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A Simple, Rapid and Efficient Protocol for the Selective Phosphorylation of Phenols with Dibenzyl Phosphite[1]

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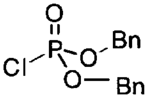
Abstract: Phosphorylation of phenols with dibenzyl phosphite, carbon tetrachloride, *N,N*-diisopropylethylamine, and catalytic DMAP in acetonitrile at -10°C is rapid, mild, clean, high yielding, and selective.

Dibenzyl chlorophosphate **1** is a commonly used reagent for the phosphorylation of alcohols.[2]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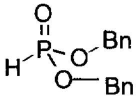
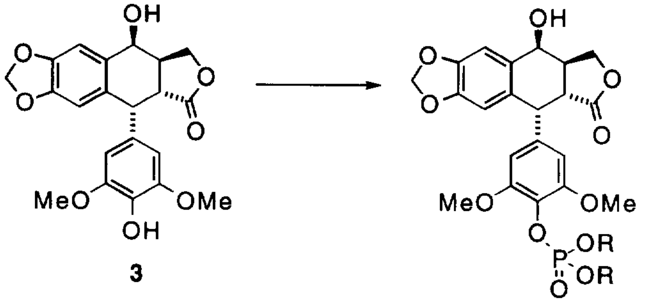

2

This unstable reagent is usually prepared in a separate reaction shortly before usage by chlorination of dibenzyl phosphite **2**. [2,3] A more attractive approach is *in situ* generation of **1**. This method was first attempted by Atherton and coworkers,[4] who reported that ethanol could be phosphorylated by a mixture of **2**, trichlorobromomethane (to give dibenzyl bromophosphate *in situ*), and a tertiary amine base,[4a] although when carbon tetrachloride was used, the reaction failed.[4b] Steinberg,[5] following Atherton's lead, reported the reaction of other dialkyl phosphites with aliphatic alcohols in the presence of triethylamine in carbon tetrachloride to give trialkylphosphates in moderate yield. Kenner and Williams[6] used this same system for the phosphorylation of phenols with diethyl phosphite. The reactions took overnight at room temperature and gave excellent yields in the 78-98% range. Other variations, including two-phase systems, have been reported by Zwierzak,[7] Purnanand,[8] and Corcoran.[9] Widlanski and Stowell recently reported near quantitative yields using trialkylphosphites, including tribenzylphosphite, and iodine to phosphorylate alcohols and phenols.[10]

In the course of developing a process for the synthesis of etoposide-4'-phosphate,[11] an antitumor prodrug, we required a method for selective phosphorylation at the phenolic hydroxyl of 4'-demethyl-4-epipodophyllotoxin **3**[12] (Equation 1). Phosphorylation of **3** was first reported by Saulnier *et al,*[13] using both diphenylchlorophosphate and **1** separately prepared from **2** and N-chlorosuccinimide, but yields of only 30% and 38% respectively were achieved. We chose to make the dibenzyl phosphate since the benzyl groups are readily removed by either hydrogenation[14] or catalytic transfer hydrogenolysis.[13, 15] In this letter, we wish to present a protocol for the phosphorylation of phenols with **2** which proceeds rapidly in one pot under mild conditions and in high yield.



3

(1)

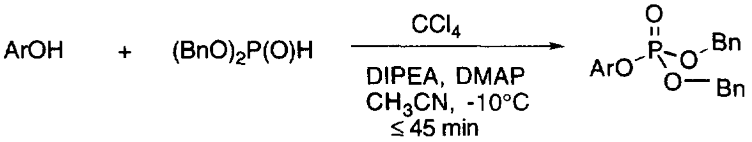
We investigated a number of different substrates (Table 1) for this phosphorylation. The main drawbacks of the method described by Kenner and Williams are the long reaction times and use of CCl_4 as solvent. We found that when the phosphorylations were run in acetonitrile using only reagent quantities of CCl_4 and catalytic amounts of *N,N*-dimethylaminopyridine (DMAP),[11c, 13, 16, 17a] the reactions were very rapid. Under these conditions, running the reactions at room temperature typically produced coloration which was minimized by lowering the temperature to -10°C. On all phenols examined, the phosphorylation performed exceedingly well and was complete within 45 minutes. Specifically, the reaction was best run using 1.45 eq. of **2**, 5 eq. of CCl_4, 2.1 eq of *N,N*-diisopropylethylamine (DIPEA), and 0.1 eq. of DMAP in acetonitrile at -10°C. The reaction required at least 1.4 eq. of **2** and as little as 2 eq. of CCl_4 to reach completion. The reaction also proceeded well with CBr_4 in place of CCl_4 (e.g., 77% yield of **15** from **3**), and it is likely[4,10,17] that other tetrahalomethanes will work.

In cases where there was a competing aliphatic alcohol, high chemoselectivity towards the phenol was observed. In the case of **3**, no phosphorylation was observed at the benzylic *sec*-alcohol. 4-Hydroxyphenethyl alcohol **7**, despite having a primary alcohol, gave a 95:5 ratio (by ^1H NMR of the crude product) of monophosphate **13**:bis-phosphate. Phosphorylation of etoposide **9** produced 5% total (by HPLC) of the two bisphosphate products (2",4' and 3",4').[11c] The selectivity presumably arises due to the higher acidity of the phenolic proton. The bis-phosphate products in these cases, if any, were removed by chromatography.

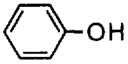
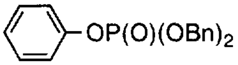
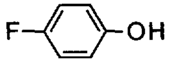
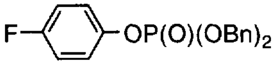
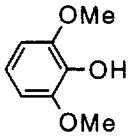
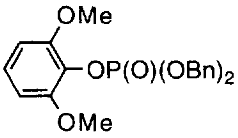
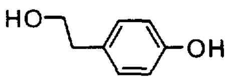
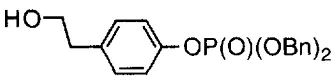
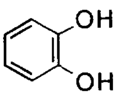
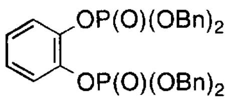
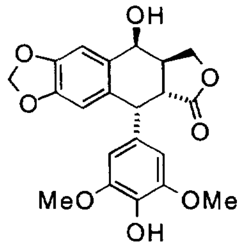
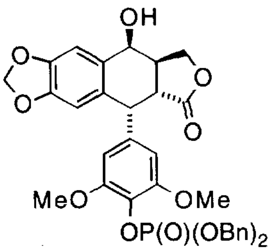
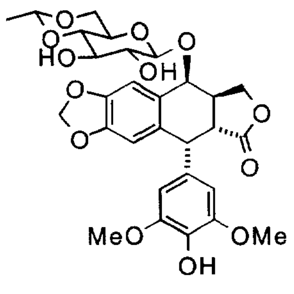
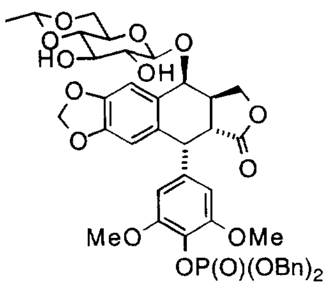
In summary, a protocol for the phosphorylation of phenols with dibenzyl phosphite has been developed that is convenient, selective, rapid, mild, clean, high yielding and amenable to scaleup.

General Experimental: A multi-necked roundbottom flask containing a stir bar was oven-dried, fitted with septa, a thermometer, and N_2 inlet. The flask was charged with the phenol (5.3 mmol) and anhydrous acetonitrile (31.25 ml). The mixture was stirred to dissolve the phenol and then cooled to -10°C. CCl_4 (5 eq.) was added and the solution stirred. N,N-diisopropylethylamine (2.1 eq.) followed by N,N-dimethylaminopyridine (0.1 eq.) were added. One minute later, dropwise addition of **2** (1.45 eq.) was begun. The reaction was exothermic and was controlled by the addition rate of **2** or by further cooling; the internal temperature was kept at or below -10°C. The reaction in some cases became light yellow. When the reaction was complete as determined by TLC or HPLC ($\leq$ 45 min after beginning addition of **2**), 0.5M aqueous KH_2PO_4 (32 ml/100 ml CH_3CN) was added and the mixture was allowed to warm to room temperature. The mixture was extracted three times with ethyl acetate. The combined organic phase was washed successively with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by chromatography or recrystallization.

Table 1. Phosphorylation of selected phenols with dibenzyl phosphite.



(2)

ArOH	#	Product[18]	#	Yield
	**4**		**10**[19]	97%[a]
	**5**		**11**	91%[a]
	**6**		**12**[20]	94%[a]
	**7**		**13**[17b]	88%[a]
	**8**		**14**	88%[a,c]
	**3**		**15**[13,21]	90%[b]
	**9**		**16**[11c,13,22]	87%[a]

a) Purified by chromatography. b) Purified by recrystallization. c) Twice as much **2**, CCl_4, DIPEA, and DMAP were used.

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18. All compounds in Table 1 were characterized by ^{1}H NMR, ^{13}C NMR, MS, and TLC or HPLC. Additional data for solid products are given in the footnotes below.
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20. Light orange solid. M.P.: 67.5-72°C.
21. White solid. Elemental Analysis: Calc.C, 63.64; H, 5.04. Found C, 63.84; H, 4.98. M.P. 207°C (DSC).
22. White solid. M.P. 198°C (decomposition) (DSC).

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