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ADVANTAGES OF USING DI(p-METHYLBENZYL) HYDROGEN PHOSPHITE IN SYNTHESIS OF AMINOPHOSPHONATES FROM ALDIMINES

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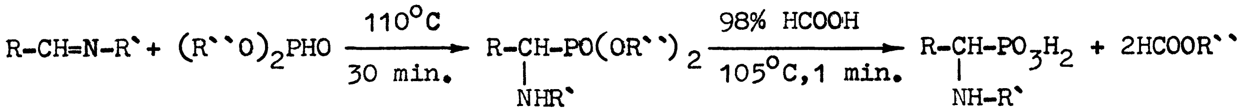
Aminophosphonic acids containing groups sensitive to hydrolysis and hydrogenation are obtained easily from aldimines by addition of di(p-methylbenzyl) hydrogen phosphite followed by selective removal of p-methylbenzyl groups by solvolysis with formic acid. Properly chosen substituens at nitrogen are also removed under these conditions and the synthesis of aminophosphonic acids with a free NH_2 group was achieved by a two-step procedure.

The p-methylbenzyl group, first proposed by Miyano and Funahashi for protection of phosphate function,1) appears not to be widely used in syntheses of phosphates or phosphonates, although it offers some advantages over the most commonly used benzyl group. Both these groups are removed by hydrogenolysis at comparable rates, but in reaction sequences starting with secondary phosphites it is advantageous to use crystalline di(p-methylbenzyl) hydrogen phosphite instead of dibenzyl phosphite which is difficult to purify. Moreover, we found that the p-methylbenzyl group is more readily removed by comparatively mild acidolysis with formic acid than the unsubstituted benzyl group.

In this communication we demonstrate the usefulness of di(p-methylbenzyl) hydrogen phosphite (2) in synthesis of aminophosphonic acids containing functions sensitive to hydrogenation and hydrolysis. Like other secondary phosphites, 2 readily adds to the C=N bond of aldimines (1), giving high yields of esters(3). Removal of p-methylbenzyl groups, achieved by brief formolysis, affords aminophosphonic acids (4) and p-methylbenzyl formate (5).

Selective removal of a p-methylbenzyl group is demonstrated by successful preparation of products 4a and 4b (Table 1) with intact methoxycarbonyl or diethoxyphosphinyl group. The presence of nitro and ester functions in these products obviously prevents removal of protecting group by hydrogenolysis or silylation.

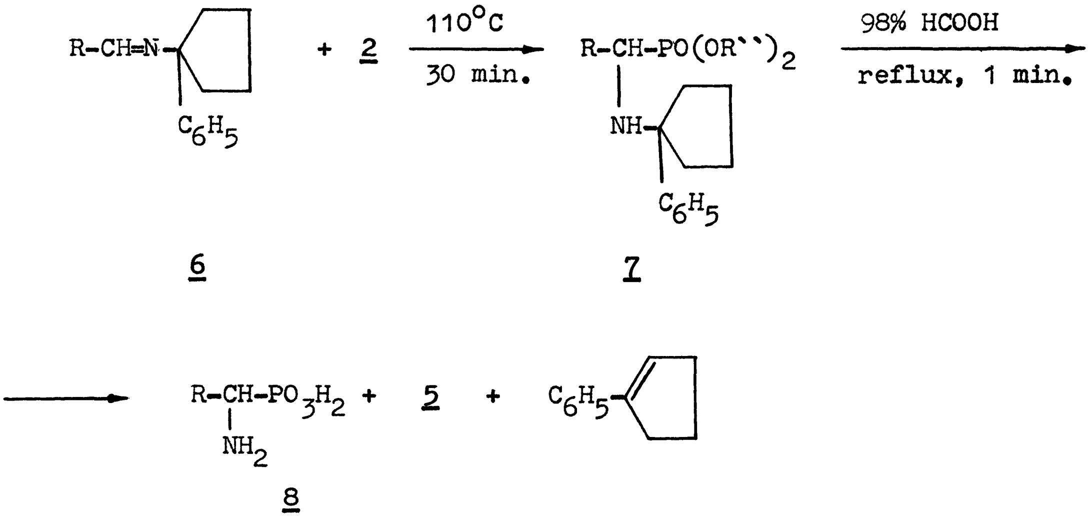


$$\underset{\mathbf{1}}{\text{R-CH=N-R}'} + \underset{\mathbf{2}}{(\text{R}''\text{O})_2\text{PHO}} \xrightarrow[30\text{ min.}]{110^\circ\text{C}} \underset{\mathbf{3}}{\underset{\text{NHR}'}{\text{R-CH-PO(OR}'')_2}} \xrightarrow[105^\circ\text{C},1\text{ min.}]{98\%\text{ HCOOH}} \underset{\mathbf{4}}{\underset{\text{NH-R}'}{\text{R-CH-PO}_3\text{H}_2}} + \underset{\mathbf{5}}{2\text{HCOOR}''}$$

R = m-$NO_2C_6H_4$ R' = CH_2COOMe 1a, 3a, 4a R' = $CH_2CH_2PO(OEt)_2$ 1b, 3b, 4b

R'' = p-$CH_3C_6H_4CH_2$

Preparation of the biochemically more interesting aminophosphonic acids with free NH_2 group from aldimines requires removable substituents at nitrogen.[2,3] Particularly useful are tertiary benzyl groups, like 1-phenyl-1-cyclopentyl,[3] removable by acidolysis under conditions necessary for removal of p-methylbenzyl from the phosphonate function. Thus, using aldimines prepared from 1-phenyl-1-cyclopentylamine and benzaldehyde, isobutyraldehyde, furfural or 2-thiophenecarbaldehyde, we were able to obtain high yields (see Table 1) of aminophosphonic acids 8a - 8d in two steps, involving addition of 2 to aldimines 6a - 6d, followed by simultaneous formolytic removal of substituents from amino and phosphonate functions. Preparation of 8a by methods involving acid hydrolysis or hydrogenolysis would obviously be difficult because of the presence of acid-sensitive furan ring.[4] Similarly, the thiophene ring in 8b would make hydrogenolysis difficult.



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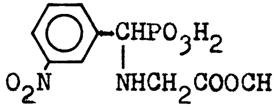
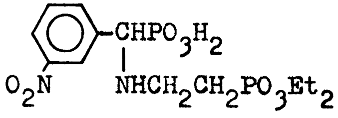
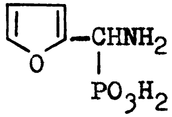
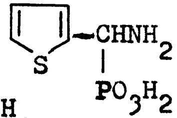
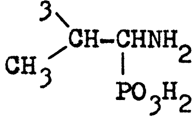
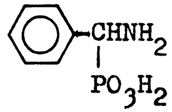
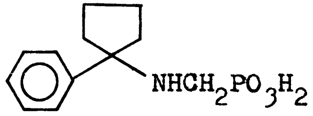
6a, 7a, 8a: R = 2-furyl 6b, 7b, 8b: R = 2-thienyl 6c, 7c, 8c: R = isopropyl

6d, 7d, 8d: R = phenyl 6e, 7e: R = H

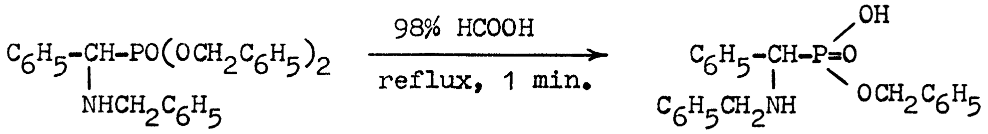
Table 1. Aminophosphonic acids obtained by di(p-methylbenzyl) hydrogen phosphite addition to aldimine and formolysis

No	Formula	Yield* (%)	Mp (^{o}C)	IR major bands (ν, cm^{-1})	^{1}H-NMR δ, ppm
4a		67	241-3(dec)	1100,1190-1210,1355,1530, 1605,1745,2300-3000	3.45(s,2H,CH$_2$),3.70(s,3H,CH$_3$),4.26(d,1H,CH, $^2J_{PH}$=17Hz),7.81-8.80(m,4H$_{ar}$); (in D$_2$O + D$_2$SO$_4$)
4b		79	200-202	1020,1085,1150,1220,1350, 1530,2400-3000	1.02-1.38(m,6H,OCH$_2$C$\underline{H}_3$),2.13-2.78(m,2H,CH$_2$P), 3.13-3.79(m,2H,CH$_2$N),3.86-4.47(m,4H,OC$\underline{H}_2$CH$_3$), 4.76-5.25(m,1H,CHP),7.45-8.63(m,4Har); (in CF$_3$COOH)
8a		82	225-7(dec)	920,1070,1225,1545, 2600-3000,3100	4.90(d,1H,CHP,$^2J_{PH}$=16Hz),6.74-7.00(m,2H$_{furyl}$) 7.88(b.s,1H$_{furyl}$); (in D$_2$O)
8b		85	248-50(dec)	720,940,1075,1155,1190,	5.20(d,1H,CHP,$^2J_{PH}$=16Hz),7.37-7.96(m,3H$_{thien.}$) (in D$_2$O + D$_2$SO$_4$)
8c		84	271-3**		
8d		77	277-9**		
***		74	257-9	890,1085,1115,1180,1210, 1225,1290,1610,2100-2700, 2960,3100	1.87-2.50(m,8H,C$\underline{H}_2$x4),2.65(d,2H,CH$_2$P, $^2J_{PH}$= 14Hz),7.82(b.s,5H$_{ar}$); (in D$_2$O + NaOD)

*Yield based on aldimines. **Identified by comparison with authentic samples prepared after Berlin$^{5)}$(8c) or Kreutzkampf$^{6)}$(8d). ***Prepared from 7e under conditions described in general procedure. In this case formolysis failed to remove substituent from nitrogen. More drastic hydrolysis was necessary to prepare aminomethanephosphonic acid from 7e in one step.$^{3)}$

General procedure: A mixture of 2 (0.01 mole) and an aldimine (0.01 mole)[3] was heated at 110-120° C for about 30 minutes. After cooling the crude reaction mixture was treated with 20 ml of formic acid (98% commercial grade, FLUKA) and was heated to boiling for 1 minute. Volatiles were then removed under reduced pressure and oily residues were extracted with anhydrous ether (3x25 ml). Resulting solid or semisolid aminophosphonic acids were recrystallized from ethanol to give pure specimens.

Unsubstituted benzyl group is not removed completely by formolysis under conditions specified above. Thus, formolysis of the dibenzyl ester 9 yielded the monobenzyl ester 10.



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