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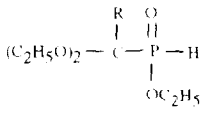
1-Hydroxy-1-Methylethylphosphinates Intermediates for the Synthesis of Functional Phosphorus Acids

E. Keith Baylis

Central Research Laboratories, Ciba-Geigy PLC,
Hulley Road, Macclesfield, Cheshire SK10 2NX, England

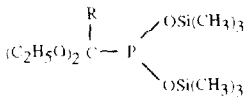
Abstract: A base-labile protecting group for hydrogen connected to phosphorus has been found. This has led to the development of hypophosphorus acid synthons.

The preceding letter[1], this issue, describes the use of synthons (1-3) containing a P-H bond protected with an acetal or ketal group. These synthons are valuable building blocks for the preparation of functional phosphorus acids.

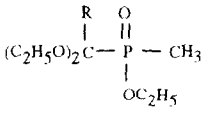


(1)

R = H or CH_3



(2)



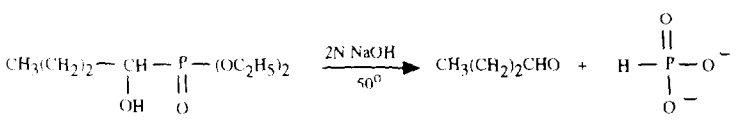
(3)

Both acetal (R=H) and ketal ($R=CH_3$) groups are removed with acid or the ketal can be removed with milder trimethylsilyl chloride in commercial chloroform. The acid lability of these protecting groups, however, precludes their use in more complex molecules which contain acid sensitive groups. There is a need therefore for a protecting group for a P-H bond which is stable to acid but can easily be removed under basic conditions. This would complement our acid-labile protection.

Kharasch et al[2] observed that in strongly alkaline media 1-hydroxyalkanephosphonates derived from aldehydes and dialkylphosphites are cleaved to regenerate the starting aldehyde.

We investigated this reaction and found that diethyl-1-hydroxy-n-butylphosphonate (4) when warmed with 2N sodium hydroxide gives n-butyraldehyde and orthophosphorus acid, thus regenerating the P-H bond. (Scheme 1)

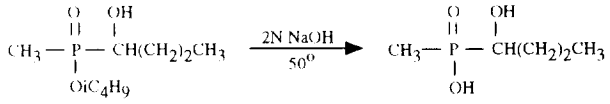
Scheme 1



(4)

However, treatment of the phosphinate (5) prepared from isobutylmethylphosphinate and n-butyraldehyde, with 2N sodium hydroxide gave only the hydrolysis product (6) of the phosphinate ester without any P-C bond cleavage. (Scheme 2)

Scheme 2

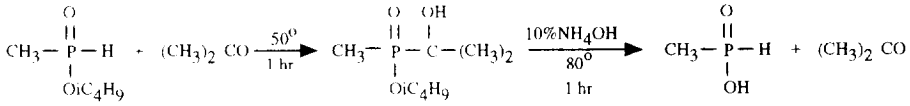


(5) (6)

Likewise, phosphinates prepared from other aldehydes, e.g. formaldehyde, are also stable to base.

Conversely, we have found that the phosphinate (7) prepared from isobutylmethylphosphinate and acetone is readily cleaved with base, e.g. ammonium hydroxide, to give acetone and regenerate the P-H bond (Scheme 3).

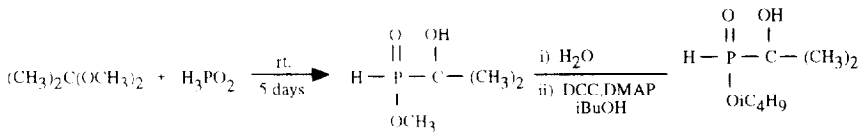
Scheme 3



(7)

This prompted us to use this P-H protection for hypophosphorous acid thus producing a synthon with base labile protecting groups. Such a compound has been described by Fitch[3] during his studies on the preparation of alkylhypophosphites. Thus, methyl-1-hydroxy-1-methylethylphosphinate (8) is the final product in the reaction of hypophosphorous acid with 2,2-dimethoxypropane (Scheme 4).

Scheme 4

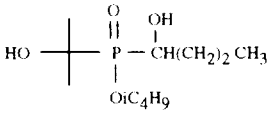
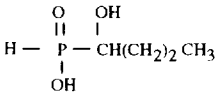
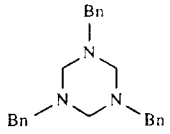
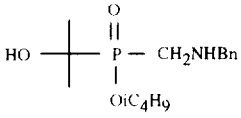
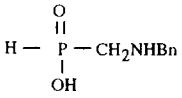
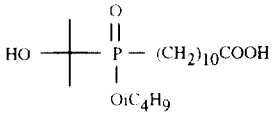
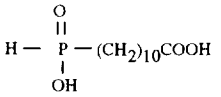


(8) (9)

Although (8) can be used as a synthon for P-C bond formation we prefer to use the more hydrolytically stable isobutyl ester (9). This is readily prepared from (8) by mild hydrolysis followed by esterification using the method of Karanewsky[4]. A typical preparation of (9) is described[5]. Alternative preparations of these new phosphinates prepared from a variety of ketones are described elsewhere[6].

Synthon (9) has been shown to undergo typical P-C bond forming reactions with aldehydes and Schiff bases and to add to double bonds under radical initiation. Deprotection to the phosphorous acid is achieved by heating with 10% ammonium hydroxide. (Table 1)

TABLE 1

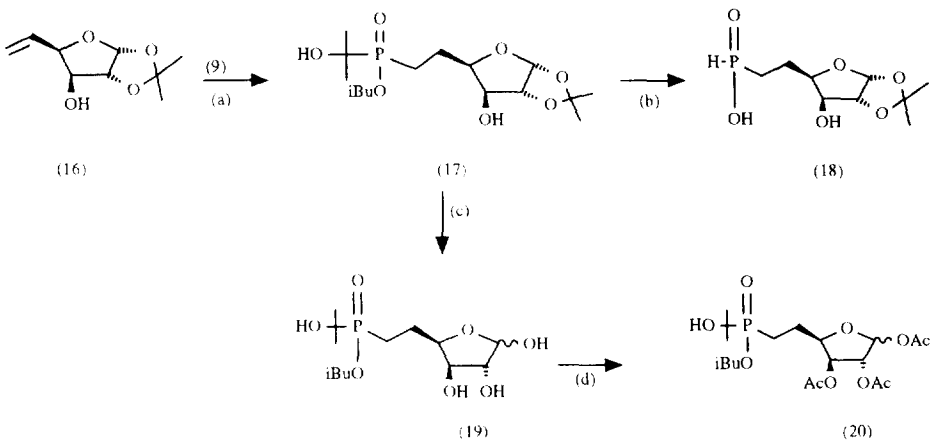
REACTANTS	PRODUCT	DEPROTECTION PRODUCT
(a) 9 + $CH_3(CH_2)_2CHO$	 (10)	 (11)
(b) 9 + 	 (12)	 (13)
(c) 9 + $CH_2=CH(CH_2)_8COOH$	 (14)	 (15)

a) DBU,Dichloromethane,r.t. 87%; b) Toluene, 100°,2h., 60%; c) Toluene, 80°, t-butylcyclohexylperdicarbonate (BCHPC), 3h, 75%

Thus, with n-butyraldehyde (9) gives phosphinate (10) which is selectively cleaved at the P-C bond containing the tertiary hydroxyl group to give the phosphonous acid (11). Reaction with the 1,3,5-hexahydrotriazine gives the α-aminophosphinate (12) and the aminophosphonous acid (13) after deprotection. With olefins (9) adds in anti-Markovnikov fashion very readily under radical initiation to give (14). That this synthon is very amenable to radical reactions provides an excellent means of controlling the reactivity of hypophosphorous acid in such reactions[7]. Its utility in more complex molecules has been demonstrated by the addition under radical initiation to the sugar olefin 5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose (16)[8]. (Scheme 5)

Phosphinate (17) is formed in excellent yield. Deprotection gives the phosphonous acid (18) retaining the acetonide protection. Alternatively, acid opening of the acetonide to triol (19) and subsequent peracetylation to give (20) has also been demonstrated. These options provide scope for further transformations to prepare disaccharide or nucleotide analogues. Our studies in these areas will be reported in due course.

Scheme 5



a) Toluene, BCHPC, 80°, 85%; b) 10%NH_4OH, 80°, 3 hr. 100%; c) Dowex 50WX2, H_2O, 70°, 6 hr. 95%; d) Ac_2O, Pyridine, r.t., 3 hr., 95%

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References and notes:

1. Tetrahedron Lett. Preceding letter.
2. Kharasch, M.S.; Mosher, R.A.; Bengelesdorf, I.S. *J.Org.Chem;* **1960**,25,1000.
3. Fitch, S.J. *J.Am.Chem.Soc;* **1964**,86,61.
4. Karanewsky, D.S.; Badia, M.C. *Tetrahedron Lett;* **1986**,27,1751.
5. Preparation of Synthon (9). Commercial hypophosphorous acid (50%) is concentrated to 94% on a rotary evaporator. A mixture of this acid (3M) and 2,2-dimethoxy propane (8.8M) is allowed to stand at room temperature for five days. The mixture is distilled to give methyl(1-hydroxy-1-methylethyl) phosphinate (8), 65%, b.p.65°/0.1mm, ^{31}Pnmr ($CDCl_3$,24.15 MHz) δ=45ppm, J_{PH}545Hz. (8) is heated with water on a steam bath until hydrolysis to the phosphonous acid is complete (monitored by ^{31}P n.m.r). The water is removed and the residue treated with isobutylalcohol, dicyclohexylcarbodiimide and dimethylamino pyridine (0.1M%) at 5° in T.H.F. On completion of the reaction (^{31}Pn.m.r.) ether is added and the dicyclohexylurea is filtered off. Evaporation of the filtrate followed by chromatography on silica gives isobutyl(1-hydroxy-1-methylethyl) phosphinate (9). C 47.0, H 9.5, P 17.1%; $C_7H_{17}O_3P$ requires C 46.7, H 9.5, P 17.2%; ^{31}Pn.m.r. $CDCl_3$, 162 MHz δ = 42.2 ppm.
6. E.P. 0614900A1 (Ciba-Geigy)
7. Kosolapoff, G.M.; Maier, L. *Organic Phosphorus Compounds*, Vol 4, Chapter 10, p261, *Wiley-Interscience*, **1972**, and references cited therein.
8. Hall, L.D.; Hough, L.; Pritchard, R.A. *J.Am.Chem.Soc.*, **1961**,83,1537.

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