A Facile Method for Synthesis of 1,2-Oxazoline Derivative of *N*-Acetylglucosamine Promoted by Potassium Fluoride

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A potassium fluoride-promoted intramolecular cyclization reaction of 2-acetamido-2-deoxy-α-D-glucopyranosyl chloride took place smoothly, giving the corresponding 1,2-oxazoline derivative in good yield. Potassium fluoride behaves as a nucleophile for anomerization of the glycosyl chloride as well as an acid captor to scavenge the protonic acid liberated. This is an extremely practical method for preparation of sugar oxazoline derivatives with simple experimental procedures.

The 1,2-oxazoline derivatives of 2-acetamido-2-deoxy sugars are the most useful key intermediates for preparation of various 2-acetamido-2-deoxy glycosides. Since Micheel et al. first reported the ''oxazoline method'' in 1958,[1] this methodology has extensively been employed in stereoselective synthesis of 1,2-*trans*-2-aminoglycosides.[2] This method is also applicable to the synthesis of natural or non-natural chitin derivatives and hyperbranched polysaccharides.[3,4] Recently, sugar oxazolines having no protecting groups were found to be recognized by an endo-*N*-acetylglucosamidase for the first time and utilized as efficient glycosyl donors for enzymatic glycosylations.[5–8]

A well-developed method for the synthesis of sugar oxazolines includes treatment of *N*-acetylated aminosugars with hydrogen chloride in acetyl chloride followed by treatment of the chloride formed with a silver salts and 2,4,6-collidine.[9] Fully acetylated aminosugars can be converted to the oxazolines by using anhydrous ferric(III) chloride, tin(IV) chloride, or trimethylsilyl triflate.[10–12] An acid-catalyzed acetolysis of the corresponding methyl glycoside has also been reported.[13]

Another promising approach is to start from an α-glycosyl chloride derivative, one of the most easily available glycosyl donor. The treatment of 2-acetamido-2-deoxy-glycosyl chlorides with sodium bicarbonate in the presence of tetraalkylammonium chloride affords the corresponding oxazoline derivatives.[14] This reaction consists of the following two processes: 1) the anomerization of α-glycosyl chloride to β-anomer by a nucleophilic attack of the chloride ion to the anomeric carbon atom of the α-glycosyl chloride and 2) the intramolecular attack of the carbonyl oxygen of the 2-acetamide group to the anomeric center as a result of proton abstraction on the nitrogen by a base. It is, therefore, necessary to utilize two kinds of reagents, quaternary ammonium salt and sodium bicarbonate, for the reaction to occur. However, the yields of these reactions are normally low. In addition, these reactions require an ammonium compound which is very difficult to be removed from the reaction mixture and consequently much organic solvent is necessary to purify the product by column chromatography. The usage of such organic compounds should be minimized from the viewpoint of green chemistry.

It is well known that an alkali metal fluoride can convert α-glycosyl bromides to the corresponding β-glycosyl fluorides with inversion of configuration.[15] It has also been established that alkali metal fluorides can act as acid captors and be utilized for many synthetic organic reactions based on its characteristic property of forming a strong hydrogen bond with various protic organic compounds.[16–19] We postulated that the utilization of a metal fluoride enabled us to develop a new method for synthesis of cyclic compounds because the metal fluoride would play two roles at the same time, a nucleophile for activation of the functional group X and a scavenger of protonic acid liberated from the group YH, leading to a cyclic compound (Figure 1).

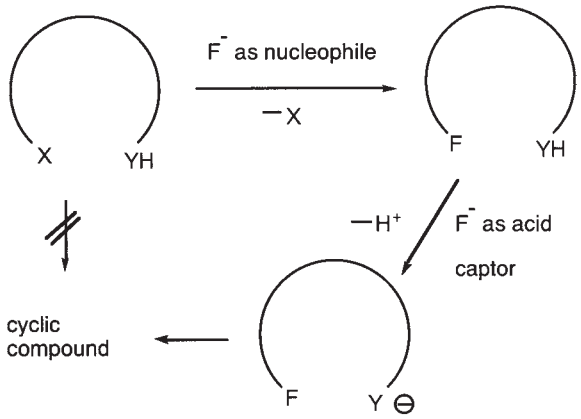
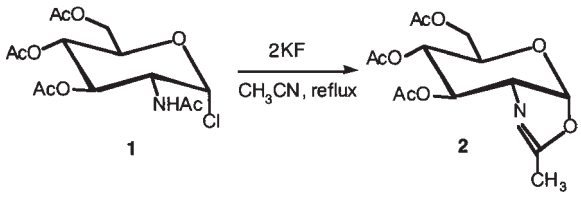


Figure 1. Fluoride ion-promoted formation of cyclic compound via nucleophilic displacement of a leaving group X and subsequent proton abstraction from the functional group YH.

Here we report an extremely convenient procedure for synthesis of the 1,2-oxazoline derivative of 2-acetamido-2-deoxy-D-glucopyranose **2** starting from peracetylated 2-acetamido-2-deoxy-D-glucopyranosyl chloride **1** promoted by potassium fluoride.



Scheme 1.

All the reactions were carried out by using acetonitrile as solvent (Table 1). The best result concerning the yield of **2** was obtained when **1** was treated with four equivalent of potassium fluoride under reflux for 15 hours (Run 1). Since the reaction proceeds in a heterogeneous system, two or one equivalent of

potassium fluoride was not sufficient and the glycosyl chloride **1** was recovered (Runs 2 and 3). The reaction did not proceed completely when carried out at room temperature (Runs 4–6). Sodium fluoride was not so effective compared with potassium fluoride probably because its poor solubility toward acetonitrile (Run 7). In case of using cesium fluoride, the reaction system becomes basic due to its higher solubility toward acetonitrile, affording the eliminated product of glycal derivative (Run 8).

Table 1. Potassium fluoride-promoted synthesis of **2**[a]

run	Metal fluoride	Equiv.	Temp/°C	Time/h	Yield/%[b]
1	KF	4	82	15	90
2	KF	2	82	15	23
3	KF	1	82	15	trace
4	KF	4	rt	48	20
5	KF	2	rt	48	29
6	KF	1	rt	48	26
7	NaF	4	82	15	55
8	CsF	4	82	15	38

[a]Solvent:acetonitrile. [b]Determined by ^{1}H NMR spectroscopy.

The typical experimental procedure is as follows: A suspension of potassium fluoride (232 mg, 4.0 mmol) and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (366 mg, 1.0 mmol) in acetonitrile (15 mL) was refluxed under argon for 15 hours with vigorous stirring. After cooling the mixture to room temperature, solid materials (KF-HF + KCl) was removed by filtration and the filtrate was evaporated to dryness to give a crude mixture of 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-d]-2-oxazoline **2** containing trace amount of β-glycosyl fluoride. 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 reactive intermediate of 2-acetamido-2-deoxy-β-D-glucopyranosyl fluoride **3** as a result of a nucleophilic attack of the fluoride ion to **1** (Figure 2). In this step, the fluoride ion behaves as a nucleophile toward the anomeric carbon atom to enhance the SN2 type reaction with the inversion of configuration. The second step involves a participation of the carbonyl oxygen of the 2-acetamido group from the α side of the pyranose ring. The resulting cyclic intermediate suffers a proton abstraction on the nitrogen by the action of another fluoride ion. This process may proceed smoothly because the acidity of the proton is increased through resonance.

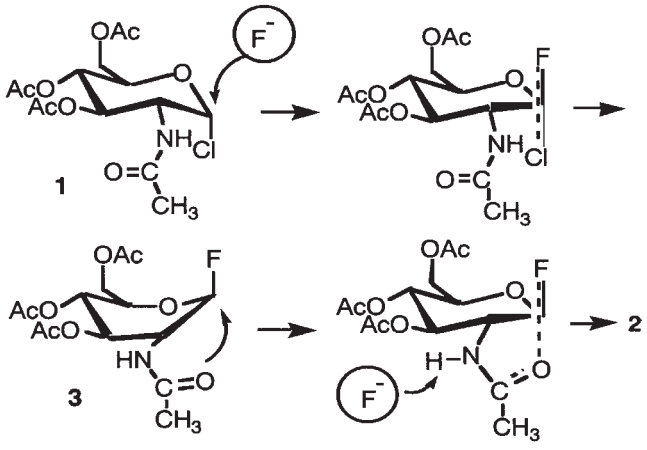


Figure 2. Proposed mechanism for formation of oxazoline ring starting from 2-acetamido-2-deoxy-α-D-glucopyranosyl chloride derivative promoted by fluoride ions which behave as nucleophile and acid captor.

According to the present method of using potassium fluoride, it is not necessary to utilize the quaternary ammonium chloride 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 KCl can easily isolate the product. The present method can be applied to synthesis of various sugar oxazoline derivatives that are important synthetic intermediates in glycotechnology.

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75 th birthday.

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