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Regioselective O-acylation of *myo*-inositol 1,3,5-orthoesters: dependence of regioselectivity on the stoichiometry of the base

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ABSTRACT

A metal mediated unusual 1–3 acyl migration from C4–O to C2–OH of *myo*-inositol 1,3,5-orthoformate was observed during the alkylation of racemic 4-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate. This has been exploited for the selective esterification of either the C4(6)–OH or the C2–OH of *myo*-inositol by varying the amount of the base used. While the use of 1 equiv of the base (sodium hydride or potassium *tert*-butoxide) for the acylation of *myo*-inositol orthoesters gives the corresponding *C*4-ester exclusively, the use of two or more equivalents of base for the same reaction gives the *C*2-ester exclusively. The relatively higher stability of the alkoxide of racemic 2-*O*-acyl-*myo*-inositol 1,3,5-orthoester as compared to the alkoxide of 4-*O*-acyl-*myo*-inositol 1,3,5-orthoester is suggested to be responsible for the observed isomerization.

1. Introduction

The chemistry and biology of phosphorylated inositols have become intense areas of research during the last two decades due to their involvement in various cellular signaling processes.[1] There are at least 26 different *myo*-inositol phosphates, 8 phosphoinositol lipids and several glycoconjugates known to occur in nature. Apart from well established roles of a few phosphoinositols in cellular signaling and protein anchoring, the biological functions of many of these phosphoinositols and glycoconjugates are far from well understood. Considering the facts that these derivatives occur in nature in very small quantities and their isolation is often tedious due to their transient nature (short half-life) and difficulty in purification, it is not surprising that these molecules have attracted the interest of synthetic chemists.[1a,2] Although methodologies for phosphoinositol synthesis starting from different starting materials have been reported,[2a,c,h,3] *myo*-inositol (**1**, Fig. 1) continues to be a frequently used starting material for the synthesis of phosphoinositols.

myo-Inositol being a cyclohexane hexol having six secondary hydroxyl groups with more or less similar chemical environment, the selective functionalization of these hydroxyl groups[4] is one of the main challenges in synthetic inositol chemistry. Often, partially protected ketals or orthoesters of inositol are used for further selective functionalization during phosphoinositol synthesis. Such a modification usually perturbs the chemical environment of different hydroxyl groups unevenly making them prone to better discrimination during synthetic manipulations. While the ketalization of *myo*-inositol gives a mixture of ketals (thus reducing the yield of the required ketal, often less than 35%), the orthoesterification provides a single product, *myo*-inositol 1,3,5-orthoester,[5] in high yield (>90%). The *myo*-inositol orthoesters (**2**–**5**, Fig. 1) have two axial hydroxyl groups and one equatorial hydroxyl group (with respect to the inositol ring) and this facilitates better discrimination among the hydroxyl groups of orthoesters. Also, the known strategies for the selective partial cleavage[4c] of the orthoester cage with reducing agents in protected *myo*-inositol orthoesters (to regenerate the C1(3)–OH or the C5–OH) make *myo*-inositol 1,3,5-orthoesters versatile intermediates for synthetic purposes. Consequently, orthoesters have become the preferred starting materials for the synthesis of phosphoinositols and their analogs in recent years.[5b,6] Several methodologies for regioselective protection of *myo*-inositol orthoester hydroxyl groups have been reported.[4c] Among various protecting groups, ester protecting groups have the advantage of mild reaction conditions for their introduction and removal, possibilities of resolution using enzymes or via diastereomeric derivatives.[5d,6] Due to these advantages, acylation of *myo*-inositol derivatives forms an important synthetic strategy. However, acyl migrations among the hydroxyl groups of *myo*-inositol are sometimes annoying during the synthesis of

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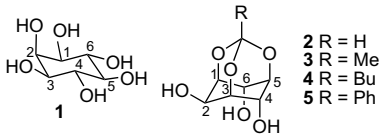
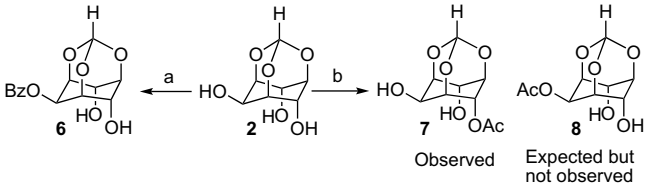


Figure 1. *myo*-Inositol and its known orthoesters.

phosphoinositols or their derivatives. Nevertheless, in a few instances, acyl migrations have been exploited for strategic and efficient synthesis of *myo*-inositol phosphates.[7]

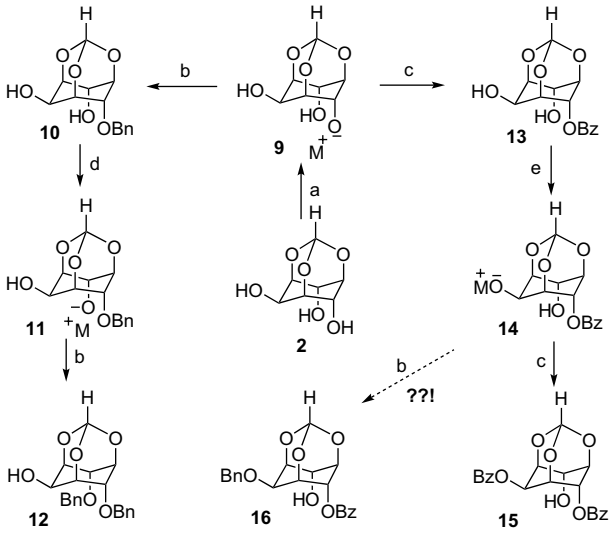
Considerable efforts have been made to understand and optimize selective acylation of the three hydroxyl groups of *myo*-inositol orthoesters.[5b,6g,8] Most of these reports deal with maximizing the yield of a particular *O*-acylated (e.g., *O*-benzoyl) derivative of a *myo*-inositol orthoester (e.g., orthoformate **2**) and hence there is no general method that could be used for the selective acylation of *C*2- or *C*4(6)-hydroxyl group in *myo*-inositol orthoesters. For instance, when we applied the reaction conditions reported for the 2-O-benzoylation[8d] of the orthoformate **2** for the preparation of the corresponding acetate, we obtained the *C*4-acetate **7** (Scheme 1). We have developed[9] simple and general methodologies for selective acylation either at the C2–OH or the C4–OH by varying the amount of the base used and the full details of this work are presented here.



Scheme 1. Acylation of **2** showing lack of generality. (a) Pyridine, benzoyl chloride;[8d] (b) pyridine, acetyl chloride.

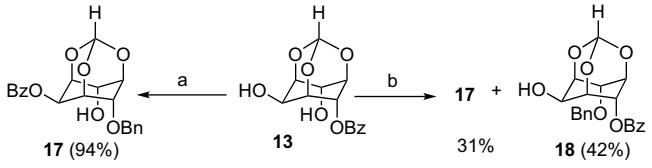
2. Results and discussion

In our efforts toward the development of simpler methods for the synthesis of inositol derivatives, we required to synthesize 2-*O*-benzyl-*myo*-inositol,[10] the precursor for *myo*-inositol 1,3,4,5,6-pentakisphosphate. Benzylation of triol **2** with 1 equiv of sodium hydride and benzyl bromide is known to give 4-*O*-benzyl ether **10** (Scheme 2) while dibenzylation gives 4,6-dibenzyl ether **12** as the major product.[6b] These results suggest that first deprotonation in **2** and **10** occurs at the *C*4- and *C*6-hydroxyl groups, respectively, on their reaction with sodium hydride. This has been attributed to the increased stability of the 4(6)-alkoxide due to chelation of the alkali metal ion.[6b] However, dibenzoylation of orthoformate **2** with potassium *tert*-butoxide and benzoyl chloride is reported to give the unsymmetrical dibenzoate **15** (in contrast to the corresponding benzylation reaction) although mono-benzoylation[11] occurs at the C4–OH (similar to mono-benzylation of **2**). A mechanism involving initial benzoylation at the C4–OH followed by the second benzoylation at the C2–OH has been proposed (Scheme 2).[11] These results imply that the treatment of the 4-benzyl ether **10** with a strong base generates *C*6-alkoxide **11** predominantly while the treatment of 4-benzoate **13** with a strong base generates *C*2-alkoxide **14** predominantly. If this is indeed the case, alkylation (benzylation) of **13** should in principle, give *C*2-*O*-alkylated product **16**. Prompted by this logic, we attempted benzylation of racemic 4-benzoate **13** in the presence of potassium *tert*-butoxide.



Scheme 2. Alkoxide mediated benzylation and benzoylation of **2**. (a) NaH or KO^{t}Bu; (b) benzyl bromide; (c) benzoyl chloride; (d) NaH (Ref. 6b); (e) KO^{t}Bu.

Benzoate **13** was treated with potassium *tert*-butoxide (or sodium hydride) for 5 min, and then allowed to react with benzyl bromide when racemic 2-*O*-benzoyl-4-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate[12] (**17**) was obtained as the only product (Scheme 3). The formation of **17** suggested migration of the benzoyl group from the C4–O to the C2–OH during benzylation. When the benzylation of **13** was carried out by the addition of sodium hydride to a previously mixed solution of benzoate **13** and benzyl bromide in DMF (the alkoxide was made to react as soon as it was formed), a mixture of racemic 4-*O*-benzoyl-6-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (**18**) and **17** were formed along with some amount of racemic **10**.[6b] Compound **18** was unambiguously characterized by its aminolysis to the known[6b] benzyl ether. No trace of the expected racemic **16** (Scheme 2) could be found in any of these experiments. These results suggested that after the generation of the alkoxide (in **13**) benzoyl migration competes with benzylation. It is interesting to note that the alkylation takes place only at the C4–OH no matter whether the acyl group has migrated or not. When **18** was treated with sodium hydride in DMF migration of the benzoyl group was not observed.



Scheme 3. Benzylation of **13**. (a) DMF, NaH, 5 min then benzyl bromide; (b) DMF, benzyl bromide, then NaH.

From these results, it was clear that the benzoyl migration occurred prior to O-alkylation, resulting in the formation of monoalkoxide **20** (Scheme 4), which underwent benzylation to give **17**. Treatment of 4-benzoate **13** with 1 equiv of sodium hydride in DMF gave 2-benzoate **6** as anticipated. Similar results were obtained when sodium hydride was replaced with potassium *tert*-butoxide for all the reactions presented above. Increasing the amount of sodium hydride or potassium *tert*-butoxide did not make any difference in the observed acyl migration. In some of the initial experiments, since the recovery of **6** was not good, it was isolated as its known[13] diacetate.

To examine the generality of this unusual 1,3-acyl migration, different racemic 4-*O*-acyl-*myo*-inositol orthoesters were required. But, there is no general method in the literature for the preparation of racemic 4-*O*-acyl-*myo*-inositol orthoesters. Based on the