N-Bromosuccinimide and Iodine Catalyzed Highly Efficient Deoxygenation of Sulfoxides to Thioethers Using 3-Mercaptopropionic Acid under Mild Reaction Conditions

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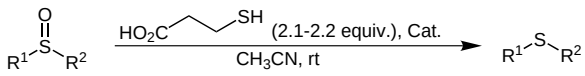
Received 12 March 2003; revised 30 May 2003

Abstract: A variety of alkyl and aryl sulfoxides have been successfully deoxygenated using 3-mercaptopropionic acid as a reducing agent and a catalytic amount of either NBS or I_2 (5–10 mol%) in MeCN at ambient temperature. Under the described reaction condition, acid sensitive substrates such as acetals remained intact after several hours.

Key words: sulfoxides, deoxygenation, thioether, catalysis

Sulfoxides are important intermediates in a variety of synthetic transformation, especially as chiral auxiliaries 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 transformations 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 remains important problems with the 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 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. In the development of new methods for functional group transformations, we are especially interested in exploring the potential use of neutral or nearly neutral catalysts.[10] Along this line, we have found that either *N*-bromosuccinimide or iodine efficiently accelerates the reduction of sulfoxides using a thiol. Thiols that were utilized in this study are thiophenol, butyl thiol, thiosalicylic acid (2-TSA), and 3-mercaptopropionic acid (3-MPA). We first examined the reduction of phenyl methyl sulfoxide (PMS) using the thiols in the presence of NBS catalyst at room temperature. Although, all of the above-mentioned thiols worked well as reducing agent, we chose 3-mercaptopropionic acid in the subsequent studies owing to the fact that the presence of the CO_2H group in this molecule allows 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, the latter is a superior reducing agent than the former from an atom economic point of view. Among different solvents such as MeCN, CH_2Cl_2, $CHCl_3$, and THF that we used for the reduction of PMS as a model substrate, MeCN 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 both I_2 and NBS as catalysts and PMS as substrate. The optimum molar ratio was found to be 1:2.1:0.05; for PMS–3-MPA–catalyst, respectively, at room temperature (Scheme 1, Table 1, entries 1, 2) (see experimental section).



Cat. = NBS or I_2 (5-10 mol%)
Method A = NBS; Method B = I_2

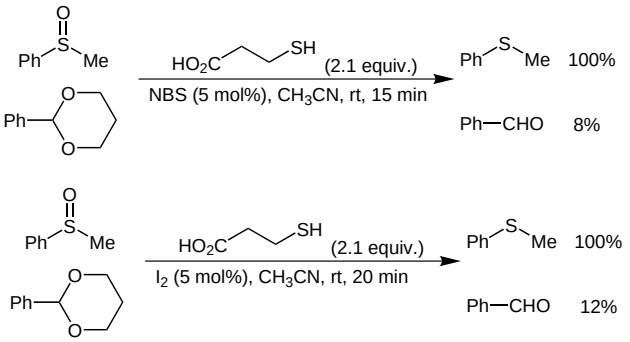
Scheme 1

In a similar way, we have also discovered that the same ratios work well for less hindered aryl alkyl and dialkyl sulfoxides. Inspection of the data, which are summarized in Table 1, clearly shows that various types of both dialkyl- and aryl alkyl including benzylic and allylic sulfoxides are rapidly deoxygenated to their sulfides in excellent yields under similar reaction conditions (Table 1, entries 3–16). Efficient deoxygenation of dibenzyl, benzyl phenyl, and allyl phenyl sulfoxides to the corresponding thioethers in excellent yields without the cleavage of the sensitive CS bond, shows the usefulness of the present method (Table 1, entries 9–14). On the other hand, it was found that in the case of diaryl sulfoxides or those substrates carrying at least one bulky group, larger amounts of 3-MPA (2.2 equiv) and the catalysts (0.1 equiv) are needed for completion of the reactions (Table 1, entries 17–32).

Synthesis 2003, No. 12, Print: 02 09 2003. Web: 30 07 2003.
Art Id.1437-210X,E;2003,0,12,1875,1877,ftx,en;Z03603SS.pdf.
DOI: 10.1055/s-2003-40981

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 1, entries 31, 32). This is presumably due to the reaction of the 3-MPA–NBS system with the nitro group.

In order to further show the mildness of the method, we have also conducted the reduction of PMS in the presence of 2-phenyl-1,3-dioxane according to protocol A and B in Scheme 2.



Scheme 2 Conversions were determined using NMR of the crude products

This result suggests that the protocols may be generally useful for the conduction of similar chemoselective deoxygenation reaction in poly-functional molecules.

In conclusion, we have demonstrated that either NBS or I_2 are excellent catalysts for convenient deoxygenation of various types of sulfoxides using 3-mercaptopropionic acid (3-MPA). Owing to the special design of the reagent system, the present protocols are superior to most of the existing thiol-based sulfoxide reduction methods in regard to its very simple work-up procedure. Moreover, the present procedure also shows good chemoselectivity, and the reaction conditions are quiet mild accompanied with the short reaction times.

General Procedure for Deoxygenation of Sulfoxides

To a solution of sulfoxide (2 mmol) and 3-MPA (4.2–4.4 mmol) in anhyd CH_2Cl_2 (10 mL), NBS or I_2 (0.1–0.2 mmol) was added, and the resulting solution was stirred at r.t. After completion of the reaction (TLC), aq NaOH (5%, 25 mL) was added and the mixture was extracted with Et_2O (3×20 mL). The organic extracts were washed successively with aq NaOH (5%, 15 mL), water (2×15 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave almost pure product(s). Further purification was achieved by vacuum distillation or recrystallization in appropriate solvent to afford pure thioether (Table 1).

Acknowledgments

The authors appreciate Institute for Advanced Studies in Basic sciences (IASBS) Research Council for support of this work.

Table 1 NBS and Iodine Catalyzed Deoxygenation of Sulfoxides to Thioethers Using 3-Mercaptopropionic Acid

Entry	R^1	R^2	A or B[a]/ time (min)	Substrate/3-MPA/Catalyst	Yield (%)[b]
1	Ph	Me	A (10)	1:2.1:0.05	96
2	Ph	Me	B (20)	1:2.1:0.05	96
3	Ph	Et	A (15)	1:2.1:0.05	95
4	Ph	Et	B (22)	1:2.1:0.05	91
5	Ph	Bu	A (15)	1:2.1:0.05	91
6	Ph	Bu	B (25)	1:2.1:0.05	93
7	Ph	$PhCH_2CH_2$	A (90)	1:2.1:0.05	95
8	Ph	$PhCH_2CH_2$	B (90)	1:2.1:0.05	93
9	$PhCH_2$	$PhCH_2$	A (80)	1:2.1:0.05	98
10	$PhCH_2$	$PhCH_2$	B (90)	1:2.1:0.05	92
11	Ph	$PhCH_2$	A (100)	1:2.1:0.05	92
12	Ph	$PhCH_2$	A (120)	1:2.1:0.05	91
13	Ph	Allyl	A (15)	1:2.1:0.05	93
14	Ph	Allyl	B (60)	1:2.1:0.05	85
15	Bu	Bu	A (20)	1:2.1:0.05	90
16	Bu	Bu	B (25)	1:2.1:0.05	93
17	Ph	*s*-Bu	A (160)	1:2.1:0.05	91
18	Ph	*s*-Bu	B (180)	1:2.1:0.1	90
19	Ph	*i*-Pr	A (200)	1:2.2:0.1	90
20	Ph	*i*-Pr	B (240)	1:2.2:0.1	89
21	3-MeC_6H_4	*i*-Pr	A (200)	1:2.2:0.1	89
22	3-MeC_6H_4	*i*-Pr	B (240)	1:2.2:0.1	85
23	Ph	*c*-C_5H_9	A (140)	1:2.2:0.1	89
24	Ph	*c*-C_5H_9	B (140)	1:2.2:0.1	89
25	Ph	*c*-C_6H_{11}	A (140)	1:2.2:0.1	87
26	Ph	*c*-C_6H_{11}	B (240)	1:2.2:0.1	85
27	Ph	Ph	A (180)	1:2.2:0.1	91
28	Ph	Ph	B (300)	1:2.2:0.1	95
29	4-MeC_6H_4	4-MeC_6H_4	A (180)	1:2.2:0.1	90
30	4-MeC_6H_4	4-MeC_6H_4	B (400)	1:2.2:0.1	89
31	*p*-$NO_2C_6H_4$	Ph	A (24)[c]	1:2.2:0.1	65
32	*p*-$NO_2C_6H_4$	Ph	B (24)[c]	1:2.2:0.1	55

[a] Method A = NBS; Method B = I_2.
[b] Isolated yields.
[c] Reaction time in hours.

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