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A SELECTIVE REMOVAL OF BENZYL PROTECTING GROUPS IN ARYLPHOSPHATE ESTERS WITH BROMOTRIMETHYLSILANE

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Abstract *: Bromotrimethylsilane (BTMS) is shown to be an effectively selective reagent for the debenzylation of dibenzyl arylphosphate esters to give the corresponding arylphosphate acids and does not affect other functional groups also present in the molecular structure.*

Naloxone and naltrexone are two potent antagonists of narcotic analgesics which have been shown to prevent the development of opiate dependence in several animal models.[1,2] The encapsulation of opioid antagonists such as naloxone or naltrexone into red blood cells appears to be a very useful mode of administration for psychologically fragile subjects because it would prevent long term repitition of detoxicative drugs.

A general method for the encapsulation of substances of biological and/or therapeutic interest into red blood tells has recently been developed and applied to a variety compounds.[3]

However, this procedure is not directly applicable to hydrophobic drugs such as naloxone and naltrexone which cross the blood-brain barrier because it causes them to strongly interact with the erythrocyte's plasma membrane, thus precluding efficient internalization. In order to circumvent this problem, prodrugs, containing ionized groups such as phosphate[4], were synthesized so as to stabilize them inside red blood cells.

Quite recently, Billington *et al.*[5] have reported the direct phosphorylation of inositol derivatives with tetrabenzyl pyrophosphate (TBPP)[6], using sodium hydride (NaH) in tetrahydrofuran (THF), to afford the dibenzyl phosphate esters. Next, the benzyl protecting groups were debenzylated by catalytic hydrogenolysis to give the corresponding phosphate acids. However, this technique cannot be applied to dibenzyl phosphate esters bearing an ethylenic bond (hydrogenation) or a C_{sp2}-X bond (hydrogenolysis).

Among the procedures described for dealkylation of phosphonate diesters affording phosphonate acids[7-14], we have selected that using BTMS.[7,8]

In the present letter, we describe the phosphorylation of various phenolic alcohols (*e.g.* naloxone, 6-β-naloxol, morphine, 2-allylphenol, cinnamic acid derivatives; 2-bromo-, 2-chloro-, and 5-chloro-3-hydroxypyridine; 7-hydroxycoumarin[15]) and the application of BTMS for the efficient removal of benzyl protecting groups.

$$\underset{1}{\text{Aryl-OH}} \xrightarrow[2)\ \text{TBPP}]{1)\ \text{NaH}} \underset{2}{\text{Aryl-OP(O)(OCH}_2\text{Ph)}_2} \xrightarrow[2)\ \text{H}_2\text{O}]{1)\ \text{BTMS}} \underset{3}{\text{Aryl-OP(O)(OH)}_2}$$

The phosphate ester was prepared by treatment of the appropriate phenolic alcohol with NaH in THF at room temperature, followed by direct phosphorylation using tetrabenzyl pyrophosphate (TBPP). The labile phosphate triester was obtained with an excellent yield (see Table I). The benzyl esters were removed rapidly by BTMS at 0°C. Then hydrolysis was accomplished in neutral water at room temperature. The crude product was purified by anion-exchange chromatography to give the pure arylphosphate in good yield (see Table II).

The structures of phosphate derivatives were determined from the ^{1}H-NMR spectra in deuterated chloroform for the dibenzyl arylphosphate esters, and in deuterated oxide for the arylphosphate as the ammonium salt.

Thus BTMS is demonstrated to be highly selective in the debenzylation of dibenzyl arylphosphate ester, without the competing formation of the allylic bromide, the reduction of double bond or halogenated pyridine, and the cleavage of the bond between the aromatic carbon and the phosphate oxygen.

The results summarized in the present work clearly show the advantage of this method for the preparation of phosphate acids of biological interest.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded at 300 MHz on a Bruker AM 300 WB spectrometer using tetramethylsilane as internal reference. T.l.c. was performed on silica gel (Merck 60 F_{254}). Column chromatography used silica gel (Merck 60 70-230 mesh). All reactions involving moisture-sensitive reagents were performed under an atmosphere of argon. Tetrahydrofuran was distilled from sodium/benzophenone. Methylene chloride was distilled from calcium hydride. All phenolic alcohols were

Table I : Spectral data of dibenzyl arylphosphate esters (**2a-i**)

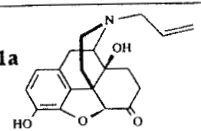
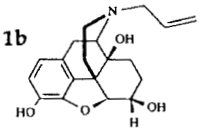
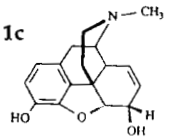
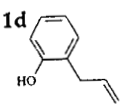
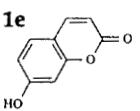
Substrate	Product	Yield (%)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)
1a 	**2a**	84	4.65 (s, 1H, H_5); 5.15-5.35 (m, 6H, 2xPhCH_2O and gem vinylic H); 5.73-5.87 (m, 1H, vinylic H); 6.61 (d, 1H, *J* = 8, H_1); 7.06 (d, 1H, *J* = 8, H_2); 7.27-7.44 (m, 10H, H_{arom}).
1b 	**2b**	95	3.37-3.50 (m, 1H, H_6); 4.50 (d, 1H, *J* = 6.1, H_5); 5.12-5.25 (m, 6H, gem vinylic H and 2xPhCH_2O); 5.69-5.85 (m, 1H, vinylic H); 6.60 (d, 1H, *J* = 8, H_1); 6.93 (d, 1H, *J* = 8, H_2); 7.25-7.41 (m, 10H, H_{arom}).
1c 	**2c**	70	4.18 (m, 1H, H_6); 4.95 (d, 1H, *J* = 7.11, H_5); 5.06 (d, 2H, *J* = 8.3, PhCH_2O); 5.20-5.26 (m, 1H, H_8); 5.29 (d, 2H, *J* = 8.3, PhCH_2O); 5.72-5.79 (m, 1H, H_7); 6.50 (d, 1H, *J* = 8, H_1); 6.69 (d, 1H, *J* = 8, H_2); 7.29-7,44 (m, 10H, H_{arom}).
1d 	**2d**	100	3.37 (d, 2H, *J* = 6.9, C-CH_2-C); 4.98-5.09 (m, 2H, C=CH_2); 5.12 (d, 4H, *J* = 8.2, 2xPhCH_2O); 5.82-5.97 (m, 1H, C=CH); 7.06-7.39 (m, 14H, H_{arom}).
1e 	**2e**	99	5.15 (d, 4H, *J* = 8.3, 2xPhCH_2O); 6.34 (d, 1H, *J* = 9.6, H_3); 7.03-7.10 (m, 2H, H_6 and H_8); 7.33 (s, 10H, H_{arom}); 7.37 (d, 1H, *J* = 8.5, H_5); 7.64 (d, 1H, *J* = 9.6, H_4).

Table I. (continued)

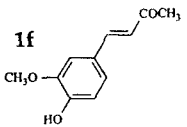
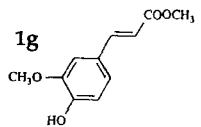
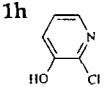
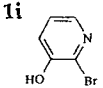
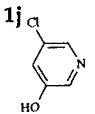
Substrate	Product	Yield (%)	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
1f 	**2f**	86	2.37 (s, 3H, CO-CH_3); 3.81 (s, 3H, O-CH_3); 5.18 (d, 4H, J = 8.3, 2xPhCH_2O); 6.64 (d, 1H, J = 16.2, H_3); 7.05 (d, 1H, J = 8,3, H_6 arom); 7.07 (s, 1H, H_2 arom); 7.23 (d, 1H, J = 8.3, H_5 arom); 7.33 (s, 10H, H_{arom}); 7.44 (d, 1H, J = 16.3, H_4).
1g 	**2g**	97	3.81 (s, 6H, 2xOCH_3); 5.18 (d, 4H, J = 8.3, 2xPhCH_2O); 6.37 (d, 1H, J = 16,2, H_2); 7.02 (d, 1H, J = 8.2, H_6 arom); 7.04 (s, 1H, H_2 arom); 7.21 (d, 1H, J = 8.4, H_5 arom); 7.33 (s, 10H, H_{arom}); 7.63 (d, 1H, J = 16.2, H_3).
1h 	**2h**	90	5.21 (d, 4H, J = 8.2, 2xPhCH_2O); 7.15 (dd, 1H, $J_{5,4}$ = 8.3, $J_{5,6}$ = 4.7, H_5); 7.34 (s, 10H, H_{arom}); 7.69 (d, 1H, J = 8.3, H_4); 8.19 (d, 1H, J = 4.7, H_6).
1i 	**2i**	90	5.19 (d, 4H, J = 8.2, 2xPhCH_2O); 7.16 (dd, 1H, $J_{5,4}$ = 8.3, $J_{5,6}$ = 4.7, H_5); 7.34 (s, 10H, H_{arom}); 7.65 (d, 1H, J = 8.3, H_4); 8.16 (d, 1H, J = 4.7, H_6).
1j 	**2j**	87	5.18 (d, 4H, J = 8.2, 2 x PhCH_2O) ; 7.35 (s, 10H, H_{arom}) ; 7.42 (s, 1H, H_4) ; 8.25 (s, 1H, H_2) ; 8.35 (s, 1H, H_6).

Table II : Spectral data of arylphosphate (**3a-i**)

Product[a]	Yield (%)	^{1}H-NMR (D_2O/TMS) δ, *J* (Hz)
3a	68	5.05 (s, 1H, H_5); 5.53-5.65 (m, 2H, gem vinylic H); 5.78-5.97 (m, 1H, vinylic H); 6.87 (d, 1H, *J* = 8, H_1); 7.26 (d, 1H, *J* = 8, H_2).
3b	78	3.63-3.74 (m, 1H, H_6); 4.68 (d, 1H, *J* = 6.2, H_5); 5.53-5.68 (m, 2H, gem vinylic H); 5.90-6.06 (m, 1H, vinylic H); 6.85 (d, 1H, *J* = 8.1, H_1); 7.32 (d, 1H, *J* = 8.1, H_2).
3c	84	4.28-4.37 (m, 1H, H_6); 5.06 (d, 1H, *J* = 7, H_5); 5.37-5.46 (m, 1H, H_8); 5.74-5.81 (m, 1H, H_7); 6.78 (d, 1H, *J* = 8, H_1); 7.17 (d, 1H, *J* = 8, H_2).
3d	72	3.43 (d, 2H, *J* = 6.9, C-CH_2-C); 5.08-5.20 (m, 2H, C=CH_2); 6.04-6.20 (m, 1H, C=CH); 7.09-7.42 (m, 4H, H_{arom}).
3e	81	6.38 (d, 1H, *J* = 9.6, H_3); 7.21 (d, 1H, *J* = 8.4, H_6); 7.23 (s, 1H, H_8); 7.62 (d, 1H, *J* = 8.4, H_5); 8.00 (d, 1H, *J* = 9.7, H_4).
3f	90	2.43 (s, 3H, CO-CH_3); 3.88 (s, 3H, O-CH_3); 6.75 (d, 1H, *J* = 16.2, H_3); 7.25 (d, 1H, *J* = 8.3, $H_{6\ arom}$); 7.33 (s, 1H, $H_{2\ arom}$); 7.36 (d, 1H, *J* = 8.3, $H_{5\ arom}$); 7.68 (d, 1H, *J* = 16,2, H_4).
3g	97	4.07 (s, 6H, 2xOCH_3); 6.63 (d, 1H, *J* = 16, H_2); 7.36 (d, 1H, *J* = 8.3, $H_{6\ arom}$); 7.46 (s, 1H, $H_{2\ arom}$); 7.51 (d, 1H, *J* = 8.3, $H_{5\ arom}$); 7.56 (d, 1H, *J* = 16, H_3).
3h	97	7.45 (dd, 1H, $J_{5,4}$ = 8.3, $J_{5,6}$ = 4.7, H_5); 7.94 (d, 1H, *J* = 8.3, H_4); 8.11 (d, 1H, *J* = 4.7, H_6).
3i	85	7.39 (dd, 1H, $J_{5,4}$ = 8.2, $J_{5,6}$ = 4.7, H_5); 7.79 (d, 1H, *J* = 8.2, H_4); 8.03 (d, 1H, *J* = 4.7, H_6).
3j	90	5.56 (s, 1H, H_4) ; 8.12 (s, 1H, H_2) ; 8,25 (s, 1H, H_6).

[a] As ammonium salt.

commercially available products, used without further purification, except 6-β-naloxol (**1b**), which was obtained from naloxone according to the procedure of Catterjie *et al.*[16] The tetrabenzyl pyrophosphate (TBPP) was formed by the dehydratation of dibenzyl phosphate with dicyclohexylcarbodiimide in accordance with the procedure of Khorana *et al.*[6] Compound **1g** was prepared by the esterification of the corresponding acid using diazomethane.

General Procedure for the Synthesis of Dibenzyl Phosphate Esters (2a-i)

To a stirred solution of the appropriate phenolic alcohol (1.2 mmol) in dry THF (20 ml) was added in one portion a sodium hydride (80% dispersion in oil; 36 mg, 1.2 mmol) under an atmosphere of argon. After 10 min, a solution of TBPP (840 mg, 1.56 mmol) in dry THF (10 ml) was added and the mixture was stirred for 10 to 18 h. The resulting precipitate was filtered and the solvent removed *in vacuo* to give the crude product which chromatographed on silica gel with (CH_2Cl_2-MeOH as eluent), afforded the dibenzyl phosphate esters (**2a-i**) in excellent yield (70-100%). Spectral data of each product are described in the Table I.

General Procedure for Debenzylation (3a-i)

A solution of the dibenzyl phosphate ester (0.64 mmol) in 7 ml of CH_2Cl_2 was treated with a solution of 0.38 ml of Me_3SiBr (2.9 mmol) and 0.31 ml of pyridine (7.28 mmol) in 5 ml of CH_2Cl_2 at 0°C for 4 to 6 h. After the addition of 14 ml of H_2O, the aqueous layer was separated and evaporated to dryness. The crude material was made alcaline with 6.4 ml of 1N NaOH (6.35 mmol) at 0°C and purified by anion-exchange chromatography on Duolite AP 143/1096 using stepwise gradient of aqueous NH_4HCO_3 (0-0.8 M). The appropriate fractions were collected, the solvent removed *in vacuo* and the residue co-evaporated with H_2O several times to give the pure product (**3a-i**) as the ammonium salt in high yields. The yields and the spectral data for new products are given in the Table II.

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