# An Efficient Synthesis of 4-Aryl-1,2,3,4-tetrahydroisoquinolines

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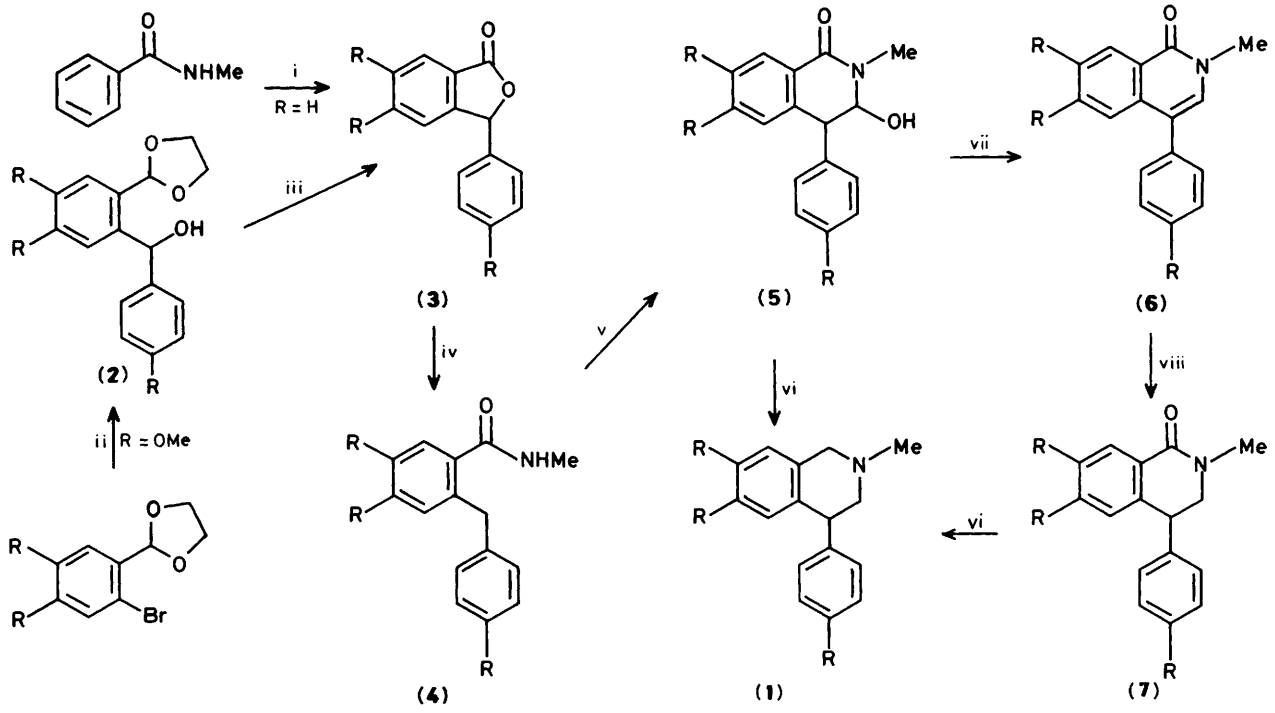
A general synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinolines from 3-aryl phthalides is described.

In this communication we describe a general synthesis of *N*-methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines. Our synthesis is illustrated for *N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**), which is an agonist for the dopamine receptor[1] and the methyl ether of cherylline (**1b**), a rare phenolic isoquinoline alkaloid[2] with an aryl substituent at the 4 position.

The starting compounds are the 3-aryl phthalides (**3**), which are obtained as shown.[3] On hydrogenolysis, the phthalides provided the *ortho*-benzyl benzoic acids. The *N*-methyl

**Table 1.**

| | | (2) | (3) | (4) | (5) | (6) | (7) | (1) |
|---|---|---|---|---|---|---|---|---|
| **a**; R = H | M.p./°C | | 114 (EtOH–$C_6H_{14}$) | 102—103 ($C_6H_{14}$–EtOAc) | 135—136 | 181—182 ($C_6H_{14}$–EtOAc) | 79—80 | 178—179 (HCl) (EtOH–$Et_2O$) Lit.,[5] 178—179 |
| | % Yield | | 70 | 75 | 80 | 90 | 75 | 50 |
| **b**; R = OMe | M.p./°C | 106—108 ($Et_2O$) | 128—129 (EtOH) | 131—132 ($C_6H_{14}$–EtOAc) | 123—126 | 179—180 (EtOAc) | | 227—228 (HCl) (MeOH–$Et_2O$) Lit.,[6] 228—229 |
| | % Yield | 80 | 65 | 80 | 75 | 90 | | 45 |




**Scheme 1.** i, Bu$^n$Li–diethyl ether, tetrahydrofuran (THF), heat; PhCHO, 0 °C; 50% HCl; ii, Bu$^n$Li–diethyl ether, −78 °C; ArCHO, −78 °C; $H_2O$; iii, 1 M $H_2SO_4$, $C_6H_6$, room temp., 3 h; $Na_2Cr_2O_7$, room temp., 3 h; iv, $H_2$–Pd/C, 90 psi: for **a**, room temp., 18 h, for **b**, 80 °C, 3 h; $SOCl_2$: for **a**, 10 min, room temp., for **b**, THF, 0 °C, 1 h; aq. $MeNH_2$, 0 °C; v, Bu$^n$Li–diethyl ether, 0 °C; DMF, 0 °C; $H_2O$; vi, $LiAlH_4$–THF, room temp., 2 h; vii, 1 M $H_2SO_4$, heat, 10 min; viii, $H_2$–Pd/C, 90 psi, 80 °C, 3 h (only for **a**).

benzamides (**4**) of the acids, on lithiation with Bu$^n$Li followed by treatment with dimethylformamide (DMF), gave the *N*-methyl-3-hydroxy-1,2,3,4-tetrahydroisoquinolone (**5**), which on dehydration and reduction or direct reduction furnished the target compounds (Table 1).†

The synthesis described above is potentially very useful, since the 3-aryl phthalides, in which the aromatic ring may be unsubstituted or substituted at any position with methoxy groups, are readily available through aromatic lithiation reactions[3] or through halogen–metal exchange reactions.[4]

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† Satisfactory i.r., $^1$H n.m.r., and analytical data were obtained for all new compounds.

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