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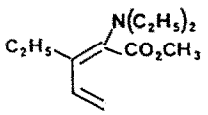
GEM-ACCEPTOR, DONOR-DISUBSTITUTED DIENES IN CYCLOADDITION FACILE [1,3] REARRANGEMENT OF NEW BICYCLO [2.2.1] HEPT-5-ENE-7-ONES

Mireille Bourhis*, Michel Goursolle, Jean-Michel Léger
Laboratoire de Chimie Physique et Analytique associé au CNRS. Université de Bordeaux II - 33076 Bordeaux France.

Jean-Georges Duboudin [a], Françoise Duboudin [b], Philippe Picard [c]
a) Ecole Nationale Supérieure de Chimie et de Physique de Bordeaux. b) Laboratoire de Chimie Organique associé au CNRS.
c) Laboratoire de Cristallographie associé au CNRS. Université de Bordeaux I - 33405 Talence France.

Summary: *The (4+2) cycloaddition of methyl 1-diethylamino-2-ethyl-1,3-butadiene-1-carboxylate was performed with acrylonitrile. The cycloadduct bridges over to form 1-diethylamino-6-ethyl-bicyclo [2.2.1] hept-5-ene-7-one-2-carbonitrile 3. We demonstrate that this latter product undergoes facile [1,3] sigmatropic rearrangement.*

There is a continued interest in being able to synthesize new aminocarboxylates for pharmacological study. In a previous note[1], we reported the original synthesis of aminobicyclo [2.2.1] heptenones **3** and aminobicyclo [3.2.0] heptenones **4**. These unexpected compounds are formed when dienaminocarboxylates **1** are mixed with acrylonitrile under thermal cycloaddition conditions. The cycloadduct **2** is not isolated.



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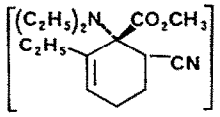

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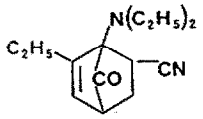

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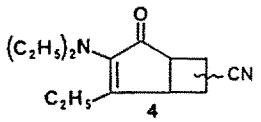

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We now report a mechanistic study of the action of methyl 1-diethylamino-2-ethyl-1,3-butadiene-1-carboxylate **1** with acrylonitrile. X-ray, ^{1}H and ^{13}C NMR analyses give the regio-and stereoisomery of the new bicycloheptenonecarbonitriles **3** and **4**. This structural assignment offers a new insight into the mechanism of the formation of bicycloheptenones.

The dienaminocarboxylate 1 (0.05 mol.) was reacted with acrylonitrile (large excess, reflux 36h). The 1-diethylamino-6-ethyl bicyclo [2.2.1] hept-5-en-7-one-2-carbonitrile 3 and the 3-diethylamino-4-ethyl bicyclo [3.2.0] hept-3-en-2-onecarbonitrile 4 were isolated (50/50) by preparative HPLC. Previously[2], we have identified compounds 3 and 4.

A single crystal X-ray analysis[3] is performed on aminobicyclo [2.2.1] heptenone 3. A drawing of the molecular structure is shown in figure 1, and shows an endo-carbonitrile stereoisomery.

Figure 1

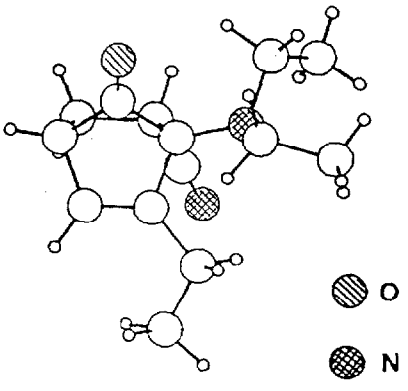
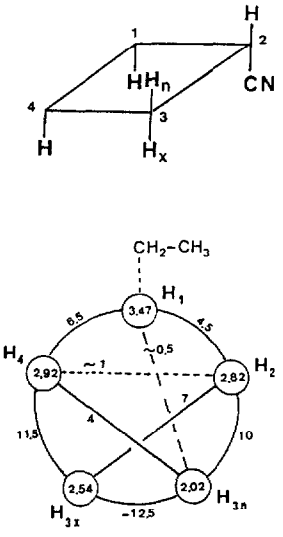


Figure 2

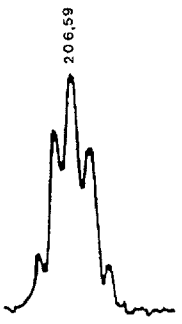


The regio- and stereochemical assignment of the aminobicyclo [3.2.0] heptenone 4 is made from ^{1}H and ^{13}C NMR.

Although difficulties have often been encountered[4] in attempts to assign the stereochemistry of the four-membered ring system, unambiguous stereochemical assignment can however be made in our aminobicyclo [3.2.0] heptenonecarbonitrile from the vicinal coupling constants between protons of the cyclobutane ring (figure 2). Indeed, we know that the two junction cycle protons must have a cis-relationship, $^{3}J_{cis}H_1H_4$ = 6.5 Hz. It can be seen that one of the junction protons (H_4) shows a cis-relationship with proton (H_{3x}) and a trans-relationship with proton (H_{3n}). It is known[4] that a very small value of ^{3}J in the four-membered ring is indicative of a trans-relationship between two vicinal protons. The relationship $^{3}J_{cis} > {}^{3}J_{trans}$ is observed in all types of four-membered ring. Accordingly, the values of the vicinal coupling constants reported in figure 2 are $^{3}J_{cis}$ = 11.5 Hz and $^{3}J_{trans}$ = 4.0 Hz.

The other junction proton (H_1) shows a ^3J coupling with proton CHCN (H_2), ^3J = 4.5 Hz. Such a small value of the vicinal coupling constant ^3J is indicative of a trans-relationship between the two vicinal protons. This result is in agreement with the values of $^3J_{cis}H_2H_{3n}$ = 10 Hz > $^3J_{trans}H_2H_{3x}$ = 7 Hz. Accordingly, the carbonitrile function, like protons (H_1) and (H_4), presents an exo-stereoisomery.

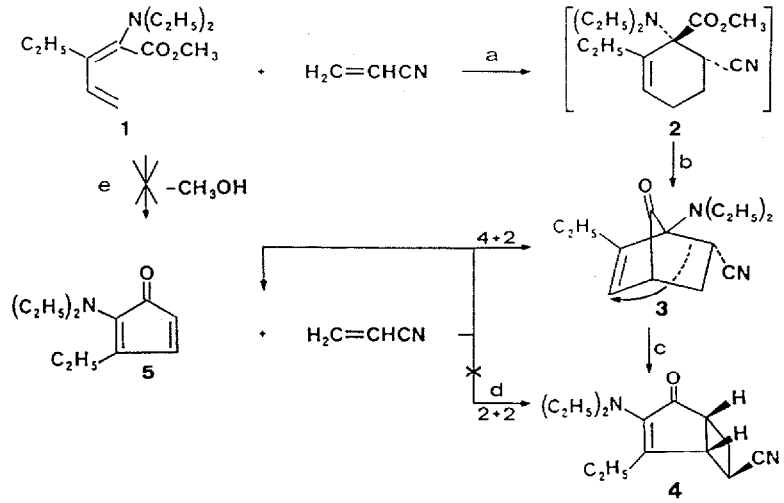
Figure 3.



The position of the cyano group in the aminobicyclo [3.2.0] heptenone **4** is found by analyzing its ^{13}C NMR spectrum (90 MHz, $CHCl_3$). The C=O signal at 206.5 ppm comprising a quintuplet (figure 3) involves four equivalent couplings (J ≈ 4.0 Hz each). It is known[5] that ^2J O=C-C-H assumes values between 5 and 8 Hz, and $^3J_{syn}$ and $^3J_{anti}$ O=C-C-C-H have similar values. The signal multiplicity is not an artefact, since a ^{13}C NMR spectrum (67.88 MHz, $CHCl_3$) shows the same multiplicity. Only the regioisomery shown in scheme 1 permits these couplings.

Thus, the following transformations may be considered :

Scheme 1.



We initially thought that aminobicyclo [2.2.1] heptenone **3** and aminobicyclo [3.2.0] heptenone **4** would result from [4+2] and [2+2] cycloaddition reactions of aminocyclopentadienone **5**. However, we now show that aminocyclopentadienone is not a reactional intermediary in the transformations studied. Indeed, aminocyclopentadienone **5** is not formed by cyclisation of dienaminocarboxylate **1** (scheme 1e).

IR, NMR spectra and gas chromatography did not reveal the formation of methanol when heating **1** at 90°C for 72 hours. The aminocyclopentadienone **5** would not lead to (scheme 1d) this site selectivity by $\pi^2+\pi^2$ cycloaddition[6]. Moreover, after heating (96h) a solution of aminobicyclo [2.2.1] heptenone **3** in a large excess of acrylonitrile at 90°C, aminobicyclo [3.2.0] heptenone **4** is quantitatively isolated. It results that **4** is very certainly formed by [1,3] sigmatropic rearrangement of aminobicyclo [2.2.1] heptenone **3** (scheme 1c) with retention of configuration in migrating group. This is according to a typical pericyclic process[7] in which the migration framework and the migrating group have widely different polarities, specially when the migrating group is substituted by a cyano group.

This study points to the following conclusions :

a- Cycloaddition (4+2) between dienaminocarboxylate **1** and acrylonitrile has taken place.

b- The aminocyclohexenecarboxylate **2** is not isolated ; his cyclisation to aminobicyclo [2.2.1] heptenone **3** may be explained by the basic environment and steric hindrance.

c- The [1,3] sigmatropic rearrangement of the aminobicyclo [2.2.1] heptenone **3** leads to conjugate aminobicyclo [3.2.0] heptenone **4**.

REFERENCES AND NOTES

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2. M. Bourhis, R. Golse, M. Goursolle, P. Picard, Tetrahedron Lett., 26, 3445, 1985.
3. The crystals of methyl 1-diethylamino-6-ethyl bicyclo [2.2.1] hept-5-ene-7-one-2-carboxylate are monoclinical, space group $P2_1/c$, a = 7.774(5), b = 15.321(7), c = 11.556(4) Å. ρ_c = 1.14 g.cm^{-3} for 4 formula units per cell. A total of 2295 independent reflexions were collected of which 1144 were accepted as statistically above background on the basis that $I \geq 3\sigma(I)$. The structure was solved by direct methods using the Multan-80 program (P.Main, S.J.Fiske, S.E.Hull, L.Lessinger, G.Germain, J.P.Declercq, M.M.Woolfson, Multan 80, Univ.York England and Louvain Belgium, 1980) and refined to a final R =0.0694.
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