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Selective Synthesis of 3-(1*H*-Tetrazol-5-yl)-indoles from 2*H*-Azirines and Arynes

Carla Grosso, Cláudia Alves, Terver J. Sase, Nuno G. Alves, Ana L. Cardoso, Américo Lemos, and Teresa M. V. D. Pinho e Melo*

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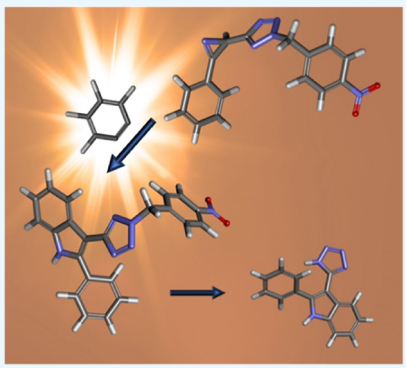
ABSTRACT: A new selective synthetic approach to indole derivatives bearing a tetrazole moiety has been developed. Arynes, generated in situ from *o*-(trimethylsilyl)aryl triflates and KF, reacted smoothly with 2-(2-benzyl-2*H*-tetrazol-5-yl)-2*H*-azirines to give 3-(2-benzyl-2*H*-tetrazol-5-yl)-indole derivatives with high selectivity. Deprotection of the tetrazole moiety gave 3-(1*H*-tetrazol-5-yl)-indole derivatives.



INTRODUCTION

The indole core is present in a significant number of natural products and across the chemical industry in fields such as agriculture, animal health, dyes and pigments, nutraceuticals and dietary supplements, flavour enhancers, and perfumes.[1] Additionally, the indole ring has become an important structural requirement in many pharmaceutical agents showing a wide range of biological activities such as antimicrobial, anti-inflammatory, antitumor, antidiabetic, antiparkinsonian, antiviral, antihistamines, and antioxidants.[2−11]

In the last decades, due to the extensive applicability of molecules embodying the indole ring, impressive new synthetic routes as well as optimization of classical methods, have been reported.[12−19] The Fischer indole synthesis,[12−15] Nenitzescu reaction,[12,13,15] Leimgruber−Batcho indole synthesis,[12,15] Reissert indole synthesis,[12,15] Bartoli indole synthesis,[12,15] Madelung synthesis,[12,13,15] synthesis from azirines,[12] and synthesis from *o*-alkynylanilines[12,15−18] are some of the synthetic routes to indoles and its derivatives. The synthesis of 3-(1*H*-tetrazol-5-yl)-indoles via Fischer indolization of tetrazolylacetaldehyde phenylhydrazones as well as a two-step synthetic route to 2-(1*H*-tetrazol-5-yl)-indoles through Ugi-tetrazole reaction followed by acid-catalyzed ring-closure have been disclosed.[20,21]

Among the functionalized indoles, 2- and 3-substituted indoles have attracted much attention from organic and medicinal chemists as valuable building blocks for the synthesis of more complex molecules with biological activity.[4,22] Also, several indole-2 and 3-carboxylic acid derivatives as well as tetrazolyl-substituted indole derivatives have shown to possess promising biological activities.[22,23] In recent years, we have been exploring the carboxylic acid/tetrazole bioisosterism as a way of finding new molecules with potential biological activity.[24,25]

2*H*-Azirines represent a versatile class of heterocyclic systems which have been extensively used as powerful building blocks for the synthesis of a plethora of N-heterocycles, including indole derivatives.[26−28] A synthetic approach toward indoles involving the reaction of 2*H*-azirines with benzyne, generated in situ by thermal decomposition from benzenodiazonium-2-carboxylate, was first described by Nair and Kim (Scheme 1a).[29] The reaction outcome was influenced by the nature of the 2*H*-azirines' substituents. Starting from 2,3-diphenyl-2*H*-azirine, a mixture of the corresponding 2,3-diphenylindole and 1,2,3-triphenylindole was obtained, whereas treatment of 2-methyl-3-phenyl-2*H*-azirine with an excess of benzyne selectively afforded 3-phenyl-2-methyl-1*H*-indole. More recently, Biju and co-workers reported a temperature-dependent reaction of arynes with 2*H*-azirines to give *N*-unsubstituted or *N*-aryl indole derivatives (Scheme 1b).[30] The use of the *o*-(trimethylsilyl)aryl triflate precursor in the presence of fluoride source and 18-crown-6 as additive allowed the generation of arynes under mild conditions. Performing the

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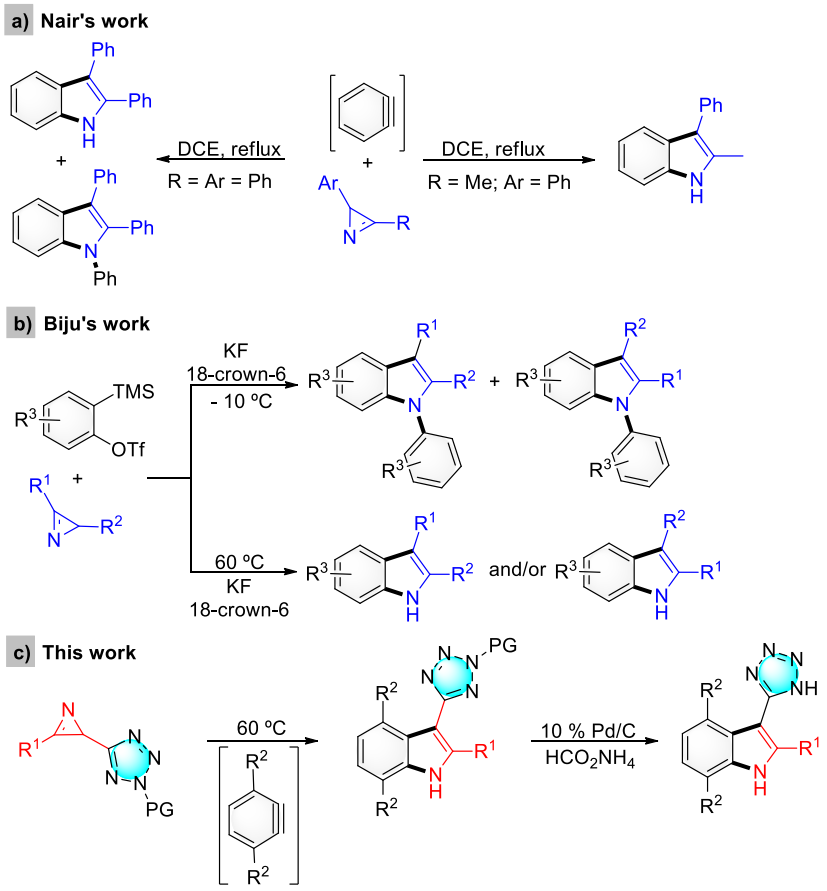
Scheme 1. Synthetic Approaches to Indoles via 2*H*-Azirines and Arynes



reaction at −10 °C led to *N*-aryl indole derivatives whereas carrying out the reaction at 60 °C led to 2,3-aryl-*N*-unsubstituted indole derivatives. However, unsymmetrical 2*H*-azirines gave rise to a mixture of regioisomers.

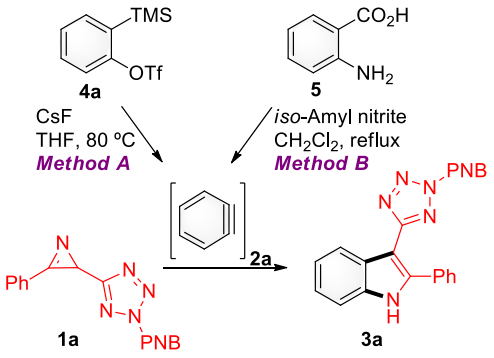
The chemistry of 2*H*-azirines has been one of our research interests.[31−33] Synthetic routes toward novel 2-(tetrazol-5-yl)-2*H*-azirines bearing phenyl, furan-2-yl, thiophen-2-yl, or 1*H*-pyrrol-2-yl substituents at C-3, based on the one-pot Neber reaction of *β*-ketooxime-tetrazoles have been disclosed, as well as the organocatalytic asymmetric Neber reaction to afford chiral 2-(tetrazol-5-yl)-2*H*-azirines.[34−36] Moreover, the reactivity of these interesting molecules toward imines in the presence of Lewis acids for the synthesis of 4-(tetrazol-5-yl)-1*H*-imidazoles was also explored.[37] In addition, we have also explored arynes as highly reactive synthetic intermediates namely in the synthesis of isoquinolines via hetero-Diels−Alder cycloaddition reaction with 1,2,4-triazines as well as in the synthesis of 1,3-dihydrothiazolo[3,4-*b*]indazoles via 1,3-dipolar cycloaddition reaction of thiazolidine-derived sydnones.[38,39]

Bringing together these two research interests, we decided to explore the reactivity of tetrazolyl-2*H*-azirines toward arynes to develop a new approach to indole derivatives bearing a tetrazole moiety (Scheme 1c).

RESULTS AND DISCUSSION

The reaction between 2-[2-(4-nitrobenzyl)-2*H*-tetrazol-5-yl]-3-phenyl-2*H*-azirine **1a** and benzyne (**2a**) was selected as the model reaction for the optimization studies (Table 1). For this purpose, two different methods of aryne generation were tested.[40,41] In the first approach (method A), benzyne (**2a**) was generated in situ from *o*-(trimethylsilyl)phenyl triflate (**4a**), using CsF as the fluoride source in THF at 80 °C for 24 h. Under these conditions and using 1.2 equiv of **4a**, indole **3a** was selectively obtained in 15% yield (Table 1, entry 1). An improvement was observed by increasing the amount of **4a** to 1.8 equiv, giving the desired indole in 44% yield (Table 1, entry 2). Attempts to further improve the efficiency of this

Table 1. Optimization of Benzyne Generation



entry	reaction conditions	precursor (equiv)	CsF (equiv)	time (h)	yield **3a** (%)
1	method A	**4a** (1.2)	2.5	24	15%
2	method A	**4a** (1.8)	2.5	24	44%
3	method A	**4a** (5.0)[a]	8.0	24	[b]
4	method B	**5** (1.0)		1	[b]

[a]Stepwise addition. [b]2*H*-Azirine recovered.

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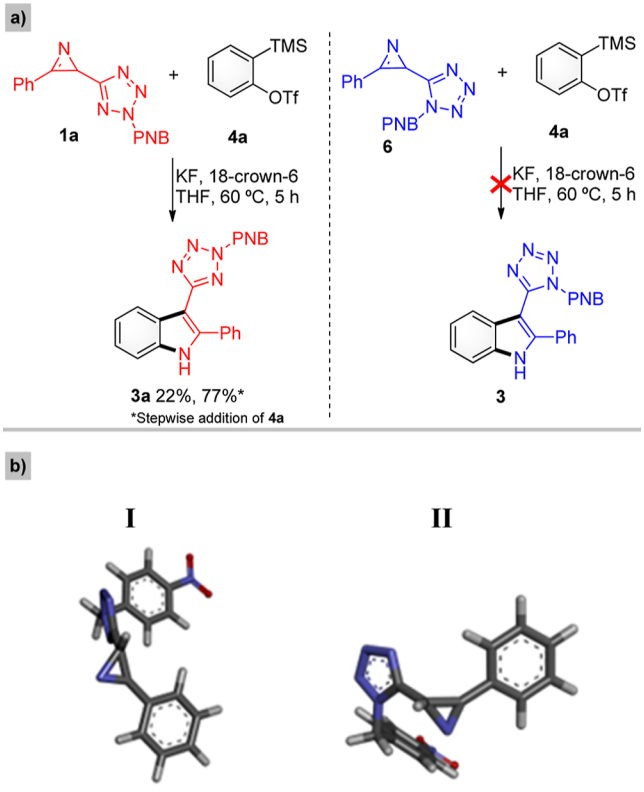
reaction, by increasing the number of equivalents of the aryne precursor **4a**, did not lead to the desired indole and only degradation products were observed (Table 1, entry 3). The generation of benzyne from anthranilic acid **5** was also investigated (Method B).[41] However, this classic strategy failed to deliver the desired product (Table 1, entry 4).

To further improve this transformation, the reaction between 2-(tetrazol-5-yl)-2*H*-azirine **1a** and benzyne **2a**, generated in situ from the *o*-(trimethylsilyl)phenyl triflate precursor (**4a**) using KF as the fluoride source and 18-crown-6 as additive, in THF at 60 °C for 5 h, was also carried out, affording the desired product in 22% yield. To our delight, the stepwise addition of aryne precursor **4a** improved the efficiency of the method and led to the isolation of indole **3a** in 77% yield (Scheme 2a). The reaction was regioselective, affording *N*-unsubstituted 3-(tetrazol-5-yl)-indole **3a** as a single product. The structural assignment of 3-(2-(4-nitrobenzyl)-2*H*-tetrazol-5-yl)-2-phenylindole **3a** was confirmed by bidimensional COSY and NOESY spectra analysis (see Figures S4 and S5). In the COSY spectrum, it was possible to observe the correlation between the H-7 (doublet at 7.69 ppm) and H-6 (pseudo triplet at 7.17 ppm) which in turn showed correlation with the H-5 proton (pseudo triplet at 7.33 ppm). On the other hand, in the NOESY spectrum, it was possible to observe connectivity between the indolés NH proton (H-1) and protons of the phenyl group.

Scheme 2. (a) Reactivity of 2-(Tetrazolyl-5-yl)-2*H*-azirines 1a and 6 toward In Situ Generated Benzyne 2a; (b) Optimized Geometries (B3LYP/6-31G(d) Level) of 2-(Tetrazol-5-yl)-2*H*-azirines 1a (I) and 6 (II)



It has been reported that the reaction at −10 °C of 2*H*-azirines with arynes generated from *o*-(trimethylsilyl)aryl triflates lead to 1,2,3-triarylindoles.[30] Therefore, we decided to investigate the effect of the temperature on our model reaction. However, carrying out the reaction at −10 °C in THF for 12 h did not lead to the formation of the target product.

Next, we decided to investigate the chemical behavior of 2-[1-(4-nitrobenzyl)-1*H*-tetrazol-5-yl]-3-phenyl-2*H*-azirine (**6**), which differs from 2*H*-azirine **1a** in the position of the *p*-nitrobenzyl protecting group, toward benzyne. Surprisingly, under the previously optimized reaction conditions, 2*H*-azirine **6** failed to react with benzyne and did not lead to the desired indole (Scheme 2a). Moreover, all attempts to perform this reaction resulted in the recovery of unreacted 2*H*-azirine **6**.

To explain the lack of reactivity of 2-tetrazolyl-2*H*-azirine **6**, quantum chemical calculations at the DFT level of theory were carried out to optimize the geometries of 2-(tetrazolyl-5-yl)-2*H*-azirines **1a** and **6** (Scheme 2b). The results showed that the approach of an incoming reagent to 2*H*-azirine **6** is significantly more hindered than that to 2*H*-azirine **1a**. This is consistent with the observed difference in the reactivity.

The study was extended to 2*H*-azirines **1b**, **1c**, and **1d** bearing a 2-thienyl, furan-2-yl, and 1*H*-pyrrol-2-yl substituent at C-3, respectively (Scheme 3). Different results were observed depending on the 2*H*-azirine heteroaromatic substituent when the reactions were carried out with in situ generated benzyne under optimal conditions. The reaction of azirine **1b** with *o*-(trimethylsilyl)phenyl triflate (**4a**) as a benzyne precursor led to 2-thienyl-3-tetrazolyl-1*H*-indole **3b** in 52% yield, after 5 h in THF at 60 °C. In contrast, the attempted reactions with 3-tetrazolyl-2*H*-azirines **1c** and **1d** bearing either the furan or 1*H*-pyrrole ring as substituents did not afford the desired products. These results demonstrate that this transformation is strongly influenced by the 2*H*-azirines' C-3 substituent.

Next, we decided to extend this reactivity further to aryne precursor **4b** (R^2 = Me). The reaction of 3,6-dimethylbenzyne with 2*H*-azirines **1a** and **1b** was slower than the reaction with benzyne leading to the target indole derivatives **3c** and **3d** in 74 and 56% yield, respectively, within 7 to 10 h of reaction. These reactions were also regioselective, affording *N*-unsubstituted 3-tetrazolyl-indoles **3** as single products (Scheme 3).

Aiming to prepare 3-tetrazolyl-indoles, tetrazole deprotection of the 3-[2-(4-nitrobenzyl)-2*H*-tetrazol-5-yl]-indoles **3** was investigated. Previously in our research group, the deprotection of tetrazoles was successfully accomplished using a general method reported for the cleavage of the benzyl group of *N*-benzylamines and 1-benzyl-1*H*-imidazoles.[37,42−44] Thus, a suspension of indole **3a** and 10% Pd/C in methanol was treated with excess of ammonium formate and heated at reflux for 1 h affording the target indole **7a**, bearing the unprotected 1*H*-tetrazolyl group, in high yield (87%) (Scheme 4). A different outcome was observed in the deprotection reaction of 2-thienyl-indoles **3b** and **3c**. Under the same reaction conditions, indole **3b** was converted into the corresponding 3-[2-(4-aminobenzyl)-2*H*-tetrazol-5-yl]-indole **8** in 83% yield, resulting from the reduction of the nitro group, showing that the deprotection reaction of 2-thienylindoles requires a longer reaction time than that of 2-phenyl-indole **3a**. In fact, the hydrogenolysis of 4,7-dimethylindole derivative **3c**, carried out for 20 h, allowed the synthesis of the target deprotected 3-(1*H*-tetrazol-5-yl)-indole derivative **7b** in moderate yield (33%).

3-Tetrazolyl-1*H*-indole **7a** could also be obtained via a two-step one-pot procedure as outlined in Scheme 5. 2*H*-Azirine **9**,

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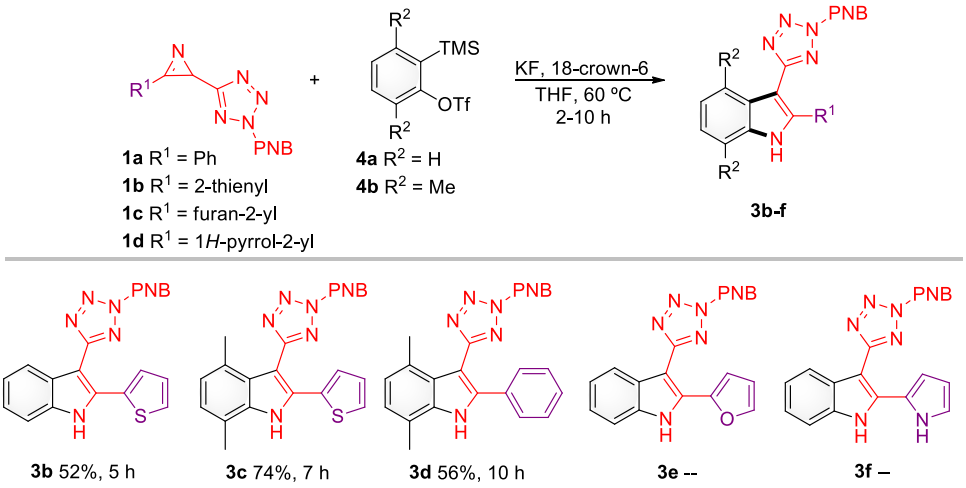
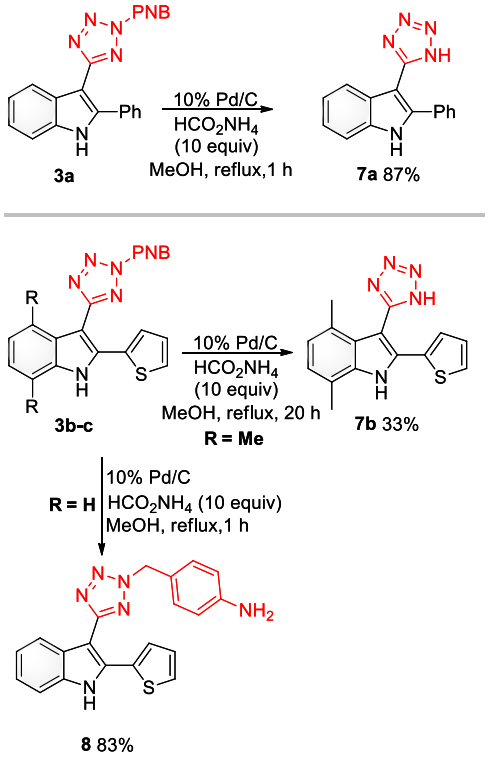
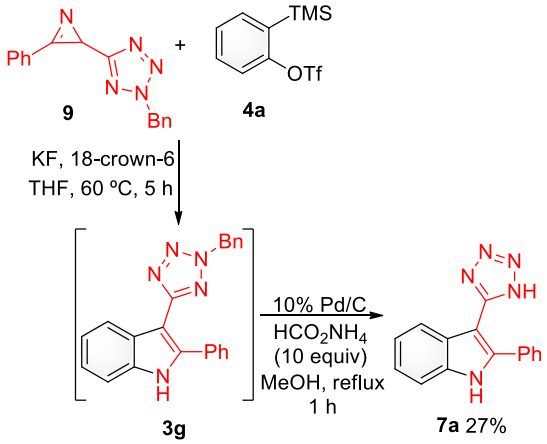
Scheme 3. Substrate Scope for the Synthesis of *N*-Unsubstituted 3-(2*H*-Tetrazolyl)-indoles



Scheme 4. Deprotection Reaction of 3-[2-(4-Nitrobenzyl)-2*H*-tetrazol-5-yl]-indoles



Scheme 5. Two-Step One-Pot Procedure toward 3-(1*H*-Tetrazol-5-yl)-indole 7a



bearing a benzyl protecting group at the N-2 position of the tetrazole ring, reacted smoothly with the in situ generated benzyne to give indole **3g** which was used without purification in the deprotection step yielding 3-tetrazolylindole **7a** in 27% overall yield.

It has been reported that the reaction of unsymmetrically substituted 2*H*-azirines with arynes leads to mixtures of regioisomers.[30] In addition, depending on the reaction conditions, *N*-unsubstituted and *N*-arylindoles can be obtained via a mechanism outlined in Scheme 6. After the initial nucleophilic addition of 2*H*-azirines onto arynes to give zwitterionic intermediate **A**, this can cyclize by two different pathways. In pathway A, the aryl anion undergoes nucleophilic attack onto the C=N bond to give intermediate **B** which can be converted into product **10** through a 1,2-hydrogen shift to nitrogen. Alternatively, compound **10** can also result from a 1,2-hydrogen shift to carbon to yield intermediate **C**, followed by another 1,3-hydrogen shift. An ene reaction of **C** with another molecule of aryne leads to *N*-arylindoles **11**. In pathway B, the nucleophilic attack of the aryl anion **A** occurs at the azirine C-2 carbon with concomitant C–N bond cleavage to generate intermediate **D**, which then affords regioisomers **13** or *N*-arylindoles **12**, by a 1,3-hydrogen shift or through an ene reaction with another molecule of aryne, respectively.

Taking into account the aforementioned studies and our experimental results, we outlined the proposed mechanism for the reaction between 2-(tetrazolyl-5-yl)-2*H*-azirines **1** and arynes **2** in Scheme 7. Arynes undergo a nucleophilic addition on reacting with 2-(tetrazolyl-5-yl)-2*H*-azirines **1** to give zwitterionic intermediate **I**. Subsequent intramolecular nucleophilic attack of the aryl anion onto the azirine C-2 carbon bearing the tetrazolyl substituent induces the C–N bond cleavage, generating 3*H*-indole derivative **II** which undergoes a 1,3-hydrogen shift to afford the indole **3**. A formal [2 + 2] cycloaddition reaction between aryne and the 2*H*-azirine imine bond must be ruled out since it would lead to 2-[2-(4-nitrobenzyl)-2*H*-tetrazol-5-yl]-indoles instead of the obtained 3-[2-(4-nitrobenzyl)-2*H*-tetrazol-5-yl]-indoles **3**. Furthermore, the regioselectivity of these transformations can be rationalized

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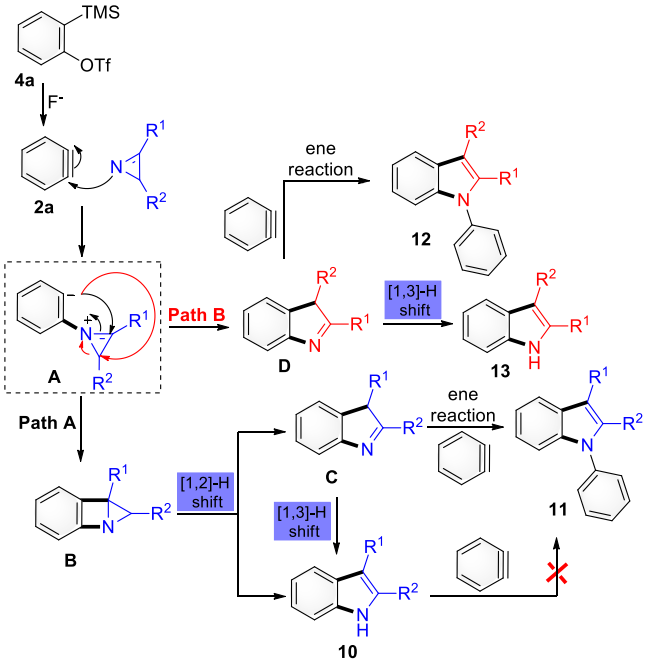
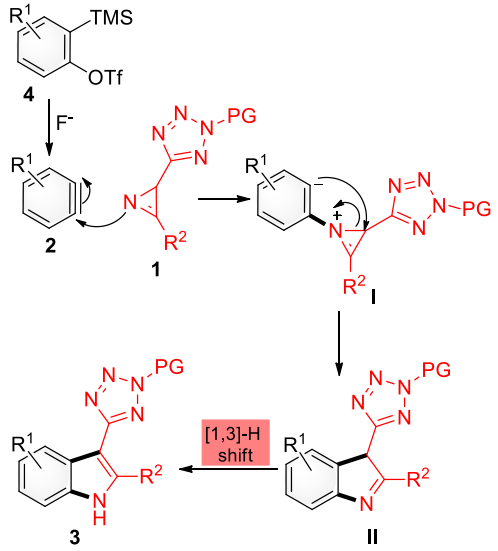
Scheme 6. Proposed Mechanism for the Synthesis of *N*-Unsubstituted and *N*-Arylindoles[30]



Scheme 7. Proposed Mechanism for the Synthesis of 3-(2*H*-Tetrazol-5-yl)-indoles from 2*H*-Azirines and Arynes



as a result of the selective nucleophilic attack of the aryl anion at 2*H*-azirine's C-2 carbon (intermediate **I**), induced by the electron-withdrawing ability of the tetrazolyl substituent to make this reactive site more electrophilic.

The different reactivity observed for phenyl- and thienyl-substituted 2-(tetrazolyl-5-yl)-2*H*-azirines **1a** and **1b** compared to furyl- and pyrrolyl derivatives **1c** and **1d** can be explained by the proposed mechanism, since the lower nucleophilicity of the latter may be detrimental to the initial nucleophilic addition on the benzyne. Additionally, our previous studies showed that 2-pyrrolyl-3-tetrazolyl-2*H*-azirine **1d** is not as stable as the other 2*H*-azirines and therefore can undergo degradation under the reaction conditions.[34,37]

CONCLUSIONS

A selective approach to the synthesis of 3-tetrazolyl-indoles involving the reaction of 2-[2-(4-nitrobenzyl)-2*H*-tetrazol-5-yl]-2*H*-azirines with arynes was developed. This methodology allows the synthesis of *N*-unsubstituted 3-(2*H*-tetrazol-5-yl)-indoles bearing phenyl and 2-thienyl substituents at C-2 in good yields. The deprotection of the tetrazole moiety of the 3-[2-(4-benzyl)-2*H*-tetrazol-5-yl]-2-phenyl-1*H*-indoles was successfully achieved giving the corresponding 3-(1*H*-tetrazol-5-yl)-2-phenyl-1*H*-indoles in excellent yield.

EXPERIMENTAL SECTION

General Methods. NMR spectra were run in deuterated chloroform ($CDCl_3$), hexadeuterodimethyl sulfoxide (DMSO-d_6), or deuterated acetone (acetone-d_6) and recorded at the following frequencies: proton (^{1}H, 400 MHz), and carbon (^{13}C, 100 MHz). Chemical shifts are expressed in parts per million related to internal TMS and coupling constants (J) are given in hertz. IR spectra were recorded on a Fourier transform spectrometer. High-resolution mass spectra (HRMS) were obtained on an electrospray (ESI)TOF mass spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase. Azirines **1a**−**d**,[34] **9**[34] and *o*-(trimethylsilyl)-aryl triflate **4b**[45] were prepared following known procedures.

General Procedure for the Synthesis of 3-(2*H*-Tetrazolyl)-indoles 3. A mixture of 18-crown-6 (0.530 g, 2.0 mmol), KF (0.116 g, 2.0 mmol), and the corresponding 2*H*-azirine **1** (0.5 mmol) under an inert atmosphere in dry THF (6 mL) was allowed to stir at 30 °C for 5 min. Then, the reaction mixture was immediately placed in a preheated oil bath at 60 °C and a stepwise addition of the appropriate aryne precursor **4** (1.0−1.5 mmol) dissolved in THF (6 mL) was performed. The progress of the reaction was monitored by TLC and upon completion the mixture was filtered through Celite; the solvent was evaporated. Subsequently, the crude residue was purified by flash column chromatography [elution with gradient ethyl acetate/hexane from (1:3) to (1:1)] to afford the corresponding 3-tetrazolyl-indoles **3**.

*3-[2-(4-Nitrobenzyl)-2H-tetrazol-5-yl]-2-phenyl-1H-indole (**3a**).* According to the general procedure: 0.160 g of azirine **1a** and 0.298 g of aryne precursor **4a** (reaction time 5 h). Yield: 70% (0.112 g), yellow solid; mp 207.7−208.3 °C (diethyl ether/hexane); IR $\tilde{\nu}$ = 3267, 1588, 1456, 1245, 1066, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (s, 2H, CH_2), 7.17 [pseudo t (two overlapping doublets), J = 8.0 Hz, J = 7.2 Hz, 1H, Ar], 7.34 [pseudo t (two overlapping doublets), J = 7.2 Hz, J = 6.8 Hz, 1H, Ar], 7.41 (d, J = 6.8 Hz, 1H, Ar), 7.44−7.48 (m, 3H, Ar), 7.53 (d, J = 8.4 Hz, 2H, Ar), 7.59−7.61 (m, 2H, Ar), 7.69 (d, J = 8.0 Hz, 1H, Ar), 8.24 (d, J = 8.8 Hz, 2H, Ar), 9.11 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.4, 119.7, 120.2, 120.7, 120.9, 124.2, 124.6, 127.2, 128.1, 128.3, 129.6, 130.5, 133.3, 136.2, 139.6, 148.3, 160.4 ppm; HRMS (ESI) calcd for $C_{22}H_{17}N_6O_2$, 397.1408 [M + H$^+$]; found, 397.1407.

*3-[2-(4-Nitrobenzyl)-2H-tetrazol-5-yl]-2-(2-thienyl)-1H-indole (**3b**).* According to the general procedure: 0.163 g of azirine **1b** and 0.298 g of aryne precursor **4a** (reaction time 5 h). Yield: 52% (0.105 g), yellow solid; mp 212.4−213.5 °C (diethyl ether/hexane); IR $\tilde{\nu}$ = 3239, 1585, 1525, 1232, 1087,

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1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 2H, CH_2), 7.16−7.22 (m, 2H, Ar), 7.32 [pseudo t (two overlapping doublets), J = 8.0 Hz, J = 7.2 Hz, 1H, Ar], 7.40−7.46 (m, 3H, Ar), 7.55 (d, J = 8.8 Hz, 2H, Ar), 7.87 (d, J = 8.0 Hz, 1H, Ar), 8.24 (d, J = 8.8 Hz, 2H, Ar), 9.25 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 111.4, 112.2, 121.0, 121.1, 124.3, 124.8, 125.5, 127.1, 128.0, 129.5, 139.6, 148.3, 160.0 ppm; HRMS (ESI) calcd for $C_{20}H_{15}N_6O_2S$, 403.0972 $[M + H]^+$; found, 403.0970.

*4,7-Dimethyl-3-[2-(4-nitrobenzyl)-2H-tetrazol-5-yl]-2-(2-thienyl)-1H-indole (**3c**).* According to the general procedure: 0.163 g of azirine **1b** and 0.326 g of aryne precursor **4b** (reaction time 7 h). Yield: 74% (0.159 g), yellow solid; mp 205.4−207.1 °C (diethyl ether/hexane); IR $\tilde{\nu}$= 3229, 1595, 1514, 1341, 807, 787, 732; ^1H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 5.77 (s, 2H, CH_2), 6.82 (d, J = 7.2 Hz, 1H, Ar), 7.00 (d, J = 7.2 Hz, 1H, Ar), 7.04−7.05 (m, 1H, Ar), 7.13−7.15 (m, 1H, Ar), 7.44−7.48 (m, 3H, Ar), 8.21 (d, J = 8.8 Hz, Ar), 9.05 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 19.0, 55.6, 112.2, 118.4, 122.6, 122.9, 124.1, 124.8, 126.1, 126.7, 127.1, 129.1, 129.6, 130.1, 135.5, 136.0, 139.5, 148.3, 159.9 ppm; HRMS (ESI) calcd for $C_{21}H_{22}N_6O_2$, 431.1271 $[M + H]^+$; found, 431.1281.

*4,7-Dimethyl-3-[2-(4-nitrobenzyl)-2H-tetrazol-5-yl]-2-phenyl-1H-indole (**3d**).* According to the general procedure: 0.160 g of azirine **1a** and 0.326 g of aryne precursor **4b** (reaction time 10 h). Yield: 56% (0.118 g), yellow solid; mp 209.2−211.0 °C (diethyl ether/hexane); IR $\tilde{\nu}$ = 3258, 1592, 1478, 1241, 808, 785, 734; ^1H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 5.72 (s, 2H, CH_2), 6.79 (d, J = 7.2 Hz, 1H, Ar), 7.00 (d, J = 7.2 Hz, 1H, Ar), 7.41−7.43 (m, 7H, Ar), 8.19 (d, J = 8.4 Hz, 1H, Ar), 8.94 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 29.3, 55.5, 118.3, 118.8, 120.8, 121.1, 122.2, 124.1, 124.7, 126.4, 127.2, 127.5, 129.6, 130.1, 131.3, 135.7, 139.5, 148.2, 160.3 ppm; HRMS (ESI) calcd for $C_{24}H_{21}N_6O_2$, 425.1721 $[M + H]^+$; found, 425.1718.

General Procedure for the Deprotection Reaction. Compounds **7a**, **7b**, and **8** were prepared following a known procedure.[42] Anhydrous ammonium formate (10 equiv) was added in a single portion to a stirred suspension of the appropriate indole **3** (1 equiv) and an equal weight of 10% Pd/C in methanol (10 mL/0.1 mmol **3**) under a nitrogen atmosphere. The resulting mixture was stirred at reflux for the appropriate time. The mixture was cooled to room temperature, and the catalyst was removed by filtration through a Celite pad, which was then washed using methanol. The combined filtrate was evaporated under reduced pressure, and the resulting crude material was dissolved in ethyl acetate (25 mL), washed using aqueous 1 M HCl (2 × 25 mL), and dried using anhydrous Na_2SO_4. The solvent was evaporated, and the product was purified by crystallization from diethyl ether.

*2-Phenyl-3-(2H-tetrazol-5-yl)-1H-indole (**7a**).* According to the general procedure: 0.040 g of indole **3a** and 0.063 g of ammonium formate (reaction time of 1 h). Yield: 87% (0.023 g), brown solid; mp > 185 °C (decomp., diethyl ether); IR $\tilde{\nu}$ = 3320, 1608, 1601, 1338, 1054, 775, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.13−7.17 (m, 1H, Ar), 7.28−7.32 (m, 1H, Ar), 7.34−7.38 (m, 1H, Ar), 7.45−7.46 (m, 4H, Ar), 7.55 (d, J = 8.0 Hz, 1H, Ar), 7.64 (d, J = 8.4 Hz, 1H, Ar), 12.09 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.7, 116.8, 120.1, 120.9, 124.3, 127.2, 127.2, 129.0, 130.0, 130.5, 133.7, 137.2 ppm; HRMS (ESI) calcd for $C_{15}H_{12}N_5$, 262.1087 $[M + H]^+$; found, 262.1087.

*4,7-Dimethyl-3-(2H-tetrazol-5-yl)-2-(2-thienyl)-1H-indole (**7b**).* According to the general procedure: 0.125 g of indole **3c** and 0.183 g of ammonium formate (reaction time of 20 h). Yield: 33% (0.028 g), brown solid; mp 181.5−182.4 °C; IR $\tilde{\nu}$ = 3274, 2968, 2921, 2859, 1700, 1601, 1363, 1041, 912, 807, 699 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 2.15 (s, 3H), 2.61 (s, 3H), 6.78 (d, J = 7.2 Hz, 1H), 7.00 (d, J = 7.2, 1H), 7.13−7.21 (m, 2H), 7.57 (dd, J = 1.6, 5.2 Hz, 1H), 10.97 (s, 1H) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ 15.9, 18.2, 111.9, 119.4, 119.5, 121.2, 122.5, 124.8, 126.9, 127.0, 127.2, 128.9, 130.0, 134.9, 136.3, 150.1 ppm; HRMS (ESI) calcd for $C_{15}H_{13}N_5S$, 318.0784 $[M + Na]^+$; found, 318.0778.

*3-[2-(4-Aminobenzyl)-2H-tetrazol-5-yl]-2-(2-thienyl)-1H-indole (**8**).* According to the general procedure: 0.040 g of indole **3b** and 0.064 g of ammonium formate (reaction time of 1 h). Yield: 83% (0.031 g), white solid; mp > 185 °C (decomp., diethyl ether); IR $\tilde{\nu}$ = 3274, 1588, 1492, 1344, 1207 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.25 (s, 2H, NH), 5.75 (s, 2H, CH_2), 6.56 (d, J = 8.4 Hz, 2H), 7.12−7.18 (m, 4H), 7.26−7.30 (m, 1H, Ar), 7.37 (dd, J = 3.6, 2.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.58 (dd, J = 5.2, 4.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 12.15 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.9, 110.6, 112.7, 114.2, 120.2, 120.8, 121.0, 121.9, 124.2, 125.8, 127.5, 127.7, 130.2, 134.8, 136.9, 149.7, 159.3 ppm; HRMS (ESI) calcd for $C_{20}H_{17}N_6S$, 373.1278 $[M + H]^+$; found, 373.1281.

One-Pot Procedure for the Synthesis of 2-Phenyl-3-(2*H*-tetrazol-5-yl)-1*H*-indole (7a). A mixture of 18-crown-6 (0.530 g, 2.0 mmol), KF (0.116 g, 2.0 mmol), and the corresponding 2*H*-azirine **9** (0.5 mmol) under an inert atmosphere in dry THF (6 mL) was allowed to stir at 30 °C for 5 min. Then, the reaction mixture was immediately placed in a preheated oil bath at 60 °C and a stepwise addition of aryne precursor **4a** (1.0 mmol) dissolved in THF (6 mL) was performed. The progress of the reaction was monitored by TLC which was completed after 5 h. The mixture was filtered through Celite, the solvent was evaporated, and the crude residue was used in the following step without further purification. Anhydrous ammonium formate (10 equiv) was added in a single portion to a stirred suspension of **3g** (1 equiv) and an equal weight of 10% Pd/C in methanol (50 mL) under a nitrogen atmosphere. The resulting mixture was stirred at reflux for 1 h. The mixture was cooled to room temperature, and the catalyst was removed by filtration through a Celite pad, which was further washed with methanol. The combined filtrate was evaporated under reduced pressure, and the resulting crude material was dissolved in ethyl acetate (25 mL), washed using aqueous 1 M HCl (2 × 25 mL), and dried using anhydrous Na_2SO_4. The solvent was evaporated, and the product was purified by crystallization from diethyl ether. Yield: 27% (0.035 g).

Minimum Energy Calculations. Quantum chemical calculations were carried out to explore the structure and preferred conformations of molecules **1a** and **6**. One initial low-energy conformer of each molecule was generated using the Open Eye Omega software.[46,47] These low-energy structures were then optimized at the DFT level of theory, using the B3LYP hybrid functional[48,49] and the standard 6-31G(d) basis set. All calculations were performed using the GAMESS program package.[50] Graphical representations were

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■ ASSOCIATED CONTENT

Supporting Information

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NMR spectra of compounds and theoretical computational calculations (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Teresa M. V. D. Pinho e Melo − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal;* orcid.org/0000-0003-3256-4954; Email: tmelo@ci.uc.pt

Authors

Carla Grosso − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal;* orcid.org/0000-0003-1999-3471

Cláudia Alves − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal*

Terver J. Sase − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal*

Nuno G. Alves − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal*

Ana L. Cardoso − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal;* orcid.org/0000-0003-0551-7255

Américo Lemos − *University of Coimbra, Coimbra Chemistry Center−Institute of Molecular Sciences (CQC-IMS) and Department of Chemistry, 3004-535 Coimbra, Portugal; FCT, University of Algarve, 8005-139 Faro, Portugal;* orcid.org/0000-0001-9588-4555

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c00305

Notes

The authors declare no competing financial interest.

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