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ORIGINAL PAPER

A one-pot synthesis of functionalized ethyl 1,3-thiazole-5-carboxylates from thioamides or thioureas and 2-chloro-1,3-dicarbonyl compounds in an ionic liquid

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Abstract A simple one-pot synthesis of functionalized ethyl 1,3-thiazole-5-carboxylates from the reaction of 2-chloro-1,3-dicarbonyl compounds with thioureas or thioamides in the presence of 1-butyl-3-methylimidazolium trifluoromethanesulfonate is described.

Keywords Heterocyclic synthesis · Ionic liquid · Thiourea · Thioamide

Introduction

Thiazole and its derivatives are useful compounds in medicinal and agricultural chemistry. The thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for decarboxylation of α-ketoacids [1]. This heterocyclic system has found broad application in drug development for the treatment of inflammation [2], hypertension [3], bacterial [4] and HIV infections [5]. Aminothiazoles are known to be ligands of estrogen receptors [6] as well as a novel class of adenosine receptor antagonists [7]. Thus, the thiazole nucleus has been much studied in organic and medicinal chemistry.

Several methods for the synthesis of thiazole derivatives have been developed. The most widely used method is Hantzsch synthesis [8, 9], involving the reaction of α-halocarbonyl compounds with thioureas or thioamides. Recently, a synthesis of thiazoles from thioamides and alkyl 2-chloro-3-oxobutanoates in organic solvents has been reported [10]. However, in spite of their potential utility, many of these methods suffer from drawbacks, such as harsh reaction conditions, unsatisfactory yields, prolonged reaction time, cumbersome product isolation procedures, polar, volatile, and hazardous organic solvents, and often expensive catalysts.

Ionic liquids (ILs) are ionic compounds that have a melting point below 100 °C. Most of the commonly used ILs are liquids at room temperature. Ionic liquids have a high polarity (usually between acetonitrile and methanol) and low vapor pressure. These features combined with the fact that most ionic liquids are immiscible with less polar organic solvents led to their use as media or co-solvent in catalysis. The importance of this area is highlighted by the increasing number of reviews and books dedicated to the topic [11–15]. Room temperature ionic liquids (RTILs), especially those based on the 1,3-di-alkylimidazolium salts, have shown great promise as an attractive alternative to conventional solvents [12]. RTILs possess the unique advantages of high thermal stability, negligible vapor pressure, immiscibility with a number of organic solvents, and recyclability [13–15].

We describe an efficient synthesis of functionalized thiazols through the reaction of thioamide/thiourea **1** and diethyl 2-chloromalonate/ethyl 2-chloro-3-oxobutanoate **2** in 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([bmin]CF_3SO_3) (Scheme 1).

Results and discussion

This reaction leads to trisubstituted thiazoles **3** in 55–95% yields. Structures of compounds **3a–3h** were assigned by

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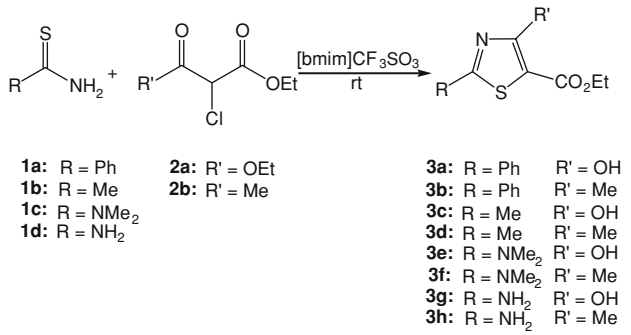
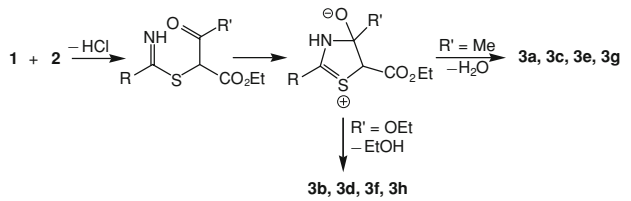


Scheme 1



Scheme 2

IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{13}C NMR spectrum of **3a** shows C=N ($\delta = 168.5$ ppm), carbonyl ($\delta = 161.2$ ppm), and aromatic ($\delta = 148.4$, 133.4, 131.1, 129.6, 128.2, and 126.9 ppm) carbons.

A tentative mechanism for this transformation is proposed in Scheme 2. The role of the IL may be postulated in terms of some Lewis/Brønsted acidity of the imidazolium cation leading to its interaction with the carbonyl oxygen of the α-halocarbonyl compound resulting in its increased polarization and electrophilicity, thus promoting the condensation and cyclization steps to give five-membered rings, which on dehydration or tautomerization afforded thiazole **3** (Scheme 2).

In conclusion, we describe a one-pot method for the synthesis of ethyl 1,3-thiazole-5-carboxylates using [bmim]CF_3SO_3 as reaction medium as well as a promoter. The important features of this procedure are enhanced reaction rate, mild reaction conditions, high yields, and green aspects, such as avoiding hazardous organic solvents, toxic catalysts, and waste, ease of recovery, and reuse of this novel reaction medium.

Experimental

Compounds **1**, **2**, and [bmim]CF_3SO_3 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-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz; δ 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. The results agreed favorably with the calculated values.

*General procedure for the preparation of compounds **3***

Thiourea or thioamide **1** (2 mmol) was added to a stirred solution of 2 mmol **2** in 2 cm^3 [bmim]CF_3SO_3 at rt. After completion of the reaction (1–2 h), as indicated by TLC (EtOAc/*n*-hexane, 2:1), the products were extracted with EtOAc (2 × 10 cm^3). The solvent was evaporated under reduced pressure to leave the crude product, which was purified by column chromatography on silica gel and eluted with a mixture of *n*-hexane:EtOAc (2:1) to afford pure thiazoles **3**. The IL was recovered by addition of 5 cm^3 water, then collected and dried under vacuum. These reactions were performed without any protective atmosphere of inert gas.

Ethyl 4-hydroxy-2-phenyl-1,3-thiazole-5-carboxylate (**3a**, $C_{12}H_{11}NO_3S$)

Brown oil: yield 0.47 g (95%); IR (KBr): $\bar{\nu} = 3{,}446$, 3,118, 1,732, 1,467, 1,442, 1,001 cm^{-1}; EI-MS: *m/z* = 249 (M^+, 4), 219 (40), 205 (52), 161 (88), 149 (36), 135 (14), 105 (100), 77 (38); ^{1}H NMR: $\delta = 1.38$ (t, $^{3}J = 6.0$, *Me*), 4.38 (q, $^{3}J = 6.0$, OCH_2), 7.5–8.1 (m, 5 CH), 8.43 (s, 1H, OH) ppm; ^{13}C NMR: $\delta = 14.2$ (*Me*), 61.1 (OCH_2), 126.9 (C), 128.2 (2 CH), 129.6 (CH), 131.1 (2 CH), 133.4 (C), 148.4 (C), 161.2 (C=O), 168.5 (C=N) ppm.

Ethyl 4-methyl-2-phenyl-1,3-thiazole-5-carboxylate (**3b**, $C_{13}H_{13}NO_2S$)

Pale yellow oil: yield 0.40 g (80%); IR (KBr): $\bar{\nu} = 3{,}406$, 3,088, 2,981, 1,720, 1,455, 1,426, 1,006 cm^{-1}; EI-MS: *m/z* = 247 (M^+, 4), 232 (34), 218 (68), 174 (14), 149 (36), 105 (100), 77 (35), 45 (25); ^{1}H NMR: $\delta = 1.37$ (t, $^{3}J = 9.0$, *Me*), 2.88 (s, 3H, *Me*), 4.35 (q, $^{3}J = 9.0$, OCH_2), 7.50–8.11 (m, 5 CH) ppm; ^{13}C NMR: $\delta = 14.1$ (*Me*), 17.1 (*Me*), 61.4 (OCH_2), 122.1 (C), 127.0 (2 CH), 129.6 (CH), 131.6 (2 CH), 133.3 (C), 161.0 (C), 162.0 (C=O), 169.7 (C=N) ppm.

Ethyl 4-hydroxy-2-methy-1,3-thiazole-5-carboxylate (**3c**, $C_7H_9NO_3S$)

White powder: yield 0.30 g (80%); m.p. 210–112 °C. IR (KBr): $\bar{\nu} = 3{,}507$, 3,157, 1,730, 1,457, 1,000 cm^{-1}; EI-MS: *m/z* = 187 (M^+, 3), 172 (87), 170 (45), 157 (35), 155 (71), 143 (65), 44 (100); ^{1}H NMR: $\delta = 1.18$ (t, $^{3}J = 9.0$, *Me*), 2.55 (s, 3H, *Me*), 4.34 (q, $^{3}J = 9.0$, OCH_2), 8.75 (s, 1H, OH) ppm; ^{13}C NMR: $\delta = 14.7$ (*Me*), 20.6 (*Me*), 61.9 (OCH_2), 96.4 (C), 166.0 (C), 169.3 (C=N), 170.7 (C=O) ppm.

Ethyl 2,4-dimethy-1,3-thiazole-5-carboxylate (**3d**, $C_8H_{11}NO_2S$)
White powder: yield 0.35 g (95%); m.p. 195-197 °C. IR (KBr): $\bar{\nu}$ = 3,542, 3,169, 1,731, 1,453, 1,030 cm^{-1}; EI-MS: *m/z* = 185 (M^+, 4), 170 (23), 155 (98), 141 (36), 114 (18), 44 (100); ^{1}H NMR: $\delta = 1.20$ (t, $^3J = 9.0$, *Me*), 2.53 (s, 3H, *Me*), 2.56 (s, 3H, *Me*), 4.16 (q, $^3J = 9.0$, OCH_2) ppm; ^{13}C NMR: $\delta = 14.5$ (*Me*), 15.5 (*Me*), 17.5 (*Me*), 63.1 (OCH_2), 136.7 (C), 152.5 (C), 159.5 (C=N), 173.8 (C=O) ppm.

Ethyl 2-(dimethylamino)-4-hydroxy-1,3-thiazole-5-carboxylate (**3e**, $C_8H_{12}N_2O_3S$)
Yellow oil: yield 0.30 g (70%); IR (KBr): $\bar{\nu}$ = 3,390, 3,118, 1,746, 1,658, 1,425, 1,030 cm^{-1}; EI-MS: *m/z* = 216 (M^+, 5), 201 (56), 199 (10), 172 (26), 145 (67), 73 (100); ^{1}H NMR: $\delta = 1.28$ (t, $^3 J = 9.0$, *Me*), 2.90 (s, 6H, 2 *Me*), 4.25 (q, $^3J = 9.0$, OCH_2), 9.11 (broad s, 1H, OH) ppm; ^{13}C NMR: δ = 13.7 (*Me*), 49.4 (2 CH_3), 62.8 (OCH_2), 123.0 (C), 152.6 (C), 166.7 (C=N), 168.4 (C=O) ppm.

Ethyl 2-(dimethylamino)-4-methyl-1,3-thiazole-5-carboxylate (**3f**, $C_9H_{14}N_2O_2S$)
Pale yellow oil: yield 0.36 g (85%); IR (KBr): $\bar{\nu}$ = 3,574, 3,111, 1,722, 1,627, 1,463, 1,029 cm^{-1}; EI-MS: *m/z* = 214 (M^+, 3), 199 (65), 184 (26), 170 (67), 73 (100); ^{1}H NMR: $\delta = 1.34$ (t, $^3J = 9.0$, *Me*), 2.73 (s, 3H, *Me*), 3.15 (s, 6H, 2 *Me*), 4.36 (q, $^3J = 9.0$, OCH_2), ppm; ^{13}C NMR: $\delta = 13.2$ (*Me*), 19.5 (CH_3), 49.6 (s, 6H, 2 *Me*), 62.1 (OCH_2), 137.2 (C), 149.3 (C), 160.7 (C=O), 167.6 (C=N) ppm.

Ethyl 2-amino-4-hydroxy-1,3-thiazole-5-carboxylate (**3g**, $C_6H_8N_2O_3S$)
Colorless oil: yield 0.21 g (55%); IR (KBr): $\bar{\nu}$ = 3,321, 3,159, 1,708, 1,633, 1,506, 1,030 cm^{-1}; EI-MS: 188 (M^+, 7); 173 (47); 172 (37); 159 (44); 142 (27); 115 (87); 45 (100). ^{1}H NMR: $\delta = 1.29$ (t, $^3J = 9.0$, *Me*), 4.33 (q, $^3J = 9.0$, OCH_2), 5.06 (broad s, 2H, NH_2), 9.12 (s, 1H, OH) ppm; ^{13}C NMR: $\delta = 13.7$ (*Me*), 62.5 (OCH_2), 122.9 (C), 143.3 (C), 161.4 (C=O), 166.4 (C=N) ppm.

Ethyl 2-amino-4-methyl-1,3-thiazole-5-carboxylate (**3h**, $C_7H_{10}N_2O_2S$)
Yellow powder: yield 0.24 g (65%); m.p. 100–102 °C. IR (KBr): $\bar{\nu}$ = 3,372, 3,153, 1,721, 1,651, 1,429, 1,030 cm^{-1}; EI-MS: *m/z* = 186 (M^+, 7), 171 (52), 170 (43), 156 (65), 141 (37), 113 (57), 45 (100); ^{1}H NMR: $\delta = 1.55$ (t, $^3J = 9.0$, *Me*), 2.64 (s, 3H, *Me*), 4.36 (q, $^3J = 9.0$, OCH_2), 5.00 (s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 13.8$ (*Me*), 14.0 (*Me*), 62.0 (OCH_2), 118.9 (C), 148.3 (C), 160.9 (C=O), 170.1 (C=N) ppm.

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