PREPARATION OF TETRAHYDROISOQUINOLINES FROM *N*-(*TERT*-BUTOXYCARBONYL)-2-METHYLBENZYLAMINES[1]

Robin D. Clark* and Jahangir

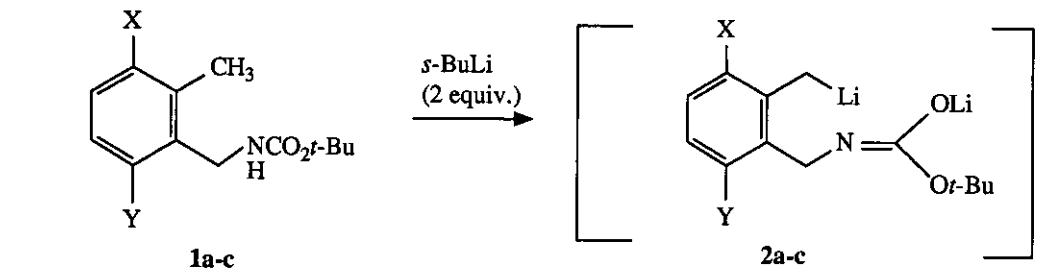
Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304, U.S.A.

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-tetrahydro-isoquinoline (**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**).

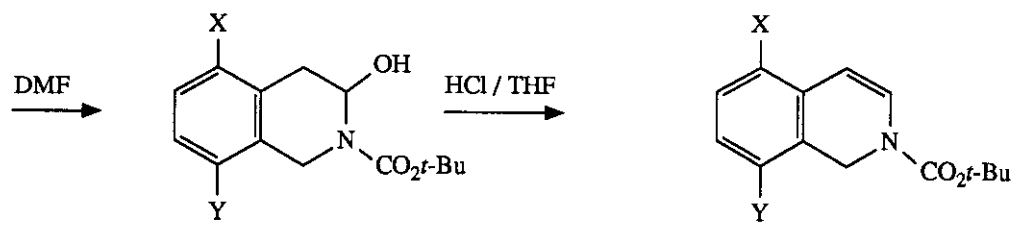
Classical syntheses of the isoquinoline ring system generally involve electrophilic cyclization onto an activated aromatic ring.[2] Thus, preparations of isoquinolines *via* the Pomeranz-Fritsch cyclization, dihydroisoquinolines *via* the Bischler-Napieralski cyclization, and tetrahydroisoquinolines *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 a 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-

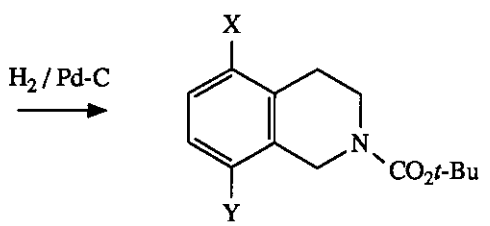
isoquinoline (**3a**)[9] as the sole product (78%, mp 97-98 °C). Brief treatment of **3a** with HCl in THF gave the somewhat unstable dihydroisoquinoline (**4a**) which afforded BOC-tetrahydroisoquinoline (**5a**) upon catalytic hydrogenation (95% from **3a**). The 8-chloro (**5b**, 76% from **1b**[10],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



1a-c **2a-c**



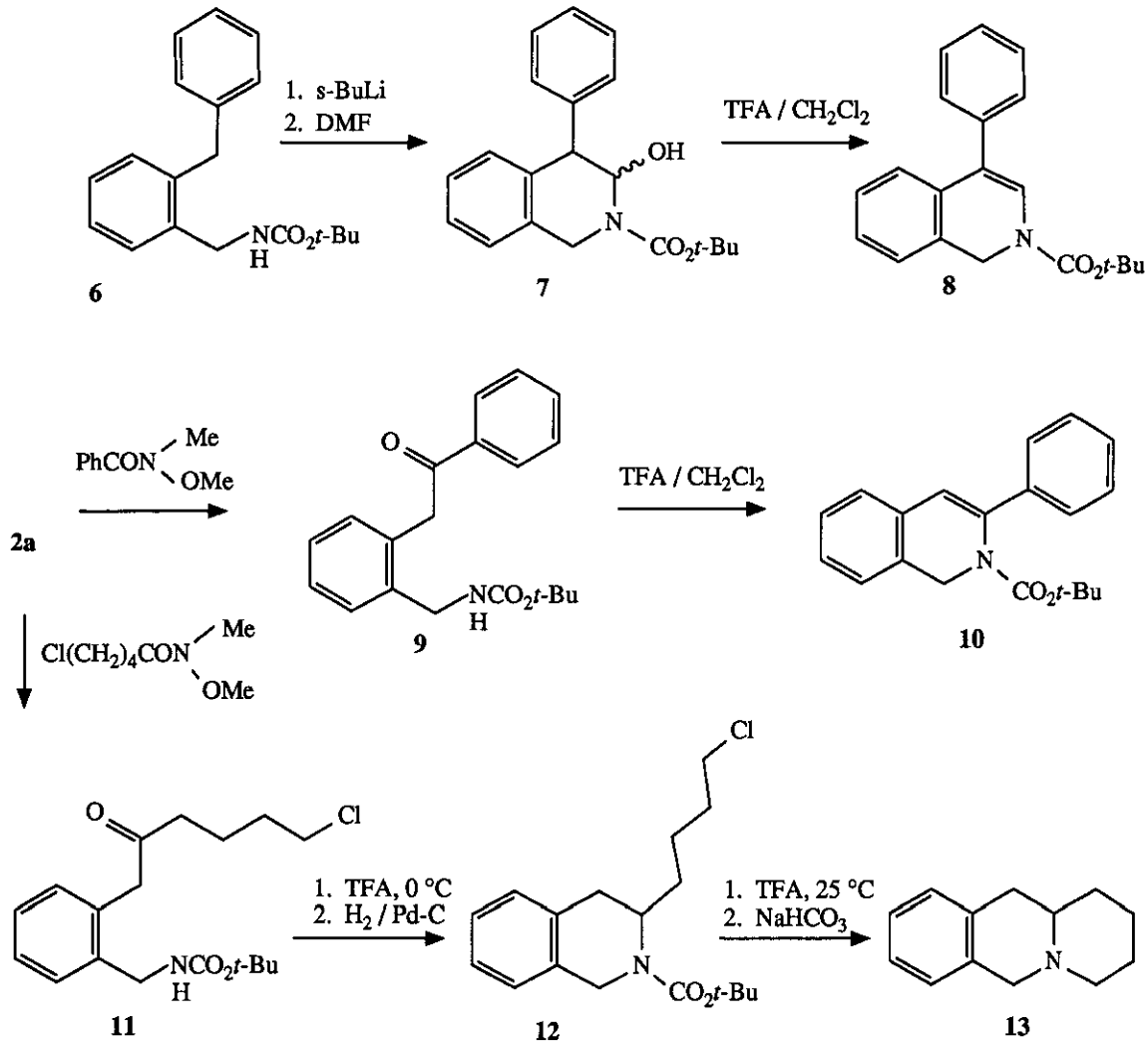
3a-c **4a-c**



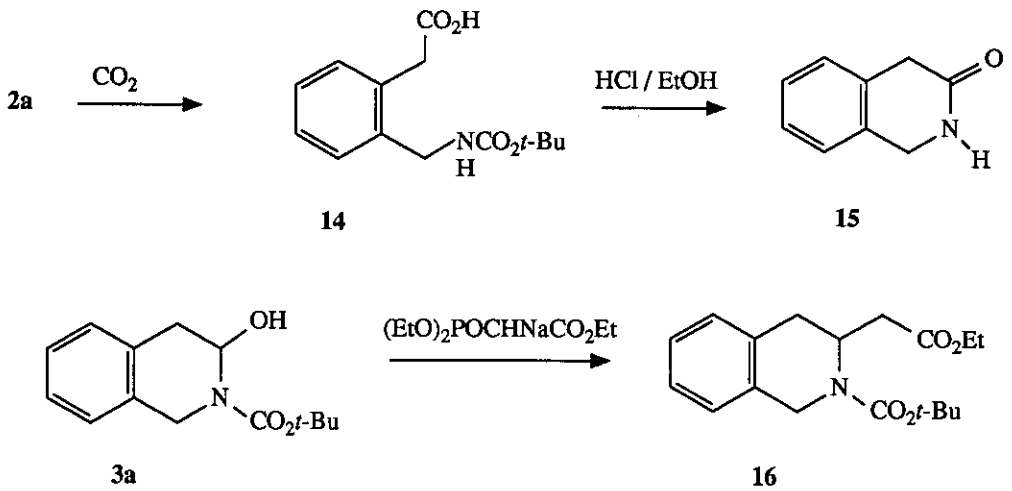
5a-c

1-5	X	Y
a	H	H
b	H	Cl
c	F	H

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*-methylbenzamide[12] 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 amidal (**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 97-98 °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 $C_{14}H_{19}NO_3$: 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% $Pd(OH)_2$ for 12 h to afford 1.1 g (95%) of BOC-tetrahydroisoquinoline (**5a**) (mp 35-36 °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.

REFERENCES AND NOTES

1. Contribution no. 836 from the Institute of Organic Chemistry.
2. D. L. Boger, C. E. Brotherton, and M. D. Kelley, *Tetrahedron*, 1981, **37**, 3977 and references cited therein.
3. E. V. Brown, *J. Org. Chem.*, 1977, **42**, 3208.
4. W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 74 and 151.
5. V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
6. Novel syntheses of 8-substituted tetrahydroisoquinolines involving *ortho*-lithiation have been reported: G. Simig and M. Schlosser, *Tetrahedron Lett.*, 1990, **31**, 3125; M. Schlosser and G. Simig, *Tetrahedron Lett.*, 1991, **32**, 1965.
7. Similar methodology has been utilized for indole synthesis: R. D. Clark, J. M. Muchowski, M. Souchet, and D. B. Repke, *Synlett*, 1990, 207.
8. G. Simig and M. Schlosser, *Tetrahedron Lett.*, 1988, **29**, 4277.
9. All new compounds gave satisfactory 300 MHz ^{1}H nmr spectra. Satisfactory elemental analyses were obtained for all compounds with the exception of the unstable dihydroisoquinolines (**4a-c**).
10. Prepared from 2-chloro-6-methylbenzonitrile (Aldrich) by reduction (BH_3•DMS) and treatment with di-*tert*-butyl dicarbonate).
11. Prepared from 3-fluoro-2-methylbenzoic acid (Aldrich) by conversion to the amide, LAH reduction, and treatment with di-*tert*-butyl dicarbonate.
12. For the use of *N*-methoxy-*N*-methylamides as acylating agents see: S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981 **22**, 3815.
13. Ketones analogous to **9** have been prepared by $S_{RN}1$ reaction of the ethyl carbamate of *ortho*-iodobenzylamine and ketone enolates. These ketones were cyclized to dihydroisoquinolines by acid treatment: R. Beugelmans, J. Chastanet, and G. Roussi, *Tetrahedron Lett.*, 1982, **23**, 2313.
14. J. M. Paton, P. L. Pauson, and T. S. Stevens, *J. Chem. Soc.(C)*, 1969, 2130.
15. R. Huisgen and J. Reinertshofer, *Liebigs Ann. Chem.*, 1952, **575**, 197.

Received, 17th June, 1991