

Synthesis and Biological Activity of 4-[5-(4-Substituted phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

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Esterification of trifluoroacetic acid with ethanol gives ethyl trifluoroacetate (1). Diazotization of sulphanilamide followed by reduction with sodium sulphite leads to the 4-(sulfamoylphenyl)hydrazine hydrochloride (2). Condensation of (1) with substituted acetophenone (3a–d) gave (4a–d), which on treatment with (2) results in the formation of 4-[5-(4-substituted phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (5a–d). The structures of the newly synthesized compounds have been established by analytical and spectral methods. These compounds have also been screened for their biological activity.

Key Words: Synthesis, Substituted benzenesulfonamide, Antibacterial and antifungal activity.

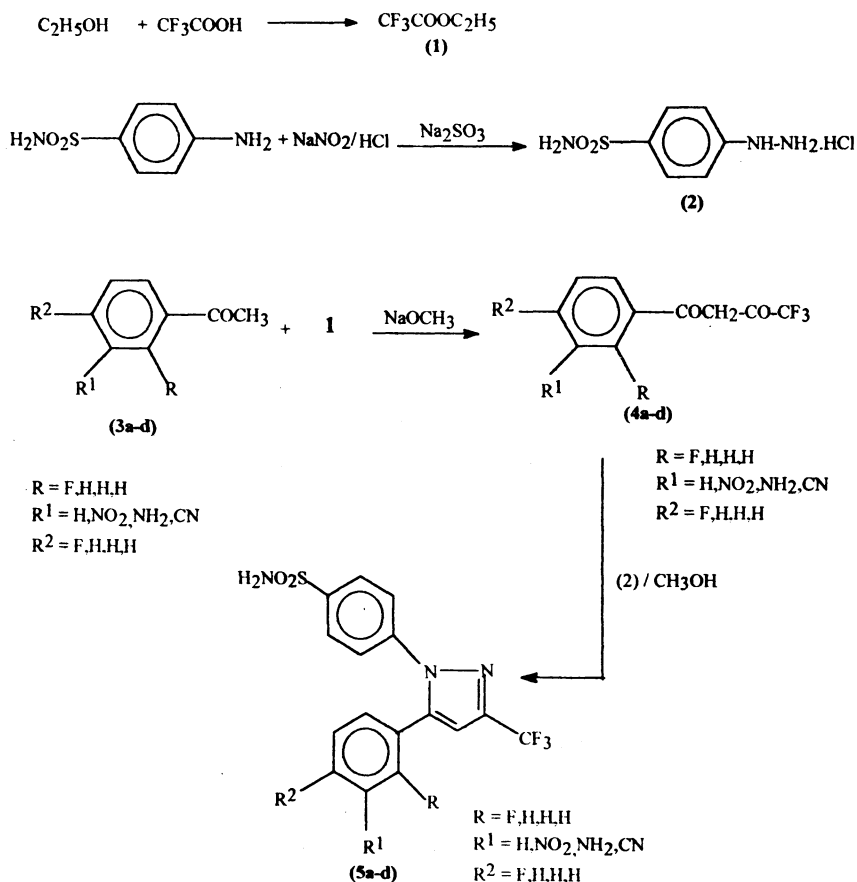
INTRODUCTION

Benzenesulfonamide derivatives possess varying degree of antibacterial¹ and antifungal² activity. Further, the pyrazole derivatives constitute an important class of compounds possessing diverse pharmacological activities including antibacterial³ and antifungal⁴ activities. In addition, pyrazole-benzenesulphonamide derivatives were recently evaluated for their ability to block cyclooxygenase-2 (COX-2)⁵.

In view of this observation and in continuation of our research for biologically active heterocycles, it was proposed to synthesize pyrazole-benzenesulfonamide derivatives (5a–d) and to evaluate their antibacterial and antifungal activity.

RESULTS AND DISCUSSION

Ethyl trifluoroacetate (1) was prepared from trifluoroacetic acid by esterification with ethanol under pressure. Sulphanilamide was diazotized at low temperature and reduction of diazonium salt was carried out using sodium sulphite to give 4-(sulfamoylphenyl)hydrazine hydrochloride (2). Claisen condensation of substituted acetophenone (3a–d) with ethyl trifluoroacetate (1) under pressure afforded (4a–d). Condensation of 4-(sulfamoylphenyl)hydrazine hydrochloride (2) with trifluorobutane-1,3-diones (4a–d) in methanol gave (5a–d) (Scheme -1).



Scheme-1

Screening for biological activity: All the compounds (**5a-d**) were screened *in vitro* for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhosa* and *Bacillus subtilis* by the ditch-plate technique⁶. The compounds synthesized were also tested for antifungal activity against *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans*, *Thielaviopsis paradoxa* by paper disc diffusion method⁷.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer FTIR spectrophotometer. ¹H NMR spectra were recorded on a Bruker 300 spectrophotometer (300 MHz) using DMSO-d₆ as solvent and TMS as internal standard (chemical shifts in 6 ppm). The purity of the compounds was monitored by thin-layer chromatography.

Ethyl trifluoroacetate (1): A mixture of trifluoroacetic acid (200 g, 1.75 mol) and absolute ethanol (88.55 g, 1.925 mol) was placed in a 500 cm³ autoclave.

The reaction mixture was heated to 70°C for 5 s. The ester⁸ was distilled off at 60-62°C (199 g, 80%), b.p. 60°C.

4-(Sulfamoylphenyl)hydrazine hydrochloride (2): Sulphanilamide (50 g, 0.29 mol) was dissolved in a mixture of water (100 mL) and 35% hydrochloric acid (65 mL, 0.62 mol) and cooled to 0°C. Sodium nitrite (22 g, 0.31 mol) was dissolved in 44 mL water at 0-5°C. The reaction mixture was poured into sodium sulphite heptahydrate (160 g, 0.63 mol) at 5-10°C and then further heated to 80°C for 3 h, cooled to room temperature and filtered. The solid obtained was again heated using 300 mL hydrochloric acid for 2 h and filtered. The product (2) obtained was crystallized from ethanol (55 g, 83%), m.p. 210°C.

1-(2,4-Difluorophenyl)-4,4,4-trifluorobutane-1,3-dione (4a): 2,4-Difluoro- acetophenone (3a, 50g, 0.32 mole) and ethyl trifluoroacetate (1) dissolved in 200 mL methanol were added to sodium methoxide (54.0 g, 1.0 mol) in an autoclave and the reaction mixture was heated to 75°C for 30 min. Methanol was completely distilled off; 10% hydrochloric acid (500 mL) was added and the product obtained was extracted with 3 × 200 mL ethyl acetate. The extract was dried over MgSO₄, filtered and concentrated to afford brown oil which was subjected to further reaction.

Other trifluorobutane-1,3-diones were prepared in a similar manner.

4-[5-(2,4-Difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (5a): The hydrazine hydrochloride (2, 40g, 0.175 mol) was added to the solution of trifluorobutane-1,3-dione (4a, 40 g, 0.158 mol) in 100 mL methanol. The reaction mixture was refluxed for 8 h. The solvent was removed under reduced pressure and 500 mL water was added to the reaction mixture. The solid precipitated out was filtered and recrystallized from isopropyl alcohol (5a).

IR (KBr) (cm⁻¹): 3374-3341 ν(-NH₂), 3231 ν(-NH₂), 3083 ν(C-H, aromatic), 1323 ν(S=O, asym.), 1141 ν(S=O, sym.), 825 ν(C-H, aromatic band.); NMR (DMSO- d₆) δ 6.94 (s, 1H, =CH), 7.49 (m, 7H, ArH), 7.96 (s, 2H, -NH₂).

Other compounds (5b-d) were prepared in an analogous way. The melting points, yields and analytical data are given in Table-1.

TABLE-1
PHYSICAL DATA OF 4-[5(4-SUBSTITUTED PHENYL)-3-(TRIFLUOROMETHYL)-1H-PYRAZOL-1-YL]BENZENESULPHONAMIDE (5a-d)

Cmpd	m.f.	R	R ¹	R ²	Crystallized form	Yield (%)	m.p. (°C)	Analysis (%) N	
								Reqd.	Found
5a	C ₁₆ H ₁₀ F ₅ N ₃ O ₂ S	F	H	F	Isopropyl alcohol	78	185	10.41	10.38
5b	C ₁₆ H ₁₁ F ₃ N ₄ O ₄ S	H	NO ₂	H	Ethanol	68	194	13.58	13.55
5c	C ₁₆ H ₁₃ F ₃ N ₄ O ₂ S	H	NH ₂	H	Ethanol	76	163	14.64	14.61
5d	C ₁₇ H ₁₁ F ₃ N ₄ O ₂ S	H	CN	H	Isopropyl alcohol	60	215	14.27	14.25

The compounds were screened using concentration of 2 and 5 mg/mL. The results of such studies are given in Table-2.

TABLE-2
BIOLOGICAL ACTIVITY DATA

Antibacterial Activity									
Compound	<i>S. aureus</i>		<i>E. coli</i>		<i>B. subtilis</i>		<i>S. typhosa</i>		
	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	
5a	+	++	+	++	+	++	+	+	
5b	+	+	-	+	+	+	-	+	
5c	+	+	+	+	-	-	+	+	
5d	+	+	+	+	-	+	-	-	

Antifungal Activity									
Compound	<i>A. niger</i>		<i>C. albicans</i>		<i>C. neoformans</i>		<i>T. paradoxa</i>		
	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	
5a	-	+	-	+	+	+	-	+	+
5b	+	+	-	-	+	+	-	+	
5c	-	+	+	+	-	+	+	+	
5d	+	+	+	+	+	+	+	+	

Inhibition zone diameter in mm: (-) <11 mm; (+) 11–14 mm (++) 15–18 mm.

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