REGIOSELECTIVE ONE-POT SYNTHESIS OF 5-CHLORO-3-METHYL-8-TRIFLUOROMETHYL-4H-1, 4-BENZOTHIAZINES

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Abstract
5-Chloro-3-methyl-8-trifluoromethyl-4H-1, 4-benzothiazines have been synthesized by an efficient synthetic method in a single step involving heterocyclization of 2-amino-3-chloro-6-trifluoromethylbenzenethiol with □-ketoesters or □-diketones. 2-Amino-3-chloro-6-trifluoromethylbenzenethiol was prepared by hydrolytic cleavage of 2-amino-4-chloro-7-trifluoromethylbenzothiazole which in turn was prepared by brominative cyclization of 2-chloro-5-trifluoromethylphenylthiourea. The phenylthiourea was prepared by the reaction of 2-chloro-5-trifluoromethylaniline with ammonium thiocyantate. The structures of the synthesized 4H-1, 4-benzothiazines have been characterized by their elemental analyses and spectral characteristics.

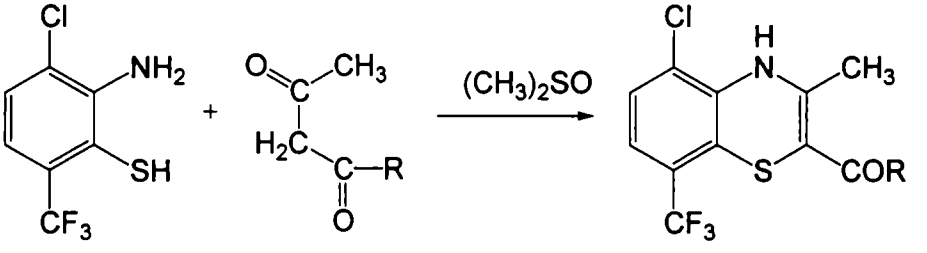
Keywords
5-chloro-3-methyl-8-trifluoromethyl-4H-1,4-benzothiazines;2-aminobenzothiazole; 2-aminobezenethiol

Introduction:
The synthesis of heterocyclic systems is of continuing interest in the field of organic chemistry because most of the compounds with biological activity are derived from the heterocyclic structures.(1-3) 1,4-Benzothiazines constitute an important class of biologically active heterocycles and have been reported as calcium channel blockers(4), phosphodiestrase inhibitors(5), 5-HT_3 antagonists (6) anticataract agents(7) , dopamine D_4 (8) , Na^+/H^+ Exchange inhibitors (9) coagulation factor Xa inhibitors(10), matrix metalloproteinase inhibitors(11), etc.1,4-Benzothiazines have also been reported to be new antiallergic(12) and antirhumatic(13) compounds. The nature of the substituent present around the scaffold substantially influences the target specificity of the compounds. Triflurometlhyl group due to its high electronegativity and unique stereoelectronic properties plays an important role in drug receptor interactions. The presence of trifluoromethyl group not only influences the physiological activity with increasing lipophilicity of the molecules but also improves the transport characterstics in vivo and avoids undesirable metabolic transformations. The introduction of trifluoromethyl group in bioactive molecules especially in the position responsible for effective drug-receptor interactions become very important direction in pharmaceutical research. The Introduction of CF_3 group in the molecule at the desired position is not always possible with direct triflurometlhylation and, therefore, easily available reactants with trifluoromethyl group are considered the best substitutes for the synthesis of heterocycles with CF_3 group. As a part of our continuing research programme of synthesizing novel heterocycles(14-19) of therapeutic interest, we have synthesized structurally flexible 4H-1,4-benzothiazines with trifluoromethyl group keeping in view the wide spectrum of biological activities associated with 1,4-benzothiazine heterosystem(20-24) and trifluoromethyl

group(25). The structural features present in the synthesized 4H-1,4-benzothiazines will of course make them to interact effectively as pharmacophores with the receptor sites of biological system by assuming the required conformation due to their structural flexibility.

Results and discussion:

2-Amino-3-chloro-6-trifluoromethylbenzenethiol was prepared by the heterolytic cleavage of 2-amino-4-chloro-7-trifluoromethylbenzothiazole which was prepared by brominative cyclization(26)of the corresponding phenyl thiourea obtained by thiocyanogenation of 2-chloro-5-trifluromethylaniline . 2-Aminobenzothiazoles have also been prepared recently by brominative cyclization of substituted phenylthioureas by using organic ammonium tribromides (OATBs) such as benzyltrimethylammonium tribromide ($PhCH_2NMe_3Br_3$) as an electrophilic bromine source (27). 5-Chloro-3-methyl-8-trifluoromethyl-4H-1,4-benzothiazines have been synthesized by heterocyclization of 2-amino-3-chloro-6-trifluoromethyl benzenethiol with □-diketone/□-ketoester in the presence of dimethyl sulphoxide involving oxidative cyclization (Scheme-1).

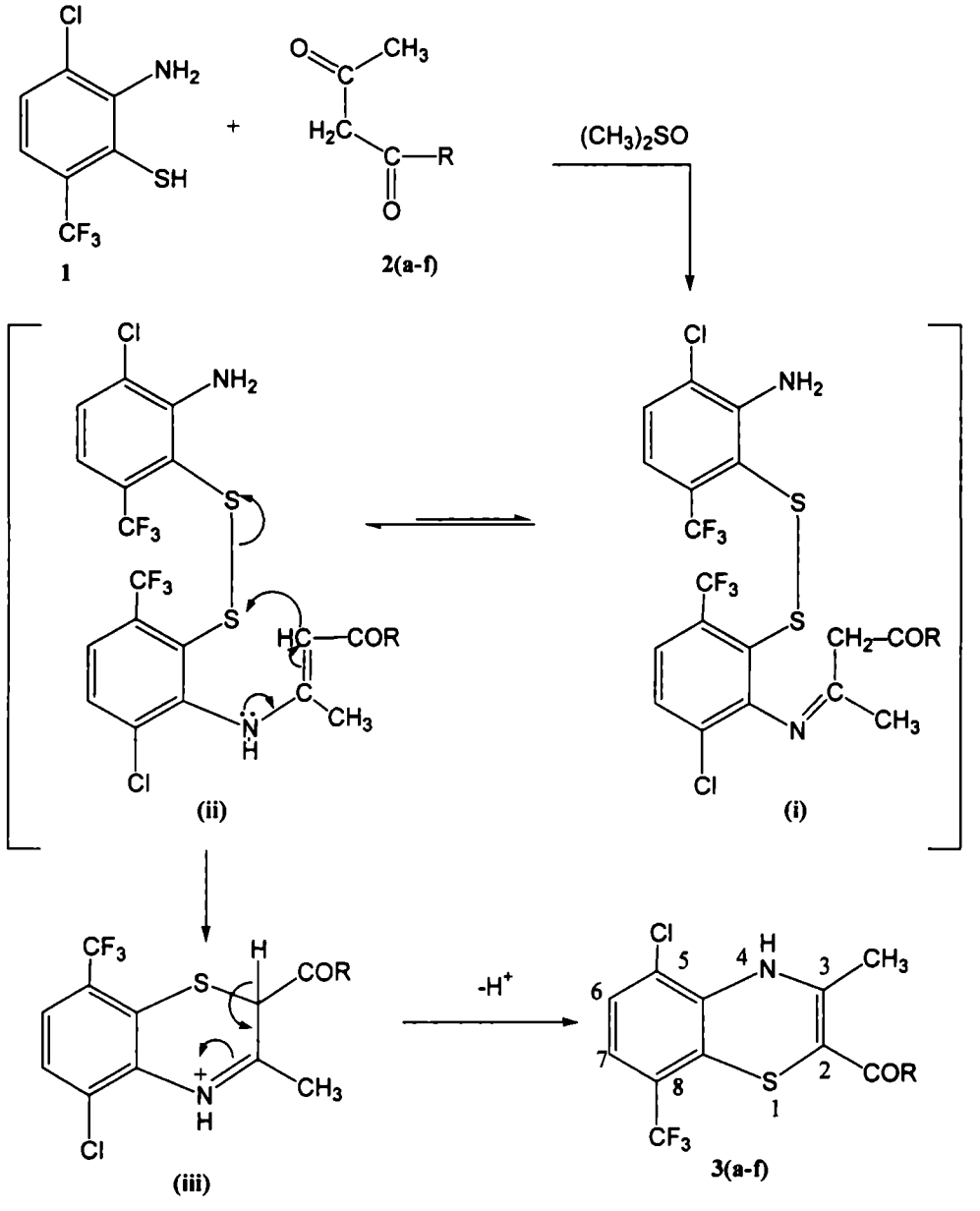


1 2(a-f) 3(a-f)

R: a = $-C_6H_5$; b = $-C_6H_4OCH_3$ (p); c= $-C_6H_4CH_3$ (m);
d = $-C_6H_3(CH_3)_2$ (2, 3); e = $-C_6H_4CH_3$ (o); f = $-OC_2H_5$

[Scheme-1]

The reaction is considered to proceed via an enaminoketone intermediate (ii) which is simultaneously cyclized to 4H-1,4-benzothiazine with the cleavage of S-S bond involving intramolecular nucleophilic attack.Thus the reaction is regioselective and occurs through the predominately keto form of □-diketone or □-ketoester (scheme-2)



Scheme -2

The structures of all the synthesized 4*H*-1,4-benzothiazines have been elucidated by their elemental analyses and spectral studies. The absence of absorption bands corresponding to -NH_2 and -SH groups and the appearance of the absorption bands corresponding to the N-H and C=O stretching vibrations in the regions, 3370-3340 cm^{-1} and 1690-1670 cm^{-1} respectively in IR spectra revealed that heterocyclization has occurred under the reaction conditions and provided 5-chloro-3-methyl-8-trifluoromethyl-4*H*-1,4-benzothiazines **(3a-f)** involving the proposed reaction mechanism (scheme-2).

The ^{1}HNMR spectra of all the synthesized 4H-1,4-benzothiazines revealed two distinct doublets centered at δ 6.95-7.02 and at δ 6.75-6.80 due to C_6-H and C_7-H respectively. The broad singlet in the region δ 8.79-8.93 indicated the presence of N-

H proton. The presence of multiplets (not in all cases) in the aromatic region was assigned to the substituted or unsubstituted benzoyl group at position-2. ^{13}C NMR spectra of all the synthesized 4H-1,4-benzothiazines; C_{4a} (δ 147.0-148.2), C_{8a} (δ 117.8-118.3) and C=O (δ 169.2-197.4), are in accordance with their structures and hence confirmed the carbon skeleton of the synthesized compounds. In the mass spectrum of representative 4H-1,4-benzothiazine **3c**, the molecular ion peak is in accordance with the molecular weight and the fragmentation pattern is according to the molecular structure. The peak at 119 ($CH_3CH_4CO^+$) has also been taken as the evidence that the reaction occurs regioselectively through keto form of β-diketone or β-ketoester with the insitu formation of disulphide.

Conclusion:

The present method enables the synthesis of structurally flexible biologically interesting heterocycles in a single step and efficiently incorporates structural diversity simply by varying the substituents or by slight structural modification in the components involved in the reaction.

Experimental:

Melting points were determined on an electric melting point apparatus and are uncorrected. The purity of synthesized compounds was checked by TLC. The IR spectra were recorded on a SHIMADZU-8400S FTIR spectophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on Jeol model Al-300 [300 MHz] in $CDCl_3$ using TMS as an internal standard. The chemical shifts are expressed as δ ppm. Mass spectrum was scanned on JEOL- SX-102 /DA-6000 mass spectrometer [FAB MS].

Synthesis of 5-chloro-3-methyl-8-trifluoromethyl-4H-1,4-benzothiazines(3a-f)

2-Amino-3-chloro-6-trifluoromethylbenzenethiol (0.01 mole) was added to the stirred suspension of □-diketone/□-ketoester (0.01 mol) in dimethyl sulphoxide and the resulting mixture was refluxed for 25 minutes. The refluxed solution was cooled down to room temperature. The solid separated out was washed well with petroleum ether. The product was recrystallized from methanol.

2-benzoyl-5-chloro-3-methyl-8-trifluoromethyl-4H-1,4-benzothiazine (3a)

Yield: 56% m.p. 180°C. IR (KBr): 1680 cm^{-1} (C=O), 3340 cm^{-1} (N-H). ^1H NMR (300 MHz, $CDCl_3$, δ ppm), 6.98 (d, 1H, C_6-H), 6.75 (d, 1H,C_7-H), 7.50-7.95 (m, 5H, Ar-H), 8.89 (s, 1H, N-H), 2.38 (s, 3H, CH_3). ^{13}C NMR [$CDCl_3$, δ ppm]: 114.8 (C-2), 139.5(C-3), 147.6($C-4_a$), 125.2(C-5), 127.4(C-6), 120.4(C-7), 131.8(C-8), 118.3($C-8_a$), 16.8(CH_3), 189.0 (C=O), 137.70, (C-1′), 130.8(C-2′), 130.29(C-3′), 135.5(C-4′). Anal. calcd for $C_{17}H_{11}ClF_3NOS$: C, 55.22, H, 3.00; N, 3.79%. Found C, 55.01; H, 3.52;N, 3.88%.

5-chloro-3-methyl-2[4′-methoxybenzoyl]-8-trifluoromethyl-4H-1,4-benzothiazine (3b) Yield 45%; m.p. 210°C. IR (KBr): 1685 cm^{-1} (C=O), 3340 cm^{-1} (NH). ^1H NMR (300 MHz, $CDCl_3$, δ ppm) : 6.95 (d, 1H, C_6-H), 6.72 (d, 1H, C_7-H), 7.85 (d, 1H, C-2 and C-6′), 7.16 (d, 1H, C-3′ and C-5′), 8.98 (br s, 1H, N-H), 2.45 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR [$CDCl_3$, δ ppm) : 114.9(C-2), 139.6(C-3), 147.3($C-4_a$), 125.5(C-5), 127.3(C-6), 131.6(C-6), 16.8(CH_3), 189.2 (C=O), 130.0(C-1′), 131.4(C-2′), 115.4(C-3′), 168.2(C-4′), 56.2(OCH_3). Anal. calcd for $C_{18}H_{13}ClF_3NO_2S$: C, 54.07; H, 3.28; N, 3.50%. Found C, 54.12; H, 3.49 N, 3.82%.

5-chloro-2-(3′-methylbenzoyl)-3-methyl-8-trifluoromethyl-4H-1,4-benzothiazine (3c) Yield: 65%; m.p. 190°C. IR (KBr): 1680 cm^{-1} (C=O), 3340 cm^{-1} (N-H). ^1H NMR (300 MHz, $CDCl_3$, δ ppm); 6.98 (d, 1H, C_6-H), 6.75 (d, 1H, C_7-H), 7.45-7.80 (m, 4H, Ar-H), 8.95 (s, 1H, N-H), 2.37 (s, 3H, C_3-CH_3), 1.79 (s, 3H, C-3′). ^{13}C NMR ($CDCl_3$, δ ppm); 114.6(C-2), 139.3(C-3), 147.0 (C-4_a), 125.2 (C-5), 126.6 (C-6), 120.6 (C-7), 132.20 (C-8), 118.5 (C-8_a), 187.0 (C=O), 137.20 (C-1′), 130.6 (C-2′), 137.5(C-3′), 135.2 (C-4′), 129.2 (C-5′), 127.6 (C-6′), 20.6 (CH_3); MS (m/z,%):382 (M^+-H,100), 263 (5), 238 (3) ,221 (80), 195 (60),161 (5),119 (60), 91 (10),69 (5); Anal. calcd. for $C_{18}H_{13}ClF_3NOS$: C, 56.33; H, 3.41, N; 3.65%. Found: C, 56.23; H, 3.52;N, 3.20%.

5-chloro-2[2′,3′-dimethylbenzoyl]-3-methyl-8-trifluoromethyl-4H-1,4- benzothiazine (3d) Yield: 75%, m.p. 205°C. IR (KBr): 1680 cm^{-1} (C=O), 3340 cm^{-1} (N-H). ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 6.98 (d, 1H, C_6-H), 6.78 (d, 1H,C_7-H), 8.93 (s, 1H, N-H), 2.35 (s, 3H, C_3-CH_3), 1.79 (s, 6H, C_2′-CH_3 and C_3′-CH_3), 7.24 (dd, 1H, C_4′-H); 7.16 (dd, 1H, C_5′-H), 7.50 (dd, 1H, C_6′-H). ^{13}C NMR ($CDCl_3$, δ ppm) ; 114.2 (C-2), 139.1 (C-3), 149.2 (C-4_a), 125.3 (C-5), 127.6 (C-6), 119.2 (C-7), 131.8 (C-8), 118.2 (C-8_a), 113.6 (CF_3), 189.6 (C=O), 19.4 (C_3-CH_3), 16.6(Ar-CH_3), 138.8(C-1′), 138.2(C-2′), 138.4(C-3′), 135.2(C-4′), 128.2 (C-5′), 128.6 (C-6′). Anal. Calcd. for $C_{19}H_{15}ClF_3NOS$; C,57.36; H, 3.80, N, 3.52%. Found: C, 57.42; H, 3.99, N, 3.49%.

5-chloro-3-methyl-2-[2′-methylbenzoyl]-8-trifluoromethyl-4H-1,4-benzothiazine (3e) Yield: 36%; m.p.194°C. IR (KBr); 1670 cm^{-1} (C=O), 3360 cm^{-1} (N-H). ^1H NMR [300 MHz, $CDCl_3$, δ ppm]: 6.98 (d, 1H, C_6-H), 6.78 (d, 1H, C_7-H), 8.92 (s, 1H, N-H), 2.38 (s, 3H, C_3-CH_3), 7.25-7.45 (m, 4H, Ar-H), 1.86 (s, 3H, C_2-CH_3). ^{13}C NMR [$CDCl_3$, δ ppm]: 114.2(C-2), 139.2(C-3), 147.1 (C-4_a), 125.2(C-5), 126.4(C-6), 121.2(C-7), 132.1(C-8), 118.2(C-8_a), 187.2 (C=O), 137.2(C-1′), 138.1(C-2′), 130.2(C-3′), 135.4(C-4′), 126.6(C-5′), 129.7(C-6′), Anal. calcd for. $C_{18}H_{13}ClF_3NO$: C, 56.33; H, 3.41; N, 3.65%. Found: C, 56.01; H, 3.22; N, 3.82%.

Ethyl- 5-chloro-3-methyl-8-trifluoromethyl-4H-1,4-benzothiazine-2 carboxylate (3f) Yield: 53%; m.p. 216°C. IR (KBr) : 1685 cm^{-1} (C=O), 3360 cm^{-1} (N-H); ^1H NMR (300 MHz, $CDCl_3$, δ ppm); 6.95 (d, 1H, C_6-H), 6.78 (d, 1H, C_7-H), 8.87 (s, 1H, N-H), 2.39 (s, 3H, CH_3) 4.95 (q, 2H, OCH_2); 1.30 (t, 3H, -OCH_2-CH_3). ^{13}C NMR [$CDCl_3$, δ ppm] : 108.3(C-2), 138.6(C-3), 148.4 (C-4_a), 124.8(C-5), 126.4(C-6), 118.0(C-7), 130.8(C-8), 117.8(C-8_a), 169.2 (C=O), 59.6(OCH_2), 16.8(CH_3). Anal calcd. for $C_{13}H_{11}ClF_3NO_2S$: C, 46.23; H, 3.28; N, 4.15%. Found: C, 46.99; H, 3.45; N, 4.65%.

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