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

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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 ¹H 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.

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 structure 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 1H 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 1H 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 1H 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).

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