

A SHORT STEP AND PRACTICAL SYNTHESIS OF *MYO*-INOSITOL 1,3,4,5-TETRAKISPHOSPHATE

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The reaction of *myo*-inositol with benzoyl chloride gave 1,3,4,5-tetra-*O*-benzoyl-*myo*-inositol as a major product which was conveniently converted to *myo*-inositol 1,3,4,5-tetrakisphosphate. The tetrabenzoate was optically resolved by means of chiral column chromatography using Chiralcel OD.

KEYWORDS *myo*-inositol 1,3,4,5-tetrakisphosphate; *myo*-inositol; benzoylation; phosphorylation; chiral column chromatography

Attempting an efficient synthesis of *myo*-inositol polyphosphates, it is important how quickly an adequately protected inositol derivative can be derived as a substrate for phosphorylation. In most cases of inositol phosphate synthesis ketals such as cyclohexylidene and isopropylidene groups were first formed from *myo*-inositol (1)¹⁾ mainly because other suitable candidates for their synthesis are difficult to prepare regioselectively from 1. Unfortunately, this route is rather indirect and tedious in some cases. In contrast, our recent work showed that 1,3-dichloro-1,1,3,3,-tetraisopropylidisiloxane reacted regioselectively with 1 to afford the 1,6:3,4-disiloxane derivative which was conveniently transformed to *myo*-inositol 1,3,4,6-tetrakisphosphate.²⁾ Such a straightforward protection of *myo*-inositol itself provides a short step synthesis of inositol phosphates. Along this line, the reaction of 1 with benzoyl chloride was examined. We report here the results and utilization of a benzoylated product for a convenient synthesis of *myo*-inositol 1,3,4,5-tetrakisphosphate (7) which apparently is an important metabolite in an intracellular signal transduction system.³⁾ An adequate supply of it has been needed for biological investigation.

Benzoylation of *myo*-inositol with 3.5 equivalent of benzoyl chloride in pyridine for 2 h afforded three main products 2. The ratio of these products varied depending on reaction temperature. Thus, the reaction at 90 °C gave 33% of 1,3,4,5-tetra-*O*-benzoyl-*myo*-inositol (2a) accompanied with 14% of 2c, a waste product. The yield of the latter increased when the reaction was conducted at 65 °C. At room temperature, the desired 2a was obtained in a lower yield at and 2c became a major product. These results may be explained in terms of the solubility of benzoylated inositols (*myo*-Inositol is sparingly soluble in pyridine at room temperature and the fewer benzoylated derivatives tend to be less soluble.).

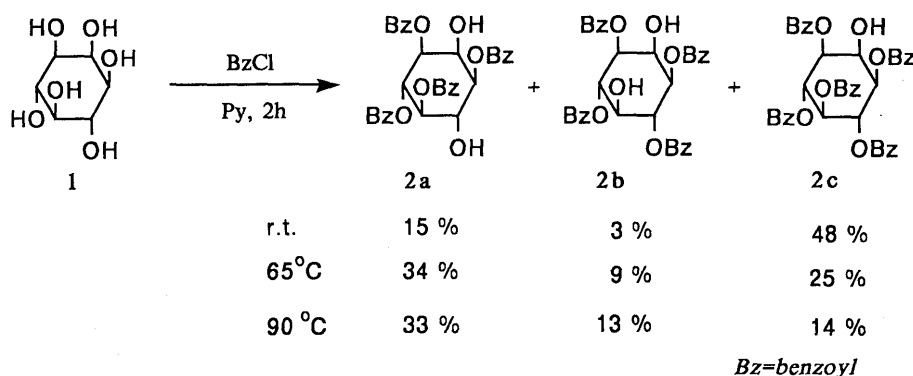


Chart 1

Since 1,3,4,5-tetrabenzoate 2a can be prepared in one step from *myo*-inositol which is readily available as a commercial chemical and its isolation in large quantities is easy, it may be quite promising as a synthetic intermediate for the synthesis of *myo*-inositol 1,3,4,5-tetrakis-phosphate (7). Thus, 2a was benzylated by the reaction with benzyl trichloroacetimidate in the presence of trifluoromethanesulfonic acid to give 2,6-dibenzyl ether 3 in 70% yield which was

then subjected to debenzoylation by the action of sodium methoxide under refluxing for 3 h to give 1,3,4,5-tetrol **4** in 72% yield. Four hydroxyl groups in **4** were then phosphorylated smoothly by the use of a new phosphitylating agent **5**.⁴⁾ Treatment of tetrol **4** with **5** (6 eq) in the presence of tetrazole (9 eq) at room temperature for 20 min formed the corresponding phosphite which after being stirred with a limited amount of water (20 eq) at the same temperature for 10 min was oxidized with *m*CPBA (9 eq) for 20 min (added at -40 °C and stirred at r.t.) to give the fully protected phosphate **6** in 90% yield. Finally, **6** was deprotected at once by hydrogenolysis (H₂, 10% Pd-C, r.t., 17 h) and *myo*-inositol 1,3,4,5-tetrakisphosphate **7** was isolated quantitatively as ammonium salt.

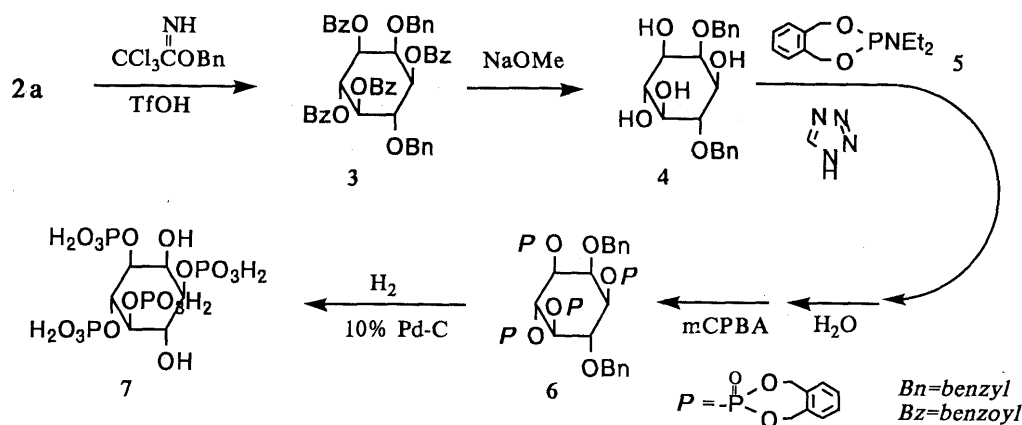


Chart 2

Optical resolution of 1,3,4,5-tetrabenzoyl was accomplished by means of a chiral column chromatography using Chiralcel OD™ (Daisel Chemical Industries, Ltd.).⁵⁾ Thus, a short-step synthesis of D- and L-**7** has been formally accomplished.

Among reported methods for synthesizing **7**,⁶⁾ some groups^{6b,e,f)} suggested the use of an orthoformate derivative of **1**. The present synthesis route provides an alternative and practical method for synthesizing optically active *myo*-inositol 1,3,4,5-tetrakisphosphate.

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