Preparation of New Phosphine Oxide Synthons: Synthesis of an Analogue of Muscarinic Antagonists

Roger G. Hall,* Peter Riebli

Novartis Crop Protection AG, Basel, Switzerland

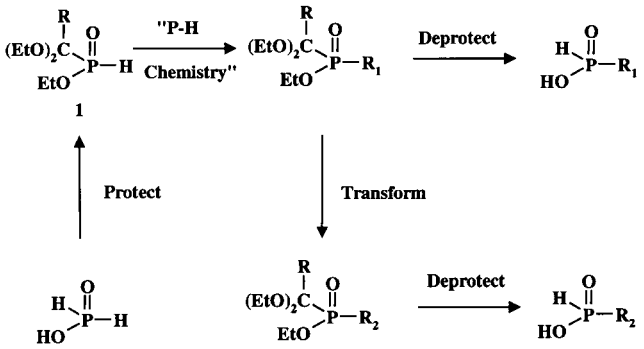
E-mail: roger_graham.hall@cp.novartis.com

Received 26 July 1999

Abstract: Protected primary phosphine oxides may be obtained by reaction of ethyl (diethoxyalkyl)phosphinates with organometallic reagents. These products, stable to chromatography or distillation, may be further elaborated into new, functional unsymmetrical secondary and tertiary phosphine oxides. A close analogue of muscarinic antagonists has been prepared using this methodology.

Key words: functional phosphine oxides, synthons, muscarinic antagonists

We have previously reported[1] the synthesis of phosphinic acid synthons **1**[2] and demonstrated their application in the preparation of novel α, β and γ - amino phosphinic acids. Such molecules are close analogues of natural amino acids, and as such have potentially useful biological properties. In addition to novel therapeutic agents,[3] such phosphinic acids have found application as tools for probing receptor sub-types.[4] The strategy, Scheme 1, relies on the use of the diethoxy - methyl (R = H) or - ethyl function (R = CH_3) as a P-H protecting group; selective transformations are performed on the exposed P-H. Functional group modifications can then be optionally performed on group R_1, thereafter a deprotection step regenerates a P-H function which can be further derivatised as required.



Scheme 1

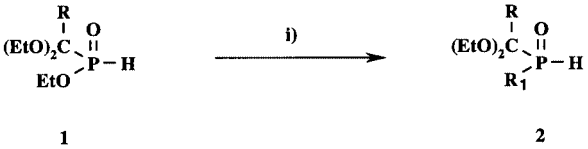
Whilst the biological properties of phosphinic acids are by now well documented, that of phosphine oxides remains relatively unexplored. This could well be due to the fact that no general method exists for the synthesis of highly functional, unsymmetrical phosphine oxides. We have now developed such a method by converting synthons **1** into phosphine oxide synthons and report our findings here.

The reaction of dialkyl phosphites with organometallic reagents has been described. Hays[5] demonstrated that symmetrical secondary phosphine oxides can be obtained from the reaction of diethyl phosphite with three equivalents of alkyl Grignard reagent, followed by acidic work-up.

We reasoned that synthons **1** might undergo a similar reaction, using only two equivalents of organometallic reagent. Thus reaction of **1** (R= H, CH_3) with two equivalents of Grignard or organolithium reagent [6] leads to phosphine oxides **2** in good to excellent yields (Table). The acetal or ketal functionality is stable under the reaction conditions. The formation of unwanted by-products $(EtO)_2C(R)\text{-}P(O)(R^1)_2$ can be minimised by inverse addition of the organometallic reagent to the phosphinates **1**, Scheme 2.

Table Preparation of Protected Primary Phosphine Oxides **2**

Compounds 2	R	R_1	% Yield
2a	H	CH_3	60 [a] (57)[b]
2b	CH_3	CH_3	80 [a]
2c	H	n-C_4H_9	70 [b]
2d	H	t-C_4H_9	97 [b]
2e	H	$CH_2Si(CH_3)_3$	72 [a]
2f	H	4-Cl-C_6H_4	43 [a]
2g	H	$CH_2C_6H_5$	55 [a]
2h	H	$C_{18}H_{37}$	36 [a]
2i	H	c-C_6H_{11}	99 [a]

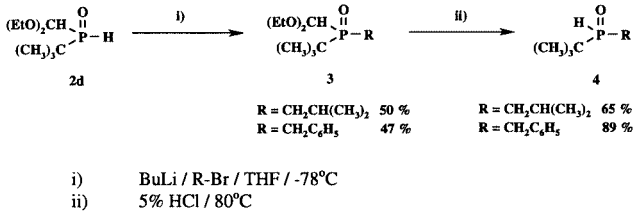


i) a) 2eq. R_1MgX / Et_2O / 10°C / 2hr, then K_2CO_3 or
b) 2eq. R_1Li / THF / -40°C / then dil HCl

Scheme 2

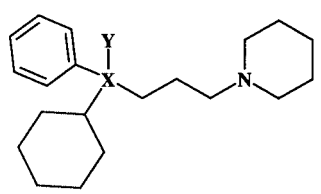
Compounds **2** can be viewed as protected primary phosphine oxides. Primary phosphine oxides are known to be unstable and decompose via disproportionation . Buckler[7] reported that either in solution or in the solid state, primary phosphine oxides decompose into primary phosphines and phosphinic acids. However, such protected species **2** are stable and may be isolated by chromatography or distillation.

Phosphine oxides **2** can be further elaborated via P-H chemistry. For example **2d** undergoes alkylation leading to compounds **3**; these tertiary phosphine oxides can in turn be deprotected under acidic conditions yielding secondary phosphine oxides **4**, Scheme 3.



Scheme 3

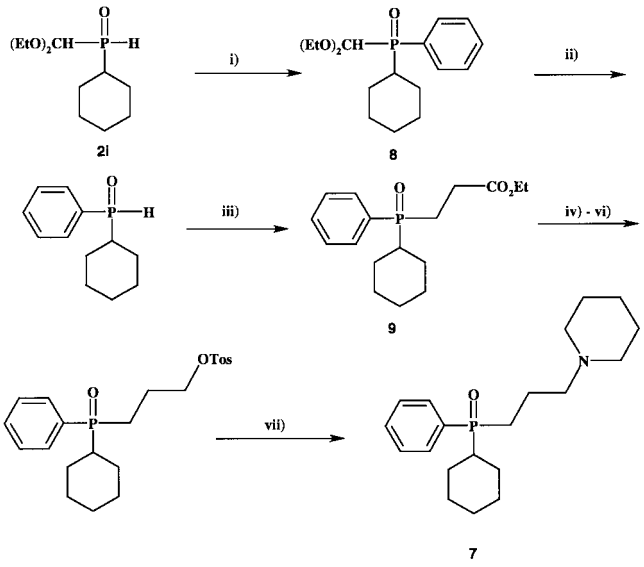
We next sought to apply this methodology to prepare novel phosphine oxides with potentially interesting biological properties. A number of interesting secondary and tertiary alcohols were identified as targets, where the C-OH could be mimicked by a P=O functionality. Hexahydro-siladiphenidol **5** is a potent anticholinergic agent which exhibits selective antagonism to muscarinic receptors.[8] The carbon analogue **6** shows a different selectivity profile to receptor sub-types, Scheme 4.



	X - Y
5	Si -OH
6	C -OH
7	P =O

Scheme 4

The synthesis of the phosphine oxide analogue **7** is shown below, Scheme 5. Reaction of cyclohexyl (diethoxymethyl)phosphine oxide **2i** with bromobenzene under palladium catalysis gave the tertiary phosphine oxide **8** in good yield. Acid deprotection liberated the P-H function for the Michael addition to ethyl acrylate to give **9**. Elaboration of the ester function via reduction to the alcohol, tosylation and displacement with piperidine gave the target molecule **7** as a racemic mixture.



Scheme 5

We have developed a synthesis of stable, protected primary phosphine oxides. These synthons can be elaborated using straightforward transformations into functional, unsymmetrical phosphine oxides of potential biological interest.

Acknowledgement

We would like to acknowledge the technical support of S. N. Bennett, K. Jones, N. Blair and N. Squirrel.

References and Notes

(1) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787.
(2) R = H, Gallagher, M. J.; Honnegar, H. *Aus. J. Chem.* **1980**, *33*, 287 ; R = CH_3, Baylis, E. K.; *Tetrahedron Lett.* **1995**, *36*, 9385.
(3) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H-R.; Rihs, G.; Vassout, A.; Waldmeier, P.C.; Bittiger, H.; *J. Med. Chem*. **1995**, *38*, 3297.
(4) Bowery, N. G.; Bittiger, H.; Olpe, H-R. (editors), *GABA-B receptors in Mammalian Function*, Wiley **1990.**
(5) Hays, H. R. *J. Org. Chem.* **1968**, *33*, 3690.
(6) Typical procedure : Ethyl diethoxymethyl phosphinate (5.0 gm, 25.5 mmol) is dissolved in 75 ml dry tetrahydrofuran and this solution is cooled to -40°C under argon. To this stirred solution is added dropwise 50 ml of methyl lithium (1.0 M solution in diethyl ether) whilst maintaining the temperature below -40°C. After the addition is complete, the reaction mixture is allowed to stand at room temperature for 12 hours. Hydrochloric acid (50 ml, 0.1M) is then carefully added and the mixture extracted with dichlormethane (3 X 100 ml). The organic extracts are combined, dried over magnesium sulfate, and the solvent removed. The crude material is purified by vacuum distillation to give methyl diethoxymethyl phosphine

oxide as a colourless liquid, b. p. 85° / 0.02 mm. ^{1}H NMR ($CDCl_3$) : 1.3 (t, J = 9Hz, 6H), 1.6 (d.d, J = 20Hz, 5.4Hz, 3H), 3.8 (m, 4H), 4.3 (m, 0.5H), 4.9 (d.d, J = 12.5Hz, 1.8Hz, 1H), 9.6 (m, 0.5H). ^{31}P NMR : 26.6ppm ($CDCl_3$) J P-H = 468.6 Hz. ^{13}C NMR ($CDCl_3$) : 10.1 (d, J = 97Hz), 15.5, 66.5 (dd, J = 9Hz), 101.2 (d, J = 184Hz). IR (CCl_4) : 2980, 2940, 2890, 2340, 1300, 1200, 1120, 1060, 965. Anal. Calcd. for $C_6H_{15}O_3P$: C 43.4%; H 9.1%. Found : C 44.0%; H 9.1%. All new compounds gave satisfactory spectroscopic data.

(7) Buckler, S. A.; Epstein, M. *Tetrahedron* **1962**, *18*, 1221.
(8) Waelbroeck, M.; Tastenoy, M.; Camus, J., Christophe, J.; Strohmann, C.; Linoh, H.; Zilch, H.; Tacke, H.; Mutschler, E.; Lambrecht, G. *Br. J. Pharmacol*. **1989**, *98*, 197.

Article Identifier:
1437-2096,E;1999,0,10,1633,1635,ftx,en;L10599ST.pdf