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Synthesis of oxazole derivatives using *N*-formylmorpholine as green solvent

Narges Ghasemi*

National Petrochemical Company (NPC), petrochemical Research and Technology Company, Arak Center, Iran

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Abstract: An efficient synthesis of oxazoles, under solvent-free conditions, is described *via* reaction between ammonium thiocyanate, acid chlorides, and ethyl bromopyruvate or ethyl 2-chloroacetoacetate in the presence of *N*-formylmorpholine.

Keywords: Oxazole, Ethyl bromopyruvate, NFM, Isothiocyanate.

Introduction

1,3-Oxazoles 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 oxazoles [1, 2]. Syntheses of oxazoles were reported using either condensation of thiocyanic acid [3-6] or isothiocyanates [7] with an *α*-hydroxycarbonyl, or condensation of thiophosgen with an aminoketone [8]. The possible balance of reactivity of *α*-hydroxycarbonyl systems with thiocyanic acid toward the formation of either oxazolesor 1,3-oxazoline-2-thione have been recently reported [9, 10].

Result and disscussion

As part of our current studies on the development of new routes in heterocyclic synthesis, we report an efficient synthetic route to functionalized oxazoles. Thus, the reaction of isothiocyanate **1**, ethyl bromopyruvate **2** in the presence of *N*-formylmorpholine (5 mL) under solvent-free conditions, produced oxazoles **3** in good yields (Scheme **1**).

Structures of compounds **3a**–**3g** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

The ^{1}H NMR spectra of **3a**–**3g** exhibited characteristic signals for methine (δ = 7.52-7.64 ppm) protons. The ^{13}C NMR spectra of the 1,3-Oxazoline-2-thione ring system of **3a** 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 **3a**–**3g** 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 NFM, 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**.

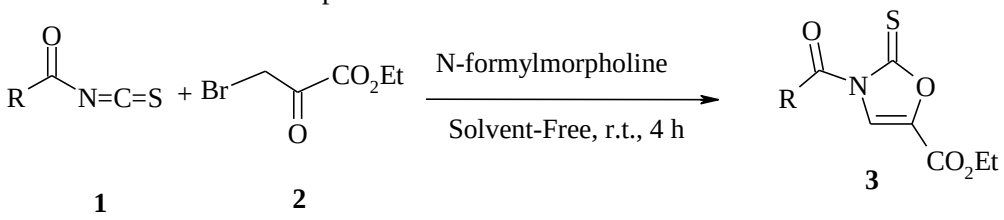
Experimental Section

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

*Corresponding author. Tel.: +98 9188616658; E-mail: naghasemi.16@gmail.com.

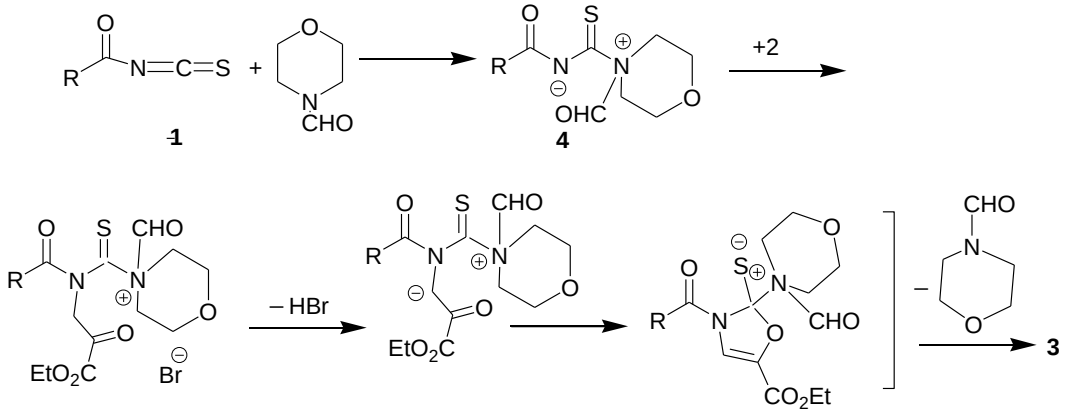
the calculated values. All chemicals were obtained from Fluka and were used without further purification.



1 **2** **3**

3	R	Yield/ % of **3**
a	Ph	85
b	p-Me-C_6H_4	95
c	P-Br-C_6H_4	75
d	p-Cl-C_6H_4	70
e	p-NO_2-C_6H_4	85
f	*t*-Bu	83
g	Et	86

Scheme 1: Synthesis of oxazol derivatives



1 **4** **5** **6** **7** **3**

Scheme 2: Proposed mechanism

General Procedure for the Preparation of Compounds 3:

A stirred mixture of isothiocyanate (2 mmol) and NFM (5 mL) as solvent for 1 h. Then, ethyl bromopyruvate (0.39 g, 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 **3a:** 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 **3b:** 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 **3c:** 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 **3d:** 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 **3e:** 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 **3f:** 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 3**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 bromopyruvate or ethyl 2-chloroacetoacetate, ammonium thiocyanate, and acid chlorides in the presence of *N-formylmorpholine* (20 mol%) led to functionalized 2-thioxo-2,3-dihydro-1,3-oxazoles 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.

Acknowledgments

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