

**PREPARATION OF TETRAHYDROISOQUINOLINES FROM
N-(*tert*-BUTOXYCARBONYL)-2-METHYLBENZYLAMINES¹**

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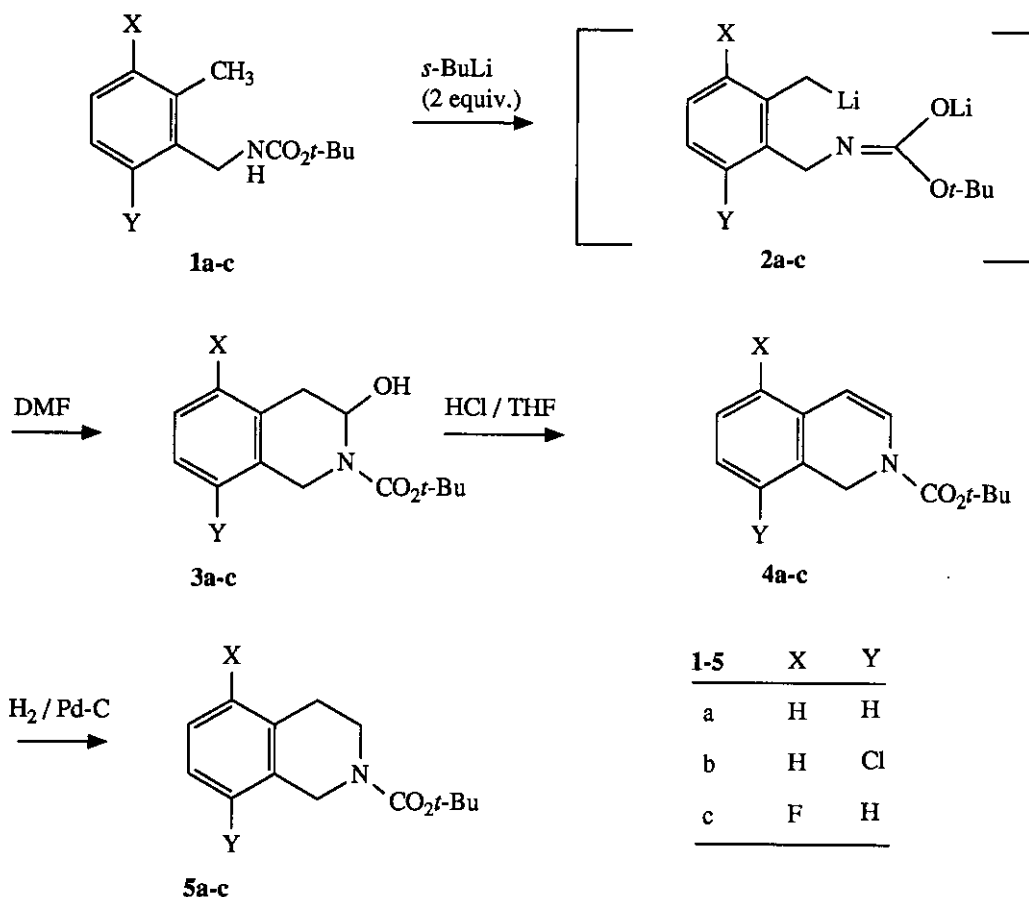
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Abstract-Dilithiation of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine (**1a**) followed by treatment with *N,N*-dimethylformamide affords 2-(*tert*-butoxycarbonyl)-3-hydroxy-tetrahydroisoquinoline (**3a**). Dehydration and reduction of **3a** afford BOC-tetrahydroisoquinoline (**5a**). The methodology is also applicable to synthesis of chloro and fluoro substituted tetrahydroisoquinolines (**5b,c**), 3 and 4 substituted derivatives (**8, 10**), and the hexahydro-2*H*-benzoquinolizine ring system (**13**).

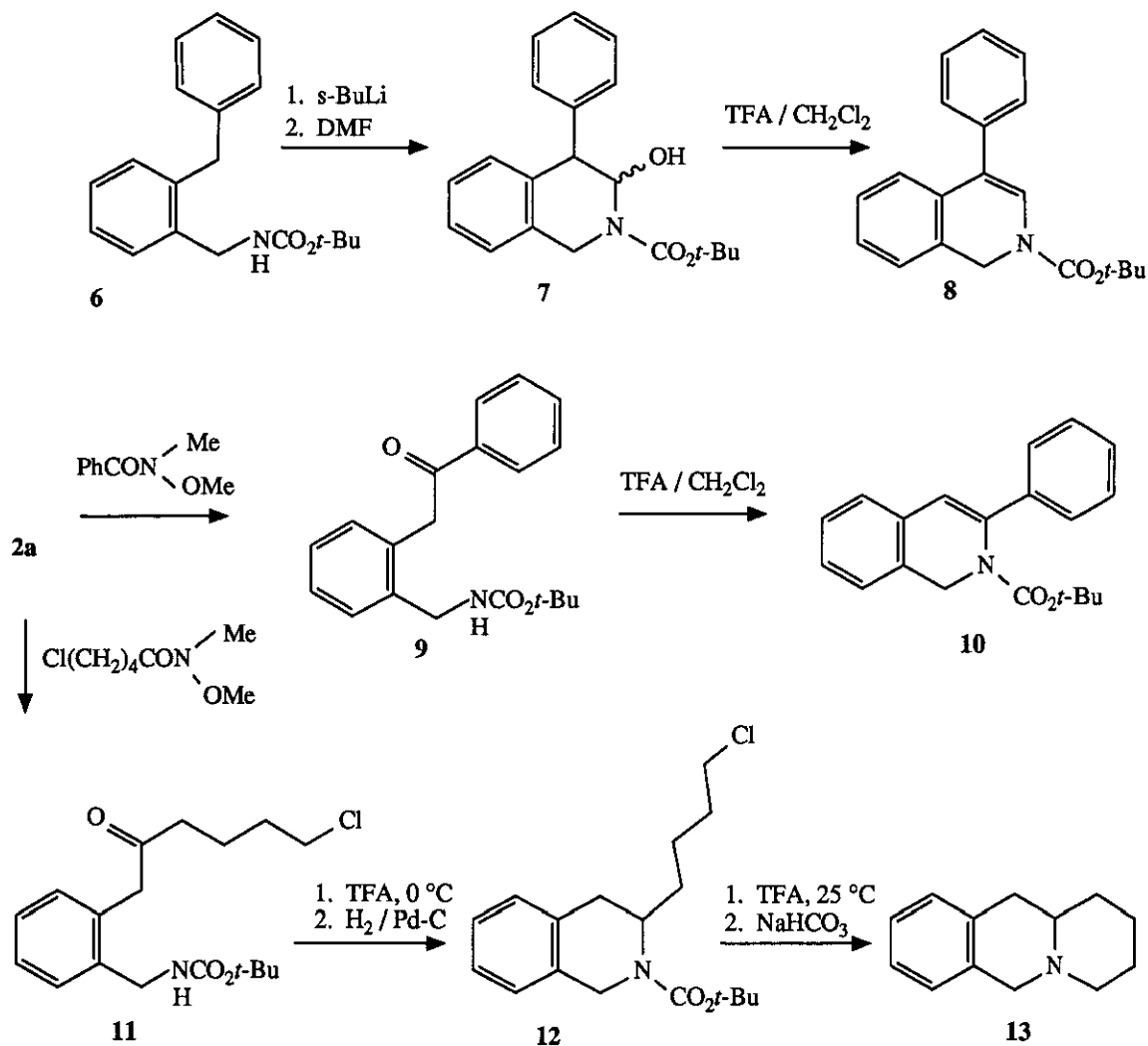
Classical syntheses of the isoquinoline ring system generally involve electrophilic cyclization onto an activated aromatic ring.² Thus, preparations of isoquinolines *via* the Pomeranz-Fritsch cyclization, dihydroisoquinolines *via* the Bischler-Napieralski cyclization, and tetrahydroisoquinolines *via* the Pictet-Spengler cyclization are often low-yielding when electron-withdrawing groups are present.^{3,4} These syntheses are also not readily applicable to substitutions at the 3- and 4-positions of the isoquinoline nucleus. We wish to report methodology for the preparation of 1,2-dihydro- and 1,2,3,4-tetrahydroisoquinolines which in certain cases overcomes these limitations. This methodology is based on condensation reactions of the dilithio species derived from heteroatom directed lithiation^{5,6} of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamines.⁷

Dilithiation of *N*-pivaloylbenzylamine has been shown to produce lithio species derived from both *ortho* and α (benzylic)-lithiation.⁸ However, treatment of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine (**1a**) with *sec*-BuLi (2 equiv.) in THF at -40 °C resulted in dilithio species (**2a**) without competing *ortho* or α -lithiation. Treatment of **2a** with *N,N*-dimethylformamide afforded *N*-(*tert*-butoxycarbonyl)-3-hydroxy-1,2,3,4-tetrahydro-

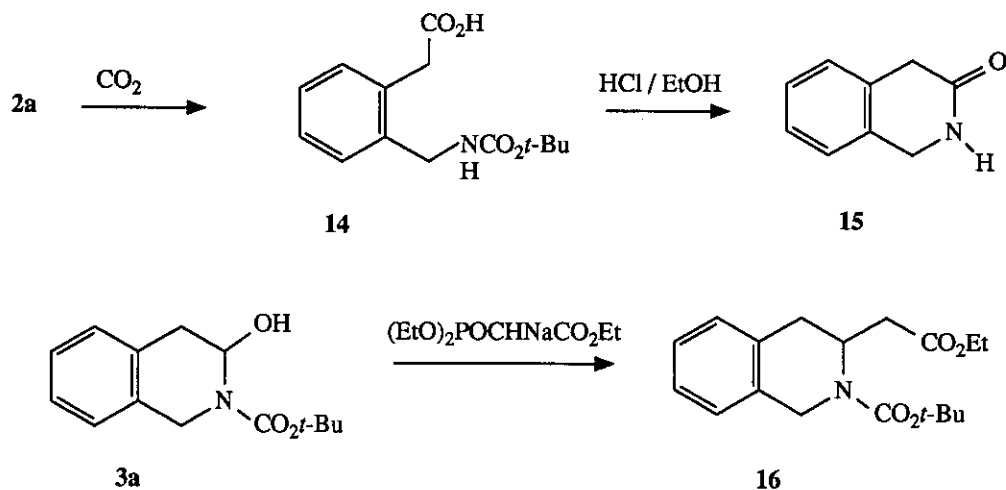
isoquinoline (**3a**)⁹ as the sole product (78%, mp 97-98 °C). Brief treatment of **3a** with HCl in THF gave the somewhat unstable dihydroisoquinoline (**4a**) which afforded BOC-tetrahydroisoquinoline (**5a**) upon catalytic hydrogenation (95% from **3a**). The 8-chloro (**5b**, 76% from **1b**¹⁰, mp 105-106 °C) and 5-fluoro (**5c**, 56% from **1c**¹¹, mp 39-40 °C) derivatives were similarly prepared.



The 4-phenyl-1,2-dihydroisoquinoline derivative (**8**) was prepared from **6** by an analogous sequence (71%, mp 96-98 °C). The 3-phenyl analogue was available from treatment of **2a** with *sec*-BuLi followed by *N*-methoxy-*N*-methylbenzamide¹² to afford ketone (**9**) (79%, mp 110-112 °C) which was cyclized (catalytic trifluoroacetic acid in dichloromethane, 0 °C) to **10** (94%, mp 105-106 °C). Condensation of **2a** with *N*-methoxy-*N*-methyl-5-chlorovaleramide gave ketone (**11**) (53%, mp 47-48 °C) which afforded 1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine (**13**, 86%, mp 42-43, lit.,¹⁴ mp 46-47 °C) after cyclization, reduction, deprotection (trifluoroacetic acid in dichloromethane, room temperature), and base treatment.



In summary, the methodology described herein affords access to tetrahydroisoquinolines substituted with electron-withdrawing groups (e.g. Cl, F) which are difficult to prepare by classical routes.² Derivatives substituted at positions 3 and 4 are also available. In addition, dilithio species (**2a**) and arnidal (**3a**) are useful for other applications. For example, treatment of **2a** with carbon dioxide afforded acid (**14**) (90%, mp 107-108 °C) which was cyclized to afford 1,4-dihydro-3(2*H*)-isoquinolone (**15**) (70%, mp 147-148 °C, lit.,¹⁵ mp 149.5-150.5 °C). Condensation of **3a** with triethyl 2-sodiophosphonacetate (2 equiv., THF, room temperature, 24 h) gave ester (**16**) (56%, oil).



A typical experimental procedure is as follows: To a solution of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine (**1a**, 11 g, 50 mmol) in 250 ml of THF at -35°C was added *sec*-BuLi (84.6 ml of 1.3 M in cyclohexane, 110 mmol). The resulting bright orange solution was stirred for 5 min and DMF (5.8 ml, 75 mmol) was added. The now colorless mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4) and evaporated to an oil. Crystallization from hexane afforded 9.8 g (78%) of **3a**, mp $97\text{--}98^\circ\text{C}$; ^1H nmr (300 MHz, CDCl_3) δ : 1.52 (9H, s), 2.98 (1H, dd, $J = 4.3, 15.4$ Hz), 3.06 (1H, dd, $J = 4.3, 15.4$ Hz), 3.65 (1H, broad s, OH), 4.46 (1H, d, $J = 15.7$ Hz), 4.54 (1H, d, $J = 15.7$ Hz), 5.80 (1H, broad m, H-3), 7.20 (4H, m); ms (m/z): 249 (M^+). *Anal.* Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.57; H, 7.82; N, 5.79.

A solution of **3a** (1.25 g, 5 mmol) in 20 ml of THF was treated with 5 drops of conc. HCl and the solution was stirred for 5 min at room temperature. The mixture was partitioned between ether layer and water and the ether was washed with aqueous NaHCO_3 and brine, dried (Na_2SO_4) and evaporated to 1.2 g of crude **4a**. This material was hydrogenated at 30 psi in 50 ml of EtOAc with 0.3 g of 20% $\text{Pd}(\text{OH})_2$ for 12 h to afford 1.1 g (95%) of BOC-tetrahydroisoquinoline (**5a**) (mp $35\text{--}36^\circ\text{C}$, hexane) which was identical (tlc, nmr, mp) with an authentic sample prepared from tetrahydroisoquinoline (di-*tert*-butyl dicarbonate, THF).

ACKNOWLEDGEMENT

We thank Dr. J.M. Muchowski for helpful discussions on this work and Lani Russell for preparation of the manuscript.

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11. Prepared from 3-fluoro-2-methylbenzoic acid (Aldrich) by conversion to the amide, LAH reduction, and treatment with di-*tert*-butyl dicarbonate.
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Received, 17th June, 1991