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# Ferrier-Type Alkynylation Reaction Mediated by Indium

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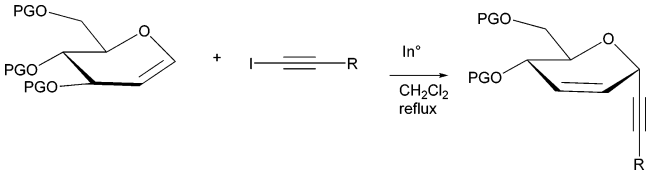
## ABSTRACT




**An efficient Ferrier-type alkynylation reaction between glycals and iodoalkynes using Barbier conditions is described. These conditions require $In^0$, $In^I$, or $In^{II}$ and lead to α-2,3-unsaturated-*C*-glycosides with good stereoselectivity. When glycosyliodoalkynes are used, trehalose-derived compounds and α-(1→6)-*C*-disaccharides are obtained.**

Addition of alkynyl derivatives to carbonyl compounds is an important reaction.[1] We have recently shown that iodoalkynes add to carbonyl compounds in the presence of a stoichiometric amount of metallic indium to afford propargylic alcohols.[2] Depending on the conditions of the reaction, an in situ oxidation of the propargylic alcohol can take place to give propargylic ketones.[3] As organoindium species were found to be tolerant of ester groups, this reaction could be applied in carbohydrate chemistry using acetate protecting groups. Thus, we realized the synthesis of *C*-glycosides[4] through the alkynylation of formylglycosides. We were also interested in the direct creation of the carbon−carbon bond at the anomeric center using indium-promoted alkynylation reaction[5] by a Ferrier rearrangement.

*C*-Glycosylation by silylacetylene addition to glucals using Lewis acids had been previously reported.[6] Iodine was also efficient as a catalyst in this reaction.[7]

Minehan's group[8] recently published the addition of triaryl, trivinyl, and trialkynylindium reagents to glycals. The authors emphasized the attraction of such reagents toward functionalized compounds and then their use in synthesis. The method[9] implies the transmetalation of trialkynylmagnesium bromide in the presence of indium trichloride, prior to the addition of the organometallic species.

We tried Barbier conditions,[10] mixing 2 equiv of iodophenylacetylene with tri-*O*-acetyl-D-glucal in the presence of 2.4 equiv of metallic indium. After 4 h under reflux of dichlo-

(1) Guillarme, S.; Plé, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355.

(2) Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* **2002**, *42*, 5255.

(3) Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* **2003**, *44*, 819.

(4) Picard, J.; Lubin-Germain, N.; Uziel, J.; Augé, J. *Synthesis* **2006**, 979.

(5) Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739.

(6) (a) Isobe, M.; Phoosaha, W.; Saeeng, R.; Kira, K.; Yenjai, C. *Org. Lett.* **2003**, *5*, 4883. (b) Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Russo, B.; Tagarelli, A. *Synthesis* **2006**, 332. (c) Yadav, J. S.; Raju, A. K.; Sunitha, V. *Tetrahedron Lett.* **2006**, *47*, 5269.

(7) (a) Yadav, J. S.; Reddy, B. V.; Rao, C. V.; Reddy, M. S. *Synthesis* **2003**, 247. (b) Saeeng, R.; Sirion, U.; Sahakipitchan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211.

(8) Price, S.; Edwards, S.; Wu, T.; Minehan, T. *Tetrahedron Lett.* **2004**, *45*, 5197.

(9) Baker, L.; Minehan, T. *J. Org. Chem.* **2004**, *69*, 3957.

(10) In a typical procedure, indium (2 g, 17.5 mmol) was stirred during 30 min under a vacuum/argon in a sealed tube. Then, a solution of iodophenylacetylene (3.35 g, 14.7 mmol) and tri-*O*-acetyl-D-glucal (2 g, 1 mmol) in anhydrous $CH_2Cl_2$ (40 mL) was introduced to the medium which was refluxed for 4 h. The mixture was treated with a saturated solution of $NaHCO_3$ (70 mL) and extracted with $CH_2Cl_2$. The combined organic phases were dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel (Cyclohexane-EtOAc, 85:15), and the compound **1b** was obtained as a yellow solid (1.83 g, 79%).

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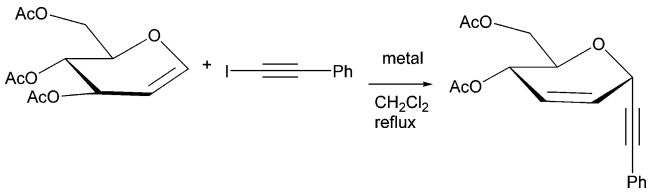
**Table 1.** Barbier Alkynylation of Tri-*O*-acetyl-D-glucal with Iodophenylacetylene




| entry | metal | time | yield (%) | α/β selectivity |
|---|---|---|---|---|
| 1 | $In^0$ | 4 h | 79 | 90/10 |
| 2 | InBr | 0.5 h | 57 | 82/18 |
| 3 | InBr[b] | 2 h | 50 | 70/30 |
| 4 | InCl | 4 h | 24 | 90/10 |
| 5 | $InCl_2$ | 4 h | 77 | 83/17 |
| 6 | $Mn^0$ | 42 h | traces | – |
| 7 | $Zn^0$ | 4 days | 30 | 88/12 |
| 8[a] | $In^0/Mn^0$ | 7 h | 46 | 84/16 |
| 9[a] | $In^0/Zn^0$ | 5 h | 35 | 83/17 |

[a] 10 mol % of $In^0$/2.4 equiv of metal. [b] Room temperature.

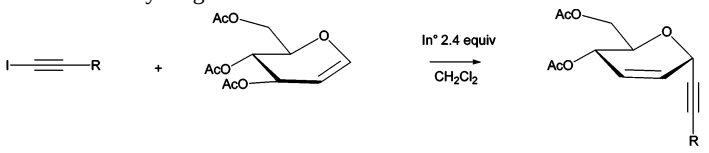
romethane, the *C*-alkynylglycoside **1b**[6b] was obtained in 79% yield with 90/10 α/*β* selectivity (Table 1). The need of the iodine atom of the alkyne was verified for this reaction as we observed the lack of reactivity when terminal alkyne was used in the presence of indium tribromide and triethylamine.[11] Concerning the choice of the solvent, this alkynylation reaction takes place efficiently in chlorinated solvents such as dichloromethane or dichloroethane,[2,3] contrary to the usual indium-mediated Barbier processes using aqueous media.

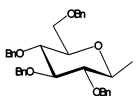
We were interested in testing indium in other oxidation states with the aim of knowing which oxidation states of the organoindium intermediates are involved in the reaction. Thus, $In^I$ was found to be very efficient for the catalysis of the reaction, and particularly, the reaction rate was increased with InBr (Table 1, entry 2). Then the reaction was performed at room temperature, but the yield did not improve (Table 1, entry 3). An $In^{II}$ salt led rapidly to the *C*-glycoside with a good yield (Table 1, entry 5). $In^{II}$ is now commercially available, and to our knowledge, it has not been mentioned in the literature in such reactions. However, the determination of the oxidation states of organoindium intermediates is under investigation.

On the other hand, as we had previously mentioned an $In^0$ catalytic system for allylation reactions,[12] we tried to transpose a similar system to the alkynylation reaction to avoid the use of a substoichiometric amount of indium. We first verified the absence or the low efficiency of $Mn^0$ and $Zn^0$ in the alkynylation (Table 1, entries 6 and 7). Then, when 10% $In^0$ was added, the *C*-glycoside was formed with modest yields (Table 1, entries 8 and 9).

In a second part of this work, we tried to apply the conditions to various alkynes. $In^0$ was chosen as the best compromise between reactivity and cost for a synthetic application (Table 2). The iodoalkynes **1a**, **2a**, **3a**, **4a**, **5a**, **6a**, **8a**, and **9a** were all prepared from the corresponding

**Table 2.** Alkynylation Reaction of Tri-*O*-acetyl-D-glucal with $In^0$

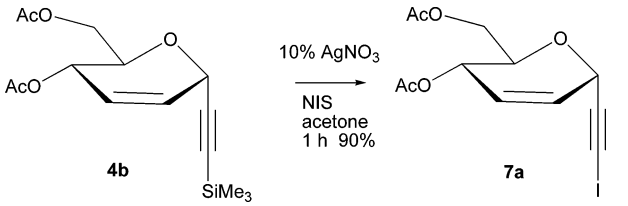



| entry | iodoalkyne | R | conditions | yield (%) | product | NMR data ppm | α/β selectivity |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | 4 h reflux | 79 | **1b** | $H_5$ 4.19<br>$C_5$ 70 | 90/10 |
| 2 | **2a** | $CH_2OAc$ | 7 h reflux | 54 | **2b** | $H_5$ 4.07<br>$C_5$ 70.4 | 88/12 |
| 3 | **3a** | $(CH_2)_5CH_3$ | 18 h reflux | 48 | **3b** | $H_5$ 4.05<br>$C_5$ 70 | >95/05 |
| 4 | **4a** | $SiMe_3$ | 24 h reflux | 82 | **4b** | $H_5$ 3.9<br>$C_5$ 70.2 | 85/15 |
| 5 | **5a** | $(CH_2)_3Cl$ | 6 h reflux | 64 | **5b** | $H_5$ 4.02<br>$C_5$ 69 | 92/08 |
| 6 | **6a** | $(CH_2)_3CN$ | 6 h rt | 75 | **6b** | $H_5$ 4.05<br>$C_5$ 70.2 | 93/07 |
| 7 | **7a** |  | 24 h reflux | 75 | **7b** | $H_5$ 4.05<br>$C_5$ 70.1 | 84/16 |
| 8 | **8a** | $(CH_2)_4$—≡—I | 16 h reflux | 34 | **8b** | $H_5$ 4.05<br>$C_5$ 70. | >95/05 |
| 9 | **9a** |  | 3 h reflux | 94 | **9b** | $H_5$ 4.05<br>$C_5$ 70 | >95/05 |

alkynes in the presence of iodine and morpholine in benzene.[4] The treatment of tri-*O*-acetyl-D-glucal with these iodoalkynes provided the *C*-pseudoglycals **1b**, **2b**,[13] **3b**, **4b**,[14] **5b**, and **6b** in a few hours under reflux of dichloromethane. In each case, the α-anomer was predominantly obtained. The determination of the α-selectivity was based on the NMR observations of H-5 and C-5. In fact, Isobe[6a,15] established an empirical rule dealing with the chemical shielding of H-5 between 4.07 and 4.09 ppm for the α-anomer and between 3.74 and 3.77 for the *β*-anomer. Moreover, the α-anomer presents a chemical shift[8] for the C-5 lower than 75 ppm. In the case of alkynylation with trimethylacetylene, Isobe explained the α selectivity by electronic effects on the oxocarbenium intermediates involved in the transformation.

To demonstrate the generality of the reaction, the trimethylsilylethynyl-*C*-glycoside **4b** was transformed into iodoethynyl-*C*-glycoside **7a** by treatment with silver nitrate and iodine (Scheme 1). The product **7a** was then involved

**Scheme 1.** Preparation of **7a**




in the Ferrier reaction with tri-*O*-acetyl-D-glucal and led to the *C*-disaccharide **7b** (Table 2, entry 7).

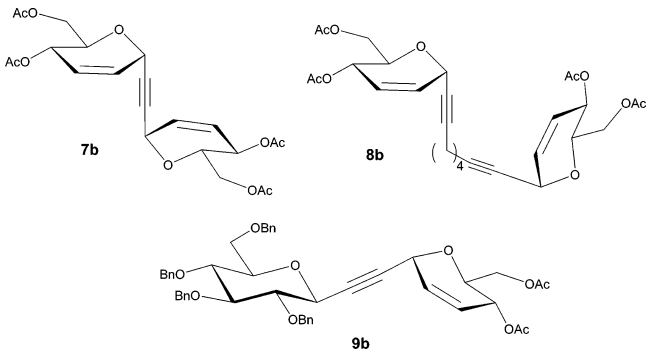
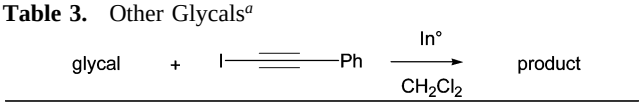


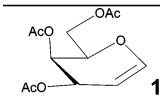
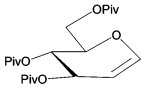
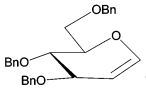
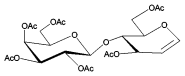

**Figure 1.** Trehalose derivatives.

Other *C*-disaccharides **8b** and **9b** (Figure 1) were obtained, by the simultaneous addition of 1,8-diiodoocta-1,7-diyne **8a** on tri-*O*-acetyl-D-glucal (Table 2, entry 8) and by addition of the organoindium species derived from **9a** on tri-*O*-acetyl-D-glucal (Table 2, entry 9).

Finally, the reaction was applied to other glycosidic electrophiles (Table 3). The first reaction was carried out with tri-*O*-acetyl-D-galactal, and the corresponding *C*-pseudogalactal **10b**[6b] was isolated with a good yield of 95%. Acetylated lactal **13a** was also found to be a good substrate for the reaction, furnishing *C*-alkynylglycoside **13b**.

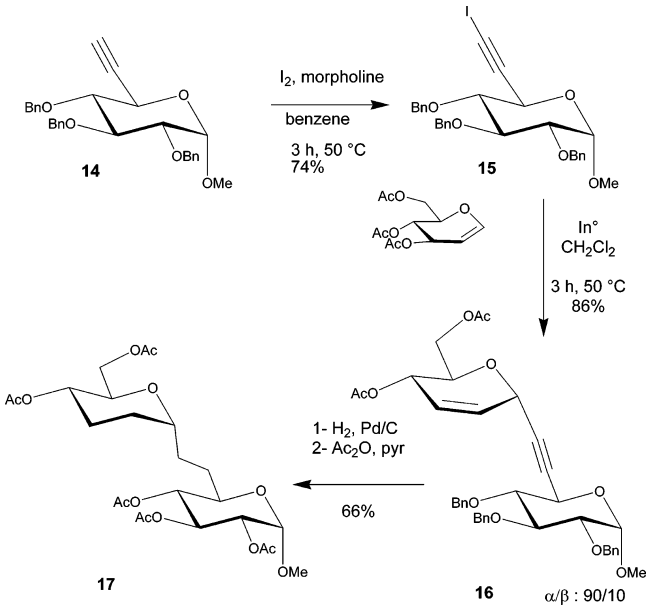
**Table 3.** Other Glycals[a]




| glycal | time | product | yield (%) | α/β selectivity |
|---|---|---|---|---|
|  **10a** | 16 h | **10b** | 95 | 83/17 |
|  **11a** | 24 h | **11b** | 93 | 85/15 |
|  **12a** | 2 days | **12b** | 67 | >95/5 |
|  **13a** | 16 h | **13b** | 65 | 78/22 |

[a] All reactions were carried out at reflux of dichloromethane (0.166 M solution) with 2 equiv of In(0) and 2.4 equiv of iodophenylacetylene.

**Scheme 2.** Synthesis of *C*-Disaccharide **17**




We also showed that pivaloyl and benzyl protecting groups could be used in this reaction, the time of reaction depending

(11) Sakai, N.; Hirasawa, M.; Konahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171. Under the conditions described here, no *C*-pseudoglucal was observed after 4 days in refluxing toluene.

(12) Augé, J.; Lubin-Germain, N.; Marque, S.; Seghrouchni, L. *J. Organomet. Chem.* **2003**, *679*, 79.

(13) Isobe, M.; Nishizawa, R.; Nishikawa, T.; Yoza, K. *Tetrahedron Lett.* **1999**, *40*, 6927.

(14) Isobe, M.; Saeeng, R.; Nishizawa, R.; Konobe, M.; Nishikawa, T. *Chem. Lett.* **1999**, *6*, 467.

(15) (a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.* **1993**, *34*, 5757. (b) Tanaka, S.; Isobe, M. *Tetrahedron* **1994**, *50*, 5633.

on the leaving-group ability of the protecting group employed. It is reasonable to think that the mechanism of the reaction is close to that given by Minehan's group[8] under Grignard conditions, as we also observed that the selectivity does not depend on the nature of the protected sugar.

To assess the scope of the reaction, we attempted the coupling with glycosyliodoalkyne with the aim to build a *C*-disaccharide (Scheme 2). Glycosyl alkyne **14**[16] was iodinated as described above, and iodoalkyne **15** was used for the coupling reaction. After 3 h, the *C*-disaccharide **16** was identified by TLC and isolated by flash chromatography in a very good yield of 84%. After hydrogenolysis−reduction in the presence of Pd/C and further acetylation, the disaccharide **17** was formed in 66% yield. The configuration was confirmed by NMR spectroscopy.

In conclusion, we have demonstrated that indium-mediated alkynylation offers a convenient access to *C*-glycosides with good yields and diastereoselectivities.

**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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(16) Chénedé, P.; Pothier, P.; Sollogoub, M.; Fairbanks, A. J.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1995**, 1373.