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A novel synthetic route for the preparation of alkyl and benzyl chloromethyl phosphates

Antti Mäntylä,[a,*] Jouko Vepsäläinen,[b] Tomi Järvinen[a] and Tapio Nevalainen[a]

[a]*Department of Pharmaceutical Chemistry, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland*
[b]*Department of Chemistry, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland*

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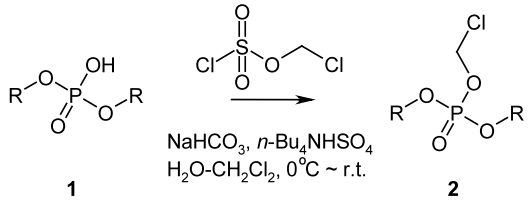
Abstract—An efficient and simple synthesis is described for the production of various chloromethyl phosphates as useful reagents for the preparation of phosphonooxymethyl prodrugs.

Modern drug discovery techniques, such as combinatorial chemistry and high-throughput pharmacological screening, often introduce new lead compounds with aqueous solubility problems. Phosphate prodrugs are widely used to enhance the aqueous solubility of parent drugs.[1,2] Phosphate promoieties are bound either directly or via a spacer group to drug molecules, especially those having an hydroxyl functionality.[3–6] However, it has been reported that phosphate moieties directly attached to a hydroxyl group are not always accessible to enzymatic cleavage, due to steric hindrance,[5,6] and consequently there has been a great interest in the development of phosphonooxymethyl prodrugs, which have been shown to be enzymatically labile.[7,8] This hydrolysis occurs via a two-step reaction; enzymatic cleavage of the ester group followed by spontaneous decomposition of the hydroxymethyl intermediate. It is important to point out that the hydroxymethyl intermediate releases the parent drug by spontaneous chemical hydrolysis, while larger hydroxyalkyl groups are not, and thus are not useful intermediates for the design of bioreversible prodrugs.[9,10]

The phosphonooxymethyl moieties are useful intermediates in the synthesis of enzymatically stable oligonucleotide analogues containing methylene acetal linkages in place of the phosphate diester bond.[11] The widely-used strategy for their preparation involves the synthesis of a methylthiomethyl ether intermediate,[12] which is converted to phosphonooxymethyl ethers by an *N*-iodosuccinimide (NIS) mediated esterification.[13] However, this method is laborious and gives low yields. Herein we report a novel, simple method for the preparation of dibutyl, dibenzyl, diallyl and di-*tert*-butyl chloromethyl phosphates, which are superior reagents for the derivatization of hydroxyl and amino groups with phosphonooxymethyl moieties (Scheme 1).

A general procedure for the preparation of dialkyl and dibenzyl (Table 1) chloromethyl phosphates is as follows: dialkyl[14,15] or dibenzyl phosphate[16] (4.76 mmol), sodium bicarbonate (19.04 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.476 mmol) were dissolved in water (40 ml). Dichloromethane (DCM, 25 ml) was added and the mixture was vigorously stirred at 0°C for



Scheme 1.

Table 1. Synthesis of dialkyl and dibenzyl chloromethyl phosphates (**2a–d**) via Scheme 1

Product	R	Yield (%)[a]
2a	$-CH_2CH_2CH_2CH_3$	84
2b	$-CH_2C_6H_5$	90
2c	$-CH_2CH{=}CH_2$	36
2d	$-C(CH_3)_3$	72[b]

[a] Isolated yield.
[b] The more laborious synthetic method gives 35% yield.[8]

* Corresponding author. Fax: +358 17 162456; e-mail: antti.mantyla@uku.fi

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10 min, followed by the addition of chloromethyl chlorosulfate[17] (5.7 mmol) in DCM (15 ml) with continuous vigorous stirring overnight at room temperature. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash silica gel column chromatography using ethyl acetate/hexanes (1:3) as eluent to give compounds **2a**–**d**. The products were identified by ^1H and ^{13}C NMR, mass spectral analysis and elemental analysis. Dibutyl chloromethyl phosphate (**2a**): ^1H NMR ($CDCl_3$), 500 MHz δ 0.94 (t, 6H, $J=7$ Hz), 1.42 (m, 4H), 1.67 (m, 4H), 4.10 (m, 4H), 5.68 (d, 2H, $J=15$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.5, 18.6, 32.1, 32.2, 68.3 (d, $J=6$ Hz), 73.5 (d, $J=7$ Hz); ^{31}P NMR ($CDCl_3$) δ −0.94 (s); MS (ESI) m/z 259 (MH^+). Anal. ($C_9H_{20}ClO_4P$) C, H: calcd 41.79, 7.79. Found 41.98, 7.86. Dibenzyl chloromethyl phosphate (**2b**): ^1H NMR ($CDCl_3$), 500 MHz δ 5.09 (d, 4H, $J=8$ Hz), 5.62 (d, 2H, $J=16$ Hz), 7.35 (10H, s); ^{13}C NMR ($CDCl_3$) δ 69.9 (d, $J=6$ Hz), 73.5 (d, $J=7$ Hz), 128.1, 128.7, 128.8, 135.2 (d, $J=7$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.08 (s); MS (ESI) m/z 327 (MH^+). Anal. ($C_{15}H_{16}ClO_4P$) C, H: calcd 55.14, 4.94. Found 55.01, 4.94. Diallyl chloromethyl phosphate (**2c**): ^1H NMR ($CDCl_3$), 500 MHz δ 4.61 (m, 4H), 5.29 (d, $J=11$ Hz, 2H), 5.39 (d, $J=17$ Hz, 2H), 5.69 (d, 2H, $J=16$ Hz), 5.91–6.00 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 68.8 (d, $J=5$ Hz), 73.5 (d, $J=7$ Hz), 118.9, 131.9 (d, $J=7$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.57 (s); MS (ESI) m/z 227 (MH^+). Anal. ($C_7H_{12}ClO_4P\cdot 0.05EtOAc$) C, H: calcd 38.37, 5.64. Found 38.35, 5.55. (identical to NMR-spectra). Di-*tert*-butyl chloromethyl phosphate (**2d**): ^1H NMR ($CDCl_3$), 500 MHz δ 1.51 (s, 18H), 5.63 (d, $J=15$ Hz, 2H), ^{13}C NMR ($CDCl_3$) δ 29.8 (d, $J=4$ Hz), 73.3 (d, $J=7$ Hz), 84.1 (d, $J=8$ Hz); ^{31}P NMR ($CDCl_3$) δ −11.24 (s); MS (ESI) m/z 259 (MH^+). Anal. ($C_9H_{20}ClO_4P$) C, H: calcd 41.79, 7.79. Found 41.51, 7.87. The results are summarized in Table 1.

With the present method, all chloromethyl phosphates were obtained in good to excellent yields (Table 1) without formation of any side products, except for the diallyl chlorophosphate, where the synthetic procedure was not optimized. Hydroxyl or amine group reacts efficiently with these reagents. After removal of the protecting group, the resulting compound works well as a water-soluble prodrug.

In conclusion, the reaction described above will be a highly useful method for the preparation of chloromethyl phosphates having various substituents. Using the present methodology, bioreversible prodrugs were obtained that enhance the aqueous solubility of poorly water-soluble compounds. It is also believed that the new method will be useful for the synthesis of enzymatically stable oligonucleotide analogues.

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