Synthesis of Phosphonates: a Modified Arbuzov Procedure

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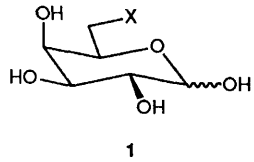
Reactions of 6-iodogalactosides with either methyl or isopropyl diphenyl phosphite lead to diphenylphosphoryl derivatives; these can be converted by ester exchange into dibenzylphosphoryl derivatives, which are convenient precursors of carbohydrate phosphonic acids.

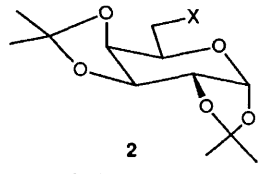
In connection with studies aimed at the synthesis of phosphonate analogues (*e.g.* **1a**) of sugar 6-phosphates (*e.g.* galactose 6-phosphate, **1b**), we have found a new method to introduce the diphenylphosphoryl group, and hence dibenzylphosphoryl group into carbohydrates. This enables the phosphonic acid of **1a** to be unmasked *in the last step* of its synthesis. Our method is based on a variant of the Arbuzov reaction[1] in which either methyl or isopropyl diphenyl phosphite is used with the iodide **2a** or **3a**.† The products from such reactions are the diphenyl phosphonates **2b** and **3b**;† compound **2b** has been converted into the corresponding dibenzyl phosphonate **2c**,† by base-catalysed ester exchange. Following acidic cleavage of acetal functions, the benzyl protecting groups can be removed cleanly by hydrogenolysis (H_2, 10% Pd/C) in tetrahydrofuran (THF)–water (1 : 1) to give a quantitative yield of **1a**† as a white foam.

We originally explored standard Arbuzov reactions of the galactosyl iodide **2a** and trifluoromethanesulphonate **2d**. Compound **2a** reacted with an excess of trimethyl phosphite at 140 °C to afford a 30% yield of **2e**.† Much better was the use of the trifluoromethanesulphonate **2d**, which reacted with the sodium salt of dibutyl phosphite in hexane (*cf.* ref. 2) or THF (reflux, 2 days) to give the corresponding dibutyl phosphonate **2f**† (81%). Conversion of **2e** or **f** into the free phosphonic acid was problematical, because it was not possible to remove the phosphonate protecting groups after all of those of the carbohydrate. For example, reaction of **2e** or **f** with an excess of bromotrimethylsilane (3 h, room temp.), followed by aqueous hydrolysis of the intermediate silyloxy compound gave a crude phosphonic acid **2g**. This was immediately



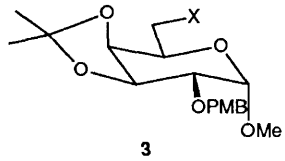
1

a; X = $PO(OH)_2$
b; X = $OPO(OH)_2$



2

a; X = I
b; X = $PO(OPh)_2$
c; X = $PO(OCH_2Ph)_2$
d; X = OSO_2CF_3
e; X = $PO(OMe)_2$
f; X = $PO(OBu)_2$
g; X = $PO(OH)_2$
h; X = *p*-$MeC_6H_4SO_3$



3

a; X = I
b; X = $PO(OPh)_2$, PMB = *p*-methoxybenzyl

† New compounds gave analytical and spectroscopic data in accord with their assigned structures.

subjected to acidic hydrolysis of the acetal functions [using either 1 : 1 THF–4 mol dm^{-3} aq. HCl (16 h, room temp.) or 1 : 1 trifluoroacetic acid–water (2 h, room temp.) (*cf.* ref 3)] to give a product that was difficult to purify and could not be readily converted into a pure sample of the phosphonic acid **1a**.

The point of using methyl or isopropyl diphenyl phosphite in place of trimethyl or triethyl phosphite in reaction with alkyl halides, is that the intermediate phosphonium species was expected to break down by iodide attack on methyl or isopropyl rather than on phenyl (*n.b.* Arbuzov and Nesterov reported[4] that the alkyl of X_2PO–alkyl is more reactive than the phenyl of X_2P–OPh). This has already been shown for the reaction of methyl diphenyl phosphite with cyanuric chloride.[5] Furthermore, the presence of phenyl groups in the product enables other dialkyl phosphites to be obtained by a simple base-catalysed exchange reaction[6,7] with an alcohol.

Our initial studies with methyl diphenyl phosphite revealed another problem: the iodomethane released reacted with methyl diphenyl phosphite (faster than **2a**) to afford diphenylmethyl phosphonate. By subjecting the reaction to continuous pumping (water pump), this side-reaction was suppressed and the yield of desired product was improved. In this way (*i.e.* heating **2a** with a fivefold excess of methyl diphenyl phosphite at 140 °C) **2b** was obtained in 68% yield (19% without pumping), and **3a** was converted into **3b** in 70% yield (41% without pumping). Alternatively, the use of isopropyl diphenyl phosphite suppressed the side-reaction because isopropyl is much less reactive to S_N2 displacement than methyl. Presumably, the decomposition of the intermediate phosphonium species, which also needs nucleophilic attack on isopropyl, is much faster than the formation of this intermediate. Arbuzov and Nesterov showed[4] that isopropyl diphenyl phosphite does not react with isopropyl iodide at 200 °C. We found that using isopropyl diphenyl phosphite (5-fold excess, 140 °C) with **2a** gave **2b** (45%), whilst **3a** gave **3b** (52%).

Methyl and isopropyl diphenyl phosphite were prepared from hexaethylphosphorotriamidite which was treated with phenol (2 mol equiv.) in glyme (reflux overnight) to afford diphenyl diethylphosphoramidite. This was treated with either methanol or propan-2-ol and tetrazole (each 1 mol equiv.) in glyme (6 h, 20 °C) to give either methyl diphenyl phosphite (69% overall) or isopropyl diphenyl phosphite (71% overall). These are better methods than those described in the literature (*cf.* ref. 8 and see also reaction of diphenyl phosphorochloridite with methanol[5]).

The iodide **2a** was prepared from toluene-*p*-sulphonate **2h**[9] by reaction with sodium iodide in *N.N*-dimethyl-*N,N*-propyleneurea (DMPU) (100 °C, 8 h). The trifluoromethanesulphonate **2d** was obtained from the corresponding alcohol.[10,11] Compound **3a** was derived (90% overall yield) from methyl-3,4-di-*O*-isopropylidene-α-D-galactoside[12] by dimethoxytritylation[13] at the 6-hydroxy, followed by *p*-methoxybenzylation (*p*-methoxybenzyl chloride, NaH in THF), removal of the dimethoxytrityl group, tosylation and replacement (see above) of OTs by I.

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