Pergamon

Tetrahedron Letters, Vol. 35, No. 43, pp. 8053-8056, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01733-6

Neighbouring Hydroxy group Assisted O-Alkylation and Solvolysis of an Unsymmetrical Diester derivative of *myo*-Inositol*

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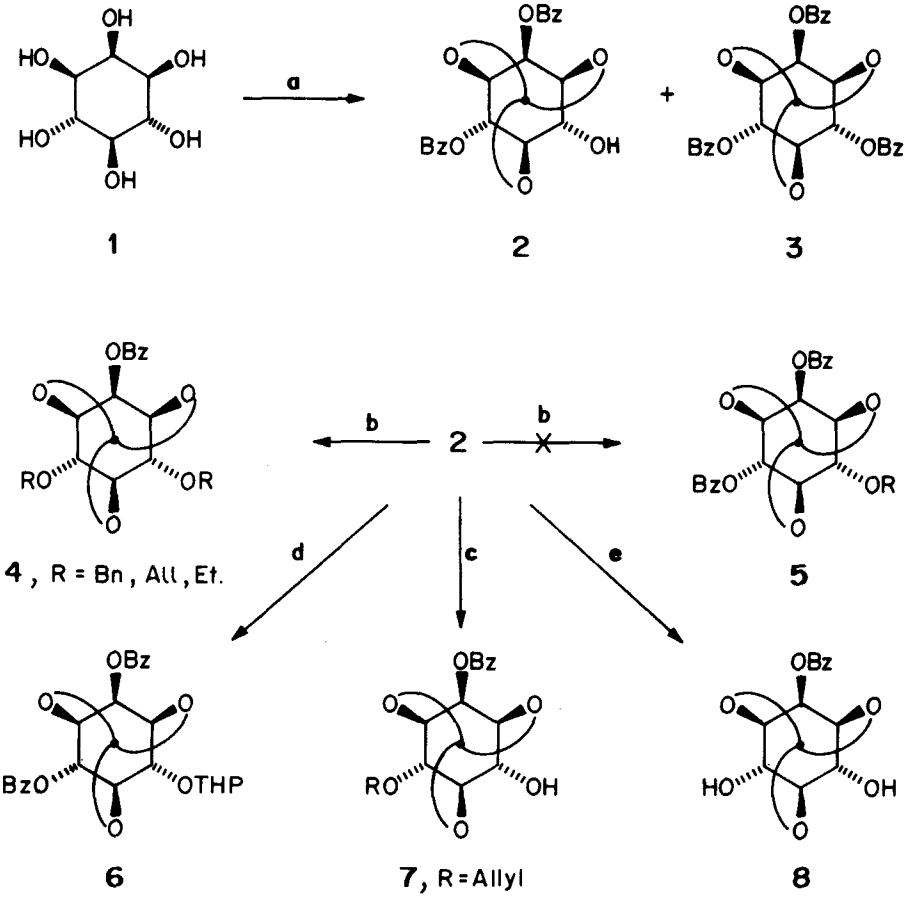
Abstract: The alkylation and solvolysis of the unsymmetrical 2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate, in the presence of silver (I) oxide and pyridine yields 2-O-benzoyl-4,6-di-O-alkyl-*myo*-inositol-1,3,5-orthoformate and 2-O-benzoyl-*myo*-inositol-1,3,5-orthoformate respectively. Both the reactions proceed with the assistance of the axial hydroxy group at the 6-position.

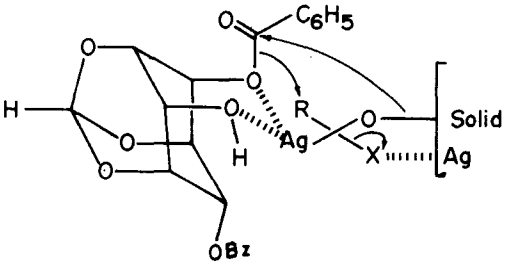
The involvement of *myo*-inositol phosphates and their glycerolipid derivatives in cellular signal transduction pathways[1] has renewed interest in the chemistry of the inositols in the recent past. Several methodologies for the synthesis of various derivatives of *myo*-inositol have been developed[2] starting from *myo*-inositol, quebrachitol, benzene etc. We required several protected *myo*-inositol derivatives for an ongoing program in our laboratory and chose to adopt a route involving *myo*-inositol orthoformate[3] for our purposes. Here, we report an unusual neighbouring hydroxy group assisted O-alkylation and solvolysis of the racemic 2,6-di-O-benzoyl-*myo*-inositol derivative **2**.

The pentaprotected *myo*-inositol derivative **2** was prepared[4] on a multi-gram scale by the sequential reaction of *myo*-inositol with triethylorthoformate and benzoyl chloride in a one pot procedure. Traces of the tribenzoate **3** formed could be easily removed by crystallization. The unsymmetrical nature of the dibenzoate **2** was established by infrared (shows two peaks for ester carbonyl groups), ^{1}H and ^{13}C NMR spectroscopy[4,5]. ^{13}C NMR spectrum of **2** showed two distinct signals for the two ester carbonyl carbons, seven signals for aromatic ring carbons and five signals for inositol ring carbons. The dibenzoate **2** could be easily converted to the known[6] *myo*-inositol-1,3,5-orthoformate by aminolysis with isobutylamine.

Benzylation of the dibenzoate **2** using excess benzylbromide in the presence of silver (I) oxide[7] yielded the dibenzyl ether **4** (R = Bn) in about 80% isolated yield, instead of the expected monobenzyl ether **5**. The equatorial ester group at the 2-position remained unaffected. Similar results were obtained on using allyl bromide and ethyl iodide. Since esters are reported to be stable under these alkylation conditions[7], we suspected that the free axial hydroxy group at the 6-position might be assisting in the cleavage of the axial ester moiety at the 4-position. Thus, we subjected the tribenzoate **3** to alkylation under identical conditions and found it to be stable. The tribenzoate **3** was recovered almost quantitatively. We also prepared the tetrahydropyranyl (THP) ether **6** and subjected it to alkylation in the presence of silver (I) oxide. A mixture of products resulted,



(a)(i) $HC(OEt)_3$ / H^+, DMF, 100°C (ii) BzCl, Py, −5°C ; (b) X'S R−X / Ag_2O, DMF; (c) 1eq. R−X / Ag_2O , DMF ; (d) DHP, PPTs, DCM ; (e) MeOH, Py, 40°C



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^{1}H NMR spectrum of which suggested the cleavage of the THP ether to some extent. About 50% of the starting material could however be isolated by column chromatography. These results strongly suggest the assistance of the axial hydroxy group at the 6-position during alkylation at the 4-position.

The reaction of **2** with one equivalent of allyl bromide in the presence of silver (I) oxide resulted in formation of monoether **7** (40%) and diether **4** (R = allyl, 20%). No 6-O-allylated product **5** could be isolated. These results suggest the intermediacy of **7** during the formation of the diether **4**. The fact that protection of the 6-hydroxy group leads to prevention of alkylation (see above), strongly favours the cleavage and alkylation of the 4-benzoate moiety prior to alkylation of the hydroxy group at the 6-position. Thus, in all probability, the monoether **7** is formed by the direct cleavage and alkylation of the ester moiety at the 4-position in **2**. The intermediacy of the diol **8**, formed by the hydrolysis (due to adsorbed water or hydroxide ions on the surface of silver (I) oxide) of **2** during alkylation could be ruled out by treating the dibenzoate **2** with only silver (I) oxide or excess of water in the presence of silver (I) oxide. The dibenzoate **2** was completely stable to such experimental conditions, and was recovered quantitatively. It is likely that silver (I) oxide forms a complex (see **9**) with the dibenzoate **2** resulting in the cleavage of the acyl-oxygen bond and O-alkylation at the 4-position. The formation of such a silver complex could reduce the nucleophilicity of the free hydroxy group at the 6-position, thereby inhibiting its alkylation. The involvement of an alkali metal chelate during the selective O-alkylation at the 4-position of the *myo*-inositol orthoformate has been suggested recently[3].

Treatment of the dibenzoate **2** with methanol and pyridine at 40°C resulted in the solvolysis of the axial 4-benzoate exclusively, resulting in the formation of the diol **8**. Solvolysis of the equatorial ester at the 2-position was not observed. It is reasonable to expect preferential solvolysis of the equatorial ester over that of the axial ester, since the formation of the tetrahedral intermediate should be easier when the ester moiety is present in the equatorial position. Again assistance by the axial hydroxy group was demonstrated by subjecting the THP ether **6** as well as the tribenzoate **3** to methanolysis as above. Both the compounds were completely resistant to solvolysis. Instances of the acceleration of ester hydrolysis by a neighbouring hydroxy group have been reported[8].

In conclusion, we report an unusual one step conversion of a carboxylic acid ester to an ether in the presence of silver (I) oxide. This route also provides convenient access to some important protected *myo*-inositol derivatives which are useful for the synthesis of *myo*-inositol-phosphates[3]. Further kinetic and mechanistic studies of the reactions reported here are in progress and will be reported in due course.

ACKNOWLEDGEMENTS: Partial financial support from the Department of Science and Technology, New Delhi, is gratefully acknowledged. One of us (TB) thank the University Grants Commission, New Delhi, for a research fellowship. We thank Dr. K.N. Ganesh for encouragement.

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4. **Preparation of 2**: *Myo*-inositol (0.06 mol), triethyl orthoformate (0.09 mol), p-toluenesulphonic acid mono hydrate (1.0 g) and dry dimethylformamide (100 ml) were heated at 100°C in a round bottomed flask for 3 hours. The reaction mixture was cooled to room temperature, triethylamine (4 ml) and dry benzene (20 ml) were added and the volatiles were removed in vacuo. The resulting solution was mixed with pyridine (24 ml) and cooled to -5°C. Benzoyl chloride (0.15 mol) was added drop-wise over a period of 30 minutes. The reaction mixture was allowed to come to room temperature and stirred for 16 hours. The resulting solution was distilled under reduced pressure and the gummy residue was triturated with dry methanol and the mixture was stored in a refrigerator over night. The precipitate obtained was washed with methanol and crystalized from dichloromethane-petroleum ether mixture to obtain **2** (5.8 g). The mother liquor was evaporated to a gum, dissolved in dichloromethane, washed with dilute hydrochloric acid followed by dilute sodium bicarbonate solution, dried over anhydrous sodium sulphate and methylenechloride was removed using a rotary evaporator. The solid product obtained was crystalized as above to obtain a further quantity (4.7 g) of **2**. m.p. 163-164°C. IR (nujol) 3500, 1726, 1711 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.70 (d, 1H, D_2O exchangeable), 4.50 (m, 1H), 4.65 (m, 2H), 4.75 (m, 1H), 5.65 (m, 2H), 5.85 (m, 1H), 7.45 (m, 4H), 7.65 (m, 2H), 8.05 (dd, 2H), 8.20 (dd, 2H). ^{13}C NMR ($CDCl_3$) δ 64.1, 67.7, 68.8, 69.9, 72.1, 103.2, 128.7, 128.9, 129.2, 129.7, 130.2, 133.8, 133.9, 165.4, 166.5. Elemental analysis: $C_{21}H_{18}O_8$ requires C, 63.31%; H, 4.55%. Found: C, 62.79%; H, 4.79%.

5. All the compounds reported are racemic and they exhibited infrared and nuclear magnetic resonance (^{13}C and ^1H, 200 MHz.) spectra consistent with their structure. The diether **4** (R = benzyl) and the monoether **7** were also converted to the known[3] 2,4-di-O-benzyl-*myo*-inositol-1,3,5-orthoformate and 4-O-allyl-*myo*-inositol-1,3,5-orthoformate respectively.

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(*Received in UK* 28 *July* 1994; *revised* 31 *August* 1994; *accepted* 2 *September* 1994)