JOC*Note*

Concise Preparation of Amino-5,6,7,8-tetrahydroquinolines and Amino-5,6,7,8-tetrahydroisoquinolines via Catalytic Hydrogenation of Acetamidoquinolines and Acetamidoisoquinolines

Krystyna A. Skupinska, Ernest J. McEachern,* Renato T. Skerlj, and Gary J. Bridger

AnorMED Inc., #200-20353 64th Avenue, Langley, BC, Canada V2Y 1N5

emceachern@anormed.com

Received July 29, 2002

Abstract: A method to prepare amino-substituted 5,6,7,8-tetrahydroquinolines and 5,6,7,8-tetrahydroisoquinolines via catalytic hydrogenation of the corresponding acetamido-substituted quinolines and isoquinolines followed by acetamide hydrolysis is described. The yields of the products are good when the acetamido substituent is present on the pyridine ring and moderate with the acetamido substituent on the benzene ring. This method has also been applied to the regioselective reduction of quinoline substrates bearing other substituents (R = OMe, CO_2Me, Ph).

As part of our medicinal chemistry research program, we required an efficient synthetic approach to a series of amino-5,6,7,8-tetrahydroquinolines and amino-5,6,7,8-tetrahydroisoquinolines. The 5,6,7,8-tetrahydroquinoline moiety is found as a subunit in numerous medicinally interesting compounds,[1] but concise methods to access usefully functionalized 5,6,7,8-tetrahydroquinolines are scarce in the literature. To our knowledge, no general method for the synthesis of amino-5,6,7,8-tetrahydroquinolines or amino-5,6,7,8-tetrahydroisoquinolines has been described.

It is well-known that catalytic hydrogenation of quinolines at neutral and weakly acidic pH (e.g., in MeOH or acetic acid) generally takes place at the pyridine ring, generating 1,2,3,4-tetrahydroquinolines.[2] It has also been shown that when the hydrogenation is performed in a strongly acidic medium (CF_3COOH, 12 N HCl) the selectivity of the saturation is reversed in favor of 5,6,7,8-tetrahydroquinolines.[3] We were cognizant of the fact, however, that the intermediate amine formed during the reduction of aminoquinolines using these conditions may be benzylic or allylic (during stepwise reduction) and therefore susceptible to hydrogenolysis, providing the unsubstituted 5,6,7,8-tetrahydroquinoline.[4] This concern was justified by experimentation; initial attempts to selectively reduce amino-substituted quinolines using catalytic amounts of PtO_2 in trifluoroacetic acid (TFA) at room temperature led to substantial hydrogenolysis of the amine substituents.

To circumvent this problem, a series of *N*-protected 8-aminoquinoline substrates were prepared and subjected to the hydrogenation conditions. While we were gratified to find that the *N*-pivaloyl, *N*-methanesulfonyl, and *N*-acetyl groups were stable to hydrogenolysis (compared to the *N*-trifluoroacetyl group which was cleaved under the reaction conditions), only moderate selectivity was observed, with significant amounts (30−40%) of the 1,2,3,4-tetrahydroquinolines being isolated in addition to the desired 5,6,7,8-tetrahydro products. Of the substrates investigated, 8-acetamidoquinoline (**1g**) showed the best selectivity for formation of the 5,6,7,8-THQ product. Unfortunately, selectivity was not improved by the choice of heterogeneous catalyst or solvent. Using 8-acetamidoquinoline as a representative substrate, we found that Rh/C, Pd/C, Ru/C, or Raney-Ni gave either starting material or decomposition products, whereas alternative solvents gave either poor selectivity (HCl/MeOH, concd H_2SO_4, H_2SO_4/HOAc), or resulted in cleavage of the acetamide (12 N HCl, 12 N HCl/EtOH, 12 N HCl/HOAc, phosphoric acid). Varying catalyst loading and hydrogen pressure also had little effect on product distribution. However, we were pleased to find that carrying out the reduction at higher temperature favored formation of the 5,6,7,8-tetrahydro product. For example, reduction of 8-acetamidoquinoline **1g** (Table 1, entry 7) with PtO_2 in trifluoroacetic acid at room temperature gave the 5,6,7,8- and 1,2,3,4-tetrahydroquinoline products **2g** and **3g** in a 1.6:1 ratio, respectively. When the temperature of this reaction was elevated to 60 °C (entry 8), the selectivity of the reaction was improved, giving **2g** and **3g** in a ratio of 4.4:1. Equally significant from a practical perspective was the fact that the reduction proceeded to completion more rapidly at higher temperature, requiring only 2.5 h at 60 °C (entry 8) compared to 7 h at ambient temperature (entry 7). With this information in hand, the selective hydrogenation of a series of substituted quinolines was undertaken; the results of this study are summarized in Table 1.

The results for the reduction of a series of *N*-acetyl-amino-substituted quinolines are shown in entries 1−9, with moderate to good yields of the desired 5,6,7,8-THQ isomers being isolated in each case. The highest yields of the desired acetamido-5,6,7,8-tetrahydro products (63−78%) were obtained with substrates **1a**−**c**, which bear substituents on the pyridine ring (Table, entries 1−3); in these cases, the 5,6,7,8-THQ products **2a**,[5] **2b**,[6] and **2c** were formed almost exclusively, with only trace amounts of the 1,2,3,4-THQ isomers detected. For sub-

* To whom correspondence should be addressed. Tel: +1 (604) 530-1057. Fax: +1 (604) 530-0976.

(1) (a) Sucheck, S. J.; Greenber, W. A.; Tolbert, T. J.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1080−1084. (b) Bosch, J.; Roca, T.; Perez, C. G.; Montanari, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 563−566. (c) Glase, S. A.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *J. Med. Chem.* **1995**, *38*, 3132−3137.

(2) Rylander, R. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; p 385.

(3) (a) Vierhapper, F. W.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 2256−2257. (b) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2729−2734. (c) Vierhapper, F. W.; Honel, M. *Monat. Chem.* **1984**, *115*, 1219−1228.

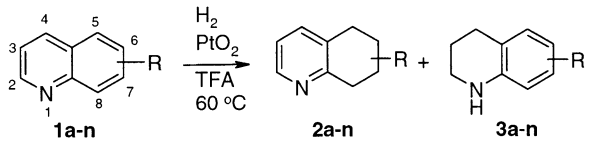
(4) Hydrogenolysis of other quinoline heterosubstituents (F, OH, OMe) has been reported under similar conditions: Vierhapper, F. W.; Honel, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1933−1939.

(5) Vijn, R. J.; Arts, H. J.; Maas, P. J.; Castelijns, A. M. *J. Am. Chem. Soc.* **1992**, *58*, 887−891.

(6) Kato, K.; Terauchi, J.; Mori, M.; Suzuki, N.; Shimomura, Y.; Takekawa, S.; Ishihara, Y. Takeda Chemical Industires Ltd. Japan; PCT Int. Appl. WO 20010211577; JP 2002003370, 2001.

10.1021/jo026258k CCC: $22.00
Published on Web 10/03/2002

TABLE 1. Hydrogenation of Substituted Quinolines 1a−n[a]



entry	compnd	R	reaction time (h)	yield of **2** (%)	yield of **3** (%)
1	**1a**	2-NHAc	18	69	0
2	**1b**	3-NHAc	3.5	63	1
3	**1c**	4-NHAc, 2-Me	20	78	0
4	**1d**	5-NHAc	4.5	45	27
5	**1e**	6-NHAc	5	49	28
6[b]	**1f**	7-NHAc	18	25	20
7[c]	**1g**	8-NHAc	7	53	34
8	**1g**	8-NHAc	2.5	62	14
9	**1h**	8-NHAc, 2-Me	3	57	15
10	**1i**	3-MeO	4	65	0[d]
11	**1j**	2-Ph	5	68	10
12	**1k**	2-COOMe	4	51	20
13	**1l**	3-COOMe	5	70	11
14	**1m**	6-COOMe	5	30	39
15	**1n**	8-COOMe	2	36	28[e]

[a] Unless otherwise noted, all reactions were performed with 0.8−1.5 mmol of **1** at 0.3 M in TFA using 5 mol % PtO_2 at 60 °C under 1 atm hydrogen. The progress of each reaction was monitored by GC and/or TLC. Yields are for isolated, purified product. [b] Yields are approximate as the reaction was performed on a small scale (30 mg **1f**) with 20% PtO_2. [c] The reaction was carried out at room temperature. [d] Trace amounts (∼2%) of hydrogenolyzed products were detected (quinoline, 1,2,3,4-THQ, 5,6,7,8-THQ). [e] 16% recovered starting material was isolated from this reaction.

strates bearing the acetamido substituent on the phenyl ring (**1d**, **1e**, **1f**, and **1g**) (entries 4−6, 8) selectivity for the 5,6,7,8-THQ isomer was diminished to the range 1.3−4.4:1, a fact reflected in the commensurately lower yields for the respective products **2d**[7], **2e**,[8] **2f**, [9] and **2g**.[10] It should be noted, however, that the desired 5,6,7,8-THQ isomer was still the major product in each case, and isolated yields for **2d**, **2e**, and **2g** were in the range of 45−62%.[11] While previous studies have indicated that methyl substitution in the 2-position favors formation of 5,6,7,8-tetrahydro products,[3a,c] the effect was not apparent in this case (compare entries 8 and 9).

The results obtained with the acetamido-substituted substrates (entries 1−9) suggest that steric factors play a dominant role in determining the selectivity of the hydrogenation. That is, the steric hindrance provided by substitution on the pyridine group renders the ring less susceptible to reduction compared to the phenyl ring, thereby improving selectivity (entries 1−3), whereas substitution on the phenyl ring makes this ring less susceptible to reduction (relative to the pyridine ring), thereby diminishing selectivity (entries 4−9). This observation is consistent with previous reports suggesting that catalytic hydrogenation of naphthalenes is sensitive to steric factors, with the less sterically encumbered ring generally being preferentially reduced;[12] it is also consistent with previous reports of hydrogenation of simple alkyl-substituted quinolines.[3a,b]

At this point, we examined a number of other substrates in an effort to probe the general utility of this reaction (entries 10−15). Functional groups that are tolerated under the reaction conditions include methoxy (entry 10), phenyl (entry 11), and methyl carboxylate (entries 12−15). Interestingly, in these cases substrates bearing substituents on the pyridine ring (**1i**−**l**) also exhibit higher selectivity for the 5,6,7,8-THQ isomers than those bearing groups on the phenyl ring (**1m**, **1n**). Correspondingly, the isolated yields for the pyridine-substituted products **2i**, **2j**,[13] **2k**,[14] and **2l** range from 51 to 70% (entries 10−13), while yields for the 6- and 8-substituted esters **2m** and **2n**[15] are 30% and 36%, respectively (entries 14−15).[16] The results from this series of substrates indicate that electronic factors may also influence the selectivity of the hydrogenation. For example, substrates **1b** and **1i**, bearing electron-donating NHAc and MeO groups at the 3-position (entries 2 and 10), exhibit almost complete selectivity for the 5,6,7,8-THQ isomers; conversely, substrate **1l**, which bears an electron-withdrawing methyl carboxylate[17] at the 3-position, exhibits a selectivity of 6.4:1. This appears to be a general observation within our data set: substrates bearing electron-donating groups on the pyridine ring (entries 1−3, 10) exhibit better selectivity for formation of 5,6,7,8-THQ products compared to substrates bearing electron-withdrawing groups on the same ring (entries 11−13). Presumably, the explanation for this trend is that the positive inductive capacity of the electron-releasing substituents renders the pyridine ring less susceptible to reduction and suppresses formation of the 1,2,3,4-THQ products. Thus, for reduction of quinoline derivatives using these reaction conditions, the combined effects of electron donating groups on the pyridine ring and an unsubstituted phenyl ring lead almost exclusively to the 5,6,7,8-THQ isomer.[18]

(7) Dukat, M.; Fiedler, M.; Dumas, D.; Damaj, I.; Martin, B. R.; Rosecrans, J. A.; James, J. R.; Glennon, R. A *Eur. J. Med. Chem.* **1996**, *31*, 875−888.

(8) Adachi, J.; Nomura, K.; Yamamoto, S.-I.; Mitsuhashi, *Chem. Pharm. Bull.* **1976**, *24*, 2876−2980.

(9) Preparation of 7-amino-5,6,7,8-tetrahydroquinoline via a different route has been described: Cliffe, I. A.; Ifill, A. D.; Mansell, H. L.; Todd, R. S.; White, A. C. *Tetrahedron Lett.* **1991**, *32*, 678−692.

(10) Preparation of enantiomerically pure 8-amino-5,6,7,8-tetrahydroquinoline has recently been described: Uenishi, J.; Hamada, M. *Synthesis* **2002**, *5*, 625−630.

(11) The 1,2,3,4-tetrahydro products **3d**, **3e**, and **3g** are known compounds: (a) Bigge, C. F.; Malone, T. C.; Boxer, P. A.; Nelson, C. B.; Ortwine, D. F.; Schelkun, R. M.; Retz, D. M.; Lescosky, L. J.; Borosky, S. A.; Vartanian, M. G.; Schwarz, R. D.; Campbell, G. W.; Robichaud, L. J.; Watjen, F. *J. Med. Chem.* **1995**, *38*, 3720−3740. (b) Reich, S. H.; Fuhry, M. A.; Nguyen, D.; Pino, M. J.; Welsh, K. M.; Webber, S.; Janson, C. A.; Jordan, S. R.; Matthews, D. A.; Smith, W. W.; Bartlett, C. A.; Booth, C. L. J.; Herrmann, S. M.; Howland, E. F.; Morse, C. A.; Ward, R. W.; White, J. *J. Med. Chem.* **1992**, *35*, 847−858. (c) Richardson, A.; Amstutz, E. D. *J. Org. Chem.* **1960**, *25*, 1138.

(12) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 438.

(13) Chelucci, G.; Cossu, S.; Soccolini, F. J. *Heterocycl. Chem.* **1986**, *23*, 1283−1286.

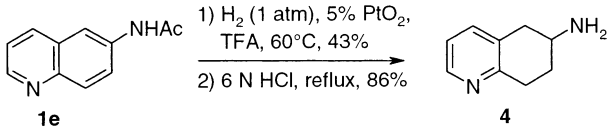
(14) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840−7850.

(15) An alternative, more efficient synthesis of **2n** has been reported: Crossley, R.; Curran, A. C. W.; Hill, D. G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 977−982.

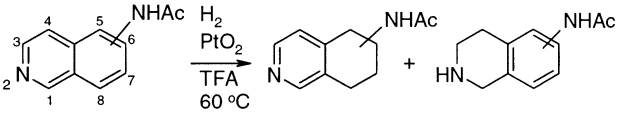
(16) The 1,2,3,4-tetrahydro products **3j**, **3k**, **3l**, and **3m** are known compounds: (a) Gogte, V. N.; El-Namaky, H. M.; Salama, M. A.; Tilak, B. D. *Tetrahedron Lett.* **1969**, *39*, 3319−3322. (b) Rao, V. A.; Jain, P. C.; Anand, N. *Indian J. Chem.* **1972**, *10*, 1134−1135. (c) Rasetti, V.; Rueeger, H.; Maibaum, J.; Mah, R., Gruetter, M.; Cohen, N. C. Ciba-Geigy A.-G., Switzerland. Eur. Pat. Appl. EP 702004, 1996. (d) Oku, T.; Kayakiri, H.; Satoh, S.; Abe, Y.; Sawada, Y.; Inoue, T.; Tanaka, H. PCT Int. Appl. WO 9604251, 1996.

(17) Methyl 5-carboxylate-5,6,7,8-tetrahydroisoquinoline was prepared via this method: Paivio, E.; Berner, M.; Tolvanen, A.; Jokela, R. *Heterocycles* **2000**, *53*, 2241−2246.

SCHEME 1



SCHEME 2



The methods described herein were readily amenable to the preparation of amino-5,6,7,8-tetrahydroquinolines in multigram quantities (see the Experimental Section for procedure). For example, reduction of 7 g of **1e** afforded the acetamide **2e** in 43% yield (Scheme 1); subsequent acid-mediated hydrolysis of the acetamide (6 N HCl, reflux) furnished 6-amino-5,6,7,8-tetrahydroquinoline **4** in 86% yield.

Finally, we applied this hydrogenation method to two acetamidoisoquinoline systems, **5a** and **5b** (Scheme 2). We obtained a good yield of 1-acetamido-5,6,7,8-tetrahydroisoquinoline **6a** along with some of the 1,2,3,4-tetrahydro product **7a**. The reaction of 5-acetamidoisoquinoline **5b** provided **6b** in 43% yield, albeit with the expected lower selectivity (20% of **7b**[19] was isolated). Amino-5,6,7,8-tetrahydroisoquinolines were also readily accessible via this protocol using the deprotection conditions described above.

As a point of general interest, it should be emphasized that the use of an acetamido-protected amino group overcomes the major limitation inherent to the previous methodology, namely, hydrogenolysis of heterosubstituents.[20] Until the present time, the use of this hydrogenation procedure has been confined to simple alkyl-substituted quinolines and isoquinolines, given the poor yields obtained when heterosubstituents are present. The ability to perform this reaction in the presence of a protected amine represents an important advance, particularly in light of the fact that many of these amino-5,6,7,8-tetrahydroquinolines and isoquinolines are not readily available via other routes, and several have not been reported previously. Moreover, the amino function can serve as a useful synthetic handle for subsequent functionalization (e.g., diazotization), which gives this new procedure a broad range of synthetic applicability.

In conclusion, we report a practical and concise method for the preparation of amino-substituted 5,6,7,8-tetrahydroquinolines and amino-5,6,7,8-tetrahydroisoquinolines by catalytic reduction of the *N*-acetylamino protected parent quinoline and isoquinoline systems at 60 °C, followed by hydrolysis. In general, the selectivity for the desired 5,6,7,8-tetrahydroquinoline isomer in the catalytic reduction step is improved by the presence of an electron donating substituent on the pyridine ring, and diminished by the presence of sterically bulky substituents on the phenyl ring.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as a solvent. Proton and carbon chemical shifts were referenced to residual solvent protons and the solvent, respectively. Flash chromatography was carried out on silica gel (230−400 mesh). Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Trifluoroacetic acid (99%) was purged with argon prior to use in hydrogenation reactions. Acetamides **1a**−**e**,**g**,**h** and **5a**,**b** were prepared from commercially available amines. 7-Acetamidoquinoline (**1f**) was obtained by acetylation of 7-aminoquinoline prepared by the reduction of 7-nitroquinoline.[21] 3-Methoxyquinoline (**1i**)[22] was prepared from commercially available 3-bromoquinoline by the method of Baker and Duke.[23] Methyl carboxylates **1k**−**n** were prepared from commercially available acids. All new products (**2c**, **2f**, **3f**, **2g**, **2h**, **3h**, **2i**, **2l**, **2m**, **3n**, **6a**, **6b**, **7a**) were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Representative Procedure for Small-Scale Hydrogenation Reactions. To a two-neck, 250 mL round-bottom flask containing a stir bar were added 8-acetamidoquinoline **1g** (186.1 mg, 0.999 mmol) and platinum oxide (11.5 mg, 0.0506 mmol, 5 mol %). Trifluoroacetic acid (3.4 mL, 0.3 M) was added via a plastic syringe into the reaction flask under an atmosphere of nitrogen. The stirred reaction mixture was flushed and the flask filled with hydrogen gas from a balloon. The reaction flask was sealed, and the reaction mixture was warmed to 60 °C for 2.5 h. The progress of the reaction was monitored by GC and/or TLC. The reaction mixture was cooled to rt, and aqueous saturated sodium hydroxide was added until the mixture was basic (or saturated sodium bicarbonate for methyl carboxylate substrates). The mixture was then extracted with CH_2Cl_2 (3 × 30 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The products **2g** and **3g** were separated by flash chromatography using 5−15% MeOH in EtOAc. Compound **2g** was obtained as an off-white solid (118.3 mg, 62%) that displayed: ^{1}H NMR δ 1.59−1.70 (m, 1H), 1.86−1.95 (m, 2H), 2.08 (s, 3H), 2.56−2.64 (m, 1H), 2.79−2.84 (m, 2H), 4.85−4.95 (m, 1H), 6.52 (br s, 1H), 7.14 (dd, 1H, J = 5, 7 Hz), 7.43 (d, 1H, J = 7 Hz), 8.41 (d, 1H, J = 5 Hz); ^{13}C NMR δ 20.3, 24.1, 28.6, 29.8, 51.5, 122.8, 133.4, 137.5, 147.2, 155.7, 170.8; MS *m*/*z*: 213 ($M + Na^+$). Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.43; N, 14.72. Found: C, 69.23; H, 7.56; N, 14.74. Compound **3g**[11c] was isolated as a pale yellow solid (26.7 mg, 14%).

Using the representative procedure for small scale reactions, **1a** (164 mg, 0.881 mmol) provided **2a**[5] (114 mg, 69%), **1b** (138 mg, 0.741 mmol) provided **2b**[6] (89 mg, 63%), **1d** (158 mg, 0.849 mmol) provided **2d**[7] (72 mg, 45%) and **3d**[11a] (44 mg, 27%), **1e** (143 mg, 0.768 mmol) provided **2e**[8] (71 mg, 49%) and **3e**[11b] (40 mg, 28%), and **1j** (162 mg, 0.781 mmol) provided **2j**[13] (111 mg, 68%) and **3j**[16a] (20 mg, 10%). Reaction of **1k** (160 mg, 0.855 mmol) following the representative procedure using saturated $NaHCO_3$ in place of NaOH in the workup provided **2k**[14] (83 mg, 51%) and **3k**[16b] (33 mg, 20%).

***N*-(2-Methyl-5,6,7,8-tetrahydroquinolin-4-yl)acetamide (2c).** Reaction of *N*-(2-methylquinolin-4-yl)acetamide (**1c**) (136 mg, 0.679 mmol) using the general procedure for small-scale hydrogenations provided **2c** (109 mg, 78%): ^{1}H NMR δ 1.83−1.90 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.46−2.2.53 (m, 2H), 2.84−2.87 (m, 2H), 7.18 (br s, 1H), 7.82 (br s, 1H); ^{13}C NMR δ

(18) For a detailed discussion on the mechanism of quinoline hydrogenation see: Okazaki, H.; Onishi, K.; Soeda, M.; Ikefuji, Y.; Tamura, R.; Mochida, I. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3167−3174; refs 4 and 3c.

(19) Bailey, Denis M.; DeGrazia, C. George; Lape, Harlan E.; Frering, Richard; Fort, Dorothy; Skulan, Thomas. *J. Med. Chem.* **1973**, *16*, 151−156.

(20) The authors acknowledge this, stating "The synthetic possibilities are severely diminished by this hydrogenolysis"; ref 4.

(21) Sharma, K. S.; Kumari, S.; Singh, R. P. *Synthesis* **1981**, 316−318.

(22) Baker, J. T.; Duke, C. C. *Aust. J. Chem.* **1976**, 29, 1023−1030.

(23) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633−3652.

22.7, 22.8, 23.5, 24.6, 25.3, 33.1, 112.3, 117.3, 143.7, 156.4, 157.3, 169.0; MS *m*/*z* 205 ($M + H^+$).

***N*-(5,6,7,8-Tetrahydroquinolin-7-yl)acetamide (2f).** Reaction of *N*-(quinol-7-yl)acetamide (**1f**) (33 mg, 0.177 mmol) using the general procedure for small-scale hydrogenations provided **2f** (8.3 mg, 25%): ^{1}H NMR δ 1.72−1.83 (m, 1H), 1.99 (s, 3H), 2.04−2.20 (m, 2H), 2.72−2.95 (m, 3H), 3.25 (dd, 1H, J = 5, 17 Hz), 4.29−4.40 (m, 1H), 5.72 (br s, 1H), 7.05 (dd, 1H, J = 4, 8 Hz), 7.38 (d, 1H, J = 8 Hz), 8.35 (d, 1H, J = 4 Hz); ^{13}C NMR δ 23.9, 26.5, 28.7, 39.0, 45.6, 121.9, 131.4, 137.0, 147.7, 154.8, 170.1; MS *m*/*z* 213 ($M + Na^+$). *N*-(1,2,3,4-Tetrahydroquinolin-7-yl)acetamide (**3f**) was also isolated (6.5 mg, 20%): ^{1}H NMR δ 1.24−1.28 (s, 1H), 1.87−1.95 (m, 2H), 2.70 (dd, 2H, J = 6, 6 Hz), 3.28 (dd, 2H, J = 5, 5 Hz), 6.46 (d, 1H, J = 8 Hz), 6.84 (d, 1H, J = 8 Hz), 6.93 (s, 1H), 7.03 (br s, 1H); ^{13}C NMR δ 22.1, 24.7, 26.6, 37.9, 105.6, 108.3, 117.6, 129.6, 136.5, 145.1, 168.1; MS *m*/*z* 213 ($M + Na^+$).

***N*-(2-Methyl-5,6,7,8-tetrahydroquinolin-8-yl)acetamide (2h).** Reaction of *N*-(2-methyl-quinol-8-yl)acetamide (**1h**) (159 mg, 0.795 mmol) using the general procedure for small-scale hydrogenations provided **2h** (92 mg, 57%): ^{1}H NMR δ 1.57−1.66 (m, 1H), 1.77−1.86 (m, 2H), 2.02 (s, 3H), 2.44 (s, 3H), 2.43−2.57 (m, 1H), 2.68−2.73 (m, 2H), 4.67−4.74 (m, 1H), 6.79 (br s, 1H), 6.92 (d, 1H, J = 8 Hz), 7.24 (d, 1H, J = 8 Hz); ^{13}C NMR δ 21.6, 25.4, 25.8, 29.6, 31.0, 53.0, 123.4, 131.4, 139.2, 155.9, 157.2, 172.2; MS *m*/*z* 227 ($M + Na^+$). *N*-(2-Methyl-1,2,3,4-tetrahydroquinolin-8-yl)acetamide (**3h**) was also isolated (25 mg, 15%) as a tautomeric mixture of acyclic and cyclized isomers in an approximately 1:2 ratio which exhibited the following data: ^{1}H NMR δ 1.21−1.25 (m), 1.45−1.61 (m), 1.90 (s), 1.90−1.95 (m), 2.20 (s), 2.71−2.91 (m), 3.32−3.43 (m), 4.00 (br s), 6.56 (dd, J = 8, 8 Hz), 6.63 (dd, J = 8, 8 Hz), 6.66 (br s), 6.83 (d, J = 8 Hz), 6.87 (d, J = 8 Hz), 6.94 (d, J = 8 Hz), 7.02 (d, J = 8 Hz), 7.06 (br s); MS *m*/*z* 205 ($M + H^+$).

3-Methoxy-5,6,7,8-tetrahydroquinoline (2i). Reaction of 3-methoxyquinoline (**1i**) (181 mg, 1.16 mmol) using the general procedure for small-scale hydrogenations provided **2i** (127 mg, 65%): ^{1}H NMR δ 1.74−1.93 (m, 4H), 2.75 (dd, 2H, J = 6, 6 Hz), 2.85 (dd, 2H, J = 6, 6 Hz), 3.82 (s, 3H), 6.88 (d, 1H, J = 3 Hz), 8.06 (d, 1H, J = 3 Hz); ^{13}C NMR δ 23.0, 23.7, 29.4, 32.0, 55.9, 121.5, 132.9, 134.9, 149.8, 154.1; MS *m*/*z* 164.1 ($M+H^+$). A mixture (5 mg) of hydrogenolyzed products (quinoline, 1,2,3,4-tetrahydroquinoline and 5,6,7,8-tetrahydroquinoline as determined by GC analysis by comparison with commercial samples) was also obtained.

5,6,7,8-Tetrahydroquinoline-3-carboxylic Acid Methyl Ester (2l). Reaction of quinoline-3-carboxylic acid methyl ester (**1l**) (170 mg, 0.908 mmol) using the general procedure (workup with saturated $NaHCO_3$ in place of NaOH) for small-scale hydrogenations provided **2l** (121 mg, 70%): ^{1}H NMR δ 1.80−1.95 (m, 4H), 2.79−2.83 (m, 2H), 2.94−2.99 (m, 2H), 3.91 (s, 3H), 7.95 (s, 1H), 8.93 (s, 1H); ^{13}C NMR δ 22.8, 23.1, 28.9, 33.1, 52.5, 123.7, 132.5, 138.0, 148.2, 162.6, 166.5; MS *m*/*z* 192 ($M + H^+$). 1,2,3,4-Tetrahydroquinoline-3-carboxylic acid methyl ester (**3l**)[16c] was also isolated (19 mg, 11%).

5,6,7,8-Tetrahydroquinoline-6-carboxylic Acid Methyl Ester (2m). Reaction of quinoline-6-carboxylic acid methyl ester (**1m**) (170 mg, 0.908 mmol) using the general procedure (workup with saturated $NaHCO_3$ in place of NaOH) for small-scale hydrogenations provided **2m** (49 mg, 30%): ^{1}H NMR δ 1.91−2.05 (m, 1H), 2.25−2.34 (m, 1H), 2.74−2.84 (m, 1H), 2.90−3.11 (m, 4H), 3.74 (s, 3H), 7.06 (dd, 1H, J = 4, 8 Hz), 7.39 (d, 1H, J = 8 Hz), 8.37 (d, 1H, J = 4 Hz); ^{13}C NMR δ 26.1, 31.2, 31.7, 39.6, 52.3, 121.6, 130.5, 137.2, 147.6, 156.3, 175.7; MS *m*/*z* 214 ($M + Na^+$). 1,2,3,4-Tetrahydroquinoline-6-carboxylic acid methyl ester (**3m**)[16d] was also isolated (66 mg, 39%).

Reaction of quinoline-8-carboxylic acid methyl ester (**1n**) (156 mg, 0.833 mmol) using the general procedure (workup with saturated $NaHCO_3$ in place of NaOH) for small-scale hydrogenations provided **2n**[15] (58 mg, 36%). 1,2,3,4-Tetrahydroquinoline-8-carboxylic acid methyl ester (**3n**) was also isolated (45 mg, 28%): ^{1}H NMR δ 1.87−1.96 (m, 2H), 2.76−2.81 (m, 2H), 3.40−3.45 (m, 2H), 3.83 (s, 3H), 6.43 (dd, 1H, J = 7, 8 Hz), 7.03 (d, 1H, J = 7 Hz), 7.69 (d, 1H, J = 8 Hz), 7.76 (br s, 1H); ^{13}C NMR δ 21.2, 28.2, 41.6, 51.7, 108.8, 113.9, 122.4, 129.8, 134.1, 148.8, 169.6; MS *m*/*z* 192 ($M + H^+$).

***N*-(5,6,7,8-Tetrahydroisoquinolin-1-yl)acetamide (6a).** Reaction of *N*-(isoquinol-1-yl)acetamide (**5a**) (159 mg, 0.854 mmol) using the general procedure for small-scale hydrogenations provided **6a** (96 mg, 59%): ^{1}H NMR δ 1.74−1.76 (m, 4H), 2.16−2.19 (m, 3H), 2.60−2.70 (m, 2H), 2.70−2.76 (m, 2H), 6.86 (d, 1H, J = 5 Hz), 8.03 (d, 1H, J = 5 Hz); ^{13}C NMR δ 22.3, 22.8, 23.8, 25.1, 29.6, 122.9, 144.4 (2C), 149.5, 150.2, 170.6; MS *m*/*z* 213 ($M + Na^+$). *N*-(1,2,3,4-Tetrahydroisoquinolin-1-yl)acetamide (**7a**) was also isolated (16 mg, 11%): ^{1}H NMR δ 2.28 (m, 3H), 2.96−3.01 (m, 2H), 3.56−3.61 (m, 2H), 7.20 (d, 1H, J = 8 Hz), 7.33−7.38 (m, 1H), 7.44−7.49 (m, 1H), 8.27 (d, 1H, J = 8 Hz); ^{13}C NMR δ 27.2, 28.7, 29.7, 39.3, 127.3, 127.5, 128.0, 132.6, 137.9, 162.8, 188.0; MS *m*/*z* 191 ($M + H^+$).

***N*-(5,6,7,8-Tetrahydroisoquinolin-5-yl)acetamide (6b).** Reaction of *N*-(isoquinol-5-yl)acetamide (**5b**) (171 mg, 0.918 mmol) using the general procedure for small-scale hydrogenations provided **6b** (79 mg, 45%): ^{1}H NMR δ 1.60−1.70 (m, 1H), 1.70−1.09 (m, 2H), 1.98 (s, 3H), 1.98−2.08 (m, 1H), 2.65−2.68 (m, 2H), 5.03−5.11(m, 1H), 6.63 (br d, 1H), 7.08 (d, 1H, J = 5 Hz), 8.17 (s, 1H), 8.20 (d, 1H, J = 5 Hz); ^{13}C NMR δ 20.7, 23.7, 26.4, 30.1, 47.1, 122.9, 133.3, 146.3, 147.5, 150.7, 170.1; MS *m*/*z* 191 ($M + H^+$). *N*-(1,2,3,4-Tetrahydroisoquinolin-5-yl)acetamide (**7b**)[19] was also isolated (35 mg, 20%).

Representative Procedure for Large-Scale Hydrogenation Reaction and Hydrolysis Reaction. To a three-neck, 500 mL round-bottom flask containing a stir bar was added 6-acetamidoquinoline (**1e**) (6.80 g, 36.5 mmol) and platinum(IV) oxide (414 mg, 5 mol %). The flask was equipped with two Teflon cannulae: one for purging of the reaction flask with nitrogen gas and introduction of hydrogen, and the other leading to a flask connected to a bubbler. Trifluoroacetic acid (110 mL) was added to the reaction flask under an atmosphere of nitrogen. The stirred reaction mixture was flushed with nitrogen gas and warmed to 60 °C. Hydrogen gas was bubbled through the stirred reaction for 5 h. The progress of the reaction was monitored by GC and/or TLC. The reaction mixture was cooled to rt and purged with nitrogen gas, and the catalyst was filtered through a pad of Celite and washed with CH_2Cl_2 (100 mL). The solvent was removed in vacuo and the residue was basified with saturated NaOH. The mixture was then extracted with CH_2Cl_2 (3 × 250 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography using 1% MeOH in EtOAc. Compound **2e**[8] was obtained as an off-white solid (3.01 g, 43%), while compound **3e**[11b] was isolated as a yellow oil (1.86 g, 26%).

6-Acetamido-5,6,7,8-tetrahydroquinoline (**2e**) (2.76 g, 14.5 mmol) was dissolved in 6 N HCl (50 mL). The mixture was heated at reflux for 1 h, and the progress of the reaction was monitored by GC. Upon completion, the reaction mixture was cooled to rt, basified with saturated NaOH and extracted with chloroform (5 × 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The crude material was purified by distillation (bp 113−115 °C at 0.20 mmHg) to yield 6-amino-5,6,7,8-tetrahydroquinoline (**4**) as a clear liquid (1.85 g, 86%) that displayed: ^{1}H NMR δ 1.40 (br s, 2H), 1.62−1.76 (m, 1H), 2.03−2.07 (m, 1H), 2.55 (dd, 1H, J = 16.2, 9.3 Hz), 2.88−3.17 (m, 3H), 3.19−3.26 (m, 1H), 6.98−7.03 (m, 1H), 7.32 (d, 1H, J = 7.5 Hz), 8.33 (d, 1H, J = 3.9 Hz); ^{13}C NMR δ 31.3, 33.1, 38.9, 47.1, 121.4, 130.7, 137.4, 147.5, 156.7; MS *m*/*z* 149 ($M + H^+$). Anal. Calcd for $C_9H_{12}N_2 \cdot 0.3H_2O$: C, 70.37; H, 8.27; N, 18.24. Found: C, 70.09; H, 8.11; N, 18.36.

Acknowledgment. We thank NSERC of Canada for an Industrial Research Fellowship to K.A.S. as well as Lucita Ramos and Roger Sun for analytical support.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **2c**, **2f**, **3f**, **2h**, **3h**, **2i**, **2l**, **2m**, **3n**, **6a**, **6b**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026258K