New 1,4-*b*enzothiazine fused heterocycles-V : Synthesis of 9*H*-thieno[3,2-*b*]benzothiazine and 4*H*-thiazolo[2,3-*b*][1,4] benzothiazine derivatives†

Lingaiah Nagarapu* and Narender Ravirala

Division of Organic Chemistry-II, Indian Institute of Chemical Technology, Hyderabad-500 007, India.

Abstract : New heterocyclic systems namely thieno [3,2-*b*] [1,4] **3** and thiazolo [2,3-*b*] [1,4] benzothiazines **5** have been syntheiszed via the reaction of substituted 3-chloro-1,4-benzothiazine-2-carbaldehyde **2** with ethyl mercapto-acetate in the presence of a base and thiourea respectively, in good yields.

Introduction

In view of the general interest in the pharmocological and biological activities of heterocyclic systems,[1-8] we are reporting here for the first time the synthesis of some hitherto unreported heterocyclic systems in which 1,4-benzoxazine ring is fused to a thiophene and thiazole ring. These compounds have been prepared from substituted *2H*-1,4-benzothiazine-3-one **1a** and its analogues **1a-c**.[9-12]

Chemistry

Reaction of the benzoxazines **1a-c** with phosphoryl chloride in dimethylformamide at 0°C gave the corresponding *N*-substituted 3-chloro-1,4-benzoxazine-2-carbaldehyde **2a-c** which on treatment with ethyl mercaptoacetate in presence of sodium ethoxide under went cyclocondensation leading to the formation of the corresponding 2-carbethoxythieno[3,2-*b*] [1,4]benzoxazine derivatives **3a-c** in good yield (90%) (**Scheme I**). The structures of **3a-c** were established on the basis of ^{1}H NMR, analytical and mass spectral data. One of the diagnostic features of ^{1}H NMR spectrum of compounds **3a-c** is the appearance of a singlet at δ 7.55 an

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equable to the said proton in the thiophene ring. The ester group in compounds **3a-c** underwent hydrolysis to give the corresponding acid **4a-c**. The structures of the compounds **4a-c** were established on the basis of their analytical, IR, ^{1}H NMR and mass spectral data.

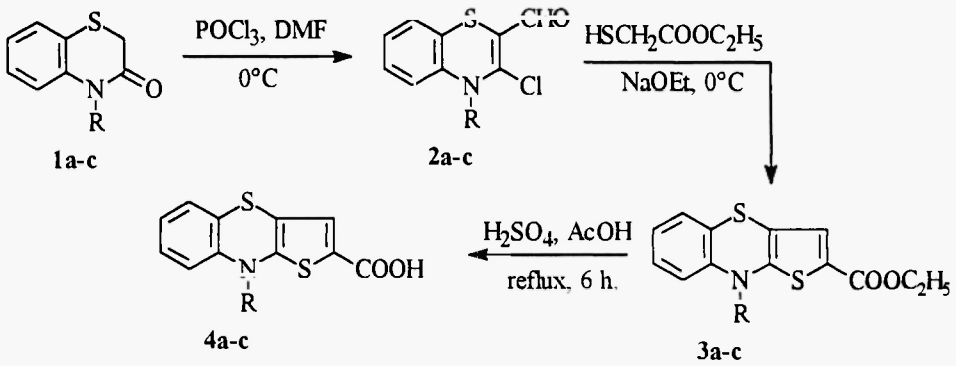
The literature survey reveals that ketones react with thiourea and halogens to give substituted phenmorpholo aminoketones.[13] This coupled with the available ketones **1a-c** obtained in this work provided a further opportunity to these systems. Reaction of **1a-c** with thiourea and iodine gave 2-amino-4N-methyl thiazolo [2,3-*b*] [1,4] benzothiazine **5a** as pale yellow needles (65%). The ^{1}H NMR spectrum of **5a** showed NH_2 as a broad singlet at δ 5.38 in DMSO-d_6, which underwent deuterium exchanged readily, and the IR spectrum containes NH_2 bands at 3380 and 3100 cm^{-1}.

As with **1a**, condensation of **1b-c** with thiourea proceeded satisfactorily yielding the corresponding thiazole derivatives **5a-c** (**Scheme-II**). Their structures were confirmed by IR, NMR, mass spectra an elemental analysis.

Experimental Section

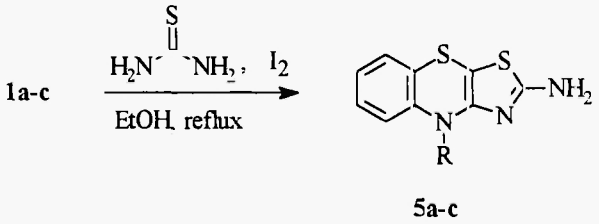
Melting points were determined in open glass capillaries on a Metler FP5 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini (200 MHz) spectrometers (chemical shifts in δ ppm using TMS as internal standard) and Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer.

Preparation of 2a-d using Vilsmeier-Haack reagent : **General procedure** : Phosphoryl chloride (5 mmol) was added dropwise with stirring and cooling to dry DMF (10 mL), at such a rate that the temperature did not exceed 5°C. *N*-methyl-*2H*-1,4-benzothiazin-3-one (1.5 mmol) was added dropwise to the resulting solution at 0-5°C and the mixture was stirred for 30 min at 0°C and for 1.5 hr at 80°C. It was then poured into cold aq. sodium acetate (20% w/z, 25 mL). The product was extracted with ether, the organic layer dried over $MgSO_4$ and the solvent was evaporated in *vacuo*. The residue obtained was purified by column chromatography on silica gel, eluting with hexane : chloroform (2:1).



a) R = CH_3, b) R = CH_2COOH; c) R = CH_2CH_2COOH

Scheme-1



Scheme-II

3-Chloro-1,4-benzothiazine-2-carbaldehyde-*N*-methyl (2a) :

Yield 78%, pale yellow powder, m.p. 78°C; IR (KBr) : ν 1665 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.11 (s, 3H, N-CH_3), 7.08-7.32 (m, 4H, Ar-H) and 9.95 (s, 1H, -CH). Found : C, 53.20; H, 6.18; N, 6.08. Calcd. for $C_{10}H_8ClNOS$: C, 53.21; H, 6.20; N, 6.20%).

3-Chloro-*N*-acetic acid-1,4-benzothiazine-2-carbaldehyde (2b) :

Yield 70%, pale yellow crystals, m.p. 156°C; IR (KBr) : ν 1670, 3425 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 4.45 (s, 2H, N-CH_3), 7.10-7.29 (m, 4H, Ar-H) and 10.00 (s, 1H, -CHO). Found : C, 48.95; H, 3.00; N, 5.20. Calcd. for $C_{11}H_8ClNO_3S$: C, 48.98; H, 2.99; N, 5.19%).

3-Chloro-*N*-propionic acid-1,4-benzothiazine-2-carbaldehyde (2c) :

Yield 88.5%, pale yellow prisms, m.p. 172.2°C; IR (KBr) : ν 1665, 3405 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 4.25 (s, 2H, N-CH_2-), 2.82 (t, 2H, -CH_2-COOH), 7.15-7.39 (m, 4H, Ar-H) and 9.90 (s, 1H, -CHO). Found : C, 50.80; H, 3.35; N, 4.90. Calcd. for $C_{12}H_{10}ClNO_3S$: C, 50.79; H, 3.55; N, 4.93%).

Preparation of 3a-c : **General procedure** : Ethyl mercaptoacetate (5 mmol) was added to a cooled stirred solution of sodium (0.01 g atom) in dry ethanol (30 mL). A solution of **2a** (5 mmol) in ethanol 30 mL) was then added dropwise during 0.5 hr at 0-5°C and the mixture was stirred overnight at room temperature, boiled for 0.5 hr, cooled, and then poured onto water. The ester **3a** obtained was collected from light petroleum (b.p. 60-80°C).

2-Carbethoxy-9*N*-methyl thieno[3,2-*b*][1,4]benzothiazine (3a) : Yield 90%, m.p. 102-103.5°C; IR (KBr) : υ 1705 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.22 (s, 3H, N-CH_3), 7.20-7.31 (m, 4H, Ar-H), 1.35 (t, 3H, -CH_3), 4.11 (q, 2H, -OCH_2-), and 7.55 (s, 1H, 3-H). Found : C, 57.72; H, 5.01; N, 4.82. Calcd. for $C_{14}H_{13}NO_2S_2$: C, 57.70; H, 4.49; N, 4.80%.

2-Carbethoxy-9*N*-acetic acid thieno[3,2-*b*][1,4]benzothiazine (3b). Yield 78.2%, m.p. 211°C; IR (KBr) : υ 1700, 3505 cm^{-1}; 1H NMR ($CDCl_3$) : δ 4.40 (s, 3H, N-CH_2-), 1.32 (t, 3H, -CH_3), 3.99 (q, 2H, -OCH_2-), 7.00-7.32 (m, 4H, Ar-H),

and 7.56 (s, 1H, 3-H). Found : C, 53.75; H, 3.91; N, 4.17. Calcd. for $C_{15}H_{13}NO_4S_2$: C, 53.71; H, 3.90; N, 4.17%.

2-Carbethoxy-9*N*-propionic acid thieno[3,2-*b*][1,4]benzothiazine (3c). Yield 78.0%, m.p. 186°C; IR (KBr) : υ 1705, 3490 cm^{-1}; 1H NMR ($CDCl_3$) : δ 4.30 (t, 2H, N-CH_2-), 2.85 (t, 2H, -COOH), 7.09-7.36 (m, 4H, Ar-H), and 7.55 (s, 1H, 3-H). Found : C, 55.00; H, 4.35; N, 3.98. Calcd. for $C_{16}H_{15}NO_4S_2$: C, 54.99; H, 4.33; N, 4.00%.

Hydrolysis of 3a-c to 4a-c. Sulfuric acid (50%, v/v 5 mL) was added dropwise to a boiling stirred solution of the ethylester **3a** (5 mmol) in acetic acid (10 mL). The mixture was then boiled for 4 hr and cooled. The corresponding acid was collected and purified by preparative TLC (Chloroform-methanol, 95:5).

2-Carboxy-9*N*-methylthiene[3,2-*b*][1,4]benzothiazine (4a). Yield 46.8%, m.p. 202°C, Found : C, 54.59; H, 3.69; N, 5.33. Calcd. for $C_{12}H_9NO_2S_2$: C, 54.58; H, 3.70; N, 5.30%.

2-Carboxy-9*N*-acetic acid thiene[3,2-*b*][1,4]benzothiazine (4b). Yield 47.9%, m.p. 188°C, Found : C, 50.65; H, 3.20; N, 4.55. Calcd. for $C_{13}H_9NO_4S_2$: C, 50.68; H, 3.17; N, 4.54%.

2-Carboxy-9*N*-propinoic acid thiene[3,2-*b*][1,4]benzothiazine (4c). Yield 52.0%, m.p. 196°C, Found : C, 52.35; H, 3.50; N, 4.38. Calcd. for $C_{14}H_{11}NO_4S_2$: C, 52.32; H, 3.45; N, 4.35%.

Preparation of 5a-c Genral Procedure. A mixture of **1a** (5 mmol), thiourea (1 mmol) and iodine (5 mmol) was refluxed for 36 hr in abs. ethanol (50 mL). At this point TLC showed only a slight change in the substrate. After prolonged refluxing (2 to 3 days until TLC showed the absence of the ketone) the resulting hydride was dissolved in hot water. The solution was filtered while hot and the clear filtrate was neutralised with a strong solution of ammonia. The resulting precipitate was washed with water and crystallized from ethanol.

2-Amino-4*N*-methylthiazolo[2,3-*b*][1,4]benzothiazine (5a). Yield 65%, m.p. 250°C (dec); ^{1}H NMR (DMSO-d_6) : δ 3.52 (s, 3H, N-CH_3), 7.12-7.35 (m, 4H, Ar-H) and 5.38 (br,s, 2H, NH_2, D_2O exchangeable). Found : C, 50.90; H, 4.15; N, 17.82. calcd. for $C_{10}H_9N_3S_2$: C, 50.88; H, 4.14; N, 17.80.

2-Amino-4*N*-acetic acid thiazolo[2,3-*b*][1,4]benzothiazine (5b). Yield 60%, m.p. 270°C (dec); ^{1}H NMR (DMSO-d_6) : δ 4.38 (s, 2H, N-CH_2-), 7.15-7.30 (m, 4H, Ar-H) and 8.00 (br,s, 2H, NH_2, D_2O exchangeable). Found : C, 47.20; H, 3.50; N, 15.02. calcd. for $C_{11}H_9N_3O_2S_2$: C, 47.17; H, 3.49; N, 15.00.

2-Amino-4*N*-propionic acid thiazolo[2,3-*b*][1,4]benzothiazine (5c). Yield 52%, m.p. 242°C (dec); ^{1}H NMR (DMSO-d_6) : δ 4.50 (t, 2H, N-CH_2-), 2.95 (t, 2H, -CH_2-COOH), 7.20-7.38 (m, 4H, Ar-H) and 5.88 (br,s, 2H, NH_2, D_2O exchangeable). Found : C, 49.20; H, 3.81; N, 14.33. calcd. for $C_{12}H_{11}N_3O_2S_2$: C, 49.13; H, 3.78; N, 14.32.

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