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Convenient "One-Pot" Synthesis of Chlorophosphonates, Chlorophosphates and Chlorophosphoramides from the Corresponding Benzyl Esters

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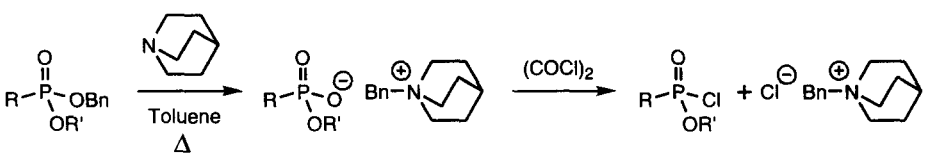
Abstract: Selective monodeprotection of alkyl phosphonate, phosphate and phosphoramide benzyl esters using quinuclidine and chlorination of the subsequent salts allows preparation of various alkyl phosphonochloridates, monochlorophosphates and monochlorophosphoramides in a convenient "one-pot" procedure.

The synthesis of mixed esters of alkyl phosphonic acids and phosphoric acids still presents a certain difficulty to the organic chemist. Transesterification methods most often are not adapted when introducing sophisticated alcohols.[1] Sequential addition of different alcohols to phosphonic acid dichlorides or phosphorus oxychloride affords poor results since displacement of chlorides by alcohols is generally too rapid to allow selective monoesterification.[2] Methods affording selective esterification of phosphonic and phosphoric acids consist in multistep procedures and the most commonly used today involve repeated sequences of monodeprotection, activation and esterification reactions.[3]

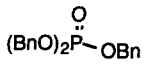
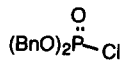
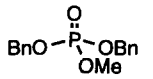
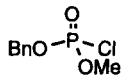
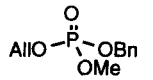
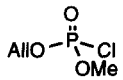
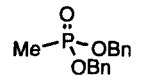
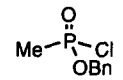
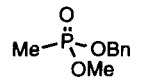
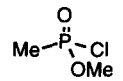
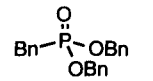
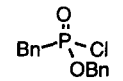
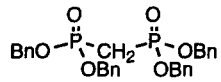
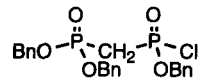
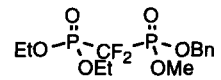
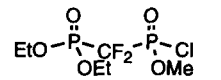
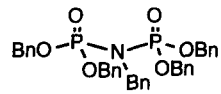
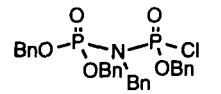
Herein, we wish to describe a convenient procedure for the preparation of alkyl-phosphonochloridates, monochlorophosphate dialkyl esters and chlorophophoramide monoalkyl esters from alkyl-phosphonate dialkyl esters, trialkyl phosphates and phosphoramide dialkyl esters. This method is based on a "one-pot" sequence involving a selective monodeprotection of a benzyl ester on the phosphonate, phosphate or phosphoramide compound using quinuclidine,[4] followed by direct chlorination of the intermediate quinuclidinium salt with oxalyl chloride (sch. 1). The reaction proceeds without formation of HCl so the procedure is especially valuable for acid sensitive substrates.



R : alkyl, O-alkyl, $N(alkyl)_2$. R' : alkyl.

Scheme 1

Some results obtained are summarized in table 1. The yield of the transformation is nearly quantitative and the chlorinated species can be directly coupled with different nucleophiles of interest (alcohols, amines, thiols...) following a number of known procedures.

Compound	Product	Yield[a] (%)
		95
		95
		98
		97
		98
		95
		98
		95
		94

[a] The yields are based upon crudes which were enough pure to be used without any purification.

Table 1

Typical experimental procedure : Benzyl phosphonic acid dibenzyl ester (1.0 g, 2.84 mmol) and quinuclidine (316 mg, 2.84 mmol) were stirred under an argon atmosphere in anhydrous refluxing toluene for 4 hours. The reaction mixture was cooled to O°C. Then oxalyl chloride (495 µl, 5.68 mmol) and a catalytic amount of anhydrous DMF (2 µl) were added. After 30 min., the white precipitate of benzyl quinuclidinium chloride was filtered off and the solvent was evaporated under vacuum to give benzyl-phosphonic acid chloride monobenzyl ester (756 mg, 95% yield) which was enough pure to be used without any purification.

These experimental conditions are especially mild and allow modifications of sensitive substrates.

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