Efficient Synthesis of Functionalized Thiazoles from Acid Chlorides, Tetramethylthiourea, Ethyl Bromopyruvate, and Ammonium Thiocyanate

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An efficient synthesis of ethyl 2-(dimethylamino)-1,3-thiazole-4-carboxylates is described *via* a four-component reaction between acid chlorides, tetramethylthiourea, ethyl bromopyruvate, and ammonium thiocyanate.

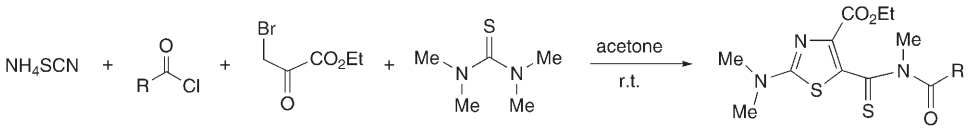
Introduction. – Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active center in the coenzyme derived from vitamin B_1 (thiamin). A large number of thiazoles obtained from microbial and marine origins exhibit important biological effects such as antitumor, antifungal, antibiotic, and antiviral activities [1]. Synthetic thiazoles also show a wide variety of biological activity [2], while others have found application as liquid crystals [3] and cosmetic sunscreens [4]. The classical method for the synthesis of thiazoles is the *Hantzsch* process, in which an α-haloketone is condensed with a thioamide [5]. 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 α-haloketone during the reaction [4][6]. As part of our current studies on the development of new routes in heterocycle synthesis [7–10], we report an efficient synthetic route to functionalized thiazoles.

Results and Discussion. – The reaction of ammonium thiocyanate (**1**), acid chlorides **2**, ethyl bromopyruvate (**3**), and tetramethylthiourea (**4**) gave ethyl 2-(dimethylamino)-5-(methylcarbamothioyl)-1,3-thiazole-4-carboxylates **5** in 78–90% yields (*Scheme 1*).

The structures of compounds **5a**–**5g** were apparent from their MS spectra, which in each case displayed the molecular-ion peak at the appropriate *m*/*z* values. The IR, ^{1}H- and ^{13}C-NMR spectra are in agreement with the proposed structures. For example, the ^{1}H-NMR spectrum of **5a** exhibited a *triplet* at 1.32 ($J = 7.2$) and a *quartet* at 4.23 ($J = 7.2$) for the ethoxycarbonyl group, and three *singlet*s for MeN groups at 3.27, 3.32, and 3.46 ppm. The C=O and C=S group resonances in the ^{13}C-NMR spectrum of **5a** appeared 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 **6** from **3** and **4**. The elimination of HBr generates **7**, which undergoes a nucleophilic attack at **8** to give **9**. Finally, H_2O elimination of **10** produces **5** (*Scheme 2*).

Scheme 1

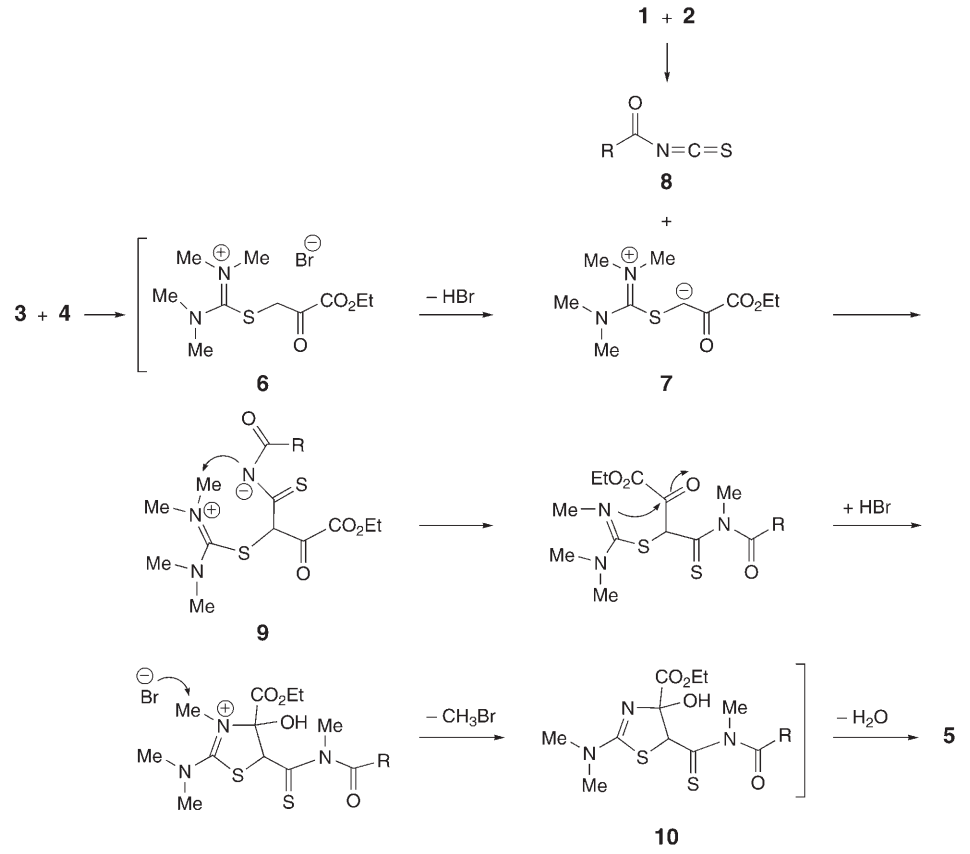


1 **2a** R = Ph; **2b** R = 4-Me-C_6H_4; **2c** R = 4-NO_2-C_6H_4; **2d** R = 4-Br-C_6H_4; **2e** R = 4-Cl-C_6H_4; **2f** R = *t*-Bu; **2g** R = Et

3 **4**

5a R = Ph 90%; **5b** R = 4-Me-C_6H_4 85%; **5c** R = 4-NO_2-C_6H_4 83%; **5d** R = 4-Br-C_6H_4 78%; **5e** R = 4-Cl-C_6H_4 82%; **5f** R = *t*-Bu 83%; **5g** R = Et 85%

Scheme 2



In conclusion, we have described a convenient route to functionalized 1,3-thiazoles from ammonium thiocyanate, acid chlorides, tetramethyl thiourea, and ethyl bromopyruvate. The advantage of the present procedure is that the reaction is performed

under neutral conditions, and the starting materials 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.

Experimental Part

General. All starting materials were obtained from *Fluka* and were used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker DRX-500 Avance* instrument, in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. EI-MS (70 eV): *Finnigan MAT-8430* MS spectrometer; in m/z. Elemental analyses (C, H, N): *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **5**. To a stirred soln. of 0.15 g of NH_4SCN (2 mmol) in 15 ml of acetone was added acid chloride (2 mmol), and the mixture was refluxed for 5 min. Then, a soln. 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 r.t. The 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-[(Benzoylmethylamino)thioxomethyl]-2-(dimethylamino)-1,3-thiazole-4-carboxylate (**5a**). Yield: 0.68 g (90%). Orange powder. M.p. 122–124°. IR (KBr): 1721, 1653, 1510, 1372, 1124. ^{1}H-NMR: 1.32 (t, ^3J = 7.2, Me); 3.27 (s, MeN); 3.32 (s, MeN); 3.46 (s, MeN); 4.23 (q, ^3J = 7.2, CH_2O); 7.43 (t, ^3J = 7.2, 2 arom. H); 7.53 (t, ^3J = 7.5, arom. H); 7.80 (d, ^3J = 7.5, 2 arom. H). ^{13}C-NMR: 14.1 (MeN); 36.4 (MeN); 36.9 (MeN); 38.7 (MeN); 62.2 (CH_2O); 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 (15, $M^{+\cdot}$), 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 2-(Dimethylamino)-5-{[methyl(4-methylbenzoyl)amino]thioxomethyl}-1,3-thiazole-4-carboxylate (**5b**). Yield: 0.66 g (85%). Yellow powder. M.p. 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, MeN); 3.26 (s, MeN); 3.53 (s, MeN); 4.42 (q, J = 7.2, CH_2O); 7.30 (d, J = 7.8, 2 arom. H); 7.52 (d, J = 7.8, 2 arom. H). ^{13}C-NMR: 13.9 (Me); 22.9 (Me); 36.4 (MeN); 38.8 (MeN); 43.1 (MeN); 62.2 (CH_2O); 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 (5, $M^{+\cdot}$), 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 2-(Dimethylamino)-5-{[methyl(4-nitrobenzoyl)amino]thioxomethyl}-1,3-thiazole-4-carboxylate (**5c**). Yield: 0.70 g (83%). Red powder. M.p. 155–157°. IR (KBr): 1715, 1679, 1599, 1369, 1176, 1116. ^{1}H-NMR: 1.39 (t, J = 7.2, Me); 3.13 (s, MeN); 3.28 (s, MeN); 3.51 (s, MeN); 4.43 (q, J = 7.2, CH_2O); 8.03 (d, J = 8.1, 2 arom. H); 8.32 (d, J = 8.1, 2 arom. H). ^{13}C-NMR: 14.0 (Me); 35.9 (MeN); 37.0 (MeN); 38.8 (MeN); 62.2 (CH_2O); 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 (10, $M^{+\cdot}$), 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]thioxomethyl}-2-(dimethylamino)-1,3-thiazole-4-carboxylate (**5d**). Yield: 0.71 g (78%). Red powder. M.p. 152–154°. IR (KBr): 1762, 1724, 1664, 1579, 1369, 1101. ^{1}H-NMR: 1.42 (t, J = 7.2, Me); 3.05 (s, MeN); 3.14 (s, MeN); 3.47 (s, MeN); 4.38 (q, J = 7.2, CH_2O); 7.59 (d, J = 7.8, 2 arom. H); 7.69 (d, J = 7.8, 2 arom. H). ^{13}C-NMR: 14.0 (Me); 36.4 (MeN); 36.9 (MeN); 38.8 (MeN); 62.2 (CH_2O); 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 (10, $M^{+\cdot}$), 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]thioxomethyl}-2-(dimethylamino)-1,3-thiazole-4-carboxylate (**5e**). Yield: 0.67 g (82%). Yellow powder. M.p. 165–167°. IR (KBr): 1759, 1721, 1665, 1584, 1354,

1027. ^{1}H-NMR: 1.42 (*t*, *J* = 7.2, Me); 3.05 (*s*, MeN); 3.14 (*s*, MeN); 3.47 (*s*, MeN); 4.38 (*q*, *J* = 7.2, CH_2O); 7.59 (*d*, *J* = 7.5, 2 arom. H); 7.69 (*d*, *J* = 7.5, 2 arom. H). ^{13}C-NMR: 14.3 (MeN); 35.7 (MeN); 37.0 (MeN); 38.8 (MeN); 62.4 (CH_2O); 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 (15, $M^{+\cdot}$), 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.

Ethyl 2-(Dimethylamino)-5-{[(2,2-dimethyl-1-oxopropyl)methylamino]thioxomethyl}-1,3-thiazole-4-carboxylate (**5f**). Yield: 0.59 g (83%). Red powder. M.p. 134–136°. IR (KBr): 1745, 1719, 1660, 1574, 1299, 1010. ^{1}H-NMR: 1.27 (*t*, *J* = 7.4, Me); 1.41 (*s*, 3 Me); 2.98 (*s*, MeN); 3.07 (*s*, MeN); 3.54 (*s*, MeN); 4.39 (*q*, *J* = 7.4, CH_2O). ^{13}C-NMR: 13.9 (Me); 27.0 (3 Me); 36.4 (Me); 38.7 (Me); 39.0 (Me); 39.7 (C); 62.2 (CH_2O); 128.7 (C); 135.4 (C); 153.9 (C); 167.1 (C=O); 177.4 (C=O); 208.4 (C=S). EI-MS: 357 (5, $M^{+\cdot}$), 313 (58), 300 (34), 283 (46), 57 (100), 44 (36). Anal. calc. for $C_{15}H_{23}N_3O_3S_2$ (357.48): C 50.40, H 6.48, N 11.75; found: C 49.95, H 6.40, N 11.68.

Ethyl 2-(Dimethylamino)-5-{[methyl(1-oxopropyl)amino]thioxomethyl}-1,3-thiazole-4-carboxylate (**5g**). Yield: 0.58 g (85%). Red powder. M.p. 138–140°. IR (KBr): 1758, 1715, 1659, 1581, 1255, 1009. ^{1}H-NMR: 1.12 (*t*, *J* = 7.6, Me); 1.43 (*t*, *J* = 7.2, Me); 2.61 (*q*, *J* = 7.6, CH_2N); 3.08 (*s*, MeN); 3.12 (*s*, MeN); 3.52 (*s*, MeN); 4.42 (*q*, ^3J = 7.2, CH_2O). ^{13}C-NMR: 13.9 (Me); 14.0 (Me); 32.4 (CH_2N); 35.8 (MeN); 36.4 (MeN); 37.0 (MeN); 62.2 (CH_2O); 132.4 (C); 153.9 (C); 160.3 (C); 167.2 (C=O); 177.4 (C=O); 208.2 (C=S). EI-MS: 343 (10, $M^{+\cdot}$), 299 (68), 272 (58), 57 (100), 44 (86). Anal. calc. for $C_{13}H_{19}N_3O_3S_2$ (329.43): C 47.40, H 5.81, N 12.76; found: C 47.32, H 5.75, N 12.70.

REFERENCES

[1] J. R. Lewis, *Nat. Prod. Rep.* **1996**, *13*, 435.
[2] J. V. Metzger, 'Thiazole and its Derivatives', John Wiley & Sons, New York, 1979.
[3] A. A. Kiryanov, P. Sampson, A. J. Seed, *J. Org. Chem.* **2001**, *66*, 7925.
[4] T. Bach, S. Heuser, *Tetrahedron Lett.* **2000**, *41*, 1707.
[5] R. H. Wiley, D. C. England, L. C. Behr, in 'Organic Reactions', John Wiley, 1951, Vol. 6, p. 367.
[6] J. S. Carter, D. J. Rogier, M. J. Graneto, K. Seibert, C. M. Koboldt, Y. Zhang, J. J. Talley, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1167.
[7] I. Yavari, H. Djahaniani, *Tetrahedron Lett.* **2006**, *47*, 2953.
[8] I. Yavari, L. Moradi, *Tetrahedron Lett.* **2006**, *47*, 1627.
[9] I. Yavari, L. Moradi, *Helv. Chim. Acta* **2006**, *89*, 1942.
[10] I. Yavari, M. Sabbaghan, Z. Hossaini, *Synlett* **2006**, 2501.

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