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# UTILIZATION OF *O*-XYLYLENE *N,N*-DIETHYLPHOSPHORAMIDITE FOR THE SYNTHESIS OF PHOSPHORIC DIESTERS

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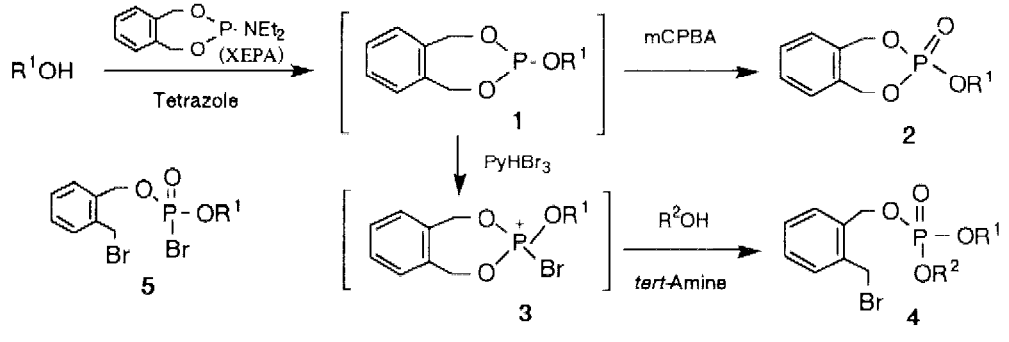
***Key Words:*** *Phosphorylation; o-xylylene N,N-diethylphosphoramidite; phosphonium salt; phosphoric diester*

**Abstract:** *o*-Xylylene alkyl phosphites which were derived by the reaction of alcohols with *o*-xylylene *N,N*-diethylphosphoramidite in the presence of 1*H*-tetrazole were reacted with second alcohols in the presence of pyridinium bromide perbromide, and a *tert*-amine, to give the corresponding triesters involving phospholipids. The esters were deprotected to phosphoric diesters by hydrogenolysis or the reaction with disodium disulfide.

In a previous paper,[1] we have reported a phosphorylation method which comprises the phosphitylation of an alcohol with a new reagent, *o*-xylylene *N,N*-diethylphosphoramidite (XEPA) in the presence of 1*H*-tetrazole and subsequent oxidation of the resultant phosphite 1 with mCPBA. The phosphorylation product 2 was converted easily to the phosphoric monoester by hydrogenolysis. The sequential procedures were utilized efficiently for the preparation of *myo*-inositol 1,4,5-tris(phosphate)[2] and other related inositol poly(phosphates)[3] which are physiologically important natural products and analogues.[4] In this communication, we wish to report the utilization of XEPA for phosphoric diester synthesis which involves transformation of 1 to phosphonium salt 3 by pyridinium bromide perbromide (PPB). Concerning phosphorylation via phosphonium salts, Mukaiyama and co-workers reported reactions of alcohols with trialkyl and dialkyl phosphites in the presence of oxidizing agents such as bromocyanoacetoamide,[5] dibromomalonamide,[6] *N*-bromosuccinimide,[7] diethyl azodicarboxylate,[8] and bromine.[9] The reaction products were converted to the phosphoric monoesters.[5b,c,d,9] However, such a phosphonium salt methodology has not been employed for the synthesis of phosphoric diesters.

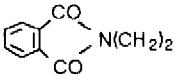
We expected that a phosphonium salt like 3 derived by the reaction of 1 with an oxidizing agent reacts with an alcohol to afford the corresponding triester like 4. Along this line, we first searched a suitable oxidizing



agent for forming the phosphonium salt and PPB was found to be much more effective than other reagents such as *N*-bromo- and *N*-chlorosuccinimide, sulfuryl chloride, *t*-butyl hypochlorite, *N*-chlorodiisopropylamine, bromine, iodine, tetrabromomethane, and diethyl azodicarboxylate. Although PPB is known to have similar properties to bromine, the yield (75%) of **4** [$R^1$=Ph$(CH_2)_2$, $R^2$=Et] in the former case was much higher than that (35%) in the latter. The second oxidation step was carried out generally at around -40 °C. The reaction conducted at 0 °C or above gave the same phosphate **4** in a poorer yield, presumably because the phosphonium salt once formed changed to phosphorobromidate **5** which in turn suffered complex decomposition. As a base in the second step, triethylamine, 2,6-lutidine, and pyridine were effective.

Thus, typically an alcohol ($R^1$OH) was first treated with XEPA in the presence of tetrazole in dichloromethane at room temperature. After removal of tetraole and diethylamine by washing with water, the phosphite **1** was reacted without purification with another alcohol ($R^2$OH) in the presence of PPB, *tert*-amine,

**Table 1.** Synthesis of **4** via phosphitylation and oxidation

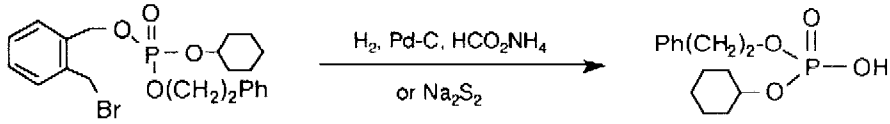
| Entry | $R^1$ (*eq*) [a] | $R^2$ (*eq*) [a] | Base (*eq*) [a] | Conditions in 2nd step | Yield of **4**, % [b] |
|---|---|---|---|---|---|
| a | $Ph(CH_2)_2$ (*1.2*) |  (*1.0*) | $Et_3N$ (*2.8*) | -40 °C/15 min then r.t./10 min | 89 |
| b | $CH_3(CH_2)_{17}$ (*1.2*) |  (*1.0*) | $Et_3N$ (*2.7*) | -10 °C/30 min | 69 |
| c | $CH_3(CH_2)_7$  $(CH_2)_8$ (*1.0*) |  (*1.3*) | $Et_3N$ (*1.1*) | -45 °C/20 min | 72 |
| d |  (*1.0*) |  (*1.3*) | $Et_3N$ (*1.2*) | -42 °C/15 min then 0 °C/10 min | 75 |
| e | DSG[c] |  (*1.0*) | $Et_3N$ (*2.6*) | -12 °C/25 min | 71 |
| f | $Ph(CH_2)_2$ (*1.1*) | **6** (*1.0*) | Lutidine (*1.3*) | -72 °C/60 min then -15 °C/60 min | 45 (70)[d] |
| g | $Ph(CH_2)_2$ (*1.1*) | **7** (*1.0*) | Lutidine (*1.3*) | -74 °C/55 min then 0 °C/5 min | 67 (97)[d] |
| h |  (*1.0*) |  (*2.4*) | $Et_3N$ (*2.4*) | -42 °C/75 min then 0 °C/15 min | 58 |

*a*: Molar equivalent. *b*: Based on the alcohol which was used in a smaller molar quantity.
*c*: 1,2-Di-*O*-stearoylglycerol. *d*: Based on the recovered alcohol.

and molecular sieves. According to this general procedure, various phosphoric triesters were prepared in good yields (Table 1).[10] The double bond in the alkenyl alcohol (Entry c in the table) was not transformed to the dibromide during oxidation. The present method also afforded a glycerophospholipid derivative (Entry e) as well as inositol phosphates (Entries f and g).

Phosphonium salt **3** and phosphorobromidate **5** which is derived from **3** by the action of the bromide ion are possible intermediates in the formation of **4** from phosphite **1**. The latter **5** is suggested not to be the major reaction intermediate by the following experiment. When 2-phenylethyl phosphite **1** [$R^1$=$Ph(CH_2)_2$] was treated similarly with excess of butyl alcohol in the presence of PPB, dibutyl 2-phenylethyl phosphate [$Ph(CH_2)_2OP(O)(On\text{-}Bu)_2$] was formed as a main product in 53% yield accompanied by 19% of a usual product **4** [$R^1$, $R^2$=$Ph(CH_2)_2$, *n*-Bu]. The dibutyl ester is not likely to be derived from **5**.

Deprotection of **4** was simply accomplished by hydrogenolysis over 5% Pd-C in the presence of ammonium formate as demonstrated in the case of **4a** where cyclohexyl 2-phenylethyl phosphate was obtained as an ammonium salt in 83% yield. In this reaction, ammonium formate was added to neutralize hydrogen bromide, otherwise the diester was obtained in a low yield. As another deprotection method, we found that sodium disulfide was quite effective. Thus, **4a** was treated with excess of the disulfide in 95% aqueous ethanol at room temperature overnight to give the diester in 90% yield. The latter deprotection method is a potent alternative, especially when hydrogenolysis conditions can not be employed.

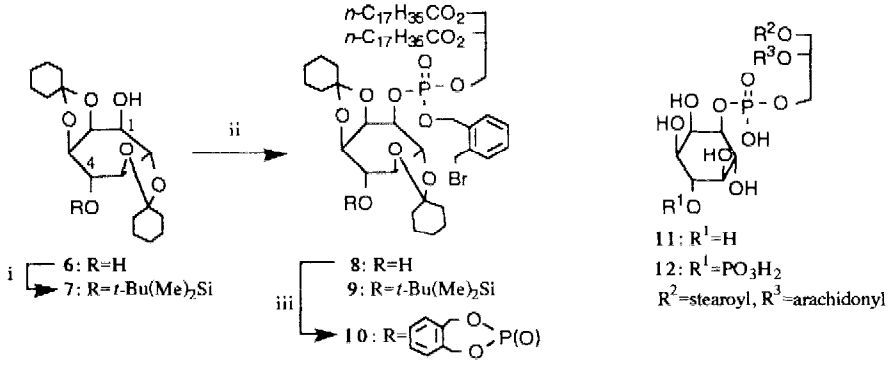



**4a**

Utilization of XEPA has been examined for synthesis of phosphatidyl inositols[11] such as **11** and **12** which are minor components in cell membranes and assumed to have important physiological roles.[12] As preliminary results, synthesis of protected derivatives **8**, **9**, and **10** with stearoyl groups as a fatty acid moiety is described here (Scheme 1). First treatment of 1,2-distearoyl glycerol (1.2 eq. based on **6**) with XEPA gave the corresponding phosphite which was then reacted with 1,2:4,5-dicyclohexylidene-*myo*-inositol (**6**) as described above to afford 1-phosphatidyl inositol derivative **8** in moderate selectivity in 43% yield accompanied by small amounts of 4-monophosphoryl (6%) and 1,4-diphosphoryl (9%) products and recovered **6** (13%). Alternatively, 4-*O*-*t*-butyldimethylsilyl derivative **7** was converted to **9** in 82% yield. Further phosphorylation of **8** according to our reported procedure[1] using XEPA and mCPBA gave **10** in 90% yield. The phosphorylation products **8**, **9**, and **10** might be derived to analogues of **11** and **12** by sequential deprotection.

In summary, XEPA was found to be utilized for the synthesis of phosphoric diesters as well as phosphoric monoester synthesis. Both of these synthetic methods have been successfully applied to the synthesis of **10**. The amidite is easily prepared from hexaethylphosphorous triamide and 1,2-di(hydroxymethyl)benzene,[13] easy to handle, and fairly stable under nitrogen atmosphere. Consequently, *o*-xylylene *N,N*-diethylphosphoramidite (XEPA) is a promising reagent for phosphoric ester synthesis.

**Scheme 1.** Synthesis of phosphatidyl inositols




i) TBDMS-OTf/2,6-Lutidine/0 °C (50%), ii) 2,3-Distearoyloxypropyl *o*-xylylene phosphite/PPB/$Et_3N$ /MS 4A/-15 °C (43% for **8** from **6**, 82% for **9** from 7), iii) XEPA/Tetrazole then mCPBA (90%)

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10. Typical procedure: A mixture of 2-phenylethanol (0.43 mmol), XEPA (0.53 mmol), and 1*H*-tetrazole (0.65 mmol) in $CH_2Cl_2$ (1.5 ml) was stirred at r.t. for 15 min and treated with water (few drops) for 5 min. After addition of ether, the organic layer was washed with 5% aq. $KHSO_4$, $NaHCO_3$, and brine, then dried ($MgSO_4$), and evaporated in vacuo. A benzene solution of the residue was prepared and distilled under reduced pressure to dryness to remove a trace of water azeotropically. The crude phosphite 1 was dissolved in $CH_2Cl_2$ (2.5 ml) together with cyclohexanol (0.35 mmol) and triethylamine (0.97 mmol), and MS (3A or 4A) was added. The mixture was cooled at -40 °C and treated with PPB (0.49 mmol) for 15 min and stirred at r.t. for an additional 10 min. An ordinary work-up procedure gave **4a**.
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