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Tetrahedron Letters 44 (2003) 1409–1411

TETRAHEDRON LETTERS

A novel one-pot synthesis of 1,2,4-triazole-3,5-diamine derivatives from isothiocyanates and mono-substituted hydrazines

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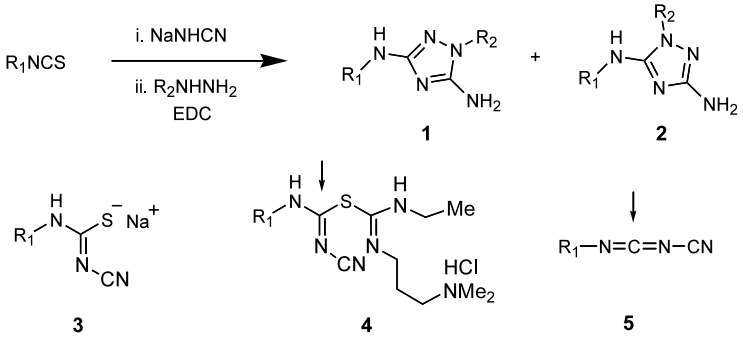
Received 30 October 2002; revised 18 December 2002; accepted 19 December 2002

Abstract—1,2,4-Triazole-3,5-diamine derivatives were synthesized in moderate to high yields in one-pot reaction from the corresponding isothiocyanates, mono-substituted hydrazines, and sodium hydrogencyanamide, in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. Typically, two target compounds were obtained, but high regioselectivities to one isomer were observed when aromatic and sterically bulky hydrazines were used. A number of examples with a detailed representative procedure are given.

1,2,4-Triazole-3,5-diamine derivatives have been identified as potential chemotherapeutic agents.[1–4] Previous synthetic methods involved the use of (a) *N*-cyanoguanidines,[5,6] which could be prepared from various commercially available reagents, (b) *S*,*S*-dimethyl-*N*-cyanodithioimidocarbonates,[6,7] or (c) diphenyl cyanocarbonimidates[8–11] as starting materials. These procedures generally required two or more synthetic steps, and overall yields were typically poor. Method b also involved the generation of malodorous methanethiol and, in some cases, the use of silver nitrate to ensure product formation.[6] In this communication, we report a facile, one-pot procedure for preparation of 1,2,4-triazole-3,5-diamines by using isothiocyanates as starting material. Treatment of isothiocyanate with commercially available sodium hydrogencyanamide in DMF provides the *N*-cyanothiourea sodium salt **3**.[12] Without isolation, **3** was reacted with a hydrazine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) to afford 1,2,4-triazole-3,5-diamine derivatives **1** and **2** (Scheme 1). The reaction presumably proceeds through intermediates **4**[12] and/or **5**.[6] Either nitrogen in the hydrazine molecule may initiate the reaction sequence by attacking the central carbon, denoted with an arrow, in either **4** or **5** (Scheme 1). The second nitrogen initiates the formation of the heterocycle, affording a mixture of two regioisomers.



Scheme 1.

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0040-4039/03/$ - see front matter
PII: S0040-4039(02)02871-X

As shown by examples arranged in Table 1, both the isothiocyanate and hydrazine can be aromatic or aliphatic. Aromatic isothiocyanates typically result in high yields (entries 1–8), whereas aliphatic isothiocyanates appear to give more side products and only moderate yields (entries 9 and 10). Both aromatic isothiocyanates and aromatic hydrazines may be substituted with either electron-donating or electron-withdrawing groups on the aromatic rings (entries 5–8). More specifically, cyano and halogen functionalities have been shown to be compatible with the reaction conditions (entries 1 and 8). Sterically hindered hydrazines do not appear to hamper the reaction (entries 3 and 9). Commercially available hydrazines are often sold as the corresponding salts. It has been demonstrated that hydrazine hydrochloride salts may be directly used as long as a base such as triethylamine is added (entries 2, 3, and 6–9).

Regioselectivity for the reaction sequence appears to be determined by the nature of hydrazine, though in all cases isomer **1** was formed in preference to isomer **2**. When the adduct of phenyl isothiocyanate and sodium hydrogencyanamide was treated with 2-cyanoethylhydrazine in the presence of EDC, triazoles **1a**[13] and **2a**[14] were produced in a ratio of 3.6:1, respectively (entry 1). The moderate regioselectivity in favour of **1a** can be understood by considering the steric environment about the reactive centers. The substituted nitrogen of the hydrazine may have the greater electron density, but it suffers on a basis of accessibility to intermediate **4** or **5** when compared to the unsubstituted nitrogen. The regioisomers were distinguished by nuclear Overhauser effect (NOE) experiments. NOEs were observed between 5-NH_2 and 1-CH_2 but not between 3-NH and 1-CH_2 in **1a**. In **2a**, on the other hand, NOEs were observed between 5-NH and 1-CH_2 but not between 3-NH_2 and 1-CH_2 (Fig. 1). By utilising cyclohexyl hydrazine hydrochloride in the presence of triethylamine in the procedure, triazoles **1b**[15] and **2b**[16] were formed in a comparable ratio of 3.0:1 (entry 2). Similar selectivities (**1g**:**2g** = 3.9:1 and **1h**:**2h** = 4.0:1) were observed in entries 7 and 8, respectively, where electron-donating and electron-withdrawing groups were present on the phenyl ring of the isothiocyanates. However, when the hydrazine was substituted with an extremely bulky *tert*-butyl residue in entries 3 and 9, the ratios of isomers **1c**[17] and **2c**,[18] and **1i** and **2i**,

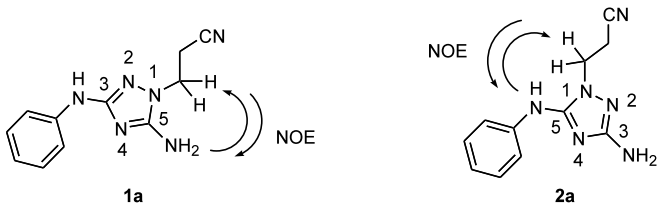
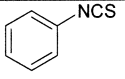
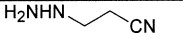
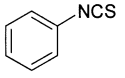
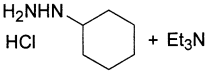
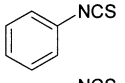
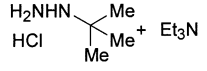
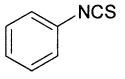
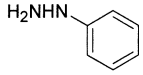
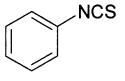
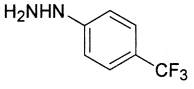
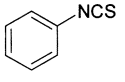
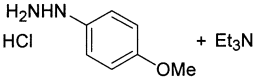
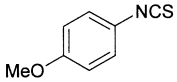
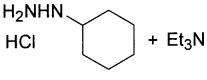
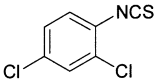
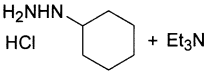
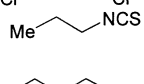
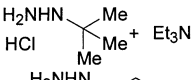
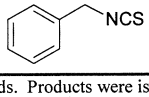
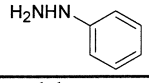


Figure 1.

Table 1. One-pot preparation of 1,2,4-triazole-3,5-diamine derivatives

entry	R_1NCS	R_2NHNH_2	Total yield (%)[a]	Ratio of **1** and **2**[b]
1			72	**1a**:**2a** = 3.6:1
2			82	**1b**:**2b** = 3.0:1
3			90	**1c**:**2c** = 20:1
4			73	**1d**:**2d** = 19:1
5			70	**1e**:**2e** = 100:0
6			79	**1f**:**2f** = 12:1
7			85	**1g**:**2g** = 3.9:1
8			90	**1h**:**2h** = 4.0:1
9			52	**1i**:**2i** = 14:1
10			42	**1j**:**2j** = 20:1

[a] Isolated yields. Products were isolated by silica gel chromatography except in the case of entry 9, where the products were isolated by preparative HPLC. [b]Crude ratio of **1** and **2**, determined by LC/MS.

increased significantly to 20:1 and 14:1, respectively. When the adduct of phenyl isothiocyanate and sodium hydrogencyanamide was reacted with phenyl hydrazine and EDC, triazoles **1d**[19] and **2d** were obtained in a ratio of 19:1 (entry 4). A very similar selectivity (**1j**:**2j** = 20:1) was observed in entry 10, where an aliphatic isothiocyanate was used. The very high preference of formation of **1d** and **1j** in entries 4 and 10 can be understood because the phenyl moiety makes the directly connected nitrogen of the hydrazine not only more hindered but also less electron rich. Entry 5 showed that when the phenyl was substituted with a 4-trifluoromethyl electron-withdrawing group, nucleophilicity of the more hindered nitrogen was further reduced and consequently the regioselectivity could be further improved. In this case, triazole **1e** was the only detected product. In entry 6, an electronic donating 4-methoxy would be expected to offset, to some extent, the electronic effect produced by the phenyl itself. As a result, a poorer selectivity for **1f** over **2f** (12:1) was encountered.

In conclusion, we have reported a convenient synthesis of 1,2,4-triazole-3,5-diamine derivatives from isothiocyanates, sodium hydrogencyanamide, and hydrazines. This procedure has the advantage of one-pot operation that gives the desired products in high yields. The method has particular utility for the preparation of triazole **1** and is far more convenient and efficient than previously reported methods.

*A representative procedure is demonstrated by the preparation of **1b** and **2b***: To a solution of phenyl isothiocyanate (0.276 g 2.00 mmol) in dry DMF was added sodium hydrogencyanamide (0.137 g, 2.10 mmol) at room temperature in one portion. The mixture was heated at 60°C for 1 h before triethylamine (0.50 mL, 3.59 mmol), cyclohexyl hydrazine hydrochloride (0.452 g, 3.00 mmol), and EDC (0.479 g, 2.50 mmol) were added at room temperature. The mixture was heated at 60°C for an additional 1 h, and diluted with ethyl acatate (100 mL), washed with water (3×25 mL) and 10% lithium chloride solution (3×30 mL). The organic solution was dried over anhydrous $MgSO_4$. A mixture of **1b** and **2b** (0.424 g, 82% yield) was isolated as a white solid by chromatography (silica gel, 5% methanol/chloroform). Analytical samples of **1b** and **2b** were obtained by preparative HPLC.

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13. Compound **1a**: ^{1}H NMR (DMSO-d_6): δ 8.72 (1H, s), 7.51 (2H, d, J = 7.9 Hz), 7.17 (2H, dd, J = 7.9, 7.2 Hz), 6.74 (1H, t, J = 7.2 Hz), 6.31 (2H, s), 4.08 (2H, t, J = 6.4 Hz), 2.92 (2H, t, J = 6.4 Hz); ^{13}C NMR (DMSO-d_6): δ 157.6, 154.4, 142.6, 128.8, 119.0, 118.9, 116.0, 41.4, 17.7.
14. Compound **2a**: ^{1}H NMR (DMSO-d_6): δ 8.78 (1H, s), 7.57 (2H, d, J = 7.7 Hz), 7.26 (2H, dd, J = 7.7, 6.9 Hz), 6.89 (1H, t, J = 6.9 Hz), 5.26 (2H, s), 4.17 (2H, t, J = 6.0 Hz), 2.93 (2H, t, J = 6.0 Hz); ^{13}C NMR (DMSO-d_6): δ 161.2, 150.4, 143.2, 141.2, 129.0, 120.9, 119.0, 117.4, 41.4, 17.9.
15. Compound **1b**: ^{1}H NMR (DMSO-d_6): δ 8.60 (1H, s), 7.48 (2H, d, J = 7.8 Hz), 7.15 (2H, dd, J = 7.8, 7.8 Hz), 6.70 (1H, t, J = 7.3 Hz), 6.04 (2H, s), 3.91 (1H, m), 1.83–1.64 (7H, m), 1.34 (2H, m), 1.18 (1H, m); ^{13}C NMR (DMSO-d_6): δ 156.9, 152.9, 143.0, 128.7, 118.5, 115.7, 53.8, 32.0, 25.4, 25.3.
16. Compound **2b**: ^{1}H NMR (DMSO-d_6): δ 8.50 (1H, s), 7.52 (2H, d, J = 7.8 Hz), 7.23 (2H, dd, J = 7.8, 7.8 Hz), 6.84 (1H, t, J = 7.3 Hz), 5.04 (2H, s), 4.12 (1H, m), 1.81–1.64 (7H, m), 1.36 (2H, m), 1.16 (1H, m); ^{13}C NMR (DMSO-d_6): δ 160.5, 148.8, 141.8, 128.9, 120.4, 117.1, 53.8, 32.4, 25.4, 25.3.
17. Compound **1c**: ^{1}H NMR (DMSO-d_6): δ 8.57 (1H, s), 7.49 (2H, d, J = 8.0 Hz), 7.14 (2H, dd, J = 8.0, 7.2 Hz), 6.70 (1H, t, J = 7.2 Hz), 5.78 (2H, s), 1.52 (9H, s); ^{13}C NMR (DMSO-d_6): δ 155.2, 152.9, 143.0, 128.7, 118.5, 115.7, 56.6, 28.9.
18. Compound **2c**: ^{1}H NMR (DMSO-d_6): δ 7.65 (1H, s), 7.18 (2H, dd, J = 8.5, 7.3 Hz), 7.08 (2H, d, J = 8.5, 7.2 Hz), 6.79 (1H, t, J = 7.2 Hz), 5.04 (2H, s), 1.52 (9H, s); ^{13}C NMR (DMSO-d_6): δ 159.6, 148.4, 143.8, 128.9, 119.9, 116.6, 57.8, 29.6.
19. Compound **1d**: ^{1}H NMR (DMSO-d_6): δ 8.92 (1H, s), 7.60–7.48 (6H, m), 7.29 (1H, t, J = 7.2 Hz), 7.20 (2H, dd, J = 7.2, 7.2 Hz), 6.77 (1H, t, J = 7.2), 6.75 (2H, s); ^{13}C NMR (DMSO-d_6): δ 158.0, 153.5, 142.4, 138.1, 129.6, 128.9, 126.0, 122.0, 119.2, 116.2.