Synthesis of Heterocyclic Compounds from *o*-Aminobenzenethiol and Ammonium Thiocarbamate [1]

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The reaction of *o*-aminobenzenethiol with carbonyl sulfide in the presence of triethylamine afforded an alternate route for the synthesis of 2-benzothiazolinone (**1**) in 97-98% yield. The reaction of ammonium thiocarbamate (**2**) with 2-chlorocyclohexanone furnished the novel 4,5,6,7-tetrahydro-2-benzothiazolinone (**3**). 3-Ethoxy-2*H*-1,4-benzothiazin-2-one (**7**) was prepared by the reaction of *o*-aminobenzenethiol with diethyl oxalate. Possible pathways and supporting nmr, ir and mass spectra are discussed.

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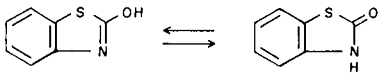
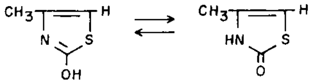
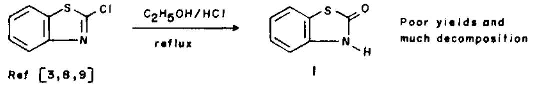
It has been stated that 2-hydroxybenzothiazole and 2-hydroxy 4-methylthiazole may also exist in their tautomeric forms 2-benzothiazolinone and 4-methyl-2-thiazolinone, respectively. Early attempts to study the above structures by comparison of their ultraviolet spectra with those of both alkylated forms failed because of the similarity of the spectra in the region investigated [2]. However, in 1935, this method was successfully applied to 2-benzothiazolinone [3] and 2-thiazolinone [4], indicating the predominance of the oxo forms for both compounds. Infrared spectral data (ν NH, ν C=O) also suggest that 2-thiazolinone [4a,5] and some of its derivatives [4b,6] exist primarily in the oxo form. In 1976, Jose Elquero and coauthors [7] stated "all available evidence suggests that five-membered heterocyclic compounds containing a potential hydroxyl group between the two heteroatoms in the 1- and 3-position predominantly exist in the oxo form".







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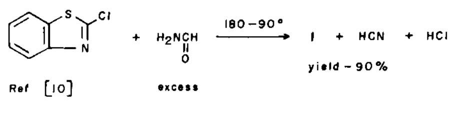

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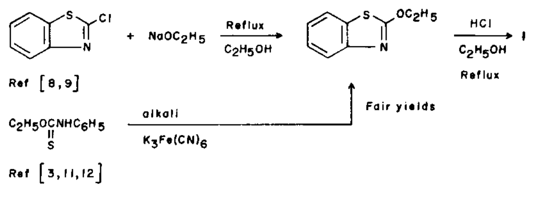

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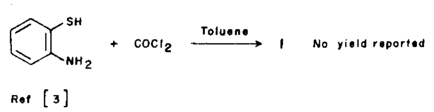

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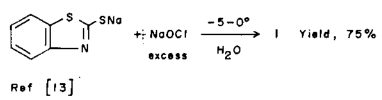

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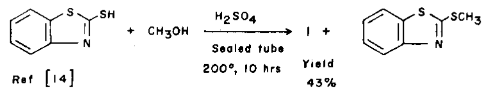

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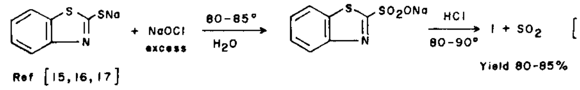

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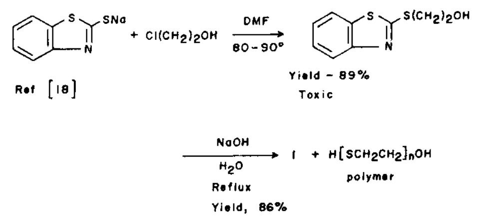
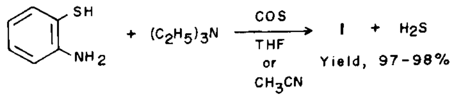


[8]

Even though there are numerous methods for preparing **1**, each suffer from various inherent drawbacks such as poor yields, the use of high temperatures, expensive and toxic intermediates.

Since *o*-aminobenzenethiol and carbonyl sulfide can easily be prepared and also are commercially available at a reasonable cost, we decided to study the reaction employing these two reactants. The outcome of this investigation afforded us a superior alternate method for the synthesis of **1** of excellent quality and yield [19]. Moreover, the recovered triethylamine and solvent can be reused.

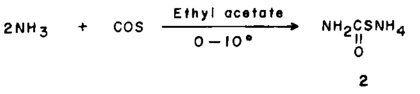


[9]

However, if triethylamine is omitted no reaction occurs and 85% of the *o*-aminobenzenethiol is recovered. In summary, our alternate route provides a synthesis of **1** that is efficient, economical, and uncomplicated by side reactions.

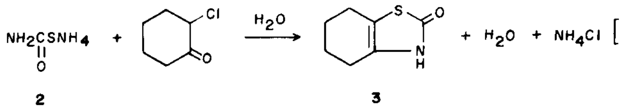
The proposed pathway for reaction 9 is depicted in Scheme I. As noted, the role of the triethylamine is to form an amine salt with the monosubstituted thiocarbamic acid which enhances the stability of this intermediate **A** prior to heating.

The intermediate ammonium thiocarbamate (**2**) was prepared in 98% yield by the reaction of carbonyl sulfide with excess ammonia at 0-10°. If **2** is allowed to dry longer than two hours or comes in contact with metals it decomposes. The preparation of **2** was briefly mentioned by Tcherniac [20] but not described in detail.



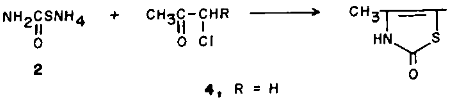
$$2NH_3 + COS \xrightarrow[0-10°]{\text{Ethyl acetate}} NH_2\overset{\displaystyle O}{\underset{\|}{C}}SNH_4 \quad [10]$$

The reaction of ammonium thiocarbamate with 2-chlorocyclohexanone afforded the novel 4,5,6,7-tetrahydro-2-benzothiazolinone (**3**). The analysis and nmr confirmed the proposed structure **3**. It is noteworthy to compare the chemical shift for -NH protons in **1** and **3**. The NH proton in **1** appeared at δ 11.50, whereas the NH proton in **3** was found at δ 10.76. The proposed pathway for reaction 11 is depicted in Scheme II.



[11]

Tcherniac [20] reported the synthesis of 4-methyl-2-thiazolinone (**4**) and Ganapathi and Venkataraman [21] reported the preparation of ethyl 4-methyl-2-thiazolinone-5-carboxylate (**5**) and 4-methyl-5-acetyl-2-thiazolinone (**6**) by the following reactions:

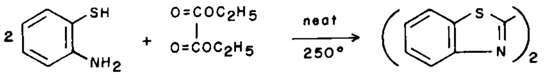


[12]

4, R = H
5, R = $-COOC_2H_5$
6, R = $-COCH_3$

We reprepared **4-6** in order to study their nmr characteristic. As expected the NH protons for **4**, **5** and **6** appeared at δ 11.35, 11.70 and 11.30 respectively. The large downfield shifts (δ 10.76-11.70) for the NH protons in **1**, **3**, **4**, **5** and **6** are due to the deshielding effect of the carbonyl group. This effect lends support for the predominance of the oxo form for these compounds.

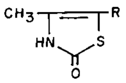
Hofmann [22] in 1880 reported the synthesis of bis-2,2'-benzothiazolyl by the reaction of *o*-aminobenzenethiol with diethyl oxalate without solvent at 250°. In 1926



[13]

No yield reported

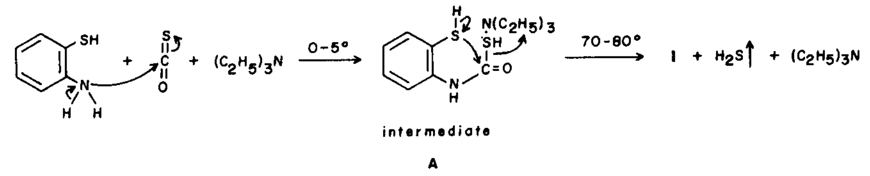
Table I



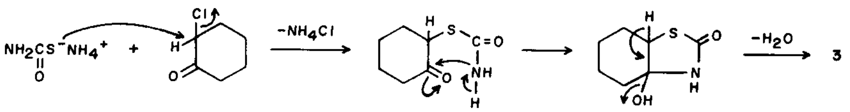
No.	R	Ml Solvent	Temperature Rise °	% Yield	Mp°	NMR, δ, ppm DMSO-d_6	Empirical Formula	Chemical Analysis	
4c	H	180 H_2O	0-77° in 1 min	90	103-104 [a]	1.99 (s, 3, $CH_3C=$) 5.85 (s, 1, =CH) 11.35 (br s, NH) exchanges with deuterium oxide	C_4H_5NOS	% C Calcd 41.72 Found 41.60 % H Calcd 4.38 Found 4.30	% N Calcd 12.16 Found 12.31 % S Calcd 27.85 Found 27.64
5d	$-COOC_2H_5$	500 H_2O	10-44° in 3 min	62	181-182 [b]	1.25 (t, 3, $-CH_2CH_3$) 2.37 (s, 3, $CH_3C=$) 4.15 (q, 2, $-CH_2CH_3$) 11.70 (br s, 1, NH) exchanges with deuterium oxide	$C_7H_9NO_3S$	% C Calcd 44.91 Found 45.11 % H Calcd 4.85 Found 4.90	% N Calcd 7.48 Found 7.26 % S Calcd 17.13 Found 16.98
6d	$-COCH_3$	500 acetone	10-44° in 1 min	34	218-219 [b]	2.32 (s, 3, $CH_3C=$) 2.40 (s, 3, $-COCH_3$) 11.30 (br s, 1 NH) exchanges with deuterium oxide	$C_6H_7NO_2S$	% C Calcd 45.85 Found 45.69 % H Calcd 4.49 Found 4.46	% S Calcd 8.91 Found 8.85 % S Calcd 20.43 Found 20.43

[a] Recrystallization from toluene. [b] Recrystallization from ethyl alcohol. [c] Ref [20] reports mp 101-102° and a 93% yield for **4**. [d] Ref [21] reports mp 175° and a 53% yield for **5** and mp 210-212° and a 48% yield for **6**.

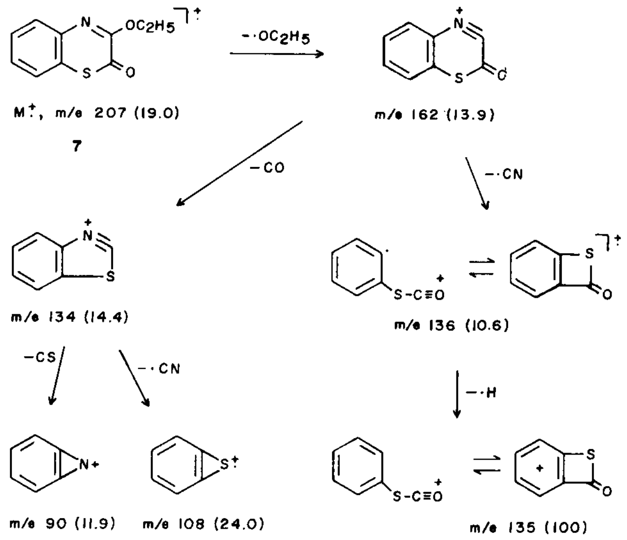
Scheme I



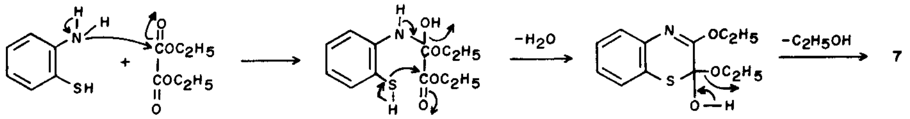
Scheme II



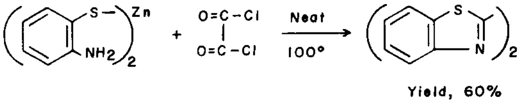
Scheme III



Scheme IV

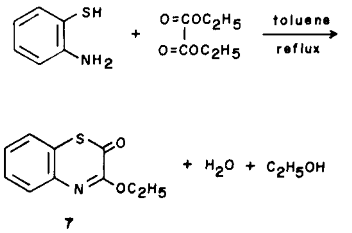


Bogert and Stull [23] disclosed the preparation of bis-2,2'-benzothiazolyl by the following reaction:



[14]

We modified Hofmann's procedure by conducting the reaction in refluxing toluene containing a catalytic amount of acetic acid. During the reflux period, the bottom water-ethyl alcohol layer was separated from toluene by means of a Dean Stark condenser. It was anticipated that the above modification of reaction conditions would have yielded bis-2,2'-benzothiazolyl. However, this was not the case, for the product isolated in 57% yield was 3-ethoxy-2H-1,4-benzothiazin-2-one (7). The analysis, nmr



[15]

and ir spectral data are in complete agreement for our proposed structure **7**. Moreover, the electron impact and isobutane chemical ionization mass spectra furnished the molecular weight data in the form of $M^{+\cdot}$ 207 and $(M+1)^+$ 208, respectively. Furthermore, the fragmentation pathway of **7** (Scheme III) is consistent with our proposed structure. The proposed pathway for reaction 15 is depicted in Scheme IV.

EXPERIMENTAL

The nmr spectra were obtained with a Varian T-60 nmr spectrometer. The chemical shifts are reported in ppm, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. The electron impact mass spectra for **7** was determined with a Varian MAT CH-7A mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 250°. This instrument was operated in the CIMS mode to obtain the chemical ionization mass spectrum of **7**. The infrared spectrum for **7** was obtained with a Beckman IR-12 spectrometer.

2-Benzothiazolinone (**1**).

To a stirred solution containing 64.5 g (0.5 mole) of 97% *o*-aminobenzenethiol in 600 ml of tetrahydrofuran or acetonitrile, 50.6 g (0.5 mole) of triethylamine was added in one portion. An exothermic reaction set in causing a temperature rise from 24° to 40° followed by the formation of a thick precipitate. After cooling the stirred slurry to 0°, 38.9 g (0.55 mole) of 85% carbonyl sulfide was added at 0-5° over a 35 to 50 minute period. External cooling was removed and the reaction mixture was stirred at 25-30° for 24 hours. After stirring at these temperatures for 5 hours a solution resulted. The stirred solution was heated at reflux for 2 hours. During this heating period hydrogen sulfide was liberated. The triethylamine and solvent were removed *in vacuo* at a maximum temperature of 80-90° at 1-2 mm. The recovered amine and solvent can be reused. To the cooled residue, 200 ml of water was added and stirred at 25-30° for 15 minutes. The solid was collected by filtration, washed with 300 ml of water and air-dried at 50°. Compound **1**, mp 135-137°, was obtained in 97-98% yield. After recrystallization from toluene it melted at 140-141°; nmr (deuteriodimethylsulfoxide): δ 7.00-7.65 (m, 4 ArH), 11.50 (br s, 1 HN) exchanges with deuterium oxide.

Anal. Calcd. for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.71; H, 3.36; N, 9.22; S, 21.35.

Without Triethylamine.

To a stirred solution containing 54.5 g (0.5 mole) of 97% *o*-aminobenzenethiol in 600 ml of tetrahydrofuran, 38.9 g (0.55 mole) of 85% carbonyl sulfide was added at 0-5° in 40 minutes. External cooling was removed and the solution (no precipitate) was stirred at 25-30° for 72 hours. The solvent was removed *in vacuo* at a maximum temperature of 60° at 10-12 mm. The residue (64 g) was distilled *in vacuo* collecting the fraction (55 g) bp 70-71° at 0.35 mm. The recovery of unreacted *o*-aminobenzenethiol, N_D^{25} = 1.6358, was 85%. Analylsis and nmr data confirmed that the distillate was unreacted *o*-aminobenzenethiol.

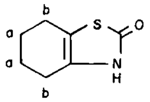
Anal. Calcd. for C_6H_7NS: C, 57.64; H, 5.64; N, 11.19; S, 25.61. Found: C, 57.30; H, 5.71; N, 11.08; S, 25.46.

Ammonium Thiocarbamate (**2**).

To a stirred solution at -20° containing 600 ml of ethyl acetate and 100 ml of ethyl alcohol, 68.2 g (4.0 moles) of anhydrous ammonia gas was added at -20° to -10° over a 30 minute period. This was followed by the addition of 140 g (2.0 moles) of 85% carbonyl sulfide at 0-10° over a 1.5 hours period. The stirred reaction mixture was maintained at 0-10° for an additional hour. The solid was collected by filtration, washed with 300 ml of diethyl ether and air-dried at 25-30° for only 1 hour. If ammonium thiocarbamate is allowed to dry longer than 2 hours or comes in contact with metals it decomposes. The salt was obtained in 98% yield and was used without any further purification.

4,5,6,7-Tetrahydro-2-benzothiazolinone (**3**).

To a stirred solution containing 103.5 g (1.1 moles) of **2** in 600 ml of water, 132 g (1.0 mole) of 2-chlorocyclocychexanone was added in one portion. A temperature rise from 20 to 31° was noted over a 4 hour period. At 25°, 100 ml of diethyl ether was added and stirring was continued at 25-30° for 3 days. The solid was collected by filtration, washed with 300 ml of diethyl ether and air-dried at 25-30°. Crude **3**, mp 137-140°, was obtained in 34% yield. After recrystallization from ethyl alcohol it melted at 144-145°; nmr (deuteriodimethylsulfoxide): δ 1.70 (m, 4, a), 2.26 (m, 4, b), 10.76 (br s, 1 NH), exchanges with deuterium oxide.



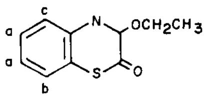
Anal. Calcd. for C_7H_9NOS: C, 54.16; H, 5.84; N, 9.02; S, 20.66. Found: C, 53.93; H, 5.66; N, 8.87; S, 20.91.

4-Methyl-2-thiazolinone (**4**), Ethyl 4-Methyl-2-thiazolinone-5-carboxylate (**5**) 4-Methyl-5-acetyl-2-thiazolinone (**6**).

Modified procedures described by Tcherniac [20] and Ganapathi and Venkataraman [21] were employed for the synthesis of **4-6**. To a stirred solution at °-10° containing 84.6 g (0.9 mole) of **2** in water or acetone-water (Table I), 0.8 mole of chloroacetone, ethyl α-chloroacetoacetate or 3-chloro-2,4-pentanedione was added in one portion. An exothermic reaction set in causing a temperature rise as specified in Table I. The reaction mixture was stirred at 25-30° for 24 hours. After cooling to 0°, 200 g ice water was added and stirring continued at 0-10° for 1 hour. The solid was collected by filtration, washed with 200 ml of heptane and air-dried at 25-30°. The data are summarized in Table I.

3-Ethoxy-2*H*-1,4-benzothiazin-2-one (**7**).

A stirred solution containing 54.5 g (0.5 mole) of 97% *o*-aminobenzenethiol, 146.2 g (1.0 mole) of diethyl oxalate, 1 g of acetic acid and 300 ml of toluene was heated at reflux for 18 hours. During the reflux period 18 ml of water and ethyl alcohol were collected *via* the Dean Stark condenser. Toluene (150 ml) was removed by distillation. To the stirred cooled residue 100 ml of heptane was added. The reaction mixture was stirred at 0-10° for 30 minutes. The solid was collected by filtration and air-dried at 25-30°. Crude **7**, mp 72.0-72.5°, was obtained in 57% yield. After recrystallization from toluene or heptane the melting point remained unchanged; ir (potassium bromide): 3030 (C-H aromatic), 2970 (C-H aliphatic), 1715 (C=O), 1505 (C=N conjugated), 1460 (CH_2 deformation) and 700 (C-H out of plane deformation of 1,2-subst phenyl group) cm^{-1}; nmr (deuteriochloroform): δ 1.47 (t, 3, $-CH_3C\mathit{H}_3$), 4.58 (q, 2, $C\mathit{H}_2CH_3$), 7.40-7.73 (m, 2, a), 7.87-8.10 (m, 1, b), 8.18-8.41 (m, 1, c); electron impact mass spectrum and m/e (rel intensity) 207 (19.0) $M^{+\cdot}$, 162 (13.9), 136 (10.6), 135 (100), 134 (14.4), 108 (24.0), 90 (11.9), 82 (6.5), 76 (2.5) and 69 (14.1); isobutane chemical ionization mass spectrum m/e 208 $(M+1)^+$.



Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.94; H, 4.38; N, 6.76; S, 15.47. Found: C, 58.03; H, 4.40; N, 6.76; S, 15.38.

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