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DESIGN AND REACTIVITY OF ORGANIC FUNCTIONAL GROUPS: THE HIGHLY CRYSTALLINE 2-ALKOXY N,N'-DIPHENYL-1,3,2-DIAZAPHOSPHOLANES AND THEIR FACILE CONVERSION INTO ALKYL HALIDES[1]

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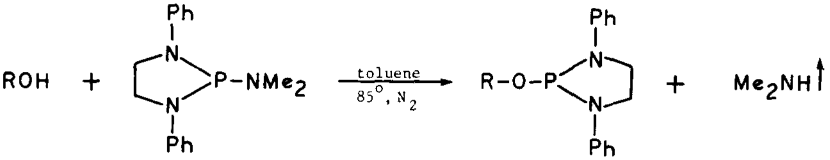
Functionalization of alcohols as 2-alkoxy N,N'-diphenyl-1,3,2-diazaphospholanes affords highly crystalline derivatives useful for characterization purposes. These tervalent phosphorus derivatives undergo facile and mild conversion into the corresponding alkyl halides with inversion of configuration.

The formation of an alkyl halide from an alcohol or appropriate derivative constitutes one of the more preparatively useful reactions involving this functional group.[2] A number of these involve organophosphorus intermediates.[3] Our continued interest in manipulating the hydroxyl group by designing novel organic functional groups and studying their reactivity[4] has led to the development of N,N'-diphenyl-1,3,2-diazaphospholanes[5] as stable derivatives of alcohols and their utility in further transformations based on the known reactivity trends of tervalent organophosphorus compounds.[6]



We find that such alkoxy diazaphospholanes are invariably highly crystalline derivatives which can be extremely useful in the crystallization and characterization of a large variety of alcohols (Table 1). Such derivatives can be easily formed from equimolar amounts of the alcohol and 2-dimethylamino N,N'-diphenyl-1,3,2-diazaphospholidine[7,8] by heating in toluene at 85°. A variety of functional groups including esters are compatible with these conditions. In many instances, the products crystallize upon evaporation of the reaction mixture. Alternatively, they can be easily isolated by column chromatography and have excellent shelf-life. Regeneration of the alcohol can be effected by treatment of the derivative with 50% aq. acetic acid at 25° (18 hr) or by methanolysis (reflux). The esters are stable under basic conditions (0.1N NaOH, several days).

In addition to the highly crystalline nature of these derivatives, they are excellent mediators for the mild and efficient conversion of alcohols into alkyl halides.

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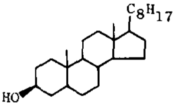
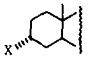
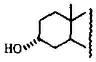
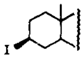
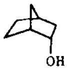
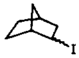
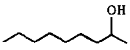
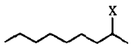
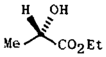
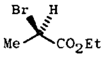
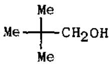
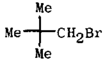
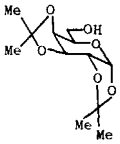
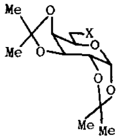
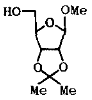
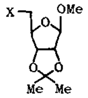
Table 1

Alcohol	Alkoxyphospholane	Halide[a]	Method[b]
	89%: mp 158-159° $[\alpha]_D$ + 4.4°	 X=Cl, 80% =Br, 85% =I, 75%	A C A
	89%; 180° dec. $[\alpha]_D$ + 3.7°	 94%	A
	94%; mp 145°	 X=Br, 81% =I, 81%	A A,C
	85%; mp 132-133°	 61%: 2:1 endo/exo	C
	91%; mp 39-40°	 X=Br, 88% =I, 74%	C B
	91%: mp 70-75°	 X=Br, 85% =I, 91%	C B
	83%; mp 49.5-51° $[\alpha]_D$ − 40.7°	 92% GC; 70% isolated $[\alpha]_D$ + 29.8°	A
 $Me_3C{-}CH_2OH$	82%, mp 127-130°	 $Me_3C{-}CH_2Br$ 30%[c]	A
	70%; mp 127.5-129° $[\alpha]_D$ − 55.3°	 X=Br, 84% =I, 91%	A A
	70%; mp 114-115° $[\alpha]_D$ − 20.1°	 72% X=Br, 86% =I, 72%	A A A

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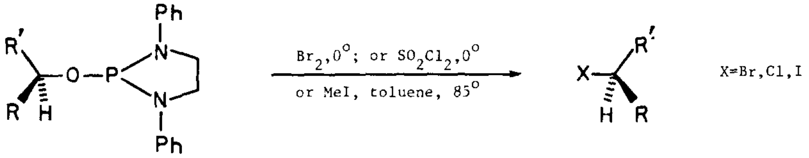
a. Yields are for isolated and characterized products which were found to be identical to authentic samples (mp, n.m.r., $[\alpha]_D$, GC, etc); b. See text for procedures; c. Isolated by distillation; analysis of the reaction mixture by n.m.r. and GC showed the presence of the bromide as a preponderant if not exclusive product.

Thus, primary and secondary alkoxyphospholanes are converted into bromides, chlorides and iodides by one of three procedures. Inversion of configuration was observed in all cases studied.[9]

METHOD A

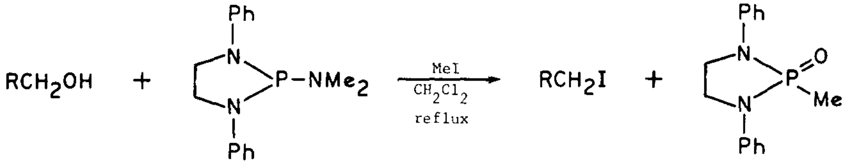


Bromides: The alkoxyphospholane (1 mmole) in 10 ml of dichloromethane is treated at 0° with a solution of bromine (1.5 mmole) in the same solvent until the color persists. Evaporation and flash column chromatography gives the bromide.

Chlorides - In the case of SO_2Cl_2 (1.5 equiv.), the reaction is done in toluene at 0° and monitored by t.l.c. until completion (usually complete within a few minutes).

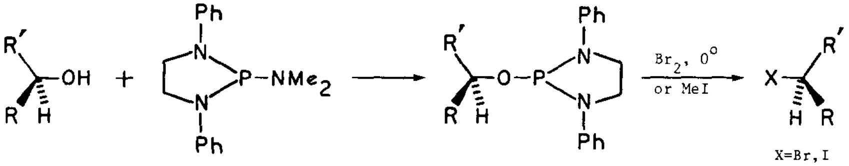
Iodides - The alkoxyphospholane (1 mmole) in 10 ml of toluene is treated with excess methyl iodide (~5 ml) and the solution is heated at 70° for 5-7 hr. The product is separated by direct crystallization or chromatography.

METHOD B (one-pot procedure)



Iodides - The alcohol (1 mmole), the phospholidine (1.1 mmole) and methyl iodide (3 ml) are mixed in 5 ml of dichloromethane and the solution is refluxed for 5h.

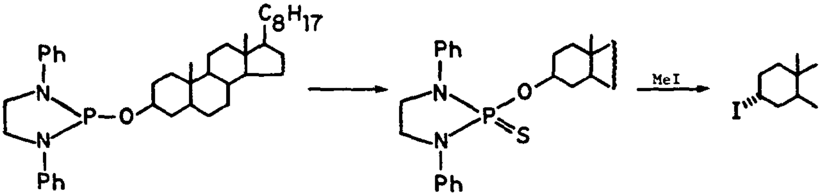
METHOD C (sequential addition)



Bromides - A solution of the alcohol (1 mmole) and the phospholidine (1.1 mmole) in 10 ml of toluene is heated at 85° for 18h. The solvent is evaporated, the residue is dissolved in 10 ml of dichloromethane, and bromine (1.2 equiv.) is added at 0° until a faint color persists.

Iodides - A solution of the alcohol (1 mmole) and the phospholidine (1.1 mmole) in 10 ml of toluene is heated at 85° for 18h. The solvent is evaporated and the residue is dissolved in 10 ml of dichloromethane containing methyl iodide (~5 ml) and refluxed for 5-6h.

The examples provided in Table I illustrate the structural variety of crystalline alkoxyphospholanes, and their facile conversions into halides under mild and essentially neutral conditions, particularly with methyl iodide as the halogen source. The alkoxyphospholanes reported herein could be easily transformed into the corresponding thiophosphoramide derivatives by treatment with elemental sulfur (1.1 equiv.) in chloroform. The derivative from β-cholestanol was thus obtained in quantitative yield, mp 183-184°; $[\alpha]_D$+8.3° ($CHCl_3$). Treatment with methyl iodide in toluene (85°, 2d) gave α-iodocholestane in 94% yield.



In conclusion, we recommend the N,N'-diphenyl-1,3,2-diazaphospholanyl group as a means of obtaining highly crystalline derivatives of alcohols and emphasize their facile conversions into alkyl halides.

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References and Notes:

1. Portions of this work were presented at the 11th Northeast Regional Meeting of the American Chemical Society; Symposium on Current Topics in Organic Chemistry, Rochester, N.Y., Oct 18-21 1981.

2. See for example, M.E. Jung and P.L. Ornstein, Tetrahedron Lett., 2659(1977); M.E. Jung and G.L. Hatfield, Tetrahedron Lett., 4483(1978) and references cited therein.

3. See for example, S.R. Landauer and H.N. Rydon, J. Chem. Soc., 2221(1953); G.A. Wiley, R.L. Hershkowitz, B.M. Rein and B.C. Chung, J. Am. Chem. Soc., 86, 964(1964); J.P.H. Verheyden and J.G. Moffatt, J. Am. Chem. Soc., 86, 2093(1964); S. Hanessian, M.M. Ponpipom and P. Lavallée, Carbohydr. Res., 24, 45(1972); H. Liu, W.H. Chan and S.P. Lee, Chemistry Lett., 929(1978); M. Lauwers, B. Regnier, M. Van Eenoo, J.N. Denis and A. Krief, Tetrahedron Lett., 1801(1979); O. Mitsunobu, Synthesis, 1(1981) and references cited therein; P.J. Garegg and B. Samuelsson, J.C.S. Chem. Comm., 978(1979).

4. S. Hanessian and J.-M. Vatèle, Tetrahedron Lett., 22, 3579(1981).

5. For related compounds, see R. Burgada, Bull. Chem. Soc. France, 186(1971).

6. R.F. Hudson, Structure and mechanism in Organophosphorus Chemistry, Academic Press, 1965; R. Greenhalgh and R.F. Hudson, Chem. Comm., 1300(1968).

7. Prepared from N,N'-diphenyl-1,2-diaminoethane (5 g, 23.6 mmoles) and tris(dimethylamino)phosphine (3.85 g., 23.6 mmoles) in refluxing toluene (24h). The product crystallizes upon cooling. Recrystallization from toluene gave pure reagent (85%), m.p. 140°; see also M.R. Marre, M. Sanchez, J.F. Brazier, R. Wolf and J. Bellan, Can. J. Chem., 60, 456 (1982).

8. New compounds gave correct microanalyses and satisfactory spectroscopic characteristics.

9. See however the case of exo-norborneol, which not unexpectedly gave some retention. Also, treatment of the N,N'-diphenyl-1,3,2-diazaphospholanyl derivative of cholesterol, mp 149-151° with N-iodosuccinimide (1.1 equiv) in toluene at 25° (15 min), gave the corresponding β-iodide (41%, non optimized) mp 105-106°; $[\alpha]_D$-12°, identical with an authentic specimen.

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