

**A SYNTHESIS OF A NOVEL HETEROCYCLIC SYSTEM:  
2H-FURO[3,2-*b*][1,4]BENZOTHAZIN-2-ONE**

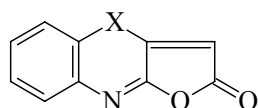
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**Abstract** – A synthesis of 3-methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**) is described. *o*-Aminothiophenols (**1a,b**) undergo condensation with citraconic anhydride followed by cyclization and oxidation of the resulting 2-(3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)propanoic acids (**5**) with thionyl chloride gives moderate yield of **10a,b**.

## INTRODUCTION

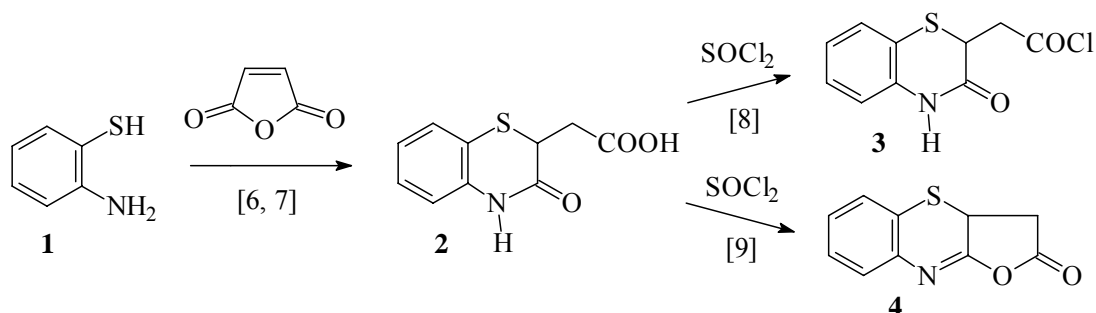
Syntheses of heterocycles having furo[2,3-*b*]quinoxalin-2-one ring system (type **A**) as well as furo[3,2-*b*][1,4]benzoxazin-2-one skeleton (type **B**) have been reported in literature.<sup>1-5</sup> However the preparation of heterocyclic system containing furo[3,2-*b*][1,4]benzothiazin-2-one (type **C**) has not been reported. Type **C** heterocycle bears a close resemblance to phenothiazine and therefore may possess potential pharmacological property. This forms the basis for the aim of the synthesis of type **C** heterocycles in this study.



- A** X = NH  
**B** X = O  
**C** X = S

3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-ylacetic acid (**2**) is known to be a product of the reaction between *o*-aminothiophenol (**1**) and maleic anhydride<sup>6, 7</sup> (Scheme 1). The reaction of the acid **2** with thionyl chloride has been reported to give the acid chloride (**3**)<sup>8</sup> or lactone (**4**)<sup>9</sup> (Scheme 1), however no spectral data have been described for **3**<sup>8</sup> and only the signal of the carbonyl group in IR spectra at 1775 cm<sup>-1</sup> has been mentioned in support of structure (**4**).<sup>9</sup> Interestingly, we have been able to demonstrate that a similar reaction of an analogous acid, with a methyl group in  $\alpha$ -position, and thionyl chloride affords a product which is different from the proposed methyl derivatives of **3** or **4**. The spectral confirmation and possible mechanism of the formation of the titled structure are discussed herein.

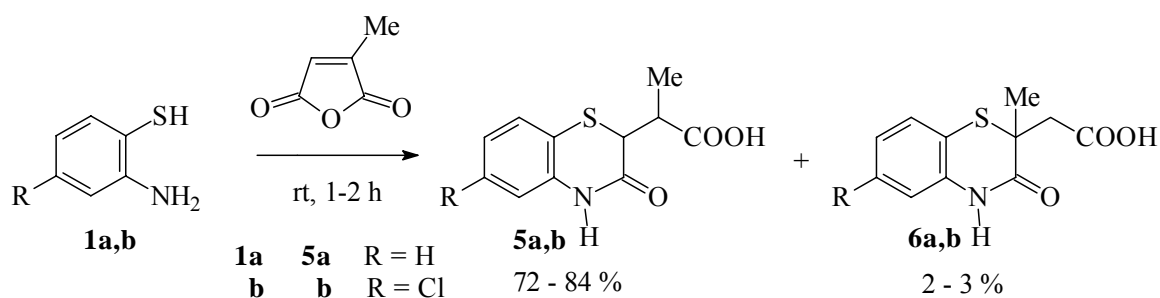
Scheme 1



## RESULTS AND DISCUSSION

From our continual investigation on reactions of maleic anhydrides that lead to the formation of heterocycles,<sup>10</sup> we now report a facile synthesis of 3-methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**) from *o*-aminothiophenols (**1a,b**). The key step of the preparation of **10a,b** involved the formation of 2-(3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)propanoic acids (**5a,b**) by the treatment of **1a,b** with citraconic anhydride (Scheme 2). This reaction afforded mixture of regioisomeric acids **5a,b** (major) and **6a,b** (minor). The ratio of the isomers was calculated using the integral value of signals of methyl groups in <sup>1</sup>H NMR spectra. Both the structure of the acids (**6a,b**) were confirmed based on signals of methyl group, methylenic group and NH in the <sup>1</sup>H NMR spectrum, *e.g.* for **6a**: 1.13 (s, Me), 3.56 (d, *J*=9.4 Hz, CH<sub>2</sub>COOH), 10.70 (s, NH). Fractional crystallizations of the mixtures provided the acids (**5a,b**).

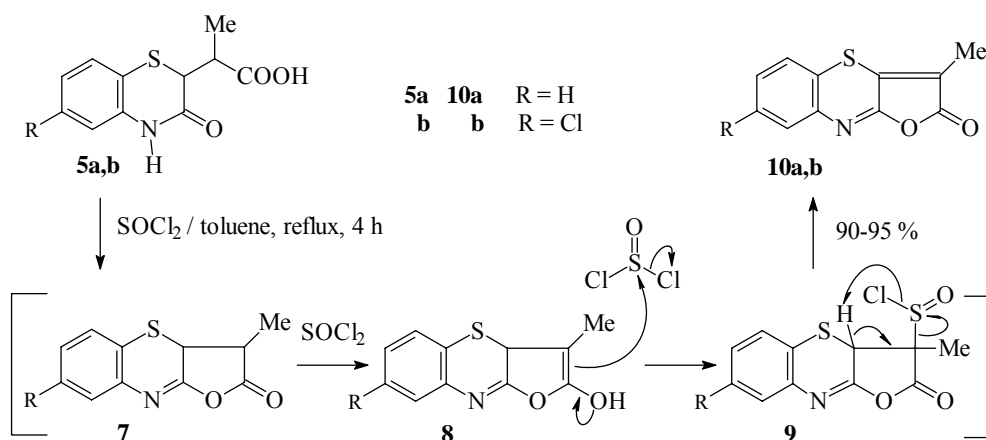
Scheme 2



Refluxing of compounds (**5a,b**) with thionyl chloride in toluene for 4 h led to the formation of 3-methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**) in moderate yields. The proposed mechanism of the formation of system (**10**) is depicted in Scheme 3. The cyclization of the acids (**5a,b**) afforded lactone (**7**), which was oxidized to **10a,b**. It was assumed that the initial step of oxidation of lactone (**7**) was an enolization step that gave **8**, followed by the addition of thionyl chloride to produce **9**. 3-Methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**) might have arisen from **9** by a concerted elimination of HCl and sulfur monoxide.

The structures of all the synthesized compounds were confirmed with elemental analyses and spectral data. The chlorine atom in compound (**10b**) showed a deshielding effect and shifted all the signals in <sup>13</sup>C NMR spectrum to lower field, except for the signal of carbonyl C2 (Table 1).

## Scheme 3

**Table 1.**  $^{13}\text{C}$  NMR spectral data of 3-methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**).

Compd	R	$^{13}\text{C}$ NMR (75 MHz, DMSO- $d_6$ , TMS) $\delta$ [ppm]										
		Me	C2=O	C3	C4	C6	C7	C8	C9	C10	C11	C13
<b>10a</b>	H	9.1	165.8	131.9	133.6	119.8	128.0	125.7	128.3	117.6	137.9	153.8
<b>10b</b>	Cl	9.2	165.5	133.1	133.9	118.4	128.1	126.5	131.4	118.1	139.1	154.7

**EXPERIMENTAL**

**General Methods.** Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DPX-300 spectrometer using TMS as an internal reference. MS spectra data were obtained using a Finnigan LCQ ion trap MS mass spectrometer. IR spectra were performed on a JASCO FT-IR-430 spectrophotometer in KBr pellets.

**2-(3,4-Dihydro-2*H*-1,4-benzothiazin-2-yl)propanoic acids (5a,b)**

To a solution of citraconic anhydride (1.12 g, 0.01 mol) in ether (20 mL) a solution of *o*-aminothiophenols (**1a,b**, 0.01 mol) in ether (10 mL) was slowly added at 0 °C (ice bath). The reaction mixture was stirred for 1-2 h at rt. The precipitation was filtered and dried to afford the products (**5a,b**) which were used for the further reactions without purification. **5a**: Yield 1.71 g (72 %); mp 251-252 °C (lit.,<sup>11</sup> 250-251 °C); IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3316 (COOH), 3198 (NH), 1689 (COOH), 1662 (C=O);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 1.16 (3H, d,  $J=7.2$  Hz, Me), 2.80 (1H, q,  $J=7.2$  Hz,  $\text{CH}(\text{Me})\text{COOH}$ ), 3.77 (1H, d,  $J=8.6$  Hz, C2-H), 6.98 (1H, dd,  $J=8.3$  and 1.5 Hz, C6-H), 6.99 (1H, td,  $J=6.8$  and 1.5 Hz, C8-H), 7.20 (1H, td,  $J=7.5$  and 1.5 Hz, C7-H), 7.34 (1H, dd,  $J=7.9$  and 1.5 Hz, C9-H), 10.66 (1H, s, NH), 12.52 (1H, br s, COOH). **5b**: Yield 1.71 g (84 %); mp 264-265 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 1.14 (3H, d,  $J=7.2$  Hz, Me), 2.57 (1H, q,  $J=7.2$  Hz,  $\text{CH}(\text{Me})\text{COOH}$ ), 3.61 (1H, d,  $J=9.4$  Hz, C2-H), 7.01 (1H, d,  $J=1.9$  Hz, C6-H), 7.05 (1H, dd,  $J=8.1$  and 2.1 Hz, C8-H), 7.36 (1H, d,  $J=8.3$  Hz, C9-H), 10.83 (1H, s, NH), 12.60 (1H, br s, COOH).

### **3-Methyl-2H-furo[3,2-b][1,4]benzothiazin-2-ones (10a,b).**

A mixture of 2-(3,4-dihydro-2H-1,4-benzothiazin-2-yl)propanoic acid (**5a,b**, 0.01 mol) and thionyl chloride (8 mL, 0.1 mol) in toluene (50 mL) was heated under reflux for 4 h. The solvent and excess thionyl chloride were removed under reduced pressure and the resulting solids were crystallized from acetone to yield **10a,b** as yellow crystals. **10a**: Yield 1.95 g (90 %); mp 199-200 °C; MS: [M+1]<sup>+</sup> 218.1; IR (KBr, v, cm<sup>-1</sup>): 1762 (C=O), 1652, 698 (C=C), 1603 (C=N), 1437, 1383 (CH<sub>3</sub>), 1288, 1227 (C-O-C); <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, δ, ppm): 1.96 (3H, s, Me), 7.45 (1H, td, J=7.2 and 1.9 Hz, C8-H), 7.51 (1H, td, J=7.5 and 1.9 Hz, C9-H), 7.66 (1H, dd, J=7.5 and 1.9 Hz, C10-H), 7.73 (1H, dd, J=7.5 and 1.9 Hz, C7-H); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ, ppm): 2.05 (3H, s, Me), 7.32-7.48 (3H, m, C7-H, C8-H, C9-H), 7.71 (1H, d, J=7.9 Hz, C10-H); Anal. Calcd for C<sub>11</sub>H<sub>7</sub>NO<sub>2</sub>S: C, 60.82; H, 3.25; N, 6.45; S, 14.76. Found: C, 60.94; H, 3.22; N, 6.42; S, 14.70. **10b**: Yield 2.40 g (95 %); mp 231-232 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ, ppm): 2.05 (3H, s, Me), 7.31 (2H, m, C7-H, C8-H), 7.70 (1H, s, C10-H); Anal. Calcd for C<sub>11</sub>H<sub>6</sub>NO<sub>2</sub>ClS: C, 52.49; H, 2.40; N, 5.57; Cl, 14.09; S, 12.74. Found: C, 52.51; H, 2.38; N, 5.61; Cl, 14.15; S, 12.66.

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