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Amine-catalyzed preparation of oxygenated derivatives of symmetric trisulfides

Mahbubeh Pourshahbaz [a], Mohammad Joshaghani [a,b,*], Ezzat Rafiee [a,b], Jahangir Shahmoradi [a], Fereshteh Emami [a], Asieh Iranpour [a]

[a] Chemistry Department, Faculty of Science, Razi University, Kermanshah, Iran
[b] Kermanshah Oil Refining Company, Kermanshah, Iran

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ABSTRACT

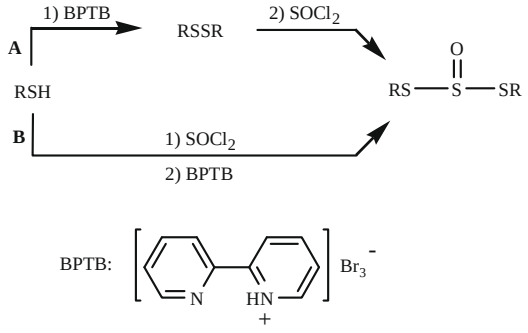
Bipyridinium tribromide reacts with thiols in the presence of thionyl chloride to yield symmetric trisulfide derivatives (RSS(O)SR) as the major products. Two possible mechanisms are advanced to explain the chemistry.

Trisulfides are important organic sulfur compounds with significant industrial and biological importance. These compounds have been found in many natural sources such as onions and garlic, brown algae and various animals.[1–4] Numerous routes have been developed for the preparation of trisulfides. The most routine are the reactions of sulfur dichloride with thiols,[5] alkyl halides with sodium trisulfide,[6] thiols with sulfur,[7] etc.[8–13] Among trisulfides, trisulfide 2-oxides have been shown to be sources of sulfur monoxide which is a challenging problem in organic and inorganic chemistry.[2b,14–16] As a result, there is still a need for the development of a general and efficient methodology to synthesize trisulfides and their oxygenated derivatives.

We recently reported that bipyridinium tribromide (BPTB) is a mild and efficient oxidant in the oxidative coupling of thiols to the corresponding symmetric disulfides.[17] The easy preparation of the reagent, short reaction times and excellent yields of the disulfide as the only product without over-oxidation made this reagent useful for the preparation of disulfides. The relative higher reactivity of BPTB compared to that of the well-known alternative, pyridine hydrobromide perbromide suggested that the unprotonated nitrogen may act as a base and remove the acid formed during the reaction. Therefore, the oxidative coupling of thiols is carried out under base-catalyzed conditions. On the other hand, base-catalyzed preparation of trisulfides from the corresponding thionyl chloride has been reported to occur in good yields.[7] Thus, we investigated the conversion of thiols into the corresponding symmetric trisulfide 2-oxides using thionyl chloride in the presence of BPTB. The effect of sequential addition of BPTB and thionyl chloride was also investigated (Scheme 1).

The results show that trisulfide 2-oxides are obtained as the major products, probably with other polysulfides as minor side products, under mild conditions at room temperature.[18]

A series of aromatic, benzylic, heterocyclic and alkyl thiols were reacted with thionyl chloride via either route **A** which proceeds by way of the corresponding symmetric disulfide intermediate, or route **B** (Table 1). Aromatic thiols containing weak electron-donating groups such as methyl and chloro were converted into the corresponding trisulfide 2-oxides in excellent yields and relatively short reaction times, (Table 1, entries 1–4). The presence of a strong electron-donating group such as NH_2 at the *ortho* position decreased the yield dramatically (Table 1, entry 6). Benzyl thiol was converted into the corresponding symmetric trisulfide 2-oxide in a similar manner but required a longer reaction time and the product was obtained in a lower yield (Table 1, entry 5). The two relatively bulky and inactive heterocyclic thiols, benzothiazole-2-thiol and 1*H*-benzimidazole-2-thiol (Table 1, entries 7 and 8) were converted in lower yields and required longer reaction times. Alkyl thiols failed to react via route **A** but were converted into the corresponding symmetric trisulfide-2-oxides via route **B** in very long reaction times (Table 1, entries 9–12). However, addition of thionyl chloride to the alkyl disulfides yielded the desired



R= Alkyl, Aryl, Heterocycle

Scheme 1.

* Corresponding author. Present address: Chemistry Department, Faculty of Science, Razi University, Kermanshah, Iran. Tel./fax: +98 831 4274559.
E-mail address: mjoshaghani@razi.ac.ir (M. Joshaghani).

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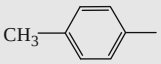
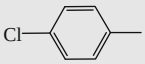
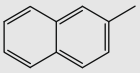
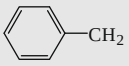
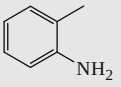
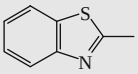
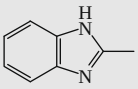
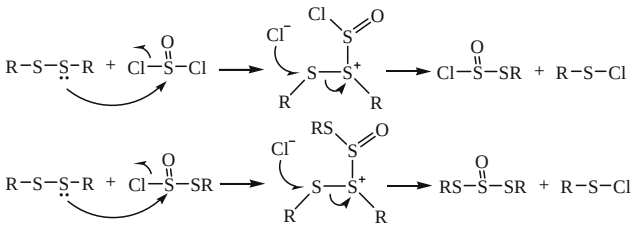
Table 1
Trisulfide-2-oxide formation via routes **A** and **B**[a]

Entry	R	Procedure **A**		Procedure **B**		Ref[c]
		Time (min)	Yield[b] (%)	Time (min)	Yield (%)	
1		15	95	20	90	15d
2		15	90	20	85	15d
3		15	90	20	85	20a
4		15	95	25	85	20b
5		20	85	30	75	–
6		180	15	180	15	–
7		25	80	35	75	–
8		25	80	35	75	–
9	n-C_4H_9–	120	75 (10)	180	80	–
10	n-C_8H_{17}–	120	70 (15)	180	80	–
11	$HOCH_2CH_2$–	–	–	360	65	–
12	$HOCH_2CH(SH)CH_2$–	–	–	720	75[d]	–
13	Me	45	85 (10)	–	–	–
14	Et	60	80 (10)	–	–	–

[a] Reaction conditions: room temperature, acetonitrile (5 ml), thiol (2 mmol), BPTB (1 mmol) and thionyl chloride (1 mmol).
[b] The figures in parentheses are the yields of the corresponding tetrasulfide-2-oxides.
[c] Known products were characterized based on literature data and the new products were characterized based on spectroscopic data as well as elemental analysis (see Supplementary data).
[d] Unresolved mixture of products.

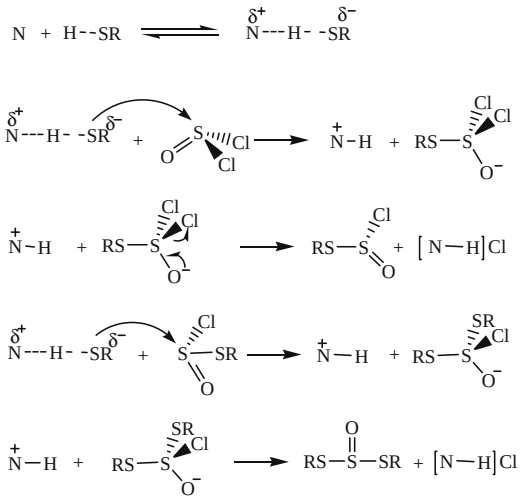


Scheme 2.

trisulfide-2-oxides along with tetrasulfide-2-oxides as side products (Table 1, entries 9, 10, 13 and 14).

Interestingly, the reaction was very sensitive to the sequence of the addition of thionyl chloride and BPTB. Addition of BPTB (Scheme 1, Procedure **A**) first resulted in the formation of the corresponding disulfide, which was converted into the trisulfide-2-oxide on addition of $SOCl_2$. The reactions failed to give trisulfide 2-oxides in the absence or in the presence of a low concentration of thionyl chloride. In these cases, the only products were the corresponding disulfides. On the other hand, trisulfide 2-oxides were formed directly on addition of $SOCl_2$ followed by BPTB (Scheme 1, Procedure **B**). In route **A**, the symmetric trisulfide-2-oxides are probably produced via a sulfur atom insertion mechanism (Scheme 2).[10]

In route **B**, a base-catalyzed mechanism may be responsible for the formation of trisulfide 2-oxides from the corresponding thiols (Scheme 3). This mechanism is similar to that proposed for the reaction of inorganic nucleophiles and sulfur[19] wherein 'N' represents the unprotonated nitrogen of BPTB. To confirm the base-catalyzed mechanism, similar reactions were carried out in the



Scheme 3.

presence of triethylamine instead of BPTB, albeit in longer reaction times. Similar results obtained confirm that BPTB may act as a base in these reactions.

The reactions are pH sensitive and were carried out in solutions of different pH. The best results were obtained in alkali media at a pH of about 9–10 using NH_3/NH_4^+ buffer.

The trisulfide 2-oxide products were isolated and characterized by FTIR and ^1H NMR spectroscopy and elemental analysis (see Supplementary data).[18] The presence of a relatively sharp band at about 1090–1130 cm^{-1} was attributed to the S=O stretching frequency. The ^1H NMR spectra were very similar to the corresponding disulfide albeit with a greater shift into the downfield region due to the presence of the relatively strong electron-withdrawing S=O group.

In conclusion, the high selectivity along with very short reaction times, simple work-up, ease of handling and significant stability of the BPTB reagent are advantages of this system.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.104.

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18. *General procedures for the preparation of trisulfide-2-oxides*: *Procedure* **A**: To a stirred solution of a thiol (2 mmol) in acetonitrile (5 ml) was added BPTB (0.4 g, 1 mmol). A pale yellow solid precipitated. Thionyl chloride (1 mmol) was added gradually and the pH of the solution was maintained at 9.5 using NH_3/NH_4^+ buffer. The mixture was stirred and the progress of the reaction was monitored by TLC (*n*-heptane–EtOAc, 3:1). After the time according to Table 1, a pale yellow solid formed which was extracted with ether (3 × 10 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was recrystallized from (*n*-heptane–EtOAc, 3:1) to afford the pure trisulfide 2-oxide product. For characterization see Supplementary data.*Procedure* **B**: A similar procedure to that described above was used for the synthesis of the trisulfide 2-oxide involving gradual addition of BPTB (1 mmol) to a stirred solution of a thiol (2 mmol) in acetonitrile (5 ml) and thionyl chloride (1 mmol).
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