ORGANIC LETTERS

2011
Vol. 13, No. 9
2330–2333

Synthesis of *S*-(2-Thioxo-1,3-dithiolan-4-yl)-methyl Dialkylcarbamothioate and *S*-Thiiran-2-ylmethyl Dialkylcarbamothioate via Intermolecular O−S Rearrangement in Water[†,‡]

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Received March 4, 2011

ABSTRACT

A facile synthesis of *S*-(2-thioxo-1,3-dithiolan-4-yl)methyl dialkylcarbamothioates (3) and *S*-thiiran-2-ylmethyl dialkylcarbamothioate (5) has been reported by the reaction of 5-(chloromethyl)-1,3-oxathiolane-2-thione (1) with sodium dialkylcarbamodithioate (2) and dialkylamine (4), respectively, through intermolecular O−S rearrangement in water. A plausible mechanism of formation of the title compounds has also been proposed.

Organosulfur compounds are important intermediates for the synthesis of various biologically active molecules.[1] Thiocarbamates, a class of organosulfur compounds are of great interest as these exhibit anesthetic,[2] fungicidal,[3] spermicidal,[4] pesticidal,[5] and anti-HIV activities.[6] In addition, these compounds are well-known for their use as commercial herbicides.[7] Organic trithiocarbonates have received much attention because of their various industrial, synthetic, and medicinal applications.[8]

[†] CDRI Communication no. 8039.

[‡] Dedicated to the International Year of Chemistry 2011.

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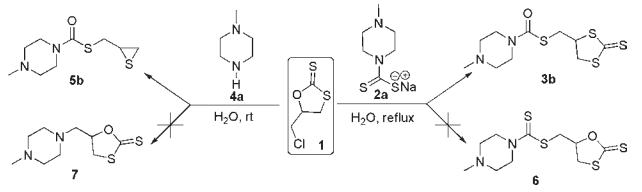
10.1021/ol2005825
Published on Web 04/01/2011

These compounds have extensively been used as pharmaceuticals,[9] agrochemicals,[10] and intermediates[8a,11] for the preparation of acyclic and cyclic compounds having two sulfur-containing functional groups on adjacent carbon atoms.[12] There are several publications illustrating intramolecular or intermolecular oxygen sulfur exchange.[13] In our ongoing efforts[4] to develop dually active vaginal microbicides, we attempted to hybridize a spermicidal pharmacophore dithiocarbamate[4,14] and microbicidal moiety thiocarbonates.[15]

Scheme 1. Reactions of 5-(chloromethyl)-1,3-oxathiolane-2-thione (**1**) with (**2a**) and (**4a**)



In a logical extension of our initial study, it was envisaged that the reaction of sodium 4-methylpiperazine-1-carbodithioate (**2a**) with 5-(chloromethyl)-1,3-oxathiolane-2-thione (**1**) would give rise to *S*-(2-thioxo-1,3-oxathiolan-5-yl)methyl 4-methylpiperazine-1-carbodithioate (**6**, Scheme 1). However, contrary to our expectation, the desired compound **6** was not obtained, and surprisingly, the major product was found to be *S*-(2-thioxo-1,3-dithiolan-4-yl)methyl 4-methylpiperazine-1-carbothioate (**3b**), isolated in 96% yield. The structural elucidation of compound **3b** revealed that oxygen−sulfur exchange between dithiocarbamate (**2a**) and cyclic dithiocarbonate (**1**) had occurred. Moreover, to study the course of the reaction, efforts were made to replace the chlorine atom of **1** with *N*-methylpiperazine (**4a**). The results obtained were again unusual as *S*-thiiran-2-ylmethyl 4-methylpiperazine-1-carbothioate (**5b**) was formed instead of **7** (Scheme 1). However, it is interesting to note that an alkyl (other than chloromethyl)-substituted 1,3-oxathiolane-2-thione reacted with amines to undergo ring-opening reaction and to obtain thiourethanes having thiol moiety.[16] There seems to be no direct precedent for this rearrangement, although there is some resemblance[17] provided the motivation to pursue the rearrangement chemistry illustrated in scheme 1. In this paper, a new route toward the synthesis of *S*-(2-thioxo-1,3-dithiolan-4-yl)methyl dialkylcarbamothioates (**3**) and *S*-thiiran-2-ylmethyl-dialkylcarbamothioate (**5**) utilizing 5-(chloromethyl)-1,3-oxathiolane-2-thione (**1**)[18] is reported where **1** has been used for the first time as the starting material.

To explore the versality of the reaction (Scheme 1), the reaction of **1** with various sodium dialkylcarbamodithioates (**2**) was studied. The reaction of sodium 4-methylpiperazine-1-carbodithioate (**2a**) with **1** was chosen as model reaction for optimization (Table 1). This model reaction was carried out in different solvents at room temperature as well as at reflux temperature. The duration of reaction and the isolated yields were observed. There was no progress in the reactions after hours at room temperature, while at reflux the reactions were completed at different time periods. Significant rate enhancement was observed in water compared to organic solvents (Table 1). This acceleration is probably due to factors such as hydrophobic effect,[19] enhanced hydrogen bonding in the transition state,[20] etc.

Table 1. Reaction of **1** with Sodium 4-Methylpiperazine-1-Carbodithioate (**2a**)[a]

entry	solvent[b]	time (h)	yield[c] (%) of **3b**
1	methanol	2	70
2	THF	8	67
3	ethyl acetate	9	62
4	acetonitrile	6.5	72
5	chloroform	7	80
6	DCM	10	77
7	water	1	96

[a] 1.2 equiv. [b] Reaction carried out at reflux temperatures. [c] Isolated yields.

The structure of **3b** was elucidated by IR, ^{1}H NMR, and ^{13}C NMR spectra. In the IR spectrum, a strong peak was observed at 1650 cm^{-1} for C=O, while in the ^{13}C NMR spectrum, there was no chemical shift for N−(C=S)−S (δ 192−195)[4] and O−(C=S)−S (δ 210)[16] while there were chemical shifts at δ 165.2 [N−(C=O)−S] and δ 226.6 [S−(C=S)−S][21] that justified the presence of thiocarbamate and trithiocarbonate groups in **3b**. Thus, the unusual product was presumably formed via oxygen sulfur swap over between **1** and **2a**. In addition, the aliquots obtained during the reaction exhibited *m*/*z* 185 ($M^+ + 1$) in the ESI−MS spectrum, which revealed the intermittent formation of intermediate **IV** (Scheme 2).

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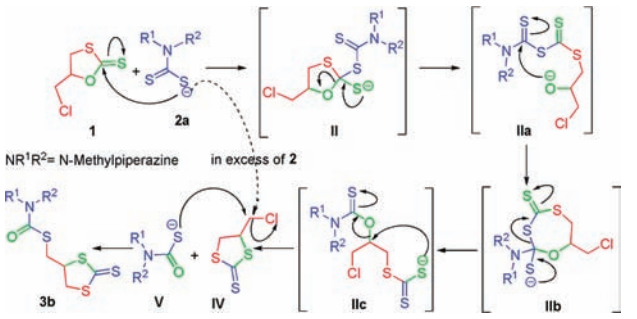
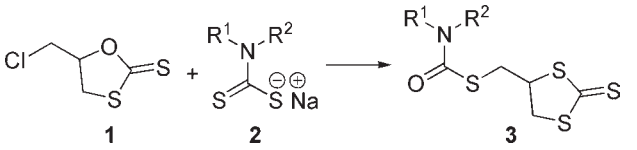
Scheme 2. Plausible Mechanism of the Reaction of **1** with **2**

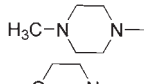
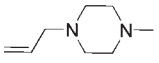
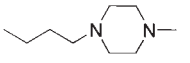
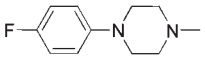
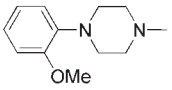
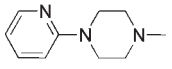
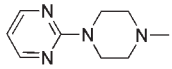


It was further supported by the observation of molecular ion peak at m/z 325 ($M^+ + 16$), when **2a** was taken in excess.

The structure of the products (Table 2) was confirmed by 2D NMR (COSY, HMBC, and HSQC) spectroscopy of **3c**. In the $^1H-^1H$ COSY spectrum, there was a correlation between C-4 proton at δ 4.50 and the protons at C-3 (δ 3.87, 4.13) as well as with protons at C-6 (δ 3.41) (A, Figure 1). In the HMBC spectrum, C-1 (δ 226.5) correlated with protons present at δ 3.87, 4.13, and 4.50. In addition, C-8 (δ 165.8) associated with the protons at δ 3.41 and 3.68. C-4 (δ 59.7) was found to correlate with the protons having chemical shifts δ 3.41, 3.87, and 4.13 while C-3 (δ 33.0)

Table 2. Synthesis of *S*-(2-Thioxo-1,3-dithiolan-4-yl)methyl Dialkylcarbamothioates[a]



entry	3	NR^1R^2	time (min)	yield[b] %
1	**3a**		55	82
2	**3b**		50	96
3	**3c**		60	80
4	**3d**		60	85
5	**3e**		60	90
6	**3f**		60	80
7	**3g**		60	82
8	**3h**		50	86
9	**3i**		50	89

[a] All reactions were carried out at 100 °C in water. [b] Isolated yields.

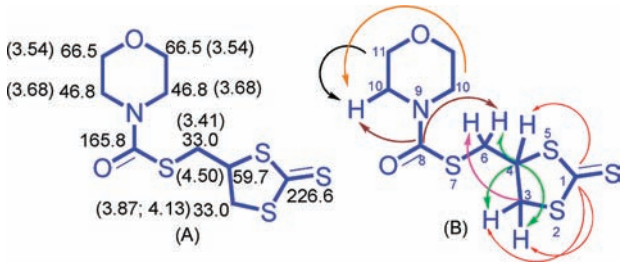


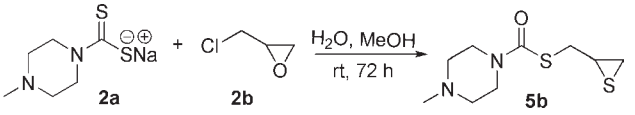
Figure 1. ^1H NMR (in parentheses) and ^{13}C NMR values (A) and ^{13}C to ^1H HMBC (B) of **3c** in $CDCl_3$.

correlated with protons at δ 3.41 and 4.50, respectively (B, Figure 1).The generality and scope of this rearrangement was established by several additional examples (Table 2).

The plausible mechanism (Scheme 2) was proposed on the basis of previous analogy[17] and the detection of the formation of intermediate **IV** and a peak at m/z 16 more than the molecular weight of **3b** in ESI-MS. It involves the initial nucleophilic attack of dithiocarbamates ion (**2a**) on C═S of **1** resulting in the intermediate **IV** via **II**−**IIc**, which finally gave rearranged product (**3b**) by straightforward nucleophilic substittution of chloride ion from **IV** with thiocarbamate ion (**V**).

To further extend this rearrangement, **1** was reacted with secondary amine (**2a** without S═C−S$^-$). Thus, treatment of *N*-methylpiperazine (**4a**, 1.2 equiv) with **1** unexpectedly gave **5b** in quantitative yield instead of the usual chlorine-substituted product **7** apparently via the oxygen−sulfur exchange (Scheme 1). The reaction occurred in ethyl acetate and methanol as well. All of the synthesized compounds through this route (Table 3) have been structurally confirmed by ^1H NMR, ^{13}C NMR, MS, and IR spectroscopy. The results are also reported in our previous publication[17] to synthesize *S*-thiiran-2-ylmethyl dialkylcarbamothioate by means of a different course (Scheme 3).

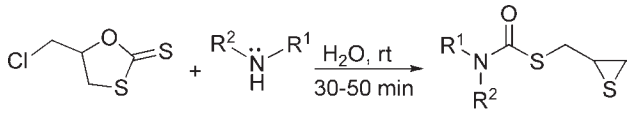
Scheme 3. Synthesis of *S*-Thiiran-2-ylmethyl-4-methylpiperazine-1-carbothioate (**5b**)



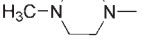
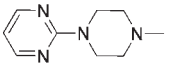
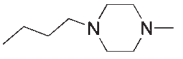
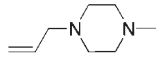
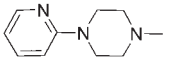
As shown in Scheme 4, the mechanism may be proposed on the basis of product obtained. The dialkyl amine (**4**) participates in nucleophilic attack to open the 1,3-oxathiolane-2-thione ring (**1**) and to give the intermediate (**IIIb**), which further cleaves in to **IVa** and **IVb** by means of oxygen sulfur rearrangement. Finally, *S*-thiiran-2-ylmethyl-dialkylcarbamothioate (**5**) yields by way of simple nucleophilic substitution.

Conclusively, two new routes (Scheme 1) for the synthesis of *S*-(2-thioxo-1,3-dithiolan-4-yl)methyl dialkylcarbamothioate

Table 3. Synthesis of *S*-Thiiran-2-ylmethyl Dialkylcarbamothioate



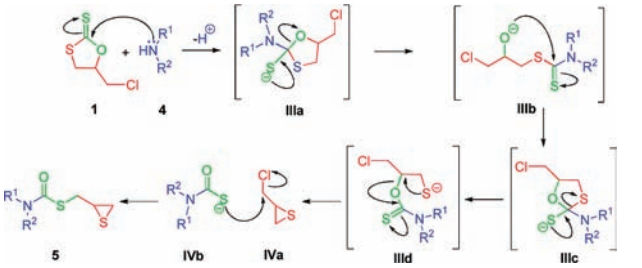
1 4 5

entry	5	NR^1R^2	time (min)	yield[a,b] %
1	**5a**		40	90 (96)[17]
2	**5b**		30	95
3	**5c**		45	76 (68)[17]
4	**5d**		45	94 (83)[17]
5	**5e**		50	83 (50)[22]
6	**5f**		50	88 (78)[17]
7	**5g**		35	76
8	**5h**		50	82
9	**5i**		50	80 (66)[17]

[a] Isolated yield. [b] Values in parentheses indicate reported % yield.

(**3**) and *S*-thiiran-2-ylmethyl dialkylcarbamothioate (**5**) using 5-(chloromethyl)-1,3-oxathiolane-2-thione (**1**) as a reactant

Scheme 4. Mechanistic Pathway of the Reaction of **1** with **4**



for the first time, are described as passing through a remarkable rearrangement. To the best of our knowledge, the so-called products derived from Scheme 1 (Table 2) have not been documented in the literature to date. The study may facilitate the synthesis of structural analogues of **3** and **5** and further biological evaluation.

Acknowledgment. We gratefully acknowledge the technical assistance received from Mrs. Tara Rawat, Technical Officer, CDRI, Lucknow and Research Fellowships from the University Grants Commission (N.L. and L.K.) and Council of Scientific and Industrial Research (A.S. and S.J.). Staff members of SAIF Division, CDRI, Lucknow, are acknowledged for providing the spectral data. This study was partly supported by a grant from the Ministry of Health and Family Welfare, Government of India.

Supporting Information Available. Spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.