Indium-Mediated Alkynylation in C-Glycoside Synthesis

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Abstract: The indium-mediated alkynylation of perbenzylated or peracetylated formylglucose is a pathway for the synthesis of various C-glycosides. Hydroxylated, ketonic, mono- or difluorinated, and methylated C-glycosides were thus obtained.

Key words: indium, alkynylation, C-glycoside, fluorination

The synthesis of non-natural glycosides, in which the glycosidic oxygen is replaced by a methylene group, has received great interest during the last decades. Numerous methods have been described for the preparation of C-glycosides.1 Moreover, the replacement of the anomeric oxygen bond by a difluoromethylene group is promising for the synthesis of new glycoconjugates, as this unit is considered bioisosteric and isoplanar to oxygen.2

We recently described the indium-mediated alkynylation of carbonyl derivatives.3 In the case of aldehyde alkynylation, this reaction allows the preparation of propargylic alcohols or ketones according to the experimental conditions depicted in Scheme 1. In refluxing dichloromethane in the presence of indium (2.4 equiv) and two equivalents of alkynyl iodide, the propargylic alcohol was obtained, whereas in refluxing dichloroethane and with the aldehyde in excess (2.3 equiv) the reaction led to the propargylic ketone via an in situ Oppenauer-type oxidation.

Continuing our work in C-glycoside synthesis,4 we applied this reaction to 2,3,4,6-tetra-O-benzyl-1-formylglucopyranose (1) and 2,3,4,6-tetra-O-acetyl-1-formylglucopyranose (2) prepared according to literature procedures.5,6 The alkynylation was accomplished by mixing the aldehyde 1 or 2 with two equivalents of phenylacetyl-ene iodide 3 in dichloromethane in the presence of indium (2.4 equiv). It led to the corresponding propargylic alcohols 4 and 5 in 87% and 71% yields, respectively; both were obtained as mixtures of diastereomers in a ratio of 65:35 (Scheme 2). In the first case, the diastereomers were separated by chromatography on silica gel; the major product was less polar than the minor product. Even though the diastereoselectivity was low, it was in the same sense as in the case of Mg, Zn, or Ce reagents described by Genêt and co-workers.7

In order to obtain the corresponding propargylic ketone 6, we first applied the conditions allowing the in situ oxidation of the alcohol (excess of aldehyde in dichloroethane). Unfortunately, the expected ketone was not obtained, which is not surprising as we showed that the indium-mediated oxidation did not always proceed in the case of enolisable aldehydes.3b On the other hand, ketone 6 was easily

Scheme 1 Indium-mediated aldehyde alkynylation

Scheme 2 Indium-mediated alkynylation of 2,3,4,6-tetra-O-benzyl-1-formylglucopyranose (1) and 2,3,4,6-tetra-O-acetyl-1-formylglucopyranose (2)
obtained in 97% yield from the mixture of propargylic alcohols 4a and 4b by an oxidation with 2-iodoxybenzoic acid (IBX) (Scheme 2).

These two compounds 4 and 6 can be fluorinated in order to lead to the corresponding mono- and gem-difluorinated derivatives. We put the fluorination of propargylic alcohol 4a into practice by treatment with commercial diethylamino-sulfur trifluoride (DAST) at room temperature in dichloromethane. The expected fluorinated derivative 7 was thus obtained in 96% yield as a mixture of diastereomers in a ratio of 62:38. Compound 4b led to 7 in 90% yield and in a similar diastereomeric ratio (68:32). Both reactions afforded the same diastereomer as main product (Scheme 3).

In the case of propargylic ketone 6 the difluorination was performed in neat DAST at 55 °C leading to 8 in 42% yield (Scheme 4). This last compound is interesting because the difluoromethylene group is isosteric to oxygen. In order to access a C-glycoside with a methylene group in β-anomeric position, we first tried the Barton–McCombie deoxygenation of alcohol 4.

Unfortunately no reduction of the xanthate intermediate or the thiocarbonyldiimidazoyl derivative occurred by treatment with Bu3SnH/AIBN. This was certainly due to the presence of the conjugated C–C triple bond. As the reduction of this triple bond by treatment with tosyl-hydrazide did not succeed, we decided to realize the synthetic pathway starting from propargylic alcohol 5 bearing acetate protecting groups on the sugar moiety. In this case, after palladium-catalyzed hydrogenation, the alcohol 9 was obtained and led to the desired dehydroxylated product by successive treatment with thiocarbonyldiimidazole and tributyltin hydride (Scheme 5).

We have shown herein the utility of the indium-mediated alkylation reaction for the synthesis of a variety of C-glycosides starting from aldehydic sugar moieties. We are presently investigating the application of this pathway for the synthesis of C-glycosylated aminoacids using an acetylenic iodide of an aminoacid derivative.

IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. 1H, 13C, and 19F NMR spectra were recorded on a Bruker Avance 250 DPX (250 MHz) spectrometer. Indium was purchased from Aldrich and was activated by stirring in vacuo for 30 min. CH2Cl2 was dried over anhyd P2O5. 2-Iodoxybenzoic acid (IBX) was prepared according to a literature procedure. Optical rotations were determined at 25 °C in CHCl3, 589 nm, on a JASPO DIP 370 instrument.

**Iodophenylacetylene (3)**

A mixture of I2 (1.218 g, 4.8 mmol) and morpholine (1.14 mL, 13.1 mmol) in benzene (5 mL) was stirred for 30 min at r.t. until the formation of an orange solution. Phenylacetylene (980 mg, 4.35 mmol) diluted in benzene (8 mL) was then added and the medium was stirred at 45 °C for 24 h. After filtration and washing with Et2O (20 mL), the organic phase was washed with aq NH4Cl soln, NaHCO3 soln, and H2O. After drying with MgSO4 and filtration, the solvent was removed under reduced pressure. The crude product was puri-
fied by flash chromatography on silica gel (PE-EtOAc, 9:1) to give 3 (2.01 g, 92%) as a yellow oil.

1H NMR (250 MHz, CDCl3): δ = 7.25 (m, 3 H), 7.42 (m, 3 H).

13C NMR (62 MHz, CDCl3): δ = 6.6, 94.1, 123.2, 128.1, 128.7, 132.2.

1-(3,4,6-Tetra-O-benzyl-d-glucopyranosyl)-3-phenyl-prop-2-yn-1-ol (4)

To activated In (276 mg, 2.40 mmol) was added a solution of iodo-phenylacetylene (3) in anhyd CH2Cl2 (2.5 mL). Aldehyde 1 (553 mg, 1.00 mmol) in CH2Cl2 (10 mL) was introduced to the medium, which was refluxed overnight. The mixture was treated with a sat. NaHCO3 soln (10 mL) and extracted with CH2Cl2 (10 × 10 mL). The combined organic phases were dried over MgSO4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE-EtOAc, 85:15) to give 4a (374 mg, 57%) and 4b (198 mg, 30%) thus separated.

4a

IR (neat): 3357, 3030, 2864, 1490 cm–1.

1H NMR (250 MHz, CDCl3): δ = 4.58–4.99 (m, 9 H, PhCH2), 5.10–5.30 (m, 3 H, H-2, C-2), 7.22–7.35 (m, 25 H, Ar).

13C NMR (62 MHz, CDCl3): δ = 7.5 (CH2), 78.3, 79.2, 79.8, 80.7 (C-2 to C-5), 86.4 (C-C), 86.8 (C-I), 122.7 (Ar-C), 126.9–128.4 (Ar-CH), 131.7 (Ar-CH), 137.8–138.4 (Ar-C).

4b

IR: 3431, 2862, 1490 cm–1.

1H NMR (250 MHz, CDCl3): δ = 3.43–3.76 (m, 7 H, H-1 to H-6, H-7), 4.53–4.85 (m, 8 H, PhCH2), 5.55 (d, J = 48 Hz, 1 H, CHF), 7.11–7.35 (m, 25 H, Ar).

13C NMR (62 MHz, CDCl3): δ = 68.4 (C-6), 73.4, 75.1, 75.2, 75.8 (PhCH2), 78.1, 78.4, 79.5, 79.9 (C-2 to C-5), 82.3 (C-C), 83.20 (d, J = 123 Hz, CHF), 86.84 (C-I), 90 (C-C), 121.5 (Ar-C), 127.4–129.0 (Ar-CH), 132.0 (Ar-CH), 137.7–138.4 (Ar-C).

13C NMR (62 MHz, CDCl3; major diastereomer): δ = 68.4 (C-6), 73.4, 75.1, 75.2, 75.8 (PhCH2), 78.1, 78.4, 79.5, 79.9 (C-2 to C-5), 82.3 (C-C), 83.20 (d, J = 123 Hz, CHF), 86.84 (C-I), 90 (C-C), 121.5 (Ar-C), 127.4–129.0 (Ar-CH), 132.0 (Ar-CH), 137.7–138.4 (Ar-C).

1F NMR (235 MHz, CDCl3; major diastereomer): δ = –185.5 (dd, J = 47, 11.8 Hz).

1F NMR (235 MHz, CDCl3; minor diastereomer): δ = –189.5 (dd, J = 47, 23.6 Hz).


3-(3,4,6-Tetra-O-benzyl-d-glucopyranosyl)-3-fluoro-1-phenyl-prop-2-yn-1-ol (7)

To a DAST soln (54 mg, 0.33 mmol) in anhyd CH2Cl2 at –78 °C was added dropwise the alcohol 4a or 4b (154 mg, 0.235 mmol) in 2 mL of CH2Cl2. After stirring for 1 h, the temperature was allowed to reach 20 °C and stirring was continued for one additional hour. The mixture was treated with MeOH (2 mL) and a spatula of NaHCO3 was added. The crude product was concentrated in vacuo and then purified by flash chromatography on silica gel (PE-EtOAc, 9:1) to give 7 as a mixture of diastereomers (149 mg, 96% starting from 4a; 139 mg, 90% starting from 4b).

1H NMR (250 MHz, CDCl3): δ = 3.47–3.70 (m, 7 H, H-1 to H-6, H-7), 4.53–4.85 (m, 8 H, PhCH2), 5.55 (d, J = 48 Hz, 1 H, CHF), 7.11–7.35 (m, 25 H, Ar).

13C NMR (62 MHz, CDCl3; major diastereomer): δ = 68.4 (C-6), 73.4, 75.1, 75.2, 75.8 (PhCH2), 78.1, 78.4, 79.5, 79.9 (C-2 to C-5), 82.3 (C-C), 83.20 (d, J = 123 Hz, CHF), 86.84 (C-I), 90 (C-C), 121.5 (Ar-C), 127.4–129.0 (Ar-CH), 132.0 (Ar-CH), 137.7–138.4 (Ar-C).

13C NMR (62 MHz, CDCl3; minor diastereomer): δ = 68.9 (C-6), 73.4, 75.1, 75.2, 75.6 (PhCH2), 77.8, 78.5, 79.5, 80.1 (C-2 to C-5), 80.4 (d, J = 123 Hz, CHF), 82.5 (C-C), 88.64 (C-I), 89.8 (C-C), 121.5 (Ar-C), 127.4–129.0 (Ar-CH), 132.0 (Ar-CH), 137.7–138.4 (Ar-C).

1F NMR (235 MHz, CDCl3; major diastereomer): δ = –185.5 (dd, J = 47, 11.8 Hz).

1F NMR (235 MHz, CDCl3; minor diastereomer): δ = –189.5 (dd, J = 47, 23.6 Hz).

HRMS (CI): m/z [M + NH4]+ calcd for C43H45NO5F: 674.3270; found: 674.3270.

3-(3,4,6-Tetra-O-benzyl-d-glucopyranosyl)-3-difluoro-1-phenyl-prop-2-yn-1-ol (8)

Compound 6 (183 mg, 0.280 mmol) and DAST (361 mg, 2.24 mmol) were heated at 55 °C for 6 h. The mixture was treated with MeOH (2 mL) and a spatula of NaHCO3 was added. The crude product was concentrated under reduced pressure and then purified by flash chromatography on silica gel (PE-EtOAc, 9:1) to give 8 as a yellow oil (80 mg, 42%); [α]25D = –0.15 (c 5.4 CHCl3).

IR (neat): 3030, 2917, 2203, 1673, 1496 cm–1.

1H NMR (250 MHz, CDCl3): δ = 5.55–3.80 (m, 6 H, H-2 to H-6, H-7), 4.03 (d, J = 9.3 Hz, 1 H, H-1), 4.56–4.92 (m, 8 H, PhCH2), 7.20–7.49 (m, 25 H, Ar).

13C NMR (62 MHz, CDCl3): δ = 68.7 (C-6), 73.5, 75.1, 74.8, (PhCH2), 78.1, 79.4, 79.5, 83.7 (C-2 to C-5), 86.4 (C-I), 87.0 (C-C), 94.5 (C-C), 119.7 (Ar-C), 127.6–128.5 (Ar-CH), 133.4 (Ar-CH), 137.5–138.3 (Ar-C), 183.3 (CO).

HRMS (CI): m/z [M + NH₄]^+ calcd for C₄₃H₄₄NO₆F₂: 692.3188; found: 692.3190.

1-(2,3,4,6-Tetra-O-acetyl-D-glucopyranosyl)-3-phenylprop-1-ol (9)
To a solution of propargylic alcohol 5 (355 mg, 0.770 mmol) in dioxane–EtOH–H₂O (2:2:1) (6 mL) was added 10% palladium on carbon (81 mg). The medium was shaken for 3 h under 1 atm of H₂, then filtered through celite and the solvents were removed under reduced pressure. Compound 9 (340 mg, 95%) was obtained as mixture of diastereomers and used without purification.

1H NMR (250 MHz, CDCl₃; 9a + 9b): δ = 1.91–2.00 (m, 14 H, OAc, CH₂CHOH), 2.45 (s, 1 H, OH), 2.58 (m, 1 H, PhCH₂H), 3.21 (d, J = 8.4 Hz, 1 H, H-1), 3.39 (s, 1 H, CHOH), 3.50–3.59 (m, 1 H, H-5), 3.97–4.22 (m, 2 H, H-6, H-6¢), 4.92–5.16 (m, 3 H, H-2 to H-4), 7.10–7.23 (m, 5 H, Ar).

13C NMR (62 MHz, CDCl₃; 9a): δ = 21.0 (CH₃COO), 32.5 (CH₂CHOH), 35.1 (PhCH₃), 62.7 (C-6), 68.0 (CHOH), 69.0, 69.5, 74.5 (C-2 to C-4), 76.2 (C-5) 79.6 (C-1), 125.5, 128.0, 128.2 (Ar-CH), 141.4 (Ar-C), 169.1, 169.9, 170.2, 170.7 (CO).

13C NMR (62 MHz, CDCl₃; 9b): δ = 21.1 (CH₃COO), 32.1 (CH₂CHOH), 33.0 (PhCH₃), 62.5 (C-6), 70.31 (CHOH), 68.6, 68.8, 74.9 (C-2 to C-4), 76.2 (C-5) 80.7 (C-1), 125.5, 128.0, 128.2 (Ar-CH), 141.4 (Ar-C), 169.1, 169.9, 170.2, 170.7 (CO).

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-phenylprop-1-ol (10)
To a solution of 9 (99 mg, 0.214 mmol) in 2 mL of THF under Ar were added thiocarbonyldiimidazole (382 mg, 2.14 mmol) and DMAP (392 mg, 3.21 mmol) and the mixture was heated at 70 °C for 5 h. The medium was then concentrated under reduced pressure and filtered through celite in order to remove the excess thiocarbonyldiimidazole and DMAP. The residue was then diluted with anhyd toluene and Bu₃SnH (577 mL, 2.14 mmol) and AIBN (35 mg, 0.21 mmol) were successively added under Ar. This mixture was heated at 85 °C for 3 h. After concentration in vacuo, the crude product was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 1:1) to give 10 (52 mg, 54%) as a colorless oil; [α] D25 –9.9 (c 3.5 CHCl₃).

1H NMR (250 MHz, CDCl₃): δ = 1.46 (m, 4 H, CH₃CH₂C₂H₂), 1.91 (m, 12 H, OAc), 2.53 (t, J = 7.6 Hz, 2 H, PhCH₂), 3.33 (m, 1 H, H-1), 3.52 (m, 1 H, H-1), 4.00 (dd, J = 12.0, 2.0 Hz, 1 H, H-6), 4.17 (dd, J = 12.3, 5.0 Hz, 1 H, H-6¢), 4.80 (t, J = 9.6 Hz, 1 H, H-2), 4.96 (t, J = 9.7 Hz, 1 H, H-3), 5.08 (t, J = 9.2 Hz, 1 H, H-4), 7.07–7.23 (m, 5 H, Ar-CH).

13C NMR (62 MHz, CDCl₃): δ = 20.7 (CH₃COO), 26.6 (CH₂CH₂), 30.5 (CH₂CH₂), 35.3 (PhCH₃), 62.3 (C-6), 68.6 (C-3), 71.8 (C-2), 74.3 (C-4), 75.6 (C-5), 77.5 (C-1), 125.7, 128.2, 128.3 (Ar-CH), 141.9 (Ar-C), 169.4, 169.6, 170.3, 170.6 (CO).


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