

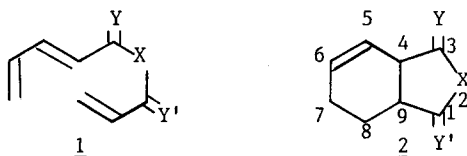
STEREOSELECTIVITY IN INTRAMOLECULAR DIELS ALDER REACTIONS I :
SYNTHESIS OF HYDROISOINDOLES

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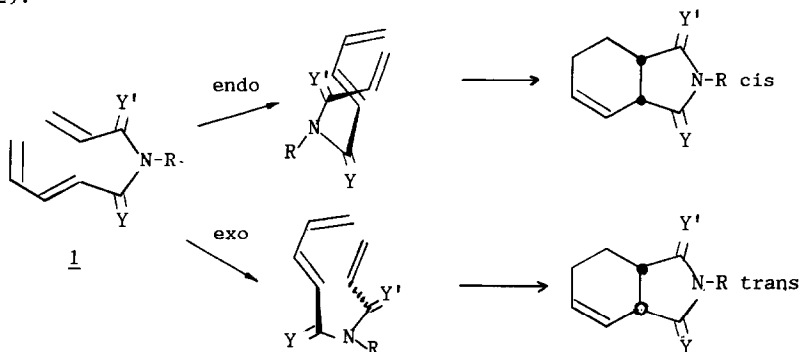
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SUMMARY : The effects of solvent, steric bulk and the nature of the electron demand (normal or inverse) on the ratio of cis vs trans isomers during intramolecular DIELS-ALDER cyclization of 4-aza-1,6,8-trienes were studied.

Cyclization of polyenes using the intramolecular DIELS-ALDER (IMDA) reaction has been the subject of much recent research (1). The products, 2, can be used for the synthesis of natural products and are therefore of considerable interest.



However the applications of IMDA reaction are rather limited since trienes 1 can react via two different transition states of similar energy and give a mixed cyclization product composed of cis and trans isomers (2).



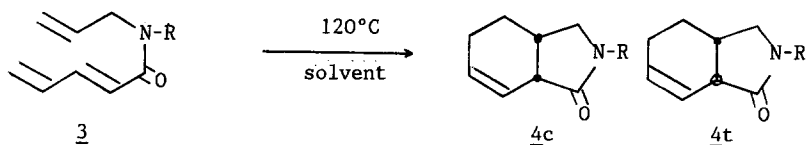
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The results of systematic studies of triene 1 cyclization, when $X = N-R$ and $Y = H_2$ or O , are described in this present communication. Trienes 3 exhibiting inverse electron demand and trienes 5 exhibiting normal electron demand (9), were prepared by MUKAIYAMA coupling (3) of corresponding amines (4) with unsaturated carboxylic acids (5). Cyclization was performed by heating a triene with an appropriate solvent in a sealed tube at $120^\circ C$ for an adequate period of time. The results (cyclization yields ; % cis and trans isomers), are presented in tables I and II according to the nature of the electron demand, nitrogen substitution and solvent. (Crude compounds were analysed, after evaporation, by NMR (90 MHz $CDCl_3$) and HPLC (hexane, ethyl acetate, SiO_2). Purification was performed by preparative TLC. All spectroscopic data are in agreement with the proposed structures and will be sent on requested).

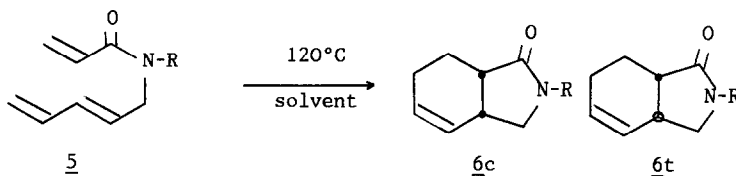
The type of solvent used affected the percentage of cis vs trans compounds obtained. This seemed to be associated with the epimerization which took place at C_9 in the presence of methanol and molecular sieves in the case of IMDA reaction with an inverse electron demand. Moreover, when a 40/60 mixture of the cis/trans adducts were treated as just described 100 % yields of the more thermodynamically stable (6) cis isomer were obtained. No isomerization of this type was observed in the case of IMDA reaction with normal electron demand, as the proton at the C_9 position could not be epimerized under these conditions.

The increased rate of reaction caused by steric hindrance at the nitrogen atom is also of interest. This phenomenon has previously been observed in carbocyclic (7) and heterocyclic systems (8). The most important finding therefore concerned the selectivity (ratio of cis vs trans isomers) of the IMDA reaction vis-à-vis type of electron demand. If it can be hypothesized that no C_9 epimerization took place when toluene was used as solvent (the composition of the mixed isomers 4c/4t or 6c/6t was unaffected by heating at $120^\circ C$ for 20 h with molecular sieves in toluene), it can be concluded that the observed selectivity reflected thermodynamic preferences for exo or endo configurations depending on electron demand.

Molecular models showed that the difference in energy levels between the exo and endo transition states of the IMDA reaction with inverse electron demand was almost negligible and accounted for the similarity between yields of cis and trans isomers. The ratio of isomer yields was biased towards the product with greater thermodynamic stability but independent of nitrogen substitution. Examination of molecular models also indicated that the interaction between the hydrogen atoms of ally-

Table 1 : IMDA cyclization of triene **3** (inverse electron demand)

R	solvent	Time	Cyclisation Yield	<u>4c</u>	<u>4t</u>
CH $\begin{cases} \text{C}_6\text{H}_5 \\ \text{Me} \end{cases}$	Toluene	20h	100 %	42 %	58 %
	Methanol	8h	100 %	100 %	-
CH $\begin{cases} \text{C}_6\text{H}_5 \\ \text{C}_6\text{H}_5 \end{cases}$	Toluene	20h	100 %	66 %	34 %
	Methanol	6h	100 %	100 %	-
H	Toluene	100h	0 %	-	-
	Methanol	100h	0 %	-	-

Table II: IMDA cyclization of triene **5** (normal electron demand)

R	solvent	Time	Cyclisation Yield	<u>4c</u>	<u>4t</u>
CH $\begin{cases} \text{C}_6\text{H}_5 \\ \text{CH}_3 \end{cases}$	Toluene	20h	100 %	56 %	44 %
	Methanol	15h	100 %	57 %	43 %
CH $\begin{cases} \text{C}_6\text{H}_5 \\ \text{C}_6\text{H}_5 \end{cases}$	Toluene	20h	100 %	39 %	61 %
	Methanol	6h	100 %	41 %	59 %

lic methylene and the benzylic carbon substituents in the endo transition state was stronger in the case of the IMDA reaction with normal electron demand. This interaction was further enhanced by steric hindrance at the nitrogen atom which explained why yields of the 6t trans isomer were predominant when the benzyl radical is replaced by a benzhydryl substituent.

In conclusion, the stereoselectivity of IMDA cyclization is regulated by extremely weak steric effects. The reaction with normal electron demand appeared to be more sensitive to these effects than the reaction with inverse electron demand. It is suggested that better knowledge of such factors would permit wider and more efficient use of this intramolecular synthetic process.

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(Received in France 22 May 1985)