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Sulfonylcarbamate as a versatile and unique hydroxy-protecting group: a protecting group stable under severe conditions and labile under mild conditions†

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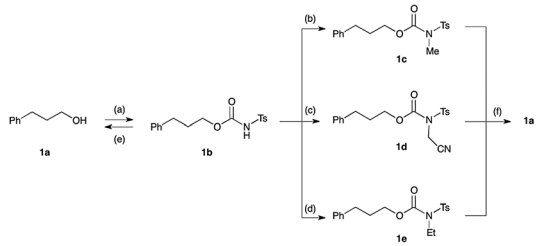
The sulfonylcarbamate group is a unique hydroxyl protecting group. In contrast to typical acyl protecting groups, the sulfonylcarbamate group is stable under harsh basic conditions, while showing labile behavior under mild basic conditions. Its compatibility with other hydroxyl protecting groups and application to carbohydrate chemistry is demonstrated.

The development of new protecting groups is highly desirable in the field of synthetic organic chemistry. The introduction and removal of protecting groups are among the most common transformations during the multistep synthesis of polyfunctional molecules.[1,2] However, protection–deprotection processes increase the number of reaction steps and can lower overall yields, especially in the synthesis of complex molecules. Consequently, there is a continuing demand for more varied, economical, and/or chemically differentiable protecting groups. Furthermore, in carbohydrate chemistry, protecting groups play an important role in controlling stereochemistry at the anomeric position, as well as in tuning the reactivity of glycosyl donors and acceptors in glycosylation reactions.[3,4] Moreover, protecting groups can change the properties of substrates, including their solubility, polarity, crystallinity, and volatility. In general, protecting groups are stable under mild conditions and are removed under severe ones. For instance, typical acyl protecting groups such as acetyl, and benzoyl groups are stable under pyridine–H_2O (weakly basic conditions), but are cleavable under aqueous NaOH (more basic conditions). Here, we report the sulfonylcarbamate moiety as a novel hydroxyl protecting group possessing unique characteristics. In contrast to conventional protecting groups, this group could be deprotected under mildly basic conditions, while being completely stable under strongly basic and other conventional reaction conditions.



Scheme 1 Protection of alcohol by the sulfonylcarbamate group and its stability under various basic conditions. *Reagents and conditions*: (a) *p*-toluenesulfonyl isocyanate, THF, quant.; (b) $TMSCHN_2$, MeOH, PhH, 90%; (c) ICH_2CN, K_2CO_3, CH_3CN, 82%; (d) EtOH, PPh_3, DEAD, THF, 92%; (e) pyridine–MeOH (7 : 3), 92%; (f) 1 M NaOH, THF quant. Ts = *p*-toluenesulfonate.

The sulfonylcarbamate group was introduced under neutral conditions in high yield using commercially available *p*-toluenesulfonyl isocyanate (Scheme 1). Sulfonylcarbamate **1b** was completely stable under strongly alkaline conditions (1 M to 5 M aqueous NaOH, 1.5 equivalents of 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane[5] in MeOH, or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in MeOH) and was recovered quantitatively. On the other hand, the sulfonylcarbamate group was removed under extremely mild basic conditions such as in pyridine–MeOH (Scheme 1(e)). It was also possible to remove the sulfonylcarbamate group using a two-step alkylation–deprotection sequence. The sulfonylcarbamate group is acidic enough to react with trimethylsilyldiazomethane ($TMSCHN_2$). After the methylation of **1b** with $TMSCHN_2$ in MeOH–benzene, deprotection could be achieved under mildly basic conditions, as well as under strongly basic ones. Similarly, after alkylation of the sulfonylcarbamate group with iodoacetonitrile in the presence of K_2CO_3 and under typical Mitsunobu conditions, it was possible to remove the sulfonylcarbamate group quantitatively under basic conditions (Scheme 1(b)–(d), and (f), respectively).

Since the protection reaction could be carried out under neutral conditions and was operationally very simple, the scope of substrates examined was wide. The protection reaction was completed within approximately 30 min in most cases. Primary alcohols **1a–5a** and **10a** and secondary alcohols **6a–8a** and **11a–13a** were

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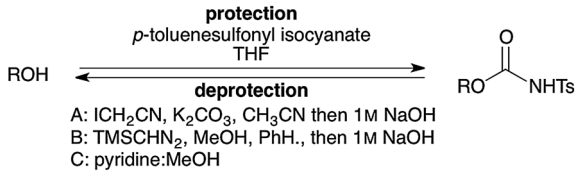
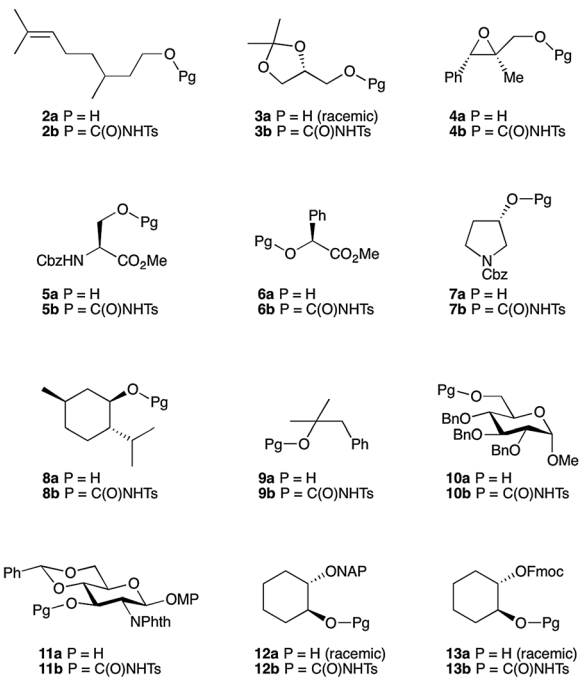
Table 1 Scope of protection and deprotection of sulfonylcarbamate-protected hydroxyl groups



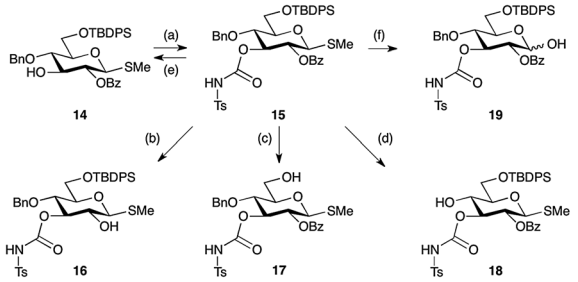
Entry	Substrate	Protection yield (%)	Deprotection yield (%)	Method
1	**2a**/**2b**	98	88	A[a]
2	**3a**/**3b**	quant.	77	B[b]
3	**4a**/**4b**	quant.	80	B[c]
4	**5a**/**5b**	quant.	quant.[d]	C
5	**6a**/**6b**	quant.	80[e]	C
6	**7a**/**7b**	quant.	95/quant.	A/C
7	**8a**/**8b**	94	90	C
8	**9a**/**9b**	85	90	C
9	**10a**/**10b**	95	90	C
10	**11a**/**11b**	95	85	C
11	**12a**/**12b**	90	89	C
12	**13a**/**13b**	94	0	C

[a] Method A: ICH_2CN, K_2CO_3, CH_3CN, then 1 M NaOH. [b] Method B: $TMSCHN_2$, MeOH, PhH, then 1 M aq. NaOH. [c] Method C: pyridine–MeOH (7 : 3), 50 °C. [d] > 99% ee by CHIRALPAK AD, hexane : i-PrOH 9 : 1 1.0 mL min^{-1}, 254 nm. [e] > 99% ee by CHIRALCEL OD-H, hexane : i-PrOH 9 : 1 1.0 mL min^{-1}, 254 nm.



Pg = protecting group.

protected in high yields (Table 1). Even the reaction involving tertiary alcohol **9a** was complete within 1 h, resulting in a satisfactory yield. In numerous cases, the protection yields were quantitative, and many functional groups such as alkenes (**2a**), acetals (**3a** (racemic) and **11a**), epoxides (**4a**), esters (**5a** and **6a**), carbamates (**5a** and **7a**), and phthalimide (**11a**) were stable under the reaction conditions. Three different methodologies were applied for the deprotection step: (a) ICH_2CN, K_2CO_3, CH_3CN, then 1 M NaOH; (b) $TMSCHN_2$, MeOH, PhH, then 1 M aq. NaOH; (c) pyridine–MeOH (7 : 3), 50 °C. The two-step sequences gave products in good yields (entries 1–3 and 6). The operationally simple one-step procedure gave satisfactory yields (entries 4–11), especially in the case of substrates with base-sensitive functional groups such as esters and Phth (entries 4, 5 and 10). Because of the mild deprotection conditions (pyridine–MeOH 7 : 3), racemization of the deprotected compounds was negligible in the cases of **5b** and **6b** (by chiral HPLC analyses). Unfortunately, the Fmoc group was removed faster than the sulfonyl carbamate group (entry 12).

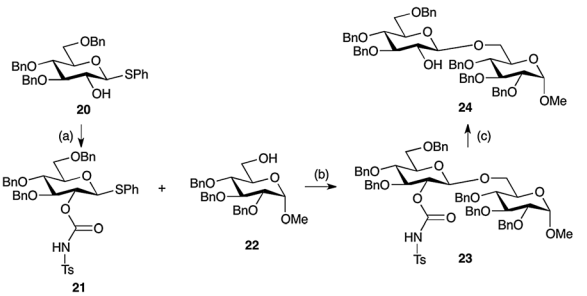


Scheme 2 A glucose scaffold with the orthogonal protecting group. *Reagents and conditions*: (a) *p*-toluenesulfonyl isocyanate, THF, quant.; (b) NaOMe, MeOH, 89%; (c) aq. HF, CH_3CN, 92%; (d) DDQ, CH_2Cl_2, H_2O, 40 °C, 68%; (e) pyridine–H_2O (7 : 3), 50 °C, 93%; (f) NBS, acetone, H_2O, 83%.

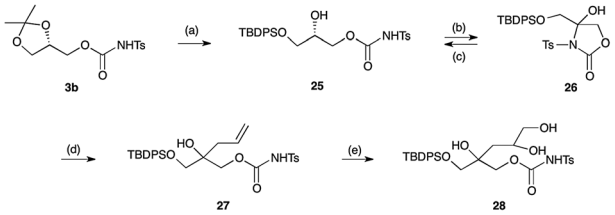
After having established ideal protection and deprotection conditions for the sulfonylcarbamate-protected hydroxyl groups, we next investigated its compatibility with other established hydroxyl protecting groups (Scheme 2). We chose **15** as a model compound because the differentially protected sugar unit would be a useful carbohydrate scaffold for further divergent synthetic manipulations.[6–10] Compound **15** was prepared from the known compound **14** in quantitative yield.[11] The benzoate of **15** was deprotected with NaOMe in MeOH, yielding **16** in quantitative yield without any removal or migration of the sulfonylcarbamate group to the C-2 position. The cleavage of the silyl group by aqueous HF afforded **17** in 92% yield. The benzyl group at the C-4 position was cleaved by the oxidation of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at 40 °C.[12] Additionally, the thioglycoside was converted to the corresponding hemiacetal **19** using *N*-bromosuccinimide (NBS) in aqueous acetone, in 83% yield. Finally, the sulfonylcarbamate group was cleaved by pyridine–MeOH without migration of the benzoate, resulting in **14** in 93% yield. Thus, a completely orthogonal set of protecting groups for glucose was established.

In the glycosylation reaction, the sulfonylcarbamate group was shown to be effective in controlling stereochemistry at the anomeric position, although it is not clear whether the sulfonylcarbamate group functions as a neighboring participating group to the oxocarbenium intermediate.[3,4] The thioglycoside donor **19** was quantitatively prepared from compound **18**. After glycosylation between donor **19** and acceptor **20** by the action of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH), only the β-disaccharide **21** was obtained in 94% yield. The sulfonylcarbamate group was then removed in 90% yield using pyridine–MeOH (Scheme 3).[13]

Furthermore, the sulfonylcarbamate group was stable under several typical reaction conditions (Scheme 4). For instance, the



Scheme 3 Utility of the sulfonylcarbamate group in glycosylation reaction. *Reagents and conditions*: (a) *p*-toluenesulfonyl isocyanate, THF, 97%; (b) NIS, TfOH, CH_2Cl_2, −40 °C, 94%; (c) pyridine–H_2O (7 : 3), 40 °C, 90%.

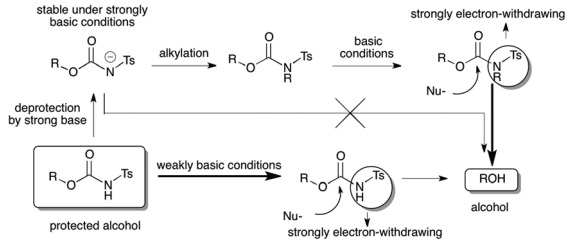


Scheme 4 Stability of the sulfonylcarbamate group under various conditions. *Reagents and conditions*: (a) (i) TFA–H_2O (1 : 1), then TBDPSCl, DMAP, pyridine, 91%; (b) Dess–Martin periodinane, CH_2Cl_2, 63% or Jones reagent, acetone, 71%; (c) $NaBH_4$, MeOH, THF, quant.; (d) allylmagnesium bromide, THF, 92%; (e) OsO_4, NMO, acetone, H_2O, 90%.

toluenesulfonylcarbamate group of compound **3b** was stable under acidic conditions (TFA–H_2O 1 : 1) for acetal removal. The secondary alcohol of **25** was oxidized using either Dess–Martin periodinane or Jones reagent to give **26**. Nucleophilic attack of the carbonyl group of compound **26** by organometallic reagents such as Grignard reagents and hydride gave corresponding compounds **27** and **25**. The sulfonylcarbamate group was also stable under OsO_4 oxidation conditions.

The underlying principle responsible for the unique characteristics of the protecting group can be explained as follows. Because of the strong electron-withdrawing nature of the sulfonyl group, nucleophilic attack on the carbonyl carbon occurs readily, and deprotection can be achieved under weakly basic conditions. However, once the rather acidic proton on the nitrogen[14] is removed by a base, nucleophilic attack is prevented. As a result, the sulfonylcarbamate group is stable under strongly basic conditions. This assumption is supported by the alkylation–cleavage sequence. After alkylation at the nitrogen atom, an acidic proton is no longer present, allowing for nucleophilic attack on the carbonyl group to occur under both weakly and strongly basic conditions (Scheme 5).

In conclusion, we have developed and established the utility of the sulfonylcarbamate group as a novel protecting group for the protection of hydroxyl moieties. The protecting group allows for simple and easy protection–deprotection under mild conditions and is compatible with other functional groups. In addition, the sulfonylcarbamate group has the unique property of being stable under severe conditions and labile under mild conditions. This unique and synthetically useful characteristic is not observed in other hydroxyl protecting groups.



Scheme 5 Mechanism underlying the unique characteristics of the sulfonylcarbamate group.

''Safety-catch'' protecting groups and linkers developed by Kenner and Ellman are typically used for carboxylic acids and require a two-step protocol for deprotection.[15] The hydroxyl protecting group described above does not necessarily require a two-step deprotection process. It has the potential to be used as a versatile protecting group in the field of synthetic organic chemistry as it can reduce the number of steps involved during the total synthesis of a variety of important compounds; the sulfonylcarbamate would be of considerable use in the final stages of a total synthesis with many functional groups.

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