Tetrahedron Letters, Vol. 33, No. 48, pp. 7291-7292, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

The Use of Diphenylmethyl as a Sulfonamide Protecting Group

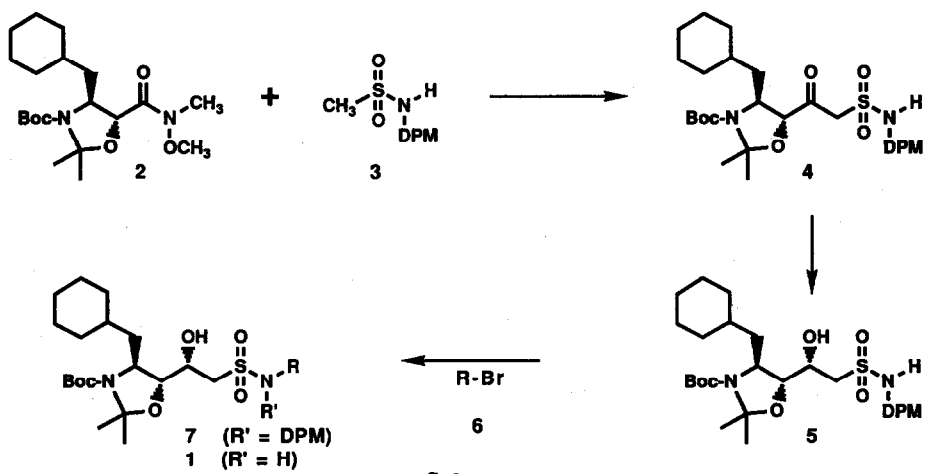
Michael A. Poss,*[1] and Joyce A. Reid

The Bristol-Myers Squibb Pharmaceutical Research Institute
P.O. Box 4000, Princeton, New Jersey 08543-4000, USA

Key Words: diphenylmethyl, hydrogenation, sulfonamide

Abstract: *The use of diphenylmethyl (DPM) as a protecting group for sulfonamides is reported.*

During our investigation of a series of renin inhibitors,[2] we sought to prepare a group of sulfonamide analogs represented by the general structure **1**. It was envisioned that the most efficient route to prepare compounds **1** would be to synthesize a protected sulfonamide intermediate such as **5**, introduce R by alkylation of the sulfonamide moiety, and then remove the protecting group to provide **1**, (Scheme).[3] Successful execution of this route, however, required a suitable sulfonamide protecting group.[4] We wish to report that diphenylmethyl (DPM) can be used as an effective sulfonamide protecting group. Diphenylmethyl is stable to both strong acid and base, but is easily removed by hydrogenation in high yield.[5]

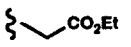
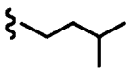
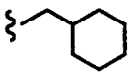
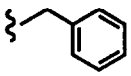


Scheme

Compound **3** was prepared from methanesulfonyl chloride and aminodiphenylmethane (Et_3N, CH_2Cl_2, 98%)[6] and treated with 4N HCl in dioxane at room temperature to determine its acid stability. After 24 hours, **3** was recovered unchanged in quantitative yield. Utilizing the dianion chemistry described by Thompson,[7] sulfonamide **3** was then coupled with amide **2**[8] (*n*-BuLi, LiCl, THF, 98%) to furnish *beta*-ketosulfonamide **4**. Reduction of ketone **4** ($KB(C_2H_5)_3H$, THF) provided alcohol **5** (57%) along with its corresponding diastereomer (20%) which were separated by chromatography.

Alkylation (K_2CO_3, DMF) of sulfonamide **5** with bromides **6a-d** gave the disubstituted sulfonamide derivatives **7a-d**, (Table). The DPM protecting group was then removed by hydrogenation (H_2, 1 atm, $Pd(OH)_2/C$, CH_3OH, THF, Et_3N, 18 hrs)[9] to furnish **1a-d**. The synthesis of **1d** demonstrates the ease of removal of DPM relative to benzyl.

Table

Entry	R	Yield of 7 (%)	Yield of 1 (%)
a		76	87
b		83	99
c		84	94
d		94	92

In summary, diphenylmethyl (DPM) has been utilized as an effective sulfonamide protecting group. This blocking group is stable to strong acid and strong base, but efficiently removed by mild hydrogenation.

Acknowledgements: *Helpful discussions with Dr. Denis E. Ryono are gratefully acknowledged.*

References and Notes:

1. Current address: The Bristol-Myers Squibb Pharmaceutical Research Institute, 1 Squibb Drive, P.O. Box 191, New Brunswick, New Jersey 08903-0191, USA.

2. Poss, M. A. U.S. Patent 5 098 924, 1992.

3. For a similar strategy to prepare *N*-monoalkylated sulfonamides, see: Gensler, W. J.; Frank, F. J.; Dheer, S. K.; Lauher, J. W. *J. Org. Chem.* **1971**, *36*, 4102.

4. For the use of phenylselenylethyl as a protecting group for sulfonamides, see: (a) Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1981**, *22*, 5027. (b) Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2869.

5. The use of benzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, and 4-nitrobenzyl as sulfonamide protecting groups was also examined. The benzyl derivatives could be removed by hydrogenation, but the reaction led to partial formation of saturated cyclohexyl derivatives and required the use of high pressure (>700 psi H_2) and acetic acid as the solvent. Removal of the 2,4-dimethoxybenzyl and 3,4-dimethoxybenzyl groups with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was also explored, but complex reaction mixtures were obtained and the yields were moderate.

6. Attempts to introduce the diphenylmethyl protecting group by alkylation of a sulfonamide with bromodiphenylmethane were unsuccessful.

7. Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700.

8. For the preparation of amide **2**, see: Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411.

9. Without the addition of a small amount of triethylamine, the reaction solutions were observed to be weakly acidic and partial deblocking of the *tert*-butoxycarbonyl and isopropylidine groups resulted.

(Received in USA 5 August 1992; accepted 9 September 1992)