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Nucleophilic Addition of Potassium Alkynyltrifluoroborates to D-Glucal Mediated by BF_3·OEt_2: Highly Stereoselective Synthesis of α-*C*-glycosides

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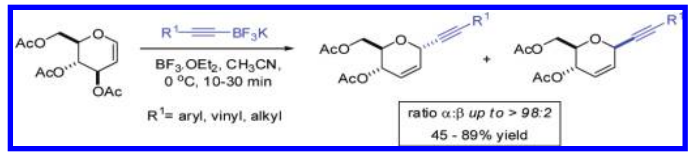
ABSTRACT



A convenient, mild and highly stereoselective method for *C*-glycosidation (alkynylation) of D-glucal with various potassium alkynyltrifluoroborates, mediated by BF_3·OEt_2 and involving oxonium intermediates, preferentially provides the α-acetylene glycoside products with good yields.

The study of glycosides has become very significant in the fields of carbohydrate and biological chemistry.[1] Glycosides containing a *C*-glycosidic bond exist in some subunits of biologically active natural products,[2] are potential inhibitors of carbohydrate processing enzymes, and are stable analogs of glycans involved in important intra- and intercellular processes.[3] These compounds are also potentially useful as chiral building blocks in organic chemistry[4] and the development of methods leading to the efficient and stereoselective syntheses of *C*-glycosides has attracted considerable attention in the recent years. *C*-glycosidation is very important in the synthesis of optically active compounds, since it allows for the introduction of carbon chains into sugar chirons and the use of sugar nuclei as chiral pools as well as carbon sources.[5] In particular, sugar acetylenes are attractive due to the presence of a triple bond that can be easily transformed into

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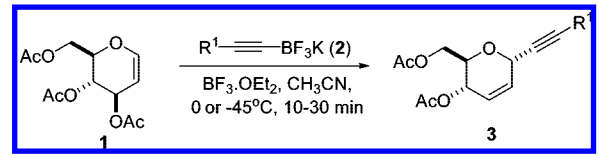
other chiral molecules and carbohydrate analogues.[6] Among the methods of *C*-glycosidation, the alkynylation reaction of sugar derivative oxocarbeniums generated from glucals such as **1** with silylacetylenes was reported by Isobe's group in 1984.[7] This reaction has been developed as an important method to prepare sugar acetylenes.[8] *C*-Glycosidation with silylacetylene compounds has been reported to proceed under various conditions and with various Lewis acids[9] such as $SnCl_4$, $(CH_3)_3SiOTf$, $BF_3{\cdot}OEt_2$, $TiCl_4$, $InBr_3$,[10] and $ZrCl_4$.[11] Iodine is also an efficient catalyst for this reaction.[12]

In recent years, organoboron compounds have become some of the most popular organometallic reagents for forming carbon−carbon bonds.[13] The organoboron compounds used most, boronic acids and boronate esters, have some drawbacks, including low stability, very high price, and high sensitivity to air and moisture. To solve these problems, organoborons have been replaced by potassium organotrifluoroborate salts,[14] which are crystalline solids, very stable in air and moisture, easily prepared from inexpensive materials, and more nucleophilic.

In connection with our research interest in the preparation and reactivity of potassium organotrifluoroborates and their potential use as intermediates in organic synthesis,[15] we report here an easy and highly diastereoselective method to synthesize *C*-glycosidate glucal **1** with potassium alkynyltrifluoroborates **2** with good yields. Although there are examples of glucals undergoing classical Ferrier-type alkynylation, to our best knowledge this is the first example of a Ferrier-type rearrangement mediated by $BF_3{\cdot}OEt_2$ using potassium alkynyltrifluoroborates as nucleophilic partners (Scheme 1).

Scheme 1. Alkynylation Reaction of 3,4,6-tri-*O*-Acetyl-D-glucal **1** with Potassium Phenylethynyltrifluoroborate



Our initial studies were focused on the development of an optimum set of reaction conditions. For initial screening experiments, 3,4,6-tri-*O*-acetyl-D-glucal **1** and potassium phenylethynyltrifluoroborate **2a** were selected as starting materials and dichloromethane was selected as the solvent.

The reaction of D-glucal **1** with potassium phenylethynyltrifluoroborate **2a** in the absence of a Lewis acid at 0 °C did not lead to the desired product, and the starting material was recovered unchanged (Table 1, entry 1).

The requirement for Lewis acidic activation strongly implies the intermediacy of oxonium ions in this kind of reaction. In view of this result, we initially chose $BF_3{\cdot}OEt_2$ as the Lewis acid because we believe that it is best for reactions involving potassium organotrifluoroborates.[14,15b]

For this purpose, the commercially available 3,4,6-tri-*O*-acetyl-D-glucal **1** was treated with potassium phenylethynyltrifluoroborate **2a** in the presence of $BF_3{\cdot}OEt_2$ (2.0 equiv) in CH_2Cl_2 at −23 °C to ensure *in situ* formation of the corresponding oxonium ion, which was formed in 15 min as evidenced by the consumption of **1** by TLC analysis. The reaction was allowed to warm to room temperature and stirred for 1 h. The corresponding alkynyl *C*-glycoside **3a** was obtained with an isolated yield of only 45% as a 90:10 mixture of the α and β anomers (Table 1, entry 2). The diastereomeric ratio was determined by GC analysis of the crude mixture. The effect of the solvent in this reaction on the yield and diastereoselectivity was noteworthy. When the reaction was performed in acetonitrile or toluene, appreciable improvements in the yield and diastereoselectivity were observed and the *C*-glycoside was obtained at 84 and 78% yield, respectively, with 95:05 α/β selectivity (Table 1, entries 3 and 4). By using *N*,*N*-dimethylformamide as the solvent, no product could be obtained, and 1,2-dichloroethane produced results similar those obtained with CH_2Cl_2 (Table 1, entries 5 and 6). This alkynylation reaction takes place efficiently with acetonitrile as the solvent, unlike the commonly used $BF_3{\cdot}OEt_2$-mediated processes, which employ chlorinated solvents.

We were interested in testing other Lewis acids in this Ferrier-type alkynylation. To our surprise, potassium phenylethynyltrifluoroborate **2a** did not react when $MgBr_2$ and $InCl_3$ were used as Lewis acids (Table 1, entries 7 and 8),

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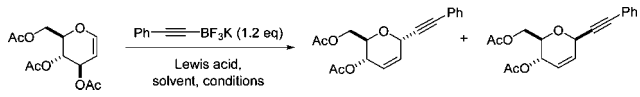
Table 1. Alkynylation Reaction of 3,4,6-tri-*O*-Acetyl-D-glucal **1** with Potassium Phenylethynyltrifluoroborate **2a**



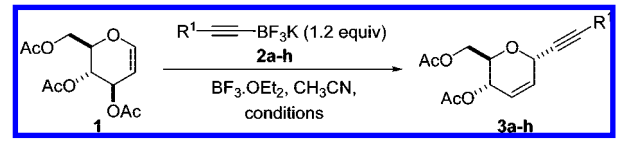
entry	Lewis acid (2 equiv)	solvent	conditions	yield (%)[a]	α/β ratio[b]
1	–	Ch_2Cl_2	1 h 0 °C	–	–
2	BF_3•OEt_2	Ch_2Cl_2	1 h r.t.	45	90:10
3	BF_3•OEt_2	CH_3CN	1 h r.t.	84	94:06
4	BF_3•OEt_2	$PhCH_3$	1 h r.t.	78	94:06
5	BF_3•OEt_2	DMF	1 h r.t.	–	–
6	BF_3•OEt_2	$(CH_2)_2Cl_2$	1 h r.t.	43	90:10
7	$MgBr_2$	CH_3CN	1 h r.t.	–	–
8	$InCl_3$	CH_3CN	1 h r.t.	–	–
9	$SnCl_4$	CH_3CN	1 h r.t.	62	85:15
10	$TiCl_4$	CH_3CN	1 h r.t.	70	80:20
11[d]	BF_3•OEt_2	CH_3CN	6 h r.t.	81	95:05
12	BF_3•OEt_2	CH_3CN	10 min 0 °C	89	94:06
13[c]	BF_3•OEt_2	CH_3CN	20 min −45 °C	85	96:04
14[e]	BF_3•OEt_2	CH_3CN	1 h r.t.	27	90:10

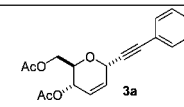
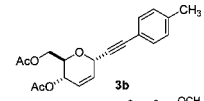
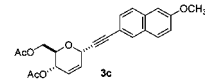
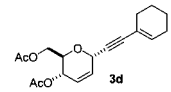
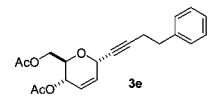
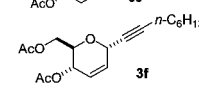
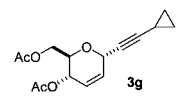
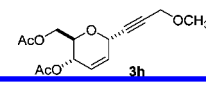
[a] Isolated yield. [b] Ratio of α and β anomers was determined by GC analysis. [c] Reaction with 4.0 equiv of BF_3•OEt_2. [d] Reaction with 5.0 equiv of BF_3•OEt_2. [e] Reaction with 1.0 equiv of BF_3•OEt_2.

and the use of $SnCl_4$ and $TiCl_4$ led to lower yields (Table 1, entries 9 and 10). The addition of BF_3•OEt_2 made this reaction very efficient, and when the reaction was performed with 4.0 equiv of Lewis acid in acetonitrile, it proceeded to completion in 20 min at −45 °C (condition a), affording the product **3a** with a very good yield and a high α/β diastereomeric ratio (Table 1, entry 13). However, a higher temperature (0 °C) dramatically reduced the reaction time to 10 min (condition b) and the required Lewis acid amount (2.0 equiv), affording the desired glycoside with an isolated yield of 89% (Table 1, entry 12). At a higher stoichiometry of the Lewis acid (5.0 equiv), no improvements in the yield or selectivity were observed, even when the reaction was performed at room temperature for 6 h (Table 1, entry 11). The use of smaller amounts of BF_3•OEt_2 resulted in lower yields (Table 1, entry 14).

Among the several reaction conditions tested, one in particular is notable: the use of 2.0 equiv of BF_3•OEt_2 as a Lewis acid and 1.2 equiv of the potassium organotrifluoroborate **2a** in CH_3CN at 0 °C for 10 min, under an anhydrous and inert atmosphere (condition b), afforded the alkynyl glycoside **3a** with an isolated yield of 89%, in a 94:06 diastereomeric ratio in favor of the α-anomer (determined by GC and ^1H NMR analysis). Furthermore, the spectral data of **3a** are identical to those reported in the literature,[10] which had previously been assigned the α-configuration at the anomeric center. These best-achieving mild conditions were applied to the reactions of 3,4,6-tri-*O*-acetyl-D-glucal **1** with various potassium alkynyltrifluoroborate salts **2b**−**h** to afford the acetylene glycoside products **3b**−**h**. All reactions were monitored by TLC until consumption of D-glucal was complete. The results are summarized in Table 2.

Table 2. BF_3•OEt_2-Mediated Alkynylation Reaction of 3,4,6-tri-*O*-Acetyl-D-glucal with Potassium Alkynyltrifluoroborates **2a**−**h**[c]



Entry	condition	Product (3)	Yield (%)[a]	α/β ratio[b]
1	a		85	96:04
	b		89	94:06
2	a		78	95:05
	b		45	93:07
3	a		64	>98:02
	b		31	>98:02
4	a		49	95:05
	b		26	93:07
5	a		78	>98:02
	b		93	>98:02
6	a		45	94:06
	b		66	93:07
7	a		23	94:06
	b		47	92:08
8	a		79	>98:02
	b		82	>98:02

[a] Isolated yield of the pure products. [b] The ratio of α and β anomers was determined by GC analysis of the crude mixture. [c] **Condition a**: 4.0 equiv BF_3•OEt_2, 20 min, −45 °C. **Condition b**: 2.0 equiv BF_3•OEt_2, 10 min, 0 °C.

All reactions showed good yields and high diastereoselectivity and the α-anomer was obtained as the predominant product in each reaction. The stereochemistries of the products **3a**−**h** were determined by ^1H and ^{13}C NMR observations of H-5 and C-5 and the correlation of the chemical shifts and coupling constants with those of similar compounds already described in the literature.[12b] In fact, Isobe[9f,16] established an empirical rule to deal with the chemical shift of H-5: the value falls between 4.07 and 4.09 ppm for the α-anomer due to the anisotropic effect of the α-acetylene at C-1, and between 3.74 and 3.77 ppm for the β-anomer. Moreover, the α-anomer exhibits a chemical shift[17] of C-5 lower than 75 ppm.

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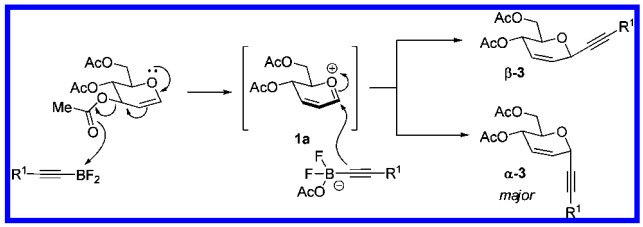
In the case of alkynylation with trimethylsilylacetylene, Isobe explained the α-selectivity by electronic effects on the oxocarbenium intermediates involved in the transformation.

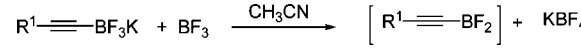
In terms of reaction mechanism, this process could involve the generation of the oxonium cation species **1a** from the Ferrier rearrangement of the Lewis acid-catalyzed *C*-glycosidation of glucal as depicted in Scheme 2.

Scheme 2. Ferrier Rearrangement Mechanism



We believe the *C*-glycosidation reaction was initiated by the reaction of BF_3 with the alkynyltrifluoroborate, to generate, as described by Kaufmann at al.,[18] organoboron difluoride, which was detected by ^{11}B NMR[18,19] (Scheme 3). The organoboron difluoride is also a Lewis acid, which is able to activate 3,4,6-tri-*O*-acetyl-D-glucal and generate oxonium and nucleophilic species. Thus, the active nucleophile in this kind of reaction may be the $[R\text{-}B(OAc)F_2]^-$

Scheme 3. $BF_3{\cdot}OEt_2$-Mediated Generation of RBF_2 Species



species, which attacks the oxonium cation at C-1 from the α-side, affording the respective α-anomer of the alkynyl *C*-glycoside.

In summary, we have developed a new and very mild method for stereoselective introduction of an alkynyl group to D-glucal, demonstrating that potassium alkynyltrifluoroborate-mediated alkynalation represents a convenient method for the production of α-*C*-glycosides with good yields and high diastereoselectivties.

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Supporting Information Available: General experimental procedures for reactions, NMR (^1H and ^{13}C) characterization data for new compounds. This material is available free of chage via Internet at http://pubs.acs.org.

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