Pergamon

Tetrahedron Letters, Vol. 36, No. 51, pp. 9385-9388, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01992-8

1,1-Diethoxyethylphosphinates and Phosphonites. Intermediates for the Synthesis of Functional Phosphorus Acids

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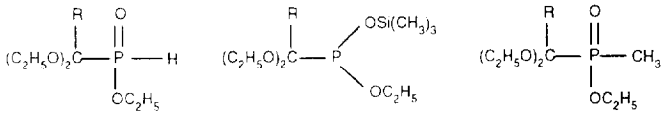
Abstract: Masked hypophosphorous and methanephosphonous acid synthons have been developed which provide functional phosphonous esters after mild deprotection.

In continuation of our studies in these laboratories aimed at the isosteric replacement of a carboxylic acid function in biologically active molecules by a phosphorus acid we now wish to report new synthons for the preparation of such functional phosphonous acids.

Our earlier report[1] describes the preparation of α-aminophosphonous acids, analogues of the protein amino acids, from Schiff bases and 100% hypophosphorous acid.

Later we described[2,3,4] the synthesis of α-, β-, and γ-aminophosphonous acids based on the use of masked hypophosphorous acid synthons (**1a**), (**2a**) and (**3a**) which have a protected form of hydrogen connected to phosphorus, i.e. a diethoxymethyl group. This latter functional group is stable to further transformations in the molecule and can ultimately be removed to liberate a phosphonous acid using dilute HCl at reflux.



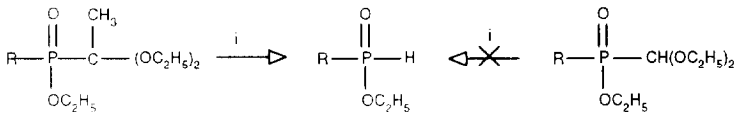
(1) (2) (3)

a) R = H[5,6] a) R = H[4] a) R = H[8]
b) R = CH_3[6] b) R = CH_3[7] b) R = CH_3[8]

These synthons obviated problems often encountered in synthesis using hypophosphorous acid which contains two P-H bonds. In addition the use of the hazardous anhydrous hypophosphorous acid is avoided[6,9]. They can be used therefore for the preparation of functional phosphonous acids which themselves are intermediates for conversion to phosphonic[1], phosphinic[10], and thiophosphonic acids[11]. Although these synthons are choice reagents for the synthesis of many functional phosphonous acids they are not suitable for those which contain groups sensitive to the vigorous acid conditions used in the subsequent removal of the protecting group.

We have found, however, that by making a small change in the protecting group to a 1,1-diethoxyethyl group, synthons (**1b**), (**2b**), and (**3b**) are obtained which undergo the same typical P-C bond forming reactions to provide functional phosphonous acids in a P-H protected form (**4**), where R is a functional group.

Moreover, the removal of this ketal protecting group is achieved using very mild conditions. Thus, reaction of **4**) with slightly more than one equivalent of trimethylsilyl chloride in commercial chloroform at ambient temperature gives the phosphinate ester (**5**) whereas corresponding acetal protection (**6**) is stable.



(4) (5) (6)

i) Trimethylsilyl chloride, chloroform, rt 1 hr >95%

That this mild deprotection retains the phosphinate ester group is advantageous in cases where further reactions of the P-H group are required. Carboxylate esters in the group R are also stable[12]. (**1b**) is readily prepared from 80-90% aqueous hypophosphorous acid, triethylorthoacetate and BF_3/etherate catalyst in good yield and high purity after distillation[6]. Silylation of ketal (**1b**) gives the new silylphosphonite (**2b**)[7] which reacts as a P^{III} nucleophile. The synthon (**3b**) is readily prepared from methylphosphonous dichloride and triethylorthoacetate[8].

Some reactions of the synthons (**1b**) - (**3b**) are outlined below (Table I)[13]. A typical deprotection procedure is carried out by treating a ketal-protected phosphonous acid with 1-2 equivalents of trimethylsilyl chloride in commercial grade chloroform containing up to 5% by weight of ethanol, under Argon and at room temperature for several hours. The reaction can be monitored by ^{31}P N.M.R. and on completion quenched with ethanol and the product isolated. The yields are almost quantitative.

Thus (**1b**) adds to the 1,3,5-hexahydrotriazine to give (**7**) which after deprotection, provides the α-aminophosphinate (**8**) which can be further functionalised through the P-H group.

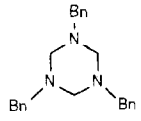
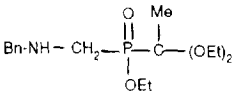
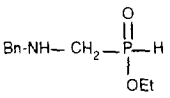
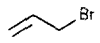
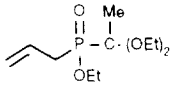
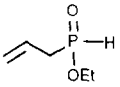
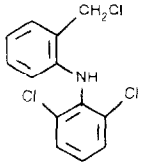
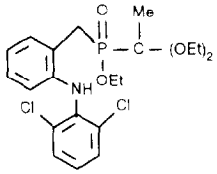
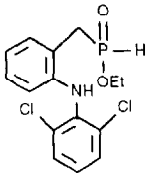
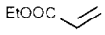
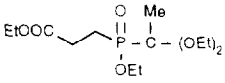
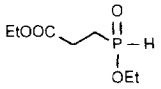
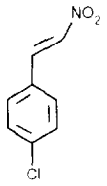
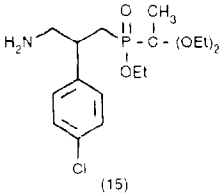
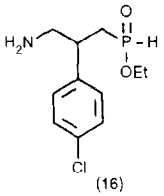
Typical Michaelis-Becker reaction of (**1b**) with allyl bromide gives the unsaturated phosphinates (**9**) and (**10**) and with α-chloro-N-(2,6-dichlorophenyl)-o-toluidine the phosphinate analogue of the non-steroidal anti-inflammatory agent Voltarol **12**) *via* the intermediate (**11**).

The P^{III} synthon (**2b**) undergoes Michael addition to ethyl acrylate to give (**13**) which on deprotection gives the phosphino-succinate having retained both ester functions.

Synthon (**3b**) is readily deprotonated and adds smoothly to 4-chloro-β-nitrostyrene to give (**15**) after reduction of the nitro group and (**16**) after deprotection. This simple three-step process to (**16**), an analogue of the muscle relaxant marketed as Lioresal®, demonstrates a reductive transformation in the presence of a protected phosphonous acid followed by mild deprotection to the γ-aminophosphinate.

Further use of these synthons in the preparation of more complex molecules of biological importance will be reported separately.

Table 1

Reactants	Product	Deprotected Product
(1b)[a] 	 (7)	 (8)
(1b)[b] 	 (9)	 (10)
(1b)[c] 	 (11)	 (12)
(2b)[d] 	 (13)	 (14)
(3b)[e,f] 	 (15)	 (16)

a) Toluene, 100°, 1h, 60%; b) Na, Toluene, 5-20°, 3h, 80%; c) Na, Toluene, 0-20°, 3h, 60%;

d) THF 60°, 3h, 95%; e) BuLi, THF, -78° $\rightarrow$0°, 1h, 60%, f) Ni, H_2, EtOH, rt, 90%.

ACKNOWLEDGEMENTS

The author wishes to thank Mr. S. Killick and Mr. S. McKown for technical assistance.

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(*Received in UK* 31 *August* 1995; *accepted* 19 *October* 1995)