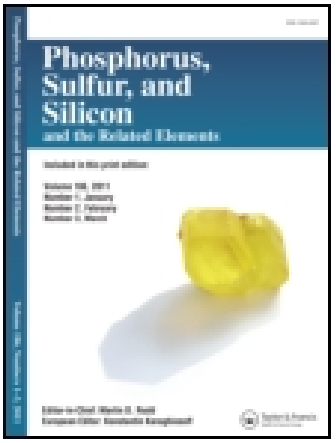


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Microwave-Assisted Synthesis of Some Substituted Sulfamides

Aliye Gediz Erturk [a] & Yunus Bekdemir [b]

[a] Faculty of Science and Arts, Department of Chemistry , Ordu University , Ordu , Turkey

[b] Canik Basari University, Department of Molecular Biology, Gurgenyatak Campus , 55080 , Canik/ Samsun , Turkey

Accepted author version posted online: 02 Sep 2013.Published online: 03 Dec 2013.

To cite this article: Aliye Gediz Erturk & Yunus Bekdemir (2014) Microwave-Assisted Synthesis of Some Substituted Sulfamides, Phosphorus, Sulfur, and Silicon and the Related Elements, 189:2, 285-292, DOI: 10.1080/10426507.2013.819868

To link to this article: http://dx.doi.org/10.1080/10426507.2013.819868

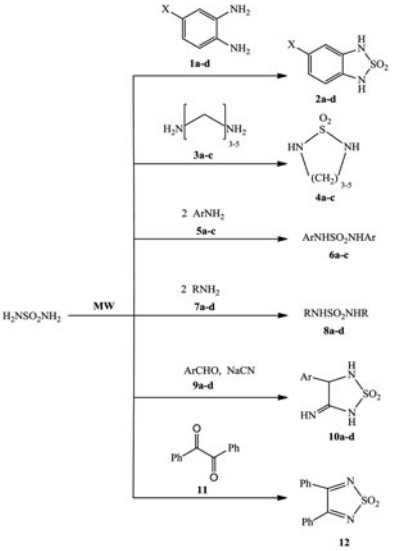
Phosphorus, Sulfur, and Silicon, 189:285–292, 2014

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2013.819868

MICROWAVE-ASSISTED SYNTHESIS OF SOME SUBSTITUTED SULFAMIDES

Aliye Gediz Erturk[1] and Yunus Bekdemir[2]
[1]Faculty of Science and Arts, Department of Chemistry, Ordu University, Ordu, Turkey
[2]Canik Basari University, Department of Molecular Biology, Gurgenyatak Campus 55080, Canik/ Samsun, Turkey

GRAPHICAL ABSTRACT



Abstract *Microwave-assisted synthesis of some substituted open-chain and cyclic sulfamides, by amine-exchange reaction, was studied in a modified domestic microwave oven. Reaction times and yields under microwave radiation were compared with classical heating. Synthesis of the sulfamides under microwave irradiation gave better yields with the desired compounds, and in considerably reduced reaction times, than those obtained by classical heating.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements for *the following free supplemental files: Additional figures.]*

Keywords Sulfamides; amine-exchange reactions; microwave irradiation

Received 3 April 2013; accepted 24 June 2013.
We would like to thank the Ondokuz Mayis University (Grant No: F-286) for financial support of this work.
Address correspondence to Aliye Gediz Erturk, Faculty of Science and Arts, Department of Chemistry, Ordu University, Ordu, Turkey. E-mail: aerturk@att.net

INTRODUCTION

There are very striking similarities between the structure of sulfamide, which is an important member of organosulfur compounds, and urea.[1] The pharmacological properties of the sulfamides have commanded the interest of organic and medicinal chemists. Compounds bearing this functionality have been investigated as agonists of the 5-HTID receptor, for their active components in epinephrine analogues, their nonhydrolizable components of peptide-mimetics and as carbonic anhydrase inhibitors.[2] In addition, previous research has considered alkyl/aryl sulfamides as new candidates for antiepileptic drugs.[3] Molecular structures with the sulfamide function are used as oral antidiabetic agents,[4] diuretics and antiglaucoma agents and it has recently emerged that they also have potential as anticonvulsant, antiobesity, anticancer, antipain, and anti-infective drugs.[5] Cyclic sulfamides, in particular, are used as components of insecticide mixtures and as myorelax-anti-inflammatory agents.[6] Aryl-substituted seven and eight-membered cyclic sulfamides inhibit HIV-1 protease, serine protease and metalloprotease.[7,8]

The synthesis of sulfamide derivatives have been summarized into two main synthetic routes in the literature[9]: (a) from the reaction of primary amines (alkyl or aryl) with thionyl and sulfuryl halides (very reactive and corrosive chemicals) in an inert solvent at low temperatures. Parnell has used this route extensively to obtain aromatic sulfamides.[4] (b) from the reaction of primary amines with sulfamides by means of amine exchange. Kirsanov and Spillane have synthesized a number of sulfamides in extremely dry diglyme or dry pyridine, in this way.[10] These two synthetic routes needed very long reaction times and the derivatives obtained were in much lower yields than desired (such as 6% and 4% for the synthesis of 5-chloro- and 5-nitro- 1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides, respectively).[11]

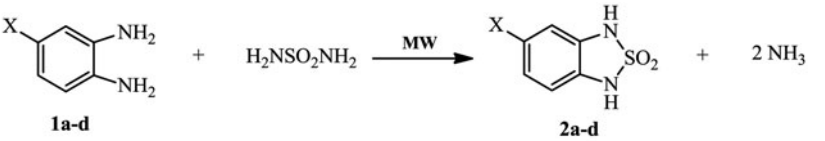
Recently, the use of microwave heating has become an area of increasing interest in both academic and industrial laboratories because it can dramatically enhance the rate of reaction and**,** in many cases**,** increase product purity and yields.[12,13] Therefore, high-speed synthesis by microwaves provides the technology for rapid optimization of reactions, efficient synthesis of new chemical entities, and for the discovery and probing of new chemical reactivity.[14] Especially, the combination of solvent-free conditions and microwave irradiation, leads to enhancement in conversions and selectivity, use of inexpensive reagents and simple product isolation procedures,[15] which are compatible with features of the environmentally-friendly technique, the so-called green chemistry.[16]

Herein, we report the facile synthesis of cyclic and acyclic substituted sulfamides by an amine exchange reaction, producing high yield using a microwave approach which proceeds more rapidly than conventional heating. Aryl, alkyl amines and diamines and also aldehydes were reacted in a modified domestic microwave with sulfamide in the presence of a solvent under reflux or solvent-free medium at 360, 900 W (2450 MHz) of microwave irradiation, resulting in shorter reaction times with higher yields when compared to classical heating.

RESULTS AND DISCUSSION

Microwave-assisted amine exchange reactions of sulfamide with substituted o-phenylenediamines were carried out in the presence of commercial diglyme under reflux. The reaction was performed at 900 W of microwave power and atmospheric pressure within

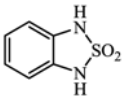
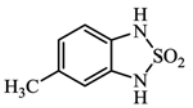
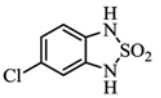
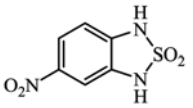
Table 1 Reaction times and yields for classical and microwave procedures in the preparation of 5-Substituted 1*H*, 3*H*-2,1,3-benzothiadiazole 2,2-dioxides



1a-d

2a-d

X: -H, -CH_3, -Cl, -NO_2

	Product	Conventional heating[17,18] Time (min)	Conventional heating[17,18] Yield (%)	Microwave irradiation[a] Time (min)	Microwave irradiation[a] Yield (%)
2a		45	64	8	80
2b		45	34	7	75
2c		45	6	7	74
2d		45	4	5	55

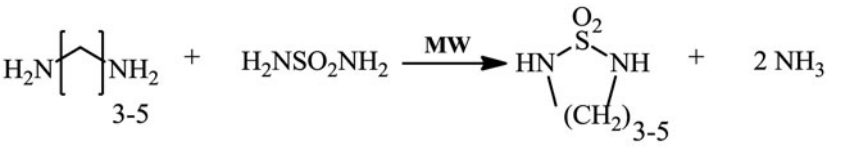
[a]MW power = 900 W.

5–8 min. Under conventional heating, when the reaction is completed, the diglyme is removed in the work-up by distillation from the filtrate at 55°C/15 mmHg. However, this was not needed since the microwave reactions were carried out using the diglyme as a neat solvent. Results and experimental conditions are summarized in Table 1.

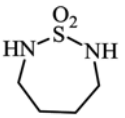
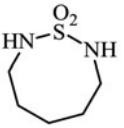
Reactions of sulfamide with open-chain diamines in a microwave oven were carried out in the presence of diglyme under reflux. The reaction was performed at 360 W of microwave power and atmospheric pressure for 20 min. Results and experimental conditions are summarized in Table 2. It has been pointed out that when the methylene chain exceeds eight carbon atoms in the reaction of the sulfamides with the diamines**,** the product formed will be polymeric in nature.[9] Microwave syntheses of compounds (4b) and (4c) were performed in diglyme to reduce formation of the polymeric by-product and shorten the reaction time.

The microwave-assisted amine exchange reactions of sulfamide with substituted aromatic and aliphatic amines were carried out in the presence of pyridine. The reaction was performed at 900–360 W of microwave power for 4–15 min. For example, in the literature, compounds (6a–c) and (8c) were not synthesized with amine exchange reactions beforehand. These compounds were obtained either from reaction of the corresponding amine with SO_2Cl_2 at –78°C[4] or from reaction of their sulfamyl chlorides[1] with their corresponding amines, respectively. Both methods include highly corrosive starting materials and take a long time. Spillane and coworkers have synthesized some sulfamides by amine exchange

Table 2 Reaction times and yields for classical and microwave procedures in the preparation of substituted of 1,2,6-thiadiazinane 1,1-dioxides



3a-c **4a-c**

		Conventional heating[19]		Microwave irradiation[a]	
	Product	Time (min)	Yield (%)	Time (min)	Yield (%)
4a		120	23[b]	20	45
4b		360	32	20	64
4c		360	13	20	18

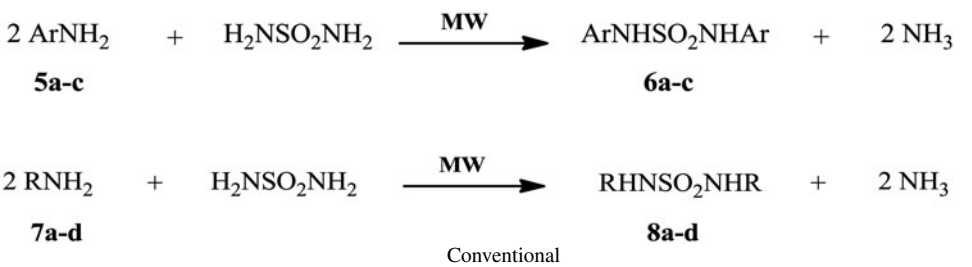
[a]MW power = 360 W, [b]Reaction was performed in triethylenediamine.

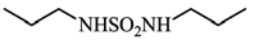
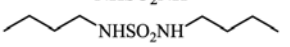
reaction in ultra-dried diglyme which was not enough to get the expected amount of the sulfamides. In our approach we used commercial diglyme (99.5%) without drying and the yields were considerably higher. Results and experimental conditions are summarized in Table 3.

In Table 4, the results and experimental conditions are given for 3-Imino-4-substituted phenyl-1,2,5-thiadiazolidine 1,1-dioxides, which were obtained from reactions of a series of benzaldehyde derivatives with sulfamide in the presence of NaCN in an aqueous ethanol mixture. In Table 5, the results are given for the preparation of 3,4-Diphenyl-1,2,5-thiadiazol 1,1-dioxide. When microwave-assisted heating was used, each product was obtained in shorter reaction times and with higher yields than with conventional heating.

In conclusion, a microwave-assisted protocol for the facile, rapid and "green" synthesis of substituted sulfamide derivatives has been developed which proceeds expeditiously through the amine exchange method at atmospheric pressure. Although catalysts or additives were not involved in the reaction, and yields of 65–90% of sulfamide derivatives were achieved, the reaction times were dramatically reduced from 45 (to 360) min by traditional heating to 3 (to 15) min under suitable conditions of microwave irradiation. The reaction not only accelerates upon exposure to microwave irradiation, thus shortening its reaction time and work-up procedure, but also eliminates the formation of any byproduct when compared to the traditional methods involving conventional heating. Furthermore, the reactions can be achieved without using dry reaction solvents.

Table 3 Reaction times and yields for classical and microwave procedures in the preparation of substituted of N,N'-diphenylsulfamides and N,N'-dialkyldulfamides



	Product	Conventional heating[20–22] Time (min)	Conventional heating[20–22] Yield (%)	Microwave irradiation[a,b] Time (min)	Microwave irradiation[a,b] Yield (%)
6a		330	84	13	87[a]
6b		330	20	5	75[a]
6c		330	15	15	40[a]
8a		330	70	8	97[b]
8b		330	79	4	93[b]
8c		330	21	15	52[b]
8d		330	73	7	93[b]

MW Power: [a]900 W, with pyridine; [b]360 W, without solvent.

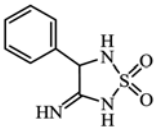
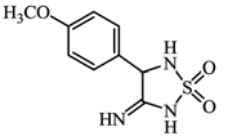
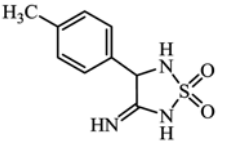
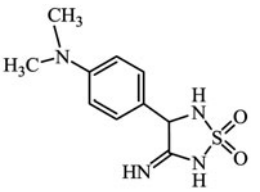
EXPERIMENTAL

Chemicals were purchased from Aldrich, Acros, Merck, and Fluka and purified by crystallization or distillation before use. Thin layer chromatography (TLC) was performed using Merck aluminum-backed plates (Kieselgel 60 F_{254}), and visualization was achieved by ultraviolet (UV) light. During the experiments to find the optimal conditions for each reaction, we took TLC of the reaction mixtures at one minute intervals in each case, until we were sure that the reaction did not proceed under prolonged microwave radiation, even with higher power. So, when the starting materials consumed, we determined the reaction time and convenient energy level. All products were characterized by comparison of their physical data with samples prepared by conventional heating. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury–400 MHz Spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ and DMSO-d_6 using TMS as the internal standard. IR Spectra were recorded with a MATTSON 1000 FTIR Spectrophotometer. Melting points were determined on an Electrothermal Digital Melting Point Apparatus. Experiments were carried out under microwave irradiation by using a domestic microwave oven (Bosch model HMT 812C 2450 MHz) that was modified by fitting a reflux system and internal camera. The domestic microwave oven operated at a frequency of 2450 MHz with power ranging

Table 4 Reaction times and yields for classical and microwave procedures in the preparation of 3-Imino-4-substituted phenyl-1,2,5-thiadiazolidine 1,1-dioxides

9a-d **10a-d**

X: -H, $-OCH_3$, $-CH_3$, $-N(CH_3)_2$

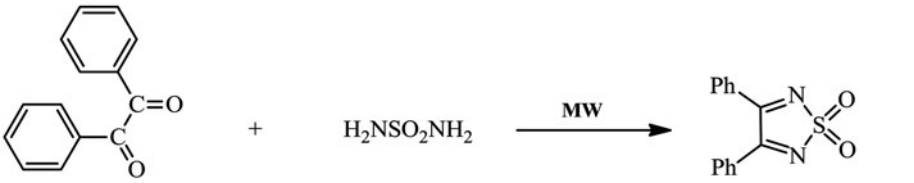
	Product	Conventional heating[23,24] Time (min)	Conventional heating[23,24] Yield (%)	Microwave irradiation[a] Time (min)	Microwave irradiation[a] Yield (%)
10a		360	35	4	92
10b		360	62	2.5	95
10c		360	41	3	96
10d		360	11	2	47

[a]MW power = 90 W

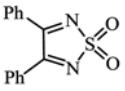
from 90 to 900 W. Elemental analysis was performed by Midwest Microlabs in Indianapolis, USA.

General Procedure for the Preparation of 5-Substituted 1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides (2a–d):[17,18] o-Phenylenediamine (280 mg, 2.6 mmol) and sulfamide (250 mg, 2.6 mmol) were dissolved in diglyme. Diglyme was used as a neat solvent. The resulting solution was placed inside a modified domestic microwave oven at 900 W and irradiated for 8 min. under reflux. The reaction was completed as determined by TLC monitoring, using ether/petroleum ether (3:1) as the eluent. The reaction mixture was then removed from the oven, cooled in ice, and filtered. The residue was dissolved in ether (20 mL) and washed successively with HCl (2 N, 3 × 5 mL) and with saturated brine (3 mL). The ether solution was dried and benzylamine (1 mL) was added. The sulfamide salt was precipitated: it was filtered off, washed with ether, and shaken with HCl (2 N, 10 mL). The acidic solution was extracted with ether (4 × 5 mL) and the combined extracts were dried and evaporated to leave the product.

Table 5 Reaction times and yields for classical and microwave procedures in the preparation of 3,4-Diphenyl-1,2,5-thiadiazol 1,1-dioxide



11 **12**

	Product	Conventional heating[25] Time (min)	Conventional heating[25] Yield (%)	Microwave irradiation[a,b] Time (min)	Microwave irradiation[a,b] Yield (%)
12		1440	57	10	66

[a]MW power = 360 W [b]reflux in abs EtOH.

General Procedure for the Preparation of Substituted 1,2,6-thiadiazinane 1,1-dioxide (4a–c):[19] Trimethylenediamine (290 mg, 3.9 mmol) and sulfamide (125 mg, 1.3 mmol) were mixed in a 25 mL flask. The mixture was refluxed in a modified oven (360 W) for 5 min. The reaction mixture was controlled by TLC at regular intervals on silica gel with a mixture of chloroform and petroleum ether (9:1) as the eluent. After cooling to room temperature, HCl (4 N, 5 mL) was added and the liquid phase was extracted using ethyl acetate. The combined extracts were dried and evaporated to product.

General Procedure for the Preparation of Substituted N,N′-diphenylsulfamides (6a–c)[20–22] and N,N'-dialkyldulfamides (8a–d):[20] Aniline (240 mg, 2.6 mmol), sulfamide (125 mg, 1.3 mmol), and pyridine (1 mL) were mixed in a 25 mL flask. The mixture was refluxed in a modified oven (360 W) for 20 min. The reaction mixture was controlled by TLC at regular intervals on silica gel with a mixture of ether and petroleum ether (4:1) as the eluent. After cooling, HCl (2 N, 5 mL) was added to obtain a mixture and was extracted with chloroform. The chloroform phase was then dried and evaporated to form the product (6a–c). Synthesis of N,N'-dialkylsulfamides (8a–d) was realized without using pyridine, under similar conditions.

General Procedure for the Preparation of 3-Imino-4-substituted phenyl-1,2,5-thiadiazolidine-1,1-dioxide (10a–d):[23,24] Sodium cyanide (35 mg, 0.72 mmol) was added to 70% aqueous alcohol solution involving benzaldehyde (70 mg, 0.66 mmol) and sulfamide (125 mg, 1.3 mmol) in a 25 mL flask. The mixture was refluxed in a modified microwave oven (90 W) for 3 min. 1 N NaOH (0.6mL) was added to the obtained mixture. The reaction mixture was monitored throughout the experiment with TLC on silica gel with a mixture of ethyl acetate and ether (4:1) as the eluent. An aqueous mixture was extracted with ethyl acetate (2 × 1.3 mL) and diethyl ether (0.7 mL). The aqueous phase was acidified with 1 N HCl (pH∼2). Precipitated solids were recrystallized with ethyl alcohol.

General Procedure for the Preparation of 3,4-Diphenyl-1,2,5-thiadiazol-1,1-dioxide (12):[25] Benzil (274 mg, 1.3 mmol), sulfamide (125 mg, 1.3 mmol), and triethylamine (0.05 mL) were mixed with absolute ethyl alcohol (3 mL) in a 25 mL flask. The mixture was refluxed in a modified microwave oven (360 W) for 120 min. Progress of the

reaction was monitored by TLC, and the eluent was acetone and petroleum ether (4:1). The reaction mixture was concentrated, washed and recrystallized with acetone. The combined extracts were dried and evaporated to form product (**12**). In order to increase the yield, the water which was formed was removed and then the reaction was renewed in a medium with anhydrous Na_2SO_4. Finally, product (**12**) was synthesized (0.118 g, 66%) at 360W for 10 min.

3-Imino-4-(4-(dimethylamino)phenyl)-1,2,5-thiadiazolidine 1,1-dioxide (10d)

Mp 208–210°C; IR (KBr): 3429, 3262, 3062, 2923, 1339, 1146 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C); $\delta = 2.88$ (s, 6H), 5.16 (s, 1H), 6.71 (d, $J = 8.00$ Hz, 2H), 7.21 (d, $J = 8.00$ Hz, 2H), 7.44 (s, 2H), 8.18 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6, 25 °C); $\delta = 40.1$, 64.3, 112.1, 124.9, 128.3, 150.4, 170.2 ppm; Anal. Calcd. For $C_{10}H_{14}N_4O_2S$: C 47.23, H 5.55, N 22.03, S 12.61. Found: C 47.48, H 5.51, N 21.80, S 12.63%.

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