

Studies on the Bromination of Pyrimidine. A Facile Synthesis of 5-Bromopyrimidine

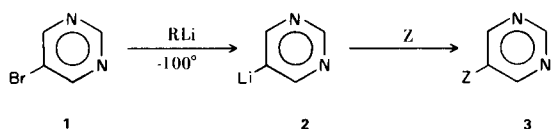
Thomas J. Kress and Larry L. Moore

The Lilly Research Laboratories, Process Research and Development Division,
Eli Lilly and Company, Indianapolis, Indiana 46206

Received December 4, 1972

Three methods for bromination of pyrimidine were investigated: (a) the bromination of pyrimidine hydrochloride in aromatic solvents, (b) the vapor phase bromination of pyrimidine, and (c) the pyrolysis of pyrimidine hydrochloride perbromide. The addition of bromine to a slurry of pyrimidine hydrochloride in nitrobenzene proved to be superior and afforded excellent yields of 5-bromopyrimidine.

Recently two groups of workers (1,2) have shown that 5-bromopyrimidine (**1**) will readily exchange with alkyl lithium salts at low temperature to afford 5-pyrimidyl lithium (**2**). This reagent (**2**) undergoes a variety of reactions characteristic of organolithium compounds, thus



giving a convenient route to a host of 5-substituted pyrimidines. Our interest in the synthesis of 5-substituted pyrimidines led us to investigate a convenient preparation

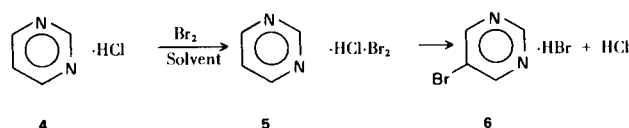
of 5-bromopyrimidine and we now wish to report the results of this study (3).

Bromination of Pyrimidine Hydrochloride in a Solvent.

We have found that the addition of bromine to a suspension of pyrimidine hydrochloride in aromatic solvents affords excellent yields of **1** (see Table I). The superiority of nitrobenzene as the solvent, we feel, was due to the fact that both the starting material and product were insoluble while the intermediate **5** was quite soluble. These properties allowed only a small concentration of reacting species in solution at one time, and also permitted the product to crystallize from the reaction mixture. The optimum conditions for the reaction in nitrobenzene were determined, and these data are described in the Experimental section.

TABLE I

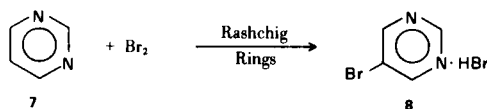
Bromination of Pyrimidine Hydrochloride in a Solvent



Solvent	Temp. (°C)	Time (hr.)	% Yield 5-Bromopyrimidine
Benzene	80	3.5	71
Chlorobenzene	105	2.0	76
<i>o</i> -Dichlorobenzene	130	3.0	84
Benzonitrile	130	2.5	80
Nitrobenzene	130	2.5	85-88

TABLE II

Vapor Phase Bromination of Pyrimidine

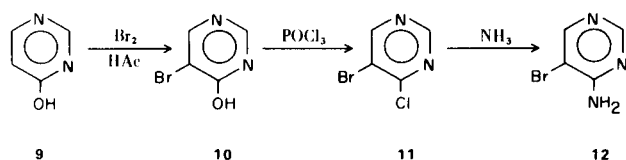


Temp. (°C)	Size Run (moles)	Addition Time of Reagents (min)	Ratio Pyrimidine/Br ₂	Column Size (cm)	Percent Yield 5-Bromopyrimidine
215	0.5	60	1.0/1.0	3.5 x 60	48
230	0.5	50	1.0/1.1	2.5 x 30	62
230	0.5	90	1.0/1.1	3.5 x 60	59
300	1.0	60	1.0/1.1	3.5 x 60	33
300	1.0	240	1.0/1.1	3.5 x 60	27

Vapor Phase Bromination of Pyrimidine.

A recent publication by van der Does and den Hertog (4) dealing with the vapor phase bromination of pyrimidine on pumice and in an empty tube prompted us to report our work on this reaction. The apparatus we used consisted of a glass column packed with Raschig rings, and the results are summarized in Table II. The maximum conversion to 5-bromopyrimidine in our study (230°, 62 percent yield) as compared with van der Does and den Hertog's (220°, 60 percent yield) is in close agreement. In our hands, the reaction at 300° led to frequent plugging of the column, and at lower temperatures starting material was recovered. Attempts to prepare larger quantities of **1** at 230° were unsatisfactory, since the column became plugged on prolonged use.

A small amount of byproduct was observed over the temperature range investigated. This substance was identified as 4-amino-5-bromopyrimidine (**12**) by its spectral data (ir, pmr, and mass spectrum), and finally by comparison with an authentic sample prepared from **9** (5). The pmr spectrum of **12** (see Table III) deserves comment since in DMSO both ring protons have identical



chemical shifts, while its spectrum in acidic solvents displays a doublet for both H₂ and H₆, due to across nitrogen coupling. The spectrum of **10** in DMSO-aqueous hydrochloric acid gave a sharp singlet for both ring protons, but in DMSO alone two singlets were observed.

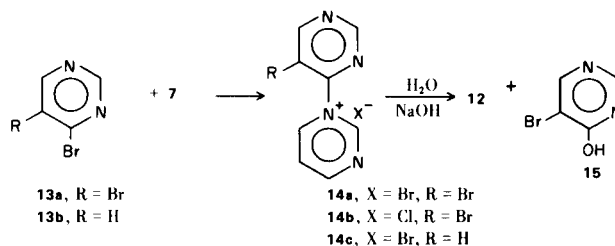
TABLE III

Pmr Spectral Data of Some Pyrimidines (c)

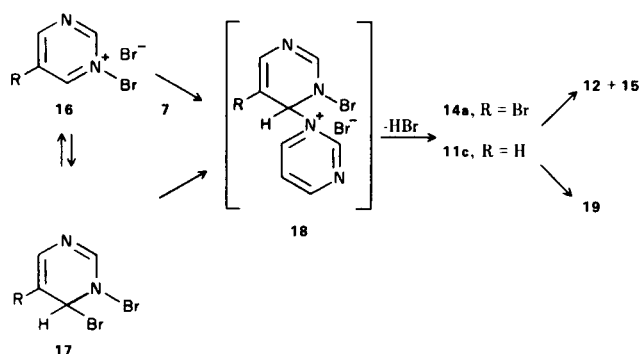
Compound	Chemical Shift (τ)				Coupling Constants (Hz)	
	H ₂	H ₅	H ₆	NH	J _{5,6}	J _{2,6}
9 (a)	1.74	3.62	2.02	0.37	7.0	
9 (b)	1.54	3.47	1.99		7.0	
10 (a)	1.66		1.73	-1.9		
10 (b)	1.54		1.54			
11 (a)	0.94		1.00			
11 (b)	0.89		0.94			
12 (a)	1.67		1.67			
12 (b)	1.22		1.30			0.5

(a) DMSO-d₆ solvent. (b) DMSO-d₆ and deuterium chloride-deuterium oxide) solvent. (c) In the assignment of H₂ and H₆ in compounds **10**, **11**, and **12** it was assumed that H₂ was the most deshielded proton.

The formation of **12** was not unprecedented since 4-aminopyrimidine was obtained as a byproduct in the vapor phase bromination of pyridine. The aminopyrimidine was presumably formed by basic hydrolysis of the condensation of 4-bromopyridine with pyridine. Analogously, **12** could arise from the reaction of 4,5-dibromopyrimidine



(13a) with pyrimidine (7) affording *N*-(5-bromo-4-pyrimidyl)pyrimidinium bromide (14a) followed by basic steam distillation. We have reacted 11 and 7 giving 14b, and subsequent refluxing in aqueous base afforded a mixture of 12 and 4-hydroxy-5-bromopyrimidine (15). Although we did not observe 15 in our studies, this byproduct was isolated by van der Does and den Hertog from bromination in an empty tube. They also obtained small amounts of 4-aminopyrimidine (19) in the empty tube reactions, but not at 300° or lower in the presence of a contact substance. This latter impurity was presumed to arise from 4-bromopyrimidine by a process similar to the formation of 12. However, these impurities need not necessarily arise in this manner, but could come from a direct reaction of the perbromide complex (16 or 17, R = Br or H) with pyrimidine as follows:



We attempted to isolate 13a as the more stable 4-ethoxy derivative by treatment of the solid from the column with sodium ethoxide in ethanol, but none was found.

Thus, if 13a was formed in the vapor phase reaction, it did not survive on the column and was converted directly to 14a.

Pyrolysis of Pyrimidine Hydrochloride Perbromide.

The fact that the vapor phase bromination was a fast reaction (contact time 25-30 seconds), led us to examine the pyrolysis of pyrimidine hydrochloride perbromide (5). Our best yield (70%) and least amount of charring of the column were found to occur at 300° using a slow addition of the complex (5), and a slight excess of bromine. The rate of production of 6 was limited to 25-30 g. an hour, and on prolonged use the reaction tube became plugged.

Of the three methods we examined, the reaction employing nitrobenzene as the solvent proved to be the most convenient laboratory procedure, and afforded the highest yield of 1.

EXPERIMENTAL (6)

Pyrimidine (7).

Pyrimidine was prepared by the method of Bredereck (7) and distilled twice through a 2.5 x 30 cm column packed with glass beads. The fraction between 124-126° (lit. value 124-126°) was collected affording a total of 3.2 Kg. This sample was used in all reactions.

Pyrimidine Hydrochloride.

Pyrimidine was dissolved in anhydrous diethyl ether (2.5 l./mole) and dry hydrogen chloride gas was bubbled through the solution until saturated. The resulting white solid was filtered, dried *in vacuo*, and stored in a desiccator over anhydrous calcium chloride, m.p. 163-165° with sublimation.

TABLE IV

Pyrolysis of Pyrimidine Hydrochloride Perbromide (a)

Temp. (°C)	Addition Time (min)	Ratio Pyrimidine-HCl/Br ₂	% Yield 5-Bromopyrimidine	Carrier Gas
230 (b)	135	1:1	43	N ₂
230 (c)	85	1:1.1	66	
230 (c)	80	1:1.1	58	N ₂
265 (d)	120	1:1.4	56	
295 (d)	105	1:1	57	
300 (d)	120	1:1.1	70	
320 (d)	80	1:1.4	59	
350 (d)	105	1:1.1	63	

(a) All of the reactions were carried out with 0.25 M of pyrimidine hydrochloride. (b) Column size 2.5 x 5.0 cm. (c) Column size 2.5 x 30 cm. (d) Column size 2.5 x 10 cm.

4-Amino-5-bromopyrimidine (**9**) (5).

Thiouracil was converted to 4-hydroxypyrimidine (**8**) (**9**). Bromination of **9** in acetic acid gave **10** which was treated with phosphorus oxychloride affording **11**. Treatment of **11** with aqueous ammonia gave **12**. Crystallization of **12** from water gave pale yellow needles, m.p. 209-211° (lit. value (5) 208-210°). The pmr spectral data on the intermediates are listed in Table III.

Method A. 5-Bromopyrimidine (**1**).

Vapor Phase Bromination of Pyrimidine.

The apparatus in which the vapor phase bromination was carried out was based on the design by Den Hertog and Wibaut (9) and consisted of a pyrex glass tube (3.5 x 70 cm) packed with Raschig rings (6 x 6 mm) to a depth of 60 cm and heated over a length of 60 cm with Nichrome V wire strung with porcelain beads. Two side-arm inlet tubes with preheater columns attached were connected to the main reaction tube by means of ground glass ball joints. The inlet tubes were mounted on opposite sides of the column, one being 3 cm above the other. On top of the reaction tube above both side-arms was an inlet for preheated nitrogen gas. The reaction tube and the two preheater columns were equilibrated to the desired temperature (see Table II) and liquid bromine and pyrimidine were added dropwise to their respective preheater columns from calibrated dropping funnels. The bromine vapor entered the reaction chamber just above the column packing and the pyrimidine vapor entered 3 cm above the bromine. Both gases were swept through the column with nitrogen gas which entered the column 6 cm above the pyrimidine inlet tube. The effluent gases from the column were condensed in a series of 2 one-liter round bottom flasks cooled by dry ice-acetone baths. The solids from the two traps were taken up into water, made alkaline with 10 percent aqueous sodium hydroxide and steam distilled. The product was isolated as in the bromination in aromatic solvents.

The pot residue from the steam distillation was continuously extracted with chloroform for 24 hours. The chloroform was separated, dried, and evaporated to dryness *in vacuo* affording 2-3 g. of a tan solid. The solid was crystallized twice from ethyl acetate and sublimed at 150°/10 mm giving pale yellow cubes, m.p. 209-211°. The high resolution mass spectrum gave the empirical formula C₄H₄BrN₃ and showed the loss of Br, NH₂, and two consecutive losses of HCN as the major fragmentation pathways. A mixed melting point with **12** was not depressed. The infrared and pmr spectra of the two samples were identical.

Attempted Isolation of 4-Ethoxy-5-bromopyrimidine from 4,5-Dibromopyrimidine.

In one experiment the contents of the dry ice-acetone traps were treated directly with sodium ethoxide in ethanol. The resulting mixture was heated on a steam bath for 30 minutes; the ethanol was removed *in vacuo*. The residue was dissolved in water and extracted affording pale yellow crystals. The pmr spectrum showed only the presence of **1** and a trace of **12**.

Method B. 5-Bromopyrimidine (**1**).Pyrolysis of Pyrimidine Hydrochloride Perbromide (**5**).

The experimental conditions used are listed in Table IV. The reaction was performed by adding pyrimidine hydrochloride to a dropping funnel followed by the desired amount of bromine. The resulting viscous red liquid was added dropwise to a glass column packed with (6 x 6 m) Raschig rings. The product was trapped in dry ice-acetone traps and isolated as in the vapor phase reaction (Method A).

Method C. 5-Bromopyrimidine (**1**).

Bromination of Pyrimidine Hydrochloride in Aromatic Solvents (see Table I).

A slurry of pyrimidine hydrochloride, 29.0 g. (0.25 mole) in 30 ml. of nitrobenzene, contained in a three-neck round bottom flask equipped with a paddle stirrer, condenser, dropping funnel, and thermometer was heated at 130°, and bromine 44.0 g. (0.275 mole) was added dropwise over 30 minutes. The mixture was allowed to stir an additional two hours at 130°, cooled to 80°, and 150 ml. of benzene was added. The resulting slurry was filtered and washed with 100 ml. of benzene and sucked dry. The tan solid (61-62 g.) was placed in 200 ml. of water, adjusted to pH 8 with saturated aqueous sodium carbonate, and steam distilled. The white solid was filtered from the chilled aqueous steam distillate and air dried overnight. The aqueous filtrate was extracted with ethyl ether (3 x 100 ml.), dried, filtered and evaporated affording an additional 1 to 3 g. of product. The average yield was 34-35 g. (85-88 percent of theory), m.p. 73-74°, identical to that prepared by Bredereck (3).

Optimum Conditions for Bromination in Nitrobenzene.

Four experiments were conducted under the conditions described in Method C. The hydrogen chloride gas evolved was measured by passing it through a series of solutions of known concentration of aqueous sodium hydroxide containing phenolphthalein indicator. The time required for the evolution of the theoretical amount of hydrogen chloride, and the corresponding yield of **1** were determined. The maximum yield was obtained at 130-135°. The results of these experiments are listed below.

TABLE V

Bromination of Pyrimidine Hydrochloride in Nitrobenzene

Temp. (°C)	Time to Evolve Theoret. Amount of HCl (hr.)	% Yield 5-Bromopyrimidine
100-110	8.0	59
130-135	2.0-2.5	85-88
140-145	1.5-2.0	70
160-165	0.5-0.75	17

4-Amino-5-bromopyrimidine (**12**) and 4-Hydroxy-5-bromopyrimidine (**15**) from Hydrolysis of *N*-(5-Bromo-4-pyrimidyl)pyrimidinium Chloride (**14b**).

A mixture of 4-chloro-5-bromopyrimidine (**11**) (7.0 g., 36.3 mmoles) and pyrimidine (2.9 g., 36.3 mmoles) were heated on a steam bath for two hours. The resulting solid was diluted with 120 ml. of 10 percent aqueous sodium hydroxide, refluxed for two hours, cooled, extracted with chloroform (3 x 75 ml.), dried over anhydrous magnesium sulfate, filtered, and evaporated affording a tan solid. Crystallization from ethyl acetate gave 0.2 g. as tan plates. Thin layer chromatography (silica gel, 1:1 ethyl acetate-benzene) showed the presence of two substances, *rf* 0.38 and 0.48 with spots of about equal intensity. The mixture was sublimed at 160°/10 mm in a test tube affording two distinct bands. The upper band, m.p. 208-210°, had identical tlc, *rf* 0.48, mass spectrum, and mixed melting point as **12**.

The lower band, m.p. 198-199°, tlc *rf* 0.38 had *m/e* M⁺ 174, 176, and identical cleavage pattern as **15**. A mixed melting point with **15** (lit. value 199-200°) was not depressed (5).

Acknowledgement.

We would like to thank Drs. L. Paquette, E. C. Taylor, and J. Baldwin for several helpful discussions, Drs. J. Occolowitz and A. Kossoy for the mass spectral determinations, and Dr. R. P. Dayton for his encouragement.

REFERENCES

- (1) S. Gronowitz and J. Roe, *Acta Chem. Scand.*, **19**, 1741 (1965).
- (2) J. D. Davenport, R. E. Hackler, and H. E. Taylor, British Patent 1,218,623; *Chem. Abstr.*, **75**, 15186h (1971).
- (3) 5-Bromopyrimidine has been prepared by heating molten pyrimidine hydrochloride perbromide in 66 percent yield [H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958)] and through the condensation of 2-bromo-1,1,3,3-tetra-methoxypropane with formamide in 64 percent yield (H. Bredereck, F. Effenberger, and E. Schweiger, *ibid.*, **95**, 803 (1962)).
- (4) L. van der Does and H. J. den Hertog, *Tetrahedron Letters*, 2183 (1972).
- (5) J. Chesterfield, J. McOmie, and E. Sayer, *J. Chem. Soc.*, 3478 (1955).
- (6) Pmr spectra were determined on a Varian T-60 and A-60 spectrometer. The high resolution mass spectra were determined on a model 21-110 Consolidated Electroynamics Corp. Spectrometer. Other mass spectra were determined on a Hitachi RMU-6E Spectrometer. Melting points were determined on a Thomas Hoover apparatus and were corrected.
- (7) H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).
- (8) D. J. Brown, *J. Soc. Chem. Ind. (London)*, **69**, 353 (1950).
- (9) H. J. den Hertog and J. P. Wibaut, *Rec. Trav. Chim.*, **51**, 381 (1932).