SYNTHESIS OF 2, 4-DIARYL-2, 3-DIHYDRO-1, 5-BENZOTHIAZEPINES

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Abstract : A new series of functionalized 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines have been synthesized by a convenient single step synthesis involving heterocyclization reaction of 2-aminobenzenethiols with α, β-unsaturated ketones in toluene in the presence of catalytic amount of glacial acetic acid. The synthesized compounds have been characterized by their elemental analyses and spectral characteristics.

Introduction

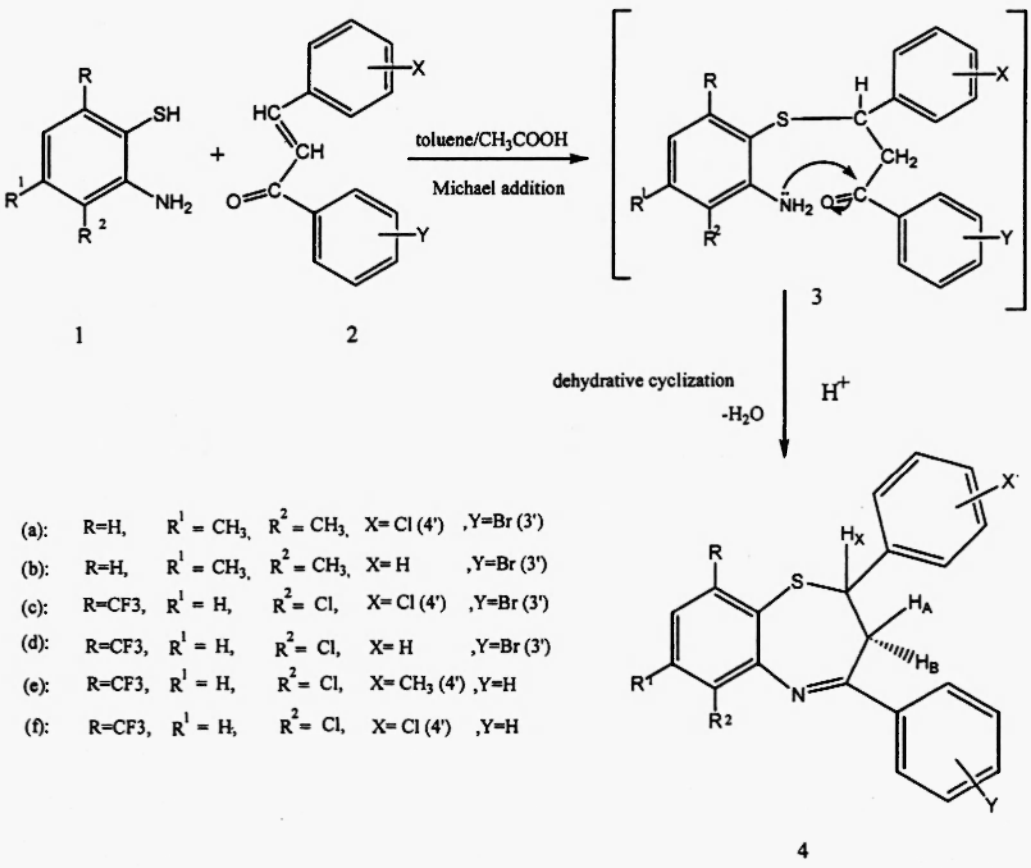
1,5-Benzothiazepines are very important N-and S- heterocycles in drug research and have been shown to exhibit, in addition to unique structural specificity ,well recognized pharmacological properties such as anti-anginal[1] and antihypertensive[2]. Diltiazem, an important cardiovascular drug, also incorporates 2,3-dihydro-1,5-benzothiazepine heterocyclic system. The chalcones; α,β-unsaturated ketones, especially 1,3-diaryl-2-propen-1-ones, required for the synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines have been considered as analogues of potent anticancer agent, combretastatin A4(CA-4)[3,4]. In accordance with CA-4,the chalcones (1,3-diaryl-2-propen-1-ones) bind to colchine site of tubulin and inhibit the formation of mitotic spindle in cancer cells[5]. The tetrazole analogue of CA-4 has been reported to exhibit significant anticancer activity[6]. The structural-activity relationship studies of chalcones have suggested that 1,3-diphenyl substituted propenone structural system is crucial for the significant cytotoxity against tumor cells[7,8]. In order to synthesize nitrogen-sulphr containing pharmacologically interesting heterocycles,especially with anticancer activity, the enone functionality has been converted into heterocyclic system (1,5-thiazepine) by heterocyclization of enone system by its reaction with 2-aminobenzenethols.The nature and arrangement of the substituents on benzene ring fused to 1,5-thiazepine heterosystem as well as the substituents on phenyl rings present on 2-and 4-positions of 1,5-thiazepine heterocyclic system, derived from 1,3-diphenylpropenone functionality will of course, influence the activity of the synthesized 2,3-dihydro-1,5-benzothiazepines.

Results and Discussion

The chalcones (1,3-diaryl-2-propen-1-ones) were prepared by Claisen-Schmidt condensation of benzaldehydes and acetophenones[9].Substituted 2-

aminobenzenethiols were prepared by hydrolytic cleavage of 2-aminobenzothiazoles which were prepared by brominative cyclization of the corresponding thioureas obtained by thiocyanogenation of substituted anilines[10].

2,4-Diaryl-2,3-dihydro-1,5-benzothiazepines were synthesized in quantitative yields in a single step involving the reaction of 2-aminobenzenethiols **1** with 1,3-diaryl-2-propen-1-ones (chalcones) **2** in toluene in the presence of catalytic amount of glacial acetic acid (Scheme-1)



Scheme-1

Under the reaction conditions the reaction is considered to proceed with the nucleophilic attack of thiol group on β-carbon atom of 1,3-diaryl-2-propen-1-one (chalcone) which is followed by dehydrative cyclization involving intramolecular nucleophilic addition of amino group on the carbonyl carbon to provide 2,3-dihydro-1,5-benzothiazepine. Acetic acid catalyzes the ring closure and hence proved to be a convenient catalyst for one-step synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines. 2,3-Dihydro-1,5-benzo-thiazepines have also been synthesized by

different methods including microwave assisted[11,12], but the present method is simplest and convenient to provide 2,3-dihydro-1,5-benzothiazepines in quantitative yields in a single step.

The structures of synthesized compounds have been confirmed by elemental analyses and their spectral characteristics. The absence of absorption bands characteristic of NH_2, SH and C=O groups in IR spectra of the synthesized compounds indicates that the heterocyclization of 2-aminobenzenethiols with 1,3-diarylpropenones (chalcones) have occurred involving Michael type addition of –SH group to the β-carbon of 1,3-diarylpropenone (α,β-unsaturated ketones) with the formation 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines. The presence of characteristic absorption bands in the regions; 1605-1635 cm^{-1} (C=N), 3010-3060 cm^{-1} (C-H of aromatic rings), 645-690 cm^{-1}(C-Br) and 740-775 cm^{-1} (C-Cl) indicates the formation of 2, 4-diaryl-2, 3-dihydro-1, 5-benzothiazepines.

In ^{1}H NMR spectra of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines chemical shifts, coupling constants and multiplicity of protons attached to C-2 and C-3 unequivocally (signals arising due to typical ABX pattern) confirm the structures of all the synthesized compounds. The ^{1}H NMR spectra of the synthesized 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines showed three distinctive double doublets for methylene protons; H_A and H_B, and for methine proton H_X. The first double doublet appeared at δ 3.12-3.15 ppm integrating for one proton with coupling constant values; J_{AB} = 15.3-16.2 H_Z and J_{AX} =11.4H_Z,was assigned to C_3-H_A (axial) proton. The second double doublet which appeared at δ 3.45 -3.50 ppm with coupling constant values; J_{AB} =15.3-16.2 H_Z and J_{BX} =5.8 H_Z was attributed to C_3-H_B (equatorial) proton. The methine proton (C_2-H_X) signal at δ 4.98-5.02 ppm also appeared as a double doublet due to splitting by two vicinal protons H_A and H_B with two coupling constants; J_{AX} =11.4 H_Z and J_{BX} =5.8 H_Z. The aromatic protons appeared as multiplet in the range of δ 7.23-7.78 ppm. The difference in the positions of signals of H_A and H_B with the coupling constant values of J_{AX} and J_{BX} may be due to the difference in the conformations of H_A and H_B (one is axial and other is equatorial).In the ^{13} C NMR spectra of synthesized compounds, the signals observed in the regions δ 38.9-39.6 ppm (C-3), δ 58.6-59.2 ppm (C-2), δ 122.6-139.6 ppm (aromatic carbon atoms), and 166.8-168.2 (C=N) also confirm the formation of 2,4-diphenyl-2,3-dihydro-1,5-benzothiazepines.In the mass spectrum of the compound (4e), the molecular ion peak is in accordance with the molecular mass of the compound.

Experimental

Melting points of the synthesized compounds were determined on an electric melting point apparatus and are uncorrected. IR spectra were recorded in KBr on SHIMADZU 8400S FTIR spectrophotometer. The ^{1}HNMR and ^{13}C NMR spectra were recorded on a model Bruker-DRX-300 NMR spectrometer at 300 MH_Z and 75 MH_Z respectively using $CDCl_3$ as a solvent and TMS as an internal standard. The Mass spectrum of the representative compound was recorded on JEOL-SX-102/DA-6000 mass spectrometer.

Synthesis of 2, 4-diaryl-2, 3-dihydro-1, 5-benzothiazepines 4(a-f)

Substituted 2-aminobenzenethiol [0.01mole] and chalcone [0.01mole] were taken in dry toluene containing glacial acetic acid (1ml) in a 50ml R.B.flask and refluxed for 3-4 hrs.The colour of the reaction mixture changed from yellow to dark yellow. The reaction mixture was cooled and neutralized with 10% NaHCO3 solution. The solid product obtained was washed with petroleum ether and crystallized from methanol.

4-[3'-Bromophenyl]-2-[4'-chlorophenyl]-6,7-dimethyl-2,3-dihydro-1,5-benzothiazepine (4a).

Obtained as yellow crystalline solid in 75% yield, m.p. 215 °C. IR (KBr): 1670 cm^{-1}(C=N).^{1}HNMR (300 MH_Z,$CDCl_3$,δ ppm): δ 7.26-7.58 (m,10H aromatic protons), δ 5.05 (dd.,1H C_2-H); δ3.12 (dd.,1H,C_3-H_A); δ 3.83 (dd.,1H,C_3-H_B); δ 2.42 (s,3H,C_6-CH_3); δ 1.68 (s,3H,C_7-CH_3); ^{13}CNMR (75MH_Z, $CDCl_3$, δ ppm):19.2 (CH_3), 20.08 (CH_3), 39.4 (C-3), 58.9 (C-2), 122.6, 124.7, 125.2, 127.6, 128.8, 129.6, 130.4, 131.3, 132.7, 134.2, 136.6, 140.1, 152.4 (aromatic carbons), 167.8 (C=N). Anal. calcd. for $C_{23}H_{19}NSClBr$: C, 60.53; H, 4.12; N, 3.00 found C, 60.59; H, 4.17; N, 3.07.

4-[3'-Bromophenyll-6-7-dimethyl-2-phenyl-2,3-dihydro-1,5-benzothiazepine (4b)

Obtained as yellow crystalline solid in 69% yield, m.p. 194 °C. IR (KBr): 1620 cm^{-1}(C=N).^{1}HNMR (300 MH_Z,$CDCl_3$,δ ppm): δ 7.25-7.62 (m,14H aromatic protons), δ 5.12 (dd.,1H C_2-H); δ3.13 (dd.,1H,C_3-H_A); δ3.80 (dd.,1H,C_3-H_B); δ 2.40 (s,3H,C_6-CH_3); δ 2.23 (s,3H,C_7-CH_3); ^{13}CNMR (75MH_Z,$CDCl_3$, δ ppm):19.3 (CH_3), 21.2 (CH_3), 39.2 (C-3), 59.2 (C-2), 122.7, 124.7, 125.8, 126.1, 127.3, 128.6, 129.4, 131.2, 132.4, 132.8, 140.3, 151.7 (aromatic carbons),166.9 (C=N). Anal. calcd. for $C_{23}H_{20}NSBr$: C, 65.44; H, 4.62; N, 3.21 found C, 65.66; H, 4.75; N, 3.33.

4-[3'-Bromophenyl]-2-[4'-chlorophenyl]-6-chloro-9-trifluromethyl-2,3-dihydro-1,5-benzothiazepine (4c)

Obtained as yellow crystalline solid in 60% yield,m.p., 210 °C. IR (KBr): 1605 cm^{-1} (C=N).^{1}HNMR (300 MH_Z,$CDCl_3$,δ ppm): δ 7.28-7.72 (m,13H aromatic protons), δ 5.06 (dd.,1H C_2-H); δ 3.11(dd.,1H,C_3-H_A); δ3.82 (dd.,1H,C_3-H_B); ^{13}CNMR (75MH_Z,$CDCl_3$, δ ppm): 39.4 (C-3), 58.6 (C-2), 121.2 (CF_3), 123.2, 125.4, 126.2, 128.1, 129.3, 130.1, 132.2, 132.8, 136.2, 139.4, 151.8 (aromatic carbons), 168.2 (C=N). Anal. calcd. for $C_{22}H_{13}NSClBrF_3$: C, 49.76; H, 2.42; N, 2.60 found C, 49.80; H, 2.45; N, 2.64.

4-[3'-Bromophenyl]-6-chloro-2-phenyl-9-trifluromethyl-2,3-dihydro-1,5-benzothiazepine (4d)

Obtained as yellow crystalline solid in 65% yield, m.p., 185 °C. IR (KBr): 1615 cm^{-1} (C=N).^{1}HNMR (300 MH_Z,$CDCl_3$,δ ppm): δ 7.15-7.78 (m,14H aromatic protons), δ 5.25 (dd.,1H C_2-H); δ3.14 (dd.,1H,C_3-H_A); δ3.72 (dd.,1H,C_3-H_B); ^{13}CNMR (75MH_Z,$CDCl_3$, δ ppm): 38.9 (C-3), 59.6 (C-2), 120.8 (CF_3), 122.6, 125.2, 126.6, 127.4, 128.5, 129.6, 130.2, 131.2,132.1, 133.7, 135.9, 140.2,152.1 (aromatic carbons),166.8 (C=N). Anal. calcd. for $C_{22}H_{14}NSClBrF_3$: C, 53.21; H, 2.78; N, 2.54 found C, 53.38; H, 2.38; N, 2.83.

6,-chloro-2-(p-tolyl)-4-phenyl-9-trifluromethyl-2,3-dihydro-1,5-benzothiazepine (4e)

Obtained as yellow crystalline solid in 75% yield, m.p., 178 °C. IR (KBr): 1625 cm^{-1} (C=N).^{1}HNMR (300 MH_Z,$CDCl_3$,δ ppm): δ 7.20-7.76 (m,17H aromatic protons), δ 5.23 (dd.,1H C_2-H); δ3.12 (dd.,1H,C_3-H_A); δ 3.82 (dd.,1H,C_3-H_B); δ 1.28 (s,3H,CH_3 at ring B); ^{13}CNMR (75MH_Z,$CDCl_3$, δ ppm): 22.7 (CH_3), 39.6 (C-3), 59.2 (C-2), 121.2 (CF_3), 124.6, 125.2, 126.3, 127.7, 128.3, 129.0, 130.1, 131.3, 134.2, 136.2, 137.6, 152.4 (aromatic carbons),167.6 (C=N). Anal. calcd. for $C_{23}H_{17}NSF_3Cl$: C, 64; H, 3.89; N, 3.20 found C, 64.10; H, 3.95; N, 3.25.

6,-chloro-2-(4'-chlorophenyl)-4-phenyl-9-trifluromethyl-2,3-dihydro-1,5-benzothiazepine (4f)

Obtained as yellow crystalline solid in 80% yield, m.p., 170 °C.IR (KBr): 1635 cm^{-1} (C=N).^{1}HNMR (300 MH_Z,$CDCl_3$,δ ppm): δ 7.18-7.62 (m,14H aromatic protons), δ 5.12 (dd.,1H C_2-H); δ 3.15 (dd.,1H,C_3-H_A); δ 3.80 (dd.,1H,C_3-H_B); ^{13}CNMR (75MH_Z,$CDCl_3$, δ ppm): 39.2 (C-3), 58.6 (C-2), 120.6 (CF_3), 125.4, 126.1, 127.3,

128.2, 128.6 ,129.3 , 129.8, 130.3, 131.2, 132.8, 134.2, 139.6, 152.3 (aromatic carbons) 168.2 (C=N). Anal. calcd. for $C_{22}H_{14}NSCl_2F_3$: C, 58.49 ; H, 3.02; N, 3.06 found C, 58.53; H, 3.10; N, 3.10.

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