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Sulfonate protecting groups. Regioselective *O*-sulfonylation of *myo*-inositol orthoesters

Kana M. Sureshan and Mysore S. Shashidhar*

Division of Organic Synthesis, National Chemical Laboratory, Pune 411 008, India

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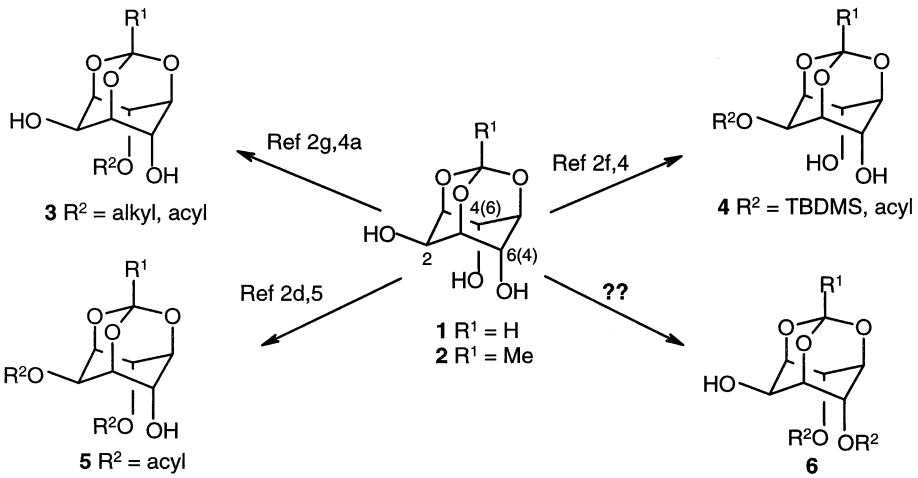
Abstract—Sulfonylation of *myo*-inositol 1,3,5-orthoesters with alkyl or aryl sulfonyl chlorides in the presence of sodium hydride gives the corresponding 4,6-di-*O*-sulfonates in good yields. These sulfonates can be cleaved with magnesium in methanol to generate the free *myo*-inositol derivative. This methodology was used for the preparation of racemic 2,4-di-*O*-benzyl-*myo*-inositol and 2-*O*-benzyl-*myo*-inositol, which are precursors for some phosphoinositols.

The continued interest in the biological role of phosphoinositols[1] has created a need for efficient methods for the synthesis of natural as well as synthetic derivatives and analogs of inositols. Orthoesters of *myo*-inositol (**1** and **2**, Scheme 1) are important intermediates for the synthesis of phosphoinositols[2] and other molecules with interesting properties.[3] In the past decade, there have been efforts to functionalize selectively the three hydroxyl groups of orthoesters **1** and **2**. Methods for the selective functionalization of (a) only the C-4 (or C-6) hydroxyl group;[2g,4a] (b) only the C-2 hydroxyl group;[2f,4] (c) the C-2 and C-4 (or C-6) hydroxyl groups[2d,5] simultaneously, in **1** and **2** were developed. However, selective functionalization of both the C-4 and C-6 hydroxyl groups (**6**) in orthoesters of *myo*-inositol, leaving the C-2 hydroxyl group undisturbed has eluded chemists. Billington and co-workers[2g] benzylated **1** and obtained a mixture of diethers (the ratio of 2,4:4,6 diethers was 1:5, isolated yield of the 4,6-diether was 27%) and the 2,4,6-triether. Most other reports[2e,f,3a,4b] on the preparation of 4,6-di-*O*-substituted derivatives of **1** resorted to protection of the C-2 hydroxyl group prior to functionalization of the C-4 and C-6 hydroxyl groups. We now report a method to



Scheme 1.

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* Corresponding author.

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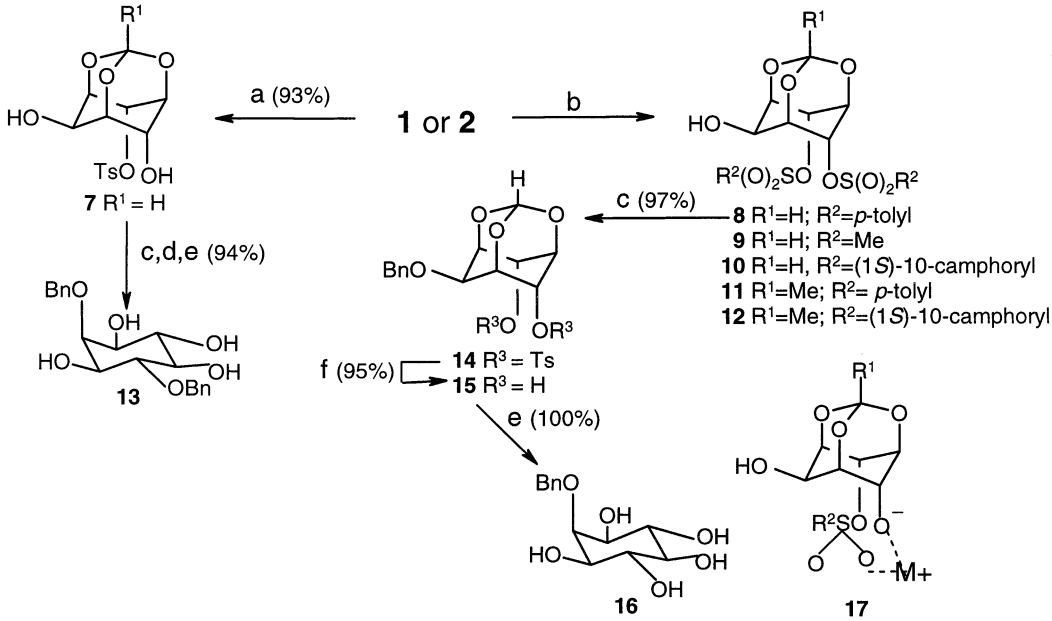


Scheme 2. (a) DMF, NaH (1 equiv.), *p*-TsCl (1 equiv.); (b) DMF, NaH (5 equiv.), R^2SO_2Cl (2.1 equiv.); (c) DMF, NaH, BnBr; (d) Mg/MeOH, 6 h; (e) TFA:water (4:1); (f) Mg/MeOH, 48 h.

achieve the selective sulfonylation of both the C-4 and C-6 hydroxyl groups in **1** and **2** leaving the C-2 hydroxyl group undisturbed.

Reaction of the orthoformate **1** with 1 equiv. of *p*-toluenesulfonyl chloride in the presence of 1 equiv. of sodium hydride gave the corresponding racemic 4-*O*-tosylate **7** (Scheme 2) as expected.[2g] The reaction of orthoesters **1** and **2** with 2 equiv. of alkyl or arylsulfonyl chloride in the presence of an excess of sodium hydride (or potassium *t*-butoxide) gave the corresponding 4,6-di-*O*-sulfonates **8**–**12** in good yields (Table 1).

To demonstrate the utility of this method, we prepared racemic 2,4-di-*O*-benzyl-*myo*-inositol (**13**) and 2-*O*-benzyl-*myo*-inositol (**16**) from **7** and **8**, respectively. The sulfonates could be removed subsequent to benzylation by treatment with Mg/MeOH.[6] The ether **13** (83% from **1**) and **16** (54% from *myo*-inositol), obtained[7] in the present work, are intermediates for the synthesis of D- and L-*myo*-inositol-1,3,4,5-tetraphosphates[8] and *myo*-inositol-1,3,4,5,6-pentaphosphate,[9] respectively. Furthermore, 2-*O*-alkylated inositol derivatives are important intermediates for the preparation of inhibitors of phosphatidylinositol-specific phospholipase C[10] and compounds that exhibit liquid crystalline properties.[11]

A plausible reason for the high regioselectivity observed for the sulfonylation reaction described above could be the involvement of chelates (**17**, Scheme 2), which stabilize the alkoxide at the axial position. This is suggested by the fact that use of THF as a solvent for the sulfonylation reaction or the presence of a crown ether in the reaction mixture while using DMF as the solvent led to loss of selectivity (Scheme 3). The requirement for the presence of the metal ion for the exclusive functionalization of the C-4 and C-6 hydroxyl groups is also revealed by the sulfonylation of the orthoformate **1** with tosyl chloride in the presence of pyridine, which leads to the formation of the unsymmetric ditosylate **19**. Exclusive ether formation at the C-4 (or C-6) hydroxyl groups in **1** on its reaction with alkyl halides in the presence of sodium hydride has been attributed to the stability of the sodium ion–orthofomate **1** chelate.[2g] We had earlier observed migration of *O*-acyl groups from the C-4 (or C-6) position to the C-2 position in **1** and **2** as a result of the differences in the stability of metal ion–inositol derived chelates.[4a]

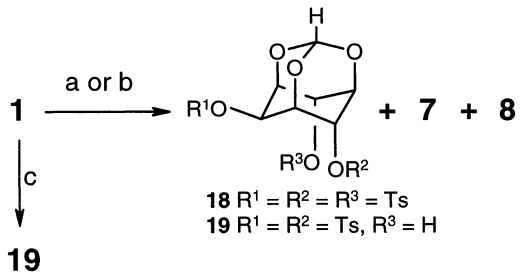
In conclusion, we have reported a simple procedure[12] for the simultaneous protection of both the C-4 and C-6 hydroxyl groups in *myo*-inositol orthoesters and demonstrated its utility by preparation of important *O*-protected *myo*-inositol derivatives. We are presently exploring the synthesis of enantiopure inositol derivatives using the methods described here, which will be reported in due course.

Table 1. Sulfonylation of *myo*-inositol orthoesters[a]

Entry	Substrate	R^2SO_2Cl	Product	Yield (%)[b]
1	**1**	*p*-Tolyl	**8**	70
2	**1**	Methyl	**9**	84
3	**1**	1(*S*)-10-Camphoryl	**10**	70
4	**2**	*p*-Tolyl	**11**	78
5	**2**	1(*S*)-10-Camphoryl	**12**	69

[a] All the new compounds reported in this communication were characterized by IR, ^1H and ^{13}C NMR spectroscopy as well as C, H analysis.

[b] Average isolated yields from several trials; range of the yields obtained for all the experiments was 65–85%.



Scheme 3. (a) THF, NaH (5 equiv.), *p*-TsCl (2.1 equiv.); (b) DMF, 18-C-6, NaH (5 equiv.), *p*-TsCl (2.1 equiv.); (c) pyridine, *p*-TsCl, 100°C, 24 h.

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7. Compound **13**: mp 120°C, lit.[2g] mp 119–120.5°C, yield (from **1**) reported in Refs. 2g and 8 are 36 and 63%, respectively. Compound **16**: mp 251°C, lit.[9] mp 248–250°C, the yield (from *myo*-inositol) reported in Ref. 9 is 10%.
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12. Procedure for sulfonylation: Sodium hydride (5 mmol, previously washed with dry petroleum ether) was suspended in dry DMF (5 mL) and stirred with the orthoester (**1** or **2**, 1 mmol) at ambient temperature under a nitrogen atmosphere (1–2 min). A solution of the sulfonyl chloride (2.1 mmol) in dry DMF (4 mL) was added in one portion with stirring. After 5 min the reaction mixture was diluted with chloroform and washed with water. The combined aqueous layers were acidified (dil. HCl) and again extracted with chloroform. The combined chloroform extracts were washed successively with cold dil. HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude product obtained was purified by crystallization or column chromatography over silica gel. The regioselectivity observed in this reaction was sensitive to the presence of moisture in the reaction mixture. Hence, all the reactions were carried out using freshly dried DMF, clean sodium hydride, and orthoester (**1** or **2**) either crystallized from dry methanol or filtered through a column of silica gel using ethyl acetate as the eluant.