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A novel method for the synthesis of 3,5-disubstituted-(NH)-1,2,4-triazoles from 3,6-diaryl-1,2,4,5-tetrazines

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ABSTRACT

The reaction of 3,6-diaryl-1,2,4,5-tetrazines and 2-aryl substituted acetonitriles, under basic conditions, leads unexpectedly to 3,5-diaryl-(NH)-1,2,4-triazoles in moderate yields. A mechanism is proposed.

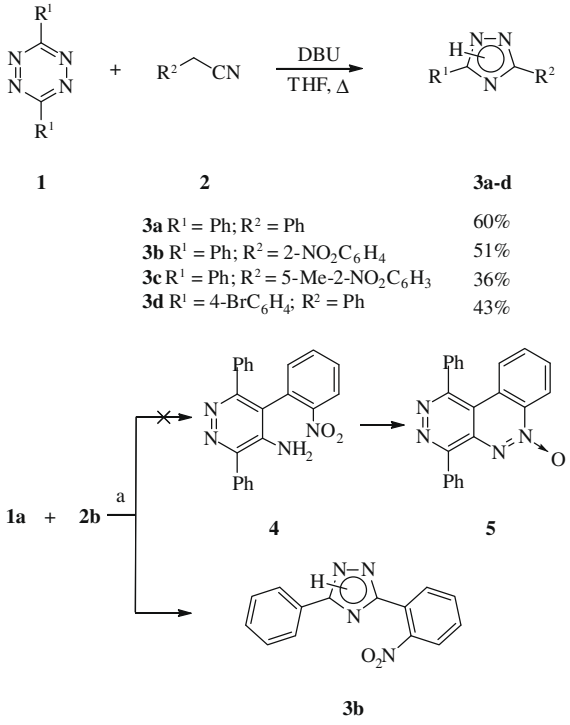
1. Introduction

The synthesis of substituted 1,2,4-triazoles has received considerable attention as these systems demonstrate a broad spectrum of biological activities such as antifungal,[1–3] anti-inflammatory,[4–6] antibacterial,[7–10] anticonvulsant,[11,12] and anticancer behavior.[13–16] Although several methods have been reported for the synthesis of 3,5-diaryl-(NH)-1,2,4-triazoles **3** via the construction of five-membered heterocycles,[17] this work presents the reaction of 3,6-diaryl-1,2,4,5-tetrazines **1** and α-substituted acetonitriles **2** under basic conditions as the first example of the transformation of a 1,2,4,5-tetrazine into a 1,2,4-triazole (Scheme 1).

The formation of **3** was unexpected. In fact, it was envisaged that, analogous to other protocols used by our group for synthesizing new derivatives of cinnoline,[18] the reaction of 1,2,4,5-tetrazine (**1a**) with *o*-nitrobenzyl cyanide (**2b**) in methanolic KOH solution would afford 5-(2-nitrophenyl)-3,6-diphenylpyridazin-4-amine (**4**), which upon ring closure should lead to the unknown pyridazino[4,5-*c*]cinnoline-5-oxide **5** (Scheme 1).[1]

Evidence in support of structure **3b** was provided by the ^{1}H NMR spectrum which showed nine aromatic protons instead of the 14 expected for **4**. In addition, the spectrum included a solvent dependent one-proton broad signal, at 12.2–14.5 ppm. This broad signal disappeared on the addition of deuterium oxide. Analysis of the ^{13}C NMR spectrum indicated that the product had only 14 carbon atoms. In essence, the structure of the product has two phenyl groups, one of which must have come from *o*-nitrobenzyl cyanide (**2b**). This is supported by the IR spectrum which includes strong sharp peaks at 1530 and 1350 cm^{-1}, consistent with the presence of a nitro group. The mass spectrum demonstrated two major peaks: a molecular ion peak, *m*/*z* 266, which fits a molecular formula of $C_{14}H_{10}N_4O_2$ and the possible structure **3b** which is unknown in the literature, and a base peak of *m*/*z* 134 (see Section 2 for HRMS details).

We next turned our attention to the synthesis of the known 3,5-diphenyl-(NH)-1,2,4-triazole (**3a**) using benzyl cyanide (**2a**) as the 2-aryl substituted acetonitrile. Indeed, the reaction of **2a** with **1a** using DBU as the base yielded the known triazole **3a**[19] as was indi-



Scheme 1. Reagents and conditions: (a) KOH (5%), MeOH, reflux, 3 h.

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cated by ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy and the melting point, all of which lent indirect support to the formation of 1,2,4-triazole **3b**.

A postulated mechanism involves the attack of a nucleophile generated from **2**, on the carbon atom of the tetrazine ring of **1**, accompanied by ring opening and ring closure in what is known as the ANRORC (addition of nucleophile, ring opening and ring closure) mechanism. This transformation is completed by the elimination of an aryl nitrile, as outlined in Scheme 2.

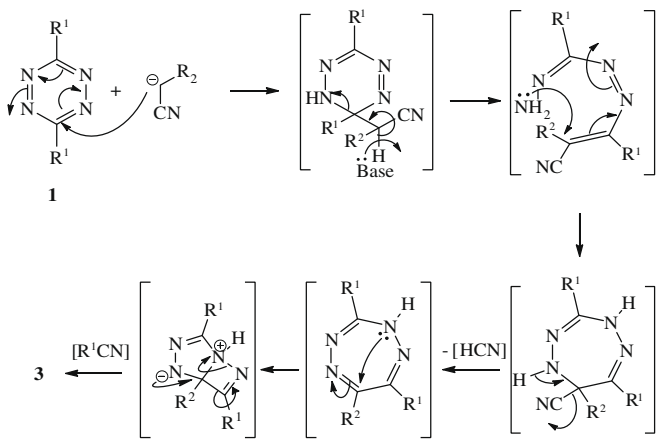
Support for the reaction mechanism was provided by GC–MS studies on two separate reactions under the same conditions (DBU/THF): one reaction mixture was between **1a** and **2b,** and the second using **1a** alone. Although benzonitrile was present in both reaction mixtures, there was a substantial difference in the quantities of benzonitrile formed where 80% excess of benzonitrile was generated in the reaction mixture of **1a** and **2b**, which is attributed to the loss of benzonitrile from the bicyclic intermediate. Loss of a nitrile moiety from a 1,2,4-triazepine ring leading to pyrazoles is established in the literature.[20] Although **1a** is reported to give benzonitrile upon heating in solution and without a solvent,[21,22] we know of no report which indicates the formation of benzonitrile from **1a** under basic conditions (THF–DBU), Scheme 3. The nucleophilicity of DBU has been demonstrated by Baidya and Mayr.[23]

These findings establish the reaction of α-substituted acetonitriles **2** with 3,6-diaryl-1,2,4,5-tetrazines **1** under basic conditions as the first example of the synthesis of 3,6-diaryl-(NH)-1,2,4-triazoles **3** via the addition of the nucleophile, ring opening, and ring closure (ANRORC).

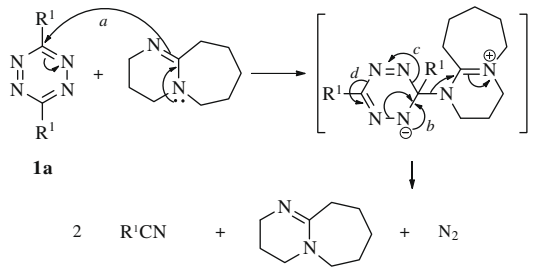
2. Experimental section

2.1. Procedure for the synthesis of 3,6-diphenyl-1,2,4,5-tetrazine (1a)

The title product was prepared according to a literature procedure.[24] Elemental sulfur (1.00 g, 31.3 mmol) was added to a solution of benzonitrile (5.00 g, 48.5 mmol) in ethanol (25 ml). Hydrazine monohydrate (3.00 g, 97.0 mmol) was added to the solution which was heated at reflux for 3 h. The resulting yellow precipitate was washed with cold ethanol (3 × 10 ml) to afford the dihydro derivative as a yellow solid (2.90 g, 51%). Glacial acetic acid (10 mL) and aqueous sodium nitrite (1.76 g, 145.5 mmol) were added to the resulting solid dihydrotetrazine and the mixture was stirred for 20 min after which time the yellowish color turned purple. The solid was collected by filtration and was washed with water and methanol. The resulting purple solid was purified using column chromatography and the fractions (hexanes/ethyl acetate, 10:1→5:1) were evaporated in vacuo to yield the title product as a purple solid (2.00 g, 70%). Mp 196–198 °C (Lit. 196–198 °C).[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67–8.62 (m, 4H), 7.68–7.58 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 132.7, 131.8, 129.3, 128.0.



Scheme 2. Postulated mechanism for the formation of **3**.



Scheme 3. Postulated mechanism for the generation of benzonitrile.

2.2. Procedure for the synthesis of 3,6-diphenyl-(NH)-1,2,4-triazole (3a)

3,6-Diphenyl-1,2,4,5-tetrazine **1a** (1.00 g, 4.2 mmol) was added to a solution of benzyl cyanide **2a** (0.50 g, 4.2 mmol) in dry THF (15 mL). Upon the addition of DBU (1 mL), the mixture was heated at reflux for 3 h. The resulting solution was evaporated under reduced pressure, and was extracted using CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water (3 × 50 mL) and with dilute HCl (5N, 3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and was evaporated in vacuo. The resulting crude solid was purified by column chromatography and the fractions (hexanes/ethyl acetate, 5:1→3:1) were evaporated in vacuo to yield the title product as a white solid (0.54 g, 60%). Mp 188–189 °C (Lit. 188–190 °C).[19] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92–8.03 (m, 4H), 7.38–7.46 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 130.0, 129.3, 128.2, 127.0. IR (KBr, cm^{-1}): ν_{max} 3400 (br, N–H). GC–MS: *m/z* (calculated M^+ 221, found M^+ 221, t_R = 22.87 min). HRMS: *m/z* ($C_{14}H_{11}N_3$) calculated M^+ 221.09530, found M^+ 221.10257.

2.3. 3-(2-Nitrophenyl)-5-phenyl-(NH)-1,2,4-triazole (3b)

White solid (580 mg, 51%). Mp 183–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.2 (br s, 1H), 8.0 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 7.96–7.92 (m, 2H), 7.81 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.65 (dt, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 7.55 (dt, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.44–7.40 (m, 3H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.77 (br s, 1H), 8.05 (d, J = 7.2 Hz, 1H), 8.02–7.97 (m, 3H), 7.92 (d, J = 7.2 Hz, 1H), 7.81 (t, J = 6.6 Hz, 1H), 7.72 (t, J = 6.6 Hz, 1H), 7.56–7.47 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 155.7, 148.7, 132.4, 130.6, 130.4, 130.2, 129.1, 128.8, 127.0, 126.1, 123.6, 123.3. IR (KBr, cm^{-1}): ν_{max} 3233 (br, N–H), 1531, 1374 (s, NO_2). GC–MS: *m/z* (calculated M^+ 266, found M^+ 266, t_R = 22.87 min). HRMS: *m/z* ($C_{14}H_{10}N_4O_2$) calculated M^+ 266.08038, found M^+ 266.07983.

2.4. 3-(5-Methyl-2-nitrophenyl)-5-phenyl-(NH)-1,2,4-triazole (3c)

White solid (115 mg, 36%). Mp 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.20 (br s, 1H), 8.00–7.93 (m, 2H), 7.79–7.76 (m, 2H), 7.44–7.40 (m, 3H), 7.36–7.33 (m, 1H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 157.2, 146.7, 143.8, 132.0, 130.8, 130.4, 129.0, 127.6, 126.5, 124.4, 124.0, 21.3. IR (KBr, cm^{-1}): ν_{max} 3389 (br, N–H), 1531, 1344 (s, NO_2). HRMS: *m/z* ($C_{15}H_{12}N_4O_2$) calculated M^+ 280.09603, found M^+ 280.09548.

2.5. 3-(4-Bromophenyl)-5-phenyl-(NH)-1,2,4-triazole (3d)

White solid (200 mg, 43%). Mp 249–251 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (dd, J_1 = 8.4, J_2 = 1.8 Hz, 2H), 8.02–7.99 (m, 2H), 7.84–

7.68 (m, 3H), 7.55–7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 131.9, 131.6, 131.4, 129.9, 129.5, 129.0, 127.9, 126.0, 125.7. IR (KBr, cm^{-1}): ν_{max} 3325 (br, N–H). GC–MS: *m/z* ($C_{14}H_{10}N_3Br$) calculated $[M+H]^+$ 300/302, found $[M+H]^+$ 300/302, t_R = 25.62 min).

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Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR, IR, GC–MS, and HRMS for compounds **3a**–**d**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.061.

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