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STEREOSELECTIVITY IN INTRAMOLECULAR DIELS-ALDER REACTION II : INFLUENCE OF ALKYL SUBSTITUENT ON CYCLIZATION OF AZATRIENES

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SUMMARY : Substitution of the allylic moiety of azatrienes by functionalized alkyl groups permits high chemical yields and stereoselectivity during I.M.D.A cyclization. Substituted hydroisoindoles, precursors for natural and pharmaceutical products were prepared with good yields and selectivity.

The intramolecular DIELS-ALDER reaction (I.M.D.A.) has been recognized as a valuable route for the synthesis of fused functionalized nitrogen heterocycles (1).

I.M.D.A. cyclization permits the formation of two CC bonds in one step and many recent papers and reviews have been devoted to this approach (2). Nevertheless, control of the diastereoselectivity of such reactions is still a problem. The production of a mixture of both cis and trans fused adducts in many cases however, limits the general use of the I.M.D.A. reaction in synthesis. It is generally thought that only prevailing steric and stereoelectronic factors or use of specific LEWIS acid activation permits stereoselective cyclization of trienes. In the case of azatrienes the basicity of the nitrogen atom limits the use of activation by LEWIS acids. In a previous publication (3), we showed that the normal electron demand (i.e. the activation of the allylic part of azatrienes) is much more efficient than reverse electron demand (i.e. the activation of the dienic part). None the less, no selective formation of a cis or trans junction between the two cycles of hydroisoindole was observed during the cycloaddition but subsequent epimerization gave the thermodynamically stable adduct.

As we wished to demonstrate the potentiality of employing the I.M.D.A. reaction as a key step in the synthesis of hydroisoindoles, we have devised a convenient synthesis of substituted azatrienes and we have demonstrated the possibility of obtaining efficient and stereoselective cyclization via steric control of an allylic substituent of non-activated azatrienes.

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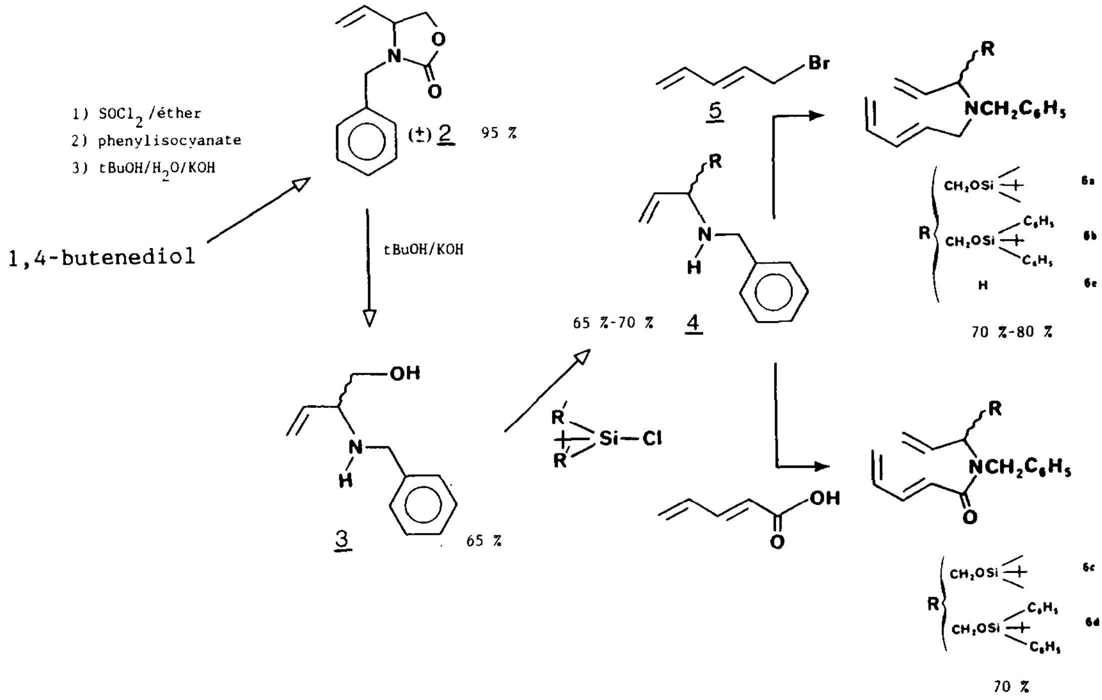
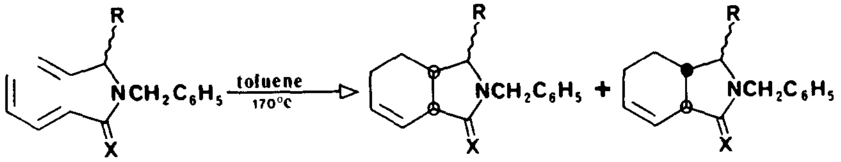
Until now, studies of the I.M.D.A reaction and its applications were largely limited because the trienes required as starting materials, are not commercially available and are also rather difficult to synthesize. These trienes were easily obtained following the sequence shown in scheme 1. The amino alcohol 3 was prepared from 1,4-butenediol via oxazolidinone 2 (4). Acylation of amines 4 by 2-E pentadienoic acid (5) was performed using the MUKAIYAMA method (6). Alkylation of amines 4 by 2-E pentadienyl bromide 5 (7) was carried out under phase transfer catalysis conditions.



Scheme 1 : Synthesis of azatrienes

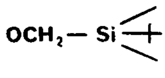
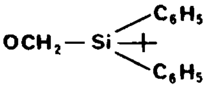
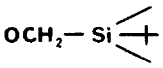
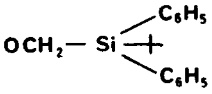
Cyclization of the triene 6 was achieved in toluene at 170°C in a sealed tube, in the presence of B.T.H. for 17 hours. Purification and analysis of the crude products were performed by HPLC on a Si60 column using ethylacetate/heptane as eluent. Structures were determined by 250 MHz ^{1}H NMR (9).



6a,b,c,d

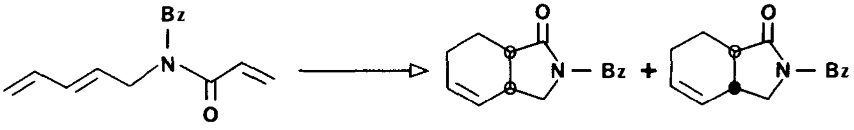
7c

7t

Azatrienes	R	X	%Cyclisation	% 7c	% 7t
6a		H_2	100	100	–
6b		H_2	100	100	–
6c		O	78	50	50
6d		O	38	50	50
6e	H	O	0	∅	∅

Scheme 2 and Table 1 : Diels Alder cyclization

As shown in table 1, substitution of the allylic part of the triene increased its reactivity dramatically, versus that of the unsubstituted allylic version. Under these reaction conditions, no cyclization was observed using N-allyl, N-2E-pentadien-2,4 yl-1 amine 6e as substrate ; in contrast, total transformation of substituted azatrienes 6a and 6b was obtained. This enhancemement of the cyclization yield was a consequence of the increasing THORPE-INGOLD effect (10) due to the allylic steric hindrance. Moreover, high stereoselectivity was observed with substrates 6a and 6b which possess 'non-activated' dienic parts : a pure cis junction was obtained during cyclization. The controlling non-bonding interactions during the closure of trienes 6a and 6b stabilised the anti-form versus the syn-form. Molecular models indicate that the silyl-alkyl side chain and the benzyl substituent are involved in the main steric interaction. In contrast, 6c and 6d which have a more rigid amide structure, exhibited a weaker and less significant interaction between the silyl-alkyl side chain and the benzyl group, as well as a lower THORPE-INGOLD activation effect. These two structural modifications affect the reaction in two opposite ways. Both reactivity and selectivity decrease with respect to substrates which are not activated by a carbonyl function as 6a and 6b. Furthermore, the products obtained from trienes activated by reverse electron demand such as 6c and 6d (3), or by normal electron demand such as 6f (scheme 3), can be epimerized easily in both basic and acidic conditions and are therefore only useful for thermodynamically stable hydroisoindole synthesis.



6f

Conditions		
toluène/20 h/120°C	52 %	48 %
MeONa/MeOH/0,1 eq/20°C	15 %	85 %

Scheme 3 : Synthesis and epimerization of trienes activated by normal electron demand

Aminoalcohols of type 3 can be prepared in enantiomeric pure form by resolution (4) or synthesis from enantiomers of methionine (8) and research on completely enantioselective synthesis of hydroisoindoles is now underway in our laboratory.

The results described in this paper demonstrate that both the reactivity and the stereoselectivity of the I.M.D.A. reaction of azatrienes are under steric control and that the use of stereochemical control elements, is the most successful way to improve the efficiency of this reaction.

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