THE REGIOSELECTIVITY OF AMINATION OF CERTAIN 4-DIMETHYLAMINOPYRIDINES

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Abstract - Under the homogeneous aminating conditions of KNH₂ in NH₃, 3-bromo-4-dimethylaminopyridine 2 affords a mixture of 2-amino-5-bromo-4-dimethylaminopyridine 3 and 3-amino-4-dimethylaminopyridine 4, along with the product of debromination, 4-dimethylaminopyridine 1. Compound 3 was debrominated with Zn in HOAc to afford 2-amino-4-dimethylaminopyridine 5. The regioselectivity observed for the homogeneous amination of 2 is precisely that predicted by an analysis of the lowest unoccupied frontier molecular orbital coefficients.

4-Dimethylaminopyridine (4-DMAP, 1) is well known as a "hypernucleophilic" catalyst for acylation reactions.¹ There appears to be some confusion in the literature concerning the course of amination reactions of 1 and structurally related pyridines. In order to assist in the understanding of this important class of heterocyclic reactions, we have investigated the amination reactions, both heterogeneous and homogeneous, of 1 and its readily accessible 3-bromo derivative.

Under the heterogeneous Chichibabin aminating reaction conditions of NaNH₂ in refluxing tetrahydrofuran, 4-DMAP was found to afford only trace amounts of both 4-aminopyridine and 2-amino-4-dimethylaminopyridine (by nmr spectral and tlc analysis).² 4-DMAP was found to be inert, however, under the homogeneous aminating conditions of KNH₂ in liquid NH₃,³ either in the presence or absence of an oxidant (KMnO₄).⁴ Based upon a report that 3-bromo-4-ethoxypyridine affords a 55-60% yield of 2-amino-4-ethoxypyridine under the KNH₂/NH₃ aminating conditions,⁵ we considered that the presence of a halogen ring substituent would activate the pyridine ring of 1 to attack by amide anion. An AM1 molecular orbital calculation⁶ on an MMPM1-minimized structure⁷ of 3-bromo-4-dimethylaminopyridine (2) revealed that ring positions 3 and 6 are predicted to be

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equally susceptible to nucleophilic attack, according to the tenets of frontier molecular orbital theory. Indeed, compound 2 reacted completely in the KNH₂/ΝΗ₃ system (no oxidant, -78 °C for 40 min, then -33 °C for 45 min) to afford three major products according to a tlc analysis of the product mixture. Two of these products, isolated by column chromatography, were identified with the aid of high-field ¹H and ¹³C nmr spectral and low- and high-resolution el mass spectral analysis as 2-amino-5-bromo-4-dimethylaminopyridine 3 (10%) and 3-amino-4-dimethylaminopyridine 4 (32%) (Scheme I). When the amination reaction time at -78 °C was shortened drastically (to less than 5 min), compound 4 was obtained in a 31% yield, but compound 3 was not detected. Surprisingly, the use of KMnO₄ (1.1 equivalents) as an in situ oxidant did not affect the distribution of products. 2-Amino-4-dimethylaminopyridine (5) was obtained by the debromination of 3 with Zn dust in HOAc (95% yield).

**Scheme I**

![Scheme I](image)

In addition to compound 3, the product of ammonia addition/oxidation, and 4, the product of $S_n(\text{AE})_{\text{ipso}}$ aminodebromination, compound 1 (debrominated 2) was invariably present (35-40% isolated yields) in the amination product mixtures. The attack of amide anion on the bromine substituent of compound 2 may be assisted by coordination of the potassium cation to the dimethylamino moiety. This effect is even more pronounced in the heterogeneous amination of compound 2, from which 1 was obtained as the sole product in a 95% yield. Conspicuously absent from the homogeneous amination mixtures, however, was compound 5, an aminodebromination product analogous to that reported for the amination of 3-bromo-4-ethoxypyridine. Although $S_n(\text{AE})_{\text{ipso}}$ and $S_n(\text{AE})_{\text{C}}$ aminodehalogenation reactions of structurally related pyridines are currently
being considered, these types of reactions do not appear to occur in the case of the 4-DMAP derivative 2.

EXPERIMENTAL

General Methods.
Melting ranges were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. All 1H and 13C nmr spectra were recorded on a General Electric GN-500, GE-300 or Nicolet NT-360 spectrometer using CDCl3 as solvent and tetramethylsilane (1H) and CHCl3 (13C) as internal references. Electron-impact mass spectra were recorded on a Varian MAT CH5 double-focusing spectrometer, and field-ionization mass spectra on a Varian MAT 731 spectrometer, each coupled with a 6201 computer and STATOS recorder. Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA), employing 10% MeOH/CHCl3 as eluent and Merck Kieselgel 60 as adsorbent. Thin-layer chromatography was performed on glass-backed silica gel Uniplates from Analtech, Newark, DE. Elemental microanalyses were performed by Josef Nemeth and his staff at the University of Illinois.

General Amination Procedure.
A 0.7 M solution of KNH2 (3-5 equivalents) in NH3 was prepared by adding K(s) in small pieces to NH3 containing a catalytic amount of Fe(NO3)3·9H2O at -78 °C, warming to -33 °C until the blue color dissipated (30 min), then cooling to -78 °C. The heterocycle (1 equivalent) was added dropwise as a 0.7 M solution in anhydrous Et2O. After the reaction was complete, the reaction mixture was quenched by the addition of NH4Cl (excess) in small portions, the NH4 allowed to evaporate at room temperature, and the residue dissolved in CH3OH and filtered from insolubles. The product mixture was purified by column and/or radial preparative-layer chromatography.

3-Bromo-4-dimethylaminopyridine (2).
A solution of 1 (5.0 g, 41 mmol) in 100 ml of CH2Cl2 was treated with sat’d. aq. K2CO3 (100 ml) and 1.3% nBu4NOH (5 ml), and the mixture stirred vigorously while a solution of Br2 (4.2 ml, 82 mmol) in 25 ml of CH2Cl2 was added dropwise over 30 min. The reaction mixture was stirred for 4 h, the layers were separated, and the organic phase was washed with H2O (3 x 100 ml), dried (Na2SO4), and rotary evaporated to a yellow oil. Purification by column chromatography (silica gel, EtOAc as eluent) followed by vacuum distillation afforded 6.16 g (75%) of 2 as a colorless liquid: bp 172 °C/1.5 mmHg (lit.14 mp 83-85 °C); 1H nmr δ 8.50 (s, 1H, H-2), 8.28 (d, J = 5.5 Hz, 1H, H-6), 6.78 (d, J = 5.5 Hz, 1H, H-5), 3.00 (s, 6H, NMe2); 13C nmr δ 156.3, 152.8, 148.3, 113.2, 111.8, 41.9. Low-resolution fi ms (8 kv), m/z: 200.0/202.0 (M+). Anal. Calcd. for C7H5N3Br: C, 41.82; H, 4.51; N, 13.93; Br, 39.74. Found: C, 41.62; H, 4.49; N, 13.96; Br,
39.59. Hydrobromide: mp 189-190.5 °C (EtOH/Et_2O); ^1H nmr δ 8.39 (s, 1H, H-2), 8.22 (d, J = 7.1 Hz, 1H, H-6), 7.02 (d, J = 7.1 Hz, 1H, H-5), 3.40 (s, 6H, NMe_3); ^13C nmr δ 158.0, 142.4, 137.0, 111.0, 102.7, 43.2. Low-resolution eims (70, 10 eV) mw: 201.0/203.0 (M-Br), 200.0/202.0 (M^-Br); 80/82 (Br). Anal. Calcd. for C_7H_4N_2Br: C, 39.82; H, 3.57; N, 9.93; Br, 56.67. Found: C, 39.67; H, 3.66; N, 9.94; Br, 56.72. Picrate: mp 180-182.5 °C (EtOH, lit. 10 mp 182-183 °C).

2-Amino-5-bromo-4-dimethylaminopyridine (3).

mp 104-106 °C (Et_2O/hexanes); tlc (silica gel, 10:10:1 CHCl_3/CH_3OH/CH_3CO_2H as eluent) Rf 0.88; ^1H nmr δ 7.98 (s, 1H, H-6), 6.01 (s, 1H, H-3), 4.39 (bs, exchanges with D_2O, 2H, NH_2), 2.97 (s, 6H, NMe_3). ^13C nmr δ 158.6, 158.3, 150.9, 102.6, 97.9, 42.5. Low-resolution eims (70, 10 eV), mw: 215.0/217.0 (M^+). High-resolution eims, calcd for C_7H_4N_2Br: 215.0055 amu; obsd: 215.0055 amu. Anal. Calcd. for C_7H_4N_2Br: C, 38.91; H, 4.66; N, 19.45; Br, 36.98. Found: C, 38.59; H, 4.72; N, 19.54; Br, 37.23.

3-Amino-4-dimethylaminopyridine (4).

mp 89-91 °C (Et_2O/hexanes, lit. 11 89 °C); tlc (above) Rf 0.60; ^1H nmr δ 8.00 (s, 1H, H-2), 7.96 (d, J = 5.2 Hz, 1H, H-6), 6.78 (d, J = 5.2 Hz, 1H, H-5), 3.70 (bs, exchanges, 2H, NH_2), 2.74 (s, 6H, NMe_3). ^13C nmr δ 146.6, 140.9, 137.1, 136.4, 112.8, 41.4. Low-resolution eims (70, 10 eV), mw: 137.1 (M^+). High-resolution eims, calcd for C_6H_5N_3: 137.0953 amu; obsd: 137.0952 amu.

2-Amino-4-dimethylaminopyridine (5).

A solution of 3 (30 mg, 0.14 mmol) in 3 ml of glacial acetic acid was treated with Zn dust (100 mg) and stirred at room temperature for 2 h. The reaction mixture was filtered, the Zn was washed with a small amount of H_2O, and the combined H_2O solutions were rotary evaporated in vacuo. The residue was treated with sat'd. aq. K_2CO_3 (10 ml), and extracted with Et_2O (6 x 25 ml). The combined Et_2O solutions were dried (MgSO_4), and rotary evaporated to afford 18 mg (95%) of 5 as a pale yellow solid; mp 126-128 °C (Et_2O/hexanes); ^1H nmr δ 7.78 (d, J = 6.1 Hz, 1H, H-6), 6.06 (d of d, J = 6.1, 2.2 Hz, 1H, H-5), 5.68 (d, 1H, J = 2.2 Hz, H-3), 4.81 (bs, exchanges, 2H, NH_2), 2.96 (s, 6H, NMe_3). ^13C nmr δ 158.9, 156.0, 146.6, 103.7, 99.5, 39.0. Low-resolution eims (70, 10 eV), mw: 137.2 (M^+). Anal. Calcd. for C_6H_5N_3: C, 61.29; H, 8.08; N, 30.63. Found: C, 61.39; H, 8.08; N, 30.60.

For comparison with the above nmr spectral data: 2-amino-4-methoxypyridine: ^1H nmr δ 7.90 (d, J = 5.9 Hz, 1H, H-6), 6.28 (d of d, J = 5.9, 2.1 Hz, 1H, H-5), 6.01 (d, J = 2.1 Hz, 1H, H-3), 4.45 (bs, exchanges, 2H, NH_2), 3.64 (s, 3H, CH_3). ^13C nmr δ 167.0, 160.3, 148.8, 102.1, 92.1, 54.6; 2-amino-4-chloropyridine: ^1H nmr δ 7.93 (d, J = 5.3 Hz, 1H, H-6), 6.63 (d, J = 5.3 Hz, 1H, H-5), 6.53 (s, 1H, H-3), 5.14 (bs, exchanges with D_2O, 2H, NH_2). ^13C nmr δ 159.1, 148.0, 145.2, 114.2, 108.4.
ACKNOWLEDGMENT

This work was supported by the National Science Foundation (NSF CHE 84-16336). Instrument support: NIH PHS 1532135 (QF-300), GM 27029 (MAT-731), NIH PHS 1531957 and NSF CHE 85-14500 (GN-500). We thank Professor Nelson J. Leonard for his encouragement and interest, and Ms. Patti Silver for her assistance in the preparation of this manuscript.

REFERENCES AND NOTES

3. Elemental potassium was purified by the Hershberg procedure and the KNH$_4$/NH$_3$ reagent was prepared in the presence of a catalytic amount of Fe(NO$_3$)$_3$; nonahydrate.
7. MMPM1 version 2.0 of the combination of N. L. Allinger's MM2 force field, R. D. Brown's VESCF MMP1 n calculation, and C. Still's MODEL parameters: Serena Software, Box 3076, Bloomington, IN 47402.
8. Squares of the AMI p$_x$ LUMO frontier molecular orbital (FMO) coefficients: N-1 (0.02), C-2 (0.16), C-3 (0.32), C-4 (0.06), C-5 (0.11), and C-6 (0.31).


Received, 12th June, 1987