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DIELS-ALDER REACTIONS OF PYRANO[3,4-b]INDOL-3-ONES WITH SUBSTITUTED ALKENES : SYNTHESIS OF 1,2-DIHYDROCARBAZOLES - PART II

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Summary - The Diels-Alder reaction of pyrano[3,4-b]indol-3-ones 1 with trisubstituted dienophiles 2 yields stable 1,2-dihydrocarbazoles 4. Electronic and steric factors, together with a gradual change in mechanism from a concerted to a more stepwise reaction, are invoked to explain the regiochemical distribution of products.

INTRODUCTION

Although many successful approaches to the synthesis of carbazoles have been developed,[1] few methods for the preparation of 1,2-dihydrocarbazoles are available.[2] In a preceding paper[3] we described a versatile route to these compounds based on the Diels-Alder reactions of pyrano[3,4-b]indol-3-ones 1 with mono- and disubstituted alkenes 2 (R^2 and/or R'^2 = H; R^3 = COR, COOMe, CN, Ar). This process can be explained by a cycloaddition followed by CO_2-extrusion and a 1,5-sigmatropic hydrogen migration towards the C-1 terminus in an intermediate indole-2,3-chinodimethane 3. In the reported synthesis of 4, two basic requirements for the olefin were 1) the presence of an electron withdrawing group R^3 stabilising 4 against aromatization to carbazoles 5 and 2) an hydrogen atom located in geminal position to R^3, required for 1,5-hydrogen migration to the C-1 terminus. In this paper we report the reaction of 1 with trisubstituted enone compounds 2 (R^2 and/or R'^2 = COR).

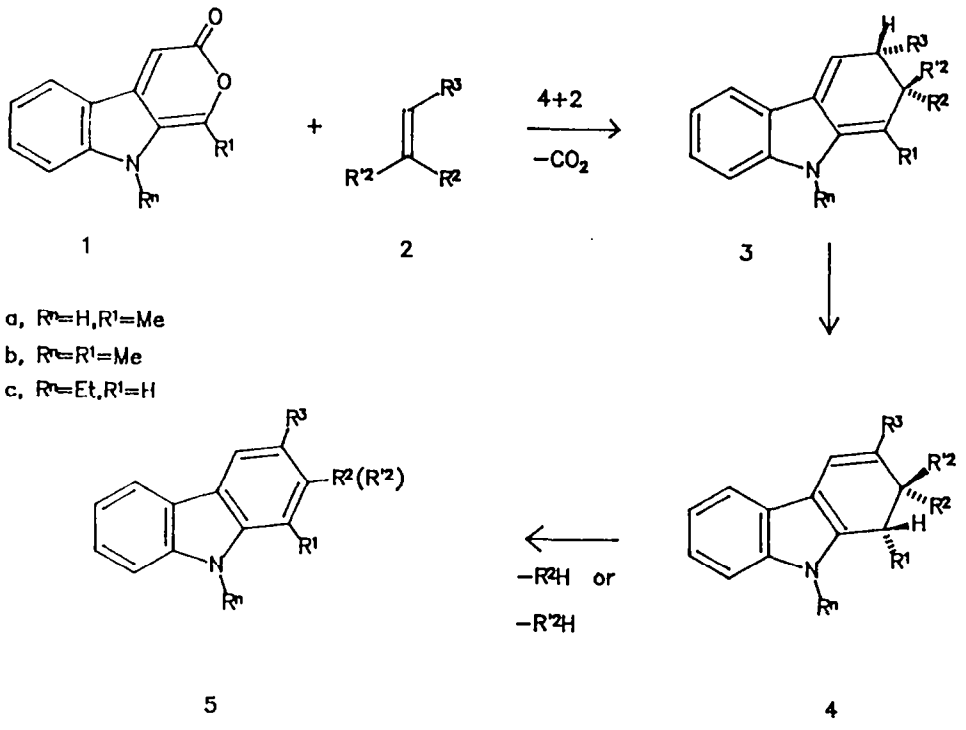
RESULTS AND DISCUSSION

For the monosubstituted alkenes 2 (R^2 = R'^2 = H) applied in our previous work,[3] the regiochemistry observed (4, R^3 = COR, CN etc) was that expected on the basis of HOMO-diene and LUMO-dienophile interactions characterized by larger coefficients for C-1 of the diene and the β-position of the enone system, respectively.[4] However, for disubstituted olefins (e.g. 2-cyclopentenone) the inverse regiochemical addition also occurred, directing the alkyl-chain substituent to the 3-position of 4 and giving rise, eventually, to carbazole 5 (R^2 = CO, R^3 = alkyl chain).

This regiochemical competition may be explained by a gradual change in mechanism from a concerted to a rather stepwise mode of addition. Concurrent with the growing steric interaction between the R^1-group of the diene (R^1 = H, Me, Et, Bn, Pr^i) and an increasingly substituted enone system, the more reactive β-carbon atom of the alkenone will attach first to the less substituted, and negatively charged C-4 position (q_1 = +0.06 ; q_4 = -0.12)[4] of the diene. In a subsequent step, linkage will occur between the sterically more congested centers, i.e. the mono- and especially (see below) the

disubstituted α-position of the enone system, and the R^1-substituted 1-position of the diene.

Scheme 1



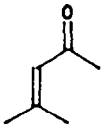
1 2 3

a, R^n=H, R^1=Me
b, R^n=R^1=Me
c, R^n=Et, R^1=H

5 4

The use of trisubstituted compounds 6-15 dealt with in the present work, and variation of the R^1-group in the diene (R^1 = H, Me) will serve to further clarify this proposal. Furthermore, the present approach to trisubstituted dihydrocarbazoles 3 (R^2, R'^2 and $R^3 \neq H$) may extend the scope of the synthesis to those members of the series which were found to be very prone to dehydrogenation, when starting from mono- or disubstituted olefins, i.e. R^1 or R^n = H or R^3 = electron donating group.

No reaction was observed between 1b and 6, 7 or 8. Apparently, disubstitution at the β-position completely blocks the reactivity of the alkenone.[5] Reaction of 1b with 9, 10 and 11 exclusively produced regioisomers 16, 17 and 18, with the original β-substituent of 9-11 located at the 3-position.



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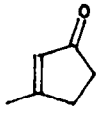

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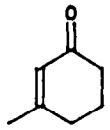

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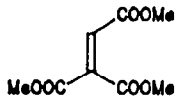

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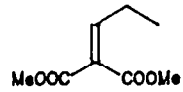

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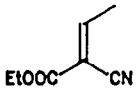

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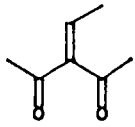

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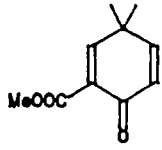

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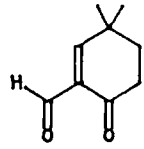

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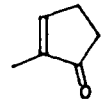

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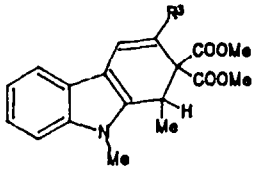
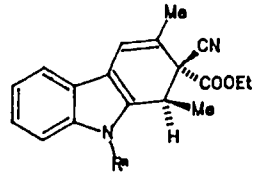


16, R^9=COOMe

17, R^9=Et



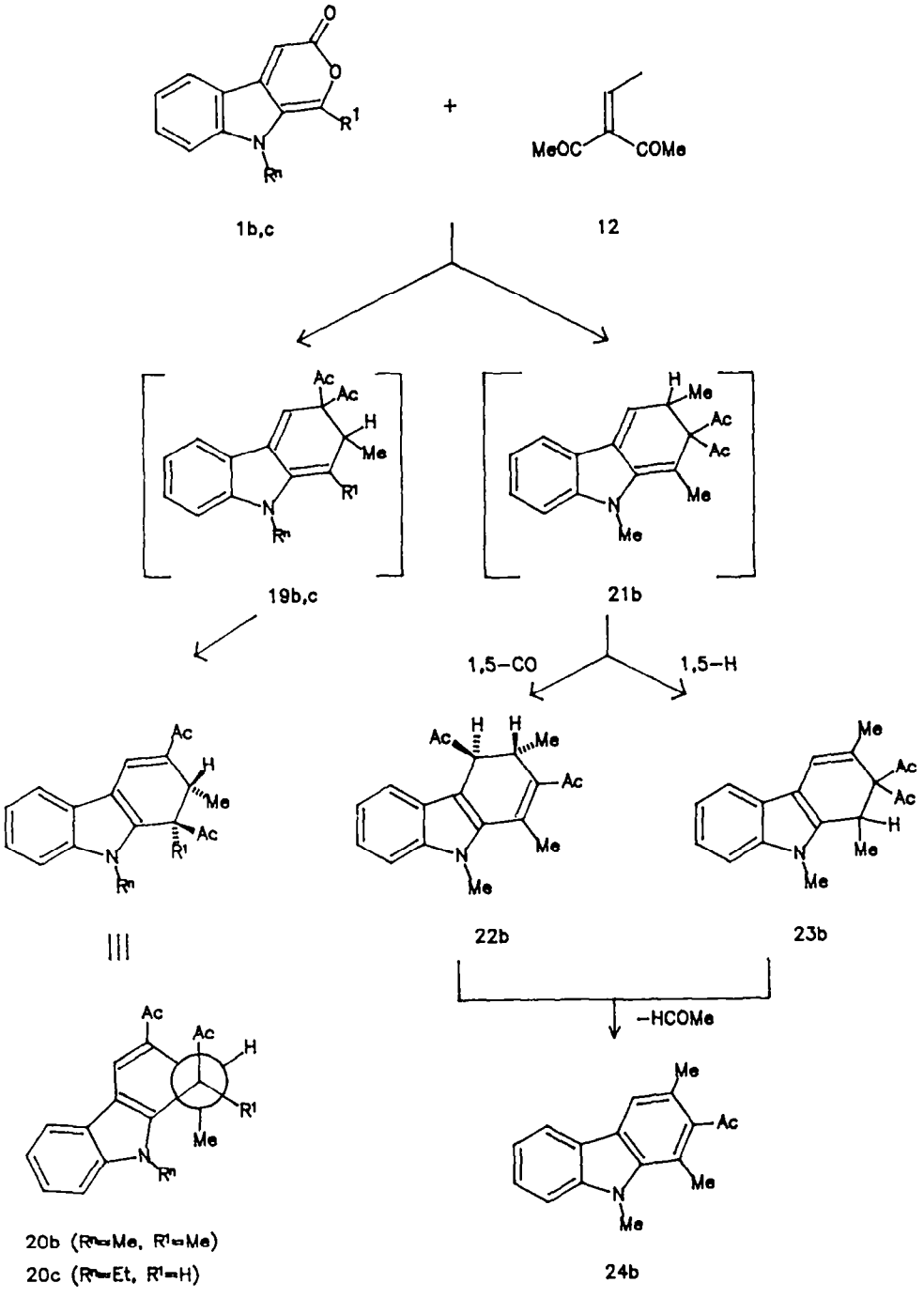
18a, R^9=H

18b, R^9=Me

Compounds 16-18 were isolated in high yield (92-97 %). Their regiochemistry was deduced from the presence of a quartet-doublet pattern in the ^{1}H-NMR spectrum, corresponding to the CH-CH_3 group, and a vinylic absorption for 4-H. The signal for this proton further showed an allylic coupling with the 3-alkyl substituent of 17 and 18. Only one diastereoisomer was detected for compounds 18a and 18b. Although the stereochemical disposition of the Me, CN and CO_2Et groups could not be determined from the ^{1}H-NMR spectra, structures 18a and 18b were inferred from the cis-relationship between Me and CN groups in 11. The validity of this supposition, however, requires syn-addition of 11 and 1 and, further, suprafacial 1,5-H-migration in the rearrangement 3 -> 4.

Reaction of 12 was performed with both 1b (R^n=R^1=Me) and 1c (R^n=Et, R^1=H). The results outlined in scheme 2 are most illustrative since regiochemical competition was observed only in the reaction of 1b. Addition of 12 on 1c exclusively yielded (67%) compound 20c, in which the 1-Ac and the 2-Me groups are trans-disposed and oriented in a pseudoaxial position ($^3J_{1H,2H}$ = 1.2 Hz, dihedral angle of ± 90°). The proton 4-H was observed as a low-field singlet at 7.47 ppm in C_6D_6 (7.81 ppm in $CDCl_3$). The absence of a long-range coupling H_2-H_4 confirmed the axial position of the 2-Me group.

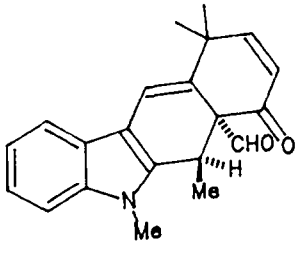
Scheme 2


1b,c
12
19b,c
21b
1,5-CO
1,5-H
22b
23b
-HCOMe
20b (R¹=Me, R¹=Me)
20c (R¹=Et, R¹=H)
24b

Compound **20c** may be formed as follows. Since C-1 of the diene is unsubstituted, addition of **12** takes the course expected on the basis of orbital-overlap considerations, producing intermediate **19c**. In the subsequent 1,5-migration of a 3-acetyl group, rearrangement of the group that is cis-disposed relative to the 2-H-atom will be favoured, yielding the trans-isomer **20c**.

In the analogous reaction of **12** with **1b**, three products **20b** (33 %), **22b** (10 %) and **23b** (53 %) were isolated (total yield 96 %). The ^{1}H-NMR-spectrum of **20b** was very similar to that of **20c**, suggesting the same trans-relationship for the 1-Ac and 2-Me groups as observed for **20c**. The other products **22b** and **23b** are derived from the inverse addition of the olefin on the diene followed by competitive 1,5-acetyl and 1,5-H-migration. Both products are unstable and lose the elements of acetaldehyde, yielding carbazole **24b**. This decomposition was inhibited by addition of hydroquinone, suggesting radical intermediates. The absence of a vinyl absorption in the 1H-NMR spectrum of **22b** indicated a 3,4-dihydrocarbazole structure. The proton 3-H showed a quartet coupling pattern with 3-Me and an additional small coupling with 4-H ($^3J_{H3,H4}$ = 1Hz), corresponding to a trans pseudoaxial orientation for the 3-Me and 4-Ac groups. The ^{1}H-NMR spectrum of **23b** showed the pattern already described before for 1,2-dihydrocarbazoles **16-18**.

The regiochemical competition observed for **1b** and the apparent lack of competition for **1c** illustrate the relative importance of steric and electronic factors mentioned before. No reaction was observed with the 2-ethoxycarbonyl substituted cyclohexadienone **13**. The more reactive 2-formyl compound **14** and (angle-strained) 2-methyl-2-cyclopentenone **15** exclusively yielded the regioisomers **25** and **26** with carbonyl substituents located at the 2-position (quartet-doublet for CH-CH_3, vinylic proton 4-H). Compound **25** readily loses CH_2O to yield the corresponding carbazole **27**. The stereochemical disposition of the methyl or formyl group could not be determined from the ^{1}H-NMR-spectrum but was assumed to be as shown in structures **25** and **26** on a kinetic basis : syn addition and suprafacial 1,5-H-migration. Syn addition of a penta- or hexa-cyclic alkenone is imposed, even for a fully stepwise mode of addition, by the steric constraints associated with the generation of a CO_2-bridged intermediate.



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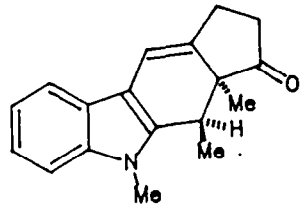

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CONCLUSION

The Diels-Alder reaction of pyrano[3,4-b]indol-3-ones **1** with trisubstituted, electron deficient olefins provides an useful extension to our work on mono- and disubstituted alkenes.[3] Previous requirements for obtaining stable 1,2-dihydrocarbazoles **4** no longer hold in the present work, i.e. crowdy substituents R^n and/or R^1 for the diene, electron withdrawing group R^3 flanked by a geminal H-atom for the alkene. Indeed, dehydrogenation of **4** is prevented by the threefold substitution (R^2, R'^2, R^3). By virtue of the inverse addition, electron donating groups are actually directed to the 3-position.

Perhaps the most convincing evidence for a change in mechanism comes from the series : methyl vinyl ketone, 2-cyclopentenone and 2-methyl-2-cyclpentenone giving rise to the normal, mixed and inverse mode of addition on **1b**, respectively. Linkage of the crowded tertiary carbon centers, in the latter case, strongly points to a stepwise reaction initiated by attachment of the oppositely charged secondary carbon centers.

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EXPERIMENTAL

IR spectra were recorded as thin films between NaCl plates or as solids in KBr-pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker WM 250 (operating at 250 MHz), on a Varian EM 390 (operating at 90 MHz) or on a Bruker UP 80 SY (operating at 80 MHz). Mass spectra were recorded on a Kratos MS 50 instrument operating at 70 eV and 150-250°C as required. Exact mass measurements were performed at a resolution 10,000. HPLC separations were performed on a Waters Associates apparatus equipped with a 6000 B pump and a RI-detector, model 403. Silicagel (Macherey Nagel Type 60) and chloroform stabilised with amylene were used for chromatographic separations. All solvents and reagents were dried and purified by standard procedures. All cycloadditions were performed under nitrogen atmosphere or in vacuo.

I. Preparation of pyrano[3,4-b]indol-3-ones 1 :

1-Methyl-, 1,9-dimethyl- and 9-ethylpyrano[3,4-b]indol-3-ones 1a-c

Compounds **1** a-b were prepared as previously described.[3,6] 9-Ethylpyrano[3,4-b]indol-3-one **1c** was generated in situ from 1-ethyl-2-formylindol-3-yl-acetic acid.[3]

II. Preparation of dienophiles

Trimethyl ethylenetricarboxylate[7] (**9**), dimethyl propylidenemalonate[8] (**10**), ethyl 2-cyano-2-butenoate[9] (**11**), 3-ethylidene-2,4-pentanedione (**12**)[10], 4,4-dimethyl-2-methoxycarbonyl-2,5-cyclohexadienone[11] (**13**), and 4,4-dimethyl-2-formyl-2,5-cyclohexadienone[12] (**14**) were prepared as described in the literature.

III. Reactions of 1 with trisubstituted olefins

General procedure : 2 mmol of 1 are heated (80-140°C) with 20 mmol dienophile in a sealed vacuum tube until complete consumption of 1. After cooling the excess of dienophile is evaporated and the residue chromatographed ($SiO_2/CHCl_3$; EtOAc).

Trimethyl 2,9-dihydro-1,9-dimethyl-1H-carbazole-2,2,3-tricarboxylate 16. 3h, 100°C, yield : 712 mg (96%); m.p. : 170°C (benzene). IR(KBr) : 1740 cm^{-1} ($\nu_{C=O}$). H-NMR δ ($CDCl_3$) : 1.16 (d, J=7.5 Hz, 3H), 3.60 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.16 (q, J=7.5 Hz, 1H), 7.2-7.4 (m, 3H), 7.60 (m, 1H), 8.05 (s, 1H),. m/z : 371 (M^+, 30%), 340 (4), 312 (10), 280 (100). Found M^+ : 371.1353, $C_{20}H_{21}NO_6$ requires M^+ : 371.1369.

Dimethyl 2,9-dihydro-1,9-dimethyl-3-ethyl-1H-carbazole-2,2-dicarboxylate 17. 5h, 80°C, yield : 628 mg (92%) as a colourless oil; IR (NaCl) : 1730 cm^{-1} ($\nu_{C=O}$); H-NMR δ ($CDCl_3$) : 1.10 (d, J=7.5 Hz, 3H), 1.23 (t, J=7.5 Hz, 3H), 2.45 (qxd, J=7.5 Hz and 1 Hz, 2H), 3.55 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 6.60 (q, J=1 Hz, 1H), 7.0-7.3 (m, 3H), 7.58 (m, 1H); m/z : 341 (M^+, 70%); 282 (100), 250 (63), 223 (47); Found M^+: 341.1623, $C_{20}H_{23}NO_4$ requires M^+ 341.1627.

Ethyl 2-cyano-2,9-dihydro-3,9-dimethyl-1H-carbazole-2-carboxylate 18a. 7h, 60°C, yield : 560 mg (95%); m.p. : 148°C (hex/$CHCl_3$). IR (KBr) : 3350 cm^{-1} (ν_{NH}), 2235 cm^{-1} (ν_{CN}), 1740 cm^{-1} ($\nu_{C=O}$). H-NMR δ ($CDCl_3$) : 1.28 (t, J=7.5 Hz, 3H), 1.42 (d, J=7 Hz, 3H), 2.10 (d, J=1 Hz, 3H), 3.88 (q, J=7 Hz, 1H), 4.35 (q, J=7.5 Hz, 2H), 6.78 (q, J=1 Hz, 1H), 7.20 (m, 3H), 7.62 (m, 1H), 8.30 (s, br, 1H). m/z : 294 (M^+, 24%), 221 (100), 206 (46). Found M^+ : 294.1361, $C_{18}H_{18}N_2O_2$ requires M^+ : 294.1368.

Ethyl 2-cyano-2,9-dihydro-1,3,9-trimethyl-1H-carbazole-2-carboxylate 18b. 7h, 60°C, yield : 600 mg (97%) as a colorless oil; IR (NaCl) : 2240 cm^{-1} (ν_{CN}); 1735 cm^{-1} ($\nu_{C=O}$); H-NMR δ ($CDCl_3$) : 1.20 (t, J=7.5 Hz, 3H), 1.38 (d, J=7 Hz, 3H), 2.26 (d, J=1 Hz, 3H), 3.73 (s, 3H), 3.82 (q, J=7 Hz, 1H), 4.15 (q, J=7.5 Hz, 2H), 6.75 (q, J=1 Hz, 1H), 7.1-7.3 (m, 3H), 7.60 (m, 1H); m/z : 308 (M^+ : 20%), 235 (100); 220 (54). Found M^+ 308.1539; $C_{19}H_{20}N_2O_2$ requires M^+ 308.1525.

1,3-Diacetyl-2,9-dihydro-9-ethyl-2-methyl-1H-carbazole 20c. 24h, 60°C, from 2 mmol 1-ethyl-2-formylindol-3-yl acetic acid and 1 ml Ac_2O with 20 mmol 12; yield : 396 mg (67%); m.p. 127°C (MeOH); IR (KBr) : 1705, 1665 cm^{-1} ($\nu_{C=O}$); H-NMR δ (C_6D_6) : 0.88 (t, J=7.5 Hz, 3H), 1.10 (d, J=7 Hz, 3H), 1.75 (s, 3H), 2.13 (s, 3H), 3.34 (d, J=1.1 Hz, 1H), 3.59 (q, J=7.5 Hz, 2H), 3.88 (qxd, J=7 Hz and 1.1 Hz, 1H), 7.00 (m, 1H), 7.20 (m, 2H), 7.17 (s, 1H), 7.62 (m, 1H); m/z : 295 (M^+, 23%); 252 (6); 210 (100); Found M^+ : 295.1563; $C_{19}H_{21}NO_2$ requires : 295.1572.

Reaction of 1b with 12 : this was carried out at 60°C and in the presence of 40 mg hydroquinone yielding compounds 20b, 22b and 23b with a total yield of 96.5% after 6h. When the reaction was performed at 100°C and during 120h, 20b and 24b were the sole products isolated in a total yield of 96%.

1,3-Diacetyl-2,9-dihydro-1,2,9-trimethyl-1H-carbazole 20b. Yield : 196 mg (33%); m.p. : 143°C (MeOH); IR (KBr) : 1710, 1640 cm^{-1} ($\nu_{C=O}$); H-NMR δ ($CDCl_3$) : 1.00 (d, J=7 Hz, 3H), 1.74 (s, 3H), 2.03 (s, 3H), 2.43 (s, 3H), 3.62 (q, J=7 Hz, 1H), 3.92 (s, 3H), 7.2-7.4 (m, 3H), 7.65 (s, 1H), 7.66 (m, 1H); m/z : 295 (M^+,14%), 252 (19), 236 (8), 210 (100); Found M^+ : 295.1570, $C_{19}H_{21}NO_2$ requires M^+ : 295.1572.

2,4-Diacetyl-4,9-dihydro-1,3,9-trimethyl-3H-carbazole 22b. Yield : 59 mg (10%) as a bright yellow oil; IR (NaCl) : 1705, 1645 cm^{-1} ($\nu_{C=O}$); H-NMR δ ($CDCl_3$) : 1.04 (d, J=7 Hz, 3H), 2.10 (s, 3H), 2.29 (s, 3H), 2.52 (s, 3H), 3.55 (qxd, J=7 and 1 Hz, 1H), 3.62 (q, J=1 Hz, 1H), 3.92 (s, 3H), 7.2-7.4 (m, 3H), 7.60 (s, 1H), 7.66 (m, 1H); m/z : 295 (M^+, 15%), 252 (17), 236 (6), 210 (100); Found M^+ : 295.1561, $C_{19}H_{21}NO_2$ requires M^+ : 295.1572.

2,2-Diacetyl-2,9-dihydro-1,3,9-trimethyl-1H-carbazole 23b. Yield : 316 mg (53.5%) as a colourless oil; IR (NaCl) : 1690, 1712 cm^{-1} ($\nu_{C=O}$) : H-NMR δ ($CDCl_3$) : 1.00 (d, J=7 Hz, 3H), 2.13 (d, J=1 Hz, 3H), 2.22 (s, 6H), 3.77 (s, 3H), 3.85 (q, J=7 Hz, 1H), 6.72 (q, J=1 Hz, 1H), 7.1-7.3 (m, 3H), 7.50 (m, 1H); m/z : 295 (M^+, 12%), 252 (21), 236 (4), 210 (100); Found M^+ : 295.1555, $C_{13}H_{21}NO_2$ requires M^+ : 295.1572.

2-Acetyl-1,3,9-trimethylcarbazole 24b. Yield : 316 mg (63%) as a colourless oil; IR (NaCl) : 1695 cm^{-1} ($\nu_{C=O}$); H-NMR δ ($CDCl_3$) : 2.42 (d, J=1 Hz, 3H), 2.58 (s, 3H), 2.72 (s, 3H), 4.08 (s, 3H), 7.2-7.4 (m, 3H), 7.75 (q, J=1 Hz, 1H), 8.00 (m, 1H); m/z : 252 (M^+, 80%) : 236 (100), 208 (53); Found M^+ : 251.1335, $C_{17}H_{17}NO$ requires 251.1310.

6a-Formyl-6,6a,7,10-tetrahydro-5,6,10,10-tetramethylbenzo[b]carbazol-7-one 25. 10h, 80°C, yield : 640 mg. Compound **25** aromatizes readily to the corresponding carbazole **27**. ^1H NMR δ ($CDCl_3$) : 1.40 (s, 3H), 1.48 (s, 3H), 1.70 (d, J=7.5 Hz, 3H), 3.33 (q, J=7.5 Hz, 1H), 3.83 (s, 3H), 6.17 (d, J=10.5 Hz, 1H), 6.56 (d, J=10.5 Hz, 1H), 6.88 (s, 1H), 7.2-7.4 (m, 3H), 8.10 (m, 1H), 9.66 (s, 1H).

2,3,3a,4-Tetrahydro-3a,4,5-trimethyl-1H-cyclopenta[b]carbazol-1-one 26. 24h, 100°C, yield : 360 mg (68%); m.p. : 152°C (MeOH); IR (KBr) : 1740 cm^{-1} ($\nu_{C=O}$); H-NMR δ ($CDCl_3$) : 0.97 (d, J=7 Hz, 3H), 1.18 (s, 3H), 2.5-2.8 (m, 4H), 2.10 (q, J=7 Hz, 1H), 3.70 (s, 3H), 6.62 (t, J=1 Hz, 1H), 7.1-7.3 (m, 3H), 7.60 (m, 1H); m/z : 265 (M^+, 100), 250 (34), 194 (29); Found M^+ : 265.1466, $C_{18}H_{19}NO$ requires M^+ : 265.1467.

7,10-Dihydro-5,6,10,10-tetramethylbenzo[b]carbazol-7-one 27. Yield : 416 mg (72%), m.p. : 141°C (hexane, benzene); IR (KBr) : 1660 cm^{-1} ($\nu_{C=O}$); H NMR δ ($CDCl_3$) : 1.58 (s, 6H), 3.20 (s, 3H), 4.12 (s, 3H), 6.35 (d, J=12 Hz, 1H), 6.83 (d, J=12 Hz, 1H), 7.2-7.4 (m, 3H), 8.07 (s, 1H), 8.10 (m, 1H). m/z : 289 (M^+, 56%), 274 (100). Found M^+ : 289.1464, $C_{20}H_{19}NO$ requires : 289.1464.

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