Synthesis of 1-Trifluoroacetyl-3-dialkylamino-methyl-5-monosubstituted Benzimidazoline-2-thiones using Trifluoroacetic Acid as an Acylating Agent

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1-Trifluoroacetyl-3-dialkylaminomethyl-5-monosubstituted benzimidazoline-2-thiones have been synthesized from *p*-substituted anilines which were acetylated with trifluoroacetic acid. The trifluoroacetanilides were nitrated, reduced and cyclised with carbon disulphide in the presence of alcoholic potassium hydroxide and finally treated with formaldehyde and suitable secondary amines to afford the Mannich bases. The compounds were characterised by their analytical and spectral (ir, pmr, ^{19}F and mass) data. The synthesized compounds have been screened for anti-inflammatory and analgesic activity and found to be active.

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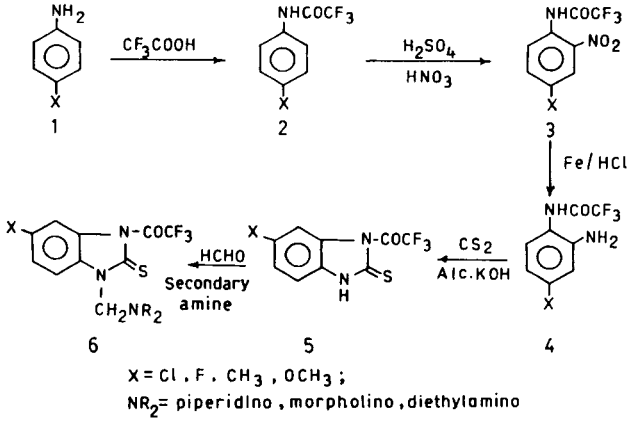
Benzimidazoles display various biological activities *viz.* anti-inflammatory [1-5], antibacterial [6], antiviral [7] and antihelmintic [8]. As a part of our comprehensive programme to synthesise novel fluorine-containing bioactive heterocycles and trifluoromethyl benzimidazoles already found to show promising activity [9], the synthesis of a series of 1-trifluoroacetyl-3-dialkylaminomethyl-5-monosubstituted benzimidazoline-2-thiones, was undertaken. It was hoped that incorporation of the trifluoroacetyl group, would lead to enhanced anti-inflammatory and analgesic activities and the group was introduced using trifluoroacetic acid in dry ether as the acylating agent. A literature survey indicates the use of trifluoroacetic anhydride [10] or a mixture of acid and anhydride [11,12] for this purpose but the acid alone in dry ether has been used for the first time by us.

The title compounds have been synthesized from *p*-substituted anilines **1** which were first acylated with trifluoroacetic acid. The trifluoroacetanilides **2** were nitrated with a mixture of concentrated nitric and sulphuric acids at 0°, the nitro group was then reduced to the amino group using iron and hydrochloric acid. The 2-amino-4-substituted trifluoroacetanilides **4**, so obtained, were cyclised with carbon disulphide in the presence of alcoholic potassium hydroxide to give 1-trifluoroacetyl-5-monosubstituted benzimidazoline-2-thiones **5** which were finally treated with formaldehyde and a suitable secondary amine to afford the title compounds, 1-trifluoroacetyl-3-dialkylaminomethyl-5-monosubstituted benzimidazoline-2-thiones **6** (Scheme 1).

Scheme 1



The formation of these compounds was confirmed by ir, ^1H nmr, ^{19}F nmr, mass spectral data and elemental analyses.

The formation of **2** was confirmed by their ir spectra (bands at 1680-1660 cm^{-1} due to the $>C=O$ group) and ^{19}F nmr spectra which show singlets in the region δ-138 to δ-141 ppm.

The formation of compounds **4a-d** was confirmed by the appearance of a broad band at 3100-3300 cm^{-1} in the ir spectra and signals at δ 9-8.7 ppm and δ 5-4.9 ppm in the ^1H nmr spectra due to $>NH$ and $-NH_2$ groups.

The cyclization of **4a-d** to give **5a-d** involves carbon disulphide and is much more rapid than the carbonyl of the trifluoroacetyl group and this was confirmed by the ir spectra in which absorption at 1200-1050 cm^{-1} due to $>C=S$ stretching appears with the disappearance of the absorption bands due to $-NH_2$ whilst those at 3300 cm^{-1} due to $>NH$ and at 1680-1660 cm^{-1} due to $>C=O$ remains unchanged. Signals at δ 8.7-8.4 ppm due to $>NH$ were also observed in the ^1H nmr spectra. Further support was obtained by the mass spectral data as the molecular ion peak M^+ at m/e 280 for **5a** corresponds to the molecular mass.

The formation of Mannich bases **6a-f** was indicated by the disappearance of the absorption band due to $>NH$ at 3300 cm^{-1} in the ir spectra. The ^1H nmr spectra showed peaks due to dialkylaminomethyl groups, *e.g.* in **6a** a singlet at δ 3.5-3 ppm due to $>N-CH_2-$, a multiplet at 2.6-2.3 ppm due to $-N-(CH_2)-CH_2-$ and another multiplet at δ 1.5-1 ppm due to $-CH_2CH_2CH_2-$ are observed. Further

Table 1

Analytical Data of 2-Nitro-4-substituted Trifluoroacetanilides **3** and 2-Amino-4-substituted Trifluoroacetanilides **4**

Compound No.	X	Yield %	Mp °C	Molecular Formula	Analysis % C (Calcd.)	H (Calcd.)	N (Calcd.)	C (Found)	H (Found)	N (Found)
3a	Cl	62	185	$C_8H_4ClF_3N_2O_3$	35.82	1.49	10.44	35.89	1.51	10.47
3b	F	64	260	$C_8H_4F_4N_2O_3$	38.09	1.58	11.11	38.12	1.61	11.23
3c	CH_3	61	101	$C_9H_7F_3N_2O_3$	43.54	2.82	11.29	43.50	2.86	11.12
3d	OCH_3	63	123	$C_9H_7F_3N_2O_4$	40.90	2.65	10.60	40.99	2.69	10.55
4a	Cl	80	70	$C_8H_6ClF_3N_2O$	40.33	2.52	11.76	40.37	2.56	11.71
4b	F	62	65	$C_8H_6F_4N_2O$	43.24	2.70	12.61	43.29	2.75	12.69
4c	CH_3	71	61	$C_9H_9F_3N_2O$	49.54	4.12	12.84	49.51	4.16	13.00
4d	OCH_3	68	67	$C_9H_9F_3N_2O_2$	46.15	3.84	11.96	46.18	3.90	12.01

Table 2a

Analytical Data of 1-Trifluoroacetyl-5-monosubstituted Benzimidazoline-2-thiones **5** and 1-Trifluoroacetyl-3-dialkylaminomethyl-5-monosubstituted Benzimidazoline-2-thiones **6**

Compound No.	X	NR_2	Yield %	Mp °C	Molecular Formula	Analysis % C (Calcd.)	H (Calcd.)	N (Calcd.)	S (Calcd.)	C (Found)	H (Found)	N (Found)	S (Found)
5a	Cl	–	65	165	$C_9H_4F_3ClN_2OS$	38.57	1.42	10.00	11.42	38.60	1.47	9.98	11.40
5b	F	–	66	173	$C_9H_4F_4N_2OS$	40.90	1.51	10.60	12.12	40.99	1.58	10.66	12.10
5c	CH_3	–	65	160	$C_{10}H_7F_3N_2OS$	46.15	2.69	10.77	12.30	46.05	2.71	10.80	12.28
5d	OCH_3	–	63	182	$C_{10}H_7F_3N_2O_2S$	43.47	2.53	10.14	11.59	43.49	2.59	10.00	11.52
6a	Cl	piperidino	61	110	$C_{15}H_{15}F_3ClN_3OS$	47.74	3.97	11.14	8.48	47.69	4.00	11.18	8.40
6b	Cl	morpholino	60	113	$C_{14}H_{13}F_3ClN_3O_2S$	44.32	3.43	11.08	8.44	44.38	3.50	11.12	8.50
6c	Cl	diethylamino	62	132	$C_{14}H_{15}F_3ClN_3OS$	46.02	4.10	11.50	8.76	46.12	4.19	11.58	8.71
6d	F	piperidino	64	130	$C_{15}H_{15}F_4N_3OS$	49.86	4.15	11.63	8.86	49.81	4.20	11.59	8.90
6e	CH_3	piperidino	64	125	$C_{16}H_{18}F_3N_3OS$	53.78	5.04	11.76	8.96	53.80	5.12	11.81	9.10
6f	OCH_3	piperidino	59	127	$C_{16}H_{18}F_3N_3O_2S$	51.47	4.82	11.26	8.57	51.44	4.79	11.30	8.60

the structures have been confirmed on the basis of ^{19}F nmr also. In compounds **6a,b,c,e,f** having X = Cl, Me, OMe a singlet at δ −140 ppm due to $>COCF_3$ group and when X = F, **6d**, singlets at δ −70 ppm and at δ −116 ppm due to $>COCF_3$ and Ar-F respectively are observed.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on Perkin Elmer (Model 557) in potassium bromide. The ^1H and ^{19}F nmr spectra were recorded on a Jeol (Model FX-90Q) using DMSO-d_6 and TFA as solvents; TMS as internal standard for ^1H nmr and perdeuteriobenzene as external standard for ^{19}F nmr. The mass spectra were recorded on Kratos 30 and 50 mass spectrometers. All compounds are homogeneous on tlc in various solvent systems.

p-Substituted Trifluoroacetanilides **2**.

A solution of trifluoroacetic acid (1 mole) in about twice its volume of dry ether was added at 0° to the solution of amine (1 mole) in a minimum volume of the same solvent. After 1 hour, the volatile matter was removed by distillation under diminished pressure. To the remaining residue ice water was added and the precipitated amide filtered and recrystallised from alcohol.

2-Nitro-4-substituted Trifluoroacetanilides **3**.

p-Substituted trifluoroacetanilide (0.12 mole) was placed in a round bottomed flask and dissolved in a minimum quantity of acetic acid by stirring until a clear solution was obtained. This solution was placed in a freezing mixture bath (ice + salt) to maintain the temperature in the vicinity of 0-5° [13]. Then nitrating mixture [concentrated sulfuric acid (13 ml) and concentrated nitric acid (6 ml)] was added dropwise with constant stirring of the solution. After complete addition, the flask was removed from the freezing bath and allowed to stand at room temperature for half an hour. The contents were then poured into cold water (200 ml) and the precipitate filtered off, washed with cold water and finally recrystallised from ethanol. The physical and analytical properties are listed in Table 1.

2-Amino-4-substituted Trifluoroacetanilides **4**.

The reduction of the nitro group was carried out by the usual method [14,15]. A flask containing iron powder (0.025 mole) and a little water was heated and the 2-nitro-4-substituted trifluoroacetanilide (0.01 mole) was added to this followed by addition of 2 ml of hydrochloric acid with vigorous stirring. The temperature was maintained at 70 ±2° throughout, and stirring was continued for 1 hour. Sodium hydroxide solution (1%) was then added to decompose any amine hydrochloride formed. The reaction mixture was filtered while still hot and the lower layer

Table 2b

Spectral Data of Compounds **5** and **6**

Compound No.	X	NR_2	IR (cm^{-1})	^1H NMR (δ ppm)	MS M^+ (m/e)
5a	Cl	–	3350 (NH), 1680 (C=O), 1140 (C=S)	8.7-8.4 (NH) 7.0-6.7 (Ar-H)	280
5b	F	–	3300 (NH), 1685 (C=O), 1160 (C=S)	8.6-8.4 (NH), 7.0-6.2 (Ar-H)	264
5c	CH_3	–	3340 (NH), 1670 (C=O), 1140 (C=S)	8.6-8.4 (NH), 7.2-6.8 (Ar-H), 2.3 (CH_3)	–
5d	OCH_3	–	3320 (NH), 1680 (C=O), 1200 (C=S)	8.7-8.5 (NH), 7.0-6.0 (Ar-H), 3.8 (OCH_3)	276
6a	Cl	piperidino	1690 (C=O), 1140 (C=S)	7.2-6.7 (Ar-H), 3.5-3.0 (N-CH_2-N), 2.6-2.3 (-N-(CH_2-)-CH_2-), 1.5-1.0 (-$CH_2CH_2CH_2$-)	377
6b	Cl	morpholino	1680 (C=O), 1170 (C=S)	–	379
6c	Cl	diethylamino	1680 (C=O), 1090 (C=S)	7.5-6.5 (Ar-H), 4.0 (N-CH_2-N), 3.8-3.5 (N-CH_2-CH_3), 2.8-2.6 (NCH_2-CH_3)	–
6d	F	piperidino	1670 (C=O), 1200 (C=S)	7.0-6.1 (Ar-H), 3.5-3.4 (N-CH_2-N), 2.7-2.4 (-N-(CH_2-)-CH_2-), 2.0-1.8 (-$CH_2CH_2CH_2$-)	361
6e	CH_3	piperidino	1675 (C=O), 1190 (C=S)	7.0-6.2 (Ar-H), 3.7-3.5 (N-CH_2-N), 2.9-2.7 (-N-(CH_2-)-CH_2-), 2.3-2.0 (-$CH_2CH_2CH_2$-), 1.8 (CH_3)	357
6f	OCH_3	piperidino	1660 (C=O), 1200 (C=S)	7.0-6.5 (Ar-H), 3.6-3.4 (N-CH_2-N), 3.2 (OCH_3), 2.9-2.7 (-N-(CH_2-)-CH_2-), 2.4-2.0 (-$CH_2CH_2CH_2$-)	373

separated. The residue was extracted with hot benzene and this extract added to the previously separated solution. This was then dried over anhydrous magnesium sulfate, filtered, and solvent removed under vacuum. This residue was recrystallised from benzene. The physical properties of the compounds are listed in Table 1.

1-Trifluoroacetyl-5-monosubstituted Benzimidazoline-2-thiones **5**.

A mixture of 2-amino-4-substituted trifluoroacetanilide (0.03 mole), potassium hydroxide (1.9 gm) and carbon disulphide (0.03 mole) in 95% ethanol (30 ml) and water (5 ml) was heated under reflux for 3 hours [16]. Norit was added to it cautiously and after refluxing for 10 minutes it was filtered hot. The hot filtrate was diluted with 30 ml of warm water and a solution of 2.4 ml of acetic acid in 5 ml of water was added with stirring. The product separated as white lumps. The mixture was refrigerated overnight and filtered. The precipitate was recrystallised from methanol-water mixture. The analytical and spectral data of compounds prepared are listed in Tables 2a and 2b repectively.

1-Trifluoroacetyl-3-dialkylaminomethyl-5-monosubstituted Benzimidazoline-2-thiones **6**.

1-Trifluoroacetyl-5-monosubstituted benzimidazoline-2-thione (0.01 mole), dissolved in the minimum amount of methanol, was treated with 2 ml of formalin (40%) and an appropriate secondary amine (0.01 mole) with brisk stirring. The mixture was further stirred for 15 minutes at room temperature and left overnight. The solid which separated was filtered off and recrystallised from methanol. The analytical and spectral data of compounds prepared are listed in Tables 2a and 2b respectively.

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