ORGANIC LETTERS

2002
Vol. 4, No. 21
3671−3673

A Simple and Effective Method for Phosphoryl Transfer Using $TiCl_4$ Catalysis

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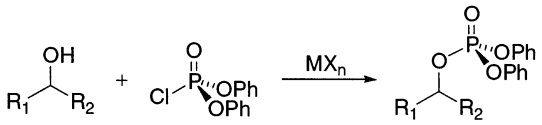
Received July 26, 2002

ABSTRACT



A number of Lewis acids have been evaluated as catalysts for the phosphoryl transfer, the most efficient being $TiCl_4$. Application of this methodology to the phosphorylation of a number of representative target alcohols is presented

Many important highly functionalized molecules in Nature contain phosphate esters, in particular, those based upon carbohydrate residues. Complex polysaccharides bearing phosphate esters are now commonly found as the structural components of cell walls and are implicated in many biological processes as varied as regulating immune response, host−pathogen interactions, and tumor metathesis.[1] Structurally related inositol phosphates are also important biological messengers that act as a second messenger in regulating transmembrane signaling.[2] As well as serving a critical role in maintaining vital biological processes, phosphate esters have been incorporated into many important pharmaceutical agents such as Honvan and Emcyt used in the treatment of cancer of the prostate. One of the primary roles that such a group has in these agents is to improve the water solubility of the agent and hence its bioavailability.

There are several approaches for the preparation of phosphate esters.[3] One of the more widely used methods in the synthesis of nucleotides is through the use of phosphoramidites, although this necessarily requires the handling of sensitive phosphorus(III) intermediates and a subsequent oxidation step. A more direct approach involves reaction of the alcohol substrate with a chlorophosphate. This can be carried out by formation of the alkoxide of the substrate, usually employing *n*-BuLi, necessarily limiting its application to those substrates with compatible functional groups. A better method is to treat the alcohol with the chlorophosphate in the presence of a proton scavenger such as triethylamine, with or without a nucleophilic catalyst.[4] This latter route offers significant advantages over the former and has been employed in the synthesis of compounds such as inositol monophosphate inhibitors,[5] D-fructose phosphate analogues,[6] and Lipid A-type pyrancarboxylic acid derivatives, among others.

Our interest in the development of methods to accomplish enantioselective phosphoryl transfer led us to consider another little explored mode of reactivity for the formation of phosphates through the use of Lewis acid catalysis. A number of groups have discussed the use of catalysts containing species such as Cu(II), La(III), Fe(III), Cr(III), Ti(IV), Zr(IV), Y(III), and Sn(IV) for the hydrolysis of fluorophosphates and phosphonate and phosphate esters,[7] while others have reported macrocyclic ligand complexes that catalyze this reaction.[8] However, only one report has

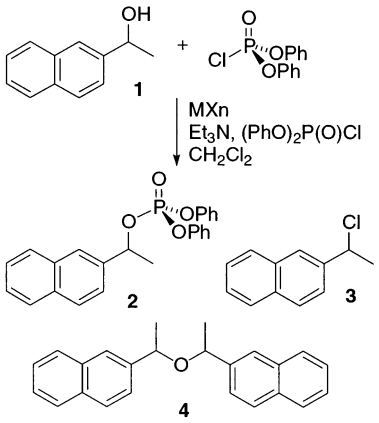
(1) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.
(2) Berridge, M. J.; Irvine, R. F. *Nature* **1984**, *312*, 315.
(3) Slotin, L. A. *Synthesis* **1977**, 737.
(4) van Boom, H. H.; de Rooy, F. M.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2513.
(5) Schulz, J.; Beaton, M. W.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 943.
(6) Mochizuki, T.; Iwano, Y.; Shiozaki, M.; Kurakata, S.-I.; Kanai, S.; Nishijima, M. *Tetrahedron* **2000**, *56*, 7691.

10.1021/ol026618q CCC: $22.00
Published on Web 09/24/2002

extended such methodology to the formation of phosphate esters using phosphoryl oxazolides as the phosphate source.[9] In this paper, we describe our studies aimed at catalyzing efficient phosphoryl transfer using chlorophosphates as the source of phosphate.

In the first instance, the catalytic activity of a number of Lewis acids was evaluated in the phosphoryl transfer from diphenylchlorophosphate to 1-(2-naphthyl)ethanol **1** (Scheme 1). All reactions were carried out with 1 equiv of Et_3N and

Scheme 1



$(PhO)_2P(O)Cl$ in CH_2Cl_2 in the presence of 20 mol % catalyst under a nitrogen atmosphere at room temperature for 2 h. The results are summarized in Table 1.

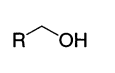
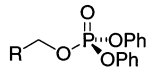
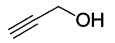
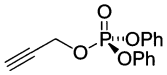
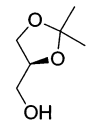
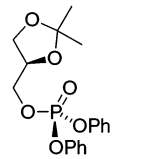
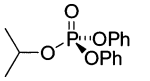
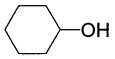
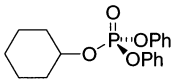
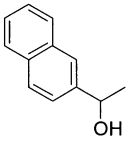
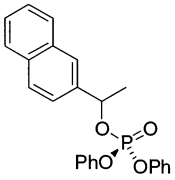
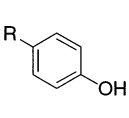
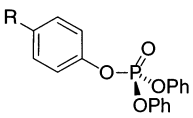
Table 1. Screening of Catalytic Activity for Phosphoryl Transfer Described in Scheme 1[a]

	conversion (%)[b]					conversion (%)[b]			
catalyst	**1**	**2**	**3**	**4**	catalyst	**1**	**2**	**3**	**4**
no catalyst	99	1	0	0	$Y(OTf)_3$	61	27	9	3
+ DIPY	92	0	5	3	+ DIPY	65	31	3	1
$Cu(OTf)_2$	15	0	0	85	$SnCl_2$	91	0	8	1
+ DIPY	90	7	0	3	+ DIPY	96	1	2	1
$Mg(OTf)_2$	88	7	0	5	$NiCl_2$	98	1	1	0
+ DIPY	97	3	0	0	+ DIPY	97	2	1	0
$La(OTf)_3$	92	0	6	2	$CrCl_3$	99	1	0	0
+ DIPY	66	13	16	5	+ DIPY	97	3	0	0
$Sc(OTf)_3$	100	0	0	0	$ZnCl_2$	98	0	1	1
+ DIPY	98	2	0	0	+ DIPY	92	7	1	0
$Eu(OTf)_3$	100	0	0	0	$TiCl_4$	55	17	26	2
+ DIPY	98	2	0	0	+ DIPY	64	26	6	4

[a] Reactions performed with 1 equiv of Et_3N and $(PhO)_2P(O)Cl$ in CH_2Cl_2 under a nitrogen atmosphere at room temperature for 2 h. All catalysts (20 mol %) and DIPY were used as appropriate. [b] Conversions calculated from integrals in the ^1H NMR spectrum.

2,2′-Dipyridyl was also evaluated as an additive in each reaction in an attempt to aid solubility of the Lewis acid. In some cases, especially with the metal chlorides, varying quantities of other components identified as the alkyl chloride

Table 2. Applicability of Optimized Reaction Conditions with $TiCl_4$[a]

alcohol	phosphate product	yield (%)[b]
		R = C_7H_{15} 94 R = Ph 96
		97
		84
		90
		97
		NA[c]
		R = H 98 R = NO_2 98 R = Br 87 R = Me 95

[a] Reactions carried out under a nitrogen atmosphere at room temperature with 2 mol % $TiCl_4$, 1.5 equiv of $(PhO)_2P(O)Cl$, and 1.5 equiv of Et_3N at a 0.2 M concentration in THF for 1 h. Standard aqueous workup conditions were employed. [b] Refers to isolated yield. [c] Product unstable to silica gel chromatography; 84% conversion from ^1H NMR spectrum.

3 and a mixture of the cis and trans isomers of the ether **4** were also observed arising from in situ nucleophilic displacement of the product phosphate **2** or an intermediate inorganic ester. The identity of each of these compounds was confirmed by independent synthesis or from literature data. Most reactions showed some catalytic enhancement compared to the background reaction, especially in the presence of DIPY. Whether this was a ligand accelerating effect or from increased solubility of the cationic species is not clear. However, the most striking catalytic enhancements giving significant quantities of products **2**, **3**, and/or **4** was with $Cu(OTf)_2$, $Y(OTf)_3$, and $TiCl_4$. Of these three systems, the $Cu(OTf)_2$ catalyst was discounted due to the excessive quantity of ether **4** formed; the $Y(OTf)_3$-catalyzed reactions

(7) Gustafson, R. L.; Chaberek, S.; Martell, A. E. *J. Am. Chem. Soc.* **1963**, *85*, 598. Butcher, W. W.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2420. Blewett, F. M.; Watts, P. *J. Chem. Soc. B* **1971**, 881. Morrow, J. R.; Trogler, W. C. *Inorg. Chem.* **1989**, *28*, 2330. Mejia-Radillo, Y.; Yatsimirsky, A. K. *Inorg. Chim. Acta* **2002**, *328*, 241. Moss, R. A.; Ragunathan, K. G. *Langmuir* **1999**, *15*, 107.

(8) Hay, R. W.; Govan, N. *Polyhedron* **1997**, *16*, 4233. Oh, S. J.; Yoon, C. W.; Park, J. W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 329.

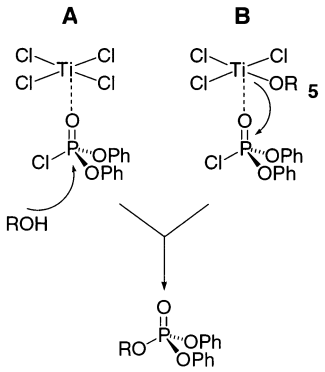
(9) Nagamatsu, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 2375.

were difficult to repeat, and the catalyst itself was nontrivial to handle. Thus, the remaining $TiCl_4$ system was optimized. The loading of catalyst could be dropped to as low as 2 mol % resulting in a significant increase in overall conversion, implying the intermediacy of a titanium ester in the catalytic cycle. Use of THF as a solvent dramatically decreased the amount of chloride **3** formed with no overall loss in conversion, while additions of a slight excess (1.5 equiv) of Et_3N as a proton scavenger and the chlorophosphate both resulted in slight increases in conversion to product **2**. No attempts were made to optimize the concentration, reaction temperature, or individual reaction times, which were generally found to be complete within 1 h. When these conditions were combined, DIPY was found to no longer serve any benefit and therefore removed from the final optimized reaction conditions, which were 2 mol % $TiCl_4$, 1.5 equiv of $(PhO)_2P(O)Cl$, and 1.5 equiv of Et_3N at a 0.2 M concentration in THF for 1 h under a nitrogen atmosphere at room temperature.

The applicability of the catalyst system was demonstrated in the phosphorylation of a number of representative alcohols (Table 2). Primary alcohols were transformed in excellent isolated yield, as were secondary alcohols and substituted phenols. Acid-sensitive functional groups such as acetals appeared to be tolerated, and although activated alcohols such as 1-(2-naphthyl)ethanol were efficiently transformed, the product was unstable to silica gel chromatography and could not be purified further. Phosphoryl transfer to *tert*-butyl alcohol failed even after prolonged reaction times presumably due to steric effects, while activated alcohols such as geraniol led to decomposition. Attempts at phosphorylation of several carbohydrate substrates gave less than 5% product in each case making this method unsuitable for the phosphorylation of these substrates at present.

The exact mechanism of these reactions is yet unclear but could proceed via one of two mechanisms (Scheme 2). In the first (**A**), $TiCl_4$ acts as a Lewis acid, coordinating to the oxygen atom of the phosphoryl chloride, increasing its electrophilicity. Intermolecular nucleophilic $S_N2(P)$ displacement then gives the phosphate product. In the second possibility (**B**), rapid formation of a titanium alkoxide **5** occurs first, followed by coordination of the phosphoryl chloride and intramolecular phosphate transfer. The second possibility seems more likely as we have observed higher conversion to product with a lower catalyst loading, implying that excess $TiCl_4$ removes the alcohol substrate from the reaction mixture and prevents it from further phosphorylation. We are currently investigating the nature of the titanium catalyst and its application to an asymmetric variant of this reaction.

Scheme 2



Acknowledgment. We thank the University of Newcastle upon Tyne for financial support.

Supporting Information Available: Typical experimental procedures and NMR data of the phosphates. This material is available free of charge via the Internet at http://pubs.acs.org.

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