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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1687–1689

Sulfonamidoglycosylation of methyl ribofuranosides: a novel approach to furanosylsulfonamides

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Received 23 November 2004; revised 12 January 2005; accepted 13 January 2005
Available online 28 January 2005

Abstract—The sulfonamidoglycosylation of benzylated methyl ribofuranosides using boron trifluoride etherate as catalyst, proceeded effectively to give the new sulfonamidofuranosides with good to high yields.

Sulfonamides have been shown to possess a wide spectrum of biological activities.[1,2] Recently several sulfonamides have been found to be inhibitors of cell proliferation, thus being potentially useful for the treatment of cancer (Fig. 1). E7010 and E7070, developed by Owa's group, are under clinical evaluation and might soon be launched as antitumor drugs.[3] The novel antimitotic sulfonamides incorporate in their molecules a common chemical motif of benzenesulfonamide. The mechanism of antitumor action of these compounds has been studied in detail and they inhibit microtubule assembly by binding to tubulin at the colchicine binding site.[4] Other sulfonamides (such as E7070), possessing a free sulfonamido moiety probably act as strong carbonic anhydrase inhibitors.[5]

Few reports deal with the synthesis of sulfonamidoglycosides. Danishefsky's group described the reaction of glycals with iodonium di-*sym*-collidine perchlorate and benzenesulfonamide to afford stereoselectively 2-β-iodo-1-α-sulfonamidohexoses.[6] This class of glycosylsulfonamides were used in the synthesis of oligosaccharides with 2-aminohexose subunits.[7] Very recently we have reported on the sulfonamidoglycosylation of glycals using a catalytic amount of triphenylphosphine hydrobromide.[8] The method afforded new glycopyranosylsulfonamides, which have been shown to be inhibitors of hepatocellular carcinoma cells in the micromolar range.

Now we turned our attention to the preparation of sulfonamidoribofuranosides. Also several methodologies for glycals synthesis have been reported, many of these approaches involve several steps or fail in the furanoid glycal series.[9] This prompted us to initiate studies designed to provide a route for the synthesis of sulfonamidoribofuranosides from more readily available starting materials such as methyl ribofuranosides. Under the catalysts of Lewis acids, the methyl glycosides are liable to generate an oxocarbenium ion at C (1). We reasoned that the addition of a sulfonamide to the ion, could afford the sulfonamidoglycoside. To the best of our knowledge, no example of sulfonamidoglycosylation of methyl glycosides is known.

Over the years several catalysts for glycosydations of methyl glycosides have been reported. Lee and Kim described the transglycosidation of methyl glucopyranosides in the presence of trimethylsilyl trifluoromethansulfonate or boron trifluoride etherate.[10] Recently Konradsson and co-workers reported on the transglycosidation of methyl glucopyranosides in ethanol or methanol catalyzed by camphorsulfonic acid.[11] Ikegami and co-workers studied the O-transglycosidation of 1-*C*-methyl hexopyranosides under the influence of several Lewis acids, the best yields were found when $SnCl_4$ was used as catalyst.[12] 1-Phenylselenylfuranosides were prepared by glycosylation of methyl glycosides with PhSeH and boron trifluoride etherate.[13]

Keywords: Sulfonamidoglycosides; Methyl glycosides; Lewis acids; Sulfonamidoglycosylation.
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doi:10.1016/j.tetlet.2005.01.065

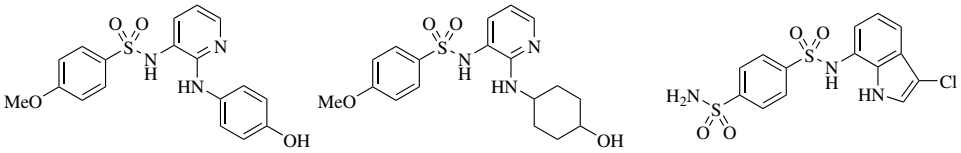


Figure 1. Antitumor sulfonamides.

We first turned our attention to the conditions for the sulfonamidoglycosylation using methyl tri-*O*-benzyl-D-ribofuranoside (**1**)[14] and *p*-toluenesulfonamide with different catalysts in dichloromethane (Table 1).

We found that the sulfonamidoglycosylation proceeded well at room temperature using 1.5 equiv of the sulfonamide and 1 equiv of boron trifluoride etherate in the presence of molecular sieves 4 A.[15]

The use of higher quantities of the catalyst only led to lower yields (entry 7) and they were not improved by using higher quantities of the sulfonamide (entry 1) or longer reaction times (entry 5). The results showed that triphenylphosphine hydrobromide and camphorsulfonic acid were not effective for catalyzing the sulfonamidoglycosylation reactions. In the case of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst, the reaction gave also the ribofuranosylsulfonamide but with lower yield (entry 8). The addition of molecular sieves was necessary for improving the sulfonamidoglycosylation by removing the generated methanol from the reaction system (entry 4).

Table 1. Reaction of *p*-toluenesulfonamide with methyl 2,3,4-tri-*O*-benzylribofuranoside **1** in CH_2Cl_2 at room temperature[a]

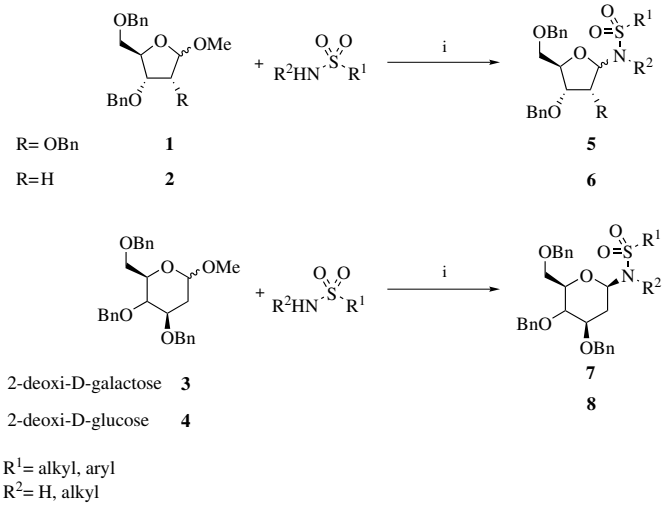
Entry	Sulfonamide (equiv)	Catalyst (equiv)	Time (min)	Ratio α:β[b]	Yield (%)
1	2	$BF_3{\cdot}Et_2O$ (1.0)	90	45.55	82
2	1.5	$BF_3{\cdot}Et_2O$ (1.0)	90	43:57	85
3	1.2	$BF_3{\cdot}Et_2O$ (1.0)	90	42:58	57
4[a]	1.5	$BF_3{\cdot}Et_2O$ (1.0)	90	40:60	67
5	1.5	$BF_3{\cdot}Et_2O$ (1.0)	120	45:55	78
6	1.5	$BF_3{\cdot}Et_2O$ (0.5)	90	40:60	35
7	1.5	$BF_3{\cdot}Et_2O$ (1.5)	90	40:60	72
8	1.5	TMSOTf	90	43:57	70
9	1.5	CSA	120	—	No reaction
10	1.5	$HBr{\cdot}PPh_3$	120	—	No reaction

[a] Without molecular sieves 4 A.
[b] Anomeric ratios were determined by ^1H NMR spectroscopy.

With this knowledge in hand, the selected conditions were applied to a variety of sulfonamides and methyl glycosides to examine the scope of the reaction (Scheme 1). The results are shown in Table 2. The α/β ratios were determined by ^1H NMR spectroscopy of the reaction mixtures.

The products were easily purified by flash chromatography. The ^1H and ^{13}C NMR and 2D COSY experiments and mass spectral data of the sulfonamides were in full accordance with their structure.[17]

The results shown in Table 2 indicated additional applications of the present reaction. Thus hindered sulfonamides (entries 3 and 4) gave the corresponding sulfonamidoglycosides with good yields. However a sulfonamide with higher steric hindrance (entry 5) afforded a poor yield of the glycosylsulfonamide. The sulfonamide **5g**, bearing a free sulfonamido moiety could be useful as carbonic anhydrase inhibitor.[18] Other methyl glycosides were also smoothly coupled to *p*-toluenesulfonamide to furnish the corresponding glycosylsulfonamides in very good yields (entries 7–9).



Scheme 1. Reagents and conditions: (i) $BF_3{\cdot}Et_2O$ (1.0 equiv), MS 4 A, room temperature, CH_2Cl_2.

Table 2. Reaction of sulfonamides with methyl glycosides[a]

Entry	Methyl glycoside	Sulfonamide	Ratio α:β[b]	Product	Yield (%)
1	**1**	Benzyl	46:54	**5b**	84
2	**1**	Ethane	48:52	**5c**	85
3	**1**	*N*-Methyl-*p*-toluene	40:60	**5d**	74
4	**1**	*N*-Butylbenzyl	50:50	**5e**	64
5	**1**	*N*-Isopropyl-*p*-toluene	45:55	**5f**	16
6[c]	**1**	Sulfamide	50:50	**5g**	70
7	**2**	*p*-Toluene	40:60	**6a**	75
8	**3**	*p*-Toluene	1:99	**7a**[d]	80 (lit. 87[e])
9	**4**	*p*-Toluene	1:99	**8a**[d]	82 (lit. 80[e])

[a] All the reactions were performed in CH_2Cl_2 using 1 equiv of $BF_3{\cdot}Et_2O$ and 1.5 equiv of sulfonamide at room temperature in the presence of MS 4 A.
[b] Anomeric ratios were determined by ^1H NMR spectroscopy.
[c] Reaction performed in CH_3CN.[16]
[d] Identified by comparison of spectral data with those reported (Ref. 8).
[e] Ref. 8.

The anomeric stereochemistry in the glycopyranose substrates was in accordance with the results previously described by us.[8] Reactions with furanoses substrates showed no stereoselectivity, which can be explained in terms of the low influence of stereoelectronic effects in the five membered carbohydrates.[19]

In conclusion, we have developed a new approach for the synthesis of sulfonamidoribofuranosides using a preparation that is quite simple and high yielding. In addition this methodology circumvents the preparation of ribofuranoid glycals. Further applications of the above method for the synthesis of other sulfonamidoglycosides will be presented in due course. Also the studies of the antiproliferative activity of the new sulfonamidoribofuranosides against human hepatocellular carcinoma cell lines Hep-G2, are currently in progress.

Acknowledgements

The authors wish to thank CIC (Pcia de Buenos Aires) for financial support, Biol. Nicolás Nuñez for experimental help, Mr. J. Rebell for NMR measurements and Dr. Albrecht Lieberknecht for valuable discussions.

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15. General procedure: To a solution or suspension of the methyl glycoside (1 mmol), the sulfonamide (1.5 mmol), and 500 mg of MS 4 A (beads) in 5 mL of dry methylenechloride was added, under argon, 1 mmol of boron trifluoride etherate at room temperature. After stirring for the time indicated, the mixture was quenched with 0.3 mL of triethylamine. The solvent was removed in vacuo and the residue was chromatographed on silica gel (eluent hexane/ethyl acetate) and/or crystallized (ethyl acetate/hexane) to afford the sulfonamidoglycosides.
16. The sulfonamidoglycosylation with sulfamide in methylenechloride afforded the *N*,*N*′-substituted product. This result can be explained in terms of the low concentration of sulfamide in the solution due to their poor solubility. When a better solvent was used (such as acetonitrile) the reaction gave the corresponding *N*-monosubstituted sulfamide.
17. 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl *p*-toluenesulfonamide **5a** *Isomer* α: solid, mp 119–120 °C ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3Ph), 3.34 (dd, 1H, J = 10.3 Hz, J = 1.5 Hz, H-5), 3.45 (dd, 1H, J = 10.3 Hz, J = 1.8 Hz, H-5), 3.95 (m, 1H, H-4), 4.12 (m, 2H, H-2, H-3), 4.32 (m, 3H, 3 × $PhCH_2O$), 4.55 (d, 1H, J = 12.8 Hz, $PhCH_2O$), 4.62 (d, 1H, J = 12.2 Hz, $PhCH_2O$), 4.72 (d, 1H, J = 12.2 Hz, $PhCH_2O$), 5.31 (dd, 1H, J = 2.1 Hz, J = 9.0 Hz, H-1), 5.50 (d, 1H, J = 9.0 Hz, NH). 7.1–7.4 (m, 17H, 3Ph, 2 × CH_3Ph), 7.61 (d, 2H, J = 8.3 Hz, 2 × CH_3Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3Ph), 68.6 (C-5), 72.0 ($PhCH_2O$), 72.2 ($PhCH_2O$), 73.5 ($PhCH_2O$), 76.0 (C-2, C-3), 81.1 (C-4), 87.5 (C-1). 126.3–129.5 (Ph), 137.7–138.5 (Ph). HRMS (EI 70 eV): calcd for $C_{33}H_{35}NO_6S$: 573.2185, found 573.2182. *Isomer* β: oil ^1H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3Ph), 3.31 (dd, 1H, J = 10.4 Hz, J = 1.0 Hz, H-5), 3.35 (dd, 1H, J = 10.4 Hz, J = 3.4 Hz, H-5), 4.0 (m, 2H, H-2, H-3), 4.10 (m, 1H, H-4), 4.35 (m, 3H, 3 × $PhCH_2O$), 4.48 (d, 1H, J = 11.6 Hz, $PhCH_2O$), 4.60 (d, 1H, J = 12.7 Hz, $PhCH_2O$), 4.70 (d, 1H, J = 12.7 Hz, $PhCH_2O$), 5.50 (dd, 1H, J = 5.4 Hz, J = 9.1 Hz, H-1), 6.25 (d, 1H, J = 9.1 Hz, NH), 7.1–7.4 (m, 17H, 3Ph, 2 × CH_3Ph), 7.77 (d, 2H, J = 8.2 Hz, 2 × CH_3Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3Ph), 68.9 (C-5), 72.4 ($PhCH_2O$), 72.8 ($PhCH_2O$), 73.5 ($PhCH_2O$), 76.8 (C-2), 76.9 (C-3), 81.5 (C-4), 83.2 (C-1). 126.9–129.4 (Ph), 137.1–138.1 (Ph). HRMS (EI 70 eV): calcd for $C_{33}H_{35}NO_6S$: 573.2185, found 573.2184.
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