Tetrahedron Letters, Vol.31, No.4, pp 501-502, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A NEW SYNTHESIS OF THIOPHOSPHORIC ACID ESTERS WITH A C-S-P BOND

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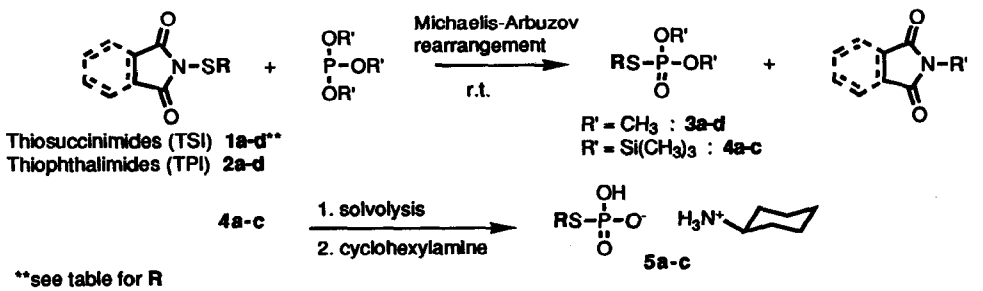
Various S-substituted thiosuccinimides **1a-d** and thiophthalimides **2a-d** were found to react with trialkylphosphites according to a Michaelis-Arbuzov type mechanism. This provides an efficient way to prepare thiophosphoric acid esters, particularly thiophospholipids, with a C-S-P bond.

Thiophosphoric acid esters with a C-S-P bond (phosphorothiolates) are of special interest as pesticides[1] and as thio-analogues of naturally occurring phospholipids with phospholipase-inhibitory,[2] cytostatic, or hypotensive activity.[3] They are often prepared by the reaction of sulfenyl halogenides with 3-coordinate phosphorus esters.[4] These sulfenyl halogenide reagents are extremely labile and their reactions often yield halogenated by-products.[5]
S-substituted thioimides are known to react as electrophilic thiol derivatives with a number of nucleophiles, such as thiols, amines, alkoxides, and pyrroles.[6] Harpp[7] used the reaction of thiophthalimides with tris(dimethylamino)-phosphine to desulfurize thioimides. We found that thiosuccinimides and thiophthalimides spontaneously react with trialkylphosphites according to a Michaelis-Arbuzov type mechanism to yield thiophosphoric acid esters and N-alkylimides. The exothermic reaction takes place extremely rapidly at any temperature and provides a convenient synthesis of thiophosphoric acid esters. Thioimides are easy-to-prepare, highly stable precursors. The reactions were carried out with two different phosphites, namely trimethylphosphite and tris(trimethylsilyl)phosphite, and various S-alkyl and -aryl thio-derivatives of two different imides, succinimide and phthalimide. Broad applicability of the new method was thereby demonstrated.



**see table for R

Thioimides were prepared as described.[8] S-substituted dimethyl phosphoric acid esters **3a-d** were obtained by slow addition of 10 mmol of freshly distilled trimethylphosphite in 10 ml toluene to 10 mmol of the appropriate thiosuccinimide (TSI) **1a-c** or thiophthalimide (TPI) **2a-d** in 20 ml toluene at r.t. The solvent was removed *in vacuo*. The product was purified by distillation (**3a,b**) or silica gel column chromatography with a dichloromethane/methanol gradient (**3c,d**).

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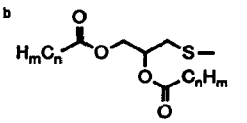
Phosphoric acid esters **5a-c** were synthesized analogously, by addition of tris(trimethylsilyl)phosphite[9] in toluene to the thioimides **1b-d**, or **2c**, respectively. After removal of the solvent *in vacuo*, the silylated phosphoric acid esters were solvolyzed by addition of 10 ml diethyl ether and 5 ml methanol. The precipitated imide was removed by filtration. The phosphoric acid esters were precipitated by addition of an appropriate amount of cyclohexylamine, collected by filtration, and recrystallized.

TABLE. Synthesis of Thiophosphoric Esters

compound	R	precursor	yield[%]	^{31}P-NMR[a] δ[ppm]	m.p.[°C] or b.p.[°C/mmHg]	lit. m.p.[°C] or b.p.[°C/mmHg]
3a	C_6H_5-	TSI **1a**	67	26.35	83/0.01	70-75/0.005[1]
		TPI **2a**	72			
3b	$C_6H_5CH_2$-	TSI **1b**	81	30.65	92/0.007	90-95/0.005[1]
		TPI **2b**	85			
3c	n-$C_{18}H_{37}$-	TSI **1c**	77	-31.89	38	
		TPI **2c**	83			
3d	TG-18[b]	TPI **2d**	74	29.74	45	46-48[11]
5a	$C_6H_5CH_2$-	TSI **1b**	83	16.77[c]	172	
5b	n-$C_{18}H_{37}$-	TSI **1c**	64	21.15	151	
5c	TG-14[b]	TSI **1d**	46	14.80	56	

[a] $CHCl_3$

[b] 
TG-14 : n=13; m=27
TG-18 : n=17; m=35

[c] $CHCl_3$:methanol 1:1

Further work is to be done on the synthesis of thiophospholipids with a C-S-P bond, *e.g.* thiophosphatidylserine and thio-analogues of Platelet Activating Factor which have up to now not been described in the literature.

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9. T. Hata and M. Sekine, *J.Am.Chem.Soc.* **96**, 7363 (1974); isolation: the reaction mixture was diluted with dry toluene and filtrated from triethylamine-HCl with exclusion of moisture. The solvents were removed under reduced pressure, followed by distillation.
10. Elemental analyses were in accordance with the proposed structures, which were confirmed by FT-IR-, ^{1}H-, and ^{13}C-NMR-spectra. Selected spectral data: **3c**: FT-IR [cm^{-1}]: 2920, 2850 (CH_2); 1263 (P=O); 1019 (P-O-C); ^{1}H-NMR ($CDCl_3$,δ): 0.88 (t,3H,CH_3); 1.26,1.44-1.93 (br s+m,34H,CH_2); 2.83 (m,2H,CH_2-S-P); 3.72 (s,3H,CH_3-O-P); 3.88 (s,3H,CH_3-O-P). **5b**: ^{1}H-NMR ($CDCl_3$,δ): 0.88 (t,3H,CH_3); 1.26,1.57-2.05 (br s+m,42H,CH_2); 2.78 (m,4H,CH_2-S-P + cyclohexylamine-C_1-H); 7.03 (s,3H,NH_3^+).
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(Received in Germany 25 September 1989)