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Efficient reduction of sulfoxides with 2,6-dihydroxypyridine

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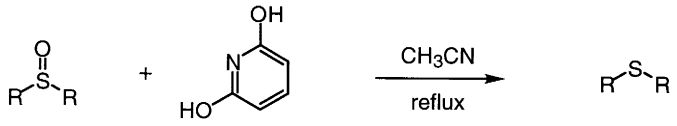
Abstract

2,6-Dihydroxypyridine was found to be an efficient reagent in the deoxygenation of sulfoxides. The mild reaction conditions were compatible with functional groups such as ester and carbamate. It was also found that approximately 0.25 equivalents of 2,6-dihydroxypyridine was required for effective reduction. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: sulfoxides; sulfides; reduction; pyridines.

During the course of our studies on the decarboxylation of orotic acid and citrazinic acid (2,6-dihydroxyisonicotinic acid) and the nature of the reaction intermediates,[1–3] we observed that citrazinic acid and related compounds react with tetramethylene sulfoxide to give the corresponding sulfide. In this communication, we report that 2,6-dihydroxypyridine (**1**) is an efficient reducing agent for the conversion of sulfoxides to sulfides.



1

Sulfoxides are important reagents in the application of organosulfur compounds in organic synthesis.[4,5] Sulfoxides are usually eliminated by a two-step process involving deoxygenation to sulfides which are then removed by catalytic hydrogenation or other chemical methods.[4] There are numerous methods available for the deoxygenation of sulfoxides; however, many of them involve reagents which are either strong acids, strong nucleophiles, or very reactive species such as carbenes.[5,6] We have found that 2,6-dihydroxypyridine (**1**) or its hydrochloride salt effects sulfoxide reduction under neutral and mild conditions.

Reductions were carried out in refluxing acetonitrile. The workup is very simple since **1** and its oxidation products are not soluble in the reaction solvent and can be filtered off. Concentration of the

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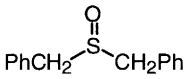
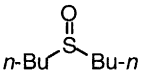
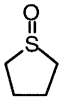
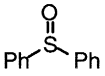
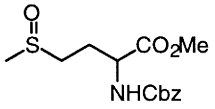
filtrate gives essentially pure sulfide.[7] The percent yields shown in Table 1 are from reactions using 0.5 equivalents of **1**. In our experiments to determine the stoichiometry of the reaction, we found that **1** could reduce approximately 4 equivalents of sulfoxide. The reaction is compatible with protective functional groups such as those examined with the methionine derivative in Table 1. Under the reaction conditions described here, diphenyl sulfoxide gave relatively low yields; however, the use of tetramethylene sulfone as solvent dramatically improved the yield. On the other hand, since it has a high boiling point and is often difficult to remove from the reaction mixture, tetramethylene sulfone is not a convenient solvent. Not surprisingly, sulfones are not reduced by **1**, as seen with many other reducing agents for sulfoxides.[4] The mechanism of this reaction remains conjectural and mechanistic studies are currently underway.†

Table 1
Reduction of sulfoxides with **1** in CH_3CN

Substrate	Time	% Yield (isolated)
	4 h	98
	5 h	98
	2 h	66[a]
	14 h	24 (96)[a,b]
	3 h	90

[a]Yields determined by gas chromatography.
[b]Yield obtained with tetramethylene sulfone (2.0 g) as solvent shown in parenthesis.

The above results have demonstrated that 2,6-dihydroxypyridine (**1**) is an efficient reducing agent for sulfoxides. Both aromatic and aliphatic, cyclic and acyclic, sulfoxides can be reduced to sulfides in high yield. Sulfoxides with other functional groups such as ester and carbamate also give good results. The reaction described here is thus a useful and convenient alternative to existing methods for sulfoxide deoxygenation.

Experimental details: Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate was prepared as reported by Carrasco et al.[8] All other reagents were obtained from commercial sources and used without further purification. The reactions were run in an open atmosphere.

Typical experimental procedure: Dibenzyl sulfoxide (2.00 g, 8.70 mmol) and 2,6-dihydroxypyridine hydrochloride (0.64 g, 4.35 mmol) were mixed in acetonitrile (20 mL) in a round-bottom flask and the mixture was refluxed for 3–5 h. Upon cooling, the reaction mixture was filtered and the filtrate was

† We were not able to identify the oxidation product of pyridine **1**, which would have provided insight on the mechanism.

concentrated to give dibenzyl sulfide (1.82 g, 98%) as the product. The identity of the product was verified by co-injection with an authentic sample onto a capillary gas chromatography column. The product was judged to be pure according to its NMR spectrum.

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References

1. Wu, W.; Ley-han, A.; Wong, F. M.; Austin, T. J.; Miller, S. M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2623–2628.
2. Nakanishi, M. P.; Wu, W. *Tetrahedron Lett.* **1998**, *39*, 6271–6272.
3. Feng, W. Y.; Austin, T. J.; Chew, F.; Gronert, S.; Wu, W. *Biochemistry* **2000**, *39*, 1778–1783.
4. March, J. *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 4th ed.; Wiley: New York, 1992.
5. For a review on reduction of sulfoxides, see: Madesclaire, M. *Tetrahedron* **1988**, *44*, 6537–6580.
6. For an earlier review, see: Drabowicz, J.; Togo, H.; Mikolajczyk, M.; Oae, S. *Org. Prep. Proc. Int.* **1984**, *16*, 171–198.
7. All products have identical NMR spectra to those of authentic samples. Many of them can be found in: Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Aldrich: Milwaukee, 1992.
8. Carrasco, M.; Jones, R. J.; Kamel, S.; Rapoport, H.; Truong, T. *Org. Synth. Coll.* **1998**, *9*, 63–67.