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APPROACH TO THE VALORIZATION OF CARBOHYDRATES AS RAW MATERIALS BY MICROWAVE-ASSISTED NEAT 1,3-DIPOLAR CYCLOADDITION

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By reaction of C,N-diphenylnitrone and carbohydrates with a crotonyl side chain at their primary or anomeric carbon position, we explore the application of sugar derivatives as raw materials and chiral inducers in microwave-assisted neat 1,3-dipolar cycloadditions.

Keywords: Carbohydrate; chiral auxiliary; 1,3-dipolar cycloaddition; microwave; neat reaction

INTRODUCTION

Cycloaddition reactions employing conventional methodologies usually require the use of harsh reaction condition. Consequently, these reactions rapidly became suitable candidates for studies using microwave (MW) irradiation.[1–3] In particular, 1,3-dipolar cycloaddition (1,3-DC) is one of the most important methods for the construction of five-membered heterocyclic rings.[4] Several dipolarophiles have been used, such as nitrones, azides, and nitrile oxides, among many others.[5,6] By the application of chiral starting materials, it is often possible to control regioselectivity, endo/exo selectivity, and diasterofacial selectivity in these reactions. Carbohydrates are good candidates in this practice[7–12] because they are highly functionalized molecules with complex stereochemistry resulting from the presence of several chiral centers. Sugars also constitute a suitable renewable source in organic synthesis: antibiotics, nucleotides, and several other optically pure noncarbohydrate natural products can be synthesized from these natural precursors.

RESULTS AND DISCUSSION

During our previous studies,[13] we applied MW-assisted neat procedures for the synthesis of a library of open-chain nitrones and isoxazolidines. As a continuation of our interest in the selective derivatization of sugars with unsaturated

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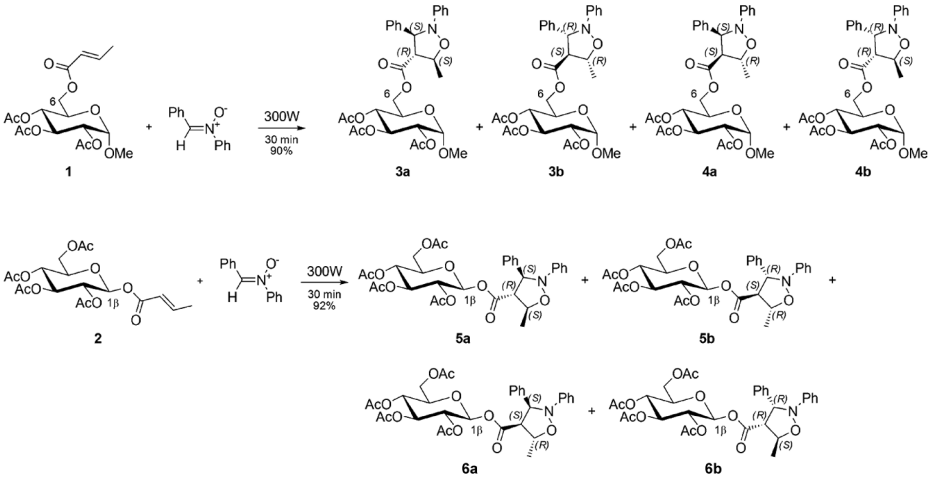
moieties,[14] we envisaged the possibility of applying 1,3-DC for the construction of asymmetric isoxazolidines using carbohydrates as chiral auxiliaries. The presence of the optically pure carbohydrate moiety has also the advantage of producing only diastereoisomers, which we are able to distinguish by analytical and spectroscopical analyses.

With this purpose, some crotonyl sugars were synthesized by applying the methodology described previously,[14] which were then reacted with *C,N*-diphenylnitrone under MW irradiation in neat conditions, producing optically active isoxazolidines.

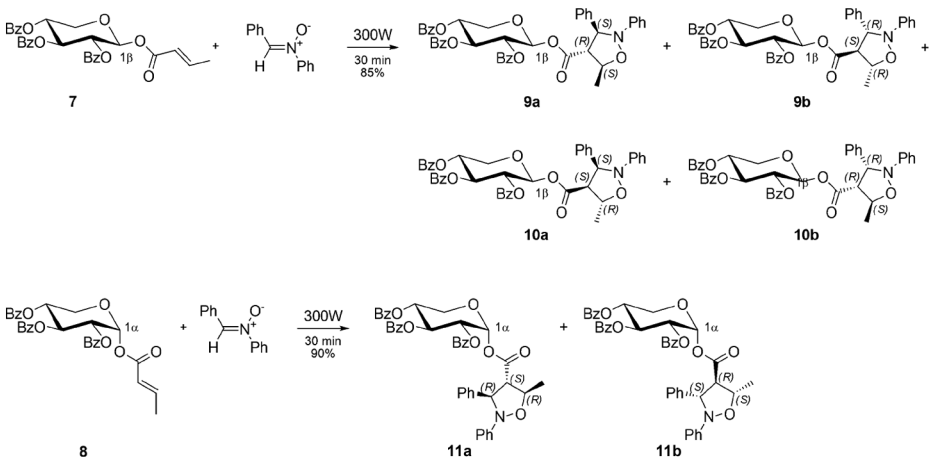
Cycloaddition to the crotonyl moiety located at the primary carbon position of glucose derivative **1** (Scheme 1) afforded two major diastereoisomeric products, **3** and **4**, in yields of more than 90%; cycloadducts **3** show a 3,4-*trans*-4,5-*trans* relationship at the heterocyclic ring, whereas **4** are 3,4-*cis*-4,5-*trans*. The ratio observed was **3**/**4** of 87:13. The ^{1}H NMR spectrum indicated the presence of two diasteriomeric products **3a** and **3b**, but their ratio could not be measured because of overlapping peaks.

Similar results were obtained at the α-anomeric position of glucose (**2**, Scheme 1) with the ratio **5**/**6** of 90:10. For this derivative, it was possible to measure the ratio of the *endo* products **5a**/**5b** as 66:44. In terms of yield and 3,4-*trans*-4,5-*trans*:3,4-*cis*-4,5-*trans* ratio, these results are similar to those found for analogous cycloaddition without the carbohydrate moiety,[15] but the sugar does seem to confer some facial selectivity to the reaction.

For xylose derivatives, different results were achieved when comparing both α and β anomers (Scheme 2). For the β-anomer (**7**), the ratio obtained for **9**/**10** could not be accurately determined because of some overlapping of signals. The two diastereoisomers, **9a** and **9b**, show a ratio of 57:43, denoting a minor facial selectivity when compared to the analogous anomer of glucose. However, when the α-anomer of xylose (**8**) was treated with *C,N*-diphenylnitrone, we could only detect the



Scheme 1. MW-neat cycloadditon using crotonyl-glucose derivatives.



Scheme 2. MW-neat cycloaddition using crotonyl-xylose derivatives.

presence of isoxazolidine isomers **11**, and the facial selectivity is improved to the ratio **11a**/**11b** of 81:19. This result is promising for further exploration the chiral assistance of the α-isomers of monosaccharides.

The previous sugar derivatives can also be interesting for biological studies after removal of all protecting groups, producing isoxazolidines linked to a hydrophilic moiety.

Furthermore, the results obtained are promising for the use of carbohydrates as chiral assistants in the asymmetric synthesis of isoxazolidines. By changing the unsaturated side chain in the carbohydrate moiety, we can synthesize a library of novel isoxazolidines linked to sugars at different carbon positions. Disaccharides, such as sucrose, are also excellent candidates for these reactions.[14]

In summary, the present study represents a potential and efficient methodology for obtaining optically active isozazolidines, by MW-assisted synthesis, in the absence of catalyst or solid supports.

EXPERIMENTAL

General Procedures

All solvents were purified before use. All reactions were monitored by thin-layer chromatography (TLC), which was performed on aluminium-backed silica-gel Merck 60 F_{254} plates, and compounds were detected by ultraviolet (UV) light or by staining with 10% solution of H_2SO_4 in ethanol followed by heating. Flash chromatography was carried out using silica gel from Macherey-Nagel (Kieselgel 60 M). Preparative-layer chromatography was performed on glass plates coated with 1 mm of silica gel (Mackerey-Nagel, Kieselgel DGF_{254}). Elemental analyses were performed on a Thermo Finnigan-CE Flash EA 1112 CHNS series analyzer. NMR spectra were recorded on a Bruker AMX 400-MHz apparatus in $CDCl_3$, using tetramethylsilane (TMS) as internal standard, with chemical shift values (δ) in parts per million (ppm). Structural assignment of all new compounds

was made by bi-dimensional NMR techniques (correlation spectroscopy 45, heteronuclear multiple quantum correlation, nuclear overhauser effect spectroscopy, total correlation spectroscopy). Microwave experiments were conducted in a Milestone MicroSynth apparatus. Temperatures were measured at the surface of the vessel with a built-in contactless infrared (IR) sensor which provides a ±1°C precision (according to the manufacturer).

Synthesis of Carbohydrate-Derived Isoxazolidines—General Method

Glucose and xylose derivatives were synthesized as described in a previous work.[14] Then 0.1 g (1 equiv.) of sugar derivative and 1.2 equiv. of nitrone were placed in an open flask. The heterogeneous solid mixture was positioned in the center of the MW cavity, over a Weflon-made support provided by the manufacturer, and irradiated for 30 min at 300 W. Reactions were monitored by thin-layer chromatography (TLC). After completion, products were purified by preparative-layer chromatography with the eluent indicated for each case.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-[3′*RS*-(3′*R**,4′*S**,5′*R**)-2′,3′-di-phenyl-5′-methyl-isoxazolidin-4′-yl]-α-D-glucopyranoside (3) and Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-[3′*RS*-(3′*R**,4′*R**,5′*S**)-2′,3′-di-phenyl-5′-methyl-isoxazolidin-4′-yl]-α-D-glucopyranoside (4)

Eluent: ether–hexane 2:1, 135.7 mg, 90%, colorless oil. Ratio **3**:**4** = 87:13. Anal. calcd. for $C_{30}H_{35}NO_{11}$: C, 61.53; N, 2.39; H, 6.02. Found: C, 61.58; N, 2.28; H, 6.20.

Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (“fake” t, J = 5.9 Hz, 3H, $CH_{3(isox)}$), 2.00, 2.02, 2.08 (3 s, 3 × 3H, 3 × CH_3), 3.21–3.27 (m, 1H, H-4′), 3.29 (s, 3H, OCH_3), 3.93 (td, J = 10.2, 3.5 Hz, 1H, H-5), 4.18 (t, J = 4.8 Hz, 2H, H-6), 4.41–4.52 (m, 1H, H-5′), 4.77 (dd, J = 10.2, 3.5 Hz, 1H, H-2), 4.85–4.91 (m, 2H, H-1, H-4), 5.20 (d, J = 6.7 Hz, 1H, H-3′), 5.44 (t, J = 9.8 Hz, 1H, H-3), 6.92 (t, J = 7.3 Hz, 1H, NPh-*H*), 7.00 (dd, J = 7.8, 4.1 Hz, 2H, NPh-*H*), 7.29 (m, 4H, NPh-*H*, Ph-*H*), 7.39 (t, J = 7.6 Hz, 2H, Ph-*H*), 7.56 (t, J = 8.2 Hz, 2H, Ph-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4 ($CH_{3(isox)}$), 20.5, 20.6 (CH_3), 55.3 (OCH_3), 62.7 (C-6), 65.4 (C-4′), 66.8 (C-5), 68.5 (C-4), 69.8 (C-3), 70.6 (C-2), 73.2 (C-3′), 77.5 (C-5′), 96.5 (C-1), 113.9, 121.4, 127.6, 128.8, 128.9, 141.7, 151.4 (*C*-Ar), 169.4, 169.9 ($C{=}O_{(Ac)}$), 170.0, 170.1 (isox-*C*=O).

Compound **4**: Detected in the isomeric mixture by ^{1}H NMR analysis (only some peaks are distinguishable). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, J = 6.1 Hz, Hz, 3H, $CH_{3(isox)}$), 4.79–4.85 (m, 2H, H-3′, H-5′).

1-*O*-[3′*RS*-(3′*R**,4′*S**,5′*R**)-2′,3′-Di-phenyl-5-methyl-isoxazolidin-4′-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (5) and 1-*O*-[3′*RS*-(3′*R**,4′*R**,5′*S**)-2′,3′-Di-phenyl-5′-methyl-isoxazolidin-4′-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (6)

Eluent: ether–hexane 1:2, 132.6 mg, 90%, colorless oil. Ratio **5**:**6** = 90:10. Anal. calcd. for $C_{31}H_{35}NO_{12}$: C, 60.68; N, 2.28; H, 5.75. Found: C, 60.49; N, 2.12; H, 5.96.

Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (d, $J = 6.0$ Hz, 3H, $CH_{3(\text{isox minor})}$), 1.55 (d, $J = 5.9$ Hz, 3H, $CH_{3(\text{isox major})}$), 1.90 (s, 3H, $CH_{3(\text{major})}$), 1.93 (s, 3H, $CH_{3(\text{minor})}$), 2.01 (s, 6H, $2 \times CH_{3(\text{Ac})}$), 2.03 (s, 6H, $2 \times CH_{3(\text{Ac})}$), 2.04 (s, 3H, $CH_{3(\text{Ac, major})}$), 2.05 (s, 3H, $CH_{3(\text{Ac, minor})}$), 3.24 (dd, $J = 8.8$, 6.8 Hz, 1H, H-4′$_{(\text{major})}$), 3.30 (dd, $J = 8.6$, 6.3 Hz, 1H, H-4′$_{(\text{minor})}$), 3.77–3.85 (m, 2H, H-5), 4.17 (ddd, $J = 12.6$, 10.1, 4.7 Hz, 2H, H-6$_{(\text{major})}$), 4.21–4.37 (m, 3H, H-5′$_{(\text{minor})}$, H-6$_{(\text{minor})}$), 4.51 (dq, $J = 8.9$, 5.9 Hz, 1H, H-5′$_{(\text{major})}$), 5.04–5.28 (m, 8H, H-3, H-3′, H-2, H-4), 5.70 (d, $J = 8.2$ Hz, Hz, 1H, H-1$_{(\text{major})}$), 5.71 (d, $J = 8.0$ Hz, 1H, H-1$_{(\text{minor})}$), 6.88–7.03 (m, 6H, NPh-*H*), 7.19–7.34 (m, 6H, Ph-*H*), 7.34–7.42 (m, 4H, NPh-*H*), 7.47–7.55 (m, 4H, Ph-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 17.7, ($CH_{3(\text{isox})}$), 20.4, 20.5, 20.7 (CH_3), 61.3 (C-6), 65.1 (C-4′), 67.7 (C-4), 70.0 (C-2), 72.6, 72.8, 73.2 (C-3, 3′, 5), 77.3 (C-5′), 92.2 (C-1), 114.0, 114.11, 115.8 121.7, 126.4, 127.8, 129.0, 141.3, 141.4, 151.0, 151.2 (*C*-Ar), 168.8, 168.9, 169.3 ($C{=}O_{(\text{Ac})}$), 170.0, 170.5 (isox-*C*=O).

Compound **5:** Detected in the isomeric mixture by ^{1}H NMR analysis (only some peaks are distinguishable). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, $J = 6.0$ Hz, Hz, 3H, ($CH_{3(\text{isox})}$), 3.33 (t, $J = 9.7$ Hz, 1H, H-4′$_{(\text{minor})}$), 3.39 (t, $J = 9.57$ Hz, 1H, H-4′$_{(\text{major})}$).

1-*O*-[3′*RS*-(3′*R**,4′*S**,5′*R**)-2′,3′-Di-phenyl-5′-methyl-isoxazolidin-4′-yl]-2,3,4-tri-*O*-benzoyl-β-D-xylopyranose (9) and 1-*O*-[3′*RS*-(3′*R**,4′*R**,5′*S**)-2′,3′-Di-phenyl-5′-methyl-isoxazolidin-4′-yl]-2,3,4-tri-*O*-benzoyl-β-D-xylopyranose (10)

Eluent: ether–hexane 1:2, colorless oil, 116.6 mg, yield 85%. Anal. calcd. for $C_{43}H_{37}NO_{10}$: C, 70.97; N, 1.92; H, 5.12. Found: C, 70.99; N, 1.81; H, 5.44.

Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, $J = 5.0$ Hz, 3H, $CH_{3(\text{isox, minor})}$), 1.45 (d, $J = 5.1$ Hz, 3H, $CH_{3(\text{isox, major})}$), 3.18 (t, $J = 7.2$ Hz, 2H, H-4′), 3.80 (dd, $J = 11.7$, 7.2 Hz, 1H, H-5$_{(\text{major})}$), 4.33 (m, 2H, H-5$_{(\text{minor})}$, H-5′), 4.48 (m, 1H, H-5′), 5.09 (d, $J = 6.1$ Hz, 1H, H-3′$_{(\text{major})}$), 5.16 (d, J=6.3 Hz, 1H, H-5$_{(\text{minor})}$), 5.33 (m, 2H, H-4), 5.46 (m, 2H, H-2), 5.79 (m, 2H, H-3), 6.07 (d, $J = 5.2$ Hz, 2H, H-1), 6.89 (t, $J = 8.4$ Hz, 6H, $6 \times$ NPh-*H*), 7.22 (m, 10H, $4 \times$ NPh-*H*, $6 \times$ Ph-*H*), 7.38 (m, 16H, $4 \times$ Ph-*H*, $12 \times$ Bz-*H*), 7.52 (m, 6H, $6 \times$ Bz-*H*), 7.95 (2d, $J = 7$ and $J = 7.4$ Hz, 12H, $12 \times$ Bz-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 17.5 (CH_3), 62.6 (C-5), 62.2 (C-4′$_{(\text{major})}$), 65.5 (C-4′$_{(\text{minor})}$), 68.6 (C-4), 69.1 (C-2$_{(\text{minor})}$), 69.2 (C-2$_{(\text{major})}$), 69.9 (C-3$_{(\text{minor})}$), 70.1 (C-3$_{(\text{major})}$), 77.5 (C-5′$_{(\text{major})}$), 77.7 (C-5′$_{(\text{minor})}$), 97.7 (C-1), 113.9, 114.1, 121.7, 126.1, 126.3, 127.7, 127.8, 128.5, 128.7, 128.8, 129.0, 129.8, 130.0, 133.6, 141.3, 151.1 (*C*-Ar), 164.9, 165.2, 165.5 ($C{=}O_{(\text{Ac})}$), 169.0, 169.1 (isox-*C*=O).

1-*O*-[3′*RS*-(3′*R**,4′*S**,5′*R**)-2′,3′-Di-phenyl-5′-methyl-isoxazolidin-4′-yl]-2,3,4-tri-*O*-benzoyl-α-D-xylopyranose (11)

Eluent: ether–hexane 1:2, colorless oil, 123.5 mg, yield 90%. Anal. calcd. for $C_{43}H_{37}NO_{10}$: C, 70.97; N, 1.92; H, 5.12. Found: C, 70.78; N, 1.93; H, 5.34. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (d, $J = 6.0$ Hz, 3H, $CH_{3(\text{isox major})}$), 1.57 (d, $J = 6.0$ Hz, 1H, $CH_{3(\text{isox minor})}$), 3.33 (m, 2H, H-4′), 3.47 (m, 1H, H-5a$_{(\text{minor})}$), 3.57 (t, $J = 10.9$ Hz, 1H, H-5a$_{(\text{major})}$), 4.13 (m, 2H H-5b), 4.38 (qd, $J = 9.4$, 6.0 Hz, 1H, H-5′$_{(\text{minor})}$), 4.54 (qd, $J = 8.8$, 6.0 Hz, 1H, H-5′$_{(\text{major})}$), 5.07 (d, $J = 6.4$ Hz, 1H, H-3′$_{(\text{major})}$), 5.24

(d, $J = 6.6$ Hz, 1H, H-3′$_{(minor)}$), 5.43 (m, 4H, H-2, H-4), 6.00 (t, $J = 10.0$ Hz, 1H, H-3$_{(minor)}$), 6.06 (t, $J = 9.9$ Hz, 1H, H-3$_{(major)}$), 6.58 (d, $J = 3.8$ Hz, 1H, H-1$_{(minor)}$), 6.59 (d, $J = 3.6$ Hz, 1H, H-1$_{(major)}$), 7.03–6.78 (m, 6H, 6 × NPh-*H*), 7.66–7.11 (m, 32H, 4 × NPh-*H*, 10 × Ph-*H*, 18 × Bz-*H*), 7.92 (m, 12H, 12 × Bz-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2 (*C*H$_3$), 60.9 (C-5), 65.5 (C-4′), 68.7 (C-4), 69.0 (C-2), 69.9 (C-3), 73.4 (C-5′), 89.9 (C-1), 113.4, 121.3, 126.0, 128.0, 128.1, 128.2, 128.7, 129.3, 129.4, 133.0, 133.2 (*C*-Ar), 165.0, 165.3 (*C*=O$_{(Ac)}$), 168.6 (isox-*C*=O).

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