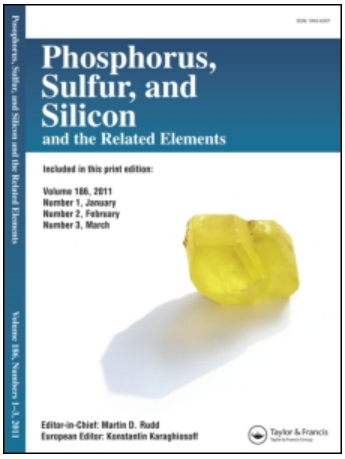

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A Green, Catalyst-Free Method for the Synthesis of Sulfonamides and Sulfonylazides

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A GREEN, CATALYST-FREE METHOD FOR THE SYNTHESIS OF SULFONAMIDES AND SULFONYLAZIDES

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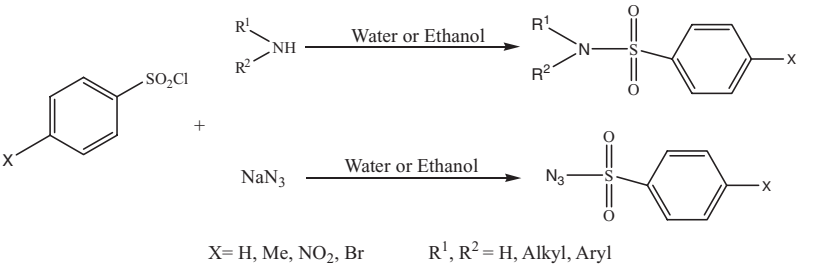
GRAPHICAL ABSTRACT



Abstract *A novel, green method for the efficient synthesis of sulfonamide and sulfonylazide derivatives by the reaction of sulfonyl chlorides with amines or sodium azide under catalyst-free conditions has been developed. The reactions proceed with high yields and excellent selectivities in short reaction times.*

Keywords Aqueous media; catalyst-free; sulfonamides; sulfonyl chloride; sulfonylazides

INTRODUCTION

Environmentally benign methods for the synthesis of pharmaceutically and industrially important compounds are in extreme demand.[1] The elimination of solvents in chemical processes or performing of the reactions in eco-friendly solvents such as water and ethanol are the procedures of choice for diminishing the environmental impacts of chemical reactions.[2]

Sulfonamides are a very important class of compounds in the pharmaceutical industry, being widely used as anticancer, anti-inflammatory, and antiviral agents.[3,4] Sulfonylazides are versatile precursors in organic chemistry,[5] and their uses in organic synthesis go well beyond the commonly used diazo[6] and azide[7] transfer reactions. The search for general and efficient synthesis of sulfonamides under mild conditions is of continuing interest for organic chemists. Although recently many efforts have been put into the development

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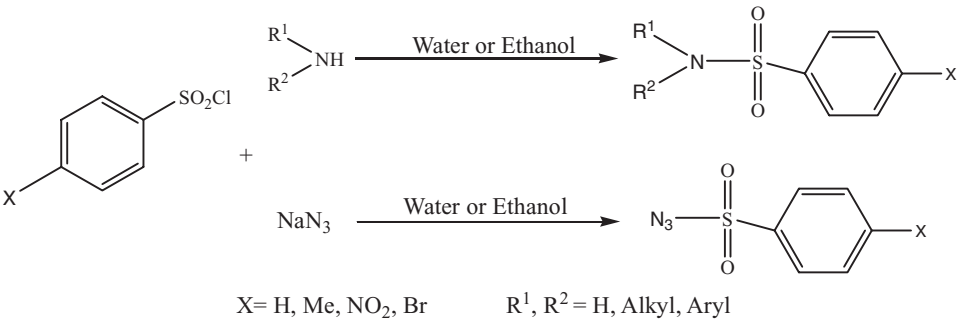
of novel sulfonamide syntheses,[8] the conventional synthesis from amino compounds and sulfonyl chlorides is still the method of choice because of the reactivity and simplicity of the method.[9] Most of the reported methods for the preparation of sulfonamides suffer from drawbacks such as formation of a bis-sulfonylation byproduct or hydrolysis of sulfonyl chlorides as the major competing reaction, which requires the use of excess of sulfonyl chloride. Thus, the isolation and purification of the sulfonamide products are not always straightforward in these protocols, resulting in diminishing yields.

According to the literature in a few reports that are available regarding the synthesis of sulfonamides in water under catalyst-free conditions, the pH control with Na_2CO_3 is necessary, and the isolation of the product involved acidification up to pH 2 with HCl[8g] and limited sulfonyl chlorides have been used.[8q]

In continuation of our ongoing research on the development of new eco-friendly organic reactions,[10] we utilized water and ethanol as green solvents to present a novel catalyst-free method for the synthesis of sulfonamides and sulfonylazides affording the desired products in excellent yields with a practical and easy workup procedure (Scheme 1).



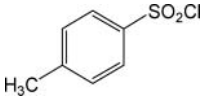
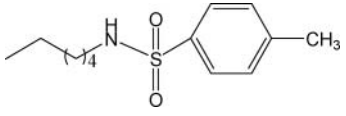
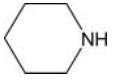
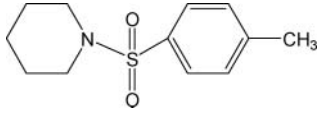
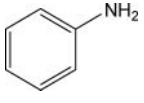
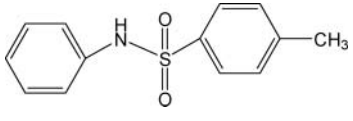
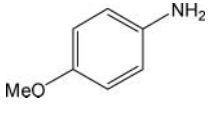
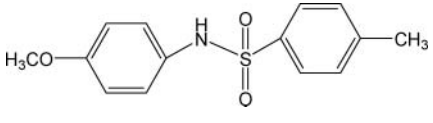
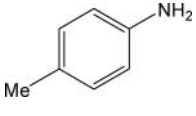
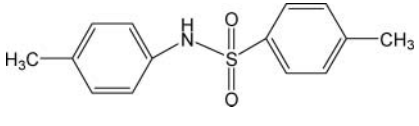
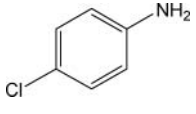
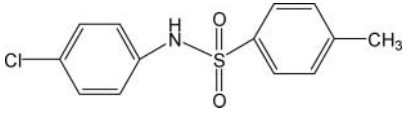
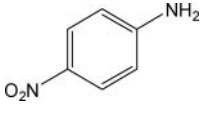
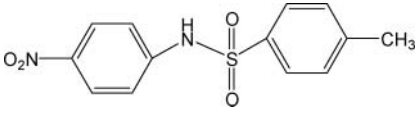
Scheme 1 Catalyst-free of synthesis of sulfonamides and sulfonylazides.

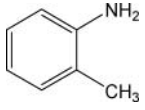
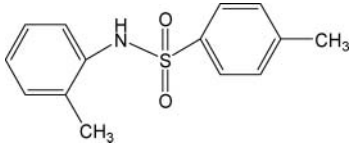
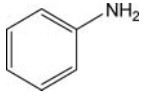
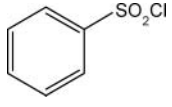
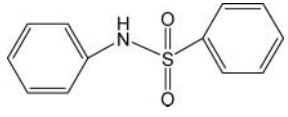
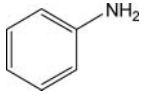
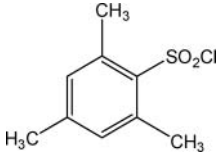
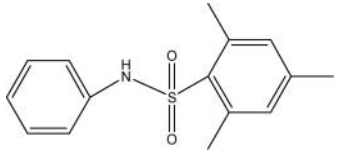
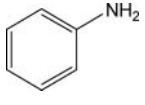
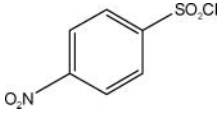
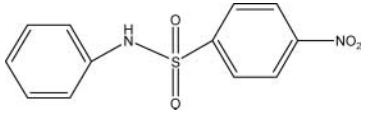
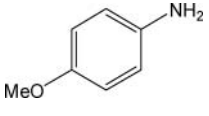
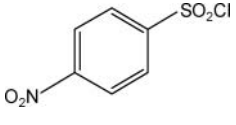
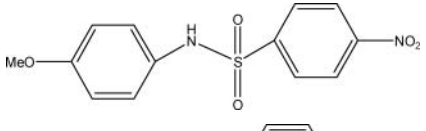
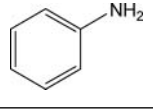
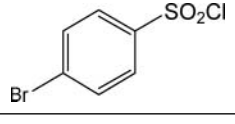
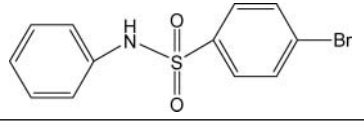
RESULTS AND DISCUSSION

To find the best reaction conditions for the synthesis of sulfonamides, the condensation of 4-toluenesulfonyl chloride with aniline was used as a model reaction. It was found that temperature changes (25°C to 80°C) did not affect the reaction yield under neat conditions, and the desired product was formed in only 50% yield (GC) after 6 h. Elongation of the reaction time also did not affect the yield of the product. Then, a similar reaction was performed in various solvents in the absence of any catalyst at a temperature range from 25°C to 80°C. The desired yields and conversion rates have been obtained at room temperature in the presence of water and ethanol, both of which are standard green media. In addition, the pronounced effect of the solvent quantity on the reaction rates has been observed. Under the optimized conditions using 4-toluenesulfonyl chloride (1 mmol) and aniline (2 mmol), the optimum yields were obtained in 2 mL of water (92%) or ethanol (96%) at room temperature.

In order to show the general applicability of this method, the reaction of structurally and electronically diverse amines and sulfonyl chlorides was examined. The results, which

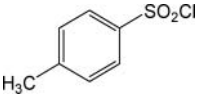
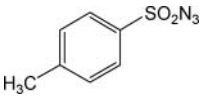
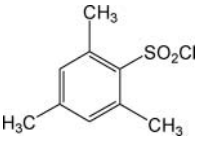
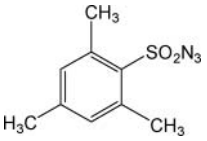
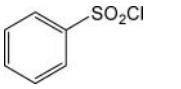
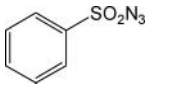
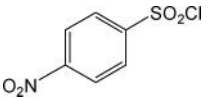
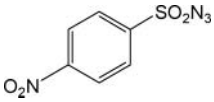
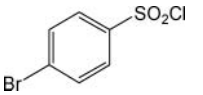
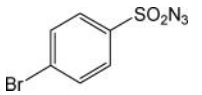
Table 1 Catalyst-free sulfonylation of amines[a]

Entry	Amine	Sulfonyl chloride	Product[b]	Time (yield%)[c] in H_2O	Time (yield%)[c] in EtOH
1				<1 min (92)	<1 min (95)
2		”		2 min (93)	<1 min (95)
3		”		5 min (92)	<1 min (96)
4		”		3 min (93)	<1 min (95)
5		”		5 min (94)	<1 min (96)
6[d]		”		20 min (96) (4/1) V/V water/ethanol	
7		”		120 min (31)[e]	120 min (45)[e]

8		”		5 min (92)	<1 min (95)
9				4 min (93)	<1 min (96)
10				5 min (94)	<1 min (96)
11				3 min (94)	<1 min (95)
12				<1 min (95)	<1 min (96)
13[d]				10 min (95) (4/1) V/V water/ethanol	

[a]The reactions were run at r.t., and the molar ratio of sulfonyl chloride/amine was 1:2 in 2 mL water or ethanol.
[b]Structural assignments of the products are based on their ^{1}H NMR, ^{13}C NMR, IR, and MS spectral data.[8]
[c]Isolated yield.
[d]The molar ratio of sulfonyl chloride:amine was 1:2 in 1.6 mL water and 0.4 mL ethanol.
[e]GC yield based on the xylene as internal standard.

Table 2 Catalyst-free azidolysis of sulfonylchlorides[a]

Entry	Sulfonyl chloride	Product[b]	Time (yield%)[c] in H_2O	Time (yield%)[c] in EtOH
1			30 min (93)	8 min (95)
2			120 min (94)	12 min (96)
3			20 min (93)	5 min (95)
4			15 min (94)	3 min (96)
5			60 min (93)	8 min (96)

[a]The reactions were run the molar ratio of sulfonyl chloride:sodium azide was 1:2.5 in 2 mL water (at reflux) or ethanol (at r.t).

[b]Structural assignments of the products are based on their spectral data.[5c]

[c]Isolated yield.

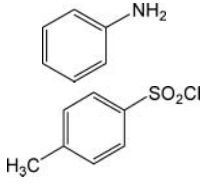
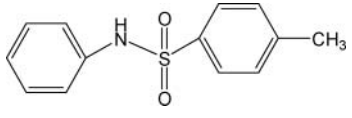
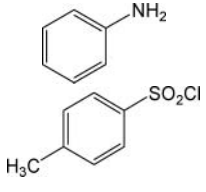
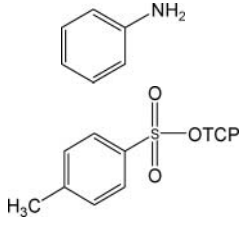
are summarized in Table 1, indicate that all reactions proceeded efficiently, and the desired sulfonamides were obtained in excellent yields in relatively short reaction times. It was observed that electronic factors play a significant role in these reactions. Aromatic amines substituted with electron-donating groups reacted faster than those having electron-withdrawing groups and provided the sulfonamides in high yields (Table 1, entries 3–8).

Encouraged by the promising results obtained in the synthesis of sulfonamides, the azidolysis of sulfonyl chlorides has also been examined by this green reaction system. The results, which are summarized in Table 2, indicate the high efficiency of this methodology for the preparation of sulfonylazides in ethanol and water under mild and reflux conditions respectively.

In order to highlight the efficiency of the presented methodology, we have compared the results obtained for the synthesis of sulfonamides in water and ethanol with some of those reported in the literature (Table 3).

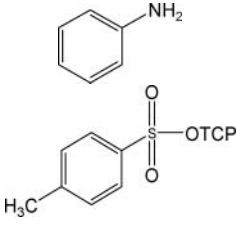
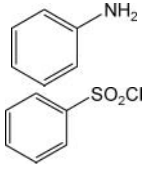
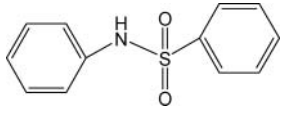
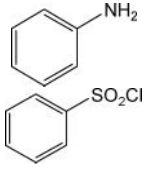
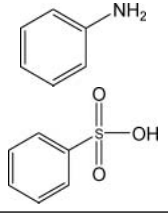
In conclusion, an operationally simple and environmentally benign protocol for sulfonylation of amines and azidolysis of sulfonyl chlorides in the absence of any catalyst is described. The mildness and eco-friendly nature of the reaction, short reaction times, and impressive yields are the considerable advantages that make the present method superior to the existing methods for the preparation of sulfonamides and sulfonylazides.

Table 3 Comparison of catalyst-free synthesis of sulfonamides in water and ethanol with other catalysts or reagents

Entry	Substrates	Reagent or catalyst	Solvent	Product	Time (isolated yield%)	Ref.
1		—	H_2O		5 min (92)	[a]
2		—	Ethanol	”	< 1 min (96)	[a]
3[b]		LHMDS[c]	THF (50°C)	”	4 h (78)	[8o]

(Continued on next page)

Table 3 Comparison of catalyst-free synthesis of sulfonamides in water and ethanol with other catalysts or reagents *(Continued)*

Entry	Substrates	Reagent or catalyst	Solvent	Product	Time (isolated yield%)	Ref.
4		NMP[d]/NEt_3	(140°C)	”	No reaction	[8o]
5		—	H_2O		4 min (93)	[a]
6		—	Ethanol	”	<1 min (96)	[a]
7		1) Cl_3CCN, PPh_3 2) Amine, 4-picoline/	CH_2Cl_2	”	2 h (93)	[8m]

[a]This work.
[b]TCP = 2,4,6-trichlorophenol.
[c]HMDS = lithium hexamethyldisilazide.
[d]*N*-methylpyrrolidone.

EXPERIMENTAL

Amines, sulfonyl chlorides, and NaN_3 were purchased from Merck or Fluka chemical companies. The progress of the reactions was monitored by TLC using silica-gel SIL G/UV 254 plates and also by GC on a Shimadzu GC-16A instrument using a 25 m CBP1-S25 (0.32 mm ID, 0.5 μm coating) capillary column. NMR spectra were recorded on a Bruker Avance DPX 250 MHz and 500 MHz instruments. Mass spectra were recorded on a Shimadzu GC-MS-QP 5050A.

General Procedure for the Synthesis of Sulfonamides in Water

To a suspension of sulfonyl chloride (1 mmol) in distilled water (2 mL), amine (2 mmol) was added at room temperature, and vigorous stirring was continued until the reaction was completed (followed by TLC). The reaction mixture was extracted with ethyl acetate, and the organic phase was separated, which was dried over $CaCl_2$. After filtration and evaporation of the solvent, surplus amine was removed by plate chromatography eluted with n-hexane/EtOAc (Table 1).

General Procedure for the Synthesis of Sulfonamides in Ethanol

To a solution of sulfonyl chloride (1 mmol) in ethanol (2 mL), amine (2 mmol) was added at room temperature, and stirring was continued until the reaction was completed (followed by TLC). After completion of the reaction, the mixture was concentrated under reduced pressure, and surplus amine was removed by plate chromatography eluted with n-hexane/EtOAc (Table 1).

General Procedure for Synthesis of Sulfonylazides in Water

To a suspension of sulfonyl chloride (1 mmol) in distilled water (2 mL), NaN_3 (2.5 mmol) was added under reflux conditions, and vigorous stirring was continued until the reaction was completed (followed by TLC). The reaction mixture was extracted with ethyl acetate, and the organic phase was separated, which was dried over $CaCl_2$. After filtration and evaporation of the solvent, the desired product was secured in high purity (Table 2).

General Procedure for Synthesis of Sulfonylazides in Ethanol

To a solution of sulfonyl chloride (1 mmol) in ethanol (2 mL), NaN_3 (2.5 mmol) was added at room temperature, and stirring was continued until the reaction was completed (followed by TLC). After completion of the reaction, the mixture was concentrated under reduced pressure, and further purification was performed by plate chromatography. The desired product was secured in high purity (Table 2).

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