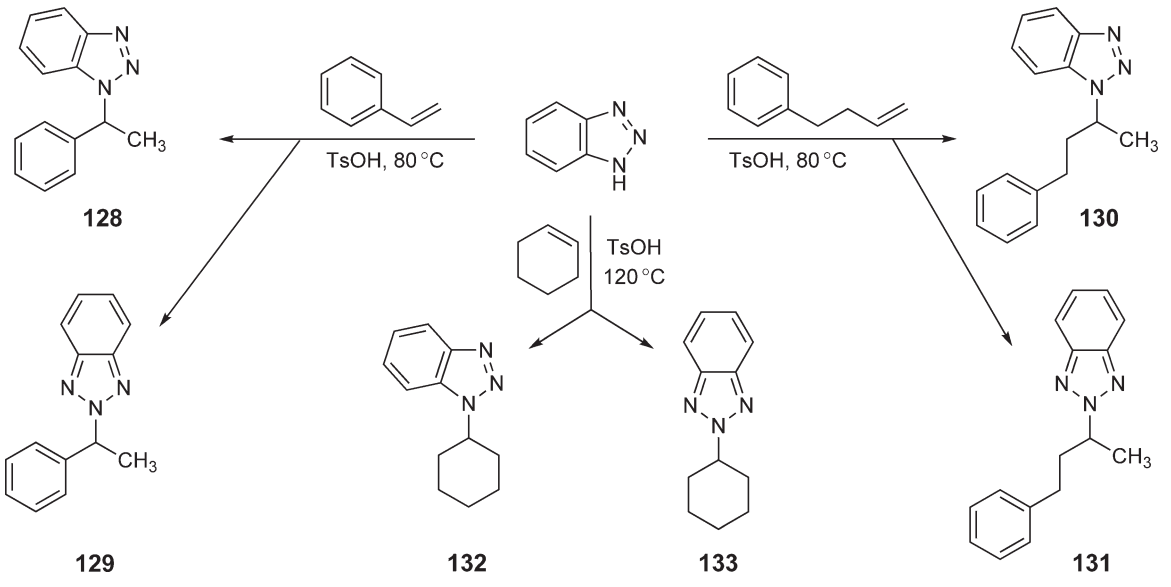
Scheme 10



Scheme 11

5.01.5.3 Addition to Multiple Bonds

Under strongly acidic conditions (10% molar equivalent of TsOH), benzotriazole adds to unactivated alkenes to afford a mixture of 1-alkyl- and 2-alkylbenzotriazoles. Because protonation of the double bond with formation of the corresponding carbocation is the first step in these additions, Markovnikov's rule is followed, and derivatives with a benzotriazolyl substituent at the terminal carbon atom are not observed. Three examples of such additions are depicted in **Scheme 12**. Thus, in a reaction with styrene, benzotriazol-1-yl **128** and -2-yl **129** are formed in a ratio of 6.5:1 and total yield of 46%. In a reaction with 4-phenylbutene, derivatives **130** and **131** are obtained in a ratio of 1.9:1 and total yield of 65%. Normal terminal alkenes give the corresponding benzotriazol-1-yl and benzotriazol-2-yl derivatives as well, but the total yields are significantly lower (25% from 1-octene and 29% from 1-decene). Increasing the amount of TsOH from 10 to 100 mol% improves slightly the overall yield, but it also results in more complex mixtures of the products due to rearrangements of the original carbocations. Cyclohexene does not react with benzotriazole at 80 °C; however, at 120 °C, a mixture of derivatives **132** and **133** is obtained in a ratio of 1.1:1 and total isolated yield of 56% <1995J(P2)1645>.



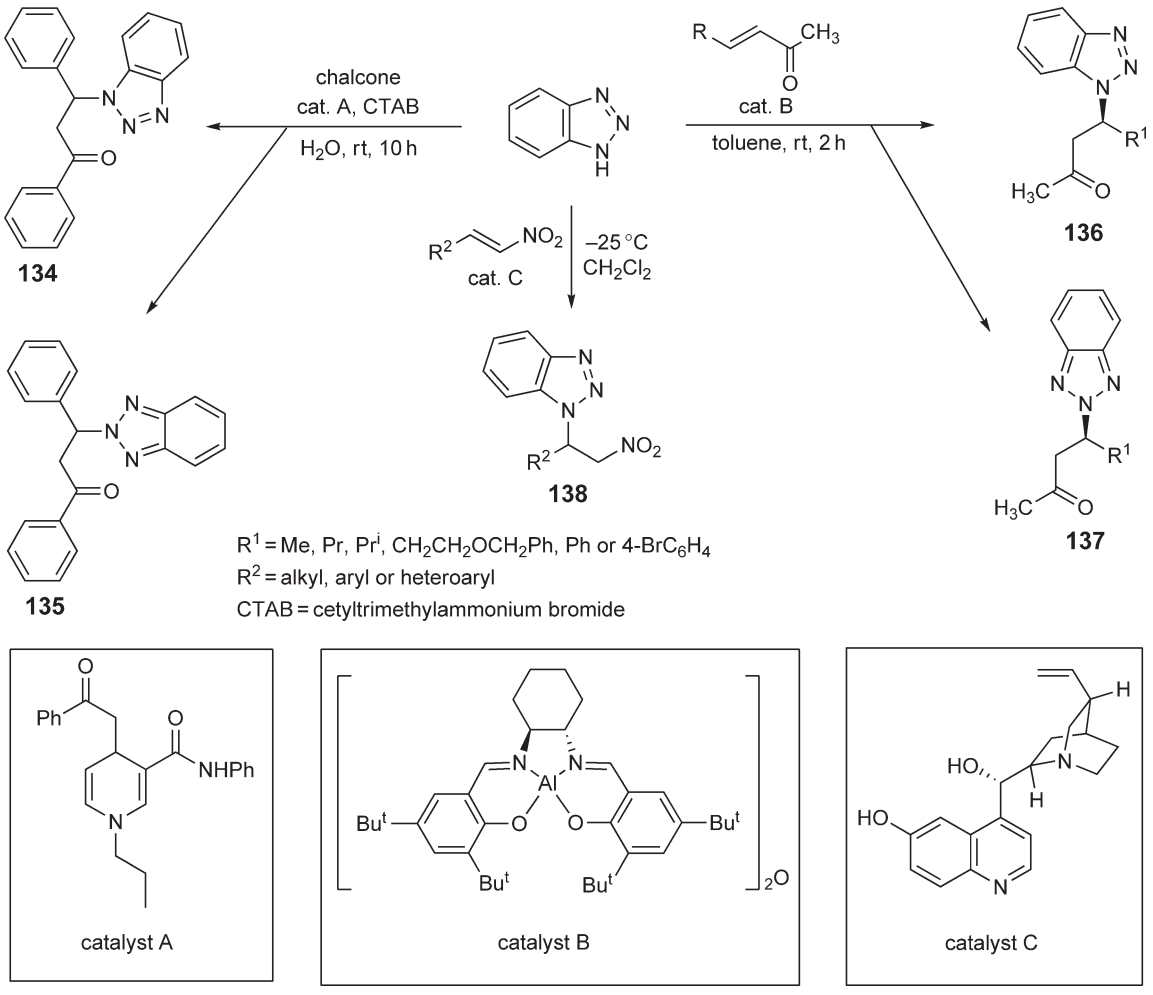
Scheme 12

Michael addition of benzotriazole to electron-deficient double bonds is described in CHEC-II(1996) <1996CHEC-II(4)1>. One of the innovations in this field is running the reaction of benzotriazole with chalcone in a micellar medium to afford a mixture of derivatives **134** and **135** in the molar ratio of 4:1 and total yield of 75% (**Scheme 13**) <2003CL1064>. Even more important innovation is running such reactions enantioselectively with application of optically active bases as catalysts. Thus, addition of benzotriazole to α,β-unsaturated ketones derived from acetone in the presence of catalyst B produces mixtures of products **136** and **137** in ratios varied from 3:1 to 2:1 with total yields in the range of 53–75% and high enantioselectivity (70–98% = ee) <2005AGE2393>. Addition of benzotriazole to 1-nitro-1-alkenes proceeds enantioselectively in the presence of catalyst C to provide exclusively benzotriazol-1-yl derivatives **138** in the average yield of 77% and high ee (64–94%) <2006OL1391>.

When the electron-deficient alkene contains a good leaving group X at the double bond, addition of benzotriazole may be followed by elimination of X (or HX) with restoration of the double bond. The total effect is a nucleophilic substitution of group X by benzotriazolide anion. Four examples of such reactions are gathered in **Scheme 14**. Thus, benzotriazolyl nitronyl nitroxide **139** must result from addition of the benzotriazolide anion to C-2 of 2-bromo-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl followed by elimination of Br^- <2004T99>. Sometimes, the intermediate adducts are stable enough to be isolated and characterized. Such is the case of adduct **140** that is obtained from a low temperature reaction of benzotriazole with methyl 2-(trifluoroacetyl)vinyl sulfone. At slightly elevated temperature, adduct **140** eliminates spontaneously methanesulfinic acid to give product **141** <2003RCB1791>. Addition of a benzotriazolide anion to carbon α of (*E*)-(2-phenylvinyl)phenyliodonium tetrafluoroborate results in unstable benzyl anion **143** that rapidly eliminates iodobenzene to afford (*E*)-1-(2-phenylvinyl)benzotriazole **142** <2002JCM388>. Heating a mixture of benzotriazole, 2-chloro-1,1,1-trifluoroethane, KOH and DMSO at 80 °C for 8 h leads to (*E*)-1-(2-chloro-1-fluorovinyl)benzotriazole **145**. The proposed mechanism for this reaction involves elimination of HF from the starting material and trapping of the evolved 2-chloro-1,1-difluoroethene by benzotriazolide anion to form intermediate anion **144** that spontaneously eliminates F^- to give product **145** <2002T4077>.

Application of catalysts allows sometimes executing this addition/elimination process even with alkenes without any electron-deficient substituent attached. Such case is illustrated by an example in **Scheme 15**. In the presence of mercury-(II) acetate and trifluoroacetic acid, 1,2,3-triazoles **146** react with vinyl acetate at 70 °C to give vinyl derivatives **148** in good yields (70–88%) <2002RJO1056>. Adducts **147** are presumed to be intermediates in this process.

In the presence of triphenylphosphine as a catalyst, benzotriazole adds readily to activated allenes. Its reaction with ethyl 2,3-butadienoate produces a mixture of adducts **149** (54%) and **150** (20%). Both derivatives form exclusively as *(E)*-isomers <2006T3710>. In a reaction of benzotriazole with dibenzoylacetylene and

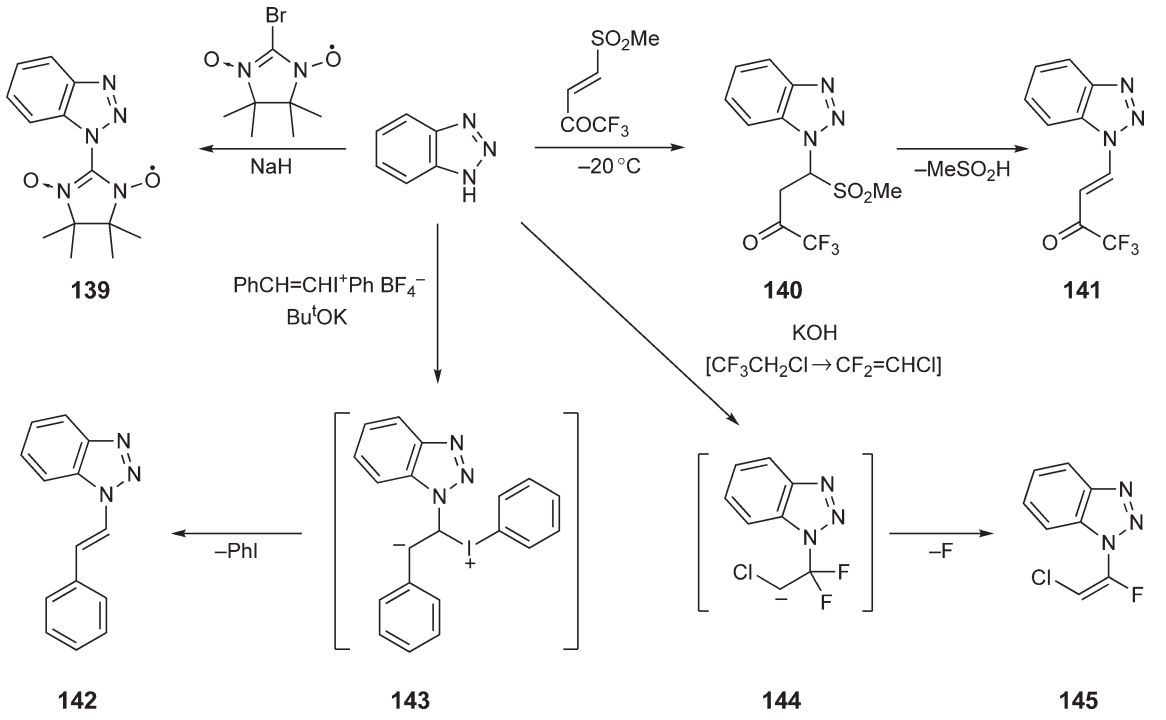


Scheme 13

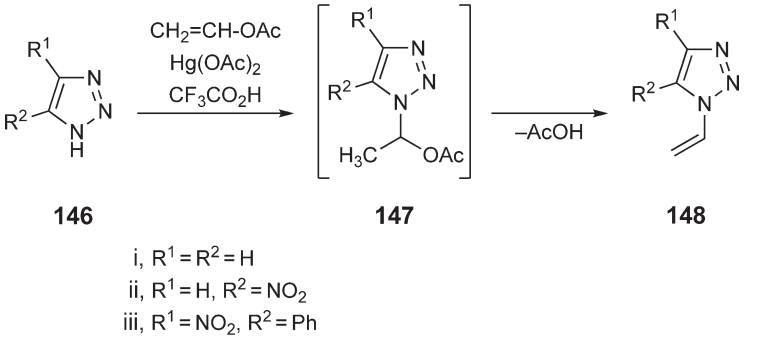
triphenylphosphine (used in the equimolar amount), a mixture of compounds **151** (40%) and **152** (45%) is obtained (**Scheme 16**). Neither open-chain benzotriazol-2-yl analog of **151** nor benzotriazol-1-yl analog of furan derivative **152** is detected <2002TL9449>. It seems to be the steric hindrance in reaction intermediates solely responsible for that distinction. To make the cyclization to a furan system possible, the molecule **151** must first assume (*E*)-configuration, and than bring the carbonyl groups to close proximity. Switching between (*Z*)- and (*E*)-configurations in compound **151** seems to be relatively easy by addition of another molecule of benzotriazole to the double bond followed by its elimination, but rotation of the α-benzoyl group would impose much strain on the molecule due to steric repulsion between its phenyl and the benzotriazolyl benzenoid ring. The less bulky benzotriazol-2-yl substituent in the original adduct of benzotriazole to the triple bond allows for such transformations without high energetic barriers.

5.01.5.4 Complexes with Borane

1-Benzylbenzotriazole **153** reacts rapidly with borane to form complex **154** in quantitative yield. Complex **154** and its analogs derived from 1-alkylbenzotriazoles are inert to water and air at room temperature and easy to handle solids. Treatment with Bu^nLi followed by iodomethane converts complex **154** into its α-methylated product **155**. In the case of a sterically hindered and less acidic substituent (compound **157**), the corresponding complex with BH_3 **158** undergoes lithiation in position 4 to afford compound **159**. Refluxing in ethanol removes the borane group from N-3 to restore the benzotriazole system (products **156** and **160**) (**Scheme 17**) <1998OPP325>.



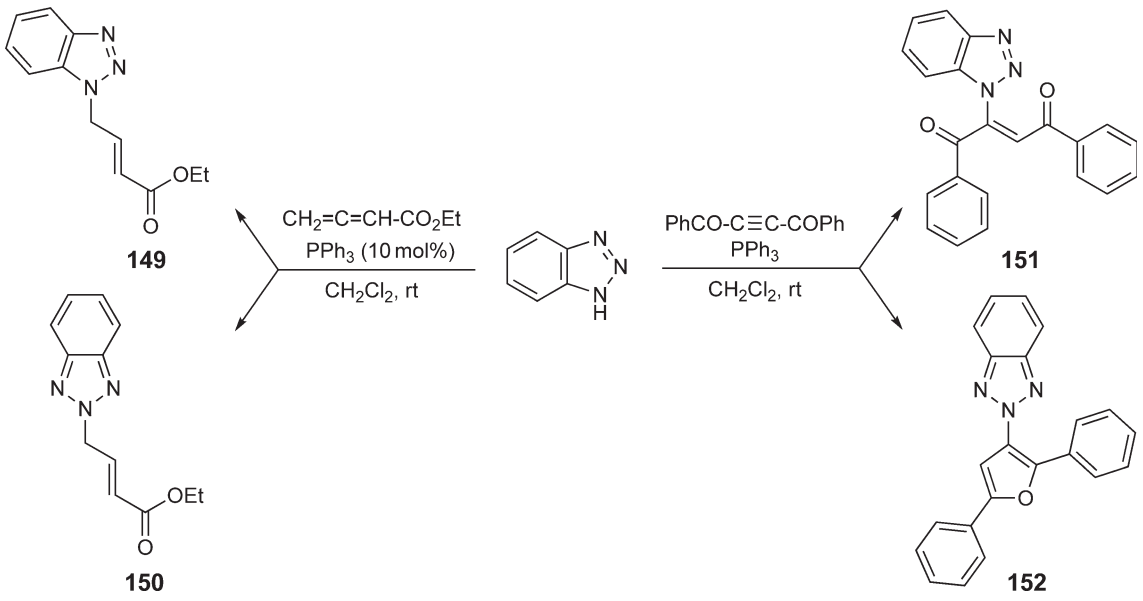
Scheme 14



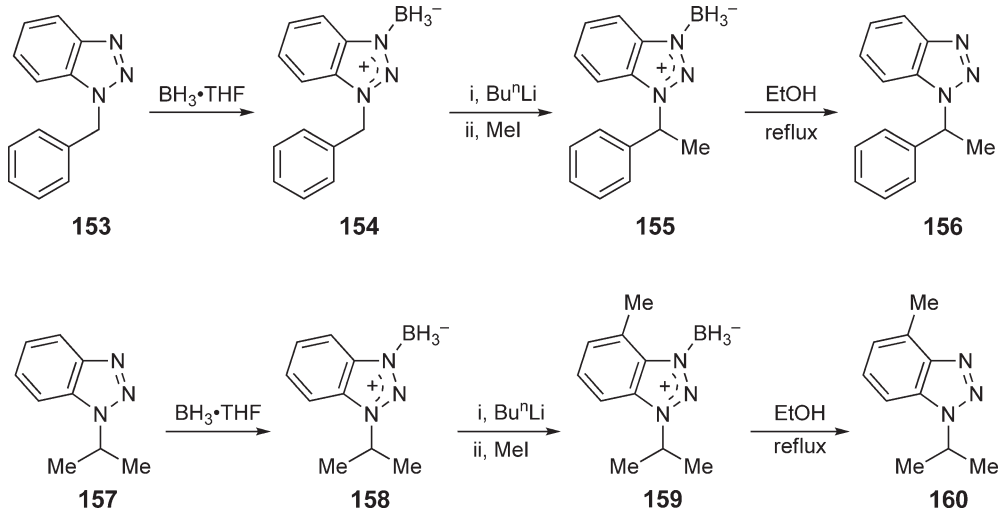
Scheme 15

5.01.5.5 N-Oxides

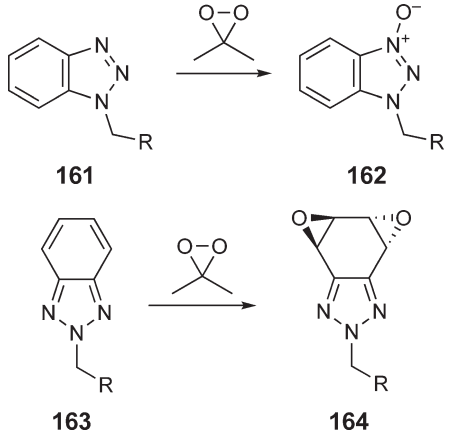
Oxidation of 1-alkylbenzotriazoles **161** with dimethyldioxirane leads to the corresponding oxides **162**, generally in high yield (Equation 4); however, in comparison with pyridine, the reaction is much slower <2001JOC5585>. Electron-deficient substituents R make the oxidation process more difficult and the yields of products **162** are compromised (e.g., 40% for R = CN). 1-Benzoylbenzotriazole is not oxidized by this reagent. n-Butyllithium lithiates oxides **162** predominantly in position 7. Refluxing in acetic anhydride converts oxides **162** into starting 1-alkylbenzotriazoles. 2-Alkylbenzotriazoles **163** react differently with dimethyldioxirane; instead of the nitrogen, carbon atoms of the benzene ring are attacked to give dioxiranes **164** (Equation 5).



Scheme 16



Scheme 17

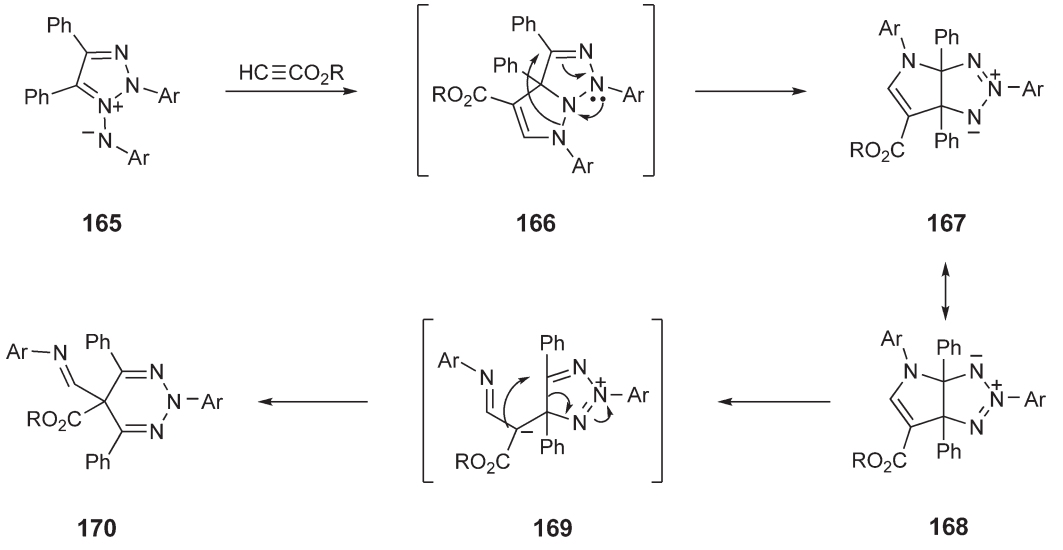


(4)

(5)

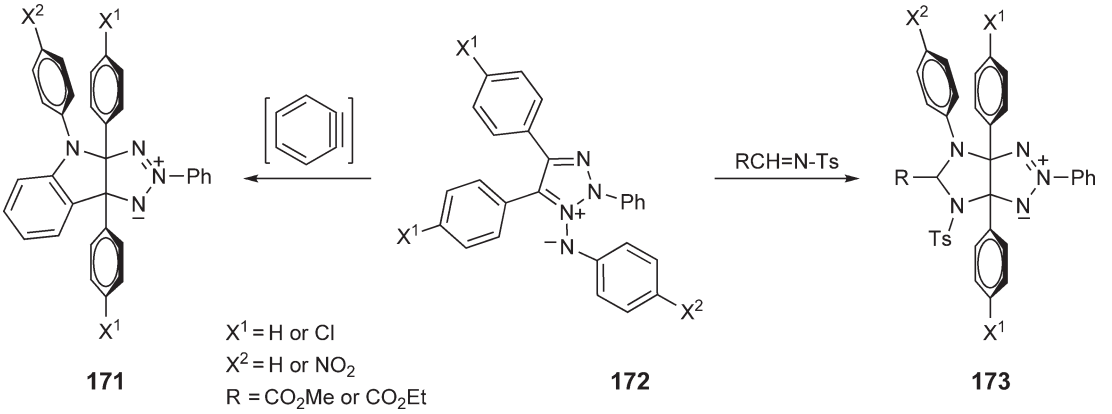
5.01.5.6 Triazolium Aminides

Aza analogs of *N*-oxides, aminides, are reactive 1-3-dipoles. In an example given in **Scheme 18**, 1,2,3-triazolium-1-aminides **165** undergo cycloaddition to esters of propiolic acid to give unstable adducts **166** that under the reaction conditions, reflux in acetone, rearrange to fused pyrrolo[2,3-*d*]-1,2,3-triazolines (mesomeric forms **167** and **168**). Prolonged heating causes cleavage of the C–N bond (between C–3a and N-4) in **168** and rearrangement of the obtained betaines **169** to more stable 2,5-dihydro-1,2,3-triazines **170**. This relatively complex process produces triazines **170** in moderate yields (35–52%) <2006TL1721, 2006JOC5679>.



Scheme 18

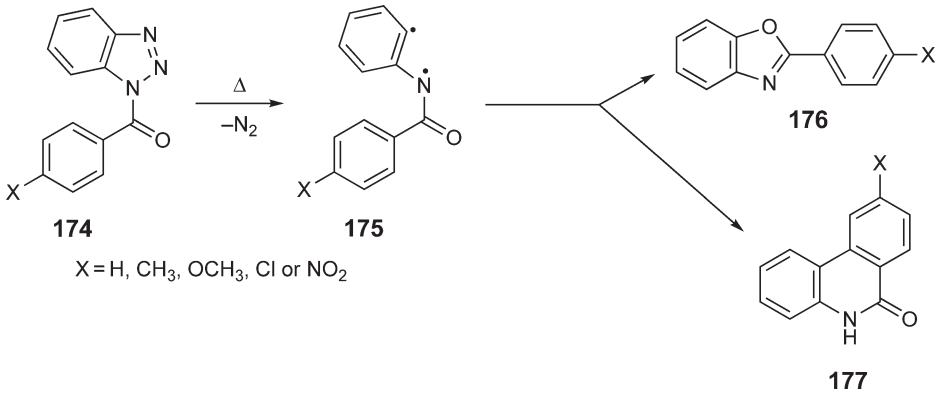
Benzyne generated *in situ* by diazotization of anthranilic acid adds readily to aminides **172** to provide cycloadducts **171**. Introduction of a nitro group into *para* position of the phenyl ring on the nitrogen terminus of the 1,3-dipole ($X^2 = NO_2$) stabilizes the system and results in higher yields of product **171** (70% vs. 50% for $X^2 = H$). Electron-deficient imines react also with aminides **172**, but the yields of isolated adducts **173** are relatively low (10–26%) (**Scheme 19**) <2003ARK(vii)110>.



Scheme 19

5.01.5.7 Thermolysis of Benzotriazole and Triazole Derivatives

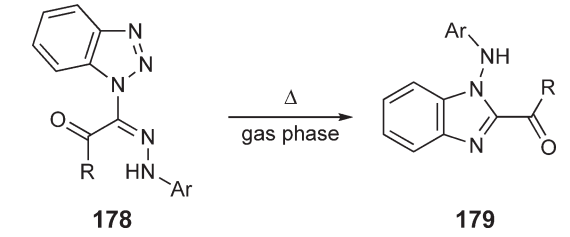
Thermolysis of benzotriazole derivatives involves cleavage of the heterocyclic ring with extrusion of a molecule of nitrogen and formation of a diradical. If the substituent at N-1 of benzotriazole is suitable for trapping radicals, cyclization to a new heterocyclic system is usually the main route for quenching the diradical. Thus, gas-phase thermolysis of 1-aryloxybenzotriazoles **174** proceeds via diradical **175**. The most favorable next step is formation of a bond between the carbonyl oxygen and the *ortho* carbon atom resulting in benzoxazole **176**. In another route, a bond forms between the ortho carbon atoms from both rings to give phenanthradinone derivative **177** (**Scheme 20**) <2005T8257>. Distribution of the products is not affected much by substituents X supporting radical mechanism of the reactions.



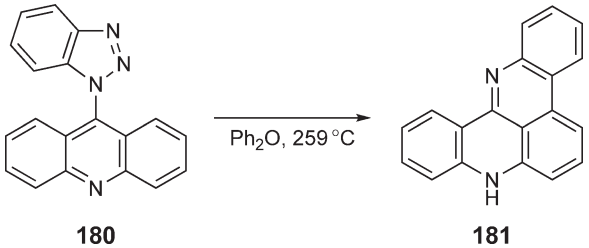
174 175 176 177

Scheme 20

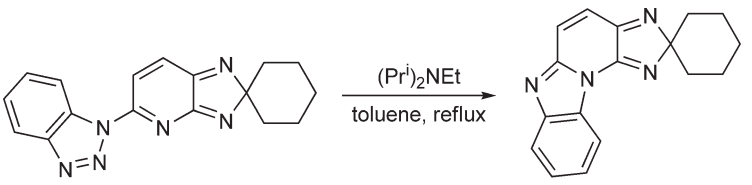
The picture can be generalized. If the substituent is attached to benzotriazolyl N-1 by an sp^2 hybridized carbon atom, the produced diradical is relatively stable, and a product resulting from simple cyclization predominates, like in an example given in **Scheme 20**. Three additional examples of such reactions are shown in Equations (6)–(8). Thus, gas-phase thermolysis of hydrazones **178** (R = Me or Ph, Ar = Ph or *para* substituted Ph) produces benzimidazoles **179** as the main products in 27–50% yields. Minor side products result mostly from cleavage of other bonds in the molecule not involving benzotriazole, and no products resulting from direct radical trapping by the carbonyl group are detected <2003T9455>. For a preparative purpose, it is more convenient to carry out pyrolysis of benzotriazole derivatives in high boiling solvents. This way, 8*H*-quino[4,3,2-*kl*]acridine **181** is obtained by refluxing a solution of 9-(1*H*-1,2,3-benzotriazol-1-yl)acridine **180** in diphenyl ether <2002JME590, 1997J(P1)2739>. Similar thermal conversions of 9-(5′-substituted-1′,2′,3′-triazol-1′-yl)acridines generate corresponding 7*H*-pyrido[4,3,2-*kl*]acridines <2003JCM75, 2001J(P1)3174>. Base catalysis may help the thermolysis, as it is illustrated by conversion of 5′-(benzotriazol-1-yl)-spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridine **182** into the corresponding fused benzimidazole derivative **183** occurring in refluxing toluene <2002JCM153>.



178 179 (6)

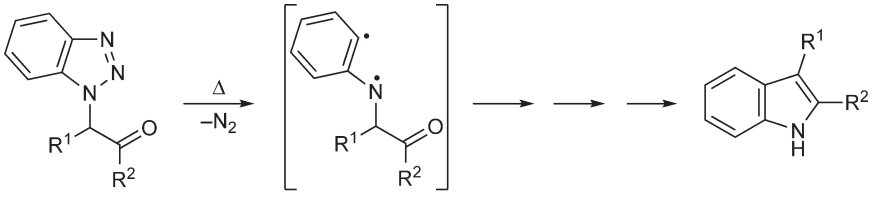


180 181 (7)



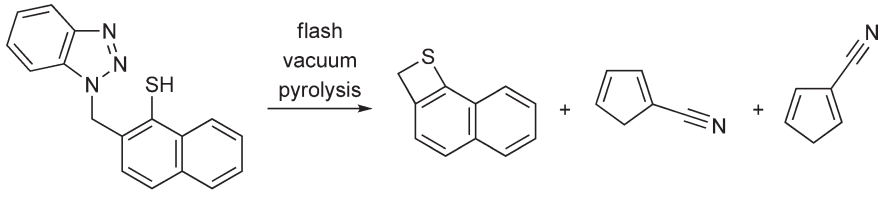
182 183 (8)

In other cases, extrusion of N_2 creates higher energy diradicals that are suitable for more complex rearrangements. Such situation is represented in **Scheme 21** by gas-phase thermolysis of ketones **184**. Diradical **185** created in the first step of this process undergoes a series of transformations that ends on stable molecule of indole **186** <2004JPO267>. Flash vacuum pyrolysis of naphthalenethiol **187** at 750 °C causes elimination of benzotriazole with formation of *2H*-naphtho[1,2-*b*]thiete **188**. Under the conditions applied, the liberated benzotriazole extrude a molecule of nitrogen end undergoes subsequent ring contraction to thermally more stable cyclopentadienecarbonitriles **189** and **190** (Equation 9) <1998JHC1505>.



184 185 186

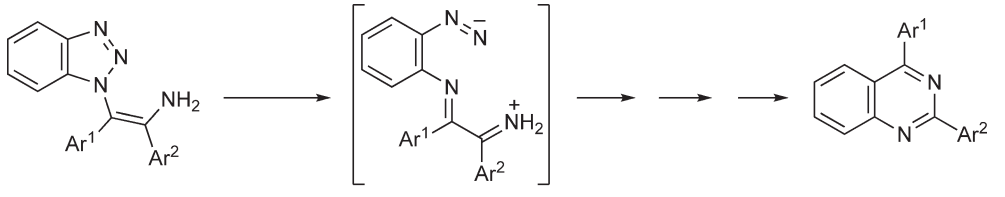
Scheme 21



187 188 189 190 (9)

5.01.5.8 Ionic and Radical Ring Opening with Loss of Nitrogen

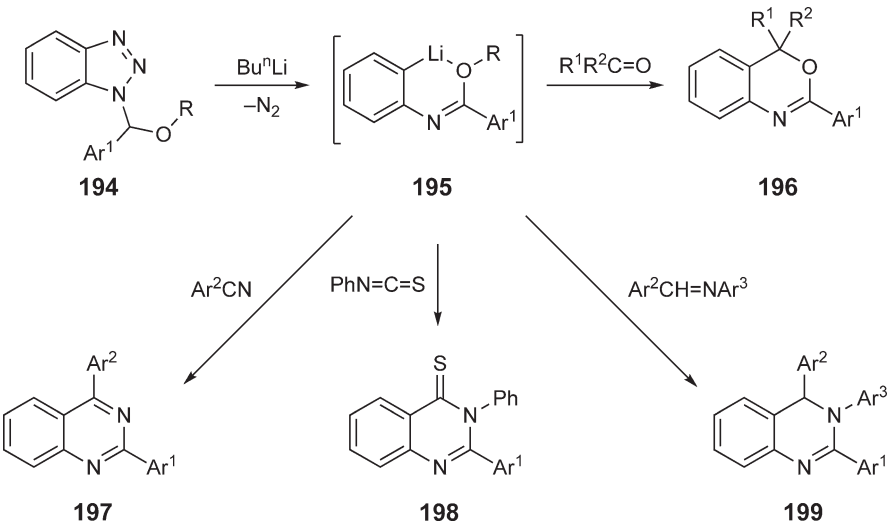
The presence of an electron-donating group adjacent to the benzotriazol-1-yl system renders the triazole ring susceptible to opening at elevated temperatures. Thus, upon heating to reflux in toluene, enamines **191** undergo ring scission between the N-1 and N-2 atoms to form betaines **192**. The consecutive loss of a molecule of nitrogen followed by cyclization and rearrangement leads to quinazolines **193** (**Scheme 22**) <1995JOC246>.



191 192 193

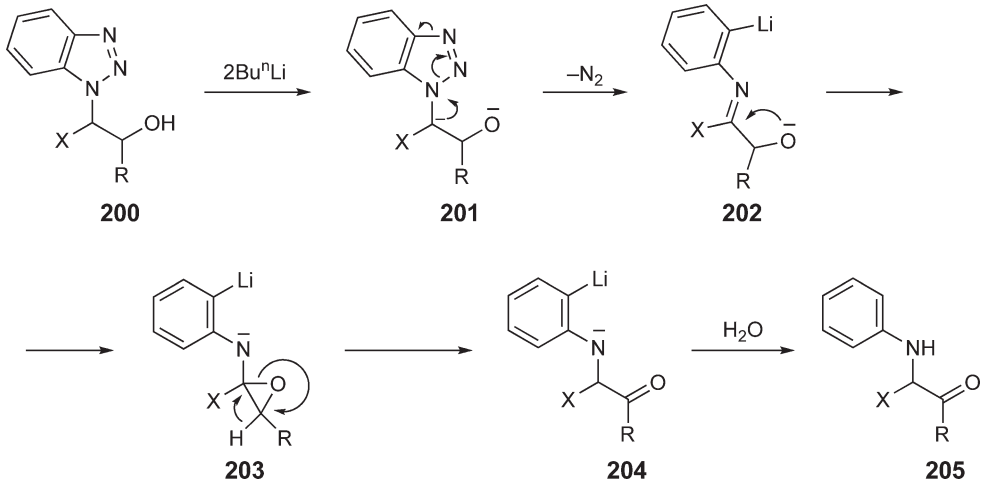
Scheme 22

Anions obtained by lithiation of 1-(α-alkoxyalkyl)benzotriazoles **194** undergo ring cleavage followed by extrusion of nitrogen to give *ortho*-iminophenyl anions **195**. These anions can be trapped by various electrophiles to provide practical synthetic methods for several heterocyclic systems **196–199** (**Scheme 23**) <1995JOC7625>.



Scheme 23

Dianion **201**, generated by treatment of alcohol **200** with 2 molar equivalents of Bu^{n}Li at −78 °C, undergoes ring opening with extrusion of N_2 and formation of new anion **202**. Cyclization to oxirane **203** and hydrogen shift creates anion **204** that is hydrolyzed during work-up to aniline derivative **205** (**Scheme 24**) <1998H(48)187>.

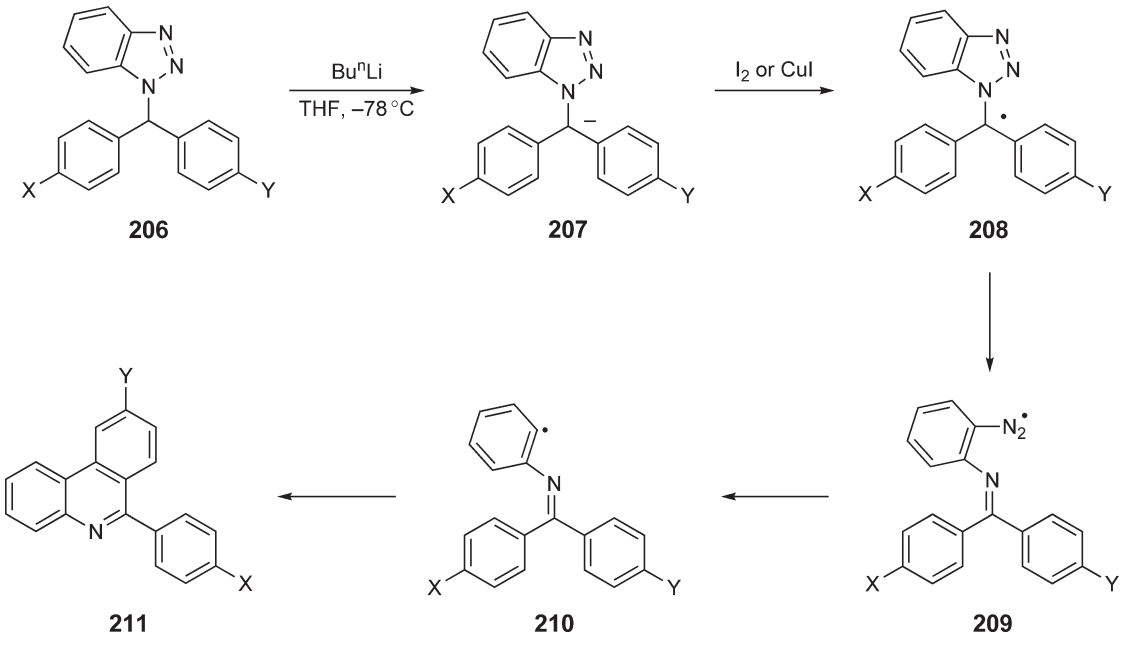


X = Ph, carbazol-9-yl or indol-1-yl
R = Ph, 4-MeC$_6$H$_4$ or *n*-C$_7$H$_{15}$

Scheme 24

Anions **207**, derived from 1-(diarylmethyl)benzotriazoles **206**, can be oxidized with mild oxidants to relatively stable triaryl radicals **208**. One of the possible reactions of radicals **208** is ring opening to give radicals **209**. Elimination of nitrogen from **209** produces unstable species **210** that undergo intramolecular cyclization to phenanthridines **211** (**Scheme 25**) <1996JHC607, 1998JOC1467>. When substituents X and Y are identical, products **211**

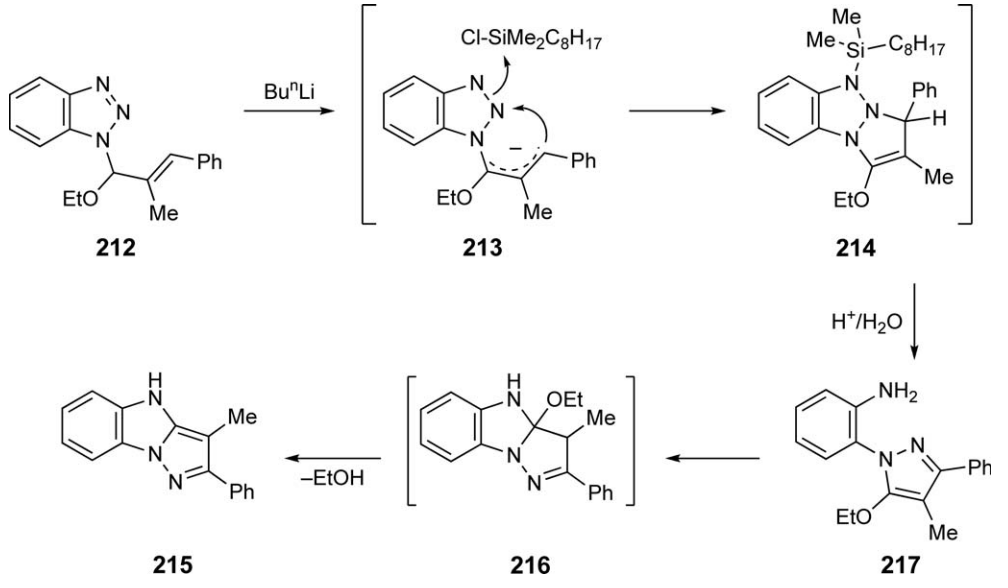
are obtained with average yield of 50%. When X and Y are different but of similar electronic character, mixtures of two isomeric phenanthridines are formed. Polycyclic phenanthridines are formed in these reactions when tricyclic analogs of **206** derived from acridine, xanthene, or thioxanthene are used as starting materials <1999JHC927>. Another possible reaction of radicals **208** is their dimerization resulting from combining one radical with another in position *para* of the aromatic ring (when X = H) <1998JOC1467>.



Scheme 25

5.01.5.9 Intramolecular Electrophilic Attack on N-2

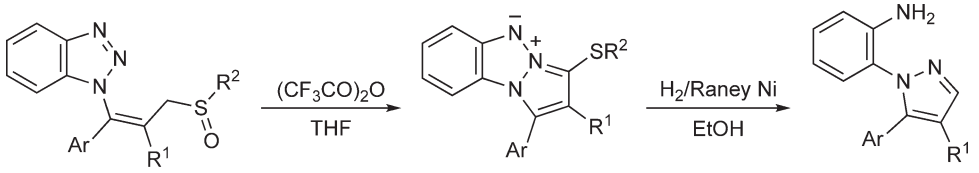
Treatment of 1-(α-ethoxyalkyl)benzotriazoles **212** with n-butyllithium and dimethyloctylsilyl chloride followed by acidic hydrolysis of the intermediates gives a mixture of pyrazoles **215** and **217** (**Scheme 26**). The probable reaction



Scheme 26

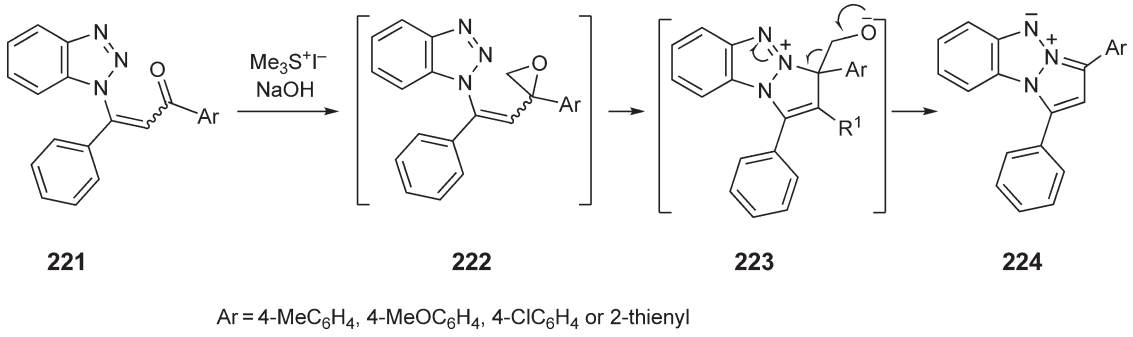
pathway involves allylic anion **213** which undergoes cycloaddition to N-2 of the benzotriazole system assisted by simultaneous reaction of N-3 with the silyl chloride to give intermediate **214**. Acidic cleavage of the bond between N-2 and N-3 leads to (2-aminophenyl)pyrazole **217**. Under acidic conditions, derivative **217** rearranges slowly to pyrazole[5,1-*b*]benzimidazole system **215**, via intermediate **216** <1996KGS775>.

Treated with trifluoroacetic anhydride, sulfoxides **218** undergo conversion to triazapentalenes **219** with high yields. The process must involve acylation of the sulfoxide oxygen atom and generation of a carbocation that attacks the N-2 atom of benzotriazole. Hydrogenation over Raney nickel cleaves the C–S and one of the N–N bonds to generate *ortho*-substituted anilines **220** (**Scheme 27**) <2002EJO493>.



Scheme 27

Addition of benzotriazole to 1-phenyl-2-aroylacetylenes gives α,β-unsaturated ketones **221** in high yields. By treatment with dimethylsulfonium ylide, ketones **221** are converted to epoxides **222**, Opening of the oxirane ring and electrophilic attack of the obtained tertiary carbocation on N-2 of the benzotriazole system leads to betaines **223** that consecutively eliminate formaldehyde to give triazapentalenes **224** (**Scheme 28**) <2004ARK(iii)109>.



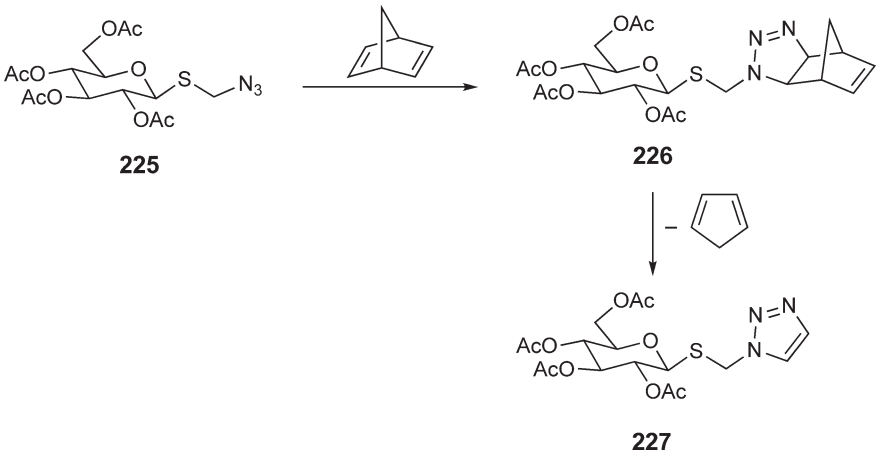
Scheme 28

5.01.6 Reactivity of Nonconjugated Rings

5.01.6.1 Conversion of Triazolines to Triazoles

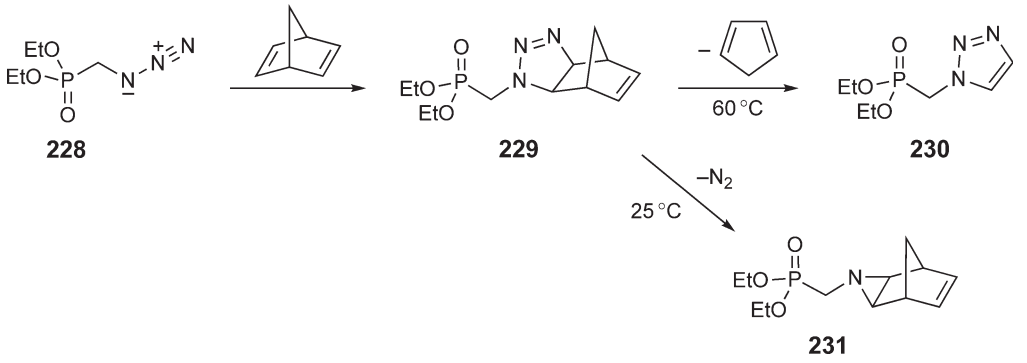
5.01.6.1.1 Retro Diels–Alder reaction

A convenient synthetic method for 1,2,3-triazoles unsubstituted at C-4 and C-5 utilizes a reaction of azides with norbornadiene, for example, **Scheme 29** <2004JOC1081>. The process is performed in refluxing dioxane. In the first step, norbornadiene undergoes 1,3-dipolar cycloaddition to glucose-derived azide **225** to give triazoline **226**. The following retro Diels–Alder reaction results in the elimination of cyclopentadiene to furnish triazole derivative **227** in 79% yield.



Scheme 29

Diethyl azidomethanephosphonate **228** reacts with norbornadiene at room temperature to give triazoline **229** in 86% yield. When heated at 60 °C, derivative **229** decomposes with elimination of cyclopentadiene to provide (1,2,3-triazol-1-yl)methanephosphonate **230** in 74% yield. However, when it is left at room temperature for an extended period of time, triazoline **229** undergoes slow conversion to aziridine **231** with elimination of nitrogen (**Scheme 30**) <1995H(40)543>.

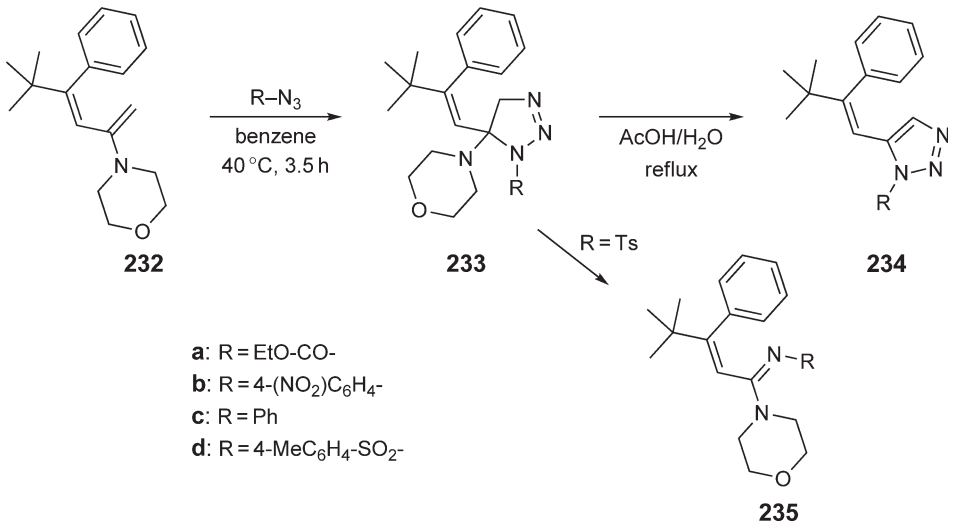


Scheme 30

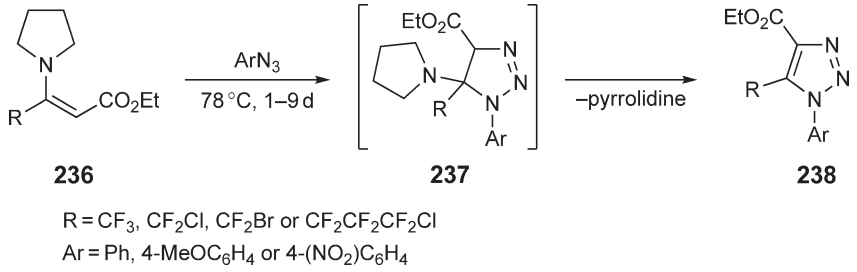
5.01.6.1.2 Elimination of amines

1,3-Dipolar cycloaddition of 2-morpholino-1,3-diene **232** to azides provides triazolines **233** (**Scheme 31**). Triazolines **233a** and **233b**, derived from 4-(ethoxycarbonyl)- and 4-nitro-phenyl azides, respectively, are stable under the reaction conditions (benzene, 40 °C); they can be isolated in good yields and fully characterized. However, phenyl derivative **233c** is less stable and spontaneously eliminates morpholine to give triazole **234c**. To eliminate morpholine from triazolines **233a** and **233b**, they are heated to reflux in aqueous acetic acid. Strong electron-withdrawing effect of the tosyl group in triazoline **233d** promotes cleavage of the ring with elimination of diazomethane to furnish α,β-unsaturated carboximidamide **235**. 1,5-Substitution of the triazole ring in derivatives **234** is confirmed by NMR studies <2005HCA1813>.

Less reactive *(Z)*-ethyl 3-fluoroalkyl-3-pyrrolidinoacrylates **236** require prolonged heating with azides to afford triazoles **238** in good yields (66–97%). The reactions give the best results when mixtures of reagents are heated neat, without any solvent added. Intermediate triazolines **237** do not survive under such conditions and spontaneously eliminate pyrrolidine to form triazoles **238**. The reactions are proved to be strictly regioselective with the ethoxycarbonyl group always located at C-4 of the triazole system (**Scheme 32**) <2003T4395>.

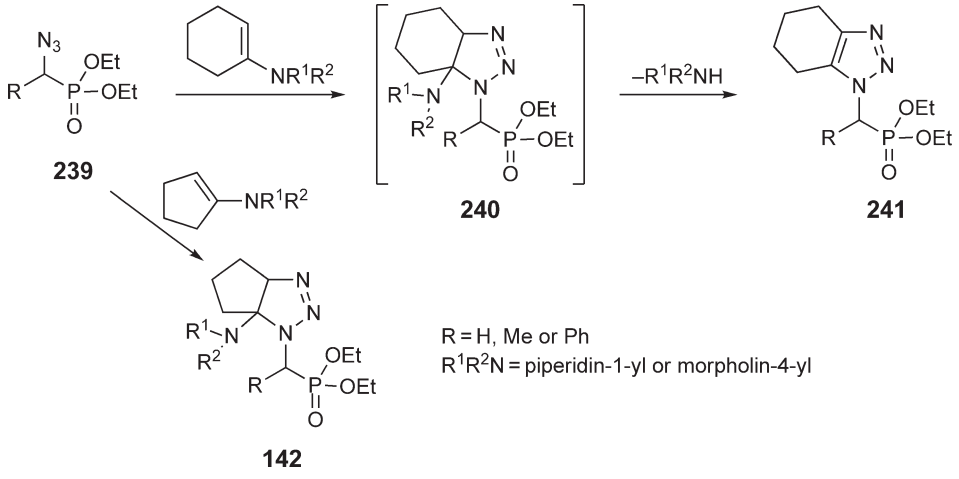


Scheme 31



Scheme 32

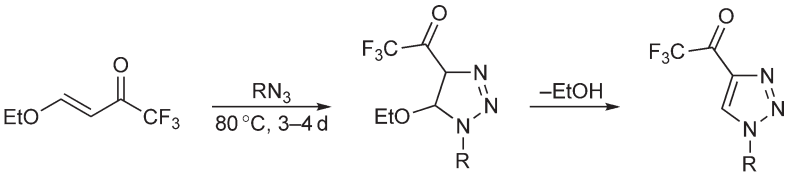
Scheme 33 illustrates the difference in reactivity between triazolines obtained from cyclohexanone and cyclopentanone enamines. Thus, the reactions of azidophosphonates **239** with cyclohexanone enamines produce unstable aminotriazolines **240** that cannot be isolated due to their spontaneous elimination of amines to provide triazoles **241**. Contrary to that, triazolines **242**, derived from cyclopentanone enamines, are isolated in good yield (76–88%) and cannot be converted to the corresponding triazoles even by thermolysis <1995H(40)543>. Probably, introduction of a double bond between two five-membered rings would involve too much molecular strain.



Scheme 33

5.01.6.1.3 Elimination of alcohols or water

2-Ethoxyvinyl trifluoromethyl ketone **243** reacts slowly at elevated temperature with aryl and benzyl azides to provide triazoles **245** in good yield (51–88%). The reactions, carried out neat, are completed usually in 2–3 d(days). However, a longer reaction time (6 d) is required for 2-methylphenyl azide due to its steric hindrance. 5-Ethoxytriazolines **244**, the expected intermediates in this process, readily eliminate ethanol under the reaction conditions and cannot be isolated (**Scheme 34**) <2002JFC(116)81>.

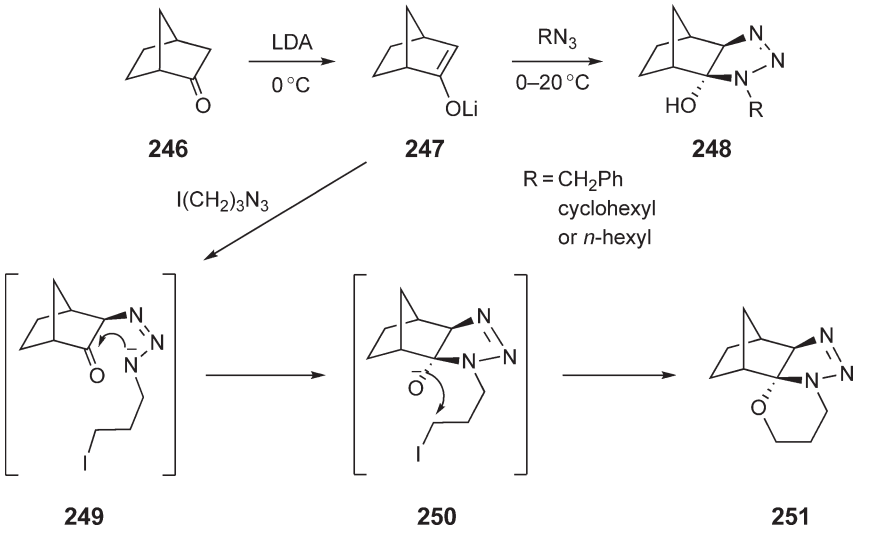


243 **244** **245**

R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-MeC_6H_4
$PhCH_2$, 4-$MeOC_6H_4CH_2$ or 4-$NO_2C_6H_4CH_2$

Scheme 34

In reactions with azides, ketones are directly converted to 5-hydroxytriazolines. Ketone enolate **247**, generated by treatment of norbornanone **246** with LDA at 0 °C, adds readily to azides to provide hydroxytriazolines **248** in 67–93% yield. Interestingly, 1-azido-3-iodopropane subjected to the reaction with enolate **247** gives tetracyclic triazoline derivative **251** in 94% yield. The reaction starts from an electrophilic attack of the azide on the ketone α-carbon atom. The following nucleophilic attack on the carbonyl group in intermediate **249** results in triazoline **250**. The process is completed by nucleophilic substitution of the iodine atom to form the tetrahydrooxazine ring of product **251** (**Scheme 35**) <2004JOC1720>.

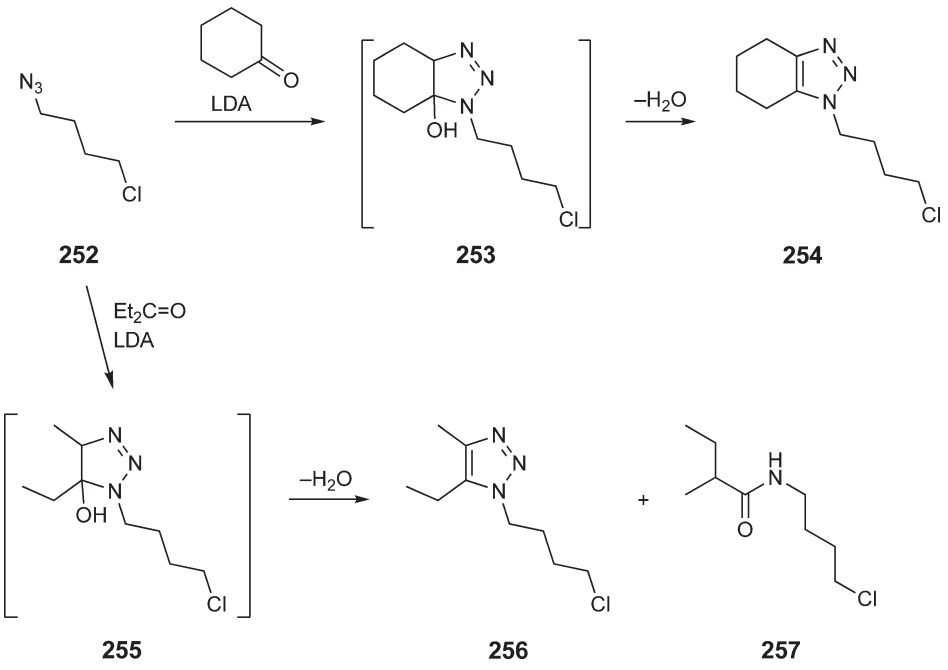


246 **247** **248**

249 **250** **251**

Scheme 35

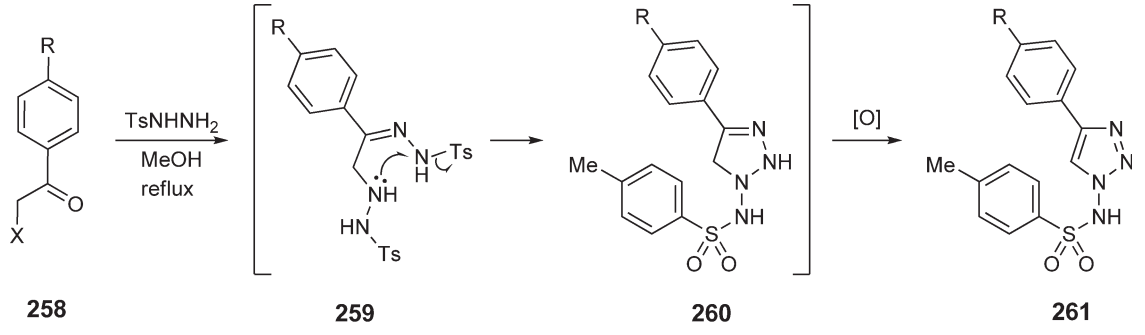
In contrast to the triazolines from **Scheme 35**, 5-hydroxytriazolines obtained from regular, unstrained ketones are unstable, eliminating rapidly water to furnish the corresponding triazoles. In an example given in **Scheme 36**, azide **252** reacts readily with cyclohexanone enolate to provide triazole **254** in 95% yield. Triazoline intermediate **253**, formed in the first step of this reaction, is very unstable and cannot be isolated. The case of open-chain ketones is illustrated by a reaction of azide **252** with diethyl ketone. Again, intermediate 5-hydroxytriazoline **255** decomposes rapidly to give, in part, triazole **256**. However, a more complex process involving elimination of nitrogen and rearrangement to amide **257** competes with the main reaction, making this synthesis less attractive <2004JOC1720>.



Scheme 36

5.01.6.1.4 Oxidation

When a solution of phenacyl halide **258** and excess tosyl hydrazide in methanol is heated to reflux, 1-(tosylamido)-4-aryltriazole **261** is formed. The reaction proceeds presumably via dihydrazide derivative **259** that subsequently undergoes intramolecular cyclocondensation to triazoline **260**. In the following step, the triazoline must be oxidized to the final triazole product **261**. Mechanism of the oxidation is not quite clear, but the probable oxidant is the starting phenacyl halide, as a half of it is converted to the corresponding acetophenone tosylhydrazone that is isolated as the main side product of the reaction (**Scheme 37**) <2004H(63)1175>.



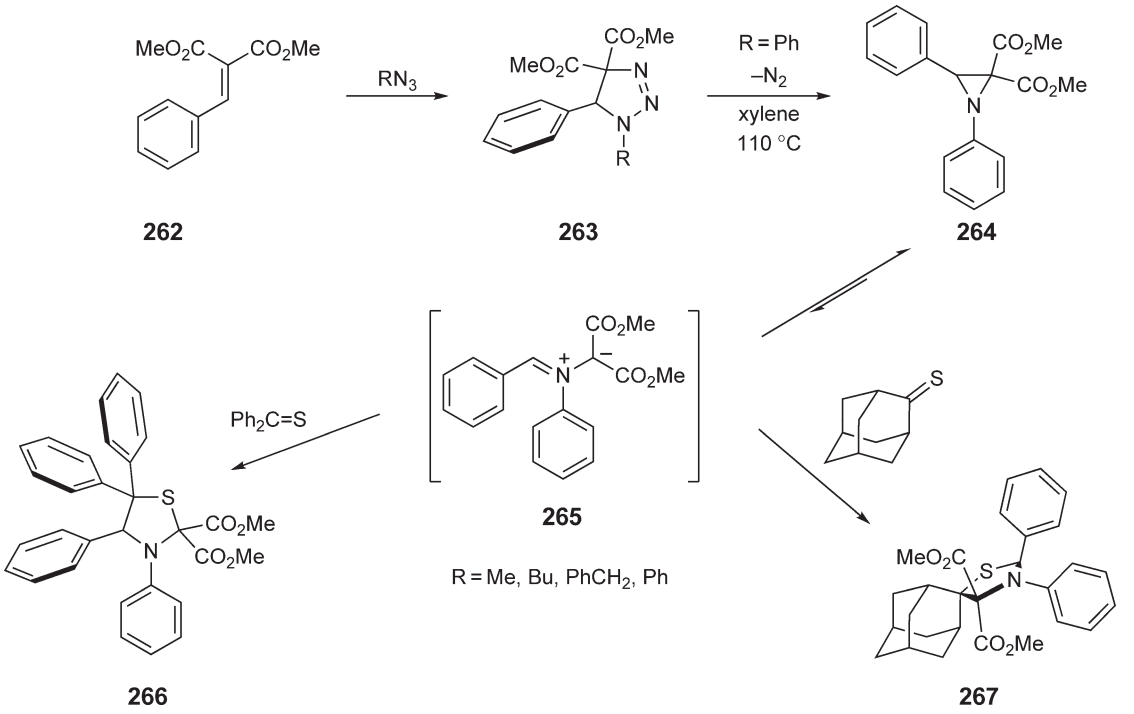
R = H, Me, Ph, MeO, Cl or F
X = Cl or F

Scheme 37

5.01.6.2 Elimination of N_2

Cycloaddition reactions of dimethyl benzylidenemalonate **262** with azides provide triazolines **263**. All compounds **263**, except one with R = Ph, are stable in xylene at 110 °C. The phenyl derivative eliminates molecular nitrogen to give dimethyl 1,3-diphenylaziridine-2,2-dicarboxylate **264**. At elevated temperature, the aziridine system is not

quite stable and may partially exist as open ylide form **265**. Thioketones added to the reaction mixture trap species **265** to provide tetrahydrothiazoles. Two examples of such reactions – with thiobenzophenone to give thiazolidine **266** and with adamantanethione to furnish derivative **267** – are presented in **Scheme 38** <2002HCA2056, 2002HCA2644>.



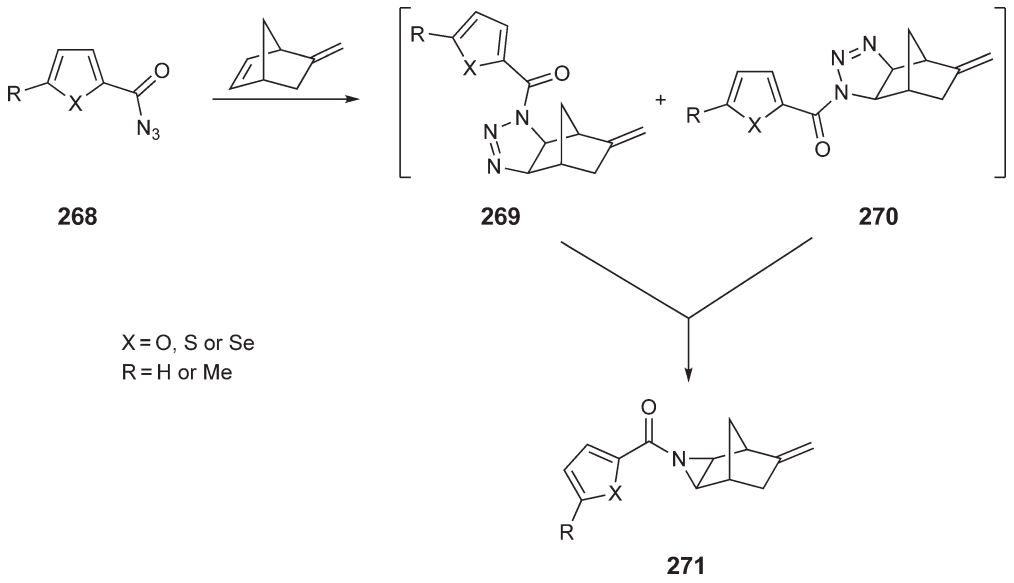
Scheme 38

Acyl azides **268**, derived from furan, thiophene and selenophene, add slowly at room temperature to the strained double bond of 5-methylenebicyclo[2.2.1]hept-2-ene. Two regioisomeric triazolines, **269** and **270**, which form in the first step, are unstable and decompose with elimination of nitrogen to provide aziridine derivatives **271**. Products **271** are isolated in good yield (73–85%). It is worthy to note that not only the terminal, unstrained double bond in the starting material, 5-methylenebicyclo[2.2.1]hept-2-ene, is unaffected, but also the typical dipolarophiles like esters of crotonic, propiolic and byt-2-ynoic acids do not react with azides **268** under these conditions (**Scheme 39**) <2002J(P1)1420>.

1-(Azidomethyl)benzotriazole **272** reacts with *N*-methylmaleinimide in refluxing toluene to give, after 3 h, exclusively triazoline derivative **273**, together with the unreacted starting materials. Prolonged heating of the starting materials results in formation of more triazoline **273**; however, products of its decomposition to derivatives **274** and **275** are also present. Refluxing of a solution of triazoline **273** in toluene for 24 h leads to a mixture of aziridine **274** and its opened isomer **275** in 4:1 ratio (**Scheme 40**) <1996JHC335>.

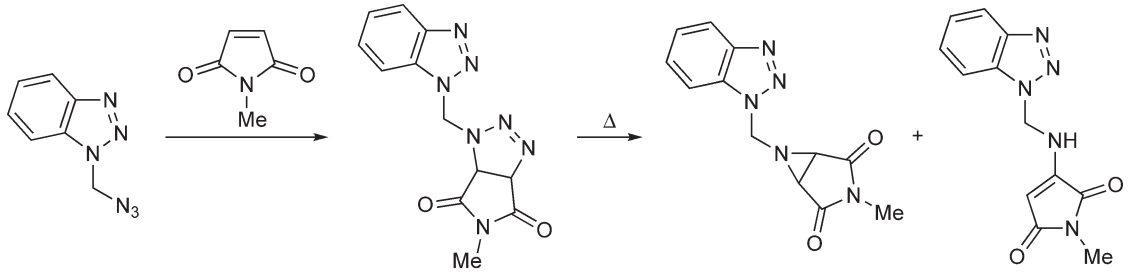
Triazolines **277** are isolated in high yield (87–94%) when the reactions of glucal **276** with azides are carried out in refluxing trimethyl or triethyl orthoformate. In all other solvents, triazolines **277** undergo immediate conversion to triazoles **278**. It is believed that the orthoformates act as nonbasic acid-scavenging solvents. Irradiated with UV light in acetone, triazolines **277** are smoothly converted to aziridines **279**. Without isolation, aziridines **279** are treated with nucleophiles in the presence of a Lewis acid to provide aminoglycosides **280** in high yield (**Scheme 41**) <2004JA8356>.

Fluoroalkanesulfonyl azides **281** add readily to vinyl ethers to provide triazolines **282** in good yield (67–84%). At room temperature, slow decomposition of the products is observed with evolution of nitrogen and formation of piperazine derivatives **284**. No other products are observed. Formation of piperazines **284** must involve cleavage of the triazoline ring with formation of zwitterionic intermediates **283** (**Scheme 42**) <2004JFC(125)445>.



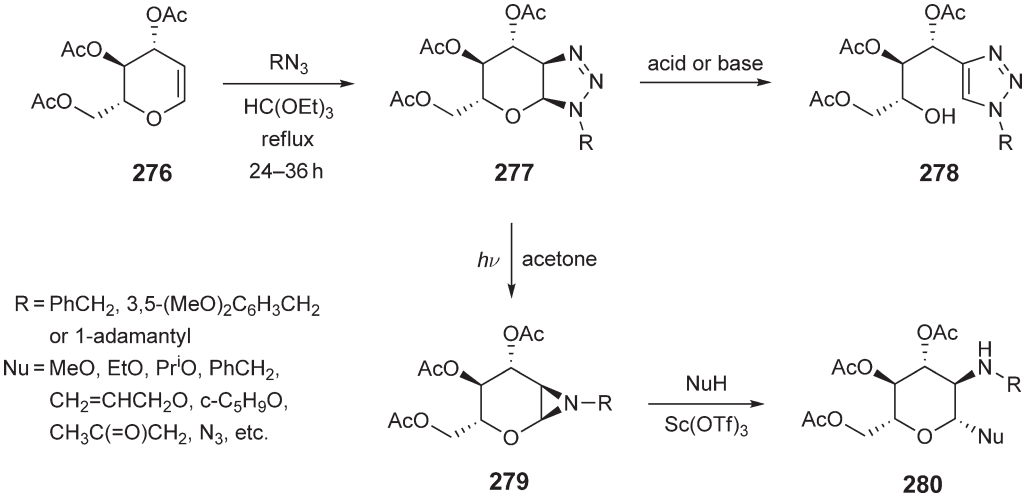
268 269 270 271

Scheme 39



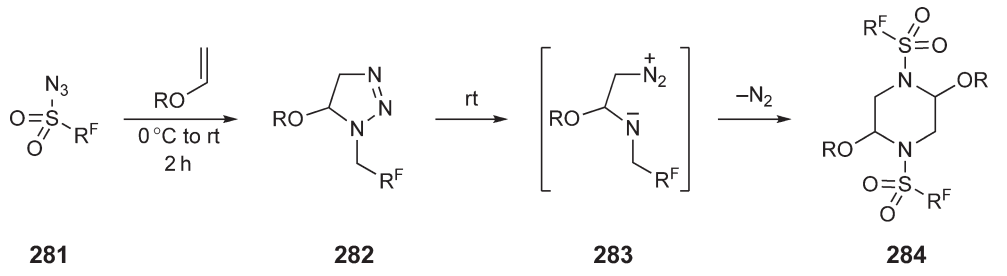
272 273 274 275

Scheme 40



276 277 278 279 280

Scheme 41

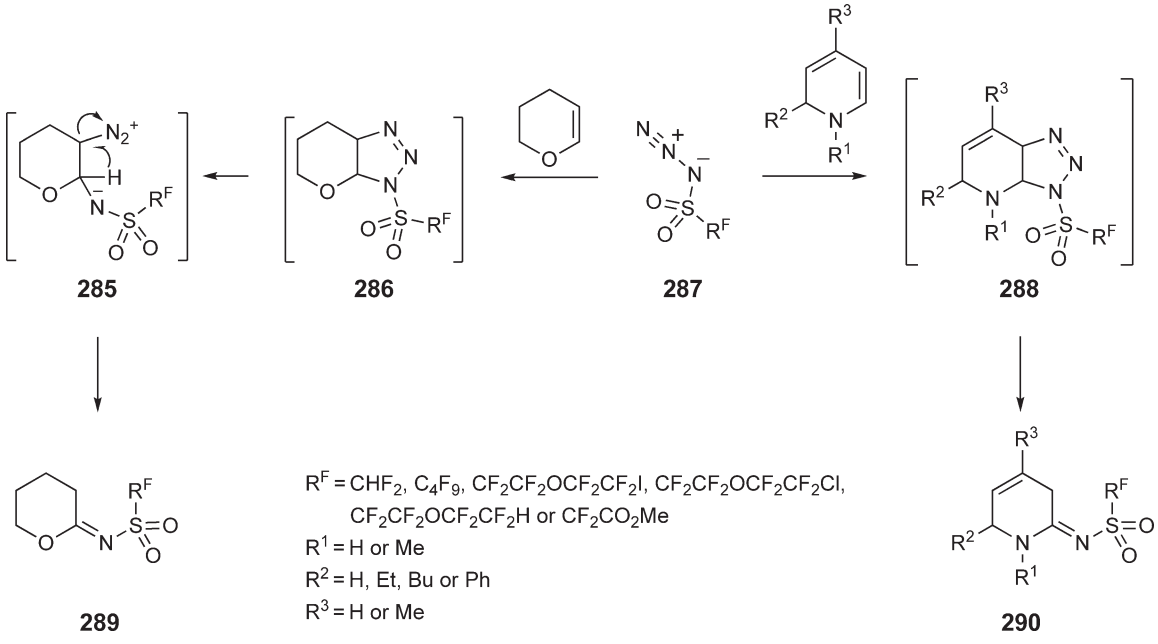


281 **282** **283** **284**

$R^F = C_4F_9$, Me_2CHOCF_2, $ClCF_2CF_2OCF_2CF_2$ or $ICF_2CF_2OCF_2CF_2$
R = Et or Me_2CHCH_2

Scheme 42

Reactions of fluoroalkanesulfonyl azides **287** with tetrahydropyran proceed fast in dichloromethane at room temperature. Evolution of nitrogen is observed together with formation of *N*-(fluoroalkanesulfonyl)-2-tetrahydropyranoimines **289**. The reactions are believed to involve 1,3-dipolar cycloaddition of tetrahydropyran to azides **287** with formation of relatively unstable triazolines **286**. Opening of the triazoline ring results in zwitterionic structure **285** that is losing molecular nitrogen and rearranges to final product **289** by 1,2-hydrogen shift <2003JFC(120)65>. In a similar manner, reactions of azides **287** with dihydropyridines lead to *N*-alkanesulfonylimines **290**, via labile triazolines **288** (**Scheme 43**) <2000JFC(106)133>.



285 **286** **287** **288** **289** **290**

$R^F = CHF_2$, C_4F_9, $CF_2CF_2OCF_2CF_2I$, $CF_2CF_2OCF_2CF_2Cl$, $CF_2CF_2OCF_2CF_2H$ or CF_2CO_2Me
R^1 = H or Me
R^2 = H, Et, Bu or Ph
R^3 = H or Me

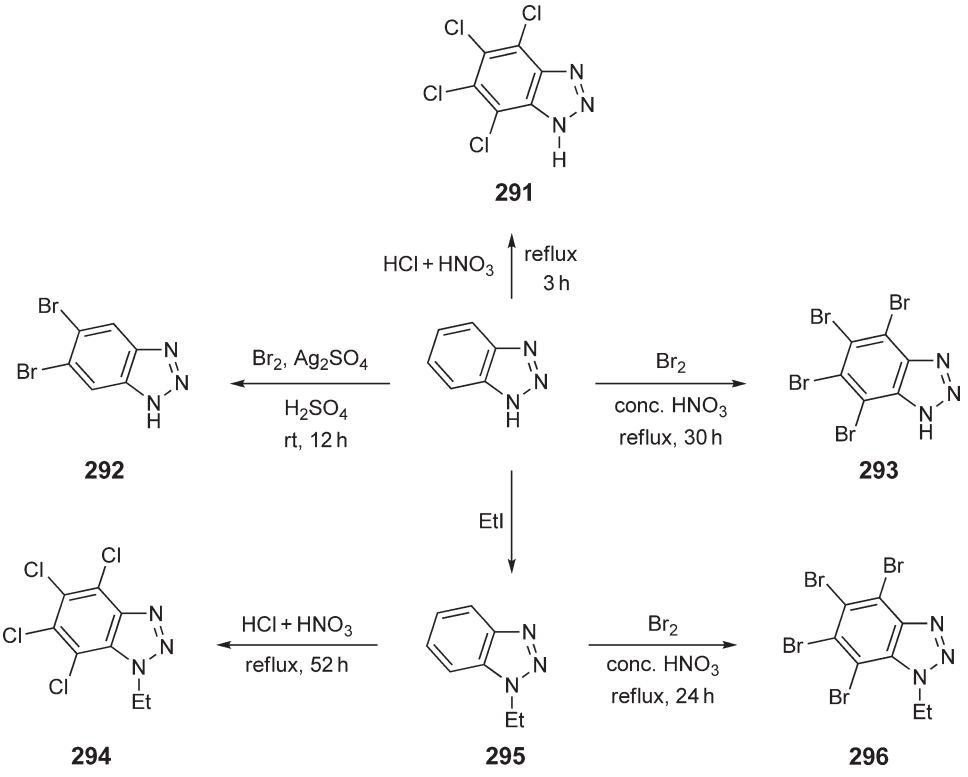
Scheme 43

5.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

5.01.7.1 Reactions of the Benzenoid Ring of Benzotriazole

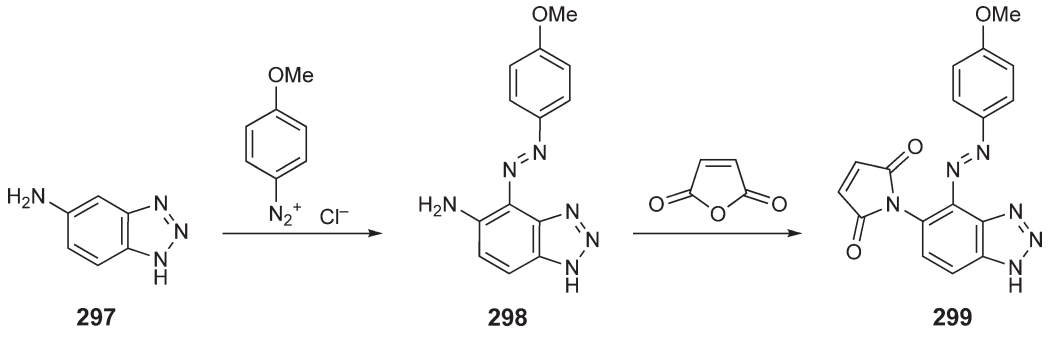
Tetrachlorobenzotriazole **291** is readily prepared in 87% yield by heating a solution of benzotriazole in a mixture of hydrochloric and nitric acids <1955JA5105>. 5,6-Dibromobenzotriazole **292** is prepared in 62% yield by treatment of benzotriazole with bromine and silver sulfate in concentrated sulfuric acid <2004BMC2617>. Under more forcing conditions, when the reaction is run in refluxing nitric acid, 4,5,6,7-tetrabromobenzotriazole **293** is formed

(**Scheme 44**) <1957JA4395>. 1-Ethylbenzotriazole **295** <1984CHEC(5)669, 1996CHEC-II(4)1> is chlorinated by refluxing in a mixture of concentrated hydrochloric and nitric acids to give 1-ethyl-4,5,6,7-tetrachlorobenzotriazole **294** in 81% yield <1957JA4395>. A reaction of derivative **295** with bromine in refluxing concentrated nitric acid provides 1-ethyl-4,5,6,7-tetrabromobenzotriazole **296** in 68% yield <1957JA4395>.



Scheme 44

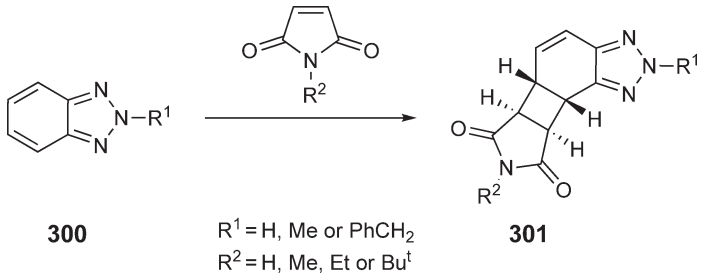
Coupling of 5-aminobenzotriazole **297** with a diazonium salt derived from 4-methoxyaniline generates diazo derivative **298**. Conversion of the amino group into maleinimide produces dye **299** (**Scheme 45**). Diels–Alder cycloadditions of dye **299** to diene tagged nucleotides allows for their efficient labeling <2002CC2100>.



Scheme 45

Benzotriazole and its 2-alkyl derivatives **300** undergo [2+2] cycloaddition to maleinimide when irradiated with UV light at λ>290 nm to give photoadducts **301** (Equation 10). In all cases, only *exo* diastereomers are formed. Since 1-alkylbenzotriazoles are completely unreactive under such conditions, unsubstituted benzotriazole must react as its

2-H tautomer. This remarkable difference in reactivity originates from a greater differentiation in bond lengths in the benzenoid ring of 2-substituted benzotriazoles in comparison with their benzotriazol-1-yl analogs. Bonds C(4)–C(5) in derivatives **300** are relatively short (1.377 Å); this renders them more double bond character and makes more susceptible to [2+2] cycloadditions <2002OL1487>.



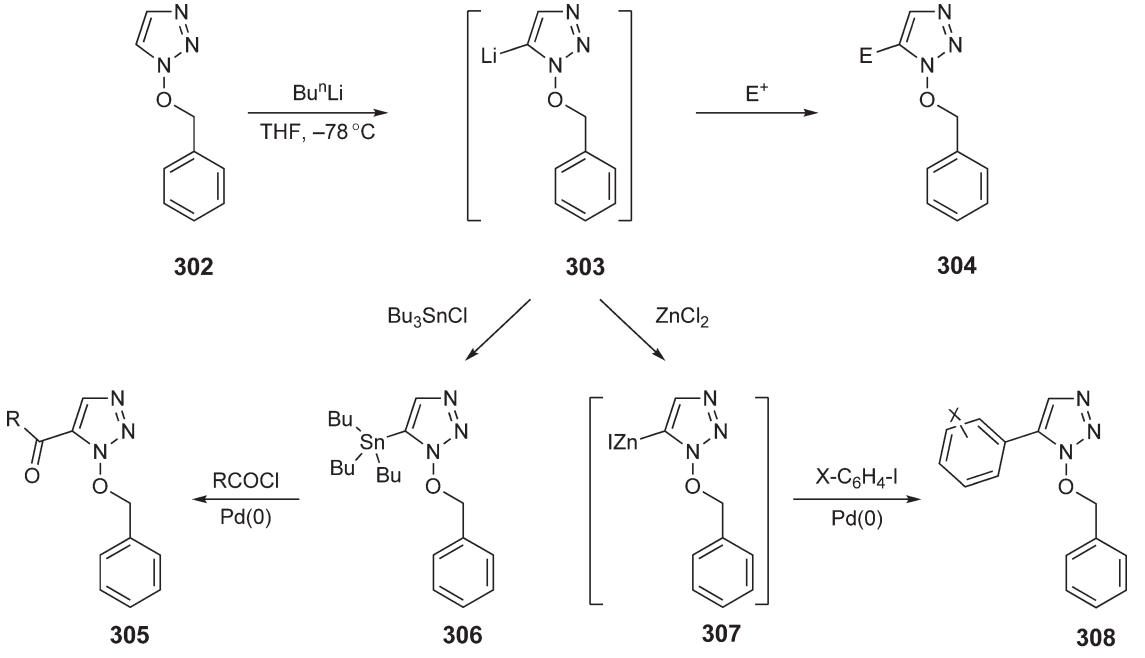
300 **301**

R^1 = H, Me or $PhCH_2$
R^2 = H, Me, Et or Bu^t

(10)

5.01.7.2 Organometallic Derivatives and Their Reactions with Electrophiles

1-Benzyloxytriazole **302** is lithiated exclusively at C-5. Treatment of lithio derivative **303** with electrophiles provides an easy access to 5-substituted triazoles **304**, which are obtained in 67–97% yield (**Scheme 46**) <1997JOC9177>. Tetrabutyltin derivative **306** becomes a convenient intermediate in the synthesis of ketones **305** (yield 59–93%) <1998S1181>. Organozinc intermediate **307** is suitable for palladium coupling with aryl iodides to provide products **308** in 71–87% yield. Apart of derivatives **308** with phenyl substituents that listed in **Scheme 46**, 5-aryltriazoles derived from pyridine, thiophene, and pyrazole are also prepared this way.

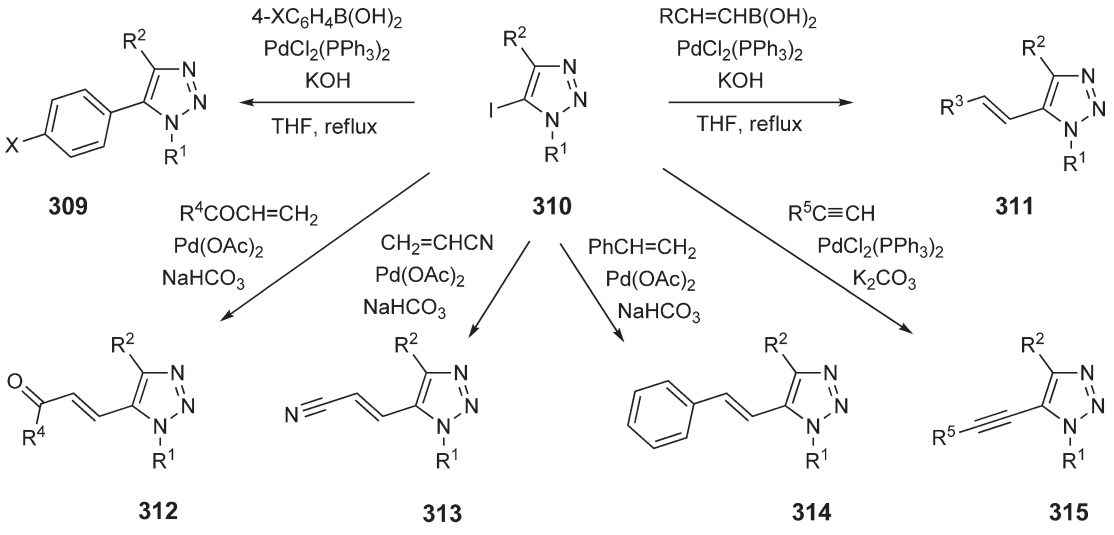


E^+ = MeI, DMF, $ClCO_2Me$, $ClCONMe_2$, C_2Cl_6, Br_2, I_2, or Me_2S_2
R = Me, *n*-$C_{11}H_{23}$, Bu^t, Ph
X = H, 2-F, 2-NH_2, 4-OH, 4-OMe, 4-NO_2

Scheme 46

5.01.7.3 Iodo Derivatives

5-Iodo-1,2,3-triazoles **310** are found to be versatile starting materials for derivatization of the triazole ring with sp^2 and sp carbon substituents. In Suzuki coupling with areneboronic acids, 5-aryltriazoles **309** are obtained in 64–98% yield. The reaction is catalyzed by palladium dichloride–triphenylphosphine complex and proceeds well in the presence of KOH as a base. In reactions with alkeneboronic acids, 5-(alken-1-yl)-1,2,3-triazoles **311** are generated in 59–95% yield. In a Heck reaction with methyl vinyl ketone, 5-iodotriazoles **310** are converted to unsaturated ketones **312** in 87–98% yield. Acrolein gives aldehyde **312** ($R^4 = H$) in only 62% yield, but the yields of products **312** obtained from a reaction of iodide **310** with methyl acrylate ($R^4 = OMe$) are much higher (92–98%). Acrylonitrile reacts well; however, mixtures of *(E)*- and *(Z)*-isomers of nitriles **313** are obtained. Heck coupling of iodide **310** with styrene is much slower, but product **314** is obtained as a single *(E)*-isomer in 92% yield. In a Sonogashira reaction, 5-iodotriazoles **310** are coupled with alkynes to provide derivatives **315** in 71–99% yield (**Scheme 47**) <2005S2730>.



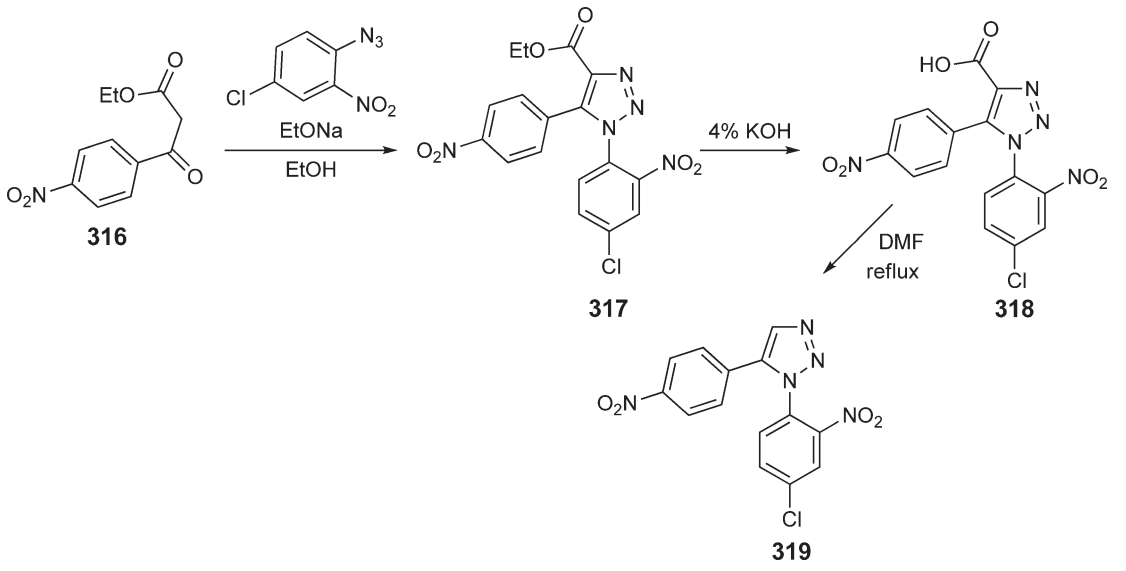
R^1 = $PhCH_2$, *n*-C_8H_{17}, CF_3CH_2, or $HCF_2CF_2CH_2$
R^2 = Ph or *n*-C_4H_9
R^3 = *n*-C_5H_{11} or $PhCH_2OCH_2$
R^4 = H, Me or MeO
R^5 = *n*-C_4H_9, Ph, $HOCH_2$, or TMS
X = H, CF_3, Cl or MeO

Scheme 47

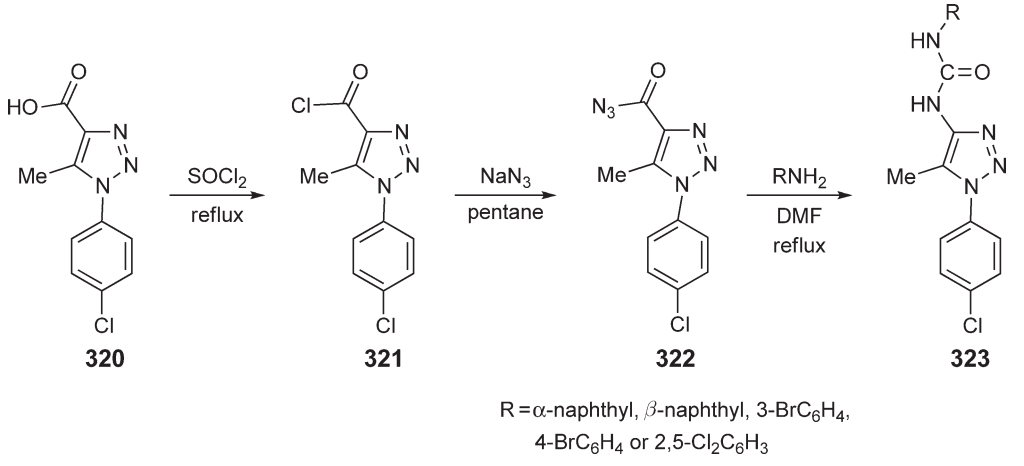
5.01.7.4 Carboxylic Acids and Their Derivatives

Esters of 1,2,3-triazolecarboxylic acids are the most common derivatives of triazole (Section 5.01.9); therefore, their conversions to other, more useful, functionalities are of great importance. In an example given in **Scheme 48**, 4-triazolecarbocylic ester **317**, obtained from a reaction of β-ketoester **316** with 4-chloro-2-nitrophenyl azide, is hydrolyzed to free acid **318** (82% yield) by 4% KOH. Heated to reflux in DMF for 3 h, acid **318** undergoes decarboxylation to triazole derivative **319** with 81% isolated yield <2004FA397>.

Acid chloride **321**, obtained in 85% yield by refluxing a solution of carboxylic acid **320** in thionyl chloride, is converted to azide **322** in 86% yield by treatment with sodium azide in pentane. Reactions of azide **322** with amines of low nucleophilicity in refluxing DMF provide ureas **323** in 24–90% yield via Curtius rearrangement. In these reactions, 3-bromo- and 4-bromoaniline give also the corresponding amides, which are formed by simple substitution of the N_3 group in azide **322** with amines, as the side products. Secondary amines and primary amines with more nucleophilic NH_2 groups (e.g., *p*-anisidine and *t*-butylamine) provide exclusively the corresponding amides (**Scheme 49**) <2003JCCS1215>.



Scheme 48

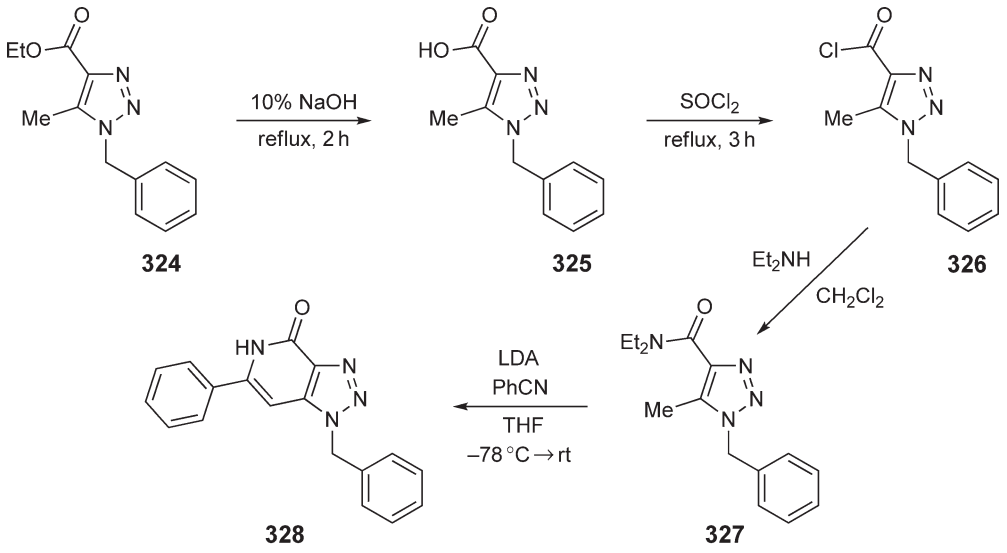


Scheme 49

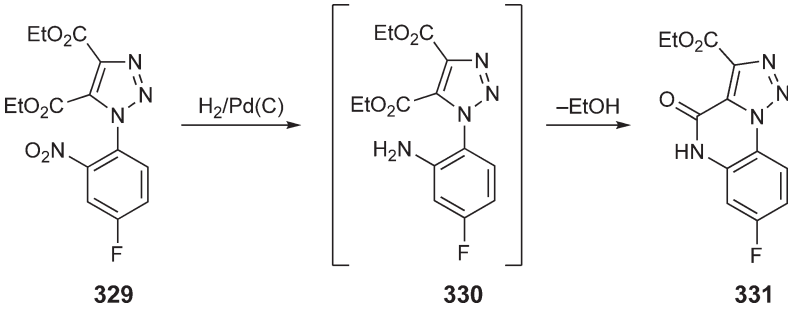
Ester **324** is hydrolyzed to acid **325** by refluxing in 10% NaOH. In a reaction with thionyl chloride, acid **325** is converted to acid chloride **326**, which is isolated as a solid in 96% yield and consecutively converted into amide **327** in 85% yield. Treatment of amide **327** with LDA extracts a proton from the methyl group. The generated anion is trapped by added benzonitrile. Subsequent cyclocondensation of the obtained imine anion with the amide group provides derivative **328** in 62% isolated yield (**Scheme 50**) <2003EJM983>.

In an example given in **Scheme 51**, tricyclic system **331** is generated by cyclocondensation between the ethoxycarbonyl group at C-5 of the triazole ring and the amino group of the substituent at N-1. The process that starts from catalytic reduction of the nitro group in derivative **329** does not stop at amine **330**, but the subsequent spontaneous cyclocondensation leads directly to product **331** that is isolated in 60% yield <2002EJM565>.

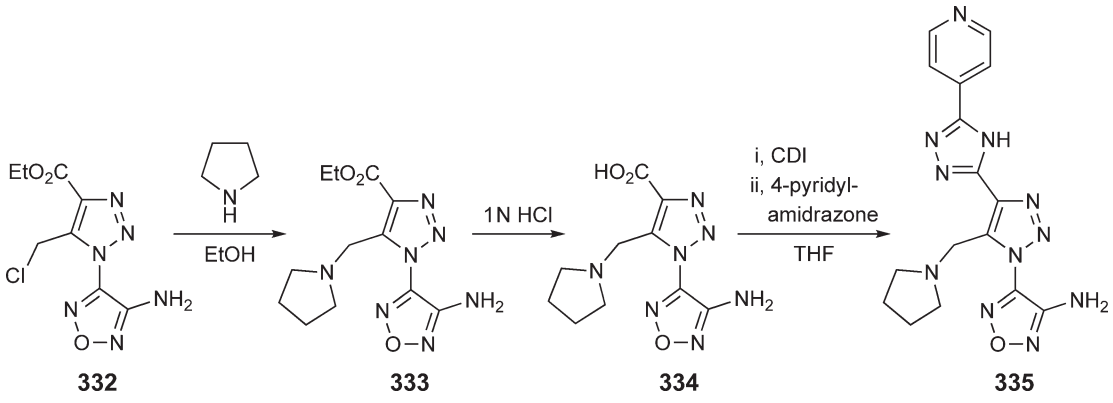
Ethyl 5-chloromethyl-1,2,3-triazole-4-carboxylate **332**, obtained by cyclocondensation of 3-amino-4-azidofurazan with ethyl 4-chloroacetoacetate, is converted to pyrrolidine derivative **333** in 97% yield. Heating at reflux with 1 N HCl deprotects the carboxylic group. The obtained acid **334** is treated with carbonyldiimidazole followed by pyridine-4-carboxylic acid amidrazone to provide product **335** in 25% yield. Compound **335** is a potent inhibitor of glycogen synthase kinase-3 (GSK-3) (**Scheme 52**) <2003JME3333>.



Scheme 50



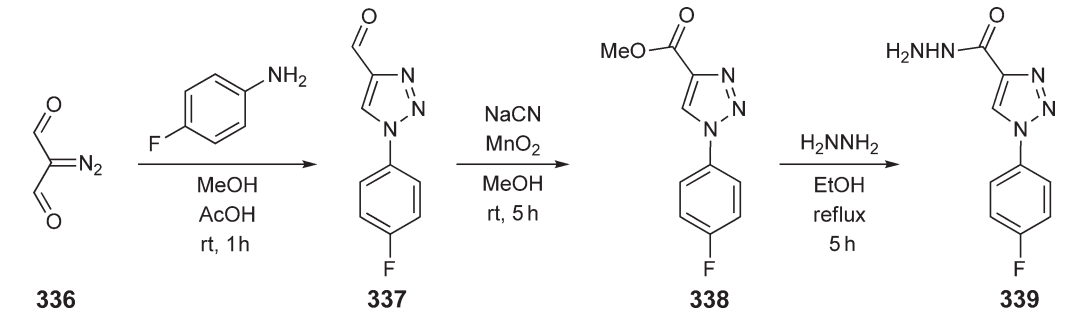
Scheme 51



Scheme 52

5.01.7.5 Carbaldehydes

Cyclocondensation of diazomalonaldehyde **336** with 4-fluoroaniline carried out in methanol-acetic acid provides 1-(4-fluorophenyl)-1,2,3-triazole-1-carbaldehyde **337** in 78% yield. Oxidation with MnO_2 in the presence of sodium cyanide in methanol converts aldehyde **337** into methyl ester **338** with 79% yield. Hydrazide **339** (84% yield) is obtained in a reaction of ester **338** with hydrazine. Product **339** reacts with various aromatic aldehydes to give hydrazones possessing interesting antiplatelet activity (**Scheme 53**) <2003BMC2051>.

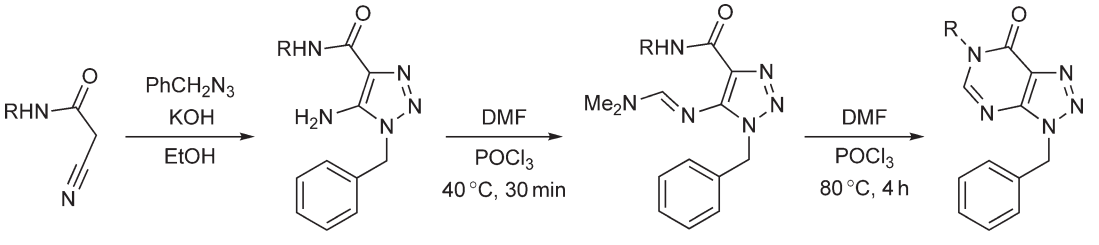


336 337 338 339

Scheme 53

5.01.7.6 Amines

1,2,3-Triazoles substituted with an amino group at C-5 are readily available from cycloaddition of nitriles to azides. They have become convenient intermediates in synthesis of biologically active compounds. In an example given in **Scheme 54**, cycloaddition of anions derived from cyanoacetamides **340** to benzyl azide provides 5-amino-1,2,3-triazole derivatives **341** in 75–91% yield. Catalyzed by phosphorus oxychloride, amines **341** undergo cyclocondensation with DMF under mild conditions (40 °C) to give amidines **242**. At higher temperature (80 °C), cyclocondensation occurs with elimination of dimethylamine to form 1,2,3-triazolo[4,5-*d*]pyrimidin-5-ones **343**, which are isolated in 71–85% yield. However, lower yield (30%) is obtained for R = 2-MeOC$_6$H$_4$. For R = H, simple heating of the corresponding amine **341** with formamide at 210 °C provides derivative **343** in good yield <2003RCB1770>.

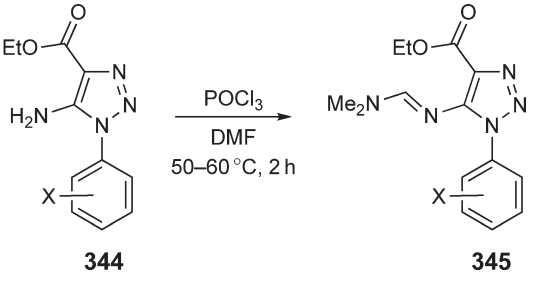


340 341 342 343

R = H, Me, PhCH$_2$, Ph, or 2-MeOC$_6$H$_4$

Scheme 54

In a synthesis similar to that depicted in **Scheme 54**, aminoesters **344** dissolved in DMF are treated with $POCl_3$ and heated at 50–60 °C for 2 h. The simple work-up procedure involves pouring into ice-water, neutralization with NaOH and separation of the precipitate by filtration to afford amidines **345** in 66–86% yield (Equation 11). Some of the obtained amidines exhibit selective antibacterial activity <2003SC3969>.

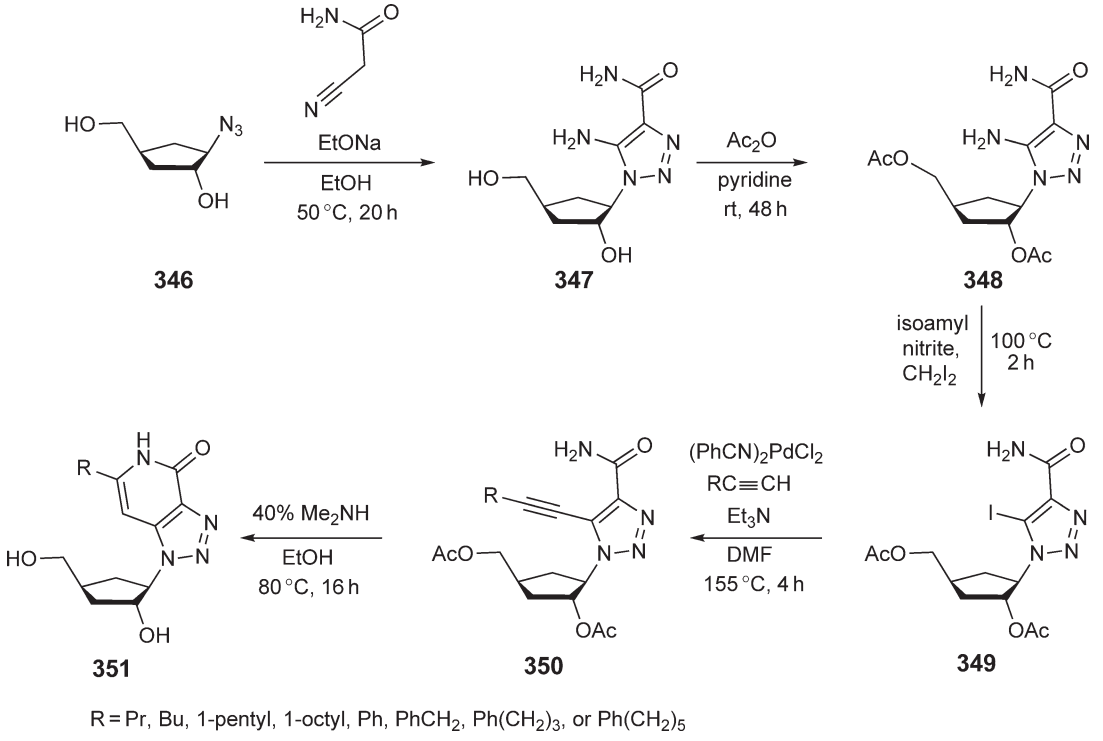


(11)

344 345

X = H, *p*-Me, *p*-MeO, *p*-EtO, *p*-MeCO, *p*-NO$_2$, *p*-Cl, *m*-F, *m*-Cl, *m*-Br, *m*-CF$_3$, or *m*-NO$_2$

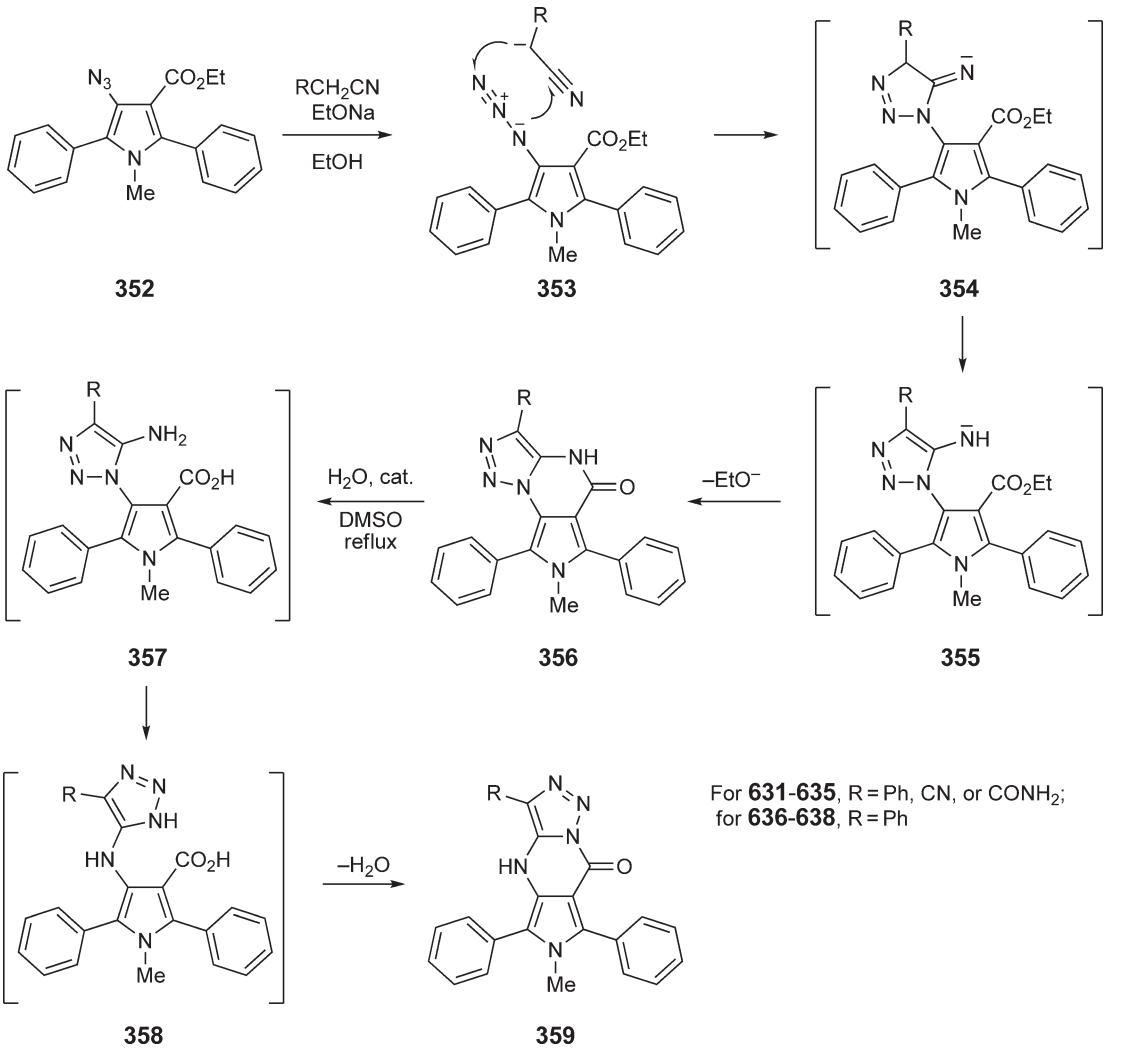
1,3-Dipolar cycloaddition of 2-cyanoacetamide to 2-azido-4-(hydroxymethyl)-cyclopentanol **346**, carried out in ethanol in the presence of sodium ethoxide, provides regioselectively 5-amino-1,2,3-triazole derivative **347** in 52% yield. In the following step, the hydroxy groups are protected by acetylation with acetic anhydride in pyridine to give diester **348** in 75% yield. Surprisingly, the amino group is not nucleophilic enough to be acetylated under such conditions. Diazotization (isoamyl nitrite) and substitution with iodide (diiodomethane) converts amine **348** into 5-iodo derivative **349** that is isolated in 55% yield. By coupling with terminal alkynes under modified Sonogashira conditions, iodide **349** is converted to alkynes **350** in 52–77% yield. Treated with 40% aqueous dimethylamine in ethanol at 80 °C in sealed tubes, amido groups in derivatives **350** undergo intramolecular cycloaddition to alkynes resulting in formation of pyridine rings. In the same step, the hydroxy groups are deprotected to provide 6-substituted 1,2,3-triazolo[4,5-*c*]pyridin-4-ones **351** in 51–72% yield (**Scheme 55**) <2005T11744>.



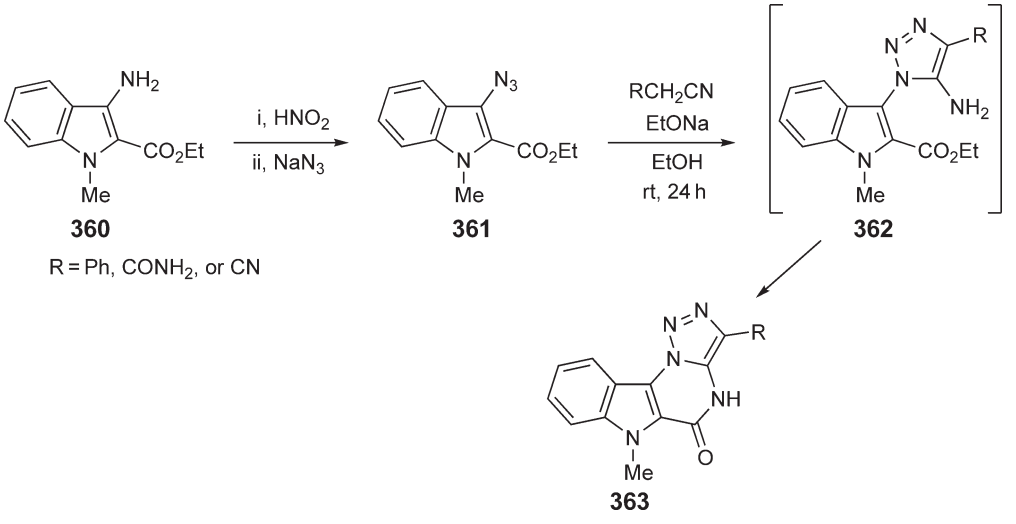
Scheme 55

When a solution of azide **352** and nitrile RCH_2CN in ethanol is treated with sodium ethoxide, the anion derived from nitrile undergoes 1,3-dipolar cycloaddition to azide **353**. Generated anion **354** tautomerizes to more stable aromatic form **355**. Nucleophilic attack of the triazoloamine anion on the ethoxycarbonyl group in intermediate **355** results in elimination of an ethoxy anion and ring closure to give pyrrolo[3,4-*e*]1,2,3-triazolo[1,5-*a*]pyrimidin-5-one **356** in high yield. Heating of compound **356** (R = Ph) in DMSO in the presence of traces of water results in its hydrolysis to aminoacid **357**. Under the reaction conditions, 5-aminotriazole system **357** undergoes Dimroth rearrangement to more stable derivative **358**. Spontaneous cyclocondensation between the carboxylic group and the triazole ring in **358** leads to 6-methyl-3,5,7-triphenyl-4,6-dihydro-8*H*-pyrrolo[3,4-*d*]1,2,3-triazolo[1,5-*a*]pyrimidin-8-one **359** that is isolated in almost quantitative yield (**Scheme 56**) <2000JHC747> . Similar transformations are reported for ethyl 1-benzyl-3-azido-4-phenylpyrrolocarboxylate <2002T9723>.

Ethyl 3-azido-1-methyl-1*H*-indole-2-carboxylate **361** is prepared in 70% yield by diazotization of amine **360** followed by substitution of the created diazonium group with sodium azide. In cycloadditions with nitrile anions, azide **361** forms triazole intermediates **362**. However, under the reaction conditions, cyclocondensation of the amino and ethoxycarbonyl groups in **362** results in formation of an additional ring. This domino process provides efficiently 4*H*-indolo[2,3-*e*]1,2,3-triazolo[1,5-*a*]pyrimidines **363** in 70–80% yield (**Scheme 57**) <2006TL2187>.

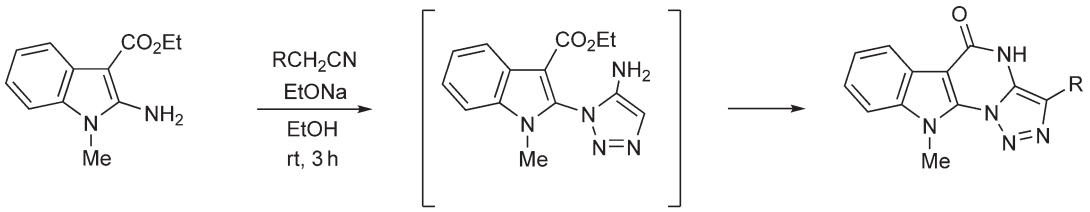


Scheme 56



Scheme 57

In a similar tandem reaction, ethyl 2-azido-1-methyl-1*H*-indole3-carboxylate **364** is converted to indolo[3,2-*e*]1,2,3-triazolo[1,5-*a*]pyrimidin-5-ones **366** via triazole intermediates **365** that are not separated (**Scheme 58**). Products **366** are obtained in 80-90% yield as potential intercalates of DNA <2003H(60)2669>.

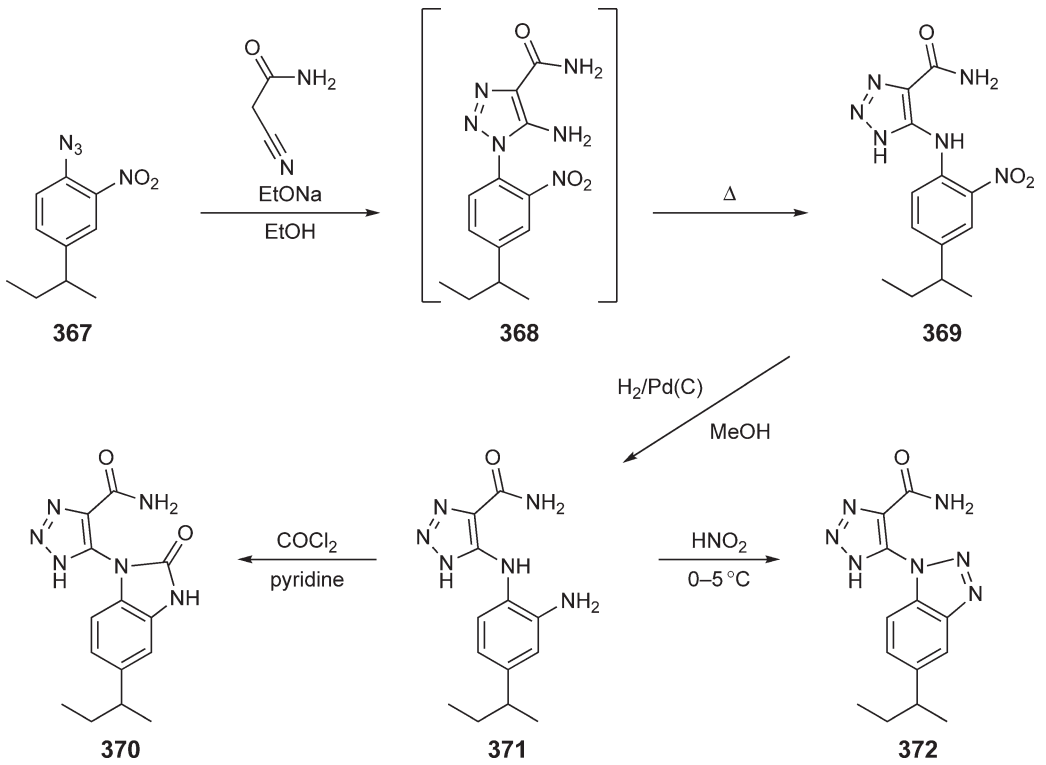


364 **365** **366**

R = Ph, $CONH_2$, CN, CO_2Me or CO_2Et

Scheme 58

Azide **367** is prepared from 4-*sec*-butyl-2-nitroaniline in 76% yield by its diazotization followed by treatment with sodium azide. In a 1,3-dipolar cycloaddition with cyanoacetamide, azide **367** is converted to triazole **368** that without separation is directly subjected to Dimroth rearrangement to give derivative **369** in 46% yield. Reduction of the nitro group provides *ortho*-phenylenediamine **371** in 91% yield <2000EJM715>. Cyclocondensation of diamine **371** with phosgene furnishes benzimidazol-2-one **370** in 39% yield, whereas its reaction with sodium nitrite in 18% HCl leads to benzotriazole derivative **372**, which is isolated in 66% yield (**Scheme 59**). Products **370** and **372** exhibit potassium channel activating ability <2001FA841>.

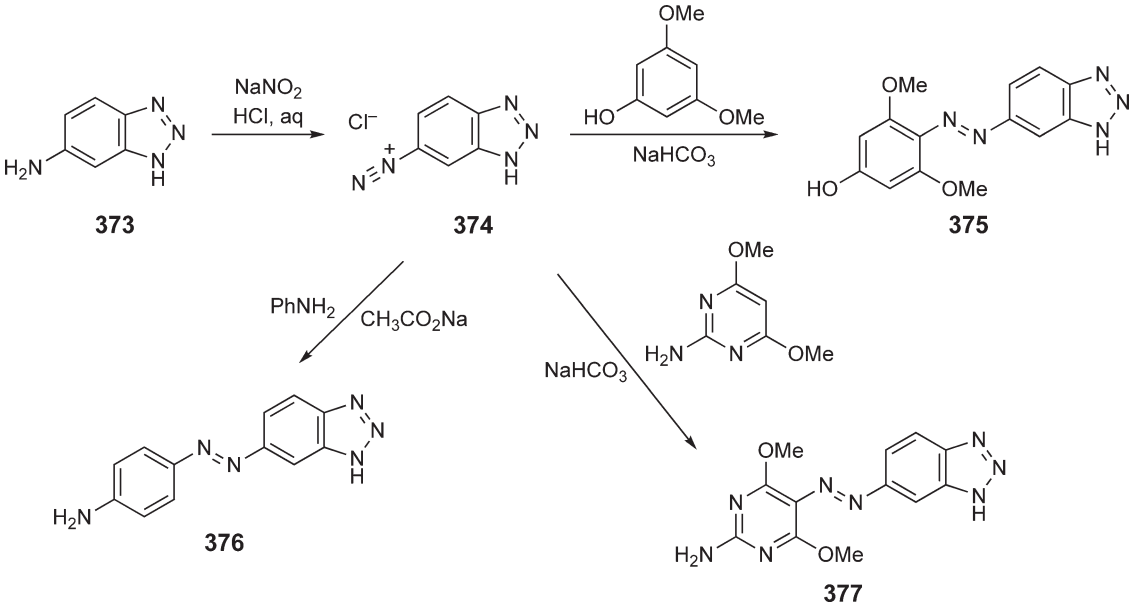


367 **368** **369**

370 **371** **372**

Scheme 59

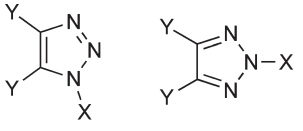
Amino groups on the benzenoid ring of benzotriazole behave similarly to those of typical aromatic amines. 4-Aminobenzotriazole **373** is readily diazotized to provide diazonium chloride **374**. In couplings with phenols or aromatic amines, diazonium derivative **374** is converted to the corresponding azo dyes. Three examples of such reactions providing dyes **375** (67%), **376** (84%) and **377** (64% yield) are shown in **Scheme 60** <2002AN838>. Dyes of this type are used for labeling of nucleotides <2003TL1339>.



Scheme 60

5.01.8 Reactivity of Substituents Attached to Ring Nitrogens

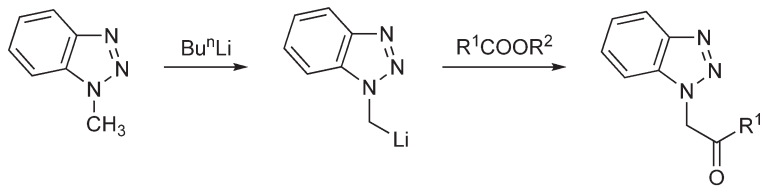
Functional groups can be attached to the ring nitrogen atoms in position 1 or 2 of unsubstituted or symmetrically substituted aromatic rings of 1,2,3-triazoles and benzotriazoles giving rise to distinctive regioisomers **378** and **379**, respectively. In most cases, isomers **378** form kinetically in predominant amounts. In some instances, there is a rapid equilibrium between isomers **378** and **379** in solution <1996CHEC-II(4)1>. For many reactions, there is no different outcome if pure isomers **378**, **379** or their mixtures are employed. For these reasons and clarity of the treatment, in the following paragraphs, only triazol-1-yl and benzotriazol-1-yl **378** isomers are depicted in schemes, even if the corresponding triazol-2-yl **379** isomers are also present in the mixtures. If the chemistry of isomers **378** and **379** differs remarkably, they are treated separately.



378 **379**

5.01.8.1 Ring N-C(sp^3)-R, R = C(sp^3), or H

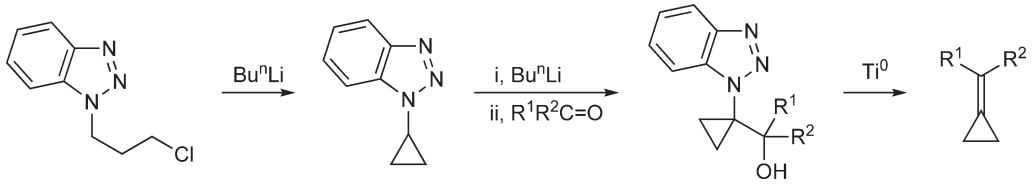
Upon treatment with n-butyllithium at −78 °C, 1-methylbenzotriazole **380** is lithiated on the methyl group to give 1-(lithiomethyl)benzotriazole **381**. Rapid addition of a carboxylic ester to the solution provides α-(benzotriazol-1-yl)alkyl ketone **382** in high yield (**Scheme 61**) <1997JOC4142>. This easy access to ketones **382** and their reactivity makes them valuable intermediates in several syntheses. Their chemistry is discussed separately in Section 5.01.8.4.



380 **381** **382**

Scheme 61

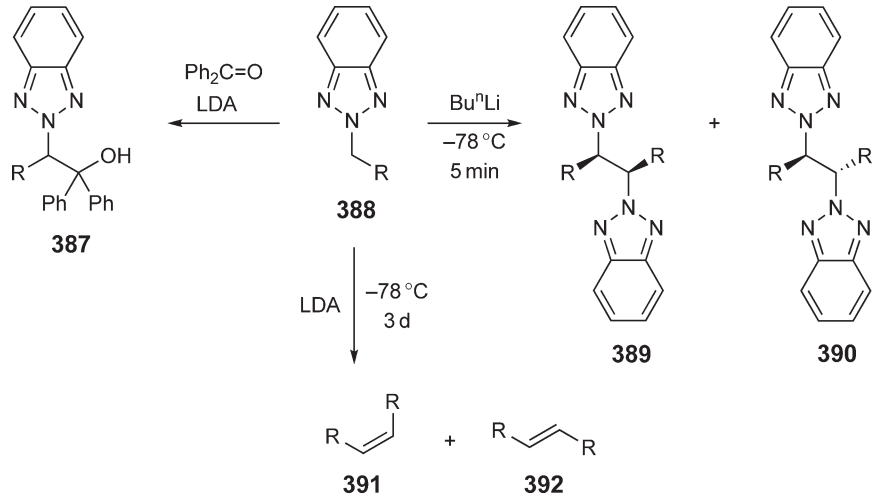
When treated with Bu^{n}Li, 1-(3-chlopropyl)benzotriazole **383**, obtained from a reaction of benzotriazole with 1-bromo-3-chloropropane and NaOH, undergoes cyclization to 1-cyclopropylbenzotriazole **384** <1998JOC6710>. Further lithiation followed by treatment with ketones provides alcohols **385** (**Scheme 62**). Upon heating at 60 °C with low valent titanium <1998JOC6704>, alcohols **385** are converted into interesting cyclopropylidene derivatives **386**. 1-(3-Chloro-2-methylpropyl)benzotriazole gives analogous products with a methyl group on the cyclopropane ring <1998JOC6710>.



383 **384** **385** **386**

Scheme 62

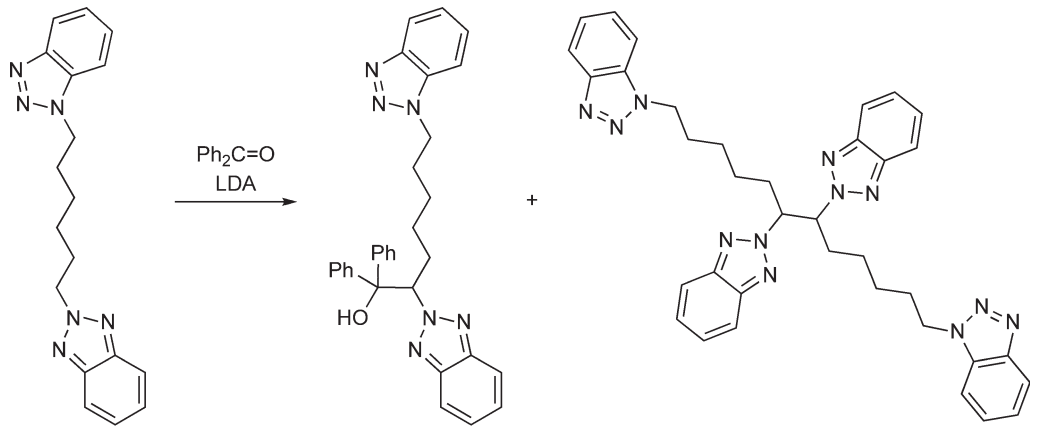
Perhaps due to oxidizing quinoid type electronic structure of benzotriazol-2-yl derivatives, some of their properties are completely different from those of isomeric benzotriazol-1-yl derivatives. Thus, anions derived from 2-alkylbenzotriazoles **388** are rapidly converted to appropriate radicals that undergo coupling to form dimers as mixtures of racemic **289** and meso **390** forms <1996LA745>. When the reaction mixture is kept for an extended period of time at −78 °C, *(Z)*- **391** and *(E)*- **392** alkenes are formed. When benzophenone is added to the reaction mixture, alcohols **387** are obtained in good yields; however, benzaldehyde does not react under these conditions (**Scheme 63**).



387 **388** **389** **390** **391** **392**

Scheme 63

In a direct comparison of the reactivity of 1-alkyl- and 2-alkylbenzotriazoles, compound **393** was lithiated in the presence of benzophenone with 1 equiv of LDA to give a mixture of alcohol **394** and dimer **395** (Equation 12) <1996LA745>. No reaction was detected at the carbon adjacent to the benzotriazol-1-yl moiety. When benzaldehyde was used instead of benzophenone, only dimer **395** was obtained. This suggests that α-benzotriazol-2-yl carbon radical reactions are much faster than those of α-benzotriazol-1-yl) carbanions.



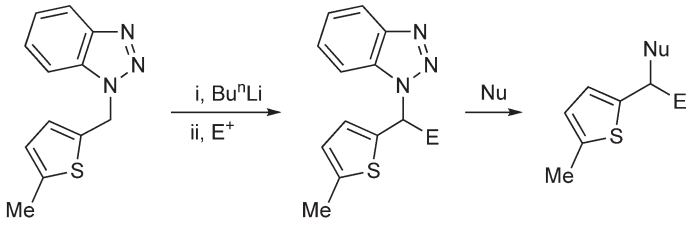
(12)

393 **394** **395**

5.01.8.2 Ring N–C(sp^3)-C=C

5.01.8.2.1 Ring N–C(sp^3)-Ar. No reaction on Ar

Easy synthesis of (benzotriazol-1-yl)methylarenes and –heteroarenes, and their reactivity, makes them convenient starting materials for further transformations. Benzotriazole assisted side-chain elaboration of alkylarenes can be illustrated by reactions carried out on 2-(benzotriazol-1-yl)methyl-5-methylthiophene **396** (**Scheme 64**). Starting material **396** can be readily obtained by refluxing a solution of 1-(hydroxymethyl)benzotriazole, 2-methylthiophene and a catalytic amount of TsOH in dioxane. α-Deprotonation of derivative **396** with Bu^{n}Li followed by treatment with an electrophile leads to product **397**. Phenyl isocyanate, phenyl isothiocyanate, benzaldehyde, alkyl iodides, benzyl bromide, and cyclohexanone have been used as electrophiles. Upon treatment with nucleophiles, the benzotriazole moiety in compounds **397** can be substituted to give products **398**. To replace the benzotriazolyl group with hydrogen, derivatives **397** are treated with zinc in refluxing acetic acid <1997JOC6215>. Similar benzotriazole-assisted side-chain transformations are reported for benzene <1997JOC721>, pyrrole <1996JOC1624, 1996TL5641>, and indole <1995JOC3401, 1995SC539, 1996JOC7558>.



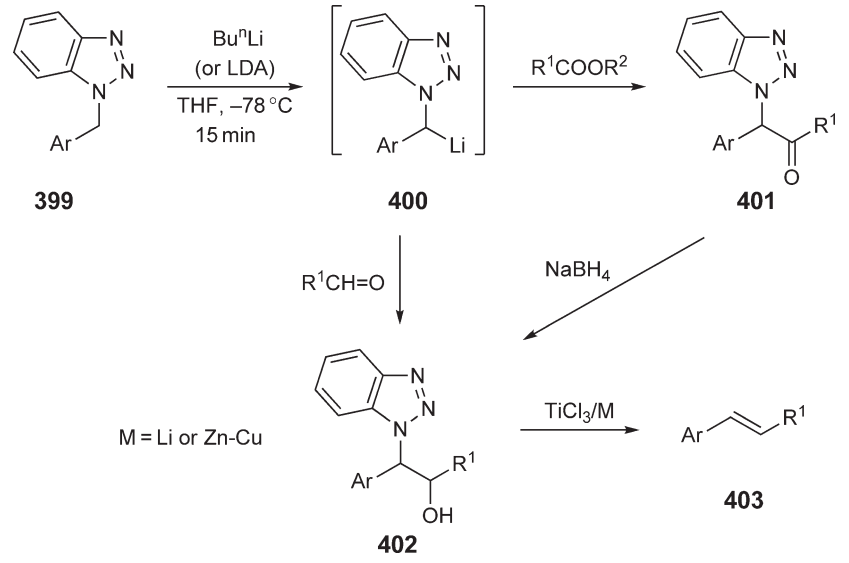
396 **397** **398**

E^+ = RI, $PhCH_2Br$, PhCH=O, PhN=C=O, PhN=C=S, and cyclohexanone

Scheme 64

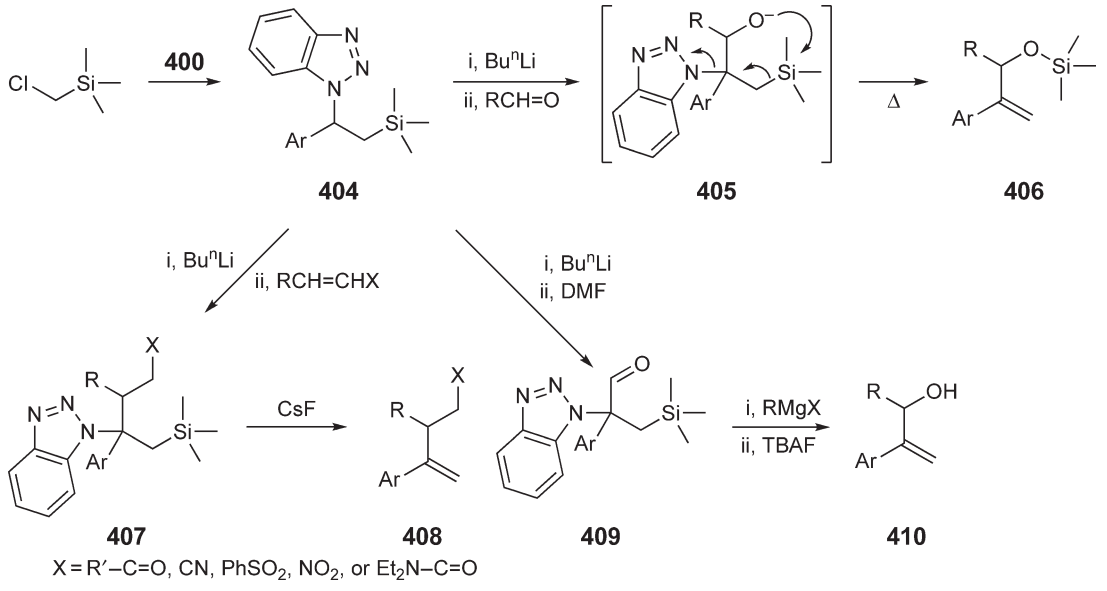
An additional stabilization of the negative charge provided by the adjacent aryl group in aryllithiomethyl intermediates **400** makes 1-(arylmethyl)benzotriazoles **399** attractive starting materials for many syntheses. Thus, reaction of anions **400** with esters of carboxylic acids leads to α-(benzotriazole-1-yl) ketones **401**, which can be easily reduced to carbinols **402**

<1998JOC3438>. In another approach, adducts **402** are produced directly by addition of anions **400** to carbonyl groups of aldehydes or ketones <1997JOC238, 1998JOC6704>. Low valent titanium, generated by reduction of $TiCl_3$ with lithium or Zn–Cu couple metals, converts carbinols **402** into olefins **403** (**Scheme 65**). The reaction sequence depicted in **Scheme 65** allows introduction of a variety of substituents R^1: for example, chiral allylamines are produced from aminoacids, or dienes are formed stereoselectively from α,β-unsaturated aldehydes or ketones. Reaction of lithio derivatives **400** with tosylhydrazones of aldehydes leads directly to *(E)*-stilbenes in a stereospecific manner <1999JOC3332>.



Scheme 65

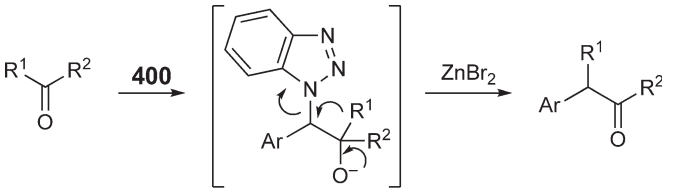
Reaction of anions **400** with chloromethyltrimethylsilane provides very useful intermediates **404** <1997JA9321>. Consecutive α-lithiation followed by addition to a carbonyl group of an aldehyde leads to alkoxide **405**. During heating, anions **405** undergo an intramolecular rearrangement with elimination of benzotriazole to produce silylated allyl alcohols **406** (**Scheme 66**) <1998JOC9978>. This approach provides a general method for the synthesis of allyl alcohols substituted with an aryl or heteroaryl group in the β position.



Scheme 66

Additions of lithiated silyl derivatives **404** to α,β-unsaturated compounds bearing electron-withdrawing substituents X provide silyl derivatives **407** with high 1,4-regioselectivity. Elimination of trimethylsilyl and benzotriazolyl groups facilitated by heating with CsF leads to γ,δ-unsaturated ketones, nitriles, sulfones, nitroalkanes, or amides **408** <1998JOC9987>. Formylation of intermediates **404** produces masked acroleins **409** that provide easy access to 2-substituted allyl alcohols **410**. Imines obtained from condensation of aldehydes **409** with arylamines can be similarly converted to the corresponding allylamines <1999JOC6080>.

Additions of anions **400** to carbonyl groups of aldehydes or ketones produce anions **411** that upon treatment with $ZnBr_2$ eliminate benzotriazole at elevated temperature and rearrange to ketones **412** (**Scheme 67**) <1996JOC7571>. This insertion of carbons carrying aryl or heteroaryl substituents provides a convenient method for one-carbon chain extension or ring expansion for aldehydes and ketones. The reaction is characterized by significant regioselectivity; of two groups R^1 and R^2, preferences for the migration are in the order: H > aryl > alkyl and *tert*-alkyl > *sec*-alkyl > n-alkyl.



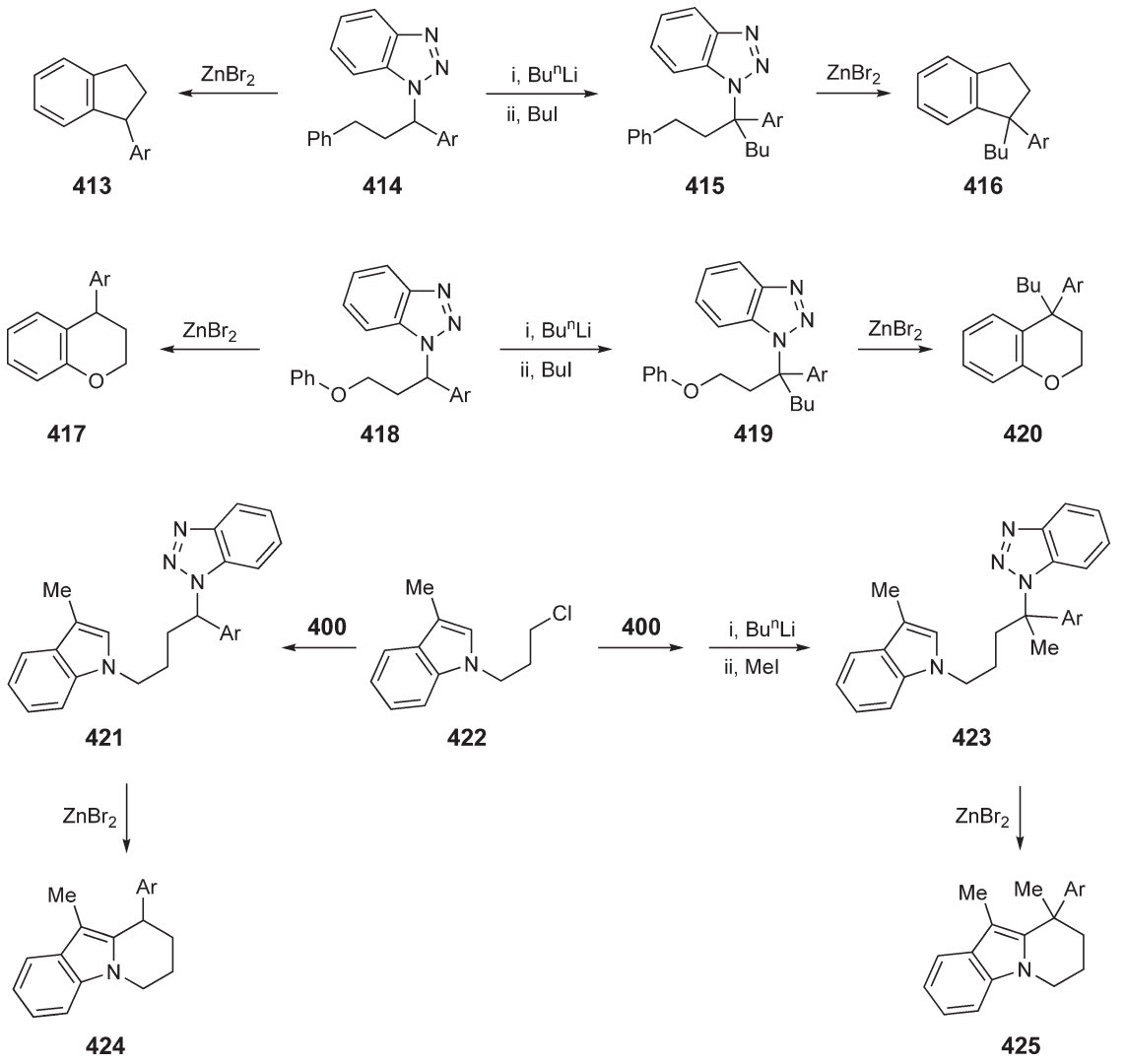
411 **412**

Scheme 67

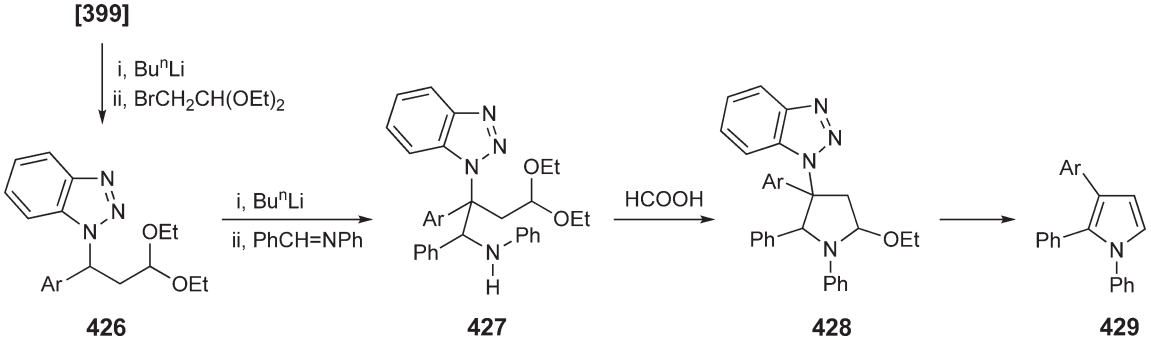
Substitution of one of the α-hydrogens in 1-(arylmethyl)benzotriazole **399** with an alkyl bearing an aromatic ring opens new frontiers. When the distance is right, an intramolecular electrophilic attack of α-carbon on an *ortho* atom of the aromatic ring is possible. Examples of such annulation reactions are given in **Scheme 68**. Thus, treatment of derivative **414**, obtained by alkylation of intermediate **400** with (2-bromoethyl)benzene, with zinc bromide results in formation of indane **413**. Alternatively, intermediate **414** can be first alkylated to product **415** and then annulated to 1,1-disubstituted indane **416**. For effective annulation, the link between the aromatic ring and α-carbon must consist of two or three atoms. Heteroatoms are also accepted, as exemplified by phenoxy derivatives **417–420**. Heterocyclic aromatic rings can be used as well; for example, annulated products **424** and **425** are obtained from 1-(3-chloropropyl)-3-methylindole **422** via intermediate **421** or its methylated analog **423**, respectively <1998JOC3445>. Similar annulation reactions involving thiophene are also described <1997JOC6215>.

Two sequential lithiations and treatments with different bifunctional electrophiles make possible one-pot syntheses of relatively complex molecules. Thus, in the [1+2+2] annulation depicted in **Scheme 69**, alkylation of 1-benzylbenzotriazole **399** with 2-bromoacetaldehyde diethyl acetal to give intermediate **426** is followed by alkylation with *N*-benzylideneaniline to produce derivative **427**. Following treatment with formic acid causes cyclization to ethoxypyrrolidine **428** that subsequently eliminates ethanol and benzotriazole to give pyrrole **429** <1997JHC1379>.

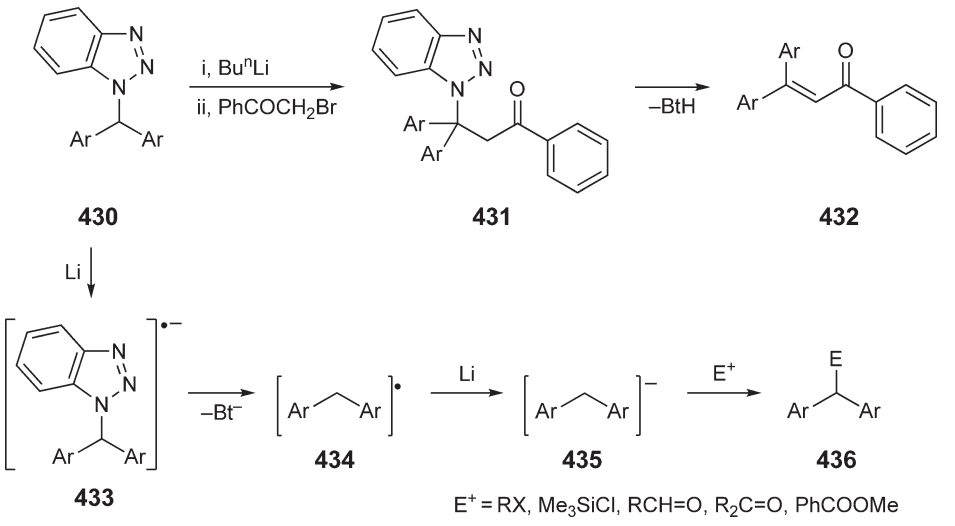
Anions derived from treatment of (diarylmethyl)benzotriazoles **430** with Bu^nLi are readily trapped by bromoacetophenone to produce ketones **431**. Increased acidity of the hydrogens in β-position, with respect to the benzotriazolyl moiety, renders derivatives **431** susceptible to elimination of benzotriazole to give diarylvinyl ketones **432** (**Scheme 70**). Both benzotriazol-1yl and -2-yl derivatives, and their mixtures, can be employed in these reactions <1998JOC3450>. Treatment of (diarylmethyl)benzotriazoles **430** with metallic lithium and electrophiles results in substitution of benzotriazole with formation of derivatives **436**. The yields are generally good, and variety of electrophiles can be employed. Some unusual outcome of these reactions can tentatively be explained by a single-electron transfer (SET) from lithium to starting compounds **430** to give radical anions **433** which eliminate benzotriazole to form relatively stable radicals **434**. Following reduction with metallic lithium (another SET) converts radicals **434** into anions **435** that are finally trapped by electrophiles to give products **436** <1997JOC4116>.



Scheme 68



Scheme 69

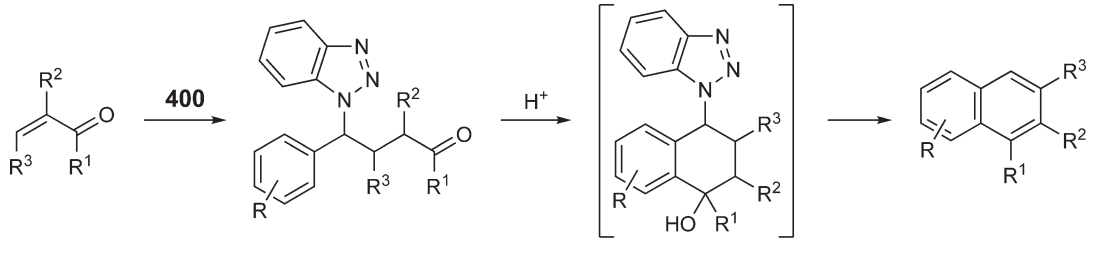


430 **431** **432** **433** **434** **435** **436**

Scheme 70

5.01.8.2.2 Ring N–C(sp^3)-Ar. Reactions on Ar

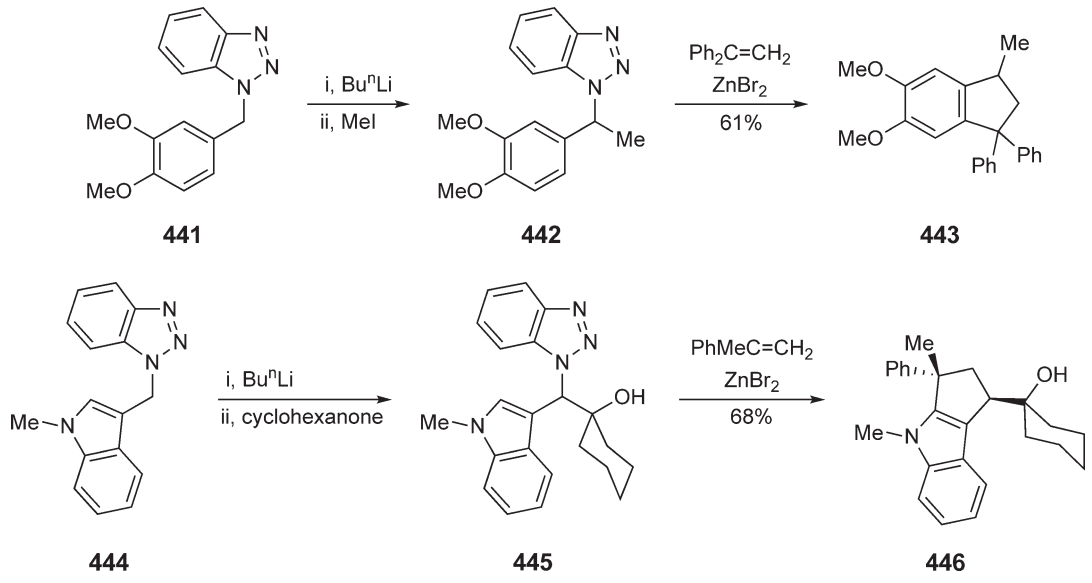
Lithiated 1-(arylmethyl)benzotriazoles **400** (Ar = phenyl, tolyl, or anisyl) readily undergo Michael additions to α,β-unsaturated aldehydes or ketones **437** to give γ-carbonyl-alkyl derivatives **438**. Upon treatment with acids, the carbonyl group of intermediate **438** is activated for an electrophilic attack on the *ortho* carbon of the ring to produce tetrahydronaphthalene derivative **439** which eliminates consecutively water and benzotriazole to give the naphthalene **440** (**Scheme 71**) <1997JOC721>. Substitution of one of the α protons in compound **400** with an alkyl group allows the introduction of substituents to C-4 of naphthalene. Analogous reactions of 1-[(1-methylindol-3-yl)methyl]-benzotriazole lead to corresponding carbazoles <1996JOC7558>. Similar [3+3] benzannulation reactions are occur for furans <1997JOC8205>, indolizines <2000JOC8059>, pyrroles <1996TL5641, 1997JOC4148>, thiazoles <2000JOC8059>, and thiophenes <1997JOC6215>; several examples of which can be found in review articles <1999T8263, 1998CCC599>.



437 **438** **439** **440**

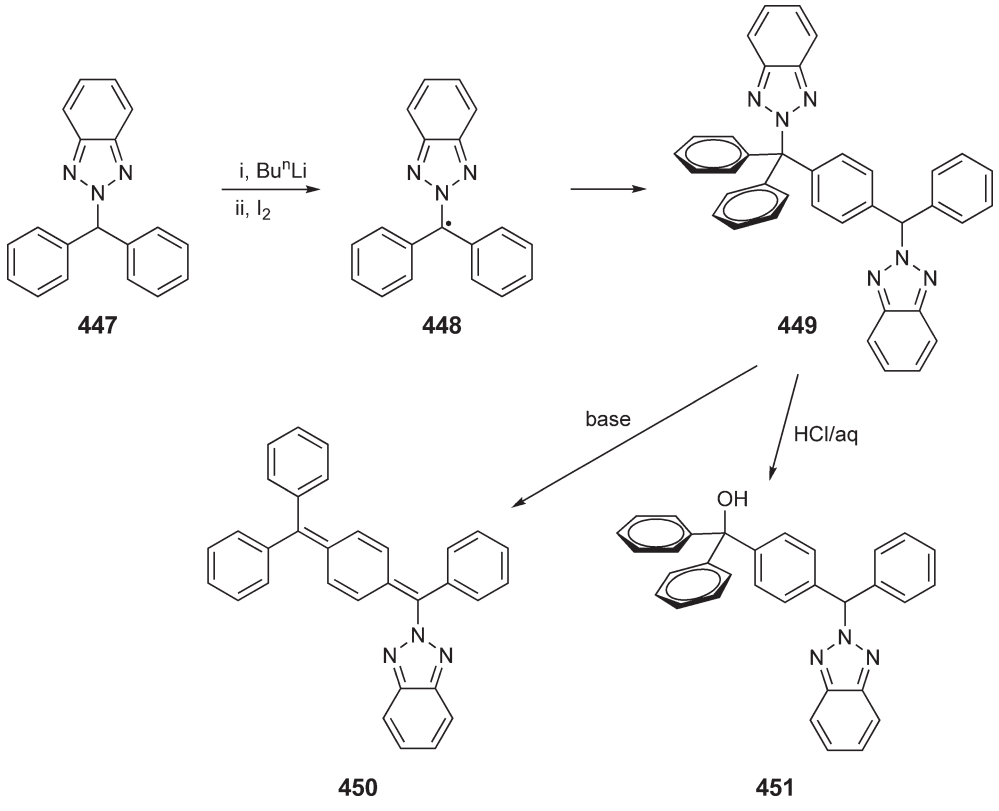
Scheme 71

Derivatives **400** containing electron-rich aromatic rings undergo readily [3+2] cycloaddition with styrenes. Two examples of such reactions are presented in **Scheme 72**. Thus, alkylation of an anion derived from benzylbenzotriazole **441** gives derivative **442**. Following treatment with $ZnBr_2$ cleaves the bond with benzotriazole to generate the corresponding benzyl cation which is then trapped by styrene to give a new cation that finally cyclizes on to the aromatic ring at its *ortho* position to furnish indan **443** <1997SC2467>. A similar process converts 1-methyl-3-[(benzotriazole-1-yl)methyl]indole **444** into tricyclic system **446**, via intermediate **445** <1996JOC7558>.



Scheme 72

Treatment of anions derived from 2-(diphenylmethyl)benzotriazole **447** with iodine generates relatively stable radicals **448** which undergo spontaneous dimerization to adducts **449** (**Scheme 73**) <1998JOC9992>. When one of the phenyl rings in starting material **447** is substituted in the *para* position, similar dimerization occurs readily, but it

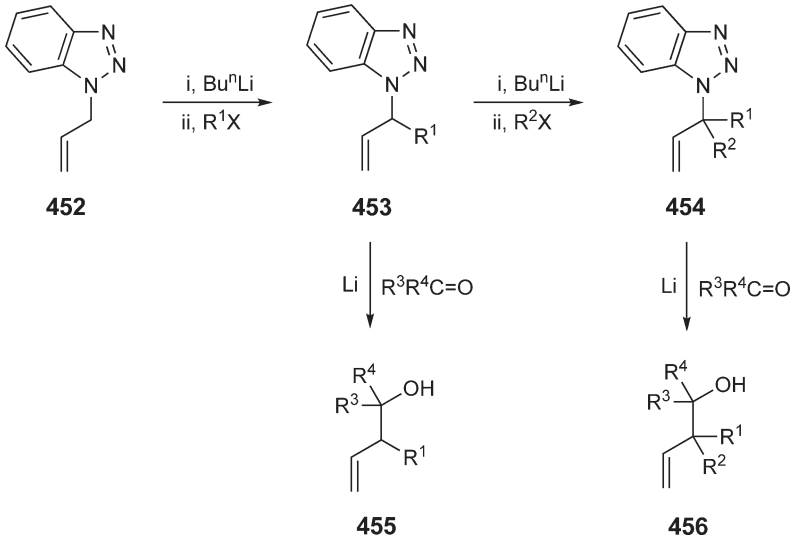


Scheme 73

is prevented by substitution of both *para* positions. Contrary to the behavior of an analogous adduct obtained by dimerization of triphenylmethyl radicals <1925CRV91, 1968TL249>, adduct **449** does not dissociate back to radicals **448**, indicating different characters of these two species. Treated with bases, adduct **449** eliminates one benzotriazole to give highly conjugated system **450**, red in color. Acidic hydrolysis converts adduct **449** into carbinol **451**. Radicals similar to **448** can be also generated from 1-(diarylmethyl)benzotriazoles, but they are less stable undergoing easily ring opening with extrusion of nitrogen <1998JOC1467>.

5.01.8.2.3 Ring N–C(sp^3)-C═C, nonaromatic

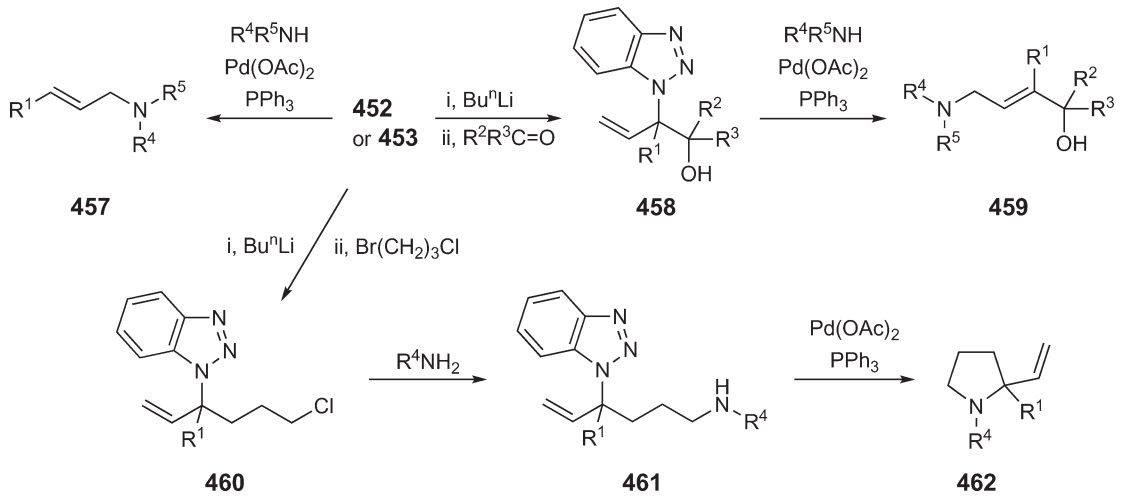
N-Allylbenzotriazoles (**452** and its benzotriazol-2-yl analog) behave somewhat similarly to *N*-benzylbenzotriazoles. Anions derived from compounds **452** upon treatment with n-butyllithium undergo alkylation exclusively at the position α to the benzotriazole moiety to give products **453** (**Scheme 74**). The lithiation and alkylation steps can be repeated to produce dialkylated derivatives **454**, possibly with two different alkyl groups. Although only benzotriazol-1yl compounds are shown in **Scheme 74**, in this case, both benzotriazol-1-yl and benzotriazol-2-yl derivatives have similar reactivity and their mixtures can be used effectively in the reactions next mentioned without separation <1998TL363>. Treatment of compounds **453** and **454** with metallic lithium in the presence of aldehydes or ketones cleaves the bonds with benzotriazole creating allylic anions that are trapped by the carbonyl groups to produce carbinols **455** and **456**, respectively, in high yields.



Scheme 74

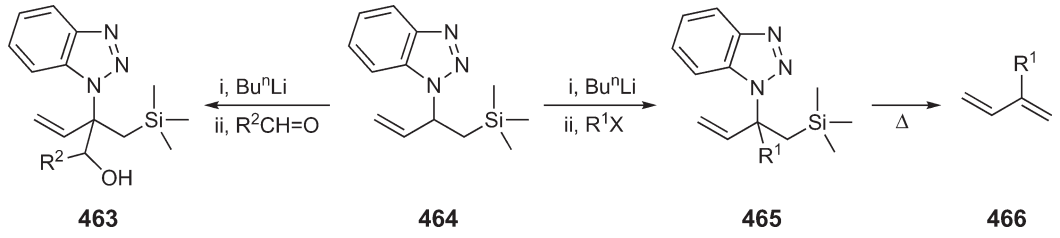
In the presence of a palladium catalyst, the benzotriazole moiety in derivatives **452**, **453** (and also in compound **454**) can be substituted with amines to give allylamines **457** (**Scheme 75**) <1998JOC5232>. Sulfonamides can also be N-allylated this way when triphenyl phosphite is used in place of triphenylphosphine as a complexing catalyst agent <2000JOC8063>. Palladium-catalyzed reactions of derivatives **453** and **454** with enamines lead to γ,δ-unsaturated ketones <1999JOC7625>. Lithiated allylbenzotriazoles **452** and **453** react with aldehydes and ketones to form alcohols **458** <2000JOC8063>. Following treatment with amines and the catalyst converts alcohols **458** into unsaturated aminoalcohols **459**.

The reaction of allylbenzotriazoles with amines can also be carried out intramolecularly. Thus, alkylation of derivatives **452** or **453** with 1-bromo-3-chloropropane gives chloropropyl derivative **460**. Subsequent substitution of the chlorine atom with an alkylamino group is easily accomplished by heating a solution of derivative **460** and amine R^4NH_2 in DMF. Intramolecular substitution of the benzotriazole moiety by the amino group in amines **461** occurs at room temperature in the presence of a palladium catalyst to furnish 2-vinylpyrrolidines **462** (**Scheme 75**) <1999JOC6066>. Similarly, alkylation of derivatives **452** and **453** with 1-bromo-4-chlorobutane and the following transformations lead to 2-vinylpiperidines <1999JOC6066>.



Scheme 75

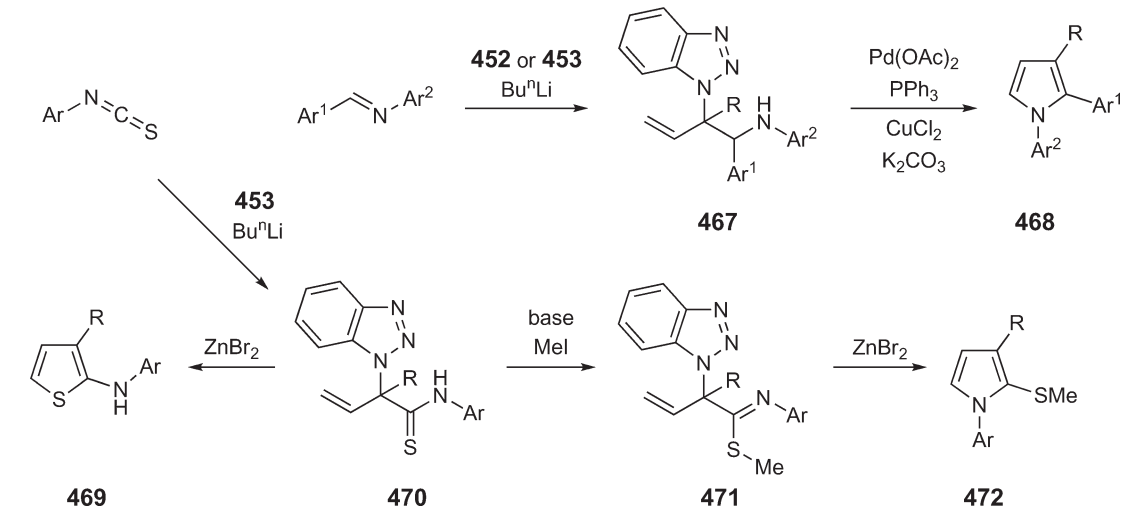
Reaction of lithiated allylbenzotriazole **452** with chloromethyltrimethylsilane yields silyl derivative **464** which can be further alkylated to give compound **465** (**Scheme 76**) <1999JOC1888>. Upon heating, product **465** is readily converted to diene **466** via vicinal elimination of benzotriazolyl and silyl substituents. Additions of lithiated silyl derivative **464** to carbonyl groups of aldehydes lead to alcohols **463** which readily eliminate benzotriazole and silane to furnish 2-(1-hydroxyalkyl)butadienes **466** (R^1 = 1-hydroxyalkyl).



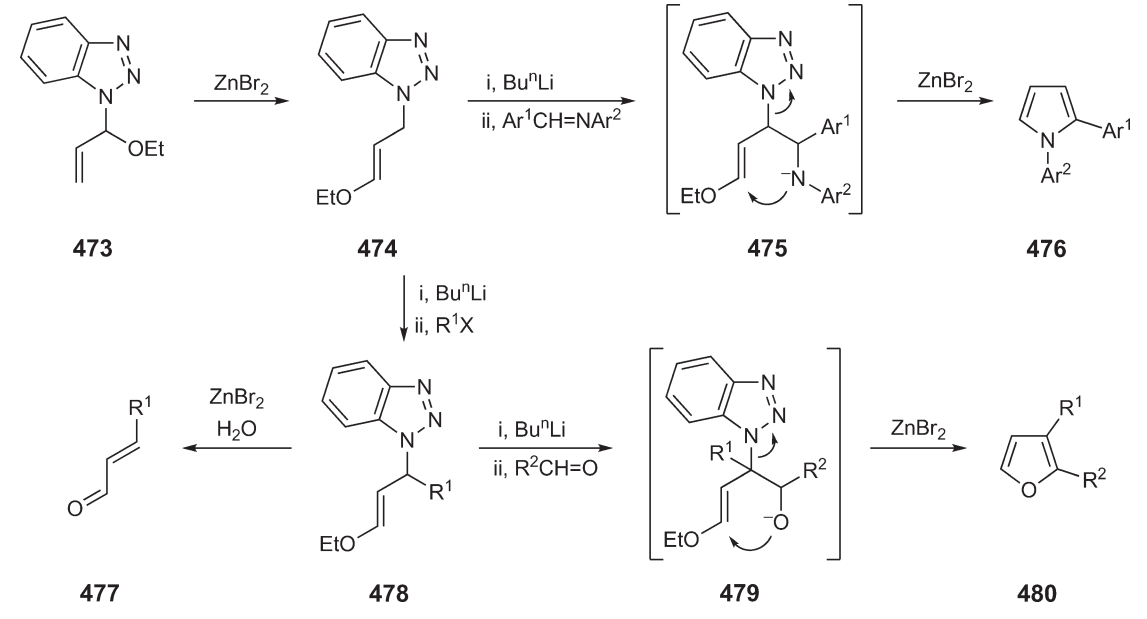
Scheme 76

Lithiated *N*-allylbenzotriazoles **452** and **453** add readily to the C=N bond of Schiff bases derived from aromatic or heteroaromatic aldehydes and amines to give amines **467**. In the presence of a palladium catalyst and copper(II) oxidizing agent, amines **467** are smoothly converted to pyrroles **468** (**Scheme 77**) <2000JOC8074>. Addition of lithiated allylbenzotriazoles **453** to the C=N bond of isothiocyanates leads to thioamides **470**. Catalyzed by $ZnBr_2$, thioamides **470** undergo cyclization to aminothiophenes **469** <2001JOC2850>. When the nucleophilic attack of the sulfur atom on the allylic system is blocked by methylation as in compound **471**, the nitrogen atom takes the leading role and 2-(methylthio)pyrroles **472** are formed instead.

When an additional leaving group is present at the allylic system, conversion of *N*-allylbenzotriazoles to five-membered heterocyclic rings is facilitated. Thus, α-ethoxy derivative **473** undergoes smooth rearrangement promoted by $ZnBr_2$ to give (γ-ethoxyallyl)benzotriazole **474**. After lithiation, the obtained anion is trapped by a Schiff base to give anion **475**. Catalyzed by $ZnBr_2$, intermediate **475** undergoes cyclization with elimination of benzotriazole and ethanol to furnish 1,2-diarylpyrrole **476** (**Scheme 78**) <1995S1315>. Alkylation of (γ-ethoxyallyl)benzotriazole **474** occurs exclusively at the carbon α producing derivatives **478**, which, in their lithiated forms, add readily to the carbonyl group of aldehydes. Obtained anions **479** are rapidly converted to 2,3-disubstituted furans **480** upon treatment with $ZnBr_2$ <1995S1315>. Treatment with $ZnBr_2$ and water converts ethoxyallyl derivatives **478** into α,β-unsaturated aldehydes **477**.



Scheme 77

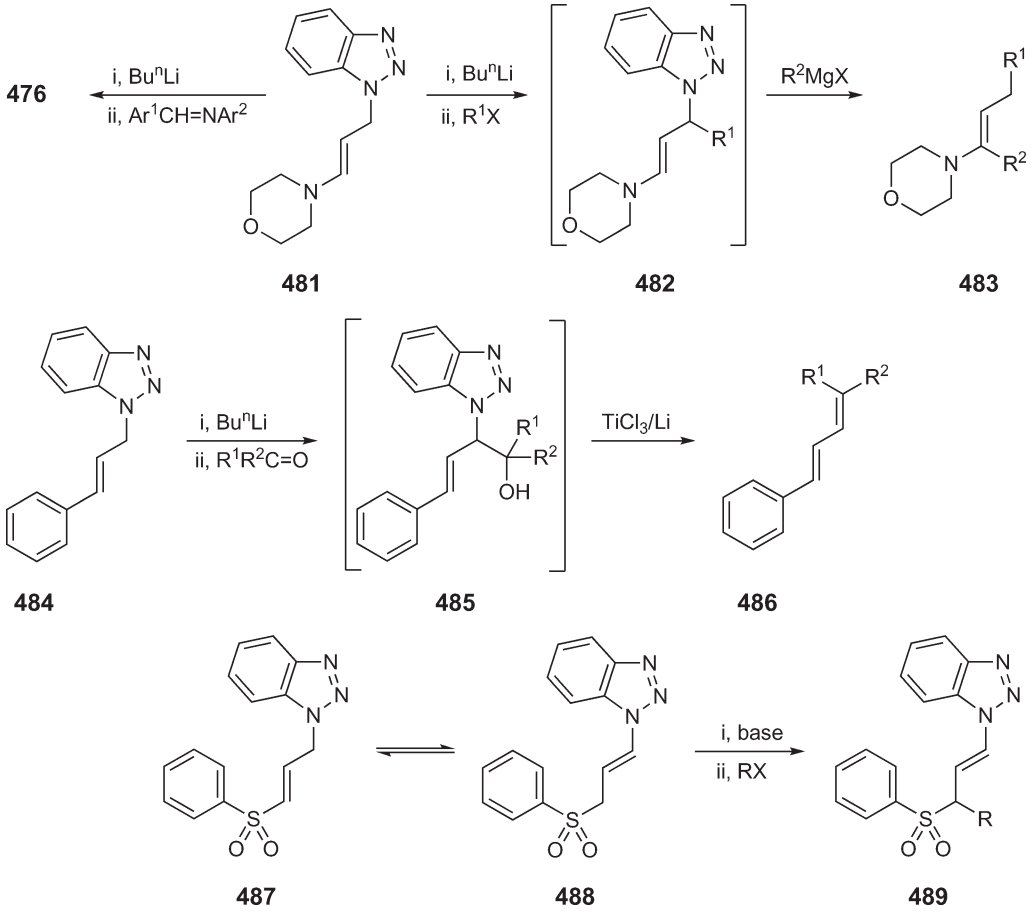


Scheme 78

The morpholin-4-yl substituent in γ-position behaves similarly to the ethoxy group. Compound **481** is easily prepared by double addition of benzotriazole to acrolein followed by elimination of one of the benzotriazolyl moieties induced by treatment with NaH. Lithiation of derivative **481** followed by addition to a Schiff base results in formation of diarylpyrrole **476**. Lithiated product **481** is alkylated exclusively at the carbon α, in relation to the benzotriazolyl substituent, giving intermediate **482**. Subsequent treatment with a Grignard reagent leads to enamine **483** (**Scheme 79**) <1995TL343>.

A phenyl substituent at the γ-carbon atom is a much weaker electron donor in comparison with the discussed above ethoxy and morpholin-4-yl groups. Nevertheless, 1-(γ-phenylallyl)benzotriazole **484** is still lithiated exclusively at the carbon α as it is evident from its reaction with aldehydes and ketones leading to dienes **486**, resulting from

elimination of benzotriazole and water from intermediate carbinols **485** <1997JOC238>. However, the strongly electron-withdrawing phenylsulfonyl group at the γ-carbon shifts the equilibrium from form **487** to form **488**, which upon its alkylation gives sole product **489** (**Scheme 79**) <1998JHC173>.

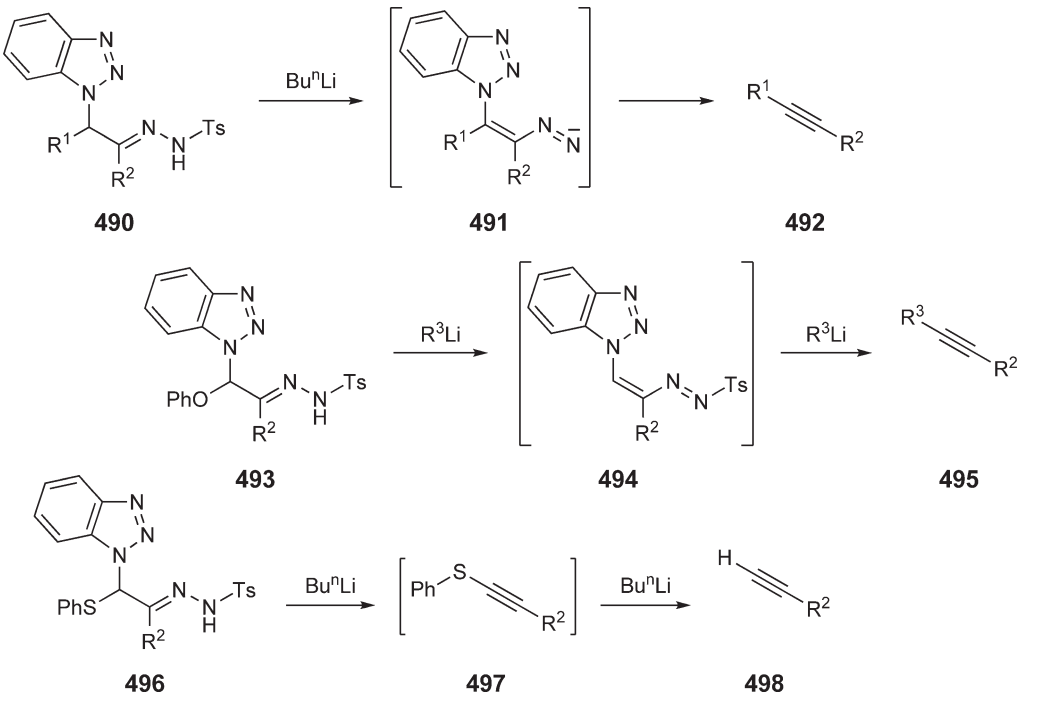


Scheme 79

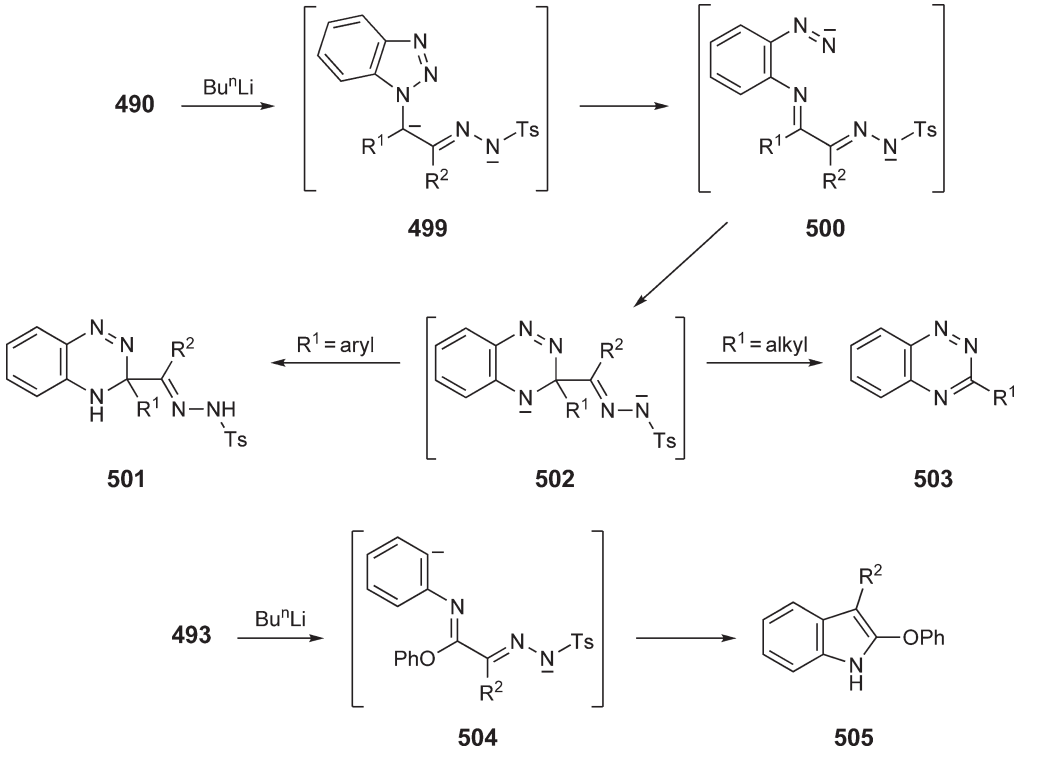
5.01.8.3 Ring N–C(sp^3)-C=N

Hydrazones **490** are readily obtained from the corresponding ketones. Upon treatment with 6 molar equivalents of n-butyllithium, they are deprotonated to dianions which lose rapidly the tosyl moiety to form anions **491** that further eliminate spontaneously N_2 and benzotriazole to give alkynes **492** (**Scheme 80**). In the special case, when R^1 = PhO (compound **493**), organolithium reagents eliminate first the phenoxy group to give intermediates **494**. Addition of group R^3 to **494** followed by elimination of tosylate, nitrogen and benzotriazole provides alkynes **495**. Due to the stronger electron-donating influence of the phenylthio group in compound **496**, the benzotriazolyl moiety is eliminated preferentially leading to unstable sulfide **497**, which is converted by excess Bu^{n}Li to acetylene **498** <1997JOC4142>.

Treated with only 3 molar equivalents of Bu^{n}Li, hydrazones **490** behave differently. Bond cleavage between N-1 and N-2 of the benzotriazole ring in the initial dianion **499** leads to dianion **500**. Following ring closure produces benzotriazine system **502**. The next step of the transformation sequence depends on substituent R^1. When R^1 is an aryl, the structure is stable enough to survive work-up as dihydrobenzotriazine **501**. When R^1 is an alkyl, the whole hydrazone group is eliminated producing benzotriazine **503** (**Scheme 81**) <1997SC3963>. When phenoxy derivative **493** is subjected to such treatment, the dianion formed, analogous to **500**, loses molecular nitrogen to give energetic dianion **504** that quickly undergoes cyclization/elimination to furnish indole **505**.

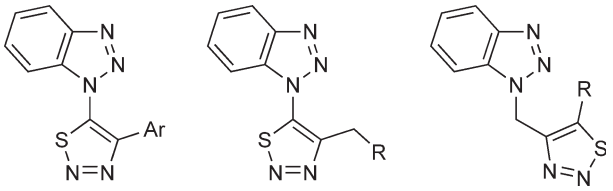


Scheme 80



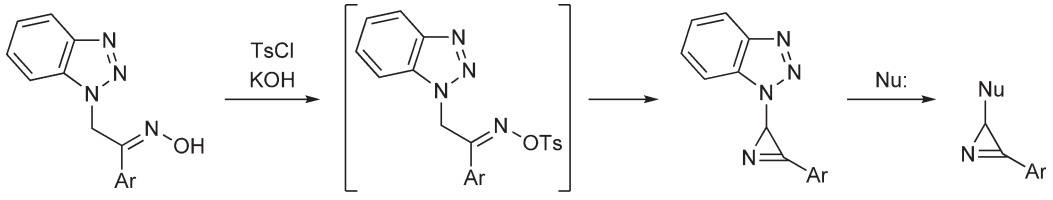
Scheme 81

Treated with thionyl chloride, hydrazones **490** ($R^1 = H$, $R^2 =$ aryl) undergo cyclocondensation to thiadiazoles **506**; whereas from aliphatic derivatives **490** ($R^1 = H$, $R^2 =$ alkyl), mixtures of thiadiazoles **507** and **508** are formed <2002H(58)311>.



506 **507** **508**

Oximes **509** can be converted to their tosylates **510**, but use of a large excess of KOH converts them directly into *2H*-azirines **511** (**Scheme 82**) <2003JOC9105>. The benzotriazolyl moiety in azirines **511** can be substituted by nucleophiles (organomagnesium reagents, potassium phthalimides, and sodium thiophenoxide) to give disubstituted azirines **512**.



509 **510** **511** **512**

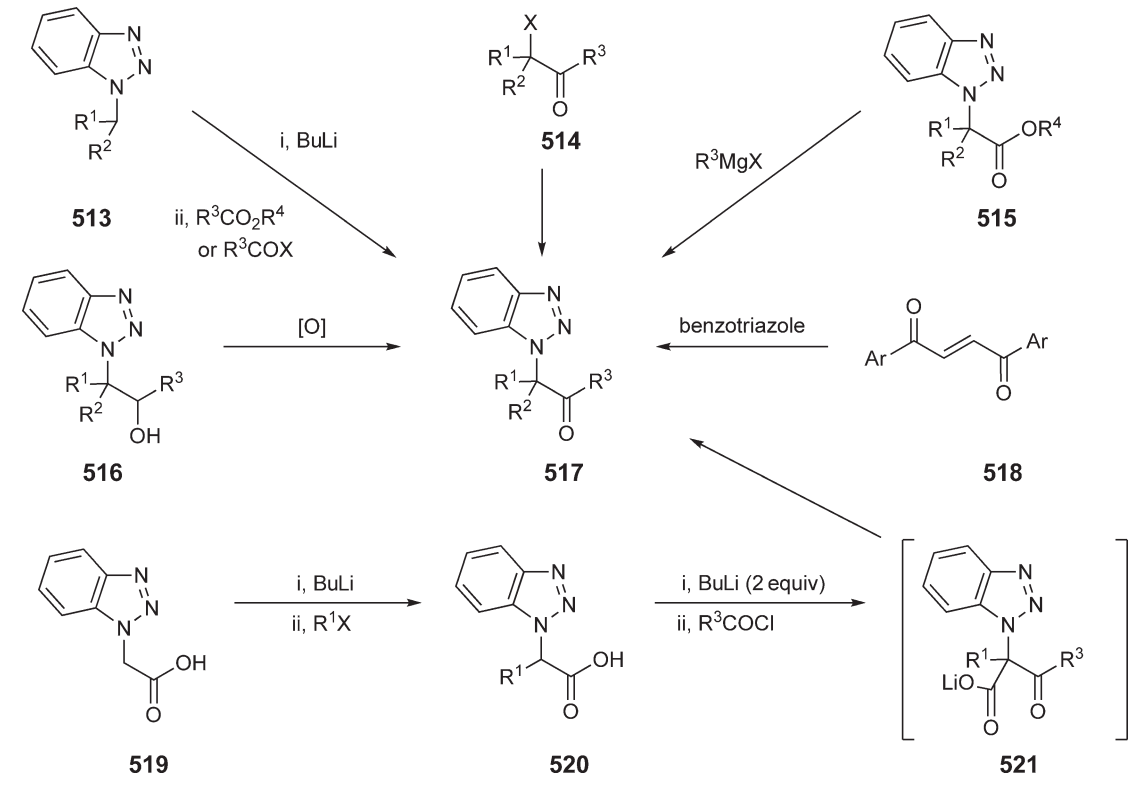
Scheme 82

5.01.8.4 Ring N–C(sp^3)-C═O

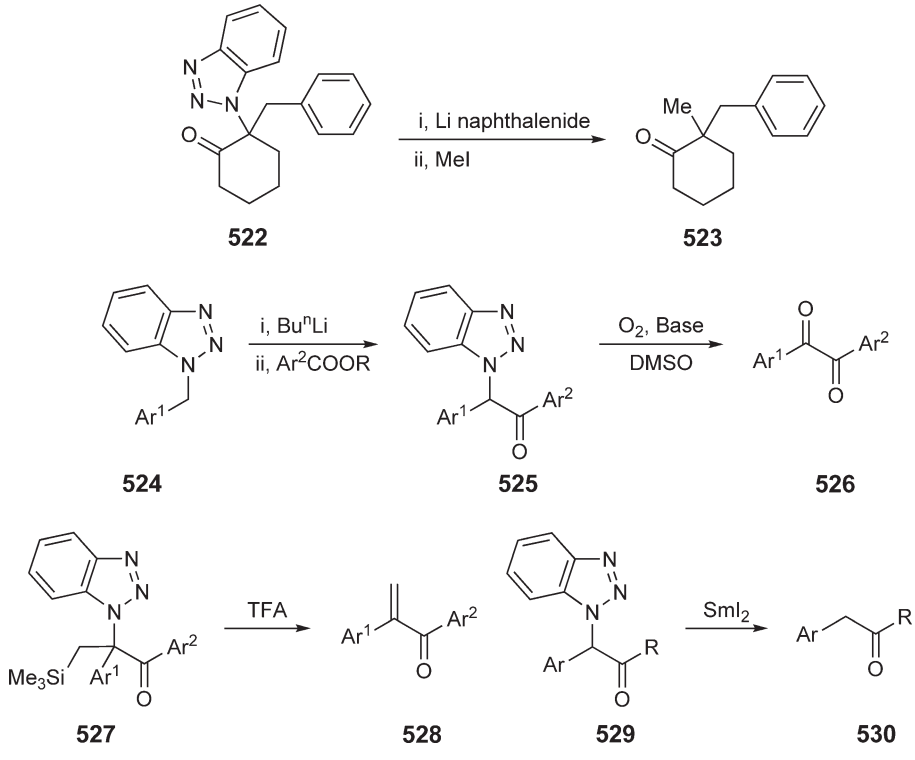
There are several methods available that lead to α-benzotriazolyl ketones **517** (**Scheme 83**). Thus, the anions derived from *N*-alkylbenzotriazoles **513** can be trapped by acid chlorides or esters <1998JOC3438, 1998H(48)1567>. Alternatively, in reactions with aldehydes, *N*-alkylbenzotriazoles **513** are converted to β-benzotriazolyl alcohols **516** that are consecutively oxidized to ketones **517** <1996LA1235>. Other approaches include substitution of halogens in α-haloketones **514** by benzotriazole, <2000JHC167, 2002ARK(iii)46>, reactions of esters of α-benzotriazolylcarboxylic acids **515** with Grignard reagents <1997JOC4142>, addition of benzotriazole to but-2-ene-1,4-diones **518** <1992PJC1633>, and reactions of *N*-chlorobenzotriazole with trimethylsilyl derivatives of the corresponding ketones <1998JCM334>. In an interesting modification of the above methods, benzotriazoleacetic acid **519** <1935LA113> is alkylated to produce carboxylic acids **520**, which are then dilithiated and treated with acyl halides to give ketones **517**, via unstable intermediates **521** <2004ARK(iii)22>.

Removal of the benzotriazole moiety from ketones **517** can be accomplished in several modes. Thus, treatment of derivative **522** with lithium naphthalenide followed by methyl iodide provides ketone **523** in 51% yield (**Scheme 84**) <2002ARK(iii)46>. Upon treatment with buthyllithium, anions derived from 1-(arylmethyl)-benzotriazoles **524** can be trapped by esters of arylcarboxylic acids to give ketones **525** which are readily oxidized with molecular oxygen under mild conditions to give diaryl 1,2-diketones **526** in good yields. This provides a convenient synthetic method for unsymmetrical 1,2-diketones, especially valuable when Ar^1 and Ar^2 are heterocyclic systems <2005JOC3271>. When trimethylsilyl derivatives **527** are treated with TFA in dichlorometane, both the trimethylsilyl and benzotriazolyl groups are eliminated to provide 1,2-diarylpropen-1-ones **528** in high yields <1998JOC9983>. Heating of ketones **527** with CsF in DMF yields also propenones **528**, but usually a rearrangement occurs and the corresponding chalcones are the main products <1998J(P2)2515>. Samarium iodide induced removal of benzotriazole from ketones **529** works well with variety of groups R to provide ketones **530** in high yield under mild reaction conditions <1998H(48)1567>.

[3+3] Annulation reaction of (benzotriazol-1-yl)acetone **531** with chalcones provides an efficient route to 3,5-diarylphenols **538**. The reaction is catalyzed by NaOH in ethanol. In the first step, Michael addition of ketone **531** to the C═C bond of a chalcone gives diketone **532**. In the second step, condensation between the carbonyl

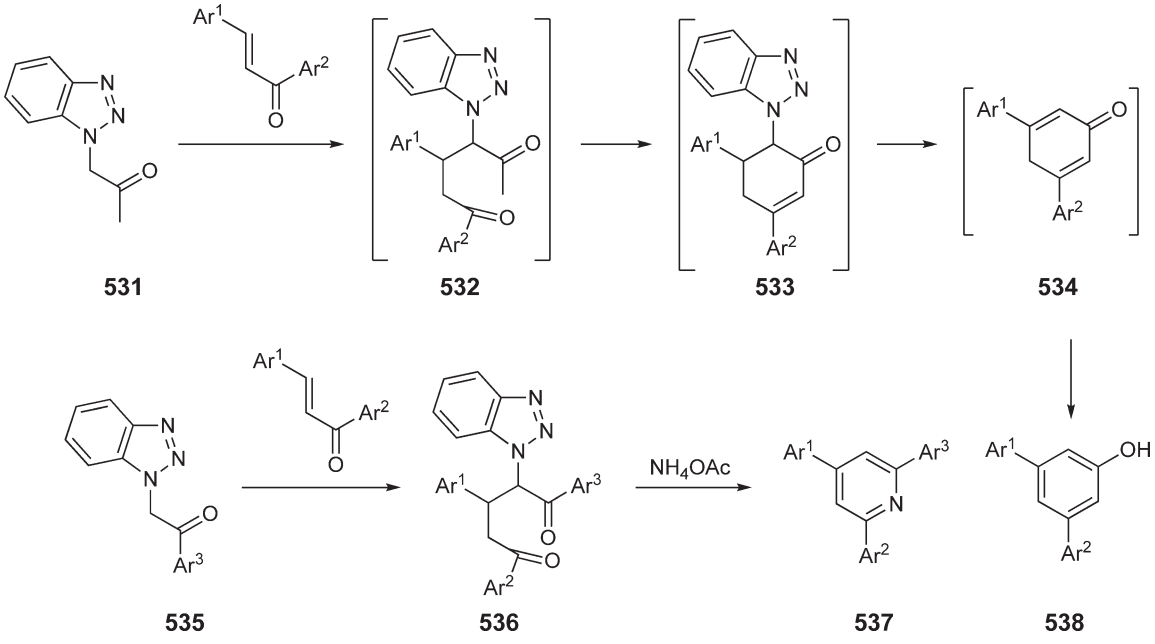


Scheme 83



Scheme 84

group at Ar^2 with the methyl group gives cyclohexenone **533**. In the following steps, benzotriazole is eliminated, and the obtained cyclohexadienone **534** rearranges to phenol **538** (**Scheme 85**) <1997JOC8215>. Diketones **536**, obtained by Michael addition of (benzotriazol-1-yl)acetophenones **535** to chalcones, cannot undergo such cyclocondensation to form phenols, but they react readily with ammonium acetate to give pyridines **537** <1999S2114>.



Scheme 85

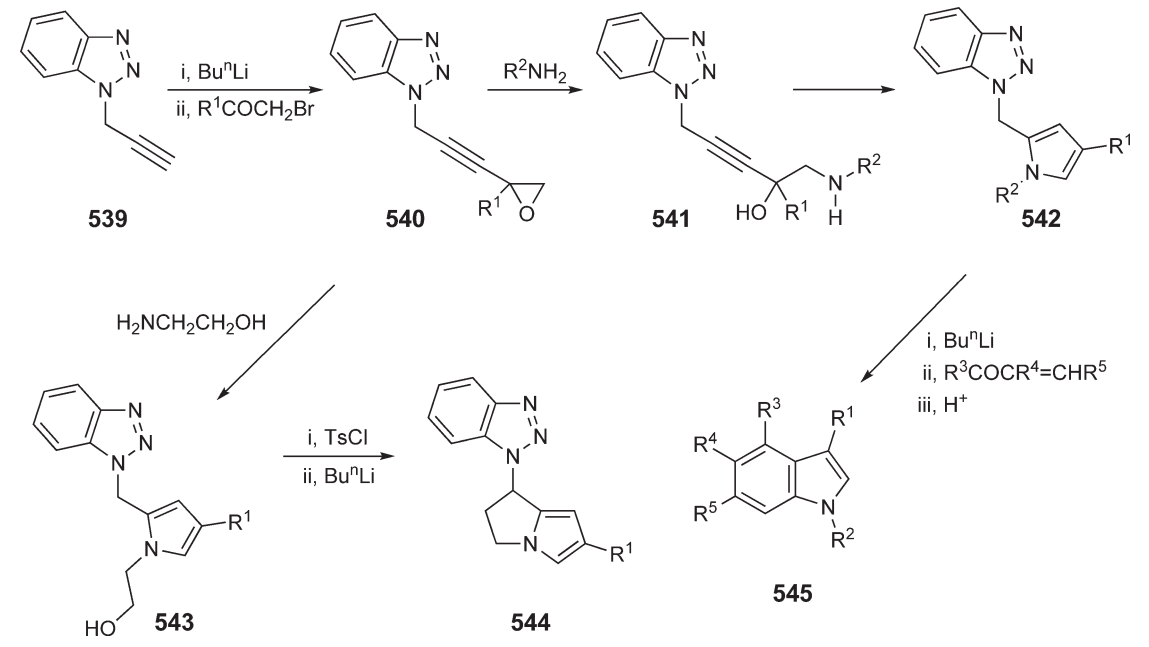
5.01.8.5 Ring N–C(sp^3)-C(sp)

Some chemistry of propargylbenzotriazole **539** and its applications in organic synthesis is already described in CHEC-II(1996) <1996CHEC-II(4)1>. Further development in this field led to very useful oxirane derivatives **540** <1995JOC638>. Primary amines in refluxing isopropanol cause opening of the oxirane ring with addition of the amine to form aminoalcohols **541** that undergo spontaneous intramolecular cyclocondensation to give pyrroles **543** (**Scheme 86**). The benzotriazolyl moiety in **542** can be directly substituted with nucleophiles or the molecule can be first lithiated at its α-carbon then treated with electrophiles and finally the benzotriazolyl group be removed to provide further classes of substituted pyrroles <1996JOC1624>.

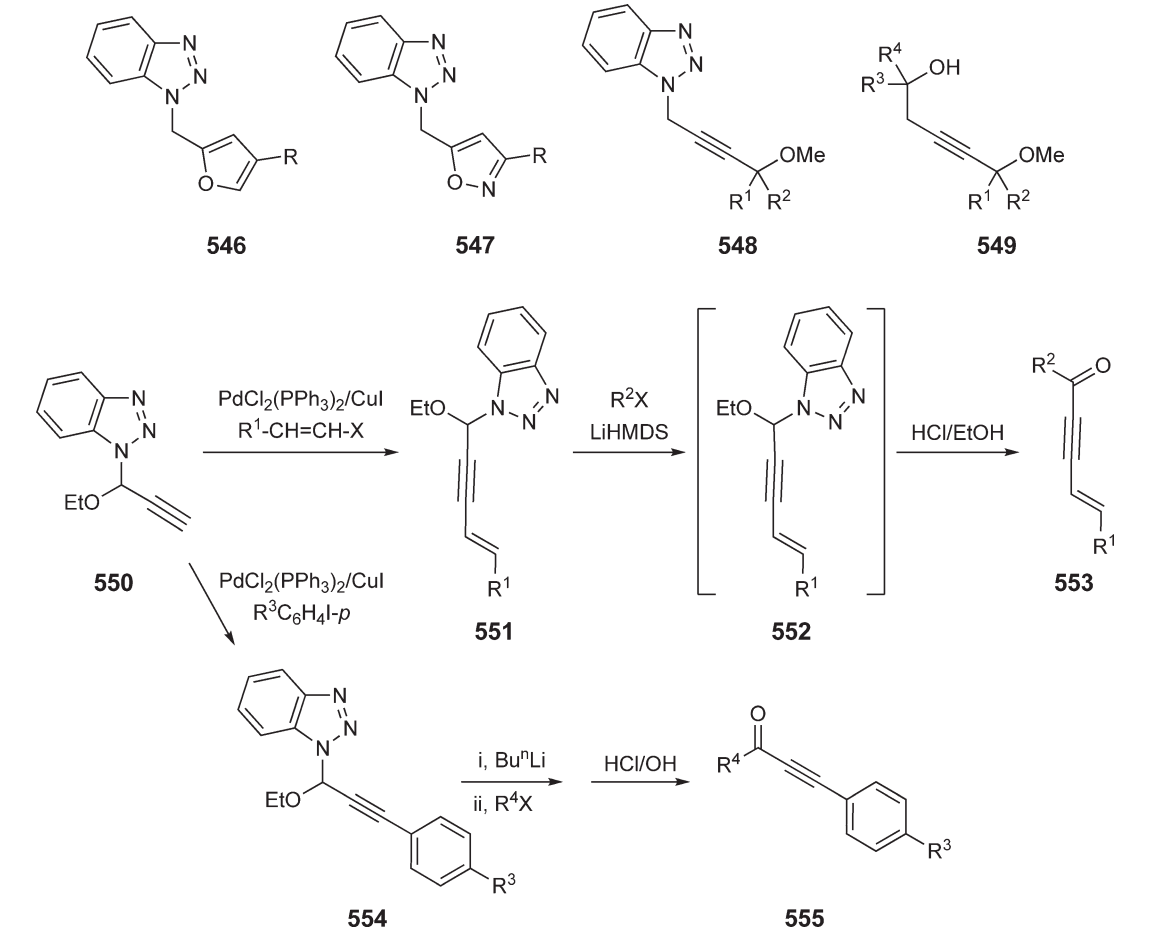
1-(2-Hydroxyethyl)pyrroles **543** obtained from reactions of oxiranes **540** with 2-aminoethanol are readily converted to 2,3-dihydro-1*H*-pyrrolo[1,2-a]pyrroles **544** <1997JOC4148>. Analogously, 1-(3-hydroxypropyl)pyrroles give homologous 5,6,7,8-tetrahydropyrrolo[1,2-a]pyridines. Easy manipulation with the benzotriazolyl moiety allows for convenient synthesis of a wide variety of fused [1,2-a]pyrroles. A similar chemistry of indoles is also described <1997JOC4148>.

Lithiated pyrrole derivative **542** undergoes Michael addition to α,β-unsaturated aldehydes or ketones, and the obtained adducts readily undergo cyclization to indoles **545** in the presence of acids as catalysts <1996TL5641>. Similarly, lithiated 2-[(benzotriazol-1-yl)methyl]furans **546**, obtained from oxiranes **540** by their cyclization promoted by Bu^{t}OK, react with α,β-unsaturated aldehydes or ketones to provide benzofurans <1997JOC8205>. 1,3-Dipolar cycloaddition of propargylbenzotriazole **539** to nitrile oxides (R-C≡C-N═O) gives oxazoles **547** in excellent yields <2000JHC1505>. Addition of lithiated propargylbenzotriazole **539** to aldehydes or ketones followed by methylation with iodomethane provides ethers **548**. Treatment with metallic lithium and the same or different aldehydes or ketones R^3R^4C═O converts ethers **548** into protected alkynediols **549** <1999TL253>.

Introduction of an alkoxy group to the α-carbon opens new possibilities regarding transformation and benzotriazole removal process from 1-propargylbenzotriazole. Thus, ether **550** <1995JOC7612> can be coupled with vinyl triflates or bromides to give enynyl products **551**. Following alkylation at the carbon α gives unstable derivatives **552** that are readily hydrolyzed to enynyl ketones **553**. In another approach, alkynes **550** are coupled with aryl iodides, and the obtained ethers **554** are alkylated and hydrolyzed to ketones **555** (**Scheme 87**) <1997JOC8201>.

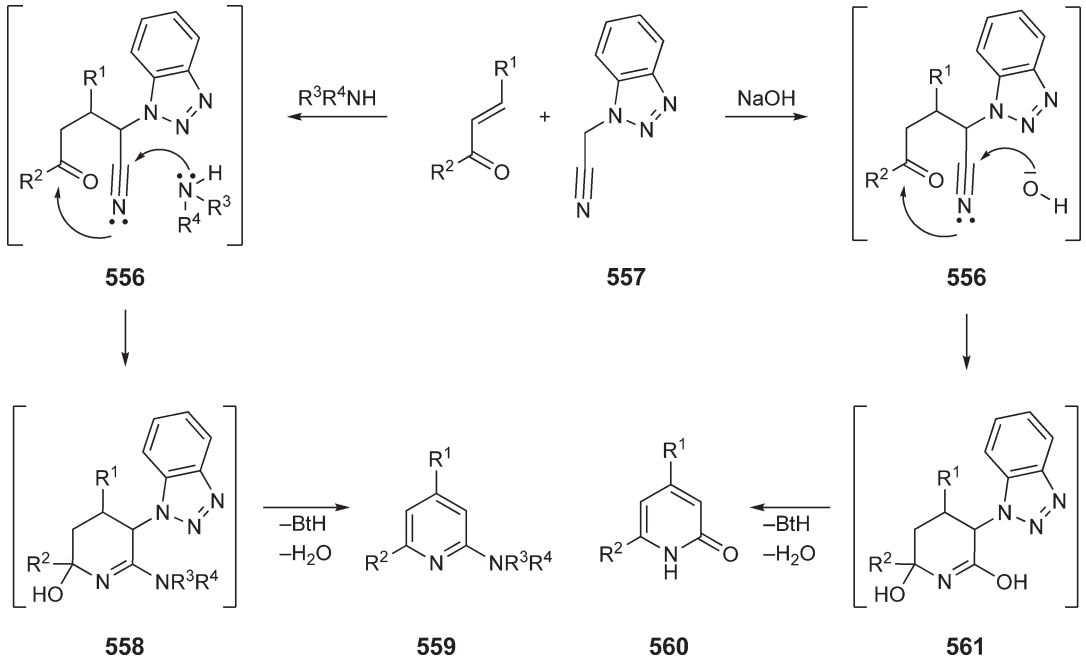


Scheme 86



Scheme 87

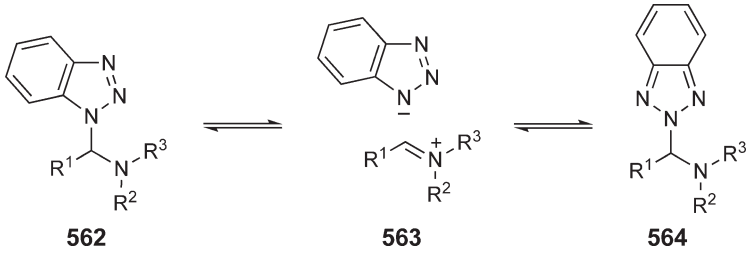
Michael addition of (benzotriazol-1-yl)acetonitrile **557** to α,β-unsaturated ketones followed by heterocyclization provides new means for preparation of 2,4,5-trisubstituted pyridines. The reaction is catalyzed by bases. In the presence of secondary amines, a nucleophilic attack of amine on the CN group in adduct **556** initiates the cyclization to tetrahydropyridine **558** that subsequently eliminates water and benzotriazole to give pyridine **559**. Analogously, in the presence of NaOH, pyridone **560** forms, via intermediate **561** (**Scheme 88**) <1997JOC6210>.



Scheme 88

5.01.8.6 Ring N–C(sp^3)-N

In solution, 1-(α-aminoalkyl)benzotriazoles **562** are in equilibrium with iminium cation **563** and hence with their benzotriazole-2-yl isomers **564** (**Scheme 89**). Protonation or complexation of the benzotriazolyl moiety (e.g., Mg, Zn, B, Al reagents) facilitates the transformation. Intermediate iminium cations **563** can be trapped by nucleophiles providing synthetic pathways to various amines. Many such reactions are described in CHEC-II(1996) <1996CHEC-II(4)1>, and some newer results are compiled in reviews <2005T2555>.

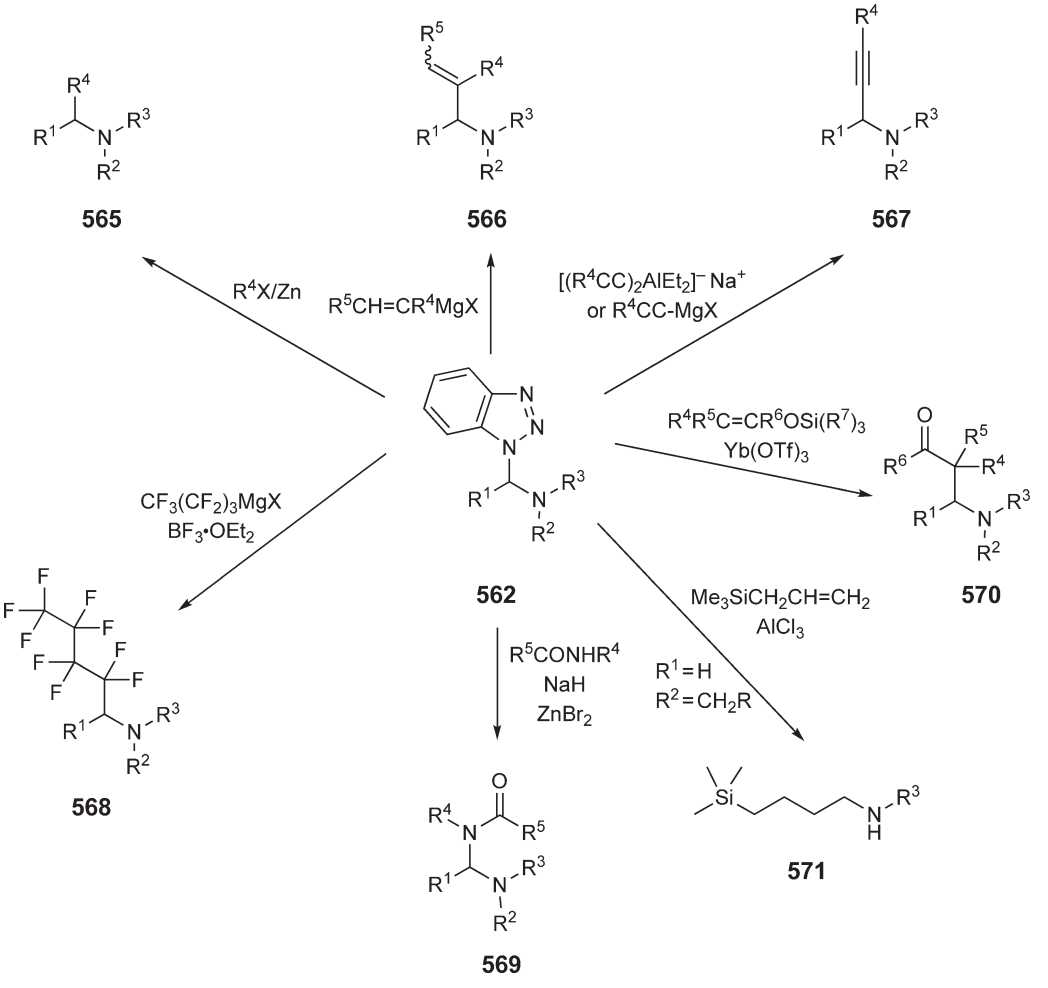


Scheme 89

For clarity, in the following schemes of this subsection, the benzotriazol-2-yl structures are often omitted when such derivatives are present in the reaction mixtures, and their chemistry is not different from that of the benzotriazol-1-yl derivatives. When there is a clear distinction in chemistry, the benzotriazol-2-yl isomers are treated separately.

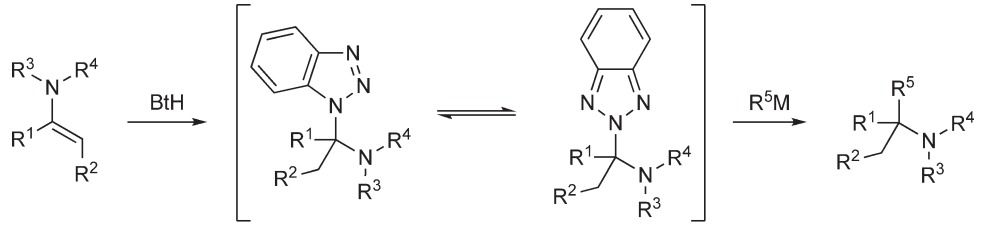
5.01.8.6.1 Substitution of benzotriazole with nucleophiles

Since the publication of CHEC-II(1996), the range of nucleophiles used for substitution of the benzotriazolyl moiety in derivatives **562** and applied reaction conditions have been widely expanded. Thus, treatment of benzotriazolyl amines **562** with organozinc bromoacetate, provides conveniently amines **565** (**Scheme 90**) <1998T7167. This extends the scope of this reaction to substituents bearing groups sensitive to organomagnesium reagents previously used for this purpose <1996CHEC-II(4)1>. Reactions of intermediates **562** with alkenylmagnesium and alkynylmagnesium reagents carried out in toluene lead to allylamines **566** and propargylamines **567** in excellent yield <2002S199>. Less stable perfluoroalkylmagnesium reagents give amines **568** when the reactions are carried out at low temperature with additional activation of derivatives **562** with trifluoroboron etherate <1997TL7015>. Propargylamines **567** can be also conveniently prepared in reactions of compound **562** with dialkynyldiethylaluminates <1999JOC488>. Treatment of benzotriazolyl derivatives **562** activated by addition of $ZnBr_2$ with sodium salts of amides allows preparation of acylaminals **569** <1998S1421>. *N*-(α-Aminoalkyl)benzotriazoles **562** react smoothly with silyl enolates in the presence of lanthanide catalysts to provide aminoketones **570** (R^6 = Ph) or aminoesters **570** (R^6 = alkoxy or phenoxy group) in practically quantitative yields <1996TL3731>. In the presence of aluminium chloride, the iminium cations derived from 1-[(dialkylamino)methyl]benzotriazoles **562** (R^1 = H) add to the C-3 atom of allyltrimethylsilane, and the obtained adducts rearrange to aminosilanes **571** via a 1,5-hydride shift from group R^2 to C-2 of the allyl system <1999OM4270>. Polymer-bound derivatives **562** provide a convenient tool for combinatorial synthesis of compound libraries <1999JCO173>.



Scheme 90

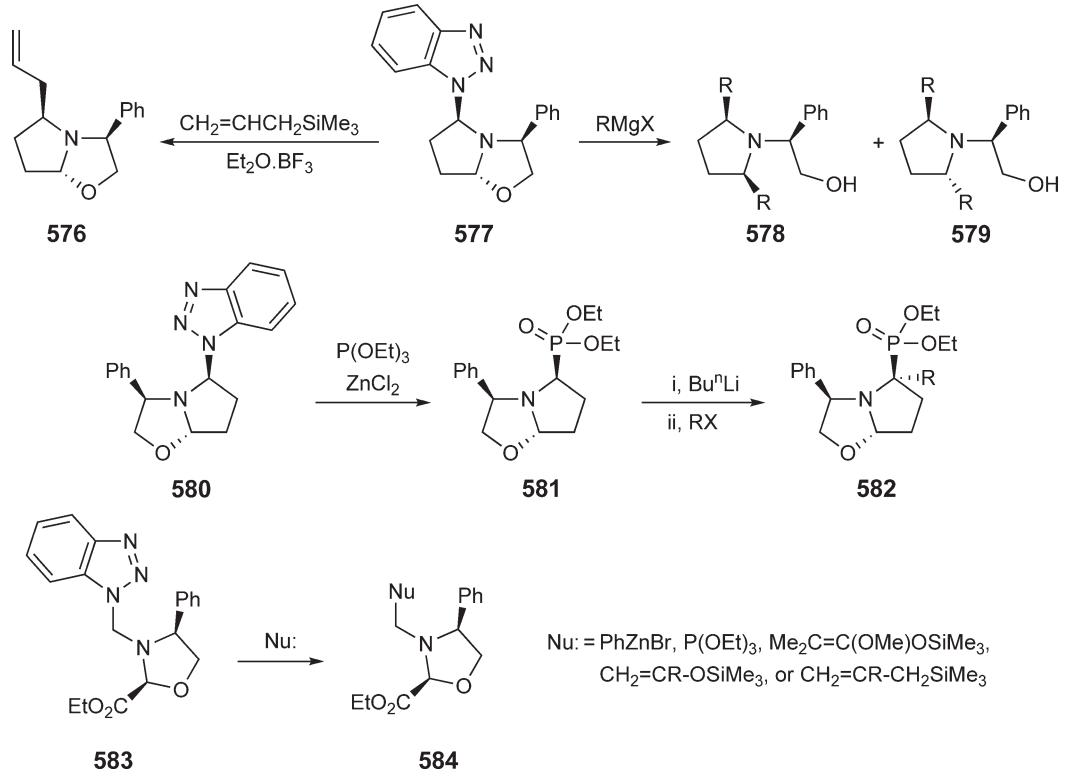
Addition of benzotriazole to enamines **572** derived from cyclic or acyclic dialkyl ketones gives α-aminoalkylbenzotriazoles **573–574**, in which the benzotriazole moiety can be easily substituted by an alkyl, aryl, alkenyl, or alkynyl group in reactions with appropriate organomagnesium or organolithium reagents to form corresponding tertiary amines **575** (**Scheme 91**). This approach extents the scope of *tert*-alkylation of secondary amines <2005JOC286>.



572 **573** **574** **575**

Scheme 91

Condensation of succinaldehyde (obtained by hydrolysis of 2,5-dimethoxyfuran) with benzotriazole and (*S*)-2-phenylglycinol provides (*3S,5R,7aR*)-5-(benzotriazole-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine **577** (**Scheme 92**). Oxazolopyrrolidine **577** is a convenient synthon for asymmetric syntheses of 2-substituted and 2,5-disubstituted pyrrolidines. Thus, in a reaction with allyltrimethylsilane, the benzotriazolyl moiety is substituted with an allyl group to provide derivative **576**. Hydrogenation of product **576** cleaves the chiral auxiliary to give (*2R*)-2-propylpyrrolidine. Alternatively, reactions of intermediate **576** with Grignard reagents lead to chiral 2,5-disubstituted pyrrolidines <1999JOC1979>. Direct treatment with organomagnesium reagents converts oxazolopyrrolidine **577** into mixtures of *cis* **578** and *trans* **579** 2,5-disubstituted pyrrolidines that can easily be separated by chromatography



576 **577** **578** **579**

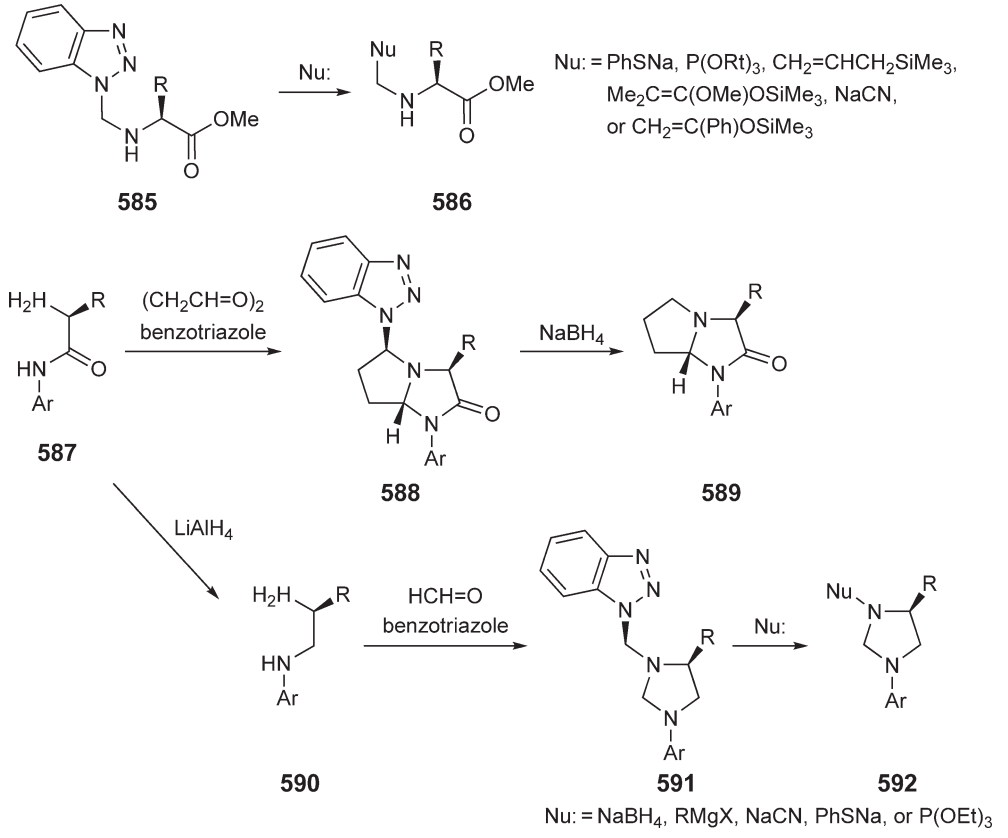
580 **581** **582**

583 **584**

Scheme 92

<1998TL1697>. Again, hydrogenation removes readily the chiral auxiliary from the nitrogen atom in intermediates **578** and **579**. Similar treatment of the piperidine analog of compound **577**, obtained by condensation of glutaraldehyde with benzotriazole and (*S*)-2-phenylglycinol leads to chiral 2,6-disubstituted piperidines <1998JOC6699>. Chiral (pyrrolidin-2-yl)-phosphonates are obtained from oxazolopyrrolidine **580** (prepared by condensation of 2,5-dimethoxytetrahydrofuran with benzotriazole and (*R*)-phenylglycinol) which reacts with triethyl phosphite to give intermediate **581** that is alkylated to produce derivatives **582** and finally deprotected by hydrogenation <2004TL5175>. Condensation of ethyl glyoxylate with (*S*)-2-phenylglycinol and formaldehyde gives *N*-[(benzotriazol-1-yl)methyl]oxazolidine **583** in which the benzotriazolyl moiety can be substituted with various nucleophiles in the presence of $ZnBr_2$ to provide chiral N-substituted oxazolidines **584** <1999JCM162>.

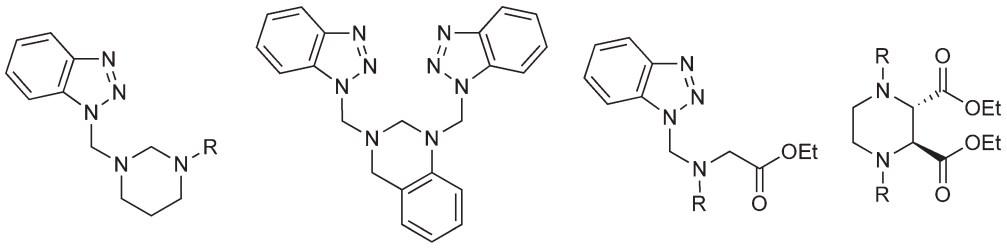
Derivatives of optically active α-aminocarboxylic acids are also used successfully in reactions with aldehydes and benzotriazole. Condensation of esters of α-aminocarboxylic acids with formaldehyde and benzotriazole gives derivatives **585** in which the benzotriazolyl moiety can be substituted by nucleophiles to give various products **586** (**Scheme 93**) <2003JOC9088>. Amides **587** derived from α-aminocarboxylic acids undergo condensation with succinaldehyde and benzotriazole to give benzotriazolyl derivatives **588** from which the benzotriazolyl group can be readily removed by treatment with sodium borohydride to furnish optically active tetrahydro-1*H*-pyrrolo[1,2-*a*]-imidazol-2-ones **589** <2002JOC4951>. Analogous reactions with glutaraldehyde provide corresponding hexahydro[1,2-*a*]pyridin-2(3*H*)-ones <2002JOC4951>. Diamines **590** obtained by reduction of amides **587** with lithium aluminium hydride undergo condensation with benzotriazole and two molecules of formaldehyde to give derivatives **591** in which the benzotriazolyl moiety is easily substituted by various nucleophiles to provide unsymmetrically substituted chiral imidazolidines **592** <2002JOC3109>.



Scheme 93

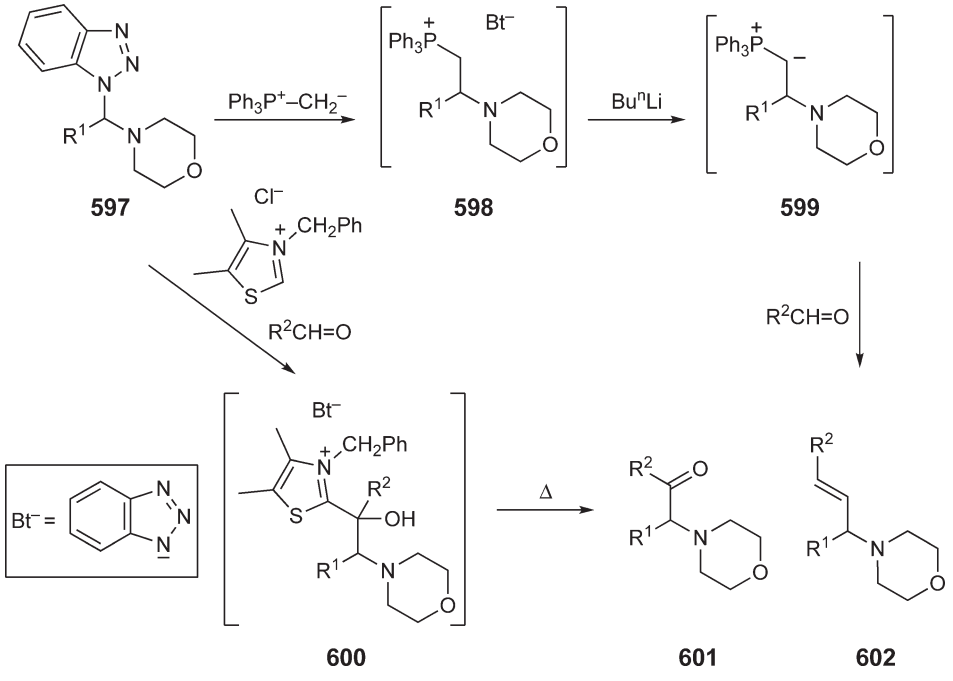
Similarly to imidazolines **591**, derivatives **593**, obtained by condensation of monosubstituted 1,3-propanediamines with formaldehyde and benzotriazole, react with organomagnesium reagents to give corresponding hexahydropyrimidines bearing two different substituents on the nitrogen atoms <2002JOC3115>. Analogously, condensation of

2-aminobenzylamine with formaldehyde and benzotriazole produces compound **594** in which the benzotriazolyl groups can be substituted by treatment with organomagnesium reagents or other strong nucleophiles. The conversion can be carried out stepwise with two different Grignard reagents, first substituting the more reactive benzotriazolyl group connected to the nitrogen atom in position 3 <2002JOC3115>. Treatment of benzotriazolyl derivatives **595**, originating from glycine, with sodium hydride in refluxing THF results in esters of *trans*-2,3-piperazinedicarboxylic acid **596**, although formation of aziridine systems could be anticipated <1996HCO1996>. The molecular structure of products **596** is confirmed by NMR and X-ray crystallographic data, but the mechanism of their formation is not yet clear.



593 **594** **595** **596**

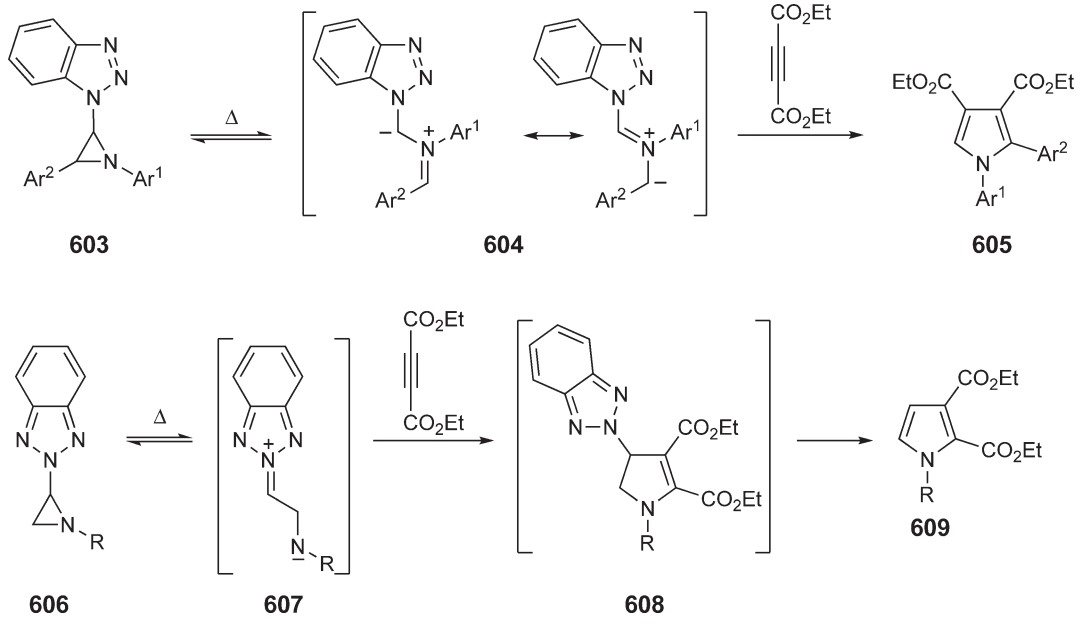
The ylide obtained from (methyl)triphenylphosphonium bromide reacts with morpholine derivatives **597** to give phosphonium salts **598** which upon treatment with *n*-butyllithium are converted to new ylides **599**. In a reaction with aldehydes, ylides **599** form *N*-(1,3-disubstituted allyl)-morpholines **602** (**Scheme 94**) <1996AQ138>. Another less common nucleophile that can be used for substitution of the benzotriazolyl moiety in *N*-(α-aminoalkyl)benzotriazoles is an adduct of *N*-benzylthiazolium salt to an aldehyde which reacts with compounds **597** to produce adducts **600**. Under the reaction conditions, refluxing in acetonitrile, salts **600** decompose to liberate aminoketones **601** <1996H(42)273>.



597 **598** **599** **600** **601** **602**

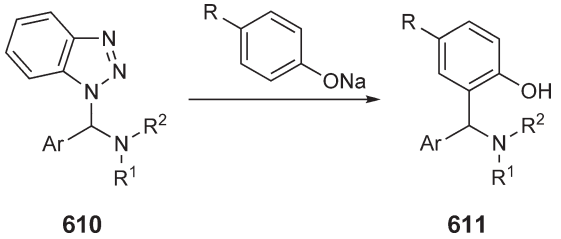
Scheme 94

Due to the high strain energy of a three-membered ring, an interesting case is represented by benzotriazolylaziridines. Upon heating, the C–C bond of the aziridine ring in (benzotriazol-1-yl)aziridines **603** is cleaved to give azomethine ylides **604** that can be trapped by diethyl acetylenedicarboxylate to form unstable pyrroline intermediates which consecutively eliminate benzotriazole to furnish pyrroles **605** (**Scheme 95**). By contrast, in (benzotriazol-2-yl)aziridines **606**, the C-N bond is cleaved, and the dipolar species **607** undergo [3+2] cycloaddition to acetylenedicarboxylate to form pyrrolines **608** that aromatize to pyrroles **609** by elimination of benzotriazole <1999JOC346>.



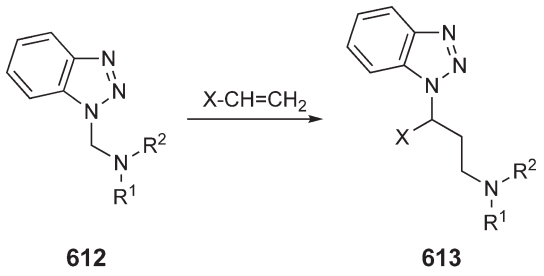
Scheme 95

1-[α-(Dialkylamino)benzyl]benzotriazoles **610**, obtained by condensation of benzaldehydes with benzotriazole and dialkylamines, react with sodium phenoxides to produce 2-[α-(dialkylamino)benzyl]phenols **611** (Equation 13). Derivatives of heterocyclic aldehydes (Ar = pyridin-4-yl, pyridin-3-yl, or thiophen-2-yl) react similarly <1999JOC6071>. As a practical example of such approach may serve derivatization of 4,13-diaza-18-crown-6-ether that is first condensed with benzotriazole and formaldehyde, and then the benzotriazolyl moiety is substituted with 7-hydroxycoumarin <1996JOC7585>.



(13)

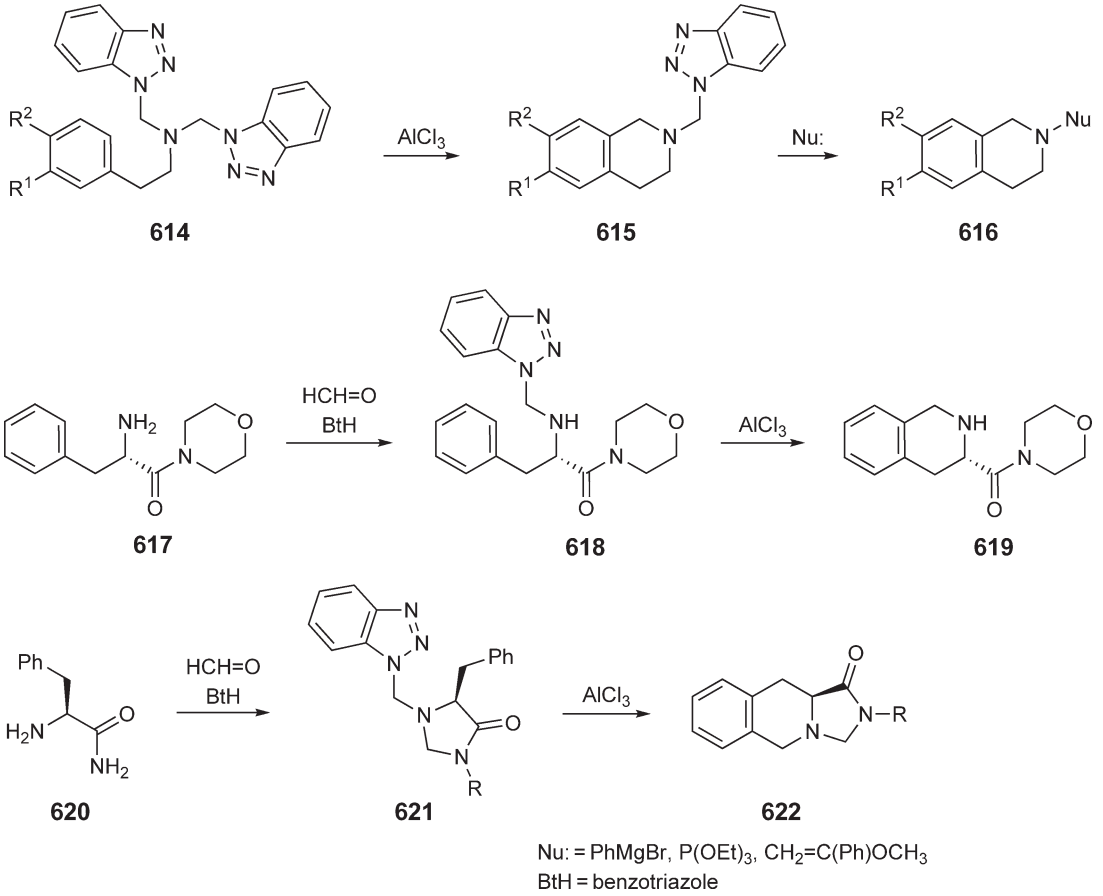
1-(Aminomethyl)benzotriazoles **612** react with electron-rich vinyl groups to give adducts **613** in which the link between the benzotriazolyl moiety and the amine nitrogen atom is extended by two atom units (Equation 14). The benzotriazolyl in its new position still can be substituted with various nucleophiles allowing rapid building of interesting molecules <1996JOC7585>.



(14)

5.01.8.6.2 Cyclocondensation

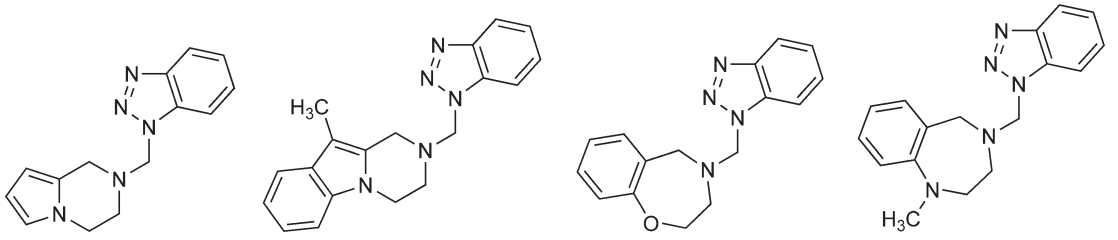
When a nucleophile is already attached to the molecule of *N*-(α-aminoalkyl)benzotriazole **562** (**Scheme 89**) as substituent R^2 or R^3, it may trap liberated iminium cation **563** with formation of a heterocyclic ring. The simplest case is represented by derivatives **562** with an electron-rich aromatic ring in a proper distance on one of the amino group substituents. Three examples of [5+1] cyclocondensation of this type (the five-atom unit comes from phenethylamines and the one atom piece comes from formaldehyde) are shown in **Scheme 96** <2001TA2427>. Thus, upon treatment with $AlCl_3$, an iminium cation generated from *N*,*N*-bis[(benzotriazol-1-yl)methyl]phenethylamine **614**, by cleavage of one of the bonds with benzotriazole, attacks the phenyl ring in its *ortho* position to produce *N*-[(benzotriazol-1-yl)methyl]-tetrahydroisoquinoline **615**. The second benzotriazolyl group can be removed by regular substitution with nucleophiles as discussed above to give tetrahydroisoquinoline **616**. Two additional



Scheme 96

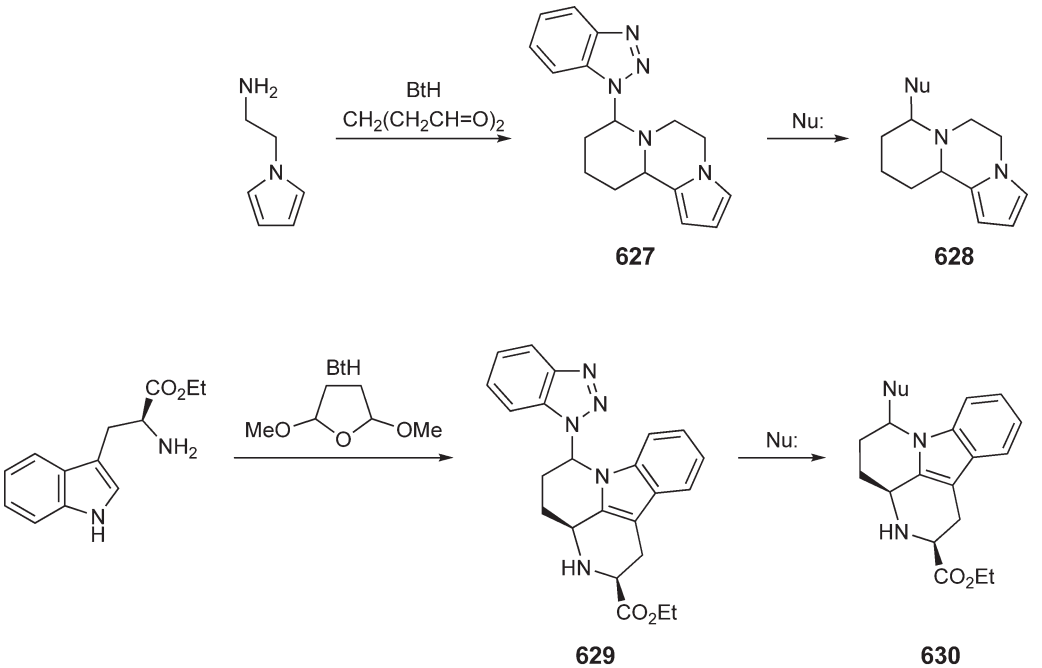
examples in **Scheme 96** show that the cyclization is not affected by even relatively complex substituents on the carbon α of the phenethylamine system, and the stereochemistry can be carried from the starting amines (**617, 620**) through the benzotriazolyl intermediates (**618, 621**) to the final products (**619, 622**) <2001TA2427, 2002JOC8224>. Some of the nucleophiles used for substitution of benzotriazole in derivatives of type **615** are listed in **Scheme 96**, but many others can be successfully employed as well <2002S601>.

Electron-rich heterocyclic rings are also used in such cyclocondensations. Thus, 1-(2-aminoethyl)pyrazole reacts with formaldehyde and benzotriazole to give bicyclic system **623** <2002JOC8220>, and an analogous reaction of 1-(2-aminoethyl)-3-methylindole leads to tricyclic system **624** <2003JOC4938>. Seven-membered rings are also formed as a result of analogous [6+1] cyclocondensations. Compound **625** was obtained from a reaction of 3-phenoxyethylamine with formaldehyde and benzotriazole, and compound **626** was obtained from a similar reaction *N*-(2-aminoethyl)-*N*-methylaniline <2002J(P1)592>. In all of these derivatives, the remaining benzotriazolyl moiety can be easily substituted with various nucleophiles.



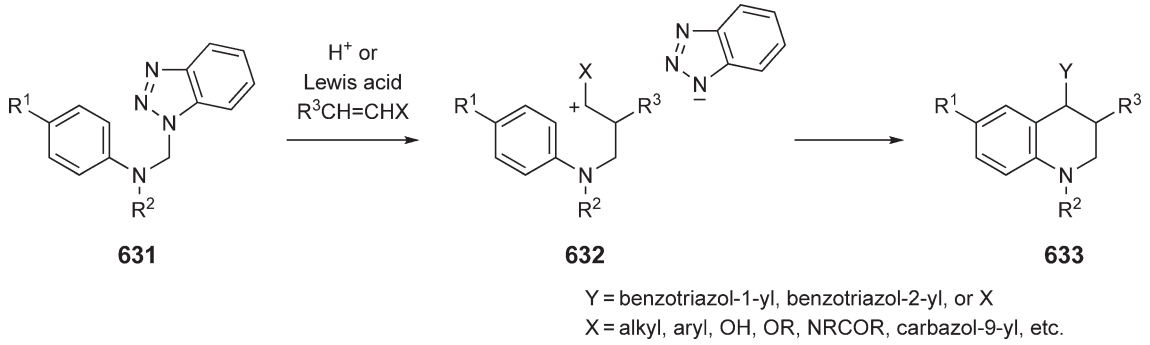
623 **624** **625** **626**

Reactions with dialdehydes allow the introduction of two additional rings in one step. Thus, condensation of 1-(2-aminoethyl)pyrrole with glutaraldehyde and benzotriazole gives tricyclic intermediate **627** in which the benzotriazolyl moiety can be readily substituted with nucleophiles to give products **628** (**Scheme 97**) <2002JOC8220>. Condensation of ethyl ester of *L*-tryptophan with 2,5-dimethoxytetrahydrofuran and benzotriazole in acetic acid gives tetracyclic intermediate **629** which upon treatment with nucleophiles (silyl derivatives) is converted to products **630** <1999T3489>.



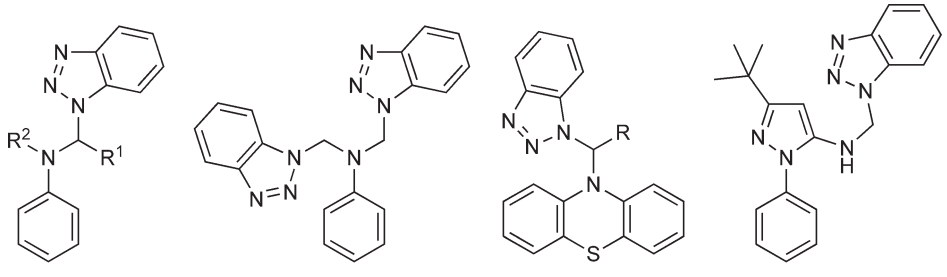
Scheme 97

Cyclocondensations of *N*-(benzotriazolylmethyl)anilines **631** with electron-rich unsaturated compounds of the type $R^3CH{=}CHX$ lead to 1,2,3,4-tetrahydroquinolines **633** (**Scheme 98**). In the first step, an iminium cation generated by dissociation of derivative **631** attacks the double bond of compound $R^3CH{=}CHX$ to generate cation **632**. In the second step, an intramolecular electrophilic attack of cation **632** on the *ortho* atom of the aniline ring furnishes tetrahydroquinoline **633**. Depending on the reaction conditions and nature of the group X, benzotriazol-1-yl (and benzotriazol-2-yl) or group X remains as the substituent in position 4 of tetrahydroquinoline **633**. For compounds lacking good leaving group, like styrenes <1997JHC1259>, alkenes <1999JHC371, 1997JHC1259>, *N*-vinylamides <1995JOC3993, 1999JHC755> and 9-vinylcarbazole <1995JOC3993>, it is the group X that remains. In the case of enolizable aldehydes <1995JOC7631> or vinyl ethers <1995JOC2588>, the benzotriazolyl moiety is usually retained as a substituent at the C-4 atom of tetrahydroquinoline **633** allowing further derivatization by substitution of benzotriazole with nucleophiles. Comparison of this new synthetic method for 1,2,3,4-tetrahydroquinolines with more classical ones has been reviewed <1996T15031>.

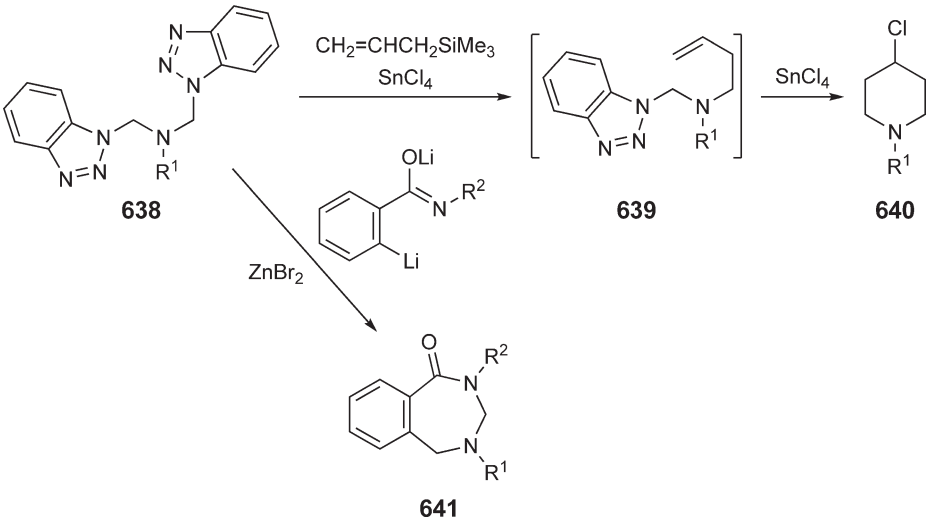


Scheme 98

Derivatives of higher aldehydes (**634**, $R^1 \neq H$) allow introduction of an additional substituent into position 2 of tetrahydroquinolines making variation of the tetrahydroquinoline system very versatile <1995JOC7631>. In *N*,*N*-bis(benzotriazolylmethyl)anilines **635**, both benzotriazolylmethyl groups may be involved in the cyclocondensation process producing julolidines <1996JOC3117, 1999JOC3328>. When the nitrogen atom supporting the benzotriazolylalkyl group is already incorporated into a ring, like in structure **636**, an additional ring is added to the heterocyclic ring system <1998S1487, 1999JHC473>. Use of alkynes instead of alkenes in the reaction depicted in **Scheme 98** results in formation of 1,2-dihydroquinolines <1998JHC467>. Derivatives of aminoheterocycles, like compound **637** <2004T8839> also undergo readily [4+2] cyclocondensation with enol ethers and vinylamides.

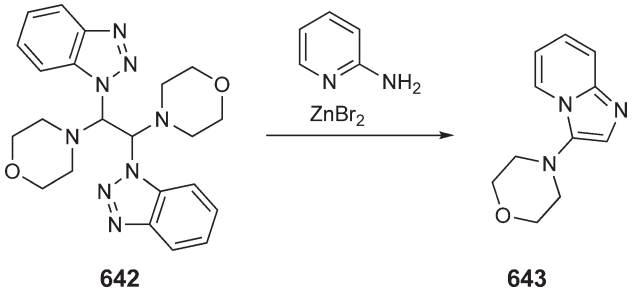


N,*N*-Bis(benzotriazolylmethyl)amines **638** derived from benzyl or phenethylamines undergo cyclocondensation with allylsilanes catalyzed by $SnCl_4$ to give 4-chloropiperidines **640** (**Scheme 99**) <1999JOC3328>. This [3+3] cyclocondensation is assumed to proceed in two steps via intermediate **639**. [3+4] cyclocondensation of derivatives **638**, originating from various aromatic and aliphatic amines, with dilithiated benzamides leads to 2,4-benzodiazepin-1-ones **641** <2002JOC8237>.



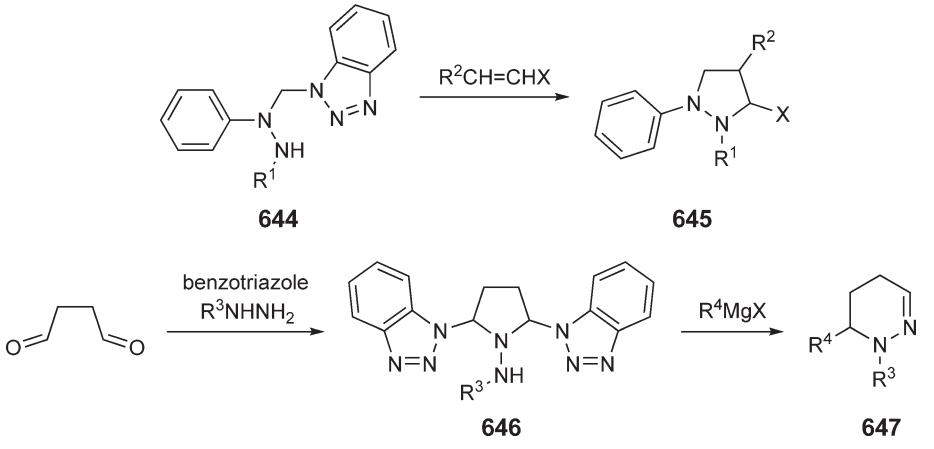
Scheme 99

Compound **642**, obtained by condensation of glyoxal with benzotriazole and morpholine undergoes interesting [2+3] cyclocondensation with 2-aminopyridine to give imidazo[1,2-*a*]pyridine **643** (Equation 15) <2003JOC4935>. Similar derivatives of piperidine and pyrrolidine are also described. 2-Amino- and 6-aminopyrimidines react similarly to give imidazo[1,2-*a*]- and imidazo[1,2-*c*]pyrimidines, respectively.



(15)

Introduction of hydrazines opens new possibilities in the cyclocondensation pattern when both nitrogen atoms of hydrazines can be involved in the process. Thus, hydrazine derivative **644** reacts with electron-rich unsaturated compounds according to [3+2] cyclocondensation pattern to produce pyrazolidines **645** (**Scheme 100**)

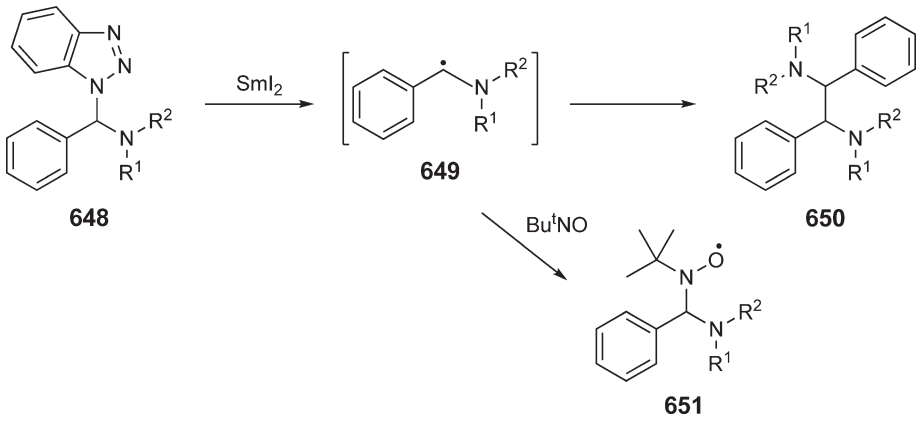


Scheme 100

<1997JOC8210>. Condensation of succinaldehyde with arylhydrazines and benzotriazole gives 1-aminopyrrolidines **646** that upon treatment with organomagnesium reagents rearrange to 1,4,5,6-tetrahydropyridazines **647** <1998S1627>.

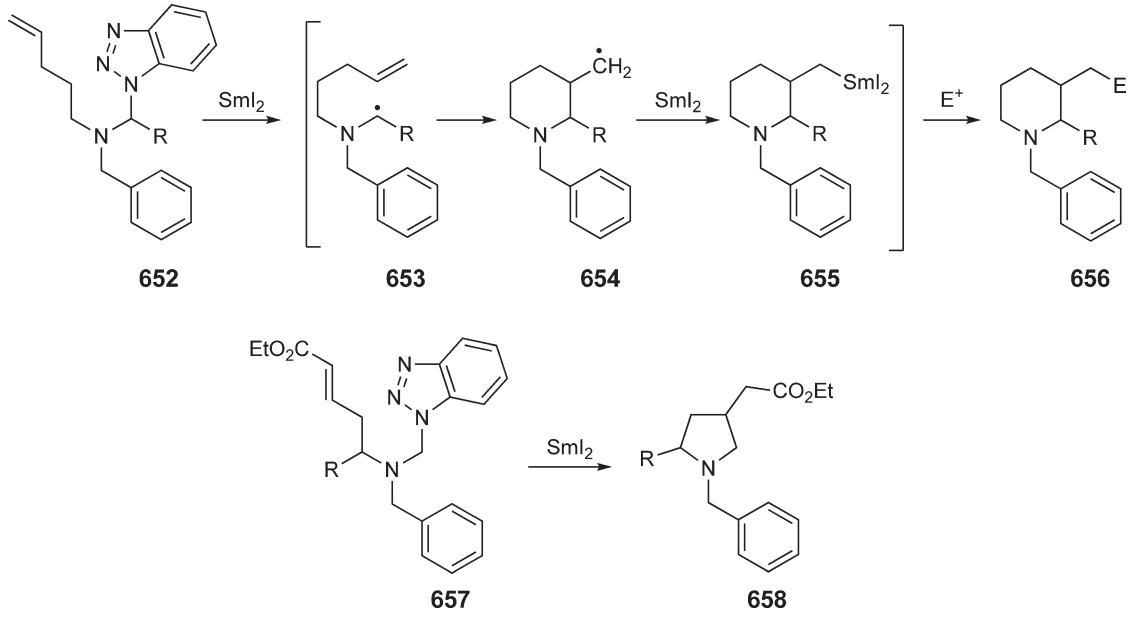
5.01.8.6.3 Reduction to α-amino radicals and α-amino anions

Treatment of *N*-(α-aminobenzyl)benzotriazoles **648** with samarium diiodide generates radicals **649** that undergo coupling to form vicinal diamines **650** (**Scheme 101**) <1992TL4763>. Formation of intermediate radicals **649** at low temperature is confirmed by EPR <1999OL1755>. Short-living radicals **649** are readily converted to more stable radicals **651** by treatment with 2-methyl-2-nitrosopropane.



Scheme 101

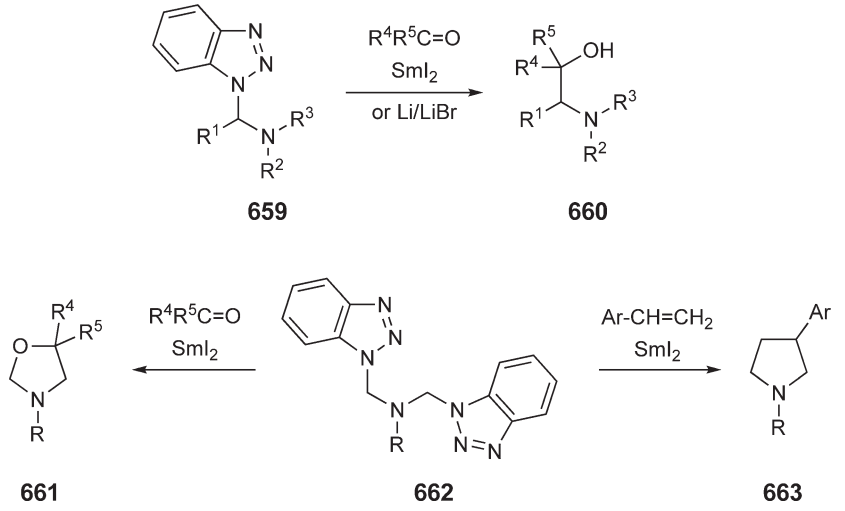
When one of the substituents on the amine nitrogen atom is ready to trap a radical formed by treatment of *N*-(α-aminoalkyl)benzotriazole with SmI_2, cyclization may occur. Such a situation is depicted in **Scheme 102**. Thus, (4-penten-1-yl)amine derivative **652** is reduced to radical **653** that is then rapidly trapped by the alkenyl group and



Scheme 102

converted to radical **654**. The following reaction with excess SmI_2 gives samarium intermediate **655**. During aqueous work-up, derivative **655** is hydrolyzed to 3-methylpiperidine **656** (E = H). Alternatively, treatment with electrophiles converts intermediate **655** to piperidines **656** with various substituents at C-3 <2000J(P2)1375>. Similarly, SmI_2 converts γ,δ-unsaturated amines **657** to pyrrolidines **658** with good yields<2002T6837>.

α-Aminocarbanions generated by treatment of *N*-(α-aminobenzyl)benzotriazoles **659** with SmI_2 (or Li/Br) can be readily trapped by aldehydes or ketones to provide β-aminoalcohols **660** (**Scheme 103**) <1997JOC4121>. A similar reaction performed on *N*,*N*-bis(benzotriazolylmethyl)amines **662** results in formation of oxazolines **661**, but the yields are low <1998TL6835>. However, when styrenes are used to trap generated radicals (or anions), pyrrolidines **663** are obtained in good yields <1998H(48)2535>.

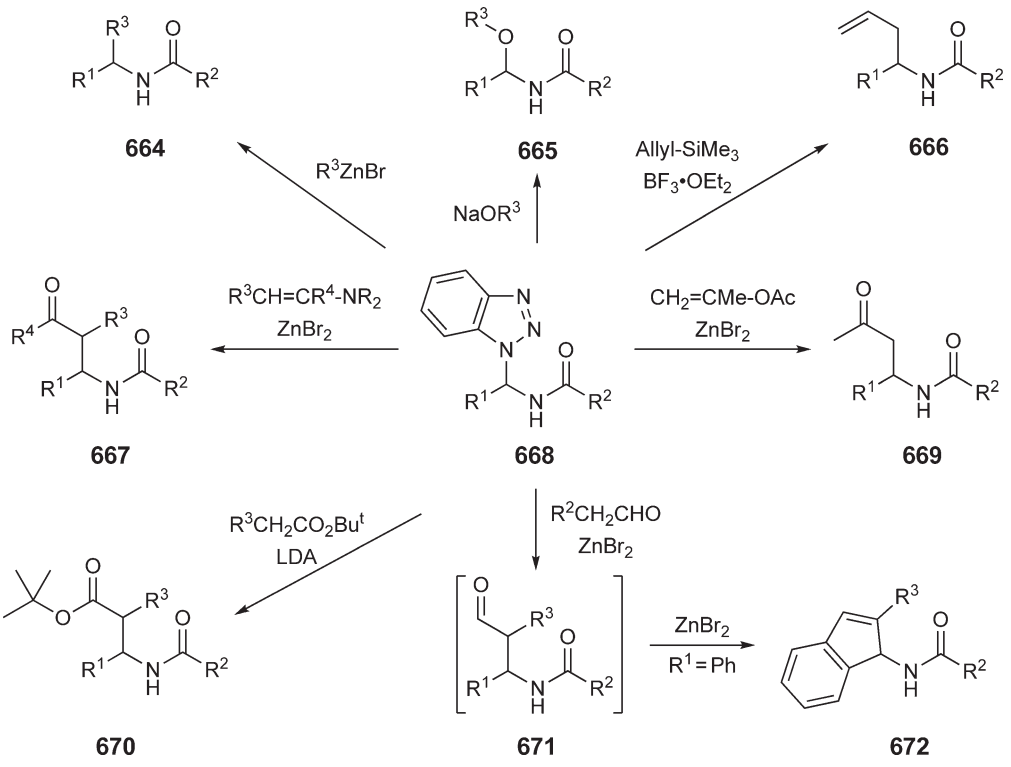


Scheme 103

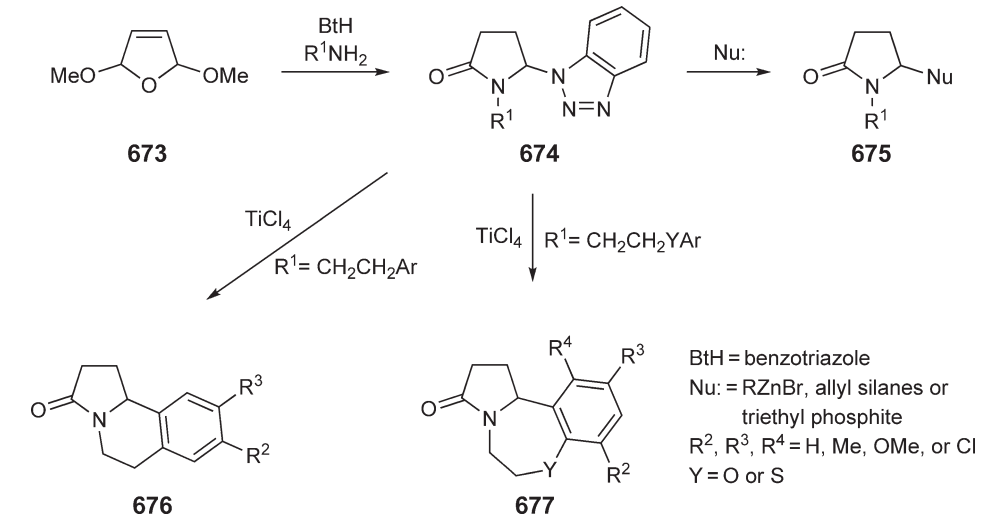
5.01.8.6.4 Derivatives of amides, thioamides, sulfonamides, and related compounds

Benzotriazolylalkyl amides **668** are easy to prepare by condensation of amides with aldehydes and benzotriazole. The chemistry of compounds **668** is to some extent similar to that of the corresponding amines discussed above; however, increased stability of derivatives **668** and higher stability of the products of their reactions bring additional synthetic possibilities. Thus, the reaction with organozinc reagents, usually prepared *in situ* from zinc powder and alkyl bromides, leading to amides **664** is analogous to the reaction of the corresponding amines (**Scheme 104**) <1998T7167, 2000TL9691>. By contrast, the reaction with sodium alkoxides producing *N*-(α-alkoxyalkyl)amides **665** is unique to derivatives **668** <1995JOC4002, 2003JOC4338>. Similarly to the amine analogs, allylation with allyltrimethylsilane converts compounds **668** to unsaturated amines **666** <1995JOC4002>, but the reaction with enamines leading to ketoamides **667** <1999JOC7622> has little precedent among the corresponding derivatives of amines. Enol esters derived from ketones react as well, as it is illustrated by the example of acetone derivative **669** <1995JOC4002>. Anions derived from *t*-butyl esters can also be used for substitution of benzotriazole to give β-amidoesters **670** <2002JOC4957>. Enolizable aldehydes can be used for substitution of benzotriazole in derivatives **668** as well. Although the original product, **671**, is unstable under the reaction conditions, in the case of R^1 being a reactive aromatic ring, subsequent cyclocondensation leads to a stable N-acylated 1-aminoindene **672** <2000JOC8066>.

Condensation of 2,5-dimethoxy-2,5-dihydrofuran **673** with benzotriazole and an amine carried out in refluxing acetic acid produces 5-benzotriazolylpyrrolidin-2-one in good yield and with strong prevalence of benzotriazol-1-yl isomer **674** <2000JOC4364>. Substitution of the benzotriazole moiety with nucleophiles gives 5-substituted 2-pyrrolidinones **675** (**Scheme 105**). When a reactive aromatic ring is attached to the nitrogen atom of 2-pyrrolidinone **674** by a two- or three-atom linker, the *ortho* carbon of the ring may serve as a nucleophile providing tricyclic systems **676** <2001JOC148> or **677** <2001JOC5590>, respectively.

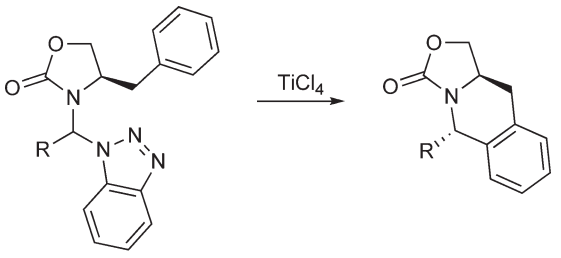


Scheme 104

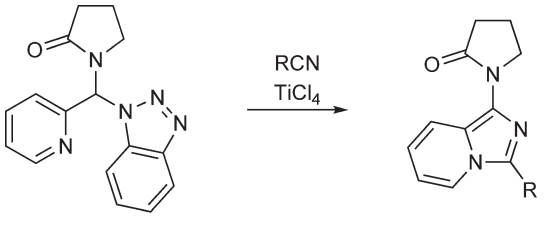


Scheme 105

Formation of polycyclic systems is also possible when benzotriazole is attached to carbon α of the nitrogen substituent in the cyclic amide. As shown in Equation (16), cyclocondensation of 5-benzyloxazolidin-2-ones **678** promoted by $TiCl_4$ stereospecifically gives tricyclic system **679** that represents the core structure of many important natural products <1999TA255, 2004EJO3611>. In a specific case of 2-pyridyl derivatives **680**, cyclocondensation with nitriles involves only the group attached to the amide nitrogen atom giving imidazo[1,5-*a*]pyridines **681** with the pyrrolidinone substituent in position 1 unchanged (Equation 17) <2001JOC2862>.

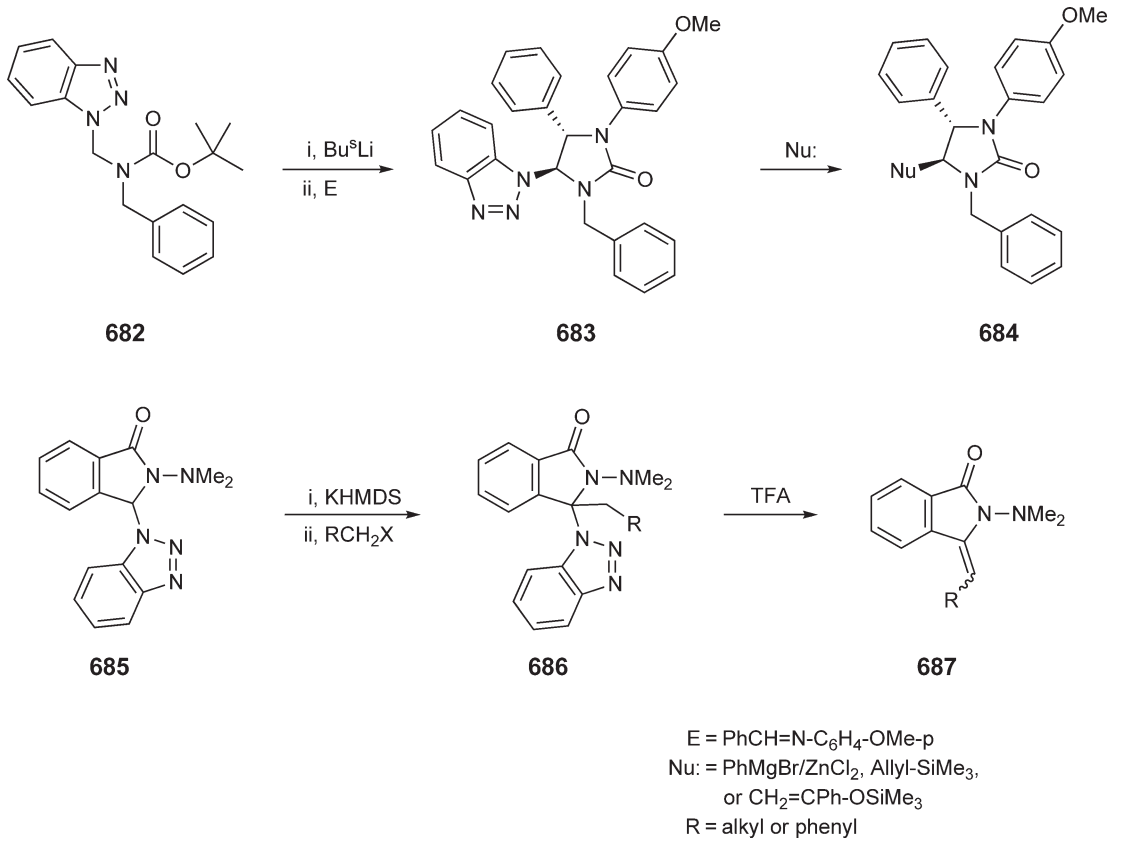


678 679 (16)



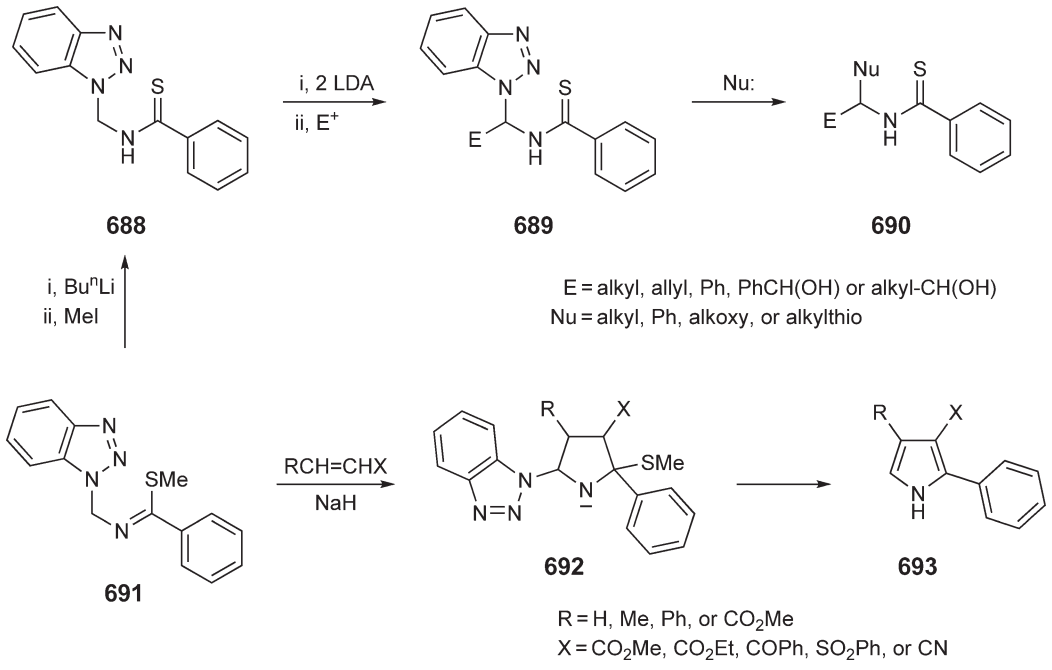
680 681 (17)

N-(Benzotriazol-1-yl)methyl derivatives of BOC-protected amines behave similarly to amides. Thus, treatment of an anion derived from compound **682** with methoxychalcone leads to 2-imidazolidinone **683** with the substituents at C-4 and C-5 oriented *trans*. Subsequent treatment with nucleophiles gives product **684** stereoselectively (**Scheme 106**) <2001JOC2858>. In the second reaction presented in **Scheme 106**, alkylation of compound **685** at the carbon α gives derivative **686** which upon treatment with TFA eliminates readily benzotriazole leading to 3-alkylidene-2,3-dihydro-1*H*-isoindolo-1-ones **687** <2002TL8055>.



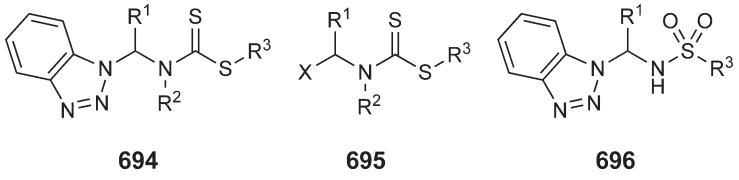
Scheme 106

The double anion, obtained from thioamide **688** upon its treatment with LDA or Bu^{n}Li, reacts with alkylating agents to give α-alkyl derivatives **689** (E = alkyl) or with aldehydes to give α-(1-hydroxyalkyl) derivatives **689** [E = RCH(OH)] (**Scheme 107**) <1995T8703>. The following substitution of benzotriazole with nucleophiles results in thioamides **690**. This simple process allows introduction of two different groups to the carbon atom attached to the thioamide nitrogen. Use of only 1 molar equivalent of the base makes possible selective methylation of the sulfur atom to give thioamidate **691**. The anion derived from compound **691** upon its treatment with sodium hydride adds readily to electron-poor double bonds to create unstable intermediate anion **692** that spontaneously eliminates benzotriazole and thiomethoxide to generate pyrrole **693** <1995T13271, 2000JOC8819>.



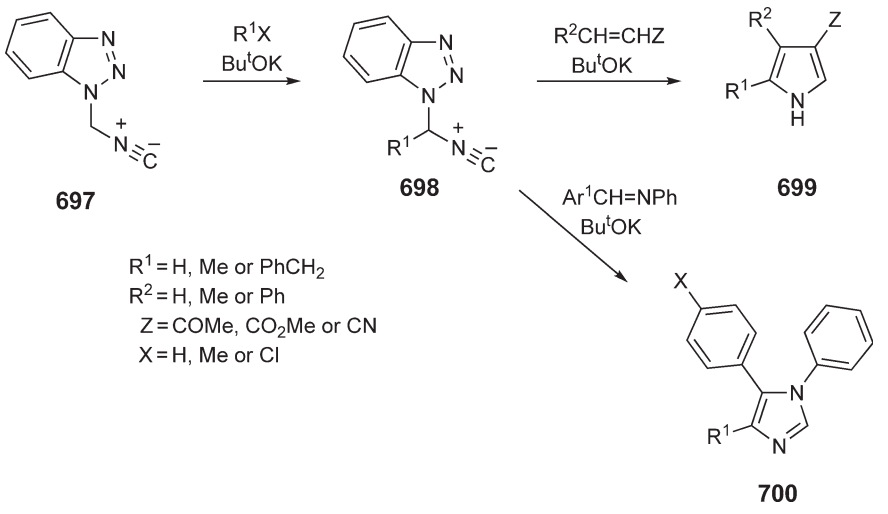
Scheme 107

In the presence of $ZnBr_2$, the benzotriazole moiety in dithiocarbamates **694** can be readily substituted by mercaptans or phosphites providing new access to derivatives **695** <2005ARK(ix)63>. Cyclic analogs of **694**, 1,3-thiazolidine-2-thione and tetrahydro-2*H*-1,3-thiazine-2-thione, react similarly. Substitution of the benzotriazolyl group in sulfonamide derivatives **696** with cyanides occurs under mild conditions in DMSO, alcohol or even water providing a good way for preparation of *N*-(α-cyanoalkyl)sulfonamides <1997SC907>.



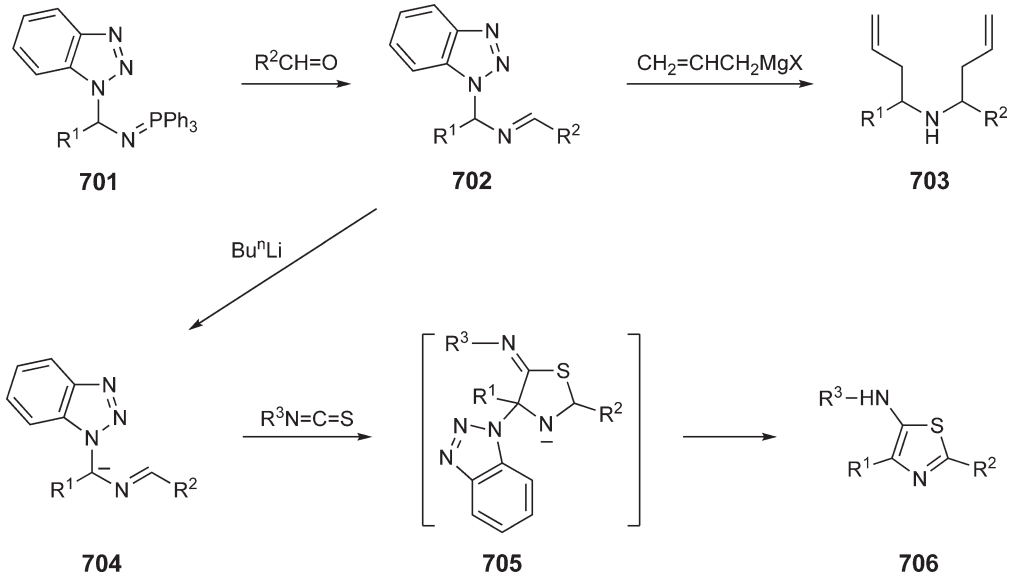
5.01.8.6.5 Imines and related compounds

In the presence of Bu^{t}OK, (benzotriazole-1-yl)methyl isocyanide (BetMIC) **697** undergoes alkylation on the methylene group to give isocyanide **698**. The anion derived from **698**, upon its treatment with Bu^{t}OK, adds to the electron-deficient double bonds of α,β-unsaturated ketones, esters or nitriles to produce pyrroles **699**. A similar reaction of isocyanide **698** with Schiff bases provides imidazoles **700**. In both cases, use of unsubstituted isonitriles **697** in the reactions leads to heterocycles **699** and **700** with R^1 = H (**Scheme 108**) <1997H(44)67>.



Scheme 108

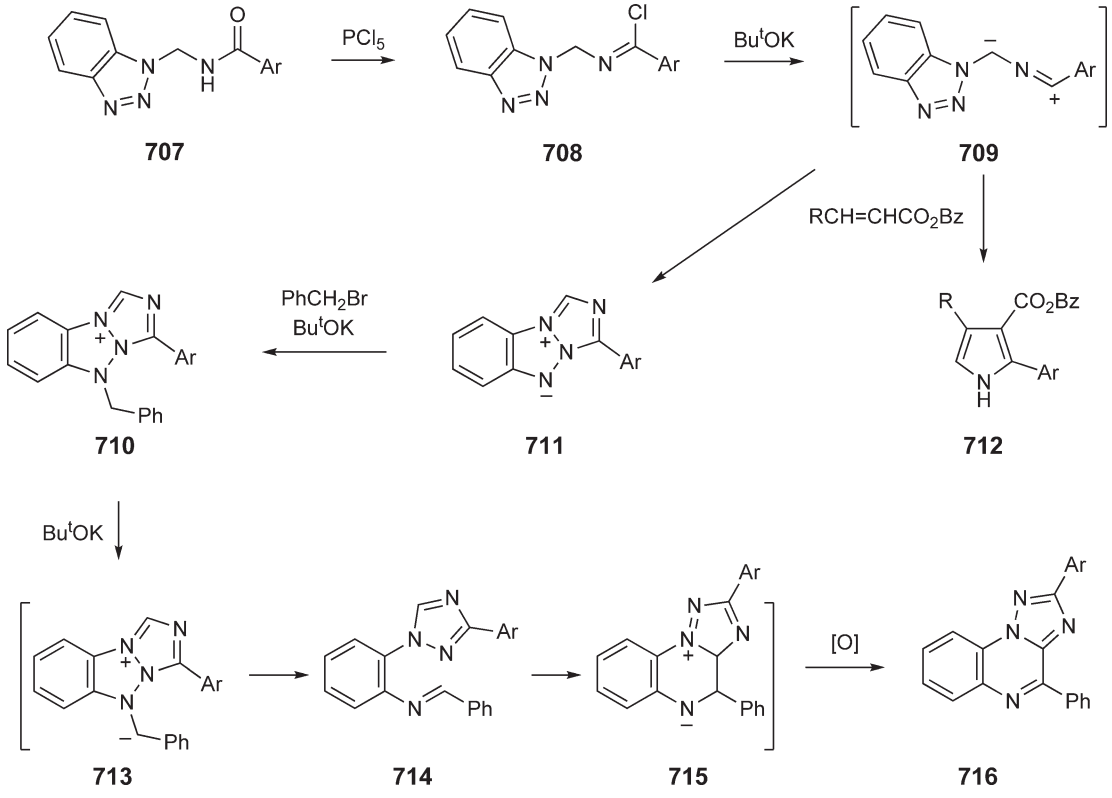
The rich chemistry of parent iminophosphorane **701** ($R^1 = H$), BetMIP, is described in CHEC-II(1996) <1996CHEC-II(4)1> and in a review article <1996JPR684>. Aza-Wittig reactions of iminophosporanes **701** with aldehydes provide imines **702**. Treated with an excess of allylmagnesium reagent, imines **702** are converted into *N*,*N*-bis(3-butenyl)amines **703**, interesting intermediates for construction of heterocyclic systems (**Scheme 109**) <2002JOC7530>. Imines **702**, particularly with $R^1 = R^2 =$ aryl, can be also conveniently prepared by direct condensation of aldehydes with benzotriazole and ammonia <2000JOC8077>. Treatment of imine **702** with *n*-butyllithium produces anion **704** that adds readily to isothiocyanates to give intermediate anion **705**. Loss of a benzotriazole anion followed by tautomerization leads to aminothiazole **706**. This way, 5-aminothiazoles **706** bearing aryl or heteroaryl substituents at C-2 and C-4 can be easily prepared in good yields <2000JOC8077>.



Scheme 109

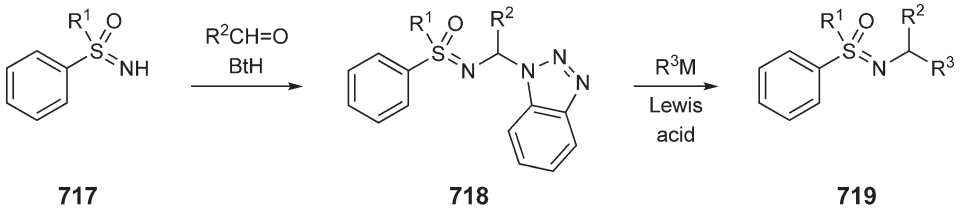
Reaction of *N*-[(benzotriazol-1-yl)methyl]amide **707** with PCl_5 gives chloroimine **708**, which upon treatment with Bu^tOK is converted to nitrile ylide **709**. Benzyl esters of α,β-unsaturated acids used as dipolarophiles trap species **709** to generate pyrroles **712** (**Scheme 110**) <2002JHC759>. When no trapping agent is added, the N-2 atom of benzotriazole act as a nucleophile, and tricyclic system **711** is formed <2001TL9109>. Addition of benzyl bromide

to the reaction mixture causes formation of a new tricyclic system that, according to the X-ray diffraction analysis, has structure **716** <2002JOC3118>. A reasonable explanation of this phenomenon is as follows. Benzylation of species **711** creates cation **710** that, affected by excess Bu^{t}OK, loses its acidic benzylic proton to form betaine **713**. Electron shift towards the positive charge causes breaking of the N–N bond. Freed 1,2,4-triazolyl group in intermediate **714** rotates to a more favorable position, and a bond between carbon atoms forms. Finally, oxidation of newly formed betaine **715**, probably by atmospheric oxygen during work-up, results in stable heterocyclic system **716**. Another possible mechanism, proposed by authors of the report <2002JOC3118>, starts from formation of the C–C bond by direct benzylation of nitrile ylide **709** that is followed by several rearrangements to produce final product **716**.



Scheme 110

Condensation of sulfoximine **717** with an aldehyde and benzotriazole produces *N*-[α-(benzotriazol-1-yl)alkyl]sulfoximine **718**. Treatment with allyl silanes in the presence of BF_3 etherate or with organozinc reagents allows substitution of the benzotriazolyl moiety in compound **718** to produce variety of substituted sulfoximines **719** (**Scheme 111**) <2003ARK(xv)115>.

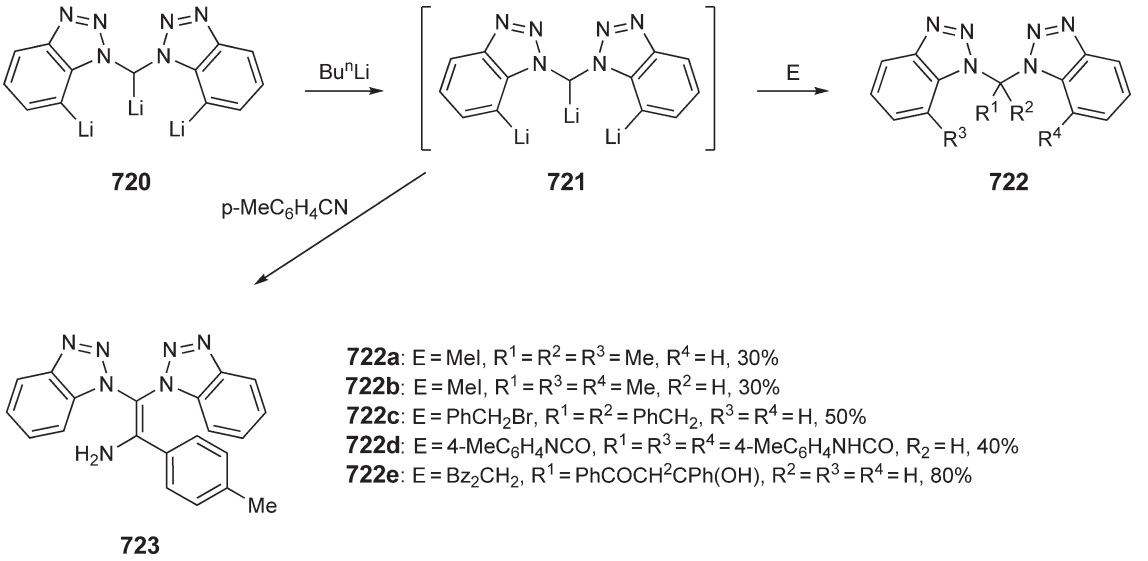


R^1 = Me or Ph
R^2 = H or CO_2Et
R^3M = CH_2=CH-CH_2SiMe_3, CH_2=CMe-CH_2SiMe_3, CH_2=CH-CH_2ZnCl, $PhCH_2ZnCl$, or PhZnCl

Scheme 111

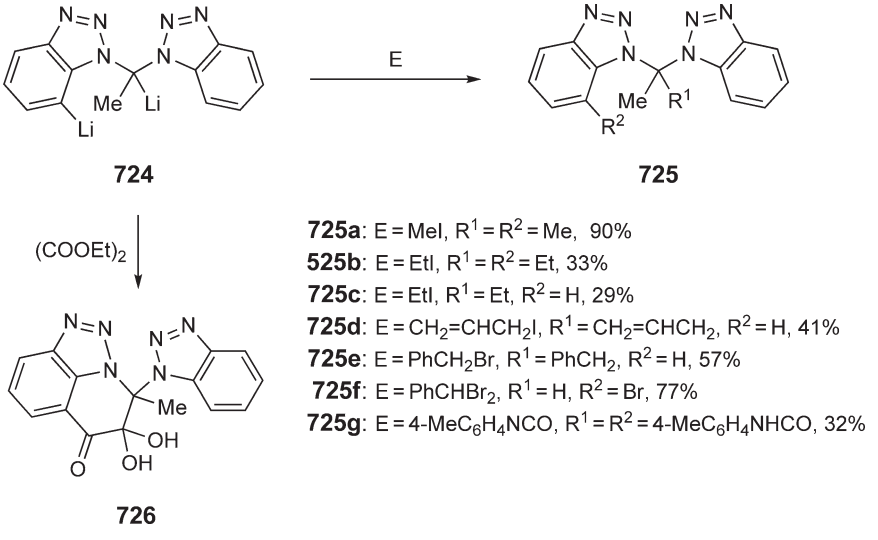
5.01.8.6.6 Bis(heterocycle-N-yl)alkanes

One of the simplest molecules belonging to this category is that of *bis*(benzotriazol-1-yl)methane **720**. Treated with an excess of Bu^nLi, molecule **720** generates polyanion **721** which, when subjected to reactions with various electrophiles, gives C-α and/or C-7 substituted derivatives **722**; an equimolar mixture of C-α, C-α, C-7 (**722a**) and C-α, C-7, C-7 (**722b**) trimethylated products forms in a reaction with iodomethane (**Scheme 112**). Under these conditions, reaction of 4-methylbenzonitrile with **721** gives enamine **723** in 70% yield <2005T3305>.



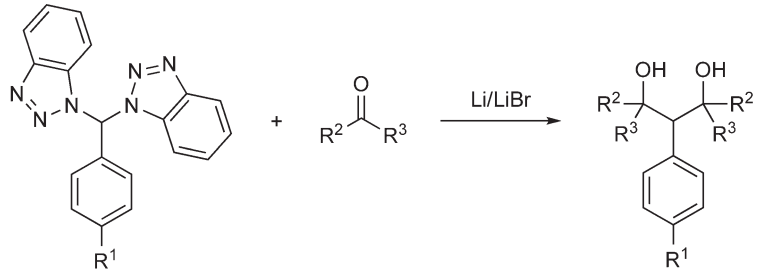
Scheme 112

1,1-Bis(benzotriazol-1-yl)ethane treated with 2 molar equivalents of BuLi undergoes lithiation at C-α and C-7 to give intermediate **724** (**Scheme 113**). Consecutive treatment of the reaction mixture with iodomethane leads to dimethylated product **725a** in high yield. In a reaction with iodoethane, apart of diethylated product **725b**, mono-ethylated derivative **725c** is also formed. Allyl iodide and benzyl bromide gives exclusively substitution at C-α (**725d** and **725e**, respectively). Reaction with benzylidene bromide leads to bromination at C-7 (**725f**). Reaction with *p*-tolyl isocyanate gives diamide **725g**, and that with diethyl oxalate produces triazoloquinolone **726** <2005T3305>.



Scheme 113

Condensation of benzaldehydes with benzotriazole in the presence of thionyl chloride readily gives α,α-*bis*(benzotriazol-1-yl)toluenes **727** that can be considered as 1,1-*gem*-dicarbanion equivalents. Thus, treatment of derivatives **727** with ketones and lithium metal suspended in THF at −78 °C generates substituted propylene glycols **728** (Equation 18) <1998TL2289>.



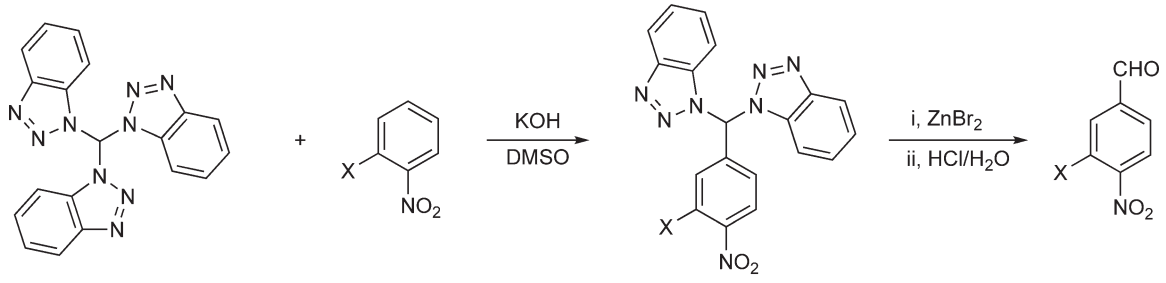
(18)

727 **728**

R^1 = H or Me;

$R^2R^3C{=}O$ = cyclopentanone, cyclohexanone, 2-pentanone, 3-pentanone, or 4-heptanone

In the presence of KOH, *tris*(benzotriazol-1-yl)methane **729** reacts with nitrobenzenes to produce *p*-[*bis*(benzotriazol-1yl)methyl]nitrobenzenes **730** (**Scheme 114**) <1996TL347>. This vicarious nucleophilic substitution of hydrogen <1991S103> can be considered as a convenient way to *p*-nitrobenzaldehydes **731**. *Meta* and *para* substituted nitrobenzenes do not react with compound **729** under these conditions, probably due to steric reasons, but 1-nitronaphthalene reacts producing a naphthalene analog of derivative **730**.



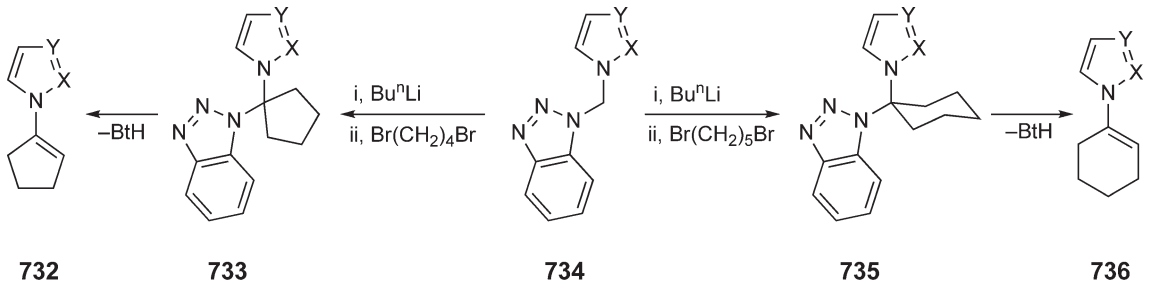
729 **730** **731**

X = H, Cl, Br, or Ph

Scheme 114

N-[(Benzotriazol-1yl)methyl]azoles **734** are dialkylated with 1,4-dibromobutane to give 1,1-disubstituted cyclopentanes **733**. 1,5-Dibromopentane reacts similarly producing cyclohexanes **735** (**Scheme 115**) <2002JOC8230>. Two alternative methods are used for elimination of benzotriazole: treatment with $ZnBr_2$ or with KOH. In some cases, acidic elimination works better, in others, basic elimination is preferred. Both methods convert cyclopentane derivatives **733** to 1-(cyclopenten-1yl)azoles **732** and their cyclohexane analogs **735** to 1-(cyclohexen-1-yl)azoles **736**.

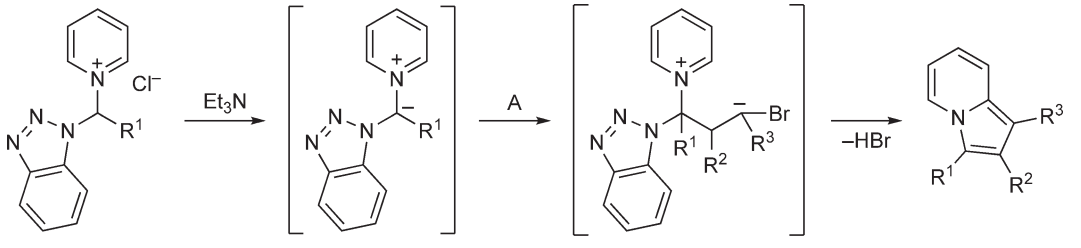
α-Protons in pyridinium salts **737** are acidic enough to be removed by weakly basic triethylamine. Obtained ylides **738** add to esters of 2-bromo-2-alkenecarboxylic acids or analogous benzonitriles to give intermediate betaines **739**. A nucleophilic attack of the anionic site on C-2 of the pyridinium system followed by elimination of HBr leads to indolizines **740** (**Scheme 116**) <1999JOC7618>. When esters of ordinary α,β-unsaturated acids (no Br at C-2) are used in these reactions, indolizines **740** are also formed but with much lower yields due to the oxidation required of the intermediate dihydro analogs of derivatives **740** that form first.



732 **733** **734** **735** **736**

a: X = Y = CH
b: X = N, Y = CH
c: X = CH, Y = N

Scheme 115

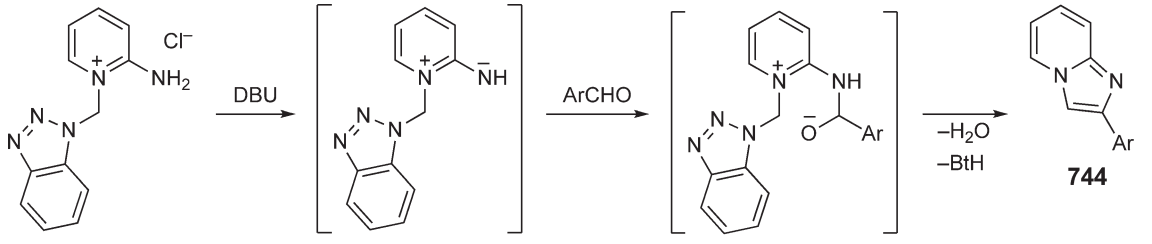


737 **738** **739** **740**

R^1 = H, Et or *p*-tolyl
A = R^2-CH=CBr-R^3
R^2 = H, Ph, CO_2Me or CO_2Et
R^3 = CO_2Me, CO_2Et or CN

Scheme 116

When treated with DBU at elevated temperature, 1-[(benzotriazol-1-yl)methyl}-2-aminopyridine salts **741** eliminate rather the N–H proton than the C–H one. Intermediates **742** can be trapped with aromatic aldehydes to create betaines **743**. The consecutive cyclocondensation and elimination of benzotriazole results in formation of imidazolo[1,2-*a*]pyridines **744** in good yields (**Scheme 117**) <2000JOC9201>. Aldehydes with enolizable α-protons fail to give bicyclic systems **744**, producing corresponding enamines instead.



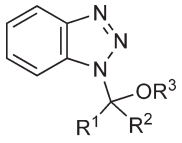
741 **742** **743** **744**

Ar = 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 2-furyl, 2-thienyl, or PhCH=CMe

Scheme 117

5.01.8.7 Ring N–C(sp^3)-O

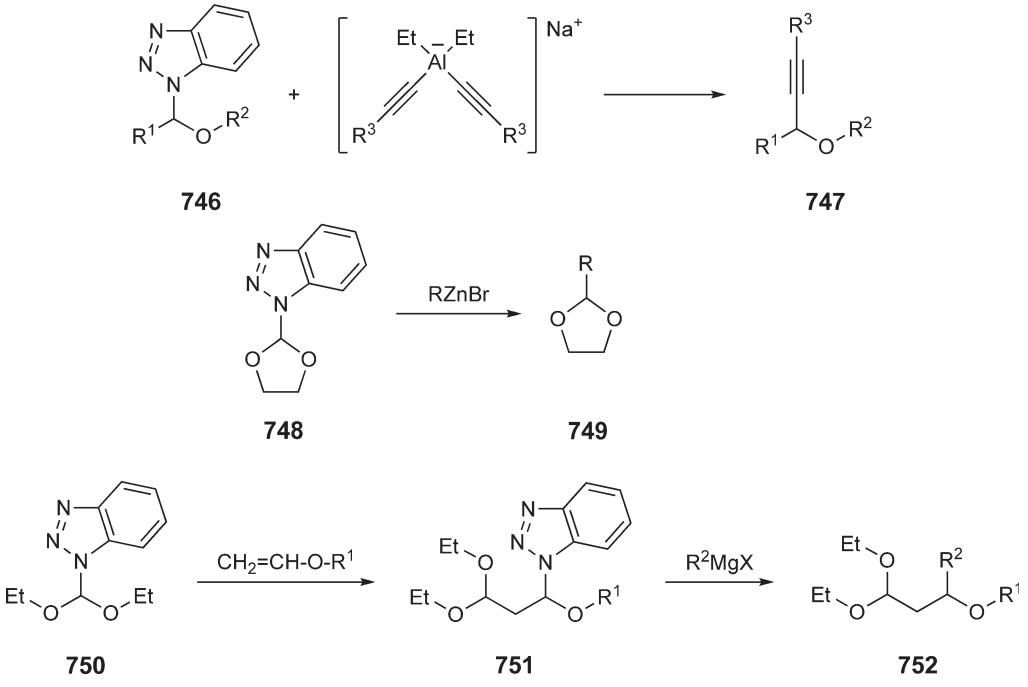
Compounds of general structure **745** (and their benzotriazol-2-yl analogs) are discussed in this subsection.



745

5.01.8.7.1 Reactions with nucleophiles

Substitution of the benzotriazole moiety in compounds **745** with organomagnesium reagents has been discussed previously <1996CHEC-II(4)1>. Newer applications of organometallic reagents to reactions with α-benzotriazolyl ethers are outlined in **Scheme 118**. Thus, reactions of benzotriazolyl ethers **746** with sodium dialkynyldiethylaluminates provide propargylic ethers **747** in high yields <1999JOC488>. 2-Benzotriazolyl-1,3-dioxolane **748** is a convenient equivalent of the formyl cation; its reactions with organozinc reagents lead to masked formylated products **749** <2000JOC1886>. In the presence of Lewis acids, *N*-(diethoxymethyl)benzotriazole **750** undergoes addition to enol ethers to produce 1-(benzotriazol-1-yl)-1,3,3-trialkoxypropanes **751**. Reactions with Grignard reagents convert derivatives **751** into β-alkoxyalkanal acetals **752** <1997JOC700>.

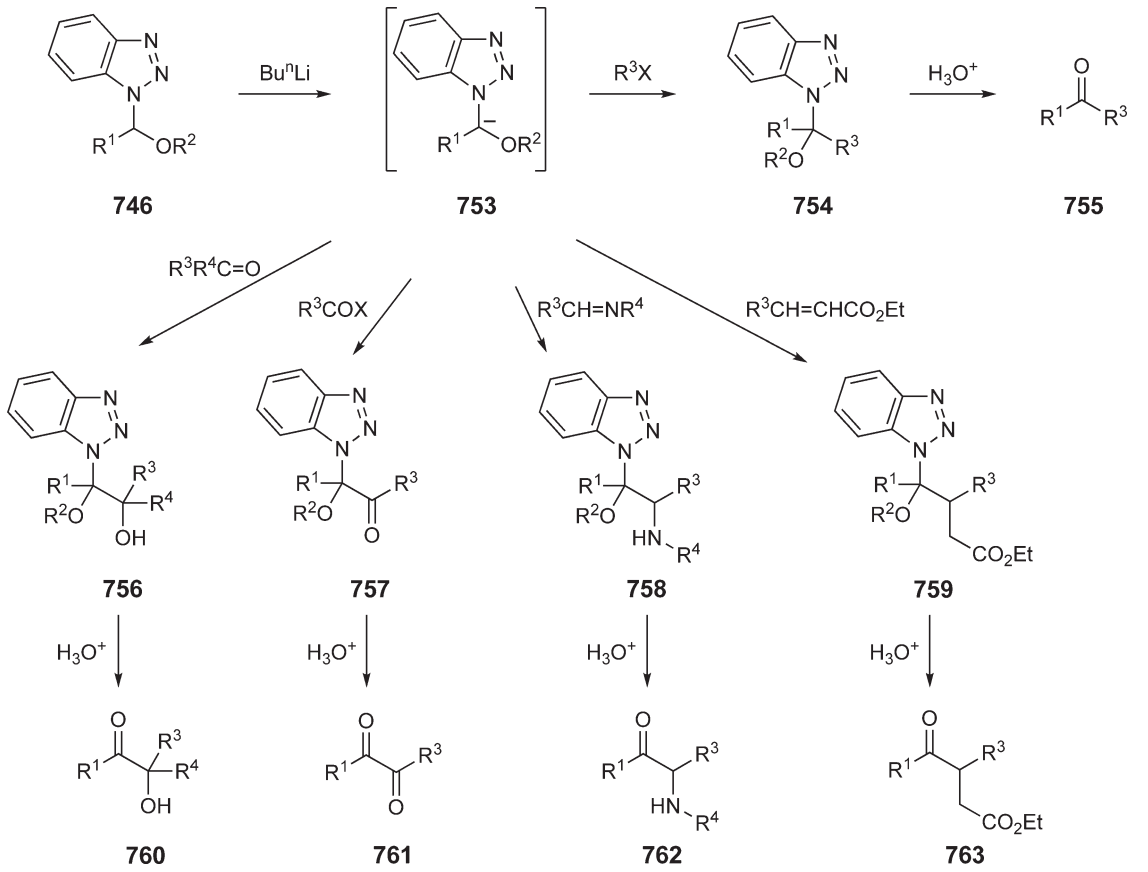


746 **747** **748** **749** **750** **751** **752**

Scheme 118

5.01.8.7.2 Reactions with electrophiles

α-Protons in alkoxy derivatives **746** are acidic enough to be pulled out by Bu^{n}Li. Nascent anions **753** can be trapped with alkylating agents to give α-alkylated products **754**. Geminal benzotriazol-1-yl and alkoxy substituents in compound **754** behave as a protected carbonyl group; they can be removed by acidic hydrolysis to furnish ketones **755** (**Scheme 119**). In this way, a conversion is made from aldehydes R^{1}CH═O (the precursor of **746**) to ketones R^{1}R^{2}C═O. Analogously, use of chlorosilanes as alkylating agents R^{3}X leads to acylsilanes **755** (R^1 = aryl, R^3 = SiMe$_2$R) in good yields <1996OM486>.



Scheme 119

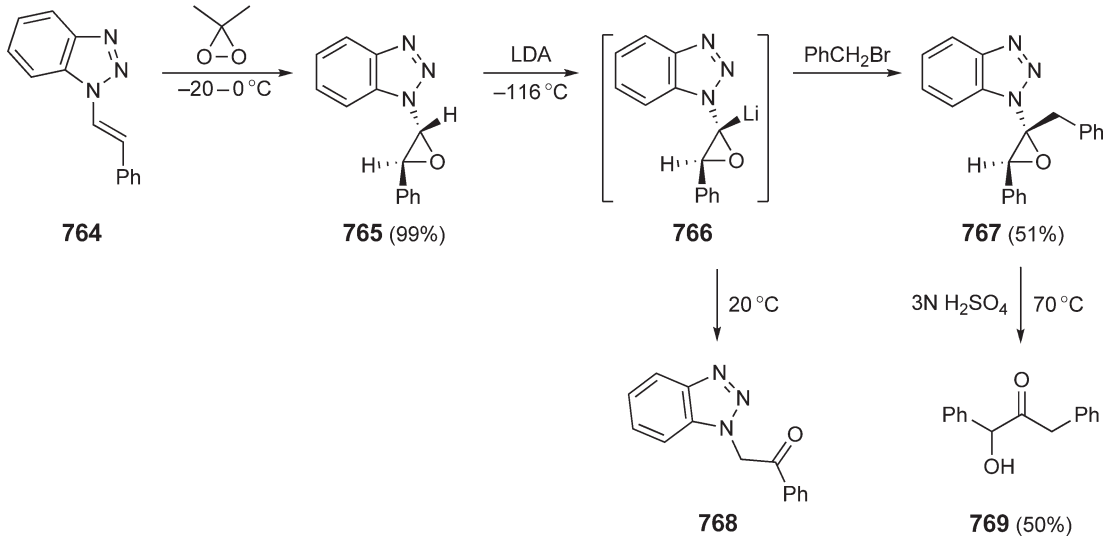
Many other electrophiles can be used to trap anions **753**; four classes of such compounds are presented in **Scheme 119**. Thus, the reactions with aldehydes or ketones lead to α-hydroxyketones **760** via intermediates **756**. The reactions with acylating agents lead to vicinal diketones **761** via intermediates **757**. The reactions with imines give α-aminoketones **762** via intermediates **758**, and those with esters of α,β-unsaturated carboxylic acids give γ-ketoacids **763** via intermediates **759**. Examples of representative products **754–763** are collected in **Table 9**. Other electrophiles used in such reactions that are not shown in **Table 9** include chlorotrimethylsilane <1995JOC7612>, isocyanates <1995JOC7612, 1998JOC1473>, isothiocyanates <1998JOC1473>, diethyl carbonate <1995JOC7612>, and ethyl chloroformate <1998JOC1473>.

Benzotriazolyloxiranes can be prepared in practically quantitative yields by epoxidation of the corresponding alkenes with dimethyldioxirane, for example, conversion of alkene **764** to oxirane **765** (**Scheme 120**). At very low temperatures, substitution of the α-proton in oxirane **765** is possible; just its treatment with LDA at −116 °C followed by benzyl bromide leads to α-benzyloxirane **767**, via lithiated intermediate **766**. At higher temperatures, rearrangement of lithiated oxirane **766** to ketone **768** is observed. Stereochemistry of the molecule is preserved during these transformations. Significant stabilization of the oxirane ring by the benzotriazolyl substituent makes its opening difficult; thus, heating in 3 N sulfuric acid was required to convert oxirane **767** into hydroxyketone **769** <2001ARK(v)68>.

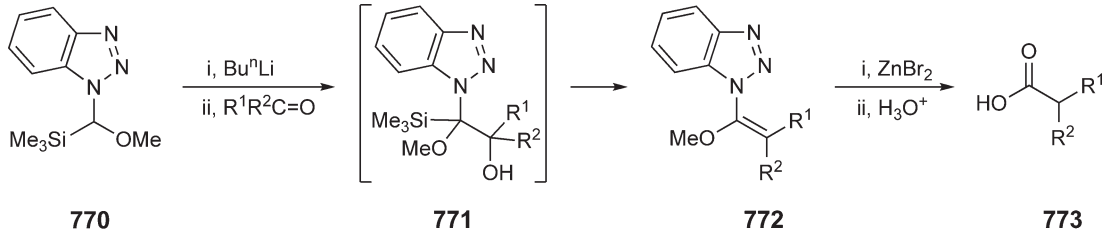
Addition of a silyl substituent into α-position of the α-(benzotriazol-1-yl)alkyl ether brings additional possibilities. Thus, lithiation of silyl ether **770** followed by treatment with an aldehyde or ketone gives unstable β-hydroxy-α-silyl-α-(benzotriazol-1-yl)alkyl ether **771** that spontaneously eliminates silanol to give vinyl ether **772** (**Scheme 121**). Treatment with $ZnBr_2$ followed by hydrolysis with a diluted acid removes both the benzotriazolyl and the methyl groups to furnish carboxylic acid **773**. In this way, in a simple manner, aldehydes and ketones are converted to one-carbon homologated carboxylic acid <1996S1425>.

Table 9 *N*-(α-Alkoxyalkyl)benzotriazoles and products of their hydrolysis

Compound	*Substituents*	*Yield (%)*	*Reference*
754a	$R^1 = Ph$, $R^2 = Me$, $R^3 = Br(CH_2)_4$	82	1999JOC2124
754b	$R^1 = PhC{\equiv}C$, $R^2 = Et$, $R^3 = Bu$	90	1996SC4049
755a	$R^1 = Ph$, $R^3 = Et$	94	1995JOC7619
755b	$R^1 = CH_2{=}CH$, $R^3 = PhCH_2CH_2$	71	1995JOC7589
755c	$R^1 = 2$-Furyl, $R^3 = Br(CH_2)_4$	89	2002JOC8489
756a	$R^1 = CH_2{=}CH$, $R^2 = Et$, $R^3 = PhCH_2$, $R^4 = H$	48	1995JOC7589
756b	$R^1 = PhC{\equiv}C$, $R^2 = Et$, $R^3 = R^4 = Me$	66	1995JOC7612
757a	$R^1 = PhC{\equiv}C$, $R^2 = Et$, $R^3 = Ph$	63	1997JOC4125
757b	$R^1 = n$-C_6H_{13}, $R^2 = Ph$, $R^3 = Bu^t$	86	1997JOC4125
758	$R^1 = PhCH(OEt)CH_2$, $R^2 = Ph$, $R^3 = p$-MeC_6H_4, $R^4 = Ph$	92	1998JOC1473
760	$R^1 = PhC{\equiv}C$, $R^3 = R^4 = Me$	100	1995JOC7612
761	$R^1 = n$-C_6H_{13}, $R^3 = Bu^t$	83	1997JOC4125
762a	$R^1 = PrCH{=}CH$, $R^2 = Et$, $R^3 = R^4 = Ph$	71	1997JOC706
762b	$R^1 = PhCH(OEt)CH_2$, $R^3 = p$-MeC_6H_4, $R^4 = Ph$	64	1998JOC1473
763	$R^1 = PrCH{=}CH$, $R^2 = Et$, $R^3 = Me$	50	1997JOC706



Scheme 120

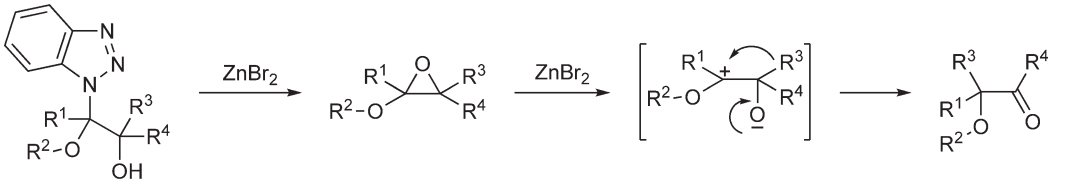


R^1 = Aryl or PhCH(Me)
R^2 = H, Me, Et or Ph
or $R^1R^2 = -C_5H_{10}-$

Scheme 121

5.01.8.7.3 Rearrangements

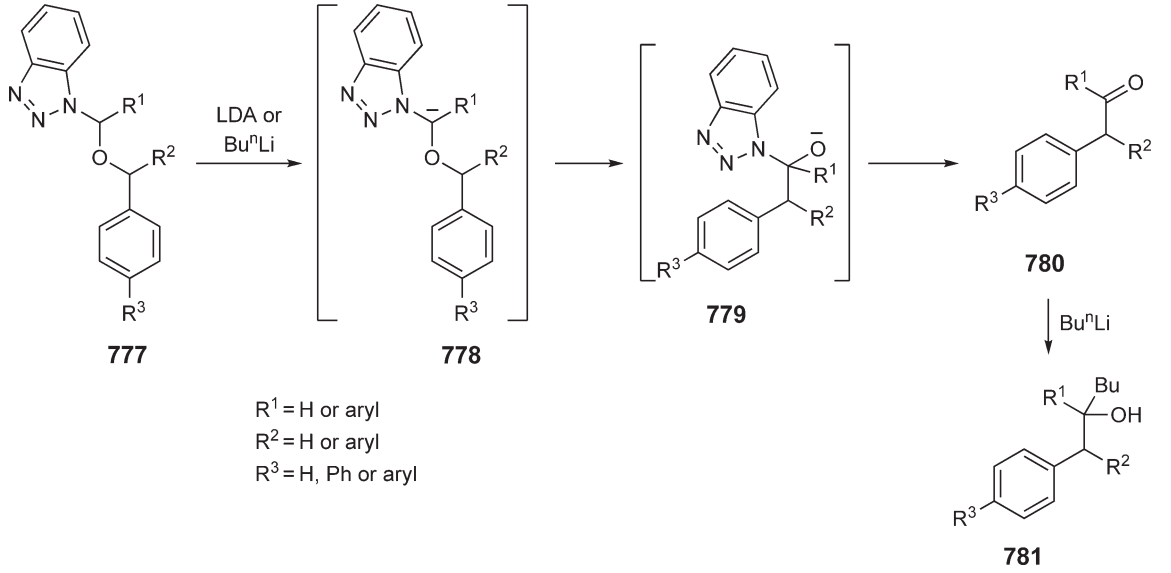
When crude reaction mixtures containing derivatives **756** (**Scheme 119**) are treated with three-fold excess of $ZnBr_2$ and heated to reflux, benzotriazole is eliminated and the products rearrange to α-alkoxyketones **776** (**Scheme 122**). The proposed mechanism involves formation of oxiranes **774** (in some cases isolated intermediates) which then open to betaines **775**. Subsequent migration of substituent R^3 furnishes α-alkoxyketone **776**. The conversion is characterized by remarkable regioselectivity with only one regioisomer formed from intermediates with $R^3 \neq R^4$ with the order of migration: H > Ar > alkyl (*tert*-alkyl > *sec*-alkyl > *n*-alkyl) <1996JOC7564>. A similar rearrangement of derivatives **756** (R^1 = H, R^2 = Ph, R^3 = H, R^4 = alkyl) is promoted by treatment with *p*-TsOH in acetic acid <1995TL841>.



756 **774** **775** **776**

Scheme 122

Treated with strong bases, α-(benzotriazol-1-yl)alkyl ethers **777** derived from benzyl alcohols undergo [1,2]-Wittig rearrangement to ketones **780** (**Scheme 123**). For the derivatives of aromatic aldehydes (R^1 = aryl), LDA is a base strong enough to pull the benzylic proton from ether **777** to give anion **778**. The subsequent [1,2]-Wittig rearrangement produces alkoxide **779** which spontaneously expels benzotriazole anion to furnish ketone **780** <2002ARK(vii)146>. In the case of formaldehyde derivatives (R^1 = H), a stronger base, Bu^nLi, is required to do the job; however, it is difficult to stop the reaction sequence at the ketone stage, and alcohols **781** are obtained as the major products <2000H(53)1783>.

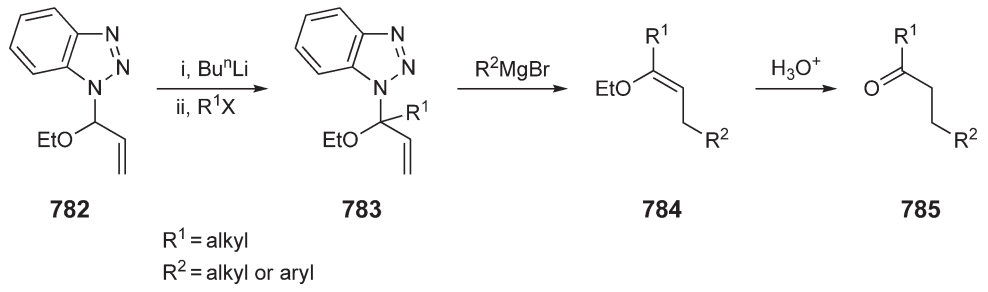


777 **778** **779** **780** **781**

Scheme 123

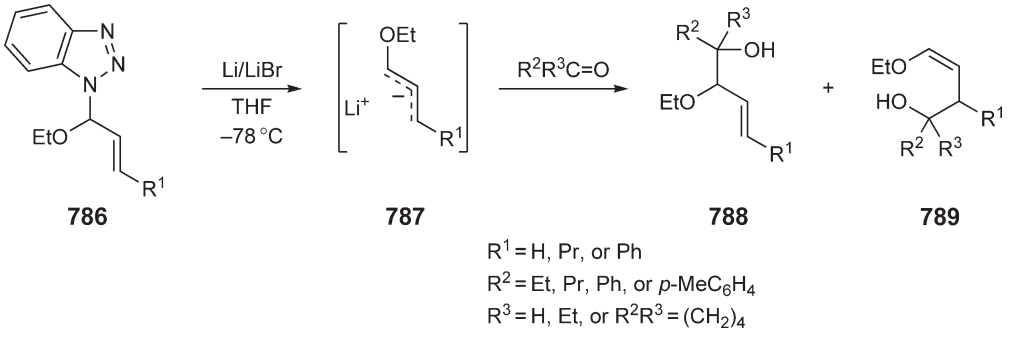
5.01.8.7.4 Allyl ethers

α-(Benzotriazol-1-yl)allyl ethyl ether **782** can be readily alkylated to give tertiary ethers **783**. Grignard reagents attack ethers **783** exclusively in γ-position (S_N2' reaction) producing enol ethers **784** which are hydrolyzed during acidic work-up to ketones **785** (**Scheme 124**). High regioselectivity of these reactions is rationalized by substitution of the α-carbon atom with bulky groups <1995JOC7605>.



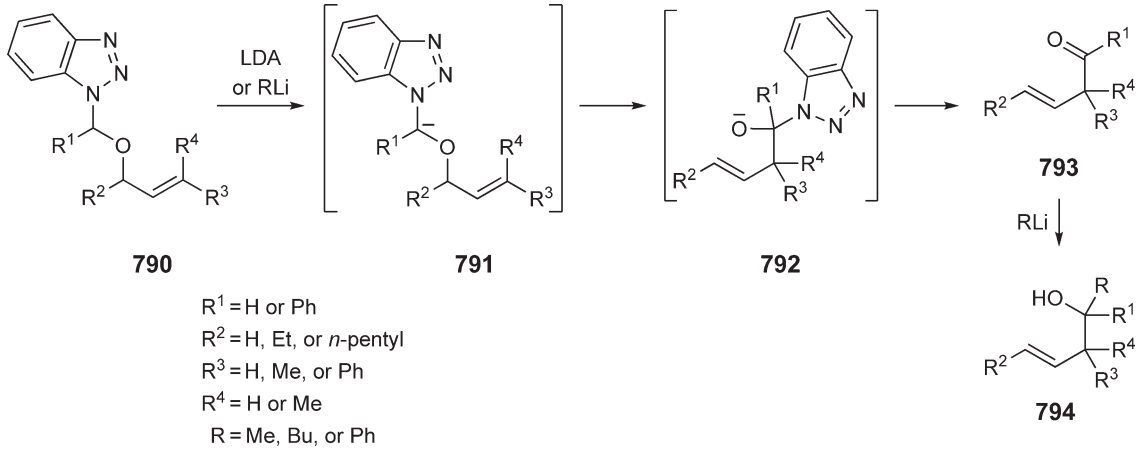
Scheme 124

Treated with a suspension of metallic lithium at low temperatures, ethers **786** are reduced to anions **787**. Addition of an aldehyde or ketone to the reaction mixture allows trapping these anions with formation of β-hydroxyethers **788** and enol ethers **789** (**Scheme 125**). For $R^1 = H$, in reactions with aliphatic aldehydes and ketones, the α-attack prevails to give hydroxyethers **788** as the major products. In other cases, products **789** resulting from the γ-attack of anion **787** on a carbonyl group become dominant. Stereochemistry of products **789** (*cis* : *trans)* also depends strongly on substituents R^1 with the *cis* geometry prevailing (98:2 to 4:2) for $R^1 = H$ or Pr. When $R^1 = Ph$, mostly *trans* isomers (1: 2) are formed <1998TL6437>.



Scheme 125

For allyl ethers **790** with $R^1 = Ph$, treatment with LDA generates anions **791** which undergo [2,3]-Wittig rearrangement to more stable alkoxides **792** (**Scheme 126**). Spontaneous expulsion of benzotriazole anion from **792** generates β,γ-unsaturated ketones **793** that are isolated in high yields (86–92%) <1996JOC4035>. In the case of

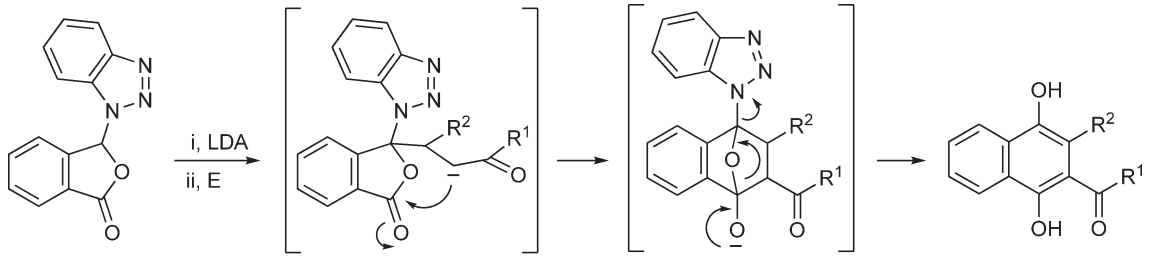


Scheme 126

R^1 = H, stronger bases required to pull the α-proton from ethers **790** react also with intermediate aldehydes **793** to convert them into alcohols **794**. In all these reactions, exclusive formation of the products with the *(E)* configuration is observed.

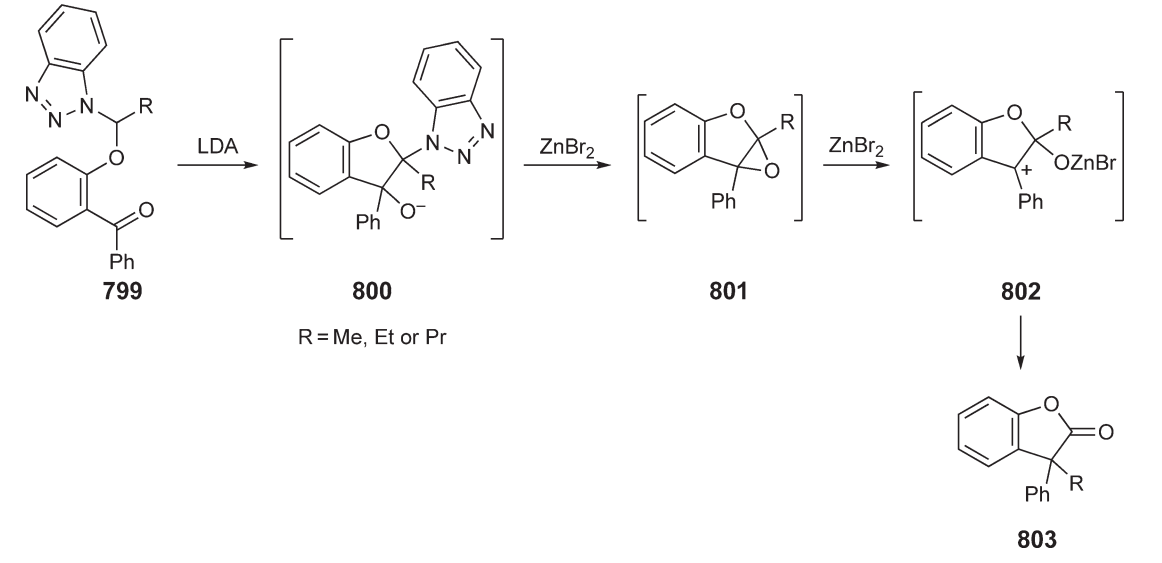
5.01.8.7.5 Cyclocondensations

Condensation of benzotriazole with 2-carboxybenzaldehyde gives 3-(benzotriazol-1-yl)phthalide **795** (**Scheme 127**). The anion derived from phthalide **795** adds to the β-carbon atom of α,β-unsaturated carbonyl compounds *E* to produce anion **796** that by intramolecular nucleophilic attack on the phthalide carbonyl group is converted to anion **797**. Spontaneous expulsion of benzotriazole from molecules **797** followed by aromatization leads to 1,4-dihydroxynaphthalenes **798** <1997SC3951>.



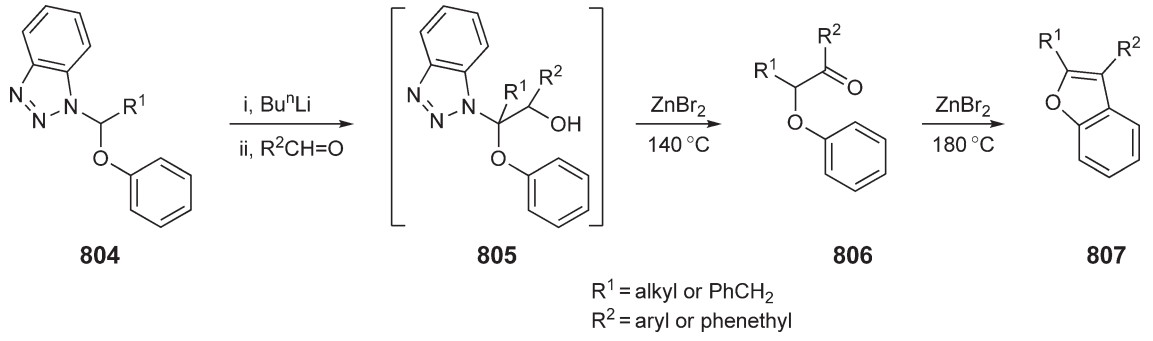
Scheme 127

Alkylation of 2-hydroxybenzophenone with 1-(α-chloroalkyl)benzotriazoles provides ethers **799**. Treated with LDA, ethers **799** lose α-proton. Nucleophilic intramolecular attack of the obtained anions on the carbonyl group leads to alkoxides **800** (**Scheme 128**). When a treatment with $ZnBr_2$ follows, an arrangement occurs resulting in formation of 2,3-dihydrobenzofuran-2-ones **803**. The suggested mechanism involves elimination of benzotriazole with formation of epoxides **801**. Promoted by $ZnBr_2$, the epoxides open to cations **802** which rearrange to final products **803** <2004ARK(vi)27>.



Scheme 128

Two examples discussed above involve participation of an *ortho* substituent on the aromatic ring in the cyclization process; however without such a substituent, α-(benzotriazol-1-yl)alkyl aryl ethers can also be employed as the starting materials for introduction of an additional ring. Thus, lithiation of ether **804** followed by treatment with an aldehyde generates β-hydroxyether **805** (**Scheme 129**). Treated with $ZnBr_2$ and heated at 140 °C, derivatives **805** eliminate benzotriazole and rearrange to α-aryloxyketones **806**. When heating with $ZnBr_2$ is continued at even higher temperature (175–180 °C), cyclocondensation of ketones **806** with involvement of the phenyl *ortho* carbon atom leads finally to benzofurans **807** <1998J(P1)1059>.



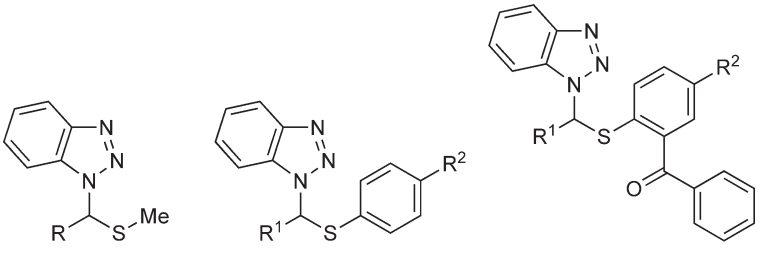
804 **805** **806** **807**

Scheme 129

5.01.8.8 Ring N–C(sp^3)-X (X = heteroatom ≠ N or O)

5.01.8.8.1 Sulfur derivatives

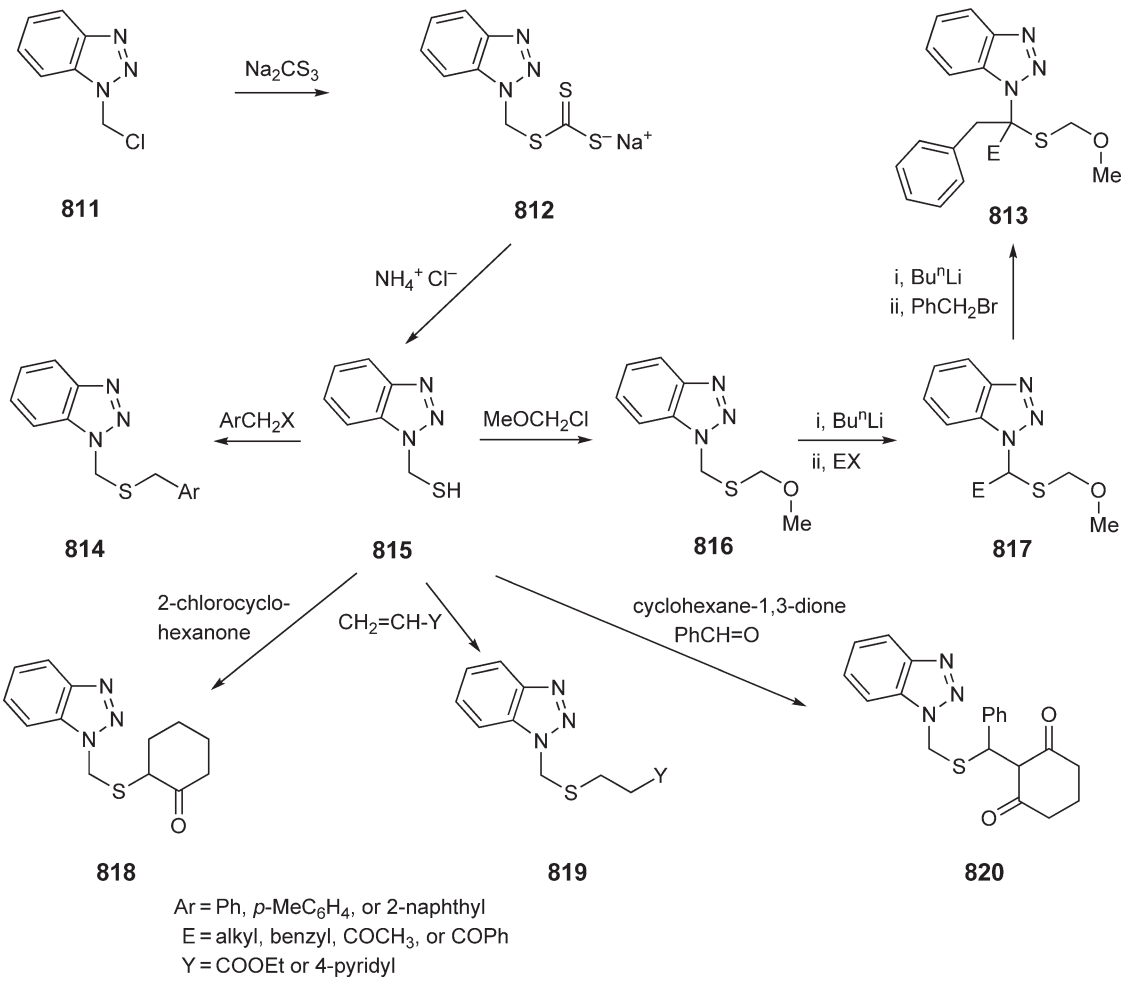
The preparation of α-(benzotriazol-1-yl)alkyl thioethers and their reactions with nucleophiles have been discussed before <1996CHEC-II(4)1>. To some extent, α-(benzotriazol-1-yl)alkyl thioethers react similarly to the related ethers. Thus, thioether **808** can be lithiated with Bu^{n}Li then treated with an aldehyde or a ketone to give a sulfur analog of α-(benzotriazol-1-yl)-β-hydroxyalkyl ether **756**. Similarly to ethers **756**, their sulfur analogs can be hydrolyzed to α-hydroxyketones **760** (**Scheme 119**) <1998JOC2110, 2004JOC303>. Lithiated, then treated with an aldehyde or ketone followed by $ZnBr_2$, thioether **809** is converted to the corresponding benzothiophene <1998J(P1)1059>, in analogy to conversion of ether **804** to benzofuran **807**. Similarly to conversion of ethers **799** to 2,3-dihydrobenzofuran-2-ones **803** (**Scheme 128**), thioethers **810** are converted to the corresponding 2,3-dihydrobenzothiophen-2-ones <2004ARK(vi)27>. In general, due to better stabilization of the adjacent carbocation than it is possible in ethers, properties of α-(benzotriazol-1-yl)alkyl thioethers resemble in some aspects those of α-(benzotriazol-1-yl)alkylamines. However, in other aspects, properties of thioethers are quite unique.



808 **809** **810**

1-(Mercaptomethyl)benzotriazole **815** is conveniently prepared by treatment of 1-(chloromethyl)benzotriazole **811** with sodium trithiocarbonate followed by hydrolysis of the obtained hemi ester **812** with ammonium chloride (**Scheme 130**). In the presence of triethylamine, mercaptan **815** reacts readily with arylmethyl halides to give sulfides **814** in high yields. Alkylation of mercaptan **815** with chloromethyl methyl ether provides methoxymethyl thioether **816** that can be substituted at the α-carbon atom by treatment with Bu^{n}Li followed by an electrophile to

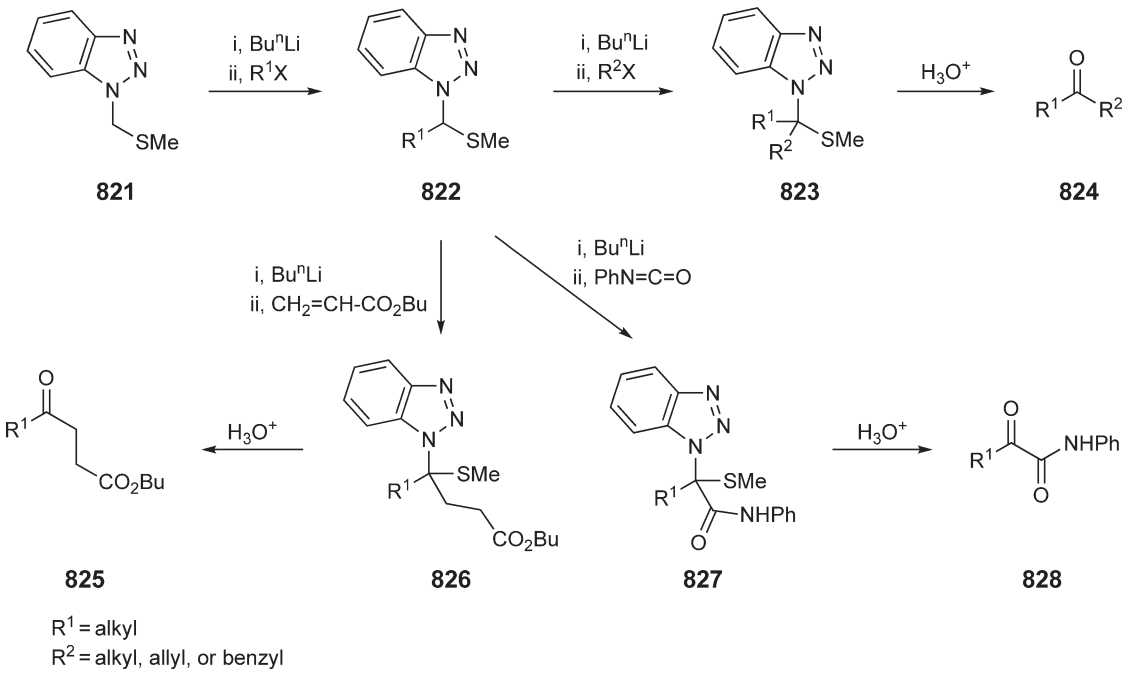
furnish thioethers **817**. Repeated treatment with Bu^nLi and an electrophile (benzyl bromide) allows substitution of the remaining α-proton to get derivative **813**. Among other reactions performed on mercaptan **815** are substitution of the chlorine atom in 2-chlorocyclohexanone to give product **818**, addition to electron deficient vinyl groups (products **819**) and condensation/addition with 1,3-cyclohexanedione and benzaldehyde to produce derivative **820** <1996JHC1927>.



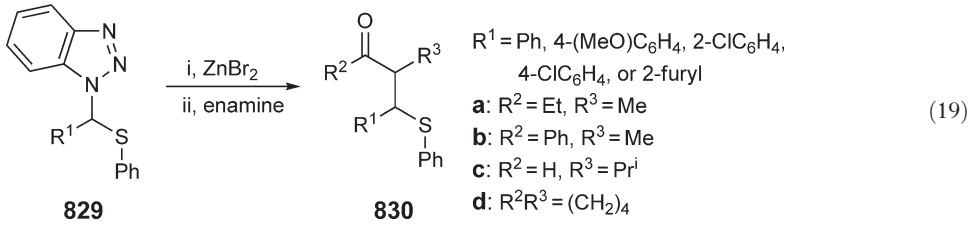
Scheme 130

The readily available benzotriazolyl derivative of dimethyl sulfide, compound **821**, can be alkylated on α-carbon in a stepwise manner to provide (α,α-disubstituted)alkyl thioethers **823** (**Scheme 131**). Hydrolysis of these thioethers under mild conditions (5% H_2SO_4 at room temperature) furnishes ketones **824** in high yields. The anion derived from mono substituted (benzotriazol-1-yl)methyl thioether **822** adds to butyl acrylate to give intermediate **826** that can be hydrolyzed to γ-ketoester **825**. In another example of reactivity of α-(benzotriazol-1-yl)alkyl thioethers, treatment of thioether **822** with Bu^nLi followed by phenyl isocyanate converts it into α-ketoanilide **828**, via intermediate adduct **827** <1998JOC2110>.

Treated with $ZnBr_2$ followed by enamines, phenyl thioethers **829** derived from aryl aldehydes are converted to β-(phenylthio)alkyl ketones or aldehydes **830** in moderate to good yields (Equation 19). Enamines used in these syntheses are: (1) morpholine enamine derived from diethyl ketone, (2) diethylamine enamine of propiophenone, (3) piperidine enamine derived from isovaleraldehyde, and (4) pyrrolidine enamine of cyclohexanone <2000H(53)331>.



Scheme 131

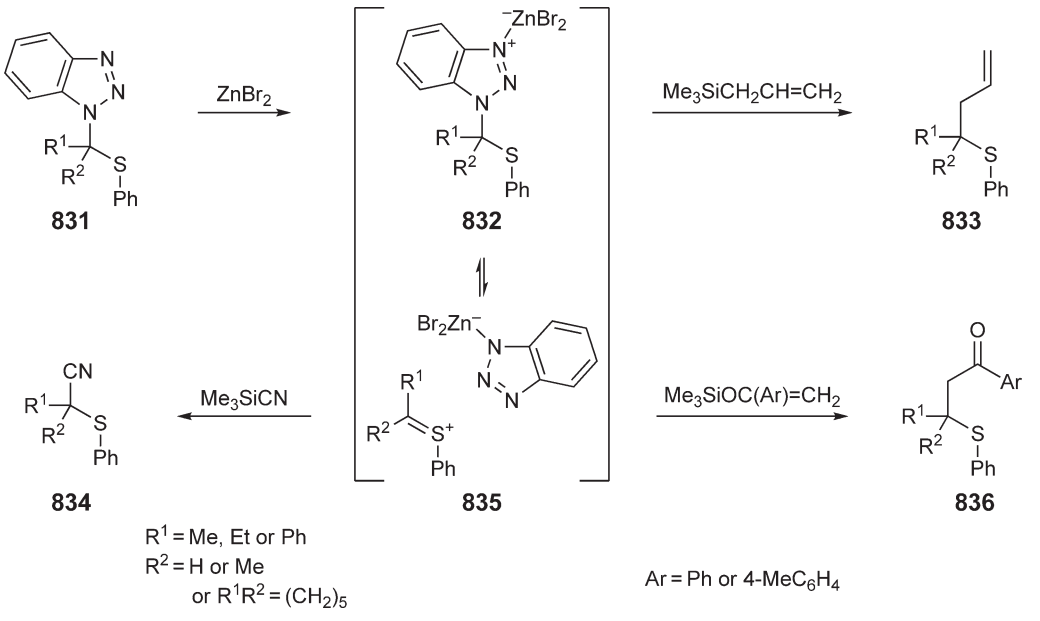


(19)

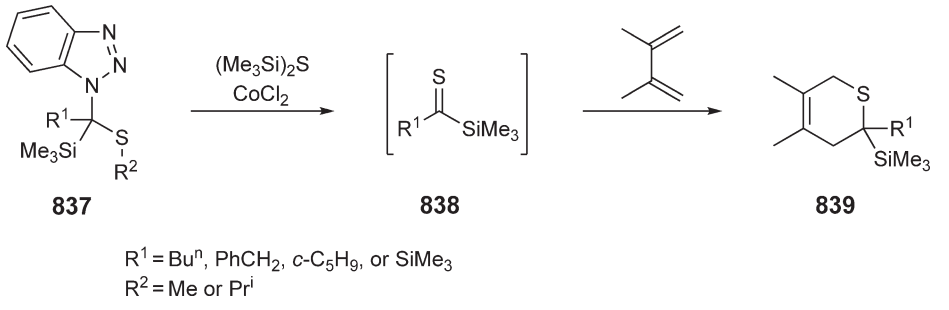
Treatment of α-(benzotriazol-1-yl)alkyl thioethers **831** with $ZnBr_2$ weakens the bond with benzotriazole, and the obtained complex **832** may partially dissociate to thionium cation **835** that can be trapped by even mild nucleophiles. Thus, trimethylsilyl cyanide added to the reaction mixture causes substitution of the benzotriazole moiety by the CN group to give α-(phenylthio)carbonitrile **834**. In a similar manner, treatment with allylsilane leads to γ,δ-unsaturated thioether **833**. Addition of species **835** to the double bond of a trimethylsilyl α-arylvinyl ether followed by hydrolysis of the silyloxy group furnishes β-(phenylthio)alkyl aryl ketones **836** (**Scheme 132**) <1996TL6631>.

Introduction of trimethylsilyl substituents attached directly to the α-carbon atom of α-(benzotriazol-1-yl)alkyl thioethers provide new opportunities. Thus, treatment of lithiated monosubstituted α-(benzotriazol-1-yl)alkyl thioethers with chlorotrimethylsilane produces α-(trimethylsilyl)alkyl thioethers **837**. In reactions with hexamethyldisilathiane and cobalt dichloride, thioethers **837** are converted to thioacylsilanes **838** that can be trapped in a Diels–Alder reaction with 2,3-dimethylbutadiene to form 2-alkyl-4,5-dimethyl-2-trimethylsilyl-3,6-dihydro-2*H*-thiopyrans **839** (**Scheme 133**) <2000JOC9206>.

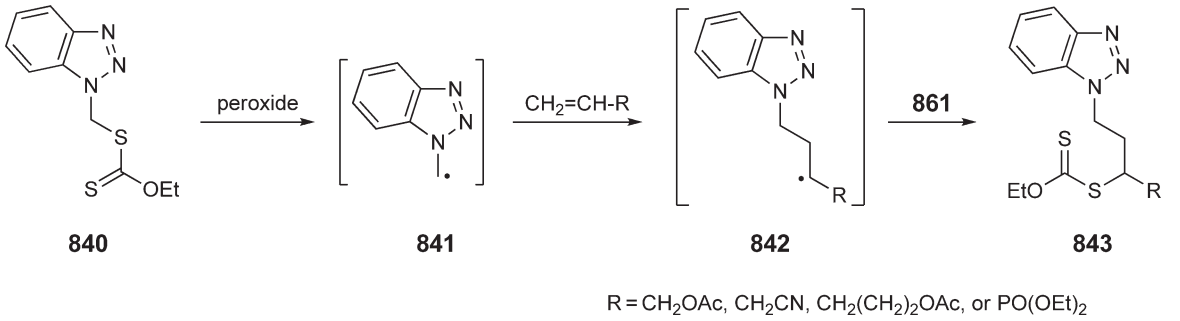
All reactions of benzotriazole derivatives of the type Bt-CR^1R^2-S discussed above are based on electrophilic or nucleophilic substitutions at the α-carbon, but radical reactions are also possible. Thus, the first report on unsubstituted carbon-centered (benzotriazol-1-yl)methyl radical **841** involves derivatives of (benzotriazol-1-yl)methyl mercaptan. *S*-(Benzotriazol-1-yl)methyl-*O*-ethyl xanthate **840** is readily prepared in a reaction of 1-(chloromethyl)-benzotriazole with commercially available potassium *O*-ethyl xanthate. Upon treatment with radical initiators (lauroyl peroxide), the C–S bond is cleaved to generate radical **841** that can be trapped by alkenes to generate new radicals **842**. By taking the xanthate moiety from the starting material, radicals **842** are converted to final products **843** with regeneration of radicals **841** allowing repetition of the process (**Scheme 134**). Maleinimides are also satisfactorily used as radical traps in these reactions <2001H(54)301>.



Scheme 132



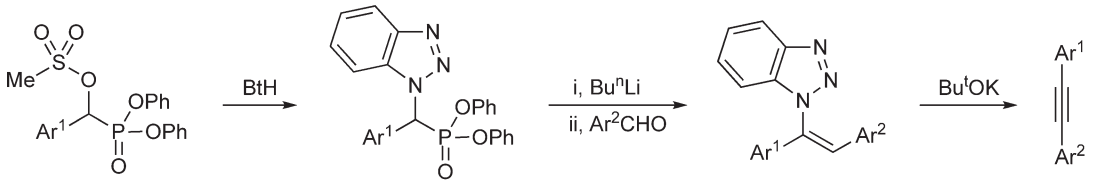
Scheme 133



Scheme 134

5.01.8.8.2 Phosphorus derivatives

Methanesulfonates **844**, obtained by addition of diphenyl phosphite to aldehydes Ar^1CHO and mesylation of the hydroxyl group of the adducts, react with benzotriazole to give diphenyl α-(benzotriazol-1-yl)benzylphosphonates **845**. Lithiation and treatment with aldehydes Ar^2CHO converts phosphonates **845** into stilbenes **846**, which can eliminate benzotriazole to give diarylacetylenes **847** (**Scheme 135**) <2002ARK(xiii)17>.

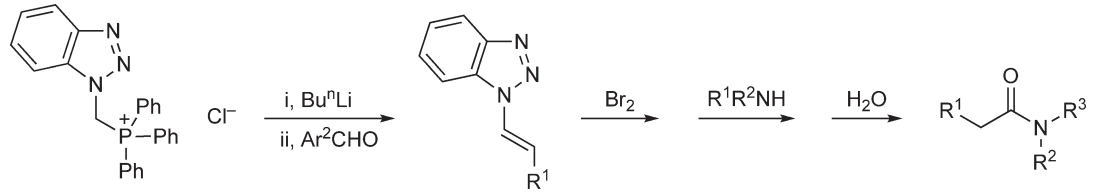


844 **845** **846** **847**

BtH = benzotriazole
Ar^1 = Ph, 4-MeC_6H_4, or 4-ClC_6H_4
Ar^2 = Ph, 4-MeC_6H_4, 4-$(NO_2)C_6H_4$, 1-naphthyl, 2-furyl, 2-thienyl, 2-pyridyl, or 3-pyridyl

Scheme 135

[(Benzotriazol-1-yl)methyl]triphenylphosphonium chloride **848** reacts with Bu^{n}Li and aldehydes to give 1-(alken-1-yl)benzotriazoles **849**. Addition of bromine to the double bond of derivatives **849** followed by a reaction with amines furnishes amides **850**. A variety of primary or secondary amines can be used. This way aldehydes are conveniently homologated and converted to amides with a one-atom longer chain (**Scheme 136**) <2004ARK(ix)44.



848 **849** **850**

R^1 = Et, Pr^i, Ph, or 2-thienyl
R^2 = various alkyl, aryl or heteroaryl, and R^3 = H
or R^1R^2 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, or $(CH_2)_2NMe(CH_2)_2$

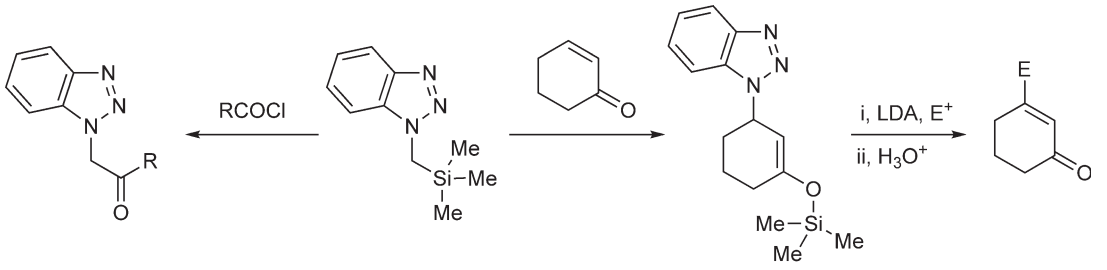
Scheme 136

5.01.8.8.3 Silicon derivatives

[(Benzotriazol-1yl)methyl]trimethylsilane **852** reacts with acyl chlorides under mild conditions to provide (benzotriazol-1-yl)methyl ketones **851** in high yields (**Scheme 137**) <2001J(P1)2483, 2001JOC5606>. Reactivity of benzotriazolyl derivatives of type **851** and their application in organic synthesis are discussed in Section 5.01.8.4. 1,4-Adition of silane **852** to 2-cyclohexen-1-one produces derivative **853** that is unstable to the air; however, direct treatment of the reaction mixture with a base generates an anion that can be trapped by various electrophiles. Final hydrolysis of the silyloxy group and elimination of benzotriazole give rise to 3-substituted 2-cyclohexen-1-ones **854** <1995TL5491>.

5.01.8.8.4 1-(Chloromethyl)benzotriazole

1-(Chloromethyl)benzotriazole **856** is an important starting material for preparation of many derivatives of benzotriazole that are discussed in this section. All these reactions rely on the nucleophilic substitution of chlorine in **856** with nucleophiles to give derivatives **855** <1996CHEC-II(4)1>. However, it appears that compound **856** can also be converted into its anion by treatment with LDA at −40 °C. The anions generated this way can be trapped by ketones to provide a convenient method for the synthesis of (benzotriazol-1-yl)oxiranes **857** (**Scheme 138**) <2003JOC407>.

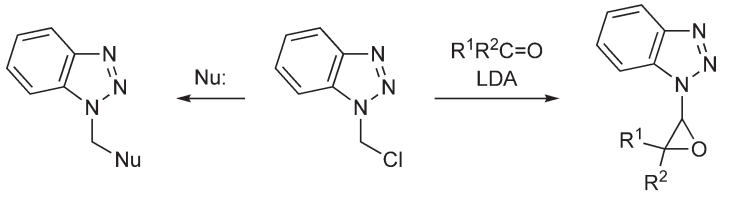


851 **852** **853** **854**

R = alkyl, aryl, or $ClCH_2$

E = alkyl, $ArCH_2$, PhCO, PhCHOH, Ph_2COH, or ArNHCS

Scheme 137



855 **856** **857**

R^1 = Me, Et, Ph, 4-MeC_6H_4 or 4-ClC_6H_4

R^2 = Et or Ph, or

$R^1R^2 = (CH_2)_5$

Scheme 138

5.01.8.9 Ring N–C(sp^2)═C

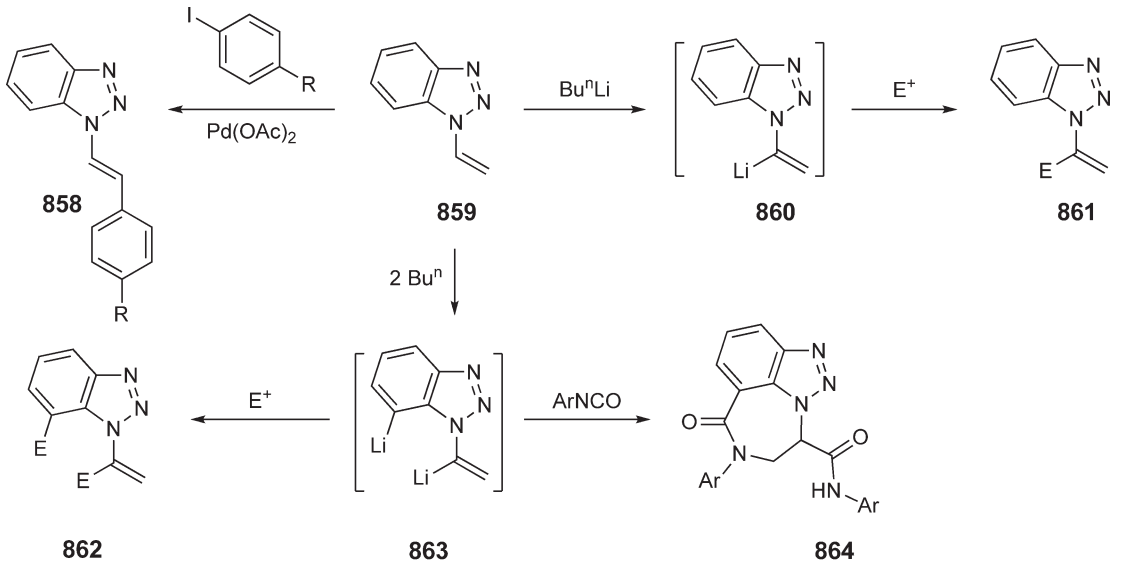
5.01.8.9.1 Alkenyl group not activated

In the presence of a palladium catalyst, 1-vinylbenzotriazole **859** reacts with iodoarenes to give derivatives **858** (**Scheme 139**). Exclusive addition to the β-carbon and *(E)* geometry of molecules **858** are confirmed by NMR data <1999H(50)767>. To introduce substituents on the α-carbon, 1-vinylbenzotiazole is lithiated first with 1 molar equivalent of Bu^{n}Li to give intermediate **860** and then treated with electrophiles to furnish products **861** <2003JOC5713>. Use of *2* equiv of Bu^{n}Li produces dilithiated intermediate **863** giving rise to disubstituted products **862**. When reagents with two electrophilic centers are used, like $(PhCO)_2$ or $(PhCO)_2CH_2$, an additional ring is added to the heterocyclic system involving atoms C-*α* and C-7. Initial addition of two isocyanate groups to C-*α* and C-7 is followed by an intramolecular nucleophilic addition of the amide N-H to the vinyl bond resulting in products **864** <2003JOC5713>.

1-Alkenylbenzotriazoles **865** are readily prepared by isomerization of the corresponding allyl derivatives catalyzed by Bu^{t}OK. Lithiated compounds **865** are treated with electrophiles to provide α-substituted derivatives **866**. Epoxidation of the double bond with *m*-chloroperbenzoic acid converts intermediates **866** into oxiranes **867** that can be hydrolyzed to furnish α-hydroxyketones **868** in good yields (**Scheme 140**) <1996SC2657>.

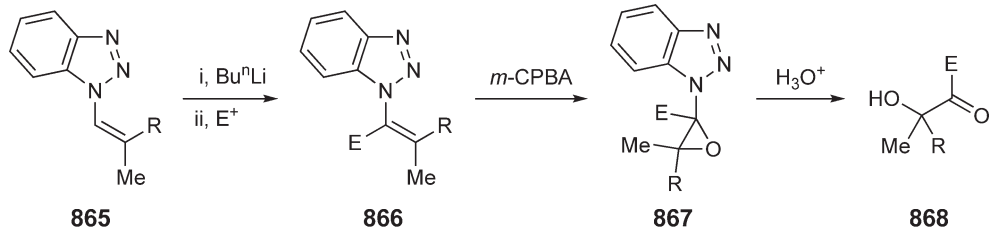
5.01.8.9.2 Electron-withdrawing substituents

Compounds of this type with an electron-withdrawing substituent at C-α can be easily prepared by condensation of 2-(benzotriazol-1-yl)acetophenone **869** with aldehydes. Exclusively *(E)* isomers of α,β-unsaturated ketones **870** are formed. Treatment with hydrazines converts derivatives **870** into pyrazolines **871**. Elimination of benzotriazole from **871** in the presence of mild bases furnishes pyrazoles **872**. When in these reactions hydroxylamine is used instead of hydrazines, the corresponding isoxazoles are obtained (**Scheme 141**) <2001JOC6787>.



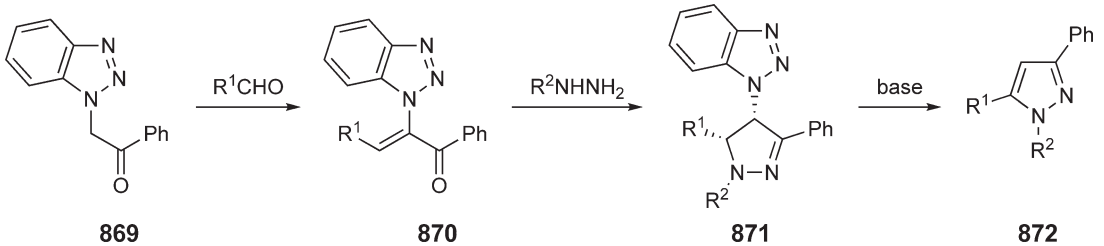
R = Me or OMe
E^+ = 4-MeC_6H_4CHO, PhCOCH=CHPh, or 4-MeC_6H_4NCO
Ar = Ph or 4-MeC_6H_4

Scheme 139



R = H or Me
E = octyl, 4-$BrC_6H_4CH_2$, PhCHOH, Ph_2COH, or 1-hydroxycyclohexyl

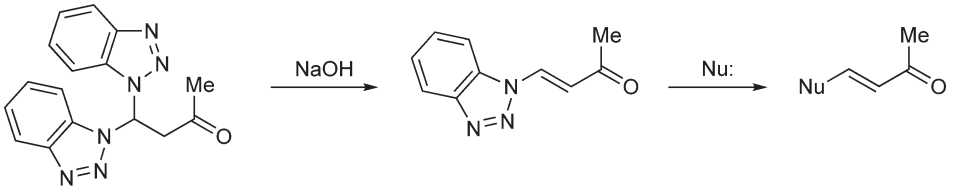
Scheme 140



R^1 = Pr^i, Ph, 4-MeC_6H_4, or 3-pyridyl
R^2 = Me or Ph

Scheme 141

Compound **874**, as a representative of derivatives with an electron-withdrawing substituent at C-β of the vinyl group, is easily prepared by elimination of one benzotriazole from 2,2-*bis*(benzotriazol-1-yl)ethyl methyl ketone **873**. The stereoselective elimination catalyzed by NaOH gives exclusively the *(E)* isomer of derivative **874**. Addition of nucleophiles to the double bond of vinyl ketone **874** followed by elimination of benzotriazole leads to α,β-unsaturated ketones **875**. Amines used as nucleophiles do not need any catalysis, but reactions with carbon and sulfur nucleophiles require addition of a base. The total effect is nucleophilic substitution of the benzotriazolyl group at the β-carbon of α,β-unsaturated ketone (**Scheme 142**) <1996SC3773>.



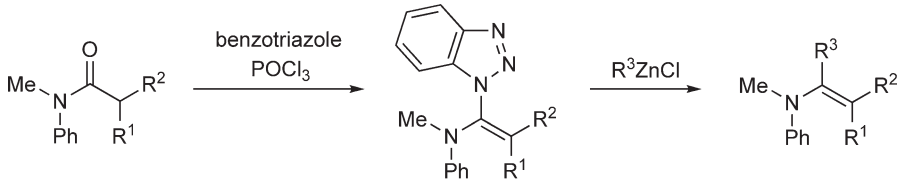
873 **874** **875**

Nu: = piperidine, morpholine, 2-nitropropane, $MeCH(CO_2Et)_2$, $Ph(CH_2)_3CN$, or PhSH

Scheme 142

5.01.8.9.3 Electron-donating substituents

α-(Benzotriazol-1-yl)enamines **877** can be conveniently prepared in reactions of amides **876** with benzotriazole and $POCl_3$. Enamines **877** are stable enough to be separated by column chromatography as pure stereoisomers; however, their long storage in a solution showed partial isomerization between benzotriazol-1-yl and benzotriazol-2-yl isomers. Nucleophilic substitution of benzotriazole with organozinc reagents furnishes enamines **878** (**Scheme 143**) <2000ARK(v)667>.

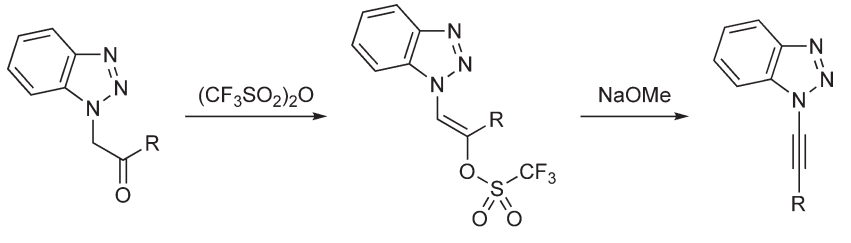


876 **877** **878**

R^1 = H or Me
R^2 = Me or Et
R^3 = Me or PhCC

Scheme 143

Triflate **880** can be formally considered as an ester of the enol form of ketone **879**. Treatment with a base causes elimination of the triflate group to afford 1-(benzotriazol-1-yl)alkynes **881** (**Scheme 144**) <2000OL3789>.



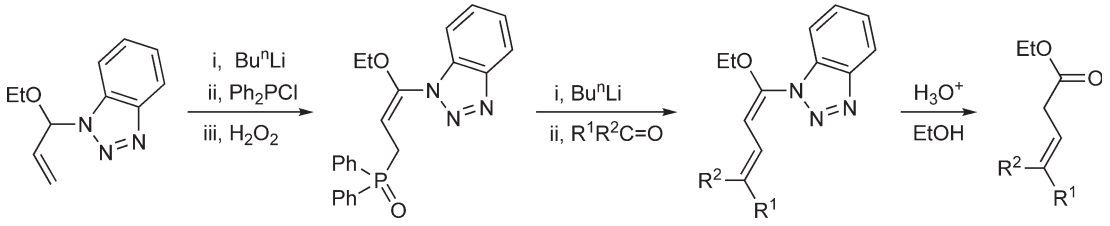
879 **880** **881**

R = alkyl or aryl

Scheme 144

5.01.8.9.4 Allylic derivatives

The benzotriazolyl derivative of acrolein acetal, compound **882**, is lithiated, treated with chlorodiphenylphosphine, and the obtained intermediate is oxidized with hydrogen peroxide to phosphine oxide **883** (**Scheme 145**). The relatively acidic proton in derivative **883** is easily removed by a base, and the obtained anion adds to a carbonyl group of aldehyde or ketone. Subsequent rearrangement and elimination of the phosphorane group generates diene **884**. For the derivatives of aldehydes (**884**, $R^2 = H$), *(E)–(E)* stereoselectivity of the elimination is observed. Acidic alcoholysis of dienes **884** affords esters of β,γ-unsaturated carboxylic acids **885** < 1997JOC4131>.

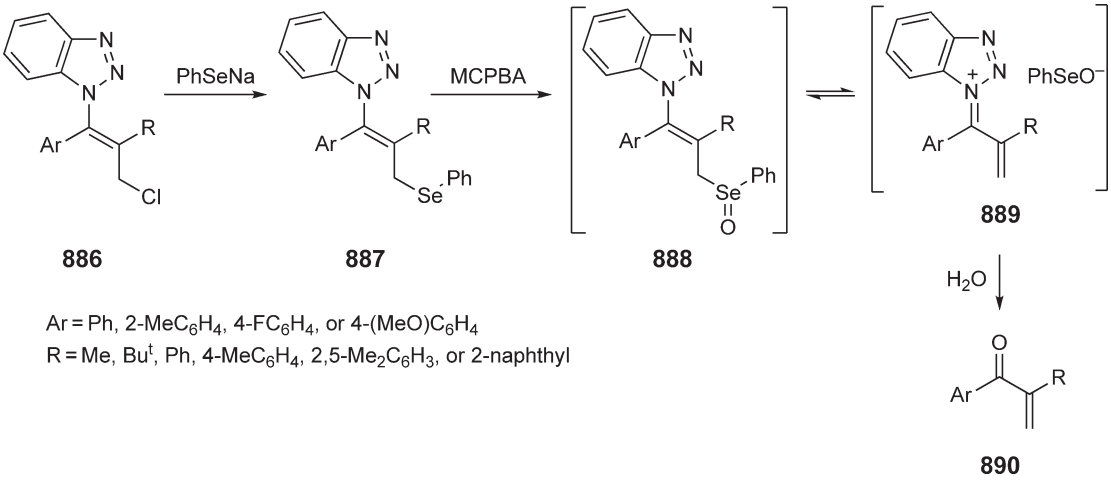


882 **883** **884** **885**

R^1 = *n*-C_3H_7, *n*-C_7H_{15}, Ph, or $PhCH_2CH_2$
R^2 = H, Me, *n*-C_3H_7, or Ph, or
$R^1R^2 = (CH_2)_5$

Scheme 145

The allylic chlorine atom in derivatives **886** can be easily substituted by nucleophiles <2002EJO493>. Reactions of chlorides **886** with sodium benzeneselenide provide allylic selenides **887**. Oxidation of the selenium atom in selenides **887** with *m*-chloroperbenzoic acid generates unstable selenoxides **888**. Contrary to the corresponding sulfoxides <2002EJO493>, and due to good leaving ability of the benzeneselenate moiety, selenoxides **888** may dissociate to cations **889** that are readily hydrolyzed to vinyl ketones **890** (**Scheme 146**) <2002TL3021>.



886 **887** **888** **889** **890**

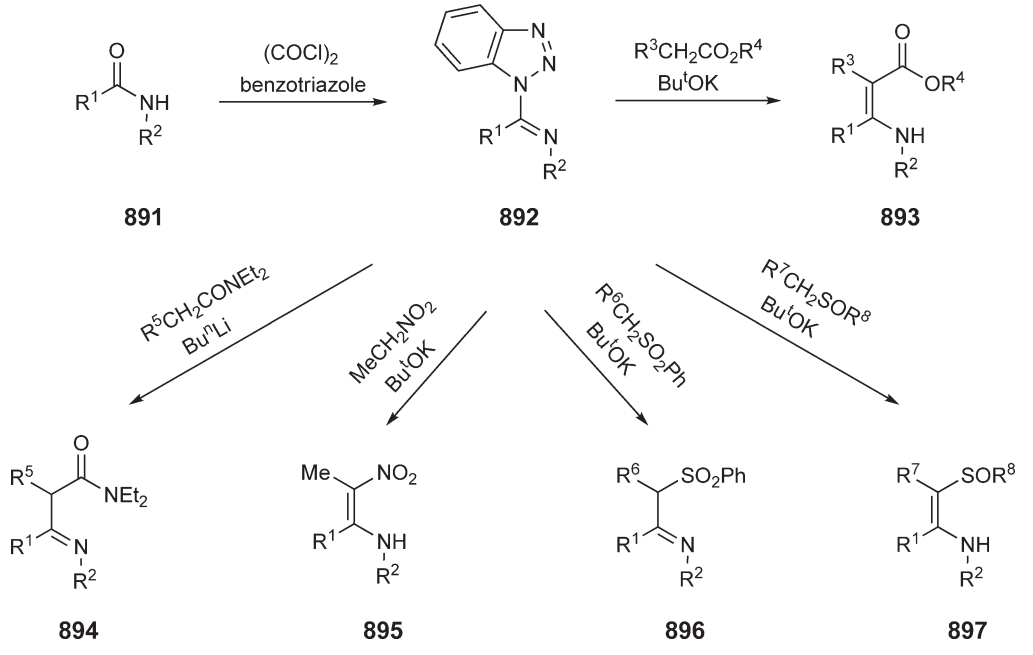
Ar = Ph, 2-MeC_6H_4, 4-FC_6H_4, or 4-$(MeO)C_6H_4$
R = Me, Bu^t, Ph, 4-MeC_6H_4, 2,5-$Me_2C_6H_3$, or 2-naphthyl

Scheme 146

5.01.8.10 Ring N–C(sp^2)═N

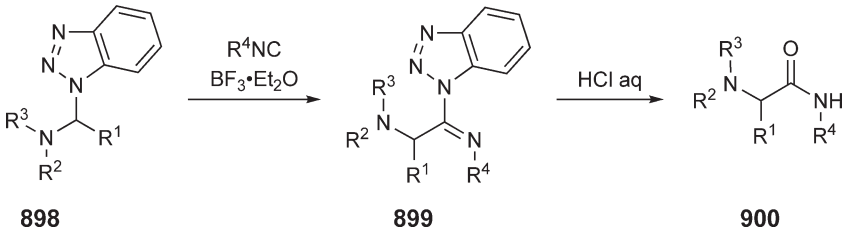
1-Imidoylbenzotriazoles **892** are prepared in good yield (50–90%) in reactions of amides **891** with benzotriazole and oxalyl chloride in the presence of pyridine <2006JOC3375>. Derivatives **892** are convenient reagents for imidoylation of methylene groups activated by electron-withdrawing substituents. Thus, in their reactions with ester enolates,

generated from the corresponding esters by addition of Bu^{t}OK, 1-imidoylbenzotriazoles **892** give β-enaminoesters **893** in 77–88% yield. Similarly, β-iminoamides **894** are obtained in 48–69% from reactions of compounds **892** with amides deprotonated by Bu^{n}Li. The anions generated from nitroethane, alkyl phenyl sulfones, or sulfoxides by action of Bu^{t}OK react with 1-imidoylbenzotriazoles **892** to provide derivatives **895**, **896**, and **897**, respectively, in generally good yields. All of these products can exist in equilibria between the enamine and imine forms; however, the NMR data indicate that the enamine forms are strongly predominant for derivatives **893**, **895**, and **897** (**Scheme 147**) <2007ARK(v)263>.



Scheme 147

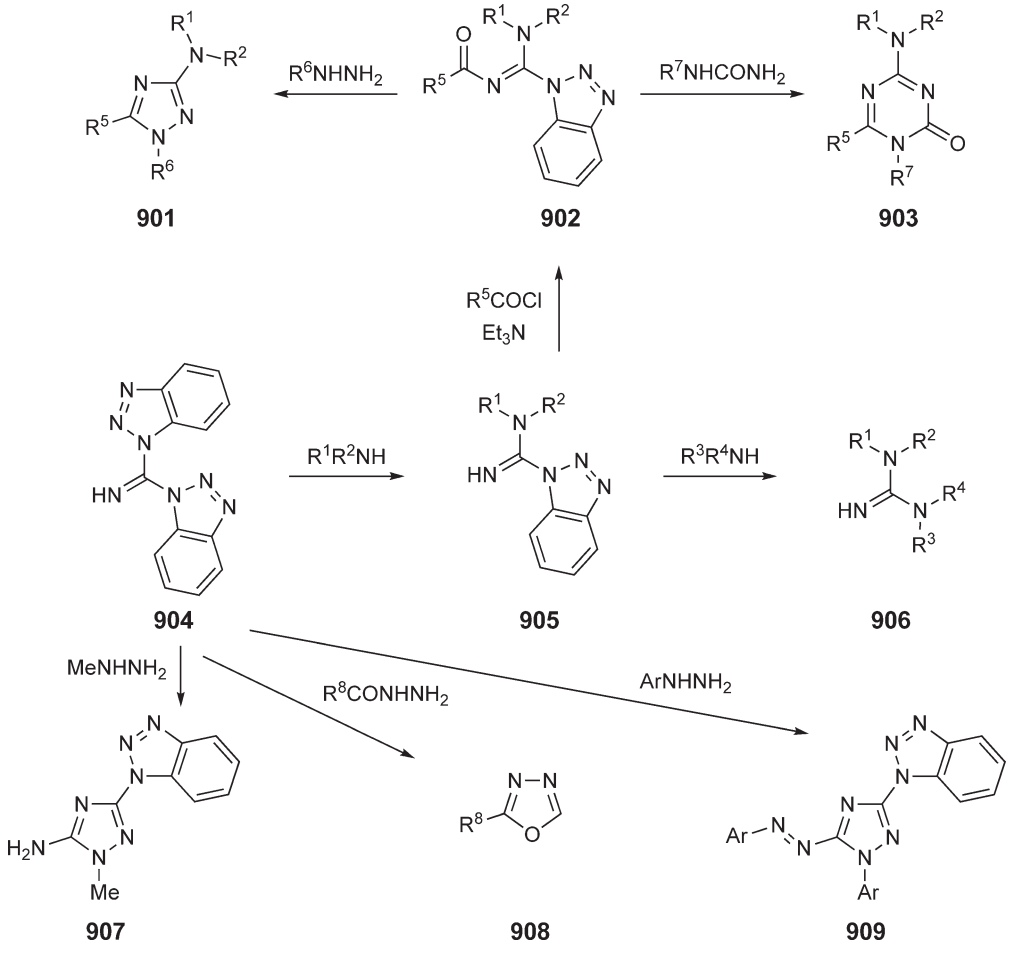
Reactions of *N*-(α-aminoalkyl)benzotriazoles **898** with isonitriles catalyzed by boron trifluoride etherate give *N*-(α-aminoalkylimidoyl)benzotriazoles **899** in high yield. Upon treatment with hydrochloric acid, derivatives **899** are conveniently converted to α-aminoamides **900** (**Scheme 148**) <2005JSC319>.



Scheme 148

A reaction of benzotriazole with cyanogen bromide carried out in ethanol in the presence of NaOH provides dibenzotriazolylmethanimine **904** as a mixture of benzotriazol-1-yl and 2-yl isomers <1996POL4011, 2000JOC8080>. To simplify the picture, only the benzotriazol-1-yl isomer is shown in **Scheme 149**. Treatment with amines converts methanimine **904** under mild conditions into carboxyimidamides **905** as sole benzotriazol-1-yl isomers. Upon treatment with other amines at slightly elevated temperature, the second benzotriazolyl moiety can be replaced to provide guanidines **906** bearing up to four different groups <2000JOC8080>. Acyl derivatives **902** undergo cyclocondensation with alkyl or aryl hydrazines to give 3-amino-1,2,4-triazoles **901** in good yields

<2001S897>. Cyclocondensation of derivative **902** with ureas provides 1,3,5-triazin-2-ones **903**, whereas a similar reaction with thioureas gives 1,3,5-triazin-2-thiones <2001JOC6797>. Hydrazides derived from aromatic carboxylic acids react with imine **904** to give oxadiazoles **908** almost quantitatively, whereas only 42% yield was achieved in an analogous reaction of acetyl hydrazide <2002ARK(vi)82>. Cyclocondensation of imine **904** with methylhydrazine produces 1,2,4-triazole **907**; however, in the case of arylhydrazines, a more complex process involving condensation of **904** with two molecules of hydrazine, elimination of ammonia and oxidation with atmospheric oxygen leads to azo derivatives **909** <2002ARK(vi)82>.

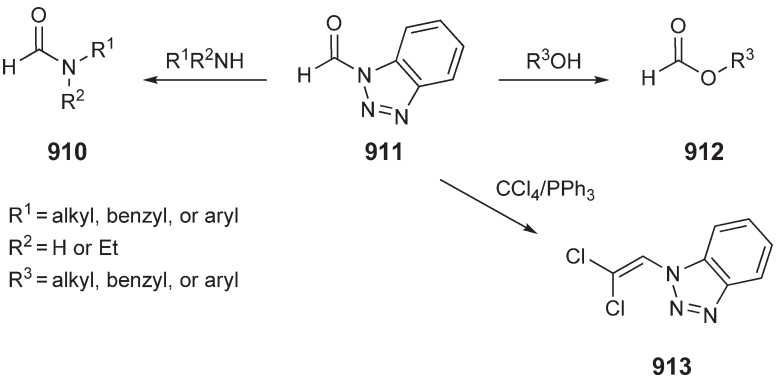


Scheme 149

5.01.8.11 Ring N–C(sp^2)═O

5.01.8.11.1 Ring N–(C═O)-H

Considering benzotriazolyl moiety in compounds of the general structure R-(C═O)-X (X = benzotriazol-1-yl or benzotriazol-2-yl) as a synthetic equivalent of a halogen atom, the formyl derivative (R = H) is of special interest due to unavailability of the halogen analogs. 1-Formylbenzotriazole **911** can be conveniently prepared in a reaction of benzotriazole with formic acid in the presence of dicyclohexylcarbodiimide <1995S503>. Its reactions with amines provide conveniently formamides **910** under mild conditions <1995S503, 2002JA12950>. Even unreactive 2-nitroaniline and 2-aminopyridine can be efficiently formylated this way (**Scheme 150**) <1995S503>. In reactions of 1-formylbenzotriazole **911** with alcohols, the corresponding formates **912** are readily obtained <1995S503>. Treatment of compound **911** with triphenylphosphine and CCl_4 results in formation of 1-(2,2-dichlorovinyl)benzotriazole **913**, a convenient starting material in the synthesis of 1-ethynylbenzotriazoles (see Section 5.01.8.13) <2006T3794>.

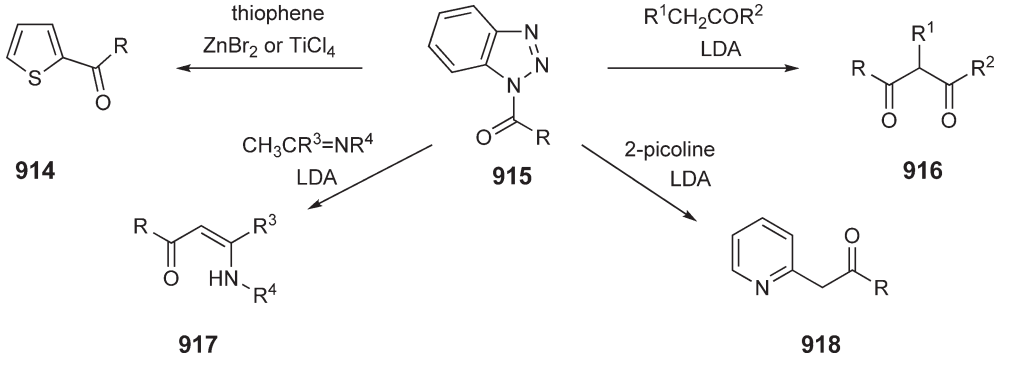


Scheme 150

5.01.8.11.2 Ring N-(C═O)-R, C-acylation

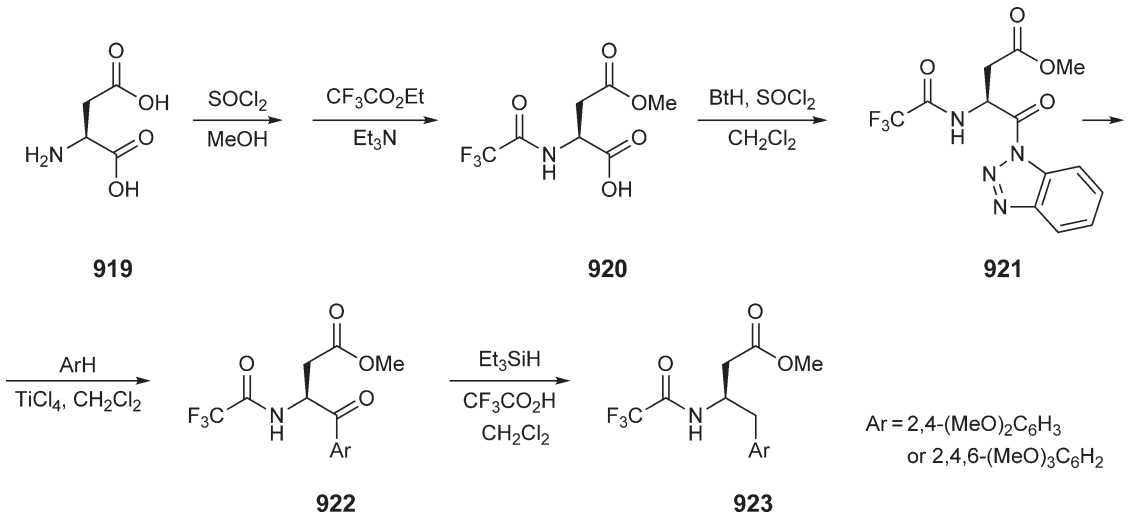
A wide range of *N*-acylbenzotriazoles **915** have been prepared under mild conditions in reactions of carboxylic acids with thionyl chloride in the presence of fourfold excess of benzotriazole, including R = alkyl, α-haloalkyl, α-alkoxyalkyl, alkenyl, alkinyl, aryl, and heteroaryl <2003S2795, 2004RQM275>. They represent convenient acylating agents for variety of nucleophiles. Synthetic applications of such compounds have been reviewed <2005SL1656>.

Some examples of C-acylation by 1-acylbenzotriazoles **915** are collected in **Scheme 151**. Thus, acylation of aromatic rings involves reactions of derivatives **915** with thiophene in the presence of $ZnBr_2$ or $TiCl_4$ to give corresponding 2-acylthiophenes **914** in high yield <2004CCA175>. Furan reacts similarly. C-2 acylation of pyrroles and C-3 acylation of indoles under these conditions does not require N-protection <2003JOC5720>. Ketones are acylated in the presence of LDA to give β-diketones **916** <2000JOC3679>; the reaction can also be carried out on a polymer support <2001JCO167>. Acylation of aliphatic nitriles leads to the corresponding β-ketonitriles <2003JOC4932> and that of sulfones to β-ketosulfones <2003JOC1443>. Imines delivered from methyl ketones are effectively acylated by derivatives **915** on their methyl groups to give enaminones **917** <2000S2029>. 2-Picoline is readily acylated by **915** to produce (pyridin-2-yl)methyl ketones **918**; 4-picoline, 4-methylquinoline and the corresponding benzyl derivatives react similarly <2005ARK(vi)329>.



Scheme 151

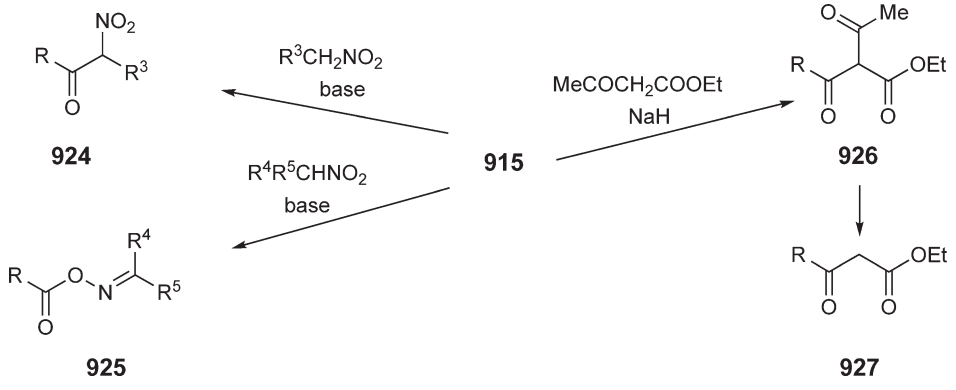
In a reaction with thionyl chloride and methanol, L-aspartic acid **919** is converted to its monoester, which is subsequently treated with ethyl trifluoroacetate to give N-protected aminoacid **920**. Upon treatment with benzotriazole and thionyl chloride, acid **920** is converted to 1-acylbenzotriazole **921** that can be used as an acylating agent for electron-rich aromatics. Thus, in its reaction with di- and trimethoxybenzene, the corresponding γ-keto-β-aminocarboxylic acid esters **922** are obtained in 35% and 50% yield, respectively. Ketones **922** are smoothly reduced with triethylsilane to β-aminoacid derivatives **923** (78–79% yield). Higher yields of ketones **922** (54–89%) are obtained from reactions of acylating agent **921** with reactive heteroaromatics like pyrrole, indole and their *N*-methyl derivatives. Starting from glutamic acid, an analogous reaction sequence provides derivatives of the corresponding γ-aminoacids (**Scheme 152**) <2007JOC407>.



919 **920** **921** **922** **923**

Scheme 152

N-Acylbenzotriazoles **915** delivered from aliphatic, aromatic or N-protected α-amino carboxylic acids react with primary nitroalkanes under basic conditions to give corresponding α-nitroalkanes **924** in good yields <2005JOC9211>. Under similar conditions, secondary nitroalkanes are converted to O-acylated oximes **925**. Treatment of ethyl acetoacetate with aromatic *N*-acylbenzotriazoles **915** (R = Ar) leads to 3-aryl-β-ketoesters **927**, presumably via three-carbonyl intermediates **926** (**Scheme 153**) <2004JOC6617>. Analogous reactions of α-acetylketones produce higher β-diketones.

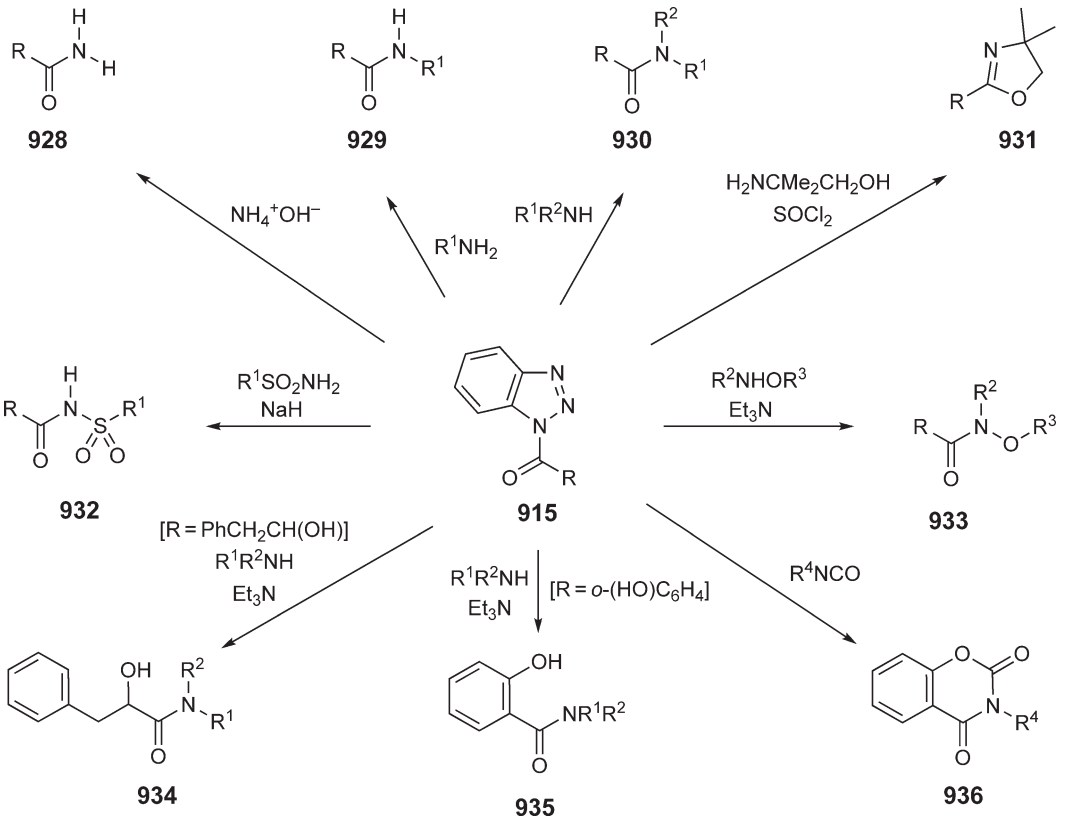


924 **915** **926** **925** **927**

Scheme 153

5.01.8.11.3 Ring N-(C═O)-R, N-acylation

Acylbenzotriazoles **915** are convenient acylating agents for all kinds of amines. Thus, in their reactions with ammonia (30% aqueous solution), primary amides **928** are formed in high to quantitative yields. Primary amines react similarly well to give amides **929**. In the case of secondary amines, the yields of amides **930** are generally high, except when there is too much steric hindrance; for example, *N*-ethylisopropylamine does not react at all (**Scheme 154**) <2000JOC8210>. Reactions of compounds **915** with 2,2-dimethyl-2-aminoethanol produce oxazolines **931** <2004JOC811>. Analogously, thiazolines are formed in reactions of acylbenzotriazoles **915** with 2-aminoethanethiol <2004JOC811>. Due to simplicity and high efficiency of these reactions, 1-acylbenzotriazoles **915** are currently used in drug derivatization <2001IJP129, 2003CCA335> and preparation of ^{14}C-labeled compounds <2003JLR449>. The synthesis of amides **928–930** can be further facilitated by application of microwaves <2006JOC3375> or a solid phase support <2002BML1809>.



Scheme 154

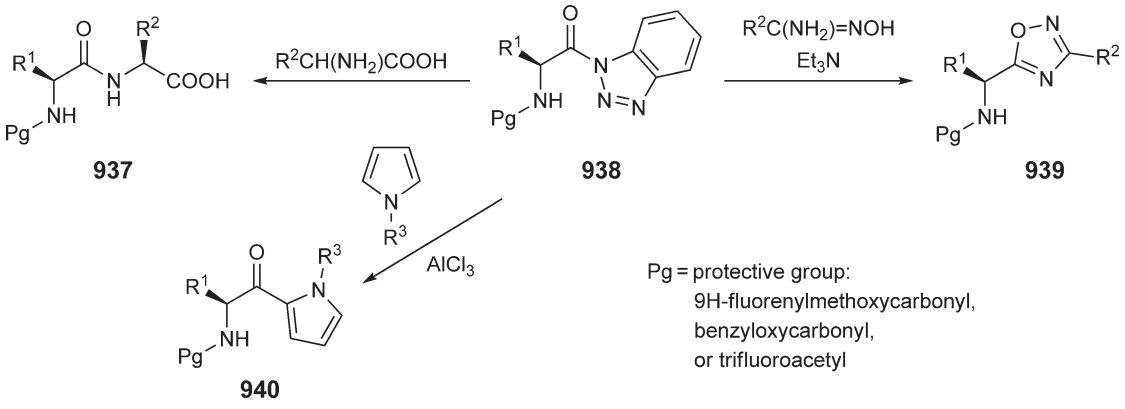
N-Acylation by derivatives **915** is applicable to the formation of *N*-acylsulfonamides **932** <2004ARK(xii)14>, hydroxamic acids and Weinreb amides **933** <2002ARK(xi)39, 2003S2777> in high yields (**Scheme 154**). Application of this methodology allows direct conversion of hydroxy carboxylic acids into their amides without any protection on the hydroxy group. Thus, in reactions with amines, compound **915** derived from 2-hydroxy-3-phenylpropionic acid gives amides **934** in 72–75% yield <2006JOC3364>. 1-Acylbenzotriazole **915** derived from salicylic acid reacts smoothly with amines to give salicylamides **935** <2006JOC3364> and with isocyanates to afford benzoxazine-2,4-diones **936** <2007ARK(vi)6>. Many other hydroxy carboxylic acids, with various distances between the hydroxy and carboxylic groups, produce similarly good results <2006JOC3364>.

N-Protected 1-(α-aminoacyl)benzotriazoles **938** derived from chiral α-aminocarboxylic acids can be conveniently prepared by mixing 4 molar equivalents of benzotriazole with 1 equiv of thionyl chloride followed by addition of 1 equiv of N-protected α-aminocarboxylic acid. Acylbenzotriazoles **938** react with chiral amines to give corresponding amides with retention of chirality <2002ARK(viii)134>. Condensation of **938** with unprotected α-aminocarboxylic acids in MeCN/H_2O in the presence of triethylamine at room temperature gives readily chiral dipeptides **937** <2004S2645, 2005S397, 2005TL6537>. The methodology can be readily extended to tripeptides <2006S411>. Reactions of derivatives **938** with amidoximes lead to 5-(α-aminoalkyl)-1,2,4-oxadiazoles **939** in high yields and with preservation of chirality <2005ARK(vii)36> (**Scheme 155**). Reactions of aminoacylbenzotriazoles **938** with pyrrole and *N*-methylpyrrole in the presence of $AlCl_3$ give chiral 2-(aminoacyl)pyrroles **940**. Analogous reactions with indoles lead to their 3-(aminoacyl) derivatives <2005JOC4993>.

5.01.8.11.4 Ring N-(C═O)-R, O-, and S-acylation

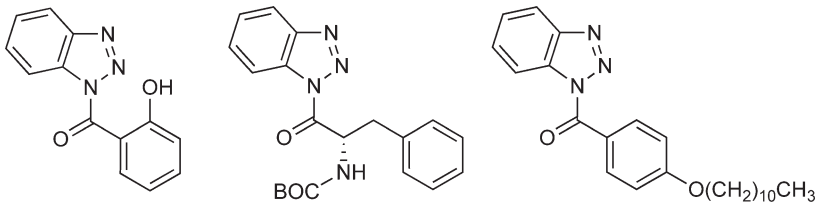
Despite the many simple methods for preparation of carboxylic esters and thioesters, in some instances, use of 1-acylbenzotriazoles **915** as O and S acylating agents may be advantageous. For example, easy to prepare salicylic acid derivative **941** reacts with cyclopentanol under microwave irradiation to give 92% yield of cyclopentyl salicylate in 10 min <2006JOC3364>. In another example, L-phenylalanine derivative **942** reacts with benzyl mercaptan

and triethylamine at 25 °C for 1 h to produce the corresponding thioester in 97% yield <2004S1806>. 1-(4-Undecyloxybenzoyl)benzotriazole **943** is conveniently used for acylation of a complex phenol in preparation of liquid crystals <2004JA1161>. Esters are also formed with good yields in reactions of 1-acylbenzotriazoles **915** with organozinc reagents in the presence of a palladium catalyst <2001ARK(xi)41>. The unusual course of these reactions must involve oxidation of the intermediates with atmospheric oxygen.



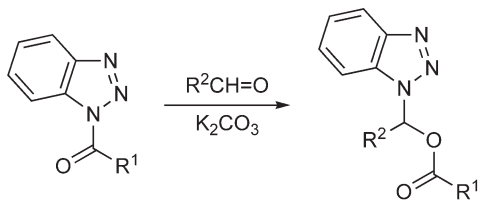
937 **938** **939** **940**

Scheme 155



941 **942** **943**

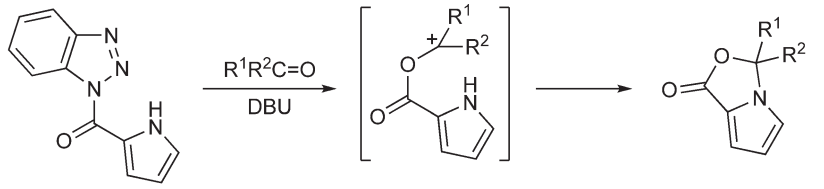
Carbonyl oxygen atoms of aldehydes can also be efficiently acylated by 1-acylbenzotriazoles **915** in the presence of mild bases (K_2CO_3, Et_3N). The released benzotriazolide anions are consecutively attached to the aldehyde carbonyl carbon atoms to produce esters **944** (Equation 20). Aliphatic aldehydes react quickly at room temperature, but aromatic aldehydes require elevated temperatures. The yields are good to quantitative. The amounts of benzotriazol-2-yl isomers of esters **944** in the products mixtures is strongly dependent on the reaction conditions and the character of groups R^1 and R^2, and it may vary from 5% to 25% <1999JHC777>.



915 **944** (20)

R^1 = Me, Bu^t, $ClCH_2$, $Cl(CH_2)_3$, Ph, 4-$MeOC_6H_4$, or 2-furyl
R^2 = Et, Pr, Bu^t, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$(CN)C_6H_4$, 4-$(NO_2)C_6H_4$, 4-$(CO_2Me)C_6H_4$, 2-furyl, or 3-furyl

Similarly to the reaction depicted in Equation (20), acylation of the oxygen atom of aldehydes or ketones by pyrrole derivative **945** produces intermediate cations **946**. However, instead of being trapped by benzotriazole to give ester **944**, the intramolecular electrophilic attack of the cation on the pyrrole nitrogen atom produces pyrrolo[1,2-oxazol-1-one] **947**. According to an alternative path, the adduct of pyrrole to the carbonyl group of aldehyde is formed first, and then its oxygen atom is intramolecularly acylated to give product **947**. The reaction is catalyzed by DBU. The indole analog of **945** reacts similarly with aldehydes and ketones to produce tricyclic systems (**Scheme 156**) <2004JOC9313>.

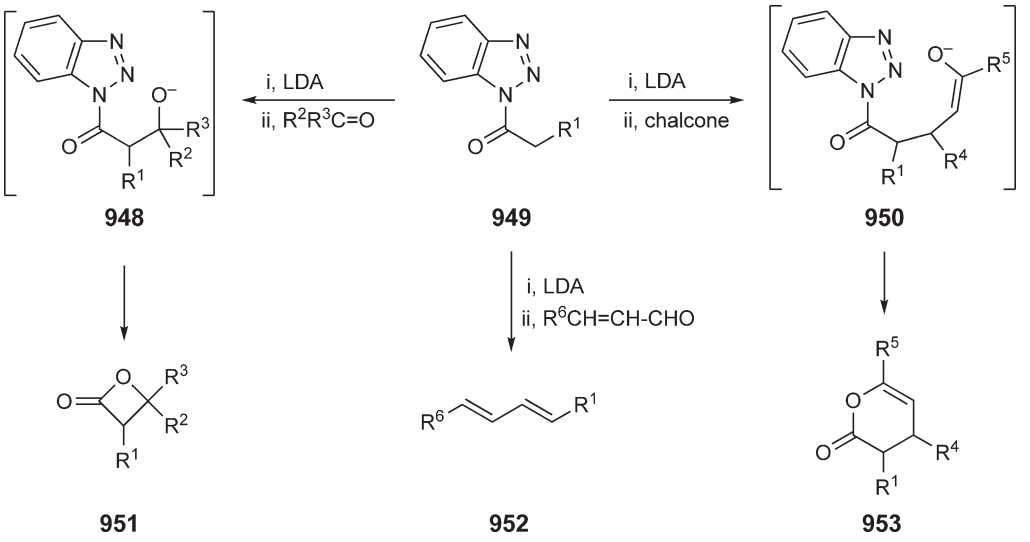


945 **946** **947**

$R^1R^2C{=}O$ = $Pr^iCH{=}O$, 4-$MeC_6H_4CH{=}O$, 2-furyl-CH=O, $Me_2C{=}O$, $Et_2C{=}O$, cyclohexanone, or acetophenone

Scheme 156

Intramolecular acylation of oxygen atoms plays also an important role in reactions of carbanions derived from acylbenzotriazoles **949** with aldehydes and ketones. Thus, anion **948** obtained in the first step undergoes intramolecular cyclocondensation to β-lactone **951** (**Scheme 157**) <1996LA881>. A similar addition of anions derived from acylbenzotriazoles **949** to cinnamaldehydes provide unstable β-lactones that undergo spontaneous ring opening and decarboxylation to dienes **952** (a mixture of (*E*,*E*) and (*E*,*Z*) isomers). However, in the case of chalcones, the nucleophilic attack goes on the β-carbon atom to yield 3,4-dihydropyran-2-ones **953**, via intramolecular acylation of the oxygen atom in anionic intermediates **950** <2002JOC3104>.



948 **949** **950**

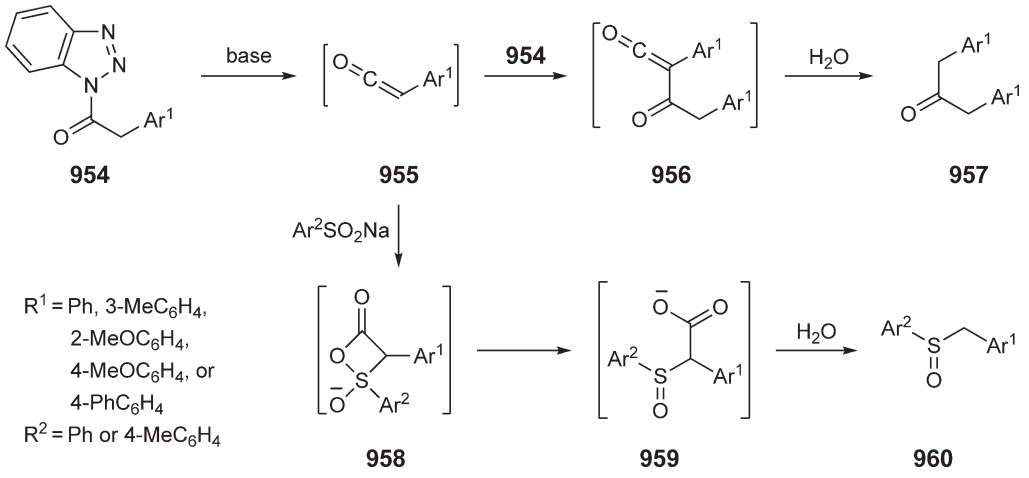
951 **952** **953**

Scheme 157

5.01.8.11.5 Ring N-(C═O)-R, elimination of benzotriazole

Treated with a base, 1-(arylacetyl)benzotriazoles **954** eliminate benzotriazole to form ketenes **955**. When no other reagent is added, ketene **955** is acylated by another molecule of **954** to produce α-ketoketene **956** which upon addition of water and decarboxylation during the work-up is converted to symmetrical dibenzyl ketone **957**

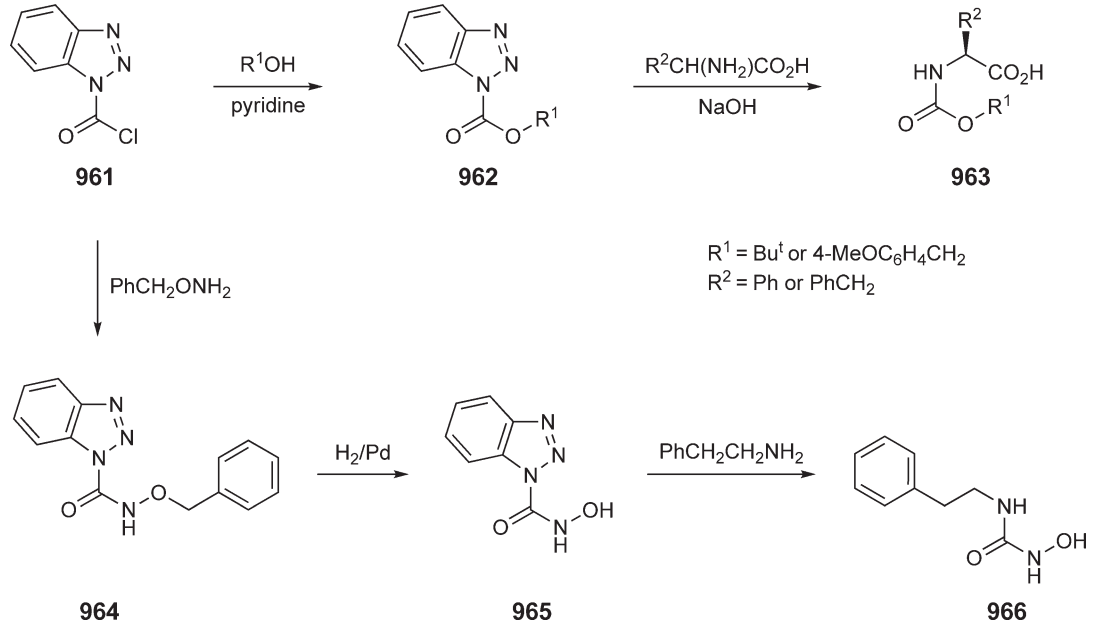
(**Scheme 158**) <1996HAC365>. Trapping of ketenes **955** by arenesulfinates generates unstable adducts **958** that consecutively undergo ring opening (intermediate **959**) and decarboxylation to aryl benzyl sulfoxides **960** <1996SL701>. Upon heating at 210 °C, even simple acylbenzotriazoles **949** (R^1 = alkyl) eliminate benzotriazole and generate corresponding ketenes that can be conveniently trapped by isocyanates <2000JOC8069>.



Scheme 158

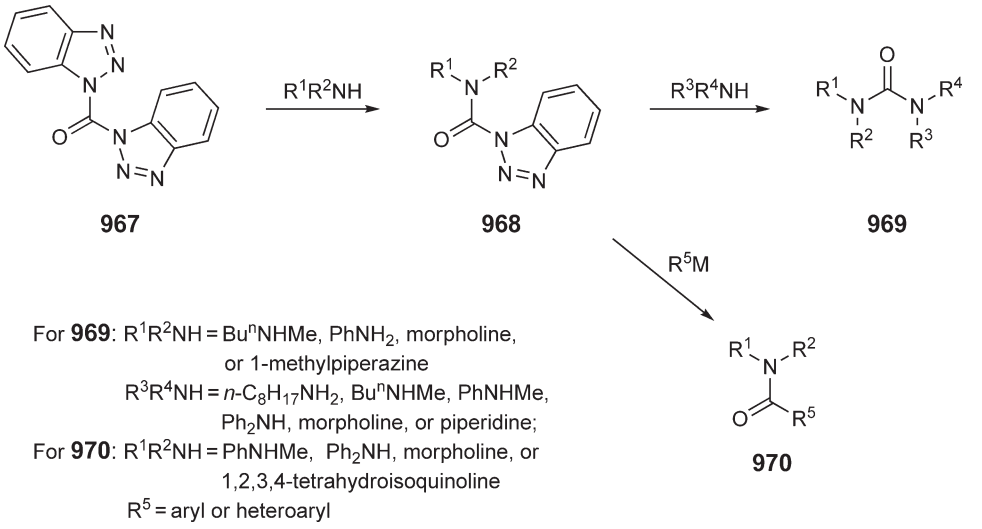
5.01.8.11.6 Ring N-(C═O)-X

1-Chloroformylbenzotriazole **961** is prepared in a reaction of benzotriazole with phosgene <1997SC1623, 2000CCA569> or more conveniently with triphosgene <2003CCA217>. In reactions with alcohols in the presence of pyridine, the chlorine atom in derivative **961** is substituted by an alkoxy group. Obtained esters **962** react with aminoacids to provide their N-protected forms **963** (**Scheme 159**) <1997SC1623>. The reaction of compound **961** with benzyloxyamine provides 1-(benzyloxycarbamoyl)benzotriazole **964**. Deprotection of the hydroxy group by hydrogenation gives acid **965** that is treated then with phenethylamine to afford *N*-hydroxy-*N*′-phenethylurea **966** <2000CCA569>.



Scheme 159

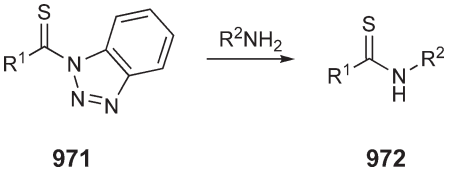
1,1′-Carbonyldibenzotriazole **967** is conveniently prepared by stirring a THF solution of 2 molar equivalents of benzotriazole and 1 equiv of phosgene for 3 d. Successive treatment with two different amines provides an efficient synthetic method for asymmetrically substituted ureas **969** via intermediate amidobenzotriazoles **968** (**Scheme 160**) <1997JOC4155>. The benzotriazole moiety in amides **968** can be readily displaced by aryl and heteroaryl organomagnesium or organolithium reagents to provide benzamides (or heterocyclic amides) **970** in moderate to good yields <1999JCM230>.



Scheme 160

5.01.8.12 Ring N-C(sp^2)═S

Benzotriazole thioamides **971** react with amines to produce thioamides **972** under mild conditions (Equation 21). It is the preferred route to thioamides with reactive groups R^1 and R^2 where direct conversion of the corresponding amides to thioamides **971** is not feasible <2002J(P1)2243>. More stable 6-nitrobenzotriazolyl analogs of **971** are more convenient to use in some instances <2005TA1905, 2005JOC7866>. A significant drawback of this method is lengthy preparation of derivatives **971** <2002J(P1)2243> or their 6-nitrobenzotriazolyl analogs <2005JOC7866> involving several steps that start from the corresponding *ortho*-phenylenediamine and include formation of the triazole ring (see Section 5.01.9).

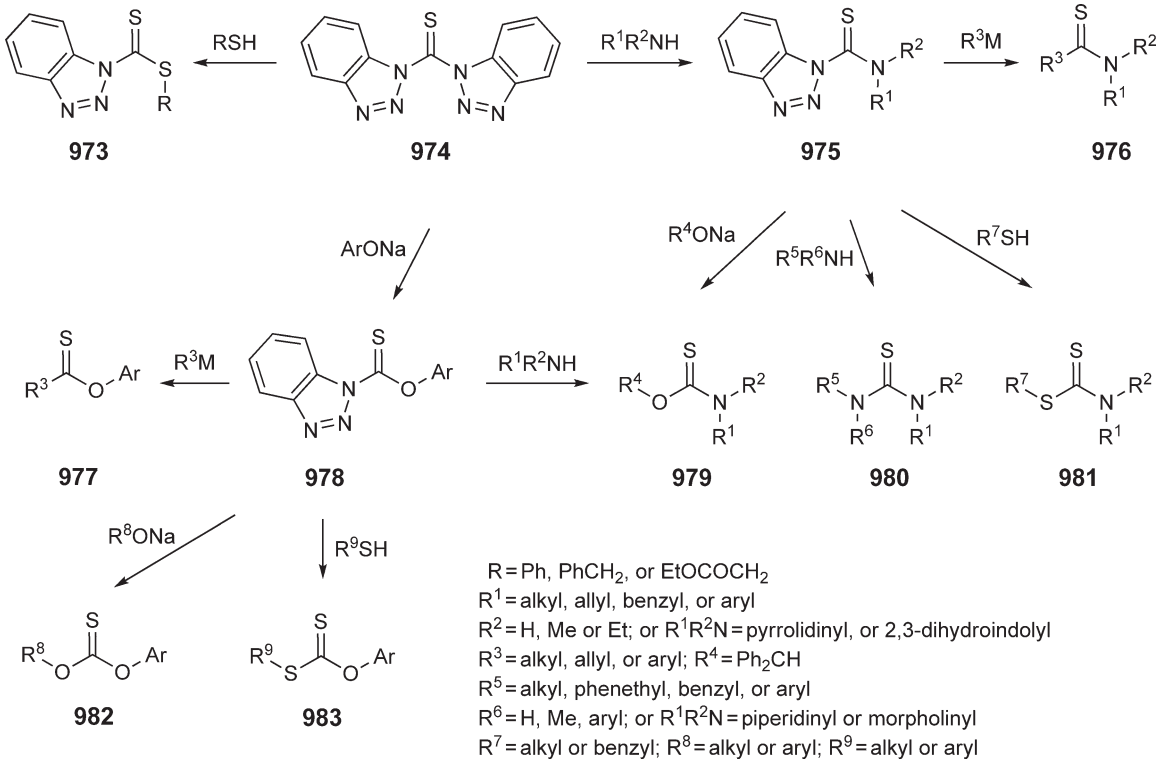


(21)

Bis(benzotriazol-1yl)methanethione **974** is easily prepared from thiophosgene and 1-(trimethylsilyl)benzotriazole <1978JOC337>. In reactions with thiols and triethylamine, thiones **974** are converted to derivatives **973** in modest yields; the main side products result from nucleophilic attacks of the thiolate anions on the thione sulfur atom to produce disulfides <2005JOC7866>. In reactions with amines, compounds **974** are smoothly converted to 1-(thiocarbamoyl)benzotriazoles **975** <2004JOC2976>. Substitution of one of the benzotriazolyl groups in **974** by phenolate anions yields 1-(aryloxythioacyl)benzotriazoles **978** (**Scheme 161**) <2005JOC7866>.

Reactions of thiocarbamoyl benzotriazoles **975** with organolithium or Grignard reagents provide thioamides **976** in moderate to good yields <2005JOC7866>. Substitution of the benzotriazolyl moiety in **975** by alkoxide anions leads to thiocarbamates **979** <2005JOC7866>. In reactions with amines, substitution of the first benzotriazolyl group in

bis(benzotriazol-1yl)methanethione **974** occurs readily at room temperature to give 1-(thiocarbamoyl)benzotriazoles **975**. However, when the amines are used in 2:1 molar ratio, and the reaction mixtures in dichloromethane are heated at reflux, symmetrical thioureas **980** ($R^1 = R^6$ and $R^2 = R^5$) are obtained. Unsymmetrical thioureas **980** are prepared in good yields by reactions of intermediates **975** with different amines <2004JOC2976, 2005JOC7866>. In the presence of triethylamine, 1-(thiocarbamoyl)benzotriazoles **975** react with mercaptans to give dithiocarbamates **981** <2005JOC7866>. Similarly to their amine analogs **975**, the benzotriazolyl moiety in oxygen derivatives **978** can be readily substituted with organometallic reagents to provide thionoesters **977**, with amines to give thiocarbamates **979**, with alkoxides to afford thiocarbonates **982** and with mercaptans to yield dithiocarbonates **983** (**Scheme 161**) <2005JOC7866>.



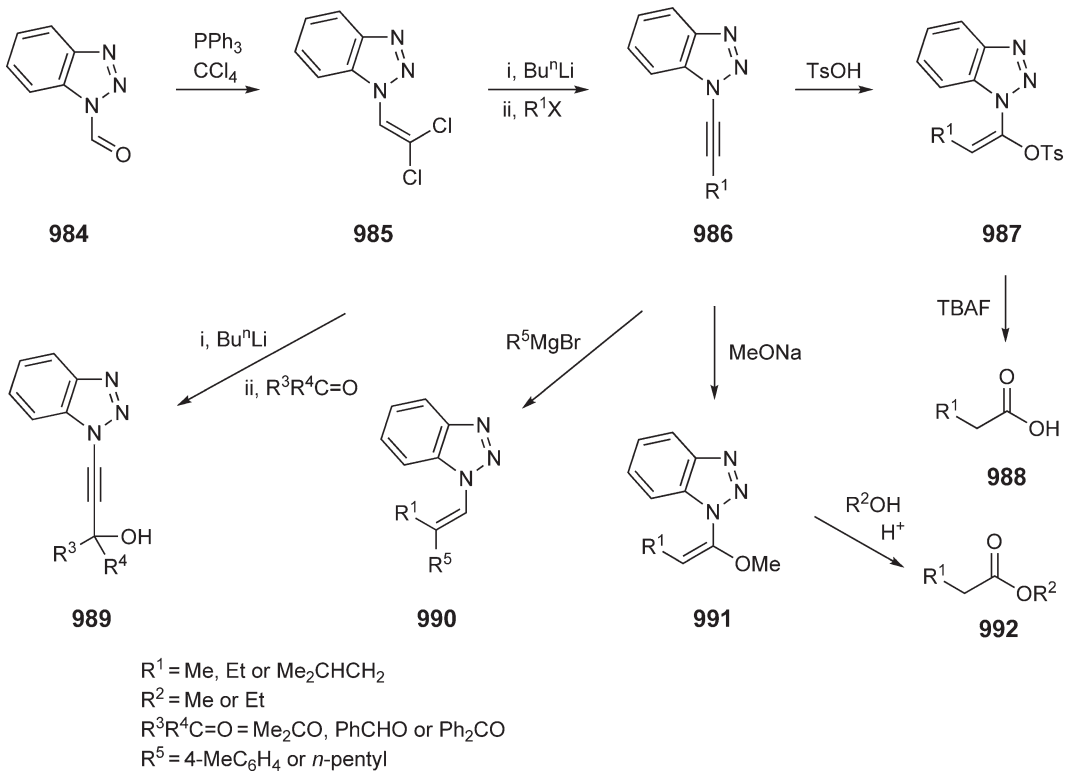
Scheme 161

5.01.8.13 Ring N–C(sp)

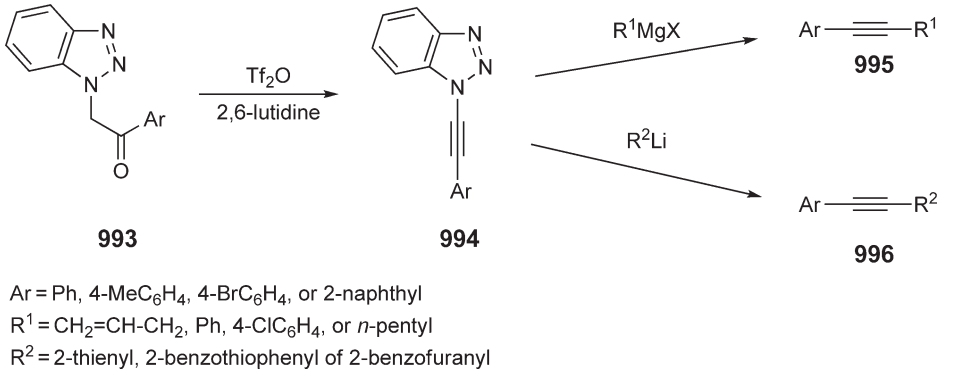
5.01.8.13.1 Ring N–C≡C–R

1-Formylbenzotriazole **984** reacts with triphenylphosphine and CCl_4 to provide 1-(2,2-dichloroethenyl)benzotriazole **985** in 68% yield as a crystalline solid. Treatment of derivative **985** with 2 molar equivalents of Bu^nLi followed by alkylating agents leads to 1-alkynylbenzotriazoles **986** in 58–84% yield. Alternatively, propargyl alcohols **989** (32–84% yield) are obtained in a reaction of **985** with Bu^nLi and aldehydes or ketones. *p*-Toluenesulfonic acid adds readily to the triple bond of derivatives **986** to give intermediates **987** that are easily hydrolyzed to carboxylic acids **988**. Similarly, esters **992** are obtained by addition of methanol to derivatives **986** under basic conditions followed by acidic alcoholysis of intermediate **991**. Addition of Grignard reagents to alkynes **986** provides alkenes **990** in 72-91% yield (**Scheme 162**) <2000OL3789, 2002JOC7526, 2006T3794>.

1-(Arylethynyl)benzotriazoles **994** are prepared conveniently in a reaction of aryl (benzotriazol-1-yl)methyl ketones **993** with triflic anhydride in the presence of 2,6-lutidine. Nucleophilic attacks in derivatives **994** occur on the C-α atoms; thus, their reactions with Grignard reagents give alkynes **995** in 51–83% yield. Lithiated heteroaromatics react similarly to give alkynes **996** in 58–70% yield (**Scheme 163**) <2002JOC7526>.



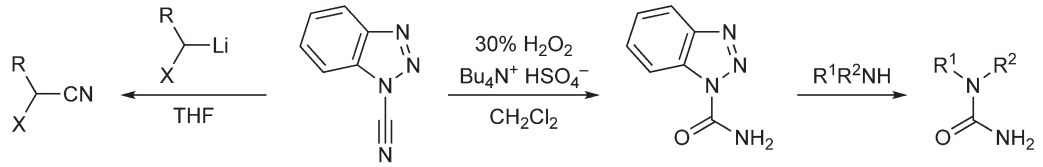
Scheme 162



Scheme 163

5.01.8.13.2 Ring N–C≡N

1-Cyanobenzotriazole **998** is readily prepared in 92% yield by treatment of benzotriazole with sodium hydride followed by cyanogen bromide. Solid and stable derivative **998** is a convenient reagent for introduction of the nitrile functional group into activated methylene compounds R-CH_2-X, which are lithiated with LDA prior to the reaction. Less acidic materials such as Ph-CH_2-Ph and 2-pyridyl-CH_2-Me are lithiated with Bu^nLi. Nitriles **997** are obtained under mild conditions in average 65% yield (**Scheme 15**) <2007ARK(iii)5>. Hydrolysis of 1-cyanobenzotriazole **998** with 30% H_2O_2 provides (benzotriazol-1-yl)carboxylic acid amide(**999** in 79% yield. Substitution of the benzotriazolyl moiety in product **999** by amines occurs readily at room temperature to furnish ureas **1000** in 61–96% yield (**Scheme 164**) <2003ARK(viii)8>.



997 **998** **999** **1000**

R-CH_2-X = Ph-CH_2-CN, $PhCH_2$-CH_2-CN, Ph-CH_2-CO_2Et, 1-naphthyl-CH_2-CO_2Me, Ph-CH_2-COPh, Ph-CH_2-Ph, 2-pyridyl-CH_2-Me, Ph-CH_2-SO_2Ph, $PhCH_2$-CH_2-SO_2Ph, or 2-tolyl-CH_2-SO_2Ph

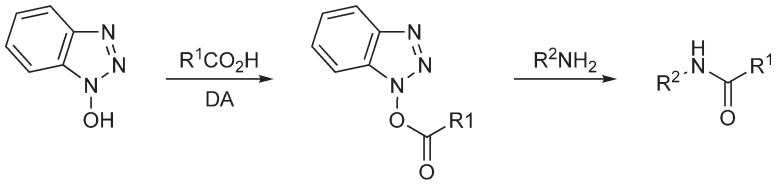
R^1R^2NH = 4-$MeOC_6H_4NH_2$, $PhCH_2NH_2$, $PhCH_2CH_2NH_2$, *n*-pentyl-NH_2, Bu_2NH, Pr^i_2NH, or $(PhCH_2)_2NH$

Scheme 164

5.01.8.14 Ring N–X (X = heteroatom)

5.01.8.14.1 Ring N–O

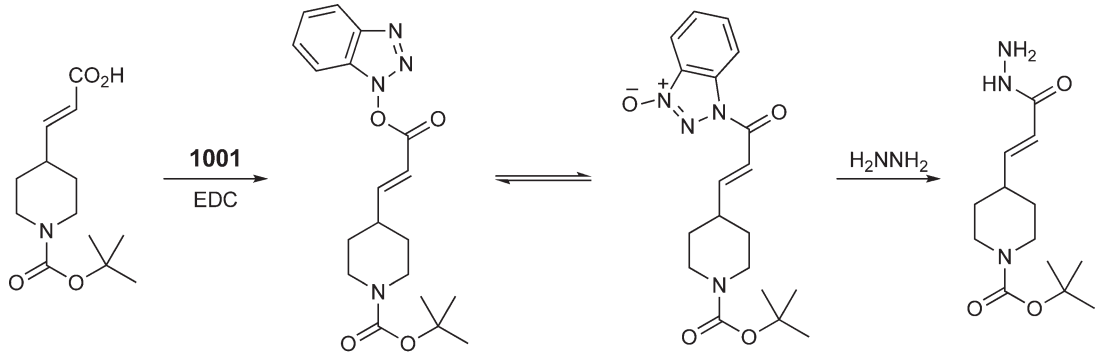
Due to its wide application in peptide synthesis, 1-hydroxybenzotriazole **1001** is the most commonly used benzotriazole derivative with hundreds of references in *Chemical Abstracts* each year. Utility of compound **1001** comes from its readiness to form esters with carboxylic acids in the presence of dehydrating agents (DAs). Obtained esters **1002** react eagerly with amines to produce amides **1003** in high yields (**Scheme 165**). More details about this application are given in Section 5.01.12.



1001 **1002** **1003**

Scheme 165

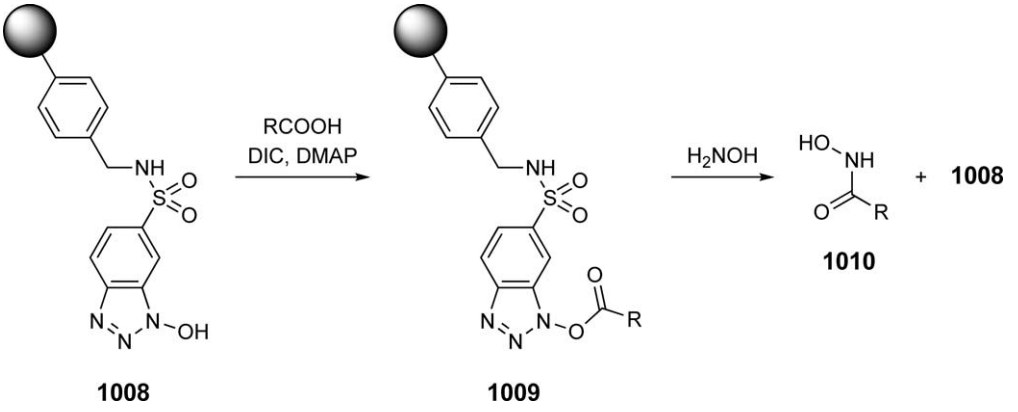
Scheme 166 shows application of this methodology for preparation of hydrazide **1007**. Thus, the reaction of acid **1004** with 1-hydroxybenzotriazole and EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] gives ester **1005** that can be separated and characterized, but it rearranges slowly to isomeric form **1006** in solutions. However, both derivatives, **1005** and **1006**, are found to be equally reactive toward hydrazine and afford hydrazide **1007** in 98% isolated yield <2002JOC9471>.



1004 **1005** **1006** **1007**

Scheme 166

Polymer-bound 1-hydroxybenzotriazole **1008** reacts with carboxylic acids in the presence of 1,3-diisopropylcarbodiimide (1,3-DIC) and DMAP to produce esters **1009**. Treated with hydroxylamine, esters **1009** are converted to hydroxamic acids **1010** (**Scheme 167**) <2003OBC850>. Starting 1-hydroxybenzotriazole **1008** is recycled in the process and can be used for other syntheses. This method is well suited for automated synthesis of a library of hydroxamic acids. In similar applications of polymer-supported 1-hydroxybenzotriazole **1008**, a wide variety of amides is synthesized <1997JOC2594, 2002JCO576>.



Scheme 167

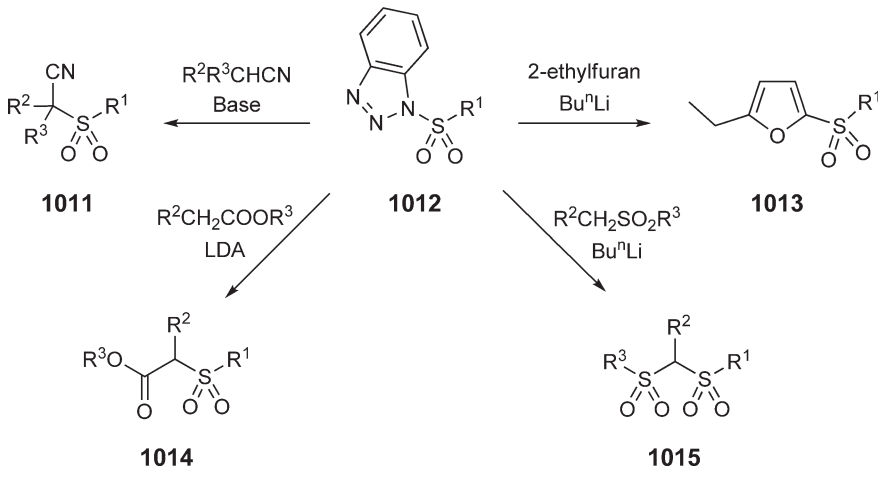
Although most common, application of esters **1002** is not limited to formation of C–N bonds. Such esters are also effectively used for regioselective benzoylation of sugars <2004CEJ399> and even for acylation of activated methylene groups <2003S2015>. Biological activity of some esters of the 1-hydroxybenzotriazole against SARS virus is attributed to their ability to acylate the cysteine sulfur atom in a key viral enzyme <2006CBO261>. Esters of 1-hydroxybenzotriazole **1001** with phosphoric acid are used for phosphorylation of nucleosides in a viral genome linked peptide <2003T1589>.

5.01.8.14.2 Ring N–S

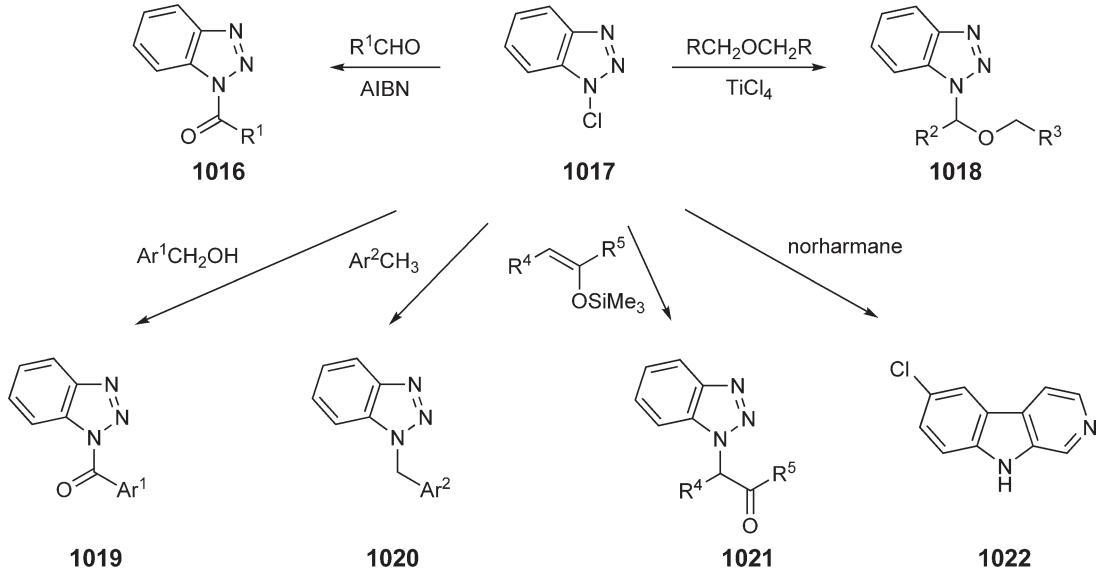
1-Sulfonylbenzotriazoles **1012** are readily available from reactions of benzotriazole with sulfonyl chlorides <2000JOC8210> or reactions of 1-chlorobenzotriazole with sulfinic acids <2004JOC1849>. Condensation of **1012** with primary or secondary nitriles under basic conditions provides corresponding α-cyanoalkyl sulfones **1011** in good to excellent yields (**Scheme 168**). In a convenient manner, sulfonyl derivatives **1012** convert lithiated heterocycles into heterocyclic sulfones; for example, 2-ethylfuran is converted to sulfone **1013**. In similar reactions, alkylheterocycles give α-(sulfonylalkyl)heterocycles, enolizable carboxylic esters give α-sulfonylcarboxylic esters **1014**, and sulfones give α-sulfonylalkyl sulfones **1015** <2005JOC9191>.

5.01.8.14.3 Ring N–Cl

1-Chorobenzotriazole **1017** is known as a mild oxidizing and chlorinating agent. Its reactions with aldehydes in the presence of catalytic amounts of AIBN lead to acylbenzotriazoles **1016** (**Scheme 169**) <2003ARK(xiv)131>. 1-Benzoylbenzotriazoles **1019** can also be obtained by oxidation of the corresponding benzyl alcohols with 2 equiv of compound **1017** <2003ARK(xiv)131>. Under similar conditions, toluenes are converted to the corresponding benzylbenzotriazoles **1020** <2003ARK(xiv)131>. Catalyzed by $TiCl_4$ and other Lewis acids, reactions of chlorobenzotriazole **1017** with ethers provide 1-(α-alkoxyalkyl)benzotriazoles **1018** <1999H(50)1877>. Reactions of **1017** with ketone silyl enol ethers give 1-(α-acylalkyl)benzotriazoles **1021** <1998JCM334>. Reactive aromatic rings can be efficiently chlorinated by chlorobenzotriazole **1017** as it is demonstrated by chlorination of norharmane, one of β-carbolines, to its chloro-derivative **1022** in 83% yield <2003JHC419>.



Scheme 168



R^1 = alkyl, aryl, or heteroaryl; Ar^1 = Ph or 4-PhC_6H_4; Ar^2 = Ph, 4-ClC_6H_4, or 4-$(NC)C_6H_4$
$R^2CH_2OCH_2R^3$ = Et_2O, $Bu^n{}_2O$, $(ClCH_2CH_2)_2O$, $(PhCH_2)_2O$, Bu^nOEt, dioxane, THF, THP, or isochroman
R^4 = H, Me, or Ph; R^5 = alkyl, aryl, or heteroaryl; or R^4R^5 = 2-$C_6H_4CH_2$, or 2-$C_6H_4CH_2CH_2$

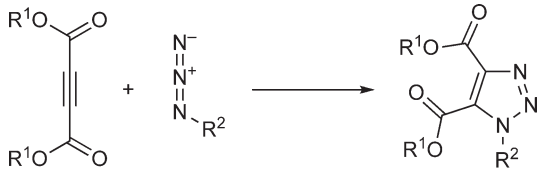
Scheme 169

5.01.9 Ring Synthesis from Acyclic Compounds

5.01.9.1 Ring Synthesis from Acetylenedicarboxylates

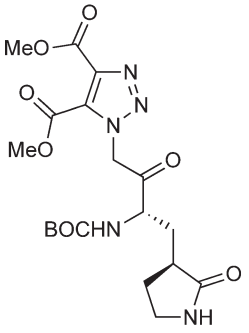
Cycloadditions of azides to alkynes and their derivatives <1996CHEC-II(4)1> continue to be the main synthetic route to 1,2,3-triazoles. Some aspects of these reactions with focus on cycloadditions at low temperature are discussed in a review <2003H(60)1225>. Recent advances in this area make the synthesis easy and high yielding to allow quick assembly of complex structures from relatively simple fragments. Drug design, proteomics, and nanotechnology are the scientific fields of great contemporary interest in such synthesis.

Esters of acetylenedicarboxylic acid **1023** are commercially readily available, are very reactive as dipolarophiles, and the carboxylic groups in products of their reactions can be easily converted to many other functionalities. Therefore, they are often the first choice as substrates for 1,3-dipolar cycloaddition to azides **1024** (Huisgen reaction). The reactions are carried out at room or elevated temperature, and the yields of 1,2,3-triazoles **1025** are usually high to quantitative (Equation 22). Several products obtained in this way are presented as structures **1026–1034**. Some details about the reactions leading to these products are given in **Table 10**.

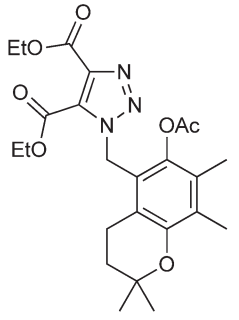


(22)

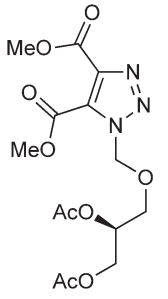
1023 **1024** **1025**



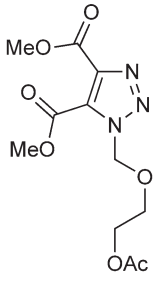
1026



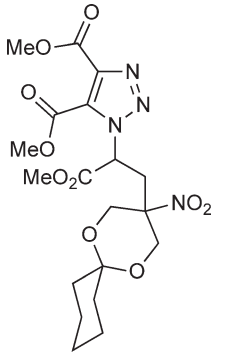
1027



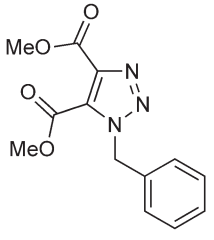
1028



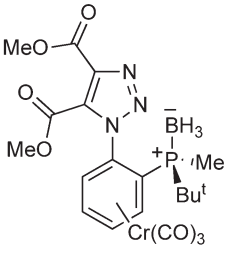
1029



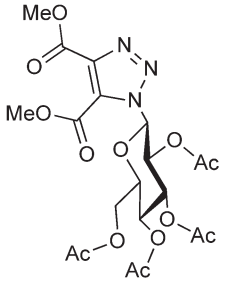
1030



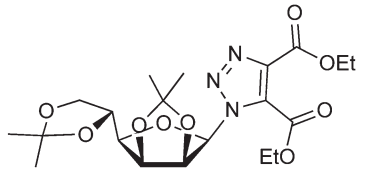
1031



1032



1033

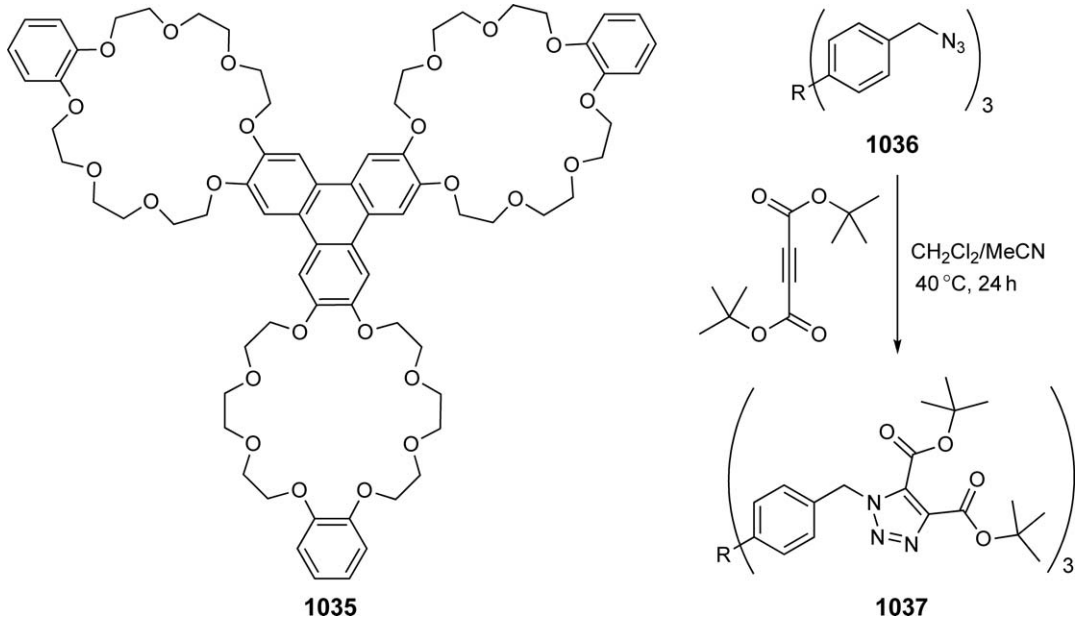


1034

Table 10 [3+2] Cycloaddition reactions of azides with acetylenedicarboxylates

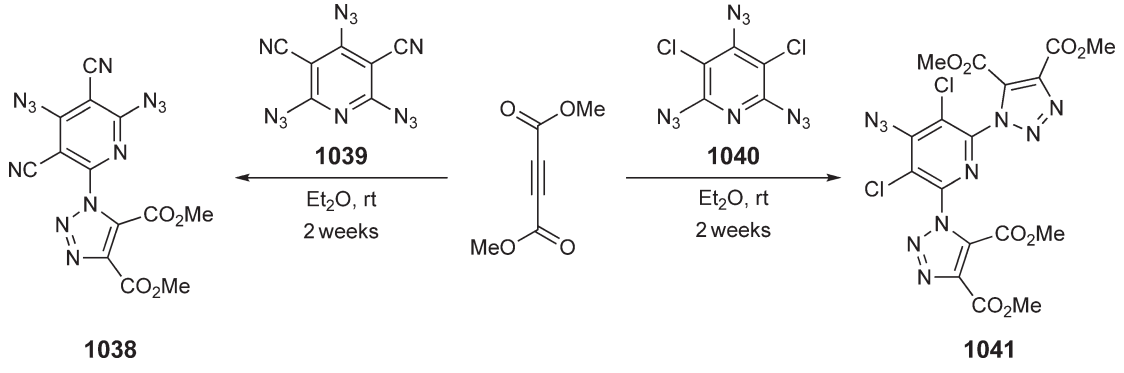
Product	*Reaction conditions*	*Yield (%)*	*Purpose*	*Reference*
1026	toluene, r.t., 72 h	100	inhibitor of hepatitis A virus 3C proteinase	2004BML3655
1027	toluene, reflux, 24 h	90	derivatives of α-tocopherol	2006EJO2081
1028	toluene, reflux, 72 h	73	nucleoside analogs	2002BKC437
1029	toluene, reflux, 72 h	73	nucleoside analogs	2002JCM264
1030	benzene, reflux, 3 h	100	nucleoside analogs	2002TL8351
1031	toluene, μw, 10 min	95	study of microwave methodology	2003MDV171
1032	toluene, 130 °C, 40 h	65	asymmetric catalysis	2005T4701
1033	toluene, 80 °C, 24 h	84	antitumor nucleoside analog	2002NN361
1034	toluene, reflux, 24 h	90	disaccharide carbohybrids	2005H(65)1035
(1,2,3-triazol-1-yl)calix[4]arenes	CH_2Cl_2, reflux, 6 h	84	molecular hosts	2002JOC6136

An example of application of the [1,3]-dipolar cycloaddition reactions between azides and esters of acetylenedicarboxylic acid in nanotechnology is given in **Scheme 170**. In solutions, molecules of tris(crown ether) **1035** and tris(benzyl azide) **1036**, where R is a large template of C_3 symmetry, are self-assembled into a bundle with benzyl azide groups poking through the crown-ether rings. When di(*tert*-butyl) acetylenedicarboxylate is added, the azide groups are converted to triazoles **1037**, that are too bulky to be pulled out of the crown-ether rings, and the assembly remains permanently mechanically interlocked <2004CEJ1926>.



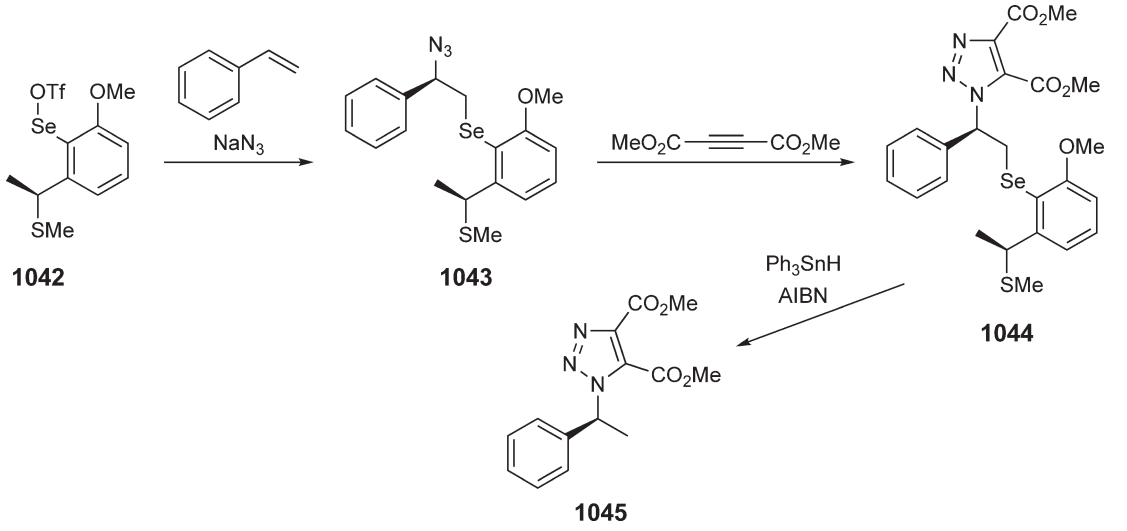
Scheme 170

Reactivity of azides towards acetylenedicarboxylates is very dependent on their electron density (energy HOMO). Thus, strongly electron-deficient 3,5-dicyano-2,4,6-triazidopyridine **1039** reacts slowly with dimethyl acetylenedicarboxylate to give triazole derivative **1038** in 34% yield with most of the starting material recovered unchanged. Under comparable conditions, less electron-deficient 3,5-dichloro-2,4,6-triazidopyridine **1040** reacts with dimethyl acetylenedicarboxylate to provide 2,6-bis(1,2,3-triazol-1yl)pyridine derivative **1041** in 75% yield (**Scheme 171**) <2001CHE861>.



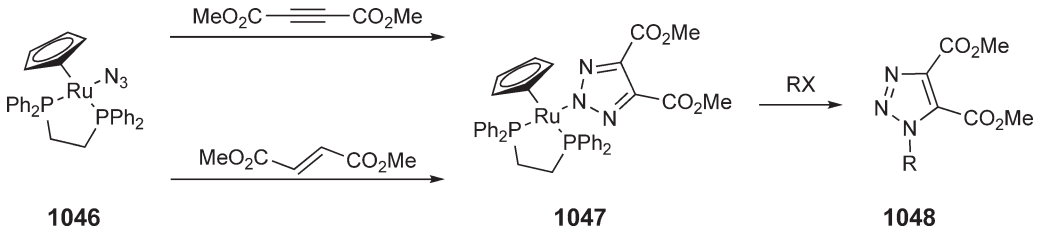
Scheme 171

An example of asymmetric synthesis involving cycloaddition of an azide to dimethyl acetylenedicarboxylate is depicted in **Scheme 172**. Thus, asymmetric auxiliary **1042** reacts with styrene and sodium azide to generate azide **1043** in 90% yield and 94% diastereomeric purity. The following reaction (**Scheme 172**) with dimethyl acetylenedicarboxylate converts azide **1043** into triazole **1044** in 75% yield. Finally, the bond with selenium is cleaved by treatment with triphenyltin hydride and AIBN to furnish triazole **1045** in 80% yield and preserved optical purity (94%) <2003AGE3131>.



Scheme 172

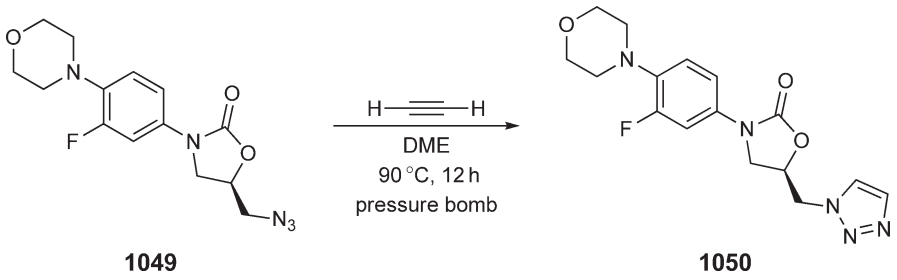
Treatment of ruthenium azido complex **1046** with dimethyl acetylenedicarboxylate in CH_2Cl_2 at room temperature for 24 h results in ruthenium triazole complex **1047** with 90% isolated yield. Surprisingly, product **1047** forms also in reactions of complex **1046** with dimethyl fumarate and dimethyl maleate in comparable yields, but the reactions are slower and require one week for completion. Presumably, the intermediate that forms in cycloaddition of azide **1046** to the double bond of fumarate undergoes consecutive dehydrogenation catalyzed by ruthenium. Treatment with alkylating agents cleaves the ruthenium–nitrogen bond and releases N-1 alkylated triazoles **1048** (**Scheme 173**) <2003OM3107>.



Scheme 173

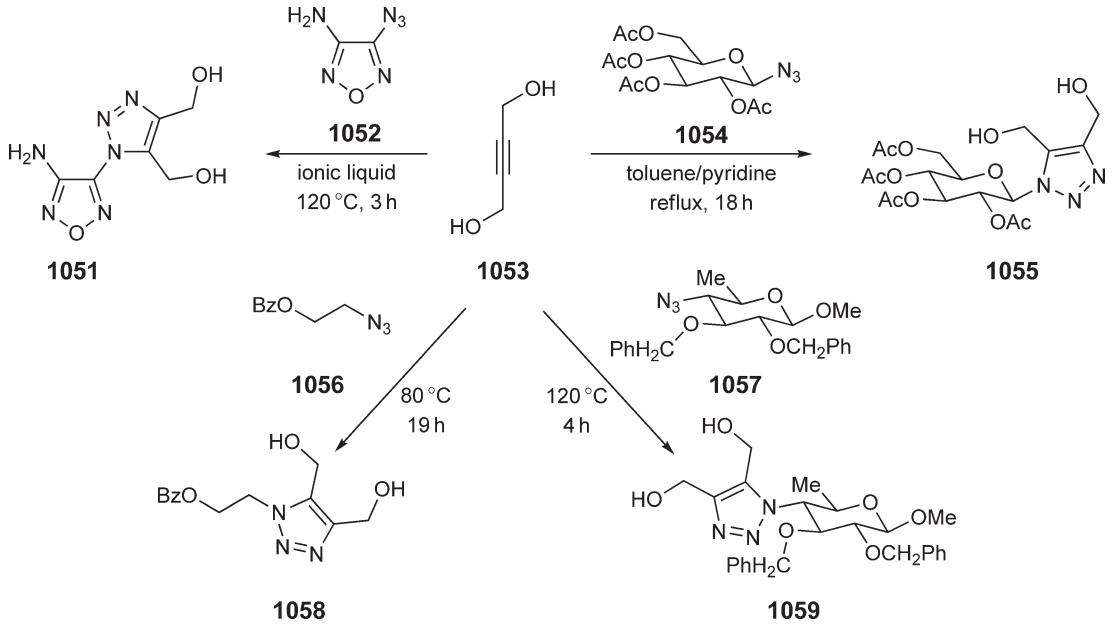
5.01.9.2 From other Symmetrically Substituted Acetylenes

Use of unsubstituted acetylene as a substrate in 1,3-dipolar cycloadditions with azides results in 4,5-unsubstituted triazoles. The reactions have to be carried out under pressure. In an example given in Equation (23) showing synthesis of an antibacterial agent, a solution of azide **1049** in dimethoxyethane is transferred to a pressure bomb that is then charged with acetylene and heated at 90 °C for 12 h to give triazole derivative **1050** in 74% yield <2003BMC35>.



1049 1050 (23)

2-Butyn-1,4-diol **1053** is a common 1,3-dipolarophile used in cycloadditions with azides; however, its reactivity is lower in comparison with esters of acetylenedicarboxylic acid, and the yields of its cycloaddition products are also lower. The advantage of using it in syntheses is direct introduction of two hydroxymethyl groups in positions 4 and 5 of the triazole system that may be useful as anchoring points for assembly of more complex structures. In the first example given in **Scheme 174**, cycloaddition of alkyne **1053** to 3-azido-4-aminofurazan **1052** is carried out in an ionic liquid at 120 °C to give triazole **1051** in 65% yield <2002MC83>.

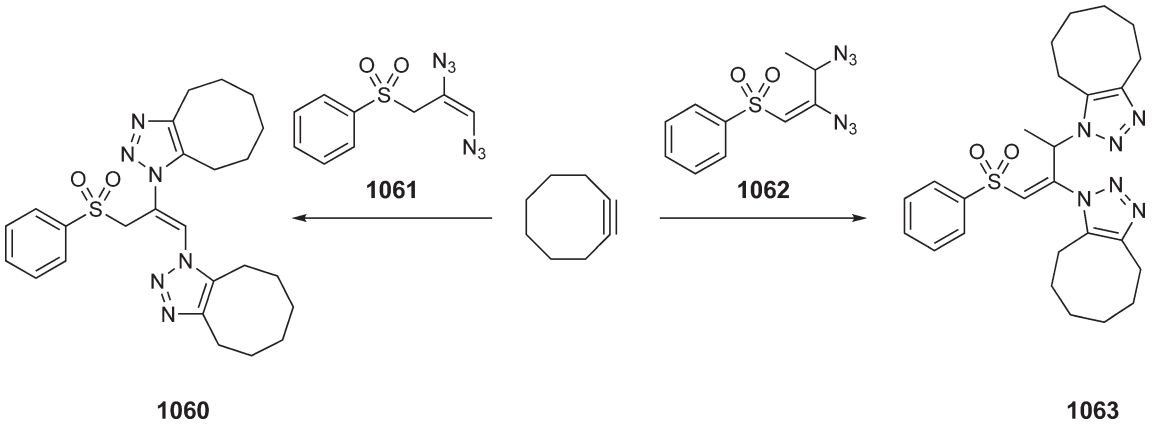


Scheme 174

In the second example, azide **1054** derived from acetylated glucose reacts with alkyne **1053** in refluxing toluene/pyridine mixture to afford triazole derivative **1055** in 38% yield which is used as an intermediate in synthesis of anticancer agents <2002TL4021>. Alternatively, the same final product is obtained when more reactive dimethyl acetylenedicarboxylate is used as the polarophile in cycloaddition with the glucose derived azide, and the carbomethoxy groups are consecutively reduced to hydroxymethyls. However, in the second approach, a different protection of the hydroxy groups in glucose is required adding a couple of additional steps to the process <2002TL4021>.

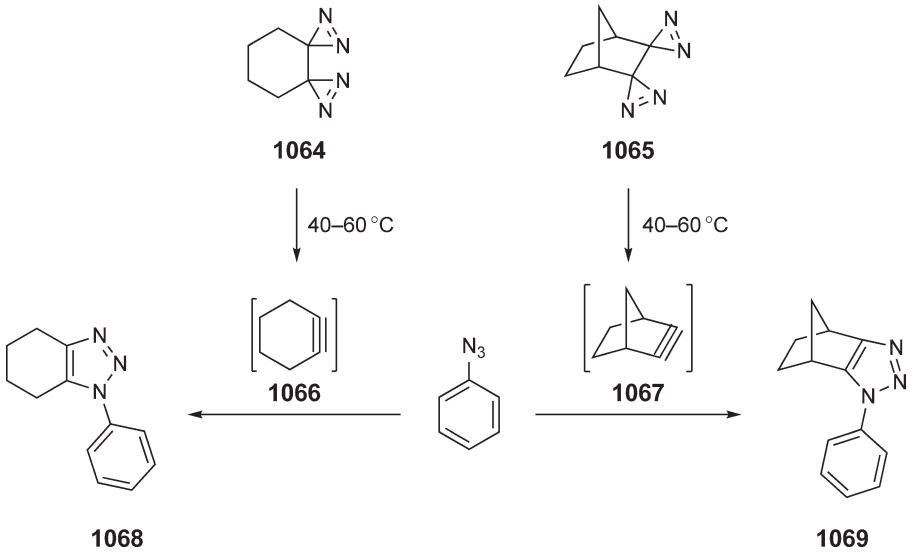
In the third example, the reaction of alkyne **1053** with protected hydroxyethylazide **1056** is carried out by heating a neat mixture of the reagents at 80 °C to give triazole **1058** in 65% yield <2005T9118>. The same neat approach is used in synthesis of sugar derivative **1059** that is obtained in 85% yield from a reaction of alkyne **1053** with protected sugar azide **1057** <2005T9118>.

Due to molecular strain, cyclooctyne is a very reactive species. Its reactions with azides proceed rapidly even at room temperature making it a convenient tool for probing structures of unstable azides. Thus, the reaction of cyclooctyne with diazide **1061** carried out in CH_2Cl_2 at room temperature is accomplished within 2 h and provides ditriazolyl derivative **1060** in 76% yield. A similar reaction of cyclooctyne with diazide **1062** leads to ditriazolyl derivative **1063** in 90% yield (**Scheme 175**) <2005T8904>.



Scheme 175

Scheme 176 represents the opposite situation, with stable phenyl azide used as a probe to trap very reactive and short living alkynes. Thus, diazirine **1064** generates cyclohexyne **1066** that is too reactive to be isolated and characterized. However, when phenyl azide is added to the reaction mixture, it traps species **1066** *in situ* to give triazole **1068** in 84% yield. Similarly, even more strained norbornyne **1067**, generated from diazirine **1065**, is trapped by phenyl azide to afford triazole **1069** in 22% yield <2006AGE309>.

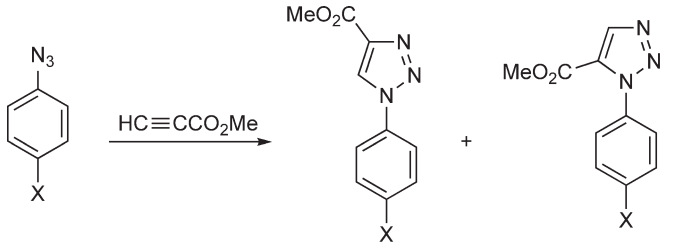


Scheme 176

5.01.9.3 From Nonsymmetrical Acetylenes – Problem of Regioisomers

After acetylenedicarboxylates, esters of propiolic acid are the second common group of reagents for 1,3-dipolar cycloaddition with azides. They react fast, and the yields of products are high. However, because the reacting

partners can approach each other in two ways, two regioisomers are formed, with the 4-alkoxycarbonyl derivative usually strongly predominant. The results of an interesting study investigating influence of substituents in arylazides **1070** on a cycloaddition reaction with methyl propiolate are presented in Equation (24). The reactions are carried out in refluxing CCl_4, and the combined yields of products **1071** and **1072** are 91–96%. To explain product distribution between the regioisomers, authors calculate chemical potential differences between the reactants and energies of their transition states <2003CEJ2770>.

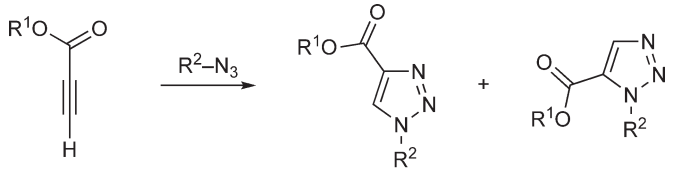


1070 **1071** **1072**

X	1071/1072
H	75:25
Me	73:27
MeO	68:32
F	70:30
Cl	68:32
NO_2	55:45

(24)

Some examples of the reactions between propiolates **1073** and azides leading to triazoles **1074** and **1075** (Equation 25) are collected in **Table 11**. As can be seen (entries 1 and 2), water as a reaction medium can improve the product yield, but it does not improve the regioselectivity. Microwave assisted synthesis (entry 3) can reduce dramatically the reaction time, but the regioselectivity is poor. Larger aliphatic groups in azides do not affect much the reactions (entries 4–7). An interesting novel approach to the problem of regioselectivity represents entry 8 where cycloaddition between 2-aminophenyl azide and ethyl propiolate is carried out in polymer nanocavities imprinted by regioisomer **1074** used as a template. In comparison with a regular reaction carried out in a solvent (entry 9), entry 8 shows a great improvement.



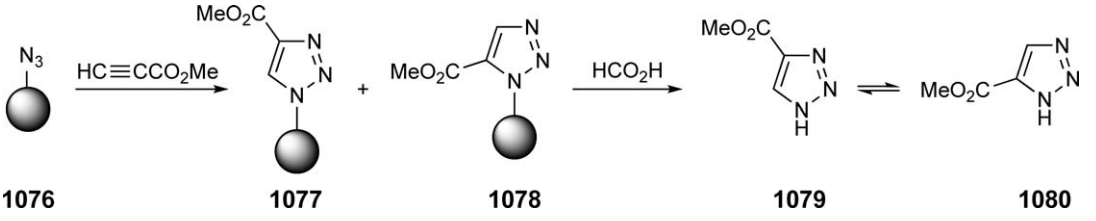
1073 **1074** **1075**

(25)

Table 11 Reactions of propiolates **1073** with azides

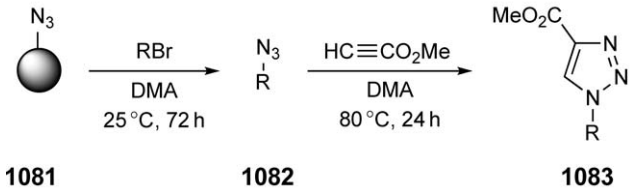
Entry	R^1	R^2	*Reaction conditions*	*Total yield(%)and ratio of* **1074**:**1075**	*Reference*
1	Et	Ph	EtOH, reflux, 8 h	69, 83:17	2004AP156
2	Et	Ph	H_2O, 120 °C, 24 h	90, 85:15	2003CC2450
3	Et	$PhCH_2$	Toluene, μW, 5 min	89, 64:36	2003MDV171
4	Me	$AcO(CH_2)_2OCH_2$	Toluene, reflux, 72 h	66, 92:8	2002JCM264
5	Me	$MeO(CH_2)_2O(CH_2)_2$	Toluene, 65 °C, 48 h	83, 80:20	2005T4983
6	Me	(1*S*,2*S*) $(MeO)_2P(O)$-CH(OH)CH(OBn)CH_2	Toluene, 100 °C, 4 h	98, 80:20	2004TA1457
7	Me	(1*R*,2*S*) $(MeO)_2P(O)$-CH(OH)CH(OBn)CH_2	Toluene, 100 °C, 4 h	100, 86:14	2004TA1457
8	Et	2-NH_2-C_6H_4	Imprinted polymer nanoreactor	94:6	2006JA4178
9	Et	2-NH_2-C_6H_4	In solution	70:30	2006JA4178

In a new approach to the synthesis of 1,2,3-triazoles, polymer supported azide **1076**, based on monomethyl ether of polyethylene glycol with molecular weight of 5000 Da, reacts with methyl propiolate in refluxing toluene to give a mixture of two regioisomeric triazoles **1077** and **1078** in 98% yield. However, the ratio of isomer **1077** to **1078**, 83:17, is not improved and remains comparable to that observed in simple addition of alkyl azides to methyl propiolate. The advantage of this method is high yield of the products and easy separation by precipitation from a solution in diethyl ether. Deprotection from the polymer is easily accomplished by treatment the mixture with formic acid. Both regioisomers give the same monosubstituted product which is a rapidly equilibrating mixture of tautomers **1079** and **1080** (**Scheme 177**) <2003TL1133, 2005T4983>.



Scheme 177

A simple procedure is developed for conversion of aliphatic bromides into methyl 1-alkyl-1,2,3-triazole-4-carboxylates **1083**. In the first step, alkyl bromide reacts with polymer-supported azide **1081** to provide a solution of azide **1082** in DMA. The best results are obtained with Merrifield resin. After the first step, the resin is simply filtered off, and the solution of azide **1082** is used directly in the next step for a reaction with methyl propiolate. In this way, the procedure is significantly simplified, and alkyl azides, that may be explosive in a concentrated form, do not require any additional work-up. As can be seen from the examples given in **Scheme 178**, the yield and purity of products **1083** are high <2003TL2153>.

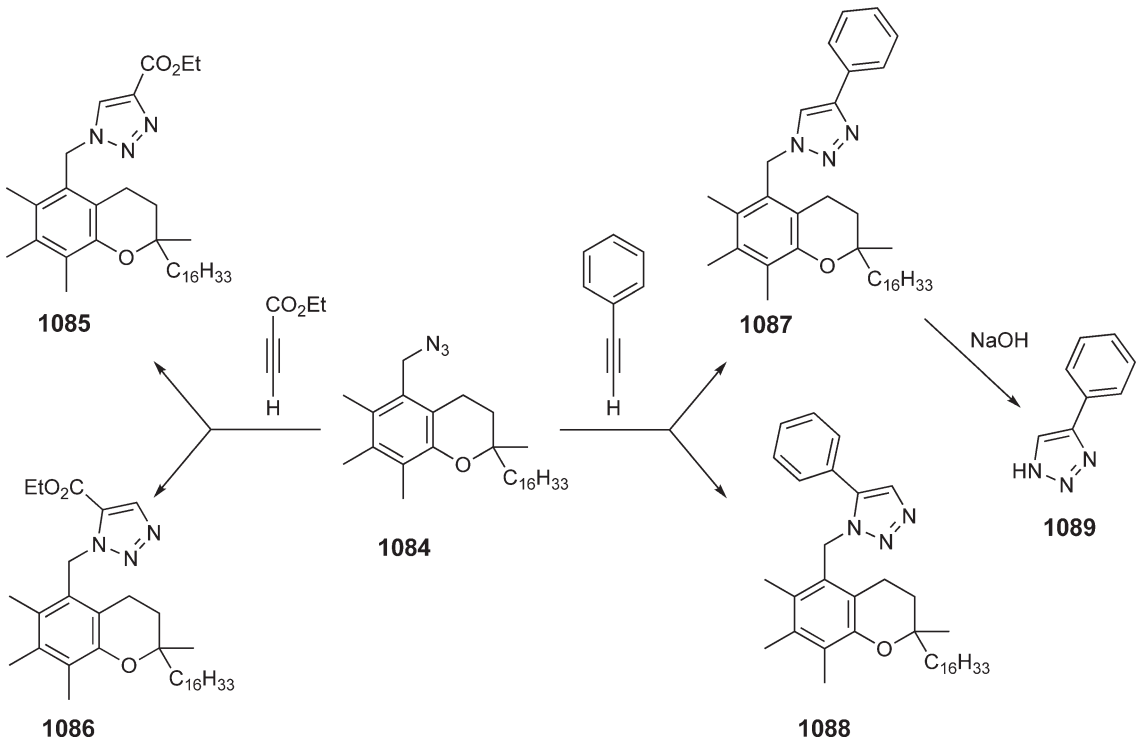


Entry	*R*	**1083** *Yield (%)*	**1083** *Purity (%)*
1	$Me_2CHCH_2CH_2$	73	99
2	c-$C_6H_{11}CH_2CH_2$	99	95
3	$Me_2C{=}CHCH_2$	88	84
4	$MeO_2C(CH_2)_4$	99	85
5	$PhCH_2$	98	97
6	$PhOCH_2CH_2$	100	75

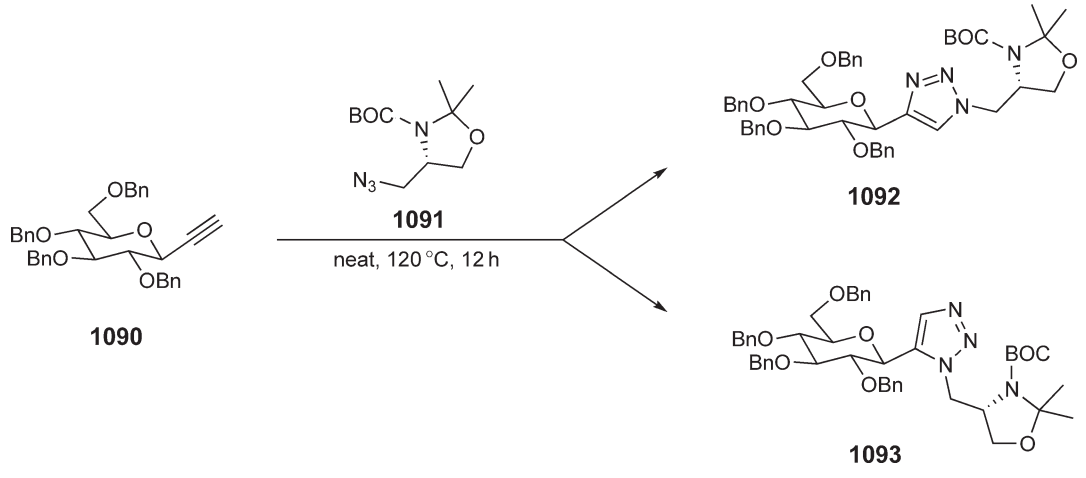
Scheme 178

Regioselectivity in reactions of acetylenes with azides depends strongly on electronic and steric factors of both reagents. Usually less electron-deficient and therefore less reactive acetylenes tend to be less regioselective. To compare reactivity of ethyl propiolate and phenylacetylene, reactions of both with tocopheryl azide **1084** are presented in **Scheme 179**. The reactions are carried out in refluxing toluene for 1–3 d. From the reaction with ethyl propiolate, 1,4-disubstituted triazole **1085** is obtained in 55% isolated yield and 1,5-disubstituted derivative **1086** in 28% yield. For phenylacetylene, the regioselectivity is slightly higher in this reaction, although the isolated yields of products are lower: 52% for derivative **1087** and 18% for isomer **1088**. Hydrolysis of derivative **1087** with 10% NaOH in methanol cleaves the bond with tocopherol releasing 4-phenyl-1,2,3-triazole **1089** <2006EJO2081>.

Not always 1,4-regioisomers are predominant in 1,3-cycloadditions of azides to alkynes. Thus, in preparation of new building blocks for glycopeptides, ethynyl *C*-glucoside **1090** is subjected to a reaction with azide **1091** to give a mixture of triazole derivatives **1092** (32%) and **1093** (48%). For the ethynyl *C*-galactoside analog of **1090**, the ratio between the products is shifted even more towards the 1,5-regioisomer (**Scheme 180**) <2004OL2929>.



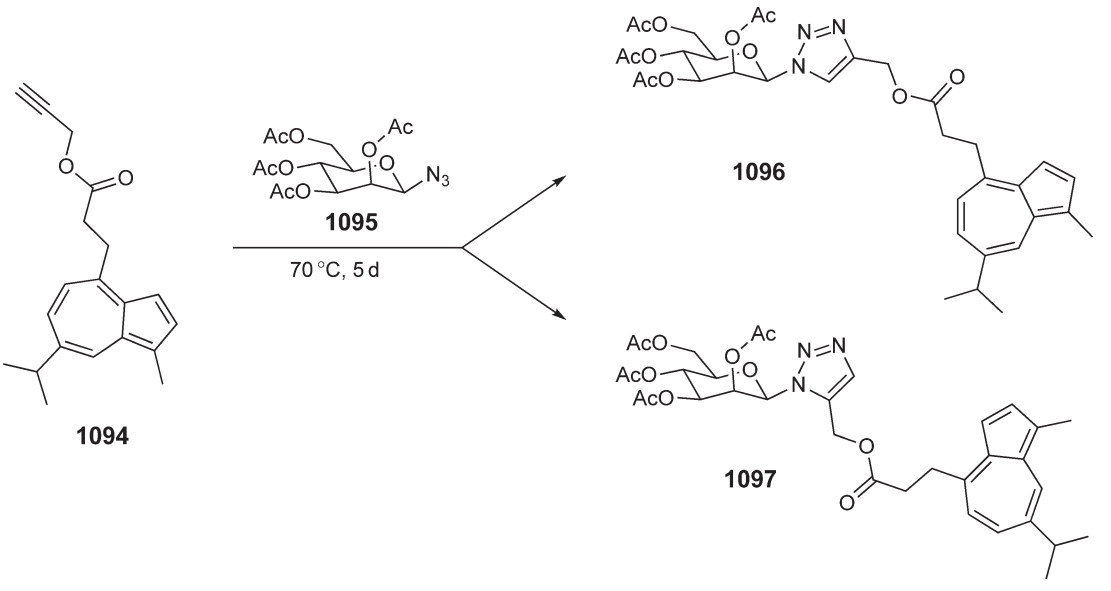
Scheme 179



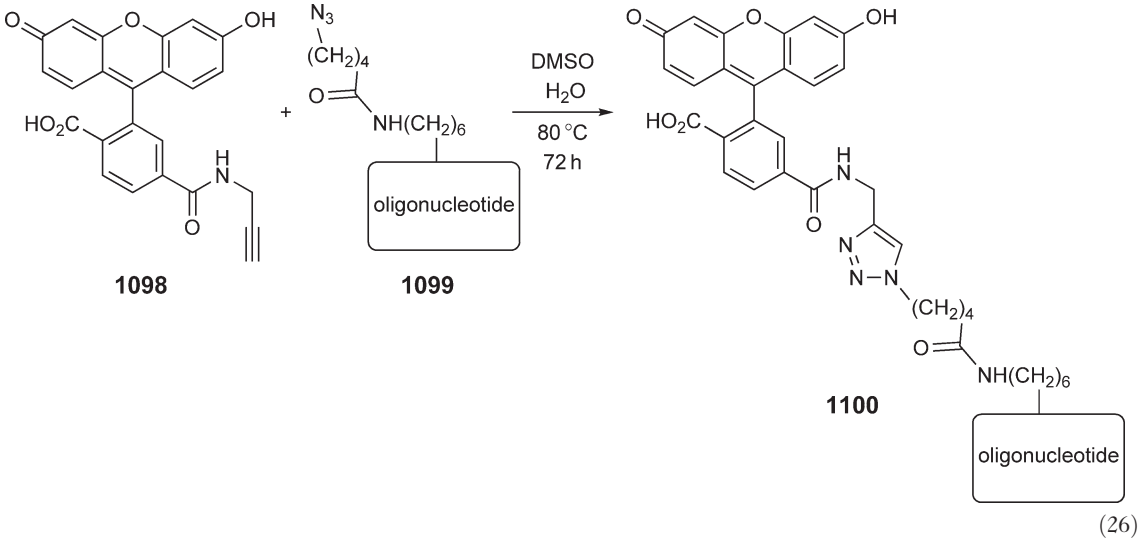
Scheme 180

To facilitate parallel synthesis and purification of triazolyl derivatives of sugars, the products are tagged with an azulene chromophore. For this purpose, guajazulene, an inexpensive azulene, is converted to propargylic ester **1094** and reacted with mannose derivative **1095** to provide a mixture of regioisomers **1096** (44%) and **1097** (32%). Separation of the products can be easily achieved by chromatography because they are visible on the column (**Scheme 181**) <2006EJO1103>.

To facilitate DNA sequencing, oligonucleotides are tagged with fluorophores. For this purpose, azido-labeled DNA **1099** is subjected to a reaction with alkyne **1098**, derived from 6-carboxyfluorescein and propargylamine, to give derivative **1100** (together with its 1,5-regioisomer) in 91% total isolated yield (Equation 26) <2003JOC609>.



Scheme 181

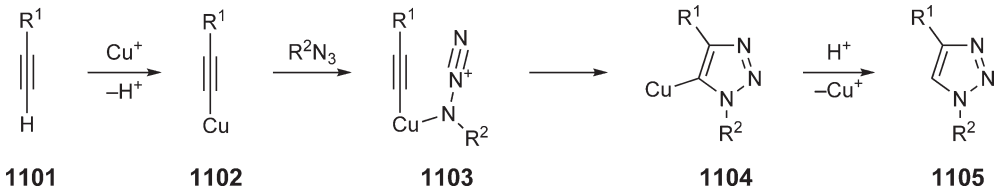


(26)

5.01.9.4 Copper Catalysis in Cycloadditions of Alkynes to Azides

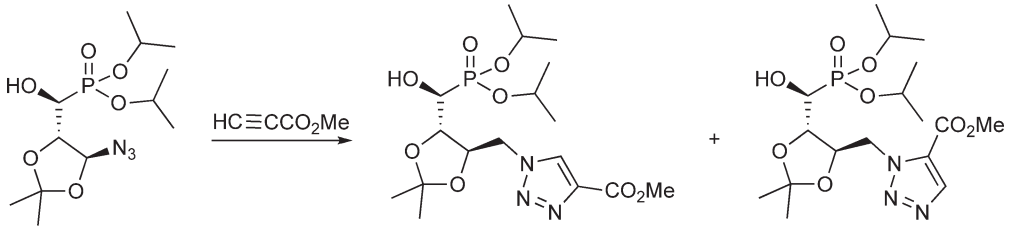
Discovery of copper(I) catalysis in 1,3-dipolar cycloadditions of terminal alkynes to azides in 2002 <2002AGE2596, 2002JOC3057> has revolutionized the field. The so-called 'click chemistry' has become very popular creating a new 'gold rush' resulting in hundreds of scientific publications on the subject. It is not only that the catalyzed reactions proceed faster under mild conditions, but full regioselectivity of the products is achieved as well. Terminal alkynes generate only 1,4-disubstituted triazoles. Some aspects of this new methodology are discussed in a recent review <2007ALD7>.

The fact that only reactions of terminal alkynes with azides are catalyzed by Cu(I) suggests participation of Cu acetylenides in the catalytic process. This conclusion is supported quantum-mechanical calculations of the transition state energies <2005JA210>. Brief outline of the reaction mechanism is given in **Scheme 182**. Thus, alkyne **1101** reacts with Cu^{+} to give copper(I) acetylenide **1102**. In the key step, copper coordinates additionally a molecule of azide to form a complex **1103**. Both entities brought to close proximity undergo facile cycloaddition to give triazole organocopper derivative **1104**. Final exchange with proton generates neutral triazole **1105** and releases the copper catalyst.



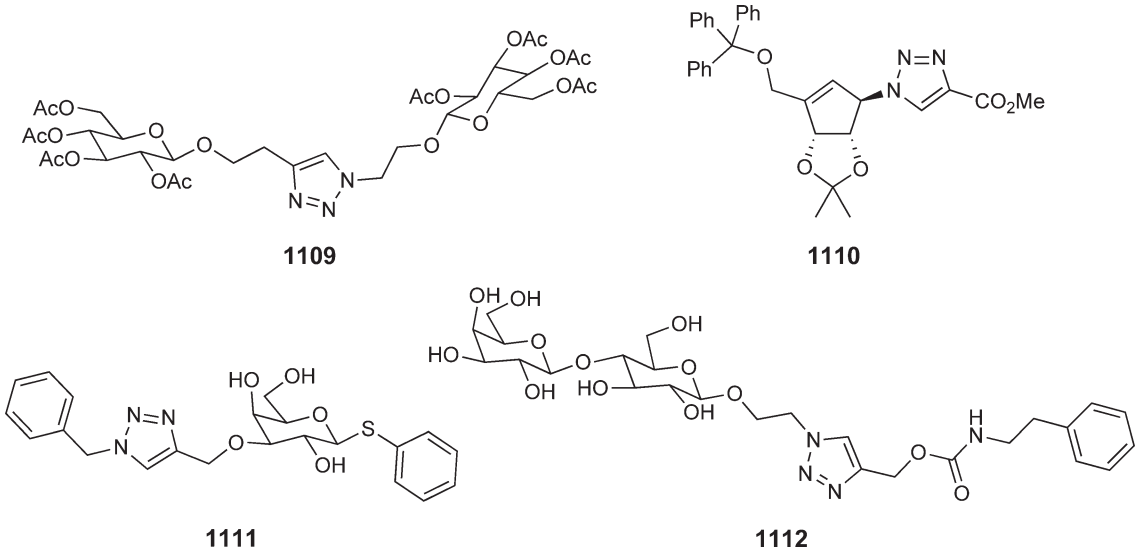
Scheme 182

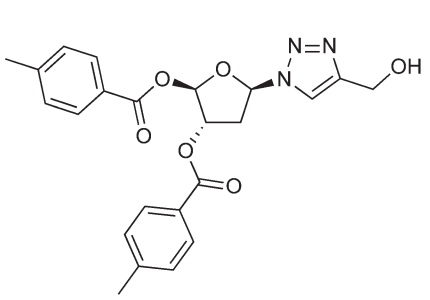
There are many studies comparing thermal and catalytic 1,3-dipolar cycloadditions between alkynes and azides. In an example given in Equation (27), azide **1106** reacts with methyl propiolate in refluxing toluene to give a mixture of regioisomeric triazoles **1107** and **1108** in total yield of 59% and the ratio of 75:25, respectively. The same reaction carried out in water at room temperature with 10 mol% of a CuI catalyst, added as a suspension, results in exclusive formation of regioisomer **1107** with 94% isolated yield (Equation 27) <2005TA4056>.



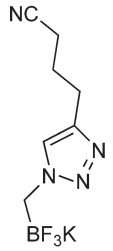
(27)

In one approach to catalytic synthesis of 1,2,3-triazoles, copper(I) is introduced to the reaction mixture as CuI. Compounds **1109–1115** are obtained this way. As can be seen in **Table 12**, a tertiary amine is often added as a base. The reaction conditions are mild and yields of the products are high. In some cases, the reaction can be carried out in water (compound **1115**). For the synthesis of triazole **1116**, addition of Cu powder is enough to generate catalytic amounts of Cu(I).

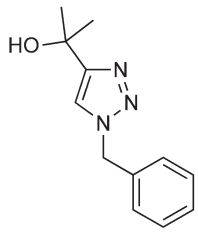




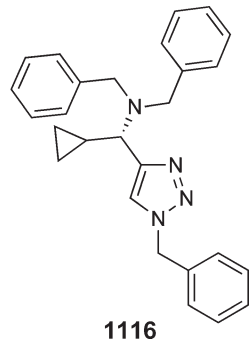
1113



1114



1115

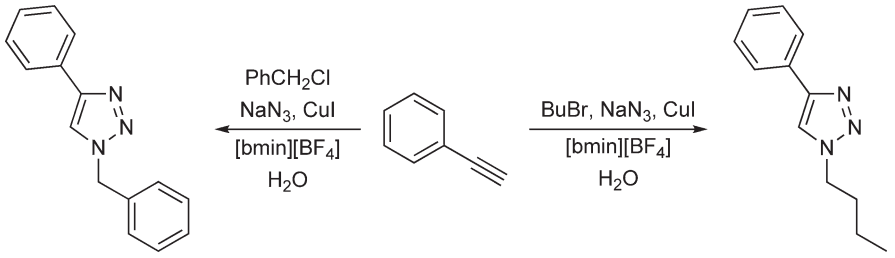


1116

Table 12 Synthesis of triazoles **1109–1116**

Product	*Reaction conditions*	*Yield (%)*	*Purpose of synthesis*	*Reference*
1109	CuI, Pr^i_2NEt, MeCN, rt, 2 h	96	Bioactive glycoconjugates	2006JOC3664
1110	CuI, Et_3N, THF, rt, 12 h	98	Antiviral nucleosides	2006JME1140
1111	CuI, Pr^i_2NEt, THF	97	Inhibitors of galectins-1 and -3	2006CC2379
1112	CuI, Pr^i_2NEt, MeCN, rt, 6 d	80	Inhibitors of galectin-1	2006CAR1353
1113	CuI, Pr^i_2NEt, silica gel, microwave	95	Triazolyl nucleosides	2006TL4807
1114	CuI, DMSO, 80 °C, 1 h	90	Novel organotrifluoro-borates	2006OL2767
1115	CuI, H_2O, rt, 20 h	100	Synthesis of 1,2,3-triazoles in water	2006SL957
1116	Cu powder, BuOH/H_2O (2:1), 40 °C, 24 h	95	Chiral 4-(α-aminoalkyl)-1,2,3-triazoles	2005SL2796

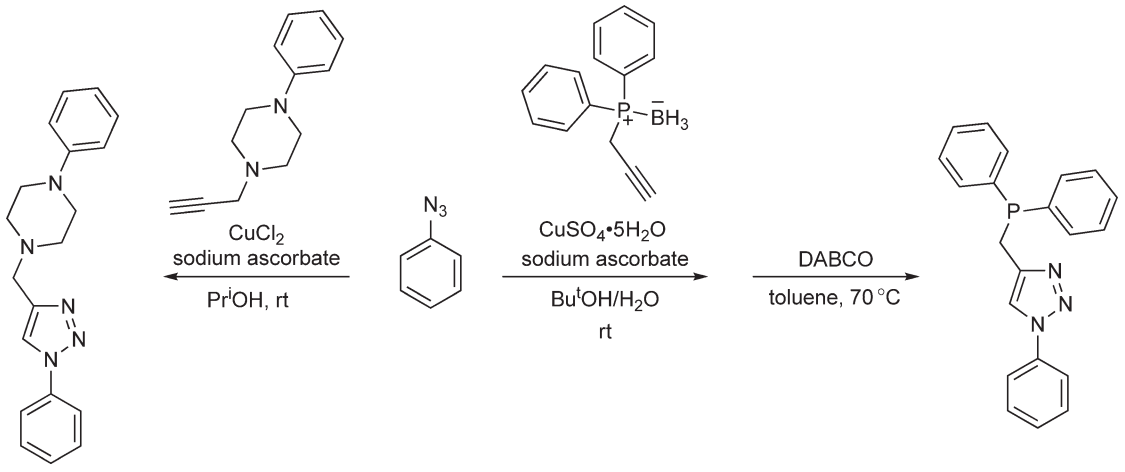
A separate preparation of azides is not always necessary. **Scheme 183** illustrates a case where azides are generated *in situ* from the corresponding halides. The reactions are carried out in ionic liquid–water system. Triazole **1117** is obtained in 94% yield from a reaction carried out at room temperature for 4 h. Butyl derivative **1118** is obtained in 90% yield under similar conditions <2006TL1545>.



1117 1118

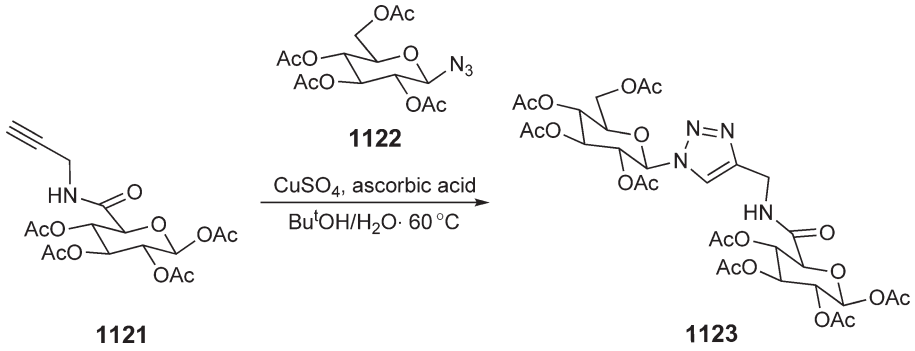
Scheme 183

In another approach, Cu(II) salts which are more soluble and easier to handle are used together with reducing agents to generate catalytic amounts of Cu(I) in reacting mixtures. In the first such example, presented in **Scheme 184**, phenylazide reacts with 1-phenyl-4-propargylpiperazine in isopropanol to give triazole **1119** in 65% yield <2006BML2955>. The reaction is catalyzed by the $CuCl_2$–sodium ascorbate system. In the second example, borane complex with propargyl-diphenylphosphine reacts with phenyl azide in a mixture of *tert*-butanol and water. The reaction is catalyzed by $CuSO_4$–sodium ascorbate and provides triazole derivative **1120**–borane complex in 96% yield. Treatment of the product with DABCO removes borane protection to give free triazole **1120** in 89% yield <2006OL3227>. In one more example of the reaction catalyzed by copper(II)–ascorbic acid system, propargylamide **1121**, derived from protected glucoronic acid, reacts with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **1122** to give triazole derivative **1123** in 91% yield (Equation 28) <2006CAR1081>.



1119 **1120**

Scheme 184

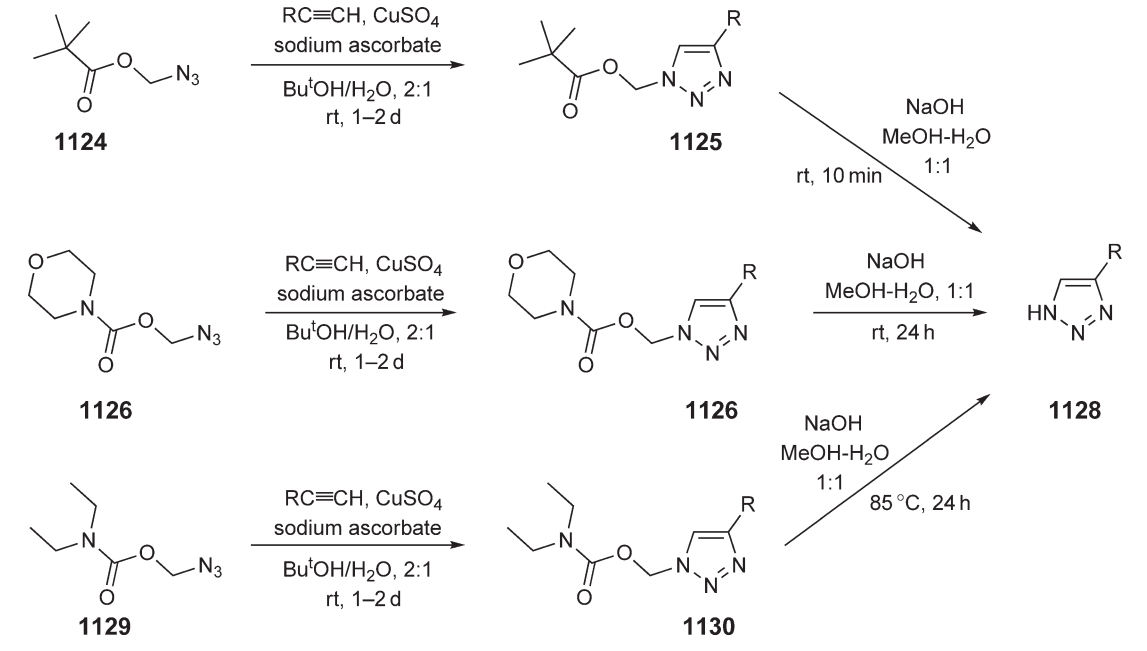


1121 **1122** **1123**

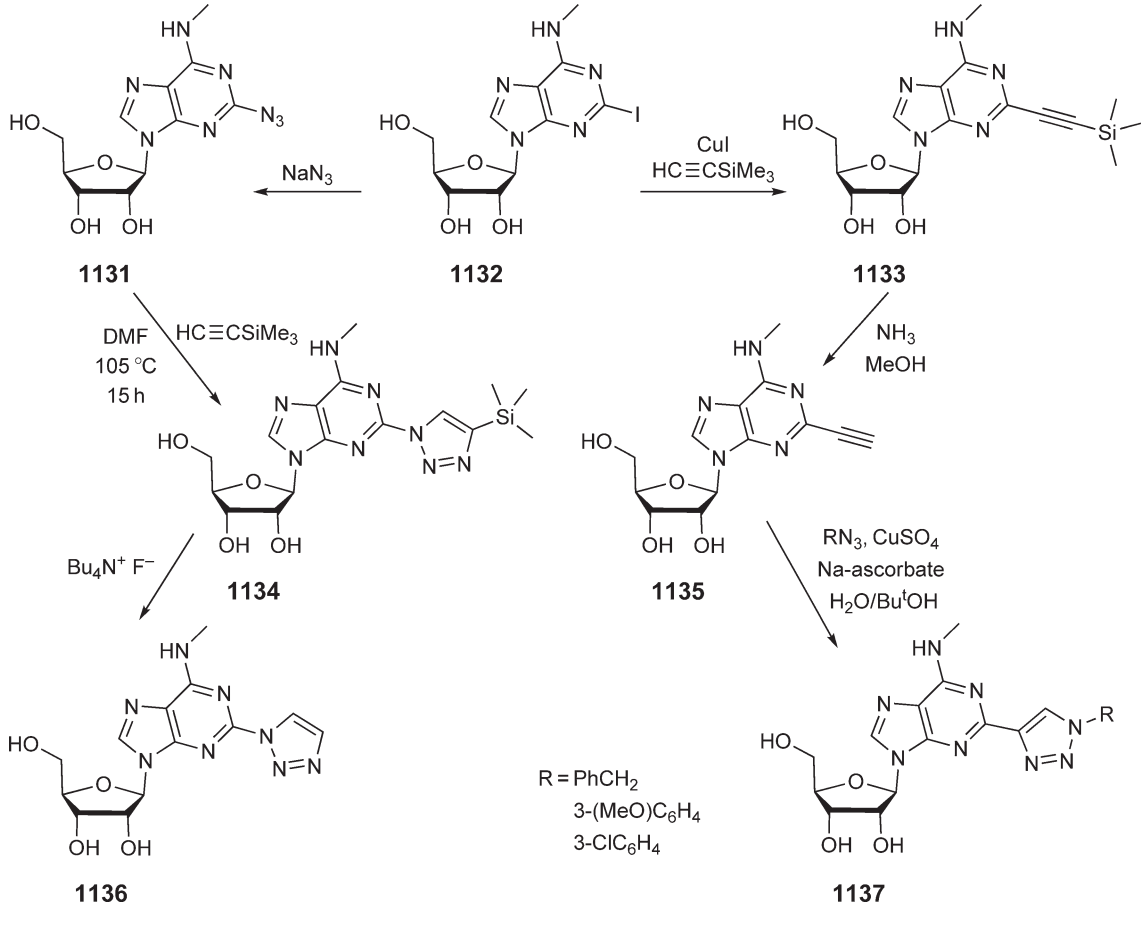
(28)

To obtain N-unsubstituted triazoles by this method, readily available azidomethyl *tert*-butyrate **1124** or carbamates **1126** and **1129** are treated with alkynes to provide triazolyl derivatives **1125**, **1127**, or **1130**, respectively. The N-protecting groups can be easily removed by treatment with NaOH to give monosubstituted triazoles **1128**. Compound **1125** is very sensitive to bases and loses its protecting group after 10 min treatment with 2.2 molar equivalents of NaOH in methanol–water. Deprotection of derivative **1127** is much slower under these conditions, and deprotection of **1130** requires heating at 85 °C. For base sensitive groups R, use of protection **1125** gives the best results. However, in other cases, more stable protections **1127** and **1130** provide better yield of products **1128** (**Scheme 185**) <2005SL2847>.

(Trimethylsilyl)acetylene is a versatile reagent in triazole synthesis. Two ways of its application in synthesis of adenosine agonists are depicted in **Scheme 186** <2006JME7373>. Thus, iodide **1132** is first treated with sodium azide to be converted to azide **1131**. Thermal cycloaddition of (trimethylsilyl)acetylene to azide **1131** gives C-silylated triazole **1134** (and possibly its regioisomer). Regioselectivity in this reaction is not important because the trimethylsilyl group is subsequently removed by treatment with tetrabutylammonium fluoride to give triazol-1-yl derivative **1136** without additional substituents on the ring. Alternatively, iodide **1132** is treated with (trimethylsilyl)acetylene in the presence of CuI and a palladium–phosphine complex as a catalyst to give (trimethylsilyl)ethynyl derivative **1133**. Removal of the silyl protection by treatment with methanolic ammonia to give compound **1135** followed by regular cycloadditions with benzyl azides, catalyzed by $CuSO_4$–sodium ascorbate, furnishes triazolyl derivatives **1137** in 73–80% yield.



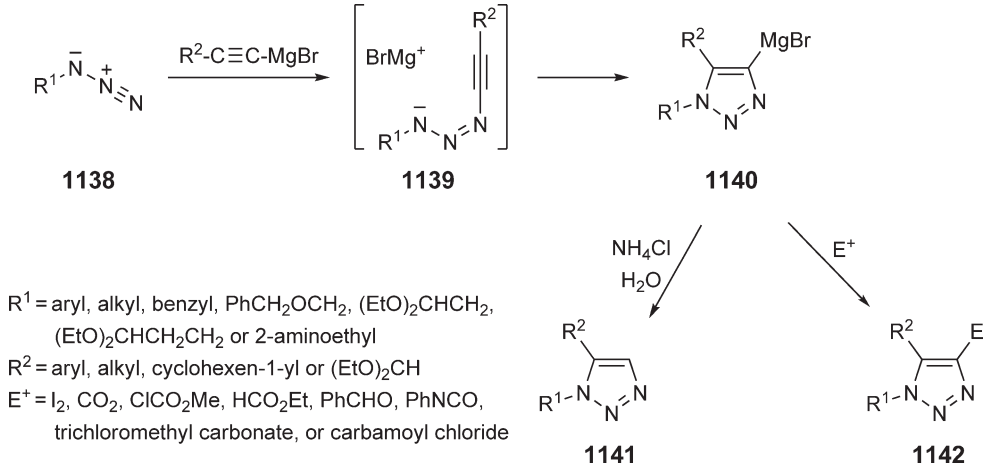
Scheme 185



Scheme 186

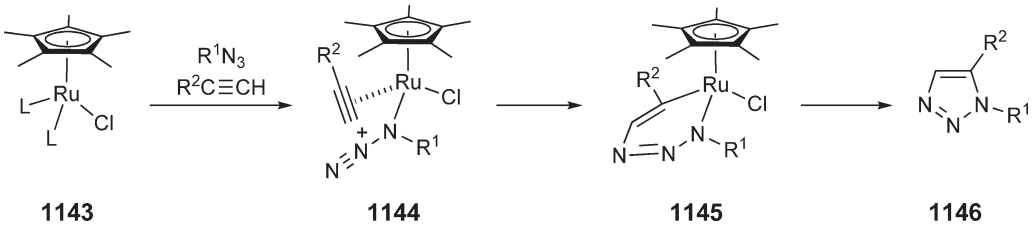
5.01.9.5 Reverse Regioselectivity

1,5-Disubstituted 1,2,3-triazoles are the minor products of thermal cycloaddition of terminal alkynes to azides, and they are completely absent when the reactions are catalyzed by Cu(I). However, under strongly basic conditions, when magnesium or lithium acetylenides are used as the substrates, reverse regioselectivity is observed, and 1,5-disubstituted triazoles are separated as the only products. The proposed mechanism begins with a nucleophilic attack of the alkyne anion on the terminal nitrogen atom of azide **1138**. The resulting intermediate anion **1139** undergoes spontaneous cyclization to organomagnesium derivative **1140**. Work-up with aqueous ammonium chloride furnishes 1,5-disubstituted triazoles **1141**. When instead of work-up, the reaction mixture is treated with an electrophile, 1,4,5-trisubstituted triazoles **1142** are obtained (**Scheme 187**) <2004OL1237>. The reactions are typically carried out in THF at room temperature. In the case of more reactive azides with electron-deficient groups R^1, the reactions are exothermic and can be accomplished in less then 1 h. Less reactive azides require longer, 1 d, time to completion. The yields are high to quantitative <2004OL1237, 2005OL4907, 2006JOC3928>.



Scheme 187

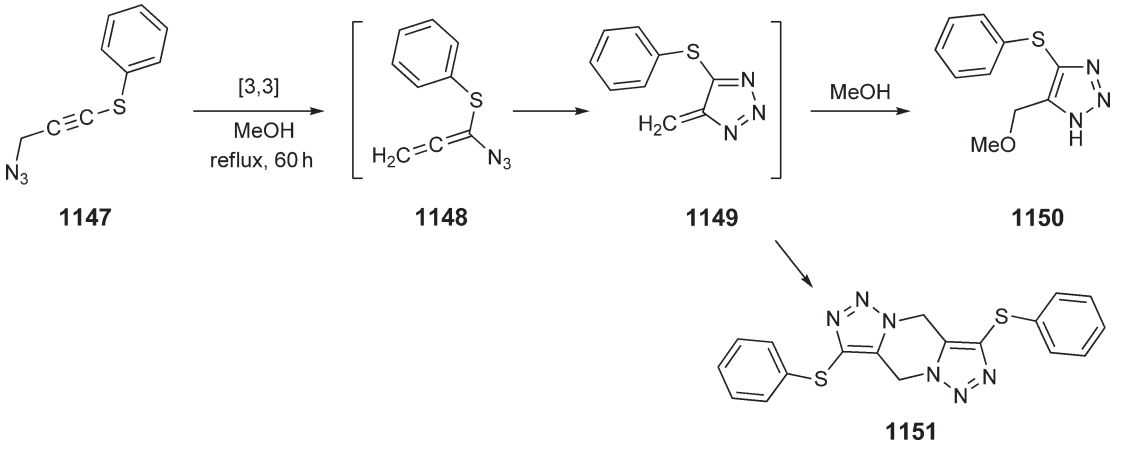
According to the recent finding <2005JA15998>, catalysis by ruthenium complexes used in 1 mol% amounts leads also exclusively to 1,5-disubstituted 1,2,3-triazoles. The reactions, carried out in benzene or dioxane, are relatively fast (typically 2–4 h) and high yielding (80–94%). The method tolerates groups that may not be compatible with organomagnesium reagents. Contrary to the copper(I) catalysis, this method works also well with disubstituted acetylenes to provide 1,4,5-trisubstituted 1,2,3-triazoles. The suggested mechanism <2005JA15998> is presented in **Scheme 188**. Simultaneous replacement of two ligands in ruthenium catalyst **1143** (e.g., triphenylphosphine) by the azide and alkyne molecules generates active transition state **1144** promoting bond formation between the terminal atoms of the new ligands to give a six-membered ruthenocycle **1145**. Finally, formation of the second bond between the reacting partners releases a molecule of triazole **1146** and recycles the catalyst.



Scheme 188

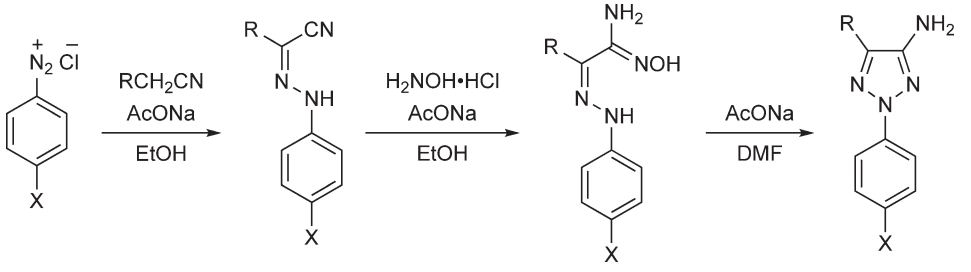
5.01.9.6 Other Synthetic Methods for 1,2,3-Triazoles

Heated in methanol for an extended period of time, propargyl azide **1147** experiences a [3,3] sigmatropic shift to allenyl azide **1148** that undergoes rapid cyclization to triazafulvene **1149**. Addition of a molecule of methanol converts reactive intermediate **1149** to triazole **1150** that is isolated in 68% yield. In concentrated solutions, two molecules of intermediate **1149** may undergo cycloaddition to form dimer **1151** as a side product (**Scheme 189**) <2005EJO3704>.



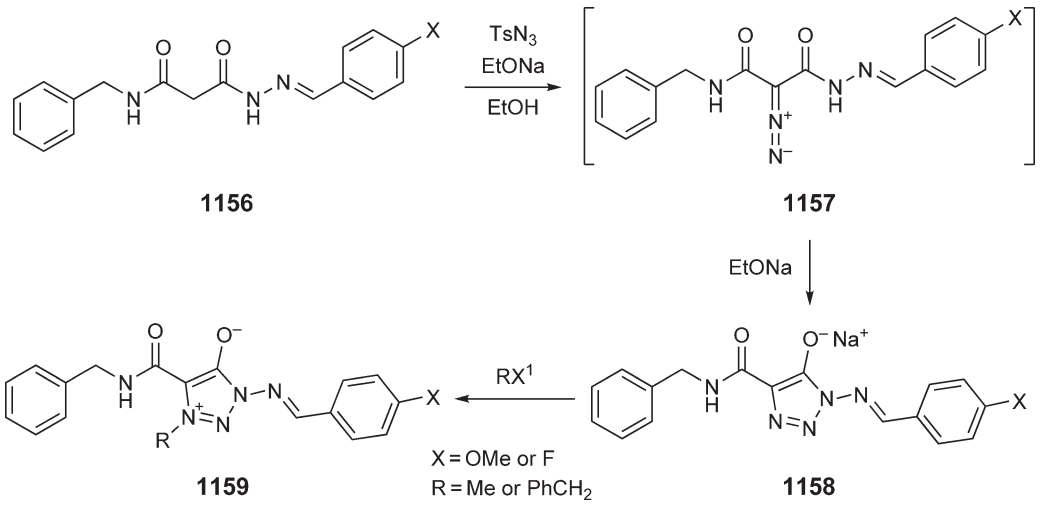
Scheme 189

Condensation of diazonium salts **1152** with activated nitriles provides hydrazones **1153**. Treatment of hydrazones **1153** with hydroxylamine affords amidoximes **1154** in high yield. Upon heating with anhydrous sodium acetate in refluxing DMF, compounds **1154** undergo intramolecular cyclocondensation to provide 5-substituted 4-amino-2-aryl-2*H*-1,2,3-triazoles **1155** in 75–85% yield (**Scheme 190**) <2006ARK(xv)53>.



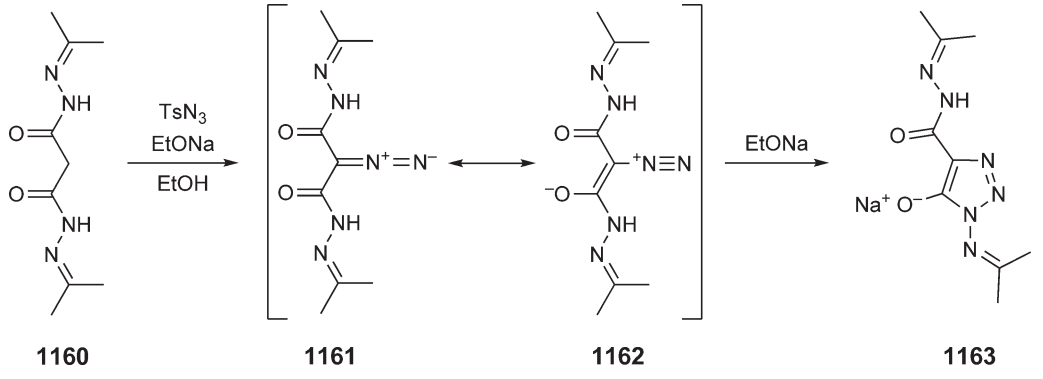
Scheme 190

Upon heating with tosyl azide and sodium ethoxide in ethanol, amidohydrazides **1156** derived from malonic acid are converted into diazo compounds **1157**. Under the reaction conditions, derivatives **1157** undergo cyclization to triazoles **1158**. Salts **1158** are isolated in good yield (52% for X = OMe and 82% for X = F). Methylation and benzylation of products **1158** occurs selectively on the triazole N-3 atom giving rise to mesoionic systems **1159** (**Scheme 191**) <2002J(P1)211>. Under similar reaction conditions, dihydrazide **1160** is converted to triazole **1163** via intermediate diazo derivative **1161** (**Scheme 192**) <2004T5367>. Resonance form **1162** and others with definitely positive charge on the diazo nitrogen atoms seem to be responsible for the cyclization.



1156 1157 1158 1159

Scheme 191



1160 1161 1162 1163

Scheme 192

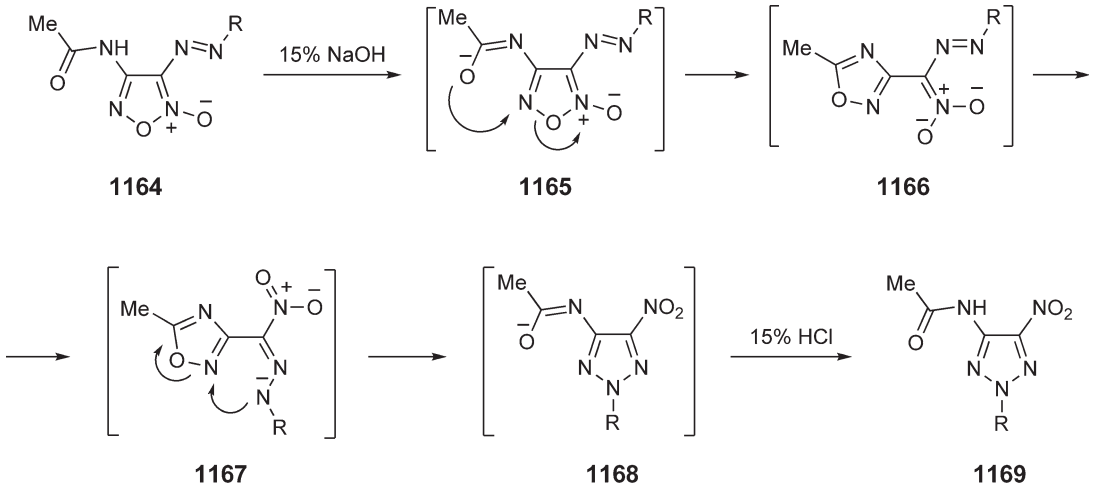
5.01.10 Ring Syntheses by Transformation of Other Rings

5.01.10.1 1,2,3-2H-Triazoles from 1,2,5-Oxadiazoles

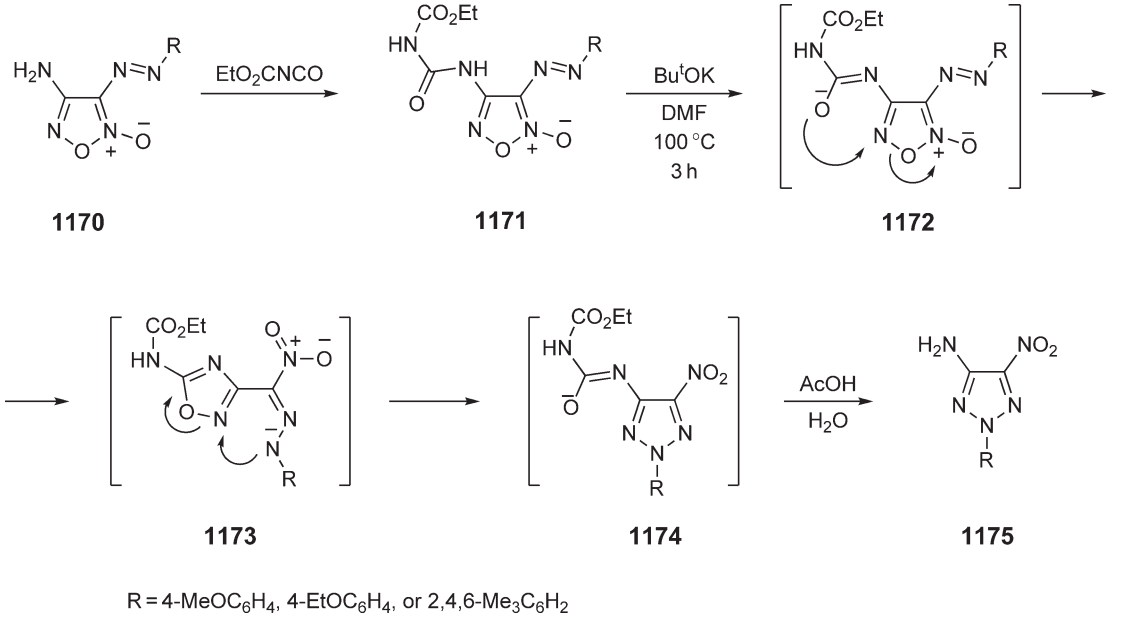
Treatment of 4-acetamido-3-arylazo-1,2,5-oxadiazole 2-oxides (furoxans) **1164** with aqueous NaOH results in formation of 4-acetamido-2-aryl-5-nitro-2*H*-1,2,3-triazoles **1169**. According to the proposed mechanism, the anion derived from the acetamido group attacks N-5 of the furoxan system (form **1165**) causing ring opening and formation of another oxadiazole ring (form **1166**). Rotation of the large substituent at C-3 in oxadiazole **1166** brings the arylazo group to proximity of the ring (form **1167**). In the following step, which is reverse to that shown as form **1165**, an intramolecular attack of the arylazo group on oxadiazole **1167** causes ring opening with release of the acetamido group and formation of a new ring (form **1168**). Acidification with hydrochloric acid stabilizes the system as triazole derivative **1169**. This cascade rearrangement is fast (20 min at room temperature) and provides triazoles **1169** in 54–62% yield (**Scheme 193**) <2001MC230>.

Reaction of amines **1170** with ethoxycarbonyl isocyanate, carried out in ethyl acetate at −20 °C, provides 3-arylazo-4-(3-ethoxycarbonylureido)furoxans **1171** in 82–86% yield. Compounds **1171** are much less reactive than their acetamido analogs **1164**. To promote a cascade rearrangement similar to that depicted in **Scheme 193**, furoxans **1171** have to be heated with potassium *tert*-butoxide in DMF. The probable reason for reduced reactivity of anion **1172** is the fact that it can exist in several tautomeric and resonance forms rendering the carbonyl oxygen atom less nucleophilic. However, at 100 °C, a nucleophilic attack of the oxygen atom on N-5 of the furoxan system results in its ring opening and formation of a new ring of oxadiazole **1173**. By rotation of the substituent at C-3, the arylazo group comes to a suitable position for

nucleophilic attack on N-2 resulting in opening of the oxadiazole ring and formation of triazole **1174**. During work-up, even under very mild conditions, the ureido group is hydrolyzed and 3-amino-2-aryl-4-nitro-2*H*-1,2,3-triazole **1175** is obtained. Compounds **1175** are isolated in 45–65% yield (**Scheme 194**) <2003RCB1829>.

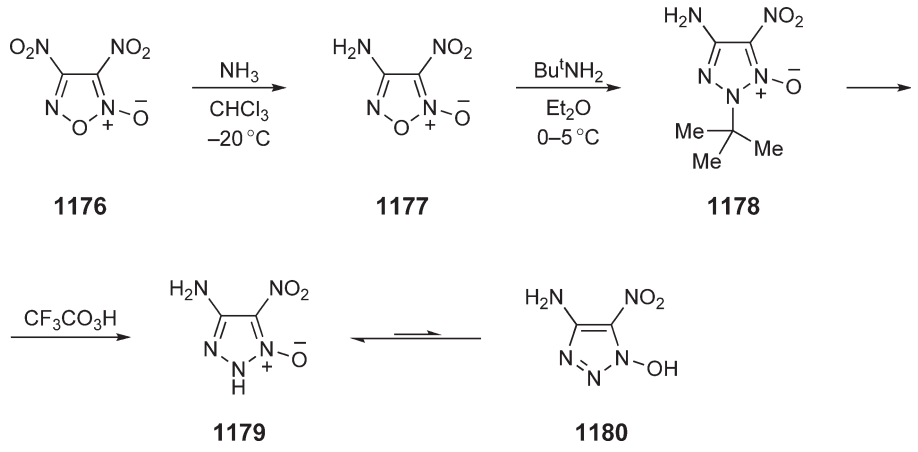


Scheme 193



Scheme 194

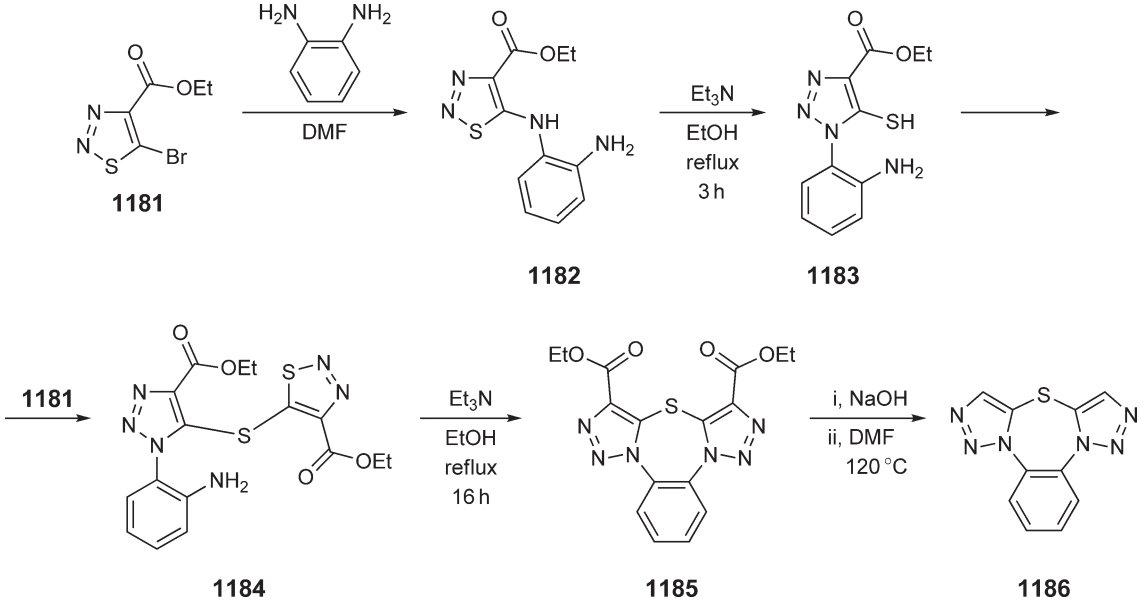
Substitution of the 4-nitro group in 3,4-dinitrofuroxan **1176** by ammonia occurs readily, even at low temperature. Subsequent treatment of the obtained amine, product **1177**, with *t*-butylamine results in formation of 4-amino-2-(*t*-butyl)-5-nitro-1,2,3-triazole 1-oxide **1178**. However, there must be some additional side products in the reaction mixture, as the isolated yield of compound **1178** is only 17%. Upon treatment with trifluoroperacetic acid, the *t*-butyl group is removed. The obtained triazole system can exist in two tautomeric forms, **1179** and **1180**; however, the 1-oxide form **1179** is strongly favored (**Scheme 195**) <2003CHE608>.



Scheme 195

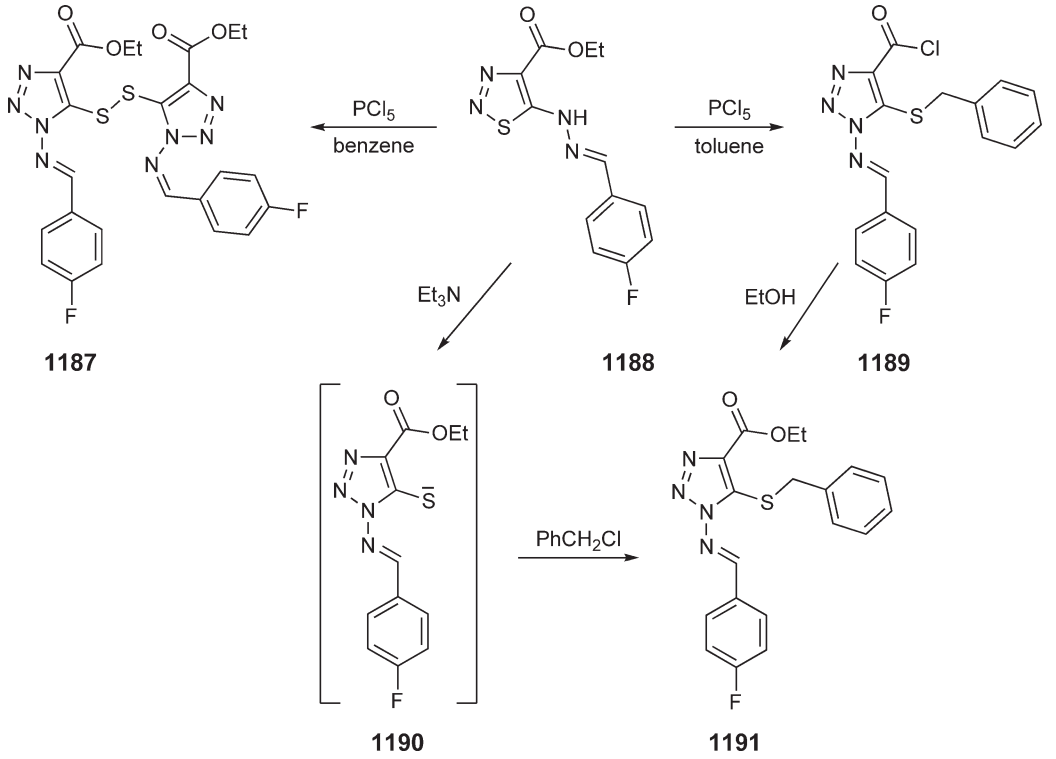
5.01.10.2 1,2,3-1H-Triazoles from 1,2,3-Thiadiazoles

In a reaction with *ortho*-phenylenediamine, carried out in DMF at room temperature, ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate **1181** is converted to ethyl 5-[(2-aminophenyl)amino]-1,2,3-thiadiazole-4-carboxylate **1182** with 76% yield. Upon treatment with a mild base, amine **1182** undergoes Dimroth rearrangement to 5-mercapto-1,2,3-triazole **1183** (isolated in 93% yield). In a reaction with second molecule of bromide **1181**, mercaptan **1183** is converted to sulfide **1184** (93% yield). Treatment of derivative **1184** with Et_3N in refluxing ethanol leads to a nucleophilic attack of the amino group on the thiadiazole ring resulting in elimination of hydrogen sulfide and formation of the second benzotriazole ring. Benzothiadiazepine **1185** obtained this way is isolated in 54% yield. Hydrolysis of the carbethoxy groups in derivative **1185** followed by decarboxylation of the obtained acid furnishes di[1,2,3]triazolo[1,5-*a*:5′1′-*d*][3,1,5]benzothiadiazepine **1186** (**Scheme 196**) <2002J(P1)1574>.



Scheme 196

Treatment of 1,2,3-thiadiazole derivative **1188** with PCl_5 in refluxing benzene results in formation of the 1,2,3-triazol-5-yl disulfide **1187**. The reaction must proceed by Dimroth rearrangement of the thiadiazole ring followed by oxidation of the obtained thiol, possibly with PCl_5. However, when the reaction is carried out in refluxing toluene, triazole derivative **1189** is obtained instead (isolated yield 65%). In this case, apart of Dimroth rearrangement of the starting material, a reaction of PCl_5 with the solvent generates benzyl chloride that benzylates the thiol group. Hydrogen chloride released in this reaction converts the ethoxycarbonyl group into an acid chloride function in product **1189**. To prove the structure of derivative **1189**, it is converted to ester **1191**, which appears to be the same compound as the product obtained by regular Dimroth rearrangement of thiadiazole **1188** catalyzed by Et_3N followed by treatment of intermediate **1190** with benzyl chloride (**Scheme 197**) <2003CHE126>.

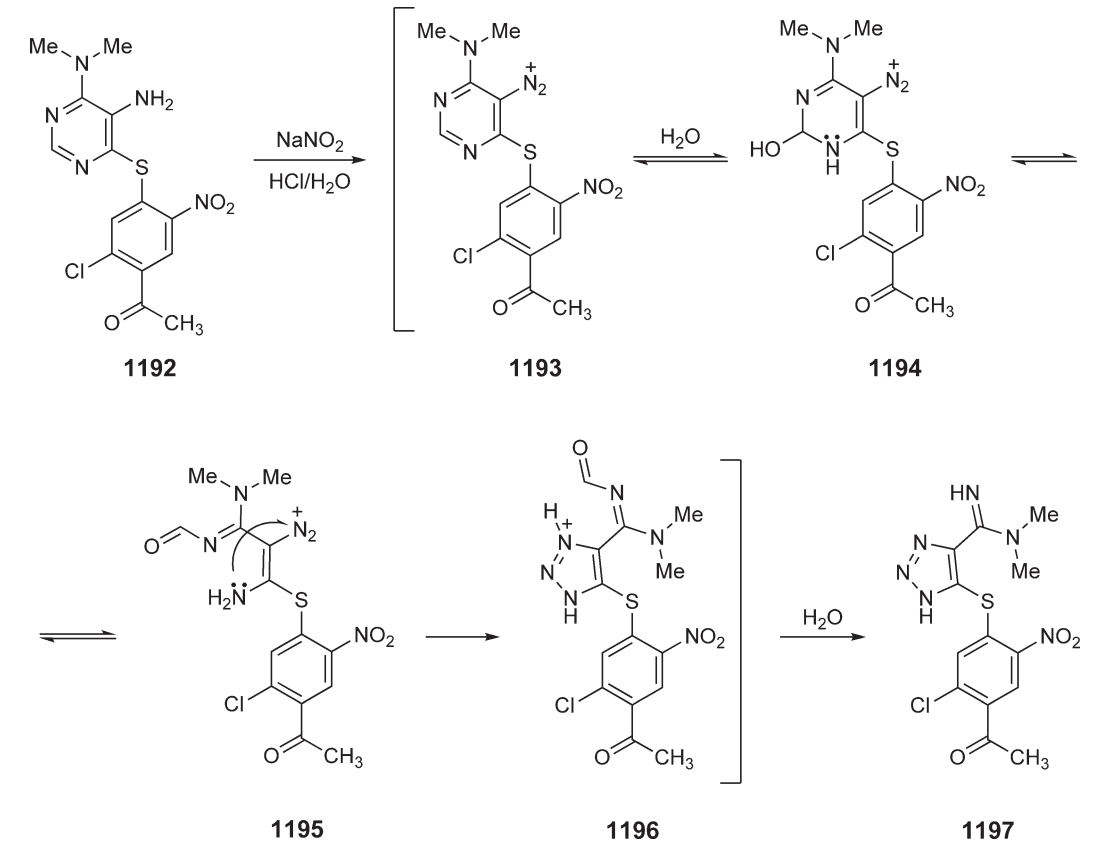


Scheme 197

5.01.10.3 1,2,3-Triazoles from Pyrimidine Derivatives

Diazotization of the 5-aminopyrimidine **1192** gives the diazonium cation **1193**. Due to strong electron deficiency at C-2 of the pyrimidine system, species **1193** exists partially as the covalent hydrate **1194**. Under acidic conditions, the 1,2-dihydropyrimidine ring of intermediate **1194** can be easily opened. One of such open forms is structure **1195**. Among many tautomeric forms of species **1195**, there are structures with a single bond between the carbon atoms, which allow free rotation to bring the NH_2 and N_2^+ groups to close proximity. Nucleophilic intramolecular attack of the amine N atom on the diazonium group leads to triazolyl derivative **1196**. In the aqueous hydrochloric acid reaction medium, **1196** is hydrolyzed to (1,2,3-triazol-4-yl)amidine **1197** (**Scheme 198**) <2003PCJ298>.

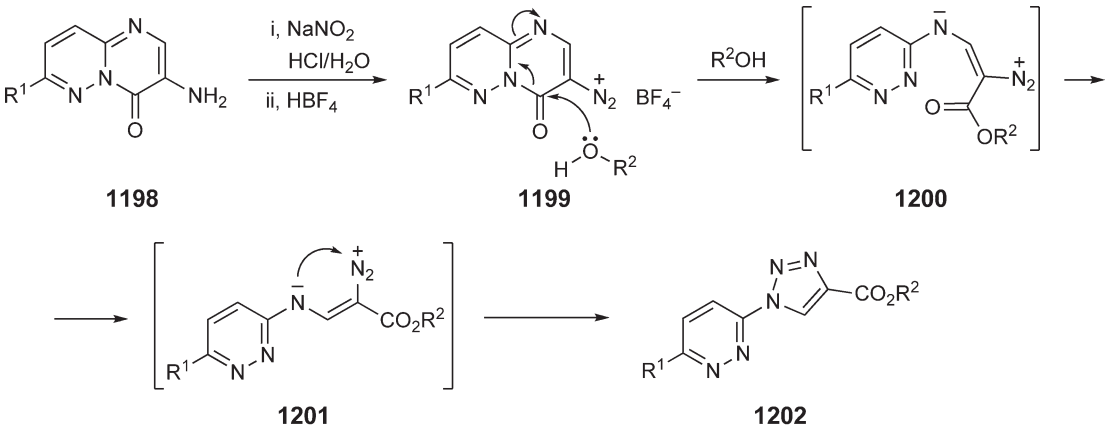
As shown in **Scheme 199**, the 5-aminopyrimidine structure may be also incorporated into a more complex bicyclic system. Thus, diazotization of 3-amino-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazines **1198** followed by treatment with 50% aqueous tetrafluoroboric acid results in precipitation of salts **1199**. When heated with alcohols, nucleophilic attack on the carbonyl group opens the pyrimidine ring. The obtained species **1200** assume conformation **1201** that is more suitable for bond formation between the opposite charged nitrogen atoms. Alkyl 1-(pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates **1202** are obtained in 31–66% yield <2002ARK(viii)143>.



1192 1193 1194

1195 1196 1197

Scheme 198



1198 1199 1200

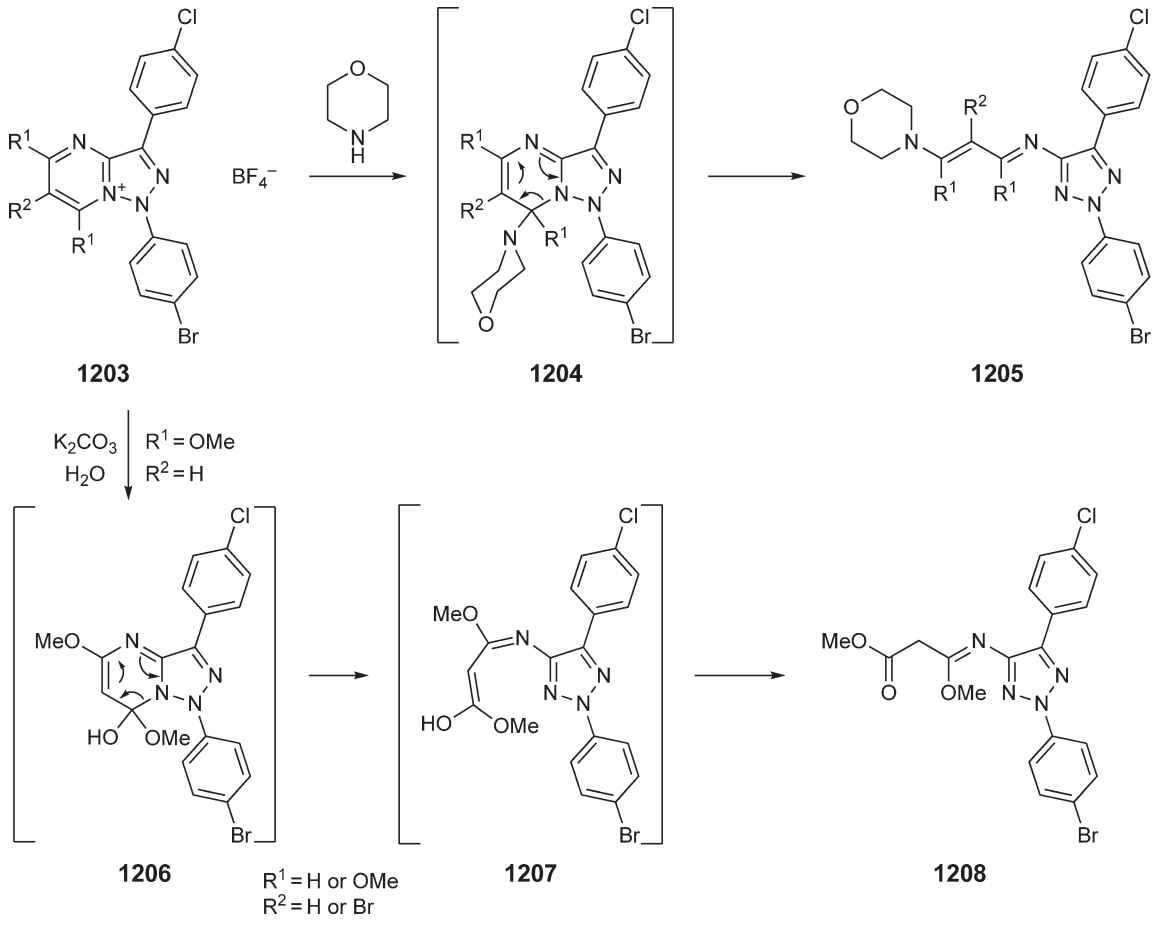
1201 1202

R^1 = H or Ph

R^2 = Me, Et, Pr^n, Bu^n, or *n*-pentyl

Scheme 199

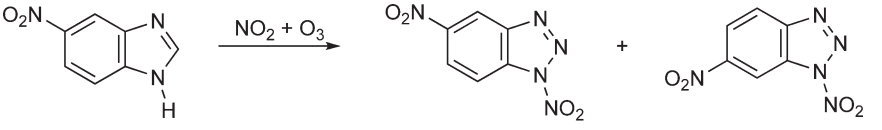
A nucleophilic attack of morpholine on the pyrimidine ring in 1,2,3-triazolo[1,5-*a*]pyrimidinium salts **1203** leads to unstable intermediates **1204**. Spontaneous opening of the pyrimidine ring results in formation of 1,2,3-triazole derivatives **1205** that are isolated in 80–85% yield. A similar nucleophilic attack of the hydroxide anion (from aq. K_2CO_3) on dimethoxy derivative **1203** provides transition species **1206** that opens to intermediate **1207**, and finally tautomerizes to ester **1208**, isolated in 87% yield (**Scheme 200**) <2003T4297>.



Scheme 200

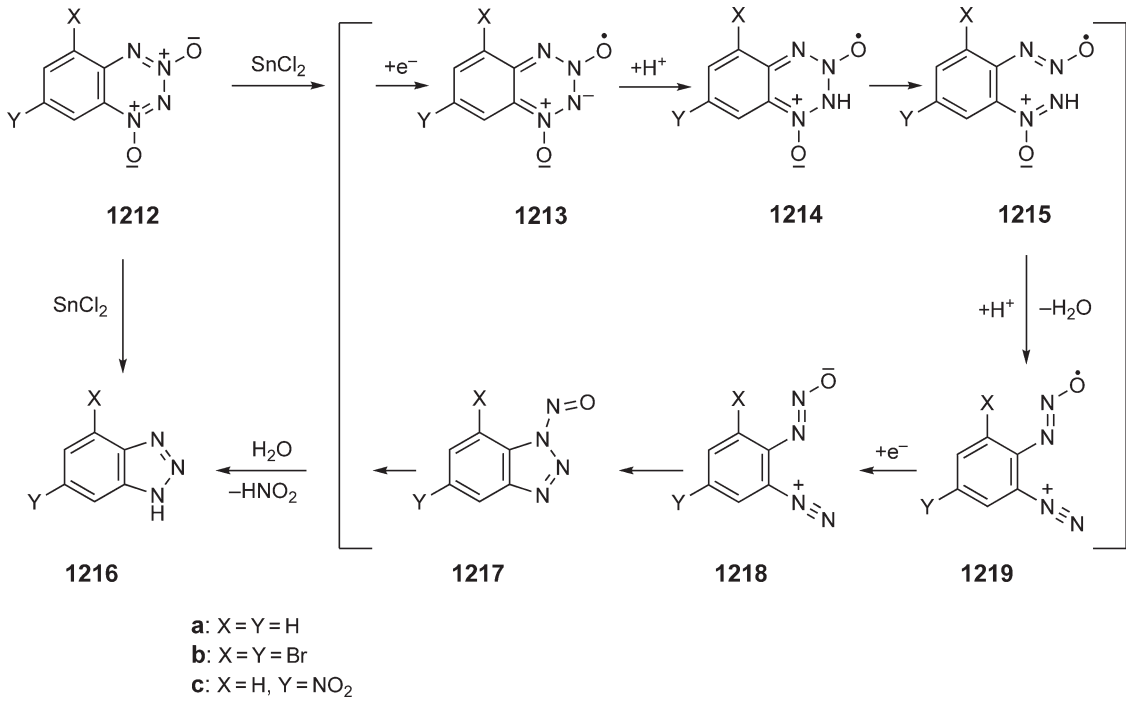
5.01.10.4 Benzotriazoles and Higher Fused Systems

Treatment of benzimidazole with ozone and NO_2 results in a complex mixture of mono- and di-nitrated benzimidazoles and triazoles. However, nitration of 5-nitrobenzimidazole **1209** under such conditions leads to two major products, benzotriazoles **1210** and **1211**. The mechanism of ring conversion from benzimidazole to benzotriazole is not clear (Equation 29) <2004CPB570>.



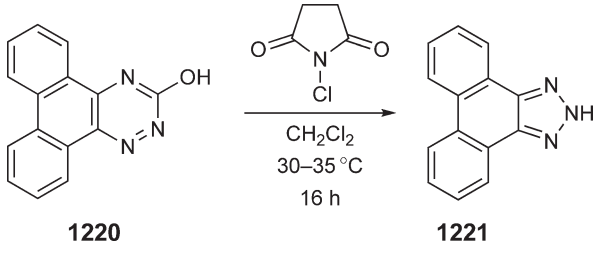
1209 **1210** **1211** (29)

Reduction of benzo-1,2,3,4-tetrazine 1,3-diones **1212** results in formation of benzotriazoles **1216**, which are isolated in high yield (95–98%). Common agents used for reduction of nitro groups, $Na_2S_2O_4$, $SnCl_2$, or Fe/HCl, work well here; however, the required reaction conditions are milder allowing a nitro group survive untouched in product **1216c**. The proposed mechanism starts from a single electron transfer with generation of radical **1213**. After protonation leading to intermediate **1214**, the N(2)–N(3) bond is cleaved furnishing form **1215**. Another protonation and elimination of water leads to diazonium ion **1219**. Transfer of a second electron converts radical **1219** into anion **1218** that is in position to undergo cyclization to *N*-nitrosobenzotriazole **1217**. Under the reaction conditions, intermediate **1217** hydrolyzes to benzotriazole **1216**. Intermediacy of nitroso derivatives **1217** is proven by running the reaction in the presence of morpholine with 4-nitrosomorpholine being isolated as the only side product (**Scheme 201**) <2002OL3227>.



Scheme 201

1,2,3-Triazoles fused with larger aromatic systems can be also obtained this way. Thus, in an example given in Equation (30), 2*H*-phenanthro[9,10-*d*]-1,2,3-triazole **1221** is obtained in 84% yield from a reaction of 3-hydroxyphenanthro-1,2,4-triazine **1220** with NCS <2000H(53)203>.



(30)

5.01.11 Synthesis of Particular Classes of Compounds

5.01.11.1 Derivatives of 1,2,3-Triazole

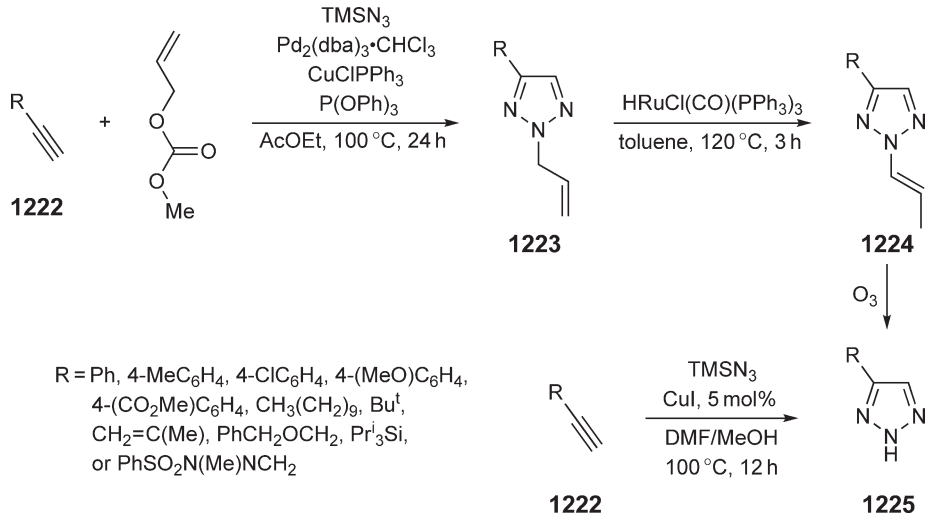
5.01.11.1.1 N-Substituted 1,2,3-triazoles

Reactions of salts of 1,2,3-triazole with electrophiles provide an easy access to 1,2,3-triazol-*N*-yl derivatives; although, usually mixtures of N-1 and N-2 substituted triazoles are obtained that have to be separated (see Section 5.01.5). Another simple method for synthesis of such derivatives is addition of 1,2,3-triazole to carbon–carbon multiple bonds (Section 5.01.5). N-1 Substituted 1,2,3-triazoles can be selectively prepared by 1,3-dipolar cycloaddition of acetylene or (trimethylsilyl)acetylene to alkyl or aryl azides (Section 5.01.9).

5.01.11.1.2 C-Substituted 1,2,3-triazoles

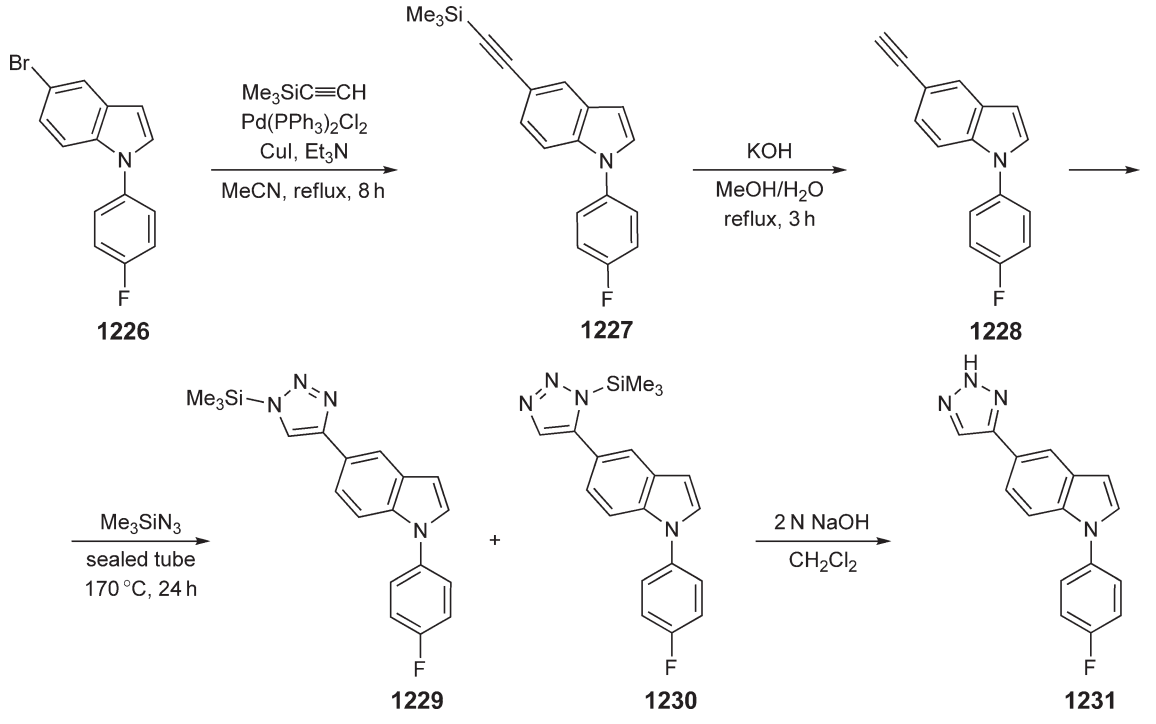
In the presence of copper and palladium catalysts, terminal alkynes **1222** react with trimethylsilyl azide and allyl methyl carbonate to provide 2,4-disubstituted 1,2,3-triazoles **1223** in moderate to good yield. Isomerization of the allyl substituent in the presence of a ruthenium catalyst gives 4-substituted 2-(1-propen-1-yl)-2*H*-1,2,3-triazoles **1224**.

Deprotection of N-2 by ozonolysis furnishes triazoles **1225** (**Scheme 202**) <2003JA7786>. Finding that 1,3-dipolar cycloaddition of alkynes **1222** to trimethylsilyl azide, carried out in DMF/MeOH in the presence of CuI as a catalyst, leads directly to products **1225** with much higher yields provides a significant progress to the synthesis of N-unsubstituted 1,2,3-triazoles <2004EJO3789>.



Scheme 202

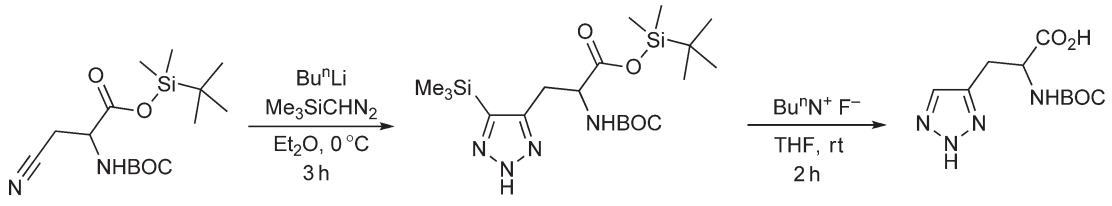
Scheme 203 provides a methodology for the conversion of aryl bromides onto 4-aryl-1,2,3-triazoles. In the given example, palladium–copper catalyzed substitution of the bromine atom in indole **1226** by trimethylsilylacetylene provides intermediate **1227**. Hydrolysis of the trimethylsilyl protecting group releases terminal alkyne **1228**, isolated



Scheme 203

in 35% yield (two steps). 1,3-Dipolar cycloaddition of alkyne **1228** to trimethylsilyl azide leads to a mixture of regioisomeric triazoles **1229** and **1230**, which is directly hydrolyzed by 2 N NaOH to give quantitatively triazole **1231** <2003JME265>.

In a quite different approach, shown in **Scheme 204**, cycloaddition of nitrile **1232** to trimethylsilyldiazomethane provides silylated triazole **1233**, isolated in 75% yield. Treatment with tetrabutylammonium fluoride removes the trimethylsilyl group and simultaneously the silyl protection of the carboxylic group to afford 4-substituted triazole derivative **1234** in 81% yield <2003PEN699>.



1232 **1233** **1234**

Scheme 204

5.01.11.1.3 1,4-Disubstituted 1,2,3-triazoles

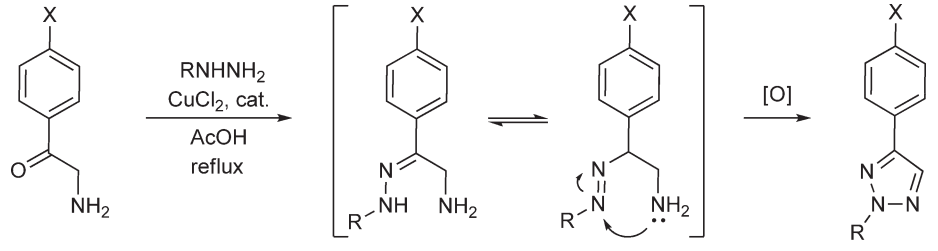
1,4-Disubstituted 1,2,3-triazoles are exclusive products of copper catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. A variety of substituents can be introduced in this way. Many examples of such reactions are discussed in Section 5.01.9.

5.01.11.1.4 1,5-Disubstituted 1,2,3-triazoles

1,5-Disubstituted 1,2,3-triazoles are formed in 1,3-dipolar cycloaddition of alkynylmagnesium reagents to azides. This reverse regioselectivity is also achieved in ruthenium-catalyzed cycloadditions. Examples of such reactions can be found in Section 5.01.9.

5.01.11.1.5 2,4-Disubstituted 1,2,3-triazoles

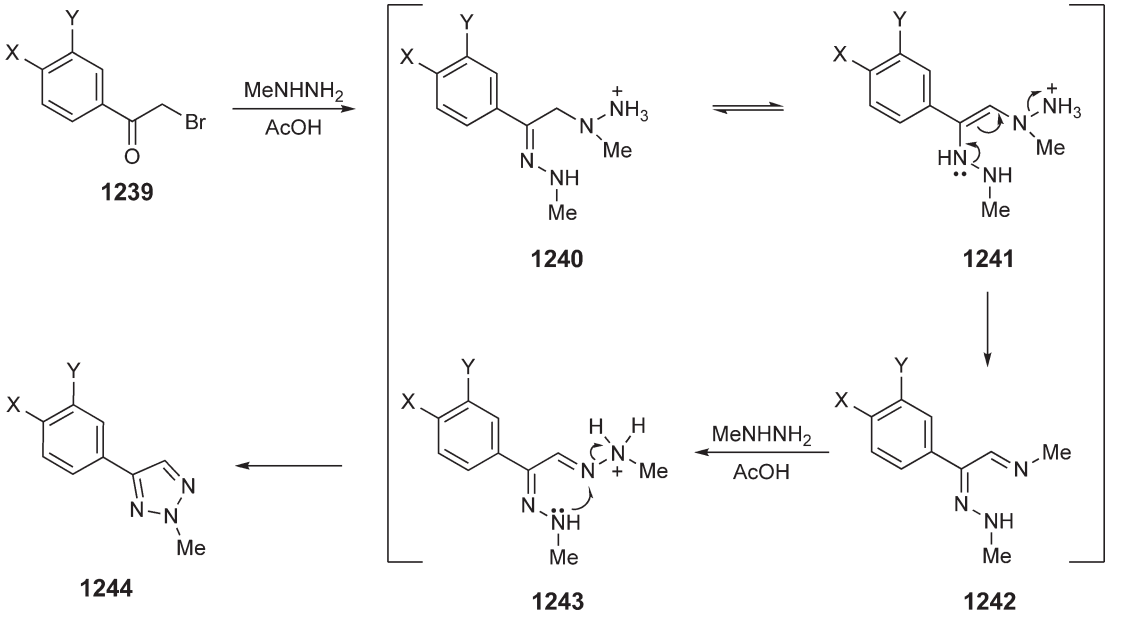
2,4-Disubstituted 1,2,3-triazoles are usually minor components in the product mixtures obtained from reactions of triazole with electrophiles (see Section 5.01.5). The few regioselective syntheses of such compounds include a reaction of aminoacetophenones **1235** with hydrazines. The reaction with methylhydrazine proceeds well without any catalysis, but that with phenylhydrazine requires cupric chloride as a catalyst. It is assumed that hydrazone **1236** that forms in the first step is in a tautomeric equilibrium with its azo form **1237**. However, it is not clear how bond formation between the nitrogen atoms and oxidation to the triazole system occurs. 4-Aryltriazoles **1238** are obtained in 50–66% yield (**Scheme 205**) <2003SC3513>.



1235 **1236** **1237** **1238**

Scheme 205

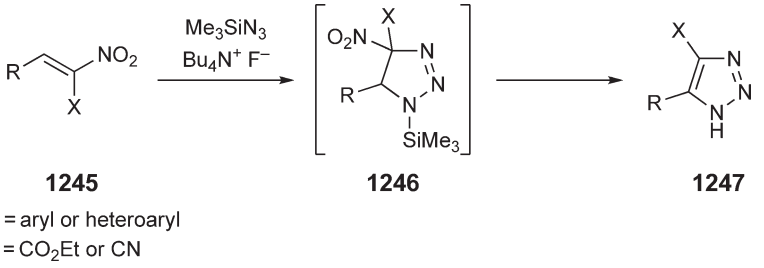
It appears that treatment of phenacyl bromides **1239** with methylhydrazine in refluxing acetic acid leads also to 1,4-disubstituted triazoles **1244**. Fivefold excess of methylhydrazine is used in these reactions. According to the proposed mechanism, structures **1240–1243**, methylhydrazine has a double role, as a condensing agent and an oxidant. In the final account, three molecules of methylhydrazine have to be used to produce one molecule of triazole **1244**, two molecules of methylamine and one molecule of ammonia. The basic triazole **1244** (X = Y = H) is separated in 59% yield. The reactions go well with electron-donating substituents (for X = OH, the yield is 81%), but electron-withdrawing substituents can lower the yield dramatically (11% for $X = NO_2$) (**Scheme 206**) <2003JCM96>.



Scheme 206

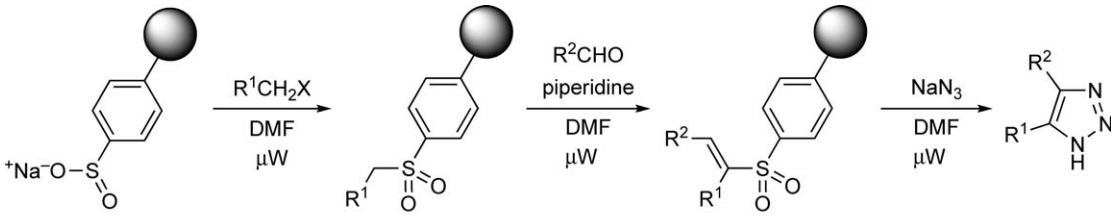
5.01.11.1.6 4,5-Disubstituted 1,2,3-triazoles

A simple procedure for the synthesis of 4,5-disubstituted 1,2,3-triazoles **1247** involves stirring a mixture of nitroethene **1245** with trimethylsilyl azide and tetrabutylammonium fluoride at 30 °C for 3 h. No solvent is needed. Triazoline **1246**, which forms in the first step of the reaction, eliminates nitrous acid, and the trimethylsilyl group is cleaved off by the fluoride anion to afford triazole **1247**. Various aryl and heteroaryl substituents R are used providing triazoles **1247** in 70–90% yield (**Scheme 207**) <2005JOC6526>.



Scheme 207

The synthesis of 4,5-disubstituted triazoles shown in **Scheme 208**, carried out on a polymer support with microwave assistance, is based on a similar principle. In the first step, sulfinate **1248** is converted to sulfone **1249**. Condensation with aldehydes provides vinyl sulfones **1250**. Cyclocondensation of sulfones **1250** with sodium azide generates corresponding triazoline intermediates that eliminate sulfinate **1248** to provide triazoles **1251** in moderate to good yield <2006OL3283>.

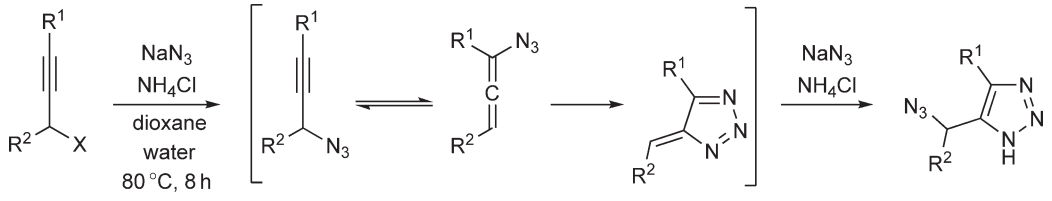


1248 **1249** **1250** **1251**

R^1 = CN, Ac, CO_2Me or $CONH_2$
R^2 = Ph, 4-$(NO_2)C_6H_4$, 2-pyridyl, 3-pyridyl, 2-furyl or 2-thienyl

Scheme 208

Azides **1253** obtained from propargyl halides or sulfonates **1252** undergo sigmatropic rearrangement to azidoallenes **1254**, which subsequently undergo cyclization to triazafulvenes **1255**. Under the reaction conditions, species **1255** react with another molecule of sodium azide to furnish triazoles **1256**. Products **1256** are isolated in 65–97% yield (**Scheme 209**) <2005S1514>.



1252 **1253** **1254** **1255** **1256**

R^1 = H, Et, Ph, CH_2OH, CH_2Cl, *n*-C_5H_{11}, or phthalimidyl-CH_2
R^2 = H, Me, or Pr
X = Cl, Br, MsO, or TsO

Scheme 209

5.01.11.1.7 Tri-substituted 1,2,3-triazoles

Compounds of this type are the most common products obtained from thermal 1,3-dipolar cycloaddition of disubstituted alkynes to azides. Many examples of such reactions can be found in Section 5.01.9.

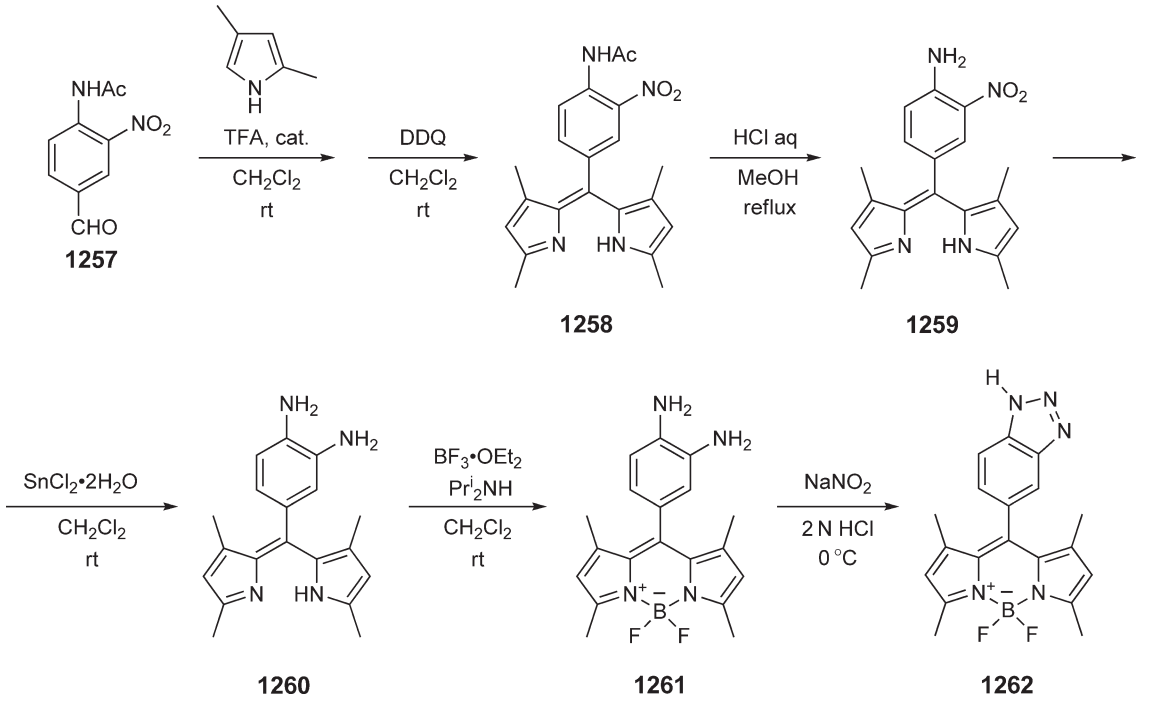
5.01.11.2 Derivatives of Benzotriazole

5.01.11.2.1 N-Substituted benzotriazoles

Preparation of benzotriazolyl derivatives substituted at N-1 (or N-2) with variety of functional groups is described in detail in Sections 5.01.5 and 5.01.8. The basic strategy starts from a reaction of benzotriazole with an electrophile. In most cases, the reaction produces a mixture of benzotriazol-1-yl and benzotriazol-2-yl derivatives that is not difficult to separate. Further modification of the substituent in subsequent steps leads to the desired product.

5.01.11.2.2 C-Substituted benzotriazoles

There are only few commercially available C-substituted benzotriazoles. In some situations, the substituents can be readily converted to more complex groups in the desired products. However, in many instances, it is more convenient to design first the right substituent and build the heterocyclic ring later. An example of such approach is shown in **Scheme 210**. Thus, in a reaction with 2,4-dimethylpyrrole, followed by treatment with DDQ, benzaldehyde **1257** is converted to product **1258** in 26% overall yield. Deprotection of the amino group gives *ortho*-nitroaniline **1259** that is subsequently reduced to *ortho*-phenylenediamine **1260** with 95% yield. Complexation of the dipyrrolyl moiety with boron trifluoride gives product **1261** (71% yield), which by treatment with sodium nitrite in 2 N HCl is converted to desired triazole derivative **1262** in 29% yield <2004JA3357>.

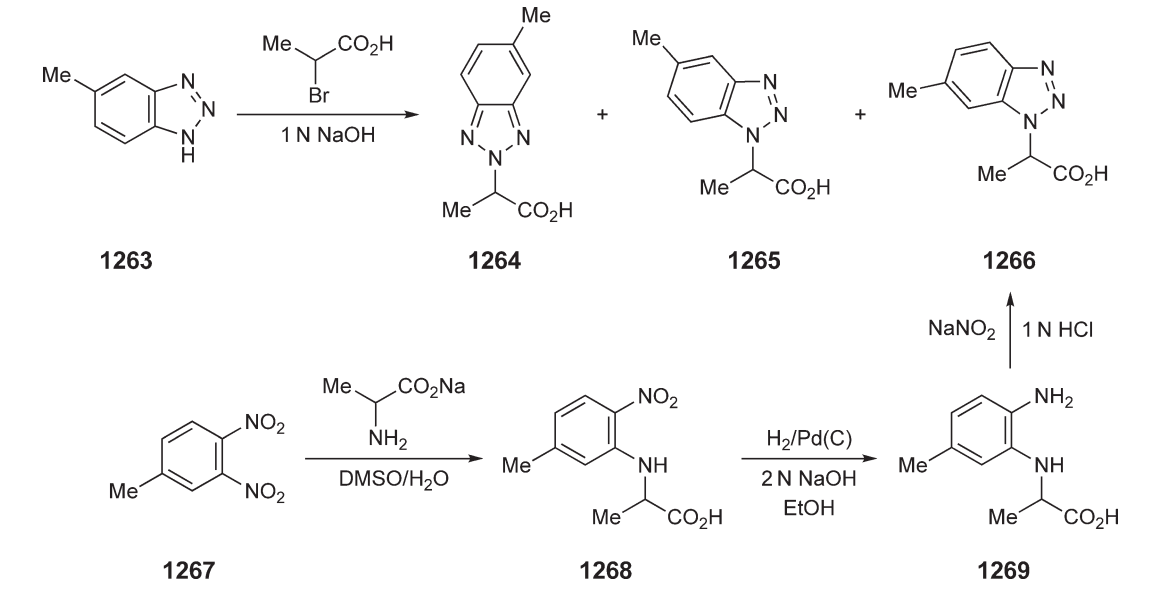


Scheme 210

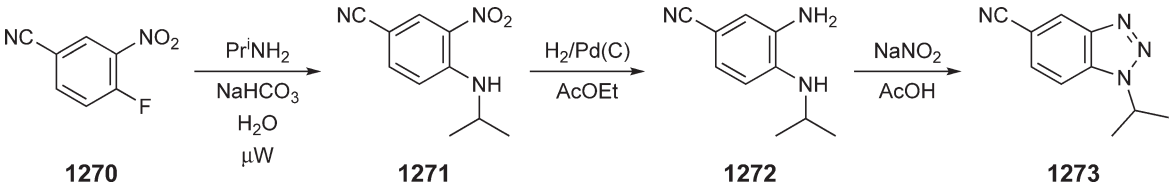
5.01.11.2.3 C,N-Disubstituted benzotriazoles

Direct N-substitution of benzotriazole in its reactions with electrophiles is a common practice. However, that strategy usually does not work well when a C-substituted benzotriazole is used as the starting material. Thus, in an example shown in **Scheme 211**, reaction of 5-methylbenzotriazole **1263** with 2-bromopropionic acid provides a mixture of three products **1264–1266** with the N(2)-substituted benzotriazole derivative **1264** being strongly predominant. Thus, the use of this approach for the synthesis of desired compound **1266**, which appears to be the least abundant in the mixture, is very impractical. Synthesis of the benzotriazole system starting from 3,4-dinitrotoluene **1267** is a much better alternative. In the first step, heating of a solution of compound **1267** and sodium 2-aminopropionate in DMSO allows for selective substitution of the nitro group in position *meta* to provide 2-nitroaniline **1268**. Reduction of the remaining nitro group to give diamine **1269** followed by cyclocondensation with nitrous acid furnishes the desired product **1266** <2003FA33>.

A similar approach, synthesis of a selectively substituted benzotriazole from the corresponding *ortho*-nitroaniline, is depicted in **Scheme 212**. The process starts from a microwave-assisted substitution of the fluorine atom in 4-fluoro-3-nitrobenzonitrile **1270** by isopropylamine to give *ortho*-nitroaniline **1271** in 99% yield. Reduction of the nitro group provides *ortho*-phenylenediamine **1272** that is directly converted to 5-cyano-1-isopropylbenzotriazole **1273**, which is isolated in 83% yield <2006JME1227>.



Scheme 211



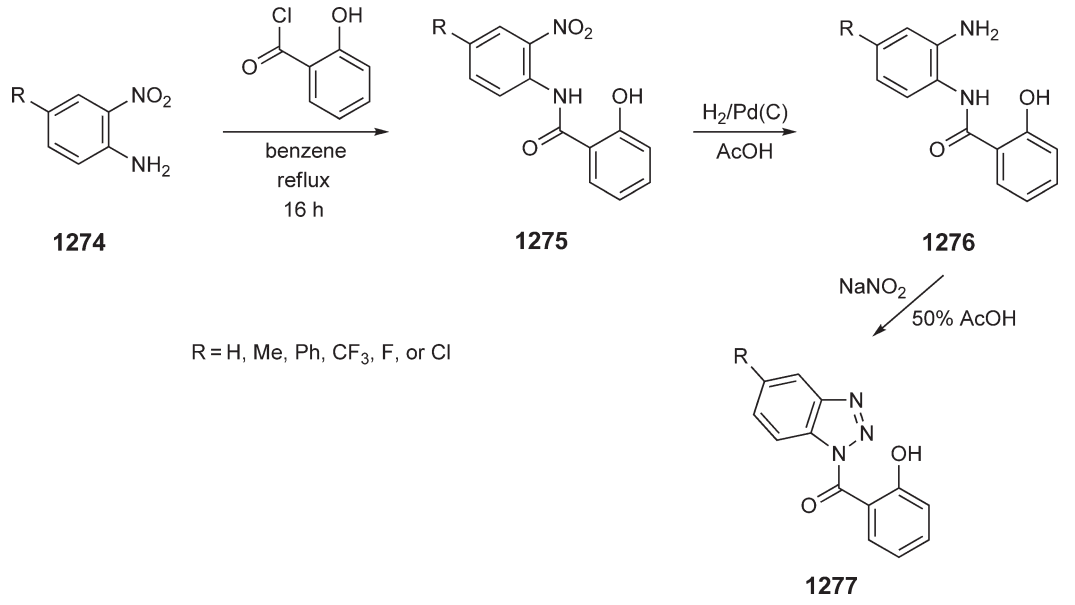
Scheme 212

A series of *para*-substituted *ortho*-nitroanilines **1274** is converted in this way to benzotriazolyl derivatives **1277**, which are of interest as potassium channel activators. In the first step, nitroanilines **1274** are treated with salicylyl chloride to provide salicylamides **1275** in 70–95% yield. The nitro group is catalytically reduced, and the obtained intermediates **1276** are subjected to a reaction with nitrous acid, generated *in situ* from $NaNO_2$, to afford 5-substituted 1-(2-hydroxybenzoyl)-1*H*-benzotriazoles **1277** in 52–96% yield (**Scheme 213**) <2001FA827>.

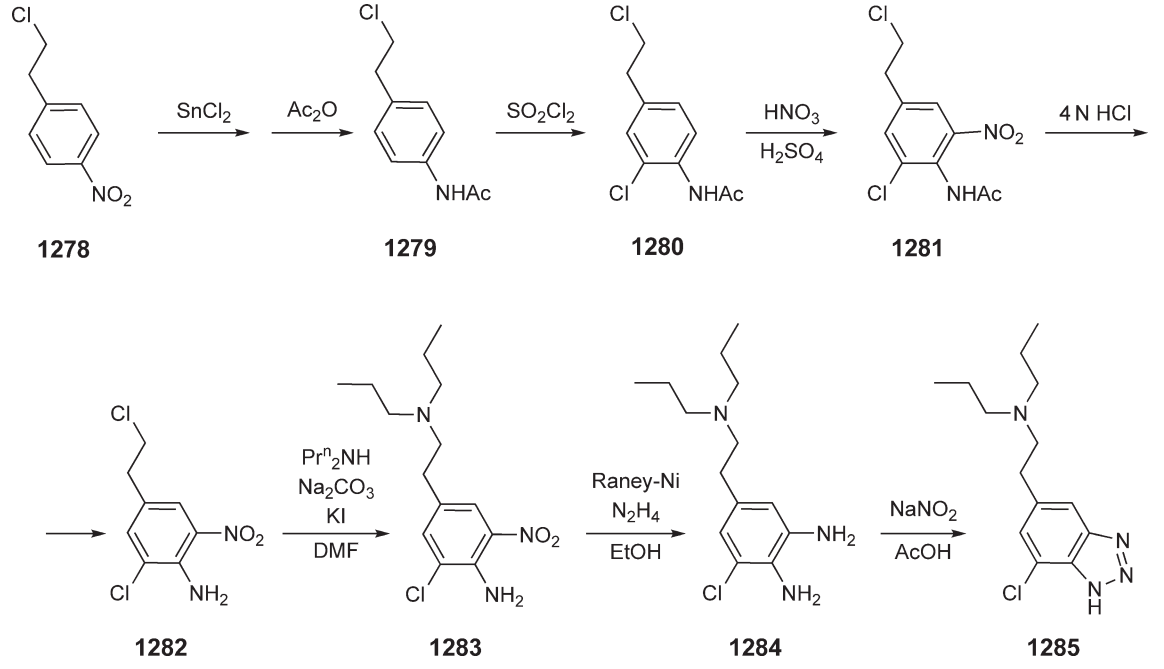
5.01.11.2.4 C,C-Disubstituted benzotriazoles

C-Derivatization of benzotriazole is rather difficult, and a benzotriazole system selectively substituted at the benzenoid ring is usually constructed from scratch. An illustration of this case is depicted in **Scheme 214**. The process starts from a relatively simple molecule of 4-(2-chloroethyl)nitrobenzene **1278** that is reduced to the corresponding aniline and acetylated to give acetanilide **1279**. Chlorination with $SOCl_2$ provides derivative **1280** in 75% yield that is subsequently nitrated to give product **1281** in 70% yield. Deprotection of the amino group gives nitroaniline **1282**, In the following steps, the 2-chloroethyl substituent is converted into 2-(dipropylamino)-ethyl group (compound **1283**), the nitro group is reduced, and the obtained *ortho*-phenylenediamine **1284** is subjected to cyclocondensation with nitrous acid to furnish benzotriazole **1285** with the last step yield of 61% <2004AP376>.

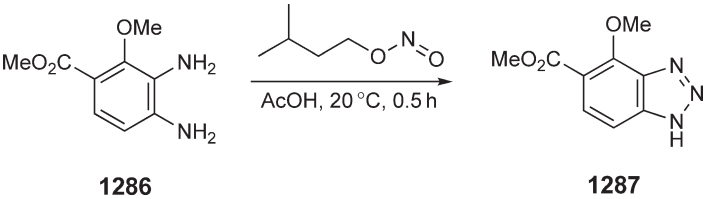
Instead of sodium nitrite, isoamyl nitrite is sometimes used as a nitrosating agent in synthesis of the benzotriazole ring. With this reagent, the reaction conditions are very mild allowing survival of acid sensitive groups. In an example of such a reaction, methyl 3,4-diamino-2-methoxybenzoate **1286** is treated with isoamyl nitrite at room temperature. The reaction is fast and provides methyl 4-methoxybenzotriazole-5-carboxylate **1287** in 62% yield, isolated by simple filtration off the precipitate (Equation 31) <2006JME4762>.



Scheme 213



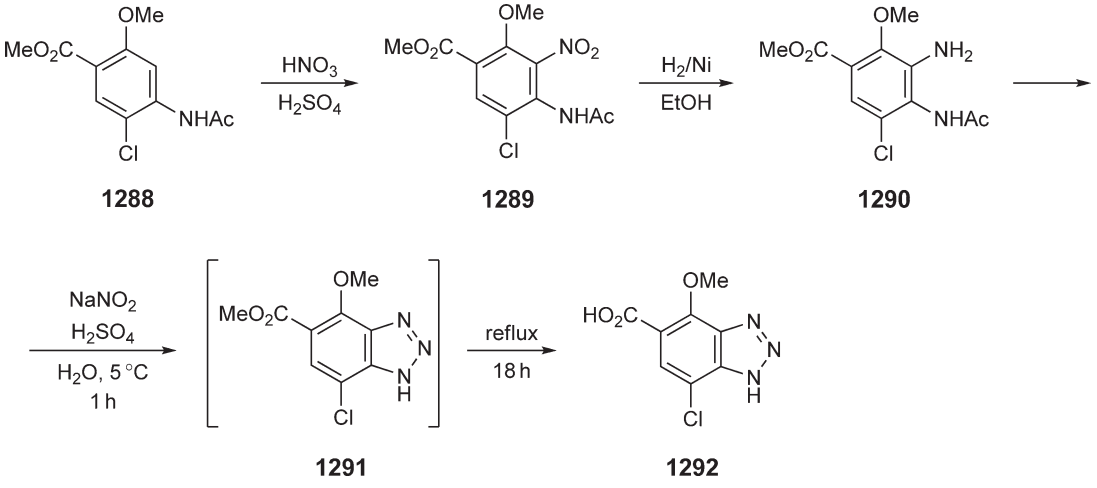
Scheme 214



(31)

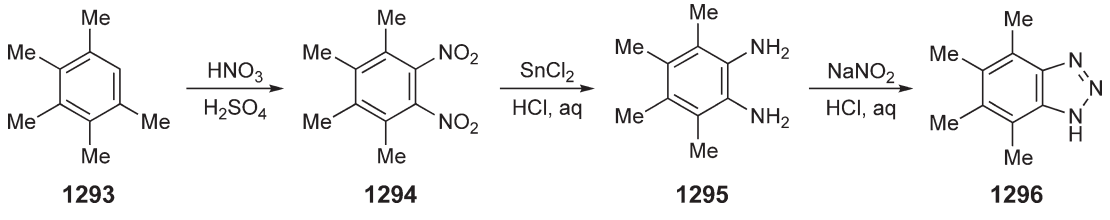
5.01.11.2.5 Three or more substituents

To get a complex set of substituents by direct derivatization of benzotriazole is not feasible. In such situations, it is better to have all the substituents in place first and later construct the heterocyclic ring. High reactivity of anilines and their well-developed chemistry makes them good stating materials. In an example shown in **Scheme 215**, acetanilide **1288** is nitrated to afford nitro derivative **1289** in 73% yield. Catalytic reduction of the nitro group provides methyl 4-acetylamino-3-amino-5-chloro-2-methoxybenzoate **1290** in 96% yield. Nitrosation of compound **1290** in diluted sulfuric acid leads to intermediate **1291**, which without separation is heated to be converted to 7-chloro-4-methoxy-1*H*-benzotriazole-5-carboxylic acid **1292**, isolated in 64% yield <2002CPB941>.



Scheme 215

Preparation of 4,5,6,7-tetrabromobenzotriazole and its tetrachloro analog by direct bromination or chlorination of benzotriazole is described in Section 5.01.7. However, other tetra-substituted benzotriazoles have to be constructed from a suitably substituted benzene ring. Thus, treatment of pentamethylbenzene **1293** with fuming nitric acid in concentrated sulfuric acid provides 3,4,5,6-tetramethyl-1,2-dinitrobenzene **1294** in 66% yield. Using routine procedures, derivative **1294** is reduced with $SnCl_2$ in aqueous HCl, and the obtained diamine **1295** is subsequently treated with $NaNO_2$ (in aq. HCl) to provide 4,5,6,7-tetramethyl-1*H*-benzotriazole **1296** (**Scheme 216**) <2004BMC2617>.



Scheme 216

5.01.12 Important Compounds and Applications

5.01.12.1 Benzotriazole Methodology in Organic Synthesis

The last two decades have witnessed rapid development of organic synthetic methods based on benzotriazole derivatives. Thus, introduction of benzotriazole moiety to organic molecules provides several practical advantages. Among other benefits, a benzotriazolyl substituent activates the reaction center, stabilizes intermediates, increases regio- and stereoselectivity, and simplifies separation and purification of the products. After the desired molecular assembly is constructed, the bond with benzotriazole is cleaved off to provide the final product. A vast variety of

molecular structures is conveniently prepared in this way. The largest section of this chapter (Section 5.01.8) is devoted specifically to this topic. For this reason, benzotriazole itself and a hundred of its basic derivatives that are commercially available now have become important materials in organic synthesis.

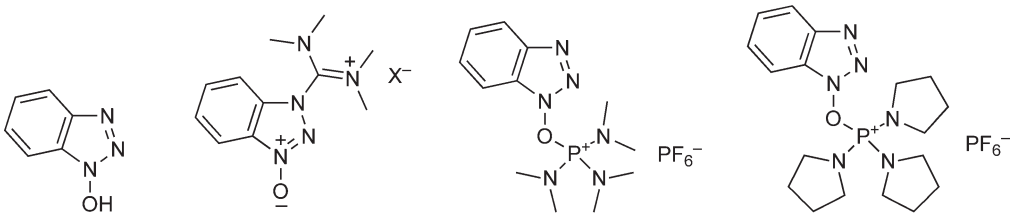
5.01.12.2 Peptide Coupling Reagents

I-Hydroxybenzotriazole (HOBt) **1297** <1996CHEC-II(4)1> has become an everyday reagent in many chemistry labs, and the number of reports of its application in organic synthesis is boosted to hundreds per year. Combined with a dehydrating agent and a tertiary amine, HOBt is an excellent auxiliary in preparation of amides (**Table 13**). The mechanism of its interaction with carboxylic acids is discussed in Section 5.01.8. Some of the dehydrating agents used in the process are also derivatives of HOBt **1298–1301**. In some instances, these derivatives, HBTU **1298** <2002JOC1184, 2004NAR623>, TBTU **1299** <2005HCA447, 2005HCA1040, 2005TL6239, 2006OL2851, 2006TL1737> and BOP **1300** <2005JA17894, 2005JOC3660, 2006JA3011, 2006OL239, 2006OL511> are used alone without addition of HOBt. Combinations of HOBt with dehydrating agents, especially DIC <2005JOC9622, 2005TL7443, 2006JCO150, 2006JME1833, 2006JME2388>, HBTU <2005AGE2534, 2005JCO697, 2005JOC7654, 2005TL4053, 2006TL2671> and BOP <2002BML2855, 2005AGE2887, 2005JCO703> are common reagents in solid-phase synthesis of peptides. Use of HOBt together with DCC <2005CEJ6666, 2005JOC5339, 2005JOC6313, 2005TL4377, 2005TL6791>, EDC <2005AGE5710, 2006JME2333, 2006OL531, 2006OL797, 2006SC1317> or HBTU <2001NN1347, 2006JME2593> in preparation of carboxylic esters is also relatively common. HOBt can likewise promote formation of C–C bonds in coupling of carboxylic acids with cyanoacetates <2002BCJ2691> and acetoacetates <2002SL1736>. In the presence of HBTU, aminoacids react with diazomethane to give their higher homologs <2003PES230>.

Table 13 Some of the recent applications of 1-hydroxybenzotriazole in the synthesis of amides

Example	*Character of* R^1COOH	*Character of* R^2NH_2	*Dehydr. agent*	R^1CONHR^2 *application*	*Yield (%)*	*Reference*
1	Aminoacid	Aminoacid	EDC	Peptide	97	2005CC4908
2	Aminoacid	Peptide	EDC	Cyclic peptide	90	2005JOC9626
3	Dipeptide	Amino thioester	DCC	Peptide thioacid	93	2006OL823
4	Oxazolidine-COOH	L-Ser-OMe	DDC	Telomerase inhibitor	79	2006S1289
5	Fmoc-Leu-OH	PS-R-NH_2	TBTU	Oxazole tripeptide	87	2006OL2417
6	Cyclopentane-carboxylic acid	Methyl glycinate	TBTU	Peptides	98	2005HCA1711
7	Aminosugar acid	Aminosugar	HBTU	Oligosaccharide mimic	89	2005AGE2096
8	Arenoxyacetic acid	Methyl glycinate	DCC	Heteroditopic receptors	71	2006CJC58
9	Aminoacid	Aminoacid	DCC	Opioid receptor agonist	96	2006JME1773
10	Aminoacid	Aminosugar	EDC	Antibiotics	91	2006OL887
11	Succinic acid	Ar-1,3-di-[$O(CH_2)_3$]-NH_2	EDC	Dentronized polymer	76	2006JA5091
12	RCH(Bu^t)-COOH	$ArCH_2NHNH_2$	EDC	HIV protease inhibitor	76	2006JME1828
13	Fmoc-Gly-OH	$R_2C(CO_2Me)$-NH_2	DIC	6-Spiro-1,4-diazepane	98	2005EJO907
14	ArCOCOOH	$R^1R^2NH_2$	EDC	FKBP12 ligand	68	2006JME1202
15	ArCOOH	Morpholine	EDC	Growth factor-β inhibitor	73	2006JME2210
16	2-Indole-carboxylic acid	2,3-Dihydro-indole	EDC	Antitumor antibiotic	96	2006JA7136

DCC = 1,3-dicyclohexylcarbodiimide, DIC = 1,3-diisopropyl-carbodiimide, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.



1297

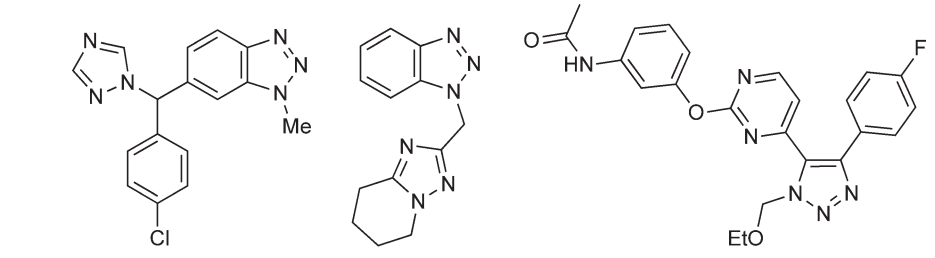
1298: $X^- = PF_6^-$ (HBTU)
1299: $X^- = BF_4^-$ (TBTU)

1300: BOP

1301: PyBOP

5.01.12.3 Biologically Active Derivatives

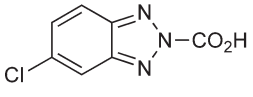
Due to their easy access and high enzymatic stability, benzotriazole and 1,2,3-triazole systems are frequently used as building blocks in drug design. Among antitumor agents, vorozole (structure **1302**) is a high-affinity competitive aromatase inhibitor, designed for inhibiting estrogen synthesis in patients with breast cancer <2001CNR8452, 2002JON1026, 2003STE1139>. Benzotriazole derivative **1303** exhibits remarkable activity against leukemia, ovarian, renal, and lung cancers <2003BMC1701>. The structures may be complex, like compound **1304** <2003BML1665>, or simple, like compound **1305** <2003FA33>, both of them exhibiting anti-inflammatory activities, although based on different principles. Nucleoside analog **1306** inhibits strongly helicase activity of hepatitis C virus <2003EJB1645>, whereas compound **1307** and several of its analogs show strong activity against respiratory syncytial virus (RSV) <2003BML2141>.



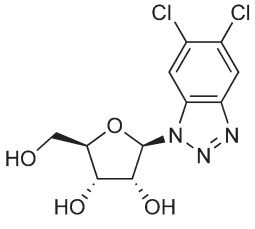
1302

1303

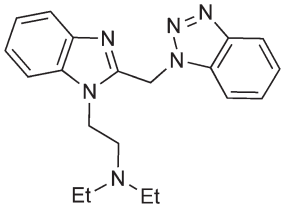
1304



1305



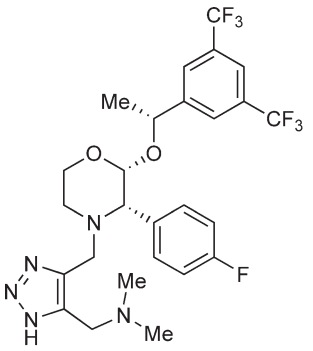
1306



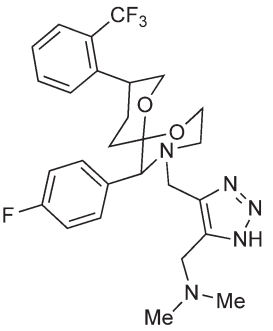
1307

Very simple derivatives of benzotriazole with biological activity include 5,6-dimethylbenzotriazole, a very effective agent against cysts of *Acanthamoeba castellanii* <2004BMC2617>, tetrabromobenzotriazole, which provides selective inhibition of protein kinase CK2 <2001PSC2200> and induces apoptosis of Jurkat cells <2002BJ41>, 1-salicylyl-4-methylbenzotriazole, potassium channel activator <2001FA827> and 1-isopropyl-1*H*-benzotriazole-4-carboxylic acid, a selective agonist of human orphan G-protein-coupled receptor GPR109b <2006JME1227>.

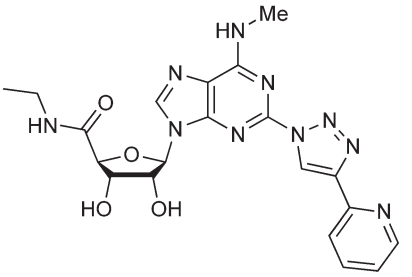
Several 1,2,3-triazole derivatives have been designed to target G-protein-coupled receptors. Among them are neurokine NK_1 antagonists **1308** <2001JME4296, 2002JEP536> and **1309** <2002BML2515>, selective A_3 adenosine receptor agonist **1310** <2006JME7373> and highly selective α_1 adrenoreceptor antagonists <2003JME265>. Other 1,2,3-triazole derivatives are of interest as inhibitors of some key enzymes: acetylcholinesterase <2004JA12809>, glycogen synthase kinase-3 <2003JME3333>, glycosidase <2005T9118>, galectin-1 <2006CAR1353, 2006CC2379> and α-2,3-sialyltransferase <2006CC629>.



1308



1309



1310

There are also 1,2,3-triazoles with antiviral <2006BML2693, 2006JME1140>, antibacterial <2002BML2771, 2003BMC35>, antithrombotic <2004AP156>, or antiplatelet <2003BMC2051> activities. Some triazoles work as potassium channel activators <2004FA397>, others as calcium signal transduction inhibitors <2002CLC86>. 1,5-Diaryl-Δ^2-1,2,3-triazolines are recognized anticonvulsant agents <2003CME2081, 2004JLR31>. Among biologically active benzotriazoles are also inactivators of the severe acute respiratory syndrome 3CL protease <2006CBO1261>, trichostatin suppressors <2003CBO397>, antagonists of the gonadotropin releasing hormone <2002BML827>, and nonpeptide inhibitors of protein tyrosine phosphatase 1B <2004BML1043>.

5.01.12.4 Other Applications

Due to strong complexing affinities to copper and some other ions, benzotriazole and its derivatives have found wide application in anticorrosion formulations. Hundreds of patents covering this subject are registered each year. One of the major applications of such formulations is in electronics that include thiol passivation of copper interconnects during semiconductor manufacturing, grinding composition for polishing of semiconductor devices, corrosion-preventing agents for etching of insulator films in manufacture of semiconductor devices, cleaning solutions for electrohydrodynamic cleaning of semiconductors, components of polymer coatings for silver-plated circuits, and in dispersants for preparation of nickel-coated copper powder for electricity-conducting inks. Benzotriazole is also commonly used as an unticlogging agent in jet inks for forming high-quality images.

Anticorrosion abilities of benzotriazole and its derivatives are also widely utilized in fluids for all kind of machinery. They are important antifriction–antiwear additives for engine oils, components of antirusting grease for aircraft, biodegradable lubricants for turbines, brake liquids based on polyoxyalkylene synthetic oils, metal corrosion inhibitors in aqueous coolants containing acetic acid and propylene glycol, grease for gas compressors for fuel cell systems, emulsifiable oil for preparation of noncombustible oil–water hydraulic emulsions for coal mining, environment-protecting lubricating oil for refrigerators, antifreeze composition for diesel engines, and lubricating oil compositions for hot rolling aluminium plates. Benzotriazole derivatives can be also found in machine dishwashing detergents containing nonionic surfactants, corrosion inhibitors for thermoplastic polyurethanes in contact with metals, and in anticorrosion polymer coatings for guitar strings.

Due to strong UV absorption, benzotriazole derivatives have found application in cosmetic formulas for skin photoprotection, in cosmetic sunscreen compositions, in multifunctional eyeglass lenses with UV absorbers, in UV protecting films for radiation detectors in personal instant alert dosimeters, in polyester compositions reducing UV light penetration for production of bottles, in UV absorbers for decorative polyolefin sheets with improved weather resistance, in protective coatings containing UV absorbers for microporous sheets, in UV absorbers for plant protecting covers, in photographic emulsion of light-sensitive materials, and as UV absorber for a multilayer golf ball with a translucent cover.

5.01.13 Further Developments

Novel applications of benzotriazole methodology in organic synthesis include regiospecific preparation of 1,4,5-trisubstituted pyrazoles <2007ARK(i)9>, efficient synthesis of 1,5-disubstituted tetrazoles <2007SL1204>,

amidoalkylations of nitroalkanes, nitriles, alkynes, and esters <2007ARK(xi)96>, thioamidoalkylation of 1,3-dicarbonyl compounds, enol silyl ethers, and enamines <2007S1655>, C-aminoimidoylation and C-thiocarbamoylation of esters, sulfones, and ketones <2007JOC6742>, synthesis of cyano derivatives of *N*-alky and *N*-aryl piperazines <2007EJM471>, and preparation of polyfunctional acyl azides <2007JOC5802>. *N*-Acyl derivatives of benzotriazole are used for efficient peptide coupling of sterically hindered aminoacids <2007JOC5794> and 5-amino-1-methyl-1*H*-[1,2,4]-triazole-3-carboxylic acid <2007SC1917, expedient synthesis of *N*-*Z*-pyroglutamyl-aminoacid derivatives <2007BML6000>, synthesis of (+)-aphanorphine <2007H(72)497>, and as Mosher-Bt reagents <2007JOC4268>.

References

1925CRV91 M. Gomberg, *Chem. Rev.*, 1925, **1**, 91.
1935LA113 F. Krollpfeiffer, A. Rosenberg, and C. Muhlhausen, *Liebigs Ann. Chem.*, 1935, 113.
1955JA5105 R. H. Wiley, K. H. Hussung, and J. Moffat, *J. Am. Chem. Soc.*, 1955, **77**, 5105.
1957JA4395 R. H. Wiley and K. F. Hussung, *J. Am. Chem. Soc.*, 1957, **79**, 4395.
1968TL249 H. Lankamp, W. T. Nauta, and C. MacLean, *Tetrahedron Lett.*, 1968, **9**, 249.
1978JOC337 C. Larsen, K. Steliou, and D. N. Harpp, *J. Org. Chem.*, 1978, **43**, 337.
1984CHEC-I(5)669 H. Wamhoff; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 5, p. 669.
1991S103 M. Makosza, *Synthesis*, 1991, 103.
1992PJC1633 A. R. Katritzky, S. Rachwal, C. V. Hughes, and Z. Wang, *Pol. J. Chem.*, 1992, **66**, 1633.
1992TL4763 J. M. Aurrecoechea and A. Fernandez-Acebes, *Tetrahedron Lett.*, 1992, **33**, 4763.
1995H(40)543 F. Palacios, A. M. Ochoa de Retana, and J. Pagalday, *Heterocycles*, 1995, **40**, 543.
1995JOC246 A. R. Katritzky, B. Yang, J. Jiang, and P. J. Steel, *J. Org. Chem.*, 1995, **60**, 246.
1995JOC638 A. R. Katritzky and J. Li, *J. Org. Chem.*, 1995, **60**, 638.
1995JOC2588 A. R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 2588.
1995JOC3401 A. R. Katritzky, J. Li, and C. V. Stevens, *J. Org. Chem.*, 1995, **60**, 3401.
1995JOC3993 A. R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 3993.
1995JOC4002 A. R. Katritzky, A. V. Ignatchenko, and H. Lang, *J. Org. Chem.*, 1995, **60**, 4002.
1995JOC7589 A. R. Katritzky, G. Zhang, and J. Jiang, *J. Org. Chem.*, 1995, **60**, 7589.
1995JOC7605 A. R. Katritzky, G. Zhang, and J. Jiang, *J. Org. Chem.*, 1995, **60**, 7605.
1995JOC7612 A. R. Katritzky and H. Lang, *J. Org. Chem.*, 1995, **60**, 7612.
1995JOC7619 A. R. Katritzky, H. Lang, Z. Wang, Z. Zhang, and H. Song, *J. Org. Chem.*, 1995, **60**, 7619.
1995JOC7625 A. R. Katritzky, G. Zhang, J. Jiang, and P. J. Steel, *J. Org. Chem.*, 1995, **60**, 7625.
1995JOC7631 A. R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 7631.
1995J(P2)1645 A. R. Katritzky, I. B. Puschmann, C. V. Stevens, and A. P. Wells, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1645.
1995S503 A. R. Katritzky, H. X. Chang, and B. Yang, *Synthesis*, 1995, 503.
1995S1315 A. R. Katritzky, H. Wu, L. Xie, S. Rachwal, B. Rachwal, J. Jiang, G. Zhang, and H. Lang, *Synthesis*, 1995, 1315.
1995SC539 A. R. Katritzky, l. Xie, and D. Cundy, *Synth. Commun.*, 1995, **25**, 539.
1995T8703 A. R. Katritzky, O. Denisko, and H. Lang, *Tetrahedron*, 1995, **51**, 8703.
1995T13271 A. R. Katritzky, L. Zhu, H. Lang, O. Denisko, and Z. Wang, *Tetrahedron*, 1995, **51**, 13271.
1995TL343 A. R. Katritzky, H. X. Chang, and S. V. Verin, *Tetrahedron Lett.*, 1995, **36**, 343.
1995TL841 A. R. Katritzky, Z. Yang, and J. L. Moutou, *Tetrahedron Lett.*, 1995, **36**, 841.
1995TL5491 A. R. Katritzky, J. Soloducho, R. P. Musgrave, and J. C. Breytenbach, *Tetrahedron Lett.*, 1995, **36**, 5491.
1996AQ138 A. R. Katritzky, Q. Hong, J. Chen, Z. Yang, and S. A. Belyakov, *An. Quim.*, 1996, **92**, 138.
1996CHE775 A. R. Katritzky, Z. Wang, H. Lang, and P. J. Steel, *Chem. Heterocycl. Compd. (English Transl.)*, 1996, **31**, 775.
1996CHEC-II(4)1 W. Q. Fan and A. R. Katritzky; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 4, p. 1.
1996H(42)273 A. R. Katritzky, D. Cheng, and R. P. Musgrave, *Heterocycles*, 1996, **42**, 273.
1996HAC365 A. R. Katritzky, M. Soleiman, and B. Yang, *Heteroatom Chem.*, 1996, **7**, 365.
1996HCO1996 A. R. Katritzky, Z. Wang, and H. Lang, *Heterocycl. Commun.*, 1996, **2**, 1996.
1996LA1235 R. Faust and C. Weber, *Liebigs Ann.*, 1996, 1235.
1996JHC335 A. R. Katritzky, C. N. Fali, I. V. Shcherbakova, and S. V. Verin, *J. Heterocycl. Chem.*, 1996, **33**, 335.
1996JHC607 A. R. Katritzky and B. Yang, *J. Heterocycl. Chem.*, 1996, **33**, 607.
1996JHC1927 A. R. Katritzky, I. Ghiviriga, D. C. Oniciu, and F. Soti, *J. Heterocycl. Chem.*, 1996, **33**, 1927.
1996JOC1624 A. R. Katritzky and J. Li, *J. Org. Chem.*, 1996, **61**, 1624.
1996JOC3117 A. R. Katritzky, B. Rachwal, S. Rachwal, and K. A. Abboud, *J. Org. Chem.*, 1996, **61**, 3117.
1996JOC4035 A. R. Katritzky, H. Wu, and L. Xie, *J. Org. Chem.*, 1996, **61**, 4035.
1996JOC7558 A. R. Katritzky, G. Zhang, L. Xie, and I. Ghiviriga, *J. Org. Chem.*, 1996, **61**, 7558.
1996JOC7564 A. R. Katritzky, L. Xie, and L. Serdyuk, *J. Org. Chem.*, 1996, **61**, 7564.
1996JOC7571 A. R. Katritzky, D. Toader, and L. Xie, *J. Org. Chem.*, 1996, **61**, 7571.
1996JOC7585 A. R. Katritzky, S. A. Belyakov, A. Sorochinsky, P. J. Steel, O. F. Schall, and G. W. Gokel, *J. Org. Chem.*, 1996, **61**, 7585.
1996JPR684 A. R. Katritzky and J. Jiang, *J. Prakt. Chem.*, 1996, **338**, 684.
1996LA745 A. R. Katritzky, A. Jesorka, J. Wang, B. Yang, J. Wu, and P. J. Steel, *Liebigs Ann.*, 1996, 745.
1996LA881 C. Wedler, K. Kleiner, A. Kunath, and H. Schick, *Liebigs Ann.*, 1996, 881.
1996LA1235 R. Faust and C. Weber, *Liebigs Ann.*, 1996, 1235.
1996OM486 A. R. Katritzky, Z. Wang, and H. Lang, *Organometallics*, 1996, **15**, 486.

1996POL4011 S. Thambidurai, K. Jeyasubramanian, and S. K. Ramalingam, *Polyhedron*, 1996, **15**, 4011.
1996S1425 A. R. Katritzky, D. Toader, and L. Xie, *Synthesis*, 1996, 1425.
1996SC2657 A. R. Katritzky, K. A. Heck, J. Li, A. Wells, and C. Garot, *Synth. Commun*, 1996, **26**, 2657.
1996SC3773 A. R. Katritzky, T. Blitzke, and J. Li, *Synth. Commun*, 1996, **26**, 3773.
1996SC4049 A. R. Katritzky, Z. Zhang, and H. Lang, *Synth. Commun*, 1996, **26**, 4049.
1996SL701 A. R. Katritzky, B. Yang, and Y. Qian, *Synlett*, 1996, 701.
1996T15031 A. R. Katritzky, S. Rachwal, and B. Rachwal, *Tetrahedron*, 1996, **48**, 15031.
1996TL347 A. R. Katritzky and L. Xie, *Tetrahedron Lett.*, 1996, **37**, 347.
1996TL3731 S. Kobayashi, H. Ishitani, S. Komiyama, D. C. Oniciu, and A. R. Katritzky, *Tetrahedron Lett.*, 1996, **37**, 3731.
1996TL5641 A. R. Katritzky, J. R. Levell, and J. Li, *Tetrahedron Lett.*, 1996, **37**, 5641.
1996TL6631 A. R. Katritzky, J. Chen, and S. A. Belyakov, *Tetrahedron Lett.*, 1996, **37**, 6631.
1997H(44)67 A. R. Katritzky, D. Cheng, and R. P. Musgrave, *Heterocycles*, 1997, **44**, 67.
1997JA9321 A. R. Katritzky and A. R. Toader, *J. Am. Chem. Soc.*, 1997, **119**, 9321.
1997JHC1259 A. R. Katritzky, D. A. Nichols, M. Qi, and B. Yang, *J. Heterocycl. Chem.*, 1997, **34**, 1259.
1997JHC1379 A. R. Katritzky, Z. Wang, J. Li, and J. R. Levell, *J. Heterocycl. Chem.*, 1997, **34**, 1379.
1997JOC238 A. R. Katritzky and J. Li, *J. Org. Chem.*, 1997, **62**, 238.
1997JOC700 A. R. Katritzky, S. A. Belyakov, B. Rachwal, and J. L. Moutou, *J. Org. Chem.*, 1997, **62**, 700.
1997JOC706 A. R. Katritzky, D. Feng, and H. Lang, *J. Org. Chem.*, 1997, **62**, 706.
1997JOC721 A. R. Katritzky, G. Zhang, and L. Xie, *J. Org. Chem.*, 1997, **62**, 721.
1997JOC2594 I. E. Pop, B. P. Deprez, and A. L. Tartar, *J. Org. Chem.*, 1997, **62**, 2594.
1997JOC4116 A. R. Katritzky and M. Qi, *J. Org. Chem.*, 1997, **62**, 4116.
1997JOC4121 A. R. Katritzky, M. Qi, D. Feng, and D. A. Nichols, *J. Org. Chem.*, 1997, **62**, 4121.
1997JOC4125 A. R. Katritzky, Z. Wang, H. Lang, and D. Feng, *J. Org. Chem.*, 1997, **62**, 4125.
1997JOC4131 A. R. Katritzky, D. Feng, and H. Lang, *J. Org. Chem.*, 1997, **62**, 4131.
1997JOC4142 A. R. Katritzky, J. Wang, N. Karodia, and J. Li, *J. Org. Chem.*, 1997, **62**, 4142.
1997JOC4148 A. R. Katritzky, C. N. Fali, and J. Li, *J. Org. Chem.*, 1997, **62**, 4148.
1997JOC4155 A. R. Katritzky, D. P. M. Pleynet, and B. Yang, *J. Org. Chem.*, 1997, **62**, 4155.
1997JOC6210 A. R. Katritzky, S. A. Belyakov, A. E. Sorochinsky, S. A. Henderson, and J. Chen, *J. Org. Chem.*, 1997, **62**, 6210.
1997JOC6215 A. R. Katritzky, L. Serdyuk, L. Xie, and I. Ghiviriga, *J. Org. Chem.*, 1997, **62**, 6215.
1997JOC8198 A. R. Katritzky, P. Czerney, and J. R. Levell, *J. Org. Chem.*, 1997, **62**, 8198.
1997JOC8201 A. R. Katritzky, J. Yao, and M. Qi, *J. Org. Chem.*, 1997, **62**, 8201.
1997JOC8205 A. R. Katritzky, C. N. Fali, and J. Li, *J. Org. Chem.*, 1997, **62**, 8205.
1997JOC8210 A. R. Katritzky, G. Qiu, and B. Yang, *J. Org. Chem.*, 1997, **62**, 8210.
1997JOC8215 A. R. Katritzky, S. A. Belyakov, S. A. Henderson, and P. J. Steel, *J. Org. Chem.*, 1997, **62**, 8215.
1997JOC9177 P. Uhlmann, J. Felding, P. Vedso, and M. Begtrup, *J. Org. Chem.*, 1997, **62**, 9177.
1997J(P1)2739 D. J. Hagan, E. Gimenez-Arnau, C. H. Schwalbe, and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans 1*, 1997, 2739.
1997SC907 A. R. Katritzky, D. C. Oniciu, and I. Ghiviriga, *Synth. Commun.*, 1997, **27**, 907.
1997SC1613 A. R. Katritzky, D. C. Oniciu, and I. Ghiviriga, *Synth. Commun.*, 1997, **27**, 1613.
1997SC1623 A. R. Katritzky, C. N. Fali, J. Li, D. J. Ager, and I. Prakash, *Synth. Commun.*, 1997, **27**, 1623.
1997SC2467 A. R. Katritzky, G. Zhang, and L. Xie, *Synth. Commun.*, 1997, **27**, 2467.
1997SC3951 A. R. Katritzky, G. Zhang, and L. Xie, *Synth. Commun.*, 1997, **27**, 3951.
1997SC3963 A. R. Katritzky, J. Wang, N. Karodia, and L. Li, *Synth. Commun.*, 1997, **27**, 3963.
1997TL7015 A. R. Katritzky, Z. Zhang, and M. Qi, *Tetrahedron Lett.*, 1997, **38**, 7015.
1998ALD33 A. R. Katritzky and S. A. Belyakov, *Aldrichim. Acta*, 1998, **31**, 33.
1998CCC599 A. R. Katritzky and M. Qi, *Collect. Czech. Chem. Commun.*, 1998, **63**, 599.
1998CRV409 A. R. Katritzky, X. Lan, J. Z. Yang, and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409.
1998EJO2623 A. R. Katritzky, P. Czerney, J. R. Levell, and W. Du, *Eur. J. Org. Chem.*, 1998, 2623.
1998H(48)187 A. R. Katritzky, Z. Zhang, H. Lang, and L. Xie, *Heterocycles*, 1998, **48**, 187.
1998H(48)1567 A. R. Katritzky, J. Wang, and S. A. Henderson, *Heterocycles*, 1998, **48**, 1567.
1998H(48)2535 A. R. Katritzky, Y. Fang, M. Qi, and D. Feng, *Heterocycles*, 1998, **48**, 2535.
1998JCM334 A. R. Katritzky, A. A. Abdel-Fattah, S. A. Belyakov, and A. F. M. Fahmy, *J. Chem. Res. (S)*, 1998, 334.
1998JHC173 A. R. Katritzky, D. A. Nichols, and M. Qi, *J. Hetеterocycl. Chem.*, 1998, **35**, 173.
1998JHC467 A. R. Katritzky, D. Semenzin, B. Yang, and D. Pleynet, *J. Hetеterocycl. Chem.*, 1998, **35**, 467.
1998JOC1467 A. R. Katritzky, B. Yang, and N. S. Dalal, *J. Org. Chem.*, 1998, **63**, 1467.
1998JOC1473 A. R. Katritzky, D. Feng, and M. Qi, *J. Org. Chem.*, 1998, **63**, 1473.
1998JHC1505 N. Rumpf, D. Groschl, H. Meier, D. C. Oniciu, and A. R. Katritzky, *J. Hetеterocycl. Chem.*, 1998, **35**, 1505.
1998JOC2110 A. R. Katritzky, D. C. Oniciu, I. Ghiviriga, and F. Soti, *J. Org. Chem.*, 1998, **63**, 2110.
1998JOC3438 A. R. Katritzky, D. Cheng, and J. Li, *J. Org. Chem.*, 1998, **63**, 3438.
1998JOC3445 A. R. Katritzky, X. Wang, L. Xie, and D. Toader, *J. Org. Chem.*, 1998, **63**, 3445.
1998JOC3450 A. R. Katritzky, S. N. Denisenko, D. C. Oniciu, and I. Ghiviriga, *J. Org. Chem.*, 1998, **63**, 3450.
1998JOC5232 A. R. Katritzky, J. Yao, and M. Qi, *J. Org. Chem.*, 1998, **63**, 5232.
1998JOC6699 A. R. Katritzky, B. Yang, G. Qiu, and P. J. Steel, *J. Org. Chem.*, 1998, **63**, 6699.
1998JOC6704 A. R. Katritzky, D. Cheng, S. A. Henderson, and J. Li, *J. Org. Chem.*, 1998, **63**, 6704.
1998JOC6710 A. R. Katritzky, W. Du, J. R. Levell, and J. Li, *J. Org. Chem.*, 1998, **63**, 6710.
1998JOC9978 A. R. Katritzky, D. Toader, and X. Wang, *J. Org. Chem.*, 1998, **63**, 9978.
1998JOC9983 A. R. Katritzky, D. Toader, and C. Chassaing, *J. Org. Chem.*, 1998, **63**, 9983.
1998JOC9987 A. R. Katritzky, M. V. Voronkov, and D. Toader, *J. Org. Chem.*, 1998, **63**, 9987.
1998JOC9992 A. R. Katritzky, B. Yang, and D. P. M. Pleynet, *J. Org. Chem.*, 1998, **63**, 9992.
1998J(P1)1059 A. R. Katritzky, L. Serdyuk, and L. Xie, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1059.

1998J(P2)2515 A. R. Katritzky, M. V. Voronkov, and D. Toader, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2515.
1998OPP325 A. R. Katritzky, Y. Fang, and S. A. Belyakov, *Org. Prep. Proced. Int.*, 1998, 325.
1998S1181 J. Felding, P. Uhlmann, J. Kristensen, P. Vedso, and M. Begtrup, *Synthesis*, 1998, 1181.
1998S1421 A. R. Katritzky, C. N. Fali, W. Bao, and M. Qi, *Synthesis*, 1998, 1421.
1998S1487 A. R. Katritzky, R. Abonia, B. Yang, M. Qi, and B. Insuasty, *Synthesis*, 1998, 1487.
1998S1627 A. R. Katritzky, D. P. M. Pleynet, B. Yang, and J. Yao, *Synthesis*, 1998, 1627.
1998T2647 A. R. Katritzky and M. Qi, *Tetrahedron*, 1998, **54**, 2647.
1998T7167 A. R. Katritzky, S. Strah, and S. A. Belyakov, *Tetrahedron*, 1998, **54**, 7167.
1998TL363 A. R. Katritzky, C. N. Fali, and M. Qi, *Tetrahedron Lett.*, 1998, **39**, 363.
1998TL1697 A. R. Katritzky, X. L. Cui, B. Yang, and P. J. Steel, *Tetrahedron Lett.*, 1998, **39**, 1697.
1998TL2289 A. R. Katritzky, C. N. Fali, and M. Qi, *Tetrahedron Lett.*, 1998, **39**, 2289.
1998TL6437 A. R. Katritzky, W. Bao, M. Qi, C. N. Fali, and I. Prakash, *Tetrahedron Lett.*, 1998, **39**, 6437.
1998TL6835 A. R. Katritzky, D. Feng, and M. Qi, *Tetrahedron Lett.*, 1998, **39**, 6835.
1999H(50)767 A. R. Katritzky, A. E. R. Ferwanah, and S. N. Denisenko, *Heterocycles*, 1999, **50**, 767.
1999H(50)1877 A. R. Katritzky, M. V. Voronkov, A. Pastor, and D. Tatham, *Heterocycles*, 1999, **50**, 1877.
1999JCO173 A. R. Katritzky, S. A. Belyakov, and D. Tymoshenko, *J. Comb. Chem.*, 1999, **1**, 173.
1999JCM162 A. R. Katritzky, J. Cobo-Domingo, B. Yang, and P. J. Steel, *J. Chem. Res. (S)*, 1999, 162.
1999JCM230 A. R. Katritzky, D. A. Monteux, D. O. Tymoshenko, and S. A. Belyakov, *J. Chem. Res. (S)*, 1999, 230.
1999JHC371 A. R. Katritzky, X. Cui, and Q. Long, *J. Heterocycl. Chem.*, 1999, **36**, 371.
1999JHC473 A. R. Katritzky, S. Agamy, B. Yang, and G. Qiu, *J. Heterocycl. Chem.*, 1999, **36**, 473.
1999JHC755 A. R. Katritzky, S. Strah, and D. O. Tymoshenko, *J. Heterocycl. Chem.*, 1999, **36**, 755.
1999JHC777 A. R. Katritzky, A. Pastor, and M. V. Voronkov, *J. Heterocycl. Chem.*, 1999, **36**, 777.
1999JHC927 A. R. Katritzky, W. Du, Y. Matsukawa, I. Ghiviriga, and S. N. Denisenko, *J. Heterocycl. Chem.*, 1999, **36**, 927.
1999JOC346 A. R. Katritzky, J. Yao, W. Bao, M. Qi, and P. J. Steel, *J. Org. Chem.*, 1999, **64**, 346.
1999JOC488 J. H. Ahn, M. J. Joung, N. M. Yoon, D. C. Oniciu, and A. R. Katritzky, *J. Org. Chem.*, 1999, **64**, 488.
1999JOC1888 A. R. Katritzky, L. Serdyuk, D. Toader, and X. Wang, *J. Org. Chem.*, 1999, **64**, 1888.
1999JOC1979 A. R. Katritzky, X. L. Cui, B. Yang, and P. J. Steel, *J. Org. Chem.*, 1999, **64**, 1979.
1999JOC2124 A. R. Katritzky, Z. Huang, Y. Fang, and I. Prakash, *J. Org. Chem.*, 1999, **64**, 2124.
1999JOC3328 A. R. Katritzky, Z. Luo, and X. L. Cui, *J. Org. Chem.*, 1999, **64**, 3328.
1999JOC3332 A. R. Katritzky, D. O. Tymoshenko, and S. A. Belyakov, *J. Org. Chem.*, 1999, **64**, 3332.
1999JOC6066 A. R. Katritzky, J. Yao, and B. Yang, *J. Org. Chem.*, 1999, **64**, 6066.
1999JOC6071 A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko, S. A. Belyakov, I. Ghiviriga, and P. J. Steel, *J. Org. Chem.*, 1999, **64**, 6071.
1999JOC6080 A. R. Katritzky, D. Toader, C. Chassaing, and D. C. Aslan, *J. Org. Chem.*, 1999, **64**, 6080.
1999JOC7618 A. R. Katritzky, G. Qiu, B. Yang, and H. Y. He, *J. Org. Chem.*, 1999, **64**, 7618.
1999JOC7622 A. R. Katritzky, Y. Fang, and A. Silina, *J. Org. Chem.*, 1999, **64**, 7622.
1999JOC7625 A. R. Katritzky, Z. Huang, and Y. Fang, *J. Org. Chem.*, 1999, **64**, 7625.
1999JPR152 A. R. Katritzky, W. Du, S. N. Denisenko, P. Czerney, and P. J. Steel, *J. Prakt. Chem.*, 1999, **341**, 152.
1999OL1755 A. R. Katritzky, H. Y. He, G. Qiu, P. J. Bratt, S. H. Parrish, and A. Angerhofer, *Org. Lett.*, 1999, **1**, 1755.
1999OM4270 C. Churlaud, J. Pornet, D. C. Oniciu, and A. R. Katritzky, *Organometallics*, 1999, **18**, 4270.
1999S2114 A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko, and S. A. Essawy, *Synthesis*, 1999, 2114.
1999T3489 A. R. Katritzky, G. Qiu, B. Yang, and P. J. Steel, *Tetrahedron*, 1999, **55**, 3489.
1999T8263 A. R. Katritzky, J. Li, and L. Xie, *Tetrahedron*, 1999, **55**, 8263.
1999TA255 A. R. Katritzky, J. Cobo-Domingo, B. Yang, and P. J. Steel, *Tetrahedron Asymmetry*, 1999, **10**, 255.
1999TL253 A. R. Katritzky, W. Bao, Y. Fang, M. Qi, and I. Prakash, *Tetrahedron Lett.*, 1999, **40**, 253.
2000ARK(v)667 A. R. Katritzky, D. A. Nichols, and M. V. Voronkov, *Arkivoc*, 2000, **v**, 667.
2000CCA569 I. Butula and M. J. M. Takac, *Croat. Chem. Acta*, 2000, **73**, 569.
2000EJM715 G. Biagi, V. Calderone, I. Giorgi, O. Livi, V. Scartoni, B. Baragatti, and E. Martinotti, *Eur. J. Med. Chem.*, 2000, **35**, 715.
2000H(53)203 A. R. Katritzky, B. Yang, D. P. M. Pleynet, and J. Wang, *Heterocycles*, 2000, **53**, 203.
2000H(53)331 A. R. Katritzky, Y. Fang, D. Feng, A. Silina, and I. Prakash, *Heterocycles*, 2000, **53**, 331.
2000H(53)1783 A. R. Katritzky and Y. Fang, *Heterocycles*, 2000, **53**, 1783.
2000JFC(106)133 Y. Xu, Y. Wang, S. Zhu, G. Zhu, Y. Jia, and Q. Huang, *J. Fluorine Chem.*, 2000, **106**, 133.
2000JHC167 F. Al-Omran, N. Al-Awadl, O. Yousef, and M. H. Elnagdi, *J. Heterocycl. Chem.*, 2000, **37**, 167.
2000JHC747 A. Lauria, P. Diana, P. Barraja, A. M. Almerico, G. Cirrincione, and G. Dattolo, *J. Heterocycl. Chem.*, 2000, **37**, 747.
2000JHC1505 A. R. Katritzky, M. A. C. Button, and S. N. Denisenko, *J. Heterocycl. Chem.*, 2000, **37**, 1505.
2000JOC1886 A. R. Katritzky, H. Odens, and M. V. Voronkov, *J. Org. Chem.*, 2000, **65**, 1886.
2000JOC3679 A. R. Katritzky and A. Pastor, *J. Org. Chem.*, 2000, **65**, 3679.
2000JOC4364 A. R. Katritzky, S. Mehta, H. Y. He, and X. Cui, *J. Org. Chem.*, 2000, **65**, 4364.
2000JOC8059 A. R. Katritzky, D. O. Tymoshenko, D. Monteux, V. Vvedensky, G. Nikonov, C. B. Cooper, and M. Deshpande, *J. Org. Chem.*, 2000, **65**, 8059.
2000JOC8063 A. R. Katritzky, J. Yao, and O. V. Denisko, *J. Org. Chem.*, 2000, **65**, 8063.
2000JOC8066 A. R. Katritzky, O. V. Denisko, and S. Busont, *J. Org. Chem.*, 2000, **65**, 8066.
2000JOC8069 A. R. Katritzky, T. B. Huang, M. V. Voronkov, and P. J. Steel, *J. Org. Chem.*, 2000, **65**, 8069.
2000JOC8074 A. R. Katritzky, L. Zhang, J. Yao, and O. V. Denisko, *J. Org. Chem.*, 2000, **65**, 8074.
2000JOC8077 A. R. Katritzky, X. Wang, and R. Maimait, *J. Org. Chem.*, 2000, **65**, 8077.
2000JOC8080 A. R. Katritzky, B. V. Rogovoy, C. Chassaing, and V. Vvedensky, *J. Org. Chem.*, 2000, **65**, 8080.
2000JOC8210 A. R. Katritzky, H. Y. He, and K. Suzuki, *J. Org. Chem.*, 2000, **65**, 8210.
2000JOC8819 A. R. Katritzky, T. B. Huang, M. V. Voronkov, M. Wang, and H. Kolb, *J. Org. Chem.*, 2000, **65**, 8819.
2000JOC9201 A. R. Katritzky, G. Qiu, Q. H. Long, H. Y. He, and P. J. Steel, *J. Org. Chem.*, 2000, **65**, 9201.

2000JOC9206 A. Degl'Innocenti, A. Capperucci, D. C. Oniciu, and A. R. Katritzky, *J. Org. Chem.*, 2000, **65**, 9206.

2000J(P2)1375 A. R. Katritzky, Z. Luo, Y. Fang, D. Feng, and I. Ghiviriga, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1375.

2000OL3789 A. R. Katritzky, S. Zhang, and Y. Fang, *Org. Lett.*, 2000, **2**, 3789.

2000PAC1597 A. R. Katritzky and O. V. Denisko, *Pure Appl. Chem.*, 2000, **72**, 1597.

2000S2029 A. R. Katritzky, Y. Fang, A. Donkor, and J. Xu, *Synthesis*, 2000, 2029.

2000TL9691 A. R. Katritzky, Z. Luo, and Y. Fang, *Tetrahedron Lett.*, 2000, **41**, 9691.

2001ARK(v)68 A. R. Katritzky, R. Maimait, A. Denisenko, and S. N. Denisenko, *ARKIVOC*, 2001, **v**, 68.

2001ARK(xi)41 A. R. Katritzky, O. V. Denisko, Y. Fang, L. Zhang, and Z. Wang, *ARKIVOC*, 2001, **xi**, 41.

2001BCJ2133 S. H. Mashraqui, S. Kumar, and C. D. Mudaliar, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 2133.

2001CNR8452 M. Dowsett, C. Harper-Wynne, I. Boeddinghaus, J. Salter, M. Hills, M. Dixon, S. Ebbs, G. Gui, N. Sacks, and I. Smith, *Cancer Res.*, 2001, **61**, 8452.

2001CHE470 V. M. Timoshenko, Ya. V. Nikolin, A. N. Chernega, E. B. Rusanov, and Yu. G. Shermolovich, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 470.

2001CHE861 S. V. Chapyshev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 861.

2001CJC1655 A. R. Katritzky, N. G. Akhmedov, S. N. Denisenko, and S. Perumal, *Can. J. Chem.*, 2001, **79**, 1655.

2001EJI3005 C. M. Thomas, A. Neels, H. Stoeckli-Evans, and G. Sus-Fink, *Eur. J. Inorg. Chem.*, 2001, 3005.

2001FA827 G. Biagi, I. Giorgi, O. Livi, V. Scartoni, P. L. Barili, V. Calderone, and E. Martinotti, *Farmaco*, 2001, **56**, 827.

2001FA841 G. Biagi, V. Calderone, I. Giorgi, O. Livi, V. Scartoni, B. Baragatti, and E. Martinotti, *Farmaco*, 2001, **56**, 841.

2001H(54)301 A. R. Katritzky, M. A. C. Button, and S. N. Denisko, *Heterocycles*, 2001, **54**, 301.

2001IJP129 M. Zovko, B. Zorc, M. Lovrek, and B. Boneschans, *Int. J. Pharm.*, 2001, **228**, 129.

2001JCX217 M. A. Mendez-Rojas, S. G. Bodige, K. Ejsmont, and W. H. Watson, *J. Chem. Crystallogr.*, 2001, **31**, 217.

2001JCO167 A. R. Katritzky, A. Pastor, M. Voronkov, and D. Tymoshenko, *J. Comb. Chem.*, 2001, **3**, 167.

2001JME4296 T. Harrison, A. P. Owens, B. J. Williams, C. J. Swain, A. Williams, E. J. Carlson, W. Rycroft, F. D. Tattersall, M. A. Cascieri, G. G. Chicchi, S. Sadowski, N. M. J. Rupniak, and R. J. Hargreaves, *J. Med. Chem.*, 2001, **44**, 4296.

2001JOC148 A. R. Katritzky, S. Mehta, and H. Y. He, *J. Org. Chem.*, 2001, **66**, 148.

2001JOC2850 A. R. Katritzky, X. Wang, and A. Denisenko, *J. Org. Chem.*, 2001, **66**, 2850.

2001JOC2858 A. R. Katritzky, Z. Luo, and Y. Fang, *J. Org. Chem.*, 2001, **66**, 2858.

2001JOC2862 A. R. Katritzky and G. Qiu, *J. Org. Chem.*, 2001, **66**, 2862.

2001JOC5585 A. R. Katritzky, R. Maimait, S. N. Denisenko, P. J. Steel, and N. G. Akhmedov, *J. Org. Chem.*, 2001, **66**, 5585.

2001JOC5590 A. R. Katritzky, Y. J. Xu, H. Y. He, and S. Mehta, *J. Org. Chem.*, 2001, **66**, 5590.

2001JOC5606 A. R. Katritzky, S. Zhang, A. H. M. Hussein, Y. Fang, and P. J. Steel, *J. Org. Chem.*, 2001, **66**, 5606.

2001JOC6787 A. R. Katritzky, M. Wang, S. Zhang, M. V. Voronkov, and P. J. Steel, *J. Org. Chem.*, 2001, **66**, 6787.

2001JOC6797 A. R. Katritzky, B. V. Rogovoy, V. Y. Vvedensky, N. Hebert, and B. Forood, *J. Org. Chem.*, 2001, **66**, 6797.

2001J(P1)2483 A. R. Katritzky, V. Y. Vvedensky, and D. O. Tymoshenko, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2483.

2001J(P1)3174 M. J. Ellis and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3174.

2001MC230 E. L. Baryshnikova, A. S. Kulikov, I. V. Ovchinnikov, V. V. Solomentsev, and N. N. Makhova, *Mendeleev Commun., Engl. Version*, 2001, 230.

2001NN1347 N. Calcerrada-Munoz, I. O'Neil, and R. Cosstick, *Nucleos., Nucleot. Nucleic Acids*, 2001, **20**, 1347.

2001PSC2200 R. Battistutta, E. De Moliner, S. Sarno, G. Zanotti, and L. A. Pinna, *Protein Sci.*, 2001, **10**, 2200.

2001RCB1630 A. G. Korepin, P. V. Galkin, N. M. Glushakova, V. P. Lodygina, I. L. Eremenko, S. E. Nefedov, and L. T. Eremenko, *Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1630.

2001RJO1762 V. G. Tsypin, M. S. Pevzner, and E. L. Golod, *Russ. J. Org. Chem. (Engl. Transl.)*, 2001, **37**, 1762.

2001S897 A. R. Katritzky, B. V. Rogovoy, V. Y. Vvedensky, K. Kovalenko, P. J. Steel, V. I. Markov, and B. Forood, *Synthesis*, 2001, 897.

2001SL458 A. R. Katritzky and D. Toader, *Synlett*, 2001, 458.

2001TA2427 A. R. Katritzky, H. Y. He, R. Jiang, and Q. Long, *Tetrahedron Asymmetry*, 2001, **12**, 2427.

2001TL9109 A. R. Katritzky, T. B. Huang, and P. J. Steel, *Tetrahedron Lett.*, 2001, **42**, 9109.

2002AGE2596 V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2596.

2002AN838 G. McAnally, C. McLaughlin, R. Brown, D. C. Robson, K. Faulds, D. R. Tackley, W. E. Smith, and D. Graham, *Analyst*, 2002, **127**, 838.

2002ARK(iii)46 A. R. Katritzky, Z. Wang, Y. Ji, and Y. Fang, *ARKIVOC*, 2002, **iii**, 46.

2002ARK(vi)82 A. R. Katritzky, V. Vvedensky, X. Cai, B. Rogovoy, and P. J. Steel, *ARKIVOC*, 2002, **vi**, 82.

2002ARK(vii)146 A. R. Katritzky, Y. Zhang, and S. K. Singh, *ARKIVOC*, 2002, **vii**, 146.

2002ARK(viii)134 A. R. Katritzky, M. Wang, H. Yang, S. Zhang, and N. G. Akhmedov, *ARKIVOC*, 2002, **viii**, 134.

2002ARK(viii)143 T. Kocar, S. Recnik, J. Svete, and B. Stanovnik, *ARKIVOC*, 2002, **viii**, 143.

2002ARK(xi)39 A. R. Katritzky, H. Yang, S. Zhang, and M. Wang, *ARKIVOC*, 2002, **xi**, 39.

2002ARK(xiii)17 A. R. Katritzky, B. V. Rogovoy, and A. Y. Mitrokhin, *ARKIVOC*, 2002, **xiii**, 17.

2002BCJ2691 G. Athanasellis, E. Gavrielatos, and O. Igglessi-Markopoulou, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 2691.

2002BJ41 M. Ruzzene, D. Penzo, and L. A. Pinna, *Biochem. J.*, 2002, **364**, 41.

2002BKC437 S. Radi and H. B. Lazrek, *Bull. Korean Chem. Soc.*, 2002, **23**, 437.

2002BMC947 A. K. Prasad, Himanshu, A. Bhattacharya, C. E. Olsen, and V. S. Parmar, *Bioorg. Med. Chem.*, 2002, **10**, 947.

2002BMC963 H. R. Tyagi, C. E. Olsen, W. Errington, V. S. Parmar, and A. K. Prasad, *Bioorg. Med. Chem.*, 2002, **10**, 963.

2002BML827 J. R. Young, S. X. Huang, T. F. Walsh, M. J. Wyvratt, Jr., Y. T. Yang, J. B. Yudkovitz, J. Cui, G. R. Mount, R. N. Ren, T. J. Wu, X. Shen, K. A. Lyons, A. H. Mao, J. R. Carlin, B. V. Karanam, S. H. Vincent, K. Cheng, and M. T. Goulet, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 827.

2002BML1809 A. R. Katritzky, B. V. Rogovoy, N. Kirichenko, and V. Vvedensky, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1809.

2002BML2515 E. M. Seward, E. Carlson, T. Harrison, K. E. Haworth, R. Herbert, F. J. Kelleher, M. M. Kurtz, J. Moseley, S. N. Owen, A. P. Owens, S. J. Sadowski, C. J. Swain, and B. J. Williams, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2515.

2002BML2771 M. A. Letavic, B. S. Bronk, C. D. Bertsche, J. M. Casavant, H. Cheng, K. L. Daniel, D. M. George, S. F. Hayashi, B. J. Kamicker, N. L. Kolosko, L. J. L. Norcia, V. D. Oberton, M. A. Rushing, and S. L. Santoro, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2771.

2002BML2855 S. Raghavan, Z. Yang, R. T. Mosley, W. A. Schleif, L. Gabryelski, D. B. Olsen, M. Stahlhut, L. C. Kuo, E. A. Emini, K. T. Chapman, and J. R. Tata, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2855.

2002CC2100 L. Fruk, A. Grondin, W. E. Smith, and D. Graham, *Chem. Commun.*, 2002, 2100.

2002CLC86 J. Berlin, K. D. Tutsch, R. Z. Arzoomanian, D. Alberti, K. Binger, C. Feierabend, A. Dresen, R. Marnocha, J. Pluda, and G. Wilding, *Clin. Cancer Res.*, 2002, **8**, 86.

2002CPB941 Y. Hirokawa, H. Harada, T. Yoshikawa, N. Yoshida, and S. Kato, *Chem. Pharm. Bull*, 2002, **50**, 941.

2002EJI2488 G. S. Papaefstathiou, R. Vincente, C. P. Raptopoulou, A. Terzis, A. Escuer, and S. P. Perlepes, *Eur. J. Inorg. Chem.*, 2002, 2488.

2002EJM565 G. Biagi, I. Giorgi, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, and M. L. Trincavelli, *Eur. J. Med. Chem.*, 2002, **37**, 565.

2002EJO493 T. Kim, K. Kim, and Y. J. Park, *Eur. J. Org. Chem.*, 2002, 493.

2002H(58)311 A. R. Katritzky, G. N. Nikonov, D. O. Tymoshenko, and P. J. Steel, *Heterocycles*, 2002, **58**, 311.

2002HCA2056 G. Mloston, K. Urbaniak, and H. Heimgartner, *Helv. Chim. Acta*, 2002, **85**, 2056.

2002HCA2644 G. Mloston, K. Urbaniak, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2002, **85**, 2644.

2002ICC453 L. Li, X. Wang, G. Shen, R. Wang, and D. Shen, *Inorg. Chem. Comm.*, 2002, **5**, 453.

2002JA4738 S. Komeda, M. Lutz, A. L. Spek, Y. Yamanaka, T. Sato, M. Chikuma, and J. Reedijk, *J. Am. Chem. Soc.*, 2002, **124**, 4738.

2002JA12950 P. M. Wehn and J. Du Bois, *J. Am. Chem. Soc.*, 2002, **124**, 12950.

2002JCO576 O. W. Gooding, L. Vo, S. Bhattacharyya, and J. W. Labadie, *J. Comb. Chem.*, 2002, **4**, 576.

2002JCM153 H. P. Le, R. Neidlein, and H. Suschitzky, *J. Chem. Res. (S)*, 2002, 153.

2002JCM264 S. Radi and H. B. Lazrek, *J. Chem. Res. (S)*, 2002, 264.

2002JCM388 P. F. Zhang and Z. C. Chen, *J. Chem. Res. (S)*, 2002, 388.

2002JEP536 R. A. Duffy, G. B. Varty, C. A. Morgan, and J. E. Lachowicz, *J. Pharmacol. Exp. Ther.*, 2002, **301**, 536.

2002JFC(116)81 W. M. Peng and S. Z. Zhu, *J. Fluorine Chem.*, 2002, **116**, 81.

2002JHC759 A. R. Katritzky, S. Zhang, M. Wang, H. Kolb, and P. J. Steel, *J. Heterocycl. Chem.*, 2002, **39**, 759.

2002JHC1111 A. O. Koren, *J. Heterocycl. Chem.*, 2002, **39**, 1111.

2002JME590 R. A. Heald, C. Modi, J. C. Cookson, I. Hutchinson, C. A. Laughton, S. M. Gowan, L. R. Kelland, and M. F. G. Stevens, *J. Med. Chem.*, 2002, **45**, 590.

2002JOC1184 P. Abato, C. M. Yuen, J. Y. Cubanski, and C. T. Seto, *J. Org. Chem.*, 2002, **67**, 1184.

2002JOC3057 C. W. Tornoe, C. Christensen, and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.

2002JOC3104 A. R. Katritzky and O. V. Denisko, *J. Org. Chem.*, 2002, **67**, 3104.

2002JOC3109 A. R. Katritzky, K. Suzuki, and H. Y. He, *J. Org. Chem.*, 2002, **67**, 3109.

2002JOC3115 A. R. Katritzky, S. K. Singh, and H. Y. He, *J. Org. Chem.*, 2002, **67**, 3115.

2002JOC3118 A. R. Katritzky, T. B. Huang, O. V. Denisko, and P. J. Steel, *J. Org. Chem.*, 2002, **67**, 3118.

2002JOC4951 A. R. Katritzky, H. Y. He, and J. Wang, *J. Org. Chem.*, 2002, **67**, 4951.

2002JOC4957 A. R. Katritzky, K. Kirichenko, A. M. Elsayed, Y. Ji, Y. Fang, and P. J. Steel, *J. Org. Chem.*, 2002, **67**, 4957.

2002JOC6136 S. Simaan, K. Agbaria, and S. E. Biali, *J. Org. Chem.*, 2002, **67**, 6136.

2002JOC7526 A. R. Katritzky, A. A. A. Abdel-Fattah, and M. Wang, *J. Org. Chem.*, 2002, **67**, 7526.

2002JOC7530 A. R. Katritzky, S. K. Nair, and A. Silina, *J. Org. Chem.*, 2002, **67**, 7530.

2002JOC8220 A. R. Katritzky, R. Jain, Y. J. Xu, and P. J. Steel, *J. Org. Chem.*, 2002, **67**, 8220.

2002JOC8224 A. R. Katritzky, K. Suzuki, and H. Y. He, *J. Org. Chem.*, 2002, **67**, 8224.

2002JOC8230 A. R. Katritzky, R. Maimait, Y. J. Xu, and Y. S. Gyoung, *J. Org. Chem.*, 2002, **67**, 8230.

2002JOC8237 A. R. Katritzky, S. K. Nair, V. Rodriguez-Garcia, and Y. J. Xu, *J. Org. Chem.*, 2002, **67**, 8237.

2002JOC8489 E. A. Voight, C. Rein, and S. D. Burke, *J. Org. Chem.*, 2002, **67**, 8489.

2002JOC9471 X. Zhang, M. Breslav, J. Grimm, K. Guan, A. Huang, F. Liu, C. A. Maryanoff, D. Palmer, M. Patel, Y. Qian, C. Shaw, K. Sorgi, S. Stefanick, and D. Xu, *J. Org. Chem.*, 2002, **67**, 9471.

2002JOM(658)251 C. M. Thomas, B. Therrien, A. Neels, H. Stoeckli-Evans, and G. Suss-Fink, *J. Organomet. Chem.*, 2002, **658**, 251.

2002JON1026 C. L. Harper-Wynne, N. P. M. Sacks, K. Shenton, F. A. MacNeil, P. Sauven, I. J. Laidlaw, Z. Rayter, S. Miall, A. Howes, J. Salter, M. J. Hills, F. M. Lowe, R. A'Hern, N. Nasiri, D. Doody, J. Iqbal, and M. Dowsett, *J. Clin. Oncol.*, 2002, **20**, 1026.

2002J(P1)211 Y. A. Rozin, E. A. Savel'eva, Y. Y. Morzherin, W. Dehaen, S. Toppet, L. Van Meervelt, and V. A. Bakulev, *J. Chem. Soc., Perkin Trans. 1*, 2002, 211.

2002J(P1)592 A. R. Katritzky, Y. J. Xu, and H. Y. He, *J. Chem. Soc., Perkin Trans. 1*, 2002, 592.

2002J(P1)1420 P. Zanirato, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1420.

2002J(P1)1574 N. N. Volkova, E. V. Tarasov, L. Van Meervelt, S. Toppet, W. Dehaen, and V. A. Bakulev, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1547.

2002J(P1)2243 J. C. Muir, G. Pattenden, and T. Ye, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2243.

2002J(P2)126 K. Banert, J. Lehmann, H. Quast, G. Meichsner, D. Regnat, and B. Seiferling, *J. Chem. Soc., Perkin Trans. 2*, 2002, 126.

2002MC83 I. V. Seregin, L. V. Batog, and N. N. Makhova, *Mendeleev Commun.*, 2002, 83.

2002NN73 M. Andrzejewska, J. Kaminski, and Z. Kazimierczuk, *Nucleos. Nucleot. Nucleic Acids*, 2002, **21**, 73.

2002NN361 N. A. Al-Masoudi and Y. A. Al-Soud, *Nucleos. Nucleot. Nucleic Acids*, 2002, **21**, 361.

2002OL1487 K. I. Booker-Milburn, P. M. Wood, R. F. Dainty, M. W. Urquhart, A. J. White, H. J. Lyon, and J. P. H. Charmant, *Org. Lett.*, 2002, **4**, 1487.

2002OL3227 M. O. Ratnikov, D. L. Lipilin, A. M. Churakov, Y. A. Strelenko, and V. A. Tartakovsky, *Org. Lett.*, 2002, **4**, 3227.

2002RJO1056 V. N. Kizhnyaev, F. A. Pokatilov, N. A. Tsypina, G. V. Ratovskii, L. I. Vereshchagin, and A. I. Smirnov, *Russ. J. Org. Chem. (Engl. Transl.)*, 2002, **38**, 1056.

2002S199 A. R. Katritzky, S. K. Nair, and G. Qiu, *Synthesis*, 2002, 199.

2002S601 A. R. Katritzky, R. Maimait, Y. J. Xu, and R. G. Akhmedova, *Synthesis*, 2002, 601.

2002SL1736 G. Athanasellis, O. Igglessi-Markopoulou, and J. Markopoulos, *Synlett*, 2002, 1736.

2002SRI265 Z. Liu and Y. Tu, *Synth. React. Inorg. Met.-Org. Chem.*, 2002, **32**, 265.

2002T4077 K. Wu and Q. Y. Chen, *Tetrahedron*, 2002, **58**, 4077.

2002T6837 F. Bustos, J. M. Gorgojo, R. Suero, and J. M. Aurrecoechea, *Tetrahedron*, 2002, **58**, 6837.

2002T9089 N. Jagerovic, M. L. Jimeno, I. Alkorta, J. Elguero, and R. M. Claramunt, *Tetrahedron*, 2002, **58**, 9089.
2002T9723 A. Lauria, P. Diana, P. Barraja, A. Montalbano, G. Cirrincione, G. Dattolo, and A. M. Almerico, *Tetrahedron*, 2002, **58**, 9723.
2002TL3021 T. Kim and K. Kim, *Tetrahedron Lett.*, 2002, **43**, 3021.
2002TL4021 N. A. Al-Masoudi and Y. A. Al-Soud, *Tetrahedron Lett.*, 2002, **43**, 4021.
2002TL8055 E. Deniau and D. Enders, *Tetrahedron Lett.*, 2002, **43**, 8055.
2002TL8351 E. Mironiuk-Puchalska, E. Kolaczkowska, and W. Sas, *Tetrahedron Lett.*, 2002, **43**, 8351.
2002TL9449 I. Yavari, A. Alizadeh, and M. Anary-Abbasinejad, *Tetrahedron Lett.*, 2002, **43**, 9449.
2002TMC377 E. Diamantopoulou, S. P. Perlepes, D. Raptis, and C. P. Raptopoulou, *Transition Met. Chem.*, 2002, **27**, 377.
2003AGE3131 M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, and A. Temperini, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3131.
2003ANS973 I. Takahashi, M. Tsuzuki, H. Kitajima, M. Hatanaka, S. Maeda, A. Yamano, T. Ohta, and S. Hosoi, *Anal. Sci.*, 2003, **19**, 973.
2003ARK(vii)110 M. Sheridan, P. James, and C. Healy, *ARKIVOC*, 2003, **vii**, 110.
2003ARK(viii)8 A. R. Katritzky, N. Kirichenko, and B. V. Rogovoy, *ARKIVOC*, 2003, **viii**, 8.
2003ARK(xiii)125 M. G. Voronkov, O. M. Trofimova, E. I. Brodskaya, Y. I. Bolgova, L. I. Larina, L. V. Klyba, E. A. Zelbst, and N. F. Chernov, *ARKIVOC*, 2003, **xiii**, 125.
2003ARK(xiv)131 A. R. Katritzky, A. V. Vakulenko, and R. Jain, *ARKIVOC*, 2003, **xiv**, 131.
2003ARK(xv)115 A. R. Katritzky, Y. Zhang, S. K. Singh, and Y. P. Le Gall, *ARKIVOC*, 2003, **xv**, 115.
2003BMC35 O. A. Phillips, E. E. Udo, A. A. M. Ali, and N. Al-Hassawi, *Bioorg. Med. Chem.*, 2003, **11**, 35.
2003BMC1701 Y. A. Al-Soud, N. A. Al-Masoudi, and A. E. R. S. Ferwanah, *Bioorg. Med. Chem.*, 2003, **11**, 1701.
2003BMC2051 A. C. Cunha, J. M. Figueiredo, J. L. M. Tributino, A. L. P. Miranda, H. C. Castro, R. B. Zingali, C. A. M. Fraga, M. C. B. V. de Souza, V. F. Ferreira, and E. J. Barreiro, *Bioorg. Med. Chem.*, 2003, **11**, 2051.
2003BML1665 J. S. Tullis, J. C. VanRens, M. G. Natchus, M. P. Clark, B. De, L. C. Hsieh, and M. J. Janusz, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1665.
2003BML2141 K. L. Yu, Y. Zhang, R. L. Civiello, K. F. Kadow, C. Cianci, M. Krystal, and N. A. Meanwell, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2141.
2003CBO397 K. M. Koeller, S. J. Haggarty, B. D. Perkins, I. Leykin, J. C. Wong, M. C. J. Kao, and S. L. Schreiber, *Chem. Biol.*, 2003, **10**, 397.
2003CC2450 Z. X. Wang and H. L. Qin, *Chem. Commun.*, 2003, 2450.
2003CCA217 I. Kalcic, M. Zovko, M. J. M. Takac, B. Zorc, and I. Butula, *Croat. Chem. Acta*, 2003, **76**, 217.
2003CCA335 M. Zovko, B. Zorc, M. J. M. Takac, B. Metelko, and P. Novak, *Croat. Chem. Acta*, 2003, **76**, 335.
2003CEJ2770 G. Molteni and A. Ponti, *Chem. Eur. J.*, 2003, **9**, 2770.
2003CEJ3383 J. K. C. Lau, C. H. S. Wong, P. S. Ng, F. M. Siu, N. L. Ma, and C. W. Tsang, *Chem. Eur. J.*, 2003, **9**, 3383.
2003CEJ4587 A. R. Katritzky and B. V. Rogovoy, *Chem. Eur. J.*, 2003, **9**, 4587.
2003CHE71 T. J. Kikalishvili and J. A. Kereselidze, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 71.
2003CHE126 T. V. Glukhareva, L. V. Dyudya, Yu. Yu. Morzherin, A. V. Tkachev, and V. A. Bakulev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 126.
2003CHE168 Yu. Yu. Morzherin, Yu. A. Rozin, E. A. Savel'eva, and V. A. Bakulev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 168.
2003CHE608 T. I. Godovikova, S. A. Vozchikova, E. L. Ignat'eva, L. I. Khmel'nitskii, and B. L. Korsunskii, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 608.
2003CHE1639 M. G. Voronkov, O. M. Trofimova, Y. I. Bolgova, L. V. Klyba, L. I. Larina, A. I. Albanov, V. A. Pestunovich, N. F. Chernov, and K. B. Petrushenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 1639.
2003CL1064 S. H. Mashraqui and M. A. Karnik, *Chem. Lett.*, 2003, **32**, 1064.
2003CME2081 P. K. Kadaba, *Curr. Med. Chem.*, 2003, **10**, 2081.
2003EJB1645 P. Borowski, J. Deinert, S. Schalinski, M. Bretner, K. Ginalski, T. Kulikowski, and D. Shugar, *Eur. J. Biochem.*, 2003, **270**, 1645.
2003EJM983 G. Biagi, I. Giorgi, O. Livi, A. Nardi, F. Pacchini, V. Scartoni, and A. Lucacchini, *Eur. J. Med. Chem.*, 2003, **38**, 983.
2003H(60)1225 A. R. Katritzky, Y. Zhang, and S. K. Singh, *Heterocycles*, 2003, **60**, 1225.
2003H(60)2669 A. Lauria, C. Patella, P. Diana, P. Barraja, A. Montalbano, G. Cirrincione, G. Dattolo, and A. M. Almerico, *Heterocycles*, 2003, **60**, 2669.
2003FA33 A. Boido, I. Vazzana, F. Mattioli, and F. Sparatore, *Farmaco*, 2003, **58**, 33.
2003IJQ572 V. Ludwig, K. Coutinho, A. C. Borin, and S. Canuto, *Int. J. Quantum Chem.*, 2003, **96**, 572.
2003JA7786 S. Kamijo, T. Jin, Z. Huo, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 7786.
2003JCCS1215 H. S. Dong and S. Q. Liu, *J. Chin. Chem. Soc.*, 2003, **50**, 1215.
2003JCD992 C. Richardson and P. J. Steel, *J. Chem. Soc., Dalton Trans.*, 2003, 992.
2003JCM75 M. J. Ellis and M. F. G. Stevens, *J. Chem. Res. (S)*, 2003, 75.
2003JCM96 B. Xu and Y. Hu, *J. Chem. Res. (S)*, 2003, 96.
2003JFC(120)65 S. Z. Zhu, G. F. Jin, and J. W. Zhao, *J. Fluorine Chem.*, 2003, **120**, 65.
2003JHC419 M. A. Ponce, O. I. Tarzi, and R. Erra-Balsells, *J. Heterocycl. Chem.*, 2003, **40**, 419.
2003JLR449 J. B. Kristensen, M. L. Pedersen, U. D. Larsen, L. Martiny, L. B. Hansen, and C. Foged, *J. Label. Compd. Radiopharm.*, 2003, **46**, 499.
2003JME265 T. Balle, J. Perregaard, M. T. Ramirez, A. K. Larsen, K. K. Soby, T. Liljefors, and K. Andersen, *J. Med. Chem.*, 2003, **46**, 265.
2003JME1116 L. Sun, C. Liang, S. Shirazian, Y. Zhou, T. Miller, J. Cui, J. Y. Fukuda, J. Y. Chu, A. Nematalla, X. Wang, H. Chen, A. Sistla, T. C. Luu, F. Tang, J. Wei, and C. Tang, *J. Med. Chem.*, 2003, **46**, 1116.
2003JME3333 P. H. Olesen, A. R. Sorensen, B. Urso, P. Kurtzhals, A. N. Bowler, U. Ehrbar, and B. F. Hansen, *J. Med. Chem.*, 2003, **46**, 3333.
2003JOC407 A. R. Katritzky, K. Manju, and P. J. Steel, *J. Org. Chem.*, 2003, **68**, 407.
2003JOC609 T. S. Seo, Z. Li, H. Ruparel, and J. Ju, *J. Org. Chem.*, 2003, **68**, 609.
2003JOC1443 A. R. Katritzky, A. A. A. Abdel-Fattah, and M. Wang, *J. Org. Chem.*, 2003, **68**, 1443.
2003JOC1480 R. Taboada, G. G. Ordonio, A. J. Ndakala, A. R. Howell, and P. R. Rablen, *J. Org. Chem.*, 2003, **68**, 1480.
2003JOC4338 P. Gizecki, R. Dhal, C. Poulard, P. Gosselin, and G. Dujardin, *J. Org. Chem.*, 2003, **68**, 4338.

2003JOC4932 A. R. Katritzky, A. A. A. Abdel-Fattah, and M. Wang, *J. Org. Chem.*, 2003, **68**, 4932.
2003JOC4935 A. R. Katritzky, Y. J. Xu, and H. Tu, *J. Org. Chem.*, 2003, **68**, 4935.
2003JOC4938 A. R. Katritzky, A. K. Verma, H. Y. He, and R. Chandra, *J. Org. Chem.*, 2003, **68**, 4938.
2003JOC5713 A. R. Katritzky, S. Bobrov, K. Kirichenko, Y. Ji, and P. J. Steel, *J. Org. Chem.*, 2003, **68**, 5713.
2003JOC5720 A. R. Katritzky, K. Suzuki, S. K. Singh, and H. Y. He, *J. Org. Chem.*, 2003, **68**, 5720.
2003JOC9088 A. R. Katritzky, N. Kirichenko, B. V. Rogovoy, and H. Y. He, *J. Org. Chem.*, 2003, **68**, 9088.
2003JOC9105 A. R. Katritzky, M. Wang, C. R. Wilkerson, and H. Yang, *J. Org. Chem.*, 2003, **68**, 9105.
2003JPO158 A. R. Katritzky, N. G. Akhmedov, I. Ghiviriga, O. V. Denisko, and P. Steel, *J. Phys. Org. Chem.*, 2003, **16**, 158.
2003JPO883 Y. Feng, J. T. Wang, L. Liu, and Q. X. Guo, *J. Phys. Org. Chem.*, 2003, **16**, 883.
2003JPY699 S. C. Nayak, P. K. Das, and K. K. Sahoo, *J. Anal. Appl. Pyrolysis*, 2003, **70**, 699.
2003OBC850 M. Devocelle, B. M. McLoughlin, C. T. Sharkey, D. J. Fitzgerald, and K. B. Nolan, *Org. Biomol. Chem.*, 2003, **1**, 850.
2003OM3107 C. W. Chang and G. H. Lee, *Organometallics*, 2003, **22**, 3107.
2003MDV171 K. A. Savin, M. Robertson, D. Gernert, S. Green, E. J. Hembre, and J. Bishop, *Mol. Diver.*, 2003, **7**, 171.
2003PCA4172 K. Jug, S. Chiodo, P. Calaminici, A. Avramopoulous, and M. G. Papadopoulous, *J. Phys. Chem. A*, 2003, **107**, 4172.
2003PCJ298 T. S. Safonova, M. P. Nemeryuk, M. M. Likhovidova, A. L. Sedov, N. A. Grineva, M. A. Keremov, N. P. Solov'eva, O. S. Anisimova, and A. S. Sokolova, *Pharm. Chem. J.*, 2003, **37**, 298.
2003PEN699 Y. Ikeda, S. Kawahara, M. Taki, A. Kuno, T. Hasegawa, and K. Taira, *Protein Eng.*, 2003, **16**, 699.
2003PES230 G. R. Vasanthakumar and V. V. S. Babu, *J. Pept. Res.*, 2003, **61**, 230.
2003RCB1770 V. P. Kislyi, E. B. Danilova, and V. V. Semenov, *Russ. Chem. Bull.*, 2003, **52**, 1770.
2003RCB1791 A. L. Krasovsky, S. A. Pissarev, V. G. Nenajdenko, and E. S. Balenkova, *Russ. Chem. Bull.*, 2003, **52**, 1791.
2003RCB1829 S. I. Molotov, A. S. Kulikov, Yu. A. Strelenko, N. N. Makhova, and K. A. Lyssenko, *Russ. Chem. Bull.*, 2003, **52**, 1829.
2003RJO1792 O. N. Verkhozina, V. N. Kizhnyaev, L. I. Vereshchagin, A. V. Rokhin, and A. I. Smirmov, *Russ. J. Org. Chem.*, 2003, **39**, 1792.
2003S2015 G. Athanasellis, A. Detsi, K. Prousis, O. Igglessi-Markopoulou, and J. Markopoulos, *Synthesis*, 2003, 2015.
2003S2777 A. R. Katritzky, N. Kirichenko, and B. V. Rogovoy, *Synthesis*, 2003, 2777.
2003S2795 A. R. Katritzky, Y. Zhang, and S. K. Singh, *Synthesis*, 2003, 2795.
2003SC2989 S. Luo, B. Zhang, P. G. Wang, and J. P. Cheng, *Synth. Commun.*, 2003, **33**, 2989.
2003SC3513 Y. Luo and Y. Hu, *Synth. Commun.*, 2003, **33**, 3513.
2003SC3969 M. Chen, Y. Zheng, G. Gao, S. Fan, S. Lu, and W. Hua, *Synth. Commun.*, 2003, **33**, 3969.
2003SPL461 Y. A. Al-Soud and N. A. Al-Masoudi, *Spectrosc. Lett.*, 2003, **36**, 461.
2003SSI129 P. Johansson, S. Beranger, M. Armand, H. Nilsson, and P. Jacobsson, *Solid State Ionics*, 2003, **156**, 129.
2003STE1139 D. Kirilovas, T. Naessen, M. Bergstrom, E. Bergstrom-Petterman, K. Carlstrom, and B. Langstrom, *Steroids*, 2003, **68**, 1139.
2003T865 E. R. Perez, A. Loupy, M. Liagre, A. M. de Guzzi Plepis, and P. J. Cordeiro, *Tetrahedron*, 2003, **59**, 865.
2003T1589 N. M. A. J. Kriek, D. V. Filippov, H. van den Elst, N. J. Meeuwenoord, G. I. Tesser, J. H. van Boom, and G. A. van der Marel, *Tetrahedron*, 2003, **59**, 1589.
2003T1657 M. K. Cyranski, P. von Rague Schleyer, T. M. Krygowski, H. Jiao, and G. Hohlneicher, *Tetrahedron*, 2003, **59**, 1657.
2003T4297 S. Batori, E. Gacs-Baitz, S. Bokotey, and A. Messmer, *Tetrahedron*, 2003, **59**, 4297.
2003T4395 W. Peng and S. Zhu, *Tetrahedron*, 2003, **59**, 4395.
2003T9455 H. H. Dib, N. A. Al-Awadi, Y. A. Ibrahim, and O. M. E. El-Dusouqui, *Tetrahedron*, 2003, **59**, 9455.
2003TL1133 L. Garanti and G. Molteni, *Tetrahedron Lett.*, 2003, **44**, 1133.
2003TL1339 R. Brown, W. E. Smith, and D. Graham, *Tetrahedron Lett.*, 2003, **44**, 1339.
2003TL2153 B. E. Blass, K. R. Coburn, A. L. Faulkner, W. L. Seibel, and A. Srivastava, *Tetrahedron Lett.*, 2003, **44**, 2153.
2004AXC250 Z. H. Shao, J. Luo, R. F. Cai, X. G. Zhou, L. H. Weng, and Z. X. Chen, *Acta Crystallogr., Sect. C*, 2004, **60**, m250.
2004AP156 A. Cwiklicki and K. Rehse, *Arch. Pharm. (Weinheim, Ger.)*, 2004, **337**, 156.
2004AP376 V. Sukalovic, D. Andric, G. Roglic, S. Kostic-Rajacic, and V. Soskic, *Arch. Pharm. (Weinheim, Ger.)*, 2004, **337**, 376.
2004ARK(iii)22 A. R. Katritzky, K. Kirichenko, P. P. Mohapatra, and I. Prakash, *ARKIVOC*, 2004, **iii**, 22.
2004ARK(iii)109 A. R. Katritzky, D. Hur, K. Kirichenko, Y. Ji, and P. J. Steel, *ARKIVOC*, 2004, **iii**, 109.
2004ARK(vi)27 A. R. Katritzky, K. Kirichenko, D. Hur, X. Zhao, Y. Ji, and P. J. Steel, *ARKIVOC*, 2004, **vi**, 27.
2004ARK(ix)44 A. R. Katritzky, R. J. Giang, L. Sommen, and S. K. Singh, *ARKIVOC*, 2004, **ix**, 44.
2004ARK(xii)14 A. R. Katritzky, S. Hoffmann, and K. Suzuki, *ARKIVOC*, 2004, **xii**, 14.
2004BMC2617 K. Kopanska, A. Najda, J. Zebrowska, L. Chomicz, J. Piekarczyk, P. Myjak, and M. Bretner, *Bioorg. Med. Chem.*, 2004, **12**, 2617.
2004BML1043 C. K. Lau, C. I. Bayly, J. Y. Gauthier, C. S. Li, M. Therien, E. Asante-Appiah, W. Cromlish, Y. Boie, F. Forghani, S. Desmarais, Q. Wang, K. Skorey, D. Waddleton, P. Payette, C. Ramachandran, B. P. Kennedy, and G. Scapin, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1043.
2004BML3655 R. P. Jain and J. C. Vederas, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3655.
2004CCA175 A. R. Katritzky, K. Suzuki, and S. K. Singh, *Croat. Chem. Acta*, 2004, **77**, 175.
2004CEJ399 J. C. Lee, S. W. Chang, C. C. Liao, F. C. Chi, C. S. Chen, Y. S. Wen, C. C. Wang, S. S. Kulkarni, R. Puranik, Y. H. Liu, and S. C. Hung, *Chem. Eur. J.*, 2004, **10**, 399.
2004CEJ1926 J. D. Badjic, V. Balzani, A. Credi, J. N. Lowe, S. Silvi, and J. F. Stoddart, *Chem. Eur. J.*, 2004, **10**, 1926.
2004CPB570 T. Kaiya, K. Nakamura, M. Tanaka, N. Miyata, and K. Kohda, *Chem. Pharm. Bull.*, 2004, **52**, 570.
2004EJO3611 O. Koepler, S. Laschat, A. Baro, P. Fischer, B. Miehlich, M. Hotfilder, and C. le Viseur, *Eur. J. Org. Chem.*, 2004, 3611.
2004EJO3789 T. Jin, S. Kamijo, and Y. Yamamoto, *Eur. J. Org. Chem.*, 2004, 3789.
2004H(63)1077 Z. G. Le, Z. C. Chen, Y. Hu, and Q. G. Zheng, *Heterocycles*, 2004, **63**, 1077.
2004H(63)1175 D. B. Batanero and E. Barba, *Heterocycles*, 2004, **63**, 1175.
2004FA397 G. Biagi, V. Calderone, I. Giorgi, O. Livi, E. Martinotti, A. Martelli, and A. Nardi, *Farmaco*, 2004, **59**, 397.
2004JA1161 J. A. McCubbin, X. Tong, R. Wang, Y. Zhao, V. Snieckus, and R. P. Lemieux, *J. Am. Chem. Soc.*, 2004, **126**, 1161.
2004JA3357 Y. Gabe, Y. Urano, K. Kikuchi, H. Kojima, and T. Nagano, *J. Am. Chem. Soc.*, 2004, **126**, 3357.
2004JA8356 R. S. Dahl and N. S. Finney, *J. Am. Chem. Soc.*, 2004, **126**, 8356.
2004JA12809 R. Manetsch, A. Krasinski, Z. Radic, J. Raushei, P. Taylor, K. B. Sharpless, and H. C. Kolb, *J. Am. Chem. Soc.*, 2004, **126**, 12809.

2004JFC(125)445 S. Z. Zhu, P. He, J. W. Zhao, and X. Cai, *J. Fluorine Chem.*, 2004, **125**, 445.
2004JHC285 I. Alkorta, J. Elguero, N. Jagerovic, A. Fruchier, and G. P. A. Yap, *J. Heterocycl. Chem.*, 2004, **41**, 285.
2004JLR31 H. Matloubi, A. Shafiee, N. Saemian, G. Shirvani, and F. J. Daha, *J. Label. Compd. Radiopharm.*, 2004, **47**, 31.
2004JOC303 A. R. Katritzky, S. Bobrov, K. Kirichenko, and Y. Ji, *J. Org. Chem.*, 2004, **69**, 303.
2004JOC811 A. R. Katritzky, C. Cai, K. Suzuki, and S. K. Singh, *J. Org. Chem.*, 2004, **69**, 811.
2004JOC1081 X. Zhu and R. R. Schmidt, *J. Org. Chem.*, 2004, **69**, 1081.
2004JOC1720 L. Yao, B. T. Smith, and J. Aube, *J. Org. Chem.*, 2004, **69**, 1720.
2004JOC1849 A. R. Katritzky, V. Rodriguez-Garcia, and S. K. Nair, *J. Org. Chem.*, 2004, **69**, 1849.
2004JOC2976 A. R. Katritzky, S. Ledoux, R. M. Witek, and S. K. Nair, *J. Org. Chem.*, 2004, **69**, 2976.
2004JOC5578 J. C. Antilla, J. M. Baskin, T. E. Barder, and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578.
2004JOC6617 A. R. Katritzky, Z. Wang, M. Wang, C. R. Wilkerson, C. D. Hall, and N. G. Akhmedov, *J. Org. Chem.*, 2004, **69**, 6617.
2004JOC9313 A. R. Katritzky, S. K. Singh, and S. Bobrov, *J. Org. Chem.*, 2004, **69**, 9313.
2004JOM(689)2473 L. V. Snegur, A. A. Simenel, Y. S. Nekrasov, E. A. Morozova, Z. A. Starikova, S. M. Peregudova, Y. V. Kuzmenko, V. N. Babin, L. A. Osrovskaya, N. V. Bluchterova, and M. M. Fomina, *J. Organomet. Chem.*, 2004, **689**, 2473.
2004JPO267 H. H. Dib, N. A. Al-Awadi, Y. A. Ibrahim, and O. M. E. El-Dusouqui, *J. Phys. Org. Chem.*, 2004, **17**, 267.
2004NAR623 R. T. Pon and S. Yu, *Nucl. Acids Res.*, 2004, **32**, 623.
2004NN521 I. Leban, M. Jeselnik, J. Sieler, and J. Kobe, *Nucleos. Nucleot. Nucleic Acids*, 2004, **23**, 521.
2004OL1237 A. Krasinski, V. V. Fokin, and K. B. Sharpless, *Org. Lett.*, 2004, **6**, 1237.
2004OL2929 A. Dondoni, P. P. Giovannini, and A. Massi, *Org. Lett.*, 2004, **6**, 2929.
2004POL1981 C. Ma, J. Zhang, and R. Zhang, *Polyhedron*, 2004, **23**, 1981.
2004RCB588 O. Y. Sapozhnikov, M. D. Dutov, M. A. Korolev, V. V. Kachala, V. I. Kadentsev, and S. A. Shevelev, *Russ. Chem. Bull.*, 2004, **53**, 588.
2004RQM275 A. R. Katritzky, N. K. Meher, C. Cai, and S. K. Singh, *Rev. Soc. Quim. Mex.*, 2004, **48**, 275.
2004S1806 A. R. Katritzky, A. A. Shestopalov, and K. Suzuki, *Synthesis*, 2004, 1806.
2004S2645 A. R. Katritzky, K. Suzuki, and S. K. Singh, *Synthesis*, 2004, 2645.
2004T99 E. V. Tretyakov, G. V. Romanenko, and V. I. Ovcharenko, *Tetrahedron*, 2004, **60**, 99.
2004T5367 E. A. Savel'eva, Y. A. Rozin, M. I. Kodess, L. Van Meervelt, W. Dehaen, Y. Y. Morzherin, and V. A. Bakulev, *Tetrahedron*, 2004, **60**, 5367.
2004T8839 R. Abonia, E. Rengifo, J. Quiroga, B. Insuasty, J. Cobo, and M. Nogueras, *Tetrahedron*, 2004, **60**, 8839.
2004TA1457 A. E. Wroblewski and I. E. Glowacka, *Tetrahedron Asymmetry*, 2004, **15**, 1457.
2004TL5175 M. Amedjkouh and K. Westerlund, *Tetrahedron Lett.*, 2004, **45**, 5175.
2004TL6129 M. S. Raghavendra and J. Lam, *Tetrahedron Lett.*, 2004, **45**, 6129.
2005AGE2096 F. Sicherl and V. Wittmann, *Angew. Chem., Int. Ed.*, 2005, **44**, 2096.
2005AGE2393 M. Gandelman and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 2393.
2005AGE2534 M. Fumoto, H. Hinou, T. Matsushita, M. Kurogochi, T. Ohta, T. Ito, K. Yamada, A. Takimoto, H. Kondo, T. Inazu, and S. Nishimura, *Angew. Chem., Int. Ed.*, 2005, **44**, 2534.
2005AGE2887 M. Lee and I. Shin, *Angew. Chem., Int. Ed.*, 2005, **44**, 2887.
2005AGE5710 R. J. Brea, M. Amorin, L. Castedo, and J. R. Granja, *Angew. Chem., Int. Ed.*, 2005, **44**, 5710.
2005ARK(vi)329 A. R. Katritzky, A. A. A. Abdel-Fattah, and R. G. Akhmedova, *ARKIVOC*, 2005, **vi**, 329.
2005ARK(vii)36 A. R. Katritzky, A. A. Shestopalov, and K. Suzuki, *ARKIVOC*, 2005, **vii**, 36.
2005ARK(ix)63 A. R. Katritzky, S. Singh, P. P. Mohapatra, N. Clemens, and K. Kirichenko, *ARKIVOC*, 2005, **ix**, 63.
2005CC4908 T. Doi, Y. Miura, S. Kawauchi, and T. Takahashi, *Chem. Commun.*, 2005, 4908.
2005CEJ6666 U. Hahn, J. J. Gonzales, E. Huerta, M. Segura, J. F. Eckert, F. Cardinali, J. de Mendoza, and J. F. Nierengarten, *Chem. Eur. J.*, 2005, **11**, 6666.
2005EJO907 L. W. A. Van Berkom, R. de Gelder, and H. W. Scheeren, *Eur. J. Org. Chem.*, 2005, 907.
2005EJO3704 J. R. Fotsing and K. Banert, *Eur. J. Org. Chem.*, 2005, 3704.
2005H(65)1035 P. L. Miner, T. R. Wagner, and P. Norris, *Heterocycles*, 2005, **65**, 1035.
2005HCA447 D. R. Staveren, P. D. Benny, R. Waibel, P. Kurz, J. K. Pak, and R. Alberto, *Helv. Chim. Acta*, 2005, **88**, 447.
2005HCA1040 J. Z. Ho, C. S. Elmore, M. A. Wallace, D. Yao, M. P. Braun, D. C. Dean, D. G. Melillo, and C. Chen, *Helv. Chim. Acta*, 2005, **88**, 1040.
2005HCA1711 I. Philipova, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2005, **88**, 1711.
2005HCA1813 M. Brunner, G. Maas, and F. G. Klarner, *Helv. Chim. Acta*, 2005, **88**, 1813.
2005JA210 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.
2005JA15998 L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, and G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998.
2005JA17894 Y. Zhao and Z. Zhong, *J. Am. Chem. Soc.*, 2005, **127**, 17894.
2005JCO490 N. Kaval, D. Ermolat'ev, P. Appukkuttan, W. Dehaen, C. O. Kappe, and E. Van der Eycken, *J. Comb. Chem.*, 2005, **7**, 490.
2005JCO697 R. A. Simon, L. Schuresko, N. Dendukuni, E. Goers, B. Murphy, and R. S. Lokey, *J. Comb. Chem.*, 2005, **7**, 697.
2005JCO703 F. El Qualid, H. van den Elst, I. M. Leroy, E. Pieterman, L. H. Cohen, B. E. A. Burm, H. S. Overkleeft, G. A. van der Marel, and M. Overhand, *J. Comb. Chem.*, 2005, **7**, 703.
2005JOC286 A. R. Katritzky, H. Yang, and S. K. Singh, *J. Org. Chem.*, 2005, **70**, 286.
2005JOC3271 A. R. Katritzky, D. Zhang, and K. Kirichenko, *J. Org. Chem.*, 2005, **70**, 3271.
2005JOC3660 J. A. Gonzalez-Vera, M. T. Garcia-Lopez, and Rosario Herranz,, *J. Org. Chem.*, 2005, **70**, 3660.
2005JOC4993 A. R. Katritzky, R. Jiang, and K. Suzuki, *J. Org. Chem.*, 2005, **70**, 4993.
2005JOC5339 Y. Matsukawa, M. Isobe, H. Kotsuki, and Y. Ichikawa, *J. Org. Chem.*, 2005, **70**, 5339.
2005JOC6313 S. Leroy-Lhez, J. Baffreau, L. Perrin, E. Levillain, M. Allain, M. J. Blesa, and P. Hudhomme, *J. Org. Chem.*, 2005, **70**, 6313.
2005JOC6526 D. Amantini, F. Fringuelli, O. Piermatti, F. P. E. Zunino, and L. Vaccaro, *J. Org. Chem.*, 2005, **70**, 6526.
2005JOC7654 J. P. Malkinson, M. K. Anim, M. Zloh, and M. Searcey, *J. Org. Chem.*, 2005, **70**, 7654.

2005JOC7866 A. R. Katritzky, R. M. Witek, V. Rodriguez-Garcia, P. P. Mohapatra, J. W. Rogers, J. Cusido, A. A. A. Abdel-Fattah, and P. J. Steel, *J. Org. Chem.*, 2005, **70**, 7866.
2005JOC9191 A. R. Katritzky, A. A. A. Abdel-Fattah, A. V. Vakulenko, and H. Tao, *J. Org. Chem.*, 2005, **70**, 9191.
2005JOC9211 A. R. Katritzky, A. A. A. Abdel-Fattah, A. V. Gromova, R. Witek, and P. J. Steel, *J. Org. Chem.*, 2005, **70**, 9211.
2005JOC9622 A. Nefzi and R. T. Santos, *J. Org. Chem.*, 2005, **70**, 9622.
2005JOC9626 V. Balraju, D. Srinivasa Reddy, M. Periasamy, and J. Iqbal, *J. Org. Chem.*, 2005, **70**, 9626.
2005JSC319 A. R. Katritzky, P. P. Mohapatra, S. Singh, N. Clemens, and K. Kirichenko, *J. Serb. Chem. Soc.*, 2005, **70**, 319.
2005OL4907 D. Liu, W. Gao, Q. Dai, and X. Zhang, *Org. Lett.*, 2005, **7**, 4907.
2005S397 A. R. Katritzky, P. Angrish, D. Hur, and K. Suzuki, *Synthesis*, 2005, 397.
2005S1514 J. C. Loren and K. B. Sharpless, *Synthesis*, 2005, 1514.
2005S2730 J. Deng, Y. M. Wu, and Q. Y. Chen, *Synthesis*, 2005, 2730.
2005SL1656 A. R. Katritzky, K. Suzuki, and Z. Wang, *Synlett*, 2005, 1656.
2005SL2796 N. Gommermann, A. Gehring, and P. Knochel, *Synlett*, 2005, 2796.
2005SL2847 J. C. Loren, A. Krasinski, V. V. Fokin, and K. B. Sharpless, *Synlett*, 2005, 2847.
2005T2555 A. R. Katritzky, K. Manju, S. K. Singh, and N. K. Meher, *Tetrahedron*, 2005, **61**, 2555.
2005T3305 A. R. Katritzky, S. Bobrov, H. Tao, and K. Kirichenko, *Tetrahedron*, 2005, **61**, 3305.
2005T4701 K. Katagiri, H. Danjo, K. Yamaguchi, and T. Imamoto, *Tetrahedron*, 2005, **61**, 4701.
2005T4983 G. Molteni and P. Del Buttero, *Tetrahedron*, 2005, **61**, 4983.
2005T8257 N. A. Al-Awadi, B. J. George, H. H. Dib, M. R. Ibrahim, Y. A. Ibrahim, and O. M. E. El-Dusouqui, *Tetrahedron*, 2005, **61**, 8257.
2005T8904 J. R. Fotsing, M. Hagedorn, and K. Banert, *Tetrahedron*, 2005, **61**, 8904.
2005T9118 R. Perion, V. Ferrieres, M. I. Garcia-Moreno, C. O. Mellet, R. Duval, J. M. Garcia-Fernandez, and D. Plusquellec, *Tetrahedron*, 2005, **61**, 9118.
2005T11744 N. Joubert, R. F. Schinazi, and L. A. Agrofoglio, *Tetrahedron*, 2005, **61**, 11744.
2005TA1905 Z. Xu and T. Ye, *Tetrahedron Asymmetry*, 2005, **16**, 1905.
2005TA4056 A. E. Wroblewski and I. E. Glowacka, *Tetrahedron Asymmetry*, 2005, **16**, 4056.
2005TL4053 S. Chattopadhaya, E. W. S. Chan, and S. Q. Yao, *Tetrahedron Lett.*, 2005, **46**, 4053.
2005TL4377 Y. Xu, L. Chen, X. Duan, Y. Meng, L. Jiang, M. Li, G. Zhao, and Y. Li, *Tetrahedron Lett.*, 2005, **46**, 4377.
2005TL6239 A. Olma and A. Kudaj, *Tetrahedron Lett.*, 2005, **46**, 6239.
2005TL6537 E. R. Walker, S. Y. Leung, and A. G. M. Barrett, *Tetrahedron Lett.*, 2005, **46**, 6537.
2005TL6791 K. N. Kim, C. S. Choi, and K. Y. Kay, *Tetrahedron Lett.*, 2005, **46**, 6791.
2005TL7443 S. Dixon, X. Wang, K. S. Lam, and M. J. Kurth, *Tetrahedron Lett.*, 2005, **46**, 7443.
2006AGE309 M. Al-Omari, K. Banert, and M. Hagedorn, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 309.
2006ARK(xv)53 S. A. S. Ghozlan, I. A. Abdelhamid, H. M. Ibrahim, and M. H. Elnagdi, *ARKIVOC*, 2006, **xv**, 53.
2006BML999 S. N. Swamy, Basappa, G. Sarala, B. S. Priya, S. L. Gaonkar, J. S. Prasad, and K. S. Rangappa, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 999.
2006BML2693 Y. Xia, Z. Fan, J. Yao, Q. Liao, W. Li, F. Qu, and L. Peng, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2693.
2006BML2955 S. Lober, H. Hubner, and P. Gmeiner, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2955.
2006CAR1081 D. P. Temelkoff, M. Zeller, and P. Norris, *Carbohydr. Res.*, 2006, **341**, 1081.
2006CAR1353 J. Tejler, E. Tullberg, T. Frejd, H. Leffler, and U. J. Nilsson, *Carbohydr. Res.*, 2006, **341**, 1353.
2006CBO261 C. Y. Wu, K. Y. King, C. J. Kuo, J. M. Fang, Y. T. Wu, M. Y. Ho, C. L. Liao, J. J. Shie, P. H. Liang, and C. H. Wong, *Chem. Biol.*, 2006, **13**, 261.
2006CC629 K. H. Chang, L. Lee, J. Chen, and W. S. Li, *Chem. Commun.*, 2006, 629.
2006CC2379 D. Giguere, R. Patnam, M. A. Bellefleur, C. St-Pierre, S. Sato, and R. Roy, *Chem. Commun.*, 2006, 2379.
2006CJC58 T. Yamato, S. Rahman, Z. Xi, F. Kitajima, and J. T. Gil, *Can. J. Chem.*, 2006, **84**, 58.
2006EJO1103 I. Aumuller and T. K. Lindhorst, *Eur. J. Org. Chem.*, 2006, 1103.
2006EJO2081 C. Adelwohrer, T. Rosenau, E. Kloser, K. Mereiter, and T. Netscher, *Eur. J. Org. Chem.*, 2006, 2081.
2006JA210 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, and V. V. Fokin, *J. Am. Chem. Soc.*, 2006, **128**, 210.
2006JA3011 K. M. Jude, A. L. Banerjee, M. K. Haldar, S. Manokaran, B. Roy, S. Mallik, D. K. Srivastava, and D. W. Christianson, *J. Am. Chem. Soc.*, 2006, **128**, 3011.
2006JA4178 H. Zhang, T. Piacham, M. Drew, M. Patek, K. Mosbach, and L. Ye, *J. Am. Chem. Soc.*, 2006, **128**, 4178.
2006JA5091 E. Kasemi, W. Zhuang, J. Rabe, K. Fischer, M. Schmidt, M. Colussi, H. Keul, D. Yi, H. Colfen, and A. D. Schluter, *J. Am. Chem. Soc.*, 2006, **128**, 5091.
2006JA7136 K. Okano, H. Tokuyama, and T. Fukuyama, *J. Am. Chem. Soc.*, 2006, **128**, 7136.
2006JCO150 F. K. Wallner and M. Elofsson, *J. Comb. Chem.*, 2006, **8**, 150.
2006JME1140 J. H. Cho, D. L. Bernard, R. W. Sidwell, E. R. Kern, and C. K. Chu, *J. Med. Chem.*, 2006, **49**, 1140.
2006JME1202 R. A. Hudack, Jr., N. S. Barta, C. Guo, J. Deal, L. Dong, L. K. Fay, B. Caprathe, A. Chatterjee, D. Vanderpool, C. Bigge, R. Showalter, S. Bender, C. E. Augelli-Szafran, E. Lunney, and X. Hou, *J. Med. Chem.*, 2006, **49**, 1202.
2006JME1227 G. Semple, P. J. Skinner, M. C. Cherrier, P. J. Webb, C. R. Sage, S. Y. Tamura, R. Chen, J. G. Richman, and D. T. Connolly, *J. Med. Chem.*, 2006, **49**, 1227.
2006JME1773 Y. S. Lee, R. S. Agnes, H. Badghisi, P. Davis, S. Ma, J. Lai, F. Porreca, and V. J. Hruby, *J. Med. Chem.*, 2006, **49**, 1773.
2006JME1828 J. K. Ekegren, N. Ginman, A. Johansson, H. Wallberg, M. Larhed, B. Samuelsson, T. Unge, and A. Hallberg, *J. Med. Chem.*, 2006, **49**, 1828.
2006JME1833 V. Maes, E. Garcia-Garayoa, P. Blauenstein, and D. Tourwe, *J. Med. Chem.*, 2006, **49**, 1833.
2006JME2210 F. Gellibert, A. C. de Gouville, J. Woolven, N. Mathews, V. L. Nguyen, C. Bertho-Ruault, A. Patikis, E. T. Grygielko, N. J. Laping, and S. Huet, *J. Med. Chem.*, 2006, **49**, 2210.
2006JME2333 G. Appendino, A. Minassi, L. Berton, A. S. Moriello, M. G. Cascio, L. De Petrocellis, and V. Di Marzo, *J. Med. Chem.*, 2006, **49**, 2333.

2006JME2388 S. M. Dixon, P. Li, R. Liu, H. Wolosker, K. S. Lam, M. J. Kurth, and M. D. Toney, *J. Med. Chem.*, 2006, **49**, 2388.
2006JME2593 J. Gong, J. F. Neels, X. Yu, T. W. Kensler, L. A. Peterson, and S. J. Sturla, *J. Med. Chem.*, 2006, **49**, 2593.
2006JME4762 S. Bolgumas, D. A. Clark, W. S. Hanna, P. A. Mauvais, and S. O. Pember, *J. Med. Chem.*, 2006, **49**, 4762.
2006JME7373 L. Cosyn, K. K. Palaniappan, S. K. Kim, H. T. Duong, Z. G. Gao, K. A. Jacobson, and S. Van Calenbergh, *J. Med. Chem.*, 2006, **49**, 7373.
2006JOC3364 A. R. Katritzky, S. K. Singh, C. Cai, and S. Bobrov, *J. Org. Chem.*, 2006, **71**, 3364.
2006JOC3375 A. R. Katritzky, C. Cai, and S. K. Singh, *J. Org. Chem.*, 2006, **71**, 3375.
2006JOC3664 S. Hotha and S. Kashyap, *J. Org. Chem.*, 2006, **71**, 3664.
2006JOC3928 Q. Dai, W. Gao, D. Liu, L. M. Kapes, and X. Zhang, *J. Org. Chem.*, 2006, **71**, 3928.
2006JOC5679 R. N. Butler, A. M. Fahy, A. Fox, J. C. Stephens, P. McArdle, D. Cunningham, and A. Ryder, *J. Org. Chem.*, 2006, **71**, 5679.
2006OL239 D. R. Ijzendoorn, P. N. M. Botman, and R. H. Blaauw, *Org. Lett.*, 2006, **8**, 239.
2006OL415 P. Vera-Lugue, R. Alajarin, J. Alvarez-Builla, and J. J. Vaquero, *Org. Lett.*, 2006, **8**, 415.
2006OL511 J. Adrio, C. Cuevas, I. Manzanares, and M. M. Joullie, *Org. Lett.*, 2006, **8**, 511.
2006OL531 T. Doi, Y. Numajiri, A. Munakata, and T. Takahashi, *Org. Lett.*, 2006, **8**, 531.
2006OL797 A. B. Smith, III, T. M. Razler, R. M. Meis, and G. R. Pettit, *Org. Lett.*, 2006, **8**, 797.
2006OL823 K. N. Barlett, R. V. Kolakowski, S. Katukojvala, and L. J. Williams, *Org. Lett.*, 2006, **8**, 823.
2006OL887 R. Rai, H. N. Chen, P. G. Czyryca, J. Li, and C. W. T. Chang, *Org. Lett.*, 2006, **8**, 887.
2006OL1391 J. Wang, H. Li, L. Zu, and W. Wang, *Org. Lett.*, 2006, **8**, 1391.
2006OL2417 E. Biron, J. Chatterjee, and H. Kessler, *Org. Lett.*, 2006, **8**, 2417.
2006OL2767 G. A. Molander and J. Ham, *Org. Lett.*, 2006, **8**, 2767.
2006OL2851 S. Surprenant and W. D. Lubell, *Org. Lett.*, 2006, **8**, 2851.
2006OL3227 R. J. Detz, S. A. Heras, R. de Gelder, P. W. N. M. van Leeuwen, H. Hiemstra, J. N. H. Reek, and J. H. van Maarseveen, *Org. Lett.*, 2006, **8**, 3227.
2006OL3283 Y. Gao and Y. Lam, *Org. Lett.*, 2006, **8**, 3283.
2006OM416 N. Mantovani, P. Bergamini, A. Marchi, L. Marvelli, R. Rossi, V. Bertolasi, V. Ferretti, I. de los Rios, and M. Peruzzini, *Organometallics*, 2006, **25**, 416.
2006POL360 L. F. Jones, L. O'Dea, D. A. Offermann, P. Jensen, B. Moubaraki, and K. S. Murray, *Polyhedron*, 2006, **25**, 360.
2006S411 A. R. Katritzky, P. Angrish, and K. Suzuki, *Synthesis*, 2006, 411.
2006S654 P. Rajakumar and M. Dhanasekaran, *Synthesis*, 2006, 654.
2006S1289 S. K. Chattopadhyay, S. Biswas, and B. K. Pal, *Synthesis*, 2006, 1289.
2006SC951 G. Conte, R. Cristiano, F. Ely, and H. Gallardo, *Synth. Commun.*, 2006, **36**, 951.
2006SC1317 S. R. Gondi and D. Y. Son, *Synth. Commun.*, 2006, **36**, 1317.
2006SL957 K. R. Reddy, K. Rajgopal, and M. L. Kantam, *Synlett*, 2006, 957.
2006T1895 A. Beauchard, H. Chabane, S. Sinbandhit, P. Guenot, V. Thiery, and T. Besson, *Tetrahedron*, 2006, **62**, 1895.
2006T3710 D. Virieux, A. F. Guillouzic, and H. J. Cristau, *Tetrahedron*, 2006, **62**, 3710.
2006T3794 A. R. Katritzky, S. K. Singh, and R. Jiang, *Tetrahedron*, 2006, **62**, 3794.
2006T8115 B. L. Wilkinson, L. F. Bornaghi, S. A. Poulsen, and T. A. Houston, *Tetrahedron*, 2006, **62**, 8115.
2006TL1545 Y. B. Zhao, Z. Y. Yan, and Y. M. Liang, *Tetrahedron Lett.*, 2006, **47**, 1545.
2006TL1721 R. N. Butler, A. M. Fahy, A. Fox, J. C. Stephens, P. McArdle, D. Cunningham, and A. G. Ryder, *Tetrahedron Lett.*, 2006, **47**, 1721.
2006TL1737 P. Styring and S. S. F. Chong, *Tetrahedron Lett.*, 2006, **47**, 1737.
2006TL2187 A. Lauria, C. Patella, P. Diana, P. Barraja, A. Montalbano, G. Cirrincione, G. Dattolo, and A. M. Almerico, *Tetrahedron Lett.*, 2006, **47**, 2187.
2006TL2671 M. Lumbierres, J. M. Palomo, G. Kragol, and H. Waldmann, *Tetrahedron Lett.*, 2006, **47**, 2671.
2006TL4807 R. Guezguez, K. Bougrin, K. El Akri, and R. Benhida, *Tetrahedron Lett.*, 2006, **47**, 4807.
2007ALD7 P. Wu and V. V. Fokin, *Aldrichim. Acta*, 2007, **40**, 7.
2007ARK(i)9 A. R. Katritzky, A. V. Vakulenko, R. Akue-Gedu, A. V. Gromova, R. Witek, and J. W. Rogers, *ARKIVOC*, 2007, **i**, 9.
2007ARK(iii)5 A. R. Katritzky, R. Akue-Gedu, and A. V. Vakulenko, *ARKIVOC*, 2007, **iii**, 5.
2007ARK(v)263 A. R. Katritzky, N. M. Khashab, and A. Singh, *ARKIVOC*, 2007, **v**, 263.
2007ARK(vi)6 A. R. Katritzky, S. K. Singh, R. Akhmedova, C. Cai, and S. Bobrov, *ARKIVOC*, 2007, **vi**, 6.
2007ARK(x)142 A. R. Katritzky, H. Tao, and K. Kirichenko, *ARKIVOC*, 2007, **x**, 142.
2007ARK(xi)96 A. R. Katritzky, A. A. A. Abdel-Fattah, and I. Celik, *ARKIVOC*, 2007, **xi**, 96.
2007BML6000 A. R. Katritzky, P. Angrish, E. Todadze, and I. Ghiviriga, *Bioorganic Med. Chem. Lett.*, 2007, **17**, 6000.
2007EJM471 P. Chaudhary, S. Nimesh, V. Yadav, A. Kr. Verma, and R. Kumar, *Eur. J. Med. Chem.*, 2007, **42**, 471.
2007H(72)497 M. Katoh, H. Inoue, and T. Honda, *Heterocycles*, 2007, **72**, 497.
2007JOC407 A. R. Katritzky, H. Tao, R. Jiang, K. Suzuki, and K. Kirichenko, *J. Org. Chem.*, 2007, **72**, 407.
2007JOC4268 A. R. Katritzky, P. P. Mohapatra, D. Fedoseyenko, M. Duncton, and P. J. Steel, *J. Org. Chem.*, 2007, **72**, 4268.
2007JOC5794 A. R. Katritzky, E. Todadze, P. Angrish, and B. Draghici, *J. Org. Chem.*, 2007, **72**, 5794.
2007JOC5802 A. R. Katritzky, K. Widyan, and K. Kirichenko, *J. Org. Chem.*, 2007, **72**, 5802.
2007JOC6742 A. R. Katritzky, N. M. Khashab, D. N. Haase, M. Yoshioka, I. Ghiviriga, and P. J. Steel, *J. Org. Chem.*, 2007, **72**, 6742.
2007S1655 A. R. Katritzky, I. Celik, and A. A. A. Abdel-Fattah, *Synthesis*, 2007, 1655.
2007SC1917 E. Masiukiewicz, B. Rzeszotarska, I. Wawrzycka-Gorczyca, and E. Kolodziejczyk, *Synth. Commun.*, 2007, **37**, 1917.
2007SL1204 A. R. Katritzky, C. Cai, and N. K. Meher, *Synlett*, 2007, 1204.

Biographical Sketch

Stanislaw Rachwal was born in Jodlowka, Poland, in 1949 and raised in Krakow, Poland. In 1978, he received a PhD in organic chemistry from Jagiellonian University in Krakow and was nominated to a position of an Adjunct Professor at that university in 1980. His main research at that time was focused on chemistry of ferrocenophanes. During a sabbatical leave in 1984, he joined Professor Alan R. Katritzky at the University of Florida to lay a foundation for application of benzotriazole in organic synthesis. He returned to the University of Florida in 1988, where, as a group leader, he pushed forward the research on derivatives of benzotriazole. His collaboration with Professor Katritzky till 1993 resulted in 36 scientific papers on benzotriazole. Since1993, he has been working in pharmaceutical industry specializing in CNS drugs with the primary focus on heterocyclic compounds.

Alan Katritzky was born in London, UK and educated at St. Catherine's College, Oxford, of which he became, in 2006, an Honorary Fellow. He was a Founder Fellow of Churchill College, Cambridge, and then founding of Professor/Dean of the School of Chemical Sciences at the University of East Anglia before crossing the Atlantic in 1980 to become Kenan Professor and Director of The Center for Heterocyclic Compounds at the University of Florida. He has researched, published, lectured, and consulted widely in heterocyclic chemistry, synthetic methods, and QSPR. He created the not-for-profit foundation ARKAT and since 2000 has been organizing the annual 'Florida Heterocyclic and Synthetic Conferences' (Flohet) and publishes *Archive for Organic Chemistry* (Arkivoc) completely free on the Internet at arkat-usa.org. His honors from 20 countries include 14 honorary doctorates.