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Note

Zinc triflate–benzoyl bromide: a versatile reagent for the conversion of ether into benzoate protecting groups and ether glycosides into glycosyl bromides

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Abstract

A simple and efficient method is developed for the chemoselective one-pot conversion of ethers (benzyl, TBDMS and acetal) to the corresponding benzoates by zinc triflate-catalyzed deprotection and benzoylation by benzoyl bromide. In the same reaction, methyl or *p*-methoxyphenyl glycosides are converted into glycosyl bromides that are useful in glycosylation reactions. © 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Zinc triflate; Benzoyl bromide; Glycosyl bromide; Protecting groups

Selective protection and deprotection of hydroxyl groups is usual practice in the multistep strategy of carbohydrate synthesis. There are hundreds of protection groups that can be introduced and removed by a variety of methods, but new and milder methods continue to be developed for their introduction and removal. Conversion of one protection group to another is often required as demanded by the reaction conditions required in subsequent steps. Direct methods for such transformations, bypassing the intermediate steps, are important to improve overall synthetic efficiency.[1] Ethers, especially benzyl ethers, are commonly used as temporary protecting group for polyols and carbohydrates, owing to their stability under a wide variety of reactions conditions. Our laboratory has been pursuing the synthesis of natural product analogs containing *C*-linked sugars.[2] In the synthesis the *C*-glycosylic derivatives (*C*-glycosides) of the ganglioside GM4,[2] we had occasion to require the conversion of benzyl protecting groups to benzoyl protecting groups. Although there are several methods available for the one-pot transformation of ethers into acetates, these methods often necessitate harsh reaction conditions, long reaction times and excess reagents.[3–7] To the best our knowledge, a one-pot transformation of ethers into benzoates has not been reported.

We report herein a mild and efficient method for the transformation of ethers into benzoates. We initially undertook the deprotection and re-protection 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-D-glucofuranurono-6,3-lactone (Entry 1, Table 1). To a suspension of $Zn(OTf)_2$ (0.1 equiv) and 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-D-glucofuranurono-6,3-lactone (100 mg, 0.3 mmol) in dichloroethane, BzBr (6 equiv) was added at room temperature under argon. After stirring for 10 min the reaction was quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the crude product on silica gel (hexane–EtOAc) afforded the corresponding benzoate derivative in 98% yield. The mechanism of this reaction may involve zinc activation of the benzoyl bromide, followed by O-acylation, to give an oxonium ion that then dealkylates by an S_N2 mechanism with bromide ion to give benzyl bromide.

$$R–O–R^1 + PhCOBr + Zn(OTf)_2 \rightarrow PhCO_2R^1 + R–Br$$

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Per-*O*-benzylated galactose, glucose, mannose and lactose were subjected to these conditions to study the reaction scope (entries 2–6, Table 1). The structures of all products were confirmed by ^{1}H NMR analysis. Initially, a molar ratio of 1:6:0.1 sugar:BzBr:Zn(OTf)$_2$ was examined, but long reaction times were required for high yields. By adjusting the molar ratio to 1:10:1, the reactions (entries 2–6, Table 1) were complete within 30 min, affording excellent isolated yields (95–97%). The single disaccharide examined, a per-*O*-benzylated lactose derivative (entry 6, Table 1), showed cleavage of the glycosidic bond affording the benzoylated glucose and galactose derivatives. The anomeric protecting groups (OMP or OMe) in entries 2–6 were converted under these reaction conditions into the corresponding glycosyl bromide. Glycosyl halides are typically prepared from the corresponding 1-*O*-acetyl or hemiacetal derivatives. It has been previously reported that OMP and OMe glycosides can be converted into corresponding glycosyl halides in one step using Lewis acids.[7–10] These reaction conditions can be used in the presence of double bonds, as *C*-allyl 2-acetamido-6-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-α-D-galactopyranoside afforded the perbenzoylated *C*-allyl derivative in excellent yield.

1. Experimental

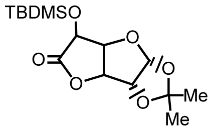
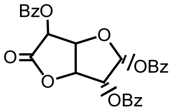
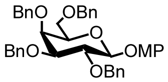
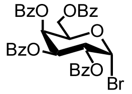
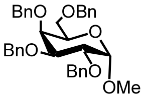
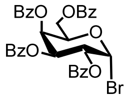
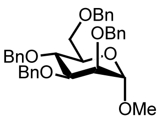
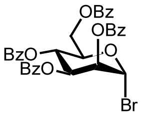
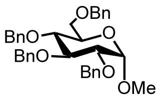
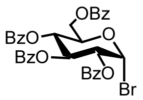
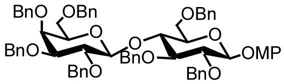
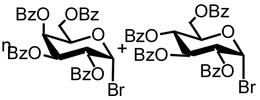
1.1. General methods

Nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 25 °C in $CDCl_3$. Chemical shifts were recorded in ppm (δ) and coupling constants in Hz, relative to Me_4Si as the internal standard. Thin-layer chromatography (TLC) was performed using E. Merck plates of Silica Gel 60 with fluorescent indicator. Visualization was effected by spraying plates with Von's reagent (1.0 g of ceric ammonium sulfate and 24.1 g of ammonium molybdate in 31 mL of H_2SO_4 and 470 mL of water), followed by heating at 140 °C. Flash chromatography was conducted with silica gel (230–430 mesh, E. Merck).

1.2. General procedure

To a suspension of Zn (OTf)$_2$ (0.1–1 equiv) and reactant (Table 1, Entry 1–6) (100 mg) in $ClCH_2CH_2Cl$ (10

Table 1
Direct conversion of alcohol ether (entries 1–6) to benzoate

Entry	Substrate[a]	Equiv of BzBr	Equiv of Zn(OTf)$_2$	Time	Product	Yield
1		6	0.1	10 min		98%
2		10	1	30 min		97%
3		10	1	30 min		96%
4		10	1	30 min		95%
5		10	1	30 min		97%
6		10	1	30 min		95%

[a] TBDMS = *tert*-butyldimethylsilyl; MP = *p*-methoxyphenyl; Bz = benzoyl; Bn = benzyl; Me = methyl

mL), BzBr (6–10 equiv) was added at room temperature under Ar. After stirring for 10 min the reaction was quenched with satd aq $NaHCO_3$ (5 mL). The organic phase was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification on silica gel (hexane–EtOAc) afforded the corresponding benzoate derivatives in 95–98% yield.

Data for the new compound, 1,2,5-tri-*O*-benzoyl-D-glucofuranurono-6,3-lactone. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (dd, 1 H, H-3), 5.37 (t, 1 H, $J_{3,4}$ 6.0 Hz, H-4), 5.47 (dd, 1 H, H-2), 5.81 (d, 1H, $J_{1,2}$ 6.5 Hz, H-1), 6.95 (d, 1H, $J_{4,5}$ 4.5 Hz, H-5), 7.45–8.02 (m, 15 H, 3 OBz). HRFABMS: m/z Calcd for $C_{27}H_{20}O_9$ $[M + Na]^+$ 488.1107; Found 488.1114.

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