Selective Monodeprotection of Phosphate, Phosphite, Phosphonate, and Phosphoramide Benzyl Esters

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Introduction

The benzyl group has found considerable use in organic chemistry as a protective group as it can be removed under neutral conditions *via* hydrogenolysis.[1-4] However, when several benzyl groups are simultaneously present on a substrate, it is often difficult, indeed impossible, to perform a monodeprotection, removing regiospecifically only one of the benzyl substituents.

Herein, we describe a procedure that allows for selective monodeprotection of various organophosphorus benzyl esters. Our investigations originated from the need to selectively introduce different ester substituents onto organophosphorus species prior to final removal of the protective groups. This was directed toward the synthesis of analogs of biologically important polyphosphorylated compounds using a strategy in which monodeprotected organophosphorus building blocks are coupled with aglycons prior to final deprotection. This strategy is exemplified with the synthesis of nonhydrolyzable nucleotide analogs (Scheme 1).

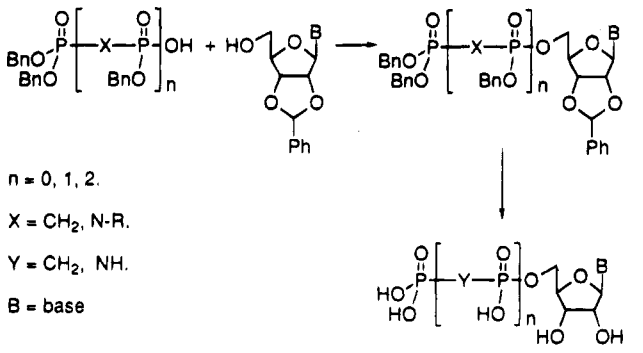
Results and Discussion

The key step of this approach resides in the monodeprotection of organophosphorus polybenzyl ester building blocks. Up to now, such a transformation was difficult to realize and most often a mixture of mono- and polydeprotected compounds was obtained, thus rendering purification very difficult. To our knowledge, the only example of selective monodeprotection of organophosphorus benzyl esters was reported in 1949[5] where tribenzyl phosphate and tetrabenzyl pyrophosphate were monodeprotected in refluxing *N*-methylmorpholine. The reaction resulted from the nucleophilic attack of one molecule of solvent on an activated benzylic position. The *N*-benzyl-*N*-methylmorpholinium salt could then be worked out in an aqueous media, yielding the corresponding acid or silver salt.

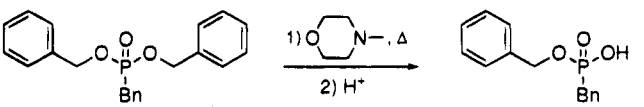
We tried to extend the latter procedure to phosphonates (Scheme 2).

Refluxing benzylphosphonic acid dibenzyl ester **1** in *N*-methylmorpholine for long periods gave only very low yields of the corresponding phosphonic acid **2**. This reveals the lower reactivity of phosphonate esters when compared to phosphates. To compensate for this lack of

Scheme 1



Scheme 2



1 **2**

reactivity, we increased the nucleophilicity of the tertiary amine. The use of quinuclidine or DABCO in refluxing benzene gave about the same result as refluxing *N*-methylmorpholine. On the other hand, the reaction could be brought to completion within a few hours when performed in refluxing anhydrous toluene. Phosphonic acid **2** could be then quantitatively obtained. These experimental conditions required only a stoichiometric amount of tertiary amine. The use of quinuclidine required a longer reaction time than DABCO but led to similar yields.

These reaction conditions were generalized to multiple organophosphorus compounds, and the results are summarized in Table 1.

With triphosphate analog **9**,[6] monodeprotection occurred regioselectively at one of the two phosphonates and not at the central phosphinate. This was ascertained by comparison with an authentic sample obtained unambiguously from the corresponding tetrabenzyl monomethyl ester.[6]

In the case of triphosphate analog **13**,[7] deprotection was not regioselective and occurred on both terminal and central phosphorus atoms to yield **14** (60%) and **15** (40%), respectively.

Under the experimental conditions described, all benzyl ethers and carboxylic esters we investigated proved to be stable.

Conclusion

It has been shown that benzylic phosphonates, phosphates, phosphites, and phosphoramides can be selectively monodeprotected under mild conditions using stoichiometric amounts of DABCO or quinuclidine in refluxing toluene. The yields are nearly quantitative, and pure compounds are obtained without any purification. In addition, with the bismethylene triphosphate analog **9**, the reaction is regioselective.

The use of these monodeprotected organophosphorus building blocks is of general interest as it provides a convenient synthetic pathway to analogs of polyphospho-

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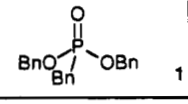
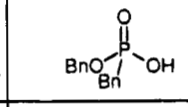
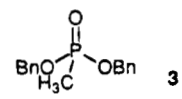
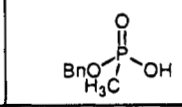
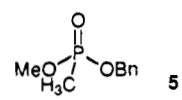
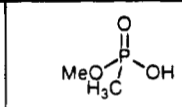
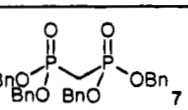
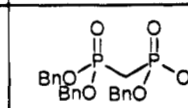
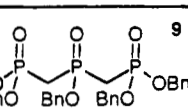
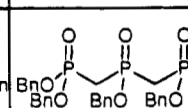
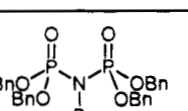
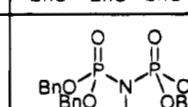
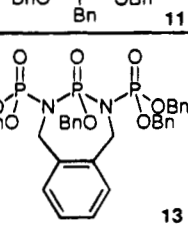
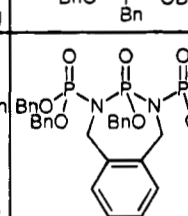
Table 1

Substrate	Product	Base[a]	Time (h)	Yield (%)
 1	 2	D	2	100
		Q	4	100
 3	 4	D	2	99
		Q	4	98
 5	 6	D	2	99
		Q	4	96
 7	 8	D	2	98
		Q	3	95
 9	 10	D	2	97
		Q	3.5	95
 11	 12	D	0.5	97
		Q	0.75	96
 13	 14	D	2	60[b]

[a] D: DABCO; Q: quinuclidine. [b] Monodeprotection was quantitative, but **14** was obtained as a mixture with its regioisomer **15** deprotected at the central phosphorus atom (40%).

rylated biological compounds where the attention of biologists is more and more devoted.

Experimental Section

General. ^{1}H-, ^{13}C-, and ^{31}P-NMR chemical shifts δ are reported in ppm relative to an internal reference (^{1}H, $CHCl_3$ at 7.27 ppm and DMSO-d_5 at 2.50 ppm; ^{13}C, $CDCl_3$ at 77.0 ppm, CD_3OD at 49.0 ppm; ^{31}P, H_3PO_4 at 0.00 ppm); J values are in hertz. IR spectra were recorded in wavenumbers (cm^{-1}). Mass spectra (MS) were recorded at chemical ionization (CI, NH_3). Mass data are reported in mass units (m/z).

Typical Procedure for Monodebenzylation. To a stirred solution of benzylphosphonic acid dibenzyl ester (**1**) (1.0 g, 2.84 mmol) in anhydrous toluene (10 mL) and under an argon atmosphere was added DABCO (318 mg, 2.84 mmol). The reaction mixture was refluxed for 2 h before the solvent was removed *in vacuo* and the residual salt was dissolved in aqueous HCl (5%). The aqueous layer was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. It was then evaporated under reduced pressure to yield benzylphosphonic acid monobenzyl ester (**2**) (744 mg, 100%) as a white powder.

Benzylphosphonic Acid Monobenzyl Ester (2). ^{1}H-NMR ($CDCl_3$, 200 MHz): 11.50 (s, 1 H), 7.35–7.22 (m, 10 H), 4.84 (d, J = 7.6, 2 H), 3.08 (d, J = 22.0, 2 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 136.56 (d, J = 5.5), 132.01 (d, J = 9.0), 129.77, 129.65, 128.13, 127.94, 127.75, 127.33, 127.24, 66.78 (d, J = 6.5), 33.91 (d, J = 136.0). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 28.55 (s). IR (CH_2Cl_2): 3090–2670, 2338, 1603, 1243, 1183, 997. MS (CI/NH_3): 280.1 (MNH_4^+), 263.0 (MH^+).

Methylphosphonic Acid Monobenzyl Ester (4). ^{1}H-NMR ($CDCl_3$, 200 MHz): 10.45 (s, 1 H), 7.39–7.33 (m, 5 H), 5.05 (d, J = 7.9, 2 H), 1.51 (d, J = 17.9, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 137.18 (d, J = 6.5), 129.32, 129.06, 128.53, 67.38 (d, J = 6.0), 12.64 (d, J = 146.1). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 34.68 (s). IR (CH_2Cl_2): 3400–2800, 1501, 1309, 1210, 1173, 1104, 996. MS (CI/NH_3): 186.9 (MH^+).

Methylphosphonic Acid Monomethyl Ester (6). ^{1}H-NMR ($CDCl_3$, 200 MHz): 11.88 (s, 1 H), 3.72 (d, J = 11.3, 3 H), 1.51 (d, J = 17.9, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 51.39 (d, J = 6.4), 11.50 (d, J = 143.5). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 33.55 (s). IR (CH_2Cl_2): 3650–2225, 1665, 1314, 1186, 1049, 990. MS (CI/NH_3): 110.9 (MH^+).

[[Bis(benzyloxy)phosphoryl]methyl]phosphonic Acid Monobenzyl Ester (8). ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.36–7.28 (m, 15 H), 5.10 (d, J = 11.9, 2 H), 5.02 (d, J = 12.0, 4 H), 2.57 (t, J = 21.1, 2 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 136.21 (d, J = 7.0), 135.86 (d, J = 6.5), 128.36, 128.31, 128.23, 128.02, 127.87, 127.46, 68.11 (d, J = 6.5), 67.30 (d, J = 6.0), 26.06 (*t*, J = 134.5). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 22.06 (d, J = 6.2), 19.79 (d, J = 6.2). MS (CI/NH_3): 446.1 (MH^+). IR (neat): 3400, 3065, 2956, 2894, 2662, 2238, 1607, 1497, 1455, 1380, 1254, 1016.

[[(Benzyloxy)[[(benzyloxy)hydroxyphosphoryl]methyl]-phosphoryl]methyl]phosphonic Acid Dibenzyl Ester (10) (Mixture of diastereomers). ^{1}H-NMR (DMSO-d_6, 200 MHz): 7.37–7.31 (m, 20 H), 5.07 (d, J = 7.2, 2 H), 4.97 (d, J = 7.4, 6 H), 2.77 (t, J = 20.1, 4 H). ^{13}C-NMR (CD_3OD, 50 MHz): 137.82–137.38 (m), 129.60–128.85 (m), 69.38 (d, J = 5.7), 68.63 (d, J = 5.7), 68.34 (d, J = 6.3), 29.61 (dd, J = 87.1, 130.6). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 41.21 (t, J = 4.9, 1 P), 18.59 (d, J = 4.9, 2 P). MS (CI/NH_3): 631.9 (MNH_4^+). IR (neat): 3064, 3033, 2953, 2897, 2635, 2306, 1668, 1498, 1455, 1382, 1216, 997.

(Benzylimido)diphosphoric Acid Tribenzyl Ester (12). ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.60–7.10 (m, 20 H), 5.15–4.80 (m, 6 H), 4.55 (t, J = 14.0, 2 H). ^{13}C-NMR (CD_3OD, 50 MHz): 136.23, 136.55 (d, J = 8.0), 135.75 (d, J = 7.7), 128.55–127.22 (m), 68.75 (d, J = 5.1), 68.05 (d, J = 4.7), 50.48. ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 5.78 (d, J = 27.6, 1 P), 3.92 (d, J = 27.6, 1 P). MS (CI/NH_3): 554.9 (MNH_4^+). IR (neat): 3112–2330, 1488, 1440, 1384, 1265, 1221, 1084, 1028.

[3-(Benzyloxy)-4-[bis(benzyloxy)phosphoryl]-3-oxo-1,3,4,5-tetrahydro-3λ^5-benzo[*e*][1,3,2]diazaphosphepin-2-yl]phosphonic Acid Monobenzyl Ester (14) (Mixture of diastereomers). ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.37–7.01 (m, 24 H), 5.12–4.82 (m, 8 H), 4.80–4.57 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 135.93–134.81 (m), 128.87–127.19 (m), 69.32–68.33 (m), 48.83–48.48 (m). ^{31}P-NMR ($CDCl_3$, 81.015 MHz):[8] 11.88 and 10.47 (tt, J = 19.7, 1 P), 5.72 and 3.81 (dd, J = 20.4, 1 P), −0.05 and −0.96 (dd, J = 19.7, 1 P). MS (CI/NH_3): 735.5 (MNH_4^+).

[4-[Bis(benzyloxy)phosphoryl]-3-hydroxy-3-oxo-1,3,4,5-tetrahydro-3λ^5-benzo[*e*][1,3,2]diazaphosphepin-2-yl]phosphonic Acid Dibenzyl Ester (15). ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.26–7.03 (m, 24 H), 4.90 (AB part of ABX system, J_{AB} = 11.7, J_{AX} = 5.6, J_{BX} = 8.0 Hz, ν_A = 4.91, ν_B = 4.86, 8 H), 4.66 (t, J = 15.2, 4 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 135.38, 135.22, 135.07, 129.07, 128.37, 128.32, 127.88, 69.06 (d, J = 5.2 Hz), 48.69. ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 6.36 (t, J = 23.4, 1 P), 4.57 (d, J = 23.4, 2 P). IR (CH_2Cl_2): 3740–3033, 1659, 1248, 1216, 1016. MS (CI/NH_3): 735.5 (MNH_4^+).

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Supplementary Material Available: ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR spectra of **2**, **4**, **6**, **8**, **10**, **12**, **14**, and **15** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, see any current masthead page for ordering information.

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(8) ^{31}P-NMR spectra of compound 14 refer to the potassium salt that offered better resolution than the acidic form.