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A one-pot selective deprotective acetylation of benzyl ethers and OTBDMS ethers using the $BF_3{\cdot}Et_2O$–NaI–Ac_2O reagent system

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Abstract—An efficient selective deprotection followed by acetylation of several benzyl ethers, including 6-*O*Bn ethers of monosaccharides, and -OTBDMS ethers has been developed by using the $BF_3{\cdot}Et_2O$–NaI–Ac_2O reagent system. In addition, both benzylidene and isopropylidene groups are deprotected to form the corresponding diacetates.

The importance of the selective introduction and removal of protecting groups in organic synthesis is well known and the suitability of a particular method largely depends on the stability of the protecting groups towards different reaction conditions in a given synthetic endeavor. Protection of hydroxy groups as ethers, especially as benzyl ethers has long been recognized as a valuable reaction. This is mainly because benzyl ethers are stable under basic and acidic reaction conditions and are relatively insensitive to various oxidizing and reducing agents. Furthermore, the wide use of benzyl ethers as protecting groups in organic synthesis is because of the easy deprotection by hydrogenolysis with palladium catalysts,[1] under essentially neutral conditions. Selective cleavage of a benzylic ether derived from a primary alcohol in the presence of other benzylic ethers, derived from secondary alcohols, as well as other protecting groups is equally useful. From the carbohydrate point of view, various bio-active natural products contain 1→6-*O*-glycosidic linkages.[2] Hence, selective deprotection of 6-*O*Bn ethers of methyl glycoside derivatives is a useful procedure for the synthesis of 1 → 6-*O*-linked oligosaccharides.

In addition to the use of catalytic hydrogenolysis, cleavage of benzylic ethers has also been reported with reagents such as Na/liq. NH_3,[3] O_3,[4] TMSI,[5] and more recently with the K/*t*-$BuNH_2$/*t*-BuOH/18-crown-6 reagent system.[6] Deprotection of a benzyl ether is often followed by the conversion of the released alcohol to another functionality. Hence, attempts have been made in carbohydrate chemistry to convert 6-*O*-benzyl ethers into the corresponding acetates using reagents like $ZnCl_2$–Ac_2O–AcOH.[7] However, this procedure requires the use of a large amount of $ZnCl_2$ and subsequent work-up becomes tedious. There are, however, a few other Lewis acids and acidic catalysts such as $FeCl_3$,[8] ZnI_2,[9] H_2SO_4[10] and TMSOTf[11] that have been employed along with Ac_2O to effect this transformation, but either the selectivity or yield is not satisfactory. Further, in some cases[11] the temperature needs to be controlled to observe selectivity.

In connection with another project, where we attempted to make use of the $ZnCl_2$–Ac_2O–AcOH procedure for converting a 6-*O*-benzyl ether to the corresponding acetate, we decided that a new procedure was required that would utilize smaller amounts of a Lewis acid to avoid a tedious work-up. Several years ago, we reported a simple procedure for the selective deprotection of benzylic, phenolic methyl and aliphatic methyl ethers using NaI–$BF_3{\cdot}Et_2O$[12] which has been well utilized[13] in organic synthesis. Our current interest[14] in carbohydrate chemistry has led us to make use of this combination along with Ac_2O to convert benzyl ethers to the corresponding acetates. Our results are shown in Table 1.

Thus, methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (Table 1, entry 1) upon treatment with the $BF_3{\cdot}Et_2O$–NaI–Ac_2O reagent system[15] gave 6-*O*-acetyl

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Keywords: Selective deprotection; Acetylation; Benzylidene; Acetonide; TBDMS ethers.

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Table 1. Selective deprotective acetylation of –OBn and –OTBDMS ethers using the $BF_3 \cdot Et_2O$–NaI–Ac_2O reagent system

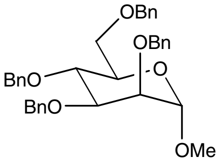
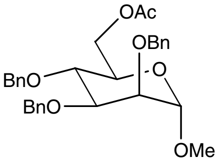
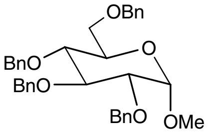
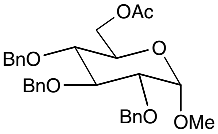
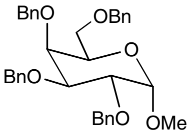
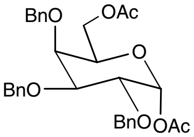
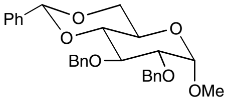
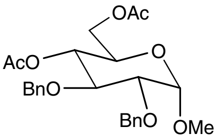
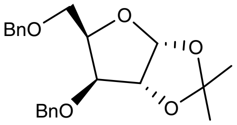
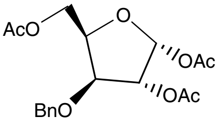
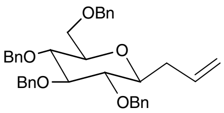
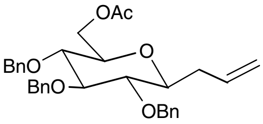
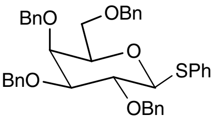
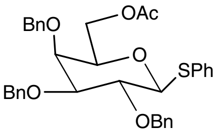
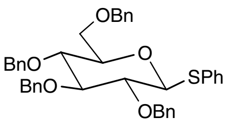
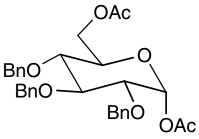
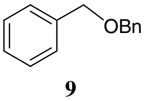
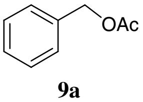
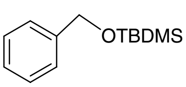
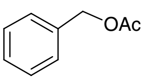
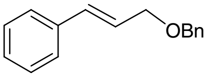
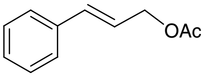
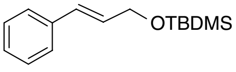
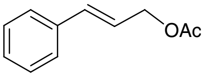
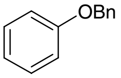
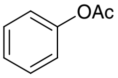
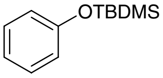
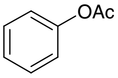
Entry	Substrate	Product	Time (h)	Yield[a] (%)	α/β
1	 **1**	 **1a**	1.5	75	—
2	 **2**	 **2a**	1.0	78[b]	—
3	 **3**	 **3a**	1.5	82	α
4	 **4**	 **4a**	1.0	80	—
5	 **5**	 **5a**	2	68	—
6	 **6**	 **6a**	1.5	77	—
7	 **7**	 **7a**	1.5	72	—
8	 **8**	 **8a**	1.5	76	α
9	 **9**	 **9a**	1.5	70	—
10	 **10**	 **10a**	1.5	70	—

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[a] (%)	α/β
11	 **11**	 **11a**	1.5	69	—
12	 **12**	 **12a**	1.2	68	—
13	 **13**	 **13a**	1.5	69	—
14	 **14**	 **14a**	1.5	65	—

[a] Isolated yields.

[b] Yield after the recovery of starting material.

product **1a**[7] in 75% yield in 1.5 h. Likewise, the acetate **2a**[16] was obtained in 78% yield (entry 2). However, methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside **3** (entry 3) produced the diacetate **3a**[17] in 82% yield where the anomeric –OMe ether was also replaced with an acetate group when the reaction was allowed to proceed to completion.[18] The stereochemistry at the anomeric centre was found to be α. It is likely that in this case since the 6-*O*Bn and the 4-*O*Bn groups are cis to each other, steric hindrance makes debenzylation of the 6-*O*Bn group somewhat slower and hence the methoxy group from the anomeric position is also cleaved in competition eventually forming the diacetate **3a**. Further, as expected, both benzylidene and isopropylidene groups were found to undergo cleavage followed by acetylation of the released alcohols. Thus, methyl 2,3-*O*-dibenzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **4** (entry 4) led to product **4a**[19] in 80% yield and 3,5-di-*O*-benzyl-1,2-*O*-isopropylidine-α-D-xylo-furanoside **5** (entry 5) gave 3-*O*-benzyl-1,2,5-triacetyl-α-D-xylo-furanoside **5a**[20] in 68% yield. The use of a smaller amount of the Lewis acid did not alter the reactivity. 3-*C*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1-propene **6** and phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside **7** (entry 7) gave the respective 6-OAc products **6a**[21] and **7a**[22] in 77% and 72% yields and in the case of **7**, the –SPh group was found to be unaffected. Surprisingly, in the case of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **8** (entry 8), the thiophenyl group was replaced with an acetate group to give **8a**[7] in 76% yield. Further, it was also found that TBDMS ethers (entries 10, 12 and 14) derived from benzylic, allylic and phenolic OH groups were also deprotected to form the corresponding acetates in good yields as shown in Table 1. Conjugated examples (entries 11 and 12) and an isolated double bond (entry 6) were not affected under the reaction conditions.

The use of $BF_3{\cdot}Et_2O$ along with Ac_2O, only in CH_2Cl_2, led to the formation of a small amount of the corresponding acetate, however, the reactions were generally slow and not clean. The reactions using the $InCl_3/Ac_2O$ reagent system, with or without NaI, were also not clean and were generally slow.

In conclusion, we have developed an efficient and selective deprotective acetylation of benzylic ethers using the $BF_3{\cdot}Et_2O$–NaI–Ac_2O reagent system. We believe that since this method involves the use of inexpensive reagents and the work-up is relatively easy, it will find further use in organic synthesis.

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15. General experimental procedure: To a stirred solution of –OBn or –OTBDMS ether (1 mmol) in dry acetic anhydride (1.5 mL) at 0 °C was added dropwise a solution of NaI (1 mmol) in acetonitrile (0.5 mL) followed by $BF_3 \cdot Et_2O$ (1 mmol). After completion of the reaction (TLC monitoring), the reaction mixture was quenched with aqueous $Na_2S_2O_3$ and extracted with ether (3×10 mL). The ethereal layer was washed with water (3×10 mL), brine (3×10 mL) and finally dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography gave the pure compound.
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18. In this reaction, it is necessary that the temperature is carefully controlled between −5 °C and 0 °C or else a small amount of the β-product starts to form as evident from its ^1H NMR spectrum.
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20. Data for **5a**: $R_f = 0.65$ (8:2 hexanes/EtOAc); yield = 68%; $[\alpha]_D^{25}$ +40.0 (c 0.75, $CHCl_3$); IR (CH_2Cl_2) ν 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 6H), 2.15 (s, 3H), 3.59–3.65 (t, $J = 10.2$ Hz, 1H), 3.91–3.96 (m, 2H), 4.68–4.74 (m, 2H), 4.95–5.03 (m, 2H), 6.21–6.22 (d, $J = 3.68$ Hz, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 29.6, 61.1, 70.2, 70.9, 74.6, 76.3, 89.6, 127.4–128.3, 137.9, 168.9, 169.6. MS (ESI): $m/z = 389$ $(M+Na)^+$.
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