RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

A Simple and Eco-Sustainable Method for the Sulfonylation of Amines Under Microwave-Assisted Solvent-Free Conditions.

Salah Lakrout, Hacène K'tir, Aïcha Amira, Malika Berredjem and Nour-Eddine Aouf

Abstract:

A new environmentally benign, simple, and efficient protocol for the chemoselective sulfonylation of various structurally amines using microwave irradiation under solvent- and catalyst-free conditions is reported. The corresponding sulfonamides were obtained in excellent yields within short reaction times. Simplicity, milder, cleaner and greener conditions, easier work-up, and lower generation of waste or pollutions are the main advantages of this method.

Keywords:

Sulfonylation, Amine, Catalyst-free, Solvent-Free, Microwave, *p*-Toluenesulfonyl chloride.

Journal Name

RSCPublishing

ARTICLE

A Simple and Eco-Sustainable Method for the Sulfonylation of Amines Under Microwave-Assisted Solvent-Free Conditions.

Cite this: DOI: 10.1039/xoxxoooooox

Received
Accepted

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Salah Lakrout,[a] Hacène K'tir,[a] Aïcha Amira,[a] Malika Berredjem,[a] and Nour-Eddine Aouf*[a]

A new environmentally benign, simple, and efficient protocol for the chemoselective sulfonylation of various structurally amines using microwave irradiation under solvent- and catalyst-free conditions is reported. The corresponding sulfonamides were obtained in excellent yields within short reaction times. Simplicity, milder, cleaner and greener conditions, easier work-up, and lower generation of waste or pollutions are the main advantages of this method.

Introduction

The development of simple, efficient, eco-friendly and economically viable processes in organic synthesis is in great demand. Sulfonylation of heteroatom is a very interesting transformation which resulted in the sulfonamide and sulfonate ester moieties as building blocks of important biologically active compounds.[1-4] Sulfonamides and sulfonate esters are very important derivatives of amines and alcohols functionalities for easy preparation under mild conditions.[5,6] Also, they are extremely useful pharmaceutical compounds because they exhibit a wide spectrum of biological activities such anticancer,[4] anti-inflammatory,[7] antiviral agents and anti VIH protease inhibitor.[8] In addition, numerous sulfonamide derivatives have been in preclinical development.

As a result of wide range of activity and importance, there are several available methods for the preparation of sulfonamides. The vast majority of sulfonamides are synthesized by the reaction of a sulfonyl/sulfuryl chloride with primary or secondary amines, usually, in the presence of a base in an aprotic solvent, or via related transformations.[9-11] The synthesis of sulfonamides can also be performed by reacting an amine with *N*-chlorosulfonyl carbamate (CSC) at 0° C.[12-14] In addition, there are a limited number of reports on the use of various catalysts to perform sulfonylation. These include CsF-Celite,[15] metal oxide (ZnO, MgO, CuO, Ag_2O),[16-18] and Zn-Al-hydrotalcite under ultrasound irradiation.[19] In addition, the use of water as solvent for the sulfonylation of amines has been described.[20]

However, most of the reported methods suffer from at least one of the limitations such as occurrence of undesired side reactions (disulfonylation with primary amines), long reaction times, effluent pollution, harsh reaction conditions, the use of toxic reagents and solvents and tedious workup procedures.[21]

Microwave has been widely used in organic synthesis.[22] Introduced by Gedye[23] and Giguere,[24] it has advantages like reduction of reaction times, enhancement of product yields, easy isolation of the final product, ability to precisely control the temperature, ect.[25]

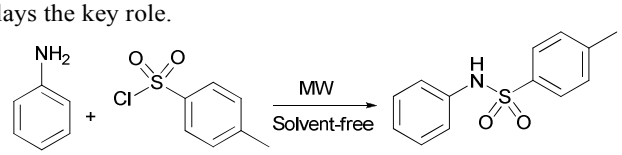
In continuation of our interest towards development of useful green synthetic methodologies,[26-30] we report the successful use of microwave irradiation for the selective sulfonylation of various structurally amines. It is a facile and eco-friendly method for the preparation of sulfonamides wherein the use of solvents and catalysts is avoided.

Results and discussion

Sulfonylation of Amines

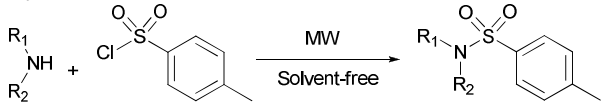
In order to investigate the optimum model reaction system, we choose aniline (Entry1, Table 1) as model substrate. It was treated with *p*-toluenesulfonyl chloride (1:1 mmol) in the absence of any catalyst with dichloromethane as a solvent under microware irradiation. The reaction was completed in 30 minutes and the expected sulfonamide was obtained in 92% yield. To find the effect of microwave irradiation, we performed the reaction (Scheme 1) without dichloromethane; the reaction showed better product yield and shorter reaction time, the time required for the completion of the reaction was reduced to 3 minutes. Thus we concluded that because of the higher concentration of the reactants, the reaction is optimal in

solvent-free conditions, and that the microwave irradiation plays the key role.



Scheme 1: Sulfonylation of aniline

Encouraged by the preliminary result and to increase the scope of this reaction, we extended this study to substituted anilines, aliphatic and heterocyclic amines (Scheme 2). The results are summarized in Table 1. In all cases, we obtained the sulfonamides with good to excellent yields. The best result was obtained with aniline as substrate, affording sulfonamide in 97% yield after 3 minutes.

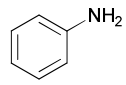
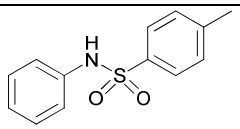
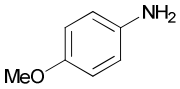
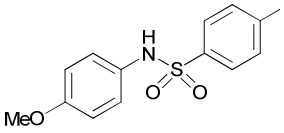
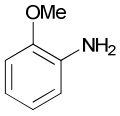
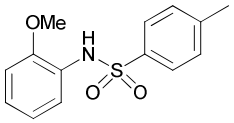
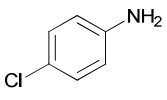
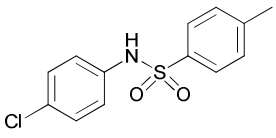
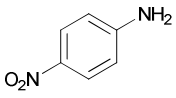
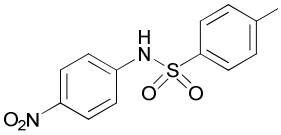
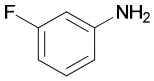
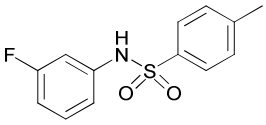
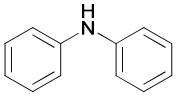
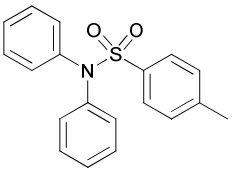
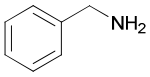
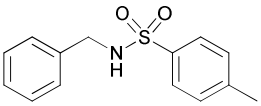
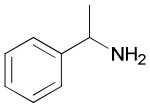
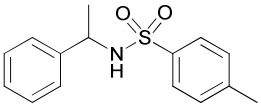
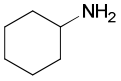
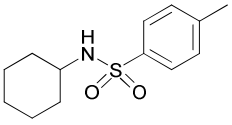
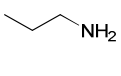
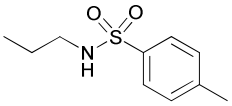
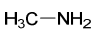
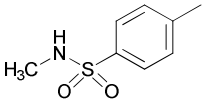
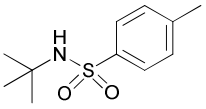
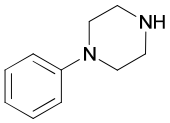
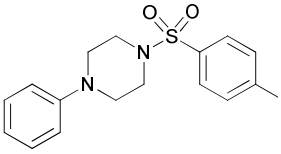
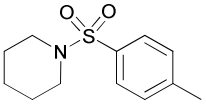
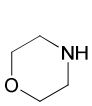
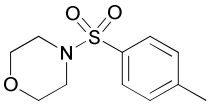
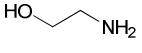
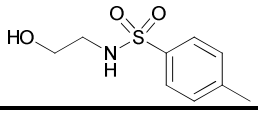


Scheme 2: Microwave-assisted sulfonylation of various structurally amines.

The reaction was compatible with a variety of primary and secondary amines (Table 1) and was rapid with all of the studied amines (1.5-7 min). However, liquid amines themselves can play the role of reactant and solvent, which explains the short reaction times comparing with solid amines (Table 1, Entry 2a, 4a, 5a, and 7a). Bis-sulfonylation compounds were not observed using this procedure for the primary amines. The formation of sulfonamide product was more rapid with primary amines when compared to secondary amines due to nucleophilicity. In the case of aromatic amines, the reaction was not affected by the nature of the substituent in the aromatic ring (Entry 2a-7a).

Further studies showed that increasing the microwave power level did not improve the yields of the products.

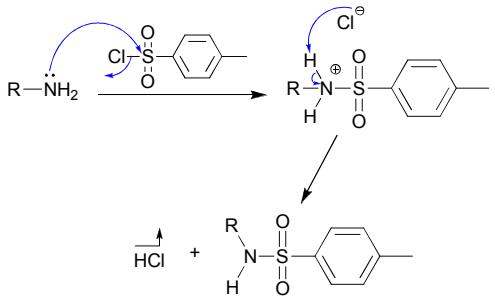
Table1: Microwave-assisted sulfonylation of amines.

Entry	Amine	Product	Time (min)	Yield (%)
1a			3	97
2a			7	93
3a			2.5	95
4a			5	92
5a			7	91
6a			3	93
7a			5	82
8a			3	89
9a			2.5	90
10a			3	86
11a			1.5	88
12a			2	89
13a			2	86
14a			3.5	81
15a			3.5	83
16a			4	85
17a			1.5	77

The structures of all the products were unambiguously confirmed by usual spectroscopic methods (^{1}H, ^{13}C NMR and IR) and comparison with known compounds. The different NMR spectra showed the appearance of a signal corresponding to the methyl protons (Ar-C<u>H</u>$_3$) between 2.3-2.4 ppm. In the IR spectrum, these compounds exhibit characteristic absorption at 1100-1370 cm^{-1} (SO_2).

Mechanistic proposal

The following mechanism can be proposed for this reaction. Microwave irradiation not only quickly heats the system to high temperature facilitating the reaction, but also activates the sulfonyl chloride, making the sulfonyl group more susceptible for nucleophilic attack by the amine, which forms an intermediate. The removal of hydrogen chloride from the intermediate leads to the formation of sulfonamide (Scheme 3).

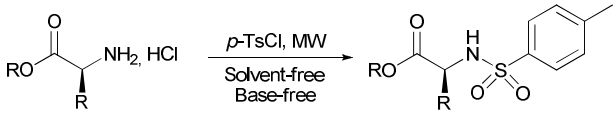


Scheme 3: Mechanistic proposal for the sulfonylation of amines.

Sulfonylation of amino acid esters

To explore the scope and limitations of this procedure, we extended our study to a variety of α-amino acid ester hydrochloride derivatives (Scheme 4). The reaction was carried out at first attempt with ethyl 2-aminoacetate hydrochloride (Table 2, Entry 1b) under the same reaction conditions and without the use of any base or catalyst.

The mildness of this procedure was next illustrated by a range of α-amino acid esters (Table 2, Entry 2b-4b).



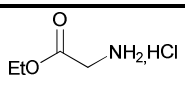
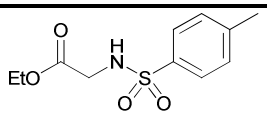
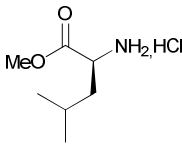
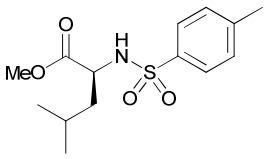
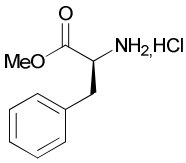
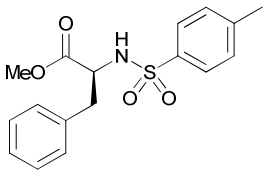
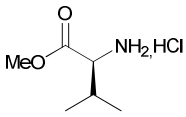
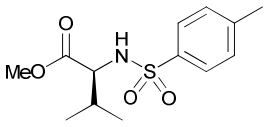
Scheme 4: Microwave-assisted sulfonylation of amino acid esters hydrochloride.

As it can be seen from results in Table 2, the reaction worked very well, and it was quite satisfactory considering that it was carried out without the use of any base. The isolated yields of products (Table 2, Entry 1b-4b) were in the range of 77-85% after 10 minutes of reaction.

It is noteworthy that the reaction preserves stereochemical integrity of *N*-tosyl amino acid esters, where the configuration of the chiral center was not affected by microwave irradiations and the optically pure sulfonamide derivatives were confirmed by optical rotation and comparison with literature.

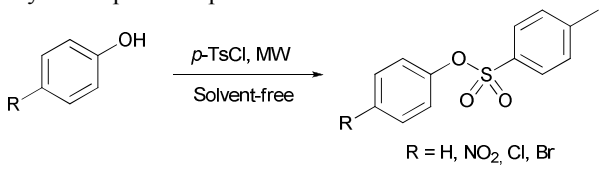
The simplicity and the selectivity of this method can be determining of its application in the organic synthesis and particularly in peptide synthesis.

Table 2: Sulfonylation of amino acid esters hydrochloride

Entry	Amine	Product	Time (min)	Yield (%)
1b			7	85
2b			10	79
3c			10	80
4c			10	77

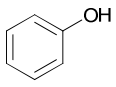
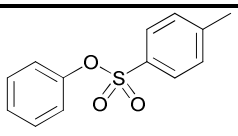
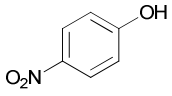
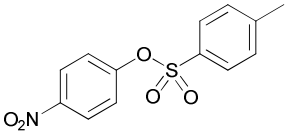
Sulfonylation of phenols

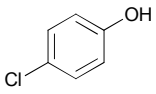
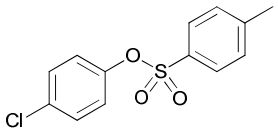
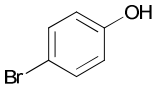
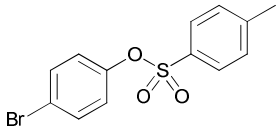
In order to expand the scope of this method to synthesize sulfonic esters, we investigated the reaction of *p*-toluenesulfonyl chloride with *p*-substituted phenols under microwave irradiation (Scheme 5). Unfortunately, a moderate yield of the corresponding sulfonic esters was obtained and requires longer reaction times (3-4 h) (Table 3). It was observed that electronic effects from aromatic ring substituents do not play any role in *O*-sulfoynation. The comparison of the results indicates that the *O*-sulfonylation reaction require a strong acidity of the phenolic proton.



Scheme 5: Microwave-assisted sulfonylation of phenols.

Table 3: Sulfonylation of phenols.

Entry	Phenol	Product	Time (h)	Yield (%)
1c			3	35
2c			4	37

3c			3.5	36
4c			4	32

Experimental

General

All chemicals were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F_{254} percolated aluminum plates and were developed by spraying with ninhydrin solution. All reactions were carried out in the LG microwave *Lightwave Oven MJ3281BCS*, using 100W of microwave power at 50 °C. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brücker spectrometer at 250, 300 or 400 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated by one of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Brücker spectrometer at 60, 75 or 100 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a SCHIMADZU FT-IR 8000 spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Typical experimental procedure for the sulfonylation of amines

p-Toluenesulfonyl chloride (1 mmol) was added to amine (1 mmol) and the mixture was exposed to microwave irradiation for the appropriate time. After completion of the reaction (monitored by TLC), the reaction mixture was treated with *n*-hexane (15-20 mL), and was allowed to stand at room temperature for 7-10 hours. The resulting crystals were collected by filtration, washed with *n*-hexane and dried.
During the reaction, the formation of hydrogen chloride (gas) was observed, confirming our mechanistic proposal.

Conclusions

In conclusion, this paper reports a new microwave assisted, efficient and green *N*-sulfonylation of various structurally amines without the use of any base or catalyst. This new protocol represents an economically advantageous and environmentally benign process; it offers advantages like short reaction times, no use of solvent, no side reactions, facile isolation of products, high yields, and is applicable to a wide range of amines substrates. This could find several applications in the synthesis of biologically important organic compounds such as sulfonamides, sulfonate esters and polyfunctional molecules.

Acknowledgements

This work was generously supported by the (*Direction Générale de la Recherche Scientifique et du Développement Technologique, DGRS-DT*), Algerian Ministry of Scientific Research, (FNR2000). Fruitful discussions with Dr. Malika Ibrahim-Ouali, Université Paul Cézanne Aix Marseille, France, are gratefully appreciated.

Notes and references

[a] Laboratory of applied organic chemistry, Bioorganic Chemistry Group, Sciences Faculty, Chemistry Department, Badji Mokhtar-Annaba University, Box 12, Annaba 23000. Algeria.

† Spectral data for sulfonamides prepared in this work are available in the supporting information joined to this manuscript.

1 C. Hanch, G. Sammes and J. B. Taylor, *Comprehensive Medicinal Chemistry*, Pergamon Press: Oxford, 1990, Vol. **2**, ch. 7.1.
2 G. Sartori and R. Maggi. *Chem. Rev*. 2010, **110**, PR1-PR54.
3 E. E. Connor, *Primary Care Update Ob/Gyn*, 1998, **5**, 32.
4 C. Supuran, A. Casini and A. Scozzafava, *Med. Res. Rev*. 2003, **23**, 535.
5 T. W. Greene and P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis*, Wiley & Sons, New York, 4th edn., 2007.
6 P. J. Kocienski, *Protecting Groups*, George Thieme Verlag, NewYork, 3rd edn., 2004.
7 A. Scozzafava, T. Owa, A. Mastrolorenzo and C. T. Supuran, *Curr. Med. Chem*., 2003, **10**, 925.
8 J. B. McMahon, R. J. Gulakowsky, O. S. Weislow, R. J. Schultz, V. L. Narayanan, D. J. Clanton, R. Pedemonte, F. W. Wassmundt, R. W. Buckheit Jr, W. D. Decker, *Antimicrob. Agents. Chemother*., 1993, **37**, 754.
9 D. A. Alonso and P. G. Andersson, *J. Org. Chem*., 1998, **63**, 9455.
10 C. S. Pak and D. S. Lim, *Synth. Commun*., 2001, **31**, 2209.
11 K. K. Andersen, in *Comprehensive Organic Chemistry*, ed. D. N. Djones. Pergamon Press: Oxford, 1979, Vol. *3*.
12 M. Berredjem, R. Bouasla, N.-E. Aouf and C. Barbey, *X-ray Structure Analysis Online*, 2010, **26**, 13.
13 C. Barbey, R. Bouasla, M. Berredjem, N. Dupont, B. Retailleau, M. Lecouvey and N.-E. Aouf, *Tetrahedron*, 2012, **68**, 9125.
14 R. Bouasla, M. Berredjem, N.-E. Aouf and C. Barbey, *Acta. Cryst.,* 2008, **E 64**, o432.
15 F. Tamaddon, A. Nasiri and S. Farokhi, *Catal. Commun*., 2011, **12**, 1477.
16 F. Tamaddon, M. Reza Sabeti, A. Ali Jafari and F. Tigir, E. Keshavarz *J. Mol. Catal. A Chem*., 2011, **41**, 41.
17 H. H. Kang, H. S. Rho, D. H. Kim and S.-G. Oh, *Tetrahedron Lett*., 2003, **44**, 7225.
18 G. A. Meshram and V. D. Patil, *Tetrahedron Lett*., 2009, **50**, 1117.
19 M. Mokhtar, T. S. Saleh, N. S. Ahmed, S. A. Al-Thabaiti and R. A. Al-Shareef, *Ultrason. Sonochem.*, 2011, **18**, 172.
20 A. Kamal, J. S. Reddy, E. V. Bharathi and D. Dastagiri, *Tetrahedron Lett*., 2008, **49**, 348.
21 J.-G. Kim and D. O. Jang, *Synlett*., 2007, 2501.
22 M. Larhed and K. Olofson, *Microwave Methods in Organic Synthesis*, Springer-Verlag, Berlin, Heidelderg, 2006.
23 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett*., 1986, **27**, 279.

24 R. J. Giguere, T. L. Bray, S. M. Duncan and G. Majetich, *Tetrahedron Lett*., 1986, **27**, 4945.
25 J. P. Tierney and P. Lidström, *Microwave Assisted Organic Synthesis*, Blackwell Publishing Ltd, Oxford, 2005.
26 A. Amira, H. K'tir, M. Berredjem and N.-E. Aouf, *Monatch Chem.*, 2014, **145**, 509.
27 R. Belghiche, Z. Cheraiet, M. Berredjem, M. Abbessi and N.-E. Aouf, *Eur. J. Chem*. 2012, **3**, 305.
28 Z. Cheraiet, S. Hessainia, S. Ouarna, M. Berredjem and N.-E. Aouf. *Green Chemistry Letters and Reviews*, 2013, Vol. **6**. No. 3, 211.
29 Z. Cheraiet, S. Ouarna, Z. Jamel, M. Berredjem and N.-E. Aouf, *Int. J. Chem*., 2012, Vol. **4**. No. 3, 73.
30 N. Klai, M. Berredjem, N. Khettache, M.-Y. Belghit, Z. Régaïnia and N.-E. Aouf, *J. Het. Chem*., 2004, **41**, 57.