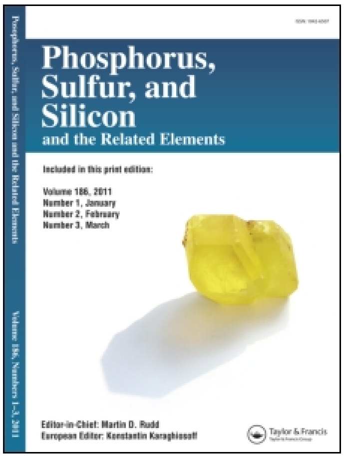

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Novel Amination of Phosphorus Diesters Promoted By Titanium Tetrakis(Diethylamide)

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SHORT COMMUNICATION

Novel Amination of Phosphorus Diesters Promoted By Titanium Tetrakis(Diethylamide)

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Reaction of titanium tetrakis(diethylamide) with phosphorus diesters results in a displacement of both ester functions by the diethylamino groups, but phosphoric triesters are inert to the title reagent.

The use of titanium tetrakis(dialkylamides) (**1**) as chemoselective protecting reagents for carbonyl substrates has been recently reported.[1] In this method nucleophilic additions can be induced to occur at ketone groups in the presence of an aldehyde function. The *in situ* protection of an aldehyde presumably involves reaction with the titanium reagent to form adducts (**2**), which revert to free carbonyl substrate upon aqueous work-up.

$$\mathrm{RC(O)R'} \underset{\mathrm{H_2O}}{\overset{\mathrm{Ti(NR''_2)_4}\ (\mathbf{1})}{\rightleftharpoons}} \mathrm{RC[OTi(NR''_2)_3](NR''_2)R'} \qquad (1)$$

(2)

Since Ti(IV) derivatives easily form adducts with a variety of organophosphorus compounds containing the phosphoryl group,[2] we decided to investigate the reactions of (**1**) with esters of typical phosphorus oxyacids. If the Lewis acid-base complex formation were to be followed by the NR_2 group transfer to phosphorus, the reaction could be expected to result in the exchange of functional groups at the phosphoryl centre. The results of the reactions between $Ti(NEt_2)_4$ (**1a**)[3] and selected organophosphorus substrates are summarized in Table I.

Treatment of dialkyl (or diaryl) phosphites (**3**) with one equivalent of (**1a**) at room temperature results in an exothermic reaction. After aqueous work-up and extraction with CH_2Cl_2, the product was purified by distillation[4] and identified as bis(diethylamino) phosphorous acid (**4**).[5]

$$\mathrm{(RO)_2P(O)H} + (\mathbf{1a}) \rightarrow \mathrm{(Et_2N)_2P(O)H} \qquad (2)$$

(**3**); R = Me, Et, Ph (**4**)

The same results are obtained at −40°C, and the ^1H n.m.r. spectra of reaction mixture show rapid disappearance of (**3**) and the appearance of new signals, consistent with product (**4**). The reaction of phosphite esters with (**1a**) (eq. 2) to our knowledge represents the first example of the direct displacement of a phosphorous acid ester function by an amino group. Although the phosphorous diamides (**4**) are useful substrates for the preparation of α-hydroxyphosphonic derivatives,[7] they were hither-to prepared by the procedures[6] which all involve the removal of one of the dialkylamino group from the tris-(dialkylamino) phosphine, $(R_2N)_3P$.

TABLE I

Reaction of (**1a**) with phosphorus compounds in benzene

Substrate	Conditions	Product	Yield (%)
$(MeO)_2P(O)H$	r.t.; −40°C	$(Et_2N)_2P(O)H$	(64; 60)
$(EtO)_2P(O)H$	r.t.	$(Et_2N)_2P(O)H$	(61)
$(PhO)_2P(O)H$	r.t.	$(Et_2N)_2P(O)H$	(49)
$(EtO)_2P(O)Cl$	r.t.	$(EtO)_2P(O)NEt_2$	(60)
$(MeO)_3PO$	45°C, 48 h	Et_2NMe	(33)
$(EtO)_3PO$	45°C, 24 h	no reaction	
$(PhO)_3PO$	45°C, 24 h	no reaction	
$(MeO)_3P$	45°C, 24 h	no reaction	
$PhCH_2P(O)(OMe)_2$	45°C, 24 h	Et_2NMe	(36)

Treatment of diethylphosphorochloridate (**5**) with (**1a**) at room temperature resulted in an exothermic reaction which, upon aqueous work-up, gave *N*,*N*-diethyldiethylphosphoramidate (**6**).[8]

$$\underset{(5)}{(EtO)_2P(O)Cl} \xrightarrow{(1a)\ r.t.} \underset{(6)}{(EtO)_2P(O)NEt_2} \qquad (3)$$

However, the amide (**6**) would be the expected product of the reaction of (**5**) with diethylamine itself.[9]

In contrast to the rapid reaction of phosphite esters (**3**) with (**1a**), phosphate triesters such as triethyl or triphenyl phosphate proved unreactive towards (**1a**) and could be recovered unchanged, without any indication of the amino group transfer. In case of the methyl esters of phosphoric or phosphonic acids, moderate yields of methyldiethylamine were obtained after the aqueous work-up of the reaction mixture.[10]

$$Y\text{—}P(O)(OMe)_2 \xrightarrow[48\ h]{(1a),\ 45°C} Et_2NMe \qquad (4)$$

$$Y = MeO,\ PhCH_2$$

This result is in agreement with the known[11] susceptibility of phosphoric methyl esters to the nucleophilic displacement. The remarkable difference between the behaviour of the phosphite and phosphate esters towards (**1a**) deserves particular attention. Since trimethyl phosphite does not react with (**1a**) even at 45°C, it is unlikely that it is the P^{III} tautomeric form of (**3**), $(RO)_2P\text{—}OH$ which is responsible for the amination reaction. We believe that the reaction involves coordination of Ti(IV) reagent to the phosphoryl oxygen, followed by the intramolecular transfer of the NEt_2 group to form the P^V intermediate, analogous to adduct (**2**) postulated for reactions of (**1**) with carbonyl compounds.[12]

In such a case, the phosphorus-nitrogen bond formation step could be subject to steric and/or stereoelectronic control,[13] thus sensitive to the nature of the substituents present at phosphorus. The mechanism of the amination, and the structural effects operating in this reaction are currently being investigated in our laboratory.

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4. $(Me_2N)_2P(O)H$ was reported to be thermally unstable: E. J. Corey and D. E. Cane, *J. Org. Chem.*, 1969, **34**, 3053. We found that (**4**) decomposed above 110°C.
5. B.p. 80–85°C/1–1.5 mm. ^1H n.m.r. ($CDCl_3$) 1.12 (12 H, t, J 7.2 Hz, 4 × CH_3); 2.99 (8 H, d of q, J_{HP} 11.7 Hz, J_{HH} 7.2 Hz , 4 × CH_2): 6.72 (1 H, d, J 570.4 Hz, PH). M.S., m/e 192 (M^+, 40%, E1). Anal. calcd. for $C_8H_{21}N_2OP$: C, 50.0; H, 10.9; N, 14.6 Found: C, 49.9; H, 10.6; N, 14.4%. Data obtained for this product (**4**) were identical to those obtained for (**4**) prepared by an independent method.[6]
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12. Ti(IV) derivative is prerequisite for the amination reaction. We have found that phosphites (**3**) do not react with Et_2NLi alone (except for the obvious deprotonation of (3)), and can be recovered unchanged after the aqueous work-up.
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