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One-pot synthesis of sulfonamides from methyl sulfinates using ultrasound

José L. García Ruano [a,*], Alejandro Parra [a], Leyre Marzo [a], Francisco Yuste [b], Virginia M. Mastranzo [b]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain*
[b] *Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Cd. Universitaria, Coyoacán 04510, México D.F., Mexico*

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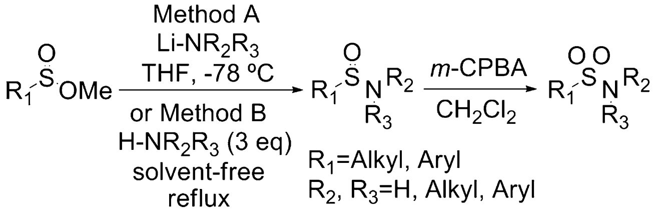
ABSTRACT

Room temperature ultrasonic irradiation of neat mixtures of methyl sulfinates and primary or secondary amines (1.5 equiv) produced sulfinamides, which on *m*-CPBA oxidation (in dichloromethane) were converted into the corresponding sulfonamides. The two steps can be accomplished in one pot, in good overall yields, when using secondary amines, but primary amines give better sulfonamide yields when the peracid oxidation is effected on the purified sulfinamide. This constitutes a mild, efficient, and potentially scalable route to sulfonamides, which obviates the use of water sensitive, often lachrymatory sulfonyl chlorides and large reagent excesses.

1. Introduction

Sulfonamides have found widespread utility in a number of applications,[1] including pharmacology and medicine,[2] agriculture,[3] and other areas,[4] and consequently there is considerable interest in devising mild, large scale, environmentally friendly syntheses thereof. The most commonly used synthesis of sulfonamides involves the reaction of sulfonyl chlorides with ammonia, a primary or secondary amine in the presence of a base.[5] This method, though effective, is associated with several undesirable features, most of which are related to the use of sulfonyl chlorides. Thus, sulfonyl chlorides can be water sensitive and lachrymatory, which are properties that imply special handling procedures and storage conditions. Furthermore, because some sulfonyl chlorides are unavailable, and/or require harsh preparative conditions, the scope of this sulfonamide synthesis is somewhat restricted. As a consequence, considerable effort has recently been devoted to the development of milder routes to sulfonyl chlorides,[6] but most of them do not obviate all of the abovementioned problems. Hence, as indicated above, the development of new, mild, and straightforward syntheses of sulfonamides has merit. In this connection, Bahrami et al.[7] reported that sulfonamides could be prepared in virtually quantitative yields, and in exceedingly short reaction times (1–3 min), by the hydrogen peroxide oxidation of mixtures of thiols or disulfides and amines in the presence of zirconium tetrachloride. We have attempted to reproduce the reported yields of several of the sulfonamides prepared by these investigators, but in our hands this methodology invariably gave sulfonamide yields lower than 20%.

We recently described a two-step synthesis of sulfonamides, which did not involve the use of sulfonyl chlorides.[8] The pivotal aspect of this process was based on the room temperature peracid oxidation of sulfinamides, which in turn were prepared from methyl sulfinates and primary or secondary amines by one of the two methods. In method A (Scheme 1) the methyl sulfinate was reacted with lithium amide at low temperature,[9] whereas in method B the sulfinate was heated (reflux temperature, or sealed tube) with an excess (3 equiv) of an amine.



Scheme 1. Synthesis of sulfonamides via sulfinamides.

Whereas method A rapidly and efficiently produced sulfinamides in good yields, the use of *n*-butyl lithium and the low temperature required are both disadvantageous for large-scale syntheses. Method B, though preferable to method A from an environmental point of view (no solvent),[10] suffers from the need to use the amine in excess as well as elevated temperatures (in some cases under sealed tube conditions) to obtain good conversions into

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[*] Corresponding author. Tel.: +34 91 497 4701; fax: +34 91 497 3966; e-mail address: joseluis.garcia.ruano@uam.es (J.L. García Ruano).

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the sulfinamides. Thus both processes have deficiencies for large-scale syntheses, as well as from an environmental point of view.

A program to develop processes for environmentally friendly multigram scale sulfonamide syntheses was undertaken by searching for conditions, which might improve each phase of the synthetic methodology involved. In this regard, we devised a very simple, inexpensive, and ecologically friendly synthesis of disulfides from the easily available thiols,[11] and also improved the reported synthetic methodology for preparing sulfinates from disulfides[12] (see Ref. 8). Herein we describe studies, which were undertaken to eliminate or minimize the problems associated with the conversion of sulfinates into sulfonamides, and to use the improved methodology for the synthesis of sulfonamides on an environmentally friendly, multigram scale.

2. Results and discussion

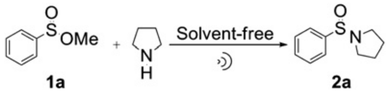
2.1. Ultrasound promoted synthesis of sulfinamides

Once we checked that the one-pot synthesis of sulfonamides from sulfinates by using method A (Scheme 1) was not successful (all the trials to use the same solvent in both steps give poor results[13]) we concentrates our efforts in improving the efficiency of the first step of method B (conversion of the sulfinates into sulfinamides), thus improving its environmental features.

Ultrasound irradiation is well known to ameliorate[14] a broad range of reactions,[15] consequently we chose to examine the effect thereof on the synthesis of sulfinamides. The influence of ultrasound on the reaction of neat methyl benzene sulfinate (**1a**) with varying equivalents of pyrrolidine was chosen as a model reaction. The results shown in Table 1 clearly indicate that ultrasound has a profound effect on the reaction rate of this reaction, quantitative conversion into the sulfonamide **2a** being achieved in 1 h in the presence of 3 equiv of pyrrolidine (entry 4). The amount of pyrrolidine could be decreased to 1.5 equiv without affecting the conversion to **2a**, although the reaction time was doubled (entry 6). The conditions of entry 6 were chosen for study in a potential one-pot synthesis of sulfonamides.

Table 1

Optimization conditions for synthesis of sulfinamide **2a** using ultrasound



Entry	Amine (equiv)	Reaction time (h)	T (°C)	Conversion[b] (%)
1	1.0	4	60	62
2	1.0	10	rt[a]	40
3	3.0	0.5	70	100
4	3.0	1	rt[a]	100
5	2.0	1.5	rt[a]	100
6	1.5	2	rt[a]	100 (80)[c]

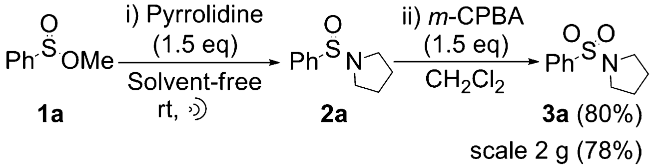
[a] Actual temperature of the bath is 35–40 °C.

[b] Measured by ^{1}H NMR.

[c] Isolate yield after chromatographic purification.

2.2. One-pot two-steps synthesis of secondary amine derived sulfonamides

After removal of the volatiles from a reaction mixture containing the sulfinamide **2a**, prepared under the conditions of entry 6, Table 1, CH_2Cl_2 and 1.5 equiv of *m*-CPBA were added. After ca. 1 h at room temperature, the sulfonamide **3a** was isolated in 80% yield following chromatographic purification (Scheme 2). This process was successfully carried out commencing with 2 g of **1a** with little diminution in the yield (78%) of **3a**.



Scheme 2. One-pot synthesis of sulfonamide **3a**.

The pleasing result obtained in the one-pot synthesis of **3a** prompted us to examine the scope of this process for the synthesis of sulfonamides derived from various methyl sulfinates (**1a**–**g**) and pyrrolidine and other secondary amines. The data shown in Table 2 clearly demonstrate that the process is tolerant of methyl phenyl sulfinates possessing an electron donating or attracting *para*-substituent (entries 2–4, 9, and 10) independent of the nature of the secondary amine used. Sulfonamides (**3e** and **4e**) derived from methyl 2-pyridyl sulfinate (**1e**) and pyrrolidine and morpholine, respectively, were also obtained with quite acceptable efficiency as were sulfonamides **3f** and **3g** stemming from pyrrolidine and the methyl alkylsulfinates **1f** and **1g**. These results indicate that this one-pot two-step synthesis of tertiary sulfonamides is likely to be generally applicable.

2.3. Two-step synthesis of primary amine derived sulfonamides

Our attempts to extend the two step one pot process to the synthesis of sulfonamides derived from primary amines indicate that this is not likely to be a useful process (Table 3).

Firstly, the methyl sulfinate to *N*-alkylsulfinamide transformation was much slower, and usually less efficient, than for secondary amines. In some cases, e.g., with cyclohexylamine (data not shown), the conversion into the corresponding sulfinamides was too low to be synthetically useful. This result must, at least in part, be a consequence of the lower nucleophilicity of primary amines. Secondly, utilization of the optimized conditions for the two step one pot process described in Table 2 for methyl benzene sulfinate and *n*-butylamine or benzylamine, produced the corresponding sulfonamides in unacceptably low yields (entries 1 and 3). If, however, the sulfinamides are first purified, then not surprisingly, the sulfonamide yields are considerably improved (entries 2, 4–6). Nevertheless, the overall sulfonamide yields do not, in general, approach those obtained from secondary amines.

3. Conclusions

In conclusion, we describe an efficient, generally applicable, two step one-pot procedure for obtaining tertiary sulfonamides by the ultrasound promoted generation of sulfinamides from neat mixtures of methyl sulfinates and secondary amines, followed by oxidation of the crude sulfinamides with *m*-CPBA. It is potentially scalable, economical, and environmentally acceptable. This method is not useful for the synthesis of sulfonamides derived from primary amines, which however, can be obtained with much lower efficiency by a two step process in which the intermediate sulfinamide is first purified.

4. Experimental section

4.1. General methods

^{1}H and ^{13}C NMR spectra were acquired at 300 or 400 MHz and 75 or 100 MHz, respectively (unless otherwise indicated) relative to $CDCl_3$ (7.26 and 77.0 ppm). Melting points were determined in open capillary tubes. For the sonication an Elma Transonic T 460/H