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Ultrasound-assisted synthesis of C-glycosides

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ABSTRACT

A significant rate enhancement was observed in the preparation of allyl and allenyl-C-glycosides from glycosyl acetate or methyl *O*-glycoside precursors when ultrasound irradiation was employed as an energy source. The C-glycosides were obtained in 77–96% yields in <20 min using TMSOTf as promoter. These results show that sonication provides rapid and efficient access to useful C-glycoside-based building blocks.

In recent years C-glycoside formation has been one of the more studied topics in carbohydrate chemistry.[1] This is due to the relative difficulty encountered in the synthesis of C-glycosides as well as the potential of such glycomimetics in medicine and biology. The C-glycoside analogues of *O*-glycosides can be resistant to glycosylhydrolases, for example.[2] It has been established that C-glycoside analogues of naturally occurring *O*-glycosides can often display interesting differences in their reactivity and biological activity in a variety of contexts.[3]

Synthesis of many different C-glycoside derivatives can commence from allyl or allenyl-C-glycoside-based precursors.[4] Methods which lead to an improvement in the yields and/or to the rates of formation of these C-glycoside building blocks would be helpful for researchers working in these areas.

Recently, ultrasonic energy[5] has been employed successfully to facilitate or improve a number of traditional reactions which include protecting group manipulations,[6] copper catalysed azide–alkyne cycloaddition reactions,[7] acyl migrations,[6] glycosylation reactions[6] and Suzuki/Heck type reactions.[8] We thus investigated the effect of ultrasonic radiation on C-glycoside formation. As part of an on-going research programme[9] we required access to a number of C-glycosides and were interested to evaluate any potential advantage of using non-traditional energy sources to carry out C-glycoside building block synthesis. In the first experiment tried we found that the allylation of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**), in the presence of TMSOTf and allyltrimethylsilane was complete within 15 min when the reaction was carried out in the presence of ultrasound radiation. This reaction was incomplete after 2 h using conventional heating showing that ultrasonic radiation significantly enhances the C-glycosidation reaction. These conditions were then tested for their suitability to prepare other protected C-glycoside derivatives (Tables 1 and 2). The rate enhancement was also observed for formation of a variety of 1-allyl- and 1-allenyl-C-glycosides with α-configuration, which were all easily obtained in <20 min from the corresponding methyl glycoside or glycosyl acetate precursor (Tables 1 and 2); the precursors **1–6** were derived from D-glucose, D-mannose and D-galactose. Increasing the reaction temperature for the preparation of such C-glycosides instead of using ultrasonic radiation was not found to be useful. The reactions of **1–6** were significantly faster in the presence of ultrasound radiation than similar reactions carried out at room temperature which generally required 24–40 h.[10] As an example, the mannoside derivative **4** was completely converted into the C-glycoside **10** (isolated yield of 95%) in just 15 min; in the absence of ultrasonication there was almost no product observed after 2 h. The α-configuration assigned to the mannoside products **10** and **16** was supported by coupling constants (J_{H1-C1} ~150 Hz), which are larger than those observed for β-anomers (J_{H1-C1} ~143 Hz) in related compounds.[11] A small amount of the β-anomer of **9** and **15** was generated from the allylation and allenylation of **3** (~7%); the β-anomers for all other C-glycosides were found to be present in yields <2%.

In a typical reaction procedure[12] the saccharide precursor (100 mg) was dissolved in acetonitrile in a Biotage microwave vial and treated with TMSOTf and the silylated nucleophile. The tube was sealed and placed in an ultrasonic cleaning bath (frequency 50/60 Hz × 230 V) until the reaction was complete by TLC. The C-glycosidation was complete within 15–20 min and the products were isolated in good yields after work-up and

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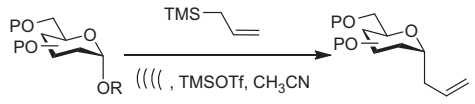
Table 1
Synthesis of l-allyl-C-glycosides from **1** to **6**



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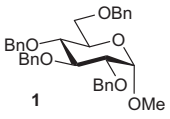
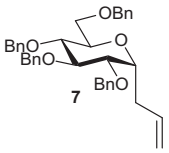
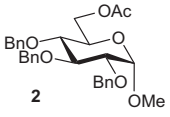
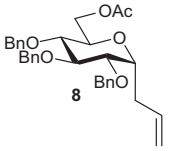
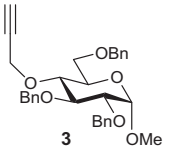
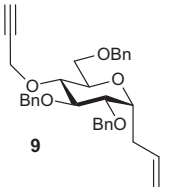
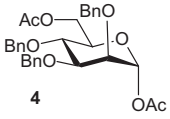
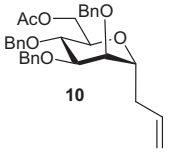
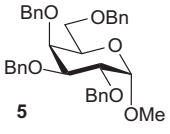
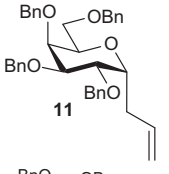
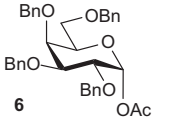
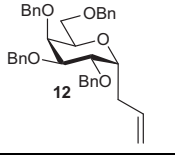
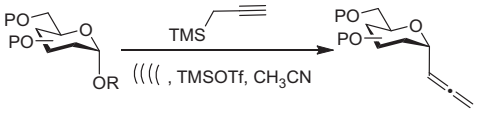
1			78	15
2			80	15
3			90	20
4			95	15
5			89	20
6			83	20

Table 2
Synthesis of l-allenyl-C-glycosides **1**–**6**



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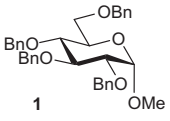
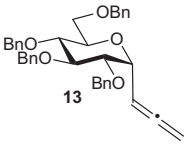
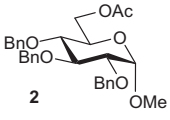
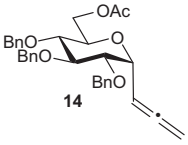
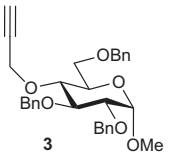
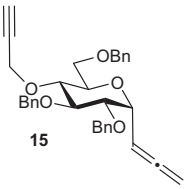
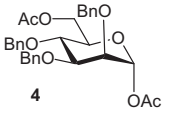
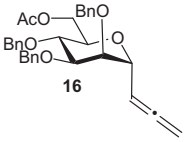
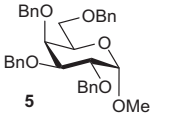
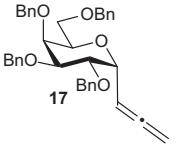
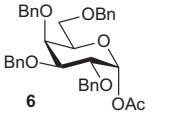
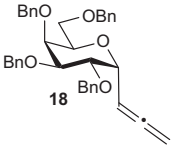
1			77	15
2			78	15
3			83	20
4			96	15
5			87	20
6			87	20

purification (see Tables 1 and 2). The structure of all new products was supported by ^{1}H NMR and ^{13}C NMR spectroscopy as well as high resolution mass spectrometry.[13] All known compounds had analytical data in agreement with those reported previously.[10,4b–e]

In conclusion, ultrasonication has led to an improvement in the reaction conditions for the preparation of C-glycosides, as has been shown in the preparation of a series of glucose, mannose and galactose derivatives. The allylation and allenylation were performed at ambient temperature with excellent enhancements of reaction rates by use of ultrasonic irradiation in a sealed tube. Under these conditions the desired stereoselectivity of the products and high yields were recorded. These building blocks are currently being used in the synthesis of new carbohydrate derivatives of biological interest.

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Supplementary data

Supplementary data (general experimental conditions and NMR spectra for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.113.

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12. To methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**) (100 mg, 0.18 mmol) in dry MeCN (2.0 mL) under N_2 at room temperature, allyl trimethylsilane or propargyltrimethylsilane (0.36 mmol) was added, followed by dropwise addition of trimethylsilyl triflate (20 mg, 0.09 mmol) before closing the vessel. The reaction mixture was then sonicated for 15 min, after which it was quenched with saturated aqueous $NaHCO_3$ (2.0 mL), diluted with EtOAc (5.0 mL) and washed with brine (3.0 mL). The separated organic extracts were combined, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give an oil. Chromatography of the oil (cyclohexane–EtOAc, 8:1) gave **7** or **13**.
13. Analytical data for selected compounds:
Compound **9**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.26 (m, 15H; aromatic H), 5.86–5.77 (m, 1H; alkene CH), 5.13–5.06 (m, 2H; alkene CH_2), 4.91 (d, J = 10.8 Hz, 1H; OCH_2Ph), 4.80 (d, J = 10.8 Hz, 1H; OCH_2Ph), 4.68 (d, J = 11.6 Hz, 1H; OCH_2Ph), 4.70 (dd, J = 11.6 Hz and 2.6 Hz, 2H; OCH_2Ph), 4.52 (d, J = 11.9 Hz, 1H; OCH_2Ph), 4.39 (dd, J = 15.1 Hz and 2.4 Hz, 1H; $OCH_2C{\equiv}$), 4.21 (dd, J = 15.1 Hz and 2.4 Hz, 1H; $OCH_2C{\equiv}$), 4.11 (ddd, J = 10 Hz, 5 Hz and 5 Hz, 1H; H-1), 3.78–3.74 (m, 1H; H-3) overlapping with 3.72–3.69 (m, 3H; H-2 and H-6), 3.60 (dt, J = 5.7 Hz and 5 Hz, 1H; H-5), 3.47 (dd, J = 10.4 Hz and 8.5 Hz, 1H; H-4), 2.50–2.46 (m, 2H; $CH_2CH{=}$), 2.40 (t, J = 2.4 Hz, 1H; C≡CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.5, 138.2, 138.1 (each s, aromatic C), 134.63 (s, CH alkene), 128.4, 128.38, 128.27, 128.0, 127.78, 127.71, 127.64, 127.51 (each s, aromatic *C*H), 116.89 (s, CH_2 alkene), 82.3, 79.99, 79.92 (3s, CH), 77.80 (s, C≡CH), 75.4, 74.2 (2s, OCH_2Ph), 73.6 (s, CH), 73.4 (s, OCH_2Ph), 73.05 (s, CH_2–C≡CH), 70.86 (s, CH), 69.14 (s, C-6), 59.89 (s, C≡CH), 29.78 (s, $CH_2CH{=}$). HRMS (ESI): found 535.2460 $[M+Na]^+$, $C_{33}H_{36}O_5Na$ requires 535.2460.
Compound **13**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31–7.24 (m, 18H; aromatic H), 7.14–7.12 (m, 2H; aromatic H), 5.44 (q, J = 5.8 Hz, 1H; allenyl CH), 4.94 (d, J = 10.9 Hz, 1H; OCH_2Ph), 4.85–4.83 (m, 2H; allenyl CH_2), 4.82–4.81 (m, 1H, OCH_2Ph), 4.8 (d, J = 11.3 Hz, 2H; OCH_2Ph), 4.66 (d, J = 3.7 Hz, 2H; OCH_2Ph), 4.61 (dd, J = 10.9 Hz and 6.4 Hz, 1H; H-1), 4.48 (dd, J = 3.2 Hz and 1.0 Hz, 2H; OCH_2Ph), 3.83–3.75 (m, overlapping signals 3H, H-3, H-2, overlapping signals 1H; H-5), overlapping signals 3.72–3.68 (m, 1H; H-4) overlapping signals 3.63 (dd, J = 8.5 Hz and 7.5 Hz, 2H; H-6). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 209.4 (allenyl =C=), 138.8, 138.2, 138.19, 138.15 (s, aromatic C), 128.4, 128.37, 128.37, 128.35, 128.33, 127.98, 127.93, 127.78, 127.75, 127.70, 127.6, 127.56 (s, aromatic CH), 85.6 (allenyl CH), 82.6, 79.9 (2s, CH), 78.1 (CH_2 allenyl), 75.5, 75.1 (2s, OCH_2Ph), 73.5 (s, CH), 72.8, 72.36 (2s, OCH_2Ph), 72.0 (s, CH), 68.9 (s, C-6). HRMS (ESI): found 585.2617 $[M+Na]^+$, $C_{37}H_{38}O_5Na$ requires 585.2617.
Compound **15**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.31 (m, 15H; aromatic H), 5.7 (q, J = 5.7 Hz, 1H; allenyl CH), 4.90 (d, J = 10.8 Hz, 1H; OCH_2Ph), 4.86–4.83 (m, 2H; allenyl CH_2), 4.80 (d, J = 10.7 Hz, 1H; OCH_2Ph), 4.72–4.70 (m, 1H; OCH_2Ph), 4.65 (d, J = 4.6 Hz, 2H; OCH_2Ph), 4.61 (dd, J = 7.4 Hz and 3.1 Hz, 1H; H-1), 4.54 (d, J = 8.7 Hz, 1H; OCH_2Ph), 4.39 (dd, J = 15.1 Hz and 2.4 Hz, 1H; $OCH_2C{\equiv}$), 4.21 (dd, J = 15.1 Hz and 2.3 Hz, 1H; $OCH_2C{\equiv}$), 3.80–3.70 (m, 5H; overlapping signals of H-3, H-2, H-5 and H-6), 3.51 (dd, J = 11.6 Hz and J = 9.7 Hz, 1H; H-4), 2.40 (t, J = 2.3 Hz, 1H; C≡CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 209.4 (allenyl =*C*=), 138.5, 138.1, 137.5 (each s, aromatic C), 128.46, 128.40, 128.38, 128.33, 128.31, 127.29, 128.09, 127.96, 127.94, 127.9, 127.8, 127.76, 127.70, 127.66, 127.56 (each s, aromatic CH), 85.5 (CH), 82.3 ($CH_2C{\equiv}$), 79.8 (s, CH_2), 77.80 (($OCH_2C{\equiv}$), 75.5, 74.26, 73.5 (3s, OCH_2Ph), 72.8, 72.02, 71.9 (3s, *C*H), 70.86 (s, *C*H), 69.08 (s, *C*-6), 60.00 (s, C≡CH), 29.70 (s, $CH_2CH{=}$). HRMS (ESI): found 533.2305 $[M+Na]^+$, $C_{33}H_{34}O_5Na$ requires 533.2304.