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STUDIES ON THE REGIOSELECTIVITY OF INTERMOLECULAR DIELS-ALDER CYCLOADDITIONS OF 1-METHYLPYRANO[3,4-b]INDOL-3-ONE AND THE N-ACETYLATED DERIVATIVE

Helena Nandin de Carvalho*, ¥, Gary I. Dmitrienko, Kent E. Nielson

Guelph-Waterloo Centre for Graduate Work in Chemistry, Waterloo Campus, University of Waterloo, N2L 3G1, Ontario, Canada

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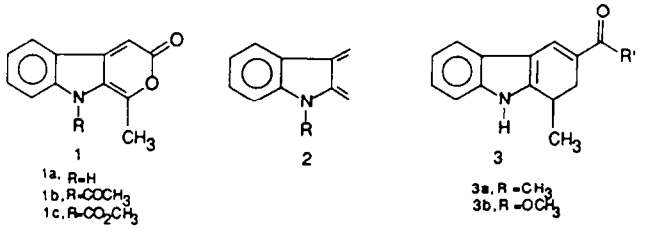
Abstract: Diels-Alder reactions of the 1-methylpyrano[3,4-b]indol-3-one **1a** with less than two equivalents of methyl acrylate and methyl vinyl ketone occur with complete regioselectivity to yield the corresponding 3-substituted 1-methyl-1,2-dihydrocarbazole derivatives **3**. Cycloadditions of the N-acetyl-1-methylpyrano[3,4-b]indol-3-one **1b** with the same dienophiles proceed at a much slower rate to yield adducts incorporating two molecules of the dienophile. In this case the regioselectivity appears to have been reversed in both steps of the Diels-Alder reaction since the bis-adducts obtained as major products have the substituents on the C_2 and $C_{2'}$ carbon. The reaction of **1a** with the symmetrical dienophile dimethylfumarate produces a mixture of the *cis* and *trans* 1-methyl-9H-1,2-dihydrocarbazole-2,3-dicarboxylic acid dimethyl esters **16** and **17** in the ratio of 1 : 3.7 respectively.

Introduction



Although Diels-Alder reactions of 1-methylpyrano[3,4-b]indol-3-one **1a**, a stable analog of indole-2,3-quinodimethanes **2**, with symmetrical dienophiles have been studied in detail[1, 2], it was not until 1985 that reactions of **1a** with unsymmetrical dienophiles were first reported thus uncovering the interesting properties of this diene. In connection with our investigations regarding the intermolecular cycloadditions of **1a** and **2** we disclosed at that time[3] that **1a** added to the unsymmetrical dienophile methyl vinyl ketone to give the corresponding 3-substituted 1,2-dihydrocarbazole **3a** in a complete regioselective reaction. Subsequently, other reports have illustrated Diels-Alder reactions of pyrones of the type **1a** with unsymmetrical dienophiles which resulted in syntheses of substituted carbazoles. However, except for one report[4], these cycloadditions were performed with acetylenic dienophiles and almost all of the

* To whom the correspondence should be addressed.

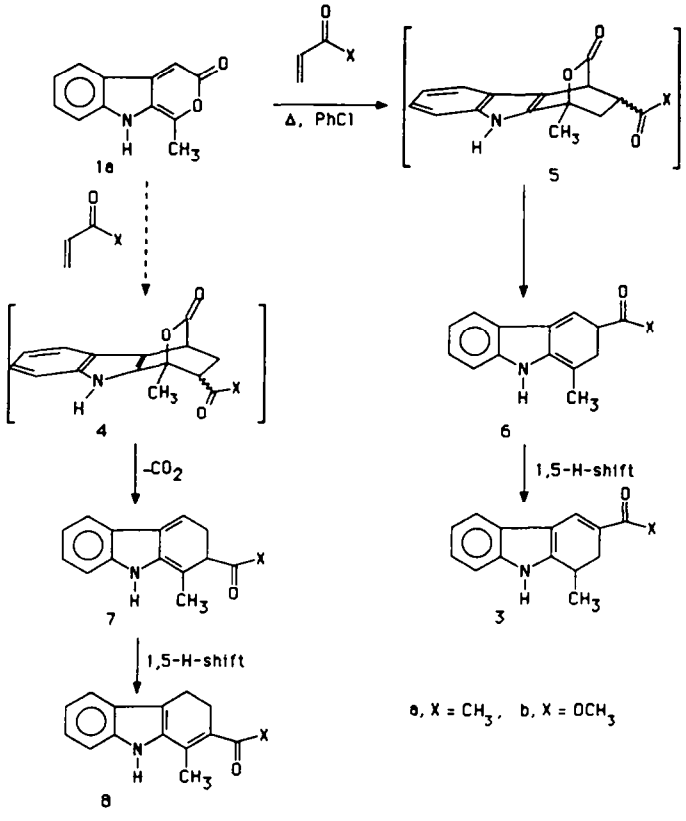
¥ Present address: University of McGill, Chemistry Department,Montreal,PQ. H3A 2K6, Canada

few reactions which were found to occur with complete regioselectivity gave the sole isomer in poor yield [5,6].

In this paper we describe investigations carried out with **1a** and the activated dienophiles, methyl vinyl ketone, methyl acrylate and dimethylfumarate which illustrate the scope of these Diels-Alder reactions as a method of preparation of selective substituted 1,2-dihydrocarbazoles. These can be further oxidized into the corresponding carbazoles. It is also shown in investigations conducted with the same unsymmetrical dienophiles, that N-acetylation of **1a** drastically reduces reactivity and reverses the regioselectivity of this diene system leading to the formation of bis-

Discussion and results

Scheme 1

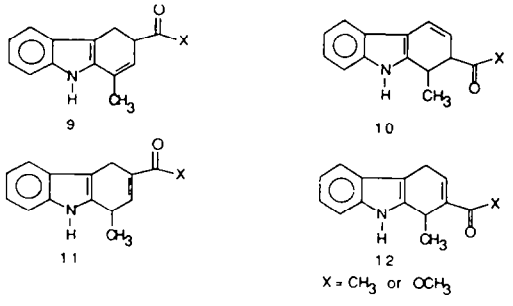


adducts. The stereochemistry of these adducts is also elucidated.

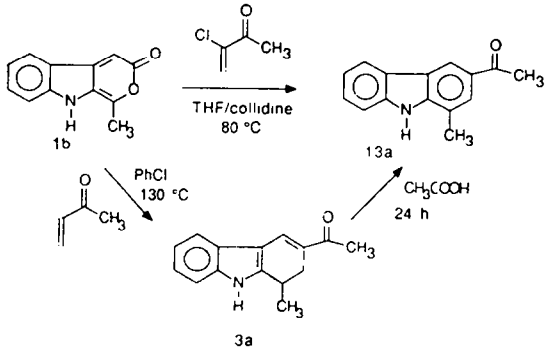
Reactions of **1a**, prepared as previously described by Plieninger [1], occurred in a 40-80% excess of the dienophile (methyl vinyl ketone and methyl acrylate) in presence of two crystals of hydroquinone at 130-150° C in DMF or, more conveniently, in chlorobenzene. The reaction with methyl vinyl ketone was over after 1-1.5 hour, but longer periods (2-2.5 hours) seemed to be necessary for a complete reaction with

methyl acrylate (scheme 1). These cycloadditions could, in principle, afford the two initial regioisomeric adducts **4** and **5** which would be expected to decarboxylate to give the indole-2,3-quinodimethane analogs **7** and **6** respectively. In practice, the crude product obtained from these reactions showed, within the limits of ^1H nmr 250 MHz detection, exclusively one adduct .

The ^1H and ^{13}C nmr spectra of these adducts were not compatible with the structures of **6** or **7** but agreed with those expected for the 1,2-dihydrocarbazoles **3**, these resulting from **6**, probably formed first, but likely to undergo a rapid 1,5-elimination-addition of a proton to give the fully conjugated isomer **3**. The presence of the 2,3-dihydrocarbazole **8** arising from **7** and the other isomeric possibilities which included the dihydrocarbazoles **9**, **10**, **11**, and **12** could also be discounted on the basis of the ^1H and ^{13}C nmr data. The 1,2-dihydrocarbazoles **3a** and **3b** could be recovered by chromatographic purification of the crude product (48% for **3a** and 23%, not optimized for **3b**). This identification was further confirmed by the conversion of **3a** and **3b** into the corresponding carbazoles **13a** and **13b** the first of which was already reported by Narisimhan and Gokhale[4] who obtained the 3-acetyl substituted aromatized carbazole directly by heating **1a** with 3-chlorobut-3-ene-2-one in THF in the presence of collidine at 80°C. We found that recrystallized **3a** and **3b** could be converted into **13a** and **13b** by treatment with acetic acid for 24 hours in an open atmosphere.



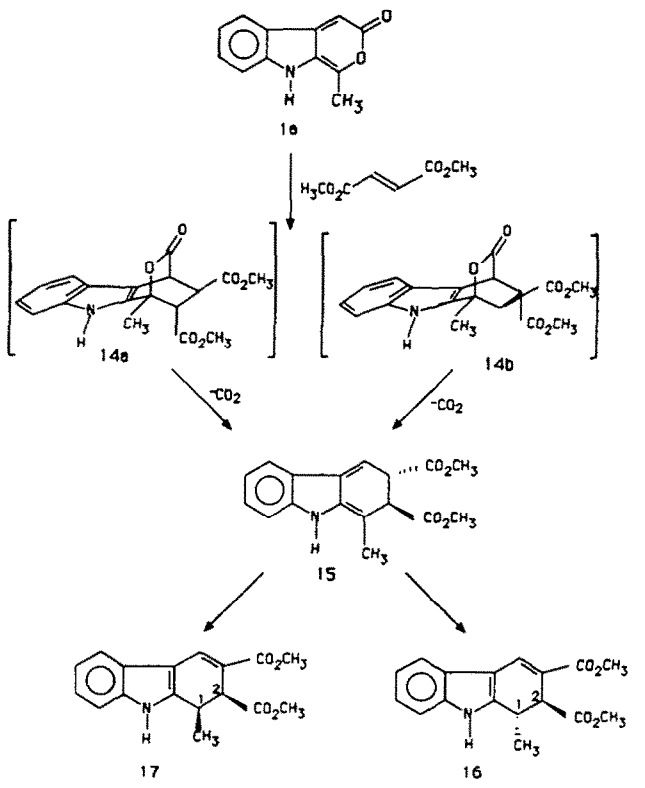
Scheme 2



The 1-methylpyrano[3,4-b]indole-3-one **1a** was also heated in chlorobenzene at 130° C for 3 hours with dimethylfumarate (only in 30% excess to avoid the possibility of bis-addition). Since the dienophile was symmetrical, this reaction would generate, in

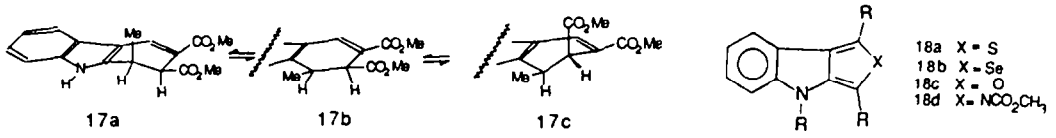
principle, two stereoisomers. Following the mechanistic considerations discussed above, the two possible racemic adducts **14a** and **14b** (scheme 3) should be expected to decarboxylate to give the *racemic* indole-2,3-quinodimethane analog **15**, which could in turn undergo a 1,5-proton elimination-addition step to yield a mixture of the *trans* **16** and the *cis* **17** 1-methyl-2,3-carbomethoxy-1,2-dihydrocarbazoles.

Scheme 3



This reaction afforded in 84% yield a crude product which upon ^1H nmr analysis revealed the presence of two doublets at 1.25 ppm and 1.54 ppm. The ratio of these signals, assigned to the C_1 methyl groups of **17** and **16**, was 3.7 : 1. The stereochemistry of the two adducts, recovered in 34% and 10% yield after two chromatographic separations, was established on the basis of the coupling constants found between H_1, and H_2, and the Karplus relationship [7]. A J value of 2.3 Hz was measured for the maior isomer, directly from the H_1 and H_2 signals which were resolved in a 400 MHz spectrum. This coupling constant, too small for an H_{axial}-H_{axial} coupling expected for the *trans* configuration **16** in which the two bulky groups occupy the more stable pseudo equatorial positions was, nevertheless, compatible with both conformations **17a** or **17c** of the *cis* isomer in which the vicinal protons H_1 and H_2 have a pseudo axial-equatorial relationship. In these puckered conformations the steric interactions between the methyl and adjacent carbomethoxy group are considerably reduced ,as compared to the planar conformation **17b.**

A larger coupling constant of 10 Hz was on the other hand measured from the H_1



signal of the 80 MHz spectrum of the minor isomer, as expected from a vicinal axial coupling between H_1 and H_2 in the *trans* configuration **16**.

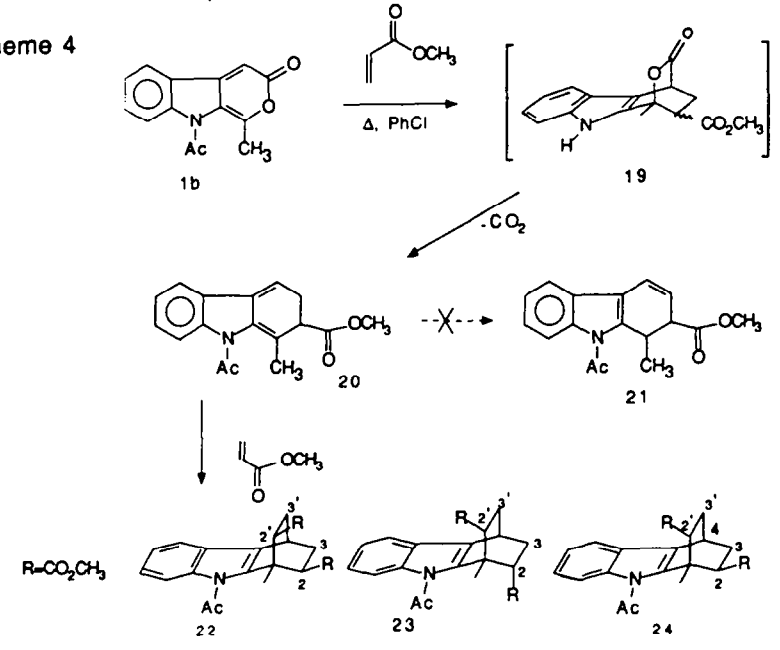
The fact that unequal amounts of the two stereoisomers, *cis* and *trans* are formed in this reaction can be interpreted as the result of a face selectivity in the proton addition step of the postulated 1,5-elimination-addition rearrangement which converts **15** into **16** and **17**. As the predominance of the *cis* isomer may suggest, this would preferentially occur on the face opposite to that bearing the C_2 carbomethoxy group.

To conclude the studies on the regioselectivity of this diene system it was decided to investigate the reactivity of the hitherto unreported N-acetyl-1-methylpyrano[3,4-b]indol-3-one **1b** prepared by treatment of **1a** with NaH/DMF followed by addition of acetic anhydride and recovered in 35% yield after chromatographic purification.

Although cycloadditions of symmetrical dienophiles with N-protected stable analogs of indole-2,3-quinodimethanes, such as the thieno (**18a**), the selenolo (**18b**), the furano (**18c**) and the pyrrolo[3,4-b]indoles (**18d**) have been reported [8,9], Diels-Alder reactions of these N-protected dienes with unsymmetrical dienophiles have not been examined yet. In fact, except for the recently described Diels-Alder reaction of the N-ethoxycarbonyl-1-methylpyrano[3,4-b]indol-3-one **1c** with ethyl propiolate[6] there are no other examples of cyclo-additions involving these type of dienes and unsymmetrical dienophiles.

Under conditions similar to those used for the parent compound **1a**, i.e. less than a two fold excess of dienophile, the N-acetylated pyrone **1b** was found to be remarkably

Scheme 4



less reactive than the parent compound **1a**. Mainly starting material was obtained in a 8 hour reaction of **1b** with 1.3 equivalents of methyl acrylate. Thus, it was necessary to heat **1b** in chlorobenzene for 10 hours with the dienophile (methyl acrylate,1.3 equivalents plus 0.5 equivalents added after 4 hours) to achieve 65% conversion of the starting material. The two products formed in approximately 1.4 : 1 ratio, as estimated by ^{1}H nmr, were not the N-acetylated analogs of **3** or its regioisomer **8**, but the bicyclic compounds derived from further Diels-Alder reaction of a postulated N-acetylated intermediate similar to **6** and **7** (scheme 4).

On the other hand, analysis of a mixture from a similar reaction (using methyl vinyl ketone, 1.6 equivalents), but interrupted after 2 hours, showed mainly starting material and also bis-adducts. Bicyclic compounds formed from **1a** were previously reported by Plieninger[1] who used a two fold excess of the symmetrical dienophiles N-phenylmaleimide and maleic anhydride. It was interesting to observe that the formation of monoadducts is not favoured in the reaction with the N-acetylated derivative despite the use of less than two fold excess of the dienophile . This seems to imply that the postulated intermediate **20**, derived from the unstable adduct **19** has, in comparison to **1a**, a higher reactivity towards further cycloaddition. On the other hand, the transformation of **20** into the fully conjugated 1,2-dihydrocarbazoles **21**, similar to **5**, appears to be significantly slowed or even blocked by the introduction of the acetyl substituent, thus suggesting in the case of **1a** the involvement of the lone pair of the indolic nitrogen on the 1,5-elimination-addition step of a proton .

The bis-adducts formed in the methyl acrylate reaction were separated by thin layer chromatography and identified by ^{1}H nmr analysis supported by decoupling experiments at 400 MHz. For both isomers, the C_4H was found to be equally coupled to 4 protons (J = 2.9 Hz) thus limiting the ten possible bis-adducts structures to **22**, **23** or **24**.

Table 1: Chemical Shifts and Coupling Constants For the Isolated Bis Adducts[a]

adduct	2'exo	2 exo	2'endo	2endo	3'endo	3endo	3'exo	3exo	4--
23 (δ)	2.68				1 55-1.62		2.73		3 60
24 "	3.42			2.64	1.47-1 62		2 31	1.97	3 60

23 (J)	2'exo,3'exo	2'exo,3'endo	2exo,3endo	2 exo,3exo	3'endo,3'exo	3exo,3endo
	11 6	4 8	4 8	11.6	12 4	12 4
24 (")	2'exo,3'exo	2'exo,3'endo	3'endo,3'exo	3exo,3endo	2 endo,3endo	2 endo,3exo
	10	4 8	13 0	12 6	11 7	5 6

[a] The assignment of the C_3 and $C_{3'}$ endo and C_3 and $C_{3'}$ exo hydrogens was made on the assumption that the bicyclic portion is seen at room temperature and in the average time scale of the nmr as a rigid structure in which is observed a dihedral angle of 0° between both the hydrogens in the 2 and 3 endo positions and the hydrogens in the 2' and 3' exo positions .

The chemical shift equivalence of the two carbomethoxy groups, of the two hydrogens at the 2, 2' positions and of the four hydrogens at the 3,3' positions, observed for the major component (table 1) indicate that this adduct must correspond to **23** or **22**, most likely **23** since the higher steric interactions between the nearby carbomethoxy groups make the formation of **22** less favoured. No chemical shift equivalence was found in the minor adduct which was then identified as **24**.

Only traces of the adducts with the carbomethoxy group on the C_2 and $C_{3'}$ or on the $C_{2'}$ and C_3 carbons could be found in the spectra of either **23** or **24.** The fact that the two major isolated bis-adducts have the carbomethoxy substituents on the C_2 and the $C_{2'}$ carbons demonstrates that this reaction is occurring, in both cycloaddition steps, with a very high degree of regioselectivety. Most interestingly the orientation of the dienophile addition is the reverse of that obtained with the unprotected indole **1a.**

Although less drastic, this same reverse effect was also recently acknowledged[6] in the reaction of N-ethoxycarbonyl-1-methylpyrano[3,4-b]indol-3-one **1c** with ethyl propiolate. In this case the two regioisomeric aromatized carbazoles were formed in the ratio of 1 : 1.4, the major adduct being the carbazole with the substituent on the 2 position. The drastic reverse effect observed in our case, is possibly related to the better electron-withdrawing properties of the N-acetyl group and the different reactivity of the dienophiles used. An adequate interpretation of the opposite directing properties observed for both diene systems **1a** and **1b** can likely be provided by a molecular orbital model. If generalizations applied to monosubstituted dienes and dienophiles to establish the preferred regioisomer[10] can be extended to multisubstituted dienes such as **1a** and **1b**, the effect of protection of the indolic nitrogen will have to be related to the energy splitting of the HOMO and LUMO of the diene and changes in the magnitudes of the coefficients of the terminal frontier orbitals at C_1 and C_4. These coefficients may have been reversed by the introduction of the N-acetyl substituent as a protecting group.

Experimental

General Procedures: Melting points were determined in a Büchi model SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded as solutions on a Beckman Acculab 10 or a Perkin-Elmer 983 infrared spectrophotometer. ^1H nmr spectra were determined on either a Bruker WP-80, Bruker AM 250 or Bruker WH 400 nuclear magnetic spectrophotometer using chloroform-d as a solvent containing tetramethylsilane as the internal standard. Mass spectra were recorded on a VG-7070 mass spectrometer. ^{13}C nmr assignments are based on information obtained in the literature [11]. Reactions were monitored by thin layer chromatography which was performed on aluminium-backed sheets precoated with silica gel (Merck , 60, F_{254},); preparative thin layer chromatography was carried out on glass plates precoated with silica gel (GF, Analtech Uniplate) to a thickness of 500 or 1000 microns. Silica gel (0.063-0.20 mm 70-230 mesh ASTM, E. Merck) column chromatography was used and medium pressure (nitrogen carrier gas) applied to columns to improve resolution.

Preparation of 3-acetyl-1-methyl-9H-1,2-dihydrocarbazole 3a

To a heated solution (40-60 $^\circ$ C) of the recrystallized pyrone **1a** (0.130 g; 0.65 mmoles) in DMF (6 ml, distiled over calcium hydride) was added hydroquinone (two crystals) and methyl vinyl ketone (0.068 g; 1.5 eq.). This solution was heated at 140-150° C for 1.5 hours. The excess of dienophile was evaporated in *vacuum* and the mixture partitioned between water and ether. The organic phase was washed with water and saturated solution of sodium chloride. Drying over anhydrous sodium sulfate and evaporation of the solvent in *vacuum* yielded the indole **3a** as yellow flakes (0.140 g ; 0.6 mmoles, 95% yield.),(also as an oil if

unrecrystallized starting material or a larger excess of dienophile is used) . The compound was purified by column chromatography on silica gel, eluted with hexane-ether (40 : 60, 100 ml), hexane-ether (25 : 75, 75 ml), hexane-ether (10 : 90, 200 ml) and ether (100 ml) to give a yellow solid **3a** in 48.2% yield). This was further recrystallized from ethyl acetate-hexane to give an analytically pure sample m.p. 176-178° C,(found: C 79.7; H 6.9; N 6.3%; M^+ 225, $C_{15}H_{15}NO$ calculated: C, 79.3, H 6.7; N 6.2%;); i.r. ($CHCl_3$) 3460 cm^{-1}(free N-H), 3200-3350 cm^{-1} (br, N-H, H bonding), 1636 (α, β- unsaturated ketone C=O), 1605 (α, β-unsaturated ketone, C=C). δ_H (250 MHz, $CDCl_3$), 1.35 (d, J =6.8 Hz, 3H, C_1CH_3), 2.46 (s, 3H, $COCH_3$), 2.65 (ddd, $J\,H_{2\beta},H_4$ =1.5 Hz, $J\,H_{2\beta},H_1$= 11.1 Hz, J gem= 16.4 Hz, 1H, C_2H_β), 3.02 (dd, $J\,H_{2\alpha},H_1$ =7.7 Hz, J gem=16.4 Hz, 1H, C_2H_α), 3.12-3.23 (m,1H, C_1H) 7.17-7.25 (m, 2H, C_6 and C_7H), 7.35-7.38 (m, 1H, C_5 or C_8H), 7.64-7.67 (m,1, C_5 or C_8H), 7.78 (br, s,1, C_4H) 8.54 (br s, N-H); δ_C ($CDCl_3$, J modulated spin echo)18.42 (C_{12},-$C_1\underline{C}H_3$), 25.04 (C_{11} $CO\underline{C}H_3$), 28.40 (C_1) 30.49 (C_2) 109.95 (C_{4a}), 111.66 117.80 121.30, 122.30 (C_5, C_6, C_7, C_8), 125.69, 128.69. 132.82 136.83, 145.71 (C_3, C_4,C_{5a} , C_{8a}, C_{9a}), 197.89 (C_{10}, Ketone carbonyl) .

Preparation of 1-methyl-9H-1,2-dihydrocarbazol-3-carboxylic acid methyl ester 3b

A mixture of the pyrone **1a** (0.200 g; 1 mmol) in DMF (8 ml), methyl acrylate (0.1 ml; 1.1 eq.) and hydroquinone (2 crystals) was heated at 110° C for 35 minutes. The reaction mixture was partitioned between ether and water. The organic phase was washed with water, saturated sodium chloride and dried over anhydrous sodium sulfate. Evaporation of the solvent in *vacuum* yielded the crude product as a viscous oil (0.126 g) which was purified by thin layer chromatography on silica gel with elution with hexane-ether (75% ether) to give the unreacted pyrone (0.036 g) and 1-methyl-3-carbomethoxy-1,2-dihydrocarbazole **3b** (0.055 g, 0.22 mmoles, 23% yield); No starting material was found by prolonging the reflux time to 2h 30m and adding a total of 1.7 equivalents of the dienophile (1.3 equivalents plus 0.4 equivalents in the last 30 minutes). M.p.= 181-183 ° C, i.r. ($CHCl_3$) 3462 cm^{-1}(free N-H), 3475-3450 cm^{-1}(H-bonding, N-H), 1687 (carbonyl) 1608 (α, β-unsaturated ester C=C); δ_H($CDCl_3$, 250 MHz) 1.34 (d,J =6.8 Hz, 3H, C_1CH_3) 2.54 (ddd, 1H,$J\,H_{2\beta},H_4$=0.9 Hz, $J\,H_{2\beta},H_1$=11.1 Hz, J gem=16.5 Hz, C_2H), 2.96 (dd, J_{gem}=16.5 Hz, J $H_{2\alpha},H_1$=7.8 Hz) 3.11-3.24 (m, 1H, C_1H), 3.82 (s, 3H, CO_2CH_3), 7.15-7.20 (m, 2H, C_6,7 H), 7.30-7.35 (m,1H, C_5H), 7.60-7.64 (m,1H, C_8H) 7.90 (br s,1H, C_4H), 8.44 (br s, 1H, N-H); δ_C($CDCl_3$, 250 MHz), 18.43 (C_{12} , CH_3), 28.52 (C_1), 31.83 (C_2), 51.63 (C_{11}-O$\underline{C}H_3$), 110.05 (C_{4a}), 111.38, 118.04 , 118.60 , 120.17, 121.77 (C_4, C_5, C_7, C_6, C_8),122.14, 125.68, 131.40, 136.29 (C_3, C_{5a}, C_{9a} and C_{8a}), 144.13 (C_{10}, ester carbonyl). Exact mass calculated for $C_{15}H_{15}NO_2$ 241.1098; found 241.1103;

Aromatization of 3a and 3b to 13a and 13 b

Recrystallized sample of **3a** stirred for 24 hours with acetic acid in an open atmosphere was converted into *1-(1-Methyl-9H-carbazol-3-yl)-ethanone* ***13a;*** The organic mixture was washed with water up to neutral pH and dried over sodium sulfate to give a crude product which was purified by preparative thin layer chromatography (65% recovery); i.r. ($CHCl_3$) 3469 cm^{-1} (free NH), 1655 cm^{-1}($COCH_3$), δ_H ($CDCl_3$, 250 MHz), 2.61 (s, 3H, C_1CH_3), 2.72 (s, 3H, $COCH_3$) 7.23-7.52 (m, 3H, C_5, C_6, C_7H), 7.92 (s, 1H, C_4 or C_2H) 8.12 (d,J= 7.8 Hz, 1H, C_8H) 8.26 (br s,1H, NH) 8.58 (s,1H, C_2 or C_4H). δ_C ($CDCl_3$, 250 MHz)16.95 (C_{12} $C\underline{C}H_3$), 26.77 (C_{11} $CO\underline{C}H_3$) 111.17 (C_{4a}) 119.63, 119.96 (C_2 or C_4 or C_5 or C_8) 120.61 (C_7 or C_6) 120.78 (C_7 or C_6) 122.69 (C_1) 124.12 (C_{5a} or C_{9a}) 126.85 and 126.59 (C_2 or C_4 or C_5 or C_8) 129.82 (C_{5a} or C_{9a}) 139.97 (C_{8a}) 142.13 (C_3) 198.00 (C_{10}, carbonyl). Exact mass calculated for $C_{15}H_{13}NO$: 223.0997; found: 223.0995. A recrystallized sample of **3b** stired in acetic acid under an open atmosphere for 24-48

hours was converted into **13b** *1-methyl-9H-carbazole-1-methyl-9H-carbazole-3-carboxylic acid methyl ester* which can be purified by thin layer chromatography elution ethyl acetate : hexane : toluene (30 : 50 : 70), (90% recovery), i.r. ($CHCl_3$) 3469 cm^{-1} (free N-H) 1706 cm^{-1} (ester carbonyl), δ_H*($CDCl_3$, 250 MHz), 2.60 (s,3H, C_1CH_3) 3.97 (s,3H, CO_2CH_3), 7.26-7.48 (m,3H, C_5,C_6 C_7H),7.96 (1H, s, C_4 or C_2H), 8.10 (m, 1H, J=7.9 Hz, C_8H) 8.22 (br, s, 1H, NH) 8.68 (s, 1H, C_4 or C_2H). Exact mass calculated for $C_{15}H_{13}NO_2$: 239.0946; found 239.0948.

* The chemical shifts reported in the literature[5] for a mixture of the carbazoles with the carbomethoxy groups at 2 and 3 position are compatible with those described here.

Reaction of 1-methyl-pyrano[3,4-b]indol-3-one 1a with dimethyl fumarate

A suspension of the pyran[3,4-b]indolone **1a** (0.100 g, 0.5 mmoles) in chlorobenzene (25 ml) containing dimethylfumarate (0.094 g , 1.3 eq.) and hydroquinone (1 crystal) was heated at 130 ° C for about 3 hours. The solvent was distiled off and to the residue was added a small portion of methylene chloride . The residue was further evaporated in vacuum for 18 hours to yield a crude product which upon analysis by ^{1}H nmr at 250 MHz appeared to be a mixture of the adducts **16** and **17**. The crude mixture was chromatographed on a column of silica gel and eluted successively with hexane (100 ml), hexane-ether (95 : 5, 500 ml), hexane-ether (75 : 25, 100 ml), hexane-ether (50 : 50) 100 ml. The first fraction recovered (0.123 g, 0.4 mmoles, 82.3%) contained mainly the major adduct and a small quantity of the minor adduct. A second fraction yielded mainly the minor adduct **16** (0.014 g, 0.05 mmoles, 10% yield). δ_H(80 MHz, $CDCl_3$) 1.54 (d, J =7.0 Hz, 3H, C_1CH_3), 3.58 (s, 3H, C_3 or C_2, $C0_2CH_3$), 3.70-3.90 (m, 5, C_1 and C_2H overlapping a C_2 or C_3 carbomethoxy singlet at 3.84 ppm),7.10-7.68 (m, 4H, C_5 $C_6$$C_7$ and C_8 H) 8.03 (s,1H, C_4H). The first fraction was further purified by preparative thin layer chromatography with elution first with hexane-ether (50 : 50) and then with hexane-ether (33 : 66). The major adduct recovered was the *cis-1-methyl-9H-1,2-dihydrocarbazole-2,3-dicarboxylic acid* dimethyl ester **17** (0.051g, 0.17 mmoles, 34%); i.r. ($CHCl_3$) 3457 cm^{-1}(free indole NH) 1700-1723 cm^{-1} (two overlapping CO_2CH_3) 1611 cm^{-1} (C=C of a α,β unsaturated ester). δ_H (250 MHz, $CDCl_3$) 1.17 (d, J = 7.1Hz, 3H, C_1CH_3) 3.59-3.90 (m, 8H, C_1H and C_2H signals overlapping a carbomethoxy singlet at δ=3.60 ppm (C_2 or $C_3CO_2CH_3$)(at 400 MHz this region was resolved into two carbomethoxy singlets at δ=3.61 and δ=3.86 ppm, a nearly first order multiplet (dq) between 3.72-3.78 for C_1H and a doublet at δ=3.82, J_{H_1,H_2}=2.3 Hz for C_2H. Upon irradiation of this doublet, the multiplet collapsed to a quartet of J =6.8 Hz),7.12-7.14 (m, 2H, C_6, and C_7H) 7.24-7.28 (m, 1H, C_5 or C_8H). Exact mass calculated for $C_{17}H_{17}O_4N$ 299.1157; found 299.1155.

Preparation of 1-methyl-9-acetylpyrano[3,4-b]-3-one 1b

To a cooled suspension of sodium hydride (0.350 g of a 50% mixture of sodium hydride in parafin oil, 5 equivalents, washed three times with hexane) in DMF (14 ml, over calcium hydride) was added a suspension of the pyrone **1a** (0.300 g, 1.5 mmoles) in DMF. After 10 minutes, freshly distiled acetic anhydride (0.23 g , 3.7 mmoles, 2.5 equivalents) was added and the mixture allowed to stir for 10-15 minutes at the ice-bath temperature. Water was carefully added and the mixture was partitioned between water and ether. The aqueous phase was extracted with ether and the combined ether phases were washed once with water and aqueous sodium chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in *vacuum* to yield **1b** (0.192 g, 0.80 mmoles, 53% yield) which appeared as the sole product by ^{1}H nmr

analysis. The 1-methyl-9-acetylpyran[3,4-b]indol-3-one was further purified by chromatography on silica gel with elution, initially with ether followed by ethyl acetate-ether mixtures with 10% increase in the ethyl acetate content up to 100% . The N-acetyl pyrone **1b** was obtained as a solid (65% recovery, yield based or starting material 34.7%), m.p.= 151-152° C (found : M^+ 241,); i.r. ($CHCl_3$) 1690-1730 (amide and lactone carbonyls, overlapping). ^1H nmr ($CDCl_3$) 2.62 (s, 3H, C_1CH_3), 2.79 (s, 3H, N-$COCH_3$), 5.55 (s, 1H, C_4H), 7.40-8.03 (m, 4H, ArH).

Diels-Alder cycloaddition of 1-methyl-9-acetyl[pyrano[3,4-b]indol-3-one 1b with methyl acrylate

The N-acetyl pyrone **1b** was heated with methyl acrylate (1.3 equivalents) in chlorobenzene at reflux temperature in the presence of hydroquinone (1 crystal). After 4 hours an extra amount of methyl acrylate was added (0.5 equivalents) and the reaction was continued for an extra 6 hours. The crude mixture analysed at 250 MHz, revealed that approximately 65% of the starting material had been consumed and two major components had been formed in approximately 1.4 :1 ratio. The solvent was distiled and the residue dried in *vacuum* . Minor quantities of these adducts(ir, mixture ($CDCL_3$) 1717-1728 cm^{-1} ($COCH_3$ and CO_2CH_3 overlapped) could be separated by preparative thin layer chromatography and identified as the adduct **23** and the adduct **24** on the basis of the ^1H nmr analysis at 400 MHz and decoupling experiments. Major adduct **23****: M^+ found for $C_{21}H_{23}NO_5$ 369. δ_H ($CDCl_3$): 1.63 (s, 3H, C_1CH_3), 2.79 (s, 3, $COCH_3$) 3.51(s, 6H, two CO_2CH_3) 3.60 (quintet, J =2.9 Hz ,1H , C_4H) 7.20-7.35 (m, 2H, C_7, C_6H) 7.51-7.35 (m, 1H, C_8H) 7.55-7.62 (m, 1H, C_5H). Minor adduct **24** : δ_H ($CDCl_3$): 1.53 (s, 3H, C_1CH_3), 2.80 (s, 3, $COCH_3$) 3.60 (quintet, J =2.9 Hz ,1H, C_4H), 3.47 (s, 3H, CO_2CH_3) 3.73 (s, 3H, CO_2CH_3) 7.21-7.22 (m, 2H, C_6, C_7H) 7.51-7.55 (m, 1H, C_5H) 7.56-7.63 (m,1H , C8H).

***See table in discussion and results for chemical shifts of hydrocarbon protons, at the 2, 2', 3 and 3 positions*

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