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An environmentally benign and practical synthesis of sugar orthoesters promoted by potassium fluoride

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Abstract—An extremely practical method for synthesis of sugar orthoesters has been developed without using any organic amines or heavy metals as additives. Various sugar orthoesters were prepared in good yields by the reaction of an acylated glycosyl bromide and an alcohol in the presence of potassium fluoride.

Sugar 1,2-orthoesters are one of the most useful intermediates in the synthetic field of carbohydrate chemistry.[1] The 'orthoester method' originally reported by Kochetkov and co-workers[2] has extensively been utilized at a key stage of oligosaccharide synthesis of complex structure because sugar 1,2-orthoesters can be efficiently converted to the corresponding 1,2-*trans*-glycosides by the action of protonic or Lewis acids such as trimethylsilyl trifluoromethanesulfonate.[3] The sugar 1,2-orthoester moieties are also very important for the selective protection of a pyranose ring[4] while the other acetyl groups on 3, 4, and 6 positions are converted, for example, to benzyl groups.[5] Furthermore, the hydrolysis of 1,2-orthoester leads to the formation of a 1-acetoxy pyranose or a 2-acetoxy pyranose, depending on gluco or galacto type.[6]

A well-known method for the preparation of sugar 1,2-orthoesters involves the treatment of a per-acetylated α-glycosyl bromide with an alcohol in the presence of tetrabutylammonium bromide and *sym*-collidine (2,4,6-trimethylpyridine)[7] or silver triflate and 2,4-lutidine.[3c] The former reaction consists of the following three processes: (1) the anomerization of α-glycosyl bromide to β-anomer by a nucleophilic attack of the bromide ion to the anomeric carbon atom of the α-glycosyl bromide, (2) the intramolecular attack of the carbonyl oxygen of the 2-acetoxy group to the anomeric center affording an acyloxonium ion, and (3) attack of the hydroxyl group of the alcohol to the acyloxonium ion as a result of scavenge of a proton from the hydroxyl group by a sterically hindered base. It is, therefore, necessary to utilize two kinds of reagents, quaternary ammonium salt and bulky amine compound, for the reaction to occur. However, the removal of such amine compounds from the reaction mixture is normally very difficult and consequently much organic solvent is required in order to purify the product by column chromatography. Carbohydrate 1,2-orthoesters are also obtained by treating 1-hydroxy sugars with 1-chloro-2,*N*,*N*-trimethyl-propenylamine followed by the addition of alcohols in the presence of triethylamine.[8] From the viewpoint of green and sustainable chemistry, the usage of such organic amine compounds should be minimized. This communication describes an extremely facile procedure for synthesis of 1,2-orthoesters **4** starting from peracylated glycopyranosyl bromides and alcohols promoted by potassium fluoride[9] without using any amine compounds or heavy metal salts.

All the reactions were carried out at 50 °C by using acetonitrile as solvent (Table 1). The best result concerning the yield of orthoester was obtained when the glycosyl bromide was treated with 5 or 10 equiv of potassium fluoride for 24 h (entries 3 and 4). Since the reaction proceeds in a heterogeneous system, 2 or 1 equiv of potassium fluoride was not sufficient and the glycosyl bromide was recovered (entries 1 and 2). When the reaction was carried out by using lithium fluoride, sodium fluoride, and cesium fluoride, good result could not be obtained. Sodium fluoride was not so effective

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Table 1. Synthesis of sugar orthoesters **4** by the KF-promoted reaction of peracylated glycosyl bromides and alcohols[a]

Entry	R	Alcohol	Equiv of KF	Yield %[b]
1	Me	EtOH	1.0	53
2	Me	EtOH	2.0	87
3	Me	EtOH	5.0	90[c]
4	Me	EtOH	10.0	90
5	Me	BnOH	5.0	84
6	Me	*i*-PrOH	5.0	84
7	Me	Cyclohexanol	5.0	69
8	Me	*t*-BuOH	5.0	30
9	Ph	EtOH	5.0	93

[a] The reaction was carried out at 50 °C for 24 h in the presence of molecular sieves 3 Å(100 wt% for **1**).
[b] Determined by ^{1}H NMR spectroscopy.
[c] The diastereomer ratio (*exo*-isomer:*endo*-isomer) was determined to be 5:1 by ^{1}H NMR spectroscopy.

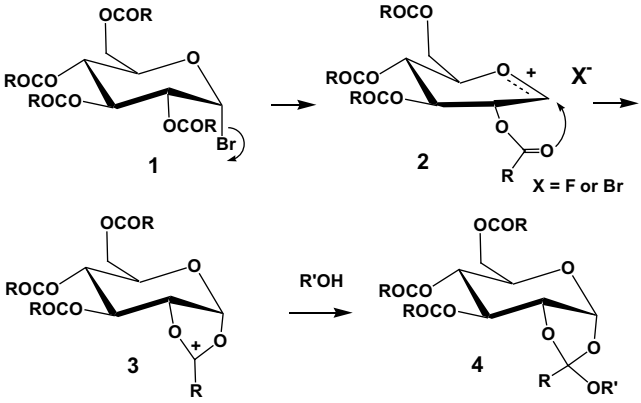

Figure 1. Proposed mechanism of the formation of 1,2-orthoester derivative starting from peracylated glucopyranosyl bromide derivative promoted by fluoride ion which behaves as acid captor.

compared with potassium fluoride probably because its poor solubility toward acetonitrile. In case of using cesium fluoride, the reaction system becomes too basic due to its higher solubility toward acetonitrile, affording the eliminated product of glycal derivative. The reaction proceeds effectively when perbenzoylated glycosyl bromide was utilized (entry 9). This method can successfully be applied to other alcohols such as benzyl alcohol, secondary alcohols, and a tertiary alcohol (entries 5–8).

The typical experimental procedure is as follows: A mixture of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide (200 mg, 0.49 mmol), ethyl alcohol (0.29 mL, 4.9 mmol), potassium fluoride (142 mg, 2.45 mmol), and molecular sieves 3 Å(200 mg) in acetonitrile (2.4 mL) was vigorously stirred under argon at 50 °C for 1 day. The solid materials (KF–HF + KBr + MS3A) were removed by filtration and the filtrate was evaporated to dryness to give a crude product of **4**. The resulting product was found to be pure enough for glycosylation reactions, which was confirmed by NMR spectroscopy.

It is assumed that the cyclization proceeds through a carbenium ion intermediate **2** as a result of S_N1 type C–Br bond cleavage (Fig. 1).[10] The second step involves a participation of the carbonyl oxygen of the 2-acetyloxy group from the α side of the pyranose ring. The resulting cyclic acyloxonium ion intermediate suffers an attack on the carbon atom by the hydroxyl group of the alcohol activated by a fluoride ion. In this reaction, alkyl glycosides could not be detected. The precise mechanism of the selective orthoester formation has not been made clear. According to the present method of using potassium fluoride, it is not necessary to utilize the quaternary ammonium salt that is very difficult to be removed from the reaction mixture. This fact makes the reaction procedure extremely simple; filtrating the complex of potassium fluoride–hydrogen fluoride (KF–HF) and KBr can easily isolate the product. The present method can be applied to synthesis of various orthoester derivatives of galactose, mannose, and lactose that are important synthetic intermediates in glycotechnology.

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