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

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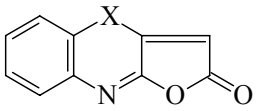
Abstract – A synthesis of 3-methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**) is described. *o*-Aminothiophenols (**1a,b**) undergo condensation with citraconic anhydride followed by cyclization and oxidation of the resulting 2-(3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)propanoic acids (**5**)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

INTRODUCTION

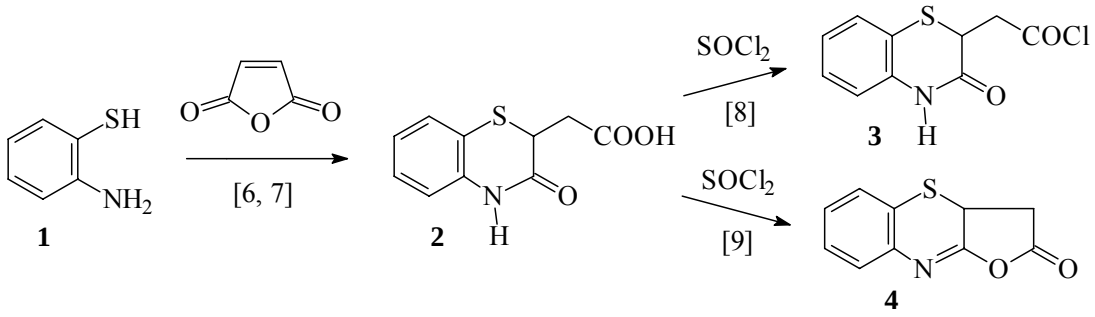
Syntheses of heterocycles having furo[2,3-*b*]quinoxalin-2-one ring system (type **A**) as well as furo[3,2-*b*][1,4]benzoxazin-2-one skeleton (type **B**) have been reported in literature.[1-5] However the preparation of heterocyclic system containing furo[3,2-*b*][1,4]benzothiazin-2-one (type **C**) 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.



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[6, 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 **3**[8] 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 α-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.

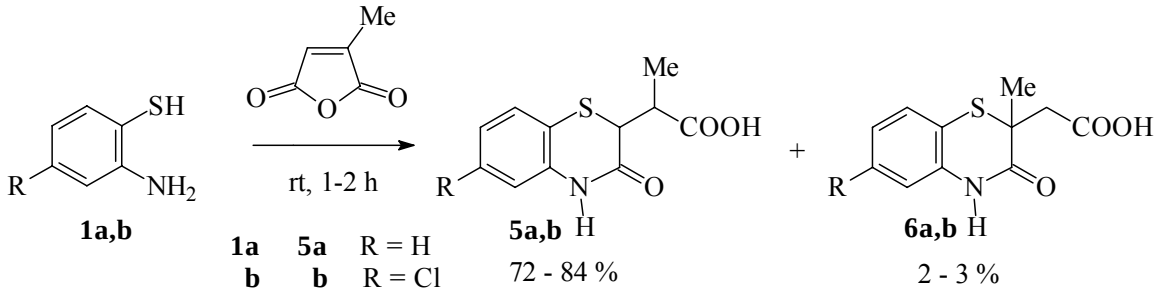
Scheme 1



RESULTS AND DISCUSSION

From our continual investigation on reactions of maleic anhydrides that lead to the formation of heterocycles,[10] 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 ^{1}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 ^{1}H NMR spectrum, *e.g.* for **6a**: 1.13 (s, Me), 3.56 (d, J=9.4 Hz, C<u>H$_2$</u>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 ^{13}C NMR spectrum to lower field, except for the signal of carbonyl C2 (Table 1).

Scheme 3

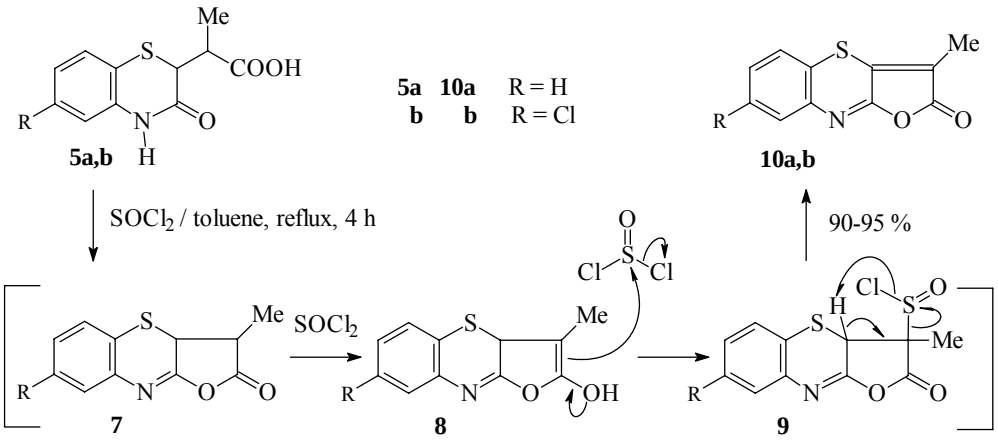


Table 1. ^{13}C NMR spectral data of 3-methyl-2*H*-furo[3,2-*b*][1,4]benzothiazin-2-ones (**10a,b**).

Compd	R	^{13}C NMR (75 MHz, DMSO-d$_6$, TMS) δ [ppm]										
		Me	C2=O	C3	C4	C6	C7	C8	C9	C10	C11	C13
10a	H	9.1	165.8	131.9	133.6	119.8	128.0	125.7	128.3	117.6	137.9	153.8
10b	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}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 (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.,[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<u>H</u>(Me)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}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, C<u>H</u>(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-2*H*-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.

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