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Three-component reaction between benzohydrazide acid, ammonium thiocyanate and acid chlorides under solvent-free conditions

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Three-component reaction between benzohydrazide acid, ammonium thiocyanate and acid chlorides under solvent-free conditions

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A novel method for 1,2,4-triazole-3-thiones formation is established using the reaction of ammonium thiocyanate and acid chlorides with benzohydrazide acid under solvent-free conditions to afford triazole-3-thiones in good yields.



Keywords: benzohydrazide acid; acid chlorides; ammonium thiocyanate; triazole-3-thiones; solvent-free

1. Introduction

Multi-component reactions have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion (1-4). 1,2,4-Triazoles are of biological interest (5) and, as a consequence, a number of synthetic methods have been developed to construct this ring system (6-9). To date, to the best of our knowledge, there has been no viable one-pot convergent synthesis 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 that illustrate the utility of the last approach (10-30). As part of our current studies on the development of new routes in organic synthesis (31, 32), we report an efficient one-pot synthesis of functionalized 1,2,4-triazole-3-thiones, employing readily available starting materials.

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2. Results and discussion

Reaction of benzohydrazide acid 1 and acid chlorides 2 with ammonium thiocyanate 3 under solvent-free conditions affords 1,2,4-triazole-3-thiones 4 in excellent yields (Scheme 1).



Scheme 1. Three-component reaction between benzohydrazide acid, ammonium thiocyanate and acid chlorides under solvent-free conditions.

Structures of compounds **4a**–**f** were confirmed by IR, ¹H- and 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 $\delta = 10.63$ ppm for the NH group, in agreement with the proposed structure. The ¹³C-NMR spectrum of **4a** showed the thiocarbonyl resonance at $\delta = 166.7$ ppm. The mass spectrum of **4a** displayed the molecular ion peak at m/z = 281.

A tentative mechanism for this transformation is proposed in Scheme 2.



Scheme 2. Suggested mechanism for the formation of compound 4.

It is conceivable that the reaction starts with the formation of aroyl thiocyanate 5 followed by the addition of benzohydrazide acid 1 to generate 6. Subsequent cyclization of intermediate 6 generates 7 which is converted to 4 by the elimination of water.

In conclusion, the reaction of ammonium thiocyanate and acid chlorides with benzohydrazide acid under solvent-free conditions led to 1,2,4-triazole-3-thiones in excellent 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.

3. Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Islamic Azad University Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.¹H- and ¹³C-NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in DMSO- d_6 using TMS as the internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

3.1. General procedure

A mixture of ammonium thiocyanate (0.15 g, 2 mmol) and an acid chloride (2 mmol) was warmed at about 50°C for 10 min. Then, benzohydrazide acid (2 mmol) was added slowly. The resulting mixture was stirred for 4 h at room temperature, and then poured into 15 ml of water. The resulting precipitate was collected by filtration on a Buchner funnel and washed with 10 ml of cold diethyl ether to afford the pure title compounds.

3.1.1. Phenyl(5-phenyl-3-thioxo-2,3-dihydro[1,2,4]triazol-1-yl)methanone (4a)

White powder, m.p. 235–237°C, IR (KBr) (ν_{max} cm⁻¹): 3192 (m), 1600 (s), 1564 (s), 1493 (s), 1456 (m), 1265 (m). Analyses: Calcd. for C₁₅H₁₁N₃OS: C, 64.04; H, 3.94; N, 14.94%. Found: C, 64.18; H, 3.79; N, 14.80. MS (m/z, %): 281 (8).

¹H-NMR (500 MHz, DMSO- d_6): δ 7.16–7.59 (10 H, m, 10 CH aromatic), 10.43 (1 H, s, NH) ppm. ¹³C-NMR (125.8 MHz, DMSO- d_6): δ 128.30, 129.41, 129.56, 130.80, 132.07, 132.56, 133.38 and 135.24 (aromatic), 165.44 (C=N), 166.28 (C=O), 166.85 (C=S) ppm.

3.1.2. Phenyl[5-(4-chlorophenyl)-3-thioxo-2,3-dihydro[1,2,4]triazol-1-yl]methanone (4b)

White powder, m.p. 226–228°C, IR (KBr) (ν_{max} cm⁻¹): 3195 (m), 1602 (s), 1564 (s), 1497 (s), 1457 (m), 1266 (m). Analyses: Calcd. for C₁₅H₁₀ClN₃OS: C, 57.05; H, 3.19; N, 13.31%. Found: C, 57.13; H, 3.35; N, 13.19. MS (m/z, %): 315 (10).

¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.52–7.96 (5 H, m, 5 CH aromatic), 7.62 (2 H, d, ³*J*_{HH} = 8 Hz, 2 CH of C₆H₄Cl), 7.97 (2 H, d, ³*J*_{HH} = 8 Hz, 2 CH of C₆H₄Cl), 10.56 (1 H, s, NH) ppm. ¹³C-NMR (125.8 MHz, DMSO-*d*₆): δ 128.33, 129.39, 129.54, 130.26, 132.18, 132.76, 133.38 and 137.62 (aromatic), 165.74 (C=N), 166.71 (C=O), 166.92 (C=S) ppm.

3.1.3. Phenyl[5-(4-bromophenyl)-3-thioxo-2,3-dihydro[1,2,4]triazol-1-yl]methanone (4c)

White powder, m.p. 211–213°C, IR (KBr) (ν_{max} cm⁻¹): 3185 (m), 1608 (s), 1577 (s), 1496 (s), 1458 (m), 1263 (m). Analyses: Calcd. for C₁₅H₁₀BrN₃OS: C, 50.01; H, 2.80; N, 11.66%. Found: C, 49.90; H, 2.68; N, 11.75. MS (m/z, %): 359 (5).

¹H-NMR (500 MHz, DMSO-*d*₆): δ 7.50–7.94 (5 H, m, 5 CH aromatic), 7.74 (2 H, d, ³*J*_{HH} = 8 Hz, 2 CH of C₆H₄Br), 7.88 (2 H, d, ³*J*_{HH} = 8 Hz, 2 CH of C₆H₄Br), 10.55 (1 H, s, NH) ppm. ¹³C-NMR (125.8 MHz, DMSO-*d*₆): δ 128.15, 129.21, 130.03, 130.97, 132.01, 132.38, 132.93 and 133.28 (aromatic), 165.44 (C=N), 166.27 (C=O), 166.94 (C=S) ppm.

3.1.4. Phenyl[5-(3-nitrophenyl)-3-thioxo-2,3-dihydro[1,2,4]triazol-1-yl]methanone (4d)

White powder, m.p. 221–223°C, IR (KBr) (ν_{max} cm⁻¹): 3226 (m), 1641 (s), 1616 (s), 1530 (s), 1487 (s), 1445 (m), 1348 (s), 1271 (m). Analyses: Calcd. for C₁₅H₁₀N₄O₃S: C, 55.21; H, 3.09; N, 17.17%. Found: C, 55.35; H, 3.16; N, 16.95. MS (m/z, %): 326 (8).

¹H-NMR (500 MHz, DMSO- d_6): δ 7.52–8.76 (5 H, m, 9 CH aromatic), 10.67 (1 H, s, NH) ppm. ¹³C-NMR (125.8 MHz, DMSO- d_6): δ 122.68, 127.04, 127.95, 129.04, 130.96, 132.47, 132.80, 134.27, 134.33 and 148.34 (aromatic), 164.34 (C=N), 166.25 (C=O), 166.98 (C=S) ppm.

3.1.5. Phenyl[5-(4-nitrophenyl)-3-thioxo-2,3-dihydro[1,2,4]triazol-1-yl]methanone (4e)

White powder, m.p. 242–244°C, IR (KBr) (ν_{max} cm⁻¹): 3205 (m), 1611 (s), 1573 (s), 1518 (s), 1458 (m), 1345 (s), 1266 (m). Analyses: Calcd. for C₁₅H₁₀N₄O₃S: C, 55.21; H, 3.09; N, 17.17%. Found: C, 55.35; H, 3.16; N, 16.95. MS (m/z, %): 326 (6).¹H-NMR (500 MHz, DMSO- d_6): δ 7.49–7.88 (5 H, m, 5 CH aromatic), 8.07 (2 H, d, $^{3}J_{HH} = 8$ Hz, 2 CH of C₆H₄NO₂), 8.33 (2 H, d, $^{3}J_{HH} = 8$ Hz, 2 CH of C₆H₄NO₂), 10.66 (1 H, s, NH) ppm. ¹³C-NMR (125.8 MHz, DMSO- d_6): δ 124.28, 127.94, 129.04, 129.47, 132.47, 132.79, 138.61 and 149.90 (aromatic), 164.81 (C=N), 166.23 (C=O), 166. 87 (C=S) ppm.

3.1.6. Phenyl(3-thioxo-5-p-tolyl-2,3-dihydro[1,2,4]triazol-1-yl)methanone (4f)

White powder, m.p. 218–220°C, IR (KBr) (ν_{max} cm⁻¹): 3172 (m), 1607 (s), 1560 (s), 1489 (s), 1443 (m), 1267 (m). Analyses: Calcd. for C₁₆H₁₃N₃OS: C, 65.06; H, 4.44; N, 14.23%. Found: C, 64.87; H, 4.60; N, 14.39. MS (m/z, %): 295 (3).

¹H-NMR (500 MHz, DMSO- d_6): δ 2.31 (3 H, s, CH₃), 7.49–7.83 (5 H, m, 5 CH aromatic), 7.45 (2 H, d, ${}^{3}J_{\text{HH}} = 8$ Hz, 2 CH of C₆H₄Cl), 7.79 (2 H, d, ${}^{3}J_{\text{HH}} = 8$ Hz, 2 CH of C₆H₄Cl), 10.48 (1 H, s, NH) ppm. ¹³C-NMR (125.8 MHz, DMSO- d_6): δ 21.9 (CH₃), 126.4, 128.05, 129.39, 129.54, 130.02, 132.18, 133.38 and 144.31 (aromatic), 164.53 (C=N), 166.21 (C=O), 166.79 (C=S) ppm.

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