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Syntheses of 1,5-Benzothiazepines: Part 48: Single Pot Syntheses and Antimicrobial Studies of 8-Substituted 4-(2,4/2,5-disubstituted aryl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic Acids

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Two substituted acrylic acids, β-(2,4-dimethylbenzoyl) acrylic acid and β-(2,5-diisopropylbenzoyl) acrylic acid were reacted with six 5-substituted 2-aminobenzenethiols, in dry ethanol containing trifluroacetic acid to obtain ten new compounds, 8-substituted 4-(2,4-dimethylphenyl/2,5-diisopropylphenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids in 53-63 % yields. The products were characterized on the basis of micro analytical data and spectral analysis comprising IR, ^{1}H NMR and mass studies. All the synthesized compounds have been screened for their antimicrobial activity against the Gram-positive bacteria, *Staphylococcus aureus* and Gram-negative bacteria, *Enterobacter cloacae*, *Klebsiella aerogenes* and fungus, *Candida albicans* with respective reference compounds.

Keywords: Acrylic acids, 5-Substituted 2-aminobenzenethiols, Antimicrobial activity.

INTRODUCTION

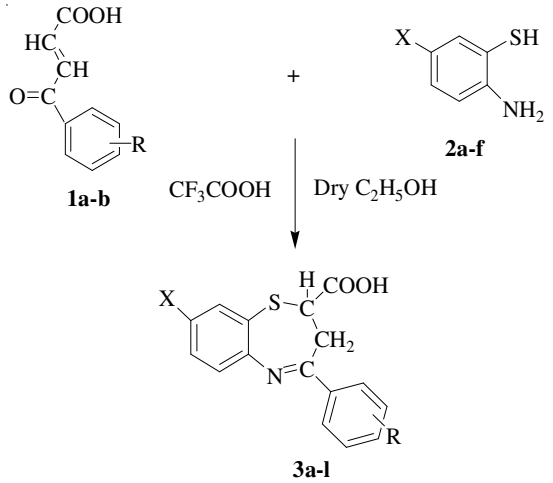
β-Aroyl acrylic acids have an antiproliferative action against the human cervix carcinoma (HeLa cells) [1], exhibit cytostatic activity which is used as an aid to study and determine factors affecting the human eye's UV filters [2], as *Aspergillus* controller [3] and inhibitors of phospholipase [4]. Moreover, they show a marked increase in *in vitro* activity against Gram-positive bacteria [5] and cancer [6]. These are used as key starting materials due to their high electrophilicity, where the β-aroyl acrylic acids react readily with nucleophiles, including nitrogen and sulfur nucleophiles, to afford either cyclic or normal Michael adducts depending on the nature of the attacking nucleophiles and the reaction medium (neutral, basic, acidic) and the Michael addition reaction may be utilized in tandem as efficient strategy for the construction of ring structures [7-9]. Therefore, this starting material has been used to prepare more interesting heterocyclic 1,5-benzothiazepine compounds having a substituent in the fused benzene ring, which may have diverse biological activities.

EXPERIMENTAL

To prepare the new series of 1,5-benzothiazepines **(3a-l, Scheme-I)**, equimolar quantities of the precursors α,β-unsaturated-β-keto acids, β-(2,4-dimethylbenzoyl/2,5-diisopropylbenzoyl) acrylic acid [1] (**1a-b**) and 5-substituted 2-aminobenzenethiols [10] **(2a-f)**, the substituents being fluoro, chloro, bromo, methyl, methoxy or ethoxy, were reacted in dry ethanol containing trifluoroacetic acid to obtain the final compounds in single step in 53-63 % yields. The purity of the final products was checked by TLC. The structures of the final products were ascertained by elemental and spectral analyses comprising IR, ^{1}H NMR and mass spectral studies. All the compounds **3a-l** were evaluated for their antimicrobial activity, comprising antibacterial and antifungal.

General procedure for the syntheses of 8-substituted 4-(2,4-dimethylphenyl/2,5-diisopropylphenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids (3a-l): To a solution of β-(2,4-dimethylbenzoyl/2,5-diisopropylbenzoyl) acrylic acid (**1**, 0.001 mol) in dry ethanol (5 mL) containing trifluoroacetic acid, was added the ethanolic solution of 5-substituted 2-aminobenzenethiols (**2**, 0.001mol) with continuous stirring. The reaction mixture after refluxing for 3-4 h followed by cooling, afforded the crude, which was filtered and crystallized from ethanol to give coloured crystals of the target compounds **(3a-l)**.

Antimicrobial activity: The antimicrobial activity of all newly synthesized compounds 8-substituted 2,3-dihydro-4-(2,4-dimethylphenyl/2,5-diisopropylphenyl)-1,5-benzothiazepine-2-carboxylic acids **(3a-l)**, were carried out using paper disc method [11] against the Gram-positive bacteria *Staphylococcus aureus* and the Gram-negative bacteria *Enterobacter cloacae*, *Klebsiella aerogenes* and antifungal activity against the fungus, *Candida albicans* at the concentration of 200 µg/disc, with vancomycin and polymixin B and fluconazole as the reference drugs, respectively. The reference compounds were used to evaluate the activity in the form of activity



Compd.	X	R	Compd.	X	R
3a	F	2,4-$(CH_3)_2$	**3g**	F	2,5-$[C(CH_3)_2]_2$
3b	Cl	2,4-$(CH_3)_2$	**3h**	Cl	2,5-$[C(CH_3)_2]_2$
3c	Br	2,4-$(CH_3)_2$	**3i**	Br	2,5-$[C(CH_3)_2]_2$
3d	CH_3	2,4-$(CH_3)_2$	**3j**	CH_3	2,5-$[C(CH_3)_2]_2$
3e	OCH_3	2,4-$(CH_3)_2$	**3k**	OCH_3	2,5-$[C(CH_3)_2]_2$
3f	OC_2H_5	2,4-$(CH_3)_2$	**3l**	OC_2H_5	2,5-$[C(CH_3)_2]_2$

Scheme-I

index. Zones of inhibition, exhibited by the reference and test compounds, were measured and compared to show relative activities in the form of activity index. The physical constants and the antimicrobial activity is given in Table-1.

Detection method: All the reported melting points are uncorrected. Purity of the compounds were checked by TLC on glass plates coated with silica gel 'G' as absorbent, using benzene : ethanol : aq. ammonia (50 %) in the ratio 7:2:1 as solvent system. The IR spectra were taken in KBr pellets on a Perkin Elmer RX1 FT IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) instrument using $CDCl_3$ as solvent and TMS as internal standard. Some of the spectral analyses and elemental analyses were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow, India.

RESULTS AND DISCUSSION

In the IR spectra of all the synthesized products, absence of characteristic absorptions bands at 3400-3300 cm^{-1} for ν(N-H) and the presence of a strong absorption signal of ν(C=N) in the range 1612-1602 cm^{-1} indicated that the amino group of the 6-substituted 2-amino benzenethiols and carbonyl group of the β-aroyl acrylic acids have reacted to form carbon nitrogen double bond and the completion of reaction in single step in the presence of acidic catalyst. The strong absorptions at 1695-1680 cm^{-1}, along with the broad absorptions in the region 3138-3025 cm^{-1} due to O-H stretching vibrations, indicated the presence of carboxylic acid group. The sharp absorption signals observed at 1434-1384 cm^{-1} indicate the presence of δ(C-O-H) in-plane bending. C-F stretching vibrations at 1201-1198 cm^{-1} in the spectra of **3a** and **3g**, C-Cl stretching vibrations at 1087-1077 cm^{-1} in **3b** and **3h** and C-Br stretching vibration at 800-760 cm^{-1} in the spectra of **3c** and **3i** were also observed.

In the ^{1}H NMR spectra, all the compounds showed a singlet at δ 7.96-8.26, which corresponds to the carboxylic acid proton. Besides, the spectra were diagnostic of the 2,3-dihydro structure as the methylene protons at C-3 and methine protons at C-2 were observed as double doublets in the ABX pattern. Each of the three double doublets were found to integrate for one proton at around δ 2.77-3.04 (dd, J_{AB} = 16 Hz and J_{AX} = 7 Hz), d 3.35-3.81 (dd, J_{AB} = 16 Hz and J_{BX} = 7 Hz) and at δ 4.27-4.98 (dd, J_{AX} = 7 Hz and J_{BX} = 7 Hz). The two methylene protons couple with each other and give rise to a doublet with the geminal coupling constant of 16 Hz. Each of the two methylene protons also couple with the methine proton, therefore the doublet signal again splits, this time with a vicinal coupling constant of 7 Hz, thus resulting in the formation of two almost similar doublets, the one which comes upfield, at δ 2.77-3.04 is assigned to H_A, which is axial and may be intramolecularly H-bonded to the COOH group at C-2, while the other double doublet at δ 3.35-3.81 may be assigned to H_B. The methine proton signal at δ 4.27-4.98, assigned to H_X, is also obtained as a double doublet due to the vicinal protons, and as it possesses two vicinal protons, the different

TABLE-1
PHYSICAL CONSTANTS AND ANTIMICROBIAL DATA OF COMPOUNDS **3a-l**

Compd. No.	m.p. (°C)	R_f	Yield (%)	Zone of inhibition (Activity index)			
				Antibacterial activity			Antifungal activity
				Staphylococcus aureus	*Klebsiella aerogenes*	*Enterobacter cloacae*	*Candida albicans*
3a	104-106	0.57	56.61	13 (0.76)	14 (1.27)	–	13 (0.52)
3b	105-107	0.53	58.85	12 (0.70)	18(1.54)	7 (0.63)	11 (0.44)
3c	110-112	0.57	56.32	–	11 (1.00)	10 (0.90)	13 (0.52)
3d	108-110	0.61	59.75	11 (0.64)	13 (1.18)	7 (0.63)	9 (0.36)
3e	87-89	0.59	60.12	10 (0.58)	12 (1.09)	8 (0.72)	12 (0.48)
3f	116-118	0.54	63.24	15 (0.88)	10 (0.90)	6 (0.54)	9 (0.36)
3g	120-122	0.71	58.32	13 (0.76)	13 (1.18)	–	15 (0.60)
3h	116-118	0.62	55.69	15 (0.88)	13 (1.18)	9 (0.81)	14 (0.56)
3i	114-116	0.59	62.97	13 (0.76)	15 (1.36)	7 (0.63)	11 (0.44)
3j	109-111	0.57	53.48	–	06 (0.54)	–	10 (0.40)
3k	120-122	0.56	59.83	10 (0.58)	14 (1.27)	–	12 (0.48)
3l	110-112	0.53	60.61	17 (1.00)	18 (1.63)	12 (1.09)	11 (0.44)

Zones of inhibition are given in mm, Values in parentheses represent activity index.

Table-2
IR (cm^{-1}) AND ^1H NMR ($CDCl_3$, δ VALUES IN ppm, *J* IN Hz) SPECTRAL DATA OF COMPOUNDS **3a-l**

Compd. No.	IR				^1H NMR				
	–COOH		ν(C=N)	ν(O–H)	C_3-H_A (dd, J_{AB} 16, J_{AX} 7, 1H)	C_3-H_B (dd, J_{AB} 16, J_{BX} 7, 1H)	C_2-H_X (dd, J_{AX} 7, J_{BX} 7, 1H)	COOH	Aromatic protons (6H, m)
	ν(O–H)	ν(C=O)							
3a	3128	1684	1613	1405	2.98	3.45	4.40	8.02	6.46-7.92
3b	3033	1689	1611	1407	3.01	3.49	4.28	8.01	6.52-7.96
3c	3132	1680	1607	1426	2.77	3.45	4.35	7.98	6.57-7.92
3d	3137	1687	1609	1393	2.89	3.56	4.28	8.00	6.53-7.97
3e	3035	1688	1610	1401	3.00	3.61	4.27	8.10	6.74-7.94
3f	3138	1690	1615	1434	3.04	3.60	4.30	8.01	6.62-7.90
3g	3124	1695	1613	1387	2.82	3.53	4.92	8.08	6.29-7.93
3h	3025	1690	1620	1384	2.84	3.68	4.87	8.26	6.30-7.89
3i	3129	1685	1611	1402	2.92	3.81	4.98	8.13	6.89-7.97
3j	3122	1693	1610	1434	2.98	3.63	4.91	8.23	6.80-7.93
3k	3033	1681	1608	1406	2.87	3.70	4.86	7.96	6.81-7.73
3l	3128	1685	1607	1386	2.88	3.35	4.80	8.09	6.85-7.67

values of coupling constant for AX and BX protons may arise due to the axial and equatorial conformations of H_A and H_B. The absorption signal in the region of δ 6.29-7.97 (m, 6H) occurred as multiplets corresponding to the aromatic protons. All the compounds, **3a-l** showed methyl group absorptions: **3a-g** showed one singlet integrating for six protons due to the two methyl groups in the region δ 2.37-2.32 due to the presence of α-phenyl ring. The spectra of **3g-l** showed methyl group protons in the upfield region of δ 1.42 to 1.25; a multiplet for two methine protons was observed in the downfield region of 3.31-3.02, indicating the presence of isopropyl group on the phenyl ring. The characteristic methyl, methoxy and ethoxy proton signals were exhibited at δ 2.26-2.35 (s, 3H), 3.76-3.88 (s, 3H), 1.25 (t, *J* = 8 Hz, 3H), 3.97-4.08 (q, *J* = 8 Hz, 2H) in the spectra of **3d** and **3j**; **3e** and **3k** and **3f** and **3l**, respectively.

In the mass spectral studies,**3b** and **3h** showed cluster of isotopic molecular ion peaks, *m/z* at 345, 346, 347 and at 401, 402, 403, respectively, while the compound **3c** showed absorptions at *m/z* 390, 391, 392 and **3i** at 446, 447, 448 which correspond to their respective M^+, $[M+2]^+$ and $[M+4]^+$. The pattern of the cluster of molecular ion peaks in the mass spectra confirmed the presence of chlorine in **3b** and **3h**, as the intensity of $[M+2]^+$, peaks was one third of that of the $[M]^+$ peak. The characteristic intensities of the $[M+2]^+$ and [M+4] peaks in 1:1 ratio in the spectra of **3c** and 3**i** indicated the presence of bromine.

For antimicrobial studies, the reference compounds were used to evaluate the activity in the form of activity index. Zones of inhibition, exhibited by the reference and test compounds were measured and compared to show relative activities in the form of activity index. Almost all the compounds showed good antibacterial activity against *Klebsiella aerogenes* at the concentration of 200 µg/disc, notable feature being the antibacterial activity of 8-ethoxy-2,3-dihydro-4-(2,4-dimethylphenyl)-1,5-benzothiazepines-2-carboxylic acid which was found to be active against the Gram-positive as well as Gram-negative bacteria studied, *i.e. Staphylococcus aureus, Klebsiella aerogenes* and *Enterobacter cloacae* (Table-1).

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