## A Convenient Synthesis of N,5-Disubstituted-4-imidazoline-2-thiones

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The preparation of N,5-disubstituted-4-imidazoline-2-thiones from readily obtainable starting materials is described. These imidazolines are synthesized by refluxing in toluene the appropriate 2-aminomethyl ketone hydrochloride with an equivalent of the desired isothiocyanate and an equivalent of triethylamine. The intermediate thiourea spontaneously eliminates water (removed from the reaction medium by a Dean-Stark trap) to form the imidazoline thione.

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We report a convenient synthesis of various N,5-disubstituted-4-imidazoline-2-thiones as shown by Reaction 1.

A similar preparation of these imidazoline thiones 3 was reported by Kjellin and Sandström (1) who refluxed  $\alpha$ -aminoacetophenone with methyl isothiocyanate in the presence of triethylamine. They isolated, however, the intermediate thiourea 4 (R = CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub>) along with the corresponding imidazoline thione 3. They then completed the cyclization of 4 to 3 by dissolving the crude product in 1 N sodium hydroxide. Two patents (2) described a similar synthesis of 3 from the ethylene ketal of 2-aminoacetone and an isothiocyanate.

We obtained imidazoline thione **3b** (R =  $CH_3$ , R' =  $(CH_3)_2CH$ ) by Kjellin's procedure. Although pure **3b** separated from the reaction mixture, the yield was only 18%.

We sought to improve this yield by investigating different solvents and organic and inorganic hydrogen chloride scavengers. We found that by removing the water that was produced during the spontaneous cyclization of the intermediate thioureas, the yields of the imidazoline thiones were greatly improved. The best yields of 3 were consistently obtained when triethylamine was used as the hydrogen chloride scavenger. Thus, a stirred mixture of equivalent amounts of 1 (3-5), 2 and triethylamine was refluxed with toluene for 18-24 hours in a flask equipped with a Dean-Stark trap. Work-up (see Experimental) and then crystallization gave generally moderate yields of 3. Increasing the reflux time to 92 hours did not significantly improve the yields of the cyclized product. A few

imidazoline thiones 3 that were prepared by this procedure are presented in Table I.

We have demonstrated a preparation in moderate yield of N,5-disubstituted-4-imidazoline-2-thiones **3** from easily obtainable starting materials. These heterocycles are readily isolated without contamination with **4**. Furthermore, a mass spectral examination of the mother liquor after crystallization of **3a** failed to show the presence of thiourea **4a** (R = CH<sub>3</sub>, R' = (CH<sub>3</sub>)<sub>3</sub>C). Conversion of **1** to its ethylene ketal before interaction with the isothiocyanate also appears to be unnecessary.

An alternative approach to N,5-disubstituted-4-imid-azoline-2-thiones (6,7) complements our procedure. Thus, an  $\alpha$ -amino acetal 5 is treated with potassium thiocyanate and hydrochloric acid to give the heterocycle (Reaction 2).

$$R'CHCH(OR'')_2 + KSCN \xrightarrow{HCI} \stackrel{H}{\Delta} \stackrel{N}{\underset{R}{}} = S$$
 (2)

## **EXPERIMENTAL**

The methyl, benzyl and allyl isothiocyanates were Eastman Organic Chemicals. Cyclohexyl isothiocyanate was obtained from the Aldrich Chemical Company. The 2-methoxyethyl and 3-methoxypropyl isothiocyanates were purchased from Trans World Chemicals, Inc., Washington, D. C. 20015. The 3-methylthiopropyl isothiocyanate was prepared according to the procedure of Moore and Crossley (8).

The mass spectra were determined with a Hitachi-Perkin-Elmer RMS-4 spectrometer. The <sup>1</sup>H nmr spectra were measured with an A60 Varian Associates, a Perkin-Elmer R-32 (90 MHz), or with a Varian Associates EM360A nmr spectrometer. Either DMSO-d<sub>6</sub> or deuteriochloroform was used as the solvent with TMS as the internal standard. The melting points were determined with a Thomas-Hoover apparatus and were uncorrected. All imidazoline thiones gave satisfactory mass and <sup>1</sup>H nmr spectra.

Representative N,5-disubstituted-4-imidazoline-2-thione synthesis is illustrated for N-(2-methoxyethyl), 5-t-butyl-4-imidazoline-2-thione (**3c**, Table I).

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Table T

N, 5-Disubstituted-4-imidazoline-2-thiones

$$\bigcap_{\substack{\text{II} \\ \text{R'CCH}_2 \text{ NH}_2 \cdot \text{HCI}}}^{\text{O}} + RN = C = S \qquad \frac{(C_2 H_5)_3 N}{C_6 H_5 C H_3, \Delta} \longrightarrow \bigcap_{\substack{\text{R'} \\ \text{R'}}}^{\text{H}} \longrightarrow S$$

Compound	R	R'	M.p. °C	Yield %	Anal. Caled.: Found:
<b>3</b> a	CH <sub>3</sub>	(CH₃)₃C	184-186	31 (a)	C, 56.4; H, 8.3; N, 16.5; S, 18.8 C, 56.4; H, 8.6; N, 16.3; S, 19.2
<b>3</b> b	CH <sub>3</sub>	(CH <sub>3</sub> )₂CH	127-129	56 (a)	C, 53.8; H, 7.7; N, 17.9; S, 20.5 C, 54.0; H, 8.0; N, 17.8; S, 20.4
3c	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	93-96	57 (a)	C, 56.1; H, 8.5; N, 13.1; S, 15.0 C, 55.7; H, 8.2; N, 12.9; S, 15.0
<b>3</b> d	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub>	(CH <sub>3</sub> )₂CH	119-122	58 (a)	C, 54.0; H, 8.1; N, 14.0; S, 16.0 C, 54.0; H, 8.2; N, 14.1; S, 16.1
<b>3</b> e	$C_6H_5CH_2$	(CH <sub>3</sub> ) <sub>3</sub> C	195-198	30 (b)	C, 68.3; H, 7.4; N, 11.4; S, 13.0 C, 68.1; H, 7.4; N, 11.1; S, 13.0
3f	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	(CH <sub>3</sub> )₂CH	172-174	36 (a)	C, 67.2; H, 6.9; N, 12.1; S, 13.8 C, 66.8; H, 7.3; N, 11.9; S, 14.2
<b>3</b> g	Cyclohexyl	(CH <sub>3</sub> )₂CH	197-199	18 (a)	C, 64.2; H, 9.0; N, 12.5; S, 14.3 C, 63.9; H, 9.0; N, 12.4; S, 14.7
<b>3</b> h	CH <sub>2</sub> =CHCH <sub>2</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	158-159	43 (b)	C, 61.2; H, 8.2; N, 14.3; S, 16.4 C, 61.2; H, 8.1; N, 14.2; S, 16.8
<b>3</b> i	CH <sub>2</sub> =CHCH <sub>2</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	109-110	36 (b)	C, 59.3; H, 7.7; N, 15.4; S, 17.6 C, 58.9; H, 7.4; N, 15.3; S, 17.6
<b>3</b> j	CH₃SCH₂CH₂CH₂	(CH <sub>3</sub> ) <sub>3</sub> C	121-122	28 (b)	C, 54.1; H, 8.2; N, 11.5 C, 54.1; H, 8.6; N, 11.6
3k	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	(CH <sub>3</sub> )₃C	125	70 (b)	C, 57.9; H, 8.8; N, 12.3 C, 57.9; H, 9.1; N, 12.2

(a) After one or more crystallizations from ethyl acetate. (b) After one or more crystallizations from ethyl acetate/n-pentane.

A stirred toluene-mixture (60 ml.) of 1-amino-3,3-dimethyl-2-butanone hydrochloride (3) (1, R' =  $(CH_3)_3C$ ) (5.0 g., 0.037 mole), 2-methoxyethyl isothiocyanate (4.3 g., 0.037 mole) and triethylamine (3.7 g., 0.037 mole) was refluxed for 24 hours. The water that was produced during the cyclization was collected by a Dean-Stark trap. Solvent was removed under reduced pressure and the semisolid residue was partitioned between dichloromethane and distilled water. The dried (magnesium sulfate) dichloromethane extract was passed through 50 g. of Florisil in a chromatographic column. The eluted compound was crystallized from ethyl acetate to give 4.5 g. (57%) of colorless crystals, m.p. 93-96°. The mass spectrum showed the parent peak at M/e 214 (Calcd, 214).

Anal. Calcd. for  $C_{10}H_{18}N_2OS$ : C, 56.1; H, 8.5; N, 13.1; S, 15.0. Found: C, 55.7; H, 8.2; N, 12.9; S, 15.0.

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