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Direct *C*-Glycosylation by Indium-Mediated Alkynylation on Sugar Anomeric Position

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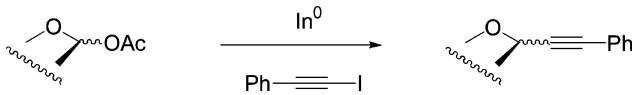
ABSTRACT



Indium-mediated alkynylation reaction was studied for the direct preparation of *C*-glycosides. Easily available starting sugar derivatives with an acetyl group at the anomeric position were tested as electrophiles toward alkynylindium reagents under Barbier conditions. Good yields and stereoselectivities were observed during the reaction. The alkynylation was applied to the synthesis of an α-(1→6)-*C*-disaccharide analogue of isomaltoside.

Over the last couple of years, indium has been receiving an increasing interest,[1] due to its smooth reactivity and its ease of use. Even though indium is particularly used in allylation reactions in polar solvents, we looked into its potential to catalyze alkynylation reactions of carbonyl compounds under Barbier conditions[2] and investigated new methods[3] to prepare *C*-glycosides. These nonhydrolyzable carbohydrate isosteres have become of great interest since they were found to have potent biological properties and to be useful building blocks. Thus, we successfully applied this reaction to *C*-glycosides synthesis,[4] using formylglucoses as electrophiles. We also demonstrated the possibility of accessing various functionalized *C*-glycosides after transformation of the resulting propargylic alcohols. The creation of the C−C bond by direct alkynylation, starting from more simple carbohydrate derivatives, represents a significant achievement. Such an alkynylation was previously carried out by the addition of ethynylmagnesium bromide and ethynylaluminium derivatives on D-glucopyranosyl bromide, which led to byproducts.[5] Organotin acetylides which are softer nucleophiles, were also used with sugar bromides,[6] but the application was limited by the toxicity of tin reagents which need to be prepared first. As a matter of fact, the most frequently used method is the addition of an organometallic reagent onto a sugar lactone.[7] The diastereoselectivity is controlled during the subsequent reduction of the lactol, leading to β isomers. An alternative to this approach is the addition of organometallic reagents to glycal epoxides. The control of the anomeric stereoselectivity is then dependent on the metal.[8] As suggested by our previous results on the indium-mediated Ferrier

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(2) Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* **2003**, *44*, 819.
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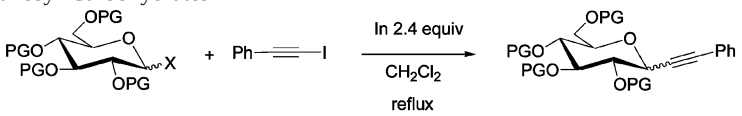
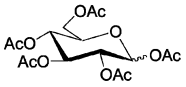
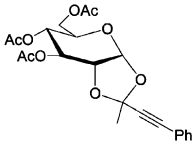
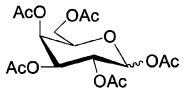
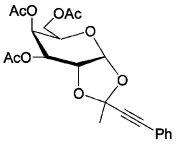
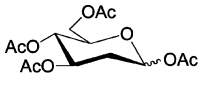
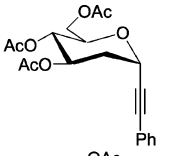
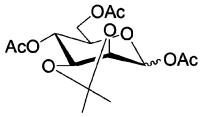
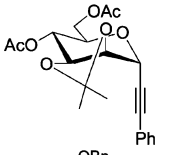
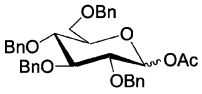
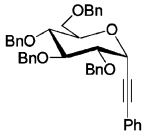
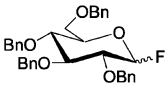
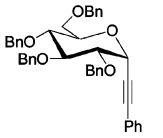
Table 1. Alkynylation of Pyranosyl Carbohydrates



entry	starting compound		anomeric mixture	time	yield %	final product		C-1 configuration
1		**1**	α/β = 20/80 α/β = 95/5	24 h 24 h	86 0		**2a**	α/β > 98/2 dr = 98/2
2		**3**	α/β > 2/98	26 h	92		**4**	α/β >98/2 dr = 89/11
3		**5**	α/β = 25/75 α/β = 88/12	16 h 48 h	70 71		**6**	α/β > 98/2
4		**7**	α/β > 98/2	24 h	66		**8**	α/β > 98/2
5		**9**	α/β = 25/75	48 h	60		**10**	α/β = 75/25
6		**11**	α/β = 10/90	16 h	52		**10**	α/β = 80/20

rearrangement,[9] we anticipated interesting reactivities of indium reagents for the anomeric center of peracetylated sugars.

We first studied this reaction with the β-D-glucopyranose pentaacetate **1**, the most accessible protected carbohydrate. The conditions determined in our previous works were followed with an excess of 2.4 equiv of metallic indium. The substrate disappeared as determined by tlc, leading to a well-defined spot. After isolation (86% yield) and characterization, the single compound was found to be the cyclic acetal **2a** and not the expected *C*-glycoside.

Compound **2a** was identified as a mixture of two α diastereomers in a 98:2 ratio resulting from the newly created quaternary stereogenic center. This compound results from the addition of the indium acetylenide species to the acetoxonium intermediate, formed by the participation of the acetate group in position 2. This participation is well-known and is generally used for 1,2-*trans* glycosylation. In fact, it was already reported by Wyatt[10] that, as opposed to the glycosylation, allenylstannanes in the presence of a Lewis acid add to the carbenium and not to the anomeric carbon. Compound **2** presents an H-1 chemical shift of 5.73 ppm inconsistent with a *C*-glycoside, but the α configuration was assigned by analogy with the NMR spectrum described by Wyatt. The same reactivity was observed with the galactose pentaacetate **3**. In this case, **4** was obtained with good yield as a mixture of α diastereomers in an 89:11 ratio (Table 1, entry 2).

In a second step, we chose to work on 2-deoxycarbohydrates to bypass this reactivity. The reaction was conducted

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(9) Lubin-Germain, N.; Hallonet, A. Huguenot, F.; Palmier, S.; Uziel, J.; Augé, J. *Org. Lett.* **2007**, *9*, 3679.

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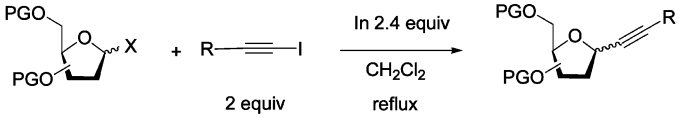
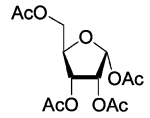
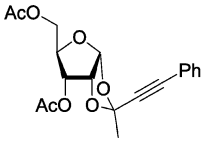
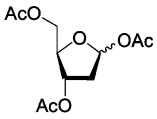
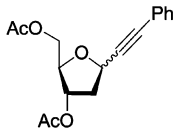
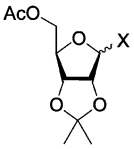
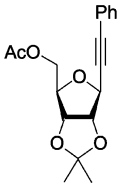
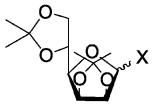
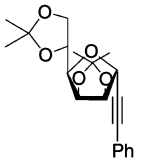
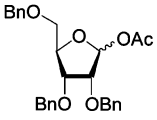
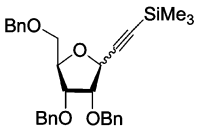
Table 2. Alkynylation of Furanosyl Carbohydrates



entry	starting compound		anomeric mixture	R	time	yield %	product		C-1 configuration
1		**13**	α/β = 30/70	Ph	27 h	68		**14**	α/β > 98/2 dr = 98/2
2		**15**	α/β = 40/60	Ph	3 h	96		**16**	dr = 32/68
3		**17a** **17b**	α/β = 14/86 α/β = 90/10	Ph Ph	24 h 24 h	60 53		**18**	α/β = 3/97 α/β = 10/90
4		**19**	α/β = 10/90	Ph	48 h	44		**20**	α/β = 94/6
5		**21**	α/β < 5/95	$SiMe_3$	16 h	67		**22**	α/β = 50/50

with tetra-*O*-acetyl-2-deoxyglucopyranose **5**. Starting from different mixtures of α/*β* anomers, we showed that the reaction rate is correlated to the anomeric mixture, i.e., to the ability to form the oxonium intermediate. The diastereoselectivity is then independent of the composition of the starting acetate. Therefore, we always observed the single α-*C*-glycoside **6** as the major product (Table 1, entry 3). The same diastereoselectivity was reported with organotin reagents.[11]

Using an acetonide as the nonparticipating protecting group, we carried out the alkynylation reaction with compound **7**. The *C*-glycoside **8** was isolated with a moderate yield but an excellent diastereoselectivity (Table 2, entry 4).

Interestingly, benzyl protected carbohydrates can also be used in this alkynylation reaction. Despite the decreased reactivity of these compounds toward organoindium species, the *C*-glycoside **10** was obtained with a moderate yield (60%). With the objective to enhance the reactivity, the fluorinated glucoside **11** was tested as a starting material. Even if the rate of the reaction increased, the yield significantly decreased (entry 6). Furthermore, as we demonstrated previously in the indium-mediated Ferrier rearrangement,[9] a significantly lower yield was observed when InBr was used instead of indium, due to the formation of compound **12** (Figure 1). We believe that this compound could result from a Friedel−Crafts-type reaction, that could

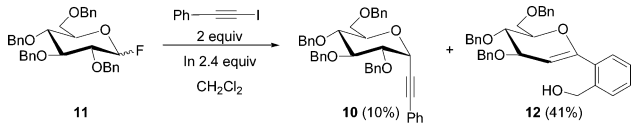


Figure 1. Friedel−Crafts reaction.

be mediated by the Lewis acid character of InBr, leading to an early oxonium transition state.

(11) Nishikawa, T.; Ishikawa, M.; Isobe, M. *Synlett* **1999**, 123.

Similar results were obtained with furanosyl compounds (Table 2). We also observed the participation of the *C*-2 acetate group with compound **13**, whereas the expected *C*-glycosylated compounds were obtained with the 2-deoxy-carbohydrate **15**[12] or with the acetonides **17**[13] and **19**, both bearing nonparticipating groups. Compounds **18**[14] and **20**[15] were isolated with moderate yields, and the stereochemistry of the *C*-glycosides depends on both the C-3 configuration[16] and the nature of the protecting group.[17] With compound **21**, a lack of selectivity was observed, resulting from equilibrium of the conformations leading to both attacks of the nucleophile.

Even if the alkynylation led to *β*-*C*-furanosylriboside (Table 2, entries 2, 3, 5), the reverse anomer could be obtained with the *manno* configuration (Table 2, entry 4). The configuration of the anomeric position of the compounds **18**[18] and **20** was determined by 2D-NMR spectroscopic analysis.

Ultimately, alkynylation conditions were applied to the synthesis of an α-(1→6)-*C*-disaccharide analogue of methyl isomaltoside. In the presence of the benzylated iodoglucopyranoside **23**,[9] the 2-deoxyglucopyranose **5** led to coupling product **24** with 53% yield. The single diastereomer obtained was transformed by treatment under hydrogen in the presence of Pd/C followed by acetylation leading to the α-(1→6)-*C*-disaccharide **25**. The stereochemistry of this compound was confirmed by reference to published data (Figure 2).[8a,19]

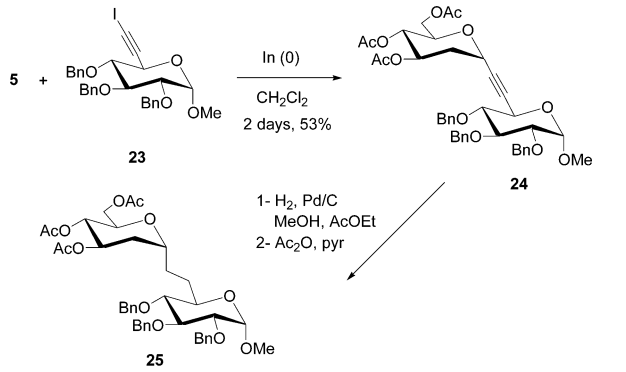


Figure 2. Methyl-2-deoxy-α-(1→6)-*C*-isomaltoside **25** synthesis.

In conclusion, we report herein a new access to *C*-glycosides from 2-deoxy acetylated carbohydrates using a new reaction in indium chemistry. For the carbohydrates bearing an oxygen atom on position 2, nonparticipating groups such as acetonide or benzyl groups, however, are required in this new indium-mediated *C*-glycosylation.

Acknowledgment. This research was supported by the French Ministry of Research and the CNRS.

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

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