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

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Abstract – A synthesis of 3-methyl-2H-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-2H-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.1-5 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.

3-Oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylacetic acid (2) is known to be a product of the reaction between o-aminothiophenol (1) and maleic anhydride6,7 (Scheme 1). The reaction of the acid 2 with thionyl chloride has been reported to give the acid chloride (3)8 or lactone (4)9 (Scheme 1), however no spectral data have been described for 38 and only the signal of the carbonyl group in IR spectra at 1775 cm\(^{-1}\) has been mentioned in support of structure (4)9. 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.
RESULTS AND DISCUSSION

From our continual investigation on reactions of maleic anhydrides that lead to the formation of heterocycles,\(^\text{10}\) we now report a facile synthesis of 3-methyl-2H-furo[3,2-b][1,4]benzothiazin-2-ones (10a,b) from \(\text{o-aminothiophenols (1a,b)}\). The key step of the preparation of 10a,b involved the formation of 2-(3,4-dihydro-2H,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 \(^1\text{H} \text{NMR} \text{spectra} \). Both the structure of the acids (6a,b) were confirmed based on signals of methyl group, methylenic group and NH in the \(^1\text{H} \text{NMR} \text{spectra} \), e.g. for 6a: 1.13 (s, Me), 3.56 (d, \(J=9.4 \text{ Hz} \), CH\(_2\)COOH), 10.70 (s, NH). Fractional crystallizations of the mixtures provided the acids (5a,b).

Refluxing of compounds (5a,b) with thionyl chloride in toluene for 4 h led to the formation of 3-methyl-2H-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-2H-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 \(^{13}\text{C} \text{NMR} \text{spectra} \) to lower field, except for the signal of carbonyl C2 (Table 1).
Table 1. $^{13}$C NMR spectral data of 3-methyl-2H-furo[3,2-b][1,4]benzothiazin-2-ones ($^{10}$a,b).

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>$^{13}$C NMR (75 MHz, DMSO-d$_6$, TMS) δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Me</td>
<td>C2=O</td>
</tr>
<tr>
<td>$^{10}$a</td>
<td>H</td>
<td>9.1</td>
</tr>
<tr>
<td>$^{10}$b</td>
<td>Cl</td>
<td>9.2</td>
</tr>
</tbody>
</table>

**EXPERIMENTAL**

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

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

To a solution of citraconic anhydride (1.12 g, 0.01 mol) in ether (20 mL) a solution of o-aminothiophenols ($^{1}$a,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 ($^{5}$a,b) which were used for the further reactions without purification. $^{5}$a: Yield 1.71 g (72 %); mp 251-252 °C (lit.,$^{11}$ 250-251 °C); IR (KBr, ν, cm$^{-1}$): 3316 (COOH), 3198 (NH), 1689 (COOH), 1662 (C=O); $^1$H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 1.16 (3H, d, J=7.2 Hz, Me), 2.80 (1H, q, J=7.2 Hz, C$_2$H), 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). $^{5}$b: Yield 1.71 g (84 %); mp 264-265 °C; $^1$H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 1.14 (3H, d, J=7.2 Hz, Me), 2.57 (1H, q, J=7.2 Hz, CH(Me)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]^+ 218.1; IR (KBr, ν, cm^{-1}): 1762 (C=O), 1652, 698 (C=C), 1603 (C=N), 1437, 1383 (CH_3), 1288, 1227 (C-O-C); \(^1^H\) NMR (300 MHz, DMSO-d_6, 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); \(^1^H\) NMR (300 MHz, CDCl_3, 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_{11}H_7NO_2S: 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. \(^1^H\) NMR (300 MHz, CDCl_3, 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_{11}H_6NO_2ClS: 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.

REFERENCES