Novel Heterocycles. 7. Reaction of 2-Chloronicotinonitrile with Thioureas. Synthesis of the Pyrido[2,3-*d*]pyrimido-[2,1-*b*][1,3]thiazine Ring System

Gary M. Coppola and Michael J. Shapiro*

Chemistry Research Department, Pharmaceutical Division, Sandoz, Inc., East Hanover, New Jersey 07936

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N,N'-Dimethylthiourea and 3,4,5,6-tetrahydro-2-pyrimidinethiol were allowed to react with 2-chloronicotinonitrile (**1**) and their products investigated by standard methods and by carbon-13 nmr. In both instances, displacement of the chlorine occurred by nitrogen not the sulfur of the thioureas. Secondary cyclizations occurred by attack of nitrogen on the nitrile to furnish **3a**, and by sulfur on the nitrile to give **4b**, a new ring system. Tricyclic **4b** was hydrolyzed in dilute acid to give **5**, or alkylated with methyl iodide in the presence of sodium hydride to give the ring opened product **6**.

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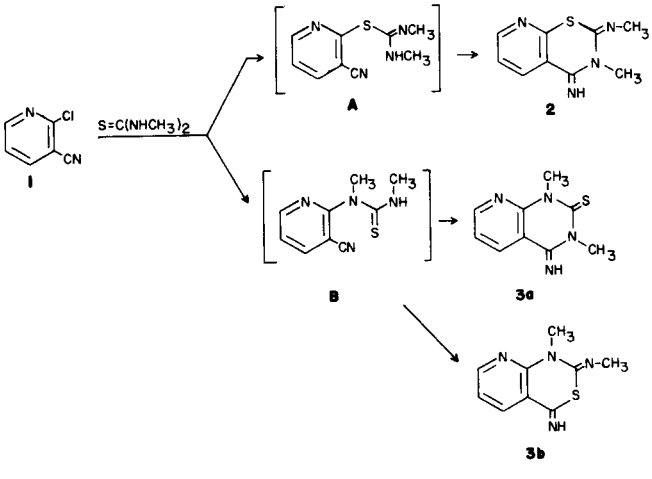
In a recent report (1), 2-chloronicotinonitrile (**1**) was used in the synthesis of the novel pyrido[2,3-*c*][1,2]thiazine ring system. We were interested in further exploring its capability to produce new polycyclic heterocycles by taking advantage of the two reactive functionalities in the 2-and 3-positions.

The interaction of **1** with a compound possessing two nucleophilic centers was considered a logical starting point. One such molecule which fulfills this requirement is a thiourea.

Thiourea itself has been shown to react readily with 2-chloro-5-nitropyridine (2,3), 2-chloro-4,6-dimethylpyrimidine (4), and 2- or 4-chloroquinolines (5) in refluxing ethanol to furnish the corresponding isothiouronium chloride in good yields.

Scheme I

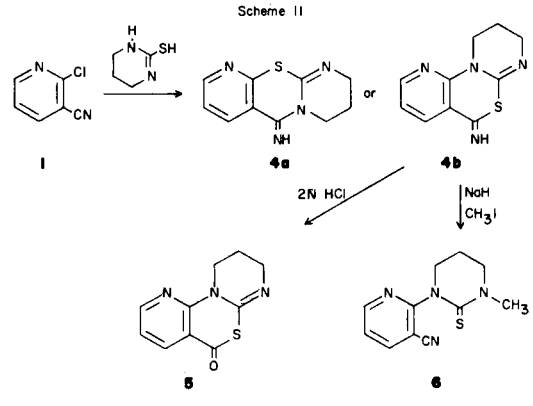


It was hoped that an analogous reaction of **1** with *N,N'*-dimethylthiourea would behave similarly and proceed through **A** (6) (Scheme I) to furnish **2** *via* attack of the amine on the nitrile. When a mixture of **1** and *N,N'*-dimethylthiourea in ethanol was refluxed, very little reaction occurred and starting materials were recovered. When the reaction was performed in dimethylacetamide in the presence of sodium hydride, a smooth reaction occurred and a compound, whose ir spectrum lacked a nitrile band, was isolated in 51% yield.

From the proton nmr, ir and mass spectral fragmentation patterns it was clear that a 1:1 adduct formed but it was not obvious whether the chlorine from **1** was displaced by the sulfur of the thiourea (proceeding through intermediate **A**) (6) to give **2**, or nitrogen (proceeding through intermediate **B**) (6) to furnish **3**.

When a cyclic thiourea (3,4,5,6-tetrahydro-2-pyrimidinethiol) was allowed to react with **1** in an analogous fashion, a 1:1 adduct (**4**) was isolated (Scheme II). Its ir spectrum (potassium bromide) also lacked a nitrile band while exhibiting absorptions at 3325, 1610 and 1585 cm^{-1}, which may be attributed to N-H and C=N vibrations in an imine functionality.

Scheme II



Treatment of **4** with 2*N* hydrochloric acid produced a compound (**5**) whose elemental analysis suggested that the imino moiety had been replaced by a carbonyl. Its ir spectrum clearly lacked the bands corresponding to the C=NH group and exhibited absorptions at 1665 and 1610 cm^{-1}.

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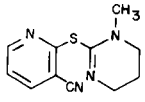
Treatment of **4** with methyl iodide in the presence of sodium hydride afforded a crystalline compound (**6**) in which a nitrile functionality was regenerated as evidenced by a band at 2235 cm^{-1} in the ir. In the nmr the appearance of the resultant methyl signal at δ 3.5 suggests that the methyl group resides on nitrogen.

Routine spectral analysis of both the hydrolysis and alkylation products could not provide a firm answer as to whether the initial product resulting from the reaction of **1** with 3,4,5,6-tetrahydro-2-pyrimidinethiol was **4a** or **4b**. We therefore decided to analyze the carbon-13 nmr spectra of the described compounds since it is much more sensitive to changes in structural features than the other techniques. In Figure I, data on model compounds are given and in Table I the data obtained for our systems. Since compounds **4** and **6** are interrelated by chemistry it was decided to look at these systems first.

In the case of compound **4**, the shift assignments for the protonated carbons in the pyridine ring were readily made by comparison with the model compounds. An error in assignment of structure (*i.e.*, **4a** for **4b**) would not affect the shift assignments given except for carbons C-2, C-6, and C-7. In any case the C-6 and C-7 assignments are tentative due to the closeness of the shifts and the lack of good model systems to evaluate them properly. Due to this difficulty it was not possible a priori to assign a structure to **4**.

However, the alkylation product derived from **4** provided shift data which was more readily interpreted. Of major importance as far as structure is concerned is the lowest field signal at δ 178.6. This observation clearly indicates that the correct structure for **6** is that shown in Scheme II and not **6a** which could be derived from alkylation of **4a** (7).



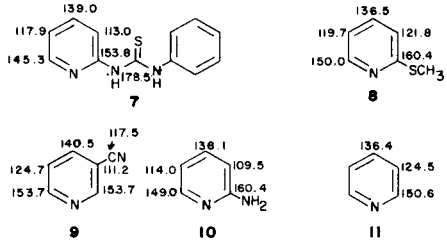
6a

This is confirmed by model compound **7**. Systems like **6a** invariably exhibit resonances for C-7 at much higher field, usually around 155 ppm. The remaining peak assignments are readily made by comparison with the models in Figure I. Now that the structure for **6** has been elucidated, it is more likely to have arisen from **4b** than **4a**.

In retrospect, the structure for the reaction product of **1** with *N,N'*-dimethylthiourea is assigned that of **3a**. The observed signal at 178.3 ppm suggests the presence of a thiocarbonyl group (7,8). This signal would not be expected in the other possible structure **3b**.

In summary, the reaction of thioureas with 2-chloronicotinonitrile in the presence of sodium hydride results in the displacement of the chlorine (6) by the nitrogen of the thiourea. In the case of *N,N'*-dimethylthiourea, subsequent attack of the nitrile by the other thiourea nitrogen furnishes **3a**. In the reaction of **1** with 3,4,5,6-tetrahydro-2-pyrimidinethiol the secondary cyclization occurs by attack of sulfur on the nitrile to produce **4b**, a new ring system.

Figure I: Model Systems for Carbon-13 NMR Analysis

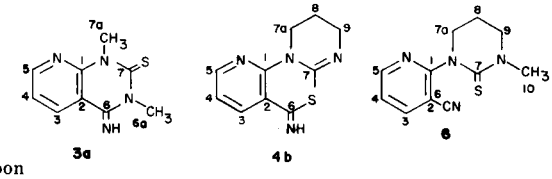


Compound **8**: Lit. ref. 8

Compound **9**, **10**, **11**: Lit. ref. 9

Table I

Carbon-13 NMR Shift Data for **3a**, **4b** and **6**



Carbon	**3a**	**4b**	**6**
1	158.0	156.4 (a)	159.2
2	112.2	120.9	110.5
3	134.7	135.2	141.6
4	119.7	120.9	122.2
5	152.2	152.0	152.5
6	148.7	154.5 (a)	115.4
7	178.3	146.8 (a)	178.6

(a) Assignments in the same column may be interchanged.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60 and EM-360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.* 0.5 molar in deuteriodimethylsulfoxide in 10 mm (od) sample tubes to which a small amount of iron III tris(pentane-2,5-dionate) was added (10). General nmr spectral and instrumental parameters employed were: internal deuterium lock to the solvent; spectral width of 5120 Hz; a pulse width of 25 μseconds, corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra 8K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to $\pm$0.05 ppm.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions. Model compounds listed in Figure I were either obtained commercially or, in the case of **7**, synthesized by reported procedures (11).

3,4-Dihydro-4-imino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2-(1*H*)thione (**3a**).

To a solution of 4.0 g. of *N,N'*-dimethylthiourea in 75 ml. of dimethylacetamide was added 1.9 g. of sodium hydride (50% in mineral oil/pentane washed) in portions. The mixture was stirred at room temperature for 1 hour; then 5.3 g. of **1** (12) was added and stirring was continued at 100° for 1 hour. The mixture was concentrated to one-half volume and then poured into water. The resulting precipitate was washed successively with water, ethanol, and then ether to give 4.0 g. (51%) of **3a**. An analytical sample was crystallized from ethanol, m.p. 192-195°; ir (potassium bromide): 3325, 1620, 1425 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 8.6-8.25 (m, 3, contains 1 exchangeable proton), 7.2 (m, 1), 4.05 (s, 3), 3.9 (s, 3); ms: (70 eV) m/e 206 (M+).

Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.4; H, 4.9; N, 27.2; S, 15.5. Found: C, 52.3; H, 5.0; N, 27.0; S, 15.7.

9,10-Dihydro-5-imino-5*H*,8*H*-pyrido[2,3-*d*]pyrimido[2,1-*b*][1,3]thiazine (**4b**).

To a solution of 3.4 g. of 3,4,5,6-tetrahydro-2-pyrimidinethiol in 50 ml. of dimethylacetamide was added 1.4 g. of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 15 minutes then 4.0 g. of **1** (12) was added in portions. The mixture was stirred at room temperature for 1 hour then at 100° for 1 hour. The solvent was removed under reduced pressure and water was added to the residue. The resulting precipitate was filtered and was washed successively with water, ethanol, then methylene chloride to give 2.6 g. (41%) of **4b**. An analytical sample was crystallized from methanol, m.p. 196-199°; ir (potassium bromide): 3325, 1610, 1585 cm^{-1}; nmr (deuteriochloroform): δ 8.7-7.8 (m, 3, contains 1 exchangeable proton), 7.25 (m, 1), 4.05 (t, 2), 3.6 (t, 2), 2.1 (m, 2); ms: 70 eV) m/e 218 (M+).

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.0; H, 4.6; N, 25.7; S, 14.7. Found: C, 55.1; H, 4.8; N, 25.5; S, 15.0.

9,10-Dihydro-5*H*,8*H*-pyrido[2,3-*d*]pyrimido[2,1-*b*][1,3]thiazin-5-one (**5**).

A solution of 5.0 g. of **4b** in 40 ml. of 2*N* hydrochloric acid was heated on a steam bath for 15 minutes. After cooling, the solution was basified with 2*N* sodium hydroxide and the resulting precipitate was filtered, washed with water, and dried to give 4.0 g. (80%) of **5**. An analytical sample was crystallized from ethanol, m.p. 192-195°; ir (chloroform): 1665, 1610, 1365 cm^{-1}; nmr (deuteriochloroform): δ 8.8-8.3 (m, 2), 7.25 (m, 1), 4.05 (t, 2), 3.7 (t, 2), 2.05 (m, 2); ^{13}C nmr (deuteriochloroform): δ 21.0, 42.5, 46.4, 120.2, 121.2, 138.4, 146.3, 153.7, 156.9, 161.3.

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.8; H, 4.1; N, 19.2; S, 14.6. Found: C, 55.0; H, 4.1; N, 19.2; S, 14.2.

2-(3,4,5,6-Tetrahydro-3-methyl-2-thioxopyrimidin-1-(2*H*)yl)nicotinonitrile (**6**).

To a suspension of 3.0 g. of **4b** in 40 ml. of dimethylacetamide was added 0.66 g. of sodium hydride (50% in mineral oil, pentane washed) and the mixture was heated at 100° for 30 minutes (hydrogen evolution occurs). After cooling to room temperature, 2.0 g. of methyl iodide was added and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and water was added to the residue. The organic material was extracted into ethyl acetate, treated with decolorizing carbon, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue crystallized from ethanol to give 0.75 g. (24%) of **6**, m.p. 150-153°; ir (chloroform): 2235, 1520, 1440, 1345, 1305 cm^{-1}; nmr (deuteriochloroform): δ 8.65 (m, 1), 8.0 (m, 1), 7.35 (m, 1), 4.0-3.4 (m, 4), 3.5 (s, 3), 2.3 (m, 2); ms: (70 eV) m/e 232 (M+).

Anal. Calcd. for $C_{11}H_{12}N_4S$: C, 56.9; H, 5.2; N, 24.1; S, 13.8. Found: C, 56.9; H, 5.4; N, 24.3; S, 13.7.

REFERENCES AND NOTES

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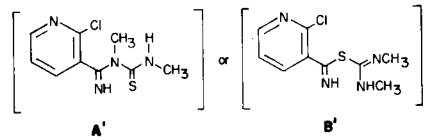
(6) Intermediates **A** or **B** have not been isolated and one cannot rule out the possibility of initial attack on the nitrile therefore giving rise to intermediates **A'** or **B'**. Displacement of the chlorine in **A'** with either



A' **B'**

the sulfur or nitrogen of the thiourea would produce either **2** or **3a** respectively. Cyclization of **B'** would give **3b**.

(7) For instance, see, J. R. Bartels-Weith, M. T. Burgess, J. M. Stevenson, *J. Org. Chem.*, **42**, 3725 (1977).

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