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An Improved Synthetic Route for the Synthesis of Sulfonamides

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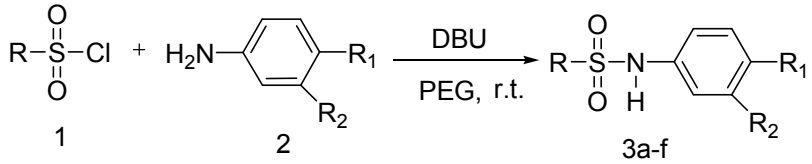
Abstract : DBU (1, 8-diazabicyclo [5,4,0]undec-7-ene) was utilized to replace pyridine, in the condensation of aryl / alkyl sulphonyl chlorides with substituted amines at room temperature in PEG. Polyethylene glycol (PEG) is found to be an inexpensive and non-toxic reaction medium for the coupling reaction of amines with aryl / alkyl sulphonyl chloride.
Keywords: Aryl Amines, sulphonamides, DBU, PEG, mild reaction condition.

Introduction:

The sulphonamides represent an important class of biologically active compounds. The antibacterial [1] sulphonamides continue to play an important role in chemotherapy alone or in the combination with other drugs [2]. Sulphonamides have many clinical applications such as diuretic [3], antiepileptic [4], hypoglycemic [5] and antitumor [6] drugs. Heteroaryl containing sulphonamides are gaining more importance as these derivatives have played a critical role for the development of several important classes of pharmacological agents [7].

Literature survey reveals that several synthetic routes have been developed to condense amines with aryl / alkyl sulphonyl chloride. The most commonly employed synthetic routes for the synthesis of N-substituted sulphonamides, are using pyridine as a catalyst as well as solvent [8], acetic anhydride in pyridine, [9], pyridine in ethanol [10] and pyridine in acetone [11]. It is observed that the reported methods used for this condensation are having one or other kind of drawbacks such as longer reaction times, high temperature and media used are found to be carcinogenic and hazardous. Thus in view of these shortcomings there is a need to develop synthetic route for the synthesis of sulphonamides.

Bicyclic amidines, such as DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) are useful reagent for dehydrohalogenation and have been termed nonnucleophilic bases [12]. On the other hand, numerous examples have been reported which demonstrate that DBU can also act as nucleophiles [13]. However, addition of DBU to the reaction mixture in some cases has found to increase the stereo selectivity and influence the rate. It has been generally assumed that this caused by specific salvation by DBU favoring more reactive aggregates [14]



Scheme 1

PEG and its monometyl ethers are known to be inexpensive, thermally stable, recoverable and non-toxic media for phase transfer catalysis [15]. The PEG is widely used in many organic reactions for conversion [16] of oxiranes to thiiranes, cross-coupling reaction [17] and Baylis-Hilman reaction [18].

Considering the synthetic, biological significance and our continuation interest [19, 20], herein, we report an improved synthetic route for the condensation of aryl / alkyl sulphonyl chlorides and amines to yield sulphonamides using DBU in PEG-400 at room temperature.

Results and discussion

In the present work, aryl / alkyl sulphonyl chlorides (**1**) were condensed with substituted amines (**2**) in the presence of DBU in PEG at room temperature and obtained sulphonamides (**3a-f**) with excellent yields.(Scheme 1).

The deployment of PEG eliminates the use of volatile solvents and provides a high yielding efficient route. The formation of substituted sulphonamides may be explained as the reaction of DBU with amines forms charge transfer complex (**4**). The nitrogen bearing negative charge attacks on the sulphur having chlorine atom in alkyl / aryl sulphonyl chlorides (**1**) forming a Meisenheimer type σ-complex. The spontaneous decomposition of σ-complex eliminates the chloride ion forming DBU HCl which is removed by washing with water.

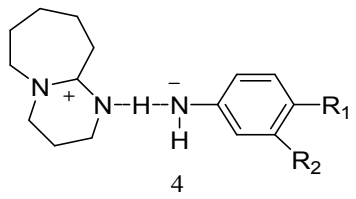


Table 1. Physical data of sulphonamides (3a-f)

Products	R	R^1	R^2	Yield (%)[a]	Mp (^oC)[b]
3a	4-$CH_3C_6H_4$	$COCH_3$	H	85	206-208
3b	4-$CH_3C_6H_4$	OH	$COCH_3$	75	152-153
3c	C_6H_5	OH	$COCH_3$	68	149-153
3d	C_6H_5	$COCH_3$	H	82	137-139
3e	CH_3	$COCH_3$	H	84	159-161
3f	4-$CH_3C_6H_4$	COOH	H	78	231-232

[a] yield of isolated product.

[b] mp was confirmed by comparison with authentic samples.

Experimental

The melting points were determined in open capillaries and are uncorrected. The IR Spectra were recorded on a FT-IR (JASCO FT-IR) Japan. The 1HMNR was measured on Bruker DRX-300, 300 MHZ FT NMR with low and high temperature in DMSO using TMS as internal reference. Mass spectra were recorded on a leo SX 102/DA- Mass spectrometer, Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer.

General procedure for the synthesis of sulphonamides, Scheme 1 (3a-f).

Aryl / alkyl sulphonyl chlorides (0.002 mol), substituted amines (0.002 mol) and DBU (0.001 mol) were dissolved in PEG (15 ml). The reaction solution was stirred at room temperature for 2.5 h. The progress of the reaction was monitored by TLC. After the completion of the reaction ethyl acetate was added until complete precipitation occurred. The obtained solid was filtered, washed with water, dried and crystallized from ethanol.

Conclusion

This method has several advantages over the existing methods such as efficient synthetic route, high yields, mild reaction conditions and nontedious workup. The data shows that a number of functional groups are tolerated in the amines and that the method can be extended to heterocyclic sulphonamides of potential biological interest.

Spectral data for selected compounds,

Compound (**3a**) Yield 85 %, mp 206-208 ^{o}C, IR (cm^{-1}) 3270, 1670, 1340 and 1159. ^{1}H NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.44 (s, 3H, $COCH_3$), 7 17 to 7.82 (m, 8H, Ar-H) and 10.77 (s, 1H, NH exchange with D_2O).Mass: (scanning mode ES^+): m/z 290 (M^+). Anal. Calcd. For $C_{15}H_{15}NO_3S$ (289): Found C 62.10, H 4.99 and N 4.90.

Compound (**3b**) Yield 75 %, mp 152-153 ^{o}C, IR (cm^{-1}) 3270, 3240, 1652, 1396 and 1161. ^{1}H NMR (DMSO-d_6) δ: 2.45 (s, 3H, CH_3), 2.61 (s, 3H, $COCH_3$), 7.18 to 7.82 (m, 7H, Ar-H), 10.77 (s, 1H, NH exchange with D_2O) and 12.17 (s, 1H, OH exchange with D_2O). Mass: (scanning mode ES^+): m/z 306 (M^+). Anal. Calcd. For $C_{15}H_{15}NO_4S$ (305): Found C 58.82, H 4.77 and N 4.62.

Compound (3e) Yield 84 %, mp 159-161 ^{o}C, IR (cm^{-1}) 3261, 1670, 1354 and 1161. ^{1}H NMR (DMSO d-$_6$) δ: 2.51 (s, 3H, $COCH_3$) 2.78 (s, 3H, CH_3), 7.17 to 7.61 (m, 4H, Ar-H) and 10.61 (s, ^{1}H, NH exchange with D_2O). Mass: (scanning mode ES^+): m/z 214 (M^+). Anal. Calcd. For $C_9H_{11}NO_3S$ (213): Found C 50.54, H 5.26 and N 6.30.

Compound (3f) Yield 78 %, mp 231-232 ^{o}C, IR (cm^{-1}) 3239, 3061, 1693, 1337 and 1160. ^{1}H NMR (DMSO d-$_6$) δ: 2.31 (s, 3H, CH_3), 7.16 to 7.76 (m, 8H, A r-H), 10.82 (s, 1H, NH exchange with D_2O) and 12.54 (s, 1H, COOH exchange with D_2O).Mass: (scanning mode ES^+): m/z 292 (M^+). Anal. Calcd. For $C_{14}H_{13}NO_4S$ (291) Found C 57.68, H 4.52 and N 4.78.

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