JOC*Note*

# Facile One-Pot Synthesis of Aromatic and Heteroaromatic Sulfonamides

Rina Pandya, Takashi Murashima, Livio Tedeschi, and Anthony G. M. Barrett*

*Department of Chemistry, Imperial College London, London SW7 2AZ, England*

*agmb@imperial.ac.uk*

*Received May 14, 2003*

**Abstract:** A series of arene and heteroarene sulfonamides were prepared in one vessel from aryl and heteroaryl bromides via conversion into the corresponding Grignard reagents using either magnesium or isopropylmagnesium chloride and subsequent reaction with sulfur dioxide, sulfuryl chloride, and an amine.

Sulfonamides are a diverse group of compounds of considerable medical importance.[1] As a class, the sulfa drugs have a veritable history of application for the treatment of bacterial infection. However, the sulfonamide functionality is much more widespread in pharmaceuticals than just in an early class of antibiotics. Medically important examples include the protease inhibitor amprenavir (**1**), the analgesic celecoxib (**2**), sildenafil (**3**) for erectile dysfunction, and the antimigraine agent sumatriptan (**4**) (Figure 1). The vast majority of sulfonamides are prepared from the reaction of a sulfonyl chloride with ammonia or primary or secondary amines or via related transformations.[2,3] In turn, arenesulfonyl chlorides are prepared from arenes by electrophilic aromatic substitution using an excess of chlorosulfonic acid or from arenesulfonic acids by reaction with phosphorus pentachloride.[4] Again, in turn, arenesulfonic acids are prepared from the electrophilic sulfonylation of arenes using concentrated sulfuric acid or oleum. Given the harshness of these reaction conditions, sulfonic acids and sulfonyl chlorides are rarely introduced into an advanced intermediate via C−S bond formation. As a consequence, the diversity of sulfonamide functionality in pharmaceutical discovery is actually limited and cannot be readily varied at both *nitrogen and sulfur* in the final stage of a library synthesis.

There is a clear need for the development of a generally useful, mild, and novel methodology for the introduction of primary, secondary, and tertiary sulfonamide groups without recourse to potent electrophiles. In 1968, Eaborn and co-workers reported the preparation of arenesulfonyl chlorides from the reaction of Grignard reagents with sulfuryl chloride.[5] Additionally, Gilbert[6] described a

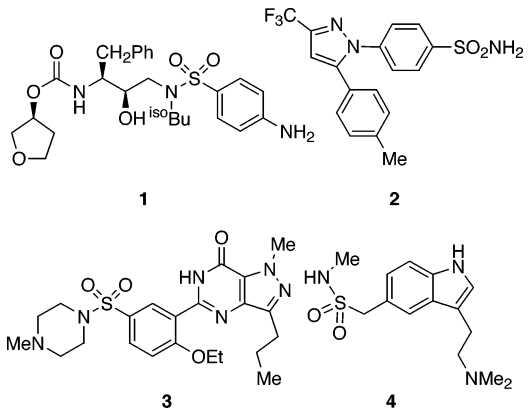



**FIGURE 1.** Important pharmaceutical drugs with sulfonamide functionality.

procedure to prepare phenylsulfonamides in moderate yields by allowing phenylmagnesium chloride to react sequentially with sulfuryl chloride in hexane and an amine at 0 °C. A limitation of the procedure was the need for careful temperature control with lower yields at lower temperatures and side reactions possibly arene chlorination above 0 °C. Moreover, the method was not applied to functionalized aryl halides. Hamada and Yonemitsu[7] showed that arenesulfonyl chlorides could be prepared in excellent yields via the addition of aryllithium reagents to sulfur dioxide at −100 °C, followed by *S*-chlorination of the arenesulfinate intermediate using sulfuryl chloride. However, this method relies on the use of reactive aryllithium intermediates, which are incompatible with polar functionality. Hence, there is a need to develop a general, mild, and efficient one-pot synthesis of sulfonamides, which could tolerate the presence of heterosubstituted aryl moieties or reactive functional groups. We therefore sought to reinvestigate the preparation of sulfonamides from aryl halides by reaction of the derived Grignard reagents with sulfur dioxide,[8] sulfuryl chloride, and an amine.

Initially, we sought to extend the scope of the Yonemitsu procedure with the synthesis of arenesulfonyl chlorides under milder reaction conditions. We found that sulfinylation of aryl-Grignard reagents **6** using sulfur dioxide afforded the sulfinates **7**, which upon direct addition of neat sulfuryl chloride at −40 °C gave the corresponding arenesulfonyl chlorides **8**. Subsequent addition of a secondary amine at room temperature gave the desired sulfonamides **9**. This one-vessel procedure gave higher yields than the synthesis of *N*,*N*-diethylbenzenesulfonamide from phenylmagnesium bromide reported by Gilbert.[6] The procedure proved to be useful for the preparation of a diverse range of sulfonamides **9a**−**k**, starting from the readily available and inexpensive aryl bromides **5** (Table 1, entries 1−11). The method was

(1) *Pharmaceutical Substances, Syntheses, Patents, Applications*; Kleemann, A., Engel, J., Kutscher, B., Reichert, D., Eds.; Thieme: Stuttgart, 1999.

(2) Cremlyn, R. *Organosulfur Chemistry: An Introduction;* J. Wiley and Sons: New York, 1996; pp 224−225.

(3) Anderson, K. K. In *Sulfonic Acids and Their Derivatives in Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Jones, D. N., Eds.; Pergamon Press, Oxford, 1979; Vol. 3, pp 331−340, 345−350.

(4) Heumann. K.; Köchlin, P. *Chem. Ber.* **1882**, *15*, 1114.

(5) Bhattacharya, S. N.; Eaborn, C.; Walton, D. R. M. *J. Chem. Soc. C* **1968**, 1265 and references therein.

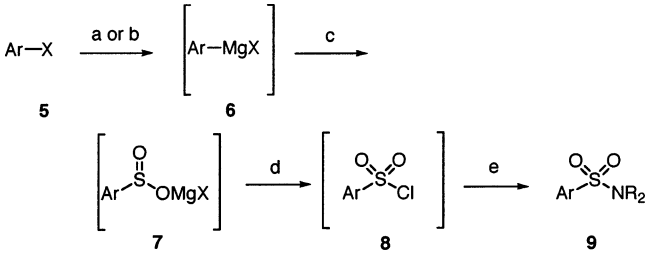
(6) Gilbert, E. E. *Synthesis* **1969**, 1.

(7) Hamada, T.; Yonemitsu, O. *Synthesis* **1986**, 852.

(8) (a) Truce, W. E.; Murphy, A. M. *Chem. Rev.* **1951**, *48*, 69. (b) Zöller, U. In *Synthesis of sulfinic acids, esters and their derivatives*; Patai, S., Ed.; J. Wiley and Sons: New York, 1990; pp 185−215.

10.1021/jo034643j CCC: $25.00 
Published on Web 09/23/2003

**TABLE 1. General One-Pot Preparation of Sulfonamides**




Reagents and conditions: a) Mg, $Et_2O$; b) $^iPrMgCl$; c) $SO_2$; d) $SO_2Cl_2$; e) $NHR_2$

| *Entry* | *Ar-X* | *$NHR_2$* | *Product* | *Yield*[a] |
|---|---|---|---|---|
| 1[b] | PhBr | $Et_2NH$ | **9a** | 80% |
| 2[b] | PhBr |  | **9b** | 85% |
| 3[b] | PhBr |  | **9c** | 88% |
| 4[b,c] | PhBr |  | **9d** | 35% |
| 5[b] | 4-$MeC_6H_4Br$ | $Et_2NH$ | **9e** | 60% |
| 6[b] | 4-$^tBuC_6H_4Br$ | $Et_2NH$ | **9f** | 61% |
| 7[b] | 4-$PhC_6H_4Br$ | $Et_2NH$ | **9g** | 62% |
| 8[b] | 2-$MeOC_6H_4Br$ | $Et_2NH$ | **9h** | 73% |
| 9[b] | 4-$MeOC_6H_4Br$ | $Et_2NH$ | **9i** | 75% |
| 10[b] | 4-$PhOC_6H_4Br$ | $Et_2NH$ | **9j** | 58% |
| 11[b] | 4-$Me_2NC_6H_5Br$ | $Et_2NH$ | **9k** | 56% |
| 12[d,e] | 4-$EtO_2CC_6H_4I$ | $Et_2NH$ | **9l** | 53% |
| 13[d,e] | 4-$NCC_6H_4I$ | $Et_2NH$ | **9m** | 67% |
| 14[d,e] | 4-$BrC_6H_4I$ | $Et_2NH$ | **9n** | 48% |
| 15[d,f] |  | $Et_2NH$ | **9o** | 68% |
| 16[d,f] |  |  | **9p** | 51% |
| 17[d,f] |  | $Et_2NH$ | **9q** | 56% |
| 18[d,f,g] |  | $Et_2NH$ | **9r** | 35% |
| 19[d,f,g] |  |  | **9s** | 48% |
| 20[d,f] |  | $Et_2NH$ | **9t** | 52% |
| 21[d,f] |  |  | **9u** | 47% |
| 22[d,g,h] |  | $Et_2NH$ | **9v** | 48% |
| 23[d,g,h] |  |  | **9w** | 30% |
| 24[d,e,i] |  | $Et_2NH$ | **9x** | 35% |
| 25[d,e] |  |  | **9y** | 47% |
| 26[b] | 1-$Me(CH_2)_4Br$ | $Et_2NH$ | **9z** | 0% |

[a] Isolated yields after column chromatography. [b] Metalation using magnesium. [c] Pure sulfonamide **9d** was isolated in low yield following chromatographic losses. [d] Metalation using isopropylmagnesium chloride. [e] Halogen−metal exchange at −30 °C. [f] Halogen−metal exchange at room temperature. [g] Major product is monobromo-monosulfonamide. [h] Halogen−metal exchange at −5 °C. [i] A superior yield was obtained with reverse addition of sulfur dioxide (35%) than with the standard addition (21%).

extended to the synthesis of three *N*,*N*-diethylsulfonamides **9l**−**n** containing an ester, nitrile, or a bromo substituent (Table 1, entries 12−14). In these examples, the requisite Grignard reagents were prepared from aryl iodides at low temperatures by iodine metal exchange using isopropylmagnesium chloride,[9,10] a procedure extensively utilized by Knochel.[11] The Knochel procedure is noteworthy since it is compatible with functional groups including esters, nitriles, and amides in the aryl iodide. In the case of sulfonamide **9l**, the extent of magnesium−iodine exchange was conveniently followed by GC/MS with a 1,3,5-tri-*tert*-butylbenzene standard. This showed that the conversion to the Grignard reagent **6l** was 73%, and therefore, the isolated yield of sulfonamide **9l** (53%) represented subsequent loss. A variety of heteroarenesulfonamides **9o**−**y** were prepared in moderate to good yield, by formation of the heteroaryl Grignard reagents **6** using isopropylmagnesium chloride,[11,12] followed by *S*-chlorination and condensation with a range of amines (Table 1, entries 15−25). The method was satisfactory for the conversion of 2,6-dibromopyridine and 2,5-dibromothiophene into the monobromosulfonamides **9r**, **9s**, **9v**, and **9w** even when using an excess of isopropylmagnesium chloride (Table 1, entries 18 and 19). Quéguiner[12] has previously reported that the second trans-metalation of 2,6-dibromopyridine is slow. Ethyl 5-bromothiophene-2-carboxylate was converted into the sulfonamides **9x** and **9y** (Table 1, entries 25 and 26) again using bromine metal exchange with isopropylmagnesium chloride.[11] Attempts were made to enhance the yields of the sulfonamides by the use of an inverse addition of the Grignard reagent to sulfur dioxide.[13] In the case of the nonfunctionalized sulfonamides **9a** and **9e** (Table 1, entries 1 and 5), yields were not significantly enhanced. However, the yield of the functionalized sulfonamide **9x** was slightly increased with reverse addition to sulfur dioxide (Table 1, entry 24). The preparation of an aliphatic sulfonamide **9z** from 1-bromopentane **5z** was not successful. Although sulfonamide **9z** was observed by GC−MS, the crude reaction mixture was intractable.

In summary, we have developed a convenient one-pot procedure for the preparation of aryl- and heteroaryl-substituted sulfonamides from commercially available and inexpensive aryl and heteroaryl bromides and iodides.

## Experimental Section

**Preparation of Sulfonamides 9. (a) Procedure GP 1.** Mg turnings (540 mg, 22.40 mmol) were activated with $I_2$ (25 mg, 0.11 mmol) in THF (5 mL). The aryl bromide **5** (11.2 mmol) in THF (15 mL) was added dropwise and the mixture heated to reflux for 1 h and recooled to −40 °C. $SO_2$ was bubbled through the solution for 5 min, and after 0.5 h, $SO_2Cl_2$ (0.90 mL, 11.20 mmol) was added. On warming to room temperature, the amine

(9) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415.
(10) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.
(11) (a) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (b) Bérillon, L.; Lepêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359. (c) Abarbri, M.; Knochel, P. *Synlett* **1999**, *10*, 1577.
(12) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339.
(13) Pinnick, H. W.; Reynolds, M. A. *J. Org. Chem.* **1979**, *44*, 160.

$R_2NH$ (112 mmol, 10 equiv) was added. After 3 h, the reaction mixture was quenched with $H_2O$ (20 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were combined and dried ($MgSO_4$), rotary evaporated, and chromatographed on silica to afford the sulfonamide **9**. **(b) Procedure GP 2.** *i*-PrMgCl in THF (2 M; 4.33 mmol) was added dropwise with stirring over 5 min to the bromide or iodide **5** (4.12 mmol) in THF (20 mL) at −30 °C, −5 °C, or room temperature (see Table 1) under argon. The resulting solution containing **6** was stirred for 30 min and allowed to react with $SO_2$, $SO_2Cl_2$, and $R_2NH$ to provide **9** following the procedure in **GP1**.

**Acknowledgment.** We thank GlaxoSmithKline for the generous endowment to A.G.M.B, the BBSRC for a studentship (to R.P.), Ehimè University, Japan for sabbatical support (to T.M.), and the Royal Society and the Wolfson Foundation for a Royal Society−Wolfson Research Merit Award (to A.G.M.B.) and for establishing the Wolfson Centre for Organic Chemistry in Medical Sciences at Imperial College.

**Supporting Information Available:** Spectroscopic data for **9a**−**y**, literature references for known sulfonamides, and copies of $^1H$ and $^{13}C$ NMR spectra for **9h**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034643J