Solvent-free One-pot Synthesis of 2,2′-dithioxo-[5,5′] bithiazolidinylidene-4,4′-diones

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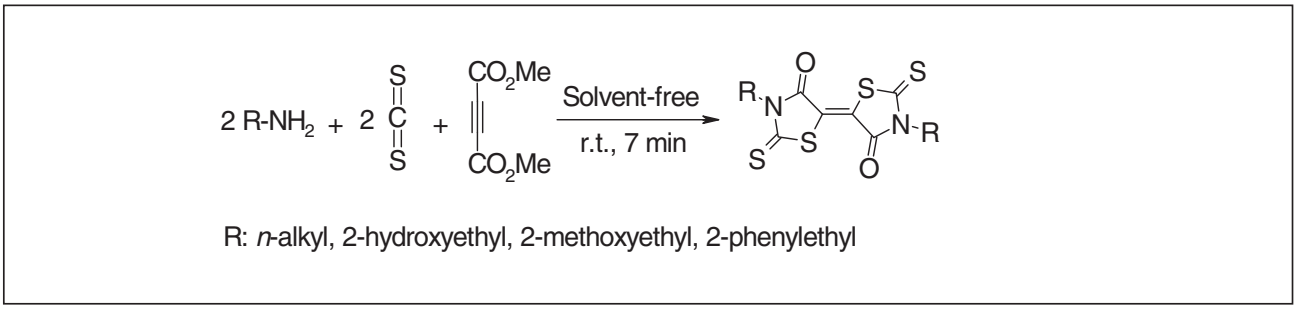

Solvent-free one-pot synthesis of 2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (birhodanine) derivatives from the reaction of primary amines and carbon disulfide in the presence of dimethyl acetylene dicarboxylate has been reported.

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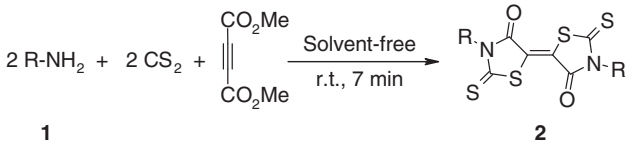
INTRODUCTION

One of the major focus areas of Green Chemistry is development of solvent-free syntheses [1]. It reduces the use of organic solvents and diminishes the formation of other waste. The reactions occur under mild conditions, and usually need simple workup procedures and easy equipment. Heterocycles are considered as a largest of the classical divisions of organic chemistry. Rhodanine-based molecules are one of the attractive heterocycles that are interested for their pharmacological activity, which include antimicrobial [2], antiviral [3], antidiabetic [4], and anticonvulsant activity [5]. Also, these compounds can inhibit numerous targets such as hepatitis C virus protease [6], aldose reductase [7], PRL-3 [8], and JSP-1 phosphatases [9]. An interesting group of rhodanines are 2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (birhodanine) derivatives. In spite of extensive developments in the synthetic methods to prepare rhodanines, little attention has been paid to the synthesis of birhodanines [10–12]. Most of the reported methods for the synthesis of these compounds require multiple-steps and/or harsh reaction conditions. For example, one route for synthesis of these compounds is reaction of alkylammonium *N*-alkyl dithiocarbamates with dimethyl acetylene dicarboxylate (DMAD), but this route is time-consuming and carried out in hazardous solvent [11]. Recently, a three-component reaction between primary amines and carbon disulfide in the presence of acetylenic esters has been reported [12]. This reaction leads to formation of thiazolidinyliden derivatives. Herein, we report one-pot and environmentally benign route for synthesis of birhodanine derivatives by the one-pot reaction of primary amines and carbon disulfide in the presence of DMAD under solvent-free condition (Scheme 1 and Table 1).

RESULTS AND DISCUSSION

The multicomponent reaction between primary amines and carbon disulfide in the presence of DMAD proceeds smoothly at room temperature under solvent-free condition to generate 3,3′-dialkyl-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione in moderate yields within 7 min. In this reaction, we added primary amines to a stirred mixture of CS_2 and DMAD in 5 min. The reaction mixture was then allowed to stir for 2 min. After completion, the product was separated as a powder by addition of EtOH. The results are given in Table 1. The structures of products were deduced from their elemental analysis and IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and mass spectrometric data. The ^{1}H NMR spectra of **2f** ($CDCl_3$) showed a singlet (δ 3.33 ppm) identified as two methoxy groups and two triplets (δ 3.69 ppm, $^3J_{HH} = 5.5$ Hz), and (δ 4.35 ppm, $^3J_{HH} = 5.5$ Hz) identified as two NCH_2 and two OCH_2 groups, respectively. The ^{1}H decoupled ^{13}C NMR spectrum of **2f** exhibited six distinct signals in agreement with the proposed structure. The mass spectra of **2f** showed molecular ion peak at *m/z* 378.

Scheme 1. Reaction between primary amines and carbon disulfide in the presence of dimethyl acetylene dicarboxylate.

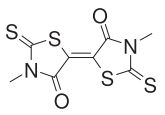
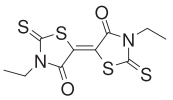
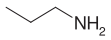
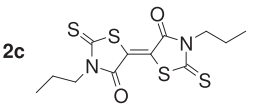
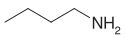
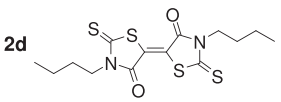
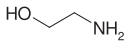
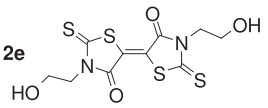
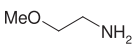
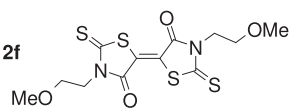
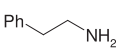
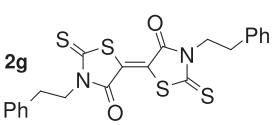


Although the mechanistic details of the aforementioned reaction are unknown, a proposed mechanism for this reaction is outlined in Scheme 2. The reaction starts by the addition of amine to carbon disulfide to form 1:1 adduct **3** [13], which subsequently attack to dimethyl acetylene dicarboxylate as a Michael-type addition and form acyclic dithiocarbamate **4**. This intermediate undergoes cyclization to generate compound **5**, which is attacked again by second molecule of **3** and produce intermediate **6**. Further cyclization of **6** results in the formation of **7** that is oxidized in air and generates compound **2** spontaneously. To approve the oxidation by air, this reaction was carried out under Ar atmosphere and seen that compound **2** was not formed.

In conclusion, the present multicomponent reaction between primary amines and carbon disulfide in the presence of dimethyl acetylene dicarboxylate provide simple entry

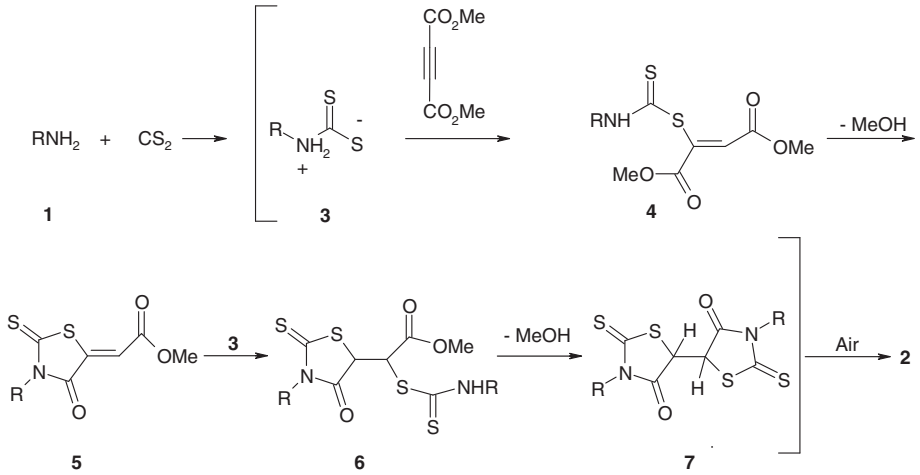
Table 1

One-pot synthesis of birhodanine derivatives under solvent-free condition.

Entry	Amine	Product	Yield (%)[a]
2a **1**	CH_3NH_2	**2a** 	50
2b **2**		**2b** 	52
2c **3**		**2c** 	54
2d **4**		**2d** 	61
2e **5**		**2e** 	56
2f **6**		**2f** 	55
2g **7**		**2g** 	56

[a]Isolated yields.

Scheme 2. Proposed mechanism for the reaction.



in to one-pot synthesis of 2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione derivatives of potential synthetic interest. The key advantages of this procedure are the mild reaction conditions, short reaction time, simple experimental, facile isolation of the desired products, and avoidance of harsh reagents.

EXPERIMENTAL

Melting points were measured with an Electrothermal 9100 apparatus (Electrotermal Engineering LTD, Rochford, UK). Elemental analyses C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer (Hanau, Germany). IR spectra were measured with a Shimadzu IR-460 spectrometer (Kyoto, Japan). NMR spectra were recorded with a Bruker DRX-250 AVANCE (Rheinstetten, Germany) instrument (250.1 MHz for ^{1}H and 62.5 MHz for ^{13}C) with $CDCl_3$ or DMSO-d_6 as solvent. Mass spectra were recorded with an Agilent-5975 C inert XL MSD mass spectrometer (Ringoes, NJ) operating at an ionization potential of 70 eV. Amines, dimethyl acetylene dicarboxylate, and carbon disulfide were obtained from Merck and were used without further purification.

Typical experimental procedure for the preparation of 3′-dimethyl-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2a). To a stirred solution of carbon disulfide (0.36 g, 4.8 mmol) and dimethyl acetylene dicarboxylate (0.28 g, 2 mmol) was added dropwise methyl amine (0.12 g, 4 mmol) in 5 min. The reaction mixture was allowed to stir for 2 min. After completion, the product was purified by addition of EtOH. Product **2a** was obtained as red powder, yield 0.29 g (50%), mp 316–317 °C; ms: *m/z* 290 (M^+, 100) [11].

3,3′-diethyl-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2b). Orange powder, yield 0.33 g (52%), mp 252–253 °C; IR (potassium bromide): 1693, 1450, 1242, 1138, 745 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ ppm 1.28 (t, 6H, J = 7.0 Hz, $2CH_3$), 4.19 (q, 4H, J = 7.0 Hz, $2CH_2$); ^{13}C NMR (deuteriochloroform): δ ppm 12.3 ($2CH_3$), 39.9 ($2CH_2$), 124.7 (2C), 166.7 (2C = O), 194.2 (2C = S); ms: *m/z* 318 (M^+, 100), 231 (9), 203 (75), 119 (38), 88 (52). *Anal*. Calcd. for $C_{10}H_{10}N_2O_2S_4$ (318.44): C, 37.72; H, 3.17; N, 8.80% found: C, 37.65; H, 3.21; N, 8.86%.

3,3′-dipropyl-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2c). Orange powder, yield 0.37 g (54%), mp 211–213 °C; IR (potassium bromide): 1688, 1344, 1285, 1220, 1134 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ ppm 0.95 (t, 6H, J = 7.3, $2CH_3$), 1.68–1.77 (m, 4H, $2CH_2$), 4.08 (t, 4H, J = 7.3 Hz, $2NCH_2$); ^{13}C NMR (deuteriochloroform): δ ppm 11.2 ($2CH_3$), 20.5 ($2CH_2$), 46.1 ($2CH_2$), 124.7 (2C), 166.9 (2C = O), 194.6 (2C = S); ms: *m/z* 346 (M^+, 100), 304 (13), 217 (67), 133 (23), 88 (38), 59 (54). *Anal*. Calcd. for $C_{12}H_{14}N_2O_2S_4$ (346.49): C, 41.59; H, 4.07; N, 8.08% found: C, 41.67; H, 4.11; N, 8.11%.

3,3′-dibutyl-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2d). Orange powder, yield 0.46 g (61%), mp 174–176 °C; IR (potassium bromide): 1680, 1432, 1268, 1205, 1139 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ ppm 0.95 (bs, 6H, $2CH_3$), 1.36–1.39 (m, 4H, $2CH_2$), 1.64–1.67 (m, 4H, $2CH_2$), 4.12 (bs, 4H, $2NCH_2$); ^{13}C NMR (deuteriochloroform): δ ppm 13.6 ($2CH_3$), 20.1 ($2CH_2$), 29.1 ($2CH_2$), 44.5 ($2NCH_2$), 124.7 (2C), 166.9 (2C = O), 194.5 (2C = S); ms: *m/z* 374 (M^+, 50), 341 (100), 285 (22), 231 (22), 198 (35), 88 (19), 64 (16). *Anal*. Calcd. for $C_{14}H_{18}N_2O_2S_4$ (374.55): C, 44.89; H, 4.84; N, 7.48% found: C, 44.95; H, 4.80; N, 7.57%.

3,3′-bis-(2-hydroxyethyl)-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2e). Orange powder, yield 0.39 g (56%), mp 236–238 °C; IR (potassium bromide): 3510, 1687, 1438, 1272, 1203, 1116 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ ppm 3.62 (bs, 4H, $2CH_2$), 4.09 (bs, 4H, $2CH_2$), 4.91 (s, 2H, 2OH); ^{13}C NMR (DMSO-d_6) δ ppm 47.2 ($2NCH_2$), 57.1 ($2OCH_2$), 124.5 (2C), 167.2 (2C = O), 196.1 (2C = S); ms: *m/z* 350 (M^+, 70), 307 (100), 263 (33), 176 (89), 116 (18), 88 (35). *Anal*. Calcd. for $C_{10}H_{10}N_2O_4S_4$ (350.44): C, 29.80; H, 1.88; N, 8.69% found: C 29.88; H 1.85; N 8.74%.

3,3′-bis-(2-methoxyethyl)-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2f). Orange powder, yield 0.42 g (55%), mp 203–205 °C; IR (potassium bromide): 1688, 1430, 1272, 1116, 747 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ ppm 3.33 (s, 6H, $2OCH_3$), 3.69 (t, 4H, J = 5.5 Hz, $2NCH_2$), 4.35 (t, 4H, J = 5.5 Hz, $2OCH_2$); ^{13}C NMR (deuteriochloroform): δ ppm 43.6 ($2NCH_2$), 58.9 ($2OCH_3$), 68.1 ($2OCH_2$), 124.7 (2C), 166.9 (2C = O), 194.8 (2C = S); ms: *m/z* 378 (M^+, 78%), 345 (25), 320 (85), 287 (52), 262 (70), 175 (60), 116 (45), 88 (43), 58 (100). *Anal*. Calcd. for $C_{12}H_{14}N_2O_4S_4$ (378.49): C, 34.27; H, 2.88; N, 7.99% found: C, 34.32; H, 2.91; N, 8.06%.

3,3′-diphenethyl-2,2′-dithioxo-[5,5′]bithiazolidinylidene-4,4′-dione (2g). Orange powder, yield 0.46 g (56%), mp 203–205 °C; IR (potassium bromide): 1692, 1449, 1255, 1173, 740 cm^{-1}; ^1H NMR (deuteriochloroform): δ ppm 2.99 (t, 4H, J = 7.8 Hz, $2CH_2$), 4.34 (t, 4H, J = 7.8 Hz, 2 NCH_2), 7.29–7.31 (m, 10H, 2Ar); ^{13}C NMR (deuteriochloroform): δ ppm 33.0 ($2CH_2$), 45.7 ($2NCH_2$), 123 (2C), 127.0 (2C-Ar), 128.7 and 128.9 (8CH-Ar), 136.9 (2CH-Ar), 166.9 (2C = O), 196.1 (2C = S). ms: *m/z* 366 (M^+-$PhCH_2CH_2$ + 1, 31), 104 (100), 91 (10), 77 (8). *Anal.* Calcd. for $C_{22}H_{18}N_2O_2S_4$ (470.63): C 56.14; H 3.85; N 5.95% found (%): C, 56.21; H, 3.79; N, 6.05%.

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