Synthesis and Antimicrobial Activity of Some New Piperazine Derivatives Containing Aryl Sulfonyloxy Group

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Abstract. Novel N-substituted piperazine derivatives containing sulfonyloxy aniline moiety have been prepared. The various 4-sulfonyloxy aniline (SA) derivatives (2a-h) have been prepared by the condensation reaction of N-Acetyl Sulfanilyl chloride (ASC) and sodium phenates followed by hydrolysis. The SA derivatives are then reacted with chloro acetyl chloride to give corresponding (N-Chloroacetyl) derivatives (3a-h). These derivatives are then reacted with N-phenyl piperazine to yield the corresponding piperazine derivatives (4a-h).

Keywords: N-Phenyl piperazine, ASC, NMR spectroscopy

Introduction

Piperazine derivatives have been extensively investigated by the organic chemists due to their close association with various types of biological activities. Moreover they have wide clinical applications in the therapy of functional diseases and exhibit Anthelmintic, antibacterial and insecticidal activities¹. Piperazine derivatives containing aryl -SO₃ group has received no attention in spite of well-defined biological activities of piperazine containing compounds. Hence it was thought interesting to synthesize novel piperazine derivatives containing aryl -SO₃ group. The present paper comprises the synthesis and characterization of piperazine derivatives as shown in **Scheme -1**.

Antibacterial activities:

Antibacterial activities of all the compounds were studied against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacteria (*E.coli* and *Salmonella typhi*) at a concentration of 100 µg/ml by Agar cup plate method. Methanol system was used as control in this method. Under similar condition using sulfanilamide as a standard for comparison carried out control experiment. The area of inhibition of zone is measured in cm. Compounds 4c, 4d and 4h were found more active against the above microbes. Other compounds found to be less or moderate active than sulfanilamide (**Table-2**).

Where	a	b	c	d	E	f	g	h
R_1	H	H	H	H	H	H	Cl	Br
R_2	H	CH_3	NO_2	Cl	OCH_3	$\text{C}(\text{CH}_3)_3$	Cl	Br
R_3	H	H	H	H	H	H	H	Br

Experimental

Melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^1H NMR spectra in CDCl_3 on Hitachi R-1500, 60 MHz spectrometer and Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. The required 4-acetamidobenzene sulfonyl chloride (ASC) was prepared by reported method². All the chemicals used were of laboratory grade.

Preparation of 4-(substituted phenyl sulfonyloxy) acetanilide (1a-h)

Sodium salts of phenols (listed Scheme-1) (0.05 mole) was dissolved in a mixture of 40ml anhydrous acetone and 1ml of dry pyridine in 250 ml R.B. flask and 11.67 gm (0.05mole) of pure 4-acetamidobenzene sulfonyl chloride (ASC) was added portion wise with stirring. Sodium bicarbonate (0.05 mole) was added as an acid acceptor. The reaction mixture is set aside overnight and almost pure 4-(substituted phenyl sulfonyloxy) acetanilide is filtered off and washed with cold water and air dried. It was then recrystallized from ethanol to give product (1a-h) in 60-70% yield. All the compounds (1a-h) were then hydrolyzed as follows.

Preparation of 4-(substituted phenyl sulfonyloxy) aniline (2a-h) by hydrolysis of (1a-h) by hydrolysis of (1a-h)

Each of the compounds (1a-h) was hydrolyzed by refluxing with 75ml of ethanol containing 15ml of conc. HCl for 4-5 hrs. It was then poured into ice-cold water and finally made just alkaline with liq. ammonia. The resultant product 4-(substituted phenyl sulfonyloxy) aniline (2a-h) is filtered off and washed with water and dried. It was then recrystallized from ethanol give products (2a-h) in 65 –75 % yield. The details of all the compounds are furnished in **Table- 1**.

Preparation of N-chloroacetyl derivatives (3a-h)

To a suspension of all the compound (2a-h) (0.005 mole), anhy. Potassium carbonate (2.5gm) and 1ml of TEA in dry chloroforms (65ml) was added chloro acetyl chloride (0.006 mole) and the mixture was refluxed for 4-5 hrs. The solvent was then evaporated and the resulting solid was washed with cold water and recrystallized using appropriate solvent affording N-chloroacetyl derivatives (3a-h) in 60 – 65% yield.

Preparation of piperazine derivatives (4a-h)

To a solution of N-chloroacetyl derivatives (3a-h) (0.005 mole) and N-phenyl piperazine 0.005 mole in dry chloroform was refluxed for 1-2 hours. The solvent was evaporated and the resulting solid was washed with cold water. The solid thus obtained was purified by column chromatography over silica gel using ethyl acetate : benzene as eluent in appropriate proportions. Recrystallization from chloroform gave corresponding (4a-h) in 50-60% yield.

Results and Discussion

The synthesis of piperazine derivatives is accomplished as shown in the **Scheme-1**. Analytical and Spectral data are given in **Table-2**.

The compound ASC was reacted with various phenolates and followed by hydrolysis³. The resultant hydrolyzed products (2a-h) have consistent values of C, H, N and S contents with the predicted structure. All the compounds (2a-h) show the diazo test for primary amine ($-\text{NH}_2$) group. The IR spectra of (2a-h) show the new bands at 3410 cm^{-1} (NH_2) and $1210\text{-}1150\text{ cm}^{-1}$ (SO_3), than the IR spectra of ASC. The compounds (2a-h) then reacted with chloro acetyl chloride in chloroform to yield corresponding N-chloroacetyl derivatives^{4,5} (3a-h) show new IR spectral absorption bands at 1550 cm^{-1} ($-\text{CONH}$). Further reaction of (3a-h) with N-phenyl piperazine afforded corresponding piperazine derivatives⁶. Their structures (4a-h) were confirmed by elemental analysis and IR spectral features and also confirms on the basis of ^1H NMR spectrum.

Table 1. Analytical and Spectral data of compounds (2 a-h)

Compd	Molecular formula	% Analysis Calculated (found)				% Yield	M.P ($^{\circ}\text{C}$)	PMR (δ ppm)
		% C	% H	% N	% S			
2a	$\text{C}_{12}\text{H}_{11}\text{O}_3\text{NS}$	57.83 (57.65)	4.41 (4.35)	5.62 (5.45)	12.85 (12.60)	70	145	4.3(2H,s, NH_2), 6.8–7.6(9H,m, aromatic)
2b	$\text{C}_{13}\text{H}_{13}\text{O}_3\text{NS}$	59.31 (59.20)	4.94 (4.75)	5.32 (5.20)	12.16 (12.95)	70	138	2.2(3H,s, CH_3),4.3(2h,s, NH_2),6.5–7.6 (8H,m, aromatic)
2c	$\text{C}_{12}\text{H}_{10}\text{O}_3\text{NSCl}$	50.79 (50.55)	3.52 (3.40)	4.93 (4.75)	11.28 (11.15)	65	120	4.3(2H,s, NH_2), 6.5–7.8(9H,m, aromatic)
2d	$\text{C}_{12}\text{H}_{10}\text{O}_5\text{N}_2\text{S}$	48.97 (48.75)	3.40 (3.25)	9.52 (9.35)	10.88 (10.70)	80	105	4.3(2H,s, NH_2), 6.8–7.8(9H,m, aromatic)
2e	$\text{C}_{13}\text{H}_{13}\text{O}_4\text{NS}$	55.91 (55.75)	4.65 (4.50)	5.01 (4.85)	11.40 (11.30)	75	125	3.8(3H,s, OCH_3), 4.3(2H,s, NH_2), 6.4–7.5 (8H,m, aromatic)
2f	$\text{C}_{16}\text{H}_{19}\text{O}_3\text{NS}$	62.95 (62.80)	6.22 (6.05)	4.59 (4.45)	10.49 (10.35)	60	118	2.2(9H,s, 3CH_3), 4.2(2H,s, NH_2), 6.4–7.8 (8H,m, aromatic)
2g	$\text{C}_{12}\text{H}_9\text{O}_3\text{NSCl}_2$	45.28 (45.10)	2.83 (2.65)	4.40 (4.20)	10.06 (9.85)	75	150	4.4(2H,s, NH_2), 6.8–8.0 (7H,m, aromatic)
2h	$\text{C}_{12}\text{H}_8\text{O}_3\text{NS Br}_3$	29.62 (29.40)	1.64 (1.50)	2.88 (2.65)	6.58 (6.45)	72	155	4.4(2H,s, NH_2),6.8–8.0 (6H,m, aromatic)

Table – 2. Analytical and Spectral data of Compounds (4a-h)

Comps	Molecular formula	% Analysis Calculated (Found)				Yield (%)	M.P. (⁰ C)	PMR (δ,ppm)
		%C	%H	%N	%S			
4a	C ₂₄ H ₂₅ O ₄ N ₃ S	63.85 (63.75)	5.54 (5.45)	9.31 (9.20)	7.09 (6.90)	170	55	2.2-3.1(10H, t+s, 5CH ₂), 6.5-7.6 (14H,m, aromatic), 9.2(1H,hump,NH,) 1.8(3H, s, CH ₃),
4b	C ₂₅ H ₂₇ O ₄ N ₃ S	64.51 (64.40)	5.80 (5.70)	9.03 (8.90)	6.88 (6.75)	165	60	2.2-3.2(10H,t+s, 5CH ₂), 6.5-7.6 (13H,m, aromatic), 9.2(1H,hump,NH,)
4c	C ₂₄ H ₂₄ O ₆ N ₃ S	58.06 (57.95)	4.83 (4.75)	11.29 (11.10)	6.45 (6.35)	205	53	2.3-3.1(10H,t+s, 5CH ₂), 6.5-7.9 (13H,m, aromatic), 9.2(1H,hump,NH,)
4d	C ₂₄ H ₂₄ O ₄ N ₃ S Cl	59.32 (59.25)	4.94 (4.80)	8.65 (8.50)	6.59 (6.50)	155	50	2.3-3.2(10H,t+s, 5CH ₂), 6.9-8.2 (13H,m, aromatic), 9.3(1H,hump,NH,)
4e	C ₂₅ H ₂₇ O ₅ N ₃ S	62.37 (62.30)	5.61 (5.50)	8.73 (8.65)	6.65 (6.55)	175	55	2.3-3.2(10H,t+s, 5CH ₂), 3.6(3H,S,OCH ₃) 6.9-8.1 (13H,m, aromatic), 9.3(1H,hump,NH,)
4f	C ₂₈ H ₃₃ O ₄ N ₃ S	66.27 (66.15)	6.50 (6.40)	8.28 (8.15)	6.31 (6.20)	167	52	1.3(9H,s, 3CH ₃), 2.2-3.1(10H,t+s, 5CH ₂), 6.8-8.1 (13H,m, aromatic), 9.2(1H,hump,NH,)
4g	C ₂₅ H ₂₃ O ₄ N ₃ Cl ₂ S	55.49 (55.40)	4.43 (4.30)	8.09 (7.90)	6.16 (6.05)	177	54	2.2-3.3(10H,t+s, 5CH ₂), 6.5-8.1 (12H,m, aromatic), 9.1(1H,hump,NH,)
4h	C ₂₄ H ₂₂ O ₄ N ₃ S Br ₃	46.15 (46.05)	3.52 (3.45)	6.73 (6.65)	5.12 (0.05)	148	55	2.3-3.1(10H,t+s, 5CH ₂), 6.8-8.3 (11H,m, aromatic), 9.2(1H,hump,NH,)

Table 3. Antibacterial Activity of compounds (4a-h)

Compounds	Zone of inhibition			
	Gram +ve		Gram –ve	
	Bacillus	Staphylococcus	Salmonella	E.Coli
	Subtillis	Aureus	Typhi	
4a	55	60	43	65
4b	42	67	52	69
4c	70	80	75	60
4d	83	70	68	55
4e	45	65	43	83
4f	65	60	62	49
4g	68	55	68	58
4h	83	69	79	72
Sulfanilamide	85	65	75	73

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References

1. Coyne W E Medicinal chemistry, edited by Alfred burger (Wiley- Interscience, New Your), 1970
2. Vogel A I A Textbook of Practical Organic Chemistry, 4th ed., 1978, 651.
3. Vogel A I A Textbook of Practical Organic Chemistry, 4th ed., 1978, 652 -653.
4. Clark N G and Hams A F *Biochem. J.* 1953, **55**, 839.
5. Arya V P, Grewal R S, Kavl C L ,David J and Honkan V *Indian J. Chem.* 1977, **15B**, 133.
6. Holinska Hana, Protiva Miroslav and Frycova Hana *Chem. Abstr.* 1990, **113**, 59226h.