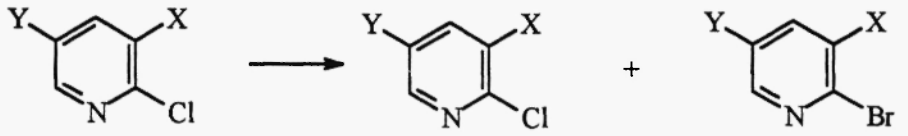
Unexpected Displacements of Chloride by Bromide Found During Sandmeyer Reactions of 3- or 5-Amino-2-chloropyridines

A. Paul Krapcho* and Simon N. Haydar
Department of Chemistry, The University of Vermont, Burlington, Vt 05405 USA

Abstract: Facile, temperature dependent displacements of chloride by bromide have been found in the diazotizations of 3-amino-2-chloropyridine (**1a**) or 5-amino-2-chloropyridine (**1b**), followed by addition of CuBr in 48% HBr, which lead to good yields of the unexpected 2,3-dibromopyridine (**3a**) or 2,5-dibromopyridine (**3b**), respectively.

We wish to report an unusually facile, temperature dependent displacement of chloride by bromide observed during a Sandmeyer reaction of 3-amino-2-chloropyridine (**1a**) in the preparation of 2-chloro-3-bromopyridine (**2a**). The diazotization of **1a** in 48% aqueous HBr at -15° to -10°C, followed by the addition of 0.9 molar equivalents of 0.7M CuBr in 48% aqueous HBr at -20° to -10°C, has been reported to yield **2a** (97%) (1). However, if the diazotization was performed at a higher temperature (25°C) (2), followed by the addition of CuBr in 48% HBr (temperature rose to 32°C), the major product obtained was 2,3-dibromopyridine (**3a**) (3) along with 2-chloro-3-bromopyridine (**2a**) in a 2.3:1 ratio, respectively. If the temperature of the mixture was kept at -30°C to -20°C, -15°C to -10°C or 0-5°C during the course of the diazotization and the addition of CuBr, the **2a**:**3a** product ratios were 100:0 (no detectable **3a** by ^{1}H nmr), 4:1 and 1:1, respectively. A control experiment in which **1a** was treated with 48% HBr and allowed to stir for 4 hours at room temperature led only to recovered starting material.



1a , X = NH_2 , Y = H
b , X = H , Y = NH_2

2a , X = Br , Y = H
b , X = H , Y = Br

3a , X = Br , Y = H
b , X = H , Y = Br

Following a similar procedure as described for **1a**, it was found that 2-chloro-5-aminopyridine (**1b**) at temperatures of -30°C to -20°C led only to **2b**. However, if the reaction was performed at 25°C, **2b** and **3b** (4) were obtained in equal amounts.

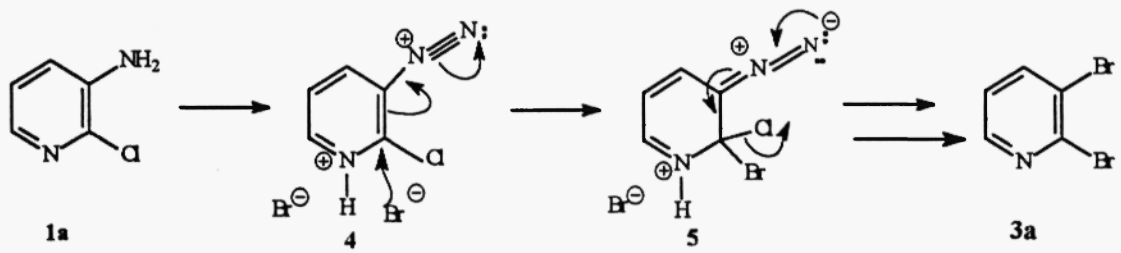
On the other hand, the diazotization and addition of CuBr to the carbocyclic models, 2-chloroaniline and 2-chloro-4-aminopyridine (5), at room temperature led only to the expected bromo analogues 2-bromo-2-chlorobenzene and 2-chloro-4-bromopyridine (6), respectively. These results point to the importance of the nitrogen atom in the ring and the position of the amino group in obtaining dibromo products **3a** and **3b** from **1a**

and 1b, respectively.

It might be noted that displacements of the chlorides from 2,6-dichloropyridine with acetic acid saturated with hydrogen bromide gas required heating at 110°C for 9 hours to prepare the corresponding dibromo analogues (7). Clearly the diazonium ion must be responsible for the high displacement rates of chloride by bromide found at higher temperatures in the cases of 1a and 1b. The rate of displacement of fluoride by methoxide in 4-fluorobenzene diazonium tetrafluoroborate and 4-fluoronitrobenzene has been reported to be 300,000 times faster for the N_2^+ group relative to the nitro group (8). In the preparation of fluoroanisoles, the diazonium ion was proposed as an efficient activator for S_NAr substitutions (9).

Diazotization of 1a would lead to 4, which at room temperature, and before loss of nitrogen could undergo nucleophilic addition of bromide to form intermediate 5 (only one resonance stucture is shown). Loss of chloride from 5, followed by replacement of the diazonium group by bromide, would lead to 3a. Similarly, an S_NAr route of this type would lead to 3b on diazotization of 1b. On the other hand, 4-amino-2-chloropyridine on diazotization has the diazonium ion in an unfavorable position for activation via an S_NAr substitution pathway and led only to the expected product 4-bromo-2-chloropyridine.

Scheme 1. Possible mechanism for S_NAr displacement of chloride by bromide.



References and Notes

1. J. D. Cook and B. J. Wakefield, J. Chem. Soc. (C) 1973 (1969).
2. All temperatures which we report are internal. Product ratios were determined by ^{1}H nmr integrations. All yields were greater than 90%, except in the case of 4-amino-2-chloropyridine which was converted to product in about 50% yield.
3. Compound 3a was prepared following the procedures described in: a) R. A. Abramovitch, F. Helmer and M. Levis, J. Org. Chem . *34*, 1730 (1969) and b) M. P. Cava and B. Weinstein, J. Org. Chem. 23, 1616 (1958). Product ratios were determined by integrations of the protons adjacent to the nitrogen atoms [δ for 2a (8.37) and 3a (8.34) ppm].
4. Compounds 1b and 3b were purchased from Aldrich. The ratios of products were determined by ^{1}H nmr integrations of the protons meta to the nitrogen atom [δ for 2b (7.79) and 3b (7.68) ppm].
5. This compound was prepared following the procedures described in: a) M. Malinowski and L. Kaczmarek, J .Prakt. Chem. 330, 154 (1988) and b) E. V. Brown, J. Am. Chem. Soc. 79, 3565 (1957).
6. M.. Mallet and G. Queguiner, Tetrahedron 42, 2253 (1986). A ^{1}H nmr is reported for this compound.
7. H. Mutterer and C. B. Weis, Helv. Chim. Acta 59, 229 (1976).
8. B. A. Bolto, M. Livens and J. Miller, J. Chem. Soc. 750 (1956).
9. N. Takechi, Y. Fukai, K. Oka and R. Huisgen, Chemistry Lett. 23 (1996).

Received on March 3, 1998