Reaction of 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole with Grignard reagents

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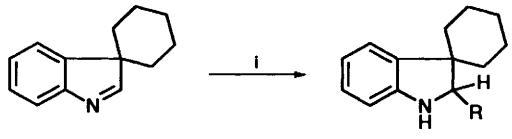
Reaction of the 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole **1** with organomagnesium halides in the presence of Cu_2Cl_2 forms only the *cis*-4a,9a-dialkylhexahydrocarbazole derivatives **2** through a radical mechanism. Characterization of the *cis*-ring junction formation was confirmed by the alkylation of an η^6-tricarbonylchromium complex of the 4a-methyl derivative **1**.

9-Dimethylaminopropyl derivatives of 4a-methyl-9a-substituted-2,3,4,4a-tetrahydrocarbazole (substituents: alkyl, allyl, benzyl, phenyl and vinyl groups) are coming to the fore as potential neuroactive drugs.

We recently reported a novel synthesis of 2'-substituted spiro[cycloalkane-1,3'-indolines].[1] This synthesis proceeded by reaction of the C=N bond in a spiro[cycloalkane-1,3'-3'*H*-indole] with an organomagnesium reagent in the presence of copper(I) chloride, to give the 2'-R substituted (R = Me, Ph) derivatives, in nearly quantitive yield,[2] Scheme 1.



Scheme 1 *Reagents and conditions:* i, RMgX, Cu_2Cl_2 (5.5% molar), dry toluene at reflux temperature

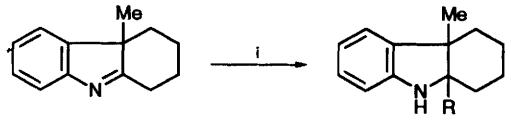
In this paper, we describe the reaction of the C=N bond of 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole **1** with an organomagnesium–Cu_2Cl_2 reagent, to give 4a,9a-disubstituted derivatives.

The structural diversity exhibited by the *cis*-fused hexahydrocarbazole system does not detract from the potency of these alkaloids, but instead leads to an impressive array of biological activity.[3]

Results and discussion

Preparation of the 4a-methylcarbazole **1** was performed either by treatment of the tetrahydrocarbazolylmagnesium iodide with methyl iodide in dry tetrahydrofuran (72%) or by the Fischer reaction from the phenylhydrazone of 2-methylcyclohexanone (70%).[4]

The reaction of the carbazole **1** with Grignard reagents in the presence of a catalytic amount of Cu_2Cl_2 has been performed in toluene (see Scheme 2 and Table 1).



1 **2**

a R = Me
b R = Bu
c R = H
d R = $CH_2CH{=}CH_2$
e R = CH_2Ph
f R = $CH{=}CH_2$
g R = Ph

Scheme 2 *Reagents and conditions:* i, RMgX–Cu_2Cl_2

Table 1 Reactivity of the carbazole **1** with Grignard reagents RMgX in presence of copper(I) chloride

RMgX R	RMgX:1	RMgX (mol dm^{-3})		Isolated compounds (%) 2	2c	1
Me	5:1	1.1	**a**	8	—	50
Me	20:1	3.0	**a**	37	—	12
Bu	20:1	5.4	**b**	18	11	13
Bu^s	20:1	5.4		0	49	16
Bu^t	20:1	5.4		0	46	15
$CH_2CH{=}CH_2$	5:1	1.0	**d**	50	—	15
$CH_2CH{=}CH_2$	20:1	3.0	**d**	92	—	—
CH_2Ph	5:1	1.0	**e**	27	—	66
CH_2Ph	20:1	3.0	**e**	69	—	—
$CH{=}CH_2$	20:1	3.0	**f**	23	15	10
Ph	20:1	3.0	**g**	53	—	10

[a] All the yields were calculated after column chromatography.

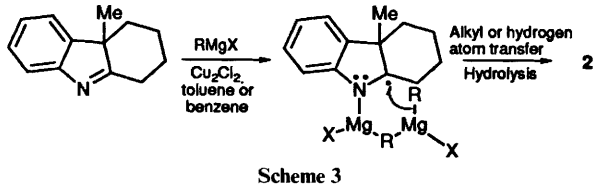
In contrast with the reaction of the spiro derivatives, the 4a-methyl derivative **1** reacted with the organometallic system to give variable yields of product, which seemed to depend upon the steric hindrance of the organic radical. Thus, reaction of compound **1** with various alkylmagnesium halides, in the presence of Cu_2Cl_2 was analysed.

Methylmagnesium iodide addition to the carbazole **1** gave the dimethyl derivative **2** in low to moderate yield with starting material as the only other isolated product.

For the butyl Grignard reagent, the 9a-butyl derivative **2b** was formed along with an appreciable yield of the reduced compound **2c**. The bulkier *sec*- and *tert*-butyl reagents gave only the compound **2c**.

The allyl and benzyl Grignard reagents were generally more reactive than the alkyl Grignards, especially when used in large excess, and afforded the 9a-allyl **2d** and the 9b-benzyl derivatives **2e** in good yield and without concomitant formation of the reduced compound **2c**. The vinyl and phenyl Grignard reagents both gave the alkylated products **2f** and **2g** in low and moderate yield, respectively; the vinyl reagent also gave rise to a small amount of the reduced compound **2c**.

The reaction presumably occurred through a free radical mechanism, utilizing the Cu_2Cl_2 as the initiator, to form the organomagnesium radical intermediate represented in Scheme 3



Scheme 3

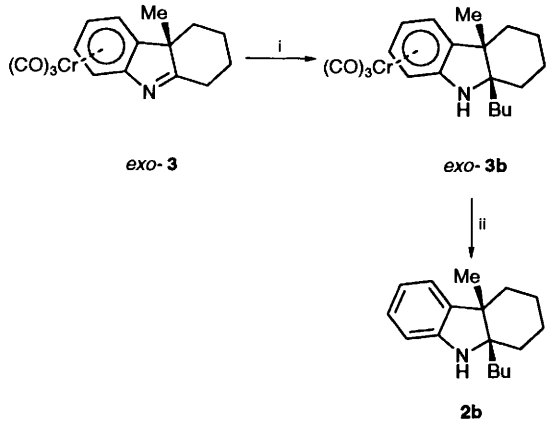
[EPR data: factor g = 2.0244, a_H = 0.325 mT (1:2:1) and a_N = 0.975 mT (1:1:1)].

The formation of the reduced compound **2c** could be explained by hydrogen atom abstraction either from the solvent [2] or from the Grignard reagent. To differentiate between these two processes, the addition of the vinyl Grignard was repeated in benzene with analogous results, whilst the addition with the *tert*-butyl Grignard in [$^2H_8$]toluene gave only the unlabelled product **2c**. These results suggest that the Grignard reagent is, in fact, the source of the hydrogen atom.

It would therefore appear that the excess of Grignard reagent is necessary in order to form the dimeric organometallic species, shown in Scheme 3, which can then serve either as the source of the hydrogen atom or the alkyl radical.

One important question concerned the stereochemistry of the product **2**; in this reaction, only the more stable *cis*-stereoisomer was ever isolated.

To improve the yield of the 9a-alkylation product, we prepared the tricarbonylchromium complex but, unfortunately, this decomposed in the presence of the organomagnesium–Cu_2Cl_2 reagent. However, evidence for the *cis*-fused ring junction in the 4a,9a derivatives was obtained by reaction of the complex **3** with butyllithium (Scheme 4).



Scheme 4 *Reagents and conditions:* i, BuLi, toluene, room temp.; ii, I_2–$Na_2S_2O_3$–H_2O

The complex **3** was obtained by treatment of the carbazole **1** with $Cr(CO)_6$ in THF–dioxane (3:10), under an argon atmosphere in a Strohmeier type system.[5] The complex **3** was isolated after silica gel column chromatography as orange crystals (38%). In this reaction was also found a yellow crystalline product that quickly decomposed. It was presumed that this was the *endo*-isomer.

The steric influence of the tricarbonylchromium moiety (crystallographic molecular models) dictates that the nucleophile must attack from the opposite face to this π-bonded group.[6] Hence, treatment of the complex with butyllithium gave only the *exo*-isomer **3b** (36%) that, upon decomplexation with I_2–$Na_2S_2O_3$–H_2O, afforded the *cis*-ring fused isomer **2b**, which was identical with the previously prepared sample.

Experimental

Mps were determined using a Reichert stage microscope and are uncorrected. IR spectra were recorded using a Perkin-Elmer 681 spectrophotometer. NMR spectra were recorded at 200 MHz using a Bruker WM-200-SY spectrometer, chemical shifts are given in δ, using TMS as internal reference. Mass spectra were recorded using a Hewlett-Packard SP85 spectrometer. Elemental analyses were performed with a LECO CHN-600.

Reaction of 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole 1 with an organomagnesium halide in the presence of copper(I) chloride

General procedure. To a solution of the alkylmagnesium halide (27 mmol), in diethyl ether, were added dry toluene (6 cm^3) and then the diethyl ether was removed by distillation. A solution of the carbazole **1** (1.35 mmol), in dry toluene (2 cm^3), followed by copper(I) chloride (1.35 mmol) were added and the mixture refluxed under argon for 20 h. After cooling, the mixture was hydrolysed with aqueous ammonium chloride and extracted with dichloromethane. The solvent was removed and the residual brown oil was purified by column chromatography using ethyl acetate–hexane as eluent.

Reaction with methylmagnesium iodide. 4a,9a-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **2a** was obtained as a yellow oil (101 mg, 37%), mp 222–225 °C (hydrochloride); δ_H 1.10 (3 H, s, Me-4a), 1.18 (3 H, s, Me-9a), 1.3–1.7 (7 H, m, $[CH_2]_n$), 1.85 (1 H, m, 1-H), 3.33 (1 H, s, NH), 6.62 (1 H, d, *J* 7.3, C-8), 6.76 (1 H, t, *J* 6.8, C-6) and 6.98 (2 H, m, C-5, 7); ν_{max} 3340 (NH) and 740 (ArH 1,2-disubstitution); *m/z* (70 eV) 201 (M^+, 30), 186 (100), 158 (19), 146 (49) and 144 (73) (Found: C, 83.4; H, 9.3; N, 7.1. $C_{19}H_{19}N$ requires C, 83.53; H, 9.51; N, 6.96%).

Reaction with butylmagnesium chloride. Two products were obtained: (4a*RS*,9a*RS*)-9a-butyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **2b** as a yellow oil (59 mg, 18%); mp 221–223 °C (hydrochloride); δ_H 0.86 (3 H, t, *J* 5.0, *Me*CH_2), 1.05 (3 H, s, Me-4a), 1.2–1.7 (13 H, m, $[CH_2]_n$), 1.85 (1 H, m, 1-H), 3.31 (s, NH), 6.52 (1 H, d, *J* 7.8, 8-H), 6.66 (1 H, t, *J* 7.2, C-6) and 6.95 (2 H, m, C-5 and C-7); ν_{max}(film) 3350 (NH) and 730 (ArH, 1,2-disubst.); *m/z* (70 eV) 243 (M^+, 10), 186 (100), 144 (28), 143 (10) and 130 (6) (Found: C, 83.6; H, 10.45; N, 5.8. $C_{17}H_{25}N$ requires C, 83.89; H, 10.35; N, 5.75%); and 4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **2c** as a yellow oil (27.5 mg, 11%); mp 115–197 °C (hydrochloride); δ_H 1.20 (3 H, s, Me-4a), 1.35 (4 H, m, $[CH_2]_n$), 1.55 (4 H, m, $[CH_2]_n$), 3.4 (1 H, t, *J* 4.0, 9a-H), 3.39 (NH, s), 6.61 (2 H, m, C-6 and C-8) and 6.98 (2 H, m, ArH); ν_{max} 3360 (NH) and 740 (ArH, 1,2-disubst.); *m/z* (70 eV) 187 (M^+, 70), 172 (69), 158 (12), 144 (100) and 130 (55) (Found: C, 83.1; H, 9.0; N, 7.5. $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48%).

Reaction with *sec*-butylmagnesium chloride. The carbazole **2c** (124 mg, 49%), was obtained, which was identical to a sample previously prepared.

Reaction of *tert*-butylmagnesium chloride. The carbazole **2c** was obtained (116 mg, 46%), which was identical to a previously prepared sample.

Reaction with allylmagnesium chloride. (*a*) Using the molar ratio of the carbazole **1**:allylmagnesium chloride as 1:20, the 9a-allyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **2d** (280 mg, 91%) was obtained as a green oil, mp 157–158 °C (hydrochloride). (*b*) With a molar ratio of 1:5 (allylmagnesium chloride, 27 mmol) in the presence of Cu_2Cl_2, after 6 h, the reaction afforded the carbazole **2d** (154 mg, 50%), as a yellow oil; δ_H 1.09 (3 H, s, Me-4a), 1.1–1.7 (7 H, m, $[CH_2]_n$), 1.9 (1 H, m, 1-H), 2.05 (2 H, m, CH_2-9a), 4.95 (1 H, m, CH=CH_2), 5.05 (1 H, m, CH=CH_2), 5.80 (1 H, m, C*H*=CH_2), 6.61 (1 H, d, *J* 8.4, ArH); 6.76 (1 H, t, *J* 7.6, ArH) and 7.01 (2 H, m, ArH); ν_{max}(KBr) 3360 (NH), 1640 (C=C), 910 (CH=CH_2) and 750 (ArH, 1,2-disubst.); *m/z* (70 eV) 228 (M^+, 1), 186 (100), 144 (19), 143 (9) and 130 (3) (Found: C, 84.3; H, 9.4; N, 6.3. $C_{16}H_{21}N$ requires C, 84.53; H, 9.31; N, 6.16%).

Reaction with benzylmagnesium chloride. (*a*) Using a molar ratio of the carbazole **1**: benzylmagnesium chloride as 1:20, 9a-benzyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **2e** (258 mg, 69%) was obtained as a white solid, mp 88–90 °C. (*b*) Using a molar ratio of the carbazole **1**: benzylmagnesium chloride as 1:5 (benzylmagnesium chloride, 6.75 mmol) in

toluene in the presence of Cu_2Cl_2, afforded the carbazole **2e** (101 mg, 27% yield) as a white solid; δ_H 1.28 (3 H, s, Me-4a), 1.3–1.6 (6 H, m, $[CH_2]_n$), 1.8 (2 H, m, CH_2), 2.73 (2 H, AB, *J* 12.8, CH_2Ph), 3.55 (1 H, s, NH), 6.63 (1 H, dd, *J* 7.2 and 1.1, 8-H), 6.75 (1 H, td, *J* 7.3 and 1.0, 6-H), 7.03 (1 H, d, *J* 7.2, 5-H) and 7.1–7.4 (6 H, m, 7-H and benzyl-Ar); ν_{max}(KBr) 3350 (NH), 750 (ArH 1,2-disubst.), 750 and 715 (ArH monosubst.); *m/z* (70 eV) 277 (M^+, 3), 186 (100), 144 (24), 130 (4) and 91 (11) (Found: C, 86.35; H, 8.45; N, 5.2. $C_{20}H_{23}N$ requires C, 86.59; H, 8.36; N, 5.05%).

Reaction with vinylmagnesium bromide. Two products were obtained; the 4a-carbazole **2c** (33 mg, 13%), which was identical to a previously prepared sample; and the 4a-methyl-9a-vinyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **2f** (66 mg, 23%), mp 172–174 °C (hydrochloride); δ_H 1.05 (3 H, s, Me-4a); 1.2–1.7 (6 H, m, $[CH_2]_n$), 1.95 (2 H, m, 1-H), 5.10 (1 H, dd, *J* 10.6 and 1.6, CH=CH_2), 5.35 (1 H, dd, *J* 16.3 and 1.6, CH=CH_2), 6.10 (1 H, dd, *J* 16.3 and 10.6, C*H*=CH_2), 6.75 (2 H, m, 6-H and 8-H) and 7.0 (2 H, m, 5-H and 7-H); ν_{max}(film) 3360 (NH), 1605 (Ar, C=C), 920 (C=C) and 750 (ArH 1,2-disubst.); *m/z* (70 eV), 213 (M^+, 5), 186 (100), 144 (18), 133 (13), 105 (20) and 91 (26) (Found: C, 84.3; H, 9.15; N, 6.5. $C_{15}H_{14}N$ requires C, 84.46; H, 8.98; N, 6.57).

Reaction with phenylmagnesium bromide. 4a-Methyl-9a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **29** (188 mg, 53%) was obtained as a yellow oil, mp 249–250 °C (hydrochloride); δ_H 0.74 (3 H, s, Me-4a), 1.4–1.9 (6 H, m, $[CH_2]_n$), 2.1 (2 H, m, CH_2), 3.9 (1 H, s, NH), 6.74 (1 H, d, *J* 7.4, 8-H), 6.77 (1 H, t, *J* 7.3, 6-H), 6.99 (1 H, d, *J* 6.8, 7-H), 7.08 (1 H, td, *J* 7.5 and 1.2, 5-H), 7.3 (2 H, m, 3′-H, 5′-H and 4′-H), 7.7 (2 H, m, 2′-H and 6′-H); ν_{max}(film) 3340 (NH), 1600 (Ar), 760, 705 and 755 (mono and disubst.); *m/z* (70 eV) 263 (M^+, 100), 248 (26), 220 (61), 207 (83), 206 (82), 186 (57), 144 (15), 130 (21) and 77 (16) (Found: C, 86.45; H, 8.15; N, 5.4. $C_{19}H_{21}N$ requires C, 86.64; H, 8.04; N, 5.32%).

Synthesis of η⁶-(4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole)-tricarbonylchromium 3

In a 250 ml flask equipped with a magnetic bar in a Strohmeier type system under an argon atmosphere and protected from the light, were placed the carbazole **1** (4 g, 22 mmol) in dry and deoxygenated THF (60 cm^3). Hexacarbonylchromium (4.76 g, 22 mmol) in dry and deoxygenated dioxane (200 cm^3) was then added. The temperature was maintained at 150 °C for 4 d then cooled and the solvent evaporated. A yellow oil was obtained and purified by column chromatography (dioxane–hexane, 1:6) to afford two products: the first one as a yellow solid that decomposed immediately, and the second was the *exo*-η⁶-(4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole)tricarbonylchromium **3** (2.71 g, 38%) as an orange solid, mp 115–120 °C; δ_H 1.22 (1 H, m, 4-H), 1.37 (2 H, s, Me), 1.52 (1 H, m, Me), 1.73 (3 H, m, 3-H and 4-H), 2.31 (2 H, m, 2-H), 2.57 (1 H, m, 1-H_{ax}), 2.72 (1 H, m 1-H_{eq}), 4.89 (1 H, m, 5-H); 5.52 (1 H, m, 6-H), 5.71 (1 H, m, 4-H) and 5.88 (1 H, m, 7-H); ν_{max}(KBr) 1940, 1850 (CO), 1590 (C=N), 665 and 625 (ArH); *m/z* (70 eV) 321 (M^-, 8), 265 (1), 237 (100), 220 (8), 195 (11), 184 (5), 80 (14) and 52 (94) (Found: C, 60.0; H, 4.4; N, 4.8. $C_{16}H_{15}CrNO_3$ requires C, 59.81; H, 4.71; N, 4.36%).

Reaction of the carbazoletricarbonylchromium 3 with butyllithium

To a solution of the chromium complex (300 mg, 0.93 mmol) in dry toluene (12 cm^3) under an argon atmosphere, was added a solution in hexane of butyllithium (1.23 cm^3, 4.65 mmol; 1.6 mol dm^{-3}). The reaction was maintained at 130 °C for 3 h, allowed to cool and then hydrolysed with THF–water (5 cm^3, 1:1), extracted with diethyl ether and then the brown oil obtained after evaporation was purified by column chromatography (diethyl ether–hexane, 1:1). Two products were obtained: the carbazole **2b** (40 mg, 18%) which was identical to a previously prepared sample and the *exo*-(4a*RS*,9a*RS*)-η⁶-(9a-butyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole)tricarbonylchromium **3b** as a yellow solid (127 mg, 36%), mp 146–148 °C; δ_H 0.96 (3 H, m, Me), 1.33 (3 H, s, Me-4a), 1.1–1.7 (8 H, m, CH_2), 1.88 (2 H, m, 1-H), 2.69 (2 H, m, CH_2), 3.49 (2 H, m, CH_2), 3.50 (1 H, m, NH), 4.68 (1 H, m, 5-H), 4.92 (1 H, m, 6-H) and 5.35 (2 H, m, 4-H and 7-H); *m/z* (70 eV) 379 (M^+, 7), 323 (4), 296 (18), 295 (64), 293 (27), 237 (9), 186 (45), 157 (6), 144 (49), 80 (26) and 52 (100) (Found: C, 63.6; H, 6.9; N, 3.75. $C_{20}H_{25}CrNO_3$ requires C, 63.31; H, 6.64; N, 3.69%).

Decomposition of the tricarbonylchromium complex

To a solution of the chromium complex **3b** (51 mg, 0.135 mmol), in THF (8 cm^3) and iodine (68.6 mg, 0.27 mmol) THF (3 cm^3), were added. After 1 h at room temperature, the residual iodine was removed using aqueous sodium thiosulfate (20%). The mixture was then extracted with diethyl ether to yield the carbazole **2b** (32 mg, 98%) as a brown oil, mp 221–223 °C (hydrochloride).

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