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Synthetic access to some new benzothiazole-based 1,3,4-thiadiazole and 1,3-thiazole derivatives

Kamal M. DAWOOD[1,*], **Eman A. RAGAB**[1], **Korany A. ALI**[2]
[1]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt
[2]Department of Applied Organic Chemistry,Center of Excellence for Advanced Science, National Research Centre, Dokki, Giza, Egypt

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Abstract: 1-(Benzothiazol-2-yl)-3-phenylthiourea **2** was prepared and treated with hydrazonoyl chlorides **3a**–**e** to yield the corresponding 5-(benzothiazol-2-ylimino)-1,3,4-thiadiazole derivatives **6a**–**e**, respectively. Reaction of the thiourea derivative **2** with ethyl 2-chloro-3-oxobutanoate **9** afforded the corresponding 2-(benzothiazol-2-ylimino)thiazole-5-carboxylate derivative **11**. The newly synthesized heterocyclic derivatives were confirmed from their elemental and spectral analyses.

Key words: Benzothiazole, thiazole, thiadiazole, thiourea, hydrazonoyl chlorides

1. Introduction

1,3,4-Thiadiazoles are among the most common heterocyclic pharmacophores. They display a broad spectrum of biological activities including antimicrobial,[1] anticancer,[2,3] antioxidant,[4] antidepressant,[5] anticonvulsant,[6,7] and antihypertensive activity,[8] as well as acetylcholinesterase inhibitors for the treatment of Alzheimer disease.[9,10] In addition, thiourea derivatives are key synthons for the synthesis of biologically active heterocycles with a broad spectrum of medicinal applications.[11] In particular, the most significant thiourea derivatives demonstrated antiviral,[12] anti-HIV,[13] antifungal,[14] and anticancer activities.[15] Benzothiazolyl thiourea derivatives have also attracted continuing interest due to their valuable biological activities such as antiinflammatory,[16] antibacterial,[17] and cytotoxic activities.[18,19] As part of our research projects aimed at the synthesis of potent biologically active 1,3,4-thiadiazole-based heterocycles,[20–32] the aim of this work was the synthesis of some new benzothiazole-based 1,3,4-thiadiazole and 1,3-thiazole derivatives utilizing 1-(benzothiazol-2-yl)-3-phenylthiourea **2** as a key starting synthon.

2. Results and discussion

1-(Benzothiazol-2-yl)-3-phenylthiourea **2** was prepared from the reaction of 2-aminobenzothiazole **1** with phenyl isothiocyanate in dimethylformamide in the presence of potassium hydroxide at room temperature according to literature procedures.[33,34] First, the reaction of 1-(benzothiazol-2-yl)-3-phenylthiourea **2** with the hydrazonoyl chloride esters **3a**–**c** was performed. The reaction of **2** with **3a** was carried out in refluxing ethanol in the presence of Et_3N to afford only one isolable product. There are two possible structures, **6a** and **8a**, for the

*Correspondence: dr_dawood@yahoo.com

reaction product either via loss of aniline from intermediate **5a** or via loss of ethanol from the intermediate **7a**, respectively (Scheme 1). The spectral data of the isolated product were completely compatible with structure **6a** and not **8a**. For example, the IR spectrum of **6a** showed a carbonyl absorption band at 1741 cm^{-1}. Its ^1H NMR showed characteristic quartet and triplet signals at δ 1.37 and 4.45 (J = 7.2 Hz) due to ethyl-ester protons in addition to the aromatic protons in the region δ 7.31–7.94. The mass spectrum of **6a** showed the molecular ion at m/z 382. In a similar way, treatment of **2** with the hydrazonoyl chloride esters **3b,c** conducted in refluxing ethanol in the presence of Et_3N afforded the corresponding ethyl 1,3,4-thiadiazole-2-carboxylate derivatives **6b,c** in high yield as shown in Scheme 1.

Next, reaction of the thiourea derivative **2** with the acetyl hydrazonoyl chloride **3d,e** in refluxing ethanol in the presence of triethylamine resulted, similarly, in the formation of only one isolable product as examined by TLC. Structures of the obtained products were established as 5-acetyl-2-(benzothiazol-2-ylimino)-4-aryl-4,5-dihydro-1,3,4-thiadiazoles **6d,e** on the basis of their elemental analyses and spectral data. As outlined in Scheme 1, the loss of aniline molecule from the intermediates **5d,e** led to the formation of compounds **6d,e**. Their IR spectra showed, in each case, an absorption band around 1680 cm^{-1} due to C=O function. The ^1H NMR spectrum of **6e** exhibited two singlet signals at δ 2.22 and 2.52 due to methyl and acetyl protons in addition to the aromatic signals. The mass spectra of **6d,e** showed, in each case, a peak due to their molecular ions.

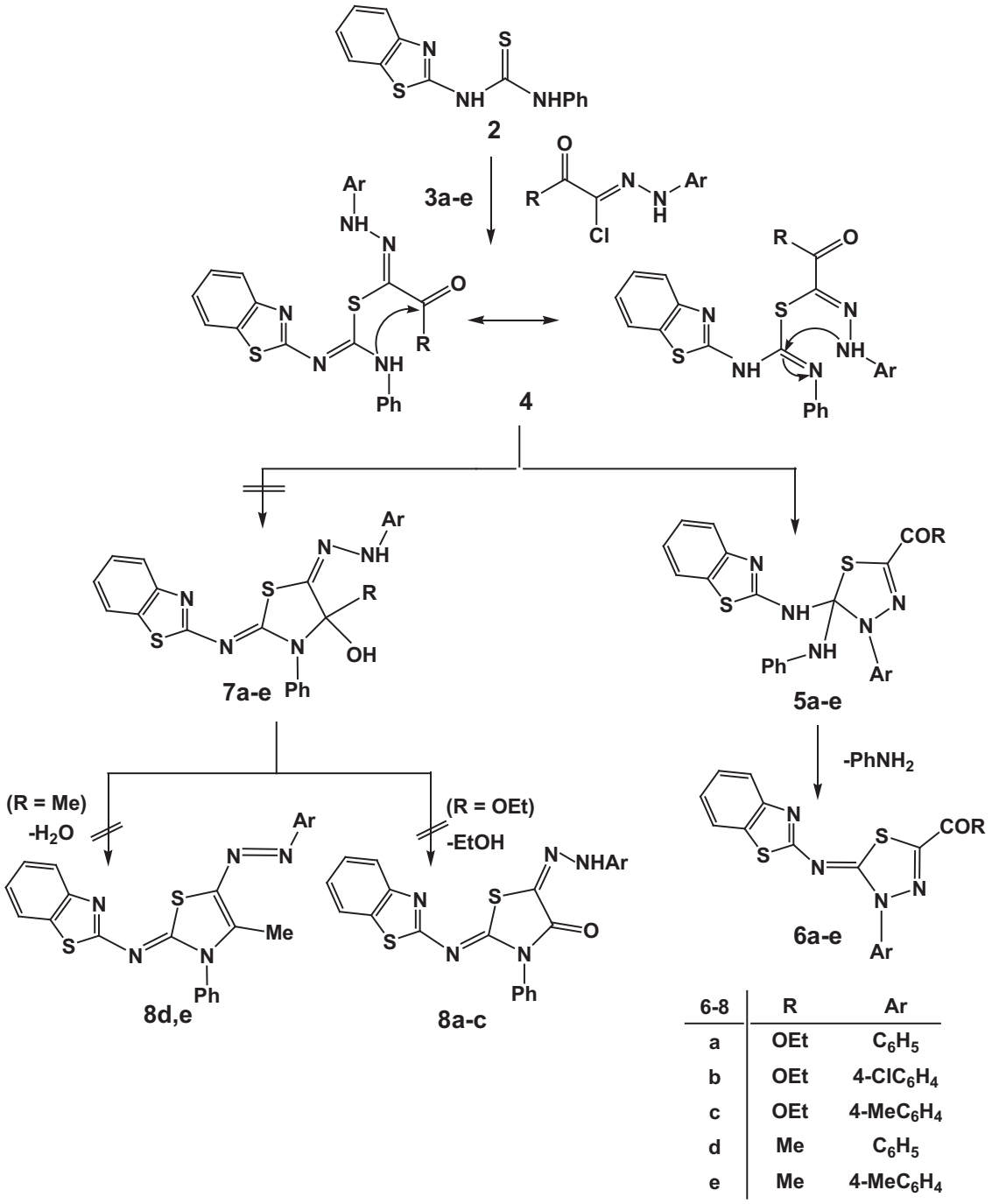
Finally, treatment of compound **2** with ethyl 2-chloro-3-oxobutanoate (**9**) in refluxing ethanol in the presence of triethylamine yielded a single product for which the structure 5-acetyl-2-(5-acetyl-4-methylthiazol-2-ylimino)-4-methyl-3-phenyl-1,3-thiazole (**11**) was assigned based on its elemental and spectral data. Formation of **11** proceeded via loss of HCl followed by water during an intramolecular cyclization of the intermediate **10**. The presence of only one carbonyl absorption band at 1686 cm^{-1} in the IR spectrum and the presence of three signals at δ 1.33, 2.24, and 4.33 assignable to the CH_3 and $CO_2CH_2CH_3$ protons in the ^1H NMR spectrum of the reaction product supported structure **11** and ruled out the other possible product **13** (Scheme 2). In addition, the mass spectrum of **11** showed a peak at m/z 395 due to its molecular ion.

3. Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^1H NMR spectra were determined in DMSO-d_6 at 300 MHz (^1H NMR) and at 75.46 MHz (^{13}C NMR) on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Benzothiazolylthiourea **2**[33] and hydrazonoyl chlorides **3a**–**c**,[35] and **3d,e**[36,37] were prepared according to procedures reported in the literature.

4. Synthesis of 5-(benzothiazol-2-ylimino)-4-aryl-1,3,4-thiadiazole derivatives 6a–e

General Procedure. To a stirred solution of 1-(benzolthiazol-2-yl)-3-phenylthiourea **2** (0.57 g, 2 mmol) in ethanol (30 ml) was added the appropriate hydrazonoyl chloride **3a**–**c** or **3d,e** (2 mmol) followed by addition of Et_3N (0.2 mL). The reaction mixture was heated at reflux for 4∼7 h, during which the starting substrates were dissolved and completely consumed and a colored product was precipitated. The solid product that formed was filtered off, washed with water and ethanol, dried, and finally recrystallized from the appropriate solvent to afford the corresponding 1,3,4-thiadiazole derivatives **6a**–**e**, respectively.

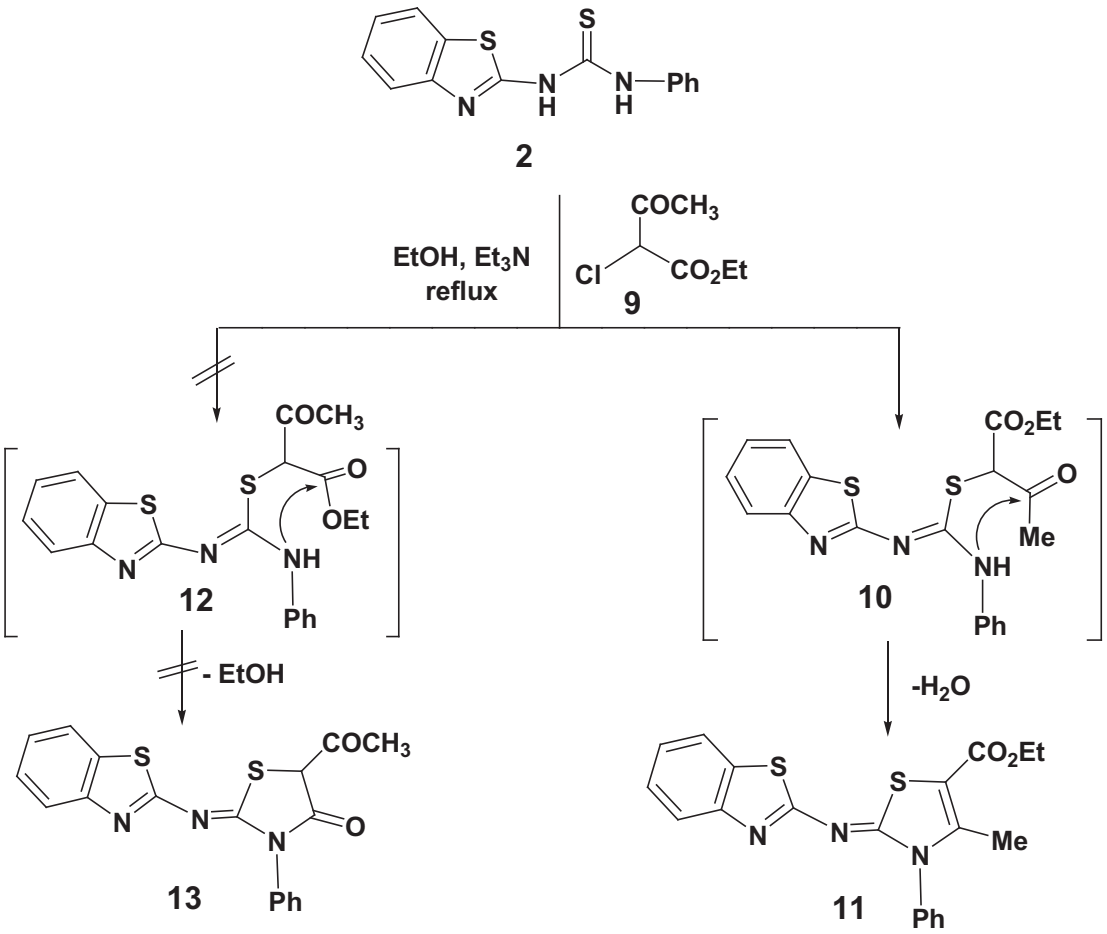


6-8	R	Ar
a	OEt	C_6H_5
b	OEt	4-ClC_6H_4
c	OEt	4-MeC_6H_4
d	Me	C_6H_5
e	Me	4-MeC_6H_4

Scheme 1. Synthesis of (benzothiazolyl)imino-1,3,4-thiadiazole derivatives **6a**–**e**.

5. Ethyl 5-(benzothiazol-2-ylimino)-4,5-dihydro-4-phenyl-1,3,4-thiadiazole-2-carboxylate (6a)

Yield (0.49 g, 64%), orange solid, mp 210–212 °C (EtOH/DMF); IR (KBr) ν (cm^{-1}): 1741 (C=O), 1592 (C=N), 1530 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.37 (t, 3H, CH_2CH_3, J = 7.2 Hz), 4.45 (q, 2H, CH_2CH_3, J = 7.2 Hz), 7.31 (t, 1H, ArH, J = 7.8 Hz), 7.45 (t, 1H, ArH, J = 7.8 Hz), 7.52–7.66 (m, 3H, ArH), 7.80–7.94 (m, 4H, ArH); MS m/z (%): 382 (M^+, 92.6), 251 (21.0), 225 (20.4), 198 (18.8), 108 (21.6), 91



Scheme 2. Synthesis of (benzothiazolyl)imino-1,3-thiazolidine derivative **11**.

(100), 77 (76.7). Anal. Calcd. for $C_{18}H_{14}N_4O_2S_2$ (382.46): C, 56.53; H, 3.69; N, 14.65; S, 16.77. Found: C, 56.27; H, 3.57; N, 14.80; S, 16.72.

6. Ethyl 5-(benzothiazol-2-ylimino)-4,5-dihydro-4-(4-chlorophenyl)-1,3,4-thiadiazole-2-carboxylate (6b)

Yield (0.63 g, 75%), yellow powder, mp 219–221 °C (EtOH/DMF); IR (KBr) ν (cm^{-1}): 1742 (C=O), 1590 (C=N), 1532 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.37 (t, 3H, CH_2CH_3, J = 7.2 Hz), 4.44 (q, 2H, CH_2CH_3, J = 7.2 Hz), 7.32 (t, 1H, ArH, J = 7.8 Hz), 7.46 (t, 1H, ArH, J = 7.8 Hz), 7.70 (d, 2H, ArH, J = 8.7 Hz), 7.87–7.95 (m, 4H, ArH); MS m/z(%): 418 (M^++2, 41.6), 417 (M^++1, 22.9) 416 (M^+, 96.0) 285 (21.6), 258 (10.2), 192 (8.9), 127 (33.1), 125 (100), 111 (17.2), 90 (24.8), 74 (14.9), 68 (10.2). Anal. Calcd for $C_{18}H_{13}ClN_4O_2S_2$ (416.90): C, 51.86; H, 3.14; N, 13.44; S, 15.38. Found: C, 52.08; H, 3.11; N, 13.16; S, 15.42.

7. Ethyl 5-(benzothiazol-2-ylimino)-4,5-dihydro-4-(4-tolyl)-1,3,4-thiadiazole-2-carboxylate (6c)

Yield (0.61 g, 77%), yellowish-orange solid, mp 202–204 °C (EtOH/DMF); IR (KBr) ν (cm^{-1}): 1742 (C=O), 1611, 1590 (C=N), 1519 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.34 (t, 3H, CH_2CH_3, J = 7.2 Hz), 2.42

(s, 3H, CH_3), 4.45 (q, 2H, CH_2CH_3, J = 7.2 Hz), 7.24–7.47 (m, 4H, ArH), 7.67 (d, 2H, ArH, J = 8.1 Hz), 7.86–7.93 (m, 2H, ArH); MS m/z(%): 396 (M^+, 100), 297 (4.9), 265 (22.1), 239 (14.6), 184 (4.8), 148 (7.2), 105 (97.5), 91 (26.9), 78 (21.6), 65 (18.4). Anal. Calcd for $C_{19}H_{16}N_4O_2S_2$ (396.49): C, 57.56; H, 4.07; N, 14.13; S, 16.17. Found: C, 57.77; H, 4.16; N, 14.01; S, 16.13.

8. 2-Acetyl-5-(benzothiazol-2-ylimino)-4,5-dihydro-4-phenyl-1,3,4-thiadiazole (6d)

Yield (0.51 g, 72%), yellow solid, mp 222–224 °C (EtOH/DMF); IR (KBr) ν (cm^{-1}): 1686 (C=O), 1595 (C=N), 1534 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.64 (s, 3H, COCH_3), 7.32 (t, 1H, ArH, J = 7.8 Hz), 7.46 (t, 1H, ArH, J = 8.1 Hz), 7.53–7.68 (m, 3H, ArH), 7.86–7.95 (m, 4H, ArH); MS m/z (%): 352 (M^+, 100), 251 (15.1), 225 (10.7), 193 (19.1), 118 (58.1), 117 (14.3), 108 (12.6), 91 (73.2), 77 (47.9). Anal. Calcd for $C_{17}H_{12}N_4OS_2$ (352.43): C, 57.93; H, 3.43; N, 15.90; S, 18.20. Found: C, 57.77; H, 3.32; N, 15.66; S, 18.28.

9. 2-Acetyl-5-(benzothiazol-2-ylimino)-4,5-dihydro-4-(4-tolyl)-1,3,4-thiadiazole (6e)

Yield (0.51 g, 70%), yellow solid, mp 233–235 °C (EtOH/DMF); IR (KBr) ν (cm^{-1}): 1679 (C=O), 1586 (C=N), 1541 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.22 (s, 3H, p-CH_3), 2.52 (s, 3H, COCH_3), 7.23 (t, 1H, ArH, J = 7.2 Hz), 7.39 (t, 1H, ArH, J = 7.5 Hz), 7.57 (d, 2H, ArH, J = 8.8 Hz), 7.65 (d, 2H, ArH, J = 8.5 Hz), 7.78–7.84 (m, 2H, ArH); MS m/z (%): 366 (M^+, 7.1), 287 (13.7), 194 (26.1), 132 (27.5), 104 (11.8), 85 (100). Anal. Calcd for $C_{18}H_{14}N_4OS_2$ (366.46): C, 58.99; H, 3.85; N, 15.29; S, 17.50. Found: C, 58.78; H, 3.77; N, 15.12; S, 17.54.

10. Ethyl 2-(benzothiazol-2-ylimino)-4-methyl-3-phenyl-2,3-dihydrothiazole-5-carboxylate (11)

To a stirred solution of 1-(benzolthiazol-2-yl)-3-phenylthiourea **2** (0.57 g, 2 mmol) in ethanol (30 mL), ethyl 2-chloro-3-oxobutanoate (**9**) (2 mmol) was added followed by adding Et_3N (0.2 mL) and the mixture was then heated at reflux for 4 h. The solvent was removed under reduced pressure and the residue was treated with crushed ice; then the precipitate was filtered off, washed with water and ethanol, dried, and finally recrystallized from DMF to give the corresponding 1,3-thiazole-5-carboxylate derivative **11**. Yield (0.55 g, 69%), yellowish-green solid, mp 206–208 °C (DMF); IR (KBr), νg(cm^{-1}): 1686 (C=O), 1594 (C=N), 1506 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.33 (t, 3H, CH_2CH_3, J = 7.2 Hz), 2.24 (s, 3H, CH_3), 4.33 (q, 2H, CH_2CH_3, J = 7.2 Hz), 7.23 (t, 1H, ArH, J = 7.8 Hz), 7.39 (t, 1H, ArH, J = 7.8 Hz), 7.51–7.64 (m, 5H, ArH), 7.78–7.84 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 13.9, 14.4, 32.4, 61.0, 64.8, 118.1, 120.6, 121.2, 121.8, 122.8, 124.6, 128.5, 129.4, 138.0, 146.9, 155.9, 168.6, 172.6. MS m/z(%): 395 (M^+, 51.5), 323 (12.5), 253 (20.7), 225 (10.8), 135 (12.9), 118 (66.7), 77 (100). Anal. Calcd for $C_{20}H_{17}N_3O_2S_2$ (395.49): C, 60.74; H, 4.33; N, 10.62; S, 16.22. Found: C, 60.65; H, 4.29; N, 10.39; S, 16.27%.

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