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A mild protocol for the deoxygenation of α-hydrogen-containing sulfoxides to the corresponding sulfides

Gurpreet S. Bhatia and Piotr P. Graczyk*

Department of Medicinal Chemistry, EISAI London Research Laboratories, University College London, Bernard Katz Building, London WC1E 6BT, United Kingdom

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Abstract—A mild method for the deoxygenation of α-hydrogen-containing sulfoxides to sulfides is reported. This synthetically useful and operationally simple protocol derives mechanistically from the Swern oxidation methodology.

Chiral sulfoxides have gained widespread use as auxiliaries in asymmetric synthesis. Their ability to control the formation of stereogenic centres mainly in carbon–carbon bond forming reactions is well documented.[1] After stereoinduction the sulfinyl moiety may be removed by deoxygenation to sulfide followed by the elimination of sulfur.

We recently required a very mild method to generate sulfides from the corresponding sulfoxides for our biological screening programmes. Examination of the literature revealed a plethora of reviews concerning this subject.[2,3] Among the numerous reagents reported for this task were hydrogen halides (HCl, HBr, HI),[4] sulfur compounds (H_2S, PhSH, MeCOSH),[5] phosphorus compounds (PBr_3, $POCl_3$, P_4S_{10}),[6] silicon compounds ($HSiCl_3$, Si_2Cl_6),[7] boranes,[8] metal hydrides ($LiAlH_4$, DIBAL-H, RedAl),[9] low-valent metal ions ($TiCl_3$, $CrCl_2$, VCl_2)[10] and other miscellaneous systems (carbenes, acid chlorides, metalloporphins and Grignard reagents).[3] More recent research in this area has demonstrated the use of $NaBH_4/I_2$[11] and $TiCl_4/In$[12] for deoxygenation of sulfoxides and the Lawesson's reagent[13] for similar systems. Unfortunately none of the current methods available were amenable to our sensitive classes of compounds[14] due to either the elevated temperatures involved, large excesses of reagents required, nondiscrimination against other functionalities present or the problematic removal of toxic and heavy metal by-products. In this context, an alternative deoxygenating protocol was sought.

The popularly used Swern reaction[15] [DMSO–$(COCl)_2$–Et_3N reagent system] employed for the oxidation of alcohols to aldehydes and ketones involves the concomitant reduction of DMSO to Me_2S. We reasoned that the replacement of DMSO with another sulfoxide and the use of a sacrificial alcohol under Swern-like conditions would afford the desired sulfide. We now report work towards this goal with our initial model system of 1-bromo-4-methanesulfinylbenzene **1** and the application of our findings to a number of other systems.

Treatment of sulfoxide **1** with oxalyl chloride (1 equiv) at −78 °C for 1 h followed by the addition of methanol (1.4 equiv) and then after a further 1 h triethylamine (2 equiv) led to only a small conversion of **1** (Table 1, entry 1, 12%)[16] into the relevant sulfide **2**. As expected, increasing the excess of reagents resulted in additional amounts of **2** being generated (entry 2). However, subsequent attempts to improve the yield of **2** by further increasing the amounts of reagents (entry 3) or by inclusion of 2% of DMAP (entries 4–5), led to little improvement.

As the observed degree of conversion might depend on the efficiency of formation of the alkoxysulfonium ion **4** (Scheme 1) and breakdown of ylide **5** into aldehyde/ketone R′RC=O and sulfide **6**, we decided to examine

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* Corresponding author. Tel.: +44-20-7413-1147; fax: +44-20-7413-1121; e-mail: piotr_graczyk@eisai.net

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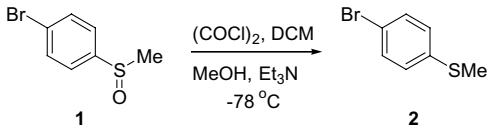
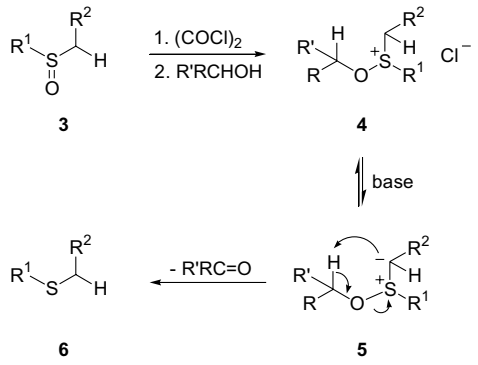
Table 1. Effect of varying amounts of $(COCl)_2$, MeOH, Et_3N and DMAP on deoxygenation of **1**



1 **2**

Entry	$(COCl)_2$ equivalents	MeOH equivalents	Et_3N equivalents	DMAP[a] equivalents	Conversion[b] (%)
1	1.0	1.4	2.0	0	12
2	1.3	2.0	3.0	0	61
3	2.0	3.0	4.0	0	68
4	3.0	8.0	10.0	0.02	69
5	4.0	10.0	12.0	0.02	68

[a] Added to the starting sulfoxide **1**.
[b] Based on the ^1H NMR ($CDCl_3$) spectrum of the reaction mixture after work-up.



3 **4** **6** **5**

Scheme 1. Swern oxidation/sulfoxide reduction mechanism.

the effect of alcohol R′RCHOH and solvent on the deoxygenation reaction.

Employment of ethanol (2 equiv) as the scavenger alcohol and Et_3N (3 equiv) in dichloromethane improved the conversion by about 5% (Table 2, entry 1, 67%; cf. Table 1, entry 2, 61%).

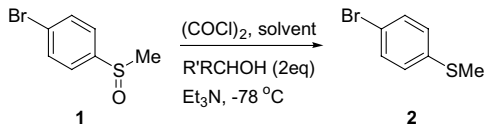
Replacement of dichloromethane with THF and a further increase in the amount of Et_3N (5 equiv) allowed 88% of **1** to be deoxygenated (Table 2, entry 2). However, further variations in the amount of oxalyl chloride (1.5–1.1 equiv; entries 3–4) and addition of DMSO (1 equiv; entry 5) showed no beneficial effect.

As the breakdown of intermediate ylide **5** could be further accelerated by increasing steric interactions between R′ and R (Scheme 1), the use of a more hindered scavenger alcohol was considered as another avenue to improve the yield of the deoxygenation product **6**. Indeed, utilization of propan-2-ol afforded almost quantitative conversion (Table 2, entry 6) with 75% isolated yield of sulfide **2**.[17]

In accordance with the mechanism presented in Scheme 1, only sulfoxides containing α-hydrogen atom(s) would be amenable to the aforementioned protocol. Thus, attempts to deoxygenate a sulfoxide not bearing an α-hydrogen such as diphenyl sulfoxide resulted in recovery of unreacted starting material. However, a number of commercially available sulfoxides bearing an α-hydrogen atom could be deoxygenated in high yield (Table 3).

In conclusion, we have developed a new protocol for the deoxygenation of α-hydrogen-containing sulfoxides to their corresponding sulfides. This technology complements those currently known for this transformation by virtue of its extremely mild (−78 °C) reaction conditions and its expected tolerance of a wide variety of functional groups.

Table 2. Effect of alcohol and solvent on deoxygenation of **1**

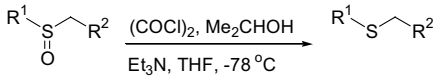


1 **2**

Entry	R′RCH	$(COCl)_2$ equivalents	Et_3N equivalents	Solvent equivalents	Conversion[a] (%)
1	Et	1.3	3.0	CH_2Cl_2	67
2	Et	1.3	5.0	THF	88
3	Et	1.5	5.0	THF	87
4	Et	1.1	5.0	THF	78
5	Et	1.3	5.0	THF[b]	82
6	Me_2CH	1.3	5.0	THF	99
7	Me_2CH	1.3	5.0	THF	99

[a] Based on the ^1H NMR ($CDCl_3$) spectrum of the reaction mixture after work-up.
[b] Contains DMSO (1 equiv).

Table 3. Sulfoxide deoxygenation examples[a]



3 **6**

Entry	R^1	R^2	GC retention times[b] (min)	Conversion (%)	
			3/6	GC	NMR[c]
1	*p*-BrC_6H_4	Me	30.21/25.70	100	100
2	*p*-BrC_6H_4	Me	30.21/25.70	100[d]	97
3	Ph	Me	25.25/19.84	99	100
4	*p*-MeC_6H_4	Me	27.70/21.80	100	100
5	$PhCH_2$	Ph	38.26/33.56	[e]	86
6	$CH_2CH_2CH_2$		22.76/10.50	99	100
7	*n*-C_4H_9	*n*-Pr	26.30/19.42	[e]	88

[a] Deoxygenation carried out in THF following the standard protocol[17] unless specified otherwise. Products were identified by reference to the corresponding commercially available sulfides.

[b] GC analysis of the crude reaction mixtures before work-up was performed on a gas chromatograph Perkin–Elmer 8500, 30M BPX5 0.32 mm I.D. wide bore capillary column; oven conditions: initial 50 °C hold for 8 min, ramp 8 °C/min, final 250 °C hold for 12 min.

[c] ^1H NMR (400 MHz, $CDCl_3$ or C_6D_6).

[d] Reaction carried out in CH_2Cl_2.

[e] Impossible to estimate due to co-elution of interfering peaks.

Acknowledgements

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16. Degree of conversion of sulfoxide into sulfide was determined based on 400 MHz ^1H NMR ($CDCl_3$) spectra after work-up.
17. Representative protocol for sulfoxide deoxygenation: To a stirred and cooled (−78 °C) solution of commercially available sulfoxide **1** (497 mg, 2.27 mmol) in THF (4 mL) under a nitrogen atmosphere was added oxalyl chloride (0.26 mL, 2.95 mmol). After 1 h, propan-2-ol (0.35 mL, 4.54 mmol) was added dropwise. The reaction mixture was stirred for a further 1 h and Et_3N (1.58 mL, 11.35 mmol) was added. After 3 min, the mixture was removed from the solid CO_2/acetone bath, allowed to warm to room temperature and partitioned between $CHCl_3$ and brine. The aqueous layer was extracted with $CHCl_3$ (2×). The combined organic solutions were dried ($MgSO_4$) and concentrated. The crude product was an 87:1 mixture of the sulfide **2** and sulfoxide **1** (based on the signals at δ 2.46 and 2.68 in the 400 MHz ^1H NMR spectrum). Purification by silica gel chromatography [hexane–propan-2-ol (100:1)] afforded **2** (343 mg, 75%) identical with a commercially available material.