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AN EFFICIENT PHOSPHORYLATION METHOD USING A NEW PHOSPHITYLATING AGENT, 2-DIETHYLAMINO-1,3,2-BENZODIOXAPHOSPHEPANE

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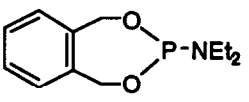
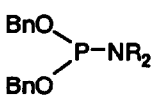
Abstract: A variety of alcohols containing polyols like inositol derivatives were efficiently phosphitylated by the reaction with 2-diethylamino-1,3,2-benzodioxaphosphepane in the presence of tetrazole and the resulting phosphites were oxidized with *m*CPBA or sulfur to yield the corresponding phosphates or thiophosphates in excellent yields.

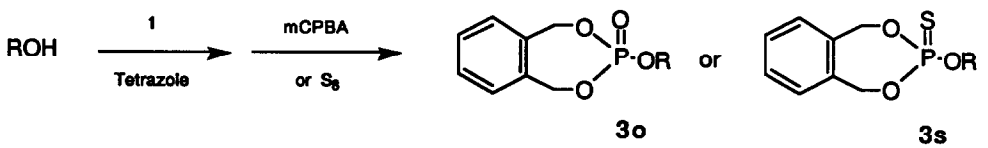
Phosphorylation of adequately protected *myo*-inositols is the crucial step for the synthesis of biologically interesting *myo*-inositol poly(phosphate) derivatives related to an intracellular signal transduction system.[1] The reaction, however, is problematic mainly because of their steric crowding and easy formation of cyclic phosphates from a vicinal diol moiety. Recent investigations on a phosphorylation of inositols have provided some effective methods which were classified into two categories; 1) the activation of alcohol function by strong bases such as butyllithium,[2] sodium hydride,[3] and potassium hydride[4] and subsequent application of tetrabenzyl pyrophosphate as a phosphorylating agent and 2) phosphitylation and oxidation.[5] In the latter methodology, N,N-dialkyl dibenzyl phosphoramidites 2 were employed preferably.[5b,c,6] We have also explored a phosphitylating agent which is analogous to 2 but easier to synthesize and purify and 2-diethylamino-1,3,2-benzodioxaphosphepane 1 has now been found to be promising. In this communication, we report a new phosphorylation method using 1.



1



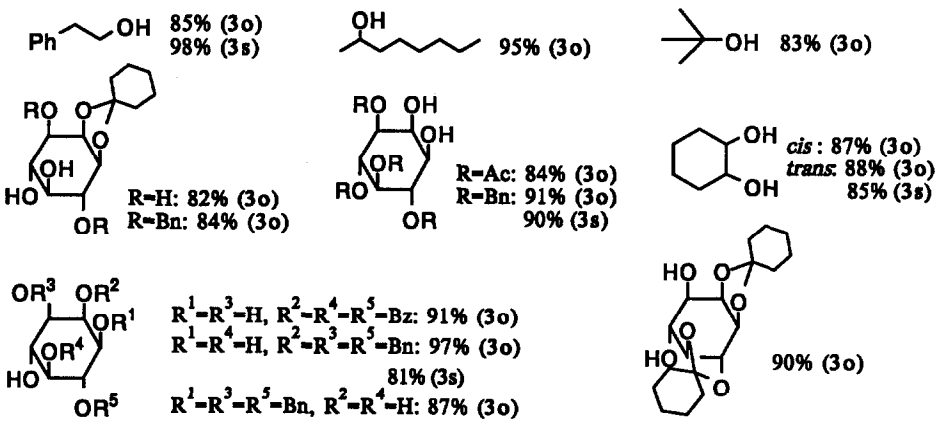
2a: R = ^{i}Pr
b: R = Et



3o 3s

Phosphepane 1 was easily prepared by the reaction of hexaethylphosphorictriamide with 1,2-dihydroxymethylbenzene as reported by Arbuzov et al.[7] and purified quite easily by distillation in vacuo. To the contrary, synthesis of dibenzyl phosphoramidites 2 requires careful reaction conditions and purification of 2a is carried out by silicagel column chromatography while that of 2b is done by distillation under high reduced pressure.

For the first time, phosphepane 1 was treated with simple alcohols such as 2-phenetyl alcohol and 2-octanol in the presence of tetrazole followed by treatment with *m*CPBA to give the corresponding triesters in excellent yields. Phosphorylation of *t*-butyl alcohol was also well accomplished by this method. Phosphitylation of polyols with 1 and subsequent oxidation proceeded also smoothly to afford the poly(phosphate) derivatives in high yields. Removal of the *o*-xylene group on phosphoric esters was accomplished easily by hydrogenolysis on Pd/C. Typically, 2,3,6-tri-O-benzyl-*myo*-inositol was treated with 1 (4.5 eq) and tetrazole (7.0 eq) in CH_2Cl_2



Note : All hydroxyl groups in each compound were phosphorylated.

at room temperature for 10 min and the excess amount of 1 was hydrolyzed by addition of a limited amount of water to the resulting solution (10 min). Oxidation with *m*CPBA (7.0 eq) was conducted at -40 °C for 10 min and then at r.t. for 10 min and simple isolation procedure using chromatography gave the trisphosphate in 97% yield which was then subjected to hydrogenolysis (10%-Pd/C in aq MeOH for 24 h) to afford *myo*-inositol 1,4,5-trisphosphate in quantitative yield.

Thiophosphates **3s** were similarly prepared in high yields by phosphitylation with 1 followed by treatment with sulfur (r.t., overnight). Thus, the protected form of *myo*-inositol 1,4,5-tris(thiophosphate) which is a biologically interesting[8] analogue of the corresponding tris(phosphate) known as a intracellular second messenger was prepared in 81% yield. Deprotection of **3s** was achieved by reduction with sodium in liq. ammonia and THF (-78 °C, ca. 30 min) or sodium naphthalide in THF (r.t., ca. 1h) to give the thiophosphates in moderate yields (not optimized).

In conclusion, the present method using a new phosphitylating agent provides an efficient tool for the synthesis of phosphoric monoesters, remarkably inositol polyphosphates.

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