

Regioselective monophosphorylation of glycols containing primary and secondary hydroxyl groups

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DOI: 10.1070/MC2000v010n01ABEH001212

A new approach to the synthesis of monophosphorylated glycols with the use of P^{III}-benzimidazolidine has been suggested.

Regioselective phosphorylation of polyhydroxyl systems is an urgent problem of fine organic synthesis. Definite progress towards this direction was achieved using the preferable interaction of primary hydroxyl groups of polyols with sterically hindered amines, which are activators of the nucleophilicity of hydroxyl groups.¹

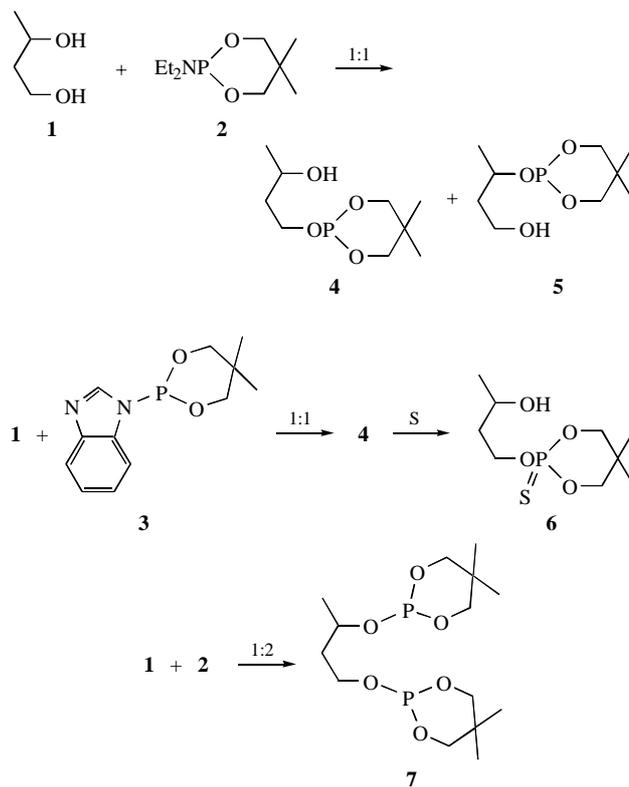
For solving this problem, we suggest another way based upon the use of commonly available and highly reactive amides of trivalent phosphorus acids (ATPA) as phosphorylating agents.² Note that in contrast to chlorophosphites and other widespread phosphorylating agents they can be dramatically different from each other in the spatial organization of a leaving (amine) group. This difference can be important in selecting reagents for the regioselective phosphorylation of nucleophiles having several reactive centres. Glycols with primary and secondary hydroxyl groups can serve as an example. ATPA with small amido groups do not exhibit selectivity with respect to such glycols. However, ATPA with bulky amido groups, which are responsible for steric hindrances during an attack on secondary hydroxyl groups, can provide high selectivity for the phosphorylation of only primary hydroxyl groups.

In this connection, we decided on phospho(III)benzimidazolidines³ in order to examine the regioselective monophosphorylation of glycols with primary and secondary hydroxyl groups. 1,3-Butylene glycol **1** was taken as a model substrate for the phosphorylation; diethylamide **2** and benzimidazolidine **3** of neopentylphosphorous acid served as phosphorylating agents.

We found that the interaction of equimolar quantities of **1** and **2** resulted in a mixture of two regioisomers **4** and **5**, which exhibit dramatically different ³¹P NMR spectra (122 and 128 ppm, respectively, the integral ratio 1:1).[†] At the same time, according to ³¹P NMR data, the interaction of equimolar quantities of **1** and **3** leads to only one product **4** (Scheme 1).

In both cases, the complete disappearance of signals of phosphorylating reagents **2** and **3** (147 and 114 ppm, respectively) in the ³¹P NMR spectra of reaction mixtures was observed. Monophosphorylation product **4** was treated with sulfur to form thiophosphate **6**, which was isolated in the individual form.[‡]

Note that diphosphite **7** was formed by the phosphorylation of glycol **1** by two moles of ATPA. The ³¹P NMR spectrum of the reaction mixture exhibited a signal at 128 ppm, which was previously observed in the phosphorylation of glycol **1** by amide



Scheme 1

2. Thus, we found that reagent **3** is capable of the regioselective phosphorylation of a primary hydroxyl group in the presence of secondary hydroxyl groups.

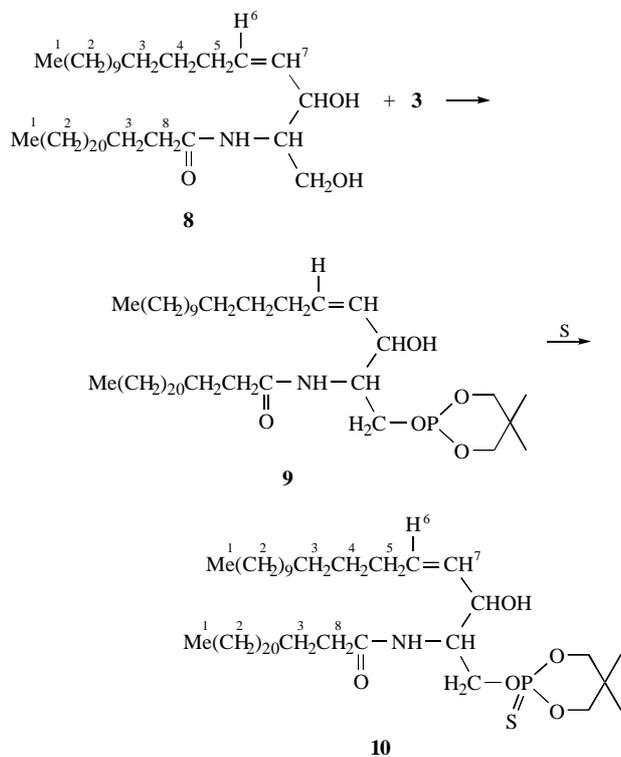
An additional confirmation for the location of a phosphorus-containing residue in compound **6** was obtained by an analysis of ¹H and ¹³C NMR spectra measured under conditions of homo- and heteronuclear double NMR. Thus, for example, spin-spin coupling constants (SSCC) of oxymethylene protons of 1,3-butylene glycol residue with phosphorus were present in the ¹H NMR spectra, and SSCC of methine proton with phosphorus were absent. Analogously, SSCC of oxymethylene carbon with phosphorus were present in ¹³C NMR spectra and SSCC of methine carbon with phosphorus were absent.[‡]

We used the found regioselectivity for the directed phosphorylation of natural ceramide **8**,[§] which is of importance for lipidology. We found that ceramide **8** was regioselectively mono-

[†] Dioxane, c 1 mol dm⁻³, 100 °C, 3 h.

[‡] An equimolar quantity of sulfur was added to the reaction mixture, and the contents were stirred at 20 °C for 12 h. Thiophosphate **6** was isolated by flash chromatography on silica gel with the eluent CHCl₃-MeOH (7:1), R_f 0.5. Yield 70%, pale yellow viscous oil. ¹H NMR (250 MHz, CDCl₃, TMS as an internal standard) δ: 0.88 (s, 3H, Me^c_{cyclo}), 1.13 (s, 3H, Me^a_{cyclo}), 1.17 (d, 3H, MeCH, ³J_{HCH} 6.4 Hz), 1.62-1.88 (m, 2H, CCH₂C), 2.34 (br. s, 1H, OH), 3.80-4.03 (m, 6H, CH₂O_{acyclo}, ³J_{HCO} 9.0 Hz; CH₂O_{cyclo}, ³J_{HCO} 8.5 Hz), 4.08-4.35 (m, 1H, CH), ¹³C NMR (50.32 MHz, CDCl₃, TMS as an internal standard) δ: 20.97 (MeCH), 21.5 (Me^c_{cyclo}), 23.44 (Me^a_{cyclo}), 32.17 (MeCMe, ³J_{CCOP} 6.6 Hz), 39.00 (CH₂CH₂CH, ³J_{CCOP} 6.9 Hz), 63.97 (CH), 65.35 (CH₂CCH₂, ²J_{COP} 5.5 Hz), 77.61 (CH₂CH₂O, ²J_{COP} 5.6 Hz). ³¹P NMR (32.4 MHz, CDCl₃, 85% H₃PO₄ as an external standard) δ: 64. The elemental analysis data are consistent with the theoretical values.

[§] We used commercial ceramide **8** (Sigma), which had the following ¹H NMR spectrum (250 MHz, CDCl₃, TMS as an internal standard) δ: 0.81 (t, 6H, Me¹, ³J_{HCH} 7.2 Hz), 1.09-1.27 (m, 58H, CH₂²), 1.42-1.60 (m, 4H, CH₂³), 1.91-2.05 (m, 2H, CH₂⁴), 2.16 (t, 2H, CH₂⁵, ³J_{HCH} 7.1 Hz), 2.56 (br. s, 1H, CH₂OH), 3.58-3.68 (m, 2H, CH₂OH), 3.76-3.90 (m, 3H, CH₂⁶, NCH), 4.25 (br. s, 1H, HCOH), 5.25-5.30 (m, 1H, CH⁶), 5.39-5.51 (m, 1H, HCOH), 5.64-5.78 (m, 1H, CH⁷), 6.17 (d, 1H, NH, ³J_{HNH} 6.8 Hz).



Scheme 2

phosphorylated by an equimolar quantity of phosphoamide **3** by analogy with the above reaction (Scheme 2).

Phosphite **9** was treated in the reaction mixture by sulfur with the formation of thiophosphate **10**, which was isolated in the individual form.[¶] Its identity and structure were determined with using the above methodology.

The synthesis of cyclothiophosphate **10** is not only principally important, but also synthetically useful since it opens the way for preparing various analogues of phosphosphingolipids (sphingomyelins).⁴

Thus, the traditional use of ATPA can find new applications, for example, to the regioselective phosphorylation of complex natural compounds containing different proton-donor groups.

This work was supported by the International Science Foundation (ISF) and the U.S. Civilian Research and Development Foundation (CRDF) (grant no. RC1-177).

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Received: 13th October 1999; Com. 99/1540

[¶] Phosphorylation conditions: dioxane-CH₂Cl₂ (4:1), *c* 0.1 mol dm⁻³, 45 °C, 12 h. ³¹P NMR of compound **9** (in the reaction mixture) δ: 122. An equimolar quantity of sulfur was added to the reaction mixture at 45 °C for 12 h. Cyclothiophosphate **10** was isolated and purified by double flash chromatography on silica gel with the eluent CHCl₃-MeOH (7:1), *R*_f 0.5; next, with the eluent C₆H₆-dioxane (3:1), *R*_f 0.6. Yield of compound **10** 50%, pale yellow amorphous solid, mp 95-96 °C. ¹H NMR (250 MHz, CDCl₃, TMS as an internal standard) δ: 0.84-0.92 (m, 9H, Me¹, Me^e_{cyclo}), 1.16-1.36 (m, 61H, CH₂², Me^a_{cyclo}), 1.56-1.70 (m, 4H, CH₂³), 1.95-2.09 (m, 2H, CH₂⁴), 2.22 (t, 2H, CH₂⁵, ³J_{HCH} 7.2 Hz), 3.67-3.73 (m, 2H, CH₂OP), 3.74-4.10 (m, 7H, CH₂⁶, NCH, CH₂O_{cyclo}), 4.31 (br. s, 1H, HCOH), 5.33-5.37 (m, 1H, CH⁶), 5.46-5.58 (m, 1H, HCOH), 5.72-5.86 (m, 1H, CH⁷), 6.23 (d, 1H, NH, ³J_{HNCH} 6.8 Hz). ³¹P NMR (32.4 MHz, CDCl₃, 85% H₃PO₄ as an external standard) δ: 63. The elemental analysis data are consistent with the theoretical values.