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Diphenyl Methylphosphonate as a Phosphonylation Reagent with High Diastereoselectivity at Phosphorus

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Abstract: Reaction of diphenyl methylphosphonate with lithium alkoxides generated in situ from alcohols and butyllithium gives phenyl alkyl methylphosphonate diesters even with hindered alcohols and with high diastereoselectivity at phosphorus. © 1997 Elsevier Science Ltd.

Unsymmetrically substituted alkylphosphonate diesters play an important role in nucleotide chemistry[1] and have been used as transition-state analogs in eliciting catalytic antibodies.[2] One of the two most frequently used methods for the preparation of the mixed phosphonate diesters employs sequential addition of different alcohols under acid (1H-tetrazole) catalysis to alkylphosphoramidites followed by oxidation of P(III) to P(V).[3] The other method[4] uses sequential addition of different alcohols to the phosphonic dichloride with 1H-tetrazole as a catalyst. Both methods result in little or no diastereoselectivities.[5] Additionally , the latter method failed in very hindered systems.[4a] Although methyl-bis-O,O-(1-benzotriazolyl)phosphonate and its trifluoromethyl analog[6] were reported to have higher reactivity towards alcohols, these reagents are not stable as pure substances and have to be used in solution (usually dioxane). Here we present a new phosphonylation methodology[7] using diphenyl methylphosphonate and featuring high diastereoselectivities and suitability for very hindered alcohol substrates. Diphenyl methylphosphonate is easily prepared from reaction of triphenyl phosphite and methyl iodide followed by treatment with sodium hydroxide,[8] or it can be obtained from commercially available methylphosphonic dichloride by treatment with phenol and triethylamine or pyridine in methylene chloride.[9]

The new method is a one-pot two-step procedure that uses the strong base n-butyllithium to react with an alcohol and the thus obtained lithium alkoxides are treated with diphenyl methylphosphonate to yield the mixed phenyl diesters. Six substrates were chosen to demonstrate the effectiveness of the method (Table 1). The hindered 2-methyl-2-propanol (**1a**) reacted with nBuLi and $MeP(O)(OPh)_2$ and gave a good isolated yield (75%) of **2a**. Reaction with dibenzylamino alcohol **1b**[10] resulted in high diastereoselectivity (95:5) and in good yield (83%). The predominant Rp-isomer of **2b** was obtained by crystallization and its configuration (Rp) was assigned by single crystal X-ray analysis (Figure 1). The amino alcohol **1c**[10] gave the same diastereoselectivity determined by ^{31}P NMR spectroscopy. Cholesterol (**1d**) likewise reacted with high diastereoselectivity (97:3) in moderate yield (57%). Although alcohol **1e** is less hindered than menthol **1f**, it gave a much higher stereoselectivity (91:9 vs. 58:42). By comparison, 2-methyl-2-propanol (**1a**) was treated with methylphosphonic dichloride followed by addition of methanol using a literature procedure[4a] but no

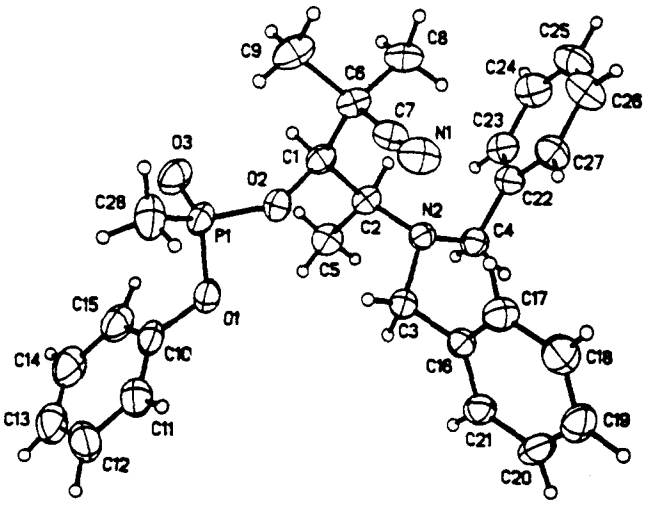
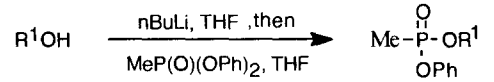
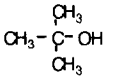
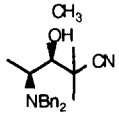
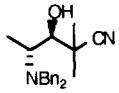
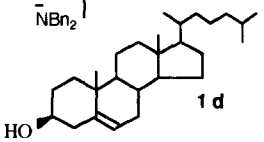
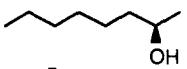
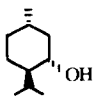


Figure 1. Molecular structure of **2b-Rp**.

Table 1.



1a-f **2a-f**

Alcohols		Yield of **2** (%)[a]	^{31}P NMR(ppm)[b]	distribution (%)[c]
	**1 a**	75	24.18	
	**1 b**	83	28.48(Rp) 27.49(Sp)	95 5
	**1 c**	60	28.80 27.72	95 5
	**1 d**	57	27.22 26.57	97 3
	**1 e**	52	29.38 27.58	9 91
	**1 f**	72	27.80 27.20	42 58

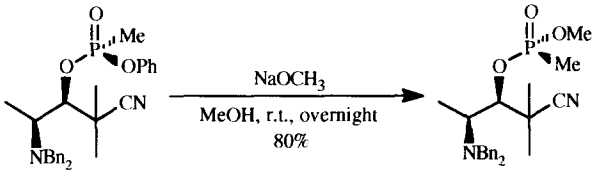
[a]Isolated yields.

[b]$CDCl_3$was used as the solvent and 85% H_3PO_4 as an external standard for ^{31}P NMR measurement. Diastereoisomers Rp and Sp of **2** were not separated except for **2b**.

[c]The Rp/Sp ratios were determined by integration of the two product peaks in ^{31}P NMR spectra.

desired product methyl 2-methyl-2-propyl methylphosphonate was obtained. When **1b**, **1c**, **1e**, and **1f** were treated respectively with methylphosphonic dichloride and methanol using the same literature procedure,[4a] the alkyl methyl methylphosphonate products were obtained in 62-93% yields but with little diastereoselectivities (the distributions of the phosphorus diastereoisomers ranged from 42:58 to 49:51).

The phenyl esters **2** can be transformed into other mixed diesters by substitution of the phenoxy group with a second alkoxy group. For example, phenyl ester **2b** was converted to methyl ester **3** in 80% yield by treatment with $NaOCH_3$ in methanol.[11] **3** was a mixture of two diastereoisomers with a ratio of 95:5 as determined by ^{31}P NMR spectroscopy. The single crystals of the predominant isomer of **3** was obtained by crystallization from ethyl acetate-hexane and its configuration was determined to be Rp by its X-ray structure (not shown). The conversion of **2b** (95% Rp, 5% Sp) to **3** (95% Rp, 5% Sp) suggested a complete inversion of configuration at phosphorus.



2b-Rp **3-Rp**

General Procedure: 3.3mL (5.27mmol) of nBuLi solution (1.6M in hexane) at 0°C was added slowly to a solution of the starting alcohol **1** (5.27mmol) in dry THF (30mL) under nitrogen. The mixture was stirred 30min at room temperature and a solution of diphenyl methylphosphonate (5.27mmol) in dry THF (30mL) was added dropwise. After stirring at room temperature for another 1hr, the reaction mixture was quenched with 60mL of saturated sodium chloride solution. The separated organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a crude product which was purified by flash column chromatography. Products were charaterized by IR, (^1H, ^{13}C, ^{31}P) NMR, and MS spectroscopy (and by elemental analysis for **2b** and **2c**). All the products showed two peaks in their ^{31}P NMR spectra and distributions of diastereoisomers were determined by integration of the two peaks corresponding to the two phosphorus diastereoisomers in the products. Single crystals of the major diastereoisomers of **2b** (and **3**) for X-ray analysis were grown with the following method: **2b** (or **3**) (ca.50mg) was dissolved in hexane (5mL) and ethyl acetate (1mL) in a vial capped with a one-hole septum. The solution was allowed to evaporate slowly through the hole in the septum at room temperature and crystals formed within a month. The rhombic single crystals were carefully picked out with a micro spatula.

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9. A solution of phenol (6.22g, 66.10mmol) and triethylamine (6.69g, 66.10mmol) in CH_2Cl_2 (15mL) at 0°C was added dropwise to a solution of $MeP(O)Cl_2$ (3.82g, 28.74mmol) in CH_2Cl_2 (25mL) and then the mixture was stirred at room temperature for 1hr. The precipitate was filtered off and the filtrate was washed with saturated sodium chloride solution (2x10mL), dried ($MgSO_4$), and concentrated in vacuo to give a light yellow oil which was applied to a silica gel column and eluted with hexane-ethyl acetate (2:1) to yield the pure diphenyl methylphosphonate as a colorless oil (6.12g, 86%). ^{1}NMR ($CDCl_3$): 1.79 (d, J=17.70Hz, 3H), 7.15-7.35ppm (m, 10H). ^{31}PNMR ($CDCl_3$): 24.52ppm.
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