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Efficient synthesis of 2,3-unsaturated sulfonamidoglycosides by Amberlyst 15

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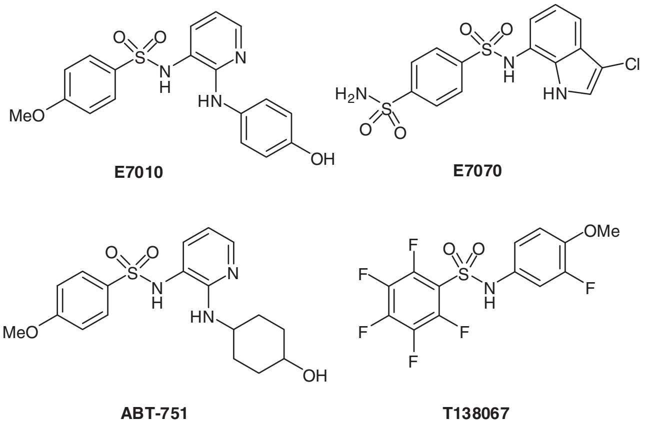
ABSTRACT

Sulfonamidoglycosylation of D-glycals in the presence of Amberlyst 15 proceeded effectively to afford the sulfonamidoglycosides in good to high yields with minimal workup and short reaction times. Two *N*-glycosyl sulfonamides were tested as inhibitors of tumor cell growth in vitro and showed antiproliferative properties in the micromolar range.

Several sulfonamides had emerged as chemotherapeutic agents for the treatment of cancer. Among them, E7010,[1] E7070,[1] ABT751,[2] and T138067[3] are under clinical evaluation and will soon be launched as antitumor drugs (Fig. 1). For several years we have been interested in the synthesis of glycosylsulfonamides.[4] Some of the sulfonamidoglycosides prepared by us showed antiproliferative activity against human hepatocellular carcinoma in the micromolar range.[4a] Recently, we have reported that *N*-glycosyl sulfonamides can be prepared by the sulfonamidoglycosylation of D-glycals on treatment with boron trifluoride etherate.[4c] One of these novel compounds, showed selectivity for inhibiting the tumor-associated isoforms carbonic anhydrase IX and XII over the ubiquitous isozyme hCA II.[5] Unfortunately, our methodology has an important drawback: boron trifluoride etherate is a highly toxic reagent. This prompted us to initiate studies designed to provide an environmentally friendlier route for the synthesis of sulfonamidoglycosides. We have shown that $HClO_4{\cdot}SiO_2$ and $HBF_4{\cdot}SiO_2$ are efficient catalysts for the sulfonamidoglycosylation of carbohydrate derivatives.[4c–e] Although fluoroboronic acid adsorbed in silica gel catalyzes the sulfonamidoglycosylation of D-glycals,[4e] the method entails the problem of a tedious workup procedure due to the presence of a large excess of nucleophile. It seems very interesting to study the use of ion exchange resins to promote the addition of sulfonamides to D-glycals. Ion exchange resins are the most widely used heterogeneous catalysts due to their advantages such as high activity and selectivity, reusability, ease of separation, no corrosion, or disposal of effluent problems.[6] Recent reports on the use of Amberlyst 15 in the preparation of 2,3-unsaturated *O*- and *S*-glycosides from 3,4,6-tri-*O*-acetyl-D-glucal via Ferrier rearrangement,[7] prompted us to investigate its use as an alternative catalyst to prepare 2,3-unsaturated sulfonamidoglycosides (Scheme 1).

The reaction of 3,4,6-tri-*O*-acetyl-D-glucal **1** and ethanesulfonamide in acetonitrile was chosen as a model reaction .[8] To study the effect of the catalyst, the reactions were carried out in the presence of variable amounts of Amberlyst 15 (Table 1).

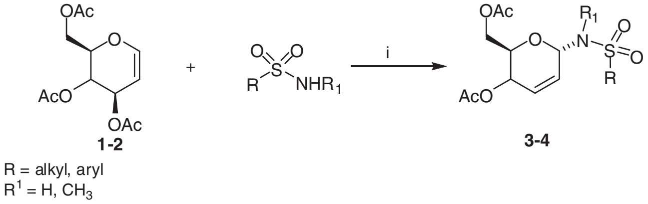
As can be seen in Table 1, the use of 30 wt % of Amberlyst 15 (entry 3) was enough for a fairly high yield. To our surprise, sulfonamidoglycosylations required a much lower amount of catalyst than the reported O- and S-glycosylations.[7] Reducing the quantity of catalyst resulted in lower yields (entries 1 and 2). Higher quantities of the catalyst only led to lower yields. In all cases the α-isomer was produced predominantly, and α/β ratios are not affected



E7010 E7070

ABT-751 T138067

Figure 1. Antimitotic sulfonamides.



Scheme 1. Reagents and condition: (i) Amberlyst 15, rt, CH_3CN.

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Table 1
Reaction of 3,4,6-tri-*O*-acetyl-D-glucal and ethanesulfonamide[a]

Entry	Wt % of Amberlyst 15	Time (min)	Temperature (°C)	$\alpha:\beta$[b]	Yield (%)
1	10	60	25	87:13	78
2	20	60	25	85:15	80
3	30	50	25	87:13	90
4	30	30	40	86:14	86
5	40	40	25	87:13	76

[a] Reactions were performed using 1 mmol of the glucal, 1.1 equiv of sulfonamide in acetonitrile.
[b] Anomeric ratios were determined by ^{1}H NMR spectroscopy.

Table 2
Reaction of 3,4,6-tri-*O*-acetyl-D-glucal **1** and 3,4,6-tri-*O*-acetyl-D-galactal **2** with different sulfonamides[a]

Entry	Glycal	Sulfonamide	Product	Time (min)	$\alpha:\beta$[b,c]	Yield[c] (%)
1	D-Glucal	Methyl	**3a**[9]	40	95:5	94
2		Ethyl	**3b**	60	87:13 (85:15)	90 (95)
3		Benzyl	**3c**	40	88:12	94
4		*p*-Toluene	**3d**	60	78:22 (87:13)	92 (95)
5		*N*-Methyl-*p*-toluene	**4e**	60	90:10 (95:5)	78 (80)
6	D-Galactal	Methyl	**4a**[10]	40	95:5	75
7		Ethyl	**4b**	50	84:16 (83:17)	88 (97)
8		Benzyl	**4c**[11]	60	95:5	72
9		*p*-Toluene	**4d**	60	90:10 (80:20)	90 (96)
10		*N*-methyl-*p*-toluene	**4e**	40	87:13 (95:5)	80 (86)

[a] Reactions were performed using 1 mmol of the glucal, 1.1 equiv of sulfonamide and 30 wt % of Amberlyst 15 in acetonitrile.
[b] Anomeric ratios were determined by ^{1}H NMR spectroscopy.
[c] Ratios and yields previously reported are shown between parentheses (Ref. 4c).

by the amount of catalyst or by the temperature. To enhance the synthetic utility of our conditions, we next tested the reaction of per-O-acetylated D-glucal **1** and D-galactal **2** with a selected group of sulfonamides using Amberlyst 15 as a catalyst (Table 2).[8]

In all the cases we examined, 4,6-di-*O*-acetyl-2,3-dideoxy-D-hex-2-enopyranosyl sulfonamides **3** and **4** were obtained in good to excellent yields and with very good α selectivity. The anomeric mixtures could be easily purified by flash chromatography or crystallization to afford the pure α anomer. ^{1}H and ^{13}C NMR data of the products confirmed the anomeric configuration of sulfonamidoglycosides. The stereochemical outcome was in accordance with the results previously described by us and could be explained in terms of a kinetically-controlled reaction.

We have studied the reaction of per-O-acetylated D-glucal **1** with methanesulfonamide over shorter times (10, 20, or 30 min) to analyze the α/β ratio. No change in the stereochemical outcome was found which suggests that sulfonamidoglycosylations take place under kinetic control and no anomerization occurred under our conditions.

Table 3
Reusability of Amberlyst 15 as Catalyst for sulfonamidoglycosylation[a]

Round	Sulfonamide	Reaction time (min)	Yield (%)
1	Ethyl	60	90
2	Ethyl	60	90
3	Ethyl	60	85

[a] Reactions were performed using 1 mmol of D-glucal, 1.1 equiv of ethanesulfonamide and 30 wt % of Amberlyst 15 in acetonitrile.

In view of green chemistry, recyclable catalysts are highly preferred. In our process, Amberlyst 15, was easily recovered from the reaction mixture by filtration and subsequently used for the next reaction cycle (Table 3). Using our conditions for the glucosylation of ethanesulfonamide with the recycled catalyst, this protocol was repeated two times, the yields were always more than 85% and no change of the anomeric selectivity was found.

The antitumor activity of sulfonamides **3b** and **4b** against human hepatocellular carcinoma cell lines Hep-G2 was assessed.[12] They act as inhibitors of growth in the 190–230 μM range, which makes them as interesting leads for the development of novel anticancer agents.

Although yields are comparable to those obtained in the sulfonamidoglycosylation of D-glycals using boron trifluoride etherate as catalyst, Amberlyst 15 is highly preferred. The present methodology has the following advantages: (a) the catalyst is inexpensive and could be reused, (b) the workup required only filtration of the catalyst followed by flash chromatography, and (c) only a slight excess of sulfonamide is used.

In conclusion, we have developed a mild and eco-friendly approach for the synthesis of *N*-glycosyl sulfonamides in the presence of Amberlyst 15. Low-cost reagents and no aqueous workup are required, and the catalyst could be recycled.

Acknowledgments

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8. Typical experimental procedure: To a solution of glycal (1 mmol) and sulfonamide (1.1 mmol) in 5 ml of dry CH$_3$CN was added, 30 wt % of resin Amberlyst 15 at room temperature. The mixture was stirred for the desired time (Table 2), until the complete disappearance of the starting materials as judged by TLC. The reaction mixture was filtered, and the resin was washed with acetone. The combined filtrate and washings were concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent hexane–EtOAc) and/or crystallized (hexane–EtOAc) to afford the products.
9. 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erithro*-hex-2-enopiranosyl methanesulfonamide (**3a**). White needles. Mp: 92–93 °C; ^{1}H RMN (200 MHz) CDCl$_3$ δ 5.86 (br d, 1H, $J = 9.2$ Hz, H-3), 5.84 (m, 2H, H-2, NH), 5.54 (br d, 1H, $J = 9.2$ Hz, H-1), 5.22 (dd, 1H, $J = 9.1$, 1.6 Hz, H-4), 3.96 (ddd, 1H, $J = 9.1$, 6.3, 2.4 Hz, H-5), 4.25 (dd, 1H, $J = 12.0$, 4.3, 2.4 Hz, H-6a), 4.11 (dd, 1H, $J = 12.0$, 6.3, 2.4 Hz, H-6b), 3.12 (s, 1H, CH_3), 2.07 (s, 3H, CH_3COO), 2.04 (s, 3H, CH_3COO); ^{13}C RMN (50 MHz) CDCl$_3$ δ 170.76 (CH$_3$*C*OO), 170.34 (CH$_3$*C*OO), 130.60 (C-3), 126.88 (C-2), 76.63 (C-1), 67.68 (C-5), 64.65 (C-4), 63.45 (C-6), 43.23 (CH$_3$), 21,15 (*C*H$_3$COO), 20.94 (*C*H$_3$COO).
10. 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopiranosyl methanesulfonamide (**4a**). White needles. Mp: 159–160 °C; ^{1}H RMN (200 MHz) CDCl$_3$ δ 6.27 (ddd, 1H, $J = 10$, 5.4, 1.6 Hz, H-3), 6.02 (dd, 1H, $J = 10.0$, 3.1 Hz, H-2), 6.01 (m, 1H, NH), 5.58 (ddd, 1H, $J = 9.1$, 3.1, 1.6 Hz, H-1), 5.03 (dd, 1H, $J = 5.3$, 1.7 Hz, H-4), 4.20 (m, 3H, H-5, 2xH-6), 3.12 (s, 3H, CH_3), 2.07 (s, 3H, CH_3COO), 2.02 (s, 3H, CH_3COO); ^{13}C RMN (50 MHz) CDCl$_3$ δ 170.79 (CH$_3$*C*OO), 170.58 (CH$_3$*C*OO), 126.71 (C-3), 129.76 (C-2), 76.65 (C-1), 67.41 (C-5), 63.36 (C-4), 62.49 (C-6), 43.38 (CH$_3$), 20,94 (*C*H$_3$COO), 21.16 (*C*H$_3$COO).
11. 4,6-Di-*O*-acetyl-2,3-dideoxi-α-D-*threo*-hex-2-enopiranosyl benzylsulfonamide (**4c**). White needles. Mp: 132–134 °C; ^{1}H RMN (200 MHz) CDCl$_3$ δ 7.41–7.35

(m, 5H, Ph), 6.17 (ddd, 1H, *J* = 9.9, 5.1, 1.91, H-3), 5.96 (dd, 1H, *J* = 9.9, 2.9 Hz, H-2), 5.75 (d, 1H, *J* = 8.7 Hz, NH), 5.60 (ddd, 1H, *J* = 8.7, 2.9, 1.7 Hz, H-1), 5.03 (appd, 1H, *J* = 5.1 Hz, H-4), 4.54 (d, 1H, *J* = 13.7 Hz, H-6a), 4.28 (m, 3H, CH_2, H-5, H-6), 2.08 (s, 3H, CH_3COO), 1.95 (s, 3H, CH_3COO); ^{13}C RMN (50 MHz) $CDCl_3$ δ 170.81 (CH_3COO), 170.57 (CH_3COO), 131.02, 129.11, 129.66, 128.87, 126.65 (Ph), 129.76 (C-2), 126.65 (C-3), 76.91 (C-1), 67.42 (C-5), 63.27 (C-4), 62.42 (C-6), 61,75 (CH_2), 21,15 (CH_3COO), 20.94 (CH_3COO).

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