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Efficient synthesis of new functionalized thiazoles using *α*-bromo ketones

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Abstract: The reaction of tetramethylguanidine with benzoylisothiocyanates or pivaloylisothiocyanate in the presence of bromopyruvate or phenacyl bromide produces functionalized thiazoles in good yield.

Keywords: Thiazole; Tetramethylguanidine; Benzoylisothiocyanate; Pivaloylisothiocyanate; Bromopyruvate; Phenacyl bromide.

Introduction

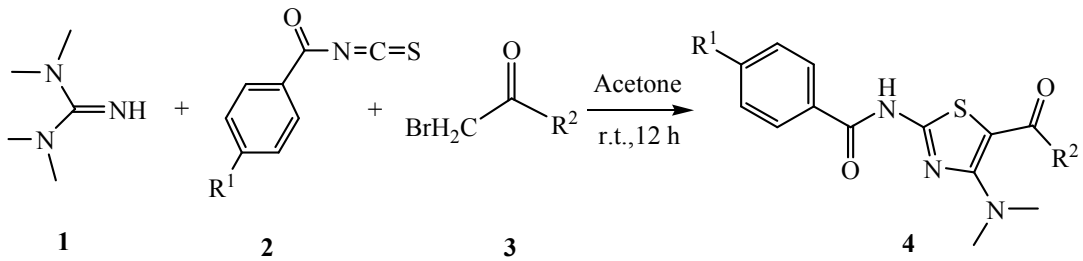
The thiazole ring system is commonly found in many pharmaceutically important molecules. Numerous natural products containing this heterocycle have been isolated and exhibit significant biological activities such as cytotoxic, immunosuppressive, antifungal, and enzyme inhibitory activity [1]. Moreover, among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process [2] and this ring structure is found in several marketed drugs.

Aminothiazoles are known to be ligands of estrogen receptors [3] as well as a novel class of adenosine receptor antagonists [4].

In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus the thiazole nucleus has been much studied in the field of organic and medicinal chemistry [6]. The classical method for the synthesis of thiazoles is the Hantzsch process, in which an R-haloketone is condensed with a thioamide [7-8]. This method gives excellent yields for simple thiazoles. As a part of our current studies on the development of new routes in heterocyclic synthesis [9-11], we report an efficient synthetic route to functionalized thiazoles with using of 1,1,3,3-Tetramethylguanidine as a nucleophilic compound.

Results and Discussion

The three-component reaction of TMG **1** and benzoyl isothiocyanate **2** in the presence of *α*-Bromo ketones **3** proceeds smoothly in acetone at room temperature to produce thiazoles **4a-4f** in good yields (Scheme **1**).



Scheme 1. Formation of compounds **4.**

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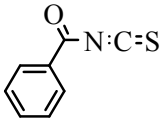
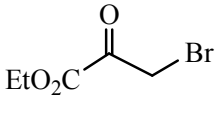
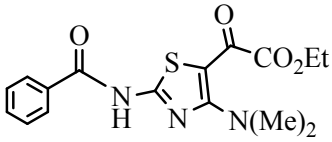
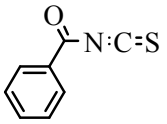
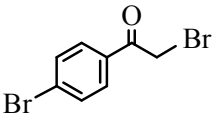
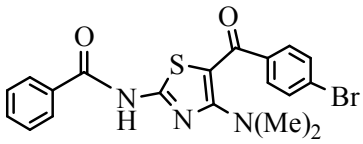
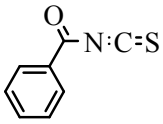
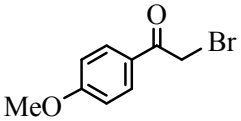
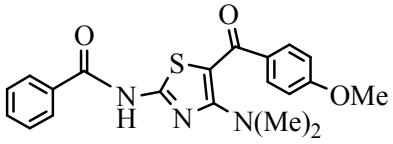
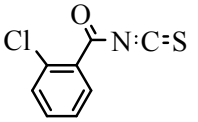
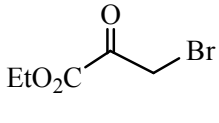
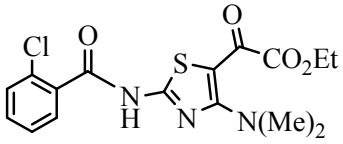
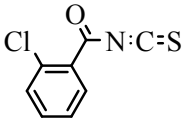
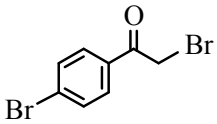
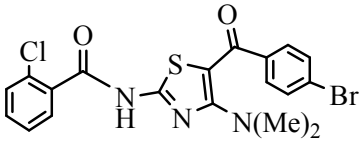
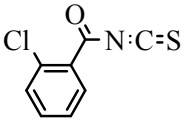
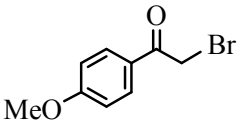
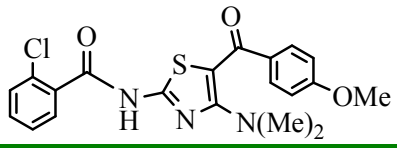
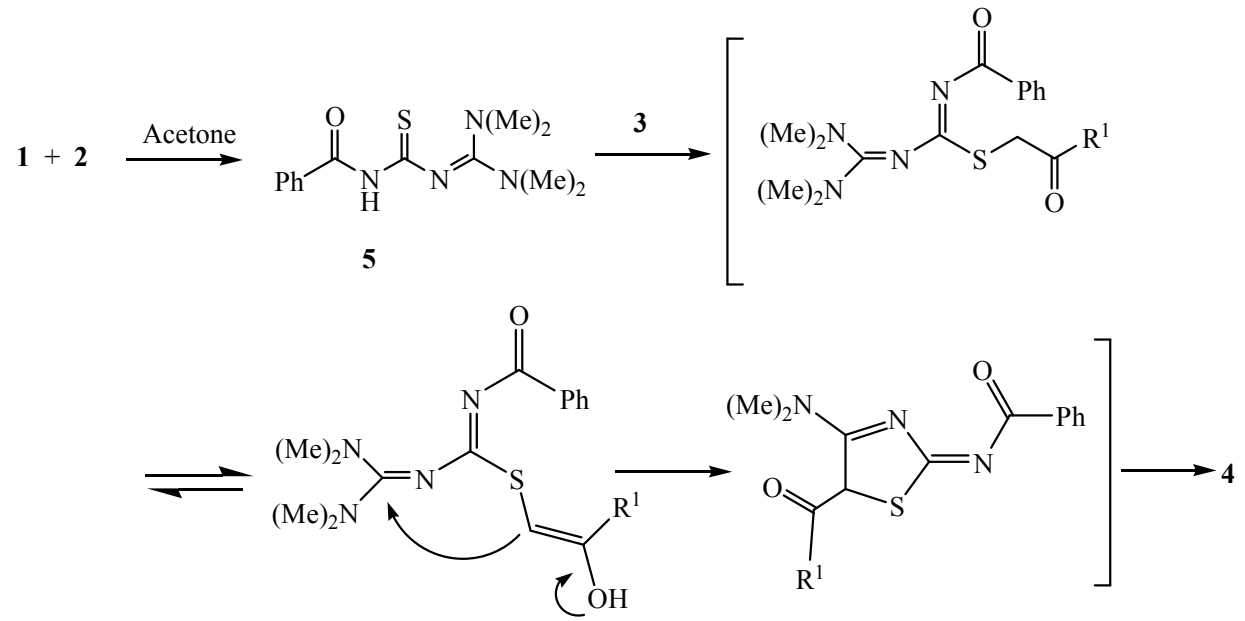
Table 1. Reaction of tetramethylguanidine **1** and benzoyl isothiocyanate **2** in the presence of *α*-Bromo ketone

Entry	Isothiocyanate	Bromoketone	Product **4**	Yield (%)
a				92
b				95
c				84
d				67
e				73
f				68

The structures of compounds **4a-4f** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed seven signals for methyl (δ = 1.38 and 3.16 ppm), OCH_2 (δ = 4.38 ppm), characteristic multiplets (δ = 7.52-8.01 ppm) for the aromatic protons, along with (δ = 9.90 ppm) for NH proton. The ^{13}C NMR spectrum of **4a** showed 13 distinct resonances in agreement with the proposed structure. The ^{1}H NMR and ^{13}C NMR spectra of **4b–m** were similar to those for **4a** except for the ketone moieties, which exhibited characteristic resonances in the appropriate regions of the spectrum. Partial assignments of these resonances are given in Experimental section.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme **2**). Presumably, addition of tetramethylguanidine **1** and isothiocyanate **2** to generate benzoylthiourea derivative **5**. Subsequent nucleophilic attack of **5** on *α*-bromo ketones **3**, which undergoes a series of cyclization and elimination reactions to generate product **4**.



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

In summery, we have reported a novel transformation involving tetramethylguanidine **1** and benzoyl isothiocyanate in the presence of α-Bromo ketones, which affords thiazole derivatives in good yields. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of new derivatives of thiazoles.

Experimental Section

Tetramethylguanidin, benzoylisothiocyanate, bromopyruvate and phenacyl bromide were obtained from Fluka and were used without further purification, IR spectra: Shimadzu IR-460 spectrometer, ^{1}H and ^{13}C NMR spectra: Bruker DRX-300AVANC instrument, in $CDCl_3$ at 300 MHz and 75 MHz, respectively, δ in ppm J in Hz, EI-MS (70 eV): Finningan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer. The mass and analyses data were in agreement with the proposed structures.

General procedure for synthesis of compounds 4

To a stirred solution of phenylisothiochanate (2 mmol) in 10 cm^3 acetone was added tetramethylguanidine **3** (2 mmol). The mixture was stirred at rt for 30 min. Then, α-Bromo ketones was added the reaction mixture at rt. The reaction mixture was then strirred for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *n*-hexane: *Et*O*Ac* = 3:1) to afford the pure title compounds.

Ethyl 2-benzoylamino-4-dimethylamino-thiazol-5-yl-oxo-acetate (**4a**)

Yield: 0.64 g (92%). Orange powder, mp.177-8ºC. IR (KBr): 3437, 1724, 1676, 1616, 1542, 1307, 1226, 1098. ^{1}H-NMR: 1.38 (*t*, ^3J = 7.1, Me), 3.16 (*s*, 2 Me), 4.38 (*q*, ^3J = 7.1, OCH_2), 7.52 (*t*, ^3J = 7.4, 2 CH), 7.64 (*t*, ^3J = 7.4, CH), 8.01 (*d*, ^3J = 7.4, 2 CH), 9.90 (*s*, NH). ^{13}C-NMR: 14.5 (Me), 43.0 (2 Me), 62.9 (OCH_2), 99.5 (C), 128.0 (2 CH), 129.5 (2 CH), 131.7 (CH), 133.8 (C), 164.1 (C), 165.2 (C), 165.4 (C=O), 166.0 (C=O), 170.5 (C=O). EI-MS, *m/z* (%): 347 (M^+, 13), 332 (38), 302 (66), 242 (21), 105 (100), 77 (39), 45 (22).

N-[5-(4-Bromo-benzoyl)-4-dimethylamino-thiazol-2-yl]-benzamide (**4b**)

Yield: 0.81 g (95%). yellow powder, mp.233-5ºC. IR (KBr): 3450, 1674, 1589, 1534, 1387, 1251, 1211, 1170. ^{1}H-NMR: 3.15 (*s*, 2 Me), 7.56 (t, ^3J = 7.3, 2 CH), 7.60 (*d*, ^3J = 8.4, 2 CH), 7.65 (*t*, ^3J = 7.3, CH), 7.73 (*d*, ^3J = 8.4, 2 CH), 7.95 (*d*, ^3J = 7.3, 2 CH), 9.90 (br *s*, NH). ^{13}C-NMR: 42.7 (2 Me), 100.1 (C), 126.7 (C), 127.9 (2 CH), 129.5 (2 CH), 130.5 (2 CH), 131.5 (C),

132.0 (2 CH), 133.8 (C), 133.9 (C), 140.5 (C), 160.9 (C), 165.1 (C=O), 184.2 (C=O). EI-MS, *m/z* (%): 431 (M^++2, 14), 429 (M^+, 13), 414 (33), 412 (30), 185 (11), 183 (11), 105 (100), 77 (43), 45 (9).

N-[4-Dimethylamino-5-(4-methoxy-benzoyl)-thiazol-2-yl]-benzamide (**4c**)

Yield: 0.64 g (84%). yellow powder, mp.217-8ºC. IR (KBr): 3445, 1679, 1591, 1520, 1367, 1221, 1157. ^{1}H-NMR: 3.11 (*s*, 2 Me), 3.89 (*s*, OMe), 6.95 (*d*, ^3J = 8.7, 2 CH), 7.53 (*d*, ^3J = 7.8, 2 CH), 7.63 (*d*, ^3J = 7.8, CH), 7.86 (*d*, ^3J = 8.7, 2 CH), 7.94 (*d*, ^3J = 7.8, 2 CH), 9.10 (br *s*, NH). ^{13}C-NMR: 42.6 (2 Me), 55.9 (OMe), 100.4 (C), 114.0 (2 CH), 127.9 (2 CH), 129.5 (2 CH), 131.6 (2 CH), 131.7 (C), 133.7 (C), 134.4 (C), 160.3 (C), 160.9 (C), 162.8 (C), 165.0 (C=O), 184.9 (C=O). EI-MS, *m/z* (%): 381 (M^+, 12), 366 (41), 276 (35), 246 (12), 135 (22), 105 (100), 77 (37), 45 (8).

Ethyl [2-(2-chloro-benzoylamino)-4-dimethylamino-thiazol-5-yl-oxo-acetate (**4d**)

Yield: 0.51 g (67%). Orange powder, mp.153-5ºC. IR (KBr): 3439, 1723, 1624, 1545, 1394, 1307, 1232, 1116. ^{1}H-NMR: 1.43 (*t*, ^3J = 7.1, Me), 3.18 (*s*, 2 Me), 4.40 (*q*, ^3J = 7.1, OCH_2), 7.41-7.92 (*m*, 4 CH), 9.85 (*s*, NH). ^{13}C-NMR: 14.5 (Me), 43.0 (2 Me), 63.0 (OCH_2), 99.4 (C), 128.0 (CH), 131.2 (CH), 131.5 (C), 131.7 (C), 131.9 (CH), 133.7 (CH), 164.0 (C), 164.2 (C), 164.3 (C=O), 165.7 (C=O), 170.5 (C=O). EI-MS, *m/z* (%): 381 (M^+, 13), 366 (45), 336 (65), 242 (14), 139 (100), 111 (18), 45 (21).

N-[5-(4-Bromo-benzoyl)-4-dimethylamino -thiazol-2-yl]-2-Chloro-benzamide (**4e**)

Yield: 0.67 g (73%). yellow powder, mp. 206-7ºC. IR (KBr): 3385, 1688, 1610, 1539, 1386, 1263, 1129. ^{1}H-NMR: 3.17 (*s*, 2 Me), 7.41-7.91 (m, 4 CH), 7.61 (*d*, ^3J = 8.4, 2 CH), 7.74 (*d*, ^3J = 8.4, 2 CH), 9.78 (br *s*, NH). ^{13}C-NMR: 42.3 (2 Me), 100.5 (C), 126.5 (C), 127.7 (CH), 128.0 (C), 130.4 (2 CH), 131.5 (CH), 132.0 (2 CH), 132.8 (CH), 132.9 (C), 133.5 (C), 140.7 (C), 162.5 (C), 164.1 (C), 166.4 (C=O), 184.2 (C=O). EI-MS, *m/z* (%): 465 (M^++2, 16), 463 (M^+, 12), 448 (45), 450 (34), 185 (21), 183 (21), 139 (100), 43 (9).

N-[4-Dimethylamino-5-(4-methoxybenzoyl)thiazol-2-yl]-2-Chloro-benzamide (**4f**)

Yield: 0.56 g (68%). yellow powder, mp.203-5ºC. IR (KBr): 3410, 1679, 1608, 1541, 1391, 1255, 1117. ^{1}H-NMR: 3.13(*s*, 2 Me), 3.89 (*s*, Me), 6.96 (*d*, ^3J = 8.7, 2 CH), 7.41-7.86 (m, 4 CH), 7.87 (*d*, ^3J = 8.7, 2 CH), 9.79 (br *s*, NH). ^{13}C-NMR: 42.5 (2 Me), 55.8 (OMe), 100.5 (C), 113.9 (2 CH), 127.9 (CH), 131.2 (2 CH), 131.5 (CH), 132.0 (CH), 132.6 (C), 133.4 (CH), 133.5 (CH), 134.4 (C), 159.6 (C), 161.8 (C), 162.8 (C), 164.1 (C=O), 184.9 (C=O). EI-MS, *m/z* (%): 417 (M^++2, 8), 415 (M^+, 20), 400 (48), 304 (33), 276 (24), 139 (100), 135 (19), 43 (10).

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