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The Halogen-Nitrile Exchange Reaction as a Route to Pyrimidinecarbonitriles (1)

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In the course of a program directed toward the synthesis of 4-aminomethyl- and 4-hydroxymethylpyrimidines, it became desirable to effect a halogen-nitrile interconversion for 4-halopyrimidines, heretofore unreported in the literature (2). The purpose of this communication is to describe the applicability of this route in the synthesis of 2-methylthio-4-pyrimidinecarbonitrile (I).

When 2-methylthio-4-chloropyrimidine (II) was treated with cuprous cyanide in refluxing pyridine there was obtained, instead of the nitrile I, only an unidentified product of empirical formula $C_{10}H_9N_3S$. MacKay and Hitchings (3) have reported that while 6-purinecarbonitrile was obtained from 6-iodopurine and cuprous cyanide in pyridine, the reaction failed when 6-chloropurine was employed. Accordingly, the hydroiodide (III) of 2-methylthio-4-iodopyrimidine was prepared by stirring II with hydroiodic acid at room temperature. Careful neutralization of III with aqueous ammonia gave 2-methylthio-4-iodopyrimidine (IV). Treatment of IV with cuprous cyanide in pyridine gave 2-methylthio-4-pyrimidinecarbonitrile (I).

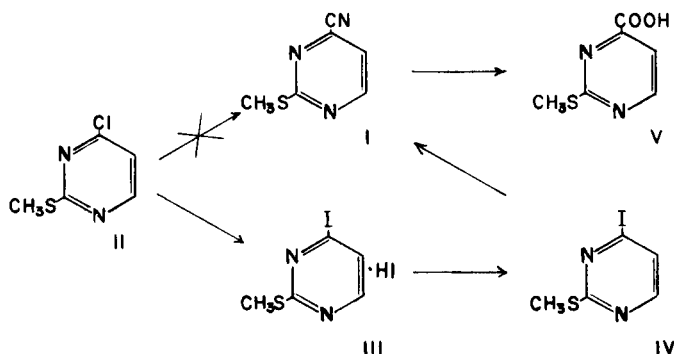
A nitrile absorption band in the infrared spectrum of I was not observed. Sensi and Gallo (4) have shown that the intensity of this band in aromatic nitriles is quenched by ortho and para electron withdrawing groups. Apparently the annular nitrogens of the pyrimidinecarbonitrile I were sufficiently

electron withdrawing to quench the cyano absorption band. Furthermore, Taylor and Jefford (5) have observed that the nitrile absorption band is not evident in a series of 2-cyano-*s*-triazines.

The structure of the nitrile I was elucidated by hydrolysis to 2-methylthio-4-pyrimidinecarboxylic acid (V). This acid exhibited an infrared spectrum identical to that of an authentic sample of V prepared by the reductive dehalogenation of 2-methylthio-5-bromo-4-pyrimidinecarboxylic acid (6).

Although this method appears suitable for the preparation of pyrimidinecarbonitriles, the treatment of 2-methylthio-4-iodo-5-carbethoxy-pyrimidine (VI) with cuprous cyanide under a variety of conditions gave only products resulting from nucleophilic displacement at C-4 during work-up. For example, when the reaction mixture from cuprous cyanide and VI in pyridine was treated with aqueous ethylenediamine to destroy metal cyanide-nitrile complexes (7) only *N,N'*-bis-(2-methylthio-5-carbethoxy-4-pyrimidinyl)-ethylenediamine (VII) was isolated.

This is suggestive that under these conditions 2-methylthio-5-carbethoxy-4-pyrimidinecarbonitrile (VIII), if formed, is susceptible to nucleophilic displacement at C-4. The enhanced reactivity of VIII in comparison to I in these displacements is attributable to the additional activating effect of the carbethoxy group in the former.



EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus. Infrared spectra were determined using a Beckman IR-5A spectrophotometer.

Materials.

2-Methylthio-4-hydroxypyrimidine (8), 2-methylthio-4-chloropyrimidine (II) (8), 2-methylthio-4-hydroxy-5-carbethoxypyrimidine (9), and 2-methylthio-4-chloro-5-carbethoxypyrimidine (9) were prepared according to the procedures described in the literature.

2-Methylthio-4-iodopyrimidine hydroiodide (III).

A mixture of 10 g. (62 mmoles) of 2-methylthio-4-chloropyrimidine (II) in 70 ml. hydroiodic acid (47-50%) was stirred for 15 minutes at room temperature and then cooled for 12 hr. The solid which formed was filtered and washed with ether to give 14.1 g. (60%) of product, m.p. 140-142°.

Anal. Calcd. for $C_5H_6I_2N_2S$: C, 15.80; H, 1.59; N, 7.37. Found: C, 15.68; H, 1.51; N, 7.50.

2-Methylthio-4-iodopyrimidine (IV).

A cooled suspension of III (14.1 g.; 37 mmoles) in 75 ml. water was made slightly alkaline with concentrated ammonium hydroxide. The resulting suspension was extracted with two 100-ml. portions of ether. Upon removal of the ether *in vacuo* there remained 6.6 g. (71%) of the crude iodopyrimidine. An analytical sample was obtained by recrystallization from low boiling petroleum ether, m.p. 45.5-47.0°.

Anal. Calcd. for $C_5H_6IN_2S$: C, 23.82; H, 2.00; N, 11.11. Found: C, 23.55; H, 1.75; N, 11.09.

2-Methylthio-4-pyrimidinecarbonitrile (I).

A mixture of 1.4 g. (5.5 mmoles) of IV, 0.50 g. (5.5 mmoles) of cuprous cyanide and 30 ml. dry pyridine was refluxed for 4 hr. The resulting suspension was cooled, filtered, and washed with ether. The filtrates and combined washings were concentrated to dryness on a rotary evaporator. The residue was extracted with two 50-ml. portions of hot water. A solid separated from the combined aqueous extracts on cooling. The suspension was extracted with ether. The residue, after removal of the ether weighed 0.45 g. (54%) and melted at 78-82°. An analytical sample was obtained by vacuum sublimation, m.p. 82-84°.

Anal. Calcd. for $C_5H_5N_3S$: C, 47.66; H, 3.33; N, 27.79. Found: C, 47.31; H, 3.01; N, 27.80.

2-Methylthio-4-pyrimidinecarboxylic acid (V).

A mixture of 0.85 g. (5.6 mmoles) of I and 6 ml. 2 N sodium hydroxide was refluxed for 2 hr. The reaction mixture was cooled and acidified with dilute (3 N) hydrochloric acid. The product, which separated (0.4 g., 43%) was recrystallized twice from benzene and once from water, m.p. 208-210° (eff.). An authentic sample of V prepared by the reductive dehalogenation of 2-methylthio-5-bromo-4-pyrimidine-carboxylic acid (6), melted at 206-210°. A mixed melting point determination gave no depression.

2-Methylthio-4-iodo-5-carbethoxypyrimidine (VI).

A mixture of 10 g. (43 mmoles) of 2-methylthio-4-chloro-5-carbethoxypyrimidine and 75 ml. hydroiodic acid (47-50%) was stirred for 5 minutes at room temperature and then cooled 2 hr. The solid which formed was filtered, washed with ether, and suspended in 100 ml. water. The suspension was made slightly alkaline with concentrated ammonium hydroxide, and the mixture was cooled for 2 hr. The product which separated (10.9 g., 79%) was recrystallized twice from low boiling ligroine, m.p. 72.5-74.0°.

Anal. Calcd. for $C_8H_9IN_2O_2S$: C, 29.64; H, 2.80; N, 8.64. Found: C, 29.89; H, 2.92; N, 8.76, 8.59.

N,N'-bis-(2-Methylthio-5-carbethoxy-4-pyrimidinyl)ethylenediamine (VII).

A mixture of 9.7 g. (30 mmoles) of VI, 3.3 g. (39 mmoles) cuprous cyanide, and 55 ml. dimethylformamide was stirred at room temperature for 2 hr. An aqueous solution of ethylenediamine (135 ml., 33%) was added and the solution was stirred at 60° for 30 minutes. The reaction mixture was extracted with four 100-ml. portions of benzene. After removal of the benzene *in vacuo*, there remained 5.3 g. of a residue which was recrystallized twice from *n*-propyl alcohol. The product, m.p. 147-148°, exhibited an infrared spectrum identical to that of N,N'-bis-(2-methylthio-5-carbethoxy-4-pyrimidinyl)ethylenediamine VII, prepared by treating 2-methylthio-4-chloro-5-carbethoxypyrimidine with ethylenediamine. A mixed melting point of the two gave no depression.

Anal. Calcd. for $C_{18}H_{24}N_6O_4S_2$: C, 47.77; H, 5.35; N, 18.57. Found: C, 48.27; H, 5.20; N, 17.82.

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