Cycloaddition Reactions of Carbodiimides. The First Example of an Intramolecular Diels–Alder Reaction of C=C-Conjugated Carbodiimides

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An one-pot preparation of α-carbolines and quinindolines from conjugated carbodiimides based on a tandem intramolecular Diels–Alder cycloaddition/oxidative aromatization is described.

In recent years there has been an upsurge of interest in the [4 + 2] cycloaddition of azadienes.[1] In spite of the important role of the intramolecular [4 + 2] cycloaddition of 2-azadienes, only one example of this reaction, involving electron-poor 2-azadienes and unactivated dienophiles, has been reported.[2] On the other hand, a number of heterocumulenes have been shown to function as 2-azadienes in [4 + 2] cycloaddition reactions, *e.g.* *N*-aryl ketenimines,[3] *N*-aryl vinylketenimines,[4] phenyl isocyanate and related isocyanates[5] react with electron-rich dienophiles by cycloaddition across the 2-azadiene system; however there have been no reports dealing with unsaturated carbodiimides as 2-azadienes, to the best of our knowledge. Continuing our interest on the preparation and synthetic applications of C=C-conjugated carbodiimides,[6] we report herein a one-pot preparation of indole derivatives, based on the strategy shown in Scheme 1. Our synthetic approach, which involves as the key step a tandem intramolecular hetero Diels–Alder cycloaddition–oxidative aromatiza-

tion has surprisingly been found to be useful in the simultaneous formation of pyrrole and pyridine rings in the synthesis of [*b*]fused pyridoindoles.

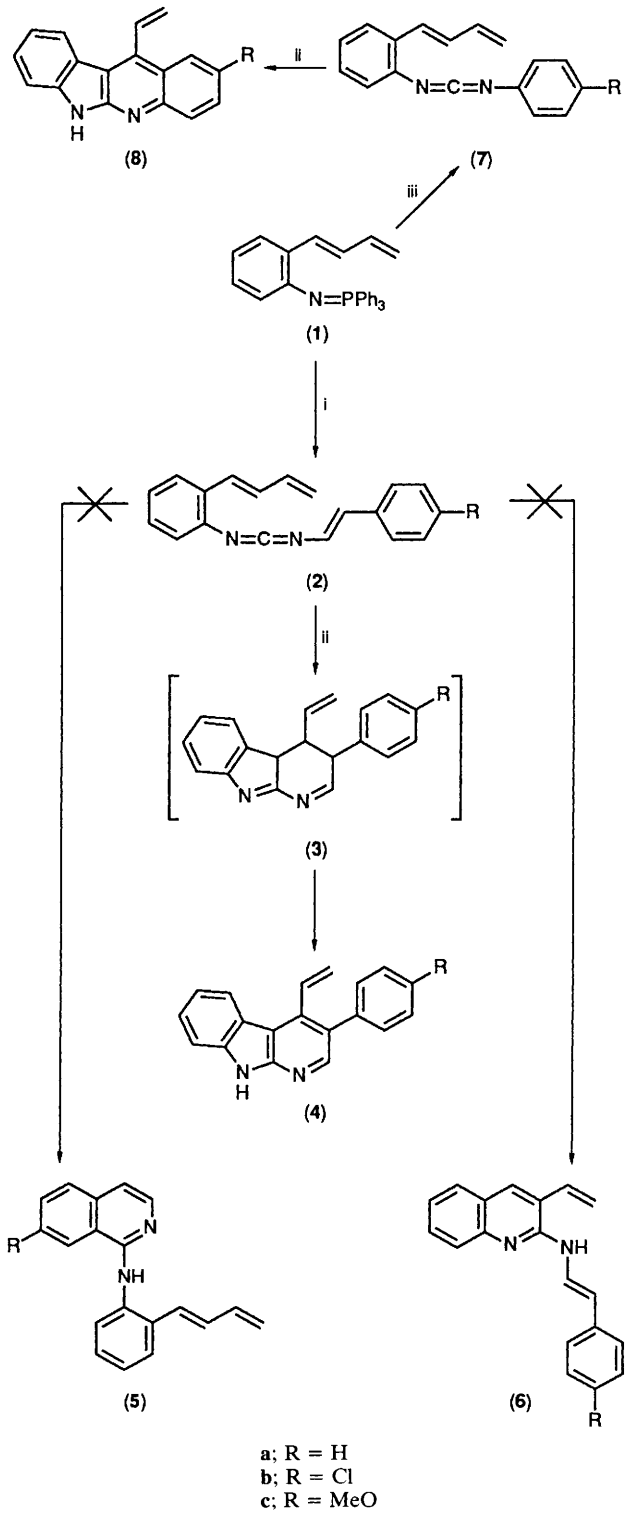
Recently, pyrido[2,3-*b*]indoles (α-carbolines) (**4**) and quinindolines (**9**) have received much attention because they are pharmacologically active compounds, displaying strong cytostatic and antitumour activity.[7]

The key intermediate (**1**) was easily prepared in 47% overall yield from 1-(*o*-nitrophenyl)buta-1,3-diene[8] (1 : 1 mixture of *E*/*Z* isomers) by standard chemistry: iodine-catalysed isomerization to the *E* isomer, reduction with the iron–acetic acid system and reaction with triphenylphosphine dibromide in the presence of triethylamine. Aza–Wittig reaction of the iminophosphorane (**1**) with styryl isocyanates in dry toluene at room temperature led to the corresponding carbodiimides (**2**) bearing a diene chain in one *ortho* position, which could be isolated as viscous oils by means of short column chromatography. When toluene solutions of (**2**) were heated at 160 °C for 16 h the corresponding tricyclic compounds (**4**) were obtained as solids, in moderate yields, after column chromatography (silica gel, ethyl acetate–n-hexane 1 : 1) accompanied by minor amounts of unidentified compounds in which neither the isoquinoline (**5**) nor quinoline (**6**) could be detected.

In the light of the behaviour of the previously reported conjugated carbodiimides,[6] the intramolecular reactivity of the carbodiimides (**2**) came as a surprise. The former compounds underwent electrocyclic ring-closure followed by 1,3-proton shift to give either isoquinoline or quinoline derivatives.

In an analogous reaction sequence, the diarylcarbodiimides (**7**), available from (**1**) and aromatic isocyanates, were converted into the corresponding tetracyclic compounds (**8**) which were isolated as crystalline solids. That conversions of the type (**2**) → (**4**) and (**7**) → (**8**) are reasonably general in nature is indicated by the examples given in Table 1. Efforts to improve the yields of (**4**) and (**8**) by heating the carbodiimides (**2**) and (**7**) in the presence of palladium–charcoal as a dehydrogenation agent were unsuccessful. In spite of the moderate yields, the syntheses of (**4**) and (**8**)† are competitive with known routes to comparable compounds, and take place in a completely periselective fashion.

These transformations include a [4 + 2] cycloaddition whereby the unsaturated carbodiimide has functioned as a 2-azadiene using one cumulative double bond and a C=C double bond adjacent to the cumulative system, whereas the C=C double bond of the *ortho*-butadienyl substituent directly linked to the aromatic ring has taken the role of the dienophile. A final oxidative aromatization followed by a



Scheme 1. *Reagents and conditions:* i, ArCH=CHNCO, toluene, room temp.; ii, sealed tube, toluene, 160 °C, 16 h; iii, ArNCO, toluene, room temp.

† *Selected spectroscopic data* for 3-(4-methoxyphenyl)-4-vinyl-9*H*-pyrido[2,3-*b*]indole (**4c**): ^{1}H NMR (200 MHz, [$^2H_6$] DMSO) δ 3.80 (s, 3H, MeO), 5.55 (dd, 1H, *J* 1.7 and 17.9 Hz, CH=C*H*$_2$), 5.73 (dd, 1H, *J* 1.7 and 11.5 Hz, CH=C*H*$_2$), 7.00 [d, 2H, *J* 8.5 Hz, H(3′) and H(5′)], 7.06—7.22 [m, 2H, C*H*=CH$_2$ and H(6)], 7.33 [d, 2H, *J* 8.6 Hz, H(2′) and H(6′)], 7.42—7.58 [m, 2H, H(7′) and H(8′)], 8.25 [d, 1H, *J* 8.1 Hz, H(5′)], 8.29 [s, 1H, H(2)], and 11.94 (s, 1H NH); ^{13}C NMR (50 MHz, [$^2H_6$] DMSO) δ 55.02 (MeO), 111.31 [C(8)], 111.69 [C(3)], 113.63 [C(3′ and 5′)], 119.14 [C(6)], 120.34 [C(4a)], 122.62 (CH=*C*H$_2$), 122.77 [C(5)], 126.31 [C(7)], 127.16 [C(4b)], 130.35 [C(1′)], 131.32 [C(2′ and 6′)], 133.05 (*C*H=CH$_2$), 139.33 [C(8a)], 139.45 [C(4)], 146.83 [C(2)], 151.48 [C(9a)], and 158.24 [C(4′)]. 2-Methoxy-11-vinyl-6*H*-quinindoline (**8c**): ^{1}H NMR (200 MHz, [$^2H_6$] DMSO) δ 3.90 (s, 3H, MeO), 5.95 (dd, 1H, *J* 1.7 and 17.8 Hz, CH=C*H*$_2$), 6.13 (dd, 1H, *J* 1.7 and 11.6 Hz, CH=C*H*$_2$), 7.16–7.67 (m, 6H, aromatic and C*H*=CH$_2$), 7.95 [d, 1H, *J* 9.1 Hz, H(4)], 8.28 [d, 1H, *J* 7.8 Hz, H(10)], and 11.68 (s, 1H, NH); ^{13}C NMR (50 MHz, [$^2H_6$] DMSO) δ 55.12 (MeO), 103.26 [C(1)], 110.67 [C(7)], 114.07 [C(11a)], 119.04 [C(9)], 120.25 [C(10b)], 120.71 [C(3)], 122.18 [C(10a)], 123.38 [C(10)], 123.48 (CH=*C*H$_2$), 127.59 [C(8)], 128.73 [C(4)], 131.95 (*C*H=CH$_2$), 137.32 [C(11)], 141.55 [C(6a)], 142.15 [C(4a)], 151.38 [C(5a)], and 154.68 [C(2)]. Values assigned by decoupling methods and 2D ^{1}H-^{13}C correlation techniques. DMSO = dimethyl sulphoxide.

Table 1. Yields of pyrido[2,3-*b*]indoles (**4**) and quinindolines (**8**).[a]

	R	Yield (%)
(**4a**)	H	37
(**4b**)	Cl	46
(**4c**)	MeO	35
(**8a**)	H	39
(**8b**)	Cl	43
(**8c**)	MeO	40

[a] All new compounds described here had spectral and microanalytical properties in agreement with the assigned structures.

1,3-proton shift in the cycloadduct furnishes the polycycle (**4**) or (**8**) respectively.‡

In conclusion, this work shows for the first time that easily available C=C-conjugated carbodiimides may react as 2-aza-dienes in intramolecular [4 + 2] cycloadditions; obviously the structural conditions in *N*-aryl(styryl), *N'*-(*o*-butadienyl)-phenyl carbodiimides provide an energetically favourable situation for this exceptional behaviour. It can be presumed that related carbodiimides may also undergo this type of cycloaddition to give nitrogen heterocycles related to the antitumour agent ellipticine.

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‡ Carbodiimide type (**7**) derived from (**1**) and 2,6-dimethylphenyl isocyanate does not undergo cycloaddition; it was recovered unaltered after prolonged heating (toluene, 160 °C, 4 days). Obviously the two methyl groups at the *ortho* positions prevent the cycloaddition step.

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