Synthesis of 1,2,3,4-Tetrahydroisoquinolines

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Several aspects of 1,2,3,4-tetrahydroisoquinoline synthesis have been examined. An improved synthesis of 2-(m-methoxyphenyl)ethylaniline (4) is reported. m-Anisaldehyde (5) was treated with potassium cyanide and ethyl chloroformate to yield O-(ethoxycarbonyl)-3-methoxymandelonitrile (7). Hydrogenation afforded 2-(m-methoxyphenyl)ethylaniline (4) in 87% yield overall. Some observations have been made regarding the reduction of 3,4-dihydroisoquinolines derived from the Bischler-Napieralski reaction. Amides 3a and 3c were cyclized with phosphorus oxychloride, followed by reduction to the corresponding tetrahydroisoquinolines 1a and 1c. It was shown that 1a and 1c were contaminated with 4% of 2a and 3% of 2c, respectively. Both 2a and 2c were independently synthesized by routes with general applicability to 8-alkoxy-1,2,3,4-tetrahydroisoquinolines.

Tetrahydroisoquinolines are among the most commonly synthesized natural products, both because of their own biological activity and as precursors to other, more complex alkaloids. Perhaps the most common approach to these compounds has been via the Bischler-Napieralski reaction (Scheme I). This method proceeds from readily available starting materials and has generally been credited with high yields of pure material. We recently had the need to prepare two alkoxylated tetrahydroisoquinolines, 1a and 1b. It soon became obvious to us that certain aspects of the Bischler-Napieralski method were still unsettled and warranted further clarification. The results of our study, as well as the synthetic methodology we developed in obtaining these results, may have potential application to the synthesis of other substituted 1,2,3,4-tetrahydroisoquinolines.

In this report, we describe (1) an improved synthesis of β-phenylethylamines, necessary precursors for the Bischler-Napieralski reaction; (2) some side products frequently formed in the reduction of the intermediate 3,4-dihydroisoquinolines 9, and the methods devised to prevent their formation; (3) the Bischler-Napieralski reaction of amides 3a and 3c (derived from unsymmetrical phenylethylamine (4) which yields a mixture of the expected para-cyclized 6-methoxy isomers 1 and 4% of the ortho-cyclized 8-methoxy isomers 2; and (4) the synthesis of ortho isomers 2a and 2c by alternative routes which are particularly applicable to the synthesis of 8-alkoxytetrahydroisoquinolines.

Synthesis of Tetrahydroisoquinolines 1a and 1b. Synthesis of 2-(m-Methoxyphenyl)ethylamine (4). Attempted preparation of 2-(m-methoxyphenyl)ethylamine (4) by reduction of nitrostyrene 6 with lithium aluminum hydride gave a product containing a persistent impurity which could be eliminated only if nitrostyrene 6 was rigorously purified. Catalytic hydrogenation of 6 gave variable results as the scale was increased. However, an efficient and convenient synthesis of phenylethylamine 4, independent of scale, proceeded in high yield from m-anisaldehyde (5) by first treatment with potassium cyanide and ethyl chloroformate to form 0-(ethoxycarbonyl)-3-

methoxymandelonitrile (7). Hydrogenation of 7 over palladium on charcoal in ethanol at atmospheric pressure gave 4 reproducibly in 92% yield (Scheme II). Bischler-Napieralski Cyclization. Amide 3c was prepared in 90% yield by refluxing a mixture of acid 8c with phenylethylamine 4 in xylene with azotropic removal of water. Treatment of amide 3c with phosphorus oxychloride in toluene at reflux for 15 min or at 80 °C for 90 min led to the formation of 9c. Upon hydrogenation catalyzed by PtO2, a mixture of the desired 1c and the cyclohexylmethyl ether 10 was isolated. Attempts to chromatographically separate 1c and 10 failed. However, further hydrogenolysis of the mixture catalyzed by 10% Pd/C led to a readily separated 2:1 mixture of 1c and 10. Reduction of 9c with NaBH4 gave only the tetrahydroisoquinoline 1c.
Attempted reduction of the dihydroisoquinoline 9c directly to 1b using 10% Pd/C resulted in acceptable yields; however, this reaction was not reliable, and the product frequently was contaminated by an impurity. The UV spectrum of the reaction product showed a strong absorption at 322 nm, indicating the presence of the fully aromatic 6-methoxytetrahydroisoquinoline (11), with some reactions yielding products containing as much as 50% of the undesired 11. Washing the crude dihydroisoquinoline 9c repeatedly with alkali to remove residual POCl₃, and other phosphorus compounds prior to hydrogenation eliminated this reaction problem. If the benzyl chloride was contaminated with 10% Pd/C, resulted in acceptable yields; however, this reaction was not reliable, and the product frequently was contaminated by an impurity. The UV spectrum of the reaction product showed a strong absorption at 322 nm, indicating the presence of the fully aromatic 6-methoxytetrahydroisoquinoline (11), with some reactions yielding products containing as much as 50% of the undesired 11. 

Similarly, heating of amine 4 with acid 8a in refluxing xylene afforded an 87% yield of amide 3a. Treatment of 3a with POCl₃ in refluxing toluene yielded the dihydroisoquinoline 9a. A basic wash of crude 9a, followed by hydrogenation (PtO₂/H₂/50 psi), afforded a 97% yield of crystalline tetrahydroisoquinoline 1a.

**Synthesis of Tetrahydroisoquinolines 2a and 2c.** Lithiation₆ (n-butyllithium, 0 °C) of benzylamine 12 in THF, followed by quenching with an equivalent of ethyl chloroformate, afforded the benzoyl ester 14. Then treatment of distilled 14 with excess ethyl chloroformate generated benzyl chloride¹⁵, which with potassium cyanide in DMF gave nitrile 16. Hydrogenation of 16 to phenylethylamine 17, which was cyclized in refluxing benzene, yielded 8-methoxy-3,4-dihydroisocarbostyril 18 (Scheme IV).

We assumed that if 18 were converted to the sulfonamide 20 it might then be susceptible to attack by the benzylmagnesium chloride 21. The amide carbonyl of 20 displays an IR absorption at 1690 cm⁻¹, more characteristic of the carbonyl of a ketone than that of amide (18 has a carbonyl absorption at 1670 cm⁻¹). When 20 was treated with 110 mol % of 21, however, no reaction occurred.

We then decided to convert amine 18 into amine 22, confident that the dihydroisoquinoline 22 would react with the benzyl Grignard reagent 21 to yield 2a. Isocarbostyril 18 was reduced to 8-methoxy-1,2,3,4-tetrahydroisoquinoline (23) with lithium aluminum hydride in 93% yield. Oxidation of tetrahydroisoquinoline 23 with MnO₂₆a in benzene led predominantly to the undesired fully aromatized 8-methoxytetrahydroisoquinoline (25). With dichloromethane as solvent, oxidation was more selective, and the desired dihydroisoquinoline 22 was the major product; γ-MnO₂₆b reacted similarly in CH₂Cl₂. Treatment of this reaction product with the benzyl Grignard reagent 21 afforded a 44% yield of 2a.

To synthesize 2c, we planned to add the Grignard reagent 26a or 26b to the dihydroisoquinoline 22. p-

Hydroxybenzaldehyde (27) was treated with benzyl chloride, generating 27b. Reduction with sodium borohydride afforded alcohol 26c, which was converted to benzylic chloride 26d with phosphorus trichloride. Alternatively, stirring alcohol 25e in ether/48% HBr yielded benzylic bromide 26e. All attempts at generating the Grignard reagents 26a and 26b from 26d and 26e, respectively, with activated magnesium¹² or magnesium turnings was unsuccessful.

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(7) Treatment of 13 with 200 mol % of ethyl chloroformate provided a 60% yield of benzyl chloride 18 contaminated with 10% of lactone 19. 200 mol % of methyl chloroformate gave a 73% yield of lactone 19. Monitoring the reaction by TLC showed that lactone formation was concomitant with chloro ester formation. Lactonization of chloro ester 15 may be facilitated by lithium chloride present in the reaction mixture of may be solely a thermal process (attempted GC purification of 15 at 180 °C yielded lactone 19). Similar results have been reported by Hinton, I. G. H.; Mann, F. G. J. Chem. Soc. 1959, 599.
successful, yielding only benzyl 26f.

Faced with these failures, we explored reversal of the role of each moiety, i.e., using the isoquinoline moiety in a nucelophilic sense and the benzyl halides 26d or 26e as the electrophilic species. Attempted synthesis of the Reissert-like compound 28 gave only 29. Treatment of tetrahydroisoquinoline 23 with benzoyl chloride gave benzamide 30a, which with LDA resulted in 10% lithiation only at C-1. The yield and regioselectivity of the metatation were determined by a deuterium quench (D₂O) and by trapping with CO₂ to form carboxylic acid 32.

Since the low yield of metatation was due, at least in part, to the insolubility of benzamide 30a in THF and other ethereal solvents, 4-tert-butylbenzamido 30b and pivalamido 30c were prepared. Both exhibited satisfactory solubility in THF, and metatation of these compounds was examined under a variety of conditions. LDA afforded 20% of 1-lithio derivatives 31b and 31c, the remainder being unreacted 30b and 30c. Use of n-butyllithium (-90 °C) resulted primarily in attack on the carbonyl. The best results were obtained with 300 mol % of LDA at -70 °C, giving 40% yields of 31b and 31c. Proceeding with the synthesis of 2e, metatation of 30b under these conditions, followed by addition of 100 mol % of benzyl bromide 26e, gave 33b in 31% yield. Hydrolysis of the 4-tert-butybenzoyl group to generate 2e proved to be surprisingly difficult. Attempted reductive cleavage with 3% sodium amalgam also failed, giving no reaction.

Assuming that the sodium amalgam reduction was sensitive to the oxidation potential of the amide carbonyl, we returned to tetrahydroisoquinoline 23 and prepared the p-phenylbenzamido 30d. Treatment with 100 mol % of tert-butyl lithium, followed by addition of 26d, afforded a 61% yield of 33d and a 20% yield of recovered starting material. The alkylated product 33d was reductively cleaved with 3% sodium amalgam to generate the desired 2c.

Isomer Analysis of Bischler–Napieralski Reaction Product. Compound 2a was separable from 1a by HPLC. Careful analysis of the total product (97% mass balance) of the Bischler–Napieralski reaction (POCl₃, refluxing toluene, followed by PtO₂-catalyzed hydrogenation) established that 4% of the tetrahydroisoquinoline present was the 8-methoxy isomer 2a. Similarly, 2c was separable from 1c by HPLC, and analysis of the total product (92% mass balance) of the reaction (POCl₃, toluene, 80–85 °C, followed by NaBH₄ reduction) showed that 3% of the tetrahydroisoquinolines present was the 8-methoxy isomer 2c. These chromatographic results, together with a comparison of the methoxy absorptions in the NMR for both the 6- and 8-isomers, are listed in Table I.

<table>
<thead>
<tr>
<th>compd</th>
<th>HPLC tR</th>
<th>NMR of aryl methyl ethers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a-HCl</td>
<td>3.87a</td>
<td>3.86 (6 H), 3.91 (3 H)c</td>
</tr>
<tr>
<td>2a-HCl</td>
<td>2.49a</td>
<td>3.68, 3.80, 3.83c</td>
</tr>
<tr>
<td>1c</td>
<td>3.9b</td>
<td>3.73d</td>
</tr>
<tr>
<td>2c</td>
<td>3.1b</td>
<td>3.82d</td>
</tr>
</tbody>
</table>

With both compounds 1a and 1c, crystallization afforded material free of the 8-methoxytetrahydroisoquinolines 2a and 2c in 85 and 82% yield, respectively. Hydrogenolysis of 1e then afforded a 97% yield of 1b, thus completing the synthesis of the desired tetrahydroisoquinoline. These results demonstrate that Bischler–Napieralski reaction products derived from unsymmetrically substituted phenylethylamines may contain the ortho-cyclized isomer. This possibility should be considered in their further application.

Experimental Section

All reactions were performed under a nitrogen atmosphere with magnetic stirring unless noted otherwise. Reaction solvents were freshly distilled as follows: CHCl₃, CH₂Cl₂, and hexane from P₂O₅. THF from potassium–benzenophenone ketyl; benzene from itself. Organic extracts were finally washed with saturated NaCl, dried over MgSO₄, and evaporated in vacuo. Melting points are corrected.

'H NMR spectra were determined with internal Me₄Si in CDCl₃ unless otherwise noted. Gas chromatographies were carried out with 50–100 mesh Chromosorb W as support on 5-ft columns with 3% OV-1 (A, glass column), 5% OV-25 (B, glass column), or 5% SE-30 (C, glass column) as the liquid phase. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

O-(Ethoxy carbonyl)-3-methoxy mandelonitrile (7). To a stirred solution of 13.6 g (0.1 mol) of m-anisaldehyde (5) and 11.9 g (0.11 mol, 10.8 mL) of ethyl chlorofomate in 20 mL of THF, cooled in an ice–water bath, was added in one portion 7.2 g (0.11 mol) of KCN dissolved in 25 mL of water. The reaction mixture was stirred for 4 h at 5 °C and then slowly warmed to room temperature overnight. Water (100 mL) was added, the aqueous solution was extracted with 3 × 40 mL of ether. The combined extracts were dried and evaporated, and the residue was Kugelrohr distilled to afford 21.4 g (0.92 mol, 92%) of nitrile (2 H, m). The combined extracts were distilled to afford 13.9 g (0.09 mol, 92%) of benzamide 2a.HCl bp 110–115 °C (0.4 mm) [lit.1 bp 113–115 °C (0.4 mm)]; GC (column A, 170 °C), tR = 2.1 min; NMR δ 1.25 (2 H, m), 3.82 (3 H, s), 4.04 (2 H, m).

2-(m-Methoxyphenyl) ethylamine (4). A solution of 23.5 g (0.1 mol) of 7 in 300 mL of absolute ethanol was added dropwise (0.5 drop/s) to a mechanically stirred solution of 300 mL of absolute ethanol containing 1.5% of 10% Pd/C catalyst and 12.9 g (0.13 mol, 7 mL) of concentrated sulfuric acid as hydrogen was bubbled through the solution. After the addition, stirring and bubbling were continued for 8 h, the reaction mixture was filtered, the filtrate was evaporated, water (100 mL) was added, and the cooled aqueous solution was made alkaline with 4 M sodium hydroxide. The solution was extracted with 4 × 50 mL of ether, the combined extracts were dried and evaporated, and the residue was Kugelrohr distilled to afford 13.9 g (0.09 mol, 92%) of phe nylethylamine 4: bp 93–95 °C (0.1 mm) [lit.4 bp 122–125 °C (1.0 mm)]; GC (column B, 140 °C), tR = 5.4 min; NMR δ 1.25 (2 H,


mmol) in 52 mL of DMF was added in one portion 20.2 g (0.413 mol) of freshly pulverized NaCN. The reaction mixture was diluted with 250 mL of water after 4 h and extracted with 4 X 80 mL of benzene. The combined organic extracts were washed, dried, and evaporated, and the residue was distilled to bulb distilled, providing 9.9 g (45.2 mmol, 88%) of nitrite 16: bp 110–112 °C (0.5 mm); NMR δ 1.35 (3 H, t, J = 7 Hz), 3.73 (2 H, s), 3.80 (3 H, s), 4.39 (2 H, q, J = 7 Hz), 6.96 (2 H, m), 7.30 (1 H, m).

3.4-DiHydro-3,4-methylisocarboxystyril (18). A solution of 9.9 g (45.2 mmol) of 2-(ethoxycarbonyl)-3-methoxyphenylacetate and 15 mL of concentrated sulfuric acid was hydrogenated over 200 mg of magnesium chloride (21) in THF. After 10 h, the solvent was removed, the residue was acidified with 15 mL of 6 M hydrochloric acid and extracted with 4 X 8 mL of CH2Cl2. The combined organic extracts were washed, dried, and evaporated, and the residue was dissolved in 1-propanol and crystallized to a fine precipitate. There was obtained 170 mg (0.49 mmol, 44%) of isoquinoline hydrochloride 2a: mp 218–219 °C after recrystallization from 1-propanol and pure by HPLC (see Table I): NMR δ 1.26–2.0 (4 H, m), 3.03 (2 H, s), 6.95 (2 H, d, J = 7.5 Hz, 3.68 (2 H, s), 7.34 (2 H, d, J = 7 Hz, 2.70 (2 H, br s). Anal. Calcd for C15H13NCl: C, 65.2; H, 6.4; Cl, 18.2. Found: C, 65.0; H, 6.3; Cl, 18.1.

1-Hydroxy-2-benzyloxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (29). To a solution of 10 mL of CH2Cl2 and 0.33 g (2.0 mmol) of 8-methoxy-3,4-dihydroisoquinoline (22) prepared as described above, stirred under 4 M HC1 for 2 h. After 2 h of vigorous stirring, the ether layer was washed, dried, and evaporated, and the resulting oil was subjected to crystalline from ethanol: mp 150–152 °C; NMR δ 7.1–7.7 (m, 6 H, Ar H), 6.6–6.9 (2 H, Ar H), 6.3 (very broad, 1 H, OH), 3.77 (3 H, OCH3), 3.1–4.0 (br, 2 H, CH2). Anal. Calcd for C20H17N07: C, 70.1; H, 6.7; N, 4.9. Found: C, 70.1; H, 6.6; N, 4.9.

2-Benzyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (30a). To a solution of 1 g (6 mmol) of 8-methoxy-1,2,3,4-tetrahydroisoquinoline (23) in 20 mL of pyridine at 0 °C was added 4 mL of benzoyl chloride over 2 h. After an additional 3 h at 0 °C, the solution was filtered, the filtrate was evaporated, and the remaining oil was taken up in CH2Cl2 and washed sequentially with 10 mL of 1 M NaOH, 2 X 10 mL of 10% HCl, and brine. The organic phase was then dried and evaporated to a solid, which was recrystallized from ethanol, yielding 1.21 g (45.5 mmol, 75%) of 30a: mp 133–135 °C; NMR δ 7.4 (s, 5 H, Ar H), 6.5–7.3 (m, 3 H, Ar H), 4.6 (br s, 2 H, Ar CH2N), 3.7 (s, 5 H, OCH3, NCH3), 2.8 (t, 2 H, Ar CH2). Anal. Calcd for C21H19N07: C, 76.4; H, 6.4; N, 5.2. Found: C, 76.4; H, 6.5; N, 5.2.

2-Pivaloyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (30c) was prepared using pivaloyl chloride and following the same procedure as described for 30a. Crude product was purified from ligroin: mp 79–80 °C; NMR δ 1.28 (9 H, C(CH3)3), 2.80 (br t, 3 H, Ar CH3), 3.8 (3 H, OCH3), 3.5–4.0 (m, 2 H, Ar CH2C), 4.65 (2 H, Ar CH2N), 6.5–7.4 (3 H, Ar H). High-resolution MS calc for C21H19N07: 247.1572. Found: 247.1584.

25 mL of CH₂Cl₂ was added at 0 °C, over a period of 0.5 h, a solution of 4-phenylbenzoyl chloride (0.83 g, 5.0 mmol) in 5 mL of CH₂Cl₂. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to 25 °C over 14 h. It was then evaporated, the residue was dissolved in 20 mL of CH₂Cl₂ and washed with 1 X 10 mL of 1 N NaOH and 2 X 10 mL of 10% HCl, and the organic phase was dried and evaporated to leave 750 mg of residue. Chromatography (SiO₂, 5% acetone/CH₂Cl₂) afforded 30d, pure by HPLC (Lichrosorb, 60% hexane/40% CHCl₃): mp 171-173 °C (after crystallization from ethyl acetate); NMR δ 2.8 (t, J = 6 Hz, 2 H, Ar CH₂), 3.73 (s, 3 H, OCH₃), 3.5-4.0 (m, 3 H, CH(N)), 4.65 (br s, 2 H, Ar CH₂CN), 6.5-7.7 (m, 12 H, Ar H). Anal. Calcd for C₂,H₂,NNO₂: C, 80.4; H, 6.2; N, 4.0.  

1-[4-(Benzyloxy)benzyl]-2-(4-tert-butylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (33b). To a solution of 200 mg (0.37 mmol) of 33d in 5 mL of THF was added 0.40 mL (0.29 g, 2.86 mmol) of diisopropylamine, followed by n-BuLi (2,3 M, 1.13 mL, 2.60 mmol) at -70 °C. After 2 h, 4-(benzyloxy)benzyl bromide (100 mol %, 240 mg, 0.87 mmol) was added as a solution in 2 mL of THF over a 5-min period. After 2 h at -70 °C, 4-(benzyloxy)benzyl bromide (100 mol %) of amide 33d in 100 mL of dry THF was cooled to -70 °C (after crystallization from ethyl acetate); NMR δ 2.8 (t, J = 6 Hz, 2 H, Ar CH₂), 3.75 (br s, 3 H, OCH₃), 4.6-5.3 (m, 3 H), 6.2-7.8 (m, 21 H, Ar H). Anal. Calcd for C₂,H₂,NNO₂: C, 80.4; H, 6.2; N, 4.0.

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Registry No. 1a, 81625-16-3; 1a-HCl, 4042-17-5; 1b, 81625-17-4; 1b-HCl, 81625-18-5; 2a, 81625-19-6; 2a-HCl, 81625-20-9; 2a-Bu, 81625-21-0; 2c, 81625-22-1; 2c-HCl, 81625-23-2; 3a, 3979-55-6; 3c, 7678-10-5; 4, 2039-67-0; 5, 591-31-1; 6, 3179-09-7; 7, 1965-74-9; 8, 172385-24-3; 9a, 93-40-3; lb-HCl, 81625-26-5; 10, 81625-27-6; 11, 15184-99-3; 12, 181625-28-9; 13, 181625-29-8; 14, 81625-30-1, 16, 81625-31-2; 17, 81625-32-3; 18, 74904-29-3; 19, 28281-58-5; 20, 81625-33-4; 21, 7306-46-9; 22, 24693-44-5; 23, 34146-58-4; 24, 24693-49-1; 25, 172385-70-2; 26a, 81625-33-4; 26b, 81625-33-4; 26c, 81625-33-4; 26d, 24923-77-3; 27, 12359-90-0; 28, 4357-53-9; 29, 81625-35-6; 30a, 81625-36-7; 30b, 81625-37-8; 30c, 81625-38-9; 30d, 81625-39-0; 33b, 81625-40-3; 33d, 81625-41-4; pivaloyl chloride, 3282-30-2; p-tert-butylbenzoyl chloride, 1710-98-1; 4-phenylbenzoyl chloride, 14002-51-8.


Enantiomeric α-Aminopropiophenones (Cathinone): Preparation and Investigation

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The preparation of the optical antipodes of α-aminohippropiophenone (cathinone) from norephedrine and an improved large-scale resolution of norephedrine are described. The characterization of cathinone and its salts and their stability in various solvents are discussed.

The chewing of the leaves of Catha edulis Forsk (Khat) by the natives of several Asian and African countries to provide rapid stimulation is extremely prevalent and has been considered to be a serious problem of drug dependence not unlike that associated with amphetamine. In fact, on the basis of the observations of Eddy et al. the United Nations Narcotics Laboratory undertook research on the chemistry of Khat and its components. Earlier in this century (+)-norpseudoephedrine, a CNS-active compound, was identified among the basic alkaloid components of Khat. Later investigations identified (+)-norpseudoephedrine as a CNS-active compound.