

Rapid Reduction of Sulfones to Sulfides using LiAlH₄-TiCl₄

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A variety of sulfones are reduced rapidly to sulfides in high yields using lithium aluminium hydride-titanium tetrachloride in tetrahydrofuran.

The use of sulfones (R¹-SO₂-R²) in organic synthesis has increased greatly over the last two decades.^{1,2} However, the subsequent rapid reduction of sulfones to sulfides has presented a difficult problem. Both alkyl and aryl sulfones are extremely resistant to the most powerful reducing agents, and many hydride reagents do not reduce ordinary sulfones. The most frequently used reducing agents are: LiAlH₄,³ (Buⁱ)₂AlH,⁴ Zn-AcOH-HCl⁵ and elemental sulfur.⁶ Reduction with these reagents requires vigorous reaction conditions and prolonged reaction times. We sought a rapid method of reducing sulfones to sulfides in high yields in a time period compatible with the synthesis of shortlived radiopharmaceuticals containing ¹¹C (20 min halflife) or ¹⁸F (110 min halflife).

Recently Handa *et al.*⁷ reported that samarium(II) iodide-tetrahydrofuran-hexamethylphosphoric triamide (SmI₂-THF-HMPA) was an effective and mild reagent for the rapid reduction of both aliphatic and aromatic sulfones to sulfides. This system led to sulfone reduction yields of <25% in 30 min as shown in Table 1.† Our findings are in agreement with those described by Künzer *et al.*¹⁰ who reported the failure of SmI₂-THF-HMPA to reduce a variety of sulfones as well as the concomitant formation of reaction products devoid of any sulfur functionality. Hasagawa and Curran¹¹ reported recently that the reduction of diphenylsulfoxide with SmI₂-THF proceeded rapidly with the addition of small amounts of water. Kamochi and Kuda¹² also observed that the reduction of pyridine to piperidine was enhanced when SmI₂ was coordinated with water. We found that the addition of water to SmI₂-THF (with and without HMPA) did not assist in the reduction of diphenylsulfone at reaction times as long as 1 h. Other deoxygenation agents such as boron tribromide, phosphorous triiodide, phosphorous tribromide and bromodimethylborane did not reduce the test sulfones despite their previously reported efficacy in reducing sulfoxides to sulfides.¹³

In our assessment of reducing reagents capable of rapidly

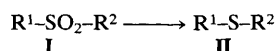


Table 1 Reduction of sulfones to sulfides using SmI₂-THF-HMPA or LiAlH₄-TiCl₄

Entry ^a	R ¹	R ²	SmI ₂ reduction (% II)	LiAlH ₄ -TiCl ₄ reduction (% II)
1	Ph	Me	18	93
2	Ph	Ph	23	80 (75) ^b
3	Ph	CHCH ₂	<5	62
4	<i>p</i> -MeC ₆ H ₄	Me	<5	81
5	<i>p</i> -MeOC ₆ H ₄	Me	<5	91
6	<i>p</i> -FC ₆ H ₄	Me	<5	73

^a The sulfones for entries 2 and 3 were purchased from Aldrich Chemical Co., and all other sulfones were synthesized according to literature procedures.¹⁶ Reduction procedures for SmI₂-THF-HMPA were performed according to Handa *et al.*⁷ and Hasewaga and Curran.¹¹ General LiAlH₄-TiCl₄ reduction methods are described below. All reduction reaction times were 30 min. ^b Isolated yield of diphenylsulfide is in parentheses, and this value compares closely to the HPLC-derived yield.

deoxygenating sulfones to sulfides, we found a mixture of LiAlH₄-TiCl₄ (2:1) to be best suited for this purpose. The active reducing species formed in this mixture is believed to be TiCl₂.¹³⁻¹⁵ The reduction yields of several test sulfones using either SmI₂-THF-HMPA or LiAlH₄-TiCl₄ are compared in Table 1.

In comparison to other available reducing methods, the use of LiAlH₄-TiCl₄ provides high reduction yields in a relatively short time which is crucial for radiosyntheses using short-lived radionuclides. LiAlH₄-TiCl₄ adds a rapid procedure to existing methodologies for the reduction of sulfones to sulfides.

General LiAlH₄-TiCl₄ reduction procedure: To a solution of TiCl₄ (0.3 ml, 3 mmol) in THF (5 ml) was added dropwise LiAlH₄ (6 ml 1 mol dm⁻³ in THF, 6 mmol) at -78°C under nitrogen. To the resulting dark-blue mixture was added the sulfone (0.3 mmol) at -78°C. The mixture was stirred for 30 min during which it was allowed to warm to room temp. The mixture was subsequently quenched with a saturated ammonium chloride solution, extracted with CH₂Cl₂ and dried over Na₂SO₄. Aliquots of the CH₂Cl₂ phase were separated by HPLC (Whatman ODS-1 column eluted with MeOH-H₂O) and the products‡ quantitated using a UV detector (254 nm). For detailed analytical purposes, the CH₂Cl₂ phase was reduced under vacuum, and the residue was purified by column chromatography (silica gel, EtOAc-hexanes).

This research was supported by USPHS/NIH grants NS-28867 and NS-22899. Technical assistance by C. P. D. Longford and Norman Simpson is gratefully acknowledged.

Received, 4th January 1994, Com. 4/00015C

Footnotes

† The reactivity of several commercially available lots of SmI₂ (Aldrich Chemical Co.) were assessed utilizing the samarium(II)-Barbier reaction.⁸ These reactions indicated that the SmI₂ was active, as 95% of the alcohol was formed. The SmI₂ used successfully for these test reactions afforded low sulfone reduction yields. Additional sulfone reduction experiments were performed with SmI₂ freshly prepared according to the procedures of Molander and Harring,⁹ and the reduction yields were not significantly different from those listed in Table 1. Careful distillation of THF and HMPA under argon over Na and CaH₂ did not significantly improve reduction yields utilizing the SmI₂-THF-HMPA reagent.

‡ The methyl sulfide chromatographic standards for entries 1-5 were purchased from Aldrich Chemical Co., and entry 6 was prepared from the corresponding commercially available thiol (Aldrich Chemical Co.) by the literature procedure.¹⁷

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