Selective Brominations in Nitrobenzene. A Convenient Synthesis of 3-Bromoquinoline, 4-Bromoisoquinoline, and 4-Phenyl-5-bromopyrimidine

Thomas J. Kress and Silvio M. Costantino

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

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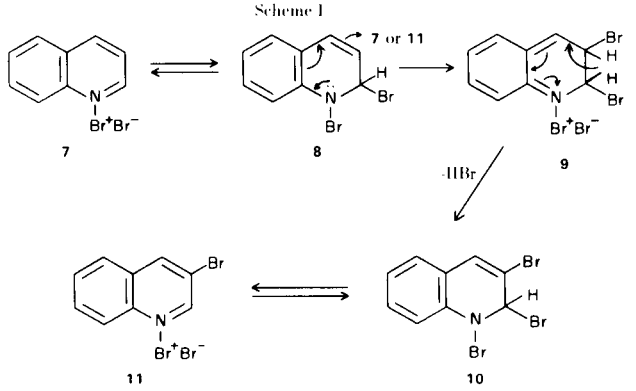
A facile synthesis of 5-bromopyrimidine, carried out by the dropwise addition of bromine to a slurry of pyrimidine hydrochloride in nitrobenzene, was recently reported by us (1). We now wish to report a modification of this technique to the selective bromination of quinoline, isoquinoline, and 4-phenylpyrimidine (2).

The bromination of both quinoline and isoquinoline as free bases has been reviewed by Eisch (3) and each requires a lengthy reaction period followed by a cumbersome work up. We have found that adding bromine to a slurry of quinoline (**2**) or isoquinoline hydrochloride (**3**) in nitrobenzene, heating for a 4-5 hour period, affords on cooling 3-bromoquinoline (**5**) or 4-bromoisoquinoline (**6**) as crystalline hydrobromide salts. The free bases **5** and **6** were isolated after neutralization in 81 and 76 percent yields, respectively (*cf.* Table I).

The selectivity of this bromination technique for substitution in the ring containing the heteroatom led us to test this reaction with 4-phenylpyrimidine hydrochloride (**1**). Van der Plas (4) reported the bromination of 4-phenylpyrimidine in fuming sulfuric acid to be unsuitable because of the vulnerability of the phenyl group to brominating agents. However, he finally prepared 5-bromo-4-phenylpyrimidine (**4**) by a six-step sequence in 16 percent overall yield. Under our conditions, **1** proved extremely stable, since 57 percent was recovered unreacted, and a 41 percent yield of **4** was obtained (*cf.* Table I).

Scheme I



In explanation of the resistance to attack of bromine in the benzenoid ring (compounds **2** and **3**) or the phenyl ring (compound **1**), we suggest the mechanism set out in Scheme I (*e.g.* quinoline).

The first step involves the reversible breakdown of complex **7** to give the addition compound **8**. This enamine **8** could then undergo an irreversible addition of bromine, affording **9**. Loss of hydrogen bromide from **9** would generate the 3-bromo-enamine **10** which is in equilibrium with the product **11**. In this bromination mechanism both product **11** and substrate **7** can serve as bromine carriers.

We have previously proposed an addition compound of type **8** to explain the formation of 4-amino-5-bromopyrimidine during the bromination of pyrimidine hydrochloride under these conditions (1). There are precedents for addition compounds such as **8** which can lead to 3-substitution. The known quinoline addition compound 1-cyano-2-hydroxy-1,2-dihydroquinoline, on treatment with bromine afforded 3-bromoquinoline (5). Tee and Banerjee have suggested intermediates similar to **8** from the bromination of *N*-substituted 2-pyrimidones (6).

EXPERIMENTAL (7)

General Bromination Procedure.

For specific reaction parameters, see Table I.

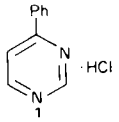
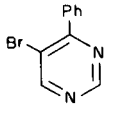
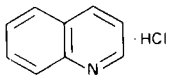
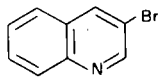
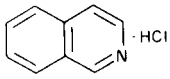
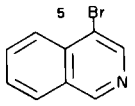
To a slurry of the appropriate heterocycle hydrochloride salt in nitrobenzene at the indicated temperature was added a 10 percent molar excess of bromine through a dropping funnel over 30 minutes. Heating and stirring were continued for the specified time. The mixture was cooled to about 80° and three volumes of benzene were added. The resulting slurry was filtered, washed with benzene, and dried. The salt was placed in water, the solution was adjusted to *p*H 8 with aqueous sodium carbonate, and the free base was isolated by extraction as described below:

3-Bromoquinoline (**5**).

The basic aqueous mixture was extracted with (4 x 200 ml.) of diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo* affording a pale yellow oil which crystallized on cooling. The solid (35.1 g., 84.5% weight yield, m.p. 12-13°, 97% pure by vpc) was identical to an authentic sample.

TABLE I

The Bromination of 4-Phenylpyrimidine, Quinoline, and Isoquinoline

Substrate	Size Run (moles)	Temperature	Nitrobenzene Solvent (ml.)	Time (hours)	Product	Percent Yield (a)
 1	0.057	150°	30	7.0	 4	41 (98)
 2	0.20	180°	50	4.5	 5	81 (93)
 3	0.20	180°	50	5.0	 6	76 (84)

(a) The yields in parenthesis were based on recovered starting material.

4-Bromoisoquinoline (**6**).

The product was isolated by the extraction procedure used for 3-bromoquinoline. Removal of solvent gave a pale yellow oil which solidified on standing. This crude material (33.6 g., 81% weight yield) was 93.5% **6** by vpc. Crystallization from petroleum ether gave needles, m.p. 41-42°, identical with an authentic sample.

5-Bromo-4-phenylpyrimidine (**4**).

The basic aqueous mixture was extracted with chloroform (3 x 100 ml.), dried over anhydrous magnesium sulfate, and evaporated affording 6.1 g. of a gum. The diluted reaction mixture (nitrobenzene-benzene) on standing overnight gave an additional 5.9 g. of solid. The combined solids were chromatographed on neutral (Brockman grade 3) alumina and eluted with carbon tetrachloride ethyl acetate (1:1) giving two distinct bands. The first band on removal of solvent gave 6.2 g. of crystalline 4-phenylpyrimidine. The latter band afforded 5.5 g. (41%) of **4**. Crystallization from cyclohexane gave white cubes; m.p. 95-97° (lit. (4) 89-90°); pmr (deuteriochloroform): τ 0.85 (s, 1H, H-2 of pyrimidine ring), τ 1.10 (s, 1H, H-6 of pyrimidine ring), τ 2.1-2.3 (m, 5H, phenyl protons); mass spectrum, P, m/e 234, 236 (100%).

Anal. Calcd. for $C_{10}H_7BrN_2$: C, 51.09; H, 3.00; N, 11.92. Found: C, 51.21; H, 2.73; N, 11.86.

Acknowledgment.

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(1) T. J. Kress and L. L. Moore, *J. Heterocyclic Chem.*, **10**, 153 (1973).

(2) Pyridine hydrochlorides gave a mixture of mono- and dibromination. Pyridazine hydrochloride afforded a small amount of an unstable yellow oil.

(3) J. J. Eisch, in "Advan. Heterocyclic Chem.," Vol. 7, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, N. Y. (1966).

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(5) M. D. Johnson and J. H, Ridd, *J. Chem. Soc.*, 283 (1962).

(6) O. S. Tee and S. Banerjee, *Chem. Commun.*, 1033 (1972); and references therein.

(7) Pmr spectra were determined on a Varian A-60 spectrometer. Elemental analyses were done by Mr. G. Maciak and associates of Eli Lilly and Company. The gas chromatographic analyses were done by Mr. M. Yager and Mr. C. Hartlage on a 5-ft. column packed with 4% XE-60 on chromasorb G (60-80 mesh) with He flow rate of 20 ml./min. at 220°. Melting points are corrected.