4-Substituted *N*-Methyl-1,2,3,4-tetrahydroisoquinolines: Synthesis *via* Stereoselective Substitution of Tricarbonyl(*N*-methyl-1,2,3,4-tetrahydroisoquinoline)chromium

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Tricarbonyl(*N*-methyl-1,2,3,4-tetrahydroisoquinoline)chromium undergoes stereoselective 4-*exo*-deprotonation and subsequent electrophilic additions to generate the corresponding 4-*exo*-derivatives which after decomplexation yield 4-alkyl-, 4-phenyl-, and 4-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinolines.

Many simple 4-substituted 1,2,3,4-tetrahydroisoquinolines exhibit interesting and important pharmacological activities. For example, 4-phenyl-*N*-methyl-1,2,3,4-tetrahydroisoquinoline is an agonist of dopamine receptors[1] and 4-hydroxy-1,2,3,4-tetrahydroisoquinoline derivatives are involved in alcohol addiction.[2] We describe here methodology for the introduction of alkyl, aryl, and hydroxy substituents into the 4-position of *N*-methyl-1,2,3,4-tetrahydroisoquinoline *via* its tricarbonylchromium complex.

Thermolysis of hexacarbonylchromium with 1,2,3,4-tetrahydroisoquinoline gave complex (**1**) (90% yield†) which was *N*-methylated by treatment with sodium hydride and

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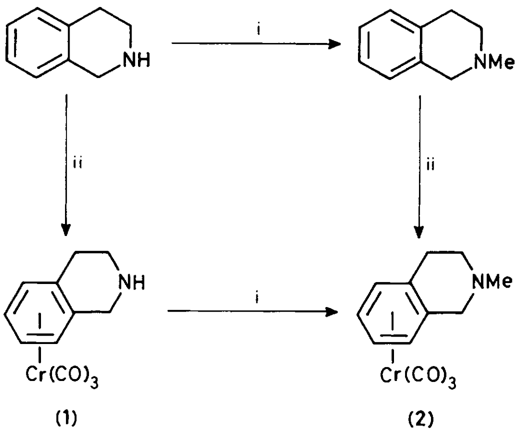
† All yields are unoptimised but refer to analytically pure material.

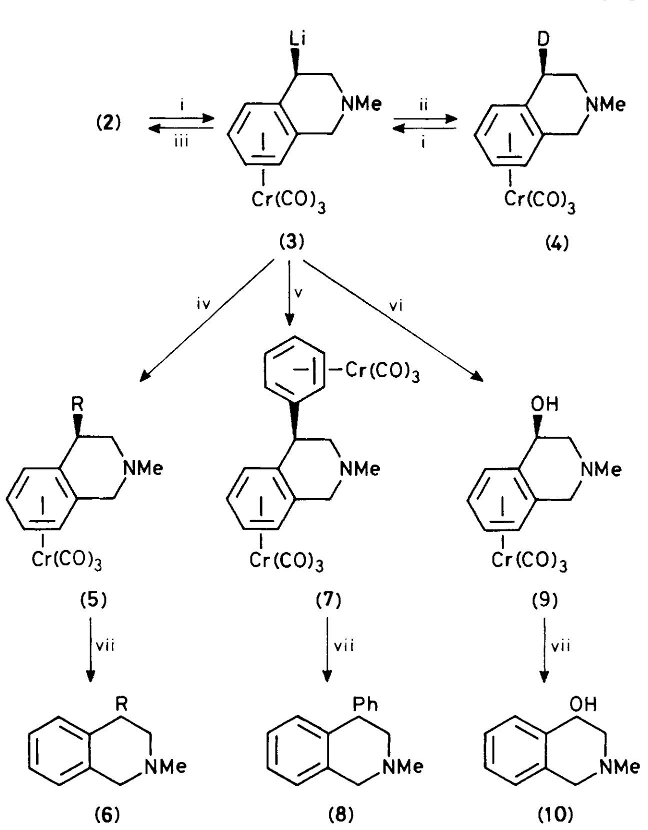


Reagents: i, NaH, MeI; ii, Cr(CO)$_6$, Bu$^n{}_2$O, reflux.

methyl iodide to give (**2**)‡ (25% yield). Alternatively complex (**2**) could be generated in 78% yield by thermolysis of hexacarbonylchromium in the presence of *N*-methyl-1,2,3,4-tetrahydroisoquinoline.

Treatment of complex (**2**) with n-butyl-lithium in tetrahydrofuran at 20 °C gave the 4-lithio derivative (**3**) which on quenching with CD_3OD gave the 4-*exo*-deuterio complex (**4**)‡ (74% yield). Only one diastereoisomer of (**4**) could be detected§ and this was assigned as *exo* by analogy with other related reactions[3] where the bulk of the tricarbonylchromium moiety protects the *endo* face. The fact that the deprotonation reaction was also stereoselective was demonstrated by treating (**4**) with n-butyl-lithium followed by quenching with methanol which completely removed the deuterium from (**4**) and regenerated complex (**2**).

Addition of benzyl bromide or methyl or ethyl iodide to (**3**) gave the 4-*exo*-alkylated derivatives (**5**)‡ in yields of 41, 65, and 65% respectively. These alkylations were also stereoselective, only one diastereoisomer being detected.§ Decomplexation of (**5**) by exposure of diethyl ether solutions to air liberated the 4-substituted *N*-methyl-1,2,3,4-tetrahydroisoquinolines (**6**) essentially quantitatively. Phenylation of (**3**) was achieved using tricarbonyl(fluorobenzene)-chromium[4] at −40 °C which generated the 4-*exo* double complex (**7**). Decomplexation as above removed both tricarbonylchromium groups and gave the known[5] 4-phenyl-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**8**)‡ (15% yield). Finally treatment of (**3**) with oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH)[6] at −40 °C introduced the 4-*exo*-hydroxy substituent in (**9**)‡ (35% yield) which after decomplexation gave 4-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**10**) [overall yield from (**2**), 35%].



Reagents: i, Bu^{n}Li; ii, CD_3OD; iii, MeOH; iv, RI, R = Me, Et; RBr, R = $PhCH_2$; v, $(C_6H_5F)Cr(CO)_3$; vi, MoOPH, Na_2SO_3; vii, air, Et_2O.

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‡ Selected ^{1}H n.m.r. data (300 MHz, $CDCl_3$): complex (**2**), δ 3.50 and 3.27 (AB system, J_{AB} 15 Hz, 2H, C-1 protons), 2.88—2.73 (m, 1H), 2.71—2.68 (m, 1H), 2.60—2.52 (m, 1H), and 2.49—2.41 (m, 1H) (C-3 and C-4 protons); complex (**4**) (^{2}H n.m.r., $CHCl_3$), δ 2.89; complex (**5**) (R = Me), δ 3.57 and 3.25 (AB system, J_{AB} 15 Hz, 2H, C-1 protons), 2.84—2.78 (m, 1H, C-4 proton), 2.59 and 2.45 (AB system, J_{AB} 12 Hz, 2H, C-3 protons), 1.36 (d, *J* 7 Hz, 3H, C-4 methyl protons); complex (**9**), δ 4.35 (s, br., 1H, C-4 proton), 3.65 and 3.30 (AB system, J_{AB} 15 Hz, 2H, C-1 protons), 2.91 and 2.68 (AB system, J_{AB} 11.5 Hz, 2H, C-3 protons); compound (**8**), δ 7.33—6.86 (m, 9H, aromatic protons), 4.31—4.26 (t, br., *J* 6 Hz, 1H, C-4 proton), 3.77 and 3.63 (AB system, J_{AB} 15 Hz, 2H, C-1 protons), 3.08—2.55 (m, 2H, C-3 protons), 2.44 (s, 3H, *N*-methyl protons), [lit.[5] (60 MHz, $CDCl_3$), δ 7.3—6.5 (m, 9H), 4.19 (t, 1H, *J* 7 Hz), 3.88 (s, 2H), 3.12—2.45 (m, 2H), 2.35 (s, 3H)].

§ ^{1}H N.m.r. data for all products were only consistent with 4-substitution and with single diastereoisomers of complexes (**5**), (**7**), and (**9**).

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