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Regioselective *O*-acylation of *myo*-inositol 1,3,5-orthoesters: the role of acyl migration

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Abstract

An efficient and general method for the preparation of 2-*O*-acylated derivatives of *myo*-inositol 1,3,5-orthoesters via isomerization of the corresponding 4(6)-*O*-acylated derivatives has been described. The isomerization involves a novel 1(axial)→3(equatorial) intramolecular acyl migration assisted by a metal ion. © 2000 Elsevier Science Ltd. All rights reserved.

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As the flow of information pertaining to the biological role of phosphorylated *myo*-inositol derivatives increases[1] so does the need for better synthetic methodologies for the selective functionalization of the six secondary hydroxyl groups present in *myo*-inositol, to enable efficient synthesis of its derivatives and their analogs. Recently, orthoesters of *myo*-inositol have emerged as useful intermediates[2] to accomplish the synthesis of *myo*-inositol derivatives with biological significance. Selective alkylation,[3] phosphorylation[3] and glycosidation[4] of one of the axial hydroxyl groups, as well as disilylation[5] and dibenzoylation[6] (to obtain unsymmetrical derivatives) has been achieved. A survey of the literature shows the observed selectivity during monoacylation[7] of **1** (Scheme 1) to be dependent on the nature of the acylating agent as well as on the reaction conditions used. The observed selectivities have been rationalized based either on the differences in the relative nucleophilicities between the axial and equatorial hydroxyl groups of **1** or on the steric bulk of the acylating agent. Flores-Mosquera et al.[7a] studied the benzoylation of **1** systematically and arrived at experimental conditions to maximize the yield of the 4-*O* or the 2-*O* benzoate (**3** or **7**). However, the yields reported were based on the gas chromatographic analysis of the crude reaction mixtures and not isolated yields of the individual isomers. We herein present results on a novel intramolecular acyl migration in 4(6)-*O*-acyl derivatives of **1** and **2** which provide convenient access to their 2-*O*-acyl derivatives (Scheme 1).

As part of an ongoing program on the chemistry of inositols[8] we required variously *O*-substituted *myo*-inositol derivatives. During this work, we found that benzoylation of the orthoformate **1** with 1

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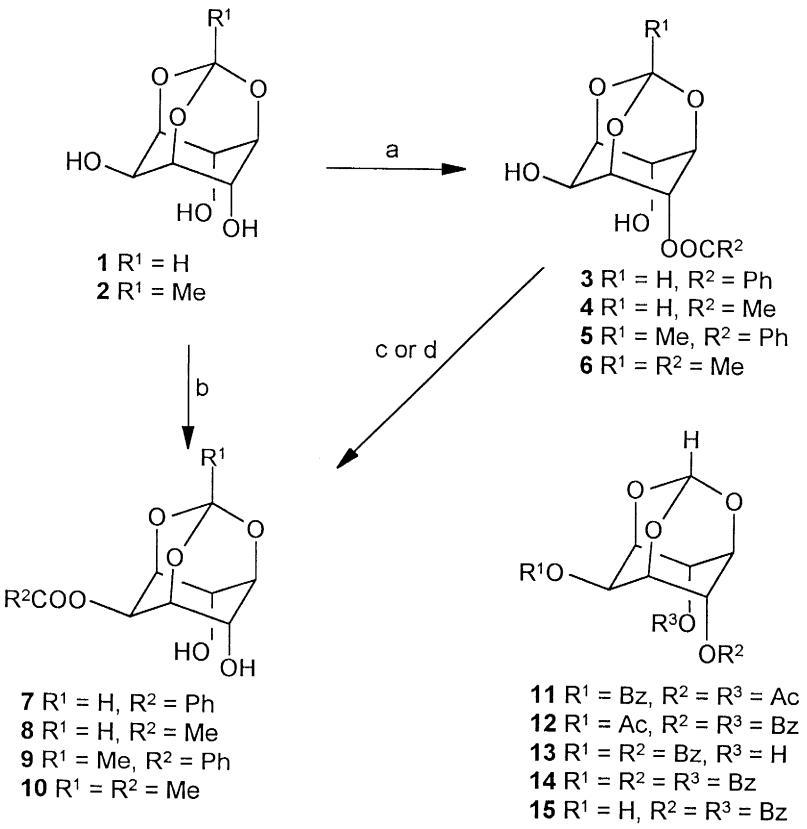


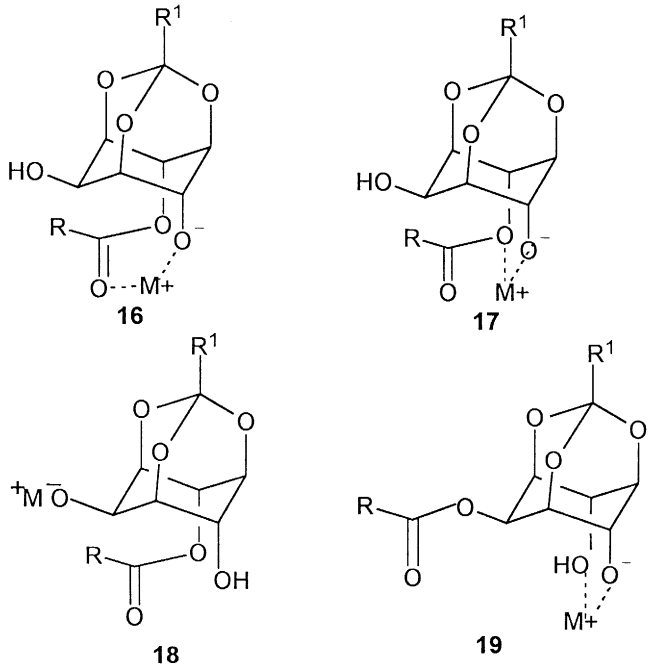
Scheme 1. Reagents and conditions: (a) DMF, NaH (1 equiv.), R^2COCl (R^2=Me, Ph), 5 min, 86–89%; (b) DMF, NaH (2 equiv.), R^2COCl (R^2=Me, Ph), 5 min, 85–97%; (c) DMF, NaH (1 equiv.), 5 min; (d) DMF, *t*-BuOK, 5 min, 90–96%

equiv. each of sodium hydride and benzoyl chloride in DMF gave the axial 4-*O*-benzoate **3**, while the use of 2 equiv. of sodium hydride and 1 equiv. of benzoyl chloride gave the equatorial 2-*O*-benzoate **7**. Hence, we suspected that the initially formed **3** might be isomerizing to **7** in the presence of the excess of sodium hydride. Treatment of the axial benzoate **3** in DMF with sodium hydride (1 equiv.) resulted in its complete isomerization to **7**. Similarly, other 4-*O*-acyl derivatives **4** and **5** could be isomerized to the corresponding 2-*O*-acyl derivatives **8** and **9** using either sodium hydride or potassium *tert*-butoxide (in some experiments **7** and **8** were isolated as their diacetate **11** and dibenzoate **12** derivatives, respectively). The 4-*O*-substituted *myo*-inositol 1,3,5-orthoesters can be easily distinguished from the corresponding 2-*O*-acylated derivatives, based on their NMR spectra since the former are asymmetric (show six separate signals for inositol ring hydrogens and carbons) and the latter are symmetric (show four signals for inositol ring hydrogens and carbons).

Since the isomerization encountered involved 1→3 migration of an acyl group from an axial position to an equatorial position which is not frequently observed, we set out to examine if the migration is inter- or intramolecular. Treatment of a mixture of 4-*O*-acetyl orthoformate **4** (0.5 mmol) and 4-*O*-benzoyl orthoacetate **5** (0.5 mmol) with sodium hydride (1 mmol) in DMF afforded the corresponding 2-*O*-acyl derivatives **8** and **9** in 91 and 96% yields, respectively. We did not observe the formation of any product (**7** or **10**) that could arise from intermolecular acyl transfer between **4** and **5**. This result strongly suggests that the observed acyl migrations are intramolecular, although a direct acyl transfer is clearly sterically impossible via the formation of a tetrahedral intermediate.

Treatment of the benzoate **3** with di-isopropylethylamine in DMF (24 h) or with sodium hydride in THF (5 min) did not result in acyl migration and **3** could be recovered quantitatively. The use of longer reaction times (24 h) for the reaction in THF gave a mixture of products (**1**, **7**, **13**–**15**) resulting from transesterification of the axial benzoate **3** as well as the dibenzoate **13** initially formed. A similar result (formation of **1**, **7**, **13**–**15**) was obtained on treating **3** with anhydrous potassium carbonate in DMF. We had earlier shown that **13** readily undergoes transesterification in the solid[8b] as well as solution[9] states to yield the diol **7** and the tribenzoate **14**.

These results indicate that formation of an anion (Scheme 2) and perhaps its chelation with a metal ion is essential for clean isomerization. A structure of the chelate that could be involved during acyl migration is shown in Scheme 2. The driving force for this isomerization could be the formation of the chelate **19** (of a 1,3-diaxial diol) which is expected to be more stable than the starting alkoxides (**16**, **17** or **18**). Involvement of a chelate during the selective *O*-alkylation (at the 4-*O*-position) of **1** has earlier been proposed.[3]



Scheme 2.

It is of interest to examine the regioselectivities reported for the *O*-acylation of the orthoformate **1**, in light of the results presented here. Benzoylation of the orthoformate **1** in the presence of potassium *tert*-butoxide is reported[7b] to give the axial benzoate **3** as well as the unsymmetrical dibenzoate **13** via successive acylations at the 4-*O* and 2-*O* positions. However, our results suggest that formation of the dibenzoate **13** could be a result of isomerization of the initially formed 4-*O*-benzoate **3** to the corresponding 2-*O*-benzoate **7** (in the presence of potassium *tert*-butoxide), and its further benzoylation at the 4-*O*-position.

In conclusion, we have described a novel and unusual 1(axial)→3(equatorial) acyl migration in orthoesters of *myo*-inositol; further work is necessary to understand the mechanism of this acyl migration. The isomerization described here provides convenient and efficient access to 2-*O*- and 4-*O*-acylated

derivatives of *myo*-inositol orthoesters† just by varying the amount of sodium hydride used for the reaction. A novelty of the method described here is that, 2-*O*-acyl derivatives of *myo*-inositol orthoesters can be obtained even when the acylating agent used (for e.g. acetyl imidazole) brings about exclusive acylation at the axial 4(6)-*O*-position in **1** or **2**.

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† All the new compounds were characterized by spectroscopy (NMR, IR) and elemental analysis.