Iranian Journal of Organic Chemistry Vol. 4, No. 3 (2012) 881-884

Solvent-free synthesis of thiazol derivatives via multi-component reaction of alkylbromide

Faramarz Rostami-Charati[a*] and Asadollah Hassankhani[b]

[a]*Department of chemistry, Facualty of Science, Gonbad Kavous University, P.O.Box 163,Gonbad, Iran*
[b]*Department of Materials Science, International Center for Science, High Technology & Environmental Sciences, PO Box 76315-117, Kerman, Iran*

Received: May 2012; Revised: June 2012; Accepted: July 2012

Abstract: The zwitterion formed from an aroyl or alkanoyl isothiocyanate and secondary amines reacts with alkyl bromids to form thiazol derivatives in relatively good yields under solvent-free conditions at room temperature without using a catalyst.

Keywords: Thiazole, Solvent-free conditions, Aroyl isothiocyanate, Secondary amine.

Introduction

Multicomponent reactions (MCRs), with three or more reactants combine in a one-pot procedure to give a single product, have become increasingly popular during the last decade [1-7]. They are economically and environmentally advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus are finding increased use in the discovery process for new drugs and agrochemicals [8]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9].

Thiazoles play a prominent role in Nature [10]. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [11, 12], anti-tumour [13] anti-hyperlipidemic [14], anti-hypertensive [15], anti-HIV infections [16], and several other biological properties [17, 18].

*Corresponding author. Tel: (+98) 172 2221802, Fax: (+98) 172 2224060, E-mail: frostami@gau.ac.ir

As part of our research on the development of new synthetic methods in heterocyclic chemistry and our interest in alkyl bromide-based multicomponent reactions, herein we describe an efficient synthesis of thiazol derivatives **4** via the reaction of alkyl bromide **1** with isothiocyanate **2** and secondary amine **3** at room temperature without using any catalyst (Scheme **1**).

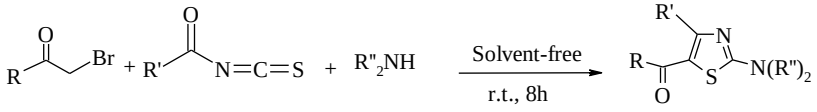
Results and discussion

The reaction of alkyl bromide **1** and isothiocyanate **2** in the presence of secondary amine **3** produced 2-(4-aryl-2-dialkylamino-1,3-thiazole-5-yl)-2-oxoacetates **4** in excellent yields.

Structures of compounds **4a-4h** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, ^{1}H NMR spectra of **4a** exhibited a singlet at δ = 2.34 ppm for the methyl protons, a singlet at δ = 3.16 ppm for NMe_2 protons along with characteristic signals for the aromatic moiety. The carbonyl group resonances in the ^{13}C NMR spectra of **4a** appear at 187.2 ppm. The mass spectra of **4a** displayed the molecular ion peaks at 246.

Mechanistically, the reaction starts with the reaction of alkanoyl or aroyl isothiocyanate 1 with secondary amine **3** to produce thiourea derivative **5**. Subsequent

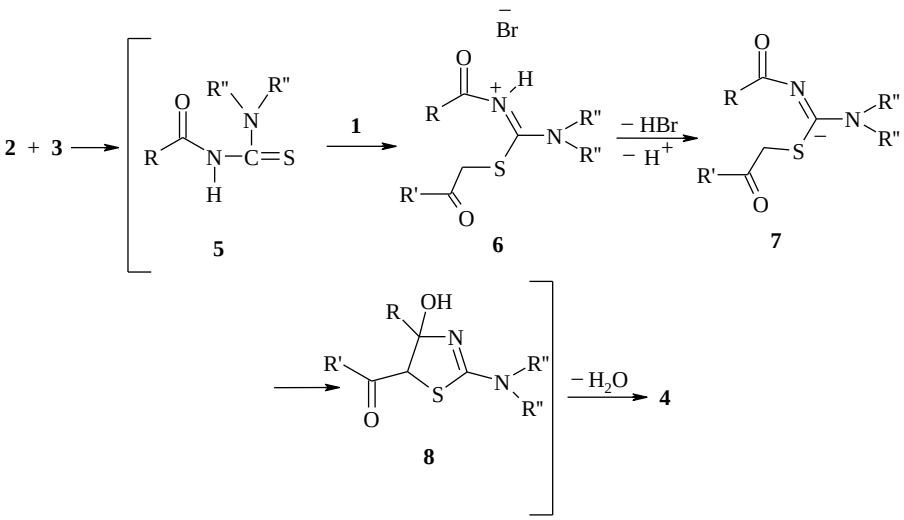
nucleophilic attacks of **5** on alkyl bromides **2** yields the 1:1 adduct **6**. Intermediate **7** undergoes HBr and hydrogen ion elimination, cyclization reaction, and loss of water to generate **4 (**Scheme **2)**.



1 **2** **3** **4**

4	R	R	R"	Yield (%) of **4**
a	Ph	CH_3	CH_3	87
b	*p*-Me-C_6H_4	$(CH_3)_3C$	$(CH_2)_5$	92
c	*p*-MeO-C_6H_4	Ph	$(CH_2)_2O(CH_2)_2$	90
d	CO_2Et	CH_3	$(CH_2)_4$	85
e	CO_2Et	*p*-NO_2-C_6H_4	CH_3	85
f	*p*-NO_2-C_6H_4	*p*-NO_2-C_6H_4	$(CH_2)_5$	90
g	CO_2Et	$(CH_3)_3C$	$(CH_2)_2O(CH_2)_2$	87
h	CO_2Et	C_2H_5	$(CH_2)_2O(CH_2)_2$	92

Scheme 1. Synthesis of thiazole derivatives



Scheme 2. Proposed mechanism for the one-pot synthesis of thiazole derivatives

Conclusion

In conclusion, we have described a convenient route to functionalized thiazols from aroyl or alkanoyl isothiocyanate and secondary amines, in the presence of alkyl bromides. The advantage of the present procedure is that the reaction is performed under solvent-free conditions by simple mixing of the starting materials. 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 thiazoles.

Experimental

Material and methods:

Alkyl bromides, acid chlorides, and secondary amines were obtained from *Fluka* and were used without further purification. Mp: Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. ^1H and ^{13}CNMR spectra: Bruker DRX-500 Avance instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; δ in parts per million, J in hertz. EIMS (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:

Mixture of the aroyl or alkanoyl isothiocyanate (2 mmol) and secondary amines was stirred for 20 min at room temperature without solvent. Then, an alkyl bromide (2 mmol) was added slowly at room temperature. The reaction mixture was then stirred for 8 h and was purified by column chromatography (SiO_2; *n*-hexane/AcOEt 8:1) to afford the pure compounds.

[2-(dimethylamino)-4-methyl-1,3-thiazole-5-yl]-phenyl methanone (4a):

Yellow crystals, yield: 0.43 g (87%), m.p. 110-112°C. IR (KBr) (ν_{max}/cm^{-1}): 1729, 1632, 1487, 1254 cm^{-1}. ^{1}H NMR: 2.34 (3 H, s, Me), 3.16 (6 H, s, NMe_2), 7.42 (2 H, t, ^3J = 7.2, 2 CH), 7.50 (1 H, t, ^3J = 7.2, CH), 7.73 (1 H, d, ^3J = 7.2, 2 CH). ^{13}C NMR: 21.2 (Me), 40.5 (NMe_2), 128.5 (2 CH), 128.7 (2 CH), 131.5 (C), 132.6 (CH), 133.4 (C), 139.4 (C), 163.4 (C), 187.2 (C=O). EI-MS: 246 (M^+, 15), 231 (25), 202 (85), 141 (68), 105 (100), 77 (46). Anal. Calcd. for $C_{13}H_{14}N_2OS$ (246.33): C 63.39, H 5.73, N 11.37, Found: C 63.32, H 5.67, N 11.30.

[2-piperidino-4-(tert)-butyl-1,3-thiazole-5-yl]-4-methyl methanone (4b):

Orange powder,Yield: 0.63 g (92%), m.p. 122-124 °C. IR (KBr) (ν_{max}/cm^{-1}): 1722, 1630, 1467, 1387 cm^{-1}. ^{1}H NMR: 1.38 (3 H, s, *Me*$_3$C), 1.67 (6 H, m, 3 CH_2), 2.45 (3 H, s, Me), 3.62 (4 H, m, 2 CH_2), 7.53 (2 H, d, ^3J = 7.8, 2 CH), 8.12 (2 H, d, ^3J = 7.8, 2 CH). ^{13}C NMR: 21.6 (Me), 22.2 (Me_3C), 23.8 (CH_2), 25.2 (2 CH_2), 31.4 (*Me*$_3$C), 49.6 (2 CH_2), 129.5 (2 CH), 131.4 (2 CH), 132.4 (C), 136.7 (C), 143.2 (C), 158.6 (C), 162.3 (C), 187.3 (C=O). Anal. Calcd. for $C_{20}H_{26}N_2OS$ (342.50): C 70.14, H 7.65, N 8.18, Found: C 70.22, H 7.74, N 8.25.

[2-morpholino-4-phenyl-1,3-thiazole-5-yl]-4-methoxy phenyl methanone (4c):

Yellow crystals, Yield: 0.68 g (90%), m.p. 127-129°C. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1620, 1548, 1437, 1267 cm^{-1}.^{1}H NMR: 3.60-3.65 (4 H, m, CH_2NCH_2), 3.75 (3 H, s, MeO), 3.82-3.87 (4 H, m, CH_2OCH_2), 7.34 (2 H, d, ^3J = 7.5, 2 CH), 7.42 (2 H, t, ^3J = 7.6, 2 CH), 7.53 (1 H, t, ^3J = 7.8, CH), 7.80 (2 H, d, ^3J = 7.8, 2 CH), 8.04 (2 H, d, ^3J = 7.5, 2 CH). ^{13}C NMR: 48.5 (CH_2NCH_2), 52.7 (MeO), 66.5 (CH_2OCH_2), 114.7 (2 CH), 128.2 (CH), 128.5 (C), 128.9 (2 CH), 129.1 (2 CH), 133.1 (C), 133.4 (2 CH), 137.4 (C), 139.2 (C), 142.4 (C), 157.6 (C), 188.4 (C=O). EI-MS: 346 (M^+, 20), 269 (86), 259 (78), 182 (52), 86 (58), 77 (100), 45 (38). Anal. Calcd. for $C_{21}H_{20}N_2O_3S$ (380.46): C 66.30, H 5.30, N 7.36, Found: C 66.37, H 5.36, N 7.42.

Ethyl 2-(2-pyrrolidino-4-methyl-1,3-thiazole-5-yl)-2-oxoacetate (4d):

Yellow crystals, Yield: 0.46 g (85%), m.p. 111-113°C. IR (KBr) (ν_{max}/cm^{-1}): 1720, 1615, 1428, 1374, 1215 cm^{-1}. ^{1}H NMR: 0.92 (3 H, t, ^3J = 7.3, Me), 2.12 (4 H, m, 2 CH_2), 2.25 (3 H, s, Me), 3.54 (4 H, m, CH_2NCH_2), 3.73 (2 H, q, ^3J = 7.2, OCH_2). ^{13}C NMR: 13.7 (Me), 17.4 (Me), 25.5 (2 CH_2), 48.8 (CH_2NCH_2), 62.7 (OCH_2), 126.5 (C), 138.7 (C), 148.7 (C), 163.2 (C=O), 185.4 (C=O). Anal. Calcd for $C_{12}H_{16}N_2O_3S$ (268.33): C 53.71, H 6.01, N 10.44, Found: C 53.64, H 5.97, N 10.36.

Ethyl 2-[2-(dimethylamino)-4-(4-nitrophenyl)-1,3-thiazole-5-yl]-2-oxoacetate (4e):

Yellow crystals, Yield: 0.59 g (85%), m.p. 132-134°C. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1631, 1567, 1425, 1378 cm^{-1}. ^{1}H NMR: 1.04 (3 H, t, ^3J = 7.2, Me), 3.20 (s, 6 H, NMe_2), 3.85 (2 H, q, ^3J = 7.2, OCH_2), 7.85 (d, 2 H, ^3J = 8.6, 2 CH), 8.25 (d, 2 H, ^3J = 8.6, 2 CH). ^{13}C NMR: 13.7 (Me), 40.5 (NMe_2), 62.0 (OCH_2), 123.6 (2 CH), 125.9 (C), 129.2 (2 CH), 144.3 (C), 149.6 (C), 149.7 (C), 162.8 (C), 172.4 (C=O), 185.5 (C=O). EI-MS: 349 (M^+, 15), 304 (48), 227 (64), 122 (100), 45 (86), 44 (56). Anal. Calcd. for $C_{15}H_{15}N_3O_5S$ (349.35): C 51.57, H 4.33, N 12.03, Found: C 51.81, H 4.26, N 12.10.

[2-piperidino-4-nitrophenyl-1,3-thiazole-5-yl]-4-nitrophenyl methanone (4f):

Yellow powder, Yield: 0.79 g (90%), m.p. 145-147°C. IR (KBr) (ν_{max}/cm^{-1}): 1726, 1682, 1459, 1110 cm^{-1}. ^{1}H NMR: 1.67-1.70 (6 H, m, 3 CH_2), 3.60-3.64 (4 H, m, CH_2NCH_2), 7.76 (2 H, d, ^3J = 7.8, 2 CH), 7.84 (2 H, d, ^3J = 7.6, 2 CH), 8.23 (2 H, d, ^3J = 7.8, 2 CH), 8.27 (2 H, d, ^3J = 7.6, 2 CH). ^{13}C NMR: 23.6 (CH_2), 25.3 (2 CH_2), 48.9 (CH_2NCH_2), 123.5 (2 CH), 124.0 (2 CH), 129.2 (2 CH), 130.4 (2 CH), 135.4 (C), 138.6 (C), 139.4 (C), 145.6 (C), 146.2 (C), 160.4 (C), 168.4 (C), 187.3 (C=O). Anal. Calcd. for $C_{21}H_{18}N_4O_5S$ (438.46): C 57.53, H 4.14, N 12.78, Found: C 57.48, H 4.08, N 12.70.

Ethyl 2-[2-morpholino-4-(tert-butyl)-1,3-thiazole-5-yl]-2-oxoacetate (4g):

Yellow powder, yield: 0.56 g (87%), m.p. 112-114°C. IR (KBr) (ν_{max}/cm^{-1}): 1730, 1719, 1699, 1640 cm^{-1}. ^{1}H NMR: 0.95 (t, 3 H, ^3J = 7.2, Me), 1.19 (s, 9 H, 3 Me), 3.42-3.47 (m, 4 H, CH_2NCH_2), 3.62-3.68 (m, 4 H, CH_2OCH_2), 3.85 (q, 2 H, ^3J = 7.2, OCH_2). ^{13}C NMR: 13.7 (Me), 26.7 (3 Me), 30.4 (C), 47.5

(CH_2NCH_2), 62.0 (OCH_2), 65.4 (CH_2OCH_2), 139.1 (C), 147.4 (C), 161.9 (C), 163.2 (C=O), 178.6 (C=O). EI-MS: 326 (M^+, 10), 281 (86), 239 (62), 57 (100), 87 (72), 45 (45). Anal. Calcd. for $C_{15}H_{22}N_2O_4S$ (326.41): C 55.20, H 6.79, N 8.58, Found: C 55.03, H 6.70, N 8.66.

Yellow *Ethyl 2-[2-morpholino-4-(ethyl)-1,3-thiazole-5-yl]-2-oxoacetate (4h):*

powder, Yield: 0.55 g (92%), m.p. 115-117°C. IR (KBr) (ν_{max}/cm^{-1}): 1729, 1714, 1658, 1587 cm^{-1}. ^1H NMR: 0.91 (t, 3 H, ^3J = 7.2, Me), 1.13 (t, 3 H, ^3J = 7.5, Me), 3.12 (q, 2 H, ^3J = 7.5, CH_2), 3.52-3.59 (m, 4 H, CH_2NCH_2), 3.89 (q, 2 H, ^3J = 7.2, OCH_2), 3.92-3.97 (m, 4 H, CH_2OCH_2). ^{13}C NMR: 13.9 (Me), 14.1 (Me), 22.6 (CH_2), 47.6 (CH_2NCH_2), 62.3 (OCH_2), 65.8 (CH_2OCH_2), 129.3 (C), 132.8 (C), 157.6 (C), 164.6 (C=O), 179.1 (C=O). EI-MS: 298 (M^+, 10), 253 (82), 211 (65), 87 (74), 45 (56), 29 (100). Anal. Calcd. for $C_{13}H_{18}N_2O_4S$ (298.36): C 52.33, H 6.08, N 9.39, Found: C 52.47, H 5.96, N 9.31.

References

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

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

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

[4] Multicomponent Reactions; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, **2005**.

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

[6] Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org.Chem.* **2003**, 4101.

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

[8] (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Ugi, I.; Domling, A. *Endeavour* **1994**, *18*, 115; (c) Heck, S.; Domling, A. *Synlett* **2000**, 424.

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

[10] Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.

[11] Miwatashi, S.; Arikawa, Y.; Kotani, E.; Miyamoto, M.; Naruo, K. I.; Kimura, H.; Tanaka, T.; Asahi, S.; Ohkawa, S. *J. Med. Chem*. **2005**, *48*, 5966.

[12] Papadopoulou, C.; Geronikaki, A.; Hadjipavlou-Litina, D. *Il Farmaco* **2005**, *60*, 969.

[13] Kumar, Y.; Green, R.; Borysko, K. Z.; Wisem, D. S.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem*. **1993**, *36*, 3843.

[14] Pereira, R.; Gaudon, C.; Iglesias, B.; Germain, P.; Gronemeyer, H.; de Lera, A. R. *Bioorg&Med. Chem. Lett.* **2006**, *16*, 49.

[15] Tsurumi, Y.; Ueda, H.; Hayashi, K.; Takase, S.; Nishikawa, M.; Kiyoto, S.; Okuhara, M. *J. Antibiotic* **1995**, *48*, 1066.

[16] Bell, F. W.; Cantrell, A. S.; Hoberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, J.; Zhang, H.; Zhou, X. X. *J. Med. Chem*. **1995**, *38*, 4929.

[17] Millan, D. S.; Prager, R. H.; Brand, C.; Hart, P. H. *Tetrahedron* **2000**, *56*, 811.

[18] Wang, W. L.; Yao, D.Y.; Gu, M.; Fan, M. Z.; Li, J. Y.; Xing, Y. C.; Nan, F. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5284.