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Green synthesis of imidazole-2-thione derivatives using ethyl 3-chloro-2-iminopropanoate

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Abstract: An efficient synthesis of imidazole-2-thione was described via multicomponent reaction of isothiocyanates, ethyl 3-chloro-2-iminopropanoate and malononitrile in water at room temperature in good yields and without any catalyst.

Keywords: Imidazole, Ethyl 3-chloro-2-iminopropanoate, Et_3N, Isothiocyanate.

Introduction

Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities such as antimalarial [1], antimicrobial [2], antitumor [3], anticancer [4], antidepressant [5], antiviral [6], antidiabetic [7] anti-inflammatory [8] and anti-HIV [9]. Moreover, they also contribute in the field of material science, [10] dyes and pigment science [11] as well as agrochemistry [12]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [13, 14]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [15–17] and could be performed in the presence of nanocatalyst and produce heterocyclic compounds [18-20].

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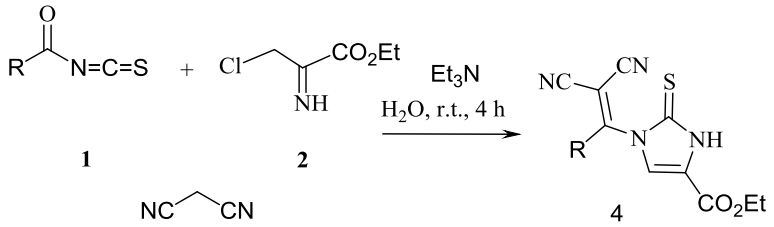
Among them imidazole represent a simple heterocyclic frame which has been scarcely explored compared to the non-aromatic counterpart oxazolesstructure. Surprisingly for this simple heterocycle, only basic structures related to acetol have been converted into imidazoles [20, 21]. Synthesis of imidazoles was reported using either condensation of thiocyanic acid [22-25] or isothiocyanates [26] with an α-hydroxycarbonyl, or condensation of thiophosgen with an aminoketone [27]. The possible balance of reactivity of α-hydroxycarbonyl systems with thiocyanic acid toward the formation of either imidazole or 1,3-imidazoline-2-thione have been recently reported [28, 29].

Result and discussion

As part of our current studies on the development of new routes in heterocyclic synthesis, we report an efficient synthetic route to functionalized imidazoles. Thus, the reaction of isothiocyanate **1**, ethyl 3-chloro-2-iminopropanoate **2** and malononitrile **3** in water at room temperature conditions, produced imidazoles **4** in good yields (Scheme **1**).

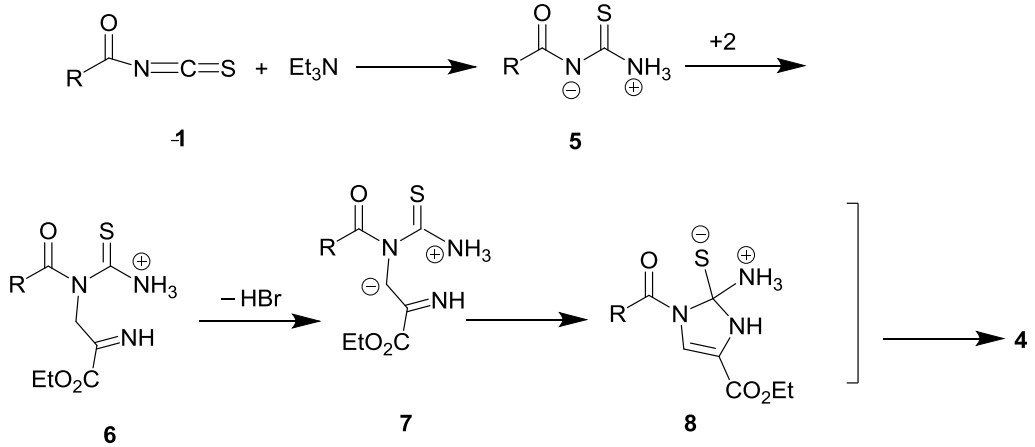
Structures of compounds **4a**–**4g** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectra of **4a**–**4g** exhibited characteristic signals for methine (δ = 7.52-7.64 ppm) protons. The ^{13}C NMR spectra of the imidazole-2-thione ring system of **4a** showed signals at 118.4 (CH), 139.8 (C), 156.6 (C=O), 176.7 (C=O), and 178.1 (C=S) ppm. The mass spectra of **4a**–**4g** displayed the molecular ion peaks at appropriate *m*/*z* values.

A tentative mechanism for this transformation is proposed in Scheme **2**. The reaction starts with reaction of benzoyl isothiocyanate **1** with triethylamine, and formation of the 1:1 adduct **4**, which is subsequently attacked by ethyl bromopyruvate to produce **5**. Intermediate **5** undergoes HBr elimination, cyclization reaction, and loss of *N*-formylmorpholine to generate **3**.



4	R	Yield/ % of 4
a	Ph	92
b	4-Me-C_6H_4	97
c	4-Br-C_6H_4	80
d	4-Cl-C_6H_4	78
e	4-NO_2-C_6H_4	90
f	*t*-Bu	89
g	Et	92

Scheme 1: Synthesis of oxazol derivatives



Scheme 2: Proposed mechanism

Experimental Section

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR)

spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. All chemicals were obtained from Fluka and were used without further purification.

General Procedure for the Preparation of imidazole 4

A stirred mixture of isothiocyanate (2 mmol) and ethyl 3-chloro-2-iminopropanoate (2 mmol) in the presence of triethylamine in water as solvent at room temperature for 1 h. Then, malononitrile (2 mmol) was added gently. The reaction mixture was stirred for 4 h and extracted by Et_2O (2 x 5 mL) to afford the pure title compounds.

Compound **4a:** Pale yellow crystals; yield: 0.38 g (85%), mp 129-131°C. IR (KBr) (ν_{max}/cm^{-1}): 1724, 1631, 1585, 1518 and 1470 cm^{-1}. ^{1}H NMR: δ 1.45 (3 H, *t*, ^3J = 7.2, Me); 4.46 (2 H, *q*, ^3J = 7.2, OCH_2); 7.52 (2 H, *t*, ^3J = 7.8, 2 CH); 7.61 (1 H, *t*, ^3J = 6.1, CH); 7.65 (1 H, *s*, CH); 7.52 (2 H, *d*, ^3J = 6.1, 2 CH). ^{13}C NMR: δ = 14.6 (Me); 63.0 (OCH_2); 118.4 (CH); 128.9 (2 CH); 130.5 (2 CH); 133.8 (CH); 134.9 (C); 139.8 (C); 156.6 (C=O); 176.7 (C=O); 178.1 (C=S). EI-MS: 227 (M$^+$, 10), 121 (20), 105 (100), 77 (90), 57 (30), 51 (64); 45 (36). Anal. Calcd for $C_{13}H_{11}NO_4S$ (277.29): C, 56.31; H, 4.00; N, 5.05%. Found: C, 56.30; H, 4.03; N, 5.00%.

Compound **4b:** Pale yellow powder; yield: 0.55 g (95%); mp 125-127°C. IR (KBr) (ν_{max}/cm^{-1}): 1720, 1635, 1580, 1520 and 1450 cm^{-1}. ^{1}H NMR: δ 1.40 (3 H, *t*, ^3J = 7.2, Me); 2.41 (3 H, *s*, Me); 4.41 (2 H, *q*, ^3J = 7.2, OCH_2); 7.26 (2 H, *d*, ^3J = 8.1, 2 CH); 7.57 (1 H, *s*, CH); 8.21 (2 H, *d*, ^3J = 8.1, 2 CH). ^{13}C NMR: δ 14.2 (Me); 21.7 (Me); 62.4 (OCH_2); 117.8 (CH); 129.2 (2 CH); 130.2 (2 CH); 132.1 (C); 139.4 (C); 144.2 (C); 156.2 (C=O); 176.2 (C=O); 177.2 (C=S). EI-MS: 291 (M$^+$, 5), 172(65), 119 (100), 99 (64), 77 (80), 45 (56). Anal. Calcd for $C_{14}H_{13}NO_4S$ (291.32): C, 57.72; H, 4.50; N, 4.81%. Found: C, 57.70; H, 4.46; N, 4.80%. Compound **4c:** Yellow crystals; yield: 0.53 g (75%), mp 135-137°C. IR (KBr): 1730, 1650, 1575, 1519 and 1450 cm^{-1}.^{1}H NMR: δ 1.37 (3 H, *t*, ^3J = 7.2, Me); 4.38 (2 H, *q*, ^3J = 7.2, OCH_2); 7.57 (2 H, *d*, ^3J = 8.5, 2 CH); 7.58 (1 H, *s*, CH); 8.13 (2 H, *d*, ^3J = 8.5, 2 CH). ^{13}C NMR: δ 14.2 (Me); 62.6 (OCH_2); 117.8 (CH); 128.5 (C); 131.5 (2 CH); 131.7 (2 CH); 133.6 (C); 139.6 (C); 156.0 (C=O); 175.4 (C=O); 177.9 (C=S). EI-MS: 356 (M$^+$, 10); 283 (45); 172 (75); 184 (100); 99 (66); 77 (64), 45 (84). Anal. Calcd for $C_{13}H_{10}BrNO_4S$ (356.19): C, 43.84; H, 2.83; N, 3.93%. Found: C, 43.80; H, 2.80; N, 3.90%.

Compound **4d:** Yellow crystals; yield: 0.43 g (70%), mp 142-144°C. IR (KBr): 1725, 1630, 1580, 1522 and 1501 cm^{-1}. ^{1}H NMR: δ 1.35 (3 H, *t*, ^3J = 7.2, Me); 4.35 (2 H, *q*, ^3J = 7.2, OCH_2); 7.56 (2 H, *d*, ^3J = 8.5, 2 CH); 7.60 (1 H, *s*, CH); 8.24 (2 H, *d*, ^3J = 8.5, 2 CH). ^{13}C NMR: δ 14.4 (Me); 62.5 (OCH_2); 118.1 (CH); 128.4 (C); 131.7 (2 CH); 132.1 (2 CH); 133.7 (C); 139.4 (C); 157.4 (C=O); 176.1 (C=O); 178.2 (C=S). EI-MS: 311 (M$^+$, 10); 238 (45); 172 (66); 139 (100), 77 (85), 45 (84). Anal. Calcd for $C_{13}H_{10}ClNO_4S$ (311.73): C, 50.09; H, 3.23; N, 4.49%. Found: C, 50.10; H, 3.20; N, 4.45%.

Compound **4e:** Yellow crystals; yield: 0.55 g (85%), mp 133-135°C. IR (KBr): 1721, 1632, 1584, 1510 and 1469 cm^{-1}. ^{1}H NMR: δ 1.41 (3 H, *t*, ^3J = 7.1, Me); 4.43 (2 H, *q*, ^3J = 7.1, OCH_2); 7.64 (1 H, *s*, CH); 8.30 (2 H, *d*, ^3J = 8.8, 2 CH); 8.47 (2 H, *d*, ^3J = 8.8, 2 CH). ^{13}C NMR: δ 14.2 (Me); 62.7 (OCH_2); 117.7 (CH); 123.6 (2 CH); 131.0 (2 CH); 139.9 (C); 140.0 (C); 150.6 (C); 155.8 (C=O); 174.4 (C=O); 179.0 (C=S). EI-MS: 322 (M$^+$, 15); 249 (55); 172 (76); 150 (100), 77 (65), 45 (52). Anal. Calcd for $C_{13}H_{10}N_2O_6S$ (322.29): C, 48.45; H, 3.13; N, 8.69%. Found: C, 48.40; H, 3.10; N, 8.65%.

Compound **4f:** Yellow crystals; yield: 0.43 g (83%), mp 124-126°C. IR (KBr): 1720, 1654, 1580, 1524 and 1460 cm^{-1}. ^{1}H NMR: δ 1.18 (9 H, s, 3 Me), 1.31 (3 H, *t*, ^3J = 7.2, Me); 4.33 (2 H, *q*, ^3J = 7.2, OCH_2); 7.53 (1 H, *s*, CH). ^{13}C NMR: δ 14.1 (Me); 27.0 (3 Me), 41.5 (C), 62.3 (OCH_2); 117.7 (CH); 138.9 (C); 156.1 (C=O); 176.9 (C=S); 190.7 (C=O). EI-MS: 257 (M$^+$, 10); 172 (85); 85 (100), 57 (86). Anal. Calcd for $C_{11}H_{15}NO_4S$ (257.30): C, 51.35; H, 5.88; N, 5.44%. Found: C, 51.30; H, 5.80; N, 5.40%.

Compound 4**g:** Yellow powder; yield: 0.39 g (86%), mp 127-129°C. IR (KBr): 1729, 1654, 1587, 1524 and 1460 cm^{-1}. ^{1}H NMR: δ 1.14 (3 H, *t*, ^3J = 7.5, Me); 1.31 (3 H, *t*, ^3J = 7.2, Me); 2.62 (2 H, *q*, ^3J = 7.5, OCH_2); 4.33 (2 H, *q*, ^3J = 7.2, OCH_2), 7.52 (1 H, *s*, CH). ^{13}C NMR: δ 8.9 (Me); 14.0 (Me); 33.6 (CH_2), 62.3 (OCH_2); 117.5 (CH); 138.9 (C); 156.0 (C=O); 176.3 (C=S); 185.9 (C=O). EI-MS: 229 (M$^+$, 10); 224 (56); 172 (56); 57 (100), 45 (42). Anal. Calcd for

$C_9H_{11}NO_4S$ (229.25): C, 47.15; H, 4.84 N, 6.11%. Found: C, 47.27; H, 4.78; N, 5.99%.

Conclusion

In conclusion, the reaction between ethyl 3-chloro-2-iminopropanoate, ammonium thiocyanate, and isothiocyanate in the presence of triethylamine (20 mol%) led to functionalized imidazoline-2-thion 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.

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