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Synthesis of Thiazole Derivatives *via* Multicomponent Reaction of Tetramethyl thiourea using Water as a Safe Solvent

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Abstract

An efficient synthesis of 1,3-thiazole drivatives is described via a three component reaction isothiocyanates, tetramethyl thiourea and ethyl bromopyruvate.

Key words: *1,3-Thiazole, Benzoyl isothiocyanate, Ethyl bromopyruvate, Tetramethyl thiourea, Ammonium thiocyanate, Acid chloride.*

Introduction

Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [1-3]. They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions frequently involving comfortable, toxic, and hazardous solvents after each step [4-7]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [8]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9].

Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [10]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [11]. Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active center in the coenzyme derived from vitamin B1 (thiamin). A large number of thiazoles obtained from microbial and marine

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origins exhibit important biological effects such as antitumor, antifungal, antibiotic, and antiviral activities [12]. Synthetic thiazoles have also been shown to exhibit a wide variety of biological activity [13], while others have found application as liquid crystals [14] and cosmetic sunscreens [15].

The classical method for the synthesis of thiazoles is the Hantzsch process, in which a γ-haloketone is condensed with a thioamide [16]. This method gives excellent yields for simple thiazoles. This method gives excellent yields for simple thiazoles; however, for some substituted examples low yields have been reported as a result of dehalogenation of the haloketone during the reaction [15, 17]. As part of our current studies on the development of new routes in heterocyclic synthesis [18-21], we report an efficient synthetic route to functionalized thiazoles.

Experimental

All compounds in these reactions were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H- and ^{13}C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; σ 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 preparation of compounds **4**

To a stirred solution of 0.15 g of ammonium thiocyanate (2 mmol) in 15 mL of acetone was added acid chloride (2 mmol), and the mixture was refluxed for 5 min. Then, a solution of 0.39 g of **3** (2 mmol) in acetone (10 mL) was added gently. Finally, 0.26 g of **4** (2 mmol) was added slowly at room temperature. The reaction mixture was then stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/AcOEt 10:1) to afford the pure title compounds.

*Ethyl 5-{[benzoyl(methylamino)]carbothioyl}-2-(dimethylamino)-1,3-thiazole-4-carboxylates (***5a***)*

Yield: 0.68 g (90%), Orange powder, mp 122-124°, IR (KBr): 17210; 1653; 1510; 1372; 1124. ^{1}H-NMR: 1.32 (t, ^{3}J = 7.2, Me); 3.27 (s, Me); 3.32 (s, Me); 3.46 (s, Me); 4.23 (q, ^{3}J = 7.2, OCH_2); 7.43 (t, ^{3}J = 7.2, 2 CH); 7.53 (t, ^{3}J = 7.5, CH); 7.80 (d, ^{3}J = 7.5, 2 CH). ^{13}C-NMR: 14.1 (Me); 36.4 (Me); 36.9 (Me); 38.7 (Me); 62.2 (OCH_2); 128.4 (2 CH); 128.6 (2 CH); 129.5 (C); 130.1 (CH); 133.5 (C); 153.9 (C); 158.2 (C); 167.1 (C=O); 177.4 (C=O); 208.2 (C=S). EI-MS: 377 (M^{+}•, 15), 272 (60), 243 (62), 223 (45), 134 (54), 105 (100), 45 (64). Anal. calc. for $C_{17}H_{19}N_3O_3S_2$ (377.74): C 54.09, H 5.07, N 11.13; found: C 54.10, H 5.05, N 11.10.

*Ethyl 5-{[4-methylbenzoyl(methylamino)] carbothioyl}-2-(dimethylamino)-1,3-thiazole-4-carboxylates (***5b***)*

Yield: 0.66 g (85%). Yellow powder, mp 130-132°, IR (KBr): 1720; 1655; 1512; 1369; 1022. ^{1}H-NMR: 1.41 (t, *J* = 7.2, Me); 2.42 (s, Me); 3.13 (s, Me); 3.26 (s, Me); 3.53 (s, Me); 4.42 (q, *J* = 7.2, OCH_2); 7.30 (d, *J* = 7.8, 2 CH); 7.52 (d, *J* = 7.8, 2 CH). ^{13}C-NMR: 13.9 (Me); 22.9 (Me); 36.4 (Me); 38.8 (Me); 43.1 (Me); 62.2 (OCH_2); 129.1 (2 CH); 129.5 (C); 130.1 (2 CH); 130.8 (C); 144.3 (C); 153.9 (C); 160.2 (C); 167.7 (C=O); 177.4 (C=O; 208.7 (C=S). EI-MS: 391 (M^+•, 5), 272 (36), 243 (85), 192 (58), 148 (76), 119 (100), 45 (48). Anal. calc. for $C_{18}H_{21}N_3O_3S_2$ (391.50): C 55.22, H 5.41, N 10.73; found: C 55.20, H 5.40, N 10.70.

*Ethyl 5-{[4-nitrobenzoyl(methylamino)] carbothioyl} -2-(dimethylamino)-1,3-thiazole-4-carboxylates (***5c***)*

Yield: 0.70 g (83%). Red powder, mp 155-157°. IR (KBr): 1715; 1679; 1599; 1369; 1176; 1116. ^{1}H-NMR: 1.39 (t, *J* = 7.2, Me); 3.13 (s, Me); 3.28 (s, Me); 3.51 (s, Me); 4.43 (q, *J* = 7.2, OCH_2); 8.03 (d, *J* = 8.1, 2 CH); 8.32 (d, *J* = 8.1, 2 CH). ^{13}C-NMR: 14.0 (Me); 35.9 (Me); 37.0 (Me); 38.8 (Me); 62.2 (OCH_2); 123.6 (C); 123.8 (2 CH); 129.3 (2 CH); 131.1 (C); 137.9 (C); 150.3 (C); 153.9 (C); 167.4 (C=O); 177.4 (C=O); 208.3 (C=S). EI-MS: 422 (M^+•, 10), 272 (66), 223 (45), 199 (62), 179 (64), 150 (100);, 45 (84). Anal. calc. for $C_{17}H_{18}N_4O_5S_2$ (422.47): C 48.33, H 4.29, N 13.26; found: C 48.30, H 4.30, N 13.25.

*Ethyl 5-{[4-bromobenzoyl(methylamino)] carbothioyl}-2-(dimethylamino)-1,3-thiazole-4-carboxylates (***5d***)*

Yield: 0.71 g (78%). Red powder, mp 152-154°. IR (KBr): 1762; 1724; 1664; 1579; 1369; 1101. ^{1}H-NMR: 1.42 (t, *J* = 7.2, Me); 3.05 (s, Me); 3.14 (s, Me); 3.47 (s, Me); 4.38 (q, *J* = 7.2, OCH_2); 7.59 (d, *J* = 7.8, 2 CH); 7.69 (d, *J* = 7.8, 2 CH). ^{13}C-NMR: 14.0 (Me); 36.4 (Me); 36.9 (Me); 38.8 (Me); 62.2 (OCH_2); 127.9 (C); 128.9 (2 CH); 129.1 (C); 129.4 (2 CH); 132.9 (C); 150.3 (C); 153.9 (C); 167.7 (C=O); 177.4 (C=O); 208.2 (C=S). EI-MS: 456 (M^+•, 10), 454 (5), 272 (44), 257 (36), 243 (60), 213 (65), 184 (100), 45 (84). Anal. calc. for $C_{17}H_{18}BrN_3O_3S_2$ (456.37): C 44.74, H 3.98, N 9.21; found: C 44.70, H 3.95, N 9.20.

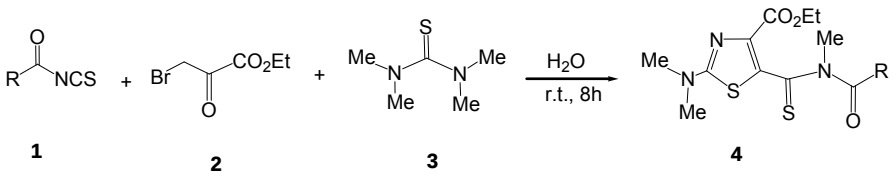
*Ethyl 5-{[4-chlorobenzoyl(methylamino)] carbothioyl}-2-(dimethylamino)-1,3-thiazole-4-carboxylates (***5e***)*

Yield: 0.67 g (82%). Yellow powder, mp 165-167°. IR (KBr): 1759; 1721; 1665; 1584; 1354; 1027. ^{1}H-NMR: 1.42 (t, *J* = 7.2, Me); 3.05 (s, Me); 3.14 (s, Me); 3.47 (s, Me); 4.38 (q, *J* = 7.2, OCH_2); 7.59 (d, *J* = 7.5, 2 CH); 7.69 (d, J = 7.5, 2 CH). ^{13}C-NMR: 14.3 (Me); 35.7 (Me); 37.0 (Me); 38.8 (Me); 62.4 (OCH_2); 128.4 (2 CH); 129.2 (C); 130.1 (2 CH); 132.5 (C); 136.4 (C); 150.4 (C); 154.0

(C); 168.2 (C=O); 177.5 (C=O); 208.4 (C=S). EI-MS: 411 (M^{+}•, 15), 243 (34), 212 (80), 199 (46), 168 (86), 139 (100), 45 (36). Anal. calc. for $C_{17}H_{18}ClN_3O_3S_2$ (411.92): C 49.57, H 4.40, N 10.20; found: C 49.55, H 4.40, N 10.21.

Results and discussion

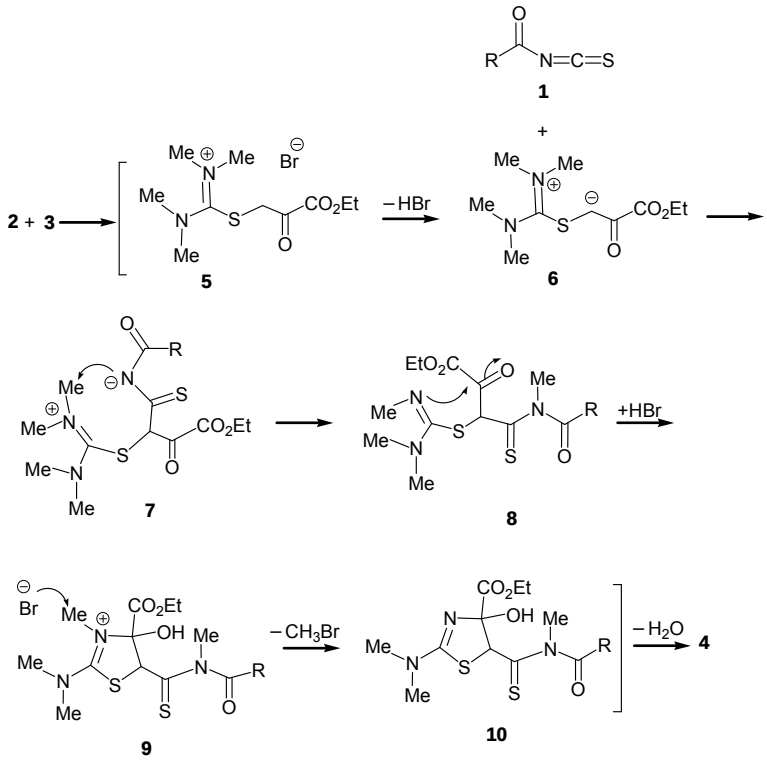
The reaction of isothiocyanate **1**, ethyl bromopyruvate **2** and tetramethyl thiourea **3** produced 1,3-thiazole derivatives **4** in 78-90% yields (Scheme 1).



1, 4	R	Yield/ % of 4
a	Ph	90
b	*p*-Me-C_6H_4	85
c	*p*-NO_2-C_6H_4	83
d	*p*-Br-C_6H_4	78
e	*p*-Cl-C_6H_4	82

Scheme 1. Synthesis of thiazole derivatives **4a-e.**

The structures of compounds **4a–4e** were apparent from their mass spectra, which displayed in each case, the molecular ion peak at the appropriate *m/z* values. The ^{1}H and ^{13}C-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. For example, the ^{1}H-NMR spectrum of **5a** exhibited one triplet at 1.32 (J = 7.2) from methyl proton, three singlet for NMe groups at 3.27, 3.32 and 3.46 and one quartet at 4.23 (J = 7.2) for OCH_2 moiety. The carbonyl and thionyl groups resonances in the ^{13}C-NMR spectra of **5a** appear at 167.1 (C=O), 177.4 (C=O) and 208.2 (C=S) ppm. The mass spectrum of **5a** displayed the molecular ion peak at *m/z* = 377. Mechanistically, it is conceivable that the reaction involves the initial formation of intermediate **5** between **2** and **3**, which elimination of HBr of **5** generate **6**. This intermediate undergoes a nucleophilic attack to **1** to produce **7**. Finally, water elimination from **10** produces 4 (Scheme 2).



Scheme 2. Proposed mechanism for the formation of **4**.

In this procedure, separation and purification of product is simple. The reaction mixture isn't busy and separation of compounds is easy.

Conclusion

In conclusion, we have described a convenient route to functionalized 1,3-thiazoles from isothiocyanate, tetramethyl thiourea and ethyl bromopyruvate. The advantage of the present procedure is that the reaction is performed in water and the starting material can be used without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here provides an acceptable one-pot method for the preparation of functionalized thiazols.

References

[1] A. Do¨mling, *Comb. Chem. High Throughput Screening*, 1, 1 (1998).

[2] A. Do¨mling, I. Ugi, *Angew. Chem., Int. Ed*., 39, 3169 (2000).

[3] L. Weber, *Drug Discovery Today*, 7, 143 (2002).

[4] J. Zhu, H. Bienayme, Eds.; Wiley-VCH: Weinheim, Germany (2005).

[5] P. Wipf, C. Kendall, *Chem. Eur. J.,* 8, 1779 (2002).

[6] G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org.Chem*., 4, 101 (2003).

[7] A. Jacobi von Wangelin, H. Neumann, D. Gordes, S. Klaus, D. Strubing, M. Beller, *Chem. Eur. J.,* 9, 4286 (2003).

[8] (a) A. Domling, I. Ugi, *Angew. Chem*., Int.

Ed., 39, 3168 (2000); (b) I. Ugi, A. Domling, Endeavour 18, 115 (1994); (c) S. Heck, A. Domling, *Synlett*., 4, 24 (2000).

[9] L. Weber, *Curr. Med. Chem*., 9, 2085 (2002).

[10] G. W. V. Cave, C. L. Raston, J. L. Scott, *Chem. Commun*., 21, 59 (2001).

[11] R. A. Sheldon, *Chem. Ind*., 12 (1997).

[12] J. R. Lewis, *Nat. Prod. Rep*., 13, 435 (1996).

[13] J. V. Metzger, *Thiazole and its Derivatives*; John Wiley & Sons: New York, (1979).

[14] A. A. Kiryanov, P. Sampson, A. J. Seed, *J. Org. Chem.,* 66, 7925 (2001).

[15] T. Bach, S. Heuser, *Tetrahedron Lett*., 41, 1707 (2000).

[16] R. H. Wiley, D. C. England, L. C. Behr, In *Organic Reactions; John Wiley*: 6, 367 (1951).

[17] J. S. Carter, D. J. Rogier, M. J. Graneto, K. Seibert, C. M. Koboldt, Y. Zhang, J. J. Talley, *Biorg. Med. Chem. Lett*., 9, 1167 (1999).

[18] I. Yavari, H. Djahaniani, *Tetrahedron Lett*., 47, 2953 (2006).

[19] I. Yavari, L. Moradi, *Tetrahedron Lett*., 47, 1627 (2006).

[20] I. Yavari, L. Moradi, Helv. *Chim. Acta,* 89, 1942 (2006).

[21] I. Yavari, M. Sabbaghan, Z. Hossaini, *Synlett*., 15, 2501 (2006).