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# INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS OF VINYLKETENIMINES . A CONVERGENT ROUTE TO CARBAZOLES AND PYRIDOCARBAZOLE ALKALOIDS

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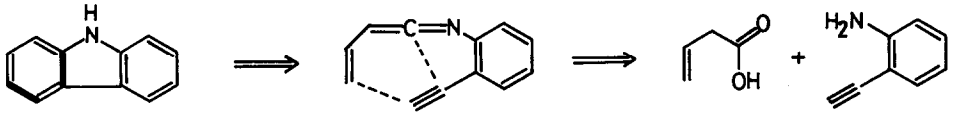
Summary : The intramolecular Diels-Alder cycloaddition of acetylenic vinylketenimines is the key step of a highly convergent synthesis of carbazoles. A facile synthesis of N-methyl-tetrahydroellipticine has been completed in five isolated steps from N-methyl piperidone.

Vinylketenimines have been shown to react as electron-rich dienes in Diels-Alder reactions[1]. Their high oxidation level at C-1 allows for the direct formation of aromatic amines from their cycloaddition to activated triple bonds. In this communication, we wish to establish the efficacy of intramolecular cycloadditions of vinylketenimines as key steps in a highly convergent synthetic approach to carbazoles[2] (Scheme 1).

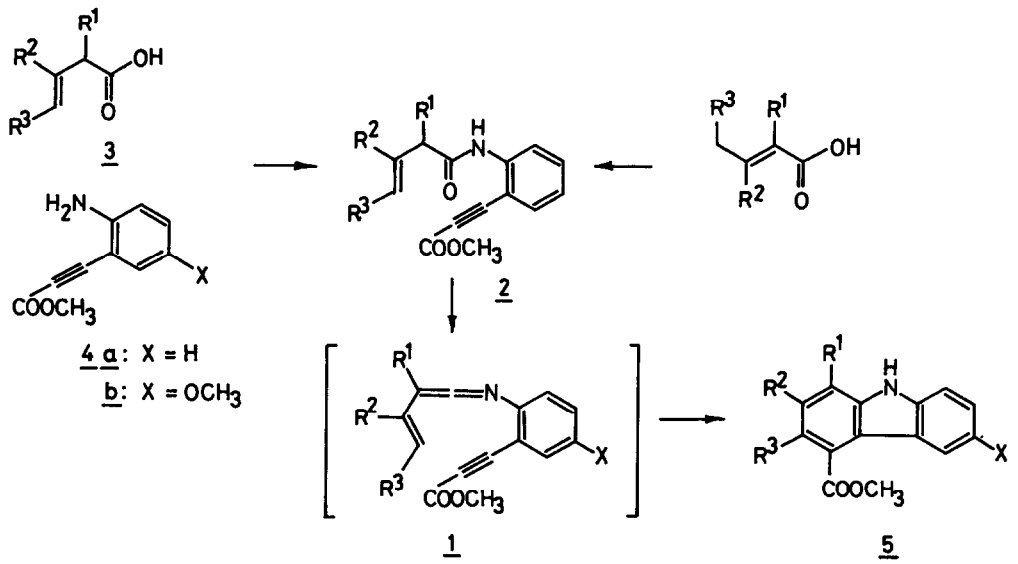



Scheme 1

The precursors of vinylketenimines 1 are the β,γ unsaturated anilides 2 (Scheme 2, Table I). Except for 2c, they were prepared by reaction of the corresponding β,γ unsaturated acids 3[3] with thionyl chloride (neat, 20°C overnight then 30 min. at 60°C) followed by treatment with the appropriate aniline derivatives 4[4] in the presence of collidine ($CH_2Cl_2$, 5°C 20°C). Under these conditions no migration of the double bond was observed. Anilide 2c was obtained from tiglyl chloride and the aniline 4a in the presence of triethylamine. These conditions led to a shift of the double bond and compound 2c was obtained as a 65 β,γ : 35 α,β mixture of isomers[5].

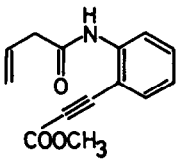
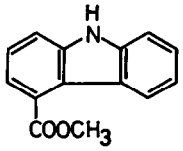
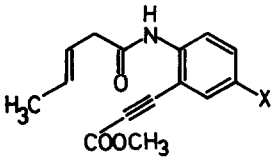
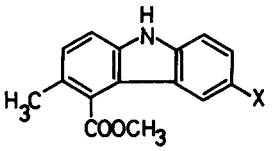
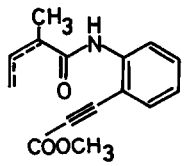
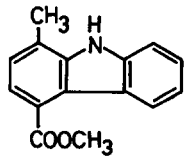
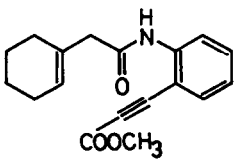
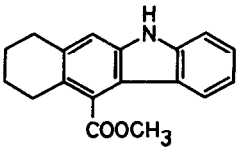
The vinylketenimines 1 were generated in situ by reacting anilides 2 with $Ph_3P$-$Br_2$ in the presence of triethylamine in refluxing dichloromethane[6]. The cycloaddition was readily monitored by following the disappearance of the characteristic infrared absorption at 2220 $cm^{-1}$

This paper is dedicated to Professor R.H. Martin for his 70th birthday



Scheme 2

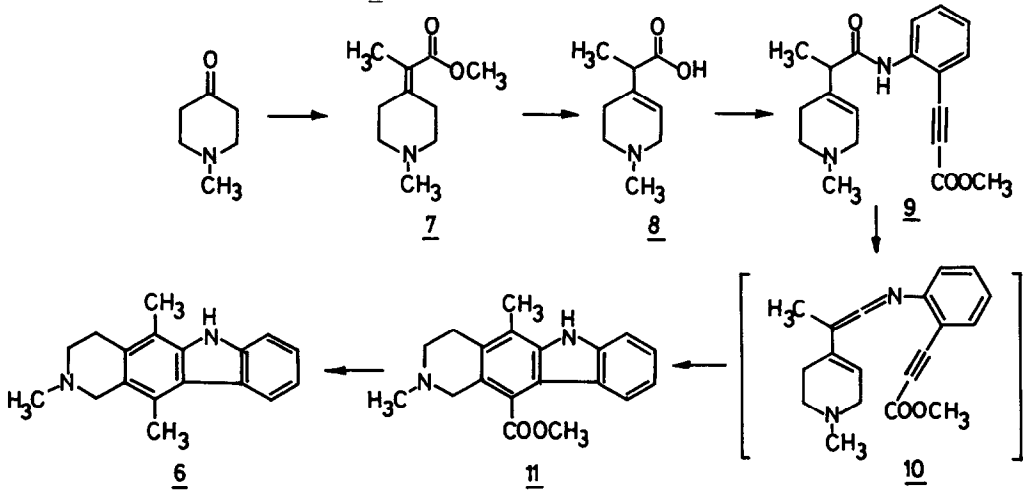
Table 1[a] : Yields of Anilides 2 and Carbazoles 5

| Entry | Anilides 2 | Yields % | Carbazoles 5 | Yields % | m.p. °C |
|---|---|---|---|---|---|
| a |  | 80 |  | 42 | 95,5-96<br>lit.[7] :96-97 |
| b |  | 80 (X=H)<br>84 (X=$OCH_3$) |  | 88 (X=H)<br>98 (X=$OCH_3$) | oil<br>oil |
| c |  | 80 |  | 68 | 151-152 |
| d |  | 71 |  | 76 | oil |

[a] All products were characterized by $^{13}C$ and $^{1}H$ NMR (200 MHz), IR, UV and mass spectrometry

The procedure for the synthesis of 5b (X=H) is illustrative : a solution of 0.2 g (0.778 mmole) of 2b (X=H) in 5 ml of dry $CH_2Cl_2$ is rapidly added to a mixture obtained by adding 44 µl (1.1 equiv.) of $Br_2$ and 0.65 ml (6 equiv.) of $Et_3N$ to a solution of 0.224 g (1.1 equiv.) of $Ph_3P$ in 10 ml of $CH_2Cl_2$. The mixture is refluxed under argon for ∿ 15 min. Addition of water, extraction with 2x15ml portions of $CH_2Cl_2$ and filtration on silica gel (15 g, $CH_2Cl_2$, 80 ml) gave 0.163 g (88 %) of carbazole 5b (X=H). As shown in Table 1, the sequence is quite general and good yields of carbazoles are obtained (table 1).

The utility of this new methodology is further illustrated by a convergent route toward N-methyl-tetrahydroellipticine 6. Ellipticine and other pyridocarbazole alkaloids show significant antitumor activity and one compound of this class is now commercialized for human use.[8] The synthetic sequence for 6 is shown in Scheme 3.



Scheme 3

N-methylpiperidone was transformed into the conjugated ester 7 (75%) by Wittig-Horner reaction[9] ($(EtO)_2P(O)CH(CH_3)CO_2CH_3$[10] + NaH in refluxing ether). Treatment of 7 with LDA (THF, -68°C, 1hr) followed by quenching with $NH_4Cl$ yielded the β,γ unsaturated ester ( ∿ 100% crude) which was directly saponified (2 equiv. 1N KOH, 2hrs, 60°C) to acid 8 (75%). Condensation of 8 with the requisite aniline derivative 4a could not be satisfactorily accomplished with the usual reagents ($ClCO_2C_2H_5$ ± DMAP; diisopropylcarbodiimide; $(C_2H_5)_2N\text{-}C{\equiv}C\text{-}CH_3$) probably as a result of the low nucleophilicity of 4a. On the other hand conversion of 8 into the corresponding acid chloride ($HCl_g$ in $CH_2Cl_2$, evaporation then 1.2 equiv. $(CH_3)_2C{=}C(Cl)N(CH_3)_2$, $CH_2Cl_2$ 20°C)[11] followed by addition of 1 equiv. of 4a in the presence of triethylamine (1 equiv.) yielded 75% of crude anilide 9. Purification of 9 was always accompanied by significant loss of material. Therefore crude 9 was directly used for the reaction with $Ph_3P\text{-}Br_2$ (2 equiv.) and $(C_2H_5)_3N$ (6 equiv.) in refluxing $CH_2Cl_2$ (2.5 hrs). These conditions generate vinylketenimine 10 which undergoes the intramolecular cycloaddition to yield carbazole 11 (50%, purification by preparative tlc on silica gel, benzene-ethylacetate-triethylamine 7:2:2). Compound 11 was readily transformed (3.5 equiv. of $LiAlH_4$, 7 equiv. of $AlCl_3$, refluxing ether, 1.25 hr, 71%)[12] into N-methyl-tetrahydroellipticine 6 (m.p.

215-218°C°;lit. 215°C[13c], 215-218°[13a]. The synthetic N-methyl-tetrahydroellipticine exhibited identical spectral properties as the natural alkaloid[13]. Its conversion into ellipticine has been reported previously[13c].

The simplicity and potential versatility of this new methodology suggests it will be valuable in the synthesis of a number of pyrido[4,3-b]carbazole alkaloids. Moreover the methodology should be readily adapted to a new indole synthesis.

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