Synthesis of Triazoles via Regioselective Reactions of Aryl Azides with Cyanoacetyl Pyrroles and Indoles

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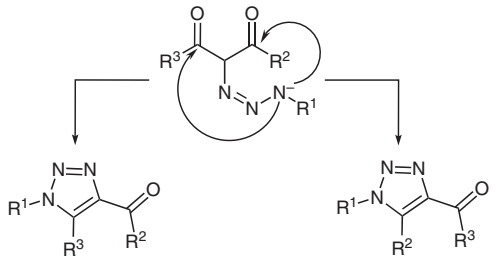
Abstract: Novel 5-aminotriazoles are prepared by the cycloaddition reactions of aryl azides with cyanoacetyl pyrroles and indoles. The regioselectivity of these reactions is discussed.

Key words: triazoles, cycloadditions, regioselectivity, pyrroles, indoles

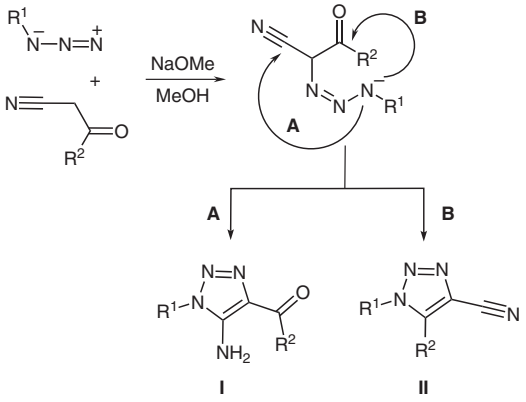
Functionalized 1,2,3-triazoles have a broad spectrum of biological activity even though they do not occur in natural compounds.[1] The antibiotic Cefatrizine is a representative example of the cephalosporins and is an effective drug against pathogenic organisms of the respiratory tract, tissue and skin.[2,3] Triazole derivatives are also used as anticonvulsants.[4] They show anti-HIV-1 activity[5] and are inhibitors of glycogen synthase kinase 3 (GSK-3) which plays an important role in the treatment of Alzheimer's disease and type 1 and 2 diabetes.[6] Antagonists of GABA receptors,[7,8] agonists of muscarinic receptors,[9] neuroleptics[10] and compounds showing cytotoxic,[11] antihistamine[12] and antiproliferative action are found among 1,2,3-triazole derivatives.[13]

The most general and versatile synthesis of 1,2,3-triazoles involves pericyclic addition of organic azides to 1,3-dipolarophiles such as alkynes.[14] A problem associated with concerted 1,3-dipolar cycloadditions is that unsymmetrical alkynes can give rise to two isomeric products, the separation of which is necessary. Moreover, organic azides undergo base-catalyzed condensation reactions with activated methylene compounds possessing neighboring carbonyl or nitrile groups to form 1,2,3-triazoles. In such reactions, high regioselectivities were obtained with the exception of reactions of azides with unsymmetrical 1,3-diketones. For example, in the reaction of benzyl azides or azidopyrimidines with benzoylacetone[15,16] mixtures of two regioisomers were obtained as a result of attack of the azido nitrogen on either one of the two carbonyl groups (Scheme 1). The different nature of the substituents on benzoylacetone (Me and Ph) does not allow the regioselectivity to be predicted. No investigation of the conditions under which regioselectivity can be achieved in these systems has been reported.



Scheme 1 Formation of regioisomers in reactions of azides with unsymmetrical 1,3-diketones

Herein, we describe a study of the regioselectivity between possible attack of the *N*-1 nitrogen atom of an azido group on the carbonyl or nitrile groups of cyanoacetyl pyrroles and cyanoacetyl indoles. It is known that cyanoacetic acid and its derivatives can serve as building blocks for 1,2,3-triazole synthesis. However, replacement of the hydroxy group with alkyl or aryl substituents results in problems of regioselectivity. Cyclization can take place at either the nitrile (path A) or the carbonyl group (path B) and the formation of two regioisomers is possible (Scheme 2). Obviously, the nature of the R^2 group will influence the direction of cyclization. The presence of an electron-donor substituent increases the probability of nitrogen attack on the nitrile group leading to the formation of a 5-amino-1*H*-1,2,3-triazole (path A). In contrast, an electron-withdrawing group should favor formation of the regioisomeric carbonitrile (path B).



Scheme 2 Formation of regioisomers **I** and **II**

Taking into account these facts we selected electron-donating pyrrole and indole derivatives **2a–c** as reaction partners for cyclization with aryl azides. It was estab-

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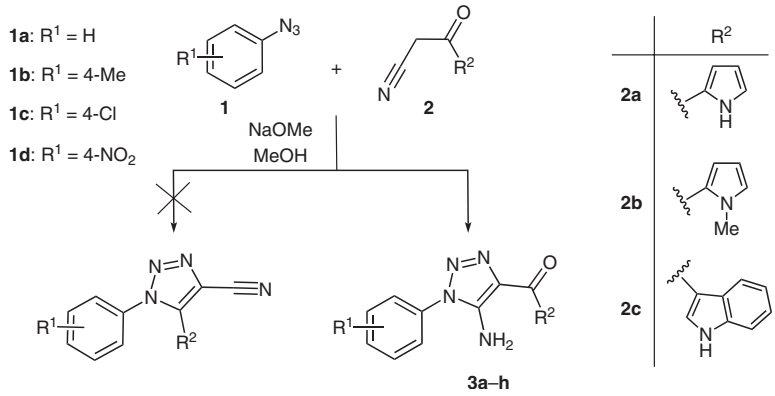


Scheme 3 Regioselective reactions between aryl azides **1** and nitriles **2**

lished that the reactions between aryl azides **1** and nitriles **2** occurred in the presence of sodium methoxide in methanol at room temperature leading to the formation of 5-amino-1*H*-1,2,3-triazoles **3** (Scheme 3 and Table 1). When aryl azides **1a–c** were reacted with 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile **2a** or 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile **2b**, the corresponding 1,2,3-triazoles **3a–d** were obtained after precipitation from the reaction medium upon addition of a few drops of water. Reactions of azides **1a–d** with 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **2c** under the same conditions gave 1,2,3-triazoles **3e–h** which precipitated in good yields from the reaction medium in one hour. The advantage of these reactions is that they occur at room temperature to afford pure products. Regioisomeric 1,2,3-triazoles of type **II** were not formed in these reactions.

Table 1 Triazoles **3a–h**

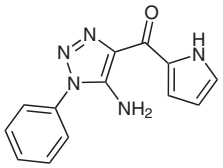
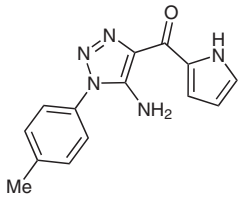
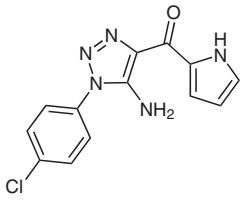
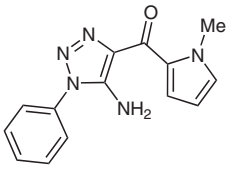
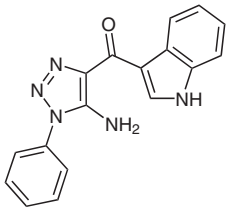
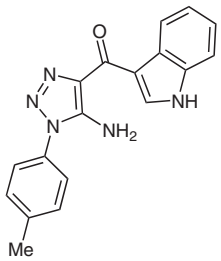
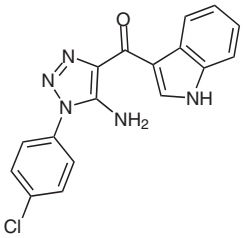
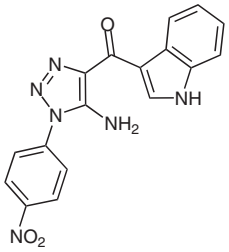
Entry	Product	Yield (%)
3a		70
3b		74
3c		81

Table 1 Triazoles **3a–h** (continued)

Entry	Product	Yield (%)
3d		77
3e		72
3f		79
3g		85
3h		86

Our results correlate well with the abovementioned influence of the R^2 substituent on the direction of cyclization. On the other hand, when 3-oxo-3-phenylpropanenitrile, which was anticipated to form regioisomer **II**, was reacted with aryl azides mixtures of regioisomers were obtained in poor yields (<10%) under the same conditions as those described for compounds **3a**–**d**. Increasing the reaction temperature led to a decrease in the triazole yields. Moreover, aryl amines, the products of reduction of the azido group, were detected.

Many indole and pyrrole derivatives are biologically active and these systems are often fragments of natural compounds and amino acids.[17] Therefore, the reported reaction represents a new method to compounds of potential pharmacological activity. Furthermore, the keto and amine groups present in these compounds provide scope for possible additional structural modifications.

In conclusion, we have reported the first example of regioselective base-catalyzed condensation reactions of azides with active methylene compounds which enables access to novel 1,2,3-triazole derivatives.

Melting points were measured with an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C, DMSO-d_6 as solvent). The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS or the deuterated solvent as internal reference. Mass spectra were obtained using an Agilent 1100 series LC/MSD in API-ES/APCI ionization mode. Compounds **2a**–**c** were prepared according to the literature procedure.[18]

Synthesis of Triazoles; General Procedure

Oxopropanenitrile **2** (10.0 mmol) was added to a solution of NaOMe (540 mg, 10.0 mmol) in dry MeOH (20 mL). Next, a solution of aryl azide **1** (10.0 mmol) in dry MeOH (5 mL) was added dropwise and the mixture was stirred in the dark for 24 h. The resulting suspension was filtered and the solid product was washed with H_2O and MeOH to give triazole **3** as a white, crystalline solid. The addition of a few drops of H_2O was necessary to precipitate triazoles **3a**–**d**.

(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)(1*H*-pyrrol-2-yl)methanone (3a)

Yield: 70%; white crystals; mp 146–147 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.22 (br s, 1 H, 4-H_{Pyr}), 6.93 (s, 2 H, NH_2), 7.06 (br s, 1 H, 3-H_{Pyr}), 7.53 (br s, 1 H, 5-H_{Pyr}), 7.60–7.67 (m, 5 H, H_{Ar}), 11.73 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 110.5 (CH_{Pyr}), 118.2 (CH_{Pyr}), 124.9 (2 × CH_{Ph}), 125.5 ($C_{Triazole}$), 127.3 (CH_{Pyr}), 129.8 (CH_{Ar}), 130.2 (C_{Pyr}), 130.4 (2 × CH_{Ar}), 135.0 (C_{Ar}), 147.1 ($C_{Triazole}$), 174.9 (CO).

MS (CI): *m/z* (%) = 254 (100%) [M + H^+].

Anal. Calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.46; H, 4.60; N, 27.51.

[5-Amino-1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl](1*H*-pyrrol-2-yl)methanone (3b)

Yield: 74%; white crystals; mp 186–187 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.46 (s, 3 H, Me), 6.21 (dd, 1 H, ^3J =3.6, ^3J = 2.0 Hz, 4-H_{Pyr}), 6.82 (s, 2 H, NH_2), 7.04 (br s, 1 H, 3-H_{Pyr}), 7.40 (d, 2 H, ^3J = 8.4 Hz, 3,5-H_{Ar}), 7.49 (d, 2 H, ^3J = 8.4 Hz, 2,6-H_{Ar}), 7.59 (br s, 1 H, 5-H_{Pyr}), 11.69 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3 (Me), 110.5 (CH_{Pyr}), 118.2 (CH_{Pyr}), 124.9 (2 × CH_{Ar}), 125.5 ($C_{Triazole}$), 127.3 (CH_{Pyr}), 130.7 (2 × CH_{Ar}), 130.8 (C_{Pyr}), 132.5 (C_{Ar}), 139.5 (C_{Ar}), 147.1 ($C_{Triazole}$), 174.9 (CO).

MS (CI): *m/z* (%) = 268 (100%) [M + H^+].

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.81; H, 4.73; N, 26.06.

[5-Amino-1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl](1*H*-pyrrol-2-yl)methanone (3c)

Yield: 81%; white crystals; mp 262–263 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.21 (m, 1 H, 4-H_{Pyr}), 6.84 (s, 2 H, NH_2), 7.04 (br s, 1 H, 3-H_{Pyr}), 7.40 (d, 2 H, ^3J = 8.8 Hz, 3,5-H_{Ar}), 7.49 (d, 2 H, ^3J = 8.8 Hz, 2,6-H_{Ar}), 7.60 (br s, 1 H, 5-H_{Pyr}), 11.69 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 110.5 (CH_{Pyr}), 118.2 (CH_{Pyr}), 125.5 ($C_{Triazole}$), 126.9 (2 × CH_{Ar}), 127.3 (CH_{Pyr}), 130.4 (2 × CH_{Ar}), 130.8 (C_{Pyr}), 134.0 (C_{Ar}), 134.2 (C_{Ar}), 147.1 ($C_{Triazole}$), 174.9 (CO).

MS (CI): *m/z* (%) = 288 (100%) [M + H^+].

Anal. Calcd for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.50; N, 24.34. Found: C, 54.49; H, 3.27; N, 24.47.

(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (3d)

Yield: 77%; white crystals; mp 150–151 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.00 (s, 3 H, Me), 6.14 (dd, 1 H, ^3J = 4.0, ^3J = 2.4 Hz, 4-H_{Pyr}), 6.91 (s, 2 H, NH_2), 7.05 (br s, 1 H, 3-H_{Pyr}), 7.53 (m, 1 H, 4-H_{Ar}), 7.61 (d, 4 H, ^3J = 8.0 Hz, 2,3,5,6-H_{Ar}), 7.85 (dd, 1 H, ^3J = 4.0, ^4J = 1.6 Hz, 5-H_{Pyr}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.9 (Me), 108.5 (CH_{Pyr}), 121.5 (CH_{Pyr}), 124.9 (2 × CH_{Ar}), 127.8 ($C_{Triazole}$), 129.4 (CH_{Pyr}), 129.7 (CH_{Ar}), 130.3 (2 × CH_{Ar}), 131.8 (C_{Pyr}), 135.0 (C_{Ar}), 147.2 ($C_{Triazole}$), 176.4 (CO).

MS (CI): *m/z* (%) = 268 (100%) [M + H^+].

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.75; H, 5.02; N, 26.44.

(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)(1*H*-indol-3-yl)methanone (3e)

Yield: 72%; white crystals; mp 278–279 °C (EtOH–H_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.91 (s, 2 H, NH_2), 7.19 (m, 2 H, 5,6-H_{Ind}), 7.49 (dd, 1 H, ^3J = 5.9, ^4J = 2.9 Hz, 4-H_{Ind}), 7.53 (t, 1 H, ^3J = 6.8 Hz, 4-H_{Ar}), 7.62 (t, 2 H, ^3J = 6.8 Hz, 3,5-H_{Ar}), 7.68 (d, 2 H, ^3J = 6.8 Hz, 2,6-H_{Ar}), 8.41 (dd, 1 H, ^3J = 5.9, ^4J = 2.9 Hz, 7-H_{Ind}), 9.04 (s, 1 H, 2-H_{Ind}), 11.82 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 112.7 (CH_{Ind}), 114.9 (C_{Ind}), 122.1 (2 × CH_{Ind}), 123.3 (CH_{Ind}), 124.9 (2 × CH_{Ar}), 127.0 (C_{Ind}), 128.5 ($C_{Triazole}$), 129.7 (C_{Ar}), 130.4 (2 × CH_{Ar}), 135.1 (C_{Ar}), 135.4 (CH_{Ind}), 136.6 (C_{Ind}), 146.6 ($C_{Triazole}$), 181.4 (CO).

MS (CI): *m/z* (%) = 304 (100%) [M + H^+].

Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.25; H, 4.40; N, 23.21.

[5-Amino-1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl](1*H*-indol-3-yl)methanone (3f)

Yield: 79%; white crystals; mp 285–286 °C (EtOH–H_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.46 (s, 3 H, Me), 6.83 (s, 2 H, NH_2), 7.17 (m, 2 H, 5,6-H_{Ind}), 7.40 (d, 2 H, ^3J = 7.8 Hz, 3,5-H_{Ar}), 7.47 (dd, 1 H, ^3J = 6.8, ^4J = 2.9 Hz, 4-H_{Ind}), 7.50 (d, 2 H, ^3J = 7.8

Hz, 2,6-H_{Ar}), 8.40 (dd, 1 H, ^3J = 6.8, ^4J = 2.9 Hz, 7-H_{Ind}), 9.04 (s, 1 H, 2-H_{Ind}), 11.81 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3 (Me), 112.7 (CH_{Ind}), 114.9 (C_{Ind}), 122.1 (2 × CH_{Ind}), 123.2 (CH_{Ind}), 124.8 (2 × CH_{Ar}), 127.0 (C_{Ind}), 128.5 ($C_{Triazole}$), 130.7 (2 × CH_{Ar}), 132.6 (C_{Ar}), 135.4 (CH_{Ind}), 136.5 (C_{Ind}), 139.4 (C_{Ar}), 146.6 ($C_{Triazole}$), 181.4 (CO).

MS (CI): *m/z* (%) = 338 (100%) [M + H$^+$].

Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.21; H, 4.58; N, 21.95.

[5-Amino-1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl](1*H*-indol-3-yl)methanone (3g)

Yield: 85%; white crystals; mp >300 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.00 (s, 2 H, NH_2), 7.18 (m, 2 H, 5,6-H_{Ind}), 7.48 (dd, 1 H, ^3J = 6.8, ^4J = 2.9 Hz, 4-H_{Ind}), 7.64 (d, 2 H, ^3J = 8.8 Hz, 3,5-H_{Ar}), 7.65 (d, 2 H, ^3J = 8.8 Hz, 2,6-H_{Ar}), 8.40 (dd, 1 H, ^3J = 6.8, ^4J = 2.9 Hz, 7-H_{Ind}), 9.03 (s, 1 H, 2-H_{Ind}), 11.83 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 112.7 (CH_{Ind}), 114.8 (C_{Ind}), 122.1 (CH_{Ind}), 122.2 (CH_{Ind}), 123.2 (CH_{Ind}), 126.9 (2 × CH_{Ar}), 127.0 (C_{Ind}), 128.5 ($C_{Triazole}$), 130.4 (2 × CH_{Ar}), 134.0 (C_{Ar}), 134.2 (C_{Ar}), 135.5 (CH_{Ind}), 136.6 (C_{Ind}), 146.8 ($C_{Triazole}$), 181.2 (CO).

MS (CI): *m/z* (%) = 339 (100%) [M + H$^+$].

Anal. Calcd for $C_{17}H_{12}ClN_5O$: C, 60.45; H, 3.58; N, 20.73. Found: C, 60.19; H, 3.55; N, 20.82.

[5-Amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl](1*H*-indol-3-yl)methanone (3h)

Yield: 86%; white crystals; mp >300 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.14 (m, 2 H, 5,6-H_{Ind}), 7.26 (s, 2 H, NH_2), 7.48 (d, 1 H, ^3J = 6.8 Hz, 4-H_{Ind}), 7.98 (d, 2 H, ^3J = 8.8 Hz, 3,5-H_{Ar}), 8.40 (d, 1 H, ^3J = 6.8 Hz, 7-H_{Ind}), 8.44 (d, 2 H, ^3J = 8.8 Hz, 2,6-H_{Ar}), 9.01 (d, 1 H, ^3J = 2.4 Hz, 2-H_{Ind}), 11.86 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.0 (CH_{Ind}), 114.6 (C_{Ind}), 116.6 (2 × CH_{Ar}), 122.0 (CH_{Ind}), 122.7 (CH_{Ind}), 123.7 (CH_{Ind}), 126.0 (2 × CH_{Ar}), 126.8 (C_{Ind}), 131.9 ($C_{Triazole}$), 136.8 (CH_{Ind}, C_{Ind}), 140.3 (C_{Ar}), 147.7 ($C_{Triazole}$), 149.0 (C_{Ar}), 181.6 (CO).

MS (CI): *m/z* (%) = 349 (100%) [M + H$^+$].

Anal. Calcd for $C_{17}H_{12}N_6O_3$: C, 58.62; H, 3.47; N, 24.13. Found: C, 58.28; H, 3.58; N, 24.04.

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