γ-ξ-CH_2O, 8 H), 3.85 (t, β-CH_2O, J = 6 Hz, 2 H), 4.40 (t, α-CH_2O, J = 6 Hz, 2 H), 4.50 (dd, H_C, J = 7, 1 Hz, 1 H), 4.85 (dd, H_B, J = 14, 1 Hz, 1 H), 6.63 (dd, H_3, J = 4, 1 Hz, 1 H), 6.45 (dd, H_5, J = 4, 1 Hz, 1 H), 7.48 (t, H_4, J = 7.5 Hz, 1 H), 7.55 (dd, H_A, J = 14, 8 Hz, 1 H); IR (neat) 2930, 1675 (amide), 1580, 1425, 1370, 1300, 1235, 1120, 1080, 790 cm^{-1}; mol wt (MS) m/e 283 (M^+, 22%).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.15; H, 7.14; N, 4.93. Found: C, 58.98; H, 7.42; N, 4.75.

Acknowledgments. We are grateful to the National Institutes of Health and the National Science Foundation for partial support of this work. We also thank Dr. Weis of CIBA-GEIGY, Basel, Switzerland, for the generous sample of 2,6-dichloronicotinic acid.

Registry No. **2**, 58584-83-1; **3**, 70290-47-0; **4**, 70445-78-2; **5**, 70290-48-1; **6**, 70290-49-2; **7**, 70445-79-3; **8**, 70290-50-5; **9**, 70290-51-6; **10a**, 70290-41-4; **10b**, 70290-42-5; **10c**, 70290-43-6; **11a**, 70290-44-7; **11b**, 70290-45-8; **11c**, 70290-46-9; **12**, 70445-80-6; **13**, 70445-81-7; **14**, 61463-74-9; **15**, 56446-73-2; **16**, 70445-82-8; **17**, 70445-83-9; pentaethylene glycol, 4792-15-8; tetraethylene glycol, 112-60-7; hexaethylene glycol, 2615-15-8; ethanol, 64-17-5.

Functionalization of 5-Methyl-2-halonicotinic Acid Derivatives

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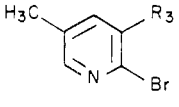
Received February 8, 1979

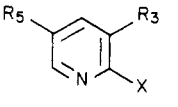
Methodology is described for the preparation of pyridines containing versatile functional groups in the 2, 3, and 5 positions via di and tri NBS brominations of the C-5 methyl group of 2-halonicotinic acid derivatives. Reductive dehalogenation of the 2-bromo substituent provides for a facile synthesis of unsymmetrical pyridines in which the oxidation state of the C-3 and C-5 groups can be effectively controlled.

Recently, we described a method for the synthesis of 5-methyl-2-halonicotinic acid derivatives of the type **1** via



1

R_3 = CO_2Et, CN



2

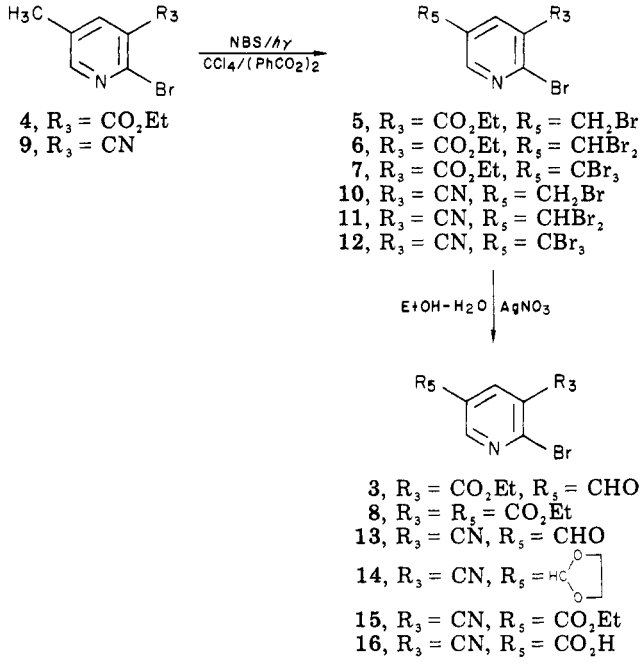
R_3 = CO_2Et, CN
R_5 = CHO, CO_2Et
X = Br, H

enamine cyclization.[1] The ready availability of **1** by this procedure prompted an investigation into the utilization of these compounds as intermediates en route to the preparation of more highly functionalized derivatives. We now report on the functionalization of the C-5 methyl group of **1** as an approach to compounds of the type **2**, a class unknown in the pyridine literature.[2]

Initially, we attempted the synthesis of ethyl 2-bromo-5-formylnicotinate (**3**) via SeO_2 oxidation of **4**. Unfortunately, SeO_2, under various conditions, failed to oxidize the C-5 methyl group. In fact, the starting material **4** was recovered quantitatively, even after prolonged treatment. This failure of the SeO_2 oxidation of **4** necessitated a search for an alternate route for the conversion of **4** to **3**. As outlined in Scheme I, this functionalization was accomplished by *N*-bromosuccinimide (NBS) bromination of the C-5 methyl group.

When **4** was treated with a slight excess over 2 equiv of NBS, ethyl 2-bromo-5-(dibromomethyl)nicotinate (**6**) was isolated as the major product in 35% yield. In addition to **6**, the mother liquors from the crystallization contained

Scheme I



varying amounts of **4**, **5**, and **7**. Chromatography of this mixture yielded **7** (6%). Although not isolated, the presence of **5** is clearly supported by the appearance of a singlet at δ 4.4 for the bromomethyl group in the ^1H NMR spectrum.

Treatment of **4** with a slight excess over 3 equiv of NBS gave ethyl 2-bromo-5-(tribromomethyl)nicotinate (**7**) in 49% yield as well as a minor amount of **6**. These compounds, **6** and **7**, were easily separated by chromatography on silica gel. Unlike the previous example, no trace of **5** could be observed in the ^1H NMR spectrum of the crude reaction mixture.

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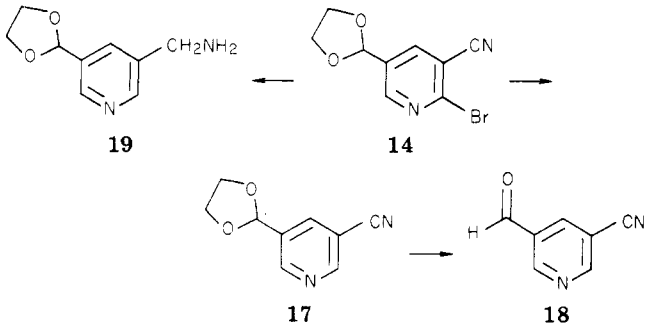
(2) R. A. Abramovitch, Ed., "Pyridine and Its Derivatives", Wiley, New York, N.Y., Parts 1-4.

0022-3263/79/1944-2702$01.00/0

Scheme II



19 14 17 18

Thus, the successful bromination of the methyl group of **4** is in direct contrast to the results obtained by Kutney,[3] who found that 3-methylpyridine failed to react with NBS. Presumably, the 2-bromo and 3-carboethoxy moieties exert a favorable electronic effect which now allows this reaction to occur.

The (dibromomethyl)pyridine **6** was readily converted to the aldehyde **3** by hydrolysis with $AgNO_3$ in EtOH–H_2O. Likewise, **7** on similar treatment gave the ester **8**.

On the basis of these results, we also investigated the NBS reaction with 2-bromo-5-methylnicotinonitrile (**9**). On reaction of **9** with a slight excess over 2 equiv of NBS, a mixture of (mono-, di-, and tribromomethyl)pyridines **10**, **11**, and **12** was obtained. Chromatography of this mixture gave **11** and **12** in 47 and 18% yield, respectively. The presence of (bromomethyl)pyridine **10** was inferred by a singlet at δ 4.4 for the bromomethyl group in the ^1H NMR spectrum of the crude reaction mixture.

Hydrolysis of **11** with $AgNO_3$ gave the aldehyde **13** in 75% yield. It is noteworthy that the (tribromomethyl)-pyridine **12** could be converted in high yield either to the ester **15** or the acid **16** by simply adjusting the EtOH–H_2O ratio in the $AgNO_3$ hydrolysis. A ratio of 5:1 EtOH to H_2O gave the ester **15** while a ratio of 1:5 provided the acid **16**.

Reductive dehalogenation of **2** (X = Br) would lead to a class of 3,5-disubstituted pyridines in which the exact nature and oxidation state of each substituent could be controlled during synthesis. Compounds of this type are in principle derivable from pyridine-3,5-dicarboxylic acid via selective functional group interconversion[4] but in fact are only obtainable in low yield by cumbersome and nonselective methodology. To explore the chemistry of such a conversion, aldehyde **13** was first protected as the acetal **14**. As illustrated in Scheme II, reductive debromination of **14** with 5% Pd on carbon in EtOH–H_2O containing MgO[5] gave 5-formylnicotinonitrile ethylene glycol acetal (**17**) in quantitative yield. Deprotection with dilute acid provided the novel 5-formylnicotinonitrile (**18**). Debromination of **14** with 5% Pd on $CaCO_3$ in EtOH[6] under more forcing conditions gave the (aminomethyl)-pyridine **19**, characterized by IR, NMR, and mass spectra. Thus, the method constitutes in theory a synthesis for potentially valuable 3,5-disubstituted pyridines in which the carbon substituents may be in the same or different oxidation state.

In summary, this method, with the ease of reaction conditions and the ready availability of starting materials, offers a relatively simple synthesis for pyridines containing versatile functional groups in the 3,5 and/or 2,3,5 positions. In addition, reductive debromination exemplified by the conversion of **14** to **18** provides the first synthetically significant method for the preparation of the potentially valuable pyridines in which the oxidation state of the 3 and 5 substituents can be effectively controlled.

Experimental Section

IR spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer, ^1H NMR spectra were recorded on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard, and mass spectra were taken on an AEI MS-902 high-resolution mass spectrometer. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Solutions were dried over Na_2SO_4 and concentrated to dryness by using a Buchi rotary evaporator under water aspirator pressure (20 mm).

Ethyl 2-Bromo-5-(dibromomethyl)nicotinate (6). A mixture of **4** (24.1 g, 0.1 mol), NBS (40 g, 0.22 mol), CCl_4 (500 mL), and dibenzoyl peroxide (1.0 g) was heated at reflux while being illuminated by a 275-W sunlamp. After 24 h, the reaction mixture was filtered and concentrated to dryness. The residue was crystallized from ligroin to yield 14 g (35%) of **6**. Recrystallization of a small sample from ligroin gave **6** of mp 88–89 °C: ^1H NMR ($CDCl_3$) δ 1.45 (3 H, t, J = 7), 4.45 (2 H, q, J = 7), 6.7 (1 H, s), 8.1 (1 H, d, J = 2), 8.4 (1 H, d, J = 2).

Anal. Calcd for $C_9H_8Br_3NO_2$: C, 26.90; H, 2.01; N, 3.48. Found: C, 26.94; H, 1.89; N, 3.76.

The mother liquor from the crystallization was concentrated to dryness and the residue chromatographed on silica gel. Elution with $CHCl_3$ gave 2.7 g (6%) of **7** and 13.1 g of a 1:1 mixture of **5** and **6** as determined by ^1H NMR spectroscopy.

Ethyl 2-Bromo-5-(tribromomethyl)nicotinate (7). A mixture of **4** (5.4 g, 0.022 mol), NBS (13 g, 0.073 mol), CCl_4 (150 mL), and dibenzoyl peroxide (0.2 g) was illuminated by a 275-W sunlamp for 24 h. Additional NBS (5 g) was then added and illumination continued for another 24 h. After the mixture had cooled to 25 °C, it was filtered and concentrated to dryness. The residue was chromatographed on silica gel and eluted with 25% C_6H_{14}–$CHCl_3$ to yield 5.1 g (49%) of **7** and 1.2 g (13%) of **6**. An analytical sample of **7** was prepared by crystallization from ligroin: mp 50–52 °C; ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t, J = 7), 4.4 (2 H, q, J = 7), 8.4 (1 H, d, J = 2), 8.8 (1 H, d, J = 2).

Anal. Calcd for $C_9H_7Br_4NO_2$: C, 22.48; H, 1.47; N, 2.91. Found: C, 22.57; H, 1.35; N, 2.92.

Ethyl 2-Bromo-5-formylnicotinate (3). A mixture of **6** (9.8 g, 0.024 mol), $AgNO_3$ (8.8 g, 0.052 mol), EtOH (100 mL), and H_2O (25 mL) was heated on a steam bath for 1 h. The yellow solid was filtered and the solution concentrated to dryness. The residue was treated with H_2O and extracted with $CHCl_3$ (3 ×). The organic layer was dried, filtered, and concentrated to dryness. Distillation of the resulting oil at 105–135 °C (0.5 mm) gave 3.0 g (48%) of **3**: ^1H NMR ($CDCl_3$) δ 1.45 (3 H, t, J = 7), 4.4 (2 H, q, J = 7), 8.6 (1 H, d, J = 2), 8.9 (1 H, d, J = 2), 10.1 (1 H, s).

Anal. Calcd for $C_9H_8BrNO_3$: C, 41.88; H, 3.12; N, 5.43. Found: C, 41.83; H, 3.37; N, 5.46.

Diethyl 2-Bromo-3,5-pyridinedicarboxylate (8). A mixture of **7** (2.3 g, 0.005 mol), $AgNO_3$ (2.5 g, 0.015 mol), and EtOH (25 mL) was heated on a steam bath. After 1 h, H_2O (25 mL) was added and the yellow solid filtered off. The solution was concentrated to dryness and the residue treated with H_2O and extracted with $CHCl_3$ (3 ×). The $CHCl_3$ layers were washed with $NaHSO_3$ solution, dried, filtered, and concentrated to dryness to yield 0.8 g (78%) of **8**: ^1H NMR ($CDCl_3$) δ 1.4 (6 H, t, J = 7), 4.45 (4 H, q, J = 7), 8.6 (1 H, d, J = 3), 9.0 (1 H, d, J = 3).

The exact mass was 300.9925 (calcd 300.9917).

2-Bromo-5-(dibromomethyl)nicotinonitrile (11) and 2-Bromo-5-(tribromomethyl)nicotinonitrile (12). A mixture of **9** (10 g, 0.05 mol), NBS (20 g, 0.11 mol), CCl_4 (500 mL), and dibenzoyl peroxide (0.5 g) was heated at reflux while being illuminated by a 275-W sunlamp for 7 h. After the mixture was allowed to stand overnight at room temperature, it was filtered and concentrated to dryness. The residue was chromatographed

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(4) (a) G. Queguiner and P. Pastour, *Bull. Soc. Chim. Fr.*, **10**, 3678 (1969); (b) *C. R. Hebd. Seances Acad. Sci., Ser. C*, **268**, 182 (1969).
(5) N. Sperber, M. Sherlock, D. Papa, and D. Kender, *J. Am. Chem. Soc.*, **81**, 704 (1959).
(6) T. A. Bryson, J. C. Wisowaty, R. B. Dunlap, R. R. Fisher, and P. D. Ellis, *J. Org. Chem.*, **39**, 3436 (1974).

on silica gel and the products were eluted with 50% C_6H_{14}–$CHCl_3$. There was obtained 3.8 g (18%) of **12** and 8.3 g (47%) of **11**. An analytical sample of **11** was prepared by crystallization from CH_2Cl_2–C_6H_{14}: mp 89–90 °C; ^1H NMR ($CDCl_3$) δ 6.6 (1 H, s), 8.15 (1 H, d, J = 3), 8.7 (1 H, d, J = 3).

Anal. Calcd for $C_7H_3Br_3N_2$: C, 23.69; H, 0.85; N, 7.89. Found: C, 23.57; H, 0.82; N, 8.24.

An analytical sample of **12** was prepared by crystallization from ligroin: mp 129–131 °C; ^1H NMR ($CDCl_3$) δ 8.3 (1 H, d, J = 3), 9.1 (1 H, d, J = 3); IR (Nujol) 2270, 1740 cm^{-1}.

Anal. Calcd for $C_7H_2Br_4N_2$: C, 19.38; H, 0.46; N, 6.46. Found: C, 19.67; H, 0.52; N, 6.50.

2-Bromo-5-formylnicotinonitrile (13). A mixture of **9** (2.1 g, 0.006 mol), $AgNO_3$ (2.2 g, 0.013 mol), EtOH (25 mL), and H_2O (5 mL) was heated on a steam bath for 1 h. After the yellow solid was filtered off, the solution was concentrated to dryness. The residue was treated with H_2O and extracted with $CHCl_3$ (3 ×). The organic layer was dried, filtered, and concentrated to dryness. The residue was treated with acetone–H_2O (10:1) and a few drops of 12 N HCl. After 1 h of heating on a steam bath, the solution was poured into saturated Na_2CO_3 and extracted with Et_2O (3 ×). The organic layer was dried, filtered, and concentrated to dryness to yield 0.9 g (75%) of **13**: mp 105-106 °C (ligroin); ^1H NMR ($CDCl_3$) δ 8.4 (1 H, d, J = 2), 9.0 (1 H, d, J = 2), 10.1 (1 H, s). The exact mass was 209.9418 (calcd 209.9429). This material was used in the next step without further purification.

2-Bromo-5-formylnicotinonitrile Ethylene Glycol Acetal (14). A mixture of **13** (0.8 g, 0.004 mol), C_6H_6 (50 mL), ethylene glycol (1 mL), and p-TsOH (0.1 g) was heated on a steam bath with the continual removal of H_2O, using a Dean–Stark trap. After 2 h, the solution was cooled and washed with saturated Na_2CO_3 solution. After separation, the aqueous layer was further extracted with Et_2O (2 ×). The combined organic extracts were dried, filtered, and concentrated to dryness to yield 1.0 g (100%) of **14**; mp 74–75 °C (ligroin); ^1H NMR ($CDCl_3$) δ 4.05 (4 H, s), 5.85 (1 H, s), 8.05 (1 H, d, J = 3), 8.65 (1 H, d, J = 3). The exact mass was 253.9670 (calcd 253.9691).

Anal. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.81; H, 2.61; N, 11.19.

Ethyl 6-Bromo-5-cyanonicotinate (15). A mixture of **12** (1.4 g, 0.003 mol), $AgNO_3$ (1.7 g, 0.01 mol), EtOH (25 mL), and H_2O (5 mL) was heated on a steam bath for 1.5 h. After the yellow solid was filtered off, the solution was concentrated to dryness to yield 0.6 g (79%) of **15**. An analytical sample was prepared by crystallization from EtOH–H_2O: mp 92–93 °C; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7), 4.35 (2 H, q, J = 7), 8.7 (1 H, d, J = 3), 8.8 (1 H, d, J = 3).

Anal. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.68; H, 2.64; N, 11.02.

6-Bromo-5-cyanonicotinic Acid (16). A mixture of **12** (2.0 g, 0.004 mol), $AgNO_3$ (2.2 g, 0.014 mol), H_2O (40 mL), and EtOH (8 mL) was heated on a steam bath for 2 h. The mixture was then poured into saturated Na_2CO_3, filtered, and extracted with $CHCl_3$ (2 ×). The aqueous layer was acidified with 12 N HCl and extracted with Et_2O (3 ×). The Et_2O layer was dried, filtered, and concentrated to dryness to yield 0.7 g (74%) of **16**: mp 170–172 °C (EtOH–H_2O); ^1H NMR (Me_2SO-d_6) δ 8.8 (1 H, d, J = 2), 9.15 (1 H, d, J = 2); IR (Nujol) 2270, 1725 cm^{-1}. The exact mass was 225.9387 (calcd 225.9378).

Anal. Calcd for $C_7H_3BrN_2O_2$: C, 37.03; H, 1.33; N, 12.34. Found: C, 37.01; H, 1.75; N, 11.85.

5-Formylnicotinonitrile Ethylene Glycol Acetal (17). A mixture of **14** (1.0 g, 0.004 mol), EtOH (75 mL), H_2O (40 mL), MgO (1 g), and 5% Pd/C (1 g) was placed on a Herschberg hydrogenation apparatus. After 100 mL of H_2 was absorbed (~10 min), the suspension was filtered under a blanket of N_2 and the volatiles were removed under reduced pressure. The resulting residue was treated with H_2O and extracted with $CHCl_3$ (3 ×). The combined organic extracts were dried, filtered, and concentrated to dryness to yield 0.7 g (100%) of **17**. An analytical sample of **17** was prepared by sublimation at 65 °C (0.2 mm): mp 73–75 °C; ^1H NMR ($CDCl_3$) δ 4.1 (4 H, s), 5.9 (1 H, s), 8.03 (1 H, t), 8.83 (2 H, bs); IR (Nujol) 2250 cm^{-1}.

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.35; H, 4.57; N, 15.90. Found: C, 61.08; H, 4.48; N, 16.24.

5-Formylnicotinonitrile (18). A solution of **17** (0.25 g, 0.0014 mol) in 1 N HCL (30 mL) was heated on a steam bath for 45 min. After the solution had cooled, it was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried, filtered, and concentrated to dryness to yield 0.16 g (89%) of **18**. An analytical sample of **18** was prepared by crystallization from CH_2Cl_2–C_6H_{14}: mp 96–98 °C; ^1H NMR ($CDCl_3$) δ 8.35 (1 H, t), 8.97 (1 H, d, J = 2), 9.2 (1 H, d, J = 2), 10.07 (1 H, t); IR (Nujol) 2250, 1700 cm^{-1}.

Anal. Calcd for $C_7H_4N_2O$: C, 63.64; H, 3.05; N, 21.20. Found: C, 63.53; H, 3.01; N, 21.58.

3-(Aminomethyl)-5-formylpyridine Ethylene Glycol Acetal (19). A mixture of **14** (1.0 g, 0.004 mol), EtOH (75 mL), and 5% Pd on $CaCO_3$ (1 g) was placed on a Herschberg hydrogenation apparatus. After 340 mL of H_2 was absorbed, the reaction was stopped. The mixture was filtered under a blanket of N_2 and the filtrate concentrated to dryness. The residue was chromatographed on silica gel, and the product eluted with $CHCl_3$ saturated with NH_3 to yield 0.34 g (50%) of **19**: ^1H NMR ($CDCl_3$) δ 2.5 (2 H, s), 3.8 (2 H, exch), 4.0 (4 H, s), 5.75 (1 H, s), 7.7 (1 H, bs), 8.4 (2 H, bs); IR (neat) 3330 cm^{-1}; mass spectrum (M^+) m/e 180.

Acknowledgments. The authors are grateful to Drs. Ralph Hirschmann and E. L. Engelhardt for their interest and encouragement throughout this work. Technical assistance was provided by Ms. J. Stranick and Mr. K. B. Streeter for analytical determinations and by Mr. R. E. Rhodes for mass spectra.

Registry No. **3**, 70416-40-9; **4**, 65996-16-9; **5**, 70416-41-0; **6**, 70416-42-1; **7**, 70416-43-2; **8**, 70416-44-3; **9**, 65996-18-1; **10**, 70416-45-4; **11**, 70416-46-5; **12**, 70416-47-6; **13**, 70416-48-7; **14**, 70416-49-8; **15**, 70416-50-1; **16**, 70416-51-2; **17**, 70416-52-3; **18**, 70416-53-4; **19**, 70416-54-5.