A simple, general and improved procedure for phosphorylation of alcohols catalyzed by indium(III) chloride[†]

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A general and efficient procedure has been developed for the preparation of dialkyl phosphate esters by indium(III) chloride catalyzed phosphoryl transfer from diethyl and diphenyl chlorophosphate to a variety of alcohols and phenols in THF in presence of triethylamine.

The phosphate esters have been the subject of current attention because of the recent reports of their widespread occurrence in nature and important role in biological processes¹. Thus, synthesis of phosphate esters is of much importance and a number of procedures have been developed². However, the simplest strategy involves direct phosphorylation of an alcohol with a chlorophosphate. This can be accomplished by the treatment of a chlorophosphate either with an alkoxide or an alcohol in the presence of a proton scavenger. However, in the first case generation of an alkoxide by an alkyl lithium may lead to complication for substrates with active centers. A direct reaction of an alcohol with diphenyl chlorophosphate catalyzed by TiCl_4 with triethylamine as proton scavenger producing phosphate ester has been reported recently³. Although this method is quite satisfactory it has its limitations toward the reaction with tertiary and activated alcohols such as allylic ones. We report here a more general and efficient method of phosphorylation of alcohols by dialkyl phosphoryl transfer from diethyl and diphenyl chlorophosphate under the catalysis of indium(III) chloride⁴ in presence of triethylamine (Scheme 1).

Scheme 1

The experimental procedure is very simple. A mixture of an alcohol (1 mmol), dialkyl chlorophosphate (1.5 mmol), triethylamine (2.5 mmol) in THF (2 cm³) was stirred in the

presence of anhydrous indium(III) chloride (5 mol%) at room temperature for the period of time required to complete the reaction (TLC). The reaction mixture was then quenched with a few drops of water and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and evaporated to leave the crude product that was reasonably pure. Further purification was done either by micro-distillation under reduced pressure or column chromatography over silica gel impregnated with triethyl amine⁵. The known compounds were identified by comparison of their spectroscopic data with those reported³, whereas a few new compounds were characterized by their IR, ¹H and ¹³C NMR spectra and elemental analysis.

A wide range of alcohols were phosphorylated by this procedure in high yields. The results are summarized in Table 1. This procedure of phosphorylation is effective for all types of alcohols such as primary (entries 1–4), secondary (entries 16–19), benzylic (entries 5, 6), phenolic (entries 22, 23) and most significantly, propargylic (entries 7, 8), allylic (entries 9–15) and tertiary (entries 20, 21) ones. Diethyl as well as diphenyl chlorophosphate has been used for phosphoryl transfer, however in general, the transfer from diethyl derivative is more facile. Although the exact mechanism of this process is not clearly understood it is established that the combination of indium(III) chloride and triethylamine is essential for an efficient reaction. In the absence of indium trichloride the progress of conversion is only marginal, whereas the presence of only indium trichloride without triethylamine also failed to initiate the reaction. Presumably, indium(III) chloride as a Lewis acid activates the phosphoryl chloride coordinating with the oxygen atom towards reaction with alcohol and triethylamine

[†]Dedicated to Professor S. M. Mukherji.

Table 1. The phosphorylation of alcohols

$$\text{ROH} + \text{Cl}-\text{P}(=\text{O})(\text{OR}^1)_2 \xrightarrow[\text{Et}_3\text{N, THF}]{\text{InCl}_3} \text{RO}-\text{P}(=\text{O})(\text{OR}^1)_2$$

Entry	R	R ¹	Time (h)	Yield (%) ^a
1	CH ₃ (CH ₂) ₈ CH ₂	Et	2.10	83
2	CH ₃ (CH ₂) ₈ CH ₂	Ph	2.30	80
3	PHCH ₂	Et	1.30	84
4	PHCH ₂	Ph	1.40	81
5		Et	1.45	85
6		Et	1.45	83
7		Et	3.20	84
8		Ph	3.50	81
9		Et	5.30	78
10		Ph	5.40	74
11		Et	4.00	82
12		Ph	4.20	80
13		Et	4.25	80
14		Ph	4.45	79
15	Me ₂ C=CH(CH ₂) ₂ C=CHCH ₂ CH ₃	Et	4.50	73
16	Me ₂ CH	Et	2.00	85
17	Me ₂ CH	Ph	2.30	81
18		Et	2.40	76
19		Ph	3.40	74
20	(Me) ₃ C	Et	5.30	73
21	(Me) ₂ (Et)C	Et	5.10	80
22	Ph	Et	2.00	85
23	Ph	Ph	2.30	81

^aYields refer to those of pure isolated products properly characterized by spectroscopic data (IR, ¹H and ¹³C NMR).

as a proton scavenger drives the process further.

In conclusion, the present procedure of phosphoryl transfer from dialkyl chlorophosphate to the alcohol catalyzed by indium(III) chloride in presence of triethylamine provides a very efficient and general methodology for the synthesis of dialkyl phosphate esters. The significant improvements offered by this procedure are general applicability to all types of alcohols including tertiary and allylic ones which are difficult to be accomplished by existing procedures^{2,3}, reaction with both diphenyl and diethyl chlorophosphate, high yield of products and simple operation.

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5. Usual chromatography over silica gel leads to decomposition of phosphate esters in a few cases. However, before loading the compound if the column is impregnated with triethyl amine by eluting the silica gel bed with a 5% solution of triethyl amine in hexane followed by one washing with hexane, decomposition is avoided completely.