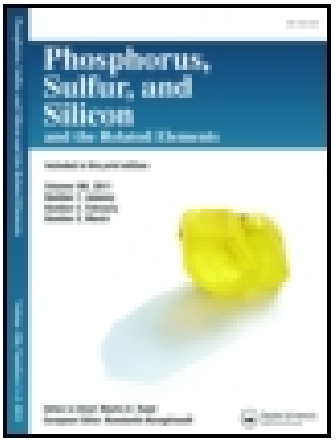

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SYNTHESIS OF 8-SUBSTITUTED-2-CARBOXY-4-(4-FLUOROPHENYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES

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SYNTHESIS OF 8-SUBSTITUTED-2-CARBOXY-4-(4-FLUOROPHENYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES

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Syntheses of six 8-substituted-2-carboxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepines having as the substituent fluoro, chloro, bromo, alkyl-methyl, alkoxyl-methoxyl and ethoxyl have been achieved by the reaction of 5-substituted-2-aminobenzenethiols with β-(*p*-fluorobenzoyl)acrylic acid in ethanol saturated with hydrogen chloride gas. The products were tested for purity by TLC. Microestimation of nitrogen, IR and ^{1}H NMR & mass spectral studies have been used for the assignment of structures to the title compounds.

Key words: 2,3-dihydro-1,5-benzothiazepines, fluorine, β-(*p*-fluorobenzoyl)acrylic acid.

In continuation of our work[1] on syntheses of 4-aryl-2-carboxy-2,3-dihydro-8-substituted-1,5-benzothiazepines and noticing the importance of analogous fluorinated heterocycles[2–12] as potential anti AIDS, anticancer agents,[13,14] we report the syntheses of six new fluoro compounds, i.e., 8-substituted-2-carboxy-2,3-dihydro-1,5-benzothiazepines having a 4-fluorophenyl group at position-4.

RESULTS AND DISCUSSION

Six 5-substituted-2-aminobenzenethiols (**1a–f**) having as substituents F, Cl, Br, CH_2, OCH_3, and OC_2H_5, have been reacted with β-(*p*-fluorophenyl)acrylic acid (**2**) to obtain 8-substituted-2-carboxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepines (**4a–f**) in a single pot syntheses. For this purpose, **1a–f** were prepared by literature[15] methods and **2** was prepared by the reaction of fluorobenzene[16] (prepared by a Balz-Shiemann reaction) with maleic anhydride in carbon disulfide in the presence of anhydrous aluminium chloride (Friedel and Craft's reaction). Six 5-substituted-2-aminobenzenethiols were reacted with β-(*p*-fluorobenzoyl)acrylic acid in acidic medium using ethanol saturated with dry hydrogen chloride gas. Evolution of carbon dioxide as brisk effervescence on addition of sodium bicarbonate to the ethanolic solution of the final products i.e. **4a–f** indicated the presence of an acidic group. The microestimation of nitrogen was found to be within the permissible limit of error of calculated values for the final products (Table I).

It has been established that the compounds having α,β-unsaturated carbonyl system react with 5-substituted-2-aminobenzenethiols in two steps.[1,17–23] In the first step initiation occurs via a nucleophilic attack[24,25] by sulfhydryl electrons[26] of 5-substituted-2-aminobenzenethiols at the β-carbon of α,β-unsaturated carbonyl system to give a Michael adduct as intermediate.[21–23,25] Stephens and Field,[21] while studying the mechanism of the reaction of 2-aminobenzenethiol with compounds having α,β-

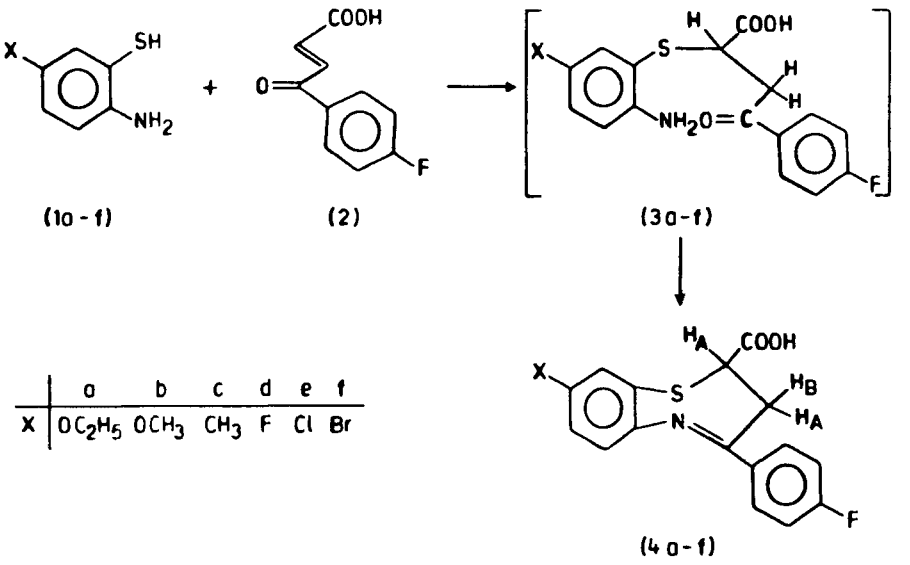
TABLE I

Physical constants and analytical data of 8-substituted-2-carboxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepines (**4b–f**)

Compound no.	X	mp (°C)	R_f	Yield (%)	Molecular formula $[M]^+$, $[M+2]^+$	Elemental analysis for N_2, found (calcd.) (%)
4b	—OCH_3	185	0.85	50	$C_{17}H_{14}NSO_3F$ (331, 333)	4.25 (4.22)
4c	—CH_3	215	0.76	48	$C_{17}H_{14}NSO_2F$	4.47 (4.44)
4d	—F	201	0.75	60	$C_{16}H_{11}NSO_2F_2$	4.40 (4.38)
4e	—Cl	214	0.75	58	$C_{16}H_{11}NSO_2FCl$	4.21 (4.17)
4f	—Br	227	0.78	55	$C_{16}H_{11}NSO_2FBr$ (379, 381)	3.66 (3.68)

unsaturated carbonyl system, isolated the Michael adduct i.e. an intermeiate in methanolic solution in the presence of piperidine as catalyst. By boiling the intermediate in methanolic solution containing catalytic amount of glacial acetic acid, they obtained the cyclized product in the second step. Reid and Marx[22] observed that the presence of catalyst markedly affects the course of reaction. They obtained[22] the final products without the isolation of the intermediate in the reaction of 2-aminobenzenethiol with variously substituted chalcones in methanol containing hydrochloric acid. It was also observed by Hideg-Hankovszky and Hideg[25] that the formation of the intermediate and the cyclized product is also affected by the presence of the type of groups or substituents present in compounds having α,β-unsaturated carbonyl system. Lévai and Bögnar[23,27] studied the reactions of a large number of chalcones with 2-aminobenzenethiols and found that intermediates of the Michael type adduct were obtained in boiling toluene. They were converted into cyclized products by boiling them in anhydrous methanol in the presence of glacial acetic acid as catalyst, in the second step. Lévai and Bögnar[23,27] also obtained the final products without isolation of the intermediate in the reactions of 2-aminobenzenethiol with chalcones by boiling in methanol containing glacial acetic acid. Since, we have carried out the reaction of 5-substituted-2-aminobenzenethiols (**1a–f**) with β-(*p*-fluorobenzoyl)-acrylic acid (**2**) in ethanol containing dry hydrogen chloride gas, we obtained the final products 8-substituted-2-carboxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepines (**4a–f**) without the isolation of the intermediate. Yet, from the evidence of the study of analogous reactions as cited above and spectral evidence,[17–27] it is presumed that the intermediates (Scheme 1, **3a–f**) are formed prior to the formation of the cyclized products (**4a–f**).

The products obtained in the present reaction conditions, showed the absence of absorption bands at 1690–1650 cm^{-1}, characteristic of ketone carbonyl absorption. Also, no absorptions were observed in the range 3500–3150 cm^{-1} as two bands due to assymmetric and symmetric stretching at around 3450 and 3350 cm^{-1}, characteristic absorptions of amino group. This indicated that the reaction between the ketone carbonyl group and amino group of the intermediate has taken place. However, the co-presence[1] of ν(C=O) at 1695–1680 cm^{-1} with very broad absorption at 3000–2600 cm^{-1} due to hydrogen bonded O—H and absorptions in the range 1390–1230



	a	b	c	d	e	f
X	OC_2H_5	OCH_3	CH_3	F	Cl	Br

SCHEME 1

due to ν(C—O) and O—H deformation were characteristic of carboxyl function (Table III). Lévai and Bögnar, while establishing the structures of benzoxazepines and benzothiazepines, have identified ν(C=N) absorption at 1610–1599 cm^{-1} as characteristic[27] occurring in cyclized products formed from the intermediate having ketone carbonyl and amino groups. The νC=N) in the region 1610–1596 cm^{-1} and ν(C—F)[28,29] absorption in the range 1020–1005 cm^{-1} correspond to our observations (Table II). In the PMR spectra, absorptions at δ 2.77–2.88 (H_A, dd, J_{AB} = 16 Hz, J_{AX} = 9 Hz, C-3 H_A), 3.26–3.38 (H_B, dd, J_{AB} = 16 Hz, J_{BX} = 8 Hz, C-3 H_B), and 3.84–3.95 (H_X, dd, J_{AX} = 9 Hz, J_{BX} = 8 Hz, C-2 H_X) were indicative of methylene protons (H_A, H_B at C-3) and a proton H_X at C-2, the three protons being in an ABX pattern.[1] In addition methyl, methoxyl and ethoxyl protons[1,17,30] were distinguished in **4c**, **4b** and **4a** respectively (Table III).

In the mass spectra of **4b**, the appearance of molecular ion peaks, m/z, $[M]^+$ and $[M + 2]^+$ at 331 and 333 and in **4f** at 379 and 381, correspond to the molecular weight of the products. The absorption peaks in IR and ^1H NMR spectra of the products, **4b–f** have been characterized (Table II and Table III).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken in KBr pellets on a Perkin-Elmer Infracord 881 Spectrophotometer, PMR spectra in $CDCl_3$ on a Jeol FT NMR 90 MHz spectrometer using TMS as internal standard, and mass spectra on a Varian Match-7 instrument at 70 eV. Purity of compounds was tested by TLC on Silica gel 'G' coated plates using toluene:ethyl acetate (1:1) as irrigant.

β-(p-Fluorobenzoyl)acrylic Acid (2)

Fluorobenzene was prepared in the laboratory by the diazotization of aniline followed by the decomposition of the diazonium fluoroborate salt.

A mixture of freshly distilled fluorobenzene (0.2 mol, 19.2 ml), powdered maleic anhydride (0.21 mol, 20.5 g) and dry CS_2 (300 ml) was kept below 5°C. To this was added anhydrous aluminium chloride

TABLE II

Characteristic IR absorption bands of 8-substituted-2-carboxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepines (**4b–f**)

Compound no.	X	IR absorption (cm^{-1}) —COOH absorptions ν(C=O)	ν(O—H)	δ(O—H)	ν(C=N)	ν(C—F)	Saturated ν(C—H)	δ(C—H)	Aromatic ν(C—H)	δ(C—H)
4b	OCH_3	1688s 1319w	3310b 3190	1238w	1608s	1019s	2974w	1434w	3048w	825w
4c	CH_3	1680s 1384w	3325b 3184	1239w	1596s	1014s	2962w	1444w	3056w	822w
4d	F	1692s 1357w	3336b 3193	1260w	1600s	1012s	2977w	1438w	3076w	865w
4e	Cl	1690 1392w	3330b 3174	1270w	1602s	1008m	2956w	1460w	3050w	859w
4f	Br	1688s 1395w	3314b 3168	1266w	1600s	1015s	2970w	1450w	3075w	846w

TABLE III

^{1}H NMR spectral data of 2-carboxy-2,3-dihydro-4-(4-fluorophenyl)-8-substituted-1,5-benzothiazepines (**4b–f**)

Compound no.	X	*J* in Hz, δ in ppm					
				C-3-H			
		COO<u>H</u>	C-2-H_x	H_A	H_B	C-8-X	Ar—H
4b	OCH_3	7.41	3.88 (J_{AX} = 9, J_{BX} = 8)	2.82 (J_{AB} = 16, J_{AX} = 9)	3.38 (J_{AB} = 16, J_{BX} = 8)	3.55 (s, 3 H)	6.16–7.54 (m, 7 H)
4c	CH_3	7.38	3.95 (J_{AX} = 9, J_{BX} = 8)	2.88 (J_{AB} = 16, J_{AX} = 9)	3.26 (J_{AB} = 16, J_{BX} = 8)	2.02 (s, 3 H)	6.21–7.58 (m, 7 H)
4d	F	7.34	3.84 (J_{AX} = 9, J_{BX} = 8)	2.78 (J_{AB} = 16, J_{AX} = 9)	3.37 (J_{AB} = 16, J_{BX} = 8)	—	6.08–7.60 (m, 7 H)
4e	Cl	7.86	3.89 (J_{AX} = 8, J_{BX} = 8)	2.80 (J_{AB} = 16, J_{AX} = 9)	3.29 (J_{AB} = 16, J_{BX} = 8)	—	6.12–7.56 (m, 7 H)
4f	Br	7.34	3.85 (J_{AX} = 8, J_{BX} = 8)	2.77 (J_{AB} = 16, J_{AX} = 9)	3.38 (J_{AB} = 16, J_{BX} = 8)	—	6.14–7.51 (m, 7 H)

(56.0 g, 0.42 mol) in small portions with stirring. The reaction mixture on workup afforded yellow crystals of β-(*p*-fluorobenzoyl)acrylic acid (mp 135°C, reported[31] 132°C–138°C; yield, 21 g 55%).

Six 5-substituted-2-aminobenzenethiols were prepared by literature[15] methods from *p*-substituted anilines by using ammonium thiocyanate or copper thiocyanate to give 6-substituted 2-aminobenzothiazoles, which, on hydrolysis with KOH and subsequent acidification following the literature[15] method, gave 5-substituted-2-aminobenzenethiols (**1a–f**).

2-Carboxy-8-ethoxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepine (**4a**)

2-Amino-5-ethoxybenzenethiol (0.001 mol, 0.16 g) and β-(*p*-fluorobenzoyl)acrylic acid (0.001 mol, 0.194 g) were refluxed with dry ethanol saturated with hydrogen chloride gas for 3 hrs whereupon the color of the reaction mixture changed from light green to black. The reaction mixture was cooled and neutralized with ammonium hydroxide in the cold. The product, obtained on concentration of benzene extract, was further crystallized from benzene and pet ether (60–80°C) to give yellow flakes of **4a**; yield, 0.16 g (46%); mp 204°C; TLC, R_f 0.77; Found: N, 4.16, $C_{18}H_{16}NSO_3F$ requires N, 4.05%. IR: 3000–2600 cm^{-1} ν(OH), 1690 ν(C=O), 1380, 1238, 1290, 920, 1600 ν(C=N), 1005, 1160 ν(C—F). PMR: δ 2.82 (H_A, dd, J_{AB} = 16 Hz, J_{AX} = 9 Hz), 3.30 (H_B, dd, J_{AB} = 16 Hz, J_{BX} = 8 Hz), 3.85 (H_X, dd, J_{AX} = 9 Hz), [1.27 (3H, t, *J* = 7 Hz), 3.7 (2H, q, *J* = 8 Hz), C-8-OC_2H_5], 7.45 (COOH), 6.10–7.38 (7H, ArH). MS: Calcd.: 345; found: m/z 345 $[M]^+$, 347 $[M + 2]^+$.

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