THE REGIOSELECTIVITY OF AMINATION OF CERTAIN 4-DIMETHYLAMINOPYRIDINES

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Abstract - Under the homogeneous aminating conditions of KNH_2 in NH_3, 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 $NaNH_2$ in refluxing tetralin, 4-DMAP was found to afford only trace amounts of <u>both</u> 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 KNH_2 in liquid NH_3,[3] either in the presence or absence of an oxidant ($KMnO_4$).[4] Based upon a report that 3-bromo-4-ethoxypyridine affords a 55-60% yield of 2-amino-4-ethoxypyridine under the KNH_2/NH_3 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 calculation[6] on an MMPMI-minimized structure[7] of 3-bromo-4-dimethylaminopyridine (**2**) revealed that ring positions 3 and 6 are predicted to be

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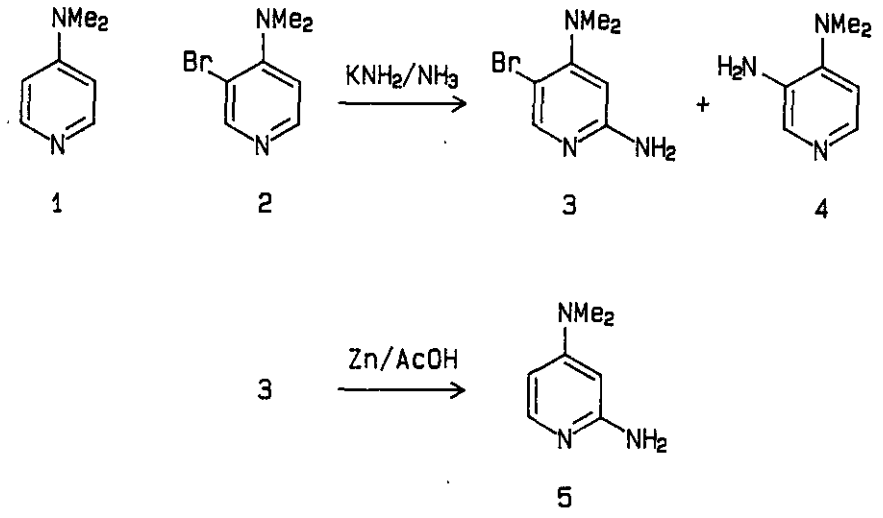
equally susceptible to nucleophilic attack, according to the tenets of frontier molecular orbital theory.[8] Indeed, compound **2**[9] reacted completely in the KNH_2/NH_3 system (no oxidant, -78 °C for 40 min, then -33 °C for 45 min) to afford three major products according to a tlc analysis of the product mixture. Two of these products, isolated by column chromatography, were identified with the aid of high-field ^1H and ^{13}C nmr spectral and low- and high-resolution ei 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 $KMnO_4$ (1.1 equivalents) as an <u>in situ</u> 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



In addition to compound **3**, the product of ammonia addition/oxidation, and **4**, the product of $S_{RN}(AE)$ *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.[24] This effect is even more pronounced in the <u>heterogeneous</u> 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 $S_{RN}(AE)$ *tele* and $S_{RN}(EA)$ *cine aminodehalogenation* reactions of structurally related pyridines are currently

being considered,[10] 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 ^{13}C nmr spectra were recorded on a General Electric GN-500, QE-300 or Nicolet NT-360 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (^1H) and $CHCl_3$ (^{13}C) 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 620I computer and STATOS recorder. Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA), employing 10% MeOH/$CHCl_3$ 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 KNH_2 (3-5 equivalents) in NH_3 was prepared by adding K(s) in small pieces to NH_3 containing a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ 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 Et_2O. After the reaction was complete, the reaction mixture was quenched by the addition of NH_4Cl (excess) in small portions, the NH_3 allowed to evaporate at room temperature, and the residue dissolved in CH_3OH 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 CH_2Cl_2 was treated with sat'd. aq. K_2CO_3 (100 ml) and 1.3% nBu_4NOH (5 ml), and the mixture stirred vigorously while a solution of Br_2 (4.2 ml, 82 mmol) in 25 ml of CH_2Cl_2 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 H_2O (3 x 100 ml), dried (Na_2SO_4), 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.[9a] 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, NMe_2); ^{13}C 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 $C_7H_9N_2Br$: 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_2); ^{13}C nmr δ 158.0, 142.4, 137.0, 111.0, 102.7, 43.2. Low-resolution ei ms (70, 10 eV) *m/z*: 201.0/203.0 ($M-Br^-$), 200.0/202.0 (M^+ -HBr), 80/82 (HBr). Anal. Calcd. for $C_7H_{10}N_2Br_2$: C, 29.82; H, 3.57; N, 9.93; Br, 56.67. Found: C, 29.67; H, 3.66; N, 9.94; Br, 56.72. Picrate: mp 180-182.5 °C (EtOH, lit.[9b] mp 182-183 °C).

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

mp 104-106 °C (Et_2O/hexanes); tlc (silica gel, 10:10:1 $CHCl_3/CH_3OH$/AcOH as eluent) R_f 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), 2.87 (s, 6H, NMe_2). ^{13}C nmr δ 158.6, 158.5, 150.9, 102.6, 97.9, 42.5. Low-resolution ei ms (70, 10 eV), *m/z*: 215.0/ 217.0 (M^+). High-resolution ei ms, calcd for $C_7H_{10}N_3Br$: 215.0058 amu; obsd: 215.0055 amu. Anal. Calcd. for $C_7H_{10}N_3Br$: 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) R_f 0.80; ^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_2). ^{13}C nmr δ 146.6, 140.9, 137.1, 136.4, 112.8, 41.4. Low-resolution ei ms (70, 10 eV), *m/z*: 137.1 (M^+). High-resolution ei ms, calcd for $C_7H_{11}N_3$: 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 HOAc, and the combined HOAc 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_2). ^{13}C nmr δ 158.9, 156.0, 146.6, 103.7, 99.5, 39.0. Low-resolution ei ms (70, 10 eV), *m/z*: 137.2 (M^+). Anal. Calcd. for $C_7H_{11}N_3$: 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:[12] ^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), 3.84 (s, 3H, CH_3). ^{13}C nmr δ 167.0, 160.3, 148.8, 102.1, 92.1, 54.6; 2-amino-4-chloropyridine:[13] ^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). ^{13}C 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 (QE-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.

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Received, 12th June, 1987