Synthesis of functionalized 1,2,4-triazole-3-thiones from potassium isothiocyanate, acid chlorides and arylhydrazines

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Abstract: An efficient synthesis of 1-aryl-5-aryl(alkyl)-1,2-dihydro-3H-1,2,4-triazole-3-thiones via reaction between potassium thiocyanate, acid chlorides, and arylhydrazines is described.

Keywords: Acid chloride; Arylhydrazine; Triazole-thione; Potassium thiocyanate; Three-component reaction.

Introduction

1,2,4-Triazoles are of biological interest 1 and as a consequence, a number of synthetic methods have been developed to construct this ring system [2-4]. To date, there have been no viable one-pot convergent syntheses reported. However, annulation reactions of suitably substituted acyclic precursors represent an attractive alternative methodology, which may allow direct regioselective preparation of the target molecule.

Recently, several new methods have been developed which illustrate the utility of the last approach [5-8]. As part of our current studies on the development of new routes in organic synthesis [9-12], we report an efficient synthesis of functionalized 1,2,4-triazoles-3-thiones, employing readily available starting materials. Thus, reaction of potassium isothiocyanate 1 with acid chlorides 2 and arylhydrazines 3 in water led to triazoles-3-thiones 4 in good yields (Scheme 1).

Scheme 1
Structures of compounds 4a-f were assigned by IR, 1H NMR, 13C NMR and mass spectral data. For example, the 1H NMR spectrum of 4a exhibited characteristic multiplets for the aromatic protons together with a singlet at \( \delta = 14.26 \) ppm for NH groups. The 13C NMR spectrum of 4a showed the thiocarbonyl resonance at \( \delta = 166.8 \) ppm. The mass spectrum of 4a displayed the molecular ion peak at \( m/z = 263 \). A tentative mechanism for this transformation is proposed in Scheme 2. The reaction starts with formation of isothiocyanate 5 followed by addition of arylhydrazine 3 to generate 6. Subsequent cyclization of intermediate 6 generates 7, which is converted into 4 by elimination of water.

\[
\begin{aligned}
1 + 2 & \rightarrow 5 \\
5 & \rightarrow 6 + 3 \\
6 & \rightarrow 7 \\
7 & \rightarrow 4 - \text{H}_2\text{O}
\end{aligned}
\]

Scheme 2

In conclusion, the reaction of acid chlorides with ammonium isothiocyanate and arylhydrazines in water led to 1-aryl-5-aryl(alkyl)-1,2-dihydro-3H-1,2,4-triazole-3-thiones in good yields. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

**Experimental**

Ammonium isothiocyanate, acid chlorides, and arylhydrazines were obtained from Merck and were used without further purification. M.p.: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu IR-460 spectrometer. 1H and 13C NMR spectra: Bruker DRX-500 AVANCE instrument; in DMSO at 500.1 and 125.7 MHz, respectively; \( \delta \) in ppm, \( J \) in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in \( m/z \). Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

**General Procedure for the Preparation of Compounds 4.**

A mixture of ammonium isothiocyanate (2 mmol) and acid chloride (2 mmol) was warmed for five min. Then, arylhydrazine was added gently. The reaction mixture was stirred for 3 h at r.t. in water. The resulting precipitate was separated by filtration to afford compounds 4a-f.

**1,5-Diphenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (4a)**

Cream powder, mp 255-257\(^\circ\), yield: (75%). IR (KBr): 3045, 1587, 1552, 1487, 1466, 1251. 1H-NMR: 7.43 (1 H, t, \( J = 7.4 \), CH), 7.52-7.57 (5 H, m, CH), 7.99-8.00 (2 H, m, 2 CH), 8.02 (2 H, d, \( J = 7.8 \), 2 CH), 14.26 (1 H, s, NH). 13C-NMR: 123.8 (2 CH), 124.7 (C), 126.0 (2 CH), 127.7 (CH), 128.6 (2 CH), 129.1 (2 CH), 131.0 (CH), 137.7 (C), 149.2 (C), 166.3 (C=S). EI-MS: 253 (M^+, 30); 167 (65); 149 (100); 146 (54), 104 (75), 77 (65); 45 (94). Anal. Caled for C_{14}H_{11}N_{3}S (253.32): C, 66.38; H, 4.38; N, 16.59; found: C, 65.82; H, 4.44; N, 16.39%.

**5-(4-Nitrophenyl)-1-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (4b)**

Yellow powder, mp 276-278\(^\circ\), yield: (70%). IR (KBr): 3050, 1586, 1551, 1487, 1465, 1426, 1251. 1H-NMR: 7.44 (1 H, t, \( J = 7.4 \), CH), 7.54 (2 H, d, \( J = 7.6 \), 2 CH), 8.00 (2 H, d, \( J = 7.9 \), 2 CH), 8.22 (2 H, d, \( J = 8.8 \), 2 CH), 8.36 (2 H, d, \( J = 8.8 \), 2 CH), 14.56 (1 H, s, NH). 13C-NMR: 123.9 (2 CH), 124.2 (2 CH), 127.2 (CH), 128.0 (CH), 128.6 (2 CH), 130.6 (1C), 137.5 (C), 147.6 (C), 148.5 (C), 166.9 (C=S). EI-MS: 298 (M^+, 15); 207 (100); 149 (54); 123 (64), 106 (78); 45 (44). Anal. Caled for C_{14}H_{10}N_{4}O_{2}S (298.31): C, 56.37; H, 3.38; N, 18.78; found: C, 55.88; H, 3.32; N, 18.90%.

**5-(4-Methylphenyl)-1-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (4c)**

Cream powder, mp 264-266\(^\circ\), yield: (65%). IR (KBr): 3030, 1586, 1551, 1487, 1465, 1426, 1251. 1H-NMR: 7.43 (1 H, t, \( J = 7.4 \), CH), 7.41 (1 H, t, \( J = 7.1 \), 1 CH), 7.51 (2 H, t, \( J = 7.1 \), 2 CH), 7.75 (2 H, d, \( J = 8.2 \), 2 CH), 8.05 (2 H, d, \( J = 8.2 \), 2 CH), 14.60 (1 H, s, NH). 13C-NMR: 20.9 (CH_{3}), 122.3 (C), 123.7 (2 CH), 125.9 (2 CH), 127.6 (C), 128.5 (2 CH), 129.6 (2 CH), 137.8 (C), 140.9 (C), 149.6 (C), 180.90%.

5-(4-Nitrophenyl)-1-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (4d)

Yellow powder, mp 276-278\(^\circ\), yield: (70%). IR (KBr): 3050, 1586, 1551, 1487, 1465, 1426, 1251. 1H-NMR: 7.44 (1 H, t, \( J = 7.4 \), CH), 7.54 (2 H, d, \( J = 7.6 \), 2 CH), 8.00 (2 H, d, \( J = 7.9 \), 2 CH), 8.22 (2 H, d, \( J = 8.8 \), 2 CH), 8.36 (2 H, d, \( J = 8.8 \), 2 CH), 14.56 (1 H, s, NH). 13C-NMR: 123.9 (2 CH), 124.2 (2 CH), 127.2 (CH), 128.0 (CH), 128.6 (2 CH), 130.6 (1C), 137.5 (C), 147.6 (C), 148.5 (C), 166.9 (C=S). EI-MS: 298 (M^+, 15); 207 (100); 149 (54); 123 (64), 106 (78); 45 (44). Anal. Caled for C_{14}H_{10}N_{4}O_{2}S (298.31): C, 56.37; H, 3.38; N, 18.78; found: C, 55.88; H, 3.32; N, 18.90%.
166.3 (C=S). EI-MS: 267 (M⁺, 10); 106 (55); 176 (76); 149 (48); 117 (100); 91 (84), 92 (45) 45 (34). Anal. Calcd for C₁₅H₁₃N₃S (267.35): C, 67.39; H, 4.90; N, 15.72; found: C, 67.22; H, 4.75; N, 5.81 %.

1-(2,4-Dinitrophenyl)-5-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (4d)
Yellow powder, mp 240-242°, yield: (58%). IR (KBr): 3043, 1582, 1554, 1398, 1466, 1251. 1H-NMR: 7.45-7.55 (3 H, m, 3 CH), 7.61 (2 H, t, J = 7.6, 2 CH), 8.28 (2 H, d, J = 7.8, 2 CH), 9.08 (1 H, s, CH), 11.12 (1 H, s, NH). 13C-NMR: 123.5 (CH), 127.3 (CH), 128.6 (2 CH), 129.0 (C), 130.3 (2 CH), 131.8 (CH), 134.4 (CH), 137.8 (C), 146.9 (C), 155.1 (C), 167.0 (C=S). EI-MS: 343 (M⁺, 20); 240 (52); 196 (100); 176 (54); 167 (60); 103 (64), 45 (74). Anal. Calcd for C₁₄H₉N₅O₄S (343.32): C, 48.98; H, 2.64; N, 20.40; found: C, 48.95; H, 2.63; N, 20.39%.

1-(2,4-Dinitrophenyl)-5-(4-methylphenyl)-1,2-dihydro-3H-1,2,4-triazole-3-thione (4e)
Yellow powder, mp 254-256°C, yield: (63%). IR (KBr): 3039, 1582, 1549, 1475, 1454, 1248. 1H-NMR: 2.39 (3 H, s, Me), 7.30 (1 H, d, J = 8.2, CH), 7.34 (2 H, d, J = 8.2, 2 CH), 7.91 (2 H, d, J = 8.2, 2 CH), 8.35 (1 H, d, J = 8.2, CH), 8.89 (1 H, s, CH), 11.69 (1 H, s, NH). 13C-NMR: 21.0 (Me), 116.1 (CH), 122.9 (CH), 128.7 (C), 128.9 (2 CH), 129.6 (2 CH), 129.2 (C), 130.0 (C), 134.2 (CH), 137.2 (C), 143.6 (C), 146.9 (C), 166.8 (C=S). EI-MS: 357 (M⁺, 15); 240 (72); 177 (89); 161 (56); 117 (100); 176 (54); 45 (54). Anal. Calcd for C₁₅H₁₁N₅O₄S (357.31): C, 48.95; H, 2.63; N, 20.39%.

1-(2,4-Dinitrophenyl)-5-(4-bromophenyl)-1,2-dihydro-3H-1,2,4-triazole-3-thione (4f)
Yellow powder, mp 232-234°, yield: (73%). IR (KBr): 3041, 1579, 1547, 1480, 1454, 1250. 1H-NMR: 7.32 (1 H, d, J = 8.5, CH), 7.75 (2 H, d, J = 8.3, 2 CH), 7.92 (2 H, d, J = 8.3, 2 CH), 8.34 (1 H, d, J = 8.5, CH), 8.91 (1 H, s, CH), 11.84 (1 H, s, NH). 13C-NMR: 115.4 (CH), 124.7 (C), 127.2 (CH), 128.7 (C), 129.0 (C), 130.0 (2 CH), 131.4 (2 CH), 133.1 (C), 134.2 (CH), 152.7 (C), 157.8 (C), 168.4 (C=S). EI-MS: 422 (M⁺, 10); 242 (100); 239 (45); 196 (86); 183 (68); 156 (65); 45 (58). Anal. Calcd for C₁₄H₉N₅O₄S (422.21): C, 50.43; H, 1.91; N, 16.59; found: C, 50.35; H, 1.90; N, 16.60%.

References