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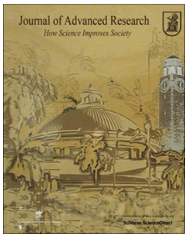

REVIEW

1,3,4-Thiadiazoles of pharmacological interest: Recent trends in their synthesis *via* tandem 1,3-dipolar cycloaddition: Review

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ABSTRACT

This review article presents a survey of the utility of a new synthetic strategy for 1,3,4-thiadiazole derivatives based on reactions of nitrilimines with various functionalized sulfur dipolarophiles which proceed *via* tandem *in situ* 1,3-dipolar cycloaddition and β-elimination of simple molecule from the initially formed cycloadduct. The biological activities of some of the compounds prepared by such a strategy are pointed out. Only the literature reports within the period from 2000 to mid 2012 are covered.

Introduction and scope of the review

A survey of the literature revealed that differently substituted 1,3,4-thiadiazoles and annelated 1,3,4-thiadiazoles have wide range of pharmacological activities such as antibacterial, antifungal, antituberculosis, antihepatitis B viral, antileishmanial, anti-inflammatory, analgesic, CNS depressant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic, analgesic, antimicrobial, antitubercular, and anticonvulsant activities [1–11]. These important biological activities encouraged several research groups to find out different methods for synthesis of new thiadiazoles using different synthones, such as thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, acylhydrazines, and bithioureas [4,7–11].

We would like to report in this review the recent developments of a new synthetic strategy for the synthesis of 1,3,4-thiadiazoles. This strategy is based on an *in situ* 1,3-dipolar cycloaddition of nitrilimines **A** to functionalized sulfur dipolarophiles **B**, followed by β-elimination of simple molecule from the initially formed cycloadducts **C** (Scheme 1). This strategy proved useful and convenient for synthesis of various functionalized 1,3,4-thiadiazole derivatives **D** (Scheme 1). Such a target

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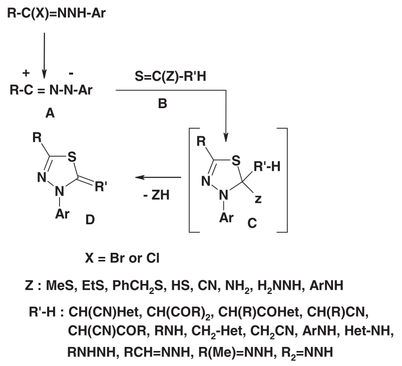


Scheme 1

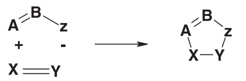


Fig. 1 1,3-Dipolar cycloaddition.

has not been covered hitherto in the foregoing review articles surveying the chemistry of both 1,3,4-thiadiazoles [1–11] and nitrilimines as well as their precursors [12–24].

Regarding the 1,3-dipolar cycloaddition, it is a process in which two reactants, namely a 1,3-dipole and a dipolarophile combine together to form a five membered ring *via* the formation of two new sigma bonds without loss of any small fragment (Fig. 1). The 1,3-dipole is basically a system of three atoms amongst which are distributed four π electrons, whereas the dipolarophile is usually an unsaturated system having two π electrons. It is usually a system with either a double or a triple bond. The 1,3-dipolar cycloaddition reactions are usually referred to either as $(4\pi + 2\pi)$cycloadditions or $(3 + 2)$cycloadditions on the basis of the number of electrons or the number of atoms in the two reactants, respectively.

Several types of 1,3-dipoles are found in the literature. One class of such 1,3-dipolar species is the so-called nitrilimines of the general formula **E.** Such nitrilimines are 1,3-dipoles readily generated *in situ* from stable precursors. They are usually generated in the presence of an appropriate dipolarophile. If they are generated in the absence of suitable dipolarophile, they undergo head-to-tail dimerization to afford the corresponding cycloadduct, namely the corresponding 1,3,4,6-tetrasubstituted-1,2,4,5-tetrazine **F** as given below.

Several convenient methods have been reported for the generation of nitrilimines [25–39]. These include (i) thermolysis of either 2,5-disubstituted tetrazoles **1**, 1,3,4-oxadiazol-5-ones **2** or 1,2,3,4-oxathiadiazol-2-oxides **3** (ii) base treatment of either hydrazonoyl halides **4**, α-nitroaldehyde hydrazones **5** or N-hydrazonoyl pyridinium salts **6** (iii) oxidation of aldehyde hydrazones **7** with lead tetracetate or ferric chloride and (iv) treatment of acid hydrazides **8** with triphenylphosphine in acetonitrile (Chart 1).

The present review covers only the papers dealing with the synthesis of 1,3,4-thiadiazoles *via* nitrilimines, generated by base-catalyzed dehydrohalogenation of hydrazonoyl halides. The various types of hydrazonoyl halides used in this synthesis are listed below in order of their citations in this review.

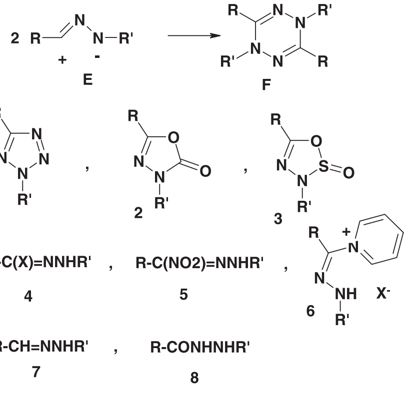
I	Ar—C(X) = NNHAr′
II	Het—COC(X) = NNHAr
III	R—C(X) = NNH—Het
IV	R—[C(X) = NNH—Ar]$_2$
V	ROOC—C(X) = NNH—Het
VI	MeCO—C(X) = NNH—Het
VII	ROOC—C(X) = NNH—Ar
VIII	Het—C(X) = NNHAr
IX	MeCOC(X) = NNHAr
X	ROOC—C(X) = NNH—Ar
XI	PhNHOC—C(X) = NNH—Ar
XII	ArCOC(X) = NNHAr
XIII	Het—C(X) = NNH—Het

Regarding the dipolarophile, it can be almost any molecule having a double or triple bond of the following types (Chart 2). In this review, only cycloaddition reactions of nitrilimines to compounds having the C=S double bond as dipolarophilic site are surveyed.

Reactions

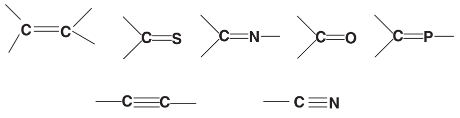
Reaction with alkyl dithiocarboxylates

Several reports on the reactions of alkyl dithiocarboxylates with nitrilimines have been published. In all cases, such reactions were carried out by stirring a mixture of the appropriate ester and hydrazonoyl halide in ethanol at room temperature in the presence of triethylamine [40–45]. For example, Abdelhamid et al. [40,41] reported that reaction of methyl 2-cyano-2-(benzoazol-2-yl)dithioacetates **9** with each of nitrilimines, derived from the corresponding hydrazonoyl halides **I** under such conditions, afforded the corresponding 1,3,4-thiadiazole derivatives **10** in 64–92% yield (Scheme 2).



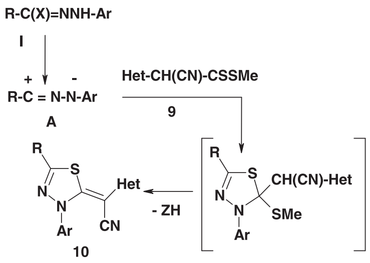
Precursors of hydrazonoyl halides

Chart 1



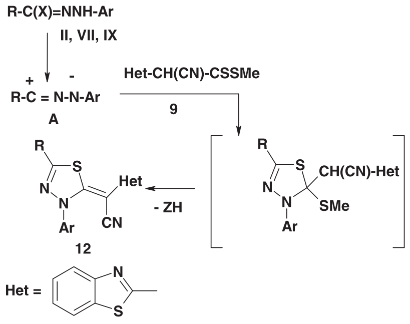
Dipolarophilic groups

Chart 2



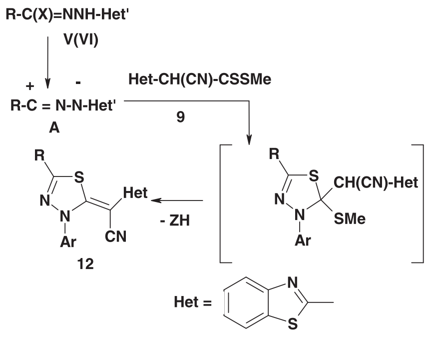
R / Ar / Het: a, 2,3-$(MeO)_2C_6H_3$ / 4-$O_2NC_6H_4$ / benzothiazol-2-yl;
b, 4-FC_6H_4 / 4-$O_2NC_6H_4$ / benzothiazol-2-yl;
c, 3-BrC_6H_4 / 4-$O_2NC_6H_4$ / benzothiazol-2-yl

Scheme 2



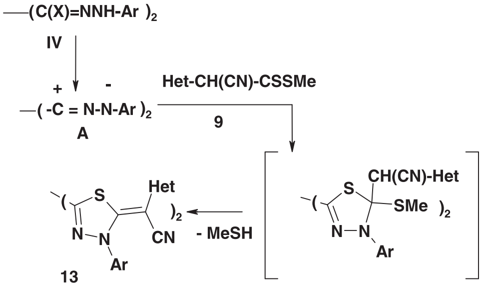
R / Ar : a, (Benzothiazol-2-yl)CO / Ph; b, (Benzothiazol-2-yl)CO / 4-ClC_6H_4;
C, EtOOC / Ph; d, MeCO / Ph

Scheme 3



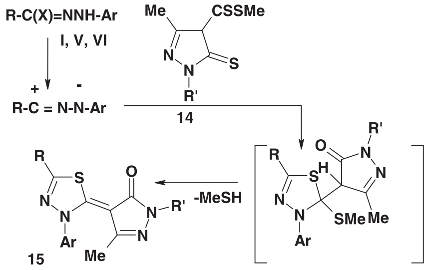
R / Ar: a, EtOOC / 3-Ph-(pyrazol-5-yl); b, MeCO / 3-Ph-(pyrazol-5-yl)

Scheme 4



Ar / Het : a, Ph / benzothiazol-2-yl; 4-ClC_6H_4 / benzothiazol-2-yl

Scheme 5 Ar/Het: a, Ph/benzothiazol-2-yl; 4-ClC_6H_4/benzothiazol-2-yl.



R / Ar / R' : a,, 4-FC_6H_4 /4-$O_2NC_6H_4$ / H; b, BrC_6H_4 / 4-$O_2NC_6H_4$ / H;
c, 4-FC_6H_4 / 4-$O_2NC_6H_4$ / Ph; d, 3-BrC_6H_4 / 4-$O_2NC_6H_4$ / Ph;
e, EtOOC / 3-Ph-pyrazol-5-yl / Ph; f, MeCO / 3-Ph-pyrazol-5-yl / Ph;

Scheme 6

Likewise, the reactions of methyl 2-cyano-2-(benzothiazol-2-yl)dithiocarboxylates **9** with hydrazonoyl chlorides **II** [42] and **VII(IX)** [43] yielded the corresponding 1,3,4-thiadiazole derivatives **11** in 92% and **12** in 52–59% yields, respectively (Scheme 3).

In another report [44], it was indicated that 1,3,4-thiadiazole derivatives **12** were formed in 55–68% yield when N-hetaryl-hydrazonoyl halides **V(VI)** were treated with methyl 2-cyano-2-(benzothiazol-2-yl)dithiocarboxylates **9** (Scheme 4).

Reaction of *bis*-nitrilimines, derived from the bis-hydrazonoyl chlorides **IV** with methyl 2-cyano-2-(hetaryl)dithiocarboxylates **9,** gave the corresponding *bis*-2,2′-(1,3,4-thiadiazole) derivatives **13** in 83–90% yield (Scheme 5) [45].

Also, the 1,3,4-thiadiazole derivatives **15** were furnished in 70–75% yield by reaction of methyl pyrazole-4-dithiocarboxylates **14** with hydrazonoyl halides **I**, **V,** and **VI** (Scheme 6) [41,44].

Reaction with thioamides

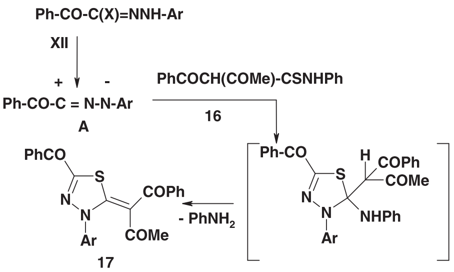
Many reactions of thioamides with nitrilimines were carried out by refluxing a mixture of the appropriate hydrazonoyl halide and thioamide in ethanol in the presence of triethylamine [49,50,54–57]. For example, when N-phenyl 2-benzoyl-3-oxothiobutanamide **16** was reacted with hydrazonoyl bromide **XII** under such reaction conditions, it afforded the corresponding 3-benzoyl-4-aryl-5-[(acetyl,benzoyl)methylene]-1,3,4-thiadiazoles **17a–c** (Scheme 7) [49].

Also, treatment of the thioanilide **18** with each of the hydrazonoyl chlorides **I** and **II** under the same reaction conditions afforded the corresponding 1,3,4-thiadiazole derivatives **19a–c** (Scheme 8) [50].

In a similar manner, the thioacetanilide **20** reacted with the hydrazonoyl halides **I**, **VII,** and **IX** gave also the corresponding 1,3,4-thiadiazole derivatives **21** in 62–68% yields (Scheme 9) [54].

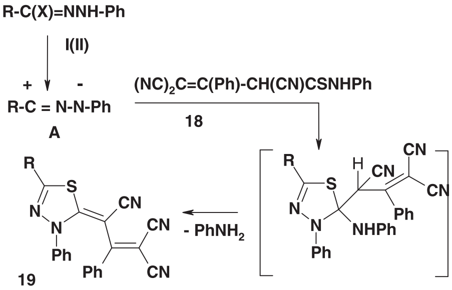
Treatment of the thioanilides **22** with the hydrazonoyl chlorides furnished also the corresponding thiadiazole derivatives **23** (Scheme 10) [55].

Likewise, the hydrazonoyl chlorides **I**, **VII**, **IX,** and **XI** were reported to react with the thioanilide **24** under the same reaction conditions and yielded the corresponding 1,3,4-thiadiazole derivatives **25** in 82–90% yields (Scheme 11) [56].



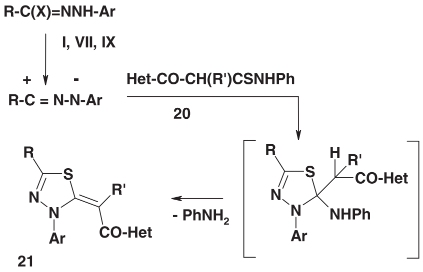
Ar : a, Ph; b, 4-MeC_6H_4; c, 4-$MeOC_6H_4$

Scheme 7



R : a, Ph; b, 4-ClC_6H_4; c, Benzothiazol-2-yl)CO-

Scheme 8



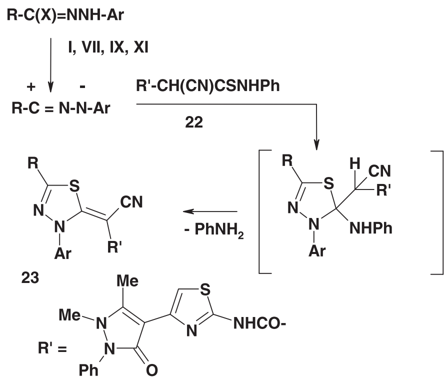
Het = Benzofuran-2-yl; R' = Benzo-1,2,3-triazol-1-yl
R / Ar : a, EtOOC / 4-MeC_6H_4; b, 4-ClC_6H_4; c, MeCO / 4-MeC_6H_4;
d, MeCO / 4-ClC_6H_4; e, Ph / Ph

Scheme 9

The reaction of the hydrazonoyl chlorides **I**, **II**, **VII**, **IX,** or **XI** with the thioanilide **26** in refluxing ethanol in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazole derivatives **27** in 73–80% yield (Scheme 12) [57].

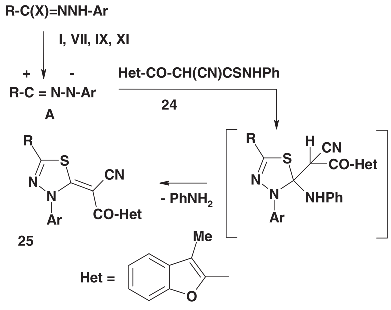
In some other reports, several 1,3,4-thiadiazole derivatives were also obtained by reaction of hydrazonoyl halides with the appropriate thioamides in ethanol containing triethylamine at room temperature. For example, the 1,3,4-thiadiazole derivatives **10** have been prepared in 64–92% yield by reaction of 2-hetaryl-cyanothioacetanilides **28** with the hydrazonoyl halides **I** and **VIII** under such reaction conditions [42] or in refluxing chloroform in the presence of triethylamine [40] (Scheme 13).

Similar treatment of each of the hydrazonoyl chlorides **VII** and **IX** with the N-methylthioacetamide derivative **29** in ethanol containing triethylamine at room temperature afforded the corresponding 1,3,4-thiadiazole derivatives **30** in 57–60% yield (Scheme 14) [59].



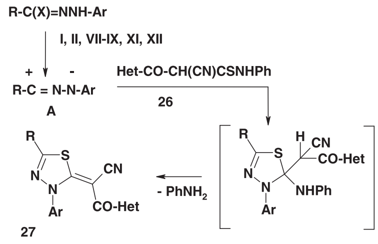
R / Ar : a, Ph / Ph; b, MeCO / Ph; c, MeCO / 4-MeC_6H_4; d, MeCO / 4-ClC_6H_4 ;
e, PhNHCO / Ph; f, PhNHCO / 4-MeC_6H_4; g, PhNHCO / 4-ClC_6H_4; h, EtOOC/ C_6H_4;
i, EtOOC/ 4-MeC_6H_4; j, EtOOC/ 4-ClC_6H_4;

Scheme 10



R / Ar: a, Ph / Ph; b, EtOOC / Ph; c, EtOOC / 4-MeC_6H_4;
d, EtOOC / 4-ClC_6H_4; e, MeCO / 4-MeC_6H_4; f, PhNHCO / Ph; g, PhNHCO / 4-MeC_6H_4;
h, PhNHCO / 4-ClC_6H_4

Scheme 11

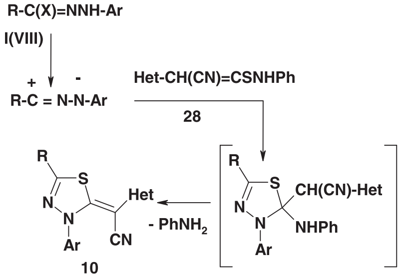


Het = 2-Ph-indol-3-yl Ar = XC_6H_4
R : Ar : a, Ph / Ph; b, PhCH=CH- / Ph; c, 2-thienyl / 4-O_2N; d, 2-Furyl / 4-O_2N; e, Ph / 4-O_2N
f, MeCO / Ph; g, MeCO / 4-Me; h, MeCO / 4-Cl; i, MeOOC / Ph; j, MeOOC / 4-Me; k,
MeOOC / 4-Cl; l, EtOOC / Ph; m, EtOOC / 4-Me; n, EtOOC / 4-Cl; o, PhCO / Ph; q, PhNHCO / 4-
Me; u, PhNHCO / 4-Cl; p, 2-Thenoyl / Ph

Scheme 12

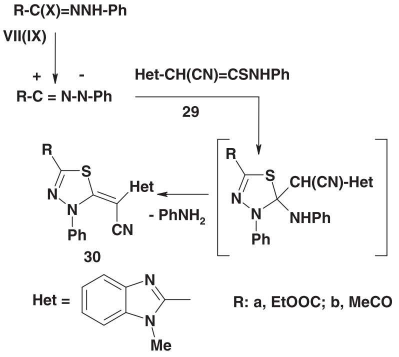
Bis-2,2′-(1,3,4-thiadiazole) derivatives **13** have been obtained in 83–90% yield by reaction of the *bis*-nitrilimines, derived from the respective *bis*-hydrazonoyl chlorides **IV**, with N-phenyl 2-cyano-2-(benzothiazol-2-yl)thioamide **29** under the same reaction conditions (Scheme 15) [45].

Only in one report [51], reaction of N-aryl-cyanothioformamides **30** with nitrilimines from hydrazonoyl halides **VII** and

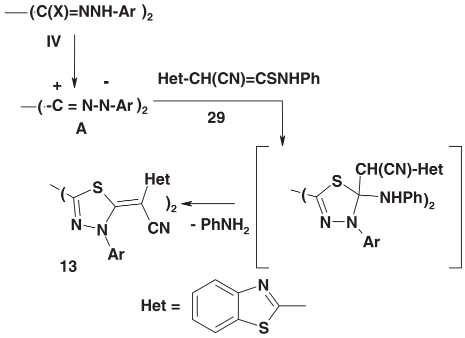


R / Ar / X : a, 2,3-$(MeO)_2C_6H_3$ / 4-$O_2NC_6H_4$ / O; b, 2,3-$(MeO)_2C_6H_4$ / 4-O_2NPh / S;
c, 2,3-$(MeO)_2C_6H_3$ / 4-$O_2NC_6H_4$ / MeN; d, (benzothiazol-2-yl)-CO- / Ph / S;
e, (benzothiazol-2-yl)-CO- / 4-ClC_6H_4 / S

Scheme 13



Scheme 14



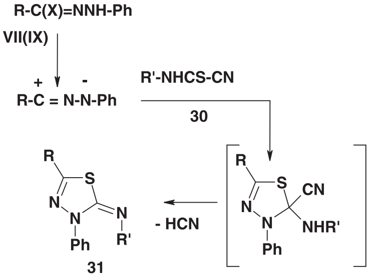
Ar / Het : a, Ph / Benzothiazol-2-yl; b, 4-ClPh / Benzothiazol-2-yl

Scheme 15

IX, when carried out in refluxing ethanol in the presence of sodium ethoxide, it afforded the corresponding 3-phenyl-5-substituted-2-N-(arylimino)-1,3,4-thiadiazoles **31** (Scheme 16) [51].

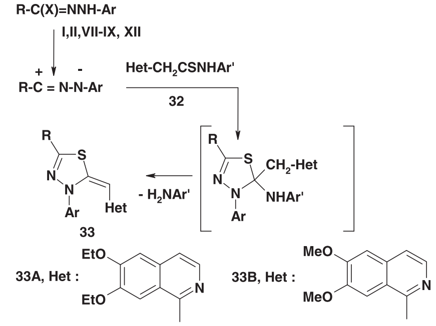
Abunada [46], Hassaneen et al. [47], and Abdallah et al. [48] demonstrated that treatment of the thioanilides **32A(B)** each with hydrazonoyl halides **I**, **II**, **VII**, **IX,** and **XII** in refluxing chloroform in the presence of triethylamine yielded thethiadiazole derivatives **33** (Scheme 17).

Similarly, the reaction of thioacetanilide **34** with various nitrilimines derived from the respective hydrazonoyl halides



R / R' : 31A: EtOOC ; 31B : MeCO
a, Ph; b, 4-MeC_6H_4; c, 4-Cl C_6H_4; d, 4-MeO C_6H_4

Scheme 16



33A , R / Ar :
a, Ph / Ph; b, EtOOC / Ph; c, PhCH=CH- / Ph; d, 2-Thienyl / 4-O_2NPh; e, MeCO / 4-O_2NPh;
f, PhCO / 4-O_2NPh; g, 2-Thenoyl / 4-O_2NPh ; h, EtOOC / Ph; b, i, EtOOC / 4-MePh;
j, EtOOC / 4-ClPh
33B , R / Ar :
33B-1, a, MeCO / Ph; b, MeCO / 4-MePh; c, MeCO / 4-Cl;
33B-2, a, PhCO / Ph; b, PhCO / 4-MePh; c, PhCO / 4-ClPh;
33B-3, a, EtOOC / Ph; b, EtOOC / 4-MePh; c, EtOOC / 4-ClPh;
33B-4, a, MeOOC / Ph; b, MeOOC / 4-MePh; c, MeOOC / 4-ClPh;
33B-5 a, PhNHCO / Ph; b, PhNHCO / 4-MePh; c, PhNHCO / 4-ClPh;
33B-6, a, Ph / 4-O_2NPh; b, 4-MePh / 4-O_2NPh; c, 4-ClPh / 4-O_2NPh; d, 2-thienyl / 4-O_2NPh;
e, 2-furyl / 4-O_2NPh;
33B-7, a, Ph / Ph; b, PhCH=CH- / Ph; f, 2-Naphthoyl / Ph; g, 2-thenoyl / Ph

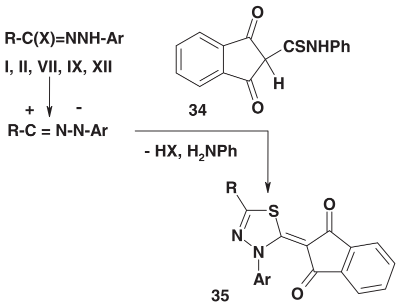
Scheme 17

I, **VII**, **IX,** and **XII** in refluxing chloroform in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazole derivatives **35** in 74–80% yield (Scheme 18) [52].

Several thioamides reacted with hydrazonoyl halides in dimethyl formamide in the presence of potassium hydroxide at room temperature to give the corresponding 1,3,4-thiadiazole derivatives [53,58,60–62]. For example, the interaction of 2-hetaryl-2-cyanothioacetanilide **36** with various nitrilimines derived from the respective hydrazonoyl halides **II**, **VII**, **IX**, **XI,** and **XII** under such reaction conditions gave mainly the 1,3,4-thiadiazole derivatives **37** in 53–60% yield (Scheme 19) [53].

Likewise, reaction of the thioanilide **38** with the hydrazonoyl chlorides **I**, **VII,** and **XI** was reported to furnish the corresponding thiadiazole derivatives **39** (Scheme 20) [58].

In another report [60], it was indicated that similar reaction of the thioanilides **40** with the *bis*-hydrazonoyl chlorides **IV** furnished the corresponding *bis*-2,2′-(1,3,4-thiadiazole) derivatives **41** in 66–70% yield (Scheme 21). In contrast to this finding, it was indicated that reaction of the same *bis*-hydrazonoyl



R = EtOOC; Ar: a, Ph; b, 4-MePh; c, 4-ClPh;

R = MeCO; Ar : a, Ph; b, 4-ClPh; c, 4-O_2NPh

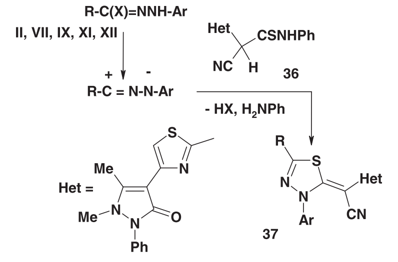
R = 2-Thenoyl; Ar : a, , Ph; b.4-ClPh; c, 4-MePh;

R = PhCO; Ar: a, Ph; b, 4-MePh;

R = Ph; Ar : a, Ph; b, 4-O_2NPh

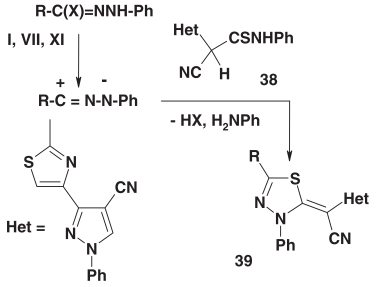
R = PhCH=CH- ; Ar : a, Ph

Scheme 18



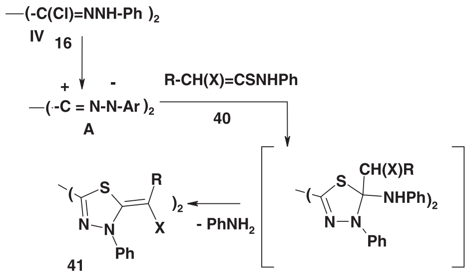
R / Ar : a, 2-Thenoyl / Ph; b, 2-furoyl / Ph; c, EtOOC / Ph; d, MeCO / Ph; e, PhNHCO / Ph; f, PhCO / Ph; g, 2-naphthoyl / Ph; H, MeCO / 4-MePh

Scheme 19



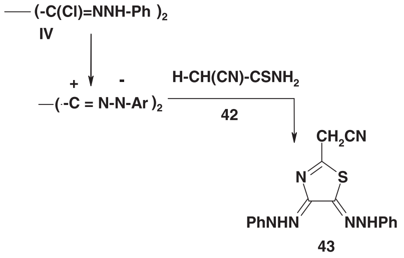
R: a, Ph; b, EtOOC; c, PhNHCO

Scheme 20

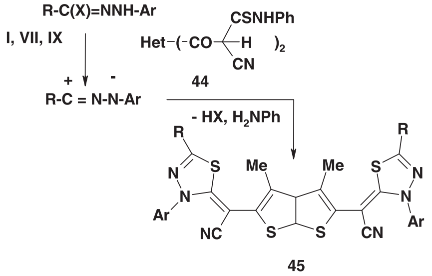


R / X : a, PhCO / CN; b, 2-Furoyl / CN; c, (Benzothiazol-2-yl)CO- / CN; d, PhCO / EtOOC

Scheme 21



Scheme 22



R = Ph; Ar : a, Ph;

R = EtOOC; Ar : a,Ph; b, 4-MePh; c, 4-ClPh

R = MeCO; Ar : a,4-MePh; b, 4-ClPh; c, 3-ClPh

Scheme 23

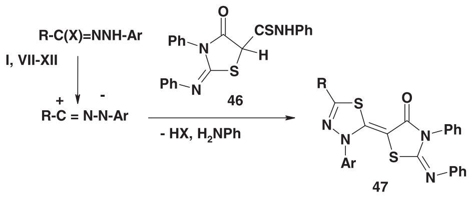
chloride with cyanothioacetamide **42** in boiling ethanol in the presence of triethylamine yielded the thiazole derivative **43** (Scheme 22) [60].

Recently, it was found that reaction of each of the hydrazonoyl halides **I**, **VII** and **IX** with the *bis*-thioanilide **44** inDMF containing KOH furnished the *bis*-1,3,4-thidiazole derivatives **45** in 49–66% yield (Scheme 23) [61].

Hassaneen et al. reported that treatment of (2-phenylimino-3-phenyl-4-oxothiazolidin-5-yl)thiocarboxanilide **46** with each of hydrazonoyl halides **I**, **VII**, **VIII**, **IX**, **XI**, and **XII** inDMF containing KOH afforded the corresponding thiadiazoline derivatives **47** (Scheme 24) [62]. Similar reaction of 1,3-diphenyl-2-thioxo-5-oxo-4-thiocarboxanilide **48** with the aforementioned hydrazonoyl halides under the same reaction conditions yielded also the corresponding 1,3,4-thiadiazole derivatives **49** (Scheme 25) [62].

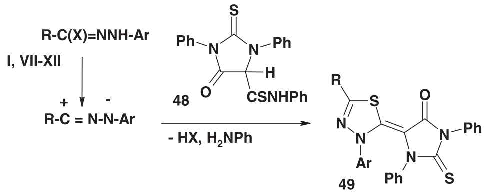
Reaction with alkyl dithiocarbamates

A number of papers have been published on reactions of alkyl dithiocarbamates with nitrilimines. In all of these papers, the reactions were carried out by stirring a mixture of the appropriate hydrazonoyl halide and the dithiocarbamate in ethanol in the presence of triethylamine at room temperature [44,63–69]. For example, 1,3,4-thiadiazole derivatives **51** were readily obtained in 68–85% yield by reaction of diarylnitrilimines derived from the respective hydrazonoyl halides **I**, **VII**, **IX**, **XI**, and **XII** under such conditions with methyl N-aryldithiocarbamates **50** (Scheme 26) [63,64].



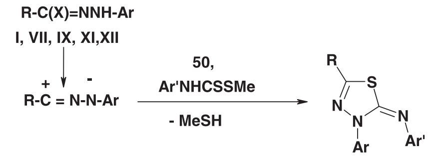
R / Ar : a, EtOOC / Ph; b, PhNHCO / Ph; c, 2-Napthoyl / Ph; d, 2-Thienyl / Ph; e, 2-Thienyl / 4-O2NPh; f, 2-thenoyl / Ph; g, MeCO / Ph; h, PhCO / Ph; i, PhCH=CH- / Ph; j, 2-furyl / 4-O_2NPh; k, Ph / Ph; l, Ph / 4-O2NPh

Scheme 24



R / Ar : a, Ph / Ph; b, EtOOC / Ph; c, MeCO / Ph; d, PhNHCO / Ph; e, PhCO / Ph; f, PhCH=CH- / Ph; 2-thienyl / Ph; b, 2-thienyl / 4-O2NPh

Scheme 25



51A-E

R / Ar / Ar' :a, PhCO / Ph / Ph; b, EtOOC / Ph / Ph; c, PhNHCO / Ph / Ph; d, MeCO / Ph / Ph; e, PhCO / Ph / 4-MePh; f, EtOOC / Ph / 4-MePh; g, PhNHCO / Ph / 4-MePh; h, MeCO / Ph / 4-MePh

Scheme 26

In like manner, the related 1,3,4-thiadiazole derivatives of type **52** were obtained in 55–87% yield by reaction of N-aryl-C-heteroyl hydrazonoyl halides **II** with methyl N-phenyldithiocarbamate **50A** (Scheme 27) [42,66–68].

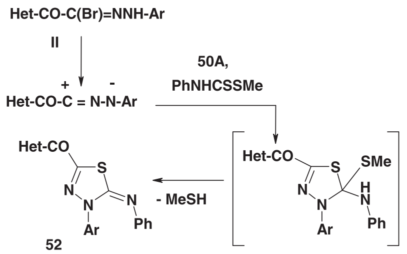
Also, reaction of hydrazonoyl chlorides **V(VI)** with methyl N-phenyldithiocarbamate **50A** in ethanolic triethylamine at room temperature furnished the corresponding 5-phenylimino-1,3,4-thiadiazole derivatives **53** in 55–65% yield (Scheme 28) [44].

Abdelhamid and Abdel-Wahab [64] and Abdelhamid et al. [69] investigated the reaction of methyl N-hetaryldithiocarbamate **54** with nitrilimines derived from the hydrazonoyl chlorides **I**, **II**, **VII**, **IX**, **XI**, and **XII** in ethanolic triethylamine at room temperature and characterized the products as 5-hetarylimino-1,3,4-thiadiazole derivatives **55**. The latter products were obtained in 50–82% yield (Scheme 29).

2-Phenylimino-1,3,4-thidiazole derivative **56** were also produced in good yield by reaction of methyl N-aryldithiocarbamates **50A** with the hydrazonoyl halide **II** in ethanolic triethylamine (Scheme 30) [66].

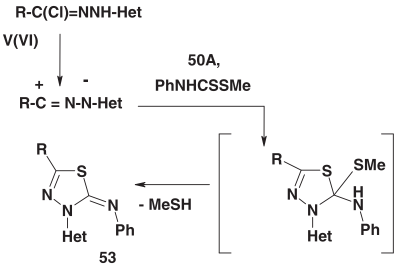
Reaction with thiourea and its derivatives

Direct synthesis of 5-phenylimino-1,3,4-thiadiazole derivatives **58** in 65–82% yield from C,N-diarylnitrilimines, derived by base-catalyzed dehydrohalogenation of the respective hydrazonoyl halides **I** in refluxing ethanol in the presence of triethylamine, and mono-substituted-thiourea and its N,N′-disubstituted derivatives **57A**,**B** were recently reported (Scheme 31) [40,63,64].



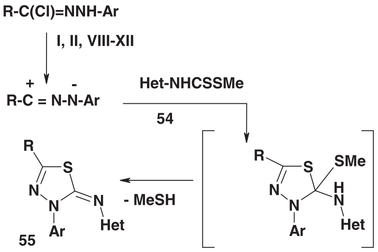
R / Ar : a, Benzenethiazol-2-yl)CO- / 4-ClPh; b, Benzenethiazol-2-yl)CO- / Ph; C, (2-Ph,4-Me-thiazol-5-yl)CO- / Ph; d, Naphtho[2,1-b]-fuan-2-yl)CO- / Ph; e, (5-Cl-benzofuran-2-yl)-CO- / Ph

Scheme 27



Het = 3-Ph-pyrazol-5-yl R : a, EtOOC; b, MeCO

Scheme 28



Het = 3-Ph-pyrazol-5-yl

R / Ar : a, Ph / Ph; EtOOC / Ph; b, PhNHCO / Ph; c, MeCO / Ph; d, PhCO / Ph; e, 2-Naphthoyl / Ph; f, 2-Thenoyl / Ph; g, 2-Naphthoyl / Ph; h, 2-Thenoyl / Ph; I, PhNHCO / 4-MePh; j, MeCO / 4-MePh; k, EtOOC / 4-MePh;

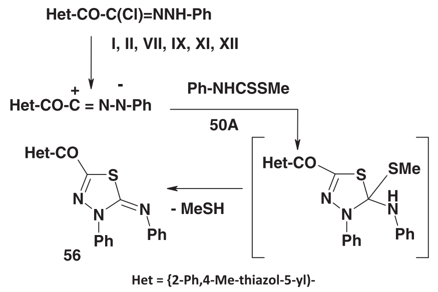
Scheme 29

Also, it was reported that N-phenyl benzenecarbohydrazonoyl bromide reacted with *bis*-thiourea **59** in refluxing pyridine and yielded the azine derivative **60** (Scheme 32) [86]. The latter was also produced by heating 2-hydrazono-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole **61** in DMF containing triethylamine as catalyst (Scheme 32) [86].

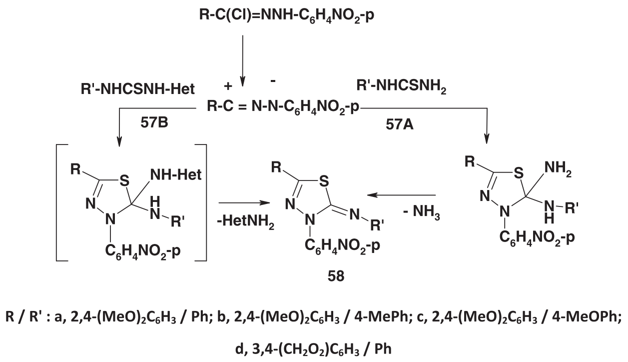
Reactions with alkyl dithiocarbazates

Unsubstituted dithiocarbazates

The thiadiazole derivatives **61a–d** were readily produced from methyl dithiocarbazate **62** through its reaction with each of the



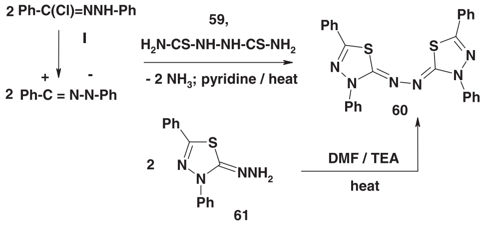
Scheme 30



R / R' : a, 2,4-(MeO)₂C₆H₃ / Ph; b, 2,4-(MeO)₂C₆H₃ / 4-MePh; c, 2,4-(MeO)₂C₆H₃ / 4-MeOPh;

d, 3,4-(CH₂O₂)C₆H₃ / Ph

Scheme 31



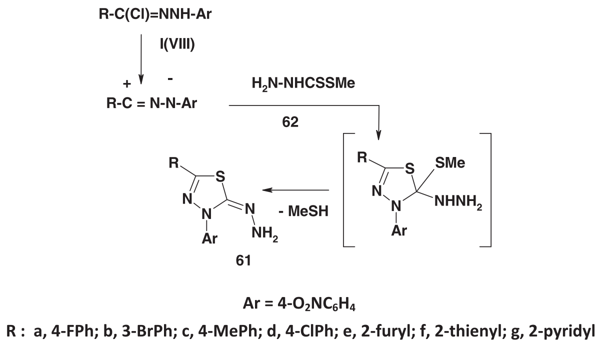
Scheme 32

hydrazonoyl bromides **I** in ethanol in the presence of triethylamine at room temperature [41]. However, the thiadiazole derivatives **61e–g** were produced by refluxing a mixture of each halide **VIII** and alkyl dithiocarbazate **62** in ethanol [70] (Scheme 33). The yields of the compounds prepared were not pointed out, however.

Likewise, reaction of N-hetaryl hydrzonoyl chlorides **V** and **VI** each with alkyl dithiocarbazates **62** in ethanol in the presence of triethylamine at room temperature furnished the corresponding thiadiazole derivatives **63** in 65% yield (Scheme 34) [40].

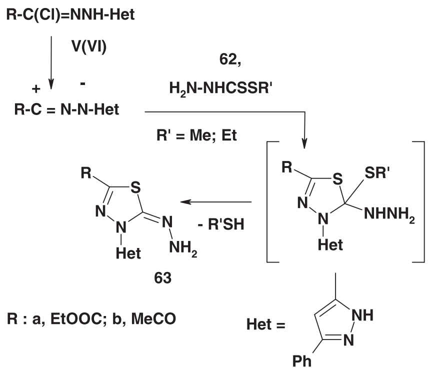
Alkyl N-aryldithiocarbazates

Reaction of methyl N-phenyldithiocarbazate **64** with the nitrilimines, generated from the N-arylC-hetaroylhydrazonoyl bromides **II** in ethanol in the presence of triethylamine, furnished the thiadiazole derivative **65** (Scheme 35) [66].



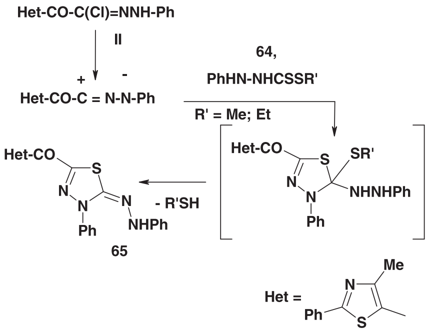
R : a, 4-FPh; b, 3-BrPh; c, 4-MePh; d, 4-ClPh; e, 2-furyl; f, 2-thienyl; g, 2-pyridyl

Scheme 33



R : a, EtOOC; b, MeCO

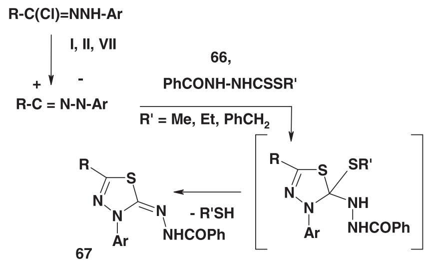
Scheme 34



Scheme 35

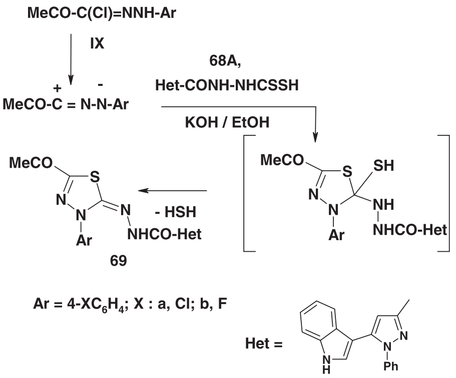
Alkyl N-acyldithiocarbazates

Several publications concerning reaction of alkyl N-acyldithiocarbazates with nitrilimines have been reported. Most of the reactions were studied by stirring a mixture of the appropriate hydrazonoyl halide and the alkyl N-acyldithiocarbazate in ethanol in the presence of Triethylamine at room temperature [42,63–65,71,72]. Only in one report [66], the reaction between the hydrazonoyl halide and alkyl N-acyldithiocarbazate was carried out in refluxing chloroform containing triethylamine. Thus, reaction of alkyl N-benzoyldithiocarbazate **66** with nitrilimines generated from various hydrazonoyl halides **I** [63,64,71], **II** [65],and **X** [42,66,72] afforded the corresponding thiadiazole derivatives **67** in 71–85% yields (Scheme 36).

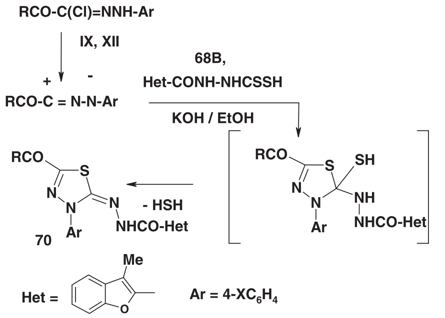


R / Ar : a, Benzothiazol-2-yl)CO- / Ph; b, Benzothiazol-2-yl)CO- / 4-ClPh;
c, 3,4-(CH_2O_2)Ph / Ph; d, 3,4-(CH_2O_2)Ph / Ph; e, 2,3-(MeO_2)Ph / 4-O_2NPh;
f, EtOOC / 4-(Benzoxazol-2-yl)Ph; g, EtOOC / 4-(Benzothiazol-2-yl)Ph;
h, (4-Me-2-Ph-thiazol-5-yl)CO- / Ph; I, 4-i-PrPh / 4-O2NPh;
j, (Benzo[f]courmarin-3-yl)-CO- / Ph

Scheme 36



Scheme 37

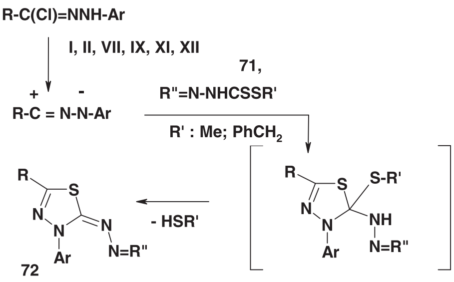


R / X : a, PhCO / H; b, MeCO / H; c, MeCO / Me; d, MeCO / Cl

Scheme 38

Furthermore, N-[5-acetyl-3-(aryl)-1,3,4-thiadiazol-2(3*H*)-ylidene]-5-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides **69** was prepared in 43–50% by direct heating the potassium salt of dithiocarbazate **68A** with hydrazonoyl chlorides **IX**in ethanol (Scheme 37) [73].

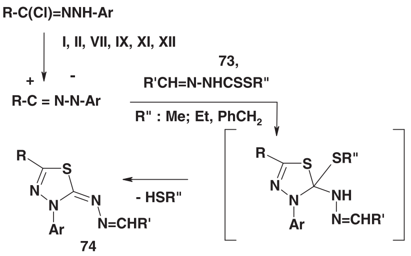
Likewise, reaction of the hydrazonoyl halides **IX** and **XII** each with potassium salt of the dithiocarbamate **68B** in refluxing ethanol yielded the corresponding 1,3,4-thidiazole derivatives **70** in 72–76% yields (Scheme 38) [74].



R" = Ph-CH=CH-CH=

R / Ar : a, 3,4-(CH_2O_2)Ph / 4-O_2NPh; b, Naphtho[2,1-b]furan-2-yl-CO- / Ph;
c, 4-i-PrPh / 4-O_2NPh; d, EtOOC / Ph; e, MeCO / Ph; f, PhCO / Ph; g, 2-furoyl / Ph;
h, 2-Naphthoyl / Ph; i, PhNHCO / Ph; j, 2-thenoyl / Ph

Scheme 39



74-1, Ar = 4-O_2NPh, R: A, 2,4-$(MeO)_2$Ph; B, 4-FPh; C, 3-BrPh; D, 3,4-(CH_2O_2)Ph;
E, 2,3-$(MeO)_2$Ph; F, 4-i-PrPh;
R' : a, Ph; b, 2-thienyl; c, 2-furyl; d, 2,3-(CH_2O_2)Ph; e, 4-i-PrPh;
f, pepirinyl; g, 3-pyridyl; h, coumarinyl; i, 2,3-(MeO)2Ph;
j, 4-MePh; k, 4-MeOPh; l, 2-pyridyl

74-2, Ar = Ph, R: A, PhCO; B, EtOOC; C, PhNHCO; D, MeCO; E, MeOOC; F, 2-Furoyl;
G, 2-Thenoyl; H, 2-Naphthoyl; I, Ph
R' : a, 2,3-$(MeO)_2$Ph; b, 4-i-PrPh; c, 2,3-(CH_2O_2)Ph; d, 2-pyrrolyl;
e, 3-indolyl; f, 2,4-$(HO)_2$Ph; g, 2-naphthoyl;
h, 2,4-Me_2-1-Ph-5-oxopyrazolin-4-yl; i, 4-Me_2NPh; j, 1-naphthyl;
k, 7-HO,2-Me,4-oxochromen-6-yl;
l, 4-MeO, 5-oxo-furo[3,2-g]chromen-6-yl

74-3, Ar = Ph, R : A, (Benzothiazol-2-yl)CO; B, (2-Ph, 4-Me-thiazol-2-yl)CO;
C, (Naphtho[2,1-b]furan-2-yl)CO; D, (5-Cl-benzo[b]furan-2-yl)CO;
E, (Benzocoumarin-3-yl)CO; F, (Bnzo[b]furan-2-yl)CO
R' : a, Ph; b, 4-FPh; c, 2-thienyl; d, 2-furyl; e, 3-pyridyl; f, 4-MeOPh;
g, 4-pyridyl

74-4, R = EtOOC; Ar : A, 4-(Benzoazol-2-yl)Ph; B, 4-(Benzothiazol-2-yl)Ph
R': a, Ph; b, 2,3-(CH2O2)Ph; c, 4-i-PrPh

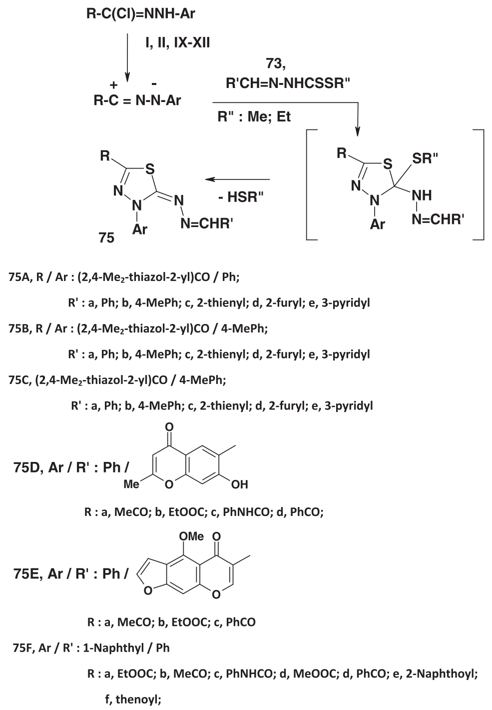
Scheme 40

Alkyl N-cinnamylidene dithiocarbazates

The azine derivatives **72** were reported to be obtained in 65–90% in yields from the interaction of alkyl styrylmethylidenedithiocarbazate **71** with various nitrilimines derived from hydrazonoyl chlorides **I**, **II**, **VII**, **IX**, **XI,** and **XII** in ethanol in the presence of triethylamine at room temperature (Scheme 39). The formation of the latter products **72** was considered to result from initial cycloaddition of nitrilimines to the C=S to form the cycloadducts which in turn underwent elimination of methanethiol [63,67,71,75].

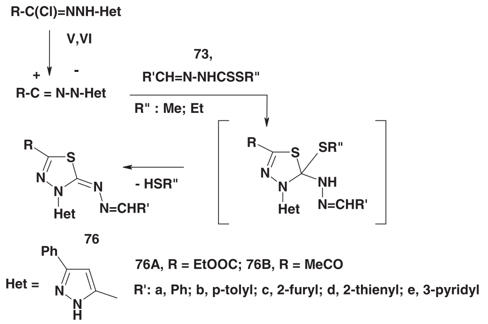
Alkyl N-arylmethylene dithiocarbazates

Several publications covering reactions of nitrilimines with alkyl N-alkylidene dithiocarbazates have been reported. In all cases examined, the reactions were carried out by stirring a mixture of the appropriate hydrazonoyl halide and alkyl



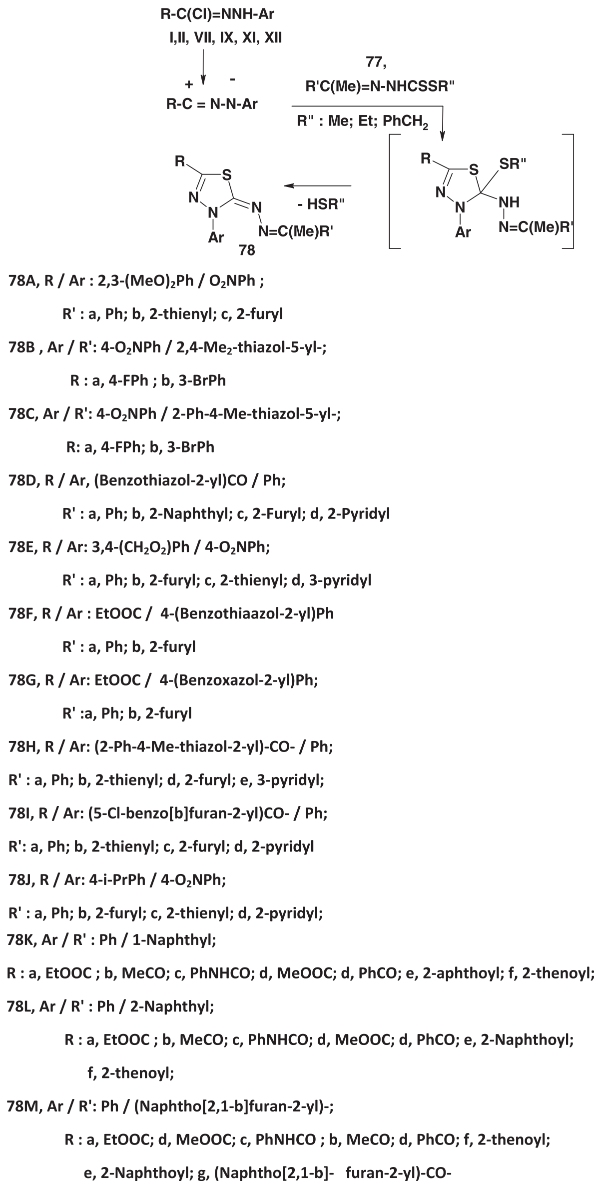
75A, R / Ar : (2,4-Me_2-thiazol-2-yl)CO / Ph;
R' : a, Ph; b, 4-MePh; c, 2-thienyl; d, 2-furyl; e, 3-pyridyl
75B, R / Ar : (2,4-Me_2-thiazol-2-yl)CO / 4-MePh;
R' : a, Ph; b, 4-MePh; c, 2-thienyl; d, 2-furyl; e, 3-pyridyl
75C, (2,4-Me_2-thiazol-2-yl)CO / 4-MePh;
R' : a, Ph; b, 4-MePh; c, 2-thienyl; d, 2-furyl; e, 3-pyridyl
75D, Ar / R' : Ph /
R : a, MeCO; b, EtOOC; c, PhNHCO; d, PhCO;
75E, Ar / R' : Ph /
R : a, MeCO; b, EtOOC; c, PhCO
75F, Ar / R' : 1-Naphthyl / Ph
R : a, EtOOC; b, MeCO; c, PhNHCO; d, MeOOC; d, PhCO; e, 2-Naphthoyl;
f, thenoyl;

Scheme 41



76A, R = EtOOC; 76B, R = MeCO
R': a, Ph; b, p-tolyl; c, 2-furyl; d, 2-thienyl; e, 3-pyridyl

Scheme 42



78A, R / Ar : 2,3-$(MeO)_2$Ph / O_2NPh ;
R' : a, Ph; b, 2-thienyl; c, 2-furyl
78B , Ar / R': 4-O_2NPh / 2,4-Me_2-thiazol-5-yl-;
R : a, 4-FPh ; b, 3-BrPh
78C, Ar / R': 4-O_2NPh / 2-Ph-4-Me-thiazol-5-yl-;
R: a, 4-FPh; b, 3-BrPh
78D, R / Ar, (Benzothiazol-2-yl)CO / Ph;
R' : a, Ph; b, 2-Naphthyl; c, 2-Furyl; d, 2-Pyridyl
78E, R / Ar: 3,4-(CH_2O_2)Ph / 4-O_2NPh;
R' : a, Ph; b, 2-furyl; c, 2-thienyl; d, 3-pyridyl
78F, R / Ar : EtOOC / 4-(Benzothiaazol-2-yl)Ph
R' : a, Ph; b, 2-furyl
78G, R / Ar: EtOOC / 4-(Benzoxazol-2-yl)Ph;
R' :a, Ph; b, 2-furyl
78H, R / Ar: (2-Ph-4-Me-thiazol-2-yl)-CO- / Ph;
R' : a, Ph; b, 2-thienyl; d, 2-furyl; e, 3-pyridyl;
78I, R / Ar: (5-Cl-benzo[b]furan-2-yl)CO- / Ph;
R': a, Ph; b, 2-thienyl; c, 2-furyl; d, 2-pyridyl
78J, R / Ar: 4-i-PrPh / 4-O_2NPh;
R' : a, Ph; b, 2-furyl; c, 2-thienyl; d, 2-pyridyl;
78K, Ar / R' : Ph / 1-Naphthyl;
R : a, EtOOC ; b, MeCO; c, PhNHCO; d, MeOOC; d, PhCO; e, 2-aphthoyl; f, 2-thenoyl;
78L, Ar / R' : Ph / 2-Naphthyl;
R : a, EtOOC ; b, MeCO; c, PhNHCO; d, MeOOC; d, PhCO; e, 2-Naphthoyl;
f, 2-thenoyl;
78M, Ar / R': Ph / (Naphtho[2,1-b]furan-2-yl)-;
R : a, EtOOC; d, MeOOC; c, PhNHCO ; b, MeCO; d, PhCO; f, 2-thenoyl;
e, 2-Naphthoyl; g, (Naphtho[2,1-b]- furan-2-yl)-CO-

Scheme 43

N-alkylidene dithiocarbazate in ethanol containing triethylamine at room temperature. For example, reactions of the dithiocarbazates **73** with nitrilimines derived from various hydrazonoyl halides **II**, **VII**, **IX**, **XI,** and **XII** [40–42,53,63–68,71,72,75,76,78,79] under such conditions furnished the corresponding azine derivatives **74** (Scheme 40).

Also, the thidiazole derivatives **75** have also been prepared by reaction of N-aryl 2-hetaryl-2-oxoethanehydrazonoyl chlorides **II** with alkyl N-arylidenedithiocarbazate **73** in ethanolic triethylamine at room temperature (Scheme 41) [71,80].

Similarly, reaction of N-hetarylhydrazonoyl chlorides **V**, VI, IX, and **X** each with alkyl N-arylidenedithiocarbazate **73** under the same reaction conditions was reported to furnish the corresponding thidiazole derivatives **76** in 60–80% yields (Scheme 42) [44].

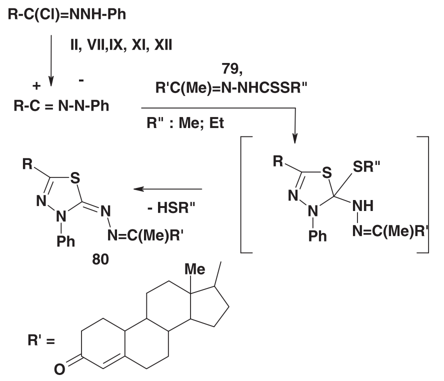
Alkyl N-(1-aryl)ethylidene dithiocarbazates

Numerous azine derivatives **78** were prepared in 56–90% yield by reactions of alkyl 1-substituted-ethylidene-dithiocarbazate **77** with various nitrilimines, generated from hydrazonoyl bromides **I**, **V**, **VII**, and **VIII** [40,41,63,71,65,66,68,71,72,77,78,81,83] in ethanol in the presence of triethylamine at room temperature (Scheme 43).

Likewise, 2,3-dihydro-1,3,4-thiadiazolyl steroids **80** were analogously prepared in 60–68% yields by reaction of alkyl dithiocarbazate **79** with various hydrazonoyl halides **II**, **VII**, **IX**, **XI,** and **XII** under the same reaction conditions (Scheme 44) [82].

Reactions of alkyl 1-substituted-ethylidene-dithiocarbazates **77** with each of N-hetaryl hydrazonoyl chlorides **V** and **VI** in ethanolic at room temperature yielded the corresponding azine derivatives **81** in 60–85% yield (Scheme 45) [44].

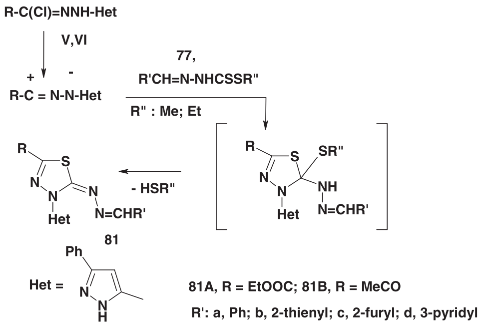
The steroidal dithiocarbazates **82A**,**B** were also reported to undergo similar reaction with hydrazonoyl halides **II**, **VII**, **IX**, **XI,** and **XII** and gave the respective 1,3,4-thiadiazoles **83A**,**B** (Scheme 46) [82].



R : a, EtOOC; b, MeOOC; c, MeCO; d, PhNHCO; e, PhCO;

f, 2-Naphthoyl; g, 2-Thenoyl

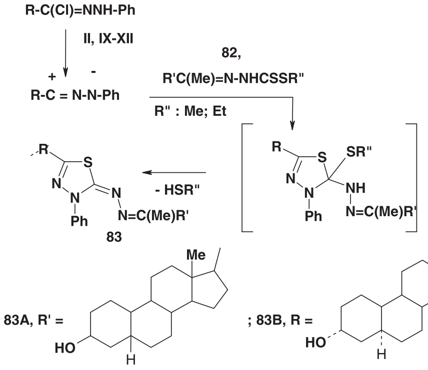
Scheme 44



81A, R = EtOOC; 81B, R = MeCO

R': a, Ph; b, 2-thienyl; c, 2-furyl; d, 3-pyridyl

Scheme 45

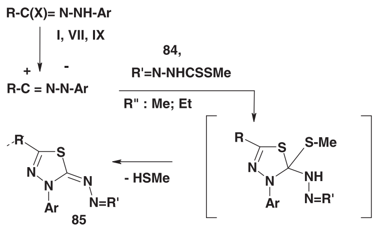


R : a, EtOOC; b, MeOOC; c, MeCO; d, PhNHCO; e, PhCO;

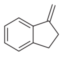
f, 2-Naphthoyl; g, 2-Thenoyl

II, IX, X,XI, XII

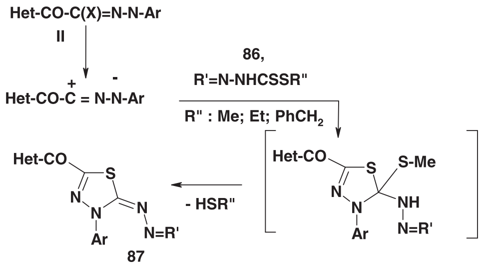
Scheme 46



R / Ar :
85A, EtOOC / 3-Ph-Pyrazol-5-yl; 85B, MeCO / 3-Ph-Pyrazol-5-yl;
85C, 3,4-(CH_2O_2)Ph / 4-O_2NPh; 85D, 4-i-PrPh / 4-O_2NPh

R' : a, $(CH_2)_4C$=; b, $(CH_2)_5C$=; c, $(CH_2)_6C$= ; d, 

Scheme 47



Het / Ar :

87A, Benzothiazol-2-yl / Ph; R' : a, $(CH_2)_4C$= ; b, 1,2-$C_6H_4(C_2H_4)C$=

87B, 2-Ph,4-Methiazol-2-yl / Ph; R': a, $(CH_2)_4C$=; b, $(CH_2)_6C$=; c, 1,2-$C_6H_4(C_2H_4)C$=

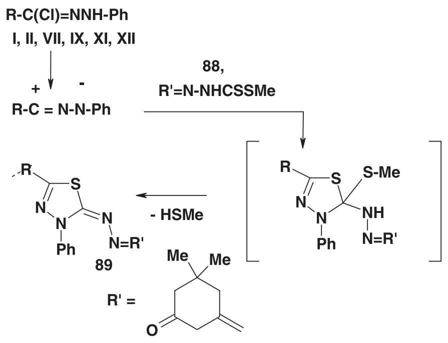
87C, Naphtho[2,1-b]furan-2-yl / Ph; R' : a, $(CH_2)_4C$=; b, $(CH_2)_5$; c, 1,2-$C_6H_4(C_2H_4)C$=

87D, 5-Cl-benzo[b]furan-2-yl / Ph; R' : a, $(CH_2)_4C$=; b, $(CH_2)_5C$=

87E, 2,4-Me2-thiazol-2-yl / Ph; R' : a, $(CH_2)_4C$=; b, $(CH_2)_5C$=

87F, 2,4-Me2-thiazol-2-yl / 4-MeC_6H_4; R' : a, $(CH_2)_4C$=; b, $(CH_2)_5C$=

Scheme 48



R : a, Ph; b, EtOOC; c, MeOOC; d, MeCO; e, PhNHCO; f, PhCO;

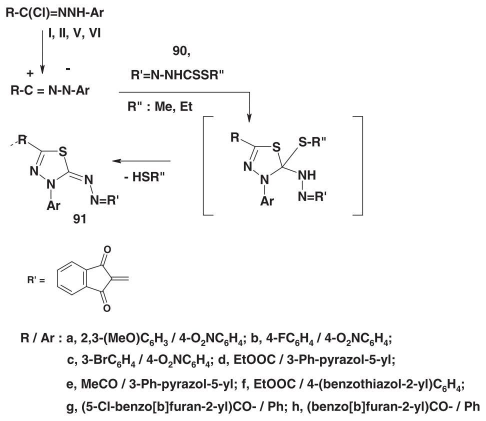
g, 2-Naphthoyl; h, 2-Thenoyl

Scheme 49

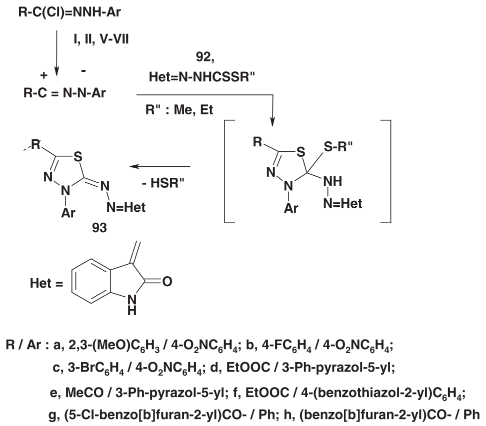
Alkyl N-cycloakylidene dithiocarbazates

Reactions of nitrilimines with alkyl cycloalkylidene dithiocarbazates have been studied by several authors. In most of these cases, the reactions were carried out by stirring the appropriate nitrilimine precursor, namely the hydrazonoyl halide, and the dithiocarbazate ester in ethanol in the presence of triethylamine at room temperature. Thus, reactions of methyl cycloalkylidene dithiocarbazates **84** with the hydrazonoyl halides **VII(IX)** [44] and **I** [63,71] under such conditions have been reported to yield the corresponding azine derivatives **85** in 50–78% yield (Scheme 47).

Also, the 1,3,4-thiadiazole derivatives **87** have been obtained in 64–88% yields by reactions of nitrilimines derived from the C-heteroyl-hydrazonoyl halides **II** with alkyl carbodithioates **86** under the same reaction conditions (Scheme 48) [43,66–68,80,83].



Scheme 50



Scheme 51

Rateb [84] reported that methyl dithiocarbazate **88** reacted with nitrilimines, derived from the hydrazonoyl halides **I**, **II**, **VII** and **IX-XII** in dimethyl formamide in the presence of potassium hydroxide at room temperature, and furnished the corresponding azine derivatives **89** in 55–67% yield (Scheme 49).

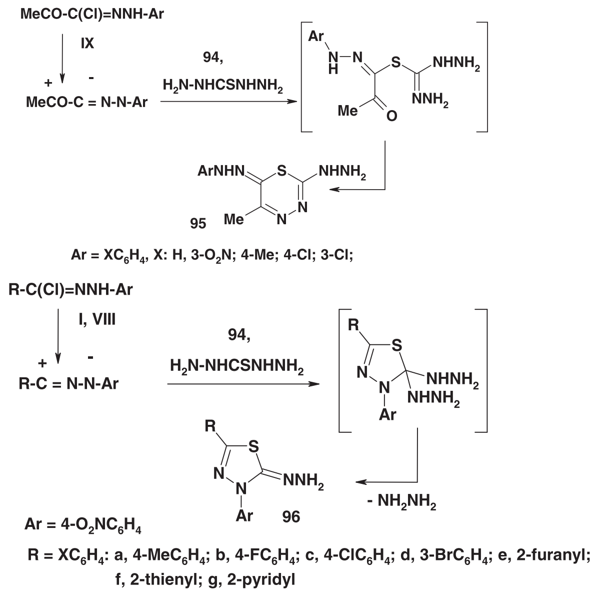
Similarly, other research groups [40,41,44,65,68] described the preparation of the thiadiazole derivatives **91** by reactions of alkyl dithiocarbazates **90** with various hydrazonoyl halides **I**, **II**, **VII,** and **IX** in ethanolic triethylamine at room temperature (Scheme 50).

Alkyl N-hetarylidene diothiocarbazates

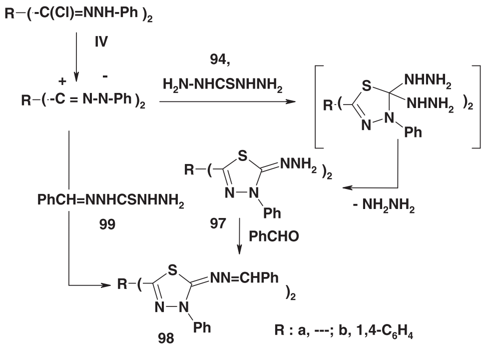
Several reports covering reactions of alkyl N-hetarylidene dithiocarbazates with nitrilimines have been published [40,41,44,65,67–69,79]. In these reports, it was indicated that reaction of alkyl dithiocarbazates **92** with various hydrazonoyl halides **I**, **II**, **VII**, **IX,** and **XI** in ethanol in the presence of triethylamine afforded the corresponding thiadiazole derivatives **93** in 65–85% yield (Scheme 51).

Reactions with carbonothioic dihydrazide

Different results were reported concerning reactions of carbonothioic dihydrazide **94** with hydrazonoyl halides. For example, Sayed [86] reported that treatment of **94** with hydrazonoyl



Scheme 52



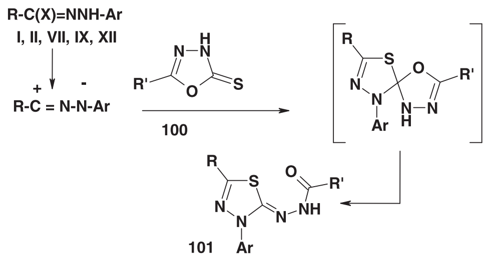
Scheme 53

chloride **IX** in boiling DMF gave the corresponding thiadiazine derivatives **95** in 64% yield (Scheme 52) [86]. In contrast, the same reaction of **94** with N-aryl arenecarbohydrazonoyl halides **I** and **VIII** in refluxing ethanol was reported earlier by the same author to afford the thiadiazole derivatives **96** [70]. No rationalization was given for such difference.

Similarly, reactions of carbonothioic dihydrazide **94** with the *bis*-hydrazonoyl chlorides **IV** in DMF in the presence of triethylamine furnished the corresponding 2,2′-*bis*(1,3,4-thiadiazole) derivatives **97** in about 60% yield (Scheme 53) [70,86]. Compound **97** reacted with benzaldehyde to give the *bis*-hydrazone **98**. The latter was also obtained by reaction of the *bis*-hydrazonoyl chloride **IV** with 2-(phenylmethylene)carbonothioic dihydrazide **99** in ethanolic triethylamine [70].

Reactions with heterocyclic thiones

In a recent review by Shawali and Farghaly [22] on reactions of hydrazonoyl halides with many heterocyclic thiones having no α-hydrogen, it has been indicated that such reactions afford only the corresponding spiro(heterocycle[n,2′]-3*H*-1,3,4-thiadiazole). More recently, several research groups have reported



R / Ar / R': a, EtOOC / 4-(benzoxazol-2-yl)C_6H_4 / Ph;
b, EtOOC / 4-(benzothiazol-2-yl)C_6H_4 / Ph;
c, Benzo[f]coumarin-3-yl)CO / Ph / Ph;
d, PhCO / Ph / 3-Me-benzo[b]furan-2-yl;
e, MeCO / Ph / 3-Me-benzo[b]furan-2-yl;
f, MeCO / 4-MeC_6H_4 / 3-Me-benzo[b]furan-2-yl;
g, MeCO / 4-ClC_6H_4 / 3-Me-benzo[b]furan-2-yl;
h, 2,4-$Me_2C_6H_4$ / 4-$O_2NC_6H_4$ / Ph

Scheme 54

that reactions of N-arylhydrazonoyl halides **I** and **X** with 5-substituted-1,3,4-oxadiazol-5(4*H*)thione **100** in boiling ethanol [65,72,74] or chloroform [64] in the presence of triethylamine furnished in all cases examined, products that were identified as the corresponding thiadiazole derivatives **101** in 72–76% yield. The latter products were assumed to be formed *via* the ring opening of the initially formed spirocycloadducts (Scheme 54). The latter products **101** were also obtained by reaction of the same hydrazonoyl halides each with alkyl N-benzoyldithiocarbazate (Scheme 54) [65,72,74].

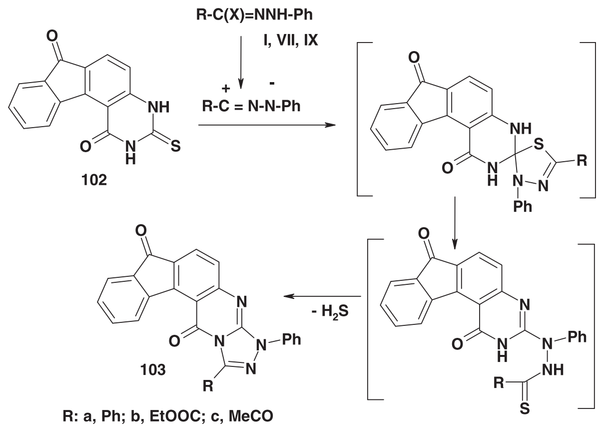
In contrast, it was reported that reactions of heterocyclic thione **102** with hydrazonoyl chlorides **I**, **VII** and **X** in chloroform in the presence of triethylamine were reported to afford the corresponding fused [1,2,4]triazoles **103** in 89–91% yields [85]. To account for the formation of the latter, it was suggested that the initially formed spiro-1,3,4-thiadiazole cycloadducts underwent tandem *in situ* rearrangement and elimination of hydrogen sulfide to give the respective fused [1,2,4]triazoles **103** as end products (Scheme 55) [85].

Biological activity

Many of the thiadiazole derivatives that have been prepared by the foregoing reactions, proved to possess wide range of pharmaceutical activities like antimicrobial, antivirus, anticancer, and molluscicidal effectiveness. In the following, a brief coverage of such activities is outlined.

Antimicrobial activities

Abdelhamid et al. [41] reported that certain 2,3-dihydro-1,3,4-thiadiazole derivatives **10a**,**b**; **15a**,**b**; **74a**,**b**; **78a**,**b**; **91** and **93** (Chart 3) possess high inhibitory activity against some strains of Gram positive bacteria, namely *Staphylococcus albus, Staphylococcus faecalis* and *Bacillus subtilis* and Gram negative bacteria *Escherichia coli*. Also compounds **74A** [76] and **74B** and **74C** [78], **74D**, **74E** and **74F** [79] and **74G**, **74H**, **74I** (Charts 4–7) [79] exhibited a high inhibition toward *Candida albicans* and *Asperills flavus* fungi. Also, 2-N-arylimino-1,3,4-thidiazole derivatives **31a** and **31b** (Chart 8) were reported to exhibit moderate activity against *Candida albicans* [51].



R: a, Ph; b, EtOOC; c, MeCO

Scheme 55

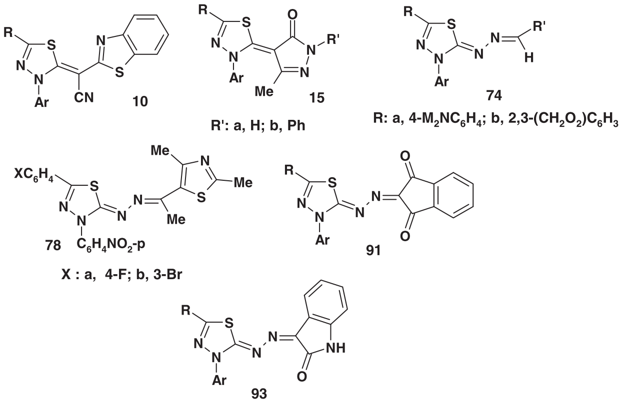
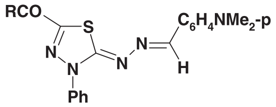


Chart 3



74, R : a, MeCO; b, EtOOC; c, PhNHCO

Chart 4

Antiviral activities

The thidiazoline derivatives **69a**,**b** (Chart 9) were reported to show no antiviral activity [73].

Anticancer and cytotoxic activity

Twelve of the azine derivatives **91** (Chart 10) were evaluated for their anticancer activity. The results showed that some of these compounds possess cytotoxicity against Ehrlich ascites carcinoma [65].

Anticonvulsant and anti-inflammatory activities

Some of the compounds **21** (Chart 11) [54] were screened for anticonvulsant activity. The results showed that **21a** and **21d** were found active in ScMet, whereas compound **21c** was active

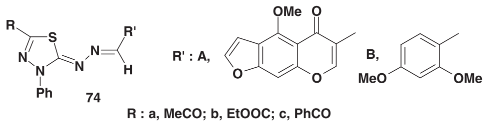


Chart 5

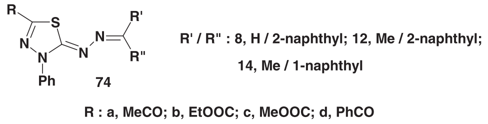


Chart 6

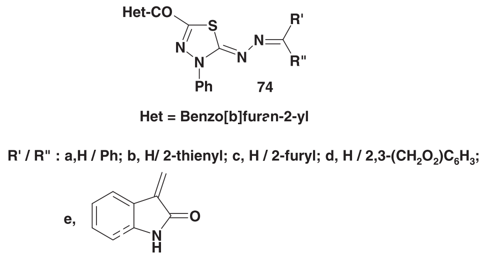


Chart 7

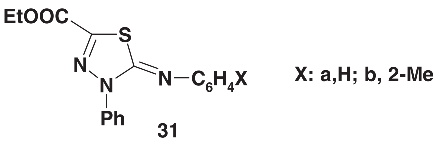


Chart 8

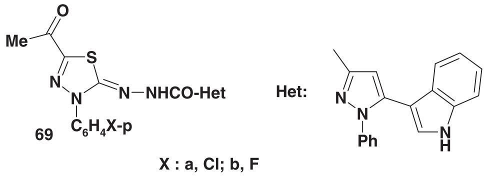


Chart 9

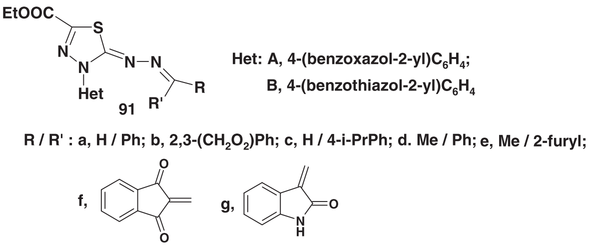


Chart 10

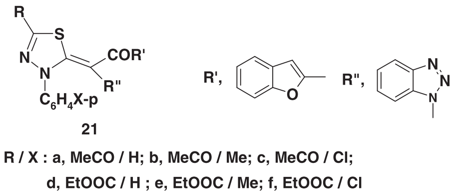


Chart 11

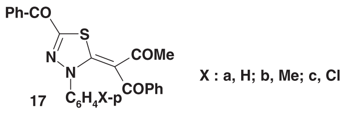


Chart 12

in MES. Also, compounds **21** were found to exhibit antinociceptive effect and the order of their activity is in the order **21f** > **21c** > **21a** > **21b** > **21d**. In addition, compounds **21** were screened for their anti-inflammatory activity. The results showed that **21a** exhibited the most potent anti-inflammatory activity and from structure–activity relationship (SAR) the order is **21a** > **21b** > **21c**.

Molluscicidal activity

The toxicity of compounds **17a–c** to *Biomphalaria alexandrinai* snails was screened, and the results showed that compound **17b** showed the highest activity (Chart 12) [49].

Conclusion

From the foregoing survey, it seems that tandem 1,3-dipolar cycloaddition of nitrilimines to functionalized sulfur dipolarophilic compounds followed by β-elimination of simple molecule such as alkanethiol from the initially formed cycloadducts provides a useful and convenient strategy for synthesis of numerous 1,3,4-thiadiazole derivatives. The subject of such reactions is still ongoing and undoubtedly will provide new fused functionalized 1,3,4-thiadiazoles of both industrial and biological interests.

Conflict of interest

The author has declared no conflict of interest.

References

[1] Siddiqui N, Ahuja P, Ahsan W, Pandeya SN, Alam MS. Thiadiazoles: progress report on biological activities. J Chem Pharm Res 2009;1:19–30.
[2] Singh AK, Mishra G, Jyoti K. Review on biological activities of 1,3,4-thiadiazole derivatives. J Appl Pharm Sci 2009;1:44–9.
[3] Kamal M, Shakya AK, Jawaid T. 1,3,4-Thiadiazole as antimicrobial agent: a review. Int J Biomed Res 2011;2:41–61.
[4] Mishra G, Singh AK, Jyoti K. Review article on 1,3,4-thiadiazole derivatives and its pharmacological activities. Int J Chem Tech Res 2011;3:1380–93.
[5] Kamal M, Shakya AK, Jawaid T. 1,3,4-Thiadiazole as antimicrobial agent: a review. Int J Biomed Res 2011;2:1–4.

[6] Kushwaha N, Kushwaha SKS, Rai AK. Biologial activities of thiadiazole derivatives: a review. Int J Chem Tech Res 2011;4:517–31.

[7] Gupta JK, Dudhey R, Sharma PK. Synthesis and pharmacological activity of substituted 1,3,4-thiadiazole derivatives. Medichemonline 2010;1:1–9.

[8] Singh AK, Mishra G, Jyoti K. Review on biological activities of 1,3,4-thiadiazolederivatives. J Appl Pharm Sci 2011;1:44–9.

[9] Ahmad T, Singh AK, Jaiswal N, Singh D. Synthesis and pharmacological activity of 1,3,4-thiadiazole derivatives: a review. Int Res J Pharm 2012;3:70–82.

[10] Bhuva H, Sahu D, Shah B, Modi DC, Patel MB. Biological profile of thiadiazole. Pharmacol Online 2011;1:528–45.

[11] Kushwaha N, Kushwaha SKS, Rai AK. Biologial activities of thiadiazole derivatives: a review. Int J Chem Tech Res 2012;4:517–31.

[12] Butler RN, Scott FL. Versatile reactive intermediates: hydrazidic halides. Chem Ind (Lond) 1970:1216–21.

[13] Shawali AS, Parkanyi C. Hydrazonoyl halides in the synthesis of hterocycles. J Heterocycl Chem 1980;17:833–54.

[14] Shawali AS. Reactions of hydrazonoyl halides with sulfur compounds. Heterocycles 1983;20:2239–85.

[15] Shawali AS. Reactions of heterocyclic compounds with nitrilimines and their precursors. Chem Rev 1993;93: 2731–77.

[16] Shawali AS, Abdallah MA. The chemistry of heterocyclic hydrazonoyl halides. Adv Heterocycl Chem 1995;63:277–338.

[17] Shawali AS, Elsheikh SM. Annelated [1,2,4,5]tetrazines. J Heterocycl Chem 2001;38:541–59.

[18] Shawali AS, Mosselhi MAN. Hydrazonoyl halides: useful building blocks for synthesis of arylazoheterocycles. J Heterocycl Chem 2003;40:725–46.

[19] Shawali AS, Mosselhi MAN. The chemistry of thiohydrazonates and their utility in organic synthesis. J Sulf Chem 2005;26:267–303.

[20] Shawali AS, Edrees MM. Reactions of nitrilimines with heterocyclic amines and enamines. Convenient methodology for synthesis and annulation of heterocycles. Arkivoc 2006;ix:292–365.

[21] Shawali AS, Sherif SM. The chemistry of hydrazonates. Curr Org Chem 2007;11:773–99.

[22] Shawali AS, Farghaly TA. Reactions of hydrazonoyl halides with heterocyclic thiones. Convenient methodology for heteroannulation, synthesis of spiroheterocycles and heterocyclic ring transformation. Arkivoc 2008;i:18–64.

[23] Shawali AS, Samy NA. Hydrazonoyl halides: their versatile biological activities. Open Bioactive Compds J 2009;2:8–16.

[24] Shawali AS, Abdelhamid AO. Synthesis of spiro-heterocycles via 1,3-dipolar cycloadditions of nitrilimines to exoheterocyclic enones. Site-, region- and stereo-selectivities overview. Curr Org Chem 2012;16:2623–39.

[25] Huisgen R, Seidel M, Sauer J, Mefarland JW, Wallbillich G. The formation of nitrile imines in the thermal breakdown of 2,5-disubstituted tetrazoles. J Org Chem 1959;24:892–3.

[26] Huisgen R, Seidel M, Wallbillich G, Knupfer H. Diphenyl-nitrilimin und seine 1.3-dipolaren additionen an alkene und alkine. Tetrahedron 1962;17:3–29.

[27] Sauer J, Mayer KK. Thermolyse und photolyse von 3. 4-Diphenyl-Δ^2-1,2,4-oxadia-zolinon-(5) und 2.4-diphenyl-Δ^2-1.3.4-oxdiazolinon-(5). Tetrahedron Lett. 1968:325–39.

[28] Grundmann C, Flory K. Uber dimesityl nitrilimin. Justus Leibigs Ann Chem 1968;721:91–100.

[29] Gladstone WAF, Aylward JP, Norman ROC. Reactions of lead tetraacetate Part XVIII. Oxidation of aldehyde hydrazones: a new method for generation of nitrilimines. J Chem Soc (C) 1969:2587–98.

[30] Reimlinger H, Vandewalle JJM, King KSD, Linger WRF, Merenyi R. 1,5-dipolare cyclisierungen, III. Kondensierte Triazole aus konjugierten Nitriliminen. Struktur und Stabilität der Produkte aus N-acylierten cyclischen Amidrazonen und Thionylchlorid. Chem Ber 1970;103:1918–33.

[31] Huseya Y, Chinune A, Ohta M. Photochemical reaction of 3,4-diphenyl-sydnone. Bull Chem Soc Jpn 1971;44:1667–8.

[32] Angadiyavar CS, George MV. Photochemical cycloadditions of 1,3-dipolar systems. 1. Addition of N.C-diphenylsydnone and 2,5-diphenyltetrazole. J Org Chem 1971;36:1589–94.

[33] Marky M, Hansen HJ, Schmid H. Photochemisches Verhalten von 3,4-Diarylsydnonen. Vorläufige Mitteilung. Helv Chem Acta 1971;54:1257–78.

[34] Huisgen R, Grashey R, Gotthardt DH, Schmidt R. 1,3-Dipolar addition of sydnones to alkynes. A new route into the pyrazole series. Angew Chem Int Ed Engl 1962;1:48–9.

[35] Lown JW, Landberg BE. Further synthetic applications of functionalized 1,3-dipoles, further synthetic applications of functionalized 1,3-dipoles. Can J Chem 1975;53:3782–90.

[36] Marky M, Meier H, Wunderli A, Heimgatner H, Schmid H, Hansen HJ. Zum photochemischen Verhalten von Sydnonen und 1,3,4-Oxadiazolin-2-onen. 56. Mitteilung über Photoreaktionen. Helv Chim Acta 1978;61:1477–510.

[37] Garanti L, Vigevani A, Zecchi G. Intramolecular carbine-type 1,1-cycloaddition by nitrile imines. Tetrahedron Lett 1976;17:1527–8.

[38] Clovis JS, Fliege W, Huisgen R. 1,3-Dipolare Cycloadditionen, 89. Neue Beiträge zur Chemie des Diphenylnitrilimins. Chem Ber 1983;116:3062–70.

[39] Molteni G. Silver(I) salts as useful reagents in pyrazole synthesis. Arkivoc 2007;ii:224–46.

[40] Abdelhamid AO, Abdel-Wahab BAM, Al-toom AA. Reactions of hydrazonoyl halides 37: synthesis of triazolo[4,3-a]pyrimidines, 1,3,4-thiadiazoles and 1,3,4-selenadiazoles. Phosp Sulf Silicon Related Elem 2004;179:601–13.

[41] Abdelhamid AO, Sayed AR, Elzanate AM. Reactions of hydrazonoyl halides 50: synthesis and antimicrobial activity of some new pyrimido[1,2-b]-[1,2,4,5]-tetrazin-6-one, tetrazino[3,2-b]quinazolin-6-one, triazolo[4,3-a]-pyrimidines and 2,3-dihydro-1,3,4-thiadiazoles. Chem J 2005;2:287–92.

[42] Abdelhamid AO, Rateb NM, Dawood KM. Reactions with hydrazonoyl halides 30: synthesis of some 2,3-dihydro-1,3,4-thiadiazoles and unsymmetrical azines containing benzothiazole moiety. Phosp Sulf Silicon 2000;167:251–8.

[43] Abdelhamid AO, Elghandour AH, Rateb NA, Awad AM. Aconvenient synthesis of 1-amino-4-methyl-4H-3-thia-4,5a,10-triazacyclopenta[a]fluoren-5-ones and some new 2,3-dihydro-1,3,4-thiadiazoles. Phosp Sulf Silicon 2006;181:1637–46.

[44] Abdelhamid AO, Al-toom A. Reactions with hydrazonoyl halides 39: sythesis of some new triazoles and 2,3-dihydro-1,3,4-thiadiazoles. Phosp Sulf Silicon 2004;179:2221–33.

[45] Dawood KM, Raslan MA, Farag AM. Synthesis of 3,3′-bi-1,2,4-triazolo[4,5-a]-benzimidazole, 5,5′-bi-1,3,4-thiadiazole and thiazolo[3,2-a]-benzimidazole derivatives. Synth Commun 2003;33:4079–86.

[46] Abunada N. Síntesis of 2-(isoquinolinemethylidene)-1,3,4-thiadiazole derivatives. J Al-Aqsa Univ 2007;11:12–21.

[47] Hassaneen HM, Hassaneen HME, Mohammed YS. Reactivity of 1-methyl-isoquinoline. Synthesis of pyrazoloyl triazoloisoquinoline and thiadiazolyl isoquinoline derivatives. Nat Sci 2011;3:651–60.

[48] Abdallah TA, Abdelhadi HA, Hassaneen HM. Reactivity of 1-methyl-isoquinoline. Synthesis of 2-(1-isoquinolinemethylidene)-1,3,4-thiadiazole derivatives. Phosp Sulf Silicon 2002;177: 59–66.

[49] Fadda AA, Abdel-Latif E, El-Mekawy R. Synthesis and molluscicidal activity of some new thiophene, thiadiazole and pyrazole derivatives. Eur J Med Chem 2009;44:1250–6.

[50] Dawood KM, Raslan MA. Fused polyaza-heterocycles and 1,3,4-thiadiazoles via a tricyano synthon. J Heteocycl Chem 2008;45:1–5.

[51] Mahran AM, Hassan NA. A one-step synthesis and antimicrobial activities of new substituted dihydro-1,3,4-thiadiazoles. Arch Pharm Res 2006;29:46–9.

[52] Elwan NM, Hassaneen HM, Hassaneen HM. Synthesis and reactions of indane-1,3-2-thiocarboxanilides with hydrazonoyl halides and active chloromethylene compounds. Heteroatom Chem 2002;13:585–91.

[53] Abdelhamid AO, Afifi MAM. Reactions with hydrazonoyl halides 61: synthesis of 2,3-dihydro-1,3,4-thiadiazoles. Phosp Sulf Silicon Related Elem 2008;183:2703–13.

[54] Dawood KM, Abdel-Gawad H, Ragab EA, Ellithey M, Mohamed HA. Synthesis, anticonvulsant and anti-inflammatory evaluation of some new benzotriazole and benzofuran-based heterocycles. Bioorg Med Chem 2006;14: 3672–80.

[55] Kandeel ZE, Dawood KM, Ragab EA, Farag AM. Simple and convenient routes to new polyheterocycles incorporating pyrazole, thiazole, thiophene and 1,3,4-thiadiazole moieties. Heteroatom Chem 2002;13:248.

[56] Dawood KM, Farag AM, Abdel-Aziz HA. Synthesis of some new benzofuran- based thiophene, 1,3-oxathiole and 1,3, 4-oxa(thia)diazole derivatives. Heteroatom Chem 2007;18: 294–300.

[57] Hassaneen HM, Hassaneen HME, Gomaa ZZA. Reactivity of 3-cyanoacetyl-indole derivatives: synthesis of 3-hydrazonopyrazolyl and 3-thiadiazolyl indole derivatives. Int J Org Chem 2011;1:97–104.

[58] Dawood KM, Ragab EA, Farag AM. Polyheterocyclic systems incorporating pyrazole, thiazole and thiadiazole moieties. J Chem Res 2003 (S) 685-686, (M) 1151-1160.

[59] Abdelhamid AO, Elghandour AH, Rateb NA, Awad AM. A convenient synthesis of1-amino-4-methyl-3-thia-4,5a,10-triazacyclopenta[a]-fluoren-5-ones and some new 2,3-dihydro-1,3,4-thiadiazoles. Phosp Sulf Silicon 2006;181:1637–46.

[60] Dawood KM, Elwan NM. Synthesis of 3,3′-bi-1,3,4-thiadiazole and fused azole systems via bishydrazonoyl chlorides. J Chem Res 2004:264–6.

[61] Kheder NA, Mabkhot YN. Synthesis and antimicrobial studies of some novel *bis*-[1,3,4]thiadiazole and *bis*-thiazole pendant to thieno[2,3-b]thiophene moiety. Int J Mol Sci 2012;13:3661.

[62] Hassaneen HM, Miqdad OA, Abunada NM, Fares AA. Reaction of thiocarboxanilide derivatives of 2-phenylimino-3-phenyl-4-thiazolidinone and 1,3-diphenyl-2-thioxo-4-imidazolone with hydrazonoyl halides and active chloromethylene compounds. Nat Sci 2011;3:199–207.

[63] Rateb NM, Abdel-Riheem NA, Al-Atoom AA, Abdelhamid AO. Reactions with hydrazonoyl halides 35: synthesis of some new 1,2,4-triazololino[4,3-a][yrimidines, 2,3-dihydro-1,3,4-thiadiazoles and 2,3-dihydro-1,3,4-selenadiazoles. Phosph Sulf Silicon 2003;178:1101–14.

[64] Abdelhamid AO, Abdel-Wahab BAM. Reactions with hydrazonoyl halides 38: synthesis of pyrrolo[3,4-c]pyrazoles, pyrazoles and 1,3,4-thiadiazoles. Affinidad 2004;61:65–73.

[65] Abdelall EKA, Mohamed MA, Abdelhamid AO. Reactions with hydrazonoyl halides 63: synthesis and anticancer activity of some new 1,3,4-thiadiazoles, 1,3,4-selenadiazoles and 1,2, 4-triazolo[4,3-a]pyrimidines. Phosp Sulf Silicon 2010;85: 1862–2010.

[66] Abdelhamid AO, Metwally NH, Bishai NS. Reactions with hydrazonoyl halides 29: synthesis of some new 1,2,4-triazolo4,3-a]-benzimidazoles, thiazolo[3,2-a]-benzimidazoles and unsymmetrical azine derivatives. J Chem Res 2000, (S)462–463, (M)1144–1154.

[67] Abdelhamid AO, Alkhodshi MAM. Reactions with hydrazonoyl halides 42: synthesis of some new 2,3-dihydro-1,3,4-thiadiazoles, 2,3-dihydro-1,3,4-selenadiazoles and triazolino[4,3-a]pyrimidines. Phosp Sulf Silicon 2005;180: 149–61.

[68] Abdelhamid AO, El-Ghandour AH, Al-Reedy AAM. Reactions with hydrazonoyl halides 56: synthesis and reactions of 1-bromo-2-(5-chlorobenzo-furanyl)ethanedione-1-phenylhydrazone. Phosp Sulf Silicon 2008;183:1272–84.

[69] Abdelhamid AO, Abdelgawad SM, El-Sharnoby SF. Reactions with hydrazonoyl halides 33: synthesis of some new 2,3-dihydro-1,3,4-thiadiazoles containing pyrazol-3-yl, indolin-2-one-3-yl and indan-1,3-dione-2-yl moieties. Phosp Sulf Silicon 2002;177:2699–709.

[70] Sayed AR. Synthesis of novel thiadiazoles and bis-thiadiazoles from carbono-thioic dihydrazide. Tetrahedron Lett 2010;51:4490–3.

[71] Abdelreheen NA, Rateb NM, Altoom AA, Abdelhamid AO. 1,3,4-Thia- and -selenadiazole and 1,2,4-triazolo[4,3-a]pyrimidine erivatives from hydrazonoyl halides. Heteroatom Chem 2003;14:421–6.

[72] Moustafa C, Abel-Reheem NA, Abdelhamid AO. Reactions with hydrazonoyl halides 40: synthesis of some new 1,3,4-thiadiazoles, pyrrolo-[3,4-c]pyrazoles, pyrazoles and pyrazolo[3,4-d]pyridazines. Synth Commun 2005;35: 249–61.

[73] Abdelgawad H, Mohamed HA, Dawood KM, Badria FA. Synthesis and antiviral activity of new indole-based heterocycles. Chem Pharm Bull 2010;58:1529–31.

[74] Dawood KM, Farag AM, Abdel-Aziz HA. Synthesis an antimicrobial evaluation of some 1,2,4-triazole, 1,3,4-oxa(thia)diazole and 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazine derivatives. Heteroatom Chem 2005;16:621–7.

[75] Abu-Team OS, Rateb NM, Abdelhamid AO. Reactions with hydrazonoyl halides 34: synthesis of some new 2,3-dihydro-1,3,4-thiadiazoles. Phosp Sulf Silicon 2003;178:2363–71.

[76] Abdelhamid AO, Sayed AR, Zaki YH. Reactions with hydrazonoyl halides 51: a facile synthesis of 5-arylthiazoles and triazolo[4,3-a]pyrimidines as antimicrobial agents. Phosp Sulf Silicon 2007;182:1447–57.

[77] Abdelhamid AO, Ismail ZH, Abdelaziem AM. Reactions with hydrazonoyl halides 58: synthesis of 2,3-dihydro-1,3,4-thiadiazoles and 5-arylazothiazoles. Phosp Sulf Silicon 2008;183:1735–45.

[78] Abdel-Gawad SM, Elgendy MS, Abdelhamid AO. Reactions with hydrazonoyl halides 46: synthesis of some new 2,3-dihydro-1,3,4-thiadiazoles and triazolino[4,3-a]pyrimidines as antimicrobial agents. J Sulf Chem 2005;25:21–31.

[79] Abdelhamid AO, Mohamed MA, Zaki YH. Reactions with hydrazonoyl halides 59: synthesis and antimicrobial activity of 2,3-dihydro-1,3,4-thiadiazole, triazolino-[4,3-a]-pyrimidine and pyrimido[1,2-b]-[1,2,4,5]tetrazin-6-one containing benzofuran moiety. Phosp Sulf Silicon 2008;183:1746–54.

[80] Abdelhamid AO, El-Ghandour AH, Hussein AM, Zaki YH. Reactions with hydrazonoyl halides 44: synthesis of some new 1,3,4-thiadiazolines, 1,3,4-selenadiazo-lines and triazolino[4,3-a]pyrimidines. J Sulfur Chem 2004;25:329–42.

[81] Abdelhamid AO, Alkhodshi MAM. Reactions with hydrazonoyl halides 43: synthesis of some new 2,3-dihydro-1,3,4-thiadiazoles, pyrazolo-[3,4-d]-pyridazines, thieno[2,3-b]-pyridines, pyrimidino[4″,5″:4,5]thieno-[2,3-b]pyridines and pyrrolo-[3,4-d]pyrazoles. J Heterocycl Chem 2005;42:527–33.

[82] Abdelhamid AO, Baghos VB, Doss SH, Halim MM. Reactions with hydrazonoyl halides 55: synthesis of 2,3-dihydro-1,3,4-thiadiazoles containing steroid moiety. Phosp Sulf Silicon 2007;182:2843–54.

[83] Abdelhamid AO, Zohdi HF, Sallam MMM, Ahmed NA. Reactions with hydrazonoyl halides 27: synthesis of some new triazolo[4,3-a]-benzimidazole and unsymmetrical azine erivatives. Phosp Sulf Silicon 2000;164:181–8.

[84] Rateb NM. Synthesis of some new thiazole, thiophene, 2,3-dihydro-1,3,4-thiadiazole and pyrimidino[1,2-b]indazole derivatives. Phosp Sulf Silicon 2005;180:2361–72.

[85] Hassaneen HM, Abdallah T, Abdelhadi HA, Hassaneen HME, Pagni RM. Polyfunctional fused heterocyclic compounds via indene-1,3-dione. Heteroatom Chem 2003;14:491–7.

[86] Sayed AR. Synthesis of 1,3,4-thiadiazines, bis-1,3,4-thiadiazoles, [1,2,4]triazino-[3,4-b][1,3,4]thiadiazine, thiazolines from carbonothioic dihydrazide. Tetrahedron 2012;68:2784–9.