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Green synthesis of morpholine-2-thione by multicomponent reaction of aziridines

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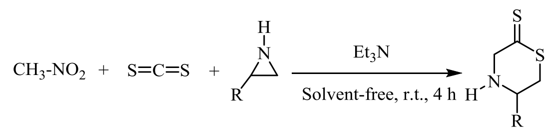
Abstract: A series of substituted morpholine-2-thione derivatives were synthesized *via* one-pot multicomponent reactions of nitromethane, carbon disulfide and aziridine in the presence of Et_3N under solvent-free conditions. Particularly valuable features of this method include high yields of products, broad substrate scope, short reaction time and straightforward procedure.

Keywords: Aziridin, Carbone disulfide, Nitro methane, 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]. Some of the 1,4-oxathiane are insecticidal and acaricidal [3] and some derivatives of 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] Aziridines 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 aziridines has been extensively studied but little work has been carried out on the aziridine 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 aziridine 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, CS_2 and substituted aziridines in the presence of Et_3N [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 aziridine **3** in the presence of N-formylmorpholine at room temperature which constitutes a direct synthesis of functionalized morpholine-2-thione **4** in good yields (Scheme **1**).



1 2 3 4

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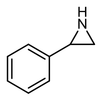
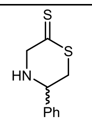
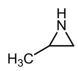
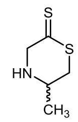
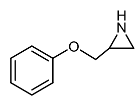
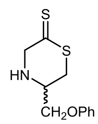
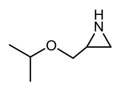
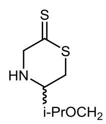
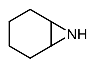
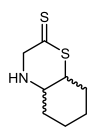
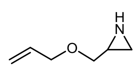
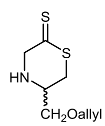
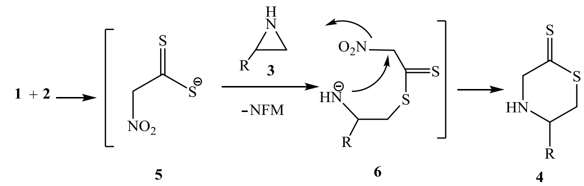
Compound **4**	Oxiran	Product	Yield (%) of **4**
a			85
b			80
c			83
d			78
e			75
f			75

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

Results and discussion

Three component reaction between nitromethane **1**, carbon disulfide **2** and aziridine **3** under solvent-free conditions at room temperature produce functionalized morpholine-2-thione **4** in good yields (Scheme **1**). The structures of compounds **4** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited sharp singlets for methine (3.38-4.64 ppm) protons, along with characteristic multipletes for the aromatic protons (7.24-7.49 ppm). The ^{13}C 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 ^{1}H NMR and ^{13}C NMR spectra of **4b-4f** were similar to those for **4a** except for the 1,4-oxathian 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 CS_2 **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 aziridine, which affords a new route to the synthesis of functionalized morpholine-2-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. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 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^{o}C). Then, aziridine (2 mmol) was added and finally, CS_2 (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**.

5-phenylthiomorpholine-2-thione (4a):

Yield: 0.16 g (78 %). Pale yellow oil. IR (KBr): 1626, 1590, 1341, 1161, 1085. ^{1}H 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 (CH_2), 85.7 (CH), 94.6 (CH_2), 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 $C_{10}H_{10}OS_2$ (210.30): C 57.11, H 4.79; Found: C 5.8, H 4.8.

5-methylthiomorpholine-2-thione (4b):

Yield: 0.12 g (85%). Pale yellow oil. IR (KBr): 1632, 1592, 1367, 1174, 1118. ^{1}H 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 (CH_2), 73.4 (CH), 94.7 (CH_2), 229.7 (CS). EI-MS: 148 (M^+, 5), 131(60), 105 (85), 89 (33), 75 (35), 42 (100), 58 (54). Anal. Calcd for $C_5H_8OS_2$ (148.23): C 40.51, H 5.44; Found: C 40.6, H 5.5.

5-(phenoxymethyl)thiomorpholine-2-thione (4c):

Yield: 0.21 g (90%). Pale yellow oil. IR (KBr): 1646, 1591, 1354, 1168, 1098. ^{1}H 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 (CH_2), 66.2 (CH_2), 84.4 (CH), 95.0 (CH_2), 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 $C_{11}H_{12}O_2S_2$ (240.33): C 54.97, H 5.03; Found: C 54.9, H 5.1.

5 cyclohexylthiomorpholine-2-thione (4d):

Yield: 0.18 g (89%). Pale yellow oil. IR (KBr): 1649, 1581, 1340, 1155, 1144. ^{1}H 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 (CH_2), 70.1 (CH_2), 72.4 (CH), 79.8 (CH), 95.0 (CH_2), 206.0 (CS). EI-MS: 206 (M^+, 15), 146 (54), 130 (47), 116 (68), 89 (100), 43 (62). Anal. Calcd for $C_8H_{14}O_2S_2$ (206.31): C 46.57, H 6.84; Found: C 46.6, H 6.9.

5-(isopropoxymethyl)thiomorpholine-2-thione (4e):

Yield: 0.16 g (87%). Pale yellow oil. IR (KBr): 1631, 1592, 1367, 1173, 1082. ^{1}H NMR: 1.77-1.82 (m, CH_2), 1.93-1.99 (m, CH_2), 2.00- 2.19 (m, CH_2), 2.19-2.23 (m, CH_2), 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 (CH_2), 25.8 (CH_2), 31.6 (CH_2), 37.5 (CH_2), 45.5 (CH), 82.1 (CH), 95.3 (CH_2), 186.8 (CS). EI-MS: 188 (M^+, 15), 112 (54), 105 (47), 98 (68), 89 (100), 75 (62). Anal. Calcd for $C_8H_{12}OS_2$ (188.30): C 51.03, H 6.42. Found: C 51.2, H 6.5.

5-(allyloxymethyl)thiomorpholine-2-thione (4f):

Yield: 0.18 g (90%). Pale yellow oil. IR (KBr): 1646, 1591, 1354, 1168, 1098. ^{1}H 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, CH_2), 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 (CH_2), 72.2 (CH_2), 74.4 (CH_2), 83.3 (CH), 95.0 (CH_2), 115.8 (CH_2), 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 $C_8H_{12}O_2S_2$ (204.30): C 47.03, H 5.92; Found: C 47.1, H 5.9.

References

[1] (a) Deiters, A.; Martin, S. F. *Chem. Rev*., **2004**, *104*, 2199; (b) Wu, X. F.; Neumann, H.; Beller, M. *Chem. Rev*. **2013**, *113*, 734.
[2] Cook, M. J. *In Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**; 3.
[3] Haubein, A. H. *J. Am. Chem. Soc*. **1959**, *81*, 144.
[4] Borkow, G.; Barnard, J.; Nguyen, T. M. A.; Belmonte, Wainberg, M. A.; Parniak, M. A. *J. Virol*. **1997**, *71*, 3023.
[5] Miyauchi, H.; Tanio, T.; Ohashi, N. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2377.
[6] Piergentili, A.; Quaglia, W.; Giannella, M.; Bello, F. D.; Bruni, B.; Buccioni, M.; Carrieric, A.; Ciattini, S. *Bioorg. Med. Chem.* **2007**, *15*, 886.
[7] (a) Parker,R. E.; Isaacs, N. S. *Chem. Rev*. **1959**, *59*, 737;(b) Buchanan, J.G.; Sable, H.Z. In. Selective Organic Transformations; Thyagarajan, B. S., Ed.; Wiley, **1972**; (c) A. Rao, S. Paknikar, S. K. Kirtane, *Tetrahedron* **1983**, *39*, 2323;(d) J. G. Smith, *Synthesis* **1984**, 629.

[8] (a) Sharpless, K. B. *Chem. Br*. **1986**, *22*, 38; (b) Pfenninger, A. *Synthesis* **1986**, 89;(c) Hanson, R. M. *Chem. Rev*. **1991**, *91*, 437.
[9] (a) R. Patel, V. P. Srivastava, L. D. S. Yadav, *Synlett* **2010,** 1797**;** (b) H. S. Park, D. W. Kwon, K. Lee, Y. H. Kim, *Tetrahedron Lett.* **2008**, *49*, 1616;(c) S. Antoniotti, E. Dunach, *Tetrahedron Lett.* **2009**, 50, 2536.
[10] Yavari, I.; Ghazanfarpour-Darjani, M.; Solgi, Y.; Ahmadian, S. *Helv. Chim. Acta.* **2011**, *94*, 639.