Benzo-fused Heterocycles and Carbocycles by Intramolecular S_NAr and Tandem S_N2-S_NAr Reactions

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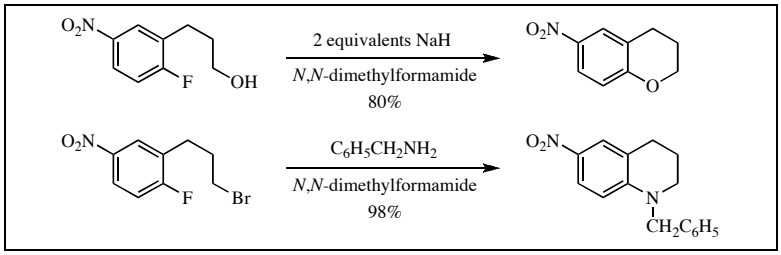

Benzo-fused heterocyclic and carbocyclic systems have been synthesized by intramolecular S_NAr and tandem S_N2-S_NAr reactions. Treatment of 3-(2-fluoro-5-nitrophenyl)-1-propanol with sodium hydride in *N*,*N*-dimethylformamide gave 6-nitrochroman in 80% yield by an intramolecular S_NAr reaction. Treatment of 2-(3-bromopropyl)-1-fluoro-4-nitrobenzene with benzylamine in *N*,*N*-dimethylformamide gave 1-benzyl-6-nitrotetrahydroquinoline in 98% yield by a tandem S_N2-S_NAr reaction. Finally, in a similar process, reaction of this same bromide with dimethyl malonate under basic conditions gave 1,1-bis(methoxycarbonyl)-6-nitro-1,2,3,4-tetrahydronaphthalene in 80% yield. Further studies exploring ring size effects are also presented.

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INTRODUCTION

Tandem reactions initiated by reduction of nitroaromatic substrates have provided an efficient route to a variety of heterocyclic systems [2]. The synthesis of these substrates has often required the use of nucleophilic aromatic substitution to introduce functionality needed to capture the resulting amino group in a ring-forming process. In the course of our work, we became interested in the possibility of generating heterocyclic systems by tandem processes terminated by a nucleophilic aromatic substitution. The current work describes our initial efforts to explore this synthetic strategy and outlines the use of an intramolecular S_NAr route to benzo-fused oxygen heterocycles and a tandem S_N2-S_NAr route to benzo-fused nitrogen heterocycles and carbocycles.

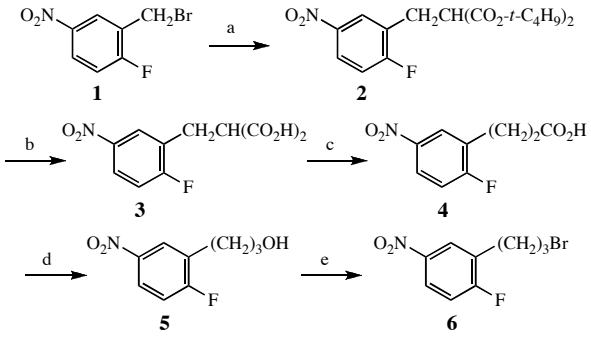
The structures accessible using the current reaction include substituted chromans, tetrahydroquinolines and tetrahydronaphthalenes. These ring systems each contain numerous derivatives that are known to express useful biological activities [3,4,5]. While we have only prepared compounds bearing substitution at C6, several other substitution patterns should also be possible. The current study also includes an evaluation of the method for the closure of five- and seven-membered rings. The results should serve to define the parameters needed for success in these reactions.

RESULTS AND DISCUSSION

The preparation of precursors for the closure of six-membered rings is depicted in Scheme 1. Starting from the known 2-fluoro-5-nitrobenzyl bromide (**1**) [6], two-carbon chain extension was accomplished by a sequence involving (1) alkylation of di-*tert*-butyl malonate to give **2**, (2) hydrolysis of the *tert*-butyl esters with trifluoroacetic acid in the presence of triethylsilane [7] to give dicarboxylic acid **3** and (3) decarboxylation at 160° to give mono-carboxylic acid **4**. Chemoselective reduction of the acid with borane-tetrahydrofuran complex gave alcohol substrate **5** [8], which was carried on to the corresponding bromide **6** by conversion to the methanesulfonate ester and treatment with lithium bromide [9]. The yields for all procedures ranged from 82-96%.

Substrates for the evaluation of ring size effects were prepared from bromides **1** and **6** using a five step

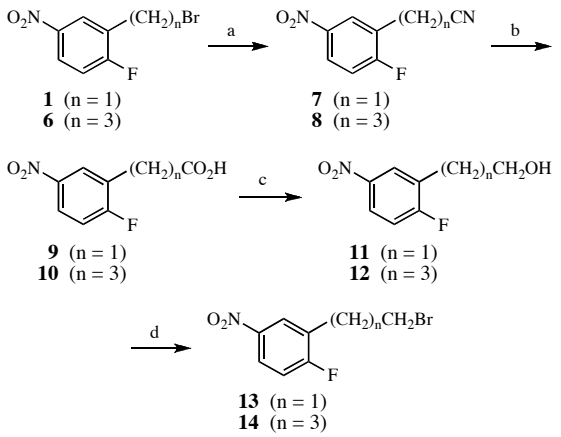
Scheme 1 [a]



[a] Key: (a) $CH_2(CO_2\text{-}t\text{-}C_4H_9)_2$, K_2CO_3, acetone, 22°, 96%; (b) CF_3CO_2H, $(C_2H_5)_3SiH$, dichloromethane, 22°, 82%; (c) 160°, neat, 94%; (d) BH_3·THF, tetrahydrofuran 0→22°, 87%; (e) *i*. CH_3SO_2Cl, $(CH_3CH_2)_3N$, CH_2Cl_2, 0°; *ii*. LiBr, 3:1 ether:acetone, 40°, 90%.

sequence that included (1) nucleophilic displacement of the bromides by cyanide to give nitriles **7** and **8** [10], (2) acid hydrolysis of the nitriles to generate carboxylic acids **9** and **10**, (3) reduction of the acids to afford alcohols **11** and **12** [8], and (4-5) treatment of the alcohols with methanesulfonyl chloride followed by lithium bromide to give bromides **13** and **14** [9]. The yield for each step in these syntheses ranged from 75-98% (Scheme 2).

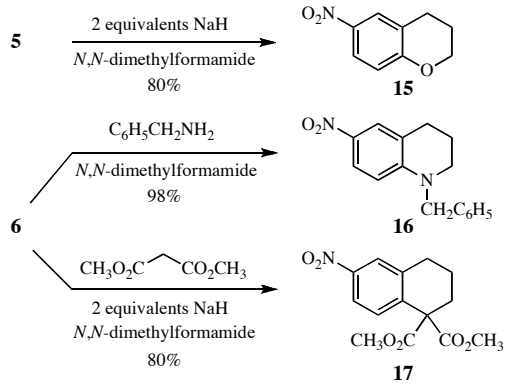
Scheme 2 [a]



[a] Key: (a) For **1**→**7**: KCN, aqueous ethanol, 22°, 91%; For **6**→**8**: KCN, dimethylsulfoxide, 22°, 98%; (b) 50% aqueous H_2SO_4, 110°; yield of **9**, 75%, **10**, 85%; (c) BH_3-THF, 0→22°; yield of **11**, 86%, **12**, 97%; (d) *i*. CH_3SO_2Cl, $(CH_3CH_2)_3N$, CH_2Cl_2, 0°; *ii*. LiBr, 3:1 ether:acetone, 40°; yield of **13**, 87%, **14**, 91%.

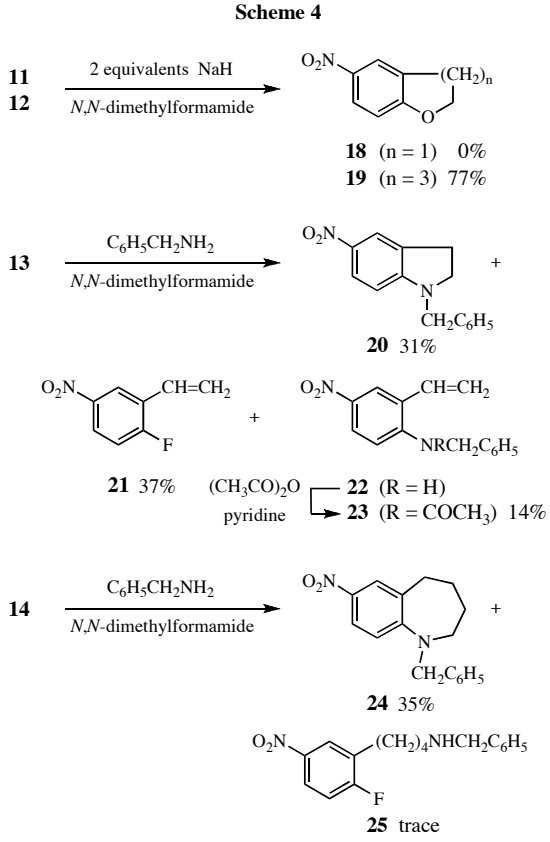
Our initial cyclization studies focused on the closure of six-membered rings (Scheme 3). Treatment of alcohol **5** with a two-fold excess of sodium hydride in *N*,*N*-dimethylformamide led to chroman **15** in 80% yield by an intramolecular S_NAr reaction [11]. Addition of two equivalents of benzylamine to bromide **6** in *N*,*N*-dimethylformamide led to a nearly quantitative yield of tetrahydroquinoline **16** by a tandem S_N2-S_NAr reaction [12]. Finally, in a similar process, carbocycle **17** was generated in 80% yield by treating **6** with dimethyl malonate in the presence of two equivalents of sodium hydride [13]. All products were readily purified by chromatography.

Scheme 3



Cyclizations to form five-membered rings were less satisfactory. Treatment of alcohol **11** with sodium hydride led to intermolecular reactions and decomposition of the substrate; none of the desired oxygen heterocycle **18** was produced. Attempts to prepare 1-benzyl-5-nitroindoline (**20**) from bromide **13** and benzylamine led to complex mixtures, which included the desired heterocycle as well as elimination and substitution products **21** and **22** derived from the basic nucleophile. The best yield of indoline **20** (31%) was achieved when the reaction was run at 0–22°, but the conversion was only 82% and elimination was still a major pathway (Scheme 4). These outcomes presumably arise because the short three-atom chain prevents the nucleophilic center from achieving the optimum orientation for addition, which must come from above (or below) the plane of the ring.

Scheme 4



Seven-membered ring closures gave more variable results. Treatment of **12** with sodium hydride as above proceeded to give benzoxepin **19** in 77% yield. Attempts to generate benzazepine **24** from **14** using benzylamine, however, gave only 35% yield. The major product in these reactions was **25**, which arises from simple S_N2 displacement of the side chain bromide without ring closure. Even when **25** was heated to 120°, little additional cyclization was noted. These rings should form more readily since the longer side chain permits approach

of the nucleophilic group with the proper trajectory for addition to the aromatic ring (Figure 1), but evidently, there is resistance to achieving the correct side chain conformation to allow this angle of approach. It should be noted that the isolation of **25** as a major product suggests that displacement of the side chain halide occurs prior to attack on the aromatic nucleus [6].

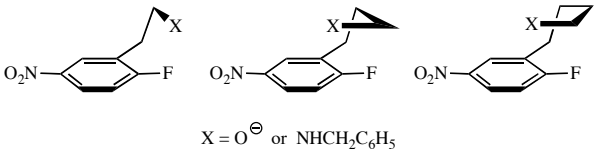


Figure 1

Calculations on the oxygen systems indicate that the five- and seven-membered heterocycles are more strained than the six-membered structure by 2.24 kcal/mole and 5.13 kcal/mole, respectively [14]. Analysis of molecular models confirms that the tether bearing the nucleophilic oxygen in the benzofuran precursor is too short to permit the optimum orientation for addition from above the plane of the ring while the side chain in the benzoxepin precursor is too long for efficient ring closure. Models also indicate that the side chain conformations required for cyclization of the five and seven-membered rings suffer from C-H and C-C eclipsing interactions, which are not present in the chair-like conformation that leads to the chroman. Similar considerations should also apply in the nitrogen series, with the added problem that basic nucleophiles strongly promote elimination in the indoline precursor.

CONCLUSION

We have developed a new approach to the synthesis of benzo-fused six- and seven-membered oxygen heterocycles involving intramolecular S_NAr addition of a three- or four-carbon side chain alkoxide to an activated aromatic fluoride positioned *ortho* to this substituent. Nitrogen-containing rings have been prepared by a tandem S_N2-S_NAr sequence involving intermolecular S_N2 reaction of an amine with a side chain primary sp^3 bromide followed by intramolecular S_NAr displacement of a similarly disposed activated aromatic fluoride. A six-membered carbocycle has been prepared in an analogous manner using the anion of dimethyl malonate. Ring size studies indicate that the length of the tether linking the aromatic ring to the nucleophile and conformational effects in the chain are critical to the success of the process. Five-membered rings are disfavored primarily by the inability of the side chain nucleophile to approach the aromatic ring with the correct geometry for addition; additionally, elimination to form the styrene is a problem in tandem S_N2-S_NAr reactions using basic nucleophiles. Six-membered rings have minimal strain and the longer tether permits intramolecular attack by the nucleophile. Seven-membered heterocycles require conformational folding of the tether, which introduces torsional strain and deters ring closure.

EXPERIMENTAL

All reactions were run under dry nitrogen in oven-dried glassware. *N*,*N*-dimethylformamide from a freshly opened bottle was stored under nitrogen over 4Å molecular sieves and syringed into reactions as needed. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed by one of the following methods: (1) flash column chromatography [15] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech 02015). Compound elution in all cases was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65-70°; petroleum ether used in crystallization and trituration procedures had a boiling range of 35-60°. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. Unless otherwise indicated, ^1H and ^{13}C nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are given in Hertz. Unless otherwise noted, mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

Di-*tert*-butyl 2-(2-Fluoro-5-nitrobenzyl)-1,3-propanedioate (2). A stirred suspension of 15.0 g (109 mmoles) of anhydrous potassium carbonate was prepared in 75 mL of anhydrous acetone. To this suspension was added 2.94 g (13.6 mmoles) of di-*tert*-butyl malonate followed by 1.50 g (6.4 mmoles) of **1** [6]. The mixture was vigorously stirred for 2 days, then filtered through Celite® and concentrated. The resulting oil was diluted with ether, washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under vacuum. The excess di-*tert*-butyl malonate was removed at 55° under high vacuum and was recycled; the remaining oil crystallized on cooling. Trituration of the crystals with 5% ether in petroleum ether and filtration gave 2.27 g (96%) of **2** as a light tan solid, mp 81-83°. The product from three runs of this reaction were combined and used directly in the next step. ir: 1727, 1530, 1350, 1249 cm^{-1}; ^1H nmr: δ 8.22-8.10 (complex, 2H), 7.17 (t, 1H, J = 8.7), 3.54 (t, 1H, J = 7.9), 3.23 (d, 2H, J = 7.9), 1.43 (s, 18H); ^{13}C nmr: δ 167.4, 164.7 (d, J = 257.4), 143.9, 127.1 (d, J = 6.6, obscures a second C signal), 124.5 (d, J = 10.0), 116.3 (d, J = 24.9), 82.2, 53.3, 27.8 (d, J = 2.3), 27.7. *Anal.* Calcd. for $C_{18}H_{24}FNO_6$: C, 58.54; H, 6.50; N, 3.79. Found: C, 58.51; H, 6.46; N, 3.83.

2-(2-Fluoro-5-nitrobenzyl)-1,3-propanedioic Acid (3). To a solution 6.75 g (18.3 mmoles) of **2** in 75 mL of dichloromethane was added 43.8 g (28.5 mL, 384 mmoles) of trifluoroacetic acid and 10.6 g (14.6 mL, 91.5 mmoles) of triethylsilane. The mixture was stirred for 3 hours and then concentrated under vacuum to give a light yellow solid. The solid was suspended in dichloromethane and filtered to give 3.86 g (82%) of **3** as an off-white powder, mp 144-146° (dec). This

compound was dried under high vacuum and used directly in the next step. ir: 3691-2123, 1713, 1527, 1350, 1249 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide-d_6): δ 12.9 (br s, 2H), 8.24 (m, 1H), 8.16 (m, 1H), 7.43 (m, 1H), 3.64 (t, 1H, J = 7.6), 3.16 (t, 2H, J = 7.6); ^{13}C nmr (deuteriodimethylsulfoxide-d_6): δ 169.7, 164.2 (d, J = 255.6), 143.7, 127.3 (d, J = 18.0), 126.8 (d, J = 6.9), 124.6 (d, J = 10.9), 116.6 (d, J = 25.2), 51.3, 27.2; ms (30 eV): *m/z* 257 (M^+). *Anal.* Calcd. for $C_{10}H_8FNO_6$: C, 46.69; H, 3.11; N, 5.45. Found: C, 46.74; H, 3.13; N, 5.41.

3-(2-Fluoro-5-nitrophenyl)propanoic Acid (4). A 100-mL flask containing 4.00 g (15.6 mmoles) of powdered **3** was heated at 160-170° under nitrogen using an oil bath. The solid liquefied and carbon dioxide was released. After 30 minutes, the evolution of gas ceased, the heat was removed and the brown product solidified. The solid was recrystallized from ether-petroleum ether to give 3.11 g (94%) of **4** as a tan solid, mp 109-110°. ir: 3374-2282, 1520, 1348, 1249 cm^{-1}; ^1H nmr: δ 9.87 (br s, 1H), 8.22-8.10 (complex, 2H), 7.18 (t, 1H, J = 9.0), 3.06 (t, 2H, J = 7.1), 2.76 (t, 2H, J = 7.1); ^{13}C nmr: δ 177.8, 164.6 (d, J = 256.8), 144.2, 128.8 (d, J = 17.8), 126.5 (d, J = 6.9), 124.5 (d, J = 10.3), 116.3 (d, J = 24.9), 33.6, 24.0; ms: *m/z* 213 (M^+). *Anal.* Calcd. for $C_9H_8FNO_4$: C, 50.70; H, 3.76; N, 6.57. Found: C, 50.71; H, 3.76; N, 6.54.

3-(2-Fluoro-5-nitrophenyl)-1-propanol (5). A solution of 2.50 g (11.7 mmoles) of **4** in 25 mL of anhydrous tetrahydrofuran was prepared and cooled to 0°. This solution was stirred and 12.2 mL of 1 *M* borane tetrahydrofuran complex (12.2 mmoles) in tetrahydrofuran was added slowly by syringe over 20 minutes. The reaction was allowed to warm to room temperature overnight. The reaction was quenched at 0° by slow addition of 10 mL of water, then transferred to a separatory funnel with ether and washed with saturated aqueous sodium chloride (three times). The combined ether layers were dried (magnesium sulfate) and concentrated under vacuum to give 2.16 g (87%) of **5** as a light yellow oil that was purified by flash chromatography on a 30-cm x 2-cm silica gel column eluted with 20% ether in hexanes. The resulting light yellow oil crystallized to a waxy solid on standing at 0°, mp 35-36°. ir: 3365, 1525, 1350, 1243 cm^{-1}; ^1H nmr: δ 8.17 (dd, 1H, J = 6.5, 3.0), 8.05 (ddd, 1H, J = 9.0, 4.3, 3.0), 7.16 (t, 1H, J = 9.0), 3.72 (t, 2H, J = 6.3), 2.85 (t, 2H, J = 7.4), 1.92 (m, 2H), 1.77 (br s, 1H); ^{13}C nmr: δ 164.7 (d, J = 256.2), 144.1, 130.5 (d, J = 18.3), 126.4 (d, J = 7.2), 123.7 (d, J = 10.3), 116.1 (d, J = 25.2), 61.7, 32.2, 25.3 (d, J = 2.3); ms: *m/z* 199 (M^+). *Anal.* Calcd. for $C_9H_{10}FNO_3$: C, 54.27; H, 5.03; N, 7.04. Found: C, 54.22; H, 5.06; N, 7.05.

2-(3-Bromopropyl)-1-fluoro-4-nitrobenzene (6). A solution of 2.00 g (10.1 mmoles) of **5** was converted to its methanesulfonate ester according to the procedure of Crossland and Servis [9], mp 58-60°. The crude ester was dissolved in 160 mL of 3:1 ether:acetone, 4.35 g (50.0 mmoles) of anhydrous lithium bromide was added and the reaction was warmed at 40° for 12 h. The reaction mixture was cooled, added to water and ether extracted (three times). The combined ether layers were washed with water and saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under vacuum. The resulting light yellow oil was flash chromatographed on a 30-cm x 2-cm silica gel column eluted with 5% ether in hexanes to give 2.38 g (90%, two steps) of bromide **6** as a light yellow oil. ir: 1525, 1349, 1243 cm^{-1}; ^1H nmr: δ 8.20-8.10 (complex, 2H), 7.18 (t, 1H, J = 8.7), 3.44 (t, 2H, J = 6.5), 2.92 (t, 2H, J = 7.5), 2.22 (m, 2H); ^{13}C nmr: δ 164.6 (d, J = 256.8), 144.2, 129.3 (d, J = 18.2), 126.5 (d, J = 7.2), 124.1 (d, J = 10.0), 116.3 (d, J = 24.9), 32.2, 32.1, 27.5 (d, J = 1.7); ms: *m/z* 261, 263 (M^+, M^++2). *Anal.* Calcd. for $C_9H_9BrFNO_2$: C, 41.22; H, 3.44; N, 5.34. Found: C, 41.31; H, 3.48; N, 5.25.

2-(2-Fluoro-5-nitrophenyl)acetonitrile (7). To a stirred solution of 1.00 g (15.4 mmoles) of potassium cyanide in 6 mL of water at 22° was slowly added a solution of 2.34 g (10.0 mmoles) of **1** in 30 mL of ethanol [10]. The reaction mixture was stirred for 4 hours, diluted with water and ether extracted (three times). The combined ether extracts were washed with saturated aqueous sodium chloride (three times), dried (magnesium sulfate) and concentrated under vacuum to afford 1.63 mg (91%) of **7** as a yellow oil. This compound was spectroscopically pure and used without further purification. ir: 2256, 1529, 1350, 1252 cm^{-1}; ^1H nmr: δ 8.41 (dd, 1H, J = 6.5, 2.7), 8.29 (ddd, 1H, J = 9.1, 4.5, 2.7), 7.32 (t, 1H, J = 9.0), 3.89 (s, 2H); ^{13}C nmr: δ 163.6 (d, J = 259.4), 144.4, 126.2 (d, J = 10.3), 125.8 (d, J = 4.9), 119.5 (d, J = 17.8), 116.8 (d, J = 23.5), 115.4, 17.7 (d, J = 4.9); ms: *m/z* 180 (M^+). *Anal.* Calcd. for $C_8H_5FN_2O_2$: C, 53.33; H, 2.78; N, 15.56. Found: C, 53.38; H, 2.83; N, 15.51.

4-(2-Fluoro-5-nitrophenyl)butanenitrile (8). To a solution of 310 mg (4.77 mmoles) of potassium cyanide in 10 mL of dimethylsulfoxide at 22° was slowly added a solution of 940 mg (3.59 mmoles) of **6** and the mixture was stirred for 3 hours [10]. The crude reaction mixture was added to saturated aqueous sodium chloride and ether extracted (three times). The combined ether layers were washed with saturated sodium chloride (three times), dried (magnesium sulfate) and concentrated under vacuum to give 734 mg (98%) of **8** as a yellow oil. This compound was spectroscopically pure and used without further purification. ir: 2247, 1527, 1351, 1243 cm^{-1}; ^1H nmr: δ 8.16 (m, 2H), 7.22 (t, 1H, J = 9.0), 2.92 (t, 2H, J = 7.0), 2.45 (t, 2H, J = 7.1), 2.05 (quintet, 2H, J = 7.1); ^{13}C nmr: δ 164.5 (d, J = 257.1), 144.2, 128.5 (d, J = 18.3), 126.3 (d, J = 6.6), 124.4 (d, J = 10.0), 118.8, 116.5 (d, J = 25.2), 27.9 (d, J = 2.0), 25.2 (d, J = 1.4), 16.7; ms: *m/z* 208 (M^+). *Anal.* Calcd. for $C_{10}H_9FN_2O_2$: C, 57.69; H, 4.33; N, 13.46. Found: C, 57.65; H, 4.34; N, 13.44.

Acid Hydrolysis of Nitriles: 2-(2-Fluoro-5-nitrophenyl)-acetic Acid (9). To 1.63 g (9.05 mmoles) of **7** was added 40 mL of 50% aqueous sulfuric acid and the mixture was boiled for 1 hour. Upon cooling, the acid crystallized from the mixture and was isolated by filtration. Drying under high vacuum gave 1.35 g (75%) of **9** as a tan solid, mp 143-144°. This compound was spectroscopically pure and used without further purification. ir: 3304-2278, 1714, 1518, 1344, 1242 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide-d_6): δ 10.96 (br s, 1H), 8.36 (dd, 1H, J = 6.3, 3.0), 8.23 (ddd, 1H, J = 8.8, 4.6, 3.0), 7.47 (t, 1H, J = 9.0), 3.81 (s, 2H); ^{13}C nmr (deuteriodimethylsulfoxide-d_6): δ 170.9, 164.4 (d, J = 255.9), 143.7, 127.5 (d, J = 6.6), 125.0 (d, J = 10.6), 124.5 (d, J = 18.6), 116.4 (d, J = 24.9), 33.8 (d, J = 1.7); ms: *m/z* 199 (M^+). *Anal.* Calcd. for $C_8H_6FNO_4$: C, 48.24; H, 3.02; N, 7.04. Found: C, 48.41; H, 3.09; N, 7.04.

4-(2-Fluoro-5-nitrophenyl)butanoic Acid (10). Using the procedure outlined for the preparation of **9**, 734 mg (3.53 mmoles) of **8** was hydrolyzed to give 682 mg (85%) of **10** as a tan solid, mp 100-101°. ir: 3683-2256, 1708, 1527, 1350, 1243 cm^{-1}; ^1H nmr: δ 9.40 (br s, 1H), 8.14 (m, 2H), 7.17 (t, 1H, J = 8.7), 2.81 (t, 2H, J = 7.5), 2.45 (t, 2H, J = 7.3), 2.01 (quintet, 2H, J = 7.5); ^{13}C nmr: δ 179.0, 164.6 (d, J = 256.5), 144.2, 129.9 (d, J = 18.6), 126.4 (d, J = 7.2), 124.1 (d, J = 10.3), 116.3 (d, J =

25.2), 33.1, 28.1 (d, J = 2.0), 24.4 (d, J = 1.1); ms: *m/z* 227 (M^+). *Anal.* Calcd. for $C_{10}H_{10}FNO_4$: C, 52.86; H, 4.41; N, 6.17. Found: C, 52.87; H, 4.42; N, 6.17.

Reduction of the Carboxylic Acids: 2-(2-Fluoro-5-nitrophenyl)ethanol (11). Using the procedure described for the preparation of **5**, 1.86 g (9.35 mmoles) of acid **9** was reduced to alcohol **11**. Purification by flash chromatography on a 30-cm x 2-cm column of silica gel eluted with 20% ether in hexanes gave 1.49 g (86%) of **11** as a light yellow oil that solidified on standing, mp 44-46°. ir: 3365, 1527.1350, 1243 cm^{-1}; ^1H nmr: δ 8.22 (dd, 1H, J = 6.3, 2.7), 8.13 (m, 1H), 7.18 (t, 1H, J = 9.0), 3.92 (q, 2H, J = 5.7), 2.99 (t, 2H, J = 6.3), 1.99 (br s, 1H); ^{13}C nmr: δ 164.8 (d, J = 256.5), 144.0, 127.6 (d, J = 18.6), 127.1 (d, J = 7.2), 124.1 (d, J = 10.3), 116.2 (d, J = 25.2), 61.5, 32.0 (d, J = 1.1); ms: *m/z* 185 (M^+). *Anal.* Calcd. for $C_8H_8FNO_3$: C, 51.89; H, 4.32; N, 7.57. Found: C, 51.94; H, 4.35; N, 7.49.

4-(2-Fluoro-5-nitrophenyl)butanol (12). Using the procedure outlined for the preparation of **5**, 702 mg (3.09 mmoles) of acid **10** was reduced to alcohol **12**. Purification by flash chromatography on a 20-cm x 2-cm column of silica gel eluted with 20% ether in hexanes gave 636 mg (97%) of **12**, mp 39-40°; ir: 3348, 1527, 1350, 1243 cm^{-1}; ^1H nmr: δ 8.14 (dd, 1H, J = 6.5, 2.7), 8.10 (m, 1H), 7.16 (t, 1H, J = 8.9), 3.70 (t, 2H, J = 6.5), 2.77 (t, 2H, J = 7.4), 1.86 (br s, 1H), 1.74 (m, 2H), 1.65 (m, 2H); ^{13}C nmr: δ 164.6 (d, J = 256.5), 144.1, 130.9 (d, J = 18.3), 126.3 (d, J = 7.4), 123.6 (d, J = 10.3), 116.1 (d, J = 25.2), 62.3, 32.0, 28.5 (d, J = 1.7), 25.9 (d, J = 1.1); ms: *m/z* 213 (M^+). *Anal.* Calcd. for $C_{10}H_{12}FNO_3$: C, 56.34; H, 5.63; N, 6.57. Found: C, 56.40; H, 5.67; N, 6.51.

2-(2-Bromoethyl)-1-fluoro-4-nitrobenzene (13). Using the procedure described for the preparation of **6**, 1.00 g (5.41 mmoles) of alcohol **11** was converted to bromide **13**. Purification by flash chromatography on a 20-cm x 2-cm silica gel column using 10% ether in hexanes gave 1.17 g (87%) of **13** as a light yellow oil that crystallized on standing at 0°, mp 24-25°. ir: 1529, 1350, 1243 cm^{-1}; ^1H nmr: δ 8.19 (m, 2H), 7.21 (t, 1H, J = 9.0), 3.63 (t, 2H, J = 7.0), 3.30 (t, 2H, J = 7.0); ^{13}C nmr: δ 164.6 (d, J = 257.4), 144.2, 127.4 (d, J = 17.8), 127.0 (d, J = 6.9), 124.8 (d, J = 10.3), 116.5 (d, J = 24.9), 32.3 (d, J = 1.7), 30.3; ms (30 eV): *m/z* 247, 249 (M^+, M^++2). *Anal.* Calcd. for $C_8H_7BrFNO_2$: C, 38.71; H, 2.82; N, 5.64. Found: C, 38.83; H, 2.87; N, 5.61.

2-(4-Bromobutyl)-1-fluoro-4-nitrobenzene (14). Using the procedure described for the preparation of **6**, 1.00 g (4.69 mmoles) of alcohol **12** was converted to bromide **14**. Purification by flash chromatography on a 20-cm x 2-cm silica gel column using 10% ether in hexanes gave 1.18 g (91%) of **14** as a light yellow oil. ir: 1525, 1350, 1242 cm^{-1}; ^1H nmr: δ 8.12 (m, 2H), 7.17 (t, 1H, J = 8.8), 3.45 (t, 2H, J = 6.3), 2.76 (t, 2H, J = 7.6), 1.93 (m, 2H), 1.83 (m, 2H); ^{13}C nmr: δ 164.6 (d, J = 256.2), 144.2, 130.4 (d, J = 18.3), 126.3 (d, J = 7.2), 123.8 (d, J = 10.3), 116.2 (d, J = 25.5), 33.0, 32.0, 28.1 (d, J = 1.1), 28.0 (d, J = 1.7); ms: *m/z* 275, 277 (M^+, M^++2). *Anal.* Calcd. for $C_{10}H_{11}BrFNO_2$: C, 43.48; H, 3.99; N, 5.07. Found: C, 43.44; H, 4.02; N, 5.10.

6-Nitrochroman (15). To a suspension of 24 mg (1.00 mmole) of oil-free sodium hydride in 2 mL of anhydrous *N*,*N*-dimethylformamide was added 100 mg (0.50 mmoles) of **5** in 3 mL of dry dimethylformamide. The reaction immediately turned brown. The mixture was stirred for 8 hours at room temperature, quenched by addition to 20 mL of saturated aqueous ammonium chloride and ether extracted (three times). The combined ether washes were washed with saturated aqueous sodium chloride (three times), dried (magnesium sulfate) and concentrated under vacuum. Purification by preparative thin layer chromatography gave 72 mg (80%) of **15** as a light yellow solid, mp 102-104° (lit [3b] mp 104°). ir: 1507, 1340 cm^{-1}; ^1H nmr: δ 8.02-7.94 (complex, 2H), 6.84 (d, 1H, J = 9.8), 4.29 (t, 2H, J = 5.3), 2.86 (t, 2H, J = 6.5), 2.05 (m, 2H); ^{13}C nmr: δ 160.4, 143.8, 125.9, 123.5, 122.6, 117.1, 67.2, 24.8, 21.5; ms: *m/z* 179 (M^+). *Anal.* Calcd. for $C_9H_9NO_3$: C, 60.34; H, 5.03; N, 7.82. Found: C, 60.33; H, 5.05; N, 7.79.

1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinoline (16). A solution of 100 mg (0.38 mmoles) of **6** in 3 mL of anhydrous *N*,*N*-dimethylformamide was treated with 82 mg (0.76 mmoles) of benzylamine in 1 mL of dry dimethylformamide. The reaction was stirred for 30 min at room temperature and for 2 hours at 45°, quenched by addition to 30 mL of saturated aqueous ammonium chloride and ether extracted (three times). The combined organic extracts were washed with saturated aqueous sodium chloride (three times), dried (magnesium sulfate) and concentrated under vacuum. Purification by preparative thin layer chromatography gave 100 mg (98%) of **16** as a bright yellow solid, mp 71-73°. ir: 1518, 1309 cm^{-1}; ^1H nmr: δ 7.88 (s, 1H), 7.87 (m, 1H), 7.39-7.24 (complex, 3H), 7.18 (d, 2H, J = 7.1), 6.42 (d, 1H, J = 9.8), 4.60 (s, 2H), 3.50 (t, 2H, J = 6.0), 2.85 (t, 2H, J = 6.0), 2.04 (quintet, 2H, J = 6.0); ^{13}C nmr: δ 150.6, 136.5, 136.4, 128.9, 127.4, 126.1, 125.0, 124.7, 121.4, 109.4, 54.8, 50.2, 27.9, 21.4; ms: *m*/z 177 (M^+-C_7H_7). *Anal.* Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.69; H, 5.95; N, 10.51.

1, 1-Bis(methoxycarbonyl)- 6- nitro-1, 2, 3, 4-tetrahydronaphthalene (17). To a suspension of 22 mg (0.90 mmoles) of oil-free sodium hydride in 3 mL of anhydrous *N*,*N*-dimethylformamide was added 60 mg (0.45 mmoles) of dimethyl malonate in 2 mL of dry dimethylformamide. The reaction mixture was stirred for 15 minutes and 100 mg (0.38 mmoles) of **6** was added as a solution in 2 mL of dry dimethylformamide. The reaction was stirred for 2 hours at room temperature and for 2 hours at 45°, then quenched by addition to 30 mL of saturated aqueous ammonium chloride and ether extracted (three times). The combined ether extracts were washed with saturated aqueous sodium chloride (three times), dried (magnesium sulfate) and concentrated under vacuum. Purification by preparative thin layer chromatography using 20% ether in hexanes gave 90 mg (80%) of **17** as a light yellow solid, mp 109-110°. ir: 1732, 1524, 1348 cm^{-1}; ^1H nmr: δ 7.99 (m, 2H), 7.56 (d, 1H, J = 9.5), 3.78 (s, 6H), 2.93 (t, 2H, J = 6.5), 2.48 (m, 2H), 1.89 (m, 2H); ^{13}C nmr: δ 170.9, 147.1, 139.0, 138.9, 131.8, 124.1, 120.3, 59.1, 53.2, 30.6, 29.3, 19.4; ms (30 eV): *m/z* 293 (M^+). *Anal.* Calcd. for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.12; N, 4.78. Found: C, 57.35; H, 5.12; N, 4.74.

Attempted Synthesis of 5-Nitro-2,3-dihydrobenzofuran (18). Attempts to cyclize **11** to **18** as described for the synthesis of **15** led to a complex mixture of products resulting from intermolecular reactions and decomposition of the substrate.

7-Nitro-2,3,4,5-tetrahydro-1-benzoxepin (19). Using the procedure described for the preparation of **15**, 100 mg (0.47 mmoles) of **12** yielded 70 mg (77%) of **19**, mp 40-41° [16]. ir: 1520, 1347 cm^{-1}; ^1H nmr: δ 8.04 (d, 1H, J = 2.8), 8.01 (dd, 1H, J = 8.6, 2.8), 7.05 (d, 1H, J = 8.6), 4.10 (t, 2H, J = 5.2), 2.91 (m, 2H), 2.01 (m, 2H), 1.80 (m, 2H); ^{13}C nmr: δ 165.3, 143.1, 135.7, 126.2, 123.2, 121.9, 73.7, 34.1, 31.4, 25.4; ms: *m/z* 193 (M^+).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.70; N, 7.25. Found: C, 62.18; H, 5.70; N, 7.27.

Attempted Synthesis of 1-Benzyl-5-nitroindoline (20). Using the procedure for the preparation of **16**, 100 mg (0.40 mmoles) of **13** was treated dropwise with benzylamine at 0° and the reaction was slowly allowed to warm to room temperature (24 hours). Workup gave a dark yellow oil that was purified by preparative thin layer chromatography using 5-20% ether in hexanes to give four bands: band 1, 2-fluoro-5-nitrostyrene (**21**); band 2, recovered **13** (18 mg, 18%); band 3, a mixture of **20** and 2-(*N*-benzylamino)-5-nitrostyrene (**22**). The compounds in band 3 were treated with excess acetic anhydride and pyridine at 85° for 12 hours to acylate the aniline then separated by preparative thin layer chromatography to give 2 bands: band 1, **20**; band 2, *N*-benzyl-*N*-(2-ethenyl-4-nitrophenyl)acetamide (**23**). The physical and spectral data for **20**, **21** and **23** are given below. Yields are based on 82% conversion of the starting material.

1-Benzyl-5-nitroindoline (20). This compound (26 mg, 31%) was isolated as a yellow solid, mp 67-68° [17]. ir: 1608, 1518, 1490, 1320 cm^{-1}; ^1H nmr: δ 8.03 (dd, 1H, J = 8.8, 1.9), 7.90 (m, 1H), 7.40-7.23 (complex, 5H), 6.35 (d, 1H, J = 8.8), 4.43 (s, 2H), 3.63 (t, 2H, J = 8.7), 3.09 (t, 2H, J = 8.7); ^{13}C nmr: δ 157.0, 138.2, 136.2, 129.7, 128.8, 127.7, 127.4, 126.7, 120.8, 103.5, 52.4, 51.0, 27.0; ms: *m/z* 163 (M^+-C_7H_7). *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.88; H, 5.53; N, 10.98.

2-Fluoro-5-nitrostyrene (21). This compound (20 mg, 37%) was isolated as a light yellow oil. ir: 1620, 1529, 1346, 1241 cm^{-1}; ^1H nmr: δ 8.41 (dd, 1H, J = 6.3, 2.7), 8.13 (ddd, 1H, J = 9.0, 4.4, 2.7), 7.19 (t, 1H, J = 9.0), 6.87 (dd, 1H, J = 17.7, 11.2), 5.99 (d, 1H, J = 17.7), 5.59 (d, 1H, J = 11.2); ^{13}C nmr: δ 163.3 (d, J = 260.5), 144.4, 127.4 (d, J = 3.1), 126.6 (d, J = 17.1), 124.6 (d, J = 10.3), 122.9 (d, J = 6.0), 119.6 (d, J = 4.6), 116.8 (d, J = 24.9); ms: *m/z* 167 (M^+). *Anal.* Calcd. for $C_8H_6FNO_2$: C, 57.49; H, 3.59; N, 8.38. Found: C, 57.47; H, 3.60; N, 8.34.

***N*- Benzyl- *N*- (2- ethenyl- 4- nitrophenyl) acetamide (23).** This compound (13 mg, 14%) was isolated as a colorless oil that crystallized on standing. Trituration with 5% ether in petroleum ether gave a light yellow solid, mp 80-82°. ir: 1669, 1610, 1525, 1346 cm^{-1}; ^1H nmr: δ 8.46 (d, 1H, J = 2.7), 8.02 (dd, 1H, J = 8.7, 2.7), 7.60-7.44 (complex, 3H), 7.38-7.25 (complex (2H), 6.94 (d, 1H, J = 8.7), 6.56 (dd, 1H, J = 17.4, 11.1), 5.93 (d, 1H, J = 17.4), 5.51 (d, 1H, J = 11.1), 5.34 (d, 1H, J = 14.0), 4.34 (d, 1H, J = 14.0), 1.80 (s, 3H); ^{13}C nmr: δ 169.6, 161.2, 145.0, 137.4, 136.1, 130.8, 129.8, 129.3, 128.6, 128.0, 123.2, 121.7, 120.2, 52.1, 22.6. *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 68.89; H, 5.44; N, 9.44.

1-Benzyl- 7-nitro-2, 3, 4, 5-tetrahydro-1*H*- 1-benzazepine (24). Using the procedure outlined for the preparation of **16**, 100 mg (0.36 mmoles) of **14** was reacted with benzylamine at 20° for 3 hours and 120° for 12 hours to give 36 mg (35%) of **24** as a yellow oil. ir: 1503, 1312 cm^{-1}; ^1H nmr: δ 7.96 (d, 1H, J = 2.7), 7.92 (dd, 1H, J = 9.0, 2.7), 7.40-7.24 (complex, 5H), 6.75 (d, 1H, J = 9.0), 4.50 (s, 2H), 3.31 (distorted t, 2H, J = 5.5), 2.96 (distorted t, 2H, J = 5.5), 1.81 (m, 4H); ^{13}C nmr: δ 157.0, 139.6, 137.5, 131.5, 128.7, 127.4, 127.3, 126.4, 123.4, 115.5, 57.6, 52.3, 33.7, 27.2, 24.6; ms: *m/z* 191 (M^+-C_7H_7). *Anal.* Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.92. Found: C, 72.39; H, 6.40; N, 9.87.

This procedure also yielded *N*-[4-(2-fluoro-5-nitrophenyl)-butyl]benzylamine (**25**) as a minor product. However, using the above procedure at 45° for 2 hours, **25** was produced as the major product (89 mg, 80%). ir: 3325, 1525, 1350, 1241 cm^{-1}; ^1H nmr: δ 8.11 (m, 1H), 8.07 (m, 1H), 7.36-7.20 (complex, 5H), 7.13 (t, 1H, J = 9.0), 3.78 (s, 2H), 2.72 (t, 2H, J = 7.1), 2.67 (t, 2H, J = 7.1), 1.70 (m, 2H), 1.58 (m, 2H), 1.36 (br s, 1H); ^{13}C nmr: δ 164.6 (d, J = 256.2), 144.2, 140.3, 131.0 (d, J = 18.6), 128.3, 128.0, 126.9, 126.3 (d, J = 7.4), 123.5 (d, J = 10.3), 116.0 (d, J = 25.5), 54.0, 48.9, 29.6, 28.7 (d, J = 2.0), 27.3. *Anal.* Calcd. for $C_{17}H_{19}FN_2O_2$: C, 67.55; H, 6.29; N, 9.27. Found: C, 67.59; H, 6.31; N, 9.22.

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