6-Nitro-1,2,3,4-tetrahydroquinolines by a Tandem Reductive Amination-S_NAr Reaction

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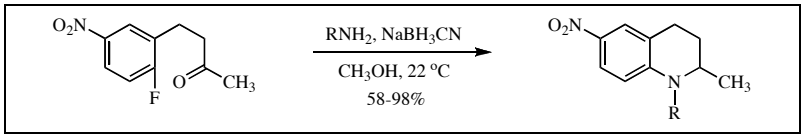
Received December 11, 2007



A tandem reductive amination-S_NAr reaction has been developed for the synthesis of 6-nitro-1,2,3,4-tetrahydroquinolines. Treatment of 4-(2-fluoro-5-nitrophenyl)-2-butanone or 3-(2-fluoro-5-nitrophenyl)-propanal with primary amines and sodium cyanoborohydride in methanol at room temperature provided good to excellent yields of the substituted tetrahydroquinolines. The reaction proceeded best with the ketone substrate using primary amines that were unbranched at the α-carbon. The aldehyde also produced the target heterocycles, but these were accompanied by 10-15% of the uncyclized side chain reductive amination products.

J. Heterocyclic Chem., **45**, 1155 (2008).

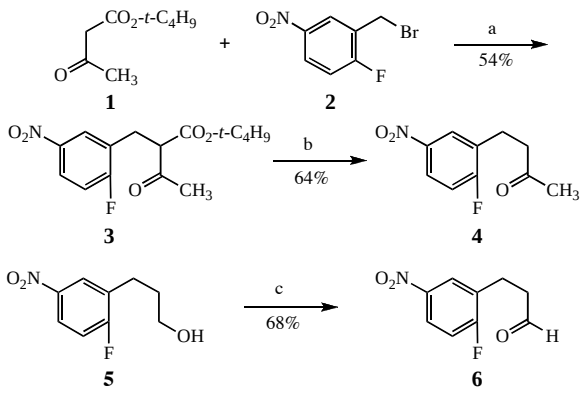
INTRODUCTION

Over the past several years, our work has led to a number of reductive cyclizations that yield 1,2,3,4-tetrahydroquinolines [2]. These earlier procedures focused on the production of derivatives with specific substitution patterns on the saturated carbons. A recent report has revealed that certain 2-substituted-6-nitro-1,2,3,4-tetrahydroquinolines promote increased bone mineral density in rats and may, thus, have use in the treatment of osteoporosis [3]. Tetrahydroquinolines bearing a nitro group at C6 would not be accessible using our previous methods, but could potentially be prepared using an S_NAr reaction coupled with an S_N2 displacement of halide [2f] or a reductive amination reaction [4]. Since the target heterocycles are substituted at C2 and therefore sterically hindered, it is unlikely that a process involving the S_N2 reaction would be successful. Thus, we sought to design systems to explore the feasibility of a tandem reductive amination-S_NAr sequence.

RESULTS AND DISCUSSION

We prepared 4-(2-fluoro-5-nitrophenyl)-2-butanone (**4**) and 3-(2-fluoro-5-nitrophenyl)propanal (**6**) to evaluate the reductive amination-S_NAr sequence as an approach to 6-nitro-1,2,3,4-tetrahydroquinolines. Ketone **4** was prepared in three steps starting from *tert*-butyl acetoacetate (**1**) and 2-fluoro-5-nitrobenzyl bromide (**2**) [5]. Monoalkylation of **1** with **2** proved difficult under standard conditions [5], but was accomplished by treating **2** with 1,8-diazabicyclo[5.4.0]undec-7-ene in benzene followed by addition of **1** [6]. This afforded a 54% yield of the desired monoalkylation product **3** after chromatography. Cleavage of the *tert*-butyl ester in **3** using trifluoroacetic acid in the presence of triethylsilane [7] and heating the resulting β-keto acid at 150 °C then gave **4** in 64% yield. Aldehyde **6** was prepared in 68% yield by oxidation of 3-(2-fluoro-5-nitrophenyl)propanol (**5**) [2f] with sodium acetate-buffered pyridinium chlorochromate [8] (see Scheme 1).

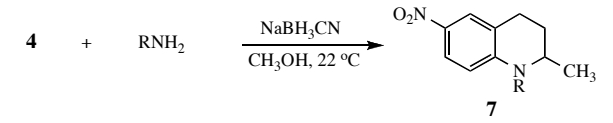
Scheme 1 [a]



[a] Key (a) 1,8-diazabicyclo[5.4.0]undec-7-ene, C_6H_6, 22 °C; (b) *i*. CF_3CO_2H, $(C_2H_5)_3SiH$, CH_2Cl_2, 22 °C; *ii*. 150°, neat; (c) $C_5H_5NH^+$ CrO_3Cl^-, NaO_2CCH_3, CH_2Cl_2, 22 °C.

The results of our reductive amination-S_NAr cyclization studies are summarized in Tables 1 and 2. Ketone **4** reacted with simple primary amines to give 6-nitro-1,2,3,4-tetrahydroquinolines in high yields. It was also possible to neutralize amine salts such as ethyl glycinate hydrochloride [9] or ammonium acetate [10] to provide amines for the reaction. Problems arose, however, in cases where branching at the α-carbon of the amine hindered its approach to the ketone. Thus, benzylamine cyclized to **7a** in 98% yield while cyclohexylamine furnished **7h** in only 12% yield and *tert*-butylamine gave no reaction at all. Aldehyde **6** afforded somewhat lower

Table 1

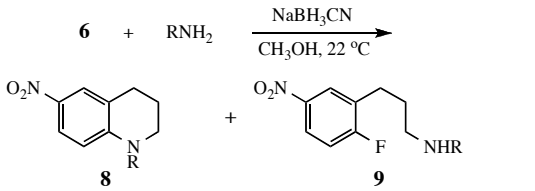


7

R	Yield (%)
Unbranched	
a $C_6H_5CH_2$	98
b $C_6H_5CH_2CH_2$	96
c *n*-C_6H_{13}	98
d *i*-C_4H_9	90
e *i*-$C_3H_7OCH_2CH_2CH_2$	88
f $CH_3CH_2O_2CCH_2$	76 [a]
g H	58 [b]
α-Branched	
h *c*-C_6H_{11}	12 [c]
i *t*-C_4H_9	0 [c]

[a] Ethyl glycinate hydrochloride was neutralized with sodium ethoxide prior to reaction. [b] Ammonium acetate was neutralized with potassium hydroxide prior to reaction. This reaction also gave 19% of (±)-4-(2-fluoro-5-nitrophenyl)-2-butanol. [c] The major product was recovered starting material.

Table 2



8 **9**

R	Yield (%) **8**	**9**
Unbranched		
a $C_6H_5CH_2$	75	13
b $C_6H_5CH_2CH_2$	72	13
c *n*-C_6H_{13}	70	12
d *i*-C_4H_9	76	15
α-Branched		
e *c*-C_6H_{11}	42	11 [a]
f *t*-C_4H_9	0	28 [a]

[a] In addition to **8** and/or **9**, these reactions gave complex and largely inseparable mixtures of products.

yields of the cyclized products accompanied by 10-15% of the uncyclized side chain reductive amination products [11]. The less hindered aldehyde gave higher yields of tetrahydroquinolines from the α-branched amine cyclohexylamine (42%), but again, failed to produce any of the target heterocycle from *tert*-butylamine. Instead, the latter gave a modest yield of **9f** (28%) along with an inseparable mixture containing the alcohol reduction product and several unidentified compounds. Finally, the aldehyde substrate was too labile to permit reaction with amine salts requiring treatment with base prior to condensation (entries **f** and **g**, Table 1) and yielded only complex mixtures of products.

Isolation of the simple reductive amination product from the reaction of **6** with *tert*-butylamine suggests that the chronology of the sequence involves initial reductive amination of the side chain carbonyl followed by nucleophilic aromatic substitution of the resulting amine at the activated fluorine on the aromatic ring. This is further supported by the observation that the reaction does not develop the deep yellow color of the cyclized 4-nitroaniline moiety until the reducing agent is added. The final ring closure likely proceeds through a chair-like conformation that permits alignment of the side chain nucleophile for addition from above (or below) the plane of the aromatic ring [2f].

The ketone substrate reacts cleanly to give high yields of the 6-nitrotetrahydroquinoline products; the aldehyde gives more side reactions, but the yields are still synthetically useful. The greater proportion of cyclized products from the ketone is puzzling, but may derive from steric interactions in a chair-like conformation possible for ring closure. The α-methyl group in the amine produced from the ketone would be expected to adopt a pseudo-equatorial orientation (Figure 1), which should orient the

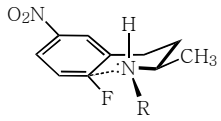


Figure 1. Possible conformation for ring closure from the ketone

reactive centers close together and promote efficient ring formation. The lack of this alkyl substituent in the aldehyde-derived amine would result in a more random orientation of the side chain that should make cyclization less favorable.

CONCLUSION

We have developed a new approach to the synthesis of 6-nitro-1,2,3,4-tetrahydroquinolines based on a novel tandem reductive amination-S_NAr reaction. The sequence gave excellent yields of the target ring system from a ketone and good yields from an aldehyde substrate. The superior results from the ketone may arise from its greater stability to the reaction conditions and from steric effects in a chair-like conformation leading to ring closure. We are pursuing further studies of this reaction in systems bearing other electron-withdrawing groups at C6 and C8 of the tetrahydroquinoline system.

EXPERIMENTAL

All reactions were run under dry nitrogen. Methanol was used from a freshly opened bottle. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521)

with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [12] 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). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65-70 °C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H 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. Mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

***tert*-Butyl (±)-2-(2-Fluoro-5-nitrobenzyl)acetoacetate (3).** To a solution of 2.37 g (15.0 mmoles) of **1** in 75 mL of benzene was added 2.28 g (15.0 mmoles) of 1,8-diazabicyclo[5.4.0]-undec-7-ene [6]. The mixture was stirred for 5 minutes and a solution of 3.50 g (15.0 mmoles) of **2** [5] in 10 mL of benzene was added dropwise. The mixture was stirred at room temperature for 15 hours, then poured into saturated aqueous ammonium chloride and extracted with ether (three times). The combined ether extracts were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under vacuum. The resulting brown oil was flash chromatographed on a 50 cm x 2 cm silica gel column eluted with 5-10% ether in hexanes to give 2.48 g (54%) of pure **3** as a light yellow oil. ir: 1734, 1715, 1529, 1350 cm^{-1}; ^{1}H nmr: δ 8.15 (m, 2H), 7.18 (t, 1H, J = 8.7), 3.76 (dd, 1H, J = 9.0, 6.3), 3.26 (dd, 1H, J = 14.7, 6.3), 3.17 (dd, 1H, J = 14.7, 9.0), 2.28 (s, 3H), 1.41 (s, 9H); ^{13}C nmr: δ 201.2, 167.4, 164.7 (d, J = 257.1), 144.0, 127.4 (d, J = 18.0), 127.2 (d, J = 6.9), 124.5 (d, J = 10.3), 116.3 (d, J = 24.6), 82.8, 60.0, 29.0, 28.1 (3C), 27.7. *Anal.* Calcd. for $C_{15}H_{18}FNO_5$: C, 57.88; H, 5.79; N, 4.50. Found: C, 57.91; H, 5.83; N, 4.44.

4-(2-Fluoro-5-nitrophenyl)-2-butanone (4). To a solution of 2.46 g (7.91 mmoles) of **3** in 20 mL of dichloromethane was added 9.02 g (5.88 mL, 79.1 mmoles) of trifluoroacetic acid and 4.58 g (6.30 mL, 39.5 mmoles) of triethylsilane [7]. The mixture was stirred at room temperature for 5 hours and then concentrated under vacuum to give a brown oil. This oil was gradually heated to 150 °C (oil bath) and maintained at this temperature until gas evolution ceased. The reaction was cooled and the product was flash chromatographed on a 35 cm x 2 cm silica gel column using 5% ether in hexanes to give 1.08 g (64%) of **4** as a light yellow oil that crystallized at 0 °C, mp 28-29 °C. ir: 1718, 1529, 1350 cm^{-1}; ^{1}H nmr: δ 8.16 (dd, 1H, J = 6.5, 2.7), 8.11 (ddd, 1H, J = 9.0, 4.4, 2.7), 7.16 (t, 1H, J = 9.0), 3.00 (t, 2H, J = 7.4), 2.83 (t, 2H, J = 7.4), 2.19 (s, 3H); ^{13}C NMR: δ 206.3, 164.6 (d, J = 256.8), 144.2, 129.7 (d, J = 18.0), 126.5 (d, J = 6.9), 124.0 (d, J = 10.0), 116.2 (d, J = 24.9), 42.5 (d, J = 1.1), 29.1, 22.9 (d, J = 2.3); ms: *m/z* 211 (M^{+}). *Anal.* Calcd. for $C_{10}H_{10}FNO_3$: C, 56.87; H, 4.74; N, 6.64. Found: C, 56.93; H, 4.79; N, 6.56.

3-(2-Fluoro-5-nitrophenyl)propanal (6). To a stirred suspension of 2.40 g (11.1 mmoles) of pyridinium chlorochromate [8] and 0.18 g (2.20 mmoles) of anhydrous sodium acetate in 25 mL of dichloromethane at room temperature was added (dropwise) a solution of 1.00 g (5.02 mmoles) of **5** [2e] in 10 mL of dichloromethane. The reaction mixture was monitored by thin layer chromatography until the alcohol was consumed, then diluted with 35 mL of hexanes and filtered through a pad of Celite®. The chromium salts remaining in the flask were washed (three times) by adding 10 mL of dichloromethane, stirring for 5 minutes, adding 10 mL of hexanes and filtering through the same Celite® pad. Concentration under vacuum and purification on a 30 cm x 2 cm silica gel column eluted with 5% ether in hexanes gave 682 mg (68%) of **6** as a light yellow oil that crystallized on standing at room temperature, mp 33.5-35.5 °C. ir: 2830, 2731, 1727, 1525, 1348, 1243 cm^{-1}; ^{1}H nmr: δ 9.84 (s, 1H), 8.17 (dd, 1H, J = 6.2, 2.7), 8.13 (ddd, 1H, J = 9.0, 4.4, 2.7), 7.18 (t, 1H, J = 9.0), 3.06 (t, 2H, J = 7.3), 2.88 (t, 2H, J = 7.3); ^{13}C nmr: δ 199.8, 164.5 (d, J = 256.8), 144.2, 129.1 (d, J = 18.0), 126.5 (d, J = 6.9), 124.2 (d, J = 10.0), 116.3 (d, J = 24.9), 43.0, 21.5 (d, J = 2.3); ms: *m/z* 196 (M^{+}-H). *Anal.* Calcd. for $C_9H_8FNO_3$: C, 54.82; H, 4.06; N, 7.11. Found: C, 54.85; H, 4.10; N, 7.03.

Representative Procedure for Ring Closures with Ketone 4: (±)-1-Benzyl-2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (7a). To a solution of 105 mg (0.50 mmoles) of **4** in 5 mL of methanol was added 64 mg (0.065 mL, 0.60 mmoles) of benzylamine. The mixture was stirred for 5 minutes and 40 mg (0.64 mmoles) of sodium cyanoborohydride was added. The mixture was stirred at room temperature for 48 hours, added to saturated sodium chloride and extracted with ether (three times). The combined ether extracts were dried (magnesium sulfate), concentrated under vacuum and purified by preparative thin layer chromatography using 20% ether in hexanes. The bright yellow band contained 138 mg (98%) of **5** as a yellow solid, mp 104-106 °C. ir: 1512, 1330 cm^{-1}; ^{1}H nmr: δ 7.91 (d, 1H, J = 2.7), 7.81 (dd, 1H, J = 9.3, 2.7), 7.36-7.22 (complex, 3H), 7.16 (d, 2H, J = 7.3), 6.33 (d, 1H, J = 9.3), 4.68 (d, 1H, J = 17.4), 4.59 (d, 1H, J = 17.4), 3.72 (m, 1H), 2.88 (ddd, 1H, J = 17.0, 12.5, 5.2), 2.80 (dt, 1H, J = 16.1, 4.1), 2.02 (m, 1H), 1.94 (m, 1H), 1.26 (d, 3H, J = 6.5); ^{13}C nmr: δ 149.8, 136.8, 136.3, 128.8, 127.2, 125.9, 125.0, 124.4, 120.9, 109.9, 53.7, 53.1, 26.9, 23.3, 19.1; 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, 9.93. Found: C, 72.32; H, 6.38; N, 9.94.

(±)-2-Methyl-6-nitro-1-(2-phenylethyl)-1,2,3,4-tetrahydroquinoline (7b). This compound (142 mg, 96%) was isolated as a yellow oil. ir: 1511, 1328 cm^{-1}; ^{1}H nmr: δ 8.01 (dd, 1H, J = 9.3, 2.7), 7.91 (d, 1H, J = 2.7), 7.36-7.17 (complex, 5H), 6.57 (d, 1H, J = 9.3), 3.76 (ddd, 1H, J = 15.0, 8.0, 5.2), 3.46 (apparent dt, 1H, J = 16.2, 8.0), 3.35 (m, 1H), 3.02-2.78 (complex, 3H), 2.70 (dt, 1H, J = 16.1, 4.0), 1.72 (m, 2H), 1.15 (d, 3H, J = 6.4); ^{13}C nmr: δ 149.0, 138.6, 136.0, 128.7 (2C), 126.7, 125.3, 124.6, 120.7, 108.8, 53.6, 51.5, 33.2, 26.4, 23.1, 18.9; ms: *m/z* 205 (M^{+}-C_7H_7). *Anal.* Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.76; N, 9.46. Found: C, 73.02; H, 6.79; N, 9.40.

(±)-1-Hexyl-2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (7c). This compound (138 mg, 94%) was isolated as a yellow oil. ir: 1512, 1328 cm^{-1}; ^{1}H nmr: δ 7.96 (dd, 1H, J = 9.3, 2.7), 7.88 (m, 1H), 6.44 (d, 1H, J = 9.3), 3.61 (m, 1H), 3.44 (ddd, 1H, J = 14.7, 8.7, 6.0), 3.22 (ddd, 1H, J = 15.0, 9.3, 7.1), 2.87 (apparent dt, 1H, J = 16.4, 9.3), 2.71 (dt 1H, J = 16.4, 4.1), 1.84 (m, 2H), 1.62 (m, 2H), 1.34 (m, 6H), 1.20 (d, 3H, J = 6.5), 0.91 (t, 3H, J = 7.0); ^{13}C nmr: δ 149.3, 135.7, 125.2, 124.6, 120.5, 108.8, 53.3, 49.9, 31.6, 26.9, 26.7, 26.6, 23.2, 22.6, 19.1, 14.0; ms: *m/z* 205 (M^{+}-C_5H_{11}). *Anal.* Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.70; N, 10.14. Found: C, 69.66; H, 8.74; N, 10.05.

(±)-1-Isobutyl-2-methyl-6-nitro-1, 2, 3, 4-tetrahydroquinoline (7d). This compound (111 mg, 90%) was isolated as a dark

yellow oil that crystallized on standing at 0 °C, mp 71-72.5 °C. ir: 1511, 1326 cm^{-1}; ^1H nmr: δ 7.94 (dd, 1H, J = 9.3, 2.7), 7.89 (m, 1H), 6.44 (d, 1H, J = 9.3), 3.62 (m, 1H), 3.46 (dd, 1H, J = 14.7, 4.9), 2.92 (ddd, 1H, J = 16.5, 13.4, 5.7), 2.83 (dd, 1H, J = 14.7, 9.7), 2.74 (dm, 1H, J = 16.5), 2.13 (m, 1H), 1.95 (tt, 1H, J = 13.4, 4.9), 1.85 (m, 1H), 1.16 (d, 3H, J = 6.6), 0.96 (d, 6H, J = 6.8); ^{13}C nmr: δ 149.6, 135.6, 125.4, 124.3, 120.1, 109.3, 57.3, 54.1, 26.7, 26.1, 22.9, 20.2, 20.1, 17.9; ms: *m/z* 205 (M^+-C_3H_7). *Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29. Found: C, 67.75; H, 8.04; N, 11.27.

(±)-1-(3-Isopropyloxypropyl)-2- methyl-6- nitro-1, 2, 3, 4-tetrahydroquinoline (7e). This compound (128 mg, 88%) was isolated as a yellow oil. ir: 1516, 1328 cm^{-1}; ^1H nmr: δ 7.96 (dd, 1H, J = 9.2, 2.6), 7.89 (d, 1H, J = 2.6), 6.56 (d, 1H, J = 9.2), 3.65 (m, 1H), 3.57 (m, 2H), 3.45 (t, 2H, J = 5.8), 3.42 (m, 1H), 2.89 (ddd, 1H, J = 17.7, 11.2, 7.5), 2.73 (dt, 1H, J = 16.3, 3.7), 1.87 (m, 4H), 1.20 (d, 3H, J = 6.6), 1.18 (d, 3H, J = 6.1), 1.17 (d, 3H, J = 6.1); ^{13}C nmr: δ 149.4, 135.7, 125.2, 124.5, 120.4, 109.1, 71.7, 64.9, 53.1, 46.7, 27.7, 26.6, 23.1, 22.1, 22.0, 18.9; ms: *m/z* 205 (M^+-$C_5H_{11}O$). *Anal.* Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.75; H, 8.22; N, 9.59. Found: C, 65.79; H, 8.26; N, 9.53.

(±)-1-Cyclohexyl-2- methyl-6- nitro-1, 2, 3, 4-tetrahydroquinoline (7h). This compound (16 mg, 12%) was isolated as a yellow oil that slowly crystallized on standing, mp 71-73 °C. ir: 1503, 1323 cm^{-1}; ^1H nmr: δ 7.95 (dd, 1H, J = 9.3, 2.7), 7.91 (d, 1H, J = 2.7), 6.63 (d, 1H, J = 9.3), 3.88 (m, 1H), 3.70 (tt, 1H, J = 11.4, 3.4), 2.93 (ddd, 1H, J = 16.5, 14.0, 6.1), 2.73 (ddm, 1H, J = 16.5, 4.3), 2.07-1.20 (complex, 12H), 1.14 (d, 3H, J = 6.4); ^{13}C nmr: δ 149.6, 135.7, 125.9, 124.3, 120.7, 110.1, 58.2, 46.0, 31.3, 30.4, 26.9, 26.2 (2C), 25.7, 23.0, 20.5; ms: *m/z* 274 (M^+). *Anal.* Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.22. Found: C, 70.14; H, 8.08; N, 10.13.

Attempted Preparation of (±)-1-*tert*-Butyl-2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (7i). Using the procedure above, reaction of **4** with *tert*-butylamine led to a 98% recovery of the starting ketone.

Ethyl (±)-2-Methyl-6-nitro-1,2,3,4-tetrahydroquinoline-1-acetate (7f). In a 50-mL round-bottomed flask, 23 mg (1.00 mmole) of sodium metal was dissolved in 5 mL of absolute ethanol. To the resulting solution was added 145 mg (1.04 mmole) of ethyl glycinate hydrochloride and the mixture was stirred for 5 minutes to give a white suspension. To this suspension was added 105 mg (0.50 mmoles) of **4** followed by 50 mg (0.79 mmoles) of sodium cyanoborohydride. To increase the solubility of the reactants, 1 mL of anhydrous tetrahydrofuran was added to the mixture. The reaction was stirred at room temperature for 5 days and the mixture turned a bright yellow color. The reaction was quenched with saturated aqueous sodium chloride and extracted with ether (three times). The combined extracts were dried (magnesium sulfate), concentrated under vacuum and purified by preparative thin layer chromatography using 30% ether in hexanes to give 105 mg (76%) of **7f** as a yellow oil that gradually crystallized at 0 °C to a waxy solid, mp 45-47 °C. ir: 1743, 1511, 1333 cm^{-1}; ^1H nmr: δ 7.95 (dd, 1H, J = 9.0, 2.7), 7.91 (d, 1H, J = 2.7), 6.31 (d, 1H, J = 9.2), 4.22 (q, 2H, J = 7.0), 4.11 (s, 2H), 3.65 (m, 1H), 2.89 (ddd, 1H, J = 16.5, 12.2, 4.9), 2.76 (dt, 1H, J = 16.2, 4.3), 1.98 (m, 1H), 1.89 (m, 1H), 1.50 (t, 3H, J = 7.0), 1.23 (d, 3H, J = 6.4); ^{13}C nmr: δ 169.6, 149.4, 137.1, 124.9, 124.3, 121.6, 109.0, 61.5, 54.5, 51.4, 26.8, 23.4, 19.2, 14.1; ms: *m/z* 205 (M^+-$C_3H_5O_2$). *Anal.* Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.48; H, 6.51; N, 9.99.

(±)-2-Methyl-6-nitro-1,2,3,4-tetrahydroquinoline (7g). To a solution of 193 mg (2.50 mmoles) of ammonium acetate in 5 mL of methanol was added 2.40 mL of 1 *M* aqueous potassium hydroxide (2.40 mmoles) and the mixture was stirred for 5 minutes. To the colorless solution was added 105 mg (0.50 mmoles) of **4** and stirring was continued for 5 minutes to give a light yellow solution. To this solution was added 40 mg (0.64 mmoles) of sodium cyanoborohydride and the reaction was stirred at room temperature for 5 days, during which time the yellow color intensified. The reaction was quenched with saturated aqueous sodium chloride and extracted with ether (three times). The combined extracts were dried (magnesium sulfate), concentrated under vacuum and purified by preparative thin layer chromatography using 25% ether in hexanes to give two major bands. Band 1 gave 56 mg (58%) of **7g** as a yellow solid, mp 135-137 °C. ir: 3352, 1528, 1322 cm^{-1}; ^1H nmr: δ 7.87 (m, 2H), 6.37 (d, 1H, J = 9.5), 4.66 (br s, 1H), 3.55 (m, 1H), 2.80 (m, 2H), 2.00 (m, 1H), 1.57 (m, 1H), 1.27 (d, 3H, J = 6.5); ^{13}C nmr: δ 150.4, 137.2, 125.8, 124.3, 119.6, 112.1, 47.4, 28.7, 26.1, 22.2; ms: *m/z* 177 (M^+-CH_3). *Anal.* Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25; N, 14.58. Found: C, 62.57; H, 6.26; N, 14.51.

Band 2 gave 20 mg (19%) of (±)-4-(2-fluoro-5-nitrophenyl)-2-butanol as a colorless oil. ir: 3369, 1527, 1350, 1245 cm^{-1}; ^1H nmr: δ 8.17 (dd, 1H, J = 6.3, 2.7), 8.10 (ddd, 1H, J = 9.0, 4.4, 2.7), 7.16 (t, 1H, J = 9.0), 3.85 (sextet, 1H, J = 6.3), 2.85 (m, 2H), 1.79 (m, 2H), 1.50 (br s, 1H), 1.27 (d, 3H, J = 6.3); ^{13}C nmr: δ 164.7 (d, J = 256.2), 144.3, 130.8 (d, J = 18.3), 126.4 (d, J = 7.2), 123.7 (d, J = 10.3), 116.1 (d, J = 25.2), 67.1, 38.7, 25.2, 23.7. *Anal.* Calcd. for $C_{10}H_{12}FNO_3$: C, 56.34; H, 5.63; N, 6.57. Found: C, 56.47; H, 5.66; N, 6.49.

Representative Procedure for Ring Closures with Aldehyde 6. To a solution of 98.5 mg (0.50 mmoles) of **6** in 5 mL of methanol was added 0.60 mmoles of the amine. The mixture was stirred for 2 hours and 8 mg (0.13 mmoles) of sodium cyanoborohydride was added. This was followed by three more 8 mg-portions of sodium cyanoborohydride at 4-hour intervals. The mixture was stirred at room temperature for 24-48 hours, added to saturated sodium chloride and extracted with ether (three times). The combined ether extracts were dried (magnesium sulfate) concentrated under vacuum and purified by preparative thin layer chromatography using 20% ether in hexanes to give two bands. Band 1 (yellow) gave the tetrahydroquinoline; band 2 (observed under ultraviolet light) gave the unclosed amine resulting from simple reductive amination.

1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinoline (8a). This compound (100 mg, 75%) was isolated as a dark yellow oil. ir: 1520, 1345 cm^{-1}; ^1H nmr: δ 7.89 (s, 1H), 7.87 (dd, 1H, J = 9.2, 2.7), 7.38-7.27 (complex, 4H), 7.18 (d, 1H, J = 8.2), 6.42 (d, 1H, J = 9.2), 4.60 (s, 2H), 3.51 (t, 2H, J = 5.8), 2.86 (t, 2H, J = 6.2), 2.04 (quintet, 2H, J = 6.0); ^{13}C nmr: δ 150.6, 136.6, 136.4, 128.9, 127.4, 126.2, 125.0, 124.7, 121.4, 109.4, 54.9, 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, 71.68; H, 5.99; N, 10.40.

***N*-Benzyl-3-(2-fluoro-5-nitrophenyl)propanamine (9a).** This compound (18 mg, 13%) was isolated as a light yellow oil. ir: 3330, 1526, 1349, 1243 cm^{-1}; ^1H nmr: δ 8.13 (m, 2H), 7.38-7.27 (complex, 5H), 7.18 (t, 1H, J = 9.1), 4.09 (d, 1H, J = 12.7), 3.83 (d, 1H, J = 12.7), 3.50 (t, 1H, J = 7.1), 2.95 (m, 3H), 2.15 (m, 2H), 1.57 (br s, 1H); ^{13}C nmr: δ 164.6 (J = 257.1), 144.4, 137.9, 128.5 (overlapping s and d, J = 18.3), 127.7, 126.4 (d, J = 6.9), 124.4 (d, J = 10.3), 119.5, 116.4 (d, J = 24.9), 51.6, 48.7,

33.1, 25.4 (d, J = 2.0); ms: *m/z* 197 (M^+-C_7H_7). *Anal.* Calcd. for $C_{16}H_{17}FN_2O_2$: C, 66.67; H, 5.90; N, 9.72. Found: C, 66.64; H, 5.91; N, 9.73.

1-(2-Phenylethyl)-6-nitro-1,2,3,4-tetrahydroquinoline (8b). This compound (102 mg, 72%) was isolated as a dark yellow oil. ir: 1519, 1335 cm^{-1}; ^1H nmr: δ 7.97 (dd, 1H, J = 9.2, 2.6), 7.85 (dt, 1H, J = 2.7, 1.1), 7.36-7.14 (complex, 5H), 6.52 (d, 1H, J = 9.2), 3.60 (t, 2H, J = 7.4), 3.22 (t, 2H, J = 5.8), 2.91 (t, 2H, J = 7.4), 2.74 (t, 2H, J = 6.2), 1.86 (quintet, 2H, J = 6.2); ^{13}C nmr: δ 150.0, 138.6, 136.2, 128.8, 128.7, 126.7, 125.2, 124.7, 121.4, 108.6, 53.3, 50.2, 32.7, 27.9, 21.1; 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, 9.93. Found: C, 72.29; H, 6.36; N, 9.91.

***N*-(2-Phenylethyl)-3-(2-fluoro-5-nitrophenyl)propanamine (9b).** This compound (21 mg, 13%) was isolated as a light yellow oil. ir: 3321, 1525, 1348, 1243 cm^{-1}; ^1H nmr: δ 8.14 (m, 2H), 7.36-7.14 (complex, 6H), 3.51 (t, 1H, J = 7.3), 3.16 (m, 1H), 3.10-2.76 (complex, 6H), 2.05 (m, 2H), 1.58 (br s, 1H); ^{13}C nmr: δ 164.6 (d, J = 257.1), 144.2, 138.9, 128.9 (d, J = 18.2), 128.6, 126.5 (overlapping s and d, J = 7.0), 124.4 (d, J = 10.3), 119.5, 116.5 (d, J = 24.9), 49.6, 48.4, 36.0, 32.9, 25.3; ms: *m/z* 211 (M^+-C_7H_7). *Anal.* Calcd. for $C_{17}H_{19}FN_2O_2$: C, 67.55; H, 6.29; N, 9.27. Found: C, 67.61; H, 6.32; N, 9.22.

1-Hexyl-6-nitro-1,2,3,4-tetrahydroquinoline (8c). This compound (92 mg, 70%), was isolated as a dark yellow oil. ir: 1520, 1338 cm^{-1}; ^1H nmr: δ 7.95 (dd, 1H, J = 9.2, 2.7), 7.83 (dt, 1H, J = 2.7, 1.1), 6.45 (d, 1H, J = 9.2), 3.41 (t, 2H, J = 5.8), 3.33 (t, 2H, J = 7.7), 2.77 (t, 2H, J = 6.2), 1.95 (quintet, 2H, J = 6.2), 1.62 (quintet, 2H, J = 7.0), 1.33 (m, 6H), 0.90 (t, 3H, J = 6.6); ^{13}C nmr: δ 150.3, 135.9, 125.1, 124.7, 121.1, 108.5, 51.6, 49.7, 31.6, 27.9, 26.7, 26.2, 22.6, 21.2, 14.0; ms: *m/z* 191 (M^+-C_5H_{11}). *Anal.* Calcd for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found: C, 68.77; H, 8.43; N, 10.64.

***N*-Hexyl-3-(2-fluoro-5-nitrophenyl)propanamine (9c).** This compound (17 mg, 12%) was isolated as a light yellow oil. ir: 3321, 1529, 1349, 1243 cm^{-1}; ^1H nmr: δ 8.15 (m, 2H), 7.19 (t, 1H, J = 9.0), 3.50 (t, 1H, J = 7.2), 2.96 (m, 1H), 2.89 (m, 1H), 2.61 (m, 1H), 2.11 (m, 2H), 1.62-1.42 (complex, 3H), 1.40-1.18 (complex, 8H), 0.90 (t, 3H, J = 6.8); ^{13}C nmr: δ 164.6 (d, J = 256.8), 144.3, 128.8 (d, J = 18.3), 126.5 (d, J = 6.9), 124.4 (d, J = 10.0), 116.4 (d, J = 24.9), 49.8, 47.7, 33.1, 31.6, 29.7, 26.8, 25.4, 22.6, 14.0; ms: *m/z* 211 (M^+-C_5H_{11}). *Anal.* Calcd. $C_{15}H_{23}FN_2O_2$: C, 63.83; H, 8.16; N, 9.92. Found: C, 63.86; H, 8.18; N, 9.86.

1-Isobutyl-6-nitro-1,2,3,4-tetrahydroquinoline (8d). This compound (89 mg, 76%) was isolated as a dark yellow oil. ir: 1520, 1335 cm^{-1}; ^1H nmr: δ 7.93 (dd, 1H, J = 9.2, 2.7), 7.84 (dt, 1H, J = 2.7, 1.1), 6.45 (d, 1H, J = 9.2), 3.43 (t, 2H, J = 5.8), 3.15 (d, 2H, J = 7.5), 2.79 (t, 2H, J = 6.2), 2.12 (nonet, 1H, J = 6.6), 1.96 (m, 2H), 0.96 (d, 6H, J = 6.6); ^{13}C nmr: δ 150.7, 135.9, 125.2, 124.5, 121.0, 109.0, 59.5, 51.1, 28.0, 26.8, 21.2, 20.3 (2C); ms: *m/z* 191 (M^+-C_3H_7). *Anal.* Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.73; H, 7.72; N, 11.89.

***N*-Isobutyl-3-(2-fluoro-5-nitrophenyl)propanamine (9d).** This compound (19 mg, 15%) was isolated as a light yellow oil. ir: 3321, 1529, 1348, 1243 cm^{-1}; ^1H nmr: δ 8.15 (m, 2H), 7.20 (t, 1H, J = 9.0), 3.49 (t, 1H, J = 7.3), 2.97 (m, 3H), 2.70 (dd, 1H, J = 11.1, 7.0), 2.42 (dd, 1H, J = 11.1, 6.6), 2.12 (m, 2H), 1.73 (nonet, 1H, J = 6.8), 1.52 (br s, 1H), 0.96 (d, 3H, J = 6.8), 0.95 (d, 3H, J = 6.8); ^{13}C nmr: δ 164.6 (d, J = 257.1), 144.2, 128.9 (d, J = 18.5), 126.5 (d, J = 6.9), 124.4 (d, J = 10.0), 116.5 (d, J = 24.9), 55.4, 49.9, 33.1, 28.5, 25.3 (d, J = 2.0), 20.6, 20.4; ms: *m/z* 211 (M^+-C_3H_7). *Anal.* Calcd. for $C_{13}H_{19}FN_2O_2$: C, 61.42; H, 7.48; N, 11.02. Found: C, 61.47; H, 7.52; N, 10.97.

1-Cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinoline (8e). This compound (55 mg, 42%) was isolated as a dark yellow oil. ir: 1511, 1344 cm^{-1}; ^1H nmr: δ 7.95 (dd, 1H, J = 9.3, 2.7), 7.83 (d, 1H, J = 2.7), 6.54 (d, 1H, J = 9.3), 3.68 (tt, 1H, J = 11.2, 3.3), 3.32 (t, 2H, J = 5.8), 2.74 (t, 2H, J = 6.2), 2.02-1.69 (complex, 6H), 1.65-1.32 (complex, 4H), 1.30-1.08 (complex, 2H); ^{13}C nmr: δ 150.6, 135.5, 125.1, 124.7, 122.1, 108.6, 57.3, 42.4, 29.5, 28.3, 25.8, 25.6, 21.5; ms: *m/z* 260 (M^+). *Anal.* Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.77. Found: C, 69.25; H, 7.65; N, 10.71.

***N*-Cyclohexyl-3-(2-fluoro-5-nitrophenyl)propanamine (9e).** This compound (15 mg, 11%) was isolated as a light yellow oil. ir: 3322, 1529, 1348, 1242 cm^{-1}; ^1H nmr: δ 8.15 (m, 2H), 7.19 (t, 1H, J = 8.9), 3.59 (t, 1H, J = 7.1), 2.96 (m, 2H), 2.75 (tt, 1H, J = 10.1, 3.5), 2.11 (m, 2H), 1.90-1.46 (complex, 6H), 1.38-1.16 (complex, 5H), 1.02 (m, 1H); ^{13}C nmr: δ 164.5 (d, J = 256.7), 144.1, 128.9 (d, J = 18.3), 126.6 (d, J = 6.9), 124.4 (d, J = 10.0), 116.4 (d, J = 24.9), 54.9, 46.6, 34.1, 33.7, 31.9, 25.9, 25.4, 24.7, 24.2; ms: *m/z* 280 (M^+). *Anal.* Calcd. for $C_{15}H_{21}FN_2O_2$: C, 64.29; H, 7.50; N, 10.00. Found: C, 64.37; H, 7.54; N, 9.93.

***N-tert*-Butyl-3-(2-fluoro-5-nitrophenyl)propanamine (9f).** This compound (35 mg, 28%) was isolated as a light yellow oil. ir: 3312, 1529, 1348, 1243 cm^{-1}; ^1H nmr: δ 8.16 (dd, 1H, J = 6.4, 2.9), 8.09 (ddd, 1H, J = 9.0, 4.4, 2.9), 7.15 (t, 1H, J = 9.0), 2.79 (t, 2H, J = 7.7), 2.61 (t, 2H, J = 7.3), 1.81 (quintet, 2H, J = 7.5), 1.10 (2s, 10H); ^{13}C nmr: δ 164.6 (d, J = 256.2), 144.2, 130.9 (d, J = 18.6), 126.4 (d, J = 7.2), 123.6 (d, J = 10.0), 116.0 (d, J = 25.2), 50.3, 41.7, 31.0, 29.1, 26.7 (3C); ms: *m/z* 239 (M^+-CH_3). *Anal.* Calcd. for $C_{13}H_{19}FN_2O_2$: C, 61.42; H, 7.48; N, 11.02. Found: C, 61.49; H, 7.51; N, 10.97.

Acknowledgment. T. N. thanks Oklahoma State University for a Niblack Scholarship and the Department of Chemistry for a Skinner Scholarship. Funding for the 300 MHz NMR spectrometer of the Oklahoma Statewide Shared NMR Facility was provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Finally, the authors wish to thank the OSU College of Arts and Sciences for funds to upgrade our departmental FTIR and GC-MS instruments.

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