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SYNTHESIS OF HYDROISOINDOLES VIA INTRAMOLECULAR DIELS-ALDER REACTIONS

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Summary : Hydroisoindoles are obtained in good yield (70-89 %) from azatrienes. The diastereoselectivity of the cycloaddition depends on the nature of the allylic and nitrogen substituents.

The synthesis of azaheterocycles by intramolecular Diels-Alder reaction (IMDA) is less well developed than the construction of carbocycles or lactones [1] by this methodology. However, the cyclization of azatrienes to hydroisoindoles proceeds readily with [2], or without [3] metal-ion catalysis. The main problem accompanying the choice of this type of strategy is the need to control the stereochemistry of cyclization. In the absence of substituted groups at the end of the triene, the syn and anti conformations are defined by the position of the chain linking the diene and dienophilic moieties. The azatriene may cyclize either via the syn transition state to give the cis-fused product, or via the anti transition state to give the trans-fused product. Chain length, chain substituents, types of diene, dienophile or catalysts are all factors influencing stereochemistry [4]. It is well recognized however that the steric interactions which are important in determining the energy of the transition state [5] are the main factors responsible for the selectivity of the reaction.

The influence of a rigid phenyl substituent in the allylic position of the dienophilic moiety was studied in order to improve our knowledge of the influence of these steric interactions. No carbonyl function was conjugated with the dienic or olefinic part of the azatriene (neutral electron demand) in order to minimize FMO effects. The electron-withdrawing trichloroacetyl group was introduced onto the nitrogen atom in order to increase the reactivity of the trienic system.

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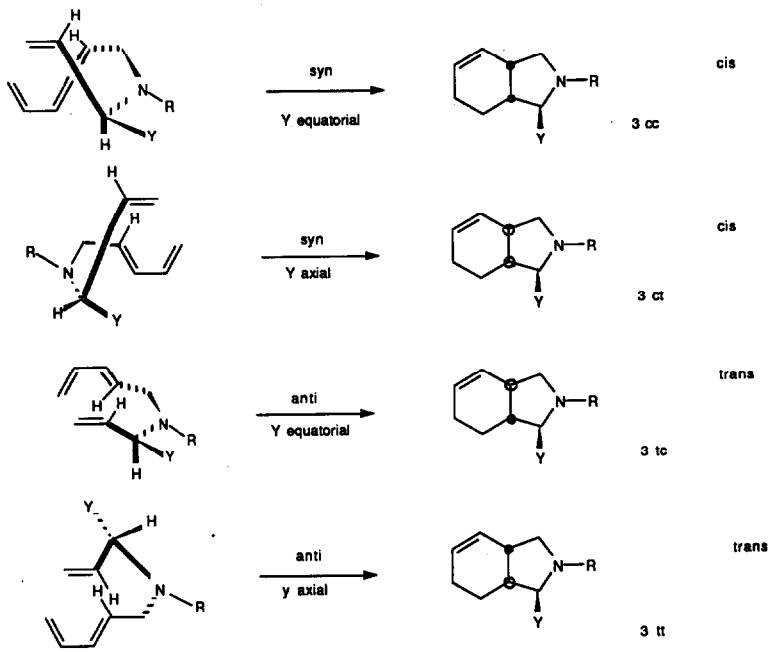
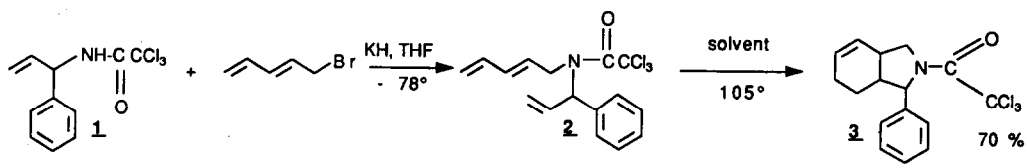
Substituted allylamides 1 were synthesized from cinnamyl alcohol by sigmatropic rearrangement of trichloroacetimidates as described by Overman [6]. Triene 2 was obtained by condensation of amide 1 with pentadienyl bromide.



Cyclisation was performed in a sealed tube maintained at 105°C for 12 h and led to the formation of a mixture of the four diastereomers.



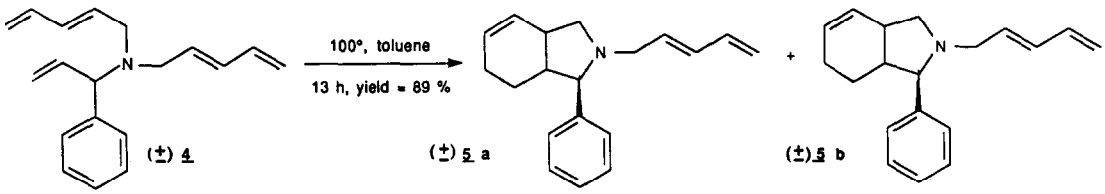
These results gave rise to certain observations :

Hydroisoindole 3	SYN axial ct	ANTI axial tt	ANTI equat. tc	SYN equat. cc
% diastereoisomer obtained in toluene	39	24,5	19,5	17
" " CH_3CN	51	30,5	11,5	7

1) the transition state with the phenyl group in the axial position was favoured in both the syn and anti conformations.

2) examination of molecular models of these two axial conformations indicates that there are fewer non-bonded interactions between the phenyl group and the trichloroacetyl substituent.

Although the percentage of product resulting from syn or anti conformation was approximately the same when the solvent was changed from toluene to the more polar acetonitrile, the difference in the degree of steric interaction between the phenyl and trichloroacetyl substituents was enhonced. Positioning of the phenyl groups in the axial position is favoured in both syn and anti conformations in acetonitrile and leads to an increased yield of the two products resulting from these two favored transition states. Solvation therefore accounts for the increase in the steric effects of the two substituents but does not alter yield or the rate of cyclization.



When the more flexible dipentadienylamine 4 is cyclized, only the two trans fused hydroisoindoles 5 are isolated. Two factors account for this selectivity. The first is the lowering of the steric interaction between the phenyl and the N pentadienyl substituent compared to the trichloroacetyl group such that neither the axial or equatorial positions of the phenyl group is favored. The second reason is statistical : the two pentadienyl groups can be cyclized with the dienophilic part more easily when in the two anti transition states.

The observed diastereofacial differentiation in these cycloadditions demonstrate that both the reactivity and the stereoselectivity of the IMDA reaction of azatrienes are principally under steric control. The choice of an adapted substituent on nitrogen either the use of stereochemical control elements are the most successful way to improve the efficiency of this reaction.

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7. The structures of the four diastereoisomers 3 have been established by IR and NMR spectroscopy using the NOE Difference between H_1, H_6 and H_7 ($CDCl_3$, δ ppm)
3 ct 1.78 (m, 2H), 2.18 (m, 2H), 2.3 (m, 1H), 2.95 (m, 1H), 4.18 (m, 2H), 5.84 (d, 1H), 5.62 (m, 1H), 5.84 (m, 1H), 7.26 (m, 5H)
3 tc 1.5-2.25 (m, 5H), 2.64-2.85 (m, 1H), 3.45-3.8 (m, 1H), 4.5-4.65 (m, 1H), 5.25 (d, 1H), 5.65-5.9 (m, 2H), 7.1-7.4 (m, 5H)
3 tt 1.62 (m, 1H), 1.75 (m, 1H), 1.92 (m, 1H), 2.26 (m, 2H), 2.44 (m, 1H), 3.51 (m, 1H), 4.54 (m, 1H), 4.63 (m, 1H), 5.78 (m, 2H), 7.29 (m, 5H)
3 cc 1.5-2.2 (m, 4H), 2.5-2.65 (m, 1H), 2.75-2.9 (m, 1H), 4.55-4.7 (m, 2H), 5.4 (d, 1H), 5.55-5.8 (m, 1H), 5.8-5.95 (m, 1H), 7.1-7.4 (m, 5H)
5 a 1.4-1.75 (m, 2H), 1.85-2.25 (m, 3H), 2.25-2.5 (m, 1H), 2.85-3.45 (m, 5H), 4.95-5.2 (m, 2H), 5.55-5.85 (m, 3H), 6.02-6.4 (m, 2H), 7.15-7.4 (m, 5H)
5 b 1.3-1.75 (m, 2H), 1.95-2.05 (m, 2H), 2.05-2.1 m, 1H), 2.1-2.25 (m, 1H), 2.55-3.55 (m, 5H), 4.95-5.2 (m, 2H), 5.6-5.85 (m, 3H), 6.05-6.4 (m, 2H), 7.15-7.45 (m, 5H)
The analysis and the separation of these different products has been done by analytical (Lichrosorb Si60 5 m, Heptane 97/dioxane 3) and preparative (Partisil M20 10/25, Heptane 98/dioxane 2) HPLC. All these compounds are isolated as oil.

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