

Green synthesis of 1,4-oxathiane-3-thiones under microwave irradiation in *N*-formylmorpholine

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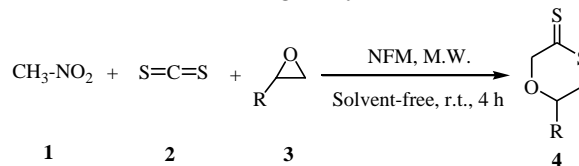
Abstract: A series of substituted oxathiane derivatives were synthesized *via* one-pot multicomponent reactions of nitromethane, carbon disulfide and oxiranes in the presence of NFM under solvent-free and microwave irradiation conditions. Particularly valuable features of this method include high yields of products, broad substrate scope, short reaction time and straightforward procedure.

Keywords: Ninhydrin, Primary amine, Arylthiocyanates, Dialkyl acetylenedicarboxylates, Multi component reaction.

Introduction

Chemistry of heterocyclic compounds has been studied in several subjects such as natural products, biologically active agrochemicals, pharmaceutical agents and organic materials [1]. 1,4-Oxathiane nucleus is the key structural motif present in certain commercial systemic fungicides broadly used in agriculture [2]. Organophosphorus derivatives of 1,4-oxathiane are insecticidal and acaricidal [3]. Some other 1,4-Oxathiane derivatives have been found to exhibit activity against tumor, HIV [4], candidosis, and aspergillosis [5]. Recently, 1,4-oxathiane nucleus has been reported as a suitable substructure for muscarinic agonists [6]. Epoxides are versatile intermediates in organic synthesis mainly due to their susceptibility to a variety of nucleophiles [7] and availability in optically pure forms [8]. Nucleophilic ring opening of epoxides has been extensively studied but little work has been carried out on the epoxide ring expansion with nucleophiles [9], although it would offer useful synthetic methods for various heterocycles.

For example, only a few attempts have been made for the synthesis of 1,4-oxathiane-2 thiones *via* an epoxide ring-opening-ring-closing reaction cascade and the results are not satisfactory in terms of yields, reaction times, number of synthetic steps, and environmental considerations. Recently reported the formation of novel functionalized oxathiolanes from reaction between malononitrile, CS₂ and substituted oxiranes in the presence of Et₃N [10]. As part of our current studies on the development of new routes in heterocyclic synthesis, we report an efficient three component reaction between nitromethane **1**, carbon disulfide **2** and epoxide **3** in the presence of *N*-formylmorpholine at room temperature which constitutes a direct synthesis of functionalized 1,4-oxathiane-3-thione **4** in good yields (Scheme 1).



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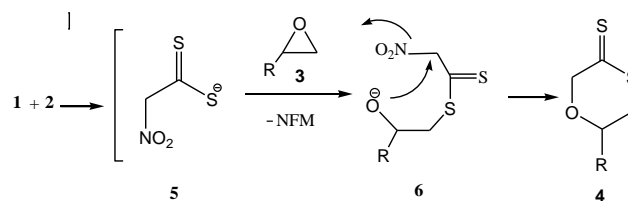
Compound 4	Oxiran	Product	Yield (%) of 4
a			95
b			90
c			92
d			90
e			90
f			93

Scheme 1: Reaction of nitromethane, carbon disulfide and oxiranes in the presence of NFM.

Results and discussion

Three component reaction between nitromethane **1**, carbon disulfide **2** and epoxide **3** in water at 70 °C produce functionalized 1,4-oxathiane-3-thione **4** in good yields (Scheme 1). The structures of compounds **4** were assigned by IR, ¹H NMR, ¹³C NMR and mass spectral data. For example, the ¹H NMR spectrum of **4a** exhibited sharp singlets for methine (3.38-4.64 ppm) protons, along with characteristic multiplets for the aromatic protons (7.24-7.49 ppm). The ¹³C NMR spectrum of **4a** exhibited 10 distinct resonances which further confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic C=S bands. The mass spectra of **4a-f** displayed the molecular ion peak at the appropriate m/z. The ¹H NMR and ¹³C NMR spectra of **4b-4f** were similar to those for **4a**

except for the 1,4-oxathiane moieties, which exhibited characteristic resonances in appropriate regions of the spectrum. Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the reaction starts with formation of the intermediate **5**, followed by addition of CS₂ **2** to generate **6**. Cyclization of this intermediates leads to **4** (Scheme 2).



Scheme 2: Proposed mechanism for the one-pot synthesis of compound **4**

Conclusion

In summary, we report a reaction involving nitromethane, carbon disulfide and epoxide, which affords a new route to the synthesis of functionalized 1,4-oxathiane-3-thione. The present procedure has the advantage that, not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ¹H, and ¹³C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ¹H, and ¹³C, spectra were obtained for solutions in CDCl₃ using TMS as internal standard or 85% H₃PO₄ as external standard.

General procedure for preparation of compounds **4a-f**:

A mixture of the (0.11g, 2 mmol) nitromethane **1** and N-formylmorpholine (2 mmol) was stirred for 30 min under microwave conditions (In power of 800 w and T=70°C). Then, oxirane (2 mmol) was added and finally, CS₂ (0.76gr, 10 mmol) was added to reaction mixture.

After completion of the reaction [4h; TLC (AcOEt/hexane 1:4) monitoring], 10 mL water was poured to the mixture of reaction. The reaction mixture was filtered and the solid residue was crystallized from ethyl acetate to afford **4**.

6-Phenyl-1,4-oxathiane-3-thione (4a):

Yield: 0.16 g (78 %). Pale yellow oil. IR (KBr): 1626, 1590, 1341, 1161, 1085. ^1H NMR: 3.38 (dd, $^2J = 11.1$, $^3J = 6.9$, CH), 3.53 (dd, $^2J = 11.1$, $^3J = 6.7$, CH), 4.63 (d, $^3J = 6.2$, CH), 4.64 (d, $^3J = 6.2$, CH), 4.93 (t, $^3J = 6.3$, CH), 7.24 (t, $^3J = 7.2$, CH), 7.34 (t, $^3J = 7.2$, 2 CH), 7.49 (d, $^3J = 7.3$, 2 CH). ^{13}C NMR: 44.8 (CH₂), 85.7 (CH), 94.6 (CH₂), 127.4 (2 CH), 127.8 (CH), 128.6 (2 CH), 141.0 (C), 229.7 (CS). EI-MS: 210 (M⁺, 15), 132 (100), 134 (80), 120 (66), 106 (64), 89 (85), 77 (84). Anal. Calcd for C₁₀H₁₀OS₂ (210.30): C 57.11, H 4.79; Found: C 5.8, H 4.8.

6-Methyl-1,4-oxathiane-3-thione (4b):

Yield: 0.12 g (85%). Pale yellow oil. IR (KBr): 1632, 1592, 1367, 1174, 1118. ^1H NMR: 1.66 (d, $^3J = 7.4$, Me), 2.40 (dd, $^2J = 12.1$, $^3J = 5.9$, CH), 3.00 (dd, $^2J = 12.1$, $^3J = 5.8$, CH), 3.68 (d, $^3J = 6.2$, CH), 3.75 (d, $^3J = 6.5$, CH), 5.24-5.29 (m, CH). ^{13}C NMR: 19.5 (Me), 44.2 (CH₂), 73.4 (CH), 94.7 (CH₂), 229.7 (CS). EI-MS: 148 (M⁺, 5), 131(60), 105 (85), 89 (33), 75 (35), 42 (100), 58 (54). Anal. Calcd for C₅H₈OS₂ (148.23): C 40.51, H 5.44; Found: C 40.6, H 5.5.

6-(Phenoxymethyl)-1,4-oxathiane-3-thione (4c):

Yield: 0.21 g (90%). Pale yellow oil. IR (KBr): 1646, 1591, 1354, 1168, 1098. ^1H NMR: 3.46 (dd, $^2J = 11.8$, $^3J = 5.7$, CH), 3.53 (dd, $^2J = 11.8$, $^3J = 5.7$, CH), 4.29 (d, $^3J = 6.4$, CH), 4.36 (dd, $^2J = 12.4$, $^3J = 5.5$, CH), 4.46 (d, $^3J = 6.5$, CH), 4.53 (dd, $^2J = 12.4$, $^3J = 6.5$, CH), 5.28-5.33 (m, CH), 6.93 (d, $^3J = 6.4$, 2 CH), 7.05 (t, $^3J = 7.5$, CH), 7.27 (d, $^3J = 7.5$, 2 CH). ^{13}C NMR: 34.1 (CH₂), 66.2 (CH₂), 84.4 (CH), 95.0 (CH₂), 114.4 (2 CH), 121.9 (CH), 129.6 (2 CH), 159.4 (C), 229.7 (CS). EI-MS: 240 (M⁺, 10), 164 (20), 146 (20), 150 (25), 103 (60), 89 (100), 77 (62). Anal. Calcd for C₁₁H₁₂O₂S₂ (240.33): C 54.97, H 5.03; Found: C 54.9, H 5.1.

6-cyclohexyl-1,4-oxathiane-3-thione (4d):

Yield: 0.18 g (89%). Pale yellow oil. IR (KBr): 1649, 1581, 1340, 1155, 1144. ^1H NMR: 1.11 (d, $^3J = 6.2$, 2 Me), 3.32 (dd, $^2J = 12.4$, $^3J = 5.7$, CH), 3.42 (dd, $^2J = 12.2$, $^3J = 5.5$, CH), 3.46-3.50 (m, CH), 3.42 (dd, $^2J = 12.4$, $^3J = 5.7$, CH), 4.76-4.77 (m, CH), 3.42 (d, $^2J = 12.2$, $^3J = 5.5$, CH), 3.42 (d, $^3J = 6.2$, CH), 3.42 (dd,

$^2J = 12.2$, $^3J = 6.2$, CH). ^{13}C NMR: 22.3 (2 Me), 39.0 (CH₂), 70.1 (CH₂), 72.4 (CH), 79.8 (CH), 95.0 (CH₂), 206.0 (CS). EI-MS: 206 (M⁺, 15), 146 (54), 130 (47), 116 (68), 89 (100), 43 (62). Anal. Calcd for C₈H₁₄O₂S₂ (206.31): C 46.57, H 6.84; Found: C 46.6, H 6.9.

6-(isopropoxymethyl)-1,4-oxathiane-3-thione (4e):

Yield: 0.16 g (87%). Pale yellow oil. IR (KBr): 1631, 1592, 1367, 1173, 1082. ^1H NMR: 1.77-1.82 (m, CH₂), 1.93-1.99 (m, CH₂), 2.00- 2.19 (m, CH₂), 2.19-2.23 (m, CH₂), 3.27 (q, CH), 3.50 (q, CH), 3.51 (d, $^3J = 6.2$, CH), 3.53 (d, $^3J = 6.2$, CH). ^{13}C NMR: 23.2 (CH₂), 25.8 (CH₂), 31.6 (CH₂), 37.5 (CH₂), 45.5 (CH), 82.1 (CH), 95.3 (CH₂), 186.8 (CS). EI-MS: 188 (M⁺, 15), 112 (54), 105 (47), 98 (68), 89 (100), 75 (62). Anal. Calcd for C₉H₁₂OS₂ (188.30): C 51.03, H 6.42. Found: C 51.2, H 6.5.

6-(allyloxymethyl)-1,4-oxathiane-3-thione (4f):

Yield: 0.18 g (90%). Pale yellow oil. IR (KBr): 1646, 1591, 1354, 1168, 1098. ^1H NMR: 3.26 (dd, $^2J = 12.5$, $^3J = 6.2$, CH), 3.33 (dd, $^2J = 12.5$, $^3J = 6.2$, CH), 3.39 (d, $^3J = 6.2$, CH), 3.46 (dd, $^2J = 12.5$, $^3J = 6.2$, CH), 3.56 (d, $^3J = 6.2$, CH), 3.59 (dd, $^2J = 12.5$, $^3J = 6.2$, CH), 3.62-3.83 (m, CH), 4.04 (d, $^3J = 6.2$, CH₂), 5.23 (dd, $^2J = 12.5$, $^3J = 6.2$, CH), 5.24 (dd, $^2J = 12.5$, $^3J = 6.2$, CH), 5.33-5.89 (m, CH). ^{13}C NMR: 35.6 (CH₂), 72.2 (CH₂), 74.4 (CH₂), 83.3 (CH), 95.0 (CH₂), 115.8 (CH₂), 134.1 (CH), 229.7 (CS). EI-MS: 204 (M⁺, 10), 132 (25), 128 (20), 114 (22), 146 (60), 71 (100), 57 (62). Anal. Calcd for C₈H₁₂O₂S₂ (204.30): C 47.03, H 5.92; Found: C 47.1, H 5.9.

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