JOC*Note*

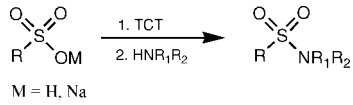
An Easy Microwave-Assisted Synthesis of Sulfonamides Directly from Sulfonic Acids

Lidia De Luca* and Giampaolo Giacomelli

Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2, I-07100 Sassari, Italy

ldeluca@uniss.it

Received February 21, 2008



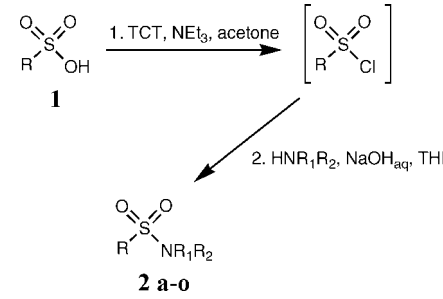
An easy and handy synthesis of sulfonamides directly from sulfonic acids or its sodium salts is reported. The reaction is performed under microwave irradiation, has shown a good functional group tolerance, and is high yielding.

Sulfonamides are an important category of pharmaceutical compounds with a broad spectrum of biological activities.[1]

Sulfonamides drugs have broad applications in many areas of clinical medicine, as good antibacterials, diuretics, anticonvulsants, hypoglycemics, and HIV protease inhibitors.[2]

In recent times, sulfonamides have been found to be powerful carbonic anhydrase,[3] COX-2,[4] and caspase inhibitors.[5] A series of aromatic sulfonamides have been prepared and crystallized as chiral crystals.[6] Typically, sulfonamides were prepared by the reaction of a sulfonyl chloride with ammonia or primary or secondary amines. However, sulfonyl chlorides have some disadvantages, as they are not handled easily and are not suitable to long-term storage.[7] Just a few of these compounds are commercially available because of their instability. Caddick and co-workers reported a suitable preparation of sulfonamides by intermolecular radical addition to pentafluorophenyl vinylsulfonate and successive aminolysis.[8] Katritzky and co-workers proposed a general and efficient synthesis of sulfonamides by the reaction between sulfonylbenzotriazoles (produced from sulfinic acid salts with *N*-chlorobenzotriazole) and various amines.[9] Recently the synthesis of heteroaryl sulfonamides via oxidation of thiols to sulfonyl chlorides or sulfonyl fluorides has been reported that were then reacted with amines to give the corresponding sulfonamides.[10] The logical way to sulfonamides could be the direct synthesis from sulfonic acid. Even if pharmaceutical compounds containing a sulfonamide group have numerous significant therapeutic applications, at present just two methodologies are reported to convert a sulfonic acid directly to a sulfonamide. The first method permits the synthesis of sulfonamides from the sulfonic acid pyridine or triethylamine salts by the use of the activating agent triphenylphosphine ditriflate.[11] The second procedure considers the reaction of a sulfonic acid with isocyanide at room temperature.[12]

SCHEME 1. Sulfonamides from Sulfonic Acids



Following our interest in the use of 2,4,6-trichloro-[1,3,5]-triazine (TCT) and [1,3,5]-triazine derivatives in organic synthesis,[13] we report here a novel, easy, and convenient method for the preparation of sulfonamides directly from easily available sulfonic acid (Scheme 1) or its sodium salt (Scheme 2), improved by microwave irradiation.

The procedure consists of the addition of 1 equiv of TCT to a mixture of 1 equiv of sulfonic acid and 1 equiv of triethylamine in acetone. Even if the reaction can be conducted in refluxing acetone (20 h), we have preferred to carry out the reaction under microwave irradiation in a sealed tube (10-mL

(1) For a review, see: Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 7.1. (b) Connor, E. E. *Sulfonamide Antibiotics prim. Care Update Ob. Gyn.* **1998**, *5*, 32. (c) Hanson, p. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.

(2) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances, Synthesis, Patents, Applications*; Thieme: Stuggart, 1999. *Guide*, 2nd ed., available from Oxford Press.

(3) (a) Winum, J.-Y.; Dogné, J.-M.; Casini, A.; de Leval, X.; Montero, J.-L.; Scozzafava, A.; Vullo, D.; Innocenti, A.; Supuran, C. T. *J. Med. Chem.* **2005**, *48*, 2121. (b) Nishimori, I.; Minakuchi, T.; Morimoto, K.; Sano, S.; Onishi, S.; Takeuchi, H.; Vullo, D.; Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2006**, *49*, 2117. (c) Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Innocenti, A.; Vullo, C.; Supuran, C. T.; Poulsen, S.-A. *J. Med. Chem.* **2007**, *50*, 1651.

(4) (a) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775. (b) Habeeb, A. G.; Praveen Rao, P. N.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039. (c) Almansa, C.; Bartrolí, J.; Belloc, J.; Cavalcanti, F. L.; Ferrando, R.; Gómez, L. A.; Ramis, I.; Carceller, E.; Merlos, M.; García-Rafanell, J. *J. Med. Chem.* **2004**, *47*, 5579.

(5) (a) Chu, W.; Zhang, J.; Zeng, C.; Rothfuss, J.; Tu, Z.; Chu, Y.; Reichert, D. E.; Welch, M. J.; Mach, R. H. *J. Med. Chem.* **2005**, *48*, 7637. (b) Chu, W.; Rothfuss, J.; d'Avignon, A.; Zeng, C.; Zhou, D.; Hotchkiss, R. S.; Mach, R. H. *J. Med. Chem.* **2007**, *50*, 3751.

(6) Kato, T.; Okamoto, I.; Tanatani, A.; Hatano, T.; Uchiyama, M.; Kagechika, H.; Masu, H.; Katagiri, K.; Tominaga, M.; Yamaguchi, K.; Azumaya, I. *Org. Lett.* **2006**, *8*, 5017.

(7) (a) Caddick, S.; Wilden, J. D.; Wadman, S. J.; Bush, H. D.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549. (b) Caddick, S.; Hamza, D.; Wadman, S.; Wilden, J. D. *Org. Lett.* **2002**, *4*, 1775.

(8) Caddick, S.; Wilden, j. D.; Bush, H. d.; Wadman, S. N.; Judd, D. N. *Org. Lett.* **2002**, *4*, 2549.

(9) Katritzky, A. R.; Rodriguez-Garcia, V.; Nair, S. K. *J. Org. Chem.* **2004**, *69*, 1849.

(10) Wright, S. W.; Hallstrom, K. N. *J. Org. Chem.* **2006**, *71*, 1080.

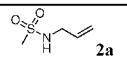
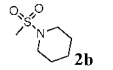
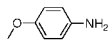
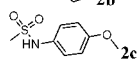
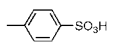
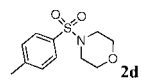
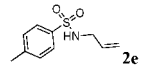
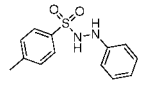
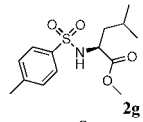
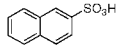
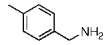
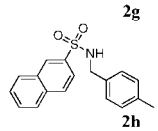
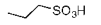
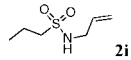
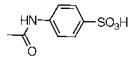
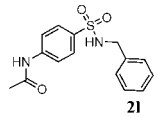
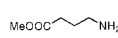
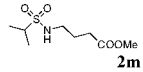
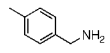
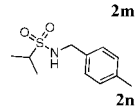
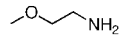
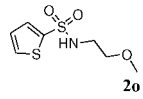
(11) Caddick, S.; Wilden, J. D.; Judd, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 1024.

(12) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 2185.

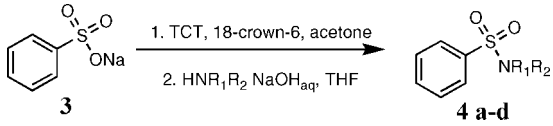
(13) (a) De Luca, L.; Giacomelli, G.; Niueddu, G. *J. Org. Chem.* **2007**, *72*, 3955. (b) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, 2570. (c) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *Synlett* **2004**, 2299. (d) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553.

10.1021/jo800424g CCC: $40.75
Published on Web 04/08/2008

TABLE 1. Sulfonic Acid and Amine Diversity in Sulfonamide Synthesis

entry	sulfonic acid	amine	product	yield %
1	H_3C-SO_3H		 **2a**	89
2	"		 **2b**	88
3	"		 **2c**	90
4			 **2d**	95
5	"		 **2e**	85
6	"		 **2f**	92
7	"		 **2g**	80
8			 **2h**	78
9			 **2i**	88
10			 **2l**	90
11			 **2m**	92
12	"		 **2n**	85
13			 **2o**	78

SCHEME 2. Sulfonamides from Sulfonic Acid Sodium Salts



3 **4 a-d**

pressure-rated reaction vial) in a self-tuning single mode irradiating synthetizer, operating at 80 °C for 20 min, for significantly shortening the reaction times and avoiding the presence of byproducts. After cooling, the precipitate formed is filtered off on Celite and the solution is added with 1.2 equiv of $NaOH_{aq}$, THF, and an amine. The reaction mixture is newly exposed to microwave irradiation for 10 min at 50 °C in a sealed tube.[14] The reaction mixture is filtered on Celite to eliminate the formed salts and then diluted with DCM and washed with water, aqueous Na_2CO_3, diluted HCl, and brine. The target product is obtained in pure form, simply by concentration of the DCM extracts at reduced pressure. Following an easy workup, the sulfonamide is obtained in a nearly quantitative yield.

It has been demonstrated that sulfonic acids, treated with TCT, in refluxing acetone for 20 h, are converted in the corresponding sulfonyl chlorides, which are recovered pure by distillation.[15] Even in our procedure the sulfonic acid (or its sodium salt) is transformed in the corresponding sulfonyl chloride; however, its isolation is not necessary as the sulfonyl chloride is directly transformed in the corresponding sulfonamide in the presence of an ammine.

As shown in Table 1, a selection of sulfamides were prepared from an array of sulfonic acids and the yields were satisfactory in all cases. The methodology is efficient and successful with aromatic, aliphatic, and heterocyclic sulfonic acids. The reaction is not limited to primary and secondary amines but works well with hydrazines and amino acid derivatives. The optical rotation value of the product **2g** (from methyl ester of L-valine) is comparable with that reported in the literature.[16] Also, anilines (entry 3) are applicable in the reaction.

We should like to extend the applicability of the methodology to sulfonic acid salts because the majority of sulfonic acids are commercially available as sodium salts. By the addition of a catalytic amount of 18-crown-6 to the reaction mixture, the procedure allows the synthesis of sulfonamides directly from sulfonic acids sodium salts (Scheme 2).

We chose to examine the reaction of benzenesulfonic acid sodium salt with a number of common amines. As reported in Table 2, the reaction is efficient with both primary and secondary amines and yields are high in all cases.

A comparison between conventional heating (oil bath) and microwave irradiation was carried out too, demonstrating a better performance of the MW-assisted process (Table 3).

TABLE 2. Synthesis of Sulfonamides from Sulfonic Acid Sodium Salts

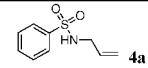
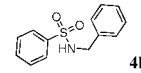
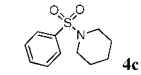
entry	amine	product	yield %
14		 **4a**	89
15		 **4b**	93
16		 **4c**	95
17		**4d**	88

TABLE 3. Comparison of Conventional and Microwave Procedures for Sulfonamide Synthesis

	% yield/purity[a]	
entry	thermal reaction[b]	microwave-assisted reaction[c]
4	80/86	95/95
9	71/85	88/98

[a] Yields determined at the end of both steps. Average purity determined by NMR on the crude product. [b] Conditions: 20 h, refluxing acetone, then 5 h, 50 °C. [c] Conditions: 20 min, 80 °C, 50 W then 10 min, 50 °C, 50 W.

(14) The same reaction carried out by conventional heating required 5 h at 50 °C. The yields of the recovered products were lower than reactions carried out under microwave irradiation.

(15) Blotny, G. *Tetrahedron Lett.* **2003**, *44*, 1499.
(16) Karrer, P.; Kehl, W. *Helv. Chim. Acta* **1924**, *7*, 740.

In conclusion, we think that the methodology described here represents a new, convenient, and handy synthesis of sulfonamides even in large scale, as it uses friendly reaction conditions and cheap and commercially available reagents. The methodology has shown a good functional group tolerance and is high yielding.

Experimental Section

General Procedure for the Synthesis of Sulfonamides from Sulfonic Acids (2a-o). *N*-Allyl-4-methylbenzene-sulfonamide 2e. The procedure for *N*-allyl-4-methyl-benzenesulfonamide (Table 1, entry 5) is representative for all sulfonamides prepared from sulfonic acids (see Supporting Information). 2,4,6-Trichloro-[1,3,5]-triazine (0.09 g, 0.49 mmol) was added at room temperature to a solution of *p*-toluenesulfonic acid (0.08 g, 0.49 mmol) in acetone dry (1 mL), followed by NEt_3 (0.07 mL, 0.49 mmol) dropwise. The resulting mixture was irradiated to 80 °C (50 W of MW power) for 20 min in a sealed tube (10 mL pressure-rated reaction vial) in a self-tuning single mode irradiating synthesizer. The mixture was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 1 min. After cooling to room temperature, the precipitate was filtered off on Celite and 0.3 mL of a 2 M solution of NaOH, THF (0.25 mL), and allylamine (0.04 mL, 0.49 mmol) were added to the solution. The reaction mixture is exposed to microwave irradiation for 10 min at 50 °C (50 W of power) in a sealed tube and then filtered on Celite to eliminate the formed salts, diluted with DCM, and washed with water, aqueous Na_2CO_3, diluted HCl, and brine. The desired product is recovered in pure form, simply by concentration of the DCM extracts at reduced pressure (0.09 g, yield 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.71 (m, 1H), 5.16 (d, J = 17.1 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 3.57 (m, 2H), 2.42 (s, 3H).[9] ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.3, 136.7, 132.9, 129.6, 126.9, 117.4, 45.6, 21.4. [9] mp: 63–66 °C (lit.,[9] 63–66 °C).

General Procedure for the Synthesis of Sulfonamides from Sulfonic Acid Sodium Salts (4a-d). *N*-allylbenzenesulfonamide 4b. The procedure for *N*-allyl-4-methylbenzenesulfonamide (Table 2, entry 15) is representative for all sulfonamides prepared from sulfonic acid sodium salts. 2,4,6-Trichloro-[1,3,5]-triazine (0.09 g, 0.49 mmol) was added at room temperature to a solution of benzenesulfonic acid sodium salt (0.09 g, 0.49 mmol) in acetone dry (1 mL) and 18-crown-6 (0.01 g, 0.04 mmol). The resulting mixture was irradiated to 80 °C (50 W of MW power) for 20 min in a sealed tube (10 mL pressure-rated reaction vial) in a self-tuning single mode irradiating synthesizer. The mixture was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 1 min. After cooling to room temperature, the precipitate formed was filtered off on Celite and to the solution were added 0.3 mL of 2 M solution of NaOH, THF (0.25 mL), and allylamine (0.04 mL, 0.49 mmol). The reaction mixture is exposed to microwave irradiation for 10 min at 50 °C (50 W of power) in a sealed tube. The reaction mixture is filtered on Celite to eliminate the formed salts, then diluted with DCM and washed with water, aqueous Na_2CO_3, diluted HCl, and brine. The desired product is recovered in pure form (0.8 g, yield 89%), simply by concentration of the DCM extracts at reduced pressure. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.89 (m, 2H), 7.56 (m, 3H), 5.61 (m, 1H), 5.13 (m, 2H), 4.67 (bs, 1H), 4.09 (d, J = 7.1 Hz, 2H).[17] ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.1, 132.6, 132.4, 129.1, 127.2, 119.3, 49.5.[14] mp: 39–42 °C (lit.,[18] 39.5–42.5 °C).

Acknowledgment. This work was financially supported by the Univeristy of Sassari and MIUR (Rome) within the project PRIN 2005.

Supporting Information Available: Characterization data of the sulfonamides. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800424G

(17) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc. Perkin Trans. 1* **1997**, *9*, 1411.
(18) Gensler, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 1843.