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A new method for the preparation of 5-bromo- and 5-chloropyrimidine from furfural has been described.

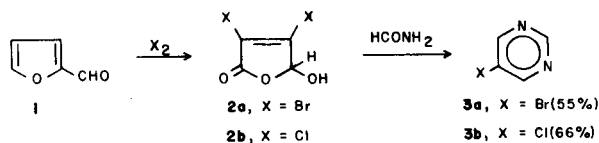
J. Heterocyclic Chem., **20**, 1721 (1983).

In a previous report, we described the preparation of 5-bromo-pyrimidine *via* the direct bromination of pyrimidine [1]. Our interest in developing a convenient synthesis of halopyrimidines from readily available and inexpensive starting materials has continued, primarily because 5-bromopyrimidine has been shown to be a key intermediate in the elaboration of the 5-position by lithium-halogen exchange [2], and more recently the 4-position by reaction with lithium diisopropylamide [3]. In this communication, we describe a convenient two-step preparation of both 5-bromopyrimidine (**3a**) and 5-chloropyrimidine (**3b**) utilizing furfural as a starting material. Prior to this report, **3b** was available only by multistep sequences in low overall yield [4], and its chemistry remains virtually unknown.

Some time ago, Kunckell [5] and later Budesinsky [6] prepared some highly functionalized 4-carboxy-5-halo-2-alkyl and aryl pyrimidines by reaction of substituted amidines with the mucohalic acids (**2a-b**) [7]. Yanagita demonstrated the reaction of **2b** with guanidine gave 4-carboxy-5-chloro-2-aminopyrimidine [8]. Both mucobromic (**2a**) and mucochloric acid (**2b**) were of particular interest to us because they were readily available in good yield by treatment of furfural (**1**) with either bromine or chlorine [9,10] and they contained the requisite three carbon unit used by Bredereck and co-workers to prepare pyrimidines by reaction with formamide [11].

We found that when **2a** or **b** was allowed to react with

formamide at 185°, the distillate from the reaction mixture contained the halopyrimidines **3a-b** which were isolated in 55 and 65 percent yield respectively. We assume the reaction proceeds by way of the 4-carboxy derivative of **3** which spontaneously decarboxylates under the reaction conditions.



The foregoing syntheses represent a simple and convenient procedure for the preparation of pivotal intermediates for functionalization of either the 4- and 5-position of pyrimidine. Some spectral data on **3a-b** are listed in Table 1.

EXPERIMENTAL

Elemental analyses were performed by Mr. G. Maciak and associates of Eli Lilly and Company. The ¹H nmr spectra were determined on a Varian T-60 spectrometer. Melting points were run on a Thomas-Hoover apparatus and are uncorrected. The ¹³C nmr spectra were determined on a Jeol FX90Q fourier transform spectrometer.

5-Bromopyrimidine (**3a**).

To a 1 l flask equipped with a mechanical stirrer, thermometer, addition funnel and distilling head leading to a 1 l receiver in an ice-alcohol bath was added 35 g (0.5 mole) of boric anhydride, and 160 ml of form-

Table 1

Spectral Data of 5-Bromo- and 5-Chloropyrimidine

| Compound | IR (Chloroform) cm ⁻¹ | ¹ H NMR (Duete- riochloroform/ TMS) ppm | ¹³ C NMR (DMSO-d ₆) ppm | UV (95% Ethanol) λ max (log ε) | MS m/e (8) |
|-----------|---|--|---|--------------------------------------|---|
| 3a | 3004, 1553, 1425, 1412, 1396, 1215, 1183, 1150, 1125, 1016, 901, | 9.15 H-2, S, 1H 8.80 H-4, 6, S, 2H | 156 C-2 157 C-4,6 120 C-5 | 260 (3.33) 216 (3.92) | 158-160 (100) 131-133 (21) 104-106 (44) |
| 3b | 3005, 1550, 1428, 1399, 1215, 1183, 1159, 1140, 1026, 901, | 9.08 H-2, S, 1H 8.73 H-4, 6, S, 2H | 156 C-2 155 C-4,6 130 C-5 | 258 (3.35) 209 (3.86) | 114-116 (100) 87-89 (76) 60-62 (71) |

amide. The mixture was heated to 180-185°, and a solution of 258 g (1.0 mole) of mucobromic acid [9] in a mixture of 240 ml of formamide and 120 ml of methanol was added dropwise over one hour. A faster addition rate resulted in product escaping the receiver. After the addition was complete, the mixture was stirred 15 minutes at 180-185°, and 200 ml of water was added dropwise over 15 minutes to steam distill any remaining product. To the slurry in the receiver was added 140 ml of heptane and the mixture was heated to reflux (50°). The organic phase was separated hot and cooled slowly to 5° affording 46.8 g of a light tan solid. The filtrate was evaporated to dryness *in vacuo* giving 12.1 g of nearly colorless solid. The aqueous phase from the reaction distillate was extracted with chloroform (3 × 75 ml). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated carefully *in vacuo* affording 29.0 g of yellow crystalline solid. All of the lots of crude 5-bromopyrimidine (87.9 g, 55%) were slurried in 400 ml water and steam distilled. The receiver was extracted with methylene chloride (3 × 100 ml), and the combined organic solutions were evaporated affording **3a**, 75.8 g (48%), mp 73-74°. A mixed melting point of **3a** with a sample of 5-bromopyrimidine prepared by the method described in reference [1] was not depressed.

5-Chloropyrimidine (**3b**).

Similarly, mucochloric acid [10] **2b** (1.0 mole) yielded 5-chloropyrimidine (**3b**) using the same procedure as for the preparation of **3a**. Careful evaporation of the methylene chloride extracts of the steam distilled product gave 74.4 g, 65% mp 34-35° (lit [4] 36.5°), as a white crystalline volatile solid.

Anal. Calcd. for C₄H₃ClN₂: C, 41.95; H, 2.64; N, 24.46. Found: C, 41.85; H, 2.82; N, 24.54.

REFERENCES AND NOTES

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[2] Metal-halogen exchange at low temperature with butyl lithium affords 5-lithiopyrimidine which undergoes numerous reactions characteristic of organolithium compounds (*c.f.*) S. Gronowitz and J. Roe, *Acta Chem. Scand.*, **19**, 1741 (1965); J. D. Davenport, R. E. Hackler and H. Taylor, British Patent 1,218,623; *Chem. Abstr.*, **75**, 15186h (1971).

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[7] A spectroscopic study (N. P. Buu-Hoi, M. Dufour and P. Jacquignon, *Bull. Soc. Chim. France*, 2999 (1971)) has demonstrated that these compounds exist in the closed ring form **2a-b** under neutral or acidic conditions and in the open ring form **i** in alkaline medium.



Due to this tautomerism, these substances have been named as derivatives of 3-formylacrylic acid, 4-oxo-2-butenic acid, malealdehydic acid, 5-hydroxy-2(5*H*)-furanone, and mucohalic acid.

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