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TRIMETHYLCHLOROSILANE (TMCS) CATALYZED EFFICIENT REDUCTION OF SULFOXIDES TO THIOETHERS USING 3-MERCAPTOPROPIONIC ACID UNDER MILD REACTION CONDITIONS

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A variety of alkyl and aryl sulfoxides were successfully deoxygenated using 3-mercaptopropionic acid as reducing agent and a catalytic amount of trimethylchlorosilane (10–20 mol%) in CH₃CN at ambient temperature.

Sulfoxides are important intermediates in a variety of synthetic transformations, especially as chiral auxiliary during many asymmetric syntheses.¹ However, in the majority of their synthetic applications, it is necessary to remove the residue of the sulfoxide moiety from the target molecules. Such a transformation can be most easily achieved by a two-step procedure that involves the deoxygenation of sulfoxides to the corresponding sulfides followed by further reductive desulfurization by treatment with either Raney nickel or dissolving metal systems such as lithium in liquid ammonia. A survey of the literature reveals that though several methods have been reported for the reduction of sulfoxides,^{2,3} there still remain the important problems of reaction, i.e., many of them need rather drastic conditions, long reaction times,³ⁱ or stoichiometric amounts of expensive reagents.^{3j,k} Among the reported protocols, sulfur compounds such as thiols,⁴ sulfides,⁵ disulfides,⁶ thionyl chloride,⁷ elemental sulfur,⁸ and 1,3-dithianes,⁹ have been used for the conversion of sulfoxides to thioethers. However, many of these methods suffer from drawbacks such as long reaction

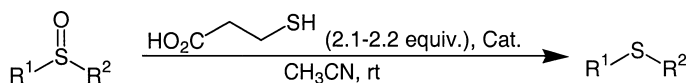
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time,⁴⁻⁶ harsh acidic conditions,^{4,7} high temperature,⁸ or difficult work-up procedures.^{4,9} Therefore, there is still a demand for the development of a new efficient method for this transformation using inexpensive and common laboratory reagents.

RESULTS AND DISCUSSION

Very recently we discovered that TMCS effectively catalyzes oxidative coupling of a variety of structurally diverse thiols to the corresponding disulfides in the presence of DMSO as the final oxidant.¹⁰ Along this line, we have found that this catalyst also efficiently accelerates the reduction of sulfoxides using a thiol. Thiols that were utilized in this study are thiophenol, butyl mercaptane, thiosalicylic acid (2-TSA), and 3-mercaptopropionic acid (3-MPA). We first examined the reduction of phenylmethyl sulfoxide (PMS) using the thiols in the presence of TMCS as catalyst at room temperature. Among all of the above-mentioned thiols, we chose 3-mercaptopropionic acid in the subsequent studies owing to its faster and cleaner reaction. Moreover, the presence of a $-\text{CO}_2\text{H}$ group in this molecule makes an easier separation of the by-product disulfide during the work-up stage through a simple aqueous NaOH washing of the reaction mixture. On the other hand, though 2-TSA has also the same property as 3-MPA; however, the latter is the superior reducing agent than the former from an atom economic point of view. among different solvents such as CH_3CN , CH_2Cl_2 , CHCl_3 , and THF that we used for the reduction of PMS as a model substrate, CH_3CN turned out to be the most suitable one. It is also worth mentioning that in CH_2Cl_2 and CHCl_3 the reactions are very sluggish. The optimum ratios of the reacting species were also studied by using TMCS as catalysts and PMS as substrate. The optimum molar ratio was found to be 1: 2.1: 0.1, for PMS:3-MPA:TMCS, respectively, at room temperature (Scheme 1, Table I, entries 1, 2).¹¹



Cat. = TMCS (10-20 mol%)

SCHEME 1

In a similar way, we have also discovered that the same ratios work well for less hindered arylalkyl- and dialkyl sulfoxides. Inspection of the data, which are summarized in Table I, clearly shows that various

TABLE I TMCS Catalyzed Deoxygenation of Sulfoxides to Thioethers Using 3-Mercaptopropionic Acid

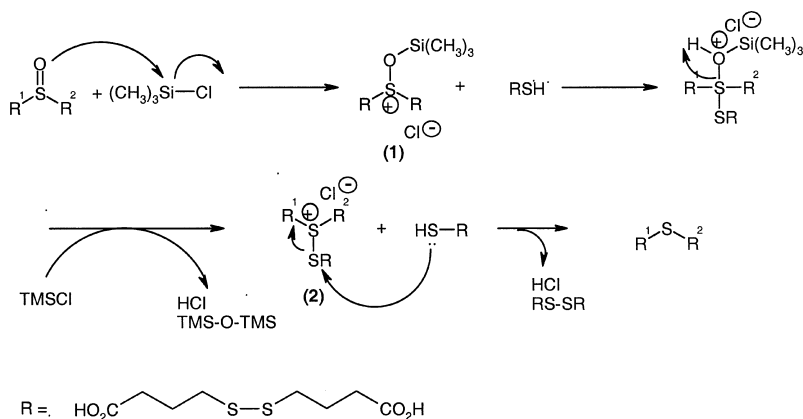
Entry	R ¹	R ²	Time (h)	Subst./3-MPA/ Catalyst	Yield (%) ^a
1	Ph	Me	1	1:2.1:0.1	93
2	Ph	Et	3	1:2.1:0.1	97
3	Ph	Bu	3	1:2.1:0.1	97
4	Ph	PhCH ₂ CH ₂	0.5	1:2.1:0.1	94
5	PhCH ₂	PhCH ₂	1	1:2.1:0.1	95
6	Ph	PhCH ₂	0.5	1:2.1:0.1	93
7	Ph	Allyl	3	1:2.1:0.1	93
8	Bu	Bu	0.5	1:2.1:0.1	96
9	Ph	<i>sec</i> -Bu	10	1:2.2:0.2	90
10	Ph	<i>i</i> -Pr	16	1:2.2:0.2	90
11	3-MeC ₆ H ₄	<i>i</i> -Pr	18	1:2.2:0.2	70
12	Ph	<i>c</i> -C ₅ H ₉	40	1:2.2:0.2	95
13	Ph	<i>c</i> -C ₆ H ₁₁	42	1:2.2:0.2	90
14	Ph	Ph	48	1:2.2:0.1	58
15	4-MeC ₆ H ₄	4-MeC ₆ H ₄	48	1:2.2:0.1	60
16	<i>p</i> -NO ₂ C ₆ H ₄	Ph	48	1:2.2:0.1	40

^aIsolated yields.

types of both dialkyl- and arylalkyl including benzylic and allylic sulfoxides, are efficiently deoxygenated to their sulfides in excellent yields under similar reaction conditions (Table I, entries 3–16). Efficient deoxygenation of dibenzyl-, benzyl phenyl-, and allylphenyl sulfoxides to the corresponding thioethers in excellent yields without the cleavage of sensitive C–S bond, shows the usefulness of the presented method (Table I entries 9–14). On the other hand, it was found that in the case of substrates bearing at least one bulky group, larger amounts of 3-MPA (2.2 equiv.) and the catalysts (0.2 equiv.) are required for completion of the reactions (Table I, entries 17–32). However, substitution of one nitro group in the case of *p*-nitrophenyl phenyl sulfoxide gave somewhat lower yields together with the formation of unidentified products (Table I, entries 31, 32). This is presumably due to the reaction of the 3-MPA/TMCS system with the nitro group.

The exact mechanism of this reaction is not clear. However, a plausible explanation for this is that at the first step of the reaction TMSCl reacts with the sulfoxide to produce an activated species **1**, which in turn reacts with the thiol (3-mercaptopropionic acid) to give the intermediate **2** with concomitant release of HCl and hexamethyldisiloxane. Then, a rapid reaction of **2** with a second molecule of the thiol leads to disulfide and evolution of dimethyl sulfide. The HCl then re-enters the reaction cycle and acts as TMCS (Scheme 2). In order to

inspect the correctness of this opinion, we examined the oxidation of thiophenol using DMSO (3 equiv.) in the presence of 10 mol% TMSCl and pyridine (2 equiv.). Interestingly, the deoxygenation reaction was completely retarded in this case.



SCHEME 2

In conclusion, we have demonstrated that TMCS is an excellent catalysts for the convenient deoxygenation of various types of sulfoxides using 3-mercaptopropionic acid (3-MPA). The present protocol is superior to most of the existing thiol-based sulfoxide reduction methods with regard to its very simple work-up procedure. Moreover, in the present procedure, the reaction conditions are quiet mild accompanied with reasonable reaction times.

EXPERIMENTAL

General Procedure for Deoxygenation of Sulfoxides

To a solution of Sulfoxide (2 mmol) and 3-MPA (4.2–4.4 mmol) in dry CH_3CN (10 mL), TMCS (0.2–0.4 mmol) was added, and the resulting solution was stirred at room temperature. After completion of the reaction (TLC), an aqueous solution of NaOH (5%, 25 mL) was added and the mixture was extracted with Et_2O (3×20 mL). The organic extracts were washed successively with NaOH (5%, 15 mL), water (2×15 mL) and dried over anhydrous Na_2SO_4 . Evaporation of the solvent under reduced pressure gave almost pure products. Further purification was performed by vacuum distillation or re-crystallization in an appropriate solvent to afford pure thioethers (Table I).

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