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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME HETEROCYCLIC SULFONAMIDE DERIVATIVES

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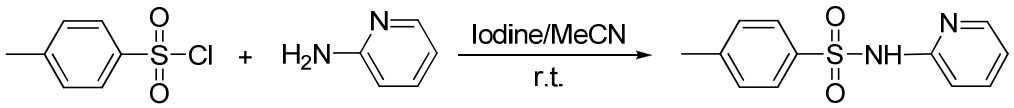
Abstract:
A facile and efficient method for synthesizing sulfonamides was developed using a catalytic amount of molecular iodine in excellent yields. The method showed a generality for substrates including less nucleophilic and sterically hindered heterocyclic amines. The remarkable selectivity under mild and neutral conditions of this commercially available inexpensive catalyst is an attractive feature of this method. In *vitro* antimicrobial activity was evaluated against the two pathogenic bacterial strains, *Escherishia coli,* and *Staphylococcus aureus* and two fungal strains, *Rhizopus oryzae* and *Candida albicans*. The compounds have shown moderate to good activity.

Keywords: Molecular Iodine, p-Toluene sulfonyl chloride, Heterocyclic amines, Sulfonamides, Antimicrobial activity.

Introduction

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds are in great demand. Sulfonamides are extremely useful pharmaceutical compounds because they exhibit a wide range of biological activities such as anticancer, anti-inflammatory and antiviral functions.[i-v] Many synthetic methods have been reported,[vi-xi] the sulfonylation of amines with sulfonyl chlorides in the presence of a base is still being used as the method of choice because of high efficiency and simplicity of the reaction.[XII] However, this approach is limited by the formation of undesired disulfonamides with primary amines and by the need of harsh reaction conditions for less nucleophilic amines such as anilines.[xiii] Additionally, side reactions take place in the presence of a base. Sulfonamides have been used as protecting groups of OH or NH functionalities for easy removal under mild conditions.[xiv-xv]

In recent years, molecular iodine has been extensively used for a plethora of organic transformations as an inexpensive, nontoxic, readily available catalyst under very mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity.[xvi-xxii] Herein we report on a mild and efficient molecular iodine catalyzed method developed for preparing sulfonamides (**Scheme 1**).



Scheme 1. Synthesis of sulfonamides

Results and discussion

We set out our studies with p-toluene sulfonyl chloride and 2-amino pyridine as model substrates (Table 2). When a solution of p-toluene sulfonyl chloride and 2-amino pyridine in acetonitrile was treated with 0.1 equivalent of molecular iodine at room temperature, resulted in the formation of the corresponding amide in 85% yield without any desulfonylated product detected (Table 2, entry 1). In order to obtain the optimal reaction conditions, we carried out several experiments under various reaction conditions. We performed the reaction with varying amounts of iodine, and found that the reaction was effective with catalytic amount of iodine without diminishing the yield of the desired product (Table 1, entry 5 & 6). The reaction did not proceed at all in the absence of molecular iodine, implying that iodine is the active promoter in the reaction and also not proceed by using other sources of iodine like 2, 2, 2-trifluoroiodomethane, bis-(2, 4, 6-trimethylpyridine) iodine (I) hexafluorophosphate. We also examined solvent effect, reaction in N, N-dimethyl formamide, ethyl acetate, tetrahedrofuran and chloroform were found to be were found less effective. Since then, we have carried out the reaction in the presence of the acetonitrile solvent to get an excellent yield 85% (Table 1, entries 5 & 6).

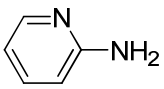
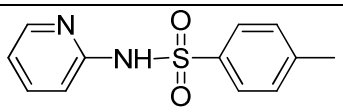
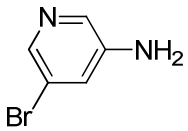
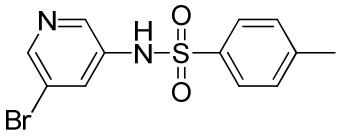
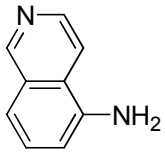
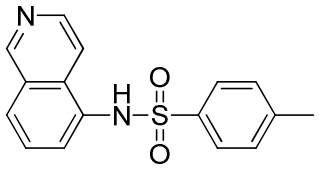
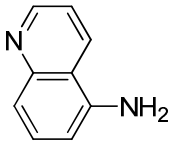
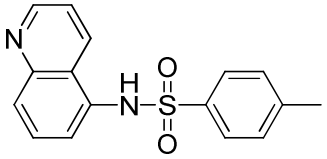
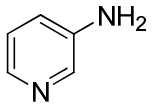
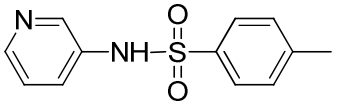
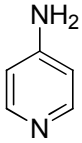
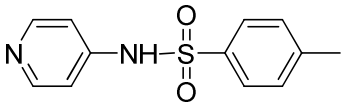
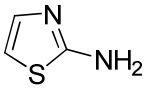
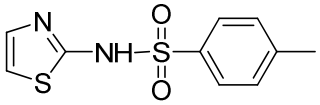
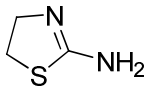
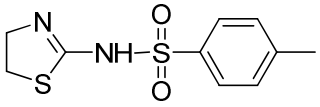
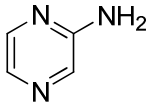
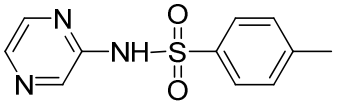
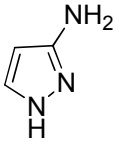
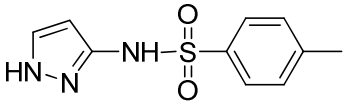
Infra red spectra of sulfonamide showed characteristic band at near region 3300-3450 cm^{-1} due to NH stretching vibration. Aromatic C-H stretch was formed near region 3040-3010 cm^{-1}. Aromatic C-C ring stretch was formed near region 1500-1600 cm^{-1}. Aromatic C-N stretching two strong bands are observed near region 1190-1360 cm^{-1} and SO_2 stretch was found near region 1350 cm^{-1}. ^1H NMR spectra of compounds were studied in $CDCl_3$ solvent showed characteristics signals δ 2.36 (s, 3H) due to CH_3 group, 6.8 -8.4 (m, ArH). The mass spectral fragmentation patterns of some representative members of the series were in good agreement with their suggested structures.

Table 1. Optimization of reaction conditions

Entry	Iodine (mmol)	Solvent	Time (h)	Temp.(°C)	Yield (%)[a]
1	0.5	DMF	6.0	80	56
2	0.5	EtOAc	8.0	reflux	55
3	0.5	THF	8.0	reflux	52
4	0.5	$CHCl_3$	7.0	reflux	68
5	0.5	CH_3CN	4.5	30	85[b]
6	**0.1**	**CH_3CN**	**4.5**	**30**	**85[b]**

[a]Isolated yield. [b]CH_3CN solvent is more effective

Table 2 Physical data of synthesized compounds (3a-j)

Entry	Amine[a]	Product[b]		Time (h)	Yield (%)[c]	M. p. (°C)
1			**3a**	4.5	85	214-216
2			**3b**	5	81	185-186
3			**3c**	4.5	83	197-199
4			**3d**	4.5	82	203-204
5			**3e**	4.5	84	191-193
6			**3f**	4.5	83	278-280
7			**3g**	5	79	220-222
8			**3h**	5	78	222-224
9			**3i**	6	82	210-211
10			**3j**	4.5	79	204-205

[a] The substrate was treated with p-toluene sulfonyl chloride (2 mmol) by using 0.1 mmol of iodine in the presence of acetonitrile under neat conditions at room temperature.
[b] All products were identified by their ^{1}H NMR spectra. [c] Isolated yields.

Anti-microbial evaluation

All the newly synthesized sulfonamides were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *Escherishia coli,* and *Staphylococcus aureus*. Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. For this, the compound whose MIC has to be determined is dissolved in serially diluted DMF. Then a standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 16–18 hrs at 37 °C. MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity.

The assessment of antifungal activity using *Rhizopus oryzae* and *Candida albicans* fungal species by spore germination method in Petri dishes was followed. Spore suspension was prepared from five days old PDA (potato dextrose agar) slope cultures. Spore suspensions were placed in small Petri dishes. Solutions of different synthesized compounds were prepared in 90:10 (vol. / vol.) water: ethanol and the concentration of compounds (150 ppm) were adjusted in spore suspensions. Petri dishes were placed for incubation period of 12 hours under moist chambers. Aqueous ethanol (90:10, vol. / vol.) served as control. Percentage germination with effect of these compounds after a period of 12 hours was recorded by observing Petri dishes directly under microscope. The results were shown in the Table 3.

Table 3. Antimicrobial activities of sulfonamides (3a-j)

Entry	Zone of inhibition in mm		% of germination after 12 hr	
	Bacteria		Fungi	
	E. coli	*S. aureus*	*R. oryzae*	*C. albicans*
3a	18	16	18	20
3b	05	04	80	90
3c	18	17	20	15
3d	18	17	25	20
3e	16	17	20	25
3f	17	18	15	10
3g	15	14	50	60
3h	12	10	60	55
3i	16	14	20	20
3j	17	18	20	30
Tetracycline	20	20	NT	NT
Greseofulvin	NT	NT	90	95

NT = Not tested.

Experimental

Melting points were determined by the melting point determination apparatus in open capillary tubes and are uncorrected. All yields refer to isolated products. The proton NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrophotometer using $CDCl_3$ as solvent. The LCMS spectra were scanned on a Shimadzu LCMS-2010 EV instrument at 70 eV. All chemicals and reagents were obtained from Aldrich (USA) and SpectroChem Pvt. Ltd. (India) and were used without further purification.

General procedure for sulfonylation of amines

A mixture of heterocyclic amines (2 mmol), p-toluene sulfonyl chloride (2 mmol) and molecular iodine (0.1 mmol) was stirred magnetically in 5 ml of acetonitrile at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with 10% aqueous sodium thiosulfate (5 mL), brine, dried over sodium sulfate and purified by column chromatography on silica gel eluting with hexane ethyl acetate to give the corresponding sulfonamide in excellent yield 78-85% (Scheme-1).

Spectral data

4-Methyl-N-(pyridine-2-yl)-benzensulfonamide (3a): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.39 (s, 3H, CH_3), 6.80 (brs, 1H, NH), 7.25 (d, 2H, ArH), 7.28 (t, 1H, ArH), 7.40 (d, 1H, ArH), 7.62 (t, 1H, ArH), 7.81 (d, 2H, ArH), 8.36 (d, 1H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) = 20.9, 109.5, 113.5, 126.4, 129.3, 138.9, 140.1, 142.4, 143.7, 152.9. LC-MS = 249.05 (M+1); Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.08; H, 4.95; N, 11.30.

N-(5-Bromopyridin-3-yl)-4-methyl benzenesulfonamide (**3b**): ^{1}H NMR (400 MHz, $CDCl_3$) = δ 2.42 (s, 3H, CH_3), 7.10 (brs, 1H, NH), 7.25-7.65 (d, 4H, ArH), 7.83-8.42 (s, 3H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) = 20.9, 119.7, 126.6, 128.6, 129.9, 135.6, 135.8, 139.4, 143.9, 145.1; LC-MS = 329.0 (M+1); Anal. Calcd for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; Br, 24.42; N, 8.56. Found: C, 44.10; H, 3.35; Br, 24.45; N, 8.58.

4-Methyl-N-(quinolin-6-yl)-benzenesulfonamide (**3c**): ^{1}H NMR (400 MHz, $CDCl_3$) = δ 2.39 (s, 3H, CH_3), 6.80 (s, 1H, NH), 7.23-7.61 (m, 7H, ArH), 8.02-8.90 (d, 3H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) = 20.8, 114.8, 122.1, 124.8, 126.8, 127.5, 128.5, 129.7, 136.3, 136.9, 138.7, 141.2, 143.5, 147.2; LC-MS = 299.1 (M+1); Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.39; H, 4.75; N, 9.36.

4-Methyl-N-(quinolin-5-yl) benzenesulfonamide (**3d**): ^{1}H NMR (400 MHz, $CDCl_3$) = δ 2.39 (s, 3H, CH_3), 7.19 (brs, 1H, NH), 7.21-7.70 (m, 7H, ArH), 8.02-8.91 (d, 3H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) = 20.9, 121.1, 123.1, 124.6, 126.7, 127.1, 129.1, 129.5, 132.1, 132.8, 136.6, 143.2, 147.7, 150.4; LC-MS = 299.1 (M+1); Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.75; N, 9.40.

Conclusion

In summary, we have demonstrated a novel and facile method for the synthesis of sulfonamides by using iodine as a promoter under mild and neutral reaction conditions. The reaction was used for the preparation of peptides with no epimerization and de-blocking protecting groups detected during the reaction. The advantages of the present method include high yields of products, simple experimental procedure, non-toxicity of the reagent, no need for dry solvent. Many of the newly synthesized compounds had good antibacterial and antifungal activity, especially those containing heterocyclic moiety and halogen substituents. We therefore believe there is ample scope for further study and our work may have a beneficial outcome.

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