Selective Transesterification of 2,2,2-Trifluoroethyl Phosphates: Synthesis of Mixed Unsymmetrical Phosphates

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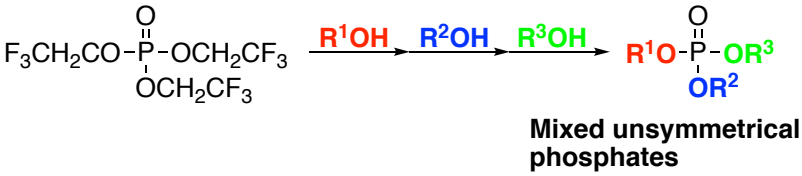
Supporting Information Placeholder

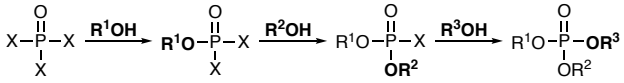
Selective Three-Step Transesterification of Trifluoroethyl phosphates



ABSTRACT: A selective transesterification starting with tris(2,2,2-trifluoroethyl) phosphate has been developed. This method involves a three-step substitution for 2,2,2-trifluoroethoxy groups and enables the facile synthesis of mixed unsymmetric phosphate triesters from three different alcohols. The substitution of the trifluoroethoxy group at the phosphorus proceeds selectively in the presence of DBU or lithium alkoxides. This method can be applied for the preparation of phospholipids.

Phosphate triesters are widely used for pharmaceuticals, agrochemicals, flame retardants, plasticizers, etc.[1] Thus, many methods for the synthesis of phosphate triesters have been developed.[2] Generally, phosphate triesters are synthesized by the reaction of alcohols with trivalent phosphorus (P(III)) compounds followed by oxidation,[3] using P(III) compounds activated under oxidative conditions[4] or reactive pentavalent phosphorus (P(V)) compounds.[5] The methods using P(III) are widely used, especially for the synthesis of oligonucleotides.[6] These methods, however, involve an oxidation step to convert P(III) to P(V) and cannot be applied to oxidizable substrates. On the other hand, reactions of P(V) compounds are useful for the direct synthesis of phosphate triesters bearing oxidizable functional groups. Most previous synthetic methods are employed for the synthesis of symmetric phosphate triesters ($P(O)(OR^1)_3$ or $P(O)(OR^1)_2(OR^2)$), whereas the selective synthesis of mixed unsymmetrical phosphate triesters ($P(O)(OR^1)(OR^2)(OR^3)$) from P(V) compounds is rare.[7,8] Moreover, reported syntheses have drawbacks such as limited functional group tolerance[7] and separate preparations of activated starting compounds.[8] Considering the drawbacks of existing approaches, we aimed to develop a new method for the synthesis of mixed unsymmetrical phosphate triesters. Three-step transesterifications of reactive phosphate triesters using three different alcohols achieve this goal if the transesterification of the three different alcohols can be managed selectively in each step (Scheme 1). Here, we report a convenient method for the synthesis of mixed unsymmetrical phosphate triesters through transesterification of P(V) compounds.

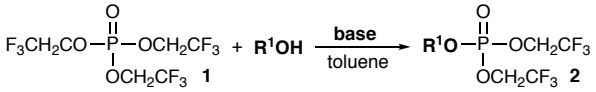
Scheme 1 Three-step transesterifications of reactive phosphate triesters

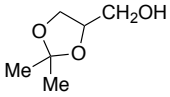
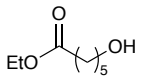
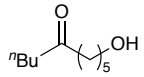
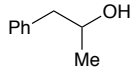
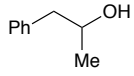
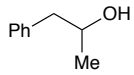


Tris(2,2,2-trifluoroethyl) phosphate (**1**) is commercially available and readily prepared from phosphorus oxychloride or phosphorus pentachloride.[9] The transesterification of **1** has not to our knowledge been previously reported. Sano *et al.* reported that transesterification of phosphonate esters bearing 2,2,2-trifluoroethoxy groups took place at the phosphorus center.[10] The phosphate **1** is expected to undergo transesterification with alcohols. To explore the desired transesterification, tris(2,2,2-trifluoroethyl) phosphate (**1**) was treated with a variety of primary alcohols in the presence of DBU. As shown in Table 1, runs 1–5, the transesterification proceeded smoothly and selectively, and the corresponding monosubstituted phosphate triesters were obtained in good yield. We found that DBU effectively promoted mono-transesterification of tris(2,2,2-trifluoroethyl) phosphate (**1**), and only trace amounts of disubstituted phosphate was detected by TLC. This reaction exhibits tolerance of several functional groups, including an acetal, ester, ketone, and Boc protected amine. Next, a secondary alcohol, 3-phenyl-2-propanol, was examined under the same conditions. This secondary alcohol reacted slower and required longer reaction time (Table 1, run 6). ^{t}BuOLi and ^{t}BuONa, which are stronger reagents than DBU, were employed, and ^{t}BuOLi proved to be more effective than DBU in promoting this reaction at a lower

temperature (runs 7,8). Compound **1** was then treated with other secondary alcohols in the presence of ^{t}BuOLi at –45°C. As shown in Table 1 (runs 9–11), ^{t}BuOLi successfully activated the alcohols, and the expected phosphate triesters were obtained in high yield. When phenols were used as an alcohol, the transesterification did not proceed at all due to the low nucleophilicity of phenoxide anions. No transesterification product was isolated from reaction of **1** and ^{t}BuOLi probably because elimination of bis(2,2,2-trifluoroethyl)phosphoric acid from the product (*tert*-butyl phosphate) occurred rapidly under basic reaction conditions.

Table 1. Mono Transesterification of Tris(2,2,2-trifluoroethyl) Phosphate[a]

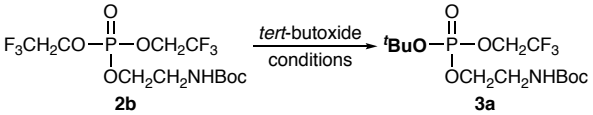


Run	Alcohol	Base	Temp.	Time (h)	Product	Yield[b] (%)
1	$PhCH_2CH_2OH$	DBU	r.t.	3	**2a**	94
2	$BocNHCH_2CH_2OH$	DBU	r.t.	5	**2b**	95
3		DBU	r.t.	8	**2c**	96
4		DBU	r.t.	6	**2d**	91
5		DBU	r.t.	8	**2e**	quant
6		DBU	r.t.	24	**2f**	70
7		^{t}BuOLi	−45°C	3	**2f**	91[c]
8		^{t}BuONa	−45°C	3	**2f**	47[c]
9	^{i}PrOH	^{t}BuOLi[d]	−45°C	3	**2g**	90[c]
10	cyclohexanol	^{t}BuOLi[d]	−45°C	3	**2h**	93[c]
11	cholesterol	^{t}BuOLi[d]	−45°C	4	**2i**	96[c]

[a]Phosphate ester **1** (1.2 equiv), alcohol **2** (1.0 equiv), and DBU (1.0 equiv) were stirred in toluene. [b]Isolated yield. [c]Phosphate ester **1** (1.2 equiv), alcohol **2** (1.0 equiv), and tert-butoxide (1.05 equiv) were stirred in toluene. [d]1.0 mol/L of hexane solution was used.

Subsequently, we investigated the transesterification of alkyl bis(2,2,2-trifluoroethyl) phosphate **2**. The reaction of **2b** with several alkali metal *tert*-butoxides was examined in THF. As shown in Table 2, runs 1–3, the transesterification proceeded, and lithium alkoxide gave the higher yields. Thus, the reaction conditions using ^{t}BuOLi were optimized. As shown in Table 2, a less polar solvent was better for this reaction, which was similar to the trend observed in typical S_N2 reactions. Employing a smaller amount of ^{t}BuOLi resulted in a lower yield (run 7) because phosphate ester **2b** had an acidic proton and a competing deprotonation by ^{t}BuOLi decreased the concentration of ^{t}BuO$^-$ in the reaction media. The best result was obtained when **2b** was treated with 2 equiv of ^{t}BuOLi in toluene at −45°C (run 6).

Table 2. Transesterification of Alkyl Bis(2,2,2-trifluoroethyl) Phosphates Using *tert*-Butoxide

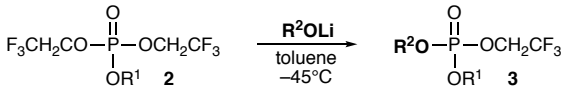


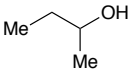
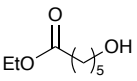
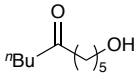
Run	*tert*-butoxide (equiv)	Temp.	Solvent	Time (h)	Yield (%)[a]
1	^{t}BuOK (2.0)	0°C	THF	2.5	14
2	^{t}BuONa (2.0)	0°C	THF	2.5	14
3	^{t}BuOLi[b] (2.0)	0°C	THF	2.5	53
4	^{t}BuOLi[b] (2.0)	0°C	THF/toluene[c]	2.5	56
5	^{t}BuOLi[b] (2.0)	–45°C	THF/toluene[c]	3	73
6	^{t}BuOLi[b] (2.0)	–45°C	toluene	3	93
7	^{t}BuOLi[b] (1.0)	–45°C	toluene	3	62

[a]Isolated yield. [b]1.0 mol/L of hexane solution was used. [c]THF/toluene = 1/1

With the optimized reaction conditions in hand, the scope of this transesterification was explored with alkyl bis(2,2,2-trifluoroethyl) phosphate **2** and lithium alkoxides, which were prepared *in situ* from the corresponding alcohols and ^{t}BuOLi. As shown in Table 3, the reaction using primary and secondary alcohols proceeded smoothly to give the corresponding phosphates in high yield. The transesterification of **2** was compatible with several functional groups, including an ester, ketone, and Boc protected amine. It is noteworthy that only trace amounts of products with dual substitution of added alcohols were observed with TLC with these reaction conditions.

Table 3. Mono Transesterification of Alkyl Bis(2,2,2-trifluoroethyl) Phosphates with Various Alcohols[a]

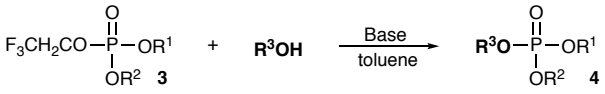


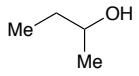
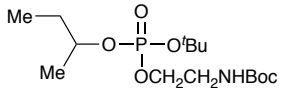
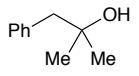
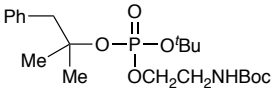
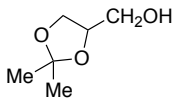
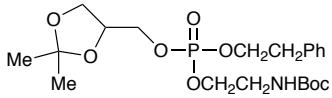
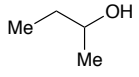
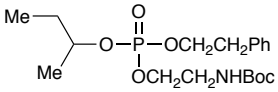
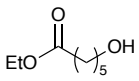
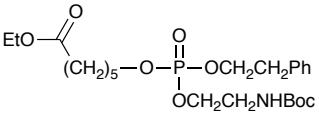
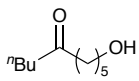
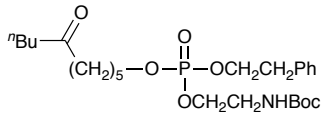
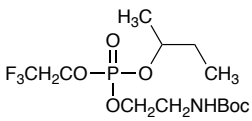
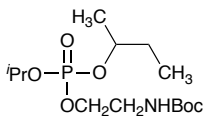
Run	**2**: R^1O	R^2OH	Time (h)	Product	Yield (%)[b]
1	**2a**: $PhCH_2CH_2O$	^{i}PrOH	4	**3b**	94
2	**2b**: $BocNHCH_2CH_2O$	EtOH	3	**3c**	92
3	**2b**: $BocNHCH_2CH_2O$	$PhCH_2CH_2OH$	3	**3d**	94
4	**2b**: $BocNHCH_2CH_2O$		3	**3e**	84
5	**2b**: $BocNHCH_2CH_2O$		3	**3f**	92
6	**2b**: $BocNHCH_2CH_2O$		4	**3g**	87
7	**2f**: ^{i}PrO	$PhCH_2CH_2OH$	4	**3b**	88

[a]Phosphate ester **2** (1.0 equiv) and 0.8–1.2 equiv of alcohol and ^{t}BuOLi (1.0 mol/L of hexane solution) were stirred in toluene at −45°C and the reaction was quenched with a toluene solution of AcOH at −45°C. [b]Isolated yield.

Lastly, we investigated the transesterification of dialkyl 2,2,2-trifluoroethyl phosphate **3** for the synthesis of mixed unsymmetrical phosphate triesters. The phosphates **3** were treated with lithium alkoxides generated *in situ* from the corresponding alcohols and ^{t}BuOLi or LDA. Since the phosphates **3** have only one leaving group, this transesterification does not need low-temperature reaction conditions. As shown in Table 4, the reaction using primary (runs 1, 4, 7, 8), secondary (runs 2, 5, 9), and tertiary alcohols (runs 3, 6) proceeded smoothly to give mixed unsymmetrical phosphate triesters **4** in good yield. Sterically demanding phosphate esters or alcohols reacted slower and more than 2 equiv of base was required to drive the reactions to completion (runs 1–3, 6). When a tertiary alcohol except *tert*-butyl alcohol was used, LDA was applied instead of ^{t}BuOLi to avoid an undesired competing reaction (run 3). The reaction using ethyl 6-hydroxyhexanoate as an alcohol required a low temperature (–45°C) to prevent lactonization of the alcohol (run 7). The transesterification of **3** was compatible with several functional groups, including an ester, ketone, acetal, and Boc protected amine.

Table 4. Transesterification of Dialkyl 2,2,2-Trifluoroethyl Phosphates with Various Alcohols[a]



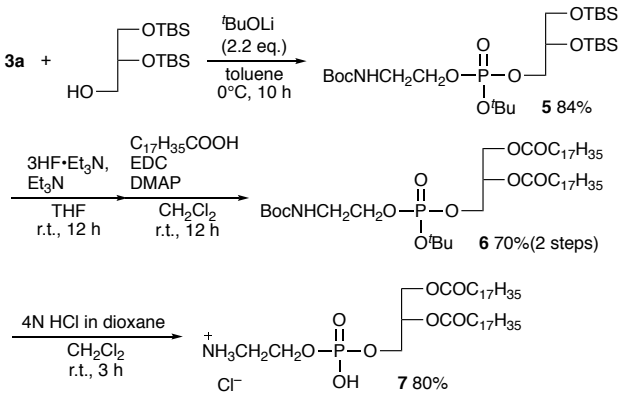
Run	3	R^3OH	Base	Temp.	Time (h)	Product	Yield (%)[b]
1	**3a**: F_3CH_2CO–P(=O)(O^tBu)–OCH_2CH_2NHBoc	$PhCH_2CH_2OH$	^{t}BuOLi[c]	0°C	5	**4a**: $PhCH_2CH_2O$–P(=O)(O^tBu)–OCH_2CH_2NHBoc	91
2	**3a**: F_3CH_2CO–P(=O)(O^tBu)–OCH_2CH_2NHBoc		^{t}BuOLi[c]	0°C	5	**4b**: 	90
3	**3a**: F_3CH_2CO–P(=O)(O^tBu)–OCH_2CH_2NHBoc		LDA[c]	0°C	5	**4c**: 	70
4	**3d**: F_3CH_2CO–P(=O)(OCH_2CH_2Ph)–OCH_2CH_2NHBoc		^{t}BuOLi	r.t.	8	**4d**: 	89
5	**3d**: F_3CH_2CO–P(=O)(OCH_2CH_2Ph)–OCH_2CH_2NHBoc		^{t}BuOLi	0°C	3	**4e**: 	92
6	**3d**: F_3CH_2CO–P(=O)(OCH_2CH_2Ph)–OCH_2CH_2NHBoc	-	^{t}BuOLi[e]	0°C	3	**4a**: $PhCH_2CH_2O$–P(=O)(O^tBu)–OCH_2CH_2NHBoc	81
7	**3d**: F_3CH_2CO–P(=O)(OCH_2CH_2Ph)–OCH_2CH_2NHBoc		^{t}BuOLi	-45°C	5	**4f:** 	70
8	**3d**: F_3CH_2CO–P(=O)(OCH_2CH_2Ph)–OCH_2CH_2NHBoc		^{t}BuOLi	r.t.	8	**4g:** 	80
9	**3e**: 	^{i}PrOH	^{t}BuOLi	r.t.	1	**4h**: 	94

[a] Phosphate ester **3** (1.0 equiv) and 0.8–1.2 equiv of alcohol and ^{t}BuOLi (1.0 mol/L of hexane solution) were stirred in toluene, unless otherwise noticed. [b] Isolated yield. [c] 2.2 equiv of base was used. [e] 2.0 equiv of ^{t}BuOLi was used.

Now that a new method for the synthesis of mixed unsymmetrical phosphate triesters starting from tris(2,2,2-trifluoroethyl) phosphate (**1**) was developed, we tried to convert dialkyl 2,2,2-trifluoroethyl phosphate **3a** to a phospholipid in order to demonstrate the synthetic utility as shown in Scheme 2. Phosphate **3a** was treated with a protected glycerol in the presence of ^{t}BuOLi and the corresponding phosphate ester **5** was obtained in 84%. After deprotection of TBS groups of **5**, esterification of the obtained diol with stearic acid gave the protected phospholipid **6** in 70% (2 steps). Deprotection of Boc and tert-

butyl groups afforded the expected phosphatidylethanolamine **7** in 80%.

Scheme 2. Synthesis of phosphatidylethanolamine 7



In summary, we have developed a new three-step method to produce mixed unsymmetrical phosphate triesters featuring the selective transesterification of 2,2,2-trifluoroethyl phosphates. Tris(2,2,2-trifluoroethyl) phosphate reacts with various alcohols in the presence of DBU or *t*BuOLi to give alkyl di(2,2,2-trifluoroethyl) phosphate in good yield. Lithium alkoxides readily undergo transesterification with alkyl di(2,2,2-trifluoroethyl) phosphates or dialkyl 2,2,2-trifluoroethyl phosphates, and the corresponding phosphate triesters are obtained selectively. This method offers three-step access to mixed unsymmetrical phosphate triesters and has the following advantages: (i) the method involves the use of a commercial starting material; (ii) the reaction proceeds under mild conditions; (iii) various functional groups can be tolerated; (iv) intermediates **2** and **3** can be isolated and purified by silica gel column chromatography; (v) the method can be applied for the preparation of phospholipids. Now we are trying to develop a simpler and more convenient three-step one-pot procedure.

ACKNOWLEDGMENT

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, and ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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