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Unexpected [3 + 2] Cycloaddition between Ethyl α-(*N*,*N*-dimethylamino)pentadienoate and Acrylonitrile

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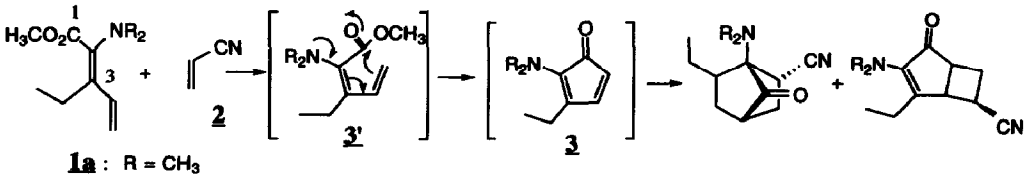
Abstract : The reaction of ethyl 2-(*N*,*N*-dimethylamino)penta-2,4-dienoate **4** with acrylonitrile **2** gave the methyl *N*-methyl-2-(2-propenyl)-3-cyano-pyrrolidine-2-carboxylate **5a** and **5b** as a [3 + 2]-atoms "cycloadducts". The putative [1,3] dipolar intermediate species azomethine ylide **4c**, results from [1,6] hydrogen shift of one N(CH_3) proton.

The access to pyrrolidine derivatives from dienaminocarboxylate **1a** and acrylonitrile **2** [under Diels-Alder reaction conditions] was not expected. For a long time, it has been known that dienamines display enhanced Diels-Alder reactivity towards electron-withdrawing olefins. Recently, a careful study was made of the regio- and stereochemistry of the reaction of (*E*)-1-(*N*,*N*-dimethylamino)-1,3-butadiene with classical dienophiles that give [4 + 2] cycloadducts[2]. The [4 + 2] cycloaddition of 1,1-bis(*N*,*N*-dimethylamino)-1,3-butadiene with acrylonitrile, for instance, requires elevated temperatures[3]. The reaction with tetracyanoethylene involves a zwitterionic intermediate that is also invoked for the reaction of (*E*)-1-(*N*,*N*-dimethylamino)-1,3-butadiene with dimethyl dicyanofumarate[4] In addition, the chemical behaviour and synthetic applications of 2-morpholinoaminobuta-1,3-dienes in typical C-alkylation or [4 + 2] cycloaddition reactions have been thoroughly studied[5].

The α-(*N*-allyl,*N*-methylamino)-dienenitrile acts as a nucleophile in [4 + 2] and [2 + 2] cycloadditions with electron-deficient double bonds[6], sometimes with cycloadduct ring opening and electrocyclization[7]. Moreover, it has been observed that methyl 2-methylthiopenta-2,4-dienoate behaves as a dienophile through its terminal double bond[8].

Nevertheless, we have found[9] that α-dienaminocarboxylates **1a**, **b**, **c** are equivalent to aminocyclopentadienones **3** in thermal cycloaddition reactions with **2** (Scheme 1).



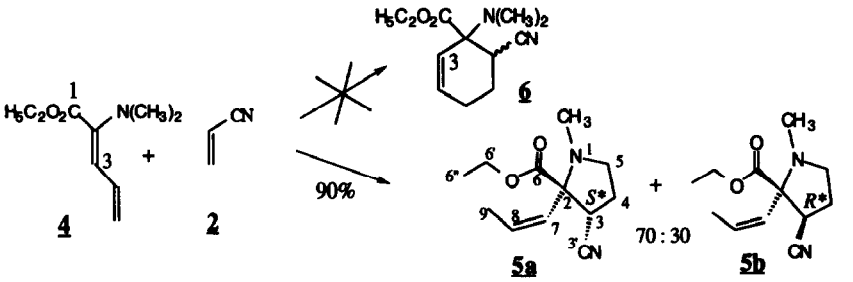
1a : R = CH_3
1b : R = C_2H_5
1c : R_2 = $(CH_2)_5$

Scheme 1

The reaction mechanism is not fully understood ([4 + 2] cycloaddition may be disfavored by steric hindrance), but transitory aminocyclopentadienone **3** could result from intramolecular nucleophilic addition of the amino group onto the carboxylate through the diene as shown in **3'**. Such a mechanism has been described in

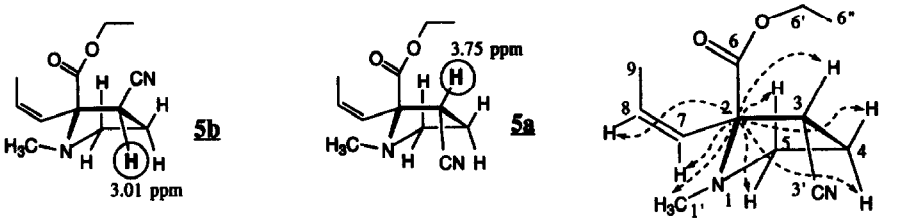
an intramolecular reaction between carboxylate and enamine[10]. In order to diminish steric hindrance at the C-3 position (compounds 1), we have prepared the dienaminocarboxylate 4 (without any substituent at this center) from ethyl *N,N*-dimethylglycinate and propargyl bromide according to Babayan[11] and Viehe[12]. The only isomer obtained had the *Z* configuration.

Compound 4 was tested against acrylonitrile (Scheme 2). Diene 4 (0.25 mol.) in presence of a large excess of acrylonitrile (20 cm^3) was refluxed (110°C) for 10 hours to afford a mixture of two compounds in 90 % yield. These products were the *rel-(S)* and *rel-(R)* cycloadducts 5a and 5b (70 : 30)[13], inseparable even after repeated column chromatography. The classical Diels-Alder product 6 was not observed.



Scheme 2

The structures of 5a and 5b were determined from their spectral data as a mixture. IR absorption at 2242 cm^{-1} due to the cyano group, clearly indicates the incorporation of 2 in the structures and absorption at 1722 cm^{-1} to the carbonyl group. In the ^1H NMR spectrum, an unexpected spin system accounting for CH_3-CH=CH- shows up and J-modulated ^{13}C NMR spectrum[14] displays a methine (δ/ppm 5a = 37.7, 5b = 38.5) and two methylenic carbons (δ/ppm 5a = 27.8 and 51.1, 5b = 26.9 and 51.4). HMQC[15] experiment allows us to assign the chemical shifts to the directly bonded protons as reported below[16]. The COSY spectrum[17] clearly indicates that only the most shielded methylenic protons (5a, δ = 2.21, 2.36 ppm ; 5b, δ = 2.33 ppm), correlate with the three other ones and thus, must be the CH_2 at C-4. As EI-HRMS gives a molecular ion at 222.1355 (corresponding to $C_{12}H_{18}N_2O_2$; calc. : 222.1368) this product is necessarily cyclic, but is not 6, the expected one resulting of a [4 + 2] cycloaddition.

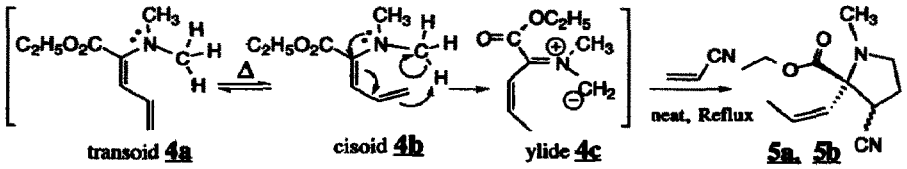


Scheme 3

Both isomers 5a and 5b have the propenyl group in a *Z* configuration as indicated by the proton NMR spectrum with $J_{H7,H8}$ values of 11.6 and 11.8 Hz, respectively[18]. On the basis of the chemical shifts of the H3 protons of these two isomers (δ = 3.75 and 3.01 ppm), we assign the "cis" relationship of this proton with the carboethoxyl group for the major isomer 5a (δ = 3.75 ppm) in which H3 is deshielded[19] (see 5a in Scheme 3) and a "trans" configuration to the minor isomer 5b, in which H3 is shielded (δ = 3.01 ppm) by the nitrogen lone pair proximity. Long range heteronuclear correlations (HMBC[20]), shown in Scheme 3 for the quaternary carbon C-2 are all in agreement with the proposed structures.

Without any doubt, such pyrrolidine systems are very interesting intermediates for the synthesis of biologically important heterocyclics[21].

The proposed reaction mechanism is shown below (Scheme 4). The basicity of the amino group leads to dipolar forms **4a** and **4b** in which the N-methyl hydrogens have an enhanced acidic character and the carboethoxyle takes part to the carbanion stabilization. Only in the case of cisoid **4b**, the [1,6] proton shift can occur, to produce in a concerted manner the azomethine ylide **4c**. The *Z* configuration of the double bond in the adducts is a good indication of participation of such an intermediate. This ylide is trapped by acrylonitrile to produce pyrrolidines **5a** and **5b**. Recently[22], some authors have reported the [1,6] hydrogen shift of an allylic proton preceding an intramolecular ring closure of an α-*N*-allylamino dienenitrile. As **5a** and **5b** are formed in 90% yield, the observed regioselectivity of the addition to acrylonitrile is further accounting for a dipole HO-controlled reacting with an electron-deficient dipolarophile[23].



Scheme 4

Conclusion

In the case of this unsubstituted dienaminocarboxylate, the formation of an alkylidene azomethine ylide seems to be straightforward, and even though this example does not allow us to elucidate the mechanism of the substituted ones, as it was aimed, this reaction constitutes an efficient pathway from dienaminocarboxylate to highly functionalized alkylidene pyrrolidine (proline derivative).

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16 Data for **5a** and **5b** (in mixture) : IR $\nu(cm^{-1})$ (film) : 1722, 2242, 3020. MS, m/z (%) (relative intensity) 222 [$M^{+\cdot}$] (16), 181 (6), 149 (100).
Data for **5a** (from the mixture of **5a** and **5b**) ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, 3H, J = 7.1 Hz, H6"), 1.63 (dd, 3H, J = 7.3, 1.7 Hz, H9), 2.21 (dddd, 1H, J = 20.0, 9.0, 7.0, 4.1 Hz, H4), 2.36 (m, 1H, H4), 2.41 (s, 3H, H1'), 2.51 (dt, 1H, J = 9.1, 3.4 Hz, H5), 3.13 (dt, 1H, J = 9.1, 7.0 Hz, H5), 3.75 (dd, 1H, J = 9.5, 4.1 Hz, H3), 4.22 (q, 2H, J = 7.1 Hz, H6'), 5.59 (dq, 1H, J = 11.6, 1.7 Hz, H7), 5.91 (dq, 1H, J = 11.6, 7.2 Hz, H8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4 (C6"), 14.7 (C9), 27.8 (C4), 35.6 (C1'), 37.7 (C3), 51.1 (C5), 61.3 (C6'), 72.2 (C2), 120.8 (C3'), 127.7 (C7), 130.6 (C8), 169.9 (C6).
Data for **5b** (from the mixture of **5a** and **5b**) ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36 (t, 3H, J = 1.3 Hz, H6"), 1.77 (dd, 3H, J = 7.4, 1.8 Hz, H9), 2.29 (s, 3H, H1'), 2.33 (m, 2H, H4), 2.72 (dt, 1H, J = 9.1, 0.9 Hz, H5), 3.01 (t, 1H, J = 9.1 Hz, H3), 3.12 (m, 1H, H5), 4.30 (q, 2H, J = 7.3 Hz, H6'), 5.46 (dq, 1H, J = 11.8, 1.8 Hz, H7), 5.85 (dq, 1H, J = 11.8, 7.4 Hz, H8) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4 (C6"), 14.9 (C9), 26.9 (C4), 35.4 (C1'), 38.5 (C3), 51.4 (C5), 61.4 (C6'), 72.8 (C2), 119.9 (C3'), 127.6 (C7), 131.1 (C8), 169.9 (C6).

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