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Short Communication

The Effect of Cesium Fluoride–DMF in the Dibutylstannylene Acetal-Mediated Selective Monobenzylation of Methyl 2,3-D-Glycerate

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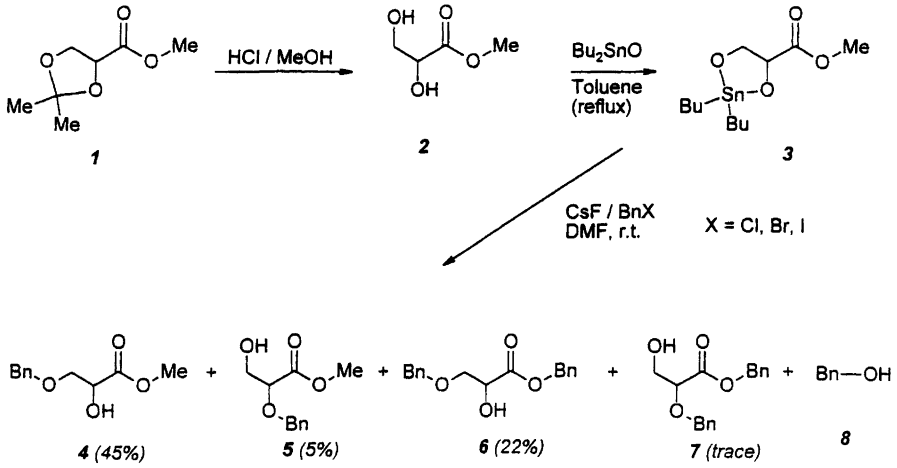
Development of methods for the mono-protection of diols are of interest in organic synthesis to provide intermediates which can be transformed into biologically important compounds.[1] Several such methods have been developed for mono-derivatisation of diols or polyols, e.g., by means of monoalkoxide sodium salts,[2a] nucleophilic opening of benzylidene-type acetals,[2b] and derivatisation catalysed by metallic sulfates or ion-exchange resins.[2c] However, over the last decade, the selective mono-transformation of diols via dialkylstannylene acetals[3] has gained wide popularity. The method is simple and tolerates a wide variety of functional groups. In general the dialkylstannylene acetal is prepared by heating at reflux a solution of a diol and dialkyltin oxide in benzene or toluene with azeotropic removal of water. Alternatively the alcohol and tin components are refluxed in chloroform and methanol without the need for removal of water.[4] In some cases commercially available dibutyltin dimethoxide[5] has been used instead of dibutyltin oxide and reacts efficiently with diols in benzene under Dean–Stark conditions to furnish the tin acetal. Recently, successful mono-functionalisation of diols has been reported using catalytic amounts of dibutyltin oxide by employing the reaction-accelerating effect of microwave heating technology.[6] Usually, the stannylene acetal, without purification, is treated with an electrophile to afford the mono-functionalised derivative after switching to a dipolar aprotic solvent. The reaction is often highly regioselective with a preference for primary hydroxy-group substitution in the presence of other alcohol arrangements.[7] Fluorides, particularly cesium fluoride, have been found to facilitate the reaction enabling it to be carried out at room temperature and in very high yields.[8]

Results and discussion

In a research program optically pure monobenzylated methyl D-glycerate was required and attention was turned to the tin-mediated procedure. The methyl glycerate **2** used as starting material was obtained by acid-catalysed deprotection of the corresponding methyl 2,3-di-*O*-isopropylidene-D-glycerate **1** using HCl anhydrous methanol. Throughout this work, the dibutylstannylene acetal **3** has sometimes been generated by the Dean–Stark method but more frequently simply by refluxing for 3 h a chloroform–methanol solution of the previously dried D-glyceric acid methyl ester **2** and dibutyltin oxide. To overcome apparent solubility difficulties in the alkylation step of the procedure *N*,*N*-dimethylformamide (DMF) has often been given as the solvent of choice in the cesium fluoride assisted benzylation of the intermediate tin acetal. However, carrying out the reaction in DMF in our laboratory resulted in the isolation of five compounds instead of the two predicted regioisomers. These are shown in Scheme 1 as **4**–**8**, together with the yields obtained. Examination of the structures of the products shows clearly that compounds **6** and **7** are transesterification products of the expected primary and secondary monobenzylated diols, **4** and **5**, respectively. The occurrence of adducts **6**, **7** and benzyl alcohol **8** was unexpected and contrasts with earlier findings.[9] Hence, using benzyl bromide as the alkylating agent, the reaction was studied in greater detail with the aim of establishing the source of these by-products.

Transformation of the methyl ester into the benzyl analogue can occur through interchange of the alkoxy moieties and involves mixing the ester and alcohol usually under acid or base catalysis.[10] The presence of benzyl alcohol in the product mixture suggests a possible source of the transesterification but the reaction takes place under neutral conditions and benzyl alcohol is not sufficiently activated to add to a carbonyl function with the displacement of a methoxy fragment. Further, analysis



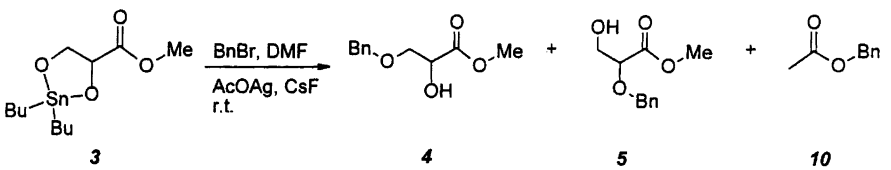
Scheme 1.

of the starting benzyl halides ruled out benzyl alcohol impurity as the precursors to **6** and **7**. Transesterification that proceeds under neutral conditions involves non-saponicative hydrolysis via cleavage of ester *O*-alkyl bond by halide ion, followed by alkylation or alcoholysis of the resulting intermediate.[11] Thus in an effort to establish the observed transesterification process, the effect of the halide in the alkylating component was initially investigated and it was found that the product distribution was the same irrespective of whether the halide used was chloride, bromide or iodide. Next, the reaction was carried out at room temperature and in the presence of one equivalent of silver acetate relative to benzyl bromide. Silver ion forms highly stable complexes with halides and would interfere in reactions involving halides or sulfides.[12] In this case, only the expected two regioisomers of monobenzylated diol and benzyl acetate **10** were formed as depicted in Scheme 2. The low conversions, which are a feature in this exploration, are comparable to the results obtained by Ohno in the reaction of benzyl bromide with the *O*-stannylene acetal of dimethyl L-tartarate without the addition of reaction accelerating agents.[8]

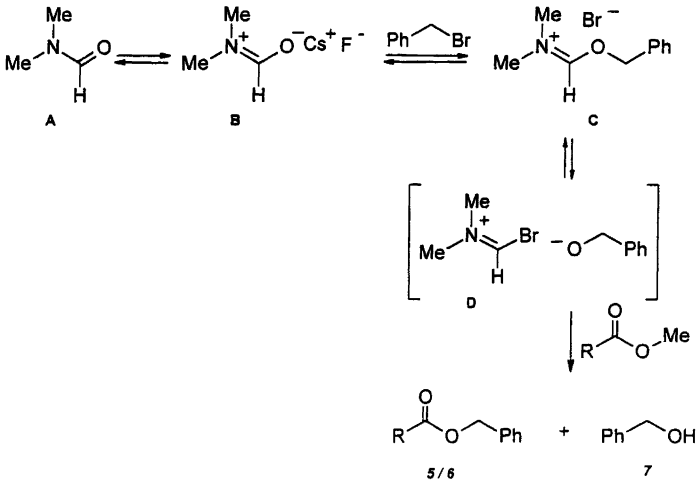
The fact that neither the transesterified products nor benzyl alcohol were observed in the reaction mixture indicated the involvement of halide ion in the side reactions. On the other hand, if partial hydrolysis of the ester function took place during reaction the formed carboxylate could be alkylated by benzyl halide and result in transesterification. Non-saponificative hydrolysis of the ester could also occur by a Taschner–Eschenmoser type[13] procedure which consists of nucleophilic attack at the methyl group of the ester by halide ion. The transesterification that would take place through this procedure would, however, certainly not account for the production of the accompanying benzyl alcohol.

Apart from the reagents, catalysts and temperature, the other key factor that may influence the outcome of a reaction is the solvent. With this consideration in mind, two other potential solvents were investigated for the benzylation of the cyclic stannylene acetal in the presence of cesium fluoride from which the results shown in Table 1 were obtained. The reaction took place in all cases and judging by the amounts and quality of product obtained, acetone seemed to be the preferred solvent for the reaction. It is worth noting that benzyl alcohol was not formed in acetone and acetonitrile. However, some transesterification took place, more in acetonitrile than in acetone, but the overall yield of compounds **4** and **5** was higher in acetone and acetonitrile than in *N,N*-dimethylformamide. This observation indicates the involvement of two separate reactions operating simultaneously and leading to the same transesterification by-products.

From these findings it therefore seems reasonable to assume that the formation of benzyl alcohol is directly related to the use of DMF as the solvent in the alkylation step, which in turn is indirectly connected to the observed transesterification products. Furthermore, the metal complexes in the reaction mixture may be functioning as transient Lewis acids efficiently catalysing transesterification reactions and formation of benzyl alcohol. Based on these assumptions, the following reaction mechanism shown in Scheme 3 is suggested as the main



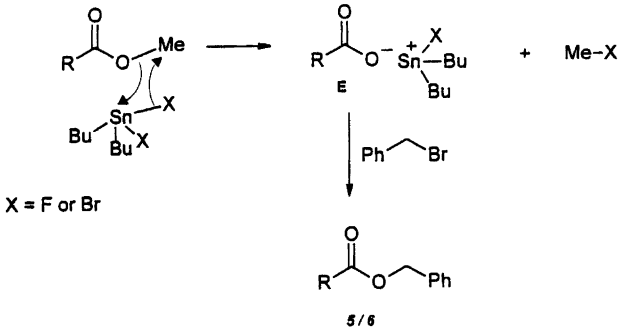
Scheme 2.



Scheme 3.

Table 1. Cesium fluoride mediated benzylation of dibutylstannylene acetal in selected solvents.

	Yield (%)	Ratio			
Solvent	**4** and **5**	**4**:**5**	**6**	**7**	**8**
Acetone	91	88:12	3%	0	0
Acetonitrile	90	84:16	5%	0	0
DMF	50	70:30	22%	Trace	≈10%



Scheme 4.

reaction pathway to transesterified products: the intermediate **C** is obtained from *O*-benzylation of the equilibrium structure of DMF **B**. In a reversible fashion *N*,*N*-dimethyl bromomethyleneiminium salt **D** is formed with displacement of phenylmethoxide by bromide ion. The phenylmethoxide counter-ion of this intermediate[14] then interchanges with the methoxy moiety of the ester function and leads to transesterification or abstracts a proton from the reaction medium to furnish benzyl alcohol. In this illustration RCO_2Me represents the glycerate part of the stannylene acetal. Consideration of the formation of the Vilsmeier formylation intermediate lends support to the formation of intermediate **D**. Usually this intermediate results from the reaction of dimethylformamide with active acid derivatives such as phosphorus oxychloride, thionyl chloride, phosgene and oxalyl chloride.[15] The case at hand therefore represents an example in which an alkylating agent reacts in a similar way to activated acid derivatives. Cesium cation may promote this reaction by forming a weak ion pair[16] with the formamide oxygen making it powerfully nucleophilic and able to react efficiently with benzyl bromide. In addition the benzyl halide could be activated by cesium fluoride through interaction of the large cesium cation with the halogen atoms allowing it to act as a template. The interaction of DMF with benzyl halide, which after hydrolysis gives formate esters, has earlier been reported in the literature.[17] Since cesium fluoride seems to be directly involved in the observed transesterification via production of phenylmethoxide, its reactivity with DMF alone was tested. NMR analysis of the oily product obtained from stirring an equimolar mixture of benzyl bromide and cesium fluoride in DMF for 17 h showed formation of benzyl alcohol which corresponded to 26 mol% of the amount of benzyl bromide. This observation strongly supports the transesterification hypothesis outlined in Scheme 3.

A proposal that explains the other reaction pathway which makes a minor contribution to transesterified products, is shown in Scheme 4. Formation of some by-products in the reactions performed in acetone and acetonitrile solvents where the formation of Vilsmeier-type intermediate is excluded can be attributed to *O*-alkyl bond cleavage of the methyl ester by halide ion. Subsequent benzylation of the resulting carboxylate **E** gives the esters **6** and **7**. The dibutyltin halide derivatives[18] which could be present in the reaction mixture as by-products may be influencing ester *O*-carbon bond breakage in a similar way to the iodotrimethylsilane methodology.[19]

Experimental

General methods. All NMR experiments were recorded on a Varian VXR-300S spectrometer using a broad-band probe with a 5 mm tube. Samples were dissolved in

$CDCl_3$ unless otherwise stated. Chemical shifts are reported relative to Me_4Si and $CDCl_3$. Flash chromatography was performed using silica gel (Merck 230–400 mesh). Thin-layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} precoated plates (0.25 mm), and spots were visualized with molybdophosphoric acid in ethanol after heating.

Materials. Ethyl acetate, light petroleum, b.p. 40–60 °C, CH_2Cl_2, MeOH, and acetonitrile were used as received. DMF was dried over 3 Å molecular sieves.

D-*Glyceric acid methyl ester* (**2**). Dry HCl gas was bubbled through absolute methanol (130 ml) for 45 min. To this was added 2,3-di-*O*-isopropylidene-D-methyl glycerate (**1**, 8.0 g, 50 mmol), and the resulting solution was stirred at ambient temperature for 1 h. The methanol was then removed *in vacuo*, and the hygroscopic product was dried over KOH in a vacuum desiccator for 3 h and kept in dry acetonitrile (60 ml) over molecular sieves 3 Å overnight. Evaporation of the solvent gave 6.0 g (100%) of **2** as colourless viscous liquid.

General procedure for regioselective benzylation of the diol. Step 1: formation of tin acetal. An equimolar mixture of D-glyceric acid methyl ester (**2**, 1.0 g, 8.33 mmol) and dibutytin oxide (2.26 g, 8.33 mmol) in 100 ml of chloroform–methanol (10:1) was refluxed for 3 h to give a clear solution. Removal of the solvents under reduced pressure gave a white solid which was mixed with cesium fluoride (2.21 g, 14.53 mmol). The solid mixture was dried overnight under high vacuum and the mixture was suspended in DMF (30 ml).

Step 2: alkylation. To a cooled (ice–water) suspension of the tin acetal in DMF was added DMF (5 ml) solution of benzyl bromide (1.0 ml, 8.33 mmol), and the mixture stirred for 17 h at ambient temperature. A mixture of ethyl acetate (60 ml) and water (1 ml) was added, the mixture stirred vigorously for 30 min and then filtered through a pad of silica gel to remove dibutyltin oxide. The solvents were evaporated off under reduced pressure to give an oily residue which was purified by flash chromatography using ethyl acetate–light petroleum (2:3) as the eluent. The following products were obtained.

Methyl 2-hydroxy-3-(benzyloxy)propionate (**4**): 755 mg (45%); ^{1}H NMR: δ 3.22 (s, 1 H, OH), 3.72–3.75, AB part of ABX (m, 2H, $C\underline{H}_2CH$), 3.76 (s, 3 H, $C\underline{H}_3$), 4.27–4.36, X part of ABX (br, 1 H, $C\underline{H}CH_2$), 4.52 and 4.60 (q, AB, *J* 12.2 Hz, 2 H, $C\underline{H}_2C_6H_5$), 7.23–7.33 (m, 5 H, C_6H_5). ^{13}C NMR: δ 52.5, 70.8, 71.3, 73.4, 127.6, 127.7, 128.4, 137.7, 173.0. IR (neat): 3477, 1745, 1496, 1454, 1236, 1126, 741 cm^{-1}. MS: 210 (M^+).

Methyl 2-benzyloxy-3-hydroxypropionate (**5**): 72 mg (5%); ^{1}H NMR: δ 2.34 (br, 1 H, OH), 3.77 (s, 3 H, $C\underline{H}_3$), 4.06–4.12 (br, 1 H, $C\underline{H}$), 3.80–3.95 (dd, 2 H, $HOC\underline{H}_2CH$), 4.50 and 4.81 (q, AB, *J* 11.4 Hz, 2 H, $C\underline{H}_2C_6H_5$), 7.30–7.40 (m, 5 H, C_6H_5). ^{13}C NMR: δ 52.1, 63.5, 72.8, 78.6, 128.1, 128.2, 128.5, 137.0, 171.0. MS: 210 (M^+). IR (neat): 3450, 1745, 1454, 1274, 1213, 1123, 748 cm^{-1}.

Benzyl 2-hydroxy-3-(benzyloxy)propionate (**6**): 465 mg (22%); ^{1}H NMR: δ 3.12 (br, 1 H, OH), 3.71–3.81 (m, AB part of ABX, 2 H, $C\underline{H}_2CH$), 4.31–4.38 (m, X part of ABX, 1 H, $C\underline{H}CH_2$), 4.56 and 4.48 (q, AB, J_{AB} 12.1 Hz) 2 H, $C_6H_5C\underline{H}_2O$), 5.20 and 5.23 (q, AB, J_{AB} 12.2 Hz, 2 H, $-OC\underline{H}_2C_6H_5$), 7.22–7.32 (m, 10 H, $C_6H_5 \times 2$). ^{13}C NMR: δ 67.4, 70.9, 71.4, 73.5, 127.6–128.6, 135.2, 137.6, 172.5. IR (neat): 3477, 1743, 1211, 1126, 741 cm^{-1}. MS: 286 (M^+).

Benzyl 2-benzyloxy-3-hydroxypropionate (**7**): trace amount. *Benzyl alcohol* (**8**): ^{1}H NMR: δ 1.80 (t, 1 H, OH), 4.67–4.69 (d, 2 H, CH_2), 7.35–7.36 (m, 5 H, C_6H_5).

In the presence of silver acetate. Reaction was carried out as described in step 2 except that a stoichiometric amount of silver acetate was added before addition of benzyl bromide. Approximately 4.0 mmol of the dibutyltin acetal were prepared. Compound (**4**) 149.44 mg (18%). Compound (**5**) 44.88 mg, (0.5%).

Benzyl acetate: 83 mg (14%); ^{1}H NMR: δ 2.082 (s, 3 H, $C\underline{H}_3$), 5.097 (s, 2 H, $C\underline{H}_2C_6H_5$), 7.30–7.36 (m, 5 H, C_6H_5).

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