Iranian Journal of Organic Chemistry Vol. 16, No. 1 (2024) 3737-3740

One pot multicomponent reaction of epoxides: Synthesis of thioxazole derivatives

Seyye Jalal Shams Najafi[a]* and Maryam Ghazvini[b]

[a]*Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad 91779-1436, I.R. Iran*
[b]*Chemistry Department, Payam Noor University, Tehran, Iran*

Received: November 2023; Revised: November 2023; Accepted: January 2024

Abstract:
An efficient synthesis of thioxazoles, under solvent-free conditions, is described *via* reaction between ammonium thiocyanate, acid chlorides, and alkyl bromids in the presence of Et_3N.

Keywords: Thioxazole, Ethyl bromopyruvate, Isothiocyanate, Acid Chloride, Epoxides.

Introduction

Thioxazoles represent a simple heterocyclic frame which has been scarcely explored compared to the non-aromatic counterpart thioxazoles structure. 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 1,3-oxazoline-2-thione have been recently reported [9, 10].

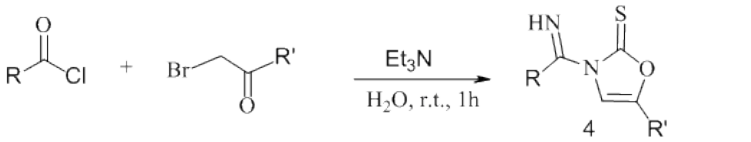
Result and disscussion

As part of our current studies on the development of new routes in heterocyclic synthesis, we report an efficient synthetic route to functionalized thioxazoles.

Thus, the reaction of acid chlorides **1**, ammonium acetate **3** and alkyl bromides **2** in the presence of Et_3N under solvent-free conditions, produced thioxazoles **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}HNMR spectra of **4a**–**g** 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 **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**–**g** displayed the molecular ion peaks at appropriate *m*/*z* values.

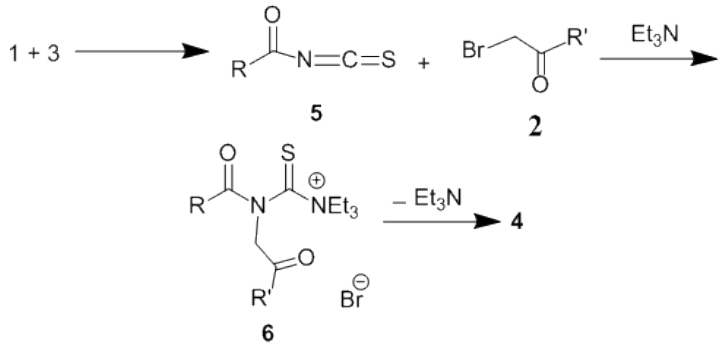
A tentative mechanism for this transformation is proposed in Scheme **2**. The reaction starts with reaction of acid chlorides **1** with ammonium acetate **3** in the presence of Et_3N to produced intermediate **5** that react with alkyl bromides **2** and by elimination of Et_3N produced thioxazoles, **4** in good yields.

*Corresponding author; E-mail: s.jalalshamsnajafi@yahoo.com.



4	R	R'	Yield/ % of 4
a	Ph	CO_2Et	90
b	p-Me-C_6H_4	p-Me-C_6H_4	97
c	P-Br-C_6H_4	P-Br-C_6H_4	78
d	p-Cl-C_6H_4	p-Cl-C_6H_4	75
e	p-NO_2-C_6H_4	p-NO_2-C_6H_4	87
f	*t*-Bu	CO_2Et	85
g	Et	CO_2Et	87

Scheme 1: Synthesis of thioxazol derivatives



Scheme 2: Proposed mechanism for the formation of thioxazole

Conclusion

In conclusion, the reaction between acid chlorides, ammonium acetate and alkyl bromides in the presence of Et_3N led to functionalized thioxazoles 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 Section

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^1H, 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 thioxazole 4:

To a stirred mixture of acid chlorides **1** (2 mmol) with ammonium acetate **3** (2 mmol) and Et_3N (5 mL) was added alkylbromides **2** (2 mmol) after 1 h. Then, The reaction mixture was stirred for 3 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}. ^1H 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 4g:

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%.

Acknowledgments

We gratefully acknowledge for supporting from the Ferdowsi University of Mashhad.

References

[1] Willems, J. F.; Vandenberghe, A. *Bull. Soc. Chim. Belg.* **1961**, *70*, 745.
[2] Lacasse, G.; Muchowki, J. M. *Can. J. Chem.* **1972**, *50*, 3082.
[3] Bradscher, C. K.; Jones, W. J. *J. Org. Chem*. **1967**, *32*, 2079.
[4] Guimon, C.; Pfister-Guillouzo, G.; Arbelot, M.; Chanon, M. *Tetrahedron* **1974**, *30*, 3831.
[5] Kapsomenos, G. S.; Akrivos, P. D. D. Can. J. Chem. **1988**, *66*, 2835.
[6] Shafer, C. M.; Molinski, T. F. *J. Org. Chem*. **1998**, *63*, 551.
[7] Gonzalez-Romero, C.; Martinez-Palou, R.; Jimenez-Vazquez, H. A.; Fuentes, A.; Jimenez, F.; Tamariz, J. *Heterocycles*, **2007**, *71*, 305.
[8] Bobosik, V.; Piklerova, A.; Maretvon, A. *Coll. Czech. Chem. Commun.* **1983**, *48*, 3421.

[9] Tatibouët, A.; Lawrence, S.; Rollin, P.; Holman, G. D. *Synlett*, **2004**, 1945.
[10] Leconte, N.; Silva, S.; Tatibouët, A.; Rauter, A. P.; Rollin, P. *Synlett*, **2006**, 301.