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Note

Mechanism of silver (I) oxide mediated *O*-alkylation of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates: effect of solvent and silver halide on the nature of the intermediates involved

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Abstract

Reaction of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate with alkyl halides in the presence of silver (I) oxide under a variety of conditions have been studied systematically and compared with the corresponding reaction of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates. The results indicate that the former is not an intermediate during the alkylation of the latter in DMF. Results obtained on alkylation of the orthoformate esters mentioned above in acetonitrile show that the alkylation of 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate which is formed via the transesterification of 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate could be a side reaction. Silver halides, which are generated during alkylation of 2,4-di-*O*-acyl-*myo*-inositol 1,3,5-orthoformates, increase their transesterification in DMF. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Cyclitols; Inositol; Alkylations; Neighboring group effects; Silver (I) oxide

We recently reported [1] an unusual silver (I) oxide mediated *O*-alkylation of the dibenzoate **1** (Scheme 1) to the corresponding 4,6-diethers, which proceeded with transannular participation of 4,6-diaxial oxygens. We had shown that methylation of the dibenzoate **1** in *N*-*N*-dimethylformamide with methyl iodide to the dimethyl ether **2** proceeds exclusively through the intermediacy of the monomethyl ether **3** and not through the diol **4**. However, such clear cut evidence could not be obtained for the reaction of *O*-acyl-*myo*-inositol 1,3,5-orthoformates with other alkyl halides and we had suggested [1] the operation of several parallel reactions leading to the formation of 4,6-diethers (Scheme 2). We herein present a comparative study on the silver (I) oxide mediated *O*-alkylation of the dibenzoate **1**, the acetate **5** as well as the diol **4** under a variety of conditions, to see if the diol is the intermediate during allylation of the dibenzoate **1**. If diol **4** is the intermediate during formation of 4,6-diethers from the dibenzoate **1**, then products

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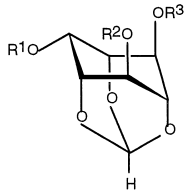
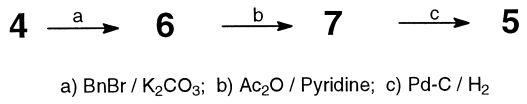


1. $R^1 = R^2 = Bz$, $R^3 = H$
2. $R^1 = Bz$, $R^2 = R^3 = Me$
3. $R^1 = R^2 = Bz$, $R^3 = Me$
4. $R^1 = Bz$, $R^2 = R^3 = H$
5. $R^1 = Bz$, $R^2 = Ac$, $R^3 = H$
6. $R^1 = Bz$, $R^2 = H$, $R^3 = Bn$
7. $R^1 = Bz$, $R^2 = Ac$, $R^3 = Bn$
8. $R^1 = Bz$, $R^2 = R^3 = All$
9. $R^1 = R^2 = Bz$, $R^3 = All$
10. $R^1 = Bz$, $R^2 = All$, $R^3 = H$
11. $R^1 = R^2 = R^3 = All$
12. $R^1 = R^2 = R^3 = H$
13. $R^1 = R^2 = R^3 = Me$
14. $R^1 = R^2 = R^3 = Bz$
15. $R^1 = Bz$, $R^2 = R^3 = Ac$
16. $R^1 = Bz$, $R^2 = Me$, $R^3 = H$
17. $R^1 = Bz$, $R^2 = Ac$, $R^3 = Me$



a) BnBr / K_2CO_3; b) Ac_2O / Pyridine; c) Pd-C / H_2

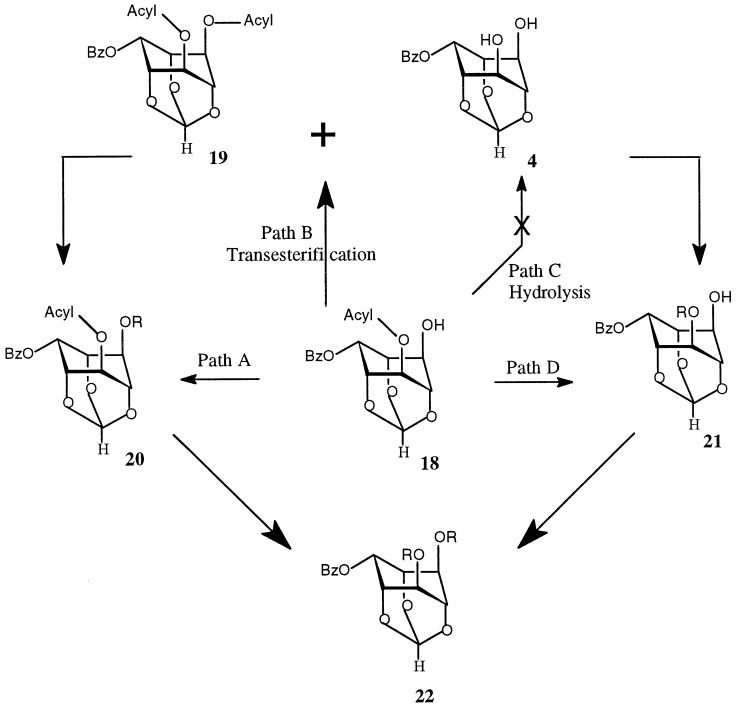
Scheme 1.

and the corresponding yields obtained from alkylation of both the dibenzoate **1** and the diol **4** should be comparable.

Reaction of the dibenzoate **1** [1] with an excess of allyl bromide in DMF gave the corresponding diallyl ether **8** as the major product, whereas the reaction with allyl chloride gave monoallyl ethers **9** and **10**. But, reaction of the diol **4** with allyl bromide in DMF yielded 2,4,6-tri-*O*-allyl-*myo*-inositol 1,3,5-orthoformate **11** as the major product (Table 1) while the major part of **4** was recovered unchanged after the reaction with allyl chloride. Control experiments in which the diol **4** was treated with silver (I) oxide alone showed that there was no hydrolysis of the equatorial 2-benzoate in **4** to generate the corresponding triol **12**, under the conditions of alkylation. Results of methylation of the dibenzoate **1** as well as the diol **4** with methyl iodide are also given in Table 1 for comparison.

Since alkylation of the diol **4** in DMF yielded the corresponding triethers **11** or **13**, we subjected diethers **2** and **8** to methylation and allylation respectively to see if triethers **11** and **13** were forming exclusively via the corresponding diethers (**4**→**2**→**13** or **4**→**8**→**11**). In all such experiments, at least 50% of diethers **2** and **8** could be recovered unchanged (Table 1, Entries 7,8). Hence, formation of larger amounts of triethers **11** and **13** from the diol **4**, as compared to those from diethers **8** and **2**, suggests operation of pathways other than those mentioned above. This is not surprising considering the biphasic nature of the reaction under scrutiny, where interfacial effects at the surface of the solid are also important.

During this study we observed that the presence of a silver halide, which is formed during



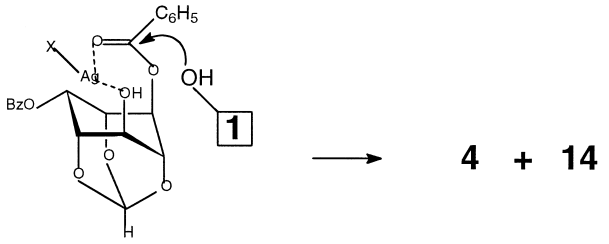
Scheme 2.

Table 1
Reaction of *myo*-inositol orthoformate derivatives with alkyl halides [a] in DMF

Entry	Reactant	RX	Products (yield % [b])
1	**1**	AllBr	**8** (74) [c]
2	**1**	AllCl	**9** (64), **10** (24) [c]
3	**4**	AllBr	**8** (14), **11** (53) [d]
4	**4**	AllCl	**1** (15), **4** (67), **10** (10)
5	**1**	MeI	**2** (80) [c]
6	**4**	MeI	**13** (76)
7	**2**	MeI	**2** (50), **13** (41)
8	**8**	AllBr	**8** (57), **11** (24)
9	**1**	None [e]	**1** (32), **4** (33), **14** (33) [f]
10	**1**	None [g]	**1** (78), **4** (10), **14** (10) [f]
11	**1**	None [h]	**1** (90), **4** (4), **14** (4) [f]
12	**3**	AllCl	**3** (97)

[a] All the reactions were carried out at ambient temperature (66 h) using a ratio of the reactant:Ag_2O:RX = 1:5:10, except in the case of allyl chloride where it was 1:5:14.
[b] Isolated, unless otherwise specified.
[c] From ref. [1].
[d] Other uncharacterized products, 25%.
[e] **1**:Ag_2O:AgI = 1:5:2.
[f] Yield by ^{1}H NMR.
[g] **1**:Ag_2O:AgBr = 1:5:2.
[h] **1**:Ag_2O:AgCl = 1:5:2.

alkylation, might lead to transesterification of the dibenzoate **1** (Scheme 2, Path B) to a small extent, thereby generating the diol **4** and the tribenzoate **14** in small amounts (Table 1, Entries 9,10,11)[1]. Perhaps silver halides function as Lewis acids and form a complex with the dibenzoate **1** and facilitate its transesterification (Scheme 3). The ability of silver halides to bring about transesterification of **1** decreased in the order AgI > AgBr > AgCl. However, the transesterification of **1** is significant only in the absence of an alkyl halide, since alkylation of **1** with one equivalent of alkyl halide [1] yielded the corresponding *O*-alkyl ethers in moderate to good yields and neither the diol **4** nor the tribenzoate **14** could be detected. Also, the amount of diol **4** formed via transesterification of **1** (Path B, Scheme 2) cannot account for the high yields of the 4,6-diethers obtained (Table 1, Entries 1,5), since



Scheme 3. Possible mechanism for the transesterification of **1** in DMF.

the rate of formation of **4** would be slow due to low levels of silver halide that would be present. If **10** is formed via the diol **4** generated through path B (during allylation of **1** with allyl chloride), then we should have isolated an equivalent amount of the tribenzoate **14** as a by product, since tri-*O*-substituted *myo*-inositol 1,3,5-orthoformates do not undergo allylation with allyl chloride in the presence of silver (I) oxide in DMF (Table 1, Entry 12 and [1]). These results suggest the noninvolvement of the diol **4** as the intermediate (Path B and C) during allylation of the dibenzoate **1** with allyl bromide and allyl chloride in DMF.

We also carried out alkylation of the dibenzoate **1** as well as the acetate **5** in acetonitrile wherein *O*-alkylation is sluggish perhaps due to complexation of silver ions by acetonitrile [2,3]. We theorized that such reaction conditions might relatively enhance the rate of transesterification of **1** and **5** and that we should be able to see the formation of the corresponding tri-*O*-acyl derivatives **14** and **15** or isolate them.

Methylation of the dibenzoate **1** as well as the acetate **5** yielded a mixture of products from which the corresponding triesters **14** and **15** could be isolated (Table 2, Entries 1–3). These experiments showed that methylation of di-*O*-acyl derivatives **1** and **5**, in acetonitrile, proceeds by a combination of several reaction pathways (Scheme 2) and that the formation of the diol **4** via transesterification (Path B) could be a competing reaction. The triesters **14** or **15** can also form through a transesterification reaction between **1** and **3** or **5** and **17**, respectively, which would give **16** as the co-product[2].

Allylation of the dibenzoate **1** with allyl bromide in acetonitrile yielded **10** as the major product along with the diallyl ether **8**, the monoallyl ether **9** and the tribenzoate **14**, as minor products. Allylation of **14** could not be carried out under identical conditions used for the allylation of **1**, due to its limited solubility in acetonitrile. Hence to check if tri-*O*-substituted *myo*-inositol 1,3,5-orthoformates

[1] It is important to note that stoichiometric amounts of silver halides (that would be present at the completion of the corresponding alkylation reaction) have been used and that the concentration of the dibenzoate **1** and that of the silver halide vary inversely during the course of alkylation. Consequently, the transesterification reactions used as controls give an over estimate of the amount of the diol **4** and the tribenzoate **14** generated during the corresponding alkylation of the dibenzoate **1**.

[2] For a discussion on the base catalyzed transesterification of **1** and **5** see [4,5].

Table 2
Reaction of *myo*-inositol orthoformate derivatives with alkyl halides [a] in acetonitrile

Entry	Reactant	RX	Products (yield % [b])
1	**1**	MeI	**2** (66), **3** (5), **14** (15), **16** (5)
2	**5**	MeI	**2** (30), **15** (5), **16** (28), **17** (30),
3	**5**	MeI [c]	**2** (21), **15** (30), **16** (14), **17** (37)
4	**3**	MeI	**2** (99)
5	**1**	AllBr	**8** (4), **9** (9), **10** (64), **14** (11),
6	**3**	AllBr	No reaction
7	**4**	AllBr	**10** (86)
8	**4**	None	No reaction [d]

[a] All the reactions were carried out at ambient temperature (80 h for MeI, 66 h for AllBr) using a ratio of the reactant: Ag_2O:RX = 1:5:10.
[b] Isolated.
[c] Reaction time 16 h.
[d] By ^{1}H NMR, however a very faint spot corresponding to **1** was visible in TLC.

undergo allylation in acetonitrile, we subjected the dibenzoate **3** (which has one axial benzoate) to allylation in acetonitrile with allyl bromide. The benzoate **3** remained unaffected and could be recovered quantitatively.

Silver (I) oxide mediated allylation of the diol **4**, in acetonitrile with allyl bromide, yielded the monoallyl ether **10** as the only isolable product. Since the product of allylation of the dibenzoate **1** as well as that from the diol **4** in acetonitrile is the same, in order to establish the contribution of Path B to the overall reaction, we had to rely upon the yields of the isolated products and the control reactions. Since transesterification of **1** is a disproportionation reaction, the maximum yield of the diol **4** and the tribenzoate **14** obtainable is 50% each. Accordingly, if **10** is formed exclusively by allylation of the diol **4** generated through transesterification of **1**, maximum yield of **10** can only be 50%. Furthermore, this sequence of reactions should yield 50% of the tribenzoate **14** as well (or a 1:1 yield of tribenzoate **14** and the monoallyl ether **10**), since **14** is stable to allylation in acetonitrile[3] (see above). These results clearly show that the intermediacy of the diol **4** formed by transesterification of the dibenzoate **1** during its allylation with allyl bromide is at best a minor side reaction. The contribution of Path B to the overall reaction (Table 2, Entry 5) is about 11% as reflected by the yield of the tribenzoate **14**. In all the alkylation reactions reported here, the possibility of involvement of water generated on the solid surface as a result of alkylation of free hydroxyl groups cannot be ruled out, especially since cleavage and alkyation of esters do not involve net consumption of water.

The dibenzoate **1** as well as the diol **4** did not undergo allylation with allyl chloride in the presence of silver (I) oxide in acetonitrile. In both the reactions, majority of the starting materials were recovered.

In conclusion, the results presented here support that the diol **4** is not an intermediate during the reaction of **1** with alkyl halides in DMF since alkylation of **4** yields the corresponding triethers. A change of solvent from DMF to acetonitrile for these alkylations leads to a complex mixture of products suggesting the operation of multiple reaction pathways in acetonitrile. *O*-Acyl-*myo*-inositol 1,3,5-orthoformates undergo intermolecular transesterification under the conditions of alkylation. The results presented here have a potential use in the preparation of *myo*-inositol derivatives of biochemical interest.

1. Experimental

General methods.—For general methods and procedure for the alkylation of *myo*-inositol orthoformate derivatives, see ref [1]. All the compounds previously known in the literature were characterized by comparison of R_f values on TLC, IR and NMR spectra as well as melting point (in the case of solids) with authentic samples. Physical, spectroscopic and analytical data for new compounds are tabulated in Table 3. Yields of products which could not be separated by column chromatography or preparative TLC were estimated by ^{1}H NMR (200 MHz) spectroscopy. IR spectra were recorded as nujol mull or in chloroform solution.

*Preparation of 4-*O*-acetyl-2-*O*-benzoyl-6-*O*-benzyl*-myo-*inositol 1,3,5-orthoformate* (**7**).—The diol **4** (1.00 g, 3.4 mmol) and benzyl bromide (1.064 g, 6.22 mmol) were dissolved in DMF (20 ml) and stirred after the addition of anhyd potassium carbonate (2.86 g, 20 mmol) for 40 h at ambient temperature. The reaction mixture was then diluted with chloroform (40 mL), washed several times with water followed by brine and dried over anhyd sodium sulfate. Solvents were

[3] One of the referees has suggested an alternate route for the formation of **10** which involves the hydrolysis of the tribenzoate **14** to the dibenzoate **1**, by water generated as a result of alkylation of the diol **4**. This sequence of reactions leads to "recycling" of **14** generated by transesterification of **1**.

Table 3
Spectroscopic data for some *myo*-inositol-1,3,5-orthoformate derivatives [a]

Compd no.	IR cm^{-1}	^1H NMR (δ in $CDCl_3$)	^{13}C NMR (δ in $CDCl_3$)
5	3442 1714	2.20 (s, 3 H, D_2O), 2.10 (d, 1 H, D_2O exchangeable), 4.50 (m, 3 H), 4.15–4.20 (m, 1 H), 5.50 (d, 1 H), 5.60 (s, 2 H), 7.10–7.15 (m, 1 H), 7.45–7.55 (m, 2 H), 8.15–8.20 (d, 2 H).	21.1, 64.3, 66.5, 68.5, 68.6, 69.4, 71.8, 102.6, 129.1, 129.7, 134.0, 155.6, 169.9[b].
6	1710	3.9 (d, 1 H, D_2O exchangeable), 4.35 (m, 1 H), 4.5 (m, 2 H), 4.65–4.90 (q, 4 H), 5.55 (m, 2 H), 7.3–7.65 (m, 8 H), 8.15–8.25 (d, 2 H).	63.7, 68.1, 68.2, 69.6, 72.6, 72.8, 74.1, 76.7, 77.3, 102.8, 128.4, 128.6, 128.9, 129.0, 129.8, 130.1, 133.5, 136.0, 166.3.
7	1730	1.9 (s, 3 H,), 4.45 (m, 2 H), 4.60 (m, 2 H), 4.70 (m, 2 H), 5.05–5.15 (m, 2 H), 5.45 (m, 1 H), 7.30–7.40 (m, 5 H), 7.45–7.70 (m, 3 H), 8.10–8.25 (d, 2 H).	20.5, 64.1, 66.7, 68.3, 69.5, 69.8, 71.6, 73.3, 76.6, 77.3, 77.9, 103.1, 127.6, 128.0, 128.4, 129.7, 129.9, 133.3, 137.2.
11		3.90 (m, 1 H), 4.00–4.20 (m, 11 H), 5.10–5.40 (m, 7 H), 5.55 (d, 1 H), 5.80–6.05 (m, 3 H).	67.5, 68.5, 70.5, 74.0, 103.5, 117.0, 117.5, 134.0, 135.0.
13		3.45 (s, 6 H), 3.55 (s, 3 H), 3.60 (m, 1 H), 4.15 (t, 2 H), 4.40 (m, 2 H), 4.50 (m, 1 H), 5.55 (d, 1 H).	56.1, 57.1, 66.9, 68.7, 68.8, 75.5, 102.7.

[a] Analytical data for **5**. Calcd for $C_{16}H_{16}O_8$: C, 57.14; H, 4.80. Found: C, 57.18; H, 4.76. **7**. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.21; H, 5.16. **13**. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.88; H, 6.88.
[b] In Me_2SO-d_6.

evaporated under reduced pressure and the product **6** (0.92 g, 68%) was isolated by column chromatography; mp 100 °C. The monobenzyl ether **6** (0.5 g, 1.3 mmol) was acetylated with acetic anhydride in pyridine under standard conditions to obtain the acetate **7** (0.55 g, 99%) as a gum.

Preparation of 4-O-acetyl-2-O-benzoyl-myo-inositol 1,3,5-orthoformate (**5**).—The monobenzyl ether **7** (0.5 g, 1.17 mmol) was dissolved in EtOAc (8 mL) and hydrogenated at 30 psi, after the addition of 10% Pd-C (0.3 g) for 24 h. The reaction mixture was then filtered and the filtrate was evaporated under reduced pressure to obtain **5** (0.39 g, 99%) as a solid[4]; mp 198 °C.

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[4] The efficiency of debenzylation of **7** varied with different batches of catalyst (Pd-C) obtained from different suppliers. The yield reported is the best obtained in several trials. Difficulties in the debenzylation of *myo*-inositol-1,3,5-orthoformate benzyl ethers have earlier been encountered [6].