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STEPWISE AND SELECTIVE DEALKYLATION OF PHOSPHOTRIESTERS WITH PHENYLTHIOTRIMETHYLSILANE

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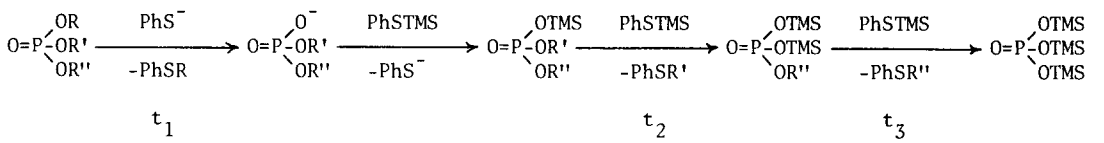
Summary Phosphotriesters were dealkylated in a stepwise manner and selectively with $PhSSiMe_3$ in the presence of PhS^- catalyst, and ease of alkyl cleavage was found to be in accord with SN-2 reactivity order of alkyl groups Other factors affecting the reaction were also described

Selective hydrolysis of protected phosphotriesters is a key reaction in the synthesis of phosphorylated compounds of biological significance Although various methods have been recorded,[1] exploitation of general as well as specific method proceeding under mild condition is still a subject of great interest Here we wish to introduce a novel method for stepwise and selective cleavage of phosphotriesters via dealkylative silylation

Recently, McKenna et al [2] reported the dealkylation of phosphonates with bromotrimethylsilane (TMSBr) We had interested in the application of the reagent for stepwise cleavage of phosphorus esters, and examined some mixed phosphotriesters for manner of the cleavage The reaction of $(EtO)_2P(O)OPh$ with 1 equiv of TMSBr at 30° followed by aqueous workup and methylation of the products with diazomethane afforded a mixture of $(EtO)_2P(O)OPh$, $MeO(EtO)P(O)OPh$, and $(MeO)_2P(O)OPh$ in a ratio of ca 1 2 1 Furthermore, in the case of $MeOP(O)(OEt)_2$ there were produced both MeBr and EtBr(ratio, ca 6 6 1) as cleavage products These results indicate that TMSBr is not practically useful for stepwise and/or selective cleavage of phosphotriesters

We then turned to the use of phenylthiotrimethylsilane(PhSTMS)[3] in light of the known monodealkylation of phosphotriester by nucleophilic mercaptide anion [4] Though the reaction of $(MeO)_3PO$ with PhSTMS did not take place at all, addition of catalytic amount of PhS^--crown ether complex induced smooth reaction giving half-life times, t_1=7 5, t_2=55 and t_3=455 min at 30° for successive methyl cleavages The reaction could be envisioned to proceed as depicted in eq 1(R= R'=R''=Me) Reaction initiated by catalytic PhS^- produces diester anion which is quenched by PhSTMS giving trimethylsilylated diester and PhS^- Silylation of dialkyl phosphate anion allows further cleavage with regenerated sulfide anion



(eq 1)

Encouraged by the appreciable difference in half-life times obtained for $(MeO)_3PO$ and isolation of intermediate products in 62-83% yields, we then subjected other phosphates to the same reaction giving the results shown in the Tables

Table 1 Reaction of Phosphotriesters with PhSTMS[a]

Phosphate	$(RO)_3PO$			$ROP(O)(OMe)_2$	$PhOP(O)(OR)_2$		$(PhO)_2P(O)OR$
Reaction Temperature	$70^o(30^o)$			10^o	$70^o(30^o)$		30^o
Half-life Time, min[b] (Group cleaved)	t_1	t_2	t_3	t_1(Me)	t_1(R)	t_2(R)	t_1(R)
R = Me	(7 5)	(55)	(455)	46	(3 5)	(132)	22
= Et	46(2450)	235	1810	122[c]	13	160	3700
= n-Pr	90(7200)	360	2350	130[c]	30	720	no change (350 hr)
= Ph	no change(500 hr)			26			

a) A mixture of phosphotriester(0 4mmol), PhSTMS(1 2mmol), and PhSK/dicyclohexyl-18-crown-6(0 2ml of 20mmol/l benzene solution) was placed in a thermostated bath For isolation experiment, the reaction mixture was subjected to aqueous workup and the dealkylated phosphates were obtained either as anilinium salts or derived methyl esters in 62-92% yields *b*) See eq 1 Half-life times were obtained by nmr spectrometry since the sulfides(PhSR) formed were easily detected *c*) No cleavage of alkyl groups other than methyl was observed

Conclusions obtained from Table 1 are (1) Ease of alkyl cleavage is in the order of Me, Et, n-Pr, no phenyl group being cleaved,[5] (2) For $(RO)_2P(O)OPh$, phenyl group accelerates the first alkyl cleavage more than twice compared with $(RO)_3PO$,[6] (3) For $ROP(O)(OPh)_2$, two phenyl groups retard the reaction,[7] (4) Difference between t_1 and t_2, or t_2 and t_3 enables one to isolate mono- or diester in good yields Additional data shown in Table 2 are also evidently indicative of stepwise and selective manner of the cleavage reaction These features clearly demonstrate that the present method is potentially useful for the preparation of phosphomono- and diesters in terms of specificity, mildness and neutrality, and facile workup of the reaction Further experiments are under way to determine the scope of the method

Table 2 Reaction of Mixed Phosphotriesters with PhSTMS[a]

Phosphate	$MeO(EtO)P(O)OPh$			$MeOP(O)(OEt)_2$			$(EtO)_2P(O)CH_2Ph$		
Half-life Time at 70,[ob] min,(Group cleaved)	t_1(Me)	t_2(Et)	t_3(Ph)	t_1(Me)	t_2(Et)	t_3(Et)	t_1($PhCH_2$)	t_2(Et)	t_3(Et)
	<0 5	180	no change (100 hr)	<2	310	1900	3	240	1800

a,b) See the corresponding footnotes in Table 1

Finally, it should be noted that PhSTMS could be also applicable to monodealkylation of phosphonate since half-life times obtained with $MeP(O)(OMe)_2$[t_1=176, t_2=2200 min at 30^o] revealed to be promising for the due purpose

References and Notes

1) V Amarnath and A D Broom, *Chem. Rev.*, 77, 183(1977)
2) C E McKenna, M T Higa, N H Cheung, and M C McKenna, *Tetrahedron Letters*, 155(1977)
3) D A Evans, L K Truesdale, K G Grimm, and S L Nesbitt, *J Am. Chem. Soc.*, 99, 5009(1977)
4) P Savignac and G Lavielle, *Bull Soc Chim. France*, 1506(1974), G W Daub and E E van Tamelen *J Am. Chem. Soc* , 99, 3526(1977)
5) This reflects a SN-2 type cleavage by PhS^- 6) This is presumably due to electron withdrawing effect of phenyl group 7) The steric hindrance of phenyl group might be responsible for the retardation

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