synthesis of $\alpha\text{-activated }\Delta^1$ pyrroline and Δ^1 piperideine : 1,3 dipolar and anionic reactivities.

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SUMMARY : The q-activated Δ^1 pyrroline <u>4</u> and Δ^1 piperideine <u>5</u> are synthesized. By thermal reaction with alkenes they give 1,3 dipolar cycloadducts and their anions lead to alkylation products.

It is well established that imine derivatives of α -aminoesters exhibit 1,3-dipolar ^[1-8] and 3⁻ + 2⁽⁸⁻¹⁰⁾ reactivities towards alkenes to give pyrrolidines and(or) alkylated imines. To our knowledge only one example of 1,3 dipolar activity is known for a cyclic imine ^[11]. We now report our results related to the 1,3-dipolar and anionic reactivities of Δ^1 -pyrroline <u>4</u> and Δ^1 -piperideine <u>5</u>. These compounds, hitherto unkown, are synthesized by alkylation of imine <u>1</u> in the presence of NaH/DMSO by the protected ketones <u>2⁽¹²⁾</u> to give <u>3</u> in quantitative yield.



The simultaneous removal of the two protecting groups (imine and dioxolane) is readily achieved by stirring 3 in ether with 1M HCl, then treating the aqueous layer by 1M NaOH in the presence of ether. After drying, evaporation gives a quantitative yield of crude 4 and 5 which are purified by short path distillation and characterization by ¹H and ¹³C NMR, mass spectrometry and elemental analysis (4 Eb_{0.03} = 110°, mp = 50°, 62 % yield; $5 \text{ Eb}_{0.03} = 130^\circ$, 66 % yield). Heating 4 and 5 in the presence of N-methyl or N-phenyl male-imide in refluxing toluene during 40 to 60 hours affords th bicyclic cycloadducts <u>6-9</u> in good yields.



These adducts are purified by short path distillation or recristallization, and characterized by $^1{\rm H}$ NMR, mass spectrometry and elemental analysis. For instance :

<u>6</u> Eb_{0.03} = 170°, mp = 174°; 70 % yield; ¹H NMR, CDCl₃, TMS : 1.83 to 2.5 (m, 5H) ; 2.9 (s, 3H) ; 3.2 (q, 2H, $J_{AB} = 7$ Hz) ; 3.9 (s, 3H) ; 7.23 to 7.45 (m, 5H). Mass spectrometry : $C_{17}H_{18}N_{2}O_{4}$ (calculated : 314.1266 ; found : 314.1260).

 $\underline{9} \ mp = 208^{\circ} \ (EtOH), \ 70^{\circ} \ yield ; \ {}^{1} H \ NMR, \ CDCl_{3}, \ TMS, \ 300 \ MHz ; \ 1.56 \ to \ 2.0 \ (m, \ 4H) ; \ 2.32 \ (m, \ 2H) ; \ 2.53 \ (s, \ 1H) ; \ 3.44 \ (q, \ 2H, \ J_{AB} = 7.3 \ Hz, \ this \ signal \ appears \ as \ a \ singlet \ at \ 80 \ MHz) ; \ 3.85 \ (s, \ 3H) ; \ 7.04 \ to \ 7.62 \ (m, \ 10 \ H). \ Mass \ spectrometry : \ C_{23}H_{22}N_{2}O_{4} \ (calculated ted : \ 390.1579 \ ; \ found \ : \ 390.1578).$

The exo configuration is suggested by analogy with the results of Grigg $^{(11)}$ and with the following results.

 Δ^1 -Piperideine <u>5</u> reacts in the same conditions or in sealed tubes in toluene at 180° during 16 h with methyl-fumarate-maleate and acrylate to give the corresponding bicyclic adducts : <u>10</u> Eb_{0.03} = 150°, 70 % yield ; <u>11</u> mp = 157° (Et₂0), 70 % yield ; <u>12</u> Eb_{0.03} = 120°, 73 % yield.



All these compounds are characterized by 1 H NMR (especially a methyl of ester group shielded at 3.18 ; 3.08 ; 3.13 ppm which implies a cis relationship with the phenyl ; for <u>10</u> J_{AB} = 7 Hz and for <u>11</u> J_{AB} = 9.6 Hz), mass spectrometry and elemental analysis.

In the same conditions, addition of $\underline{4}$ to benzylidene malonate follows a different course leading to an alkylation product $\underline{13}$. The formation of a single diastereoisomer may result from a primary 1,3-dipolar cycloaddition followed by ring chain tautomerism and prototropy.



The thermal behaviour of 5 in the presence of benzylidene malonate is initially the same but the end product is different. The reaction leads to a mixture (50/50) of two diastereoisomers 14 and 14' characterized by ¹H NMR and mass spectrometry. The formation of these compounds may also result from a primary cycloaddition giving the expected cycloadduct which undergoes ring chain tautomerism and prototropy, but the alkylated product 15 gives rise to an equilibrium imine enamine followed by nucleophilic attack of the nitrogen of the later on the carbonyl of an ester group.



This particular reaction is not observed in the case of the five membered ring probably because the imine enamine equilibrium is less favoured.

We also studied the anionic reactivity of $\underline{4}$ and $\underline{5}$ towards benzylidene malonate. The corresponding anions generated with LDA in THF at -80° lead to mixtures of diastereoisomeric alkylated compounds $\underline{13}$ and $\underline{13'}$ (69/31) starting from $\underline{4}$ and $\underline{15}$, $\underline{15'}$ (75/25) starting from 5. These structures are assigned on the basis of ${}^{1}\text{H}$ NMR and mass spectrometry.



Interestingly, an attempt to separate $\underline{15}$ and $\underline{15'}$ by distillation gave the mixture $\underline{14} + \underline{14'}$.

So Δ^1 -pyrroline and Δ^1 -pyperideine are potential azomethine-ylids which allow an easy synthesis of bicyclic cycloadducts. The anionic reactivity leads to alkylated products.

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- 12. It is necessary to use protected ketones to avoid elimination in the case of 2 n = 2, and cyclopropanation in the case of 2 n = 3.

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