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ORIGINAL PAPER

A synthesis of functionalized 2-imino-1,3-thiazoles from tetramethylguanidine, isothiocyanates, and 2-chloro-1,3-dicarbonyl compounds

Issa Yavari · Alaleh Malekafzali · Samereh Seyfi

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Abstract The Hantzsch method for thiazole synthesis is modified via the reaction of 2-chloro-1,3-dicarbonyl compounds with 2-(amidosulfanylenemethyl)-1,1,3,3-tetramethylguanidines (prepared in situ from tetramethylguanidine and isothiocyanates), to afford functionalized 2-imino-1,3-thiazoles in good yields.

Keywords 2-Imino-1,3-thiazole · Tetramethylguanidine · Isothiocyanate · 2-Chloro-1,3-dicarbonyls

Introduction

Multi-component reactions (MCRs) are economically and environmentally advantageous. MCRs are perfectly suited for combinatorial library syntheses; thus, are finding increasing use in the discovery process for new drugs and agrochemicals [1–3]. In recent years, the research into novel active organic substances and into the design of molecular electronic devices has attracted considerable interest [4]. In this respect, there are several studies involved sulfur-containing compounds because they present good conduction in organic materials or are relevant biologically.

1,3-Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active center in the coenzyme derived from vitamin B (thiamin). A large number of thiazoles obtained from microbial and marine origins exhibit important biological effects, such as antitumor, antifungal, antibiotic, and antiviral activities [5]. Synthetic thiazoles have also been shown to exhibit a wide variety of biological activity [6], while others have found application as liquid crystals [7] and cosmetic sunscreens [8]. Among these class of compounds, 2-iminothiazole, isoform of 2-aminothiazole, is an advantaged and privileged structure. In some cases, alkyl group of 2-alkyliminothiazoles is changed into other alkyl groups by isothiocyanates [9]. There are several methods for the synthesis of tiazole derivatives [10, 11]. The classical method for the synthesis of thiazoles is the Hantzsch process, in which α-haloketones are condensed with thioamides [12].

Experimental

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^{1}H and ^{13}C spectra were obtained with a BRUKER DRX-500 AVANCE instrument using $CDCl_3$ as applied solvent and TMS as internal standard at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, N were performed using a Heraeus CHN-O-Rapid analyzer.

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I. Yavari (✉) · A. Malekafzali · S. Seyfi
Department of Chemistry, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran
e-mail: yavarisa@modares.ac.ir

A. Malekafzali
e-mail: alalehmalekafzali@yahoo.com

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General procedure

To a stirred solution of the isothiocyanate **2** (2 mmol) in acetone (10 mL) was added, at room temperature, 0.23 g (2 mmol) of **1**. The mixture was stirred at room temperature for 30 min. Then, the 1,3-dicarbonyl **3** (2 mmol) was added to the reaction mixture. After completion of the reaction [8–12 h; TLC (AcOEt/hexane 2:1)], the solvent was evaporated, and the residue was purified by ether/*n*-hexane.

*1-(3-(Bis(dimethylamino)methyl)-2,3-dihydro-4-methyl-2-(phenylimino)thiazol-5-yl)ethanone chloride (**4a**)*

Pale cream powder, m.p. 121–123 °C. Yield: 0.67 g (92 %). IR (KBr): $\bar{\nu}$ = 1,637, 1,592, 1,525, 1,469, 1,407, 1,067 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.14$ (3H, s, Me), 2.33 (3H, s, Me), 2.88 (12H, s, $2Me_2N$), 7.11 (2H, t, $^3J = 7.4$, 2CH), 7.36 (1H, t, $^3J = 7.4$, CH), 7.37 (2H, d, $^3J = 7.4$, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.8$ (Me), 29.5 (Me), 40.5 ($2Me_2N$), 118.2 (C), 127.0 (2CH), 129.8 (2CH), 130.1 (CH), 134.1 (C), 143.7 (C), 163.8 (C), 166.1 (C), 188.3 (C = O). MS (EI, 70 eV): *m/z* (%) = 315 (100), 273 (26), 246 (31), 217 (33), 210 (41), 196 (29), 190 (27), 135 (31), 115(28), 85(30), 71 (97), 44 (73). Anal. calcd for $C_{17}H_{23}ClN_4OS$ (366.91): C, 55.65; H, 6.32; N, 15.27 %. Found: C, 56.15; H, 6.21; N, 15.36 %.

*N(5-Acetyl-3-di(dimethylamino)methyl)-4-methyl-2-phenylcarbonylimino-2,3-dihydro-1,3-thiazole chloride (**4b**)*

Pale cream powder, m.p. 147–150 °C. Yield: 0.51 g (67 %). IR (KBr): $\bar{\nu}$ = 2,270, 1,651, 1,610, 1,410, 1,274, 1,064 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.55$ (3H, s, Me), 2.67 (3H, s, Me), 3.05 (12H, s, $2Me_2N$), 7.48 (2H, t, $^3J = 7.4$, 2CH), 7.59 (1H, t, $^3J = 7.4$, CH), 8.15 (2H, d, $^3J = 7.4$, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.8$ (Me), 30.3 (Me), 40.3 ($2Me_2N$), 121.6 (C), 128.6 (2CH), 129.5 (2CH), 133.3 (CH), 138.2 (C), 157.5 (C), 161.8 (C), 165.6 (C), 175.0 (C = O), 189.6 (C = O). MS (EI, 70 eV): *m/z* (%) = 344 (100), 301 (26), 274 (33), 245 (28), 210 (38), 196 (36), 163 (39), 115 (25), 85 (34), 71 (94), 44 (61). Anal. calcd for $C_{18}H_{23}ClN_4O_2S$ (394.92): C, 54.74; H, 5.87; N, 14.19 %. Found: C, 54.23; H, 6.17; N, 15.02 %.

*1-(2-(4-Fluorophenylimino)-3-(bis(dimethylamino)methyl)-2,3-dihydro-4-methylthiazol-5-yl)ethanone chloride (**4c**)*

Pale cream powder, m.p. 122–123 °C. Yield: 0.66 g (86 %). IR (KBr): $\bar{\nu}$ = 2,926, 2,179, 1,598, 1,542, 1,277 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.71$ (3H, s, Me), 1.87 (3H, s, Me), 2.43 (12H, s, $2Me_2N$), 6.64 (2H, t, $^3J = 8.4$, 2CH), 6.89 (2H, t, $^3J = 8.4$, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.9$ (Me), 29.5 (Me), 40.5 ($2Me_2N$), 116.8 (d, $^2J = 22.6$, CH), 118.5 (C), 130.1 (d, $^3J = 9.0$,CH), 144.1 (C), 162.5 (d,$^1J = 251.5$, CF), 164.7 (C), 166.5 (C), 172.0 (C), 188.8 (C = O). MS (EI, 70 eV): *m/z* (%) = 334 (93), 291 (29), 264 (31), 235 (33), 210 (48), 196 (30), 153 (32), 115 (33), 85 (35), 71 (100), 44 (69). Anal. calcd for $C_{17}H_{22}ClFN_4OS$ (384.90): C, 53.05; H, 5.76; N, 14.56 %. Found: C, 53.44; H, 5.31; N, 13.97 %.

*1-(2-(4-Nitrophenylimino)-3-(bis(dimethylamino)methyl)-2,3-dihydro-4-methylthiazol-5-yl)ethanone chloride (**4d**)*

Yellow powder, m.p. 120–122 °C. Yield: 0.78 g (95 %). IR (KBr): $\bar{\nu}$ = 1,595, 1,525, 1,407, 1,352, 1,276 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.38$ (3H, s, Me), 2.52 (3H, s, Me), 3.07 (12H, s, $2Me_2N$), 7.87 (2H, d, $^3J = 8.9$, 2CH), 8.42 (2H, d, $^3J = 8.9$, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.6$ (Me), 30.1 (Me), 41.3 ($2Me_2N$), 120.0 (C), 125.6 (2CH), 130.2 (2CH), 140.1 (C), 143.5 (C), 148.7 (C), 164.4 (C), 1696. (C), 188.8 (C = O). MS (EI, 70 eV): *m/z* (%) = 361 (95), 318 (34), 291 (25), 262 (35), 236 (23), 210 (50), 196 (34), 180 (38), 115(33), 85(36), 71 (100), 44 (75). Anal. calcd for $C_{17}H_{22}ClN_5O_3S$ (411.91): C, 49.57; H, 5.38; N, 17.00 %. Found: C, 49.21; H, 5.83; N, 16.89 %.

*1-[2-(2,4-Dichlorophenylimino)-3-di(dimethylamino)methyl-4-methyl-2,3-dihydro-1,3-thiazol-5-yl]-1-ethanone chloride (**4e**)*

Pale cream powder, m.p. 214–217 °C. Yield: 0.84 g (97 %). IR (KBr): $\bar{\nu}$ = 2,929, 2,168, 1,585, 1,553, 1,267 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.36$ (3H, s, Me), 2.41 (3H, s, Me), 2.98 (12H, s, $2Me_2N$), 7.40 (1H, d, $^3J = 8.6$, CH), 8.15(1H, d, $^3J = 8.6$, CH), 8.63 (1 H, s, CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$ (Me), 30.0 (Me), 41.3 ($2Me_2N$), 96.4 (C), 128.5 (C), 129.8 (C), 132.2 (C), 133.5 (CH), 134.1 (CH), 134.8 (CH), 136.0 (C), 165.4 (C), 166.1 (C), 200.4 (C = O). MS (EI, 70 eV): *m/z* (%) = 384 (100), 341 (30), 314 (20), 285 (38), 259 (29), 210 (39), 203 (30), 196 (31), 115(37), 85(32), 71 (89), 44 (68). Anal. calcd for $C_{17}H_{21}Cl_3N_4OS$ (435.80): C, 46.85; H, 4.86; N, 12.86 %. Found: C, 46.25; H, 5.22; N, 12.46 %.

*1-(3-(Bis(dimethylamino)methyl)-2-(ethylimino)-2,3-dihydro-4-methylthiazol-5-yl)ethanone chloride (**4f**)*

Pale cream powder, m.p. 165–167 °C. Yield: 0.67 g (73 %). IR (KBr): $\bar{\nu}$ = 2,987, 2,322, 1,459, 1,404, 1,274 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.27$ (3H, t, $^3J = 7.2$, Me), 2.43 (3H, s, Me), 2.69 (3H, s, Me), 3.09

(12H, s, $2Me_2N$), 4.14 (2H, $^3J = 7.2$, q, CH_2O). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.4$ (Me), 13.9 (Me), 30.0 (Me), 41.1 ($2Me_2N$), 41.7 (OCH_2), 118.3 (C), 144.1 (C), 164.6 (C), 165.6 (C), 188.5 (C = O). MS (EI, 70 eV): *m/z* (%) = 268 (89), 225 (31), 210 (44), 198 (29), 169 (28), 143 (32), 87 (32), 115(27), 85(31), 71 (100), 44 (71), 29 (21). Anal. calcd for $C_{13}H_{23}ClN_4OS$ (318.87): C, 48.97; H, 7.27; N, 17.57 %. Found: C, 48.25; H, 7.74; N, 17.21 %.

*Ethyl 3-(bis(dimethylamino)methyl)-2,3-dihydro-4-methyl-2-(phenylimino)thiazol-5-carboxylate chloride (**4 g**)*

Yellow oil, yield: 0.56 g (68 %). IR (KBr): $\bar{\nu}$ = 1,637, 1,592, 1,525, 1,469, 1,407, 1,067 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.31$ (3H, t, $^3J = 7.1$, Me), 2.28 (3H, s, Me), 3.06 (12H, s, $2Me_2N$), 4.29 (2H, q, $^3J = 7.1$, CH_2O), 7.23 (2H, t, $^3J = 8.7$, 2CH), 7.54 (1H, t, $^3J = 8.7$, CH), 7.56 (2H, d, $^3J = 8.7$, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.2$ (Me), 23.2 (Me), 40.2 ($2Me_2N$), 57.4 (CH_2O), 107.9 (C), 127.5 (2CH), 129.4 (2CH), 134.8 (CH), 145.9 (C), 164.5 (C), 166.2 (C), 166.9 (C), 168.9 (C = O). MS (EI, 70 eV): *m/z* (%) = 345 (100), 246 (26), 240 (38), 226 (39), 190 (35), 135 (24), 115 (31), 85 (21), 71 (88), 44 (68). Anal. calcd for $C_{18}H_{25}ClN_4O_2S$ (396.93): C, 54.47; H, 6.35; N, 14.11 %. Found: C, 54.89; H, 5.93; N, 14.47 %.

*Ethyl 3-(bis(dimethylamino)methyl)-2,3-dihydro-4-methyl-2-(4-nitrophenylimino)thiazol-5-carboxylate chloride (**4 h**)*

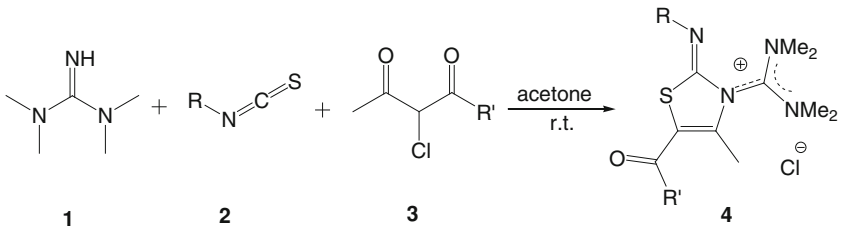
Yellow oil, yield: 0.56 g (68 %). IR (KBr): $\bar{\nu}$ = 1,637, 1,592, 1,525, 1,469, 1,407, 1,067 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.08$ (3H, t, $^3J = 7.1$, Me), 1.92 (3H, s, Me), 2.88 (12H, s, $2Me_2N$), 4.03 (2H, q, $^3J = 7.1$, CH_2O), 7.64 (2H, t, $^3J = 7.8$, 2CH), 8.04 (2H, d, $^3J = 7.8$, 2CH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.7$ (Me), 22.9 (Me), 40.7 (CH_2O), 41.1 ($2Me_2N$), 124.4 (C), 125.5 (2CH), 130.4 (2CH), 141.9 (C), 142.1 (C), 148.5 (C), 164.2 (C), 167.0 (C), 168.4 (C = O). MS (EI, 70 eV): *m/z* (%) = 390 (86), 293 (31), 236 (32), 227 (38), 210 (36), 180 (30), 115 (27), 85 (29), 71 (100), 44 (64). Anal. calcd for $C_{18}H_{24}ClN_5O_4S$ (441.93): C, 48.92; H, 5.47; N, 15.85 %. Found: C, 48.54; H, 6.21; N, 15.37 %.

Results and discussion

As a part of our current studies on the development of new routes in thiazole synthesis [13–15], we describe an efficient one-pot method for the synthesis of functionalized 2-imino-1,3-thiazoles **4** using 1,1,3,3-tetramethylguanidine (**1**) as a nucleophile. The reaction of **1** and isothiocyanates **2** in the presence of **3** in acetone at room temperature produced **4** in good yields after purification (Scheme 1). In this procedure, we have modified the Hantzsch method for thiazole synthesis via the reaction of 2-(sulfanylenemethyl)-1,1,3,3-tetramethylguanidines (**5**, see Scheme 2) with 2-chloro-1,3-dicarbonyl compounds. Thus, various thiourea derivatives were prepared from **1** and **2**. Compounds **4** were obtained from the reaction of these thioureas with **3**.

The structures of compounds **4a-h** were deduced from their IR, ^1H NMR, and ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^1H NMR spectrum of **4a** in $CDCl_3$ showed three singlets for methyl ($\delta = 2.14$ and 2.33) and dimethylamino ($\delta = 2.88$) protons. The carbonyl group resonances in the ^{13}C NMR spectra of **4a** appear at 188.3 ppm. The mass spectrum of **4a** does not display the molecular ion peak, but the fragmentation pattern confirms the proposed structure. The ^1H NMR and ^{13}C NMR spectra of **4b–h** were similar to those for **4a** except for the side chains, which exhibited characteristic resonances in the appropriate regions of the spectrum.

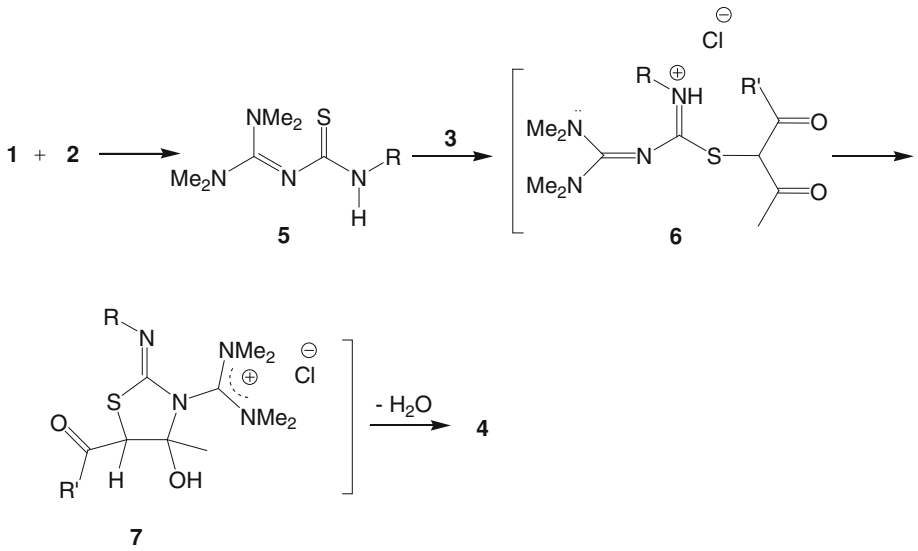
Scheme 1 Formation of compounds **4** from tetramethylguanidine, isothiocyanates, and 2-chloro-1,3-dicarbonyl compounds



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

2-4	R	R'	Yield (%) of 4
a	Ph	Me	92
b	PhCO	Me	67
c	4-F-C_6H_4	Me	86
d	4-O_2N-C_6H_4	Me	95
e	2,4-Cl_2-C_6H_3	Me	97
f	Et	Me	73
g	Ph	OEt	68
h	4-O_2N-C_6H_4	OEt	68

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



Mechanistically, the reaction starts with the formation of 2-(sulfanylenemethyl)-1,1,3,3-tetramethylguanidines (**5**) from **1** and **2**. Subsequent nucleophilic alkylation of thiourea derivative **5** with 2-chloro-1,3-dicarbonyls **3** yields intermediate **6**. Cyclization of this intermediate leads to **7**, which is converted to **4** by the elimination of water (Scheme 2).

In conclusion, we have described a convenient route to functionalized 2-imino-1,3-thiazoles from tetramethylguanidine and isothiocyanates in the presence of 2-chloro-1,3-dicarbonyl compounds. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

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