Synthesis of 1,2,3,4-Tetrahydroisoquinolines Containing Electron-Withdrawing Groups

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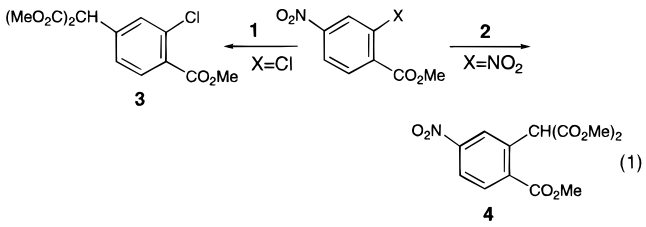
Introduction

Synthesis of tetrahydroisoquinolines containing electron-withdrawing groups in the aryl ring was required for the preparation of novel pharmaceutical agents. Unfortunately, many of the isoquinoline (Pomeranz−Fritsch)[1], dihydroisoquinoline (Bischler−Napieralski),[2] and tetrahydroisoquinoline (Pictet−Spengler)[3] routes rely on an electron-neutral or preferably an electron-rich aromatic nucleus for cyclization.[4] Modification of the Bischler−Napieralski reaction, using oxalyl chloride to generate a superior acylating agent, still provided low yields of product when a nitro group was contained in the aryl ring.[5] Thus, a method was sought to prepare tetrahydroisoquinolines containing electron-withdrawing groups.

Results and Discussion

The tetrahydroisoquinoline approach evaluated the formation of the heterocyclic ring via double displacement with a nitrogen nucleophile on a substituted benzene derivative. Access to appropriately substituted benzene derivatives was envisioned by malonate displacement.[6] To this end, reaction of methyl 2-chloro-4-nitrobenzoate (**1**) with sodium hydride and dimethyl malonate in dimethyl sulfoxide afforded **3**, wherein the leaving group was the *p*-nitro instead of the desired *o*-chloro group, eq 1. To achieve the desired regiochemistry, methyl 2,4-dinitrobenzoate (**2**) was used generating triester **4** in 39% yield.



A more efficient diethyl malonate displacement[7] of 2-bromo-4-nitrobenzoic acid was known that employed catalytic copper(I) bromide and sodium hydride as base.[8] These researchers evaluated sodium hydride, *n*-butyllithium, sodium *tert*-butoxide, and lithium *tert*-butoxide, lithium hydride and determined that only sodium hydride was effective in the displacement.[9] The sodium hydride conditions were applied to commercially available 2-chloro-4-nitrobenzoic acid to afford a 77% yield of **6a** (R = Et), Scheme 1. Although only sodium hydride was reported to be effective, alternatives were investigated prior to scale-up because of the significant exotherm and hydrogen evolution, which results on addition of this base.

Sodium methoxide was found to be an acceptable base, yielding **6a** (R = Me) in 70% yield with dimethyl malonate as solvent.[10] This was achieved by addition of sodium methoxide to 2-chloro-4-nitrobenzoic acid in dimethyl malonate followed by the addition of copper (I) bromide.[11] The reaction after 6 h at 70 °C had progressed only 5−15% and required 18−24 h for completion. Thus, an explanation for the initial slow rate was sought. No delayed exotherm was observed with a temperature chart recorder. Additives such as sodium bromide, sodium chloride, palladium acetate, and nickel acetylacetonate did not increase the reaction rate. The initial slow rate of reaction was believed to result from low solubility of the carboxylic acid sodium salt, which is predominately out of solution, gradually being solubilized as the reaction proceeds. Enhanced reaction rate (4 h) was obtained by significant increase in agitation.[12] 2,5-Dibromobenzoic acid and 2-chloro-5-(trifluoromethyl)benzoic acid similarly provided the diesters **6b** (R = Me) and **6c** (R = Me) in 77% and 83% yield, respectively, Scheme 1.

The malonate moiety in **6a**−**c** was hydrolyzed and decarboxylated with aqueous methanolic sodium hydroxide, affording the diacids **7a**−**c** in ≥88% yield. Having assembled all the carbon atoms necessary for the tetrahydroisoquinolines, borane reduction of diacids **7** into diols **8** was performed. The yield of diol **8a** obtained with borane in THF on a 3 g scale (13 mmol) of **7a** was 78%. On a larger scale, only 40−50% yields of **8a** were isolated along with lactone **10** or hydroxy acid **11**, eq 2.

This incomplete reduction, attributed in the literature to the formation of insoluble polymers halting the reac-

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(1) (a) Pomeranz, C. *Montash* **1893**, *14*, 116. (b) Gensler, W. J. *Org. Reac.* **1951**, *6*, 191−206.

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(4) (a) Grethe, G.; Bradsher, C. K.; Dyke, S. F.; Fukumoto, K.; Kametani, T. K.; Kinsman, R. G.; McDonald, E. *The Chemistry of Heterocyclic Compounds Isoquinolines Part 1*; Wiley: New York, 1981. (b) Kathawala, F. G.; Coppola, G. M.; Schuster, H. F.; Bunting, J. W.; Duarte, F. F.; Mathison, I. W.; Nair, M. D.; Popp, F. D.; Premila, M. S.; Solomons, W. E. *The Chemistry of Heterocyclic Compounds Isoquinolines Part 2*; Wiley: New York, 1990.

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(6) Bunnett, J. F.; Zahler R. E. *Chem. Rev.* **1951**, *49*, 273.

(7) (a) For copper(I)-promoted malonate coupling reaction with aryl halides, see: Setsune, J. Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett.* **1981**, 367−70. (b) Aryl halide displacements by malonate without copper catalysis see: Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51−3 and references therein.

(8) (a) Bruggink, A.; McKillop, A. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 340−1. (b) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607−19.

(9) Recovered starting material was obtained with these bases.

(10) Diethyl malonate also provided the desired product **6a** (R = Et) along with the corresponding methyl ester **6a** (R = Me) resulting from transesterification with sodium methoxide. Methyl esters are typically more crystalline than ethyl esters, as found here with melting points of 153 °C vs 104 °C, respectively.

(11) Bromobenzene is converted to anisole in 95% yield with copper(I) bromide catalysis in methanol with sodium methoxide. Aalten, H. L.; Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565−78.

(12) Toluene or tetrahydrofuran as cosolvents prevented the reaction from proceeding.

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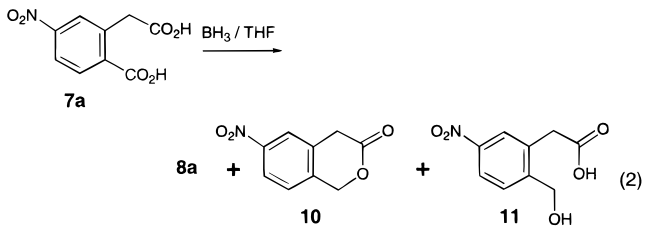
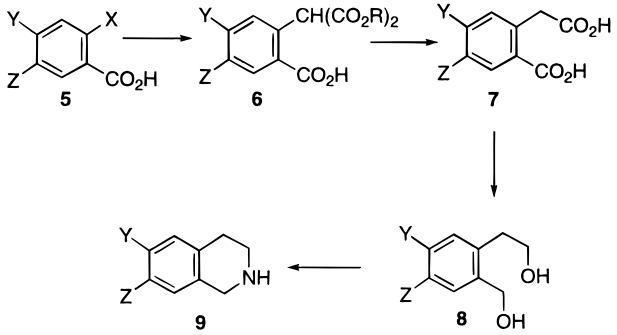


tion,[13] is a general problem when diacids are reduced with borane. Use of more reactive sodium borohydride/boron trifluoroetherate to form borane[14] or prior treatment with trimethyl borate[15] to generate the acyloxyborane did not enhance conversion of diacid **7a** into **8a**.[16] Therefore, the cyclic anhydride of **7a** was made in situ and directly reduced with borane to generate the desired diols in good yield.[17] Further investigation into direct diacid reduction revealed that small quantities (5%) of triacid **6a** (R = H) were responsible for halting the reaction. Triacid **6a** (R = H) is labile in NMR solvents such as dimethyl sulfoxide, but it could be detected in acetone where decarboxylation to **7a** occurred more slowly. HPLC was found to be the best method for monitoring the hydrolysis/decarboxylation of **6a**.[18] Extraction of the crude **6a** (R = H)/**7a** mixture into ethyl acetate and heating until the decarboxylation to **7a** was complete provided a reliable process. This borane reduction of diacid **7a**, without triacid **6a** (R = H) present, provided clean diol **8a** in 89% yield.

Formation of the heterocyclic ring by double displacement with ammonia was investigated.[19] Conversion of the alcohols into leaving groups was accomplished by mesylation.[20] Attempts to cyclize the dimesylate **12** derived from **8a** with ammonia at 1 atm employing a dry ice coldfinger to maintain ammonia throughout the reaction gave recovered starting material. Ammonia was not sufficiently nucleophilic under these conditions.[21] We hypothesized that addition of trimethylsilyl chloride would form (trimethylsilyl)amine in situ[22] and cyclization would proceed. Repeating the ammonia reaction conditions with dimesylate **12** in methylene chloride solution with 10 equiv of trimethylsilyl chloride generated **9a** in 47% yield.

An alternative explanation was that trimethylsilyl chloride's function in the cyclization was to generate ammonium chloride, which subsequently converted dimesylate **12** to the benzylic chloride **13**, and chloride **13** was more readily displaced than the benzylic mesylate **12**. To test the proposal, benzylic chloride **13** was isolated in 95% yield by allowing the mesylation of **8a** to warm to ambient temperature overnight. Treatment of **13** with ammonia at 1 atm without trimethylsilyl chloride as previously described provided recovered benzylic chloride **13**. Thus, trimethylsilyl chloride enhanced the nucleophilicity of ammonia in the cyclization at one atmosphere.

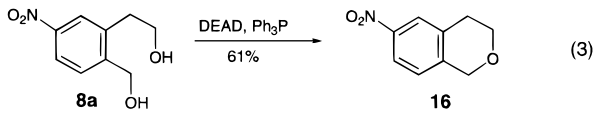
Scheme 1



Higher yields of tetrahydroisoquinoline **9a** were obtained with ammonia and tetrahydrofuran as cosolvent without trimethylsilyl chloride. The reaction was conducted at 120 psi in a Parr apparatus at ambient temperature, providing **9a** in 75% yield. These preferred cyclization conditions were employed for the dimesylates derived from **8b** and **8c**, similarly generating the tetrahydroisoquinolines **9b** and **9c**.

In contrast to the ammonia cyclizations, the ring formation reaction was more straightforward with substituted amines. Dimesylate **12** cyclized to *N*-allyl **14** in 95% yield using allylamine in methylene chloride at room temperature for 16 h. The corresponding benzylic chloride **13** proceeded to 50% conversion under the same conditions, but heating to 50 °C for 2 h completed the conversion to **14** in 71% yield, Scheme 2. Thus, the benzylic mesylate was again a better leaving group than chloride under these conditions.

Reaction of excess aniline with dimesylate **13** in tetrahydrofuran provided an 86% yield of **15** without evidence of elimination to the styrene. Diol **8a** was used to prepare isochroman **16** in 61% yield by treatment under Mitsunobu conditions.[23]



Conclusion

In summary, a method to prepare tetrahydroisoquinolines and an isochroman containing electron-withdrawing groups in the aromatic ring has been demonstrated. Sodium methoxide was employed in the copper catalyzed displacement of *o*-halobenzoic acids instead of sodium hydride. Small quantities of a tricarboxylic acid intermediate were found to halt the borane reduction of a diacid. A benzylic mesylate was demonstrated to be better than chloride as a leaving group in cyclizations

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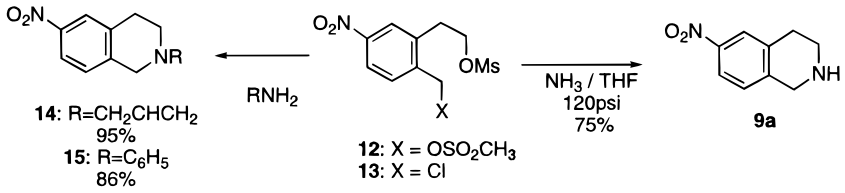
(16) Alane did not provide better conversion to the diol. Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464−72.
(17) Direct reduction of diacid **7c** with lithium aluminum hydride afforded diol **8c**; see the Experimental Section.
(18) Puresil C18, 20% acetonitrile/80% 50 mM aqueous KH_2PO_4, flow rate 1 mL/min, 280 nm.
(19) Cyclization of *o*-chloroethyl benzyl chloride with alkylamines was a precedented route to tetrahydroisoquinolines. Lusinchi, X.; Durand, S.; Delaby, R. *Compt. Rend.* **1959**, *248*, 426−8.
(20) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195−6.
(21) Pilzey, J. S. *Synthetic Reagents*; Wiley: New York, 1983; Vol. 5, p 26.
(22) (Trimethylsilyl)amine is known to disproportionate at ambient temperature into hexamethyldisilizane and ammonia. Wiberg, N.; Uhlenbrock, W. *Ber.* **1971**, *104*, 2643−45.
(23) See the Experimental Section.

Scheme 2



with nitrogen nucleophiles. Nucleophilicity of ammonia was enhanced by in situ formation of trimethylsilylamine.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Unless otherwise stated, $CDCl_3$ was used for NMR spectra, and KBr for IR spectra. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory. All reagents and solvents were obtained commercially from Aldrich and used without additional purification.

2-(Carboxy-5-nitrophenyl)malonic Acid Dimethyl Ester (6a, R = Me). A solution of 2-chloro-4-nitrobenzoic acid (75 g, 372 mmol) in dimethyl malonate (900 mL, 20 equiv) was degassed with nitrogen for 15 min. Copper(I) bromide (5.4 g, 37 mmol) was added in one portion. Sodium methoxide (48.3 g, 894 mmol) was added in one portion with stirring. This caused the reaction mixture to warm to 48 °C. After being stirred for 15 min, the reaction mixture was heated to 70 °C for 24 h. (Vigorous stirring shortens this time.) The reaction was monitored by NMR on an aliquot. Water (900 mL) was added to the cooled reaction followed by hexanes (900 mL). The aqueous layer was separated. Toluene (900 mL) was added to the aqueous layer, and the biphasic mixture was filtered through Celite to remove insolubles. The aqueous layer containing the carboxylate salt of **6a** (R = Me) was separated. (Hexane and toluene extractions served to remove the excess dimethyl malonate and thereby allow precipitation of product in the subsequent acidification.) Fresh toluene (1800 mL)[24] was added to this aqueous layer and the biphasic mixture acidified with 6 N aqueous HCl (90 mL). A white precipitate formed, and the contents were stirred for 18 h. Product **6a** (R = Me) was collected by filtration and dried to give a white solid: 78.1 g (70%, mp 153 °C); IR 2923, 2853, 1750, 1728, 1705, 1458, 1376, 1352, 1305, 1261 cm^{-1}; ^1H NMR $(CD_3)_2SO$ δ 8.37 (d, J = 2 Hz, 1H), 8.30 (d, J = 1 Hz, 2H), 5.82 (s, 1H), 3.83 (s, 6H); ^{13}C NMR $(CD_3)_2SO$ δ 168.0, 167.3, 149.4, 137.1, 135.8, 132.5, 125.4, 123.7, 54.5, 53.4. Anal. Calcd for $C_{11}H_{10}NO_8$: C, 48.49; H, 3.73; N, 4.71. Found: C, 48.27; H, 3.72; N, 4.76.

2-(4-Bromo-2-carboxyphenyl)malonic acid dimethyl ester (6b) was prepared as **6a** except the acidification was performed without toluene present: 77% yield; mp 135−6 °C; IR 2922, 2853, 1765, 1734, 1688, 1459, 1313, 1227, 1148 cm^{-1}; ^1H NMR δ 8.28 (d, J = 2 Hz, 1H), 7.73 (dd, J = 2 Hz, 1H), J = 8 Hz, 1H), 7.36 (d, J = 8 Hz, 1H), 5.78 (s, 1H), 3.79 (s, 6H); ^{13}C NMR δ 170.7, 168.4, 136.5, 134.7, 133.9, 132.1, 129.8, 122.4, 54.1, 53.0. Anal. Calcd for $C_{12}H_{11}O_6$: C, 43.53; H, 3.35. Found: C, 43.50; H, 3.07.

2-[2-Carboxy-4-(trifluoromethyl)phenyl]malonic acid dimethyl ester (6c) was prepared as for **6a** except the acidification was performed without toluene present: 83% yield: mp 140−41 °C; IR 2922, 2852, 1744, 1718, 1459, 1376, 1337, 1120 cm^{-1}; ^1H NMR δ 8.41 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 5.89 (s, 1H), 3.81 (s, 6H). Anal. Calcd for $C_{13}H_{11}F_3O_6$: C, 48.76; H, 3.46. Found: C, 48.80; H, 3.45.

2-(Carboxymethyl)-4-nitrobenzoic Acid (7a). Sodium hydroxide (10.10 g, 253 mmol) in water (120 mL) was added over 85 min to a solution of 2-(carboxy-5-nitrophenyl)malonic acid dimethyl ester, **6a** (R = Me) (15.0 g, 51 mmol), in methanol (120 mL) at ambient temperature. After 3 h, the reaction was complete, the methanol was removed under vacuum, and the contents were acidified with concentrated HCl (22.4 mL) at ambient temperature. The resulting white aqueous suspension was extracted twice with ethyl acetate (150 and 75 mL), the combined organic phases were dried with magnesium sulfate, and the volume of extracts was reduced to 55 mL. The resulting ethyl acetate slurry was heated to 65 °C for 6 h, effecting complete decarboxylation of **6a** (R = H),[18] and diacid **7a** was filtered off at ambient temperature and dried to afford 10 g of a white solid: (88%; mp 180−82 °C; IR 3080, 3055, 2983, 1707, 1611, 1585, 1516, 1491, 1424, 1358, 1298, 1237 cm^{-1}. ^1H NMR $(CD_3)_2SO$ δ 12.87 (bs, 2H), 8.25 (d, J = 2 Hz, 1H), 8.18 (dd, J = 2, 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 4.07 (s, 2H); ^{13}C NMR $(CD_3)_2SO$ δ 172.3, 167.5, 149.2, 138.8, 137.3, 132.1, 127,2, 122.4, 39.8. Anal. Calcd for $C_9H_{17}NO_6$: C, 48.01; H, 3.13; N, 6.22. Found: C, 47.67; H, 3.19; N, 6.31.

5-Bromo-2-(carboxymethyl)benzoic acid (7b) was prepared as for **13**: 96% yield; mp 210−11 °C; IR 2922, 2852, 1694, 1459, 1377, 1293 cm^{-1}; ^1H NMR $(CD_3)_2SO$ δ 12.75 (bs 2H), 7.96 (d, J = 2 Hz, 1H), 7.69 (dd, J = 2, 8 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 3.89 (s, 2H). Anal. Calcd for $C_9H_7BrO_4$: C, 41.73; H, 2.72. Found: C, 41.97; H, 2.65.

2-(Carboxymethyl)-5-(trifluoromethyl)benzoic acid (7c) was prepared as for **7a**: 95% yield: mp 173−74 °C; IR 2922, 1705, 695, 1460, 1333, 1128 cm^{-1}; ^1H NMR $(CD_3)_2SO$ δ 12.82 (bs, 2H), 8.11 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 4.03 (s, 2H).

2-[2-(Hydroxymethyl)-5-nitrophenyl]ethanol (8a). To a THF (220 mL) solution of 2-(carboxymethyl)-4-nitrobenzoic acid, **7a** (10.0 g, 44.4 mmol), was added sodium borohydride (5.06 g, 133 mmol) in portions. The contents were cooled to 0 °C, and boron trifluoride diethyl etherate (21.3 mL, 133 mmol) was added dropwise over 1 h. The contents were allowed to warm to 25 °C and stirred for 16 h. The reaction was cooled to 0 °C and cautiously quenched with aqueous sodium hydroxide (1 N, 178 mL). The contents were stirred for 3 h, THF was removed under vacuum, the resulting aqueous suspension was cooled to 0 °C, and the product was filtered off. After drying, the product was obtained as a white solid: 7.78 g (89%); mp 79−81 °C); IR 3277, 3192, 2964, 2932, 1614, 1525, 1507, 1170, 1134, 1089, 1067 cm^{-1}; ^1H NMR $(CD_3)_2SO$ δ 8.05 (d, J = 9 Hz, 1H), 8.04 (s, 1H), 7.66 (d, J = 9 Hz, 1H), 5.42 (t, J = 5 Hz, 1H), 4.74 (t, J = 5 Hz, 1H), 4.64 (d, J = 5 Hz, 2H), 3.63 (m, 2H), 2.80 (t, J = 6 Hz, 2H); ^{13}C NMR $(CD_3)_2SO$ δ 149.1, 146.6, 139.2, 127.8, 124.3, 121.3, 61.2, 60.6, 34.9. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.54; H, 5.49; N, 7.07.

2-[4-Bromo-2-(hydroxymethyl)phenyl]ethanol (8b) was prepared as for **8a** in 76% yield: mp 94−5 °C; IR 3182, 2922, 2853, 1460, 1376 cm^{-1}; ^1H NMR $(CD_3)_2SO$ δ 7.50 (d, J = 2 Hz, 1H), 7.32, (dd, J = 2 Hz, J = 8 Hz, 1H), 7.11 (d, J = 8 Hz, 1H), 5.21 (t, J = 5 Hz, 1H), 4.67 (t, J = 5 Hz, 1H), 4.50 (d, J = 5 Hz, 2H), 3.53 (m, 2H), 2.66 (t, J = 7 Hz, 2H); ^{13}C NMR $(CD_3)_2SO$ δ 143.2, 136.1, 131.7, 129.4, 129.2, 119.0, 61.3, 60.1, 34.6. Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80. Found: C, 46.80; H, 4.65.

2-[2-(Hydroxymethyl)-4-(trifluoromethyl)phenyl]ethanol (8c). A THF (30 mL) solution of diacid **7c** (3 g, 12 mmol) was added to a suspension of lithium aluminum hydride (1.4 g, 37 mmol) in THF (30 mL) at a rate to maintain gentle reflux. The contents were stirred for 16 h and quenched with water (1.4 mL), aqueous sodium hydroxide (15%, 1.4 mL), and water (4 mL). The solids were filtered off, and solvent was removed under vacuum to yield 1.34 g of the diol as an oil; IR 3294, 3197, 3054, 2924, 1620, 1483, 1456, 1375 cm^{-1}; ^1H NMR δ 7.60 (s, 1H), 7.54 (d, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 4.67 (s, 2H), 3.89 (t, J = 6 Hz, 2H), 3.54 (bs, 1H), 2.97 (t, J = 6 Hz, 2H), 2.64 (bs,

(24) Toluene prevented gumming of **6a** (R = Me) but was not essential for the corresponding bromo **6b** or trifluoromethyl **6c** derivatives.

1H). Anal. Calcd for $C_{10}H_{11}F_3$: C, 54.55; H, 5.04. Found: C, 54.78; H, 5.13.

6-Nitro-1,2,3,4-tetrahydroisoquinoline (9a). Methanesulfonyl chloride (0.9 mL, 11.63 mmol) was added dropwise over 10 min to a solution of 2-[2-(hydroxymethyl)-5-nitrophenyl]ethanol (**8a**) (1.0 g, 5.07 mmol) and triethylamine (1.8 mL, 12.91 mmol) in methylene chloride (20 mL) at <0 °C. TLC shows complete reaction after 30 min; ^{1}H NMR δ 8.17−11 (m, 2H), 7.65 (d, J = 9 Hz, 1H), 5.36 (s, 2H), 4.49 (t, J = 6 Hz, 2H), 3.25 (t, J = 6 Hz, 2H), 3.08 (s, 3H), 2.98 (s, 3H). The reaction mixture was washed with 10% aqueous HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried with magnesium sulfate, and methylene chloride was removed under vacuum. The oil was dissolved in THF (100 mL) and evaporated in vacuo (3×). The dimesylate **12** (1.9 g) was employed directly in the next reaction without further purification. Ammonia (50 mL) was added to the dimesylate (1.9 g) in THF (30 mL) at −78 °C in a Parr apparatus. The contents were warmed to 24 °C for 60 h (120 psi). Ammonia was distilled off and solvent removed under vacuum to give the crude product (786 mg, 82%). Toluene was added, the solution filtered through magnesium sulfate, and solvent removed under vacuum to yield 721 mg (75%) of an oil: IR 2928, 2831, 1672, 1514, 1345, 1123 cm^{-1}; ^{1}H NMR δ 7.97 (s, 1H), 7.95 (d, J = 9 Hz, 1H), 7.15 (d, J = 9 Hz, 1H), 4.07 (s, 2H), 3.15 (t, J = 6 Hz, 2H), 2.89 (t, J = 6 Hz, 2H), 1.98 (bs, 1H). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.48; H, 5.30; N.15.32.

7-Bromo-1,2,3,4-tetrahydroisoquinoline (9b)[25] was prepared as for **9a**: IR 3184, 3027, 2952, 2923, 1487, 1461, 1429, 1376, 1343, 1312 cm^{-1}; ^{1}H NMR δ 7.28 (d, J = 8 Hz, 1H), 7.19 (s, 1H), 6.97 (d, J = 8 Hz, 1H), 4.05 (s, 2H), 3.19 (t, J = 6 Hz, 2H), 2.82 (t, J = 6 Hz, 2H), 2.32 (bs, 1H); ^{13}C NMR $(CD_3)_2SO$ δ 136.3, 133.6, 131.5, 129.6, 129.4, 119.0, 45.8, 42.1, 26.8; EIMS, M^+ 212.0058 (calcd. 212.0074).

7-(Trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (9c) was prepared as for **9a**: IR 2929, 1622, 1587, 1465, 1432, 1383, 1373, 1332 cm^{-1}; ^{1}H NMR δ 7.38 (d, J = 8 Hz, 1H), 7.27 (s, 1H), 7.20 (d, J = 8 Hz, 1H), 4.08 (s, 2H), 3.18 (t, J = 6 Hz, 2H), 2.87 (t, J = 6 Hz, 2H), 2.05 (bs, 1H); EIMS, M^+ 202.0861 (calcd 202.0844).

Methanesulfonic acid 2-[2-(chloromethyl)-5-nitrophenyl]ethyl ester (13): IR 2922, 2853, 1460, 1347, 1259 cm^{-1}; ^{1}H NMR δ 8.15 (s, 1H), 8.10 (d, J = 7 Hz, 1H), 7.48 (d, J = 7 Hz, 1H), 4.68 (s, 2H), 4.52 (t, J = 8 Hz, 2H), 3.30 (t, J = 8 Hz, 2H), 2.98 (s, 3H); ^{13}C NMR δ 145.6, 142.9, 137.5, 131.6, 125.1, 122.6, 68.3, 42.4, 37.5, 31.9.

2-Allyl-6-nitro-1,2,3,4-tetrahydroisoquinoline (14). The dimesylate **12** was prepared as detailed in the synthesis of **9a**. Allylamine (2.3 mL, 30.6 mmol) was added to a solution of dimesylate (2.15 g, 6 mmol) in methylene chloride (30 mL), and the contents were stirred at ambient temperature for 16 h. Aqueous hydrochloric acid (1 N, 50 mL) was added, and the layers were separated. The aqueous acidic phase was treated with aqueous sodium hydroxide (5 N) until the pH was 10. Extraction of the basic aqueous phase with chloroform (150 mL), drying with magnesium sulfate, and removal of the solvent under vacuum afforded 1.26 g (95%) of the tetrahydroisoquinoline as an oil: IR 2921, 2852, 1528, 1462, 1344, 1259 cm^{-1}; ^{1}H NMR δ 7.97 (s, 1H), 7.94 (d, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 5.92 (m, 1H), 5.25 (m, 2H), 3.68 (s, 2H), 3.19 (m, 2H), 2.98 (t, J = 6 Hz, 2H), 2.76 (t, J = 6 Hz, 2H). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.23; H, 6.57; N, 12.56.

6-Nitro-2-phenyl-1,2,3,4-tetrahydroisoquinoline (15). Methanesulfonyl chloride (0.9 mL, mmol) was added dropwise to a solution of diol **8a** (1.0 g, 5 mmol) in methylene chloride (20 mL) at 0 °C. Fifteen minutes later, the reaction was complete and the organic phase successively washed with 10% aqueous HCl (20 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (20 mL). The organic layer was dried with magnesium sulfate and solvent removed under vacuum. The resulting dimesylate was dissolved in THF (20 mL), aniline (2.31 mL, 25 mmol) was added, and the contents were stirred at ambient temperature for 18 h and heated to 60 °C for 18 h. The solvent was removed under vacuum and methylene chloride (50 mL) added. The organic phase was washed with water (50 mL), saturated aqueous sodium bicarbonate (50 mL), and pH 4 buffer (50 mL). The organic phase was dried with magnesium sulfate and solvent removed under vacuum to afford 3.06 g of the crude product. Chromatography on silica eluting with 20% ethyl acetate/hexanes gave the product as a yellow solid: 1.11 g (86%); mp 137−8 °C); IR 2922, 2853, 1460, 1376, 1260 cm^{-1}; ^{1}H NMR δ 8.06−8.03 (m, 2H), 7.34−7.26 (m, 3H), 7.00 (d, J = 8 Hz, 2H), 6.89 (t, J = 7 Hz, 1H), 4.48 (s, 2H), 3.60 (t, J = 6 Hz, 2H), 3.09 (t, J = 6 Hz, 2H). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.49; H, 5.69; N, 11.19.

6-Nitroisochroman (16). To a solution of diol **8a** (200 mg, 1 mmol), succinimide (100 mg, 1 mmol), and triphenylphosphine (293 mg, 1.12 mmol) in THF (4 mL) at 0 °C was added diethyl azodicarboxylate (180 ul, 1.14 mmol) in THF (2 mL). The contents were stirred for 3.5 h, and solvent was removed under vacuum. Chromatography provided the product as a white solid: 111 mg (61%); mp 84 °C; IR 3037, 1683, 1613, 1564, 1401 cm^{-1}; ^{1}H NMR δ 8.02 (d, J = 9 Hz, 1H), 8.01 (s, 1H), 7.14 (d, J = 9 Hz, 1H), 4.83, 4.00 (t, J = 6 Hz, 2H), 2.96 (t, J = 6 Hz, 2H). Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 506; N, 7.82. Found: C, 60.69; H, 5.28; N, 7.78.

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