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A simple and effective approach to the synthesis of rhodanine derivatives via three-component reactions in water

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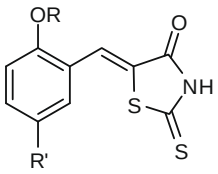
ABSTRACT

A facile and direct synthetic entry to rhodanine derivatives via the three-component coupling of carbon disulfide, primary amines, and acetylenic esters under neutral conditions in water is reported.

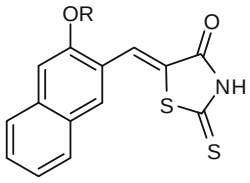
Rhodanine-based molecules are biologically active and inhibit numerous targets such as HCV NS3 protease,[1] β-lactamase,[2] PMT1 mannosyl transferase,[3] and PRL-3 and JSP-1 phosphatases (Fig. 1).[4] Classical methods for their preparation require several steps, and generally involve preparation of the rhodanine moiety followed by a Knoevenagel condensation with aldehydes.[5]

In our recent investigations,[6] treatment of an amine or its derivatives with dialkyl acetylenedicarboxylate and isocyanate (as a substituted cumulene) at room temperature led to the formation of maleimide derivatives.[7] Thus, as part of a related study on multi-component reactions, we used carbon disulfide (as a cumulene) under similar conditions for the synthesis of 5-oxo-2-thioxo-2,5-dihydro-3-thiophenecarboxylate derivatives (Scheme 1), but instead rhodanine derivatives were obtained in good yields.

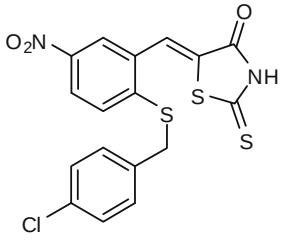
Water has many advantages over common organic solvents when used as a solvent in chemical reactions. It is economical, non-toxic, and environmentally friendly. hydrophobic reaction products can be separated by extraction with an organic solvent.[8] To our surprise, the one-pot reaction between amines and dialkyl acetylenedicarboxylates (DAAD) in the presence of carbon disulfide in water as solvent gave several rhodanine derivatives (Table 1). It should be noted that the synthesis of arylidene rhodanine derivatives reported earlier by Taran et al. proceeded via reaction between dithiocarbamates and arylpropiolates in the presence of Bu_3P as catalyst in $^{i}PrOH$.[9]



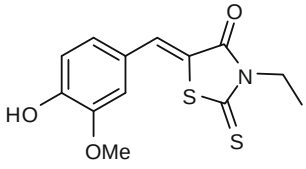
5-Arylalkylidene rhodanines
(PRL-3 inhibitors)



Naphthylidene rhodanines
(PRL-3 inhibitors)



5-Arylalkylidene rhodanine
(UDP *N*-acetylmuramate/ L-alanine ligase)



5-Arylalkylidene rhodanine
(PDE4 inhibitors)

Figure 1. Examples of biologically active rhodanine derivatives.

The reaction of carbon disulfide with amine **1** in the presence of dialkyl acetylenedicarboxylate **2** proceeded spontaneously at room temperature in water and was complete within a few hours. Table 1 lists the products of our study. The structures of

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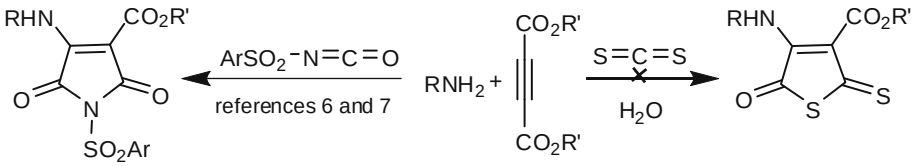
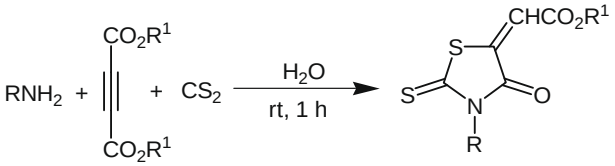
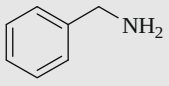
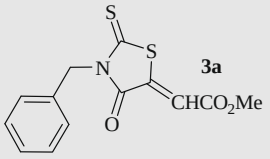
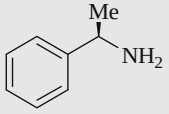
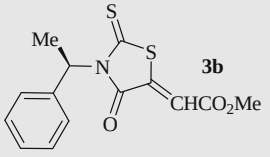
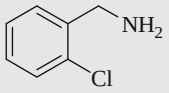
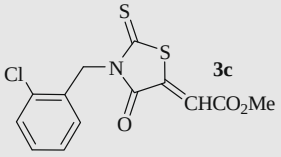
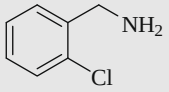
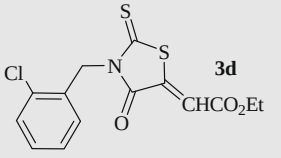
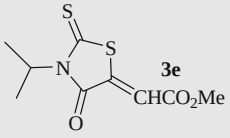
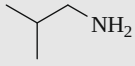
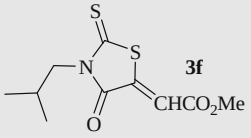
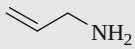
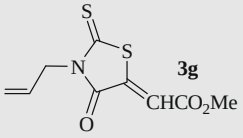


Scheme 1.

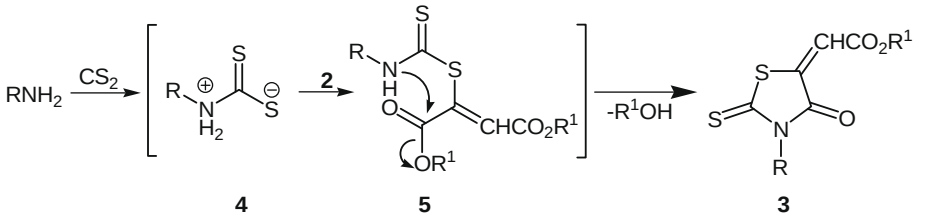
Table 1
Reaction of primary amine **1** with dialkyl acetylenedicarboxylate **2** in the presence of carbon disulfide



1 **2** **3**

Entry	Amine	R^1	Rhodanine	Yield (%)
1		Me	 **3a**	90
2		Me	 **3b**	85
3		Me	 **3c**	85
4		Et	 **3d**	86
5		Me	 **3e**	82
6		Me	 **3f**	88
7		Me	 **3g**	80

compounds **3** were deduced from their elemental analysis, mass spectra, IR, and ^{1}H and ^{13}C NMR spectra. The mass spectrum of **3a** displayed the molecular ion (M^+) at *m/z* 293. The IR spectrum of **3a** exhibited absorption bands due to the carbonyl group at 1713 cm^{-1}, the double bond at 1680 cm^{-1}, and the C=S group at 1342 and 1187 cm^{-1}



Scheme 2.

The ^{1}H NMR spectrum of **3a** exhibited three sharp singlets readily recognized as arising from the methoxy group (δ = 3.89), methylene (δ = 5.30) protons, and the vinylic CH at 6.86 ppm. The phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 11 distinct resonances in agreement with the structure of methyl 2-(4-oxo-3-(phenylmethyl)-2-thioxo-1,3-thiazolidin-5-ylidene)ethanoate. The geometry of the exocyclic double bond was not determined.

Although we have not established the mechanism of the reaction between the amines and carbon disulfide in the presence of DAAD in an experimental manner, a possible explanation is proposed in Scheme 2. Compound **3** could result from the initial addition of the amine to carbon disulfide and subsequent attack of the resulting reactive alkylammoniumcarbodithioate **4**[10] on the acetylenic ester to yield intermediate **5**. Cyclization of the intermediate **5** and subsequent loss of R^{1}OH lead to compound **3** (Scheme 2).

In summary, we have reported a one-pot method that is effective and simple for the synthesis of rhodanine derivatives of potential pharmacological and biological interest using commercially available starting materials and water as the reaction medium.[11]

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11. *Typical procedure for the preparation of methyl 2-[4-oxo-3-(phenylmethyl)-2-thioxo-1,3-thiazolidin-5-yliden)ethanoate* **3a**: Benzylamine (1 mmol) was added slowly to a mixture of CS_2 (1.2 mmol) and dimethyl acetylenedicarboxylate (1 mmol) in 3 ml of water at room temperature. The reaction mixture was stirred for 1 h. After completion of the reaction, the resulting solid was filtered and dried. Yield: 0.26 g (90%); orange powder; mp = 128–130 °C. IR (KBr) (ν_{max}, cm^{-1}): 1713 (C=O), 1680 (C=C), 1342 and 1187 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 3.89 (3H, s, OMe), 5.30 (2H, s, CH_2Ph), 6.86(1H, s, C=CH), 7.33–7.45 (5H, m, 5CH of Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 47.38 (OMe), 52.86 (CH_2Ph), 116.94 (C=CH), 128.33 (CH of Ph), 128.68 (2CH of Ph), 128.97 (2CH of Ph), 134.40 (C_{ipso}), 142.06 (*C*=CH), 165.52 (CON), 166.54 (CO_2Me), 195.49 (C=S). MS (EI), *m/z* (%): 293 (M$^+$, 19), 261 (9), 148 (22), 117 (9), 105 (9), 91 (100), 77 (8), 65 (26), 43 (15). Anal. Calcd for $C_{13}H_{11}NO_3S_2$ (293.35): C, 53.23; H, 3.78; N, 4.77. Found: C, 53.00; H, 3.75; N, 4.70. Compound **3b**: methyl 2-[3-(1-methyl-2-phenylethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-yliden]ethanoate. Yield: 0.26 g (85%); yellow powder; mp = 89–91 °C. IR (KBr) (ν_{max}, cm^{-1}): 1721 (C=O), 1689 (C=C), 1323 and 1196 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 1.94 (3H, d, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.87 (3H, s, OMe), 6.50 (1H, q, $^3J_{HH}$ = 7.2 Hz, MeCH), 6.71 (1H, s, C=CH), 7.33 (1H, t, $^3J_{HH}$ = 6.3 Hz, CH_{para} of Ph), 7.36 (2H, t, $^3J_{HH}$ = 7.6 Hz, 2 CH_{meta} of Ph), 7.46 (2H, d, $^3J_{HH}$ = 7.5 Hz, $2CH_{ortho}$ of Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 15.39 (CH_3), 52.80 (phCH), 54.97 (OMe), 116.37 (C=*C*H), 127.57 (2CH of Ph), 128.09 (CH of Ph), 128.46 (2CH of Ph), 137.8 (C_{ipso}), 141.50 (C=CH), 165.56 (CON), 165.91 (CO_2Me), 196.39 (C=S). MS (EI), *m/z* (%): 307 (M$^+$, 59), 275 (18), 204 (2), 162 (28), 105 (100), 85 (4), 77 (8), 59 (7), 51 (3). Anal. Calcd for $C_{14}H_{13}NO_3S_2$ (307.38): C, 54.71; H, 4.26; N, 4.56. Found: C, 54.50; H, 4.30; N, 4.50. Compound **3c**: methyl 2-[3-((2-chlorophenyl)methyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-yliden]ethanoate. Yield: 0.28 g (85%); yellow powder; mp = 112–114 °C. IR (KBr) (ν_{max}, cm^{-1}): 1716 (C=O), 1685 (C=C), 1330 and 1212 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 3.90 (3H, s, OMe), 5.42 (2H, s, $ArCH_2$), 6.90 (1H, s, C=CH), 6.92 (1H, t, $^3J_{HH}$ = 7.0 Hz, CH of Ar), 7.20 (1H, t, $^3J_{HH}$ = 6.6 Hz, CH of Ar), 7.23 (1H, d, $^3J_{HH}$ = 7.4 Hz, CH of Ar), 7.41 (1H, d, $^3J_{HH}$ = 7.4 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 44.85 (OMe), 52.1 ($ArCH_2$), 117.29 (C=*C*H), 126.98 (CH of Ar), 127.13 (CH of Ar), 129 (CH of Ar), 129.86 (CH of Ar), 131.45 (C_{ipso}-Cl), 132.96 (C_{ipso}-CH_2), 141.86 (*C*=CH), 165.52 (CON), 166.29 (*C*O$_2$Me), 195.14 (C=S). MS (EI), *m/z* (%): 327 (M$^+$, 2), 292 (100), 264 (7), 182 (5), 148 (12), 125 (28), 105 (7), 89 (18), 77 (4), 59 (5), 45 (4). Anal. Calcd for $C_{13}H_{10}ClNO_3S_2$ (327.80): C, 47.63; H, 3.07; N, 4.27. Found: C, 47.00; H, 3.10; N, 4.20. Compound **3d**: ethyl 2-[3-((2-chlorophenyl)methyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-yliden]ethanoate. Yield: 0.29 g (86%); yellow powder; mp = 104–106 °C. IR (KBr) (ν_{max}, cm^{-1}): 1711 (C=O), 1683 (C=C), 1335 and 1192 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 1.37 (3H, t, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 4.34 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 5.41 (2H, s, $ArCH_2$), 6.88(1H, s, C=CH), 6.90 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH of Ar), 7.18 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH of Ar), 7.23 (1H, t, $^3J_{HH}$ = 7.7 Hz, CH of Ar), 7.4 (1H, d, $^3J_{HH}$ = 7.8 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 14.15 (OCH_2CH_3), 45.10 (OCH_2CH_3), 62.23 ($ArCH_2$), 117.90 (C=CH), 126.97, 127.11, 128.98 and 129.86 (4 CH of Ar), 131.50 (C_{ipso}-Cl), 132.98 (C_{ipso}-CH_2), 141.50 (*C*=CH), 165.04 (CON), 166.35 (*C*O$_2$Et), 195.32 (C=S). MS (EI), *m/z* (%): 342 (M$^+$+1, 2), 341 (M$^+$, 2), 306 (100), 278 (26), 182 (6), 148 (7), 125 (26), 89 (14), 63 (4), 53 (4). Anal. Calcd for $C_{14}H_{12}ClNO_3S_2$ (341.83): C, 49.19; H, 3.54; N, 4.10. Found: C, 49.50; H, 3.50; N, 4.00. Compound **3e**: methyl 2-[3-(1-methylethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-yliden]ethanoate. Yield: 0.20 g (82%); yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 1725 (C=O), 1670 (C=C), 1315 and 1196 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 1.54 (6H, d, $^3J_{HH}$ = 7.0 Hz, CH*Me*$_2$), 3.88 (3H, s, OMe), 5.20 (1H, sep, $^3J_{HH}$ = 7.0 Hz, *CH*Me$_2$), 6.77 (1H, s, C=CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 18.47 (CH*Me*$_2$), 46.31 (*CH*Me$_2$), 50.10 (OMe), 115.93 (C=CH), 141.78 (*C*=CH), 165.62 (CON), 167.59 (*C*O$_2$Me), 197.44 (C=S). MS (EI), *m/z* (%): 245 (M$^+$, 76), 227 (15), 213 (26), 185 (14), 153 (22), 117 (100), 100 (78), 90 (42), 59 (40), 43 (42). Anal. Calcd for $C_9H_{11}NO_3S_2$ (245.31): C, 44.07; H, 4.52; N, 5.71. Found: C, 44.00; H, 4.40; N, 5.75. Compound **3f**: methyl 2-[3-(2-methylpropyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-yliden]ethanoate. Yield: 0.23 g (88%); yellow powder; mp = 88–90 °C. IR (KBr) (ν_{max}, cm^{-1}): 1715 (C=O), 1691 (C=C), 1325 and 1219 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 0.93 (6H, d, $^3J_{HH}$ = 6.7 Hz, CH_2CHMe_2), 2.25–2.31 (1H, m, CH_2CHMe_2), 3.87 (3H, s, OMe), 3.93 (2H, d, $^3J_{HH}$ = 7.5 Hz, CH_2CHMe_2), 6.82 (1H, s, C=CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 20.06 (CH_2CHMe_2), 26.9 (CH_2CHMe_2), 51.29 (OMe), 52.78 (CH_2CHMe_2), 116.58 (C=*C*H), 142.03 (*C*=CH), 165.55 (CON), 166.89 (CO_2Me), 196.11 (C=S). MS (EI), *m/z* (%): 259 (M$^+$, 2), 228 (14), 204 (48), 172 (16), 113 (18), 85 (38), 72 (34), 57 (86), 41 (100). Anal. Calcd for $C_{10}H_{13}NO_3S_2$ (259.34): C, 46.31; H, 5.05; N, 5.40. Found: C, 46.50; H, 5.00; N, 5.35. Compound **3g**: methyl 2-[3-(3-butenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-yliden]acetate. Yield: 0.19 g (80%); orange powder; mp = 140–142 °C. IR (KBr) (ν_{max}, cm^{-1}): 1716 (C=O), 1683 (C=C), 1331 and 1199 (C=S). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H = 3.88 (3 H, s, OMe), 4.71–4.72 (2H, m, CH_2CH=CH_2), 5.25–5.30 (2H, m, CH_2CH=CH_2), 5.75–5.90 (1H, m, CH_2CH=CH_2), 6.84 (1H, s, C=CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 46.19 (OMe), 52.83 (CH_2CH=CH_2), 116.84 (C=*C*HCO$_2$Me), 119.78 (CH_2CH=CH_2), 129.2 (CH_2CH=CH_2), 142.08 (C=CHCO$_2$Me), 165.52 (CON), 166.14 (*C*O$_2$Me), 195.15 (C=S). MS (EI), *m/z* (%): 243 (M$^+$, 47), 228 (100), 116 (28), 98 (25), 85 (79), 72 (32), 59 (26), 43 (61), 41 (79). Anal. Calcd for $C_9H_9NO_3S_2$ (243.29): C, 44.43; H, 3.73; N, 5.76. Found: C, 44.50; H, 3.60; N, 5.60.