

A new strategy for the synthesis of unsymmetrical phosphotriesters

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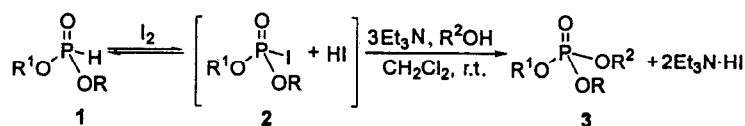
A new strategy for the synthesis of unsymmetrical phosphotriesters was reported: an alcohol was converted to unsymmetrical dialkyl phosphites firstly, which then reacted with the second alcohol or phenol to afford required unsymmetrical triesters in the presence of iodine in high yields under exceptionally mild conditions.

Keywords Unsymmetrical phosphotriesters, dialkyl phosphites, phosphorylation

Phosphotriesters are one kind of important compounds. In addition to pesticides, extracting agents and medicines, some phosphotriester-type nucleosides and oligodeoxyribo-nucleotides with *anti*-HIV activity have been reported recently.¹ Many important classes of biochemical substances are also derived *via* deprotection of the corresponding phosphotriester precursors. The phosphotriester-method has been widely used to synthesize bioactive dinucleoside phosphates and phosphatidylinositol.² The preparation of the fully unsymmetrical phosphotriesters (RO)(R¹O)(R²)PO is very important for the synthesis of bioactive molecules and pharmaceuticals, but it is far from easiness. Accordingly, efforts to construct

these compounds have extensively been made so far, providing many ways to the unsymmetrical phosphoric acid derivatives.³

An important synthetic method of phosphotriesters is coupling of triester phosphite with a target alcohol in the presence of I₂. Recently, Widlanski⁴ reported the synthesis of a mechanism-based inhibitor of Ribonuclease A, a phosphodiester compound that cannot be synthesized by using phosphoramidite methodology, can be completed by this way after subsequent deprotection. We found that dialkyl phosphite proceeded similarly in presence of I₂. We knew the reaction of dialkyl phosphite (1) with chlorine was used to prepare dialkyl chlorophosphate, but with iodine to form phosphoryl iodide (2) may be in an equilibrium,⁵ with 2 in the unfavorable position of the equilibrium. However, in present procedure the equilibrium will shift to direction of 3, when dialkyl iodophosphate reacts with hydroxylic compounds to form the phosphotriesters in the presence of a base. Thus, when the unsymmetrical dialkyl phosphites are used the reaction will give the full unsymmetrical phosphotriesters.



Results and discussion

The unsymmetrical phosphite can be prepared in a

number of ways.⁶ For example, using the mixture of 1 equivalent of a higher alcohol and 2 equivalents of simple alcohol (*e. g.* CH₃OH) would give an unsymmetrical

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methyl alkyl phosphite.⁷ We prepared some phosphites by this way in good yields (60–80%) as shown in Table 1. Probably, it is the most inexpensive and convenient method to synthesize the unsymmetrical dialkyl phosphite.

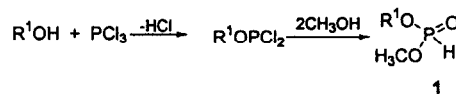

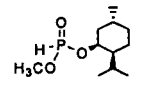
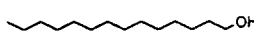
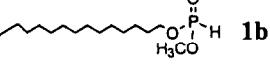
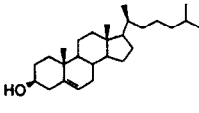
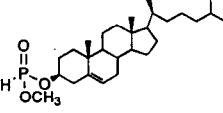

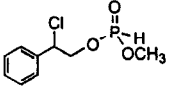


Table 1 Preparation of phosphite diesters

Entry	Substrates (R ¹ OH)	Yield (%)	Reaction time (h)	Phosphites
1		80	0.5	 1a
2		78	0.5	 1b
3		60	1	 1c
4		71	1	 1d

The transesterification of diethyl phosphites (or other reactive diesters) with an alcohol or the condensation of phosphite monoester with a hydroxylic compound in the presence of a coupling agent also afforded unsymmetrical phosphite diesters. Based on the nature of the target alcohol, an appropriate method could be chosen.

Now we can suggest a new strategy for the synthesis of unsymmetrical phosphotriesters: Firstly an alcohol is converted to unsymmetrical dialkyl phosphites, which react with the second alcohol to afford the required unsymmetrical triesters in the presence of iodine and triethylamine. The examples **3a–e** in Table 2 illustrated the potential synthetic utility. The novel procedure has some advantages over other synthetic routes and would find practical application in the preparation of pesticides and medicines with unsymmetrical phosphate structure unit because it used the inexpensive and easily available starting materials as well as easily handled phosphites as intermediates. Perhaps the new procedure will also favor the study of optically active phosphorus compounds.

Removal of the protecting group CH₃ in these phosphotriesters with TMSBr/triethylamine⁴ or thiophenol/triethylamine or other agents⁵ may easily furnish the unsymmetrical phosphate diester. A better was given when the secondary alcohol was used in the first step reaction and the primary alcohol was introduced in second step owing to

the steric hindrance effect.

Our group has reported⁶ that carbohydrates can be phosphorylated with dialkyl phosphite *via* Atherton-Todd reaction under S-L PTC condition. The reaction of the mixed dialkyl phosphite with an alcohol can also afford unsymmetrical phosphotriester. In comparison, **3f** in Table 2 was synthesized by Atherton-Todd reaction in only 63% yield. It is more important that both general and L-L or S-L PTC modified procedure of Atherton-Todd reaction are not suitable for the phosphorylation of usual secondary and tertiary alcohols.⁷ Because the intermediate iodiophosphate is more active than chlorophosphate, the present method gives better results in the preparation of phosphotriesters.


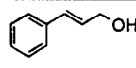
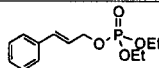

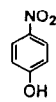
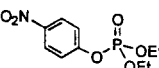
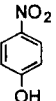
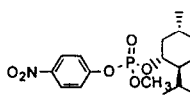
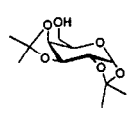
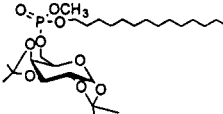
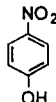
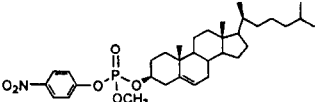
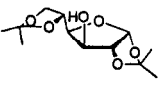
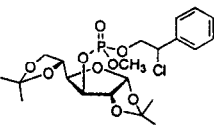
Experimental

¹H NMR spectra were recorded on a Varian EM-360A (90 MHz) spectrometer and a AM-300 (300 MHz) spectrometer in pure carbon tetrachloride (TMS as the internal reference) or in CDCl₃. ³¹P NMR spectra were recorded in CDCl₃ on DRX-400 (161.97 MHz, 85% H₃PO₄ as the external reference). Mass spectra were determined on Finnigan 4021. Elemental analyses were performed on Rapid CHN-O-S at Shanghai Institute of Organ-

ic Chemistry. CH_2Cl_2 was distilled from CaH_2 , THF from sodium benzophenone ketyl. All the reaction vessels were

flame-dried under vacuum and back-filled with N_2 , and all reactions were carried out under a N_2 atmosphere.

Table 2 Preparation of phosphotriester

Phosphites	Alcohol	Reaction time (min)	Yield (%)	Products
		30	90	 3a
		10	95	 3b
1a		10	95	 3c
1b		0.5	74	 3d
1c		10	92	 3e
1d		60	63	 3f

Dialkyl phosphites (**1a—c**) were prepared by the known method.⁸

1a Oil. δ_{H} (90 MHz, CCl_4): 6.35(d, $J = 635$ Hz, 1H), 3.7—4.2(m, 1H), 3.70(d, $J = 12$ Hz, 3H), 0.7—2.4(m, 18H). δ_{P} : 8.88, 8.27. m/z (%): 235(M + 1, 2.87), 193(4.92), 138(15.54), 123(30.27), 97(100), 81(38.70). Anal. $\text{C}_{11}\text{H}_{23}\text{O}_3\text{P}$. Calcd: C, 56.40; H, 9.89. Found: C, 56.79; H, 10.17.

1b Liquid. δ_{H} (90 MHz, CDCl_3): 6.72(d, $^1J_{\text{PH}} = 693$ Hz, 1H), 3.85—4.15(m, 2H), 3.72(d, $^3J_{\text{PH}} = 12$ Hz, 3H), 1.1—1.8(m, 24H), 0.9(t, $^3J_{\text{HH}} = 5$ Hz, 3H). δ_{P} : 9.67. m/z (%): 293(M⁺, 0.08), 137(1.14), 111(0.71), 97(100), 79(6.74), 57(5.08). HRMS: $\text{C}_{15}\text{H}_{33}\text{O}_3\text{P}$. Calcd: 293.2246. Found: 293.2251.

1c Oil, δ_{H} (90 MHz, CDCl_3): 6.83(d, $^1J_{\text{PH}} = 694$ Hz, 1H), 5.35(d, $^3J_{\text{PH}} = 2.94$, 1H), 4.30(d,

$^3J_{\text{PH}} = 12$ Hz, 3H), 2.50—0.50(m, 43H). δ_{P} : 8.105. m/z (%): 464(M⁺, 22.45), 368(76.15), 353(49.86), 255(42.48), 145(72.62), 105(92.08), 95(71.92), 81(100). Anal. $\text{C}_{28}\text{H}_{49}\text{O}_3\text{P}$. Calcd: C, 72.38; H, 10.63. Found: C, 72.60; H, 10.71.

1d The starting material was styrene oxide, the experimental procedure was the same. Liquid. δ_{H} (90 MHz, CDCl_3): 6.40(2d, $^1J_{\text{PH}} = 693$ Hz), 1H), 7.2—7.5(m, 5H), 5.04(t, $^3J_{\text{HH}} = 6$ Hz, 1H), 4.40(t, $^3J_{\text{HH}} = 6$ Hz, $^3J_{\text{PH}} = 7$ Hz, 2 H), 3.70(d, $^3J_{\text{PH}} = 12$ Hz, 3H). δ_{P} : 9.76, 9.73, 9.47, 9.44. m/z (%): 237(M + 3, 10.59), 235(M + 1, 34.75), 199(31.21), 138(100). Anal. $\text{C}_9\text{H}_{12}\text{ClO}_3\text{P}$. Calcd: C, 46.08; H, 5.15. Found: C, 46.08; H, 5.25.

General procedure for the synthesis of unsymmetrical phosphotriester

To a mixture of the dialkyl phosphite (1 mmol), hy-

droxylic compound (1 mmol) and Et_3N (4 mmol) in CH_2Cl_2 (5 mL) was added the solution of I_2 (1 mmol) in CH_2Cl_2 (10 mL) dropwise at r.t. After 0.5 h the reaction mixture was concentrated, then redissolved in Et_2O , filtered to remove the precipitate and again concentrated *in vacuo*. Flash chromatography (hexane/ethyl acetate) afforded the pure product. All reactions were carried out under nitrogen. Compounds **3a** and **3b** are known compounds, all analysis data are the same as reference.⁹

3c Oil, δ_{H} (300 MHz, CDCl_3): 7.2—8.2(m, 4H), 4.0—4.3(m, 1H), 3.95(d, $^3J_{\text{PH}} = 10.5$ Hz, 3H), 0.8—2.23(m, 18H). δ_{P} (CD_3Cl): -6.076, -6.0253, -6.268. m/z (EI, %): 371(M^+ , 5.05), 234(100), 217(6.65), 139(17.94), 123(8.88), 95(18.13). ν_{max} : 2958, 1524, 1347, 1294, 1237, 1060, 1019, 929 cm^{-1} . Anal. $\text{C}_{17}\text{H}_{26}\text{NO}_6\text{P}$. Calcd: C, 54.98; H, 7.06; N, 3.77. Found: C, 54.92; H, 7.11; N, 3.89.

3d Oil. δ_{H} (300 MHz, CDCl_3): 5.45(d, $^3J_{\text{HH}} = 5$ Hz, 2H), 4.65(dd, $^3J_{\text{HH}} = 3$ Hz, $^3J_{\text{PH}} = 9.3$ Hz, 2H), 3.97(d, $^3J_{\text{PH}} = 11$ Hz, 3H), 3.65—4.4(m, 5H), 1.1—1.6(m, 39H). m/z (EI, %): 551(M^+ , 5.65), 207(100), 185(2.73), 169(9.46), 127(17.12), 113(70.34). ν_{max} : 2925, 1467, 1235, 1064, 721 cm^{-1} . HRMS(EI) m/z (%): $\text{C}_{27}\text{H}_{51}\text{O}_9\text{P}$. Calcd: 550.3271. Found: 550.3281(M^+).

3e Mp 156 °C. δ_{H} (300 MHz, CDCl_3): 7.2—8.3(m, 4H), 5.38(t, $^3J_{\text{PH}} = 6.62$ Hz, 1H), 4.25—4.4(m, 1H), 3.90(d, $^3J_{\text{PH}} = 11.26$ Hz, 3H), 0.6—2.5(m, 43H). δ_{P} (CD_3Cl): -6.400, -6.427. m/z (EI, %): 368($\text{C}_{22}\text{H}_{44}$, 100), 353(43.51), 255(53.01), 247(82.99), 233(31.13), 213(41.38), 147(82.16), 145(99.84), 121(63.88), 95(59.79). ν_{max} : 2943, 1616, 1522, 1347, 1265, 1035, 862 cm^{-1} . Anal. $\text{C}_{34}\text{H}_{52}\text{NO}_6\text{P}$. Calcd: C, 67.86; H, 8.71; N, 2.33. Found: C, 67.73; H, 8.74; N, 2.57.

3f Oil, δ_{H} (300 MHz, CDCl_3): 7.3—7.5(m, 5H), 5.85(d, $^3J_{\text{HH}} = 3.48$ Hz, 1H), 5.10(t, $^3J_{\text{HH}} =$

6.09, 1H), 4.65—4.85(m, 2H), 4.3—4.55(m, 2H), 4.2—4.3(m, 1H), 4.0—4.2(m, 3H), 3.7—3.9(m, 3H), 1.2—1.6(m, 12H). δ_{P} (CD_3Cl): -0.891, -0.919, -1.046. MS(EI, %): 493(M^+ , 5.92), 435(52.97), 337(29.63), 339(34.35), 297(49.57), 251(29.38), 239(28.35), 138(34.29), 113(100). ν_{max} : 2989, 1375, 1262, 1218, 1075, 1036, 844 cm^{-1} . Anal. $\text{C}_{21}\text{H}_{30}\text{ClO}_9\text{P}$. Calcd: C, 51.17; H, 6.14. Found: C, 51.08; H, 6.27.

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