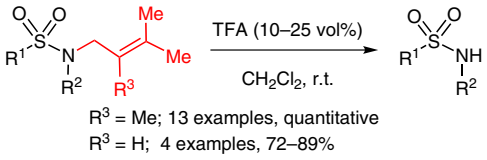
Synlett A. Nikitjuka et al. Letter

Methylprenyl and Prenyl Protection for Sulfonamides

Anna Nikitjuka
Aleksandra Nekrasova
Aigars Jirgensons*

Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga 1006, Latvia
aigars@osi.lv

Dedicated to Dr. Valerjans Kauss on the occasion of his 60th birthday



Received: 12.09.2014
Accepted after revision: 18.10.2014
Published online: 14.11.2014
DOI: 10.1055/s-0034-1379428; Art ID: st-2014-d0760-l

Abstract 2-Methylprenyl (MePre) is an efficient protection for sulfonamides. The acidic cleavage of this group leads to volatile by-products and the product can be obtained in high purity without additional purification. MePre group is resistant to Pd/C-catalysed hydrogenolysis at 1 atm, Suzuki–Miyaura reaction, Ni(0) catalysis conditions and oxidising reagents such as NIS and DDQ. The prenyl (Pre) group can also be used to protect sulfonamides in certain cases; however, the substrate scope is limited due to the side product formation.

Key words sulfonamides, protecting groups, allylation, cations, cleavage

Sulfonamide substructure is often incorporated in pharmacologically active agents.[1,2] This functionality, due to the relative acidity and nucleophilicity in the deprotonated form, may often require protection during the synthesis of complex compounds. Nevertheless, options for sulfonamide protection are limited to a few groups such as *tert*-butyl,[3–5] benzyl,[6,7] diphenylmethyl,[8] 4-methoxybenzyl,[9] 2,4-dimethoxybenzyl,[10] 2,4,6-trimethoxybenzyl[11] and allyl.[12,13] Consequently, there is a need to broaden the arsenal of sulfonamide protection with groups that are easily installed and cleaved under mild conditions generating volatile by-product(s). The prenyl-type protection has been used for alcohols,[14–20] carboxylic acids[14–16] and hydroxamic acids;[21] however, to the best of our knowledge it has not been used to protect sulfonamides. In this article, we report our investigations on the utility of prenyl and 2-methylprenyl as acid-labile sulfonamide protecting groups (Figure 1).

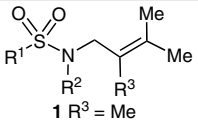
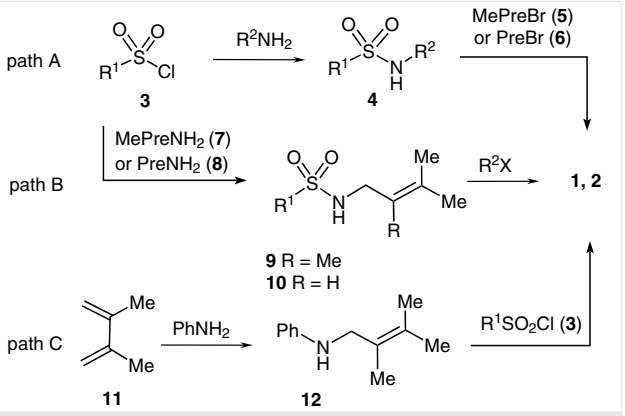


Figure 1 2-Methylprenyl (MePre)- and prenyl (Pre)-protected sulfonamides **1** and **2**

2-Methylprenyl (MePre) and prenyl (Pre) sulfonamides **1** and **2** can be obtained via several routes (Scheme 1,Table 1). Sulfonamides **4** prepared from sulfonyl chlorides **3** and amines can be alkylated with prenyl bromides **5** and **6** (path A). Sulfonamides **9** and **10** obtained from sulfonyl chlorides **3** and *N*-prenylamines **7** and **8** can be alkylated or arylated (path B). *N*-(2-Methylprenyl)anilines **12** prepared via Pd-catalysed hydroamination of dienes **11**[22] can be sulfonylated with sulfonyl chlorides **3** (Path C).

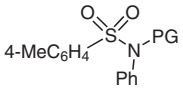
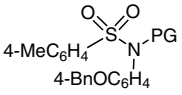
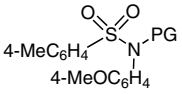
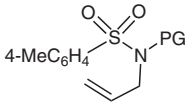
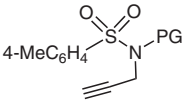
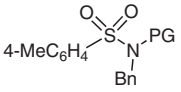
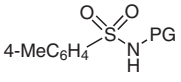
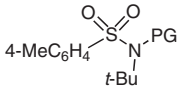
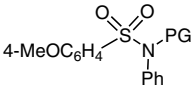
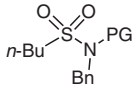
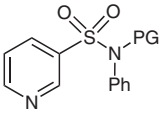
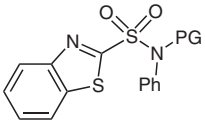
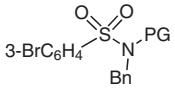


Scheme 1 Preparation of 2-methylprenyl- and prenyl-protected sulfonamides

Using the protected sulfonamides **1a** and **2a** as model substrates, we found that the cleavage of MePre and Pre groups can be achieved in acidic conditions (10 vol% TFA in CH_2Cl_2).[23] In the case of substrate **1a**, addition of triethylsilane as a cation scavenger was beneficial to achieve a clean cleavage of the MePre group. The workup required only evaporation of the reaction mixture to provide the product with high purity. In turn, the deprotection of Pre analogue **2a** in the presence of triethylsilane led to the formation of *N*-isopentylsulfonamide as a side product resulting from the Pre group reduction (ca 15%) along with the deprotected sulfonamide (Table 1, entry 2). In the absence of triethylsilane, a considerable amount of competing intramolecular Friedel–Crafts reaction was observed (ca. 40% by NMR of

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Table 1 Proteolytic Deprotection of Sulfonamides **1** and **2**[a]

Entry	Deprotection substrate (synthesis path)		PG	Reaction time, yield
1		**1a** (C)	MePre	20 min, quantitative
2		**2a** (A)	Pre	60 min,72%[b]
3		**1b** (A)	MePre	45 min, quantitative
4		**2b** (A)	Pre	12 h, 76%[b]
5		**1c** (A)	MePre	60 min, quantitative.
6		**1d** (B)	MePre	45 min, quantitative
7		**2d** (B)	Pre	60 min, 78%[b]
8		**1e** (B)	MePre	60 min, quantitative[c]
9		**2e** (B)	Pre	60 min, mixture of products
10		**1f** (B)	MePre	90 min, quantitative[c]
11		**2f** (B)	Pre	90 min, mixture of products
12		**1g** (B)	MePre	60 min, quantitative
13		**2g** (B)	Pre	12 h, mixture of products
14		**1h** (A)	MePre	12 h, mixture of products[d]
15		**1i** (C)	MePre	20 min, quantitative
16		**2i** (A)	Pre	60 min, 89%[b]
17		**1j** (A)	MePre	12 h, quantitative
18		**2j** (A)	Pre	12 h, mixture of products
19		**1k** (A)	MePre	12 h, 92%[b,c]
20		**1l** (A)	MePre	60 min, 91%[b]
21		**1m** (A)	MePre	90 min, 94%[b,c]

[a] Reaction conditions: TFA (10 vol%), triethylsilane (6 equiv), CH_2Cl_2 if not stated otherwise.
[b] Isolation of the product was achieved by flash chromatography.
[c] Amount of TFA used in CH_2Cl_2 was 25 vol%.
[d] The main components were the product of MePre group cleavage and primary sulfonamide (1:1); increasing the reaction time led to primary sulfonamide formation (full conversion was observed after 72 h).

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

crude product). Moreover, a longer reaction time was needed to achieve the complete conversion of Pre-protected sulfonamide **2a** compared to MePre analogue **1a**. The increased lability of MePre group in sulfonamides **1** can be explained by the small positive carbenium ion stabilising effect of the 2-methyl substituent.[24]

The substrate scope for MePre deprotection in sulfonamides **1** appeared to be quite broad. In the case of most examples studied, cleavage of the MePre group was efficiently achieved. An exception was *N*-*t*-Bu-substituted sulfonamide **1h** where the deprotection was accompanied by cleavage of the *t*-Bu group (Table 1, entry 14). For Pre protection the substrate scope was apparently limited: the cleavage of protecting group in sulfonamides **2** was accompanied by side product formation. Only in the case of sulfonamide **2i** did deprotection provide the desired product in high yield (Table 1, entry 15).

The stability of the prenyl-type sulfonamide protection was studied under various conditions used for the cleavage of other protecting groups. Selective O-debenzylation was achieved in the MePre-protected sulfonamide **1b** under catalytic hydrogenation conditions at 1 atm of H_2 (Table 2, entry 1). Notably, these conditions led to a complete saturation of the Pre group in the substrate **2b** (Table 2, entry 2). At the increased pressure, saturation of MePre group also took place in the substrate **1b** (Table 2, entry 3). The MePre-protected sulfonamide **1c** was resistant to NIS and DDQ (Table 2, entries 4 and 5). The allyl group could be selectively cleaved from sulfonamide **1d** under the conditions of Ni(0) catalysis[13] in the presence of MePre group (Table 2, entry 6). Strong Lewis acids such as BCl_3 promoted the cleavage of MePre group together with Bn and *t*-Bu groups in substrates **1b** and **1h** leading to primary sulfonamides in a very high yield (Table 2, entries 7 and 8).

The stability of the MePre group under the Suzuki–Miyaura coupling conditions was demonstrated in the synthesis of biphenyl intermediate **13** from protected bromophenylsulfonamide **1m** (Scheme 2). The MePre group was also stable at the stage of catalytic nitro group reduction in compound **13** to give the aniline intermediate **14**. Finally, the cleavage of the MePre group provided unprotected sulfonamide **15**.

Table 2 Stability Studies of MePre and Pre-Protected Sulfonamides **1** and **2**

Entry	Compound	Conditions	Results (yield of product)[a]
1	**1b**	Pd/C, H_2 (1atm), EtOAc	selective O-debenzylation (84%)
2	**2b**		O-debenzylation and saturation of Pre group
3	**1b**	Pd/C, H_2 (6 atm), EtOAc	O-debenzylation and saturation of MePre group
4	**1c**	NIS, CH_2Cl_2, r.t.	stable
5	**1c**	DDQ, CH_2Cl_2, H_2O, reflux	stable
6	**1d**	DIBAL-H, cat. (dppp)$NiCl_2$, toluene, r.t.	selective allyl group cleavage (89%)
7	**1b**	BCl_3 (1.5 equiv), CH_2Cl_2, r.t.	MePre and Bn cleavage (98%)
8	**1h**	BCl_3 (1.1 equiv), CH_2Cl_2, r.t.	MePre and *t*-Bu cleavage (99%)

[a] Isolated yield.

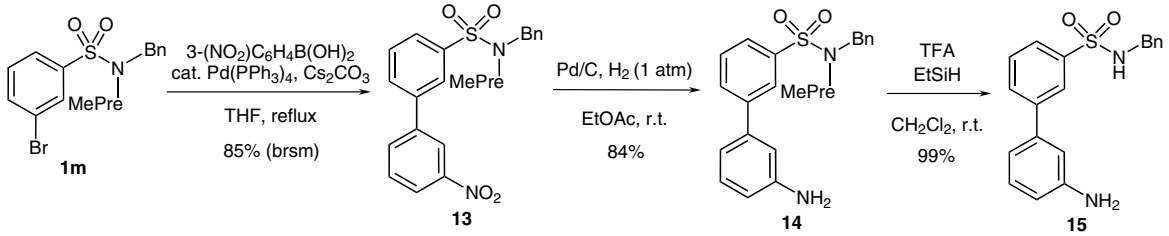
In summary, we have demonstrated that the MePre group can be used as an acid-labile protection for sulfonamides. The acid-promoted cleavage of this protecting group leads to volatile by-products and the product can be obtained in high purity after evaporation of the reaction mixture. MePre group is resistant to Pd/C-catalysed hydrogenolysis at 1 atm, Suzuki–Miyaura reaction, Ni(0) catalysis conditions, and oxidising reagents such as NIS and DDQ. The Pre group can also be used to protect sulfonamides; however, formation of side products is observed in many cases and the substrate scope is limited.

Acknowledgment

Funding from EU FP7, programme Health, project NABARSI (Grant agreement no: 601725) is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379428. Included are synthetic procedures for compounds **1a**–**m**, **2a**–**j**, **3**, **9**, **10**, **12** and **13**–**15**, their spectroscopic characterisation as well as NMR spectra of compounds **1a**–**g**, **1i**–**j** and **13**–**15**.



Scheme 2 Stability of MePre in Suzuki–Miyaura coupling and in the reduction of the nitro group

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

References and Notes

(1) Supuran, C. T.; Casini, A.; Scozzafava, A. *Med. Res. Rev.* **2003**, *23*, 535.
(2) Supuran, C. T.; Innocenti, A.; Mastrolorenzo, A.; Scozzafava, A. *Mini-Rev. Med. Chem.* **2004**, *4*, 189.
(3) Graham, S. L.; Scholz, T. H. *J. Org. Chem.* **1991**, *56*, 4260.
(4) Wan, Y.; Wu, X.; Kannan, M. A.; Alterman, M. *Tetrahedron Lett.* **2003**, *44*, 4523.
(5) Mahalingam, A. K.; Wu, X.; Wan, Y.; Alterman, M. *Synth. Commun.* **2005**, *35*, 417.
(6) Burlingham, B. T.; Widlanski, T. S. *J. Am. Chem. Soc.* **2001**, *123*, 2937.
(7) Johnson, D. C. II.; Widlanski, T. S. *Tetrahedron Lett.* **2004**, *45*, 8483.
(8) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 7291.
(9) Morris, J.; Wishka, D. G. *J. Org. Chem.* **1991**, *56*, 3549.
(10) Hill, B.; Liu, Y.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 4285.
(11) Videnov, G.; Aleksiev, B.; Stoev, M.; Paipanova, T.; Jung, G. *Liebigs Ann. Chem.* **1993**, *1993*, 941.
(12) Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355.
(13) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679.
(14) Sharma, G. V. M.; Ilangovan, A.; Mahalingam, A. K. *J. Org. Chem.* **1998**, *63*, 9103.
(15) Sharma, G. V. M.; Reddy, C. G.; Krishna, P. R. *Synlett* **2003**, *11*, 1728.
(16) Narender, T.; Venkateswarlu, K.; Madhur, G.; Reddy, K. P. *Synth. Commun.* **2012**, *43*, 26.
(17) Vatèle, J.-M. *Tetrahedron* **2002**, *58*, 5689.
(18) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 8121.
(19) Babu, K. S.; Raju, B. C.; Srinivas, P. V.; Rao, A. S.; Kumar, S. P.; Rao, J. D. *Chem. Lett.* **2003**, *32*, 704.
(20) Marković, D.; Vogel, P. *Org. Lett.* **2004**, *6*, 2693.
(21) Nikitjuka, A.; Jirgensons, A. *Synlett* **2012**, *23*, 2972.
(22) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.
(23) **General Procedure for the Cleavage of MePre Group in 1**: To a stirred solution of protected sulfonamide **1** (0.15 mmol) in CH_2Cl_2 (0.75 mL) were added triethylsilane (75 µL) and TFA (75 µL, 10 vol%). The reaction mixture was stirred at r.t. until full conversion of the starting material was observed (see Table 1). The solvent was removed in vacuo and the residue was diluted with Et_2O and the solvent was then evaporated. Dilution and evaporation was repeated twice more to give the deprotected sulfonamide.
(24) Mayr, H.; Foerner, W.; von Rague Schleyer, P. *J. Am. Chem. Soc.* **1979**, *101*, 6032.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.