212. High Acceleration and Improved Diastereoselectivity of Intramolecular Ene-Type Reactions by Diethylaluminum Chloride

Preliminary Communication

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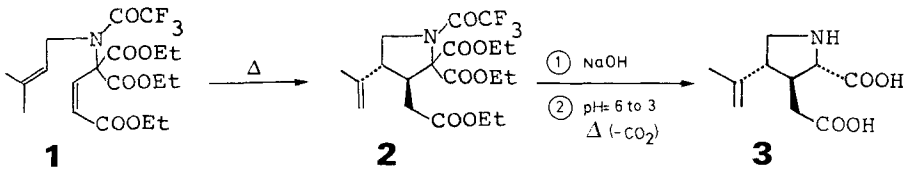
Summary

The pyrrolidines **2** and **10** were obtained by thermal ene-reactions at +70° and +180° from the (*Z*)-4-aza-1,6-diene **1** and from the (*E*)-4-aza-1,6-diene **9** in the ratios of 75:25 and 50:50, respectively. On the other hand, these cyclizations proceeded readily in the presence of diethylaluminum chloride at −78° and −35° giving in high yield the *trans*-pyrrolidine **2** from **1** with 100% and from **9** with 89% diastereoselectivity.

Recently, we have reported a simple synthesis of the racemic amino acid **3** by the sequence **1**→**2**→**3** *(Scheme 1)* [1]. In conjunction with our systematic studies of intramolecular ene reactions [2] we felt it worthwhile to re-examine the key step **1**→**2** in more detail. One important question was the extent to which the unusual 75% diastereoselectivity in favour of the *trans*-product **2**[1]) depends on the enophile geometry in **1**.

The (*Z*)-diene **1**[2])[3]) was easily accessible *via* the previously described preparation of the (*Z*)-acrylate **6** (J(AB) = 12 Hz) [3] (treatment of the *cis*-β-chloroacrylate **4**

Scheme 1



[1]) Thermal cyclization of **1** furnished a 3:1 mixture of **2** and its *cis*-isomer **10** as we found by ^{1}H-NMR. analysis of the cyclization mixture *(vide infra)* and of the aminoacid mixture obtained together with (±)-**3**.

[2]) IR., ^{1}H-NMR. ($CDCl_3$) and MS. are in full agreement with the assigned structure.

[3]) Pertinent ^{1}H-NMR. data ($CDCl_3$, internal standard TMS. ($\delta = 0$ ppm), J = spin-spin coupling constant) are listed for the 1,6-dienes **1** and **9** as follows: for **1** $\delta(H_A) = 6.13$, $\delta(H_B) = 6.29$, J(AB) = 12.5 Hz; for **9** $\delta(H_A) = 6.26$, $\delta(H_B) = 7.17$, J(AB) = 16 Hz.

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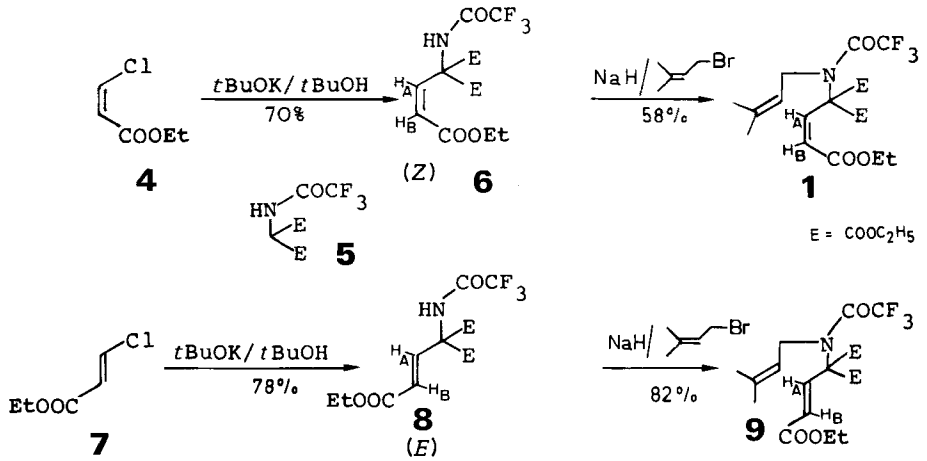
with the acylaminomalonic ester **5** in the presence of 1 mol-equiv. of *t*-BuOK) followed by *N*-alkenylation of **6**[4]) *(Scheme 2)*.

Analogous *Michael*-addition starting from the *trans-β*-chloroacrylate **7**[5]) furnished stereospecifically the (*E*)-ester **8**[2])[6]) (J(AB) = 16 Hz, 78% yield), which on alkenylation gave the (*E*)-diene **9**[2])[3]) (82% yield).

We were then kindly informed by *P. D. Kennewell* about independent careful studies of the thermolyses of the (*Z*)- and (*E*)-dienes **1** and **9** [6][7]). The British authors obtained the pyrrolidines **10** and **2** also in a ratio of 25:75 from **1** but in a ratio of 53:47 from **2**, and furthermore, characterized the products **2** and **10** after their separation by HPLC. Having a convenient stereospecific route to the (*E*)-diene in hand, we readily confirmed the lack of diastereoselectivity on thermolysis of **9**[8]) irrespective of the reaction temperature (+70 and +180°) indicating a kinetic control of the stereochemistry *(Scheme 3)*. However, the situation changed dramatically when we carried out the cyclization of **1** and **9** in the presence of diethylaluminum chloride (a mild *Lewis* acid and HCl-scavenger)[9]).

Thus, addition of Et_2AlCl (3 mol-equiv.) to a solution of the (*Z*)-diene **1** in dry CH_2Cl_2 at −78° and quenching of the reaction with water at −78° after 8 h

Scheme 2



[4]) Compound **6** was treated with NaH in the presence of an excess of 1-bromo-3-methyl-2-butene in HMPA in order to alkenylate the deprotonated amide as rapidly as possible.

[5]) Compound **7** was prepared by esterification of *trans-β*-chloroacrylic acid [4] (heating under reflux in EtOH/benzene for 40 h in the presence of a catalytic amount of toluenesulfonic acid with azeotropic removal of water).

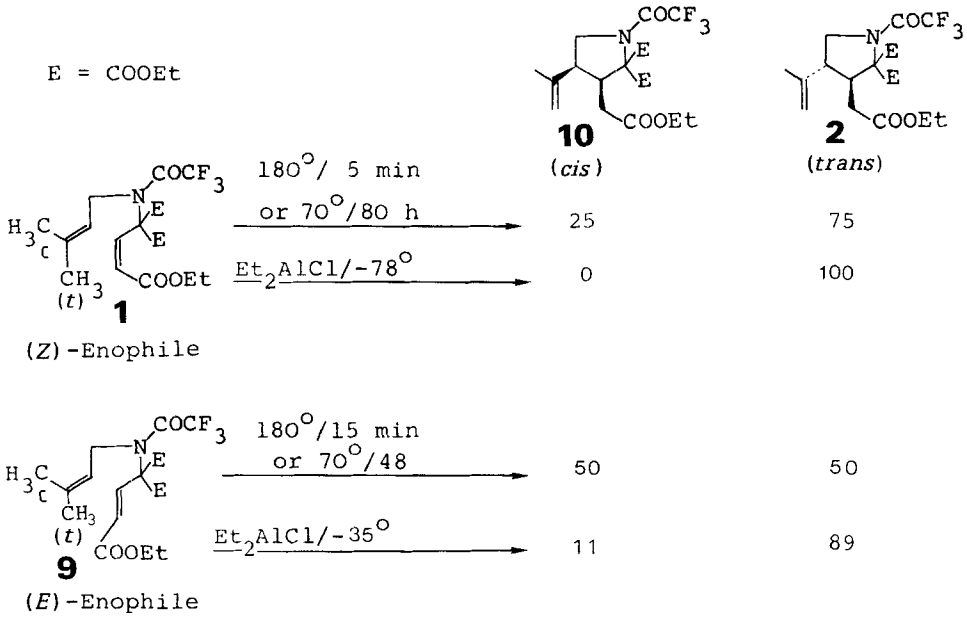
[6]) For the stereospecific substitution of *cis*- and *trans-β*-chloroacrylates by an enolate see [5].

[7]) Compounds **1** and **9** were prepared by *Michael* addition of **5** to ethylpropiolate giving a 1:3 mixture of **6** and **8**, which was separated by HPLC. prior to alkenylation.

[8]) The mixtures of **2** and **10** were analyzed by ^{1}H-NMR. measurements based on the signals of the olefinic protons by assigning a singlet at $\delta = 5.96$ to the *trans*-product **2** and two singlets at $\delta = 5.72$ and 6.05 to the *cis*-isomer **10** [6] [7].

[9]) $EtAlCl_2$ and Me_2AlCl have been recently used by *B. B. Snider* as catalysts in bimolecular ene reactions (s. [8]).

Scheme 3



yielded exclusively the *trans*-substituted pyrrolidine **2** in 90% yield[10]). Not even a trace of the *cis*-isomer **10** was found.

This enormous rate acceleration of the reaction **1**→**2** may be attributed mainly but not entirely to the complexation of the acrylic ester group with the *Lewis* acid [8] as indicated by analogous cyclizations of other 1,6-dienes containing an acrylic-ester enophile [9]. We were also pleased to find that the (*E*)-diene **9** cyclized with 89% diastereoselectivity to the *trans*-product **2** in the presence of 3 mol-equiv. of Et_2AlCl. The reaction **9**→**2** proceeded somewhat slower than the cyclization of **1**, giving after 6 h at −35° the 11:89 mixture of **10** and **2** in 78% yield. The kinetic nature of the *Lewis*-acid promoted diastereoselectivity in the reactions **1**→**2** and **9**→**2** was supported by the observation that a 1:1 mixture of **2** and **10** remained virtually unchanged on treatment with 30 mol-equiv. of Et_2AlCl in CH_2Cl_2 at 25° for 10 min. Accordingly, we attempted to rationalize the observed stereochemistry of the thermal and Et_2AlCl-mediated cyclizations of **1** and **9** by examination of the possible transition states *(Scheme 4)*[11]).

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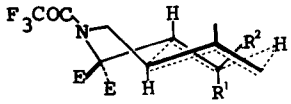
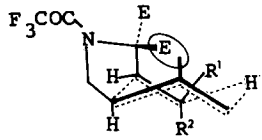
[10]) Using 30 mol-equiv. of Et_2AlCl the cyclization **1**→**2** was completed instantaneously at −78°. More conveniently the reaction was carried out with 3 mol-equiv. of Et_2AlCl at −35°, 30 min. The same diastereoselectivity was observed at −78° and −35°.

[11]) As a working model we have postulated a chair-like transition state for the ene reaction. This differs from the traditional model [10], mainly in the assumption that the migrating H-atom does not lie on the axis which joins the termini of the ene and the enophile. A chair-like transition state has been also proposed for the aldol reaction [11], which may be regarded as a version of the ene reaction.

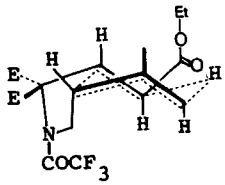
Scheme 4



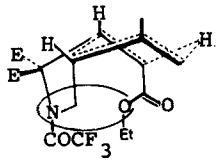
t-Ene → **2** *(trans)*
A (*Z*)-Enophile (R^1 = COOEt)
B (*E*)-Enophile (R^2 = COOEt)



t-Ene → **10** *(cis)*
C (*Z*)-Enophile (R^1 = COOEt)
D (*E*)-Enophile (R^2 = COOEt)
strong repulsion



c-Ene → **10** *(cis)*
F (*E*)-Enophile



c-Ene → **10** *(cis)*
E (*Z*)-Enophile
moderate repulsion

This analysis accounts for H-transfer from the allylic *trans*-methyl (*t*-ene) as well as *cis*-methyl (*c*-ene) groups; the latter is forced by angle strain to yield only the *cis*-substituted product **10**, whereas the former may in principle lead to both *trans*- and *cis*-pyrrolidines **2** and **10**. However, formation of the *cis*-product **10** *via* a *t*-ene unit (transition states **C** and **D**) invariably shows a strong repulsion between one of the malonic ester groups and the olefinic methyl substituent regardless of the enophile geometry. Transition state **E** is disfavoured by 1,3-diaxial perturbation which is absent in transition state **F**; the transition states **A** and **B** are virtually free from non-bonding interactions. It thus follows that thermal cyclizations of **1** (containing a (*Z*)-enophile) should prefer transition state **A** over **C** and **E** explaining the predominant formation of **2**. Thermal ene-reaction of **9** (containing an (*E*)-enophile) indicates the compatibility of the non-encumbered transition states **B** and **F** since **2** and **10** were formed in equal amounts. Although the operation of concerted ene-reactions in the *Lewis*-acid induced cyclizations of **1** and **9** remains to be proved, it agrees with the observed stereochemistry. Thus, complexation of the ester and amide units increases their steric bulk, and therefore the repulsions in the states **C**, **D**, and, somewhat less, in **F**. Consequently, it appears that in the presence of Et_2AlCl the *trans*-product **2** is formed from **1** exclusively *via* transition state **A** and from **9** preferentially *via* transition state **B**.

Although the mechanism of the *Lewis*-acid promoted ene-type reactions of the dienes **1** and **9** has not been established, these findings may prove of value in the synthesis of certain natural products[12]).

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[12]) For an application to the diastereo- and enantioselective synthesis of (+)-allokainic acid see the subsequent communication [12].

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