Synthesis of Functionalized 1,3-Thiazoles from Acid Chlorides, Primary Amines, Ethyl Bromopyruvate, and Ammonium Thiocyanate

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Abstract: An efficient synthesis of 1,3-thiazole-4(3*H*)-carboxylates is described via a four-component reaction between acid chlorides, primary amines, ethyl bromopyruvate, and ammonium thiocyanate.

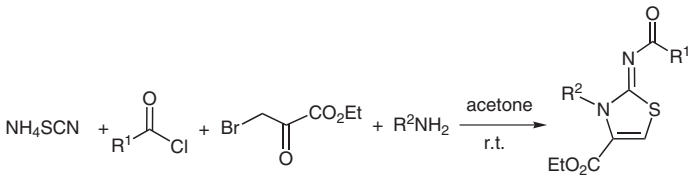
Key word: 1,3-thiazole, benzylamine, ethyl bromopyruvate, benzoyl isothiocyanate

Thiazoles play a prominent role in nature. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids.[1] Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory,[2,3] antitumour,[4,5] antihyperlipidemic,[5] and antihypertensive[6] properties. Thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Several methods[7] for the synthesis of thiazoles have been developed amongst which the most widely used method is Hantzsch's synthesis[7–9] (reaction between α-halocarbonyl compounds and thioamides, thioureas, thiocarbamic acids, or dithiocarbamic acids).

As part of our current studies on the development of new routes in heterocyclic synthesis,[10–13] we report an efficient procedure for direct synthesis of 1,3-thiazole-4(3*H*)-carboxylates **5** from ammonium thiocyanate (**1**) acid chlorides **2**, ethyl bromopyruvate (**3**), and primary amines **4** at room temperature[14] (Scheme 1).

The structures of compounds **5a–j** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **5a** exhibited a triplet at δ = 1.33 ppm (^3J = 7.2 Hz) for the methyl protons, a quartet at δ = 4.42 ppm (^3J = 7.2 Hz) for the OCH_2 moiety, and a singlet at δ = 6.07 ppm for the NCH_2 groups. The carbonyl and C=N group resonances in the ^{13}C NMR spectra of **5a** appear at δ = 158.3 (C=O), 169.3 (C=N), and 174.8 (C=O) ppm. The mass spectrum of **5a** displayed the molecular ion peak at *m/z* = 366.

A tentative mechanism for this transformation is proposed in Scheme 2. The reaction starts with formation of isothiocyanate **6** followed by addition of amine **4** to generate **7**. Subsequent nucleophilic attack of **7** on **3** yields the 1:1 adduct **8**. Intermediate **8** undergoes cyclization reaction to generate **9**, which is converted into **5** by elimination of water.



2, 4, 5	R^1	R^2	Yield (%)
a	Ph	Bn	85
b	Ph	4-Me-Bn	87
c	Ph	4-MeO-Bn	78
d	Ph	4-Cl-Bn	82
e	Ph	2-Cl-Bn	80
f	Ph	2-naphthylmethyl	75
g	Ph	*n*-Bu	80
h	4-BrC_6H_4	Bn	78
i	*t*-Bu	Bn	74
j	Et	Bn	76

Scheme 1

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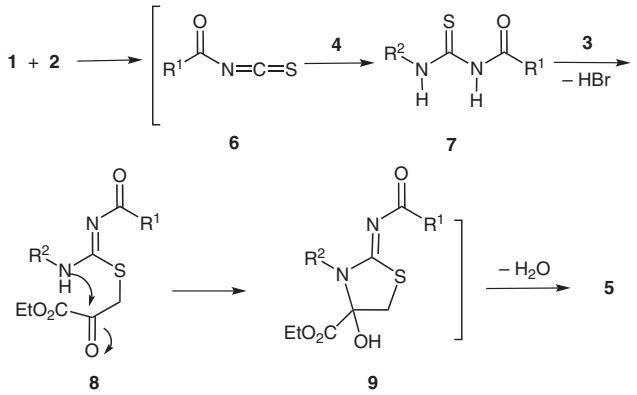

Scheme 2

In conclusion, we have described a convenient route to functionalized 1,3-thiazole-4(3*H*)-carboxylates through a four-component reaction of ammonium thiocyanate, acid chlorides, primary amines, and ethyl bromopyruvate. The advantage of the present procedure is that the reaction is performed by simple mixing of the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of functionalized 1,3-thiazole-4(3*H*)-carboxylates.

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(14) **Ethyl 2-(Benzoylimino)-3-benzyl-1,3-thiazole-4(3*H*)-carboxylate (5a); Typical Procedure**
To a stirred solution of NH_4SCN (0.15 g, 2 mmol) in acetone (15 mL) was added benzoyl chloride (0.28 g, 2 mmol), the mixture was refluxed for 5 min and a solution of ethyl bromopyruvate (0.39 g, 2 mmol) in acetone (10 mL) acetone was added dropwise. After addition of the primary amine (2 mmol) at r.t., the reaction mixture was then stirred for 24 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane–EtOAc, 9:1) to give **5a** as colorless crystals; mp 119–121 °C, yield 0.62 g (85%). IR (KBr): ν_{max} = 1716, 1658, 1587, 1477, 1429, 1369, 1369, 1304, 1231, 1105, 1054 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.33 (3 H, t, ^3J = 7.2 Hz, Me), 4.31 (2 H, q, ^3J = 7.2 Hz, OCH_2), 6.07 (2 H, s, NCH_2), 7.24–7.32 (3 H, m, 3 CH), 7.38 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.45 (2 H, t, ^3J = 7.2 Hz, CH), 7.51 (1 H, d, ^3J = 7.2 Hz, CH), 7.63 (1 H, s, CH), 8.34 (2 H, d, ^3J = 7.2 Hz, 2 CH) ppm. ^{13}C NMR (500.1 MHz, $CDCl_3$): δ = 14.0 (Me), 50.4 (CH_2), 61.9 (OCH_2), 120.8 (CH), 127.7 (2 CH), 128.1 (3 CH), 128.6 (2 CH), 129.5 (3 CH), 131.8 (C), 136.5 (C), 136.8 (C), 158.3 (C=O), 169.3 (C=N), 174.8 (C=O). MS: *m/z* (%) = 366 (10) [M^+], 293 (75), 261 (62), 105 (100), 91 (82), 45 (84). Anal. Calcd (%) for $C_{20}H_{18}N_2O_3S$ (366.43): C, 65.56; H, 4.95; N, 7.64. Found: C, 65.63; H, 4.99; N, 7.68. All other compounds **5b–j** gave satisfactory analytical and spectroscopic data.