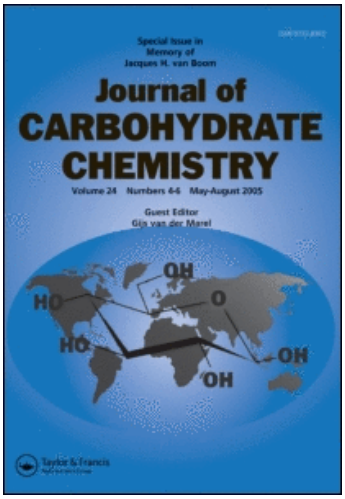

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Sulfonamidoglycosylation of Methyl Glycosides Employing Perchloric Acid Supported on Silica Gel

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The sulfonamidoglycosylation of methyl glycosides in the presence of perchloric acid immobilized on silica gel proceeded effectively to afford the corresponding sulfonamido glycosides with good to high yields with minimal workup and short reaction times. This methodology was applied to the synthesis of some *N*-glycosyl sulfamides, which showed low nanomolar activity against human carbonic anhydrase.

Keywords Sulfonamidoglycosylation, Methyl glycosides, Perchloric acid-silica

Sulfonamides, which have been clinically used for many years, have been found to possess a large number of different biological activities, including antibacterial, antiviral, antidiabetic, diuretic, and antithyroid activities.[1] They exert their diverse pharmacological effects by interacting with a wide range of different cellular targets.

In the development of new chemotherapeutic agents, several sulfonamides have emerged as useful therapeutics for the treatment of cancer. E7010,[2] E7070,[2] ABT751,[3] and T138067[4] have been found to be inhibitors of tumor cell proliferation and some of them are under clinical evaluation and will soon be launched as antitumor drugs (Fig. 1). The mechanism of antitumor action of these compounds has been studied in detail and they inhibit

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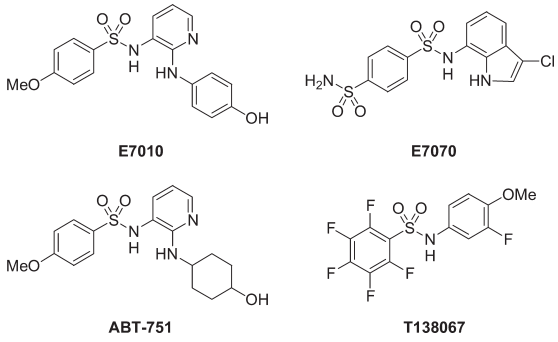
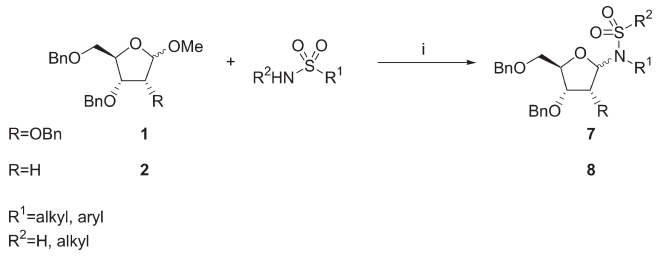


Figure 1: Antimitotic sulfonamides.

microtubule assembly by binding to tubulin at the colchicine binding site.[5] Other sulfonamides possessing a free sulfonamido moiety probably act as strong carbonic anhydrase inhibitors.[6] It was found that isozyme CA IX is overexpressed in a variety of tumor types and plays an important role in the growth and survival of tumor cells.[7] Thus, their inhibition is the target for the development of novel antitumor therapies.

Only few reports described the synthesis of sulfonamidoglycosides. Danishefsky's group reported on the reaction of glycals with iodonium di-sym-collidine perchlorate and benzenesulfonamide to afford stereoselectively 2-β-iodo-1-α-sulfonamidohexoses.[8] This class of glycosylsulfonamides were used for the preparation of oligosaccharides with the 2-aminohexose subunit.[9] Recently we reported on the stereoselective synthesis of glycosylsulfonamides via sulfonamidoglycosylation of benzylated glycals using a catalytic amount of triphenylphosphine hydrobromide.[10] The novel method afforded the β-sulfonamidoglycosides with good to high yields. Later on we developed a novel approach to ribofuranosylsulfonamides using the reaction of methyl glycosides with sulfonamides in the presence of boron trifluoride etherate.[11] Some of the glycosylsulfonamides prepared by us showed antiproliferative activity against the human hepatocellular carcinoma in the micromolar range.[10] Unfortunately, our last developed 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 sulfonamidoribofuranosides. It seems very interesting to study the use of acids supported on silica gel to promote the sulfonamidoglycosylations. The application of heterogeneous catalysts such as inorganic acids in organic synthesis is an attractive area of research.[12] Noting recent reports of the use of perchloric acid supported on silica gel[13] as an inexpensive, nontoxic, and recyclable catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity,[14] we decided to investigate $HClO_4$-SiO_2 in the sulfonamidoglycosylations.



Scheme 1: Reagents and conditions: (i) $HClO_4$-SiO_2, r t, CH_2Cl_2.

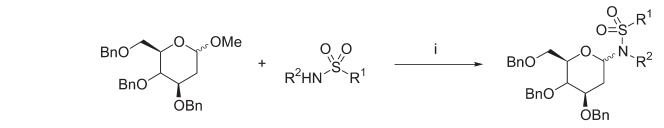
Now we wish to report that perchloric acid supported on silicagel ($HClO_4$-SiO_2 was prepared as described previously,[13] except it was dried for 2 h at 110°C.) allows the reaction of methyl glycosides with sulfonamides to give the corresponding sulfonamidoglycosides in good to high yields and in short reaction times. Further, no precautions need to be taken to exclude air from the reaction medium and the method requires minimal workup.

We first turned our attention to the conditions of sulfonamidoglycosylation using methyl tri-*O*-benzyl-D-ribofuranoside (**1**) and *p*-toluenesulfonamide (Sch. 1). (General procedure: To a solution or suspension of the methyl glycoside (1 mmol), the sulfonamide (1.5 sulfonamide) in 5 mL of dry methylenechloride was added 1.3 g of $HClO_4$-SiO_2 at rt. After stirring for the time indicated, the reaction mixture was filtered through Celite and the solvent was removed in vacuo. The residue was chromatographed on silica gel (eluent hexane/ethyl acetate) and/or crystallized (ethyl acetate/hexane) to afford the sulfonamidoglycosides.) The results are summarized in Table 1.

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

Entry	Sulfonamide (equiv.)	Promoter	Time (min)	Ratio α:β	Yield (%)
1	2	$HClO_4$-SiO_2 (1.3 g)	5	43:57	92
2	1.5	$HClO_4$-SiO_2 (1.3 g)	5	45:55[c]	90[d]
3	1.2	$HClO_4$-SiO_2 (1.3 g)	5	40:60	60
			30	42:58	58
4	1.5	$HClO_4$-SiO2 (0.65 g)	30	45:55	18
			120	45:55	25
5	1.5	$HClO_4$-SiO_2 (1.0 g)	30	43:57	78
			120	45:55	72
6	1.5	$HClO_4$-SiO_2 (1.9 g)	5	40:60	54
7	1.5	HBF_4-SiO_2 (1.3 g)	120	—	No reaction
8	1.5	SiO_2 (1.3 g)	120	—	No reaction

[a]All the reactions were performed using 1 mmol of the methyl glycoside.
[b]Anomeric ratios were determined by ^1H NMR spectroscopy.
[c]Lit. 43:57. Ref. (11).
[d]Lit 85%. Ref. (11).



2-deoxi-D-galactose **3** **9**

2-deoxi-D-glucose **4** **10**

R^1=alkyl, aryl
R^2=H, alkyl

Scheme 2: Reagents and conditions: (i) $HClO_4$-SiO_2, rt, CH_2Cl_2.

The use of higher quantities of the $HClO_4$-SiO_2 only led to lower yields (entry 6) and they were not improved by using higher quantities of the sulfonamide (entry 1). The results showed that tetrafluorboric acid was not effective for catalyzing the sulfonamidoglycosylation reactions (entry 7). The addition of molecular sieves, as is mentioned in our previous report,[11] was not necessary. The generated methanol was probably removed by the silica gel from the reaction system.

With this knowledge in hand, the selected conditions were applied to a variety of sulfonamides and methyl glycosides to analyze the scope of our methodology (Sch. 2). The results are shown in Table 2. The anomeric ratios were determined by ^{1}H NMR of the reaction mixture.

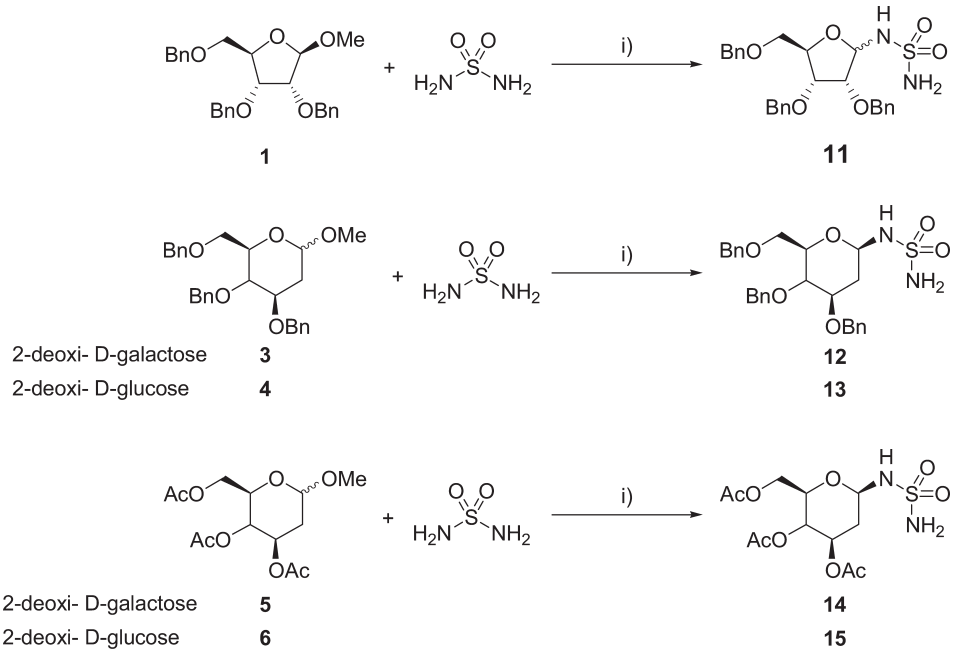
The products were easily purified by flash chromatography. The ^{1}H and ^{13}C NMR and 2D COSY experiments and mass spectral data of the sulfonamides were in full accordance with their structure.

The results shown in Table 2 indicated additional applications of the new procedure. Thus, hindered sulfonamides were also effectively coupled to the methyl ribofuranosides (entries 3 and 4). However, a sulfonamide with higher

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

Entry	Methyl glycoside	Sulfonamide	Time (min)	Ratio α:β[b,c]	Yield (%)[c]
1	**1**	Benzyl	5	45:55 (46:54)	92 (84)
2	**1**	Ethane	5	50:50 (48:52)	97 (85)
3	**1**	*N*-Methyl-*p*-toluene	10	40:60 (40:60)	89 (74)
4	**1**	*N*-Butylbenzyl	10	50:50 (50:50)	78 (64)
5	**1**	*N*-Isopropyl-*p*-toluene	10	47:53 (45:55)	15 (16)
6	**2**	*p*-Toluene	5	45:55 (40:60)	95 (75)
7	**3**	*p*-Toluene	5	1:99	97 (80, 87[d])
8	**4**	*p*-Toluene	5	1:99	98 (82, 80[d])

[a]All the reactions were performed in CH_2Cl_2 using 1.3 g of $HClO_4$-SiO_2 and 1.5 equiv. of sulfonamide at rt.
[b]Anomeric ratios were determined by ^{1}H NMR spectroscopy.
[c]Ratios and yields previously reported are shown between parenthesis (Ref. 11).
[d]Ref. (10).



Scheme 3: Reagents and conditions: i) $HClO_4$-SiO_2, rt, CH_3CN.

steric hindrance afforded a poor yield of the glycosylsulfonamide (entry 5). The methodology was also applied to methyl glycopyranosides to furnish the corresponding sulfonamidoglycosides in excellent yields (entries 7 and 8).

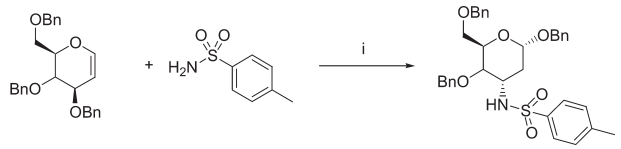
The stereochemical outcome was in accordance with the results previously described by us[10,11] and no influence of the promoter in the anomeric selectivity was found.

Very recently we have prepared a series of glycosylated sulfamides, which showed low nanomolar activity against human carbonic anhydrase.[15] The $HClO_4$-SiO_2 was applied to the synthesis of some of these *N*-glycosylsulfamides (Sch. 3). The results are shown in Table 3.

Table 3: Reaction of sulfamide with methyl glycosides[a].

Entry	Methyl glycoside	Time (min)	Product	Ratio α:β[b]	Yield (%)
1	**1**	5	11	50:50	82
2	**3**	5	12	1:99	95
3	**4**	5	13	6:94	94
4	**5**	10	14	5:95	90
5	**6**	10	15	8:92	92

[a]All the reactions were performed in CH_3CN using 1.3 g of $HClO_4$-SiO_2 and 3 equiv. of sulfamide at rt.
[b]Anomeric ratios were determined by ^1H NMR spectroscopy.



Scheme 4: Reagents and conditions: (i) $HClO_4$-SiO_2, r t, CH_2Cl_2.

Our attention next turned to the reaction of D-glycals with *p*-toluenesulfonamide using $HClO_4$-SiO_2. The addition reaction afforded the *O*-glycosides (**17**) in poor yields (Sch. 4). (The reactions were performed in methylenechloride using 0.05 equiv of $HClO_4$-SiO_2 and 1.2 equiv. of sulfonamide. Higher quantities of the promoter or the sulfonamide showed no effect on the yields (10%–14%)). Similar results using boron trifluoride etherate as catalyst were described by us.[10] The formation of this product could be explained by the reaction of sulfonamide with the carbenium ion at C(3) followed by the addition of the benzyl alcohol to the double bond.

In summary, our present methodology has the following advantages: (a) the promoter is an inexpensive noncorrosive powder, (b) the workup required only filtration of the promoter followed by flash chromatography, and (c) there were short reaction times (in order of minutes) and good to high yields. In conclusion, we have developed a mild and eco-friendly approach for the sulfonamidoglycosylation of methyl glycosides to afford the corresponding *N*-glycosyl sulfonamides. To the best of our knowledge, it is the first report of a sulfonamidoglycosylation promoted by a heterogenous reagent.

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