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AN EFFICIENT METHOD FOR POLYPHOSPHORYLATION OF INOSITOL DERIVATIVES

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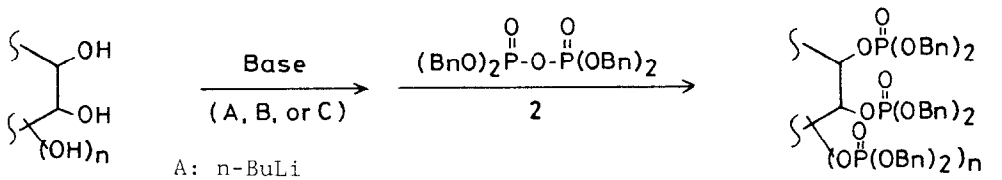
Abstract: Inositol derivatives which have vicinally situated hydroxyl groups were treated with butyl lithium or LDA and tetrabenzyl pyrophosphate to give the corresponding polyphosphates in good yields.

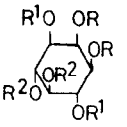
Since discovery of the role of D-myo-inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3, 1) as a cellular second messenger,[1] myo-inositol phosphates have received much attention. Synthesis of them requires an efficient phosphorylation of vicinally situated hydroxyl groups in properly protected myo-inositols. Synthesis of 1 was achieved by the use of dianilinophosphoric chloride[2] and bis(2-cyanoethyl) diethylphosphoramidite[3] as phosphorylating agents. However, there have been yet no reliable and general method for polyphosphorylation, as shown in the synthesis of Ins(2,4,5)P_3 where we employed a stepwise phosphorylation.[4] In this communication, we describe a simultaneous phosphorylation of polyhydroxyl groups in myo-inositol derivatives utilizing the corresponding alkoxides[5] and tetrabenzyl pyrophosphate (2).[5a]

According to the stepwise phosphorylation described above,[4] protection of one of vicinal hydroxyl groups as levulinic ester is necessary prior to phosphorylation. In order to avoid this first step, monolithium salt was treated with an equimolar amount of pyrophosphate 2 with expectation that monophosphate derivative once formed is inert toward 2. Contrary to our assumption, the reaction of 4,5-dihydroxy derivative 3d gave 26% yield of the corresponding bisphosphate 4d and about half of the starting diol (46%) was recovered, while the expected regioisomeric monophosphates were not isolated at all. This observation suggests employment of the dialkoxide of 3d for the synthesis of 4d. Indeed, treatment of diol 3d with 2.4 molar equivalent of butyl lithium at -78 °C followed by the reaction of the resulting dianion with 2.5 molar equivalent of 2 at 0 °C afforded 4d in 81% yield. Lithium ion was especially effective as a counter cation compared with sodium, potassium, and magnesium ions.

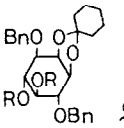
An experimental procedure is as follows: Diol 3a (0.092 mmol) in THF (1.5 ml) was treated with a 1.3M solution of butyl lithium in hexane (0.22 mmol) and diisopropylamine (0.26 mmol) at -78 °C for 10 min.[6] After direct addition of crystalline 2 (0.23 mmol), the cooling bath was replaced by an ice-salt-water bath (0 °C) and the mixture was stirred for an additional 1h. Chromatographic purification gave 90% yield of 4a.



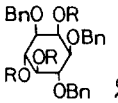
A: n-BuLi
B: n-BuLi+LDA (The latter base was derived from remained n-BuLi and diisopropylamine)
C: LDA



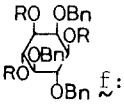
a: $R^1=R^2=Bn$ (B, 90%)
b: $R^1=Bn$, $R^2=(BnO)_2P(O)$ (C, 89%)
c: $R^1=R^2=Ac$ (C, 75%)



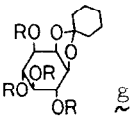
d: (A, 81%)



e: (A, 53%)



f: (A, 70%)



g: (A, 72%)

R in 3: H, R in 4: $(BnO)_2P(O)$

Bn=benzyl

Similarly, various myo-inositol derivatives were polyphosphorylated by the use of compatible molar ratio of reagents. Phosphorylation of acetyl derivative 3c gave good yield of the corresponding phosphate 4c without injuring the ester function. When the solubility of alcohols in THF was low, a small amount of DMSO was added as a co-solvent (for example; 3g → 4g).

In conclusion, the present method realizes a rapid phosphorylation of polyols. This method will become a powerful tool for the syntheses of various inositol phosphates.

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References and Notes

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5. Alkoxides were employed in the following literatures: a) P. M. Chouinard and P. A. Bartlett, J. Org. Chem., 51, 75 (1986); b) Y. Hayakawa, Y. Aso, M. Uchiyama, and R. Noyori, Tetrahedron Lett., 24, 1165 (1983) and references cited therein; Y. Watanabe and T. Mukaiyama, Chem. Lett., 1979, 389.
6. In some cases, phosphorylation with 2 was conducted immediately after addition of a base and better results were obtained.

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