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Regiospecific Intramolecular Ring-Closure of Heterocumulene-Substituted Indoles: Formation of γ-Carbolines and Pyrimido[3,4-*a*]indoles.

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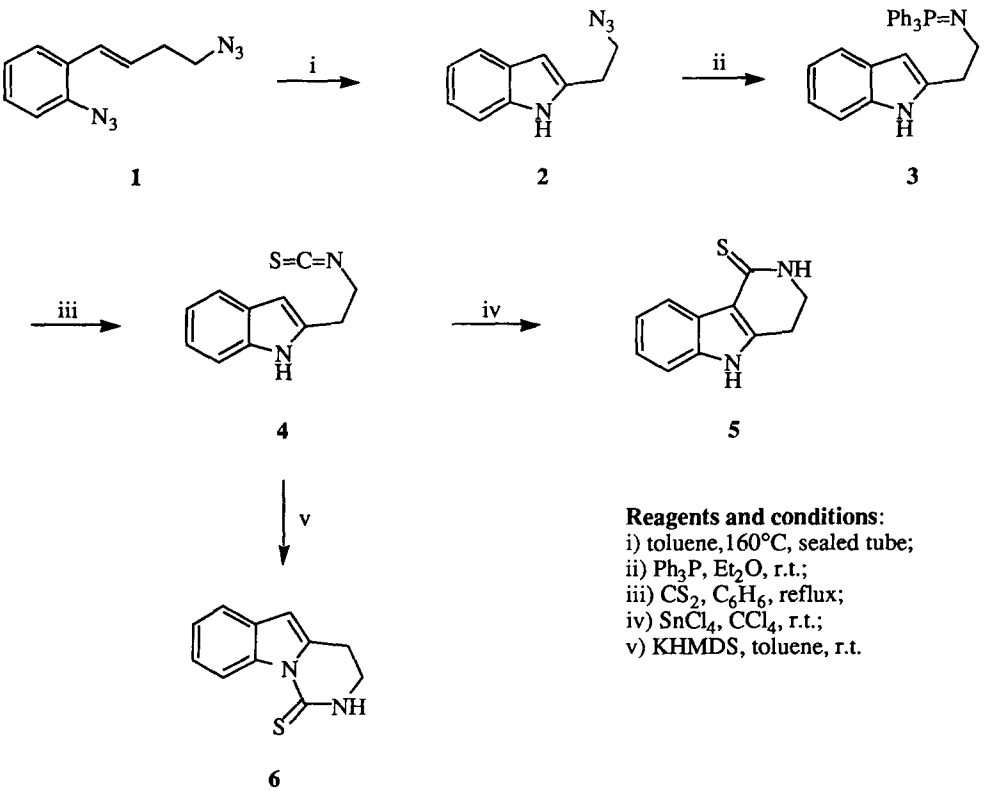
Abstract: *2-(Indol-2-yl)ethyl heterocumulenes undergo ring-closure under acid, basic and thermal conditions to give either dihydro γ-carbolines or dihydropyrimido[3,4-a]indoles in a completely regiospecific fashion. The mode of cyclization strongly depends on the cyclizating agent as well as the nature of the heterocumulene.*

Conjugated heterocumulenes exhibit a rich chemistry of unusual synthetic promise[1]. Heterocyclization reactions of such unsaturated heterocumulenic systems as ketenes, ketenimines, isocyanates, isothiocyanates, and carbodiimides provide an attractive entry to a variety of carbocycles and heterocycles. In this context, we have previously reported that β-(indol-2-yl)vinyl heterocumulenes under thermal conditions undergo electrocyclic ring-closure to give pyrido[4,3-*b*]indoles (γ-carbolines)[2], however when the indole ring is substituted at 3 position, the heterocyclization reaction takes place by nucleophilic attack of the amino group of the indole ring on the central carbon atom of the heterocumulene moiety to give pyrimido[1,6-*a*] indoles[3].

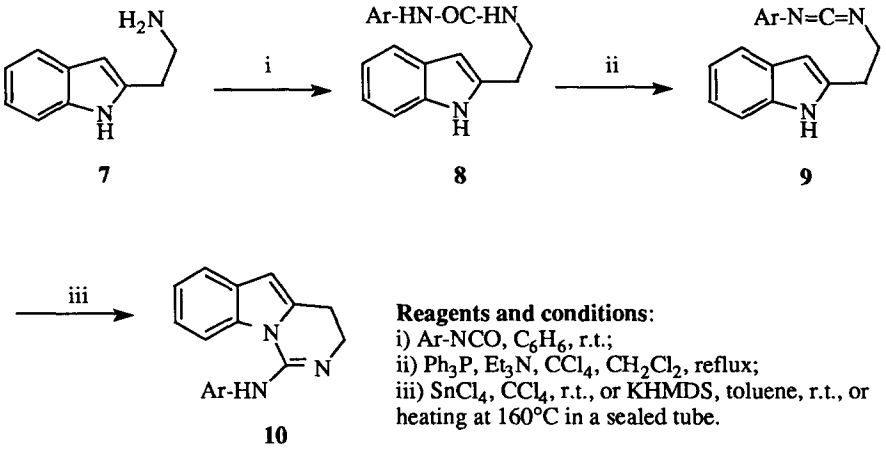
Herein, we wish to report a new regiospecific intramolecular cyclization of heterocumulene-substituted indoles in which the cumulenic portion and the indole ring are linked with a flexible alkyl chain containing two carbon atoms. At first this class of compounds could undergo two different types of cyclization, either on the 3 position of the indole ring (mode A) to give dihydro γ-carbolines or by nucleophilic attack of the indolic nitrogen atom on the central carbon atom of the heterocumulene portion (mode B) to give dihydropyrimido indoles.

The common precursor for this kind of heterocumulenes is the bis(azide) **1**, wich was prepared in 56% yield from 1,3-dibromopropane and *o*-azidobenzaldehyde according to the method previously reported for this type of compounds[4]. When compound **1** was heated at 160 °C in toluene in a sealed tube 2-(2-azidoethyl)indole **2** was obtained in 61% yield as the only reaction product and no products derived from the decomposition of the alkyl substituted azido group were observed[5]. Staudinger reaction of the azido indole **2** with triphenylphosphine in diethyl

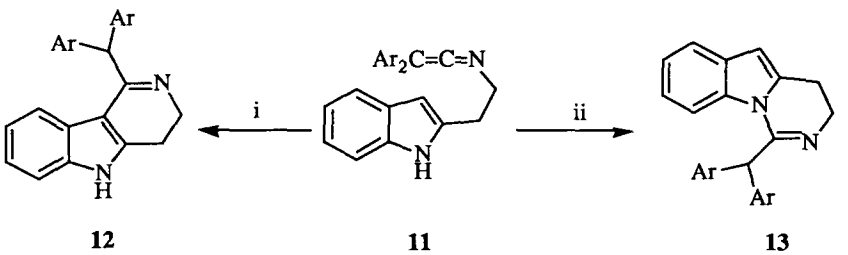
ether at room temperature provided the iminophosphorane **3** in 83% yield, which by reaction with carbon disulfide in benzene at reflux temperature afforded the isothiocyanate **4** in excellent yield (97%). All attempts to promote the thermal cyclization of the isothiocyanate **4** were unsuccessful but, when it was treated with $SnCl_4$ in carbon tetrachloride at room temperature, cyclization took place across the 3 position of the indole ring to give **5** as the only reaction product in moderate yield (45%)[6]. However, when **4** was treated with potassium bis(trimethylsilyl)amide in toluene at room temperature underwent cyclization in a completely regiospecific fashion to give **6** in 50% yield[7].



In order to investigate the scope of these processes, variations were considered. At first it was of interest to see what would happen with another type of heterocumulene such as carbodiimides. To this end, the amine **7**, readily available in 84% yield by reduction of the azide **2** with $LiAlH_4$, was treated with aryl isocyanates to give the corresponding ureas **8** in 77-83% yields, which were converted into carbodiimides **9** by the action of triphenylphosphine in the presence of triethylamine and carbon tetrachloride. Direct conversion of iminophosphorane **3** into carbodiimides **9** by reaction with aryl isocyanates failed. Regioselective cyclization of carbodiimides **9** to give **10** was achieved either by the action of $SnCl_4$ (32-38%), potassium bis(trimethylsilyl)amide (66-80%) or thermal treatment at 160 °C (43-67%)[8]. This behaviour is in sharp contrast with the observed for the closely related 2-(2-indolyl)phenyl, aryl carbodiimides, which undergo cyclization across the 3 position of the indole ring to give indolo [3,2-*c*] quinolines[3].



On the other hand, reaction of iminophosphorane **3** with diaryl ketenes provided ketenimines **11** which were isolated as viscous oils and were used for the next step without further purification. Compounds **11** were cyclized either by the action of $SnCl_4$, or thermal treatment, to give **12** albeit in low yields (20-25%), whereas treatment with potassium bis (trimethylsilyl) amide provided **13** in modest yields (38-47%).



Reagents and conditions: i)toluene, reflux or $SnCl_4$, CCl_4, r.t.; ii) KHMDS, toluene, r.t.

Several trends have surfaced from this study. First, isothiocyanate **4** and ketenimines **11**, show identical behaviour towards different cyclizating agents. They undergo cyclization across the 3 position of the indole ring under Lewis acid-catalysed conditions, whereas under strong basic conditions cyclization takes place to the indole nitrogen atom. Second, carbodiimides **9** undergo regiospecificic ring closure to give dihydropyrimido indoles under acid and basic conditions as well as by thermal treatment. These results show a detailed picture of the ability of this kind of compounds to undergo cyclization reactions under a wide variety of reaction conditions; simply by changing either the nature of the heterocumulene moeity or the cyclizating agent the reaction may be driven towards the production of dihydro γ-carbolines, or dihydropyrimido indoles.

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References and notes.

1. For reviews see: Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821; Boger, D. L. Tetrahedron **1983**, *39*, 2869; Snider, B. S. *Chem. Rev.* **1988**, *88*, 703; Arbuzov, B. A.; Zobova, N. N. *Synthesis* **1982**, 433.
2. Molina, P.; Fresneda, P. M. *J. Chem Soc. Perkin Trans. 1* **1988**, 1819.
3. Molina, P.; Alajarín, M.; Vidal, A. *Tetrahedron*, **1990**, *46*, 1063.
4. Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985**, 5747; Chhen, A.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1989**, 4953.
5. Compound **2**, oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.78 (t, 3H, J=6.6 Hz), 3.43 (t, 3H, J=6.6 Hz), 6.22 (s, 1H), 7.03-7.54 (m, 4H), 7.78 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.77, 50.86, 100.54, 110.66, 119.80, 120.01, 121.49, 128.38 (q), 135.71 (q), 135.98 (q); IR (film) 3392 (vs), 2107 (s) cm^{-1}; EI mass spectrum m/z (%) 186 (M^+, 12), 130 (100).
6. Compound **5**, m.p. 166-169°C (from chloroform/diethyl ether); ^{1}H-NMR (200 MHz, DMSO-d^6) δ 3.01 (t, 2H, J=7.3 Hz), 3.49 (dt, 2H, J=7.3, 2.5 Hz), 7.08-7.36 (m, 3H), 8.52 (s, 1H), 9.09 (s, 1H), 11.91 (br s, 1H); ^{13}C-NMR (50 MHz, DMSO-d^6) δ 21.68, 41.39, 111.15 (q), 111.57, 120.94, 120.99, 121.00, 126.42 (q), 136.17 (q), 140.36 (q), 188.67 (q); IR (Nujol) 3318 (s), 1484 (s), 1456 (vs) cm^{-1}; EI mass spectrum m/z (%) 203 (M^++1, 10), 202 (M^+, 64), 173 (100).
7. Compound **6**, m.p. 154-155°C (from chloroform/diethyl ether); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.08 (t, 2H, J=6.21 Hz), 3.44 (dt, 2H, J=6.2, 3.3 Hz), 6.33 (s, 1H), 7.24-7.30 (m, 2H), 7.47 (dd, 1H, J=6.9, 1.3 Hz), 8.27 (br s, 1H), 9.20 (dd, 1H, J=8.1, 0.9 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 22.99, 39.93, 104.75, 117.08, 120.15, 123.68, 123.85, 130.10 (q), 133.21 (q), 136.94 (q), 176.84 (q); IR (Nujol) 3217 (vs), 1454 (vs) cm^{-1}; EI mass spectrum m/z (%) 202 (M^+, 21), 130 (100).
8. Typical Procedure: To a solution of **7** (0.16g,1mmol) in benzene (5 ml) 4-methoxyphenyl isocyanate (0.15 g, 1 mmol) in benzene (5 ml),was added dropwise at room temperature. The precipitated solid was separated by filtration, washed with Et_2O and dried to give **8** in 83% yield. A mixture of **8** (0.31 g, 1mmol), triphenylphosphine (0.52 g, 2 mmol), triethylamine (0.30 g, 3 mmol) and carbon tetrachloride (0.46 g, 3 mmol) in dry CH_2Cl_2 (25ml) was heated at reflux temperature for 5h. After cooling, the solvent was removed under reduce pressure and the residual material was treated with dry toluene. The ammonium salt was separated by filtration and the filtrate was cooled at -78°C and KHMDS (1mmol, 0.5M in toluene) was added under nitrogen. The resultant solution was allowed to warm to room temperature and water (10 ml) was added. The mixture was extracted with ethyl acetate (3x10ml) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed on a silica gel column, using ethyl acetate as eluent, affording **10** in 66% yield. **10** (Ar=4-H_3CO-C_6H_4), m.p. 182-183°C (from chloroform) ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.09 (t, 2H, J=5.7 Hz), 3.37 (t, 2H, J=5.7 Hz), 3.80 (s, 3H), 4.87 (s, 1H), 6.34 (s, 1H), 6.88-6.96 (m, 4H), 7.17-7.25 (m, 2H), 7.51 (d, 1H, J=6.8 Hz), 8.69 (d, 1H, J=7.8 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.39, 39.33, 55.66, 102.11, 115.09, 116.45, 119.73, 122.18, 123.13, 123.41, 129.42 (q), 134.62 (q), 135.26 (q), 141.06 (q), 145.38 (q), 155.61 (q); IR (Nujol) 3367 (vs), 1657 (s) cm^{-1}; EI mass spectrum m/z (%) 292 (M^++1, 18), 291 (M^+, 100).

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