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Trimethylsilyl Triflate Mediated Introduction of Phospholipid Head Groups[1]

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Abstract: Trimethylsilyl triflate accelerates the nucleophilic opening of cyclic phosphates with tertiary amines. This reaction has been applied to the synthesis of ether phospholipids.

The diverse biological effects associated with ether phospholipids have attracted the attention of medicinal chemists.[3] These include the mediator of acute inflammation PAF[4] **1**, the PAF antagonist[5] **2**, the antitumor lipid[6] **3**, and the phospholipase A_2 inhibitor[7] **4** (Figure 1). In order to explore the activities of these and other lipids, a versatile synthetic scheme was desired which would enable structural substitutions in the lipophilic tail as well as in the polar head group. While the former problem has been addressed in the preparation of differentially substituted glycerols[8], the introduction of variously substituted ammonium species into the head group remained a challenge.

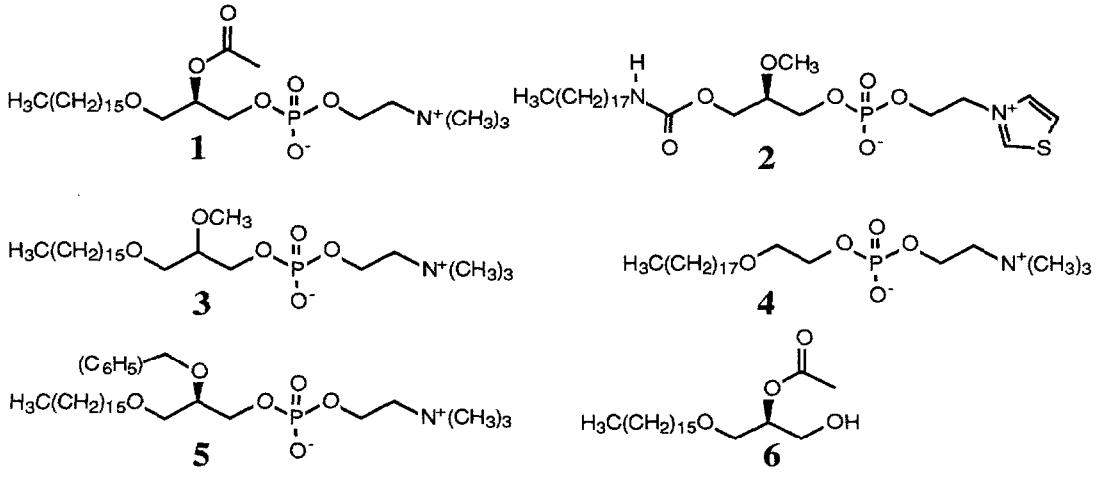
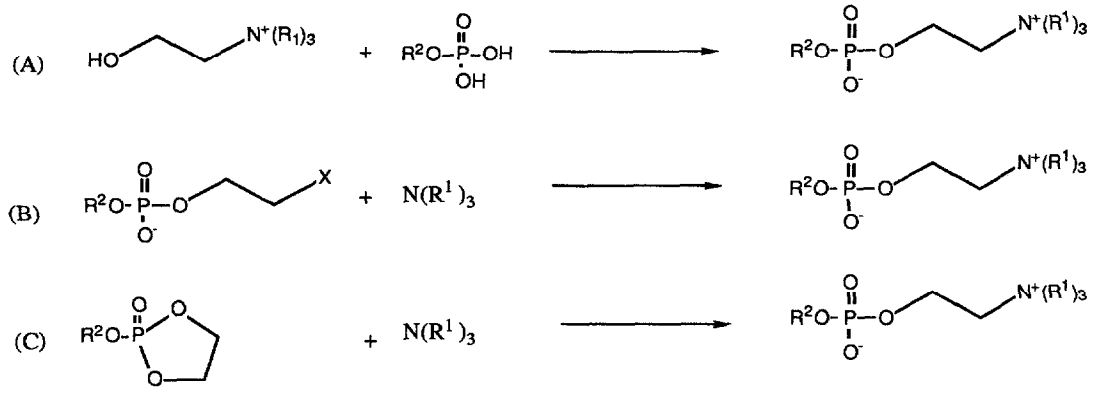


Figure 1.

Typically, the ammonium portion of a lipid is introduced in one of two fashions: (A)

prior formation of a 2-(hydroxyethyl)amine (ammonium) species and subsequent introduction of a phosphate ester;[8] or (B), nucleophilic displacement of a 2-haloethyl-phosphate ester with the appropriate amine.[9] This latter process has been extended to include the nucleophilic opening of cyclic phosphotriesters (C)[10] (Scheme 1).

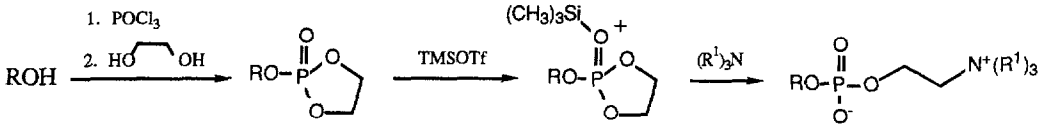
Scheme 1.



In practice, these methods failed to provide an easy entry into a variety of phospholipids. The first required the preparation of a large number of choline derivatives which proved to be difficult to isolate and purify, while the second produced complex reaction mixtures which required difficult chromatographic purifications, or failed entirely.

In an effort to avoid these problems, the nucleophilic opening of cyclic phosphotriesters (C) was explored in detail. While this approach affords phospholipids from relatively nonpolar material and without byproducts, it is a slow process requiring elevated temperatures and pressures[7,10] which fails with less nucleophilic amines (e.g. pyridine). Attempts to enhance the reactivity of the cyclic phosphate with Lewis acids (BF_3, $TiCl_4$, $SnCl_4$) failed to lead to the desired product. However, in the presence of a slight excess of trimethylsilyl triflate, the ring opening occurred at room temperature with a rate dependent on the nucleophilicity of the amine (Table 1). This procedure (Scheme 2) afforded product in high purity and allowed isolation of the phospholipid directly from the reaction mixture without chromatography.[11, 12]

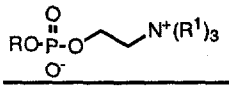
Scheme 2.



$R=(CH_2)_{17}CH_3$

The scope and limitations of this process were explored with a series of amines (Table 1). These results demonstrate a significant enhancement in the reactivity of the cyclic phosphotriester and correspond with the rates of alkylation of these bases with various electrophiles.[13]

Table 1.



	$N(R^1)_3$	Yield(%)[a]	Reaction Time	Formula[14]
7	$N(CH_3)_3$	83	15 min	$C_{23}H_{50}NO_4P$ $(4H_2O)$
8		82	1 hr	$C_{25}H_{46}NO_2P$ $(5H_2O)$
9		62	16 hr	$C_{29}H_{44}NO_4PS$ (H_2O)
10		NR[b]	48 hr	

a. R = $(CH_2)_{17}CH_3$ (Scheme 2). b. No indication of desired reaction by TLC or ^1H NMR.

The results obtained in the preparation of the ether lipids **1** through **5** (Figure 1) are summarized in Table 2. Attempts to produce PAF **1** directly from **6** lead to complex reaction mixtures. This may reflect a stabilization of the phosphonium intermediate (Scheme 2) by the acetate moiety, enabling decomposition of the starting material. However, PAF **1** was produced more successfully by a deprotection and reacylation of **5**.

Table 2.

Product	Yield(%)	mp(°C)	Formula[14]
1	13	235-6(d)	$C_{26}H_{54}NO_7P$ $(0.5H_2O)$
2	37	57-60	$C_{28}H_{53}N_2O_7PS$ $(2.5H_2O)$
3	76	225-30	$C_{27}H_{58}NO_6P$ $(0.5\ H_2O)$
4	73	80-100(d)	$C_{25}H_{54}NO_5P$ (H_2O)
5	81	170-5	$C_{31}H_{58}NO_6P$ (H_2O)

Efforts are underway to improve the yields in the case of ester containing phospholipids as well as to extend this methodology to the synthesis of phosphatidylethanolamines.

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11. *e.g.* For the preparation of **3**, 2-O-methyl-3-O-octadecylglycerol was converted to it's cyclic phosphotriester by the method of Magolda.7 A CH_2Cl_2 solution (50mL) of this material (6.21g, 13.4 mmol) was treated sequentialy with trimethylsilyl triflate (6.0g, 27mmol) and trimethylamine (450mL of gas, 20.1mmol) at 0°C. The mixture was allowed to warm to room temperature and maintained there for 3 h. The reaction mixture was diluted with $CHCl_3$ (100mL), neutralized and extracted with water (100mL). The

The resulting two layer system was allowed to diffuse together over 5 days. The colorless crystalline product **3** was isolated by filtration, 5.42g, 76%, mp 225-30°C.

12. Using this procedure, compounds **3** through **9** were isolated from reaction mixtures by crystallization. Compounds **1** and **2** were also crystallized from reaction mixtures, but required an additional chromatographic purification to afford proper combustion analyses.

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14. Elemental analyses within 0.4% of theoretical values were obtained for all compounds. All elements were determined with the exception of oxygen for each compound. Both ^1H NMR (300 MHz, CD_3OD and infra-red spectra were obtained for all compounds and were consistent with the proposed structures.

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