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Regiocontrolled Acylation of *myo*-Inositol Orthoformate

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Abstract: Reaction conditions are described that allow the monobenzoylation of *myo*-inositol 1,3,5-orthoformate at the equatorial or the axial hydroxyls in a highly regioselective way.

The receptor-controlled hydrolysis of inositol phospholipids by different phospholipases is now firmly established as a fundamental mechanism of cellular signal transduction.[1] In recent years, a new signalling pathway has been proposed in the case of insulin and a variety of neurotrophic and growth factors that implicates the generation of inositol phosphoglycans from as yet uncharacterized glycosyl phosphatidylinositols.[2] In connection with an ongoing program directed to the synthesis of inositol phosphoglycans with insulin mimetic activity,[3] we needed to prepare a series of 2-*O*-acylated derivatives of *myo*-inositol. For that purpose we chose the symmetric and readily available *myo*-inositol orthoformate (**1**)[4] as starting material. In this derivative, hydroxyl groups at positions 1, 3, and 5 are simultaneously protected and the normal axial/equatorial relationship of the remaining free hydroxyls is reversed with respect to that in free *myo*-inositol. Compound **1** can be regioselectively silylated[4,5] or benzoylated[6] at the equatorial OH-2, using TBSCl in DMF in the presence of imidazole or PhCOCl in pyridine, respectively. Alternatively, the spatial relative arrangement of the axial and enantiotopic OH-4 and OH-6 allows the highly selective alkylation or phosphorylation at these positions.[7,8] A regio- and stereoselective glycosidation of **1** at the axial hydroxyls using diazirine derived glycosylidene carbenes has also been reported.[9]

In our initial esterification experiments, we used a carboxylic acid in the presence of DCC/DMAP as coupling reagent or, alternatively, the mixed anhydride with 2,4,6-trichlorobenzoic acid in the presence of Et_3N and catalytic DMAP in DMF.[10] However, the unwanted axial monoester was obtained as the major product in both cases in contrast to the previously reported acylation with an acid chloride in pyridine.[6] This unexpected result prompted us to undertake a more systematic study of the monoacylation of **1** under different conditions. Benzoylation was chosen as a test reaction for this goal. The influence of the acylating agent (PhCOCl or $(PhCO)_2O$), solvent,[11] and base was studied. All reactions were performed by treating a solution of **1** (2 equiv)[12] with the acylating reagent (1 equiv) in the presence of an excess of base at 0 °C, and stirring for 8 h at room temperature. The ratio of product monobenzoates **2**[6,13] and (±)-**3**,[13] and dibenzoate (±)-**4**[8a,13,14] obtained in

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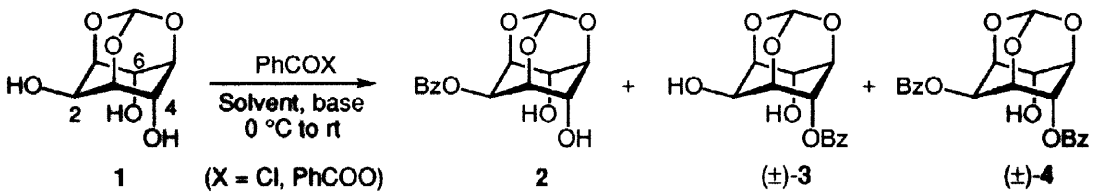


Table 1

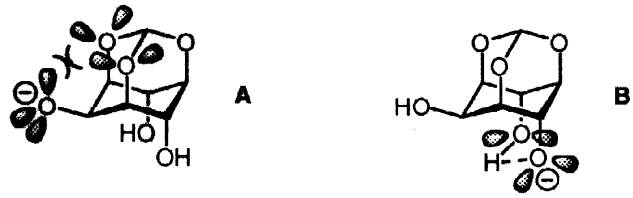
Product ratios (GC analysis) for the acylation of **1** under different conditions (see text for details).

	PhCOCl	$(PhCO)_2O$
Solvent/base	**2 : 3 : 4**	**2 : 3 : 4**
Pyridine	23 : 1 : 1.5	1 : 3 : 0.2
Pyridine/cat. DMAP	19 : 1 : 0.6	1 : 8.7 : 1.2
2,4,6-Collidine	1.7 : 1 : 0.2	1 : 2.3 : 0.2
1,4-Dioxane/Et_3N	1 : 8 : 2	1 : 27 : 0.8
DMF/Et_3N	1 : 45 : 0.4	1 : 70 : 0.9

each case was determined by GC analysis of the crude reaction mixture.[15] The results are summarized in Table 1. While $(PhCO)_2O$ gave in all conditions tested the axial benzoate (±)-**3** as major product,[16] the regioselectivity observed for PhCOCl was strongly dependent on the base used. Thus, selective acylation of the equatorial hydroxyl of **1** with PhCOCl to give **2** was observed in pyridine, as previously reported,[6] while Et_3N greatly favored formation of the axial benzoate.[17] This preference for the axial ester was higher in DMF than in the less polar solvent 1,4-dioxane. In 2,4,6-collidine, the selectivity of PhCOCl was greatly reduced, **2** being only slightly predominant. The beneficial effect of a tertiary amine base on the axial selectivity of the acylation reaction was also observed for $(PhCO)_2O$ that provided even higher axial selectivities than PhCOCl under identical reaction conditions. Again, this effect was more pronounced in DMF than in 1,4-dioxane.

The influence of the acylating reagent, base and solvent on the regioselectivity of the benzoylation reaction of **1** can be rationalized as follows.[18] In pyridine, PhCOCl forms an intermediate acylpyridinium ion that is both highly reactive and sterically hindered. This suggests that the corresponding acylation reaction proceeds through a transition state where the reacting hydroxyl group is mostly un-ionized, the selectivity being thus governed mainly by steric factors.[19,20] On the contrary, with the less reactive $(PhCO)_2O$ the acylation takes place typically via previous activation of the hydroxyl in the form of an intermediate alkoxide anion generated by the base. Of the two possible monoalkoxides that can be produced from **1** (Figure 1), **A** is destabilized by repulsive lone pair-lone pair interactions (see Figure 1), while in **B** these lone-pair repulsions are greatly reduced by a strong intramolecular hydrogen bond.[21,22] A polar solvent facilitates ionization and, therefore, enhances the observed effect.

Figure 1



In conclusion, appropriate conditions have been found that allow the monoacylation of **1** at either the equatorial or the axial hydroxyls with very high regioselectivity in both cases (see shadowed cells of Table 1).[23] The selective axial acylation conditions are particularly interesting and potentially useful for the desymmetrization of **1** using a chiral acylating reagent.[24]

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References and notes

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8. The involvement of an alkali metal chelate in the intermediate anion has been proposed to explain this axial selectivity.[7] The transannular assistance of the axial hydroxyl has been also recently claimed to explain the selective alkylation and solvolysis of the 2,4-di-*O*-benzoate (**4**) of compound **1** with BnBr/Ag_2O: (a) Banerjee, T.; Shashidhar, M. S. *Tetrahedron Lett.* **1994**, *35*, 8053-8056. (b) Das, T.; Shashidhar, M. S. *Carbohydrate Res.* **1997**, *297*, 243-249.
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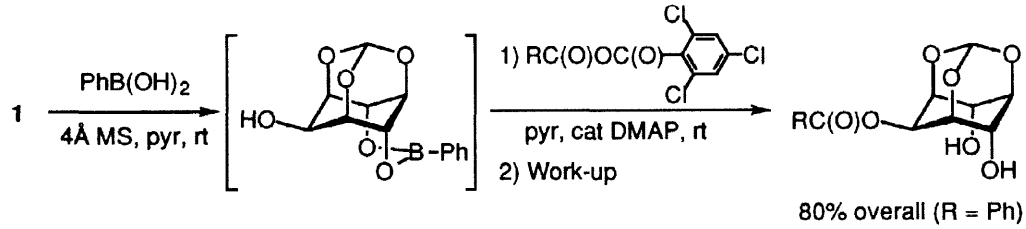
11. The intrinsic polarity of triol **1** greatly narrowed the range of solvents that could be used in this study.
12. **A two-fold excess of 1 was used to minimize formation of diester (±)-4.**
13. **Compound 2:** ^{1}**H NMR (acetone-d$_6$)** δ 8.13-8.02 (m, 2H), 7.70-7.57 (m, 3H), **5.61 (ddd, *J* = 1.8, 1.8, 1.3 Hz, 1H), 5.52 (d, *J* = 1.3 Hz, 1H),** 5.36 (br. s, 2H), 4.54 (m, 2H), 4.39 (m, **2H), 4.29 (m, 2H).** **Compound (±)-3:** ^{1}**H NMR (acetone-d$_6$)** δ 8.08-8.01 (m, 2H), 7.68-7.45 (m, 3H), **5.62 (ddd, *J* = 3.7, 3.7, 1.8 Hz, 1H), 4.80 (br. d, *J* = 4.4 Hz, 1H),** 4.58 (m, 1H), 4.47 (m, 1H), 4.39 **(br. s, 1H), 4.29** (m, 2H), 4.14 (m, 1H). Compound (±)-**4:** ^{1}H NMR (acetone-d$_6$) δ 8.14-8.09 (m, 2H), 7.70-7.34 (m, 3H), 5.77 (ddd, *J* = 1.7, 1.7, 1.3 Hz, 1H), 5.71 (m, 1H), 5.66 (d, *J* = 1.3 Hz, 1H), 5.10 (br. d, *J* = 4.2 Hz, 1H), 4.69 (m, 1H), 4.62 (m, 2H), 4.46 (m, 1H).
14. No diaxial dibenzoate was formed in a detectable amount under any of the conditions tested.
15. An aliquot of the crude reaction mixture was derivatized by treatment with *N,O*-Bis(trimethylsilyl)-trifluoroacetamide/TMSCl in pyridine at 60 °C for 2h.
16. It should be noted that formation of **3** is favored by entropic factors. Thus, if the axial and equatorial hydroxyls of **1** had comparable reactivities, a 2:1 axial/equatorial ratio of monobenzoates should be expected.
17. For a previous report on the effect of the steric hindrance of the base on the selectivity of acylation reactions see: Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.
18. For a general discussion on the relative reactivity of hydroxyl groups towards acid chlorides and acid anhydrides and the factors influencing the regioselectivity, see: (a) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11. See also: (b) Box, V. G. S. *Heterocycles* **1983**, *20*, 1641.
19. OH-2, being equatorial with respect to the cyclohexane ring and axial with respect to a 1,3-dioxane ring, is the less sterically hindered hydroxyl.
20. Formation of appreciable amounts of *N*-benzoylcollidinium chloride is expected to be hampered for steric reasons.[17]
21. The presence of a strong intramolecular hydrogen bond between the axial hydroxyls of **1**, as clearly shown by X-ray crystallography,[9] has been also demonstrated in solution by FT-IR and ^{1}H NMR studies .[5,9] The higher acidity of the axial hydroxyls follows their higher H-bonding character.
22. This preferential ionization of the axial hydroxyls explains also the axial selectivity of the alkylation of **1** under basic conditions and the glycosidation reaction using glycosylidene carbenes.[9]
23. More recently we have developed an alternative and more convenient route to equatorial monoesters of **1** using mixed anhydrides as acylating agents and *in situ* protection of the axial hydroxyls in the form of a phenyl boronic acid diester:



80% overall (R = Ph)

This approach allows the use of equimolar amounts of **1** and the acylating reagent. The formation of the intermediate symmetric phenyl boronate was checked by ^{1}H NMR in pyridine-d$_5$.

24. For a very recent example using 2 equivalents of a chiral acylating reagent see: Riley, A. M.; Mahon, M. F.; Potter, B. V. L. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1472.