Regioselective monophosphorylation of glycols containing primary and secondary hydroxyl groups

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A new approach to the synthesis of monophosphorylated glycols with the use of P^{III}-benzimidazolide 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]

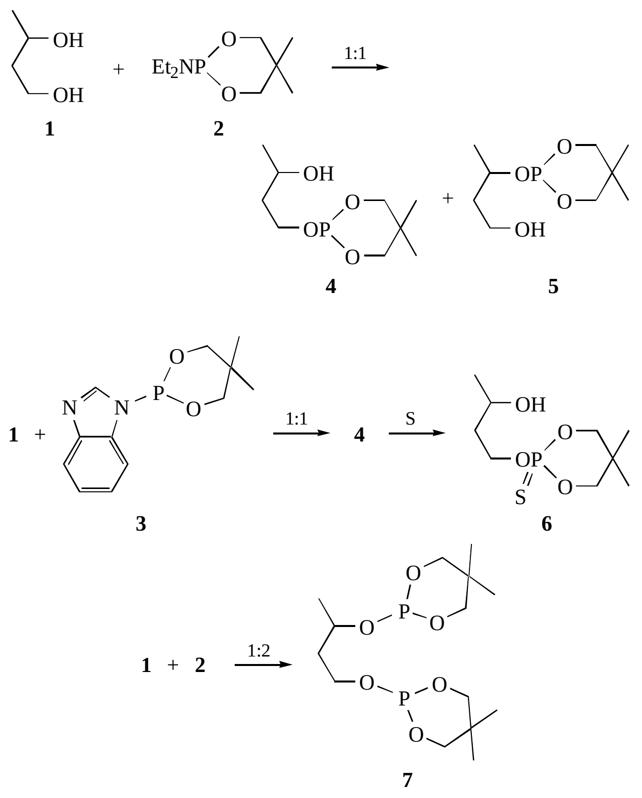
For solving this problem, we suggest another way based upon the use of commonly available and highly reactive amides of trivalent phosphorus acids (ATPA) as phosphorylating agents.[2] Note that in contrast to chlorophosphites and other widespread phosphorylating agents they can be dramatically different 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)benzimidazolides[3] 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 benzimidazolide **3** of neopentylenephosphorous acid served as phosphorylating agents.

We found that the interaction of equimolecular quantities of **1** and **2** resulted in a mixture of two regioisomers **4** and **5**, which exhibit dramatically different ^{31}P NMR spectra (122 and 128 ppm, respectively, the integral ratio 1:1).[†] At the same time, according to ^{31}P NMR data, the interaction of equimolecular 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 ^{31}P 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 ^{31}P NMR spectrum of the reaction mixture exhibited a signal at 128 ppm, which was previously observed in the phosphorylation of glycol **1** by amide **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.



Scheme 1

An additional confirmation for the location of a phosphorus-containing residue in compound **6** was obtained by an analysis of ^{1}H and ^{13}C 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 ^{1}H NMR spectra, and SSCC of methine proton with phosphorus were absent. Analogously, SSCC of oxymethylene carbon with phosphorus were present in ^{13}C 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-

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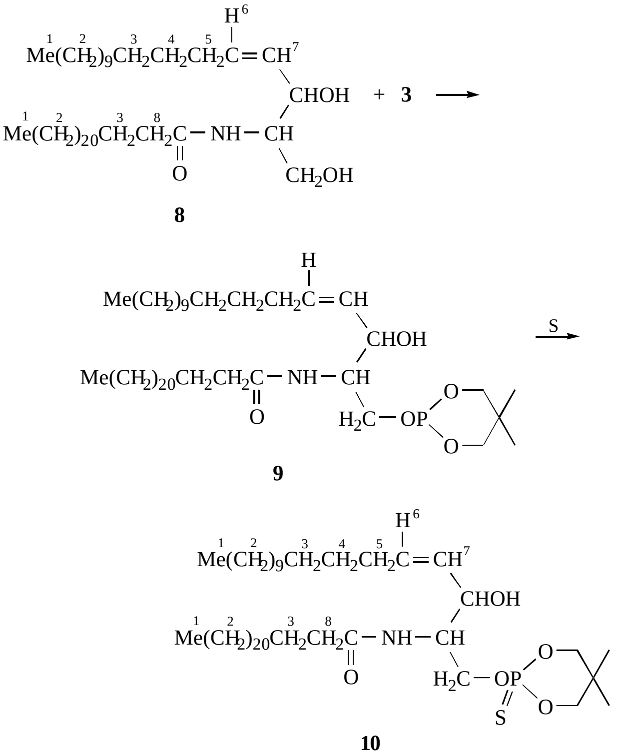
[†] Dioxane, *c* 1 mol dm^{-3}, 100 °C, 3 h.

[‡] 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 $CHCl_3$–MeOH (7:1), R_f 0.5. Yield 70%, pale yellow viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$, TMS as an internal standard) δ: 0.88 (s, 3H, Me^{e}_{cyclo}), 1.13 (s, 3H, Me^{a}_{cyclo}), 1.17 (d, 3H, MeCH, $^3J_{HCCH}$ 6.4 Hz), 1.62–1.88 (m, 2H, CCH_2C), 2.34 (br. s, 1H, OH), 3.80–4.03 (m, 6H, CH_2O_{acyclo}, $^3J_{HCOP}$ 9.0 Hz; CH_2O_{cyclo}, $^3J_{HCOP}$ 8.5 Hz), 4.08–4.35 (m, 1H, CH). ^{13}C NMR (50.32 MHz, $CDCl_3$, TMS as an internal standard) δ: 20.97 (*Me*CH), 21.5 (Me^{e}_{cyclo}), 23.44 (Me^{a}_{cyclo}), 32.17 (Me*C*Me, $^3J_{CCOP}$ 6.6 Hz), 39.00 ($CH_2\mathit{C}H_2CH$, $^3J_{CCOP}$ 6.9 Hz), 63.97 (CH), 65.35 ($\mathit{C}H_2C\mathit{C}H_2$, $^2J_{COP}$ 5.5 Hz), 77.61 ($CH_2\mathit{C}H_2O$, $^2J_{COP}$ 5.6 Hz). ^{31}P NMR (32.4 MHz, $CDCl_3$, 85% H_3PO_4 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 ^{1}H NMR spectrum (250 MHz, $CDCl_3$, TMS as an internal standard) δ: 0.81 (t, 6H, Me^1, $^3J_{HCCH}$ 7.2 Hz), 1.09–1.27 (m, 58H, CH^2_2), 1.42–1.60 (m, 4H, CH^3_2), 1.91–2.05 (m, 2H, CH^4_2), 2.16 (t, 2H, CH^8_2, $^3J_{HCCH}$ 7.1 Hz), 2.56 (br. s, 1H, $CH_2O\mathit{H}$), 3.58–3.68 (m, 2H, $C\mathit{H}_2OH$), 3.76–3.90 (m, 3H, CH^5_2, NCH), 4.25 (br. s, 1H, $HCO\mathit{H}$), 5.25–5.30 (m, 1H, CH^6), 5.39–5.51 (m, 1H, $\mathit{H}COH$), 5.64–5.78 (m, 1H, CH^7), 6.17 (d, 1H, NH, $^3J_{HNCH}$ 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.

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¶ *Phosphorylation conditions*: dioxane–CH_2Cl_2 (4:1), *c* 0.1 mol dm^{-3}, 45 °C, 12 h. ^{31}P 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 $CHCl_3$–MeOH (7:1), R_f 0.5; next, with the eluent C_6H_6–dioxane (3:1), R_f 0.6. Yield of compound **10** 50%, pale yellow amorphous solid, mp 95–96 °C. ^{1}H NMR (250 MHz, $CDCl_3$, TMS as an internal standard) δ: 0.84–0.92 (m, 9H, Me^1, Me^{e}_{cyclo}), 1.16–1.36 (m, 61H, CH^2_2, Me^{a}_{cyclo}), 1.56–1.70 (m, 4H, CH^3_2), 1.95–2.09 (m, 2H, CH^4_2), 2.22 (t, 2H, CH^8_2, $^3J_{HCCH}$ 7.2 Hz), 3.67–3.73 (m, 2H, CH_2OP), 3.74–4.10 (m, 7H, CH^5_2, NCH, CH_2O_{cyclo}), 4.31 (br. s, 1H, HCO*H*), 5.33–5.37 (m, 1H, CH^6), 5.46–5.58 (m, 1H, *H*COH), 5.72–5.86 (m, 1H, CH^7), 6.23 (d, 1H, NH, $^3J_{HNCH}$ 6.8 Hz). ^{31}P NMR (32.4 MHz, $CDCl_3$, 85% H_3PO_4 as an external standard) δ: 63. The elemental analysis data are consistent with the theoretical values.