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Alane – A Chemoselective Way to Reduce Phosphine Oxides

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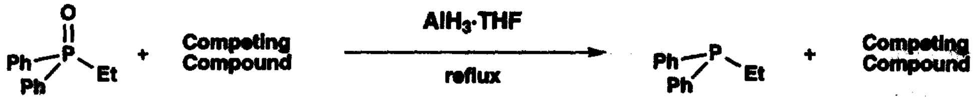
Abstract: Phosphine oxides may be chemoselectively reduced to phosphines in excellent yield in the presence of several other functional groups using alane. An aqueous workup is not required.

We recently described a new way to reduce phosphine oxides to phosphines using alane as the reducing agent.[1] Alane is known to have reactivity characteristics which differ from those of $LiAlH_4$[2,3] and we now report that the alane-mediated reductions of phosphine oxides may be performed chemoselectively. The reactions are convenient, the phosphines formed in high yield and there is no need for an aqueous workup.[4] We can thus avoid the small amount of reoxidation that always seems to accompany an aqueous workup. This is in contrast to other methods of reducing phosphine oxides — an aqueous workup is essential in the case of reductions with $HSiCl_3$ or Si_2Cl_6[5,6] and is also necessary when $LiAlH_4$ is used.

To investigate the chemoselectivity of alane for phosphine oxides, phosphine oxide **1** was mixed with compounds containing other functional groups which would compete for the reducing agent. The mixture was treated with alane·THF solution.



1 **2**

It was hoped that the competing compound would be left untouched. A solution of alane in THF is prepared by the method of Brown and Yoon[2,7] by adding **concentrated** H_2SO_4 to a solution of $LiAlH_4$ in THF (CAUTION – addition of dilute H_2SO_4 will lead to an explosion). The resulting alane·THF solution may be conveniently titrated using methanol and a gas burette.

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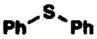
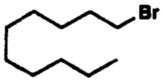
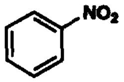
Ethyldiphenylphosphine oxide was prepared by standard methods[8] and then reduced using alane in the presence of another compound. The reactions were followed by TLC and were usually complete within 30 minutes.[9] There was no need for an aqueous workup — the reactions were quenched using anhydrous methanol and the reaction mixture filtered through celite.

Functional groups known not to react with alane

The first chemoselective advantage offered by alane is that it is known not to reduce some functional groups which are reduced by $LiAlH_4$. It should be possible to reduce phosphine oxides in the presence of such groups using alane and Table 1 summarises our findings. Chemoselective reduction of ethyldiphenylphosphine oxide **1** to ethyldiphenylphosphine **2** was achieved in good yield in the presence of diphenylsulfide, diphenylsulfone, pentyl bromide, decyl bromide and nitrobenzene.

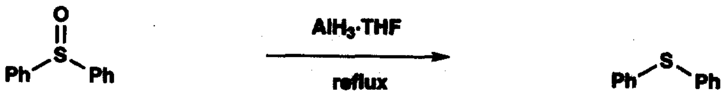
Table 1: Yield of Phosphine **2** from **1**

Compound	Equivalents of $AlH_3 \cdot THF$	Yield (%) of Phosphine	Recovered (%) Compound
	1.0	96	84
	1.05	95	93
	1.0	98	-
	1.05	96	97
	1.05	92	93

Although this represents a very useful method, there is a more interesting question – will alane chemoselectively reduce phosphine oxide **1** to phosphine **2** in the presence of functional groups which *are* known to react with alane?

Functional groups known to react with alane

Esters, amides, epoxides, disulfides and sulfoxides can all be reduced by alane.[2] Reducing a phosphine oxide in the presence of such a functional group is a challenge which, in many cases, alane meets. We reduced diphenylsulfoxide **3** (in the absence of phosphine oxide) with alane to give diphenylsulfide in a 98% yield.



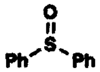
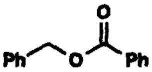
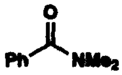
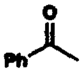
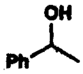
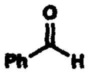
3

98%

In a competition experiment, diphenylsulfoxide and ethyldiphenylphosphine oxide **1** were treated with 1.05 equivalents of alane. Under these conditions the phosphine oxide was reduced to phosphine **2** but starting sulfoxide **3** was isolated *unreacted* from the reaction mixture (Table 2, Entry 1).[10]

Similar results were obtained with an ester, amide and epoxide (Table 2, Entries 2, 3 and 4). In other words, they all reacted in the absence of phosphine oxide but did not react appreciably in its presence. The results are summarised in Table 2. In order to achieve a chemoselective reduction of phosphine oxide **1** in the presence of diphenylaziridine, milder conditions were required and the reaction had to be performed overnight at room temperature. In some cases, however, reactions were *not* chemoselective for the phosphine oxide. For completeness we report those cases where alane failed in this respect. For instance, acetophenone (Table 2, Entry 7) is reduced to α-methylbenzyl alcohol in a 60% yield and the phosphine oxide is only partly reduced (33%).

Table 2: Yield of the Phosphine **2** from Phosphine Oxide **1**

Entry	Competing Compound	Equivalents of AlH_3·THF	Yield (%) of Phosphine	Recovered (%) Competing Compound	Other Products (Yield%)
1		1.05	**96**	93	—
2		1.05	**93**	89	—
3		1.0	**95**	90	—
4		1.0	**96**	94	—
5		1.05	**98**[a]	96[a]	
6		1.0	24	6	PhSH (36)
7		1.0	33	—	 (60)
8		1.0	5	—	 (93)

a. Stirred overnight at room temperature. Reflux led to several products.

Conclusion

We have shown that alane is a chemoselective reducing agent for phosphine oxides in the presence of several other functional groups. Reactions are high yielding and easy to perform. Given the number of phosphine ligands which contain other functionality,[11] we imagine that alane will be valuable to many organic chemists interested in preparing phosphine ligands *via* the corresponding phosphine oxides.

Acknowledgements

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References and Notes

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3. Galatsis, P., in *Encyclopedia of Reagents for Organic Synthesis* L. A. Paquette, Ed. (John Wiley & Sons, Chichester, 1995), vol. 1, pp. 161-164.
4. Coumbe, T.; Lawrence, N. J.; Muhammad, F., *Tetrahedron Lett.*, **1994**, *35*, 625-628.
5. Naumann, K.; Zon, G.; Mislow, K., *J. Am. Chem. Soc.*, **1969**, *91*, 7012-7023.
6. Alkaline hydrolysis of the reaction mixture is necessary to liberate the phosphine.
7. *Alane preparation and titration*
   $LiAlH_4$ (12.0 ml of a 1 M solution in THF, 12.0 mmol) was added to THF (10 ml) under argon. To this mixture was added conc. H_2SO_4 (321 µl, 6.03 mmol). The suspension was allowed to settle overnight. The supernatant (1 ml) was added to stirring methanol (10 ml) connected to a gas burette. More supernatant (1 ml) was added to the same methanol a second and third time. The average gas volume from second and third experiments was used to calculate the molarity of $AlH_3{\cdot}THF$. In a typical reaction, 40.4 ml of H_2 gas was evolved, corresponding to an $AlH_3{\cdot}THF$ concentration of 0.55 M.
8. Buss, A. D.; Warren, S., *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2307-2325.
9. Although all the reactions were completed under reflux, TLC often indicated a significant degree of reduction at room temperature.
10. *Competition experiment between diphenylsulfoxide (3) and ethyldiphenylphosphine oxide (1)*
    Ethyldiphenylphosphine oxide (110 mg, 0.478 mmol) and diphenylsulfoxide (96.7 mg, 0.478 mmol) were dissolved in dry THF (5 ml) under argon and $AlH_3{\cdot}THF$ (785 µl of a 0.64 M solution in THF, 0.502 mmol) was added dropwise to the stirring mixture. The mixture was refluxed for 30 min and then quenched with dry MeOH (60 µl, 1.48 mmol) and allowed to cool to room temperature. The mixture was filtered through celite which was washed with hot THF (3 × 5 ml). The organic extract was evaporated under reduced pressure and purified by flash chromatography eluting with 9:1 40/60 pet. ether-EtOAc to yield the phosphine (98 mg, 96%) R_f(9:1 40/60 pet. ether-EtOAc) 0.62; δ_H(300 MHz; $CDCl_3$) 7.48-7.31 (10 H, m, 2 × Ph), 2.09 (2 H, qd, *J* 7.7 and 0.9, CH_2) and 1.10 (3 H, dt, *J* 17.3 and 7.7, CH_3)(lit.[12]); δ_C(75 MHz, $CDCl_3$) 137.6 (*J* 9.1, *ipso*-PhC), 132.7 (*J* 18.1, *ortho*-PhC), 129.1 (*para*-PhC), 128.4 (*J* 6.8, *meta*-PhC), 20.3 (*J* 7.5, CH_2) and 9.9 (*J* 15.1, CH_3)(lit.[13]) and the sulfoxide (90 mg, 93%) which was identical to starting material, m.p. 71 °C (lit.[14] 70-71 °C); R_f(3:1 40/60 pet. ether-EtOAc) 0.16; δ_H(300 MHz; $CDCl_3$) 7.60-7.34 (10 H, m)(lit.[14]); δ_C(75 MHz; $CDCl_3$) 145.5, 131.0, 129.3 and 124.7 (lit.[15]).
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