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Phosphitylation via the Mitsunobu Reaction

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Abstract: Treatment of a dialkyl phosphite with triphenylphosphine and diisopropyl azodicarboxylate in toluene, followed by addition of an alcohol, results in the formation of the corresponding trialkyl phosphite. Similarly, dialkyl phosphonites can be synthesised from monoalkyl phosphites (alkyl phosphinates).

Introduction

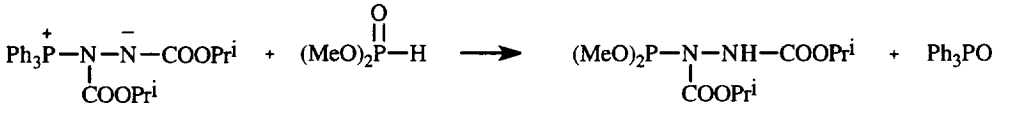
The Mitsunobu reaction[1,2] is a very useful reaction in organic synthesis[3] particularly for the synthesis of esters of carboxylic acids. The reaction can also be used for the synthesis of phosphate esters[4], but as far as we are aware, it has not been used for the synthesis of esters of trivalent phosphorus. In recent years, esters of trivalent phosphorus have become important and versatile intermediates for the synthesis of phosphate esters such as glycosyl phosphates[5] and oligodeoxyribonucleotides[6]. Phosphitylation followed by oxidation is now the method of choice for the phosphorylation of less reactive alcohols such as nucleosides.[7]

We now report that the Mitsunobu reaction provides an alternative to the more commonly used dibenzyl[8] and di-*tert*-butyl phosphoramidite[9] procedures for phosphitylation of alcohols. An example of the reaction is shown in equation (1).

$$(MeO)_2\overset{\overset{O}{\|}}{P}-H \xrightarrow[(2)\ ROH]{(1)\ Ph_3P\ /\ DIAD} (MeO)_2P-OR \qquad (1)$$

Results and Discussion

Reactions were followed by ^{31}P nmr as described for previous studies of the Mitsunobu reaction.[10-14] Thus, triphenylphosphine (TPP, 178 mg, 0.66 mmol) was dissolved in dry toluene (3ml) in an nmr tube under a nitrogen atmosphere. The solution was cooled to 0°C and diisopropyl azodicarboxylate (DIAD, 130 µl, 0.66 mmol) added dropwise. ^{31}P nmr showed the formation of the betaine **1**, δ 44.4 ppm, together with a small amount of triphenylphosphine oxide, δ 25.4 ppm, as observed previously.[10-14] Addition of dimethyl phosphite (dimethyl phosphonate, 30 µl, 0.33 mmol)[15] resulted in the immediate appearance of several broad peaks in the range δ 129-140 ppm, tentatively attributed to the phophoramidite intermediate **2**. Also present was the betaine **1**, δ 44.4, and triphenylphosphine oxide, δ 25.4 ppm. Addition of phenol (62 mg, 0.66 mmol) resulted in the formation of dimethyl phenyl phosphite, δ 135.0 ppm (lit[16]value, 135.2 ppm). The latter reaction was quite slow. Thus after 24 hours at 0°C, the yield [17] of dimethyl phenyl phosphite was 50%. When the reaction was repeated (for 24 hours) at 40°C, the yield increased to 83%. The slow appearance of the sharp phosphite peak was accompanied by a corresponding slow decrease in the broad intermediate peaks.[18]



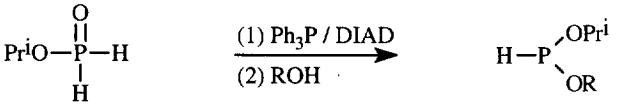
1 **2**

Analogous results were obtained when primary, secondary, and tertiary alcohols were used instead of phenol and when diethyl phosphite was used instead of dimethyl phosphite. ^{31}P nmr data for the various phosphites prepared are summarised in Table 1.

Table 1 ^{31}P nmr data for Phosphites prepared via the Mitsunobu Reaction.

Phosphite	δ_P (ppm, toluene)	δ_P (lit[16])
$(MeO)_2POMe$	141.0	140-141
$(MeO)_2POCH_2Ph$	140.7	
$(MeO)_2POCHMe_2$	139.9	
$(MeO)_2POCMe_3$	136.0	
$(MeO)_2POCH_2CMe_3$	140.4	
$(MeO)_2POC_6H_{11}$	139.7	
$(MeO)_2POPh$	135.0	135.2
$(EtO)_2POEt$	138.9	137-140
$(EtO)_2POCH_2Ph$	139.0	
$(EtO)_2POCH_2CMe_3$	139.2	137.2
$(EtO)_2POPh$	134.2	

Analogous results were also obtained when tributylphosphine / DIAD and TPP / di*tert*-butyl azodicarboxylate were used instead of TPP / DIAD for the Mitsunobu phosphitylation. Similarly it was found that when isopropyl hypophosphite (isopropyl phosphinate) was used instead of dimethyl phosphite, dialkyl phosphonites were produced (equation 2).



(2)

However, as it is difficult to obtain isopropyl phosphinate[19] free of isopropyl alcohol, the reaction was accompanied by the formation of some diisopropyl phosphonite. Also, when methanol was used, some dimethyl phosphonite was formed, indicating that the initially formed isopropyl methyl phosphonite had undergone partial transesterification. The dialkyl (and mixed alkyl/aryl) phosphonites formed all showed ^{31}P nmr doublets and J_{PH} coupling constants typical of trivalent phosphorus compounds (Table 2).

Table 2 ^{31}P nmr data for Phosphonites prepared via the Mitsunobu Reaction.

Phosphonite	δ_P (ppm, toluene)	J_{PH} (Hz)
H P(OPr^i)$_2$	151.6	201.4
H P(OPr^i) (OPh)	152.9	218.1
H P(OPr^i) (OMe)	163.4	207.0
H P(OMe)$_2$	172.6 (171[a])	201.0 (203[a])

[a] Literature values [20]

In conclusion, the Mitsunobu reaction can be used to convert (pentavalent) dialkyl phosphonates and alkyl phosphinates into (trivalent) trialkyl phosphites and dialkyl phosphonites respectively. The reaction appears to be general and can be used with primary, secondary, and tertiary alcohols. The mechanism of this novel reaction is currently being investigated.

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15. For reasons that are not yet clear, two equivalents of betaine appeared to be required. When equimolar amounts of betaine **1** and dimethyl phosphite were employed, substantial amounts of unreacted dimethyl phosphite, δ10.0 ppm, remained.

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17. The yield was determined by ^{31}P nmr and is based on integration of the phosphite product peak relative to the intermediate peaks δ 129 - 140.

18. Dimethyl phenyl phosphite was also formed cleanly by changing the order of addition, i.e. addition of dimethyl phosphite to pre-formed diphenoxytriphenylphosphorane.

19. Isopropyl "hypophosphite" was prepared from hypophosphorous acid and isopropyl alcohol by azeotropic removal of water with benzene (M.J. Gallager, M.G. Ranasinghe and I.D. Jenkins, *J.Org. Chem.*, submitted)

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