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THE INTRAMOLECULAR DIELS-ALDER CYCLOADDITION OF N-DIENOYL ACRYLIMIDATES. NEW METHODOLOGY FOR THE CONSTRUCTION OF NITROGEN HETEROCYCLES.

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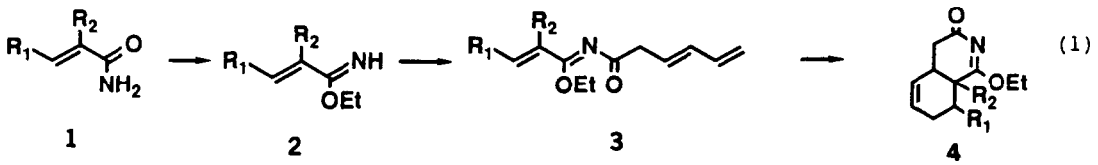
Summary: N-(3,5-Hexadienoyl)-acrylimidates, which have been synthesized by acylation of 2-ethoxy-1-aza-1,3-butadienes with 3,5-hexadienoyl chloride, are found to undergo facile intramolecular Diels-Alder cycloadditions to afford predominately cis-hexahydroisoquinolines in good yields.

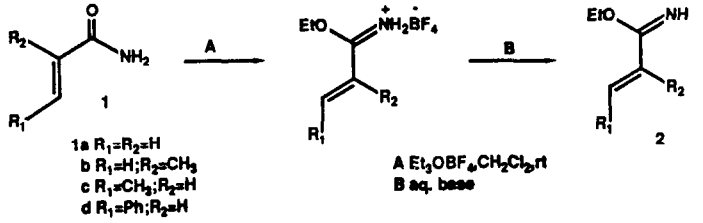
Incorporation of nitrogen into the dienophile or diene component of the Diels-Alder reaction constitutes an important synthetic route to variously substituted nitrogen heterocycles for alkaloid synthesis.[1] The intramolecular [4+2] reaction of azatrienes containing N-enoyl-1-aza-1,3-butadiene[2] or N-dienoyl imine[3] functionality has led to indolizidine and quinolizidine alkaloid precursors. A variant of the intramolecular approach, utilizing nitrogen in the tether joining the diene and dienophile, has also been applied to the synthesis of a number of functionalized hydroindole, hydroisoindole, hydroquinoline and hydroisoquinoline derivatives.[4] The latter approaches have mainly relied on the amide,[5] amine,[4] or enamide[6] functionality to serve as the link between the diene and dienophile components.[7] In contrast, the use of the imidate group as the means of introducing nitrogen into fused ring systems by the intramolecular Diels-Alder reaction has not been investigated.

In this communiction we report the facile intramolecular cycloaddition of N-(3,5-hexadienoyl)-acrylimidates, 3a-3d, which affords predominantly cis-hexahydroisoquinolones 4a-4d in good yields. The Diels-Alder precursors are readily assembled from acrylamides and the overall transformation results in a short convergent entry into nitrogen heterocycles.



(1)

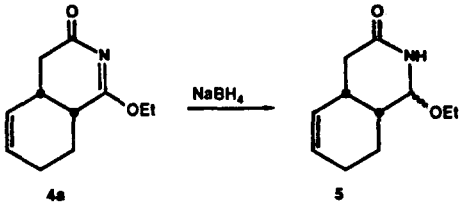
Our strategy for the construction of the Diels-Alder precursor is based upon the acylation of alkyl or aryl imidates (eq. 1), a reaction known to provide N-acyl alkyl or aryl imidates in high yield.[9] Several methods were explored for the synthesis of acryl imidates. Triethyloxonium tetrafluoroborate alkylation[10] of primary acrylamides 1a-1d followed by deprotonation of the resulting acrylimidate tetrafluoroborates with aqueous base proved to be the most expedient route, providing compounds 2a-2d in moderate yield (eq. 2, Table 1). The reaction of acrylimidate 2a with 3,5-hexadienoyl chloride[6]



(2)

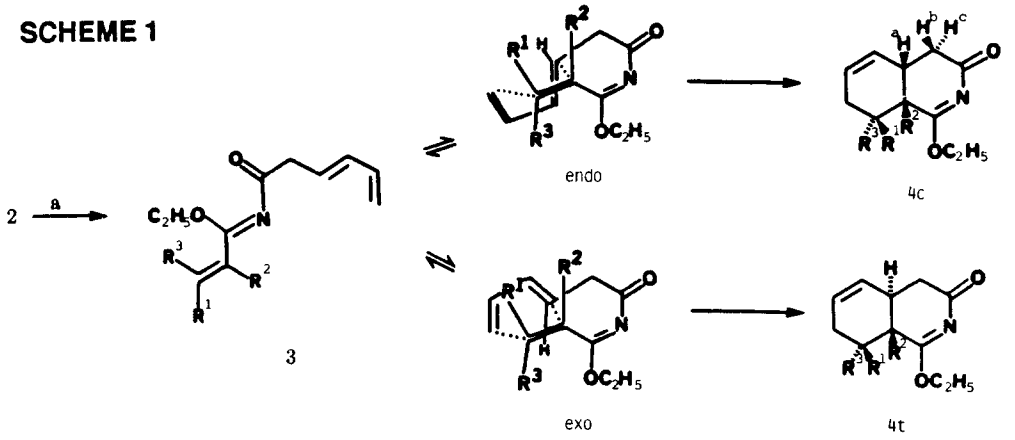
(0.95 eq) in the presence of triethyl amine (1.05 eq, C_6H_6, RT), resulted in generation of N-acyl intermediate 3a. Interestingly, NMR revealed the formation of cycloaddition products (4) even under the mild conditions of the acylation (rt). Heating the solution for 1 h at reflux completed formation of the cycloadduct 4, an N-acyl imidate, as an 8:1 mixture of stereoisomers in 80% yield. Stereochemistry of the major isomer 4c was established by conversion to the known cis-decahydroisoquinoline[11] by hydrolysis to the imide (1% HCl, MeOH/H_2O, RT), followed by reduction of the double bond (H_2, PtO_2, EtOH, RT) and imide group (LAH, THF). Analysis of the proton coupling in adducts 4a-d were also consistent with this assignment. Proton H_a splits the methylene protons of the major adduct (H_b, H_c) into two doublets of doublets (2.42, dd, J=5.2, 15.6 Hz; 2.16, dd, J=8.9, 15.6 Hz). The preponderance of cis-cycloadduct 4a implies the favored endo transition state for the cycloaddition (Scheme 1). Related systems are summarized in Table II. In all cases the cis-cycloadduct (endo) is favored.

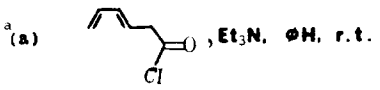
The cyclic acyl imidates 4 represent chemodifferentiated imides that are readily reduced with sodium borohydride to ethoxyamides (5, eq. 3), important intermediates for subsequent annulations.[12]



(3)

SCHEME 1





The assembly of Diels-Alder precursors from readily available acrylamides, the mild reaction conditions and high chemical yield for the cycloadditions, and the synthetic flexibility of the acyl imidate cycloadducts make this a potentially important addition to heterocyclic synthesis.

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Table I. Preparation of Acrylimidates 2a-2d.

Entry		Acrylamide R_1	R_2	Alkylation Conditions[a,b] (eq. Et_3OBF_4; time, h)	Imidate	Isolated Yield (%)	bp[c] (^oC, mm)
1	1a	H	H	1.1; 12	2a	48	70-73; 121
2	1b	H	CH_3	1.2; 3	2b	39	74-76; 100
3	1c	CH_3	H	1.3; 15	2c	44	110-120; 100
4	1d	Φ	H	1.0; 0.25	2d	59	114-115; 1

a) All alkylations were run in CH_2Cl_2 at r.t. under N_2; b) The acrylimidate tetrafluoroborate salt was treated with 12% aq. NaOH at 0°C in entries 1, 2, 3 and satd. aq. $KHCO_3$ solution at r.t. in entry 4, to liberate the imidates 2a-2d; c) Temperatures in entry 3 refers to the temperature of the air bath in a Kugelrohr distillation.

Table II. Intramolecular Diels-Alder Cycloaddition of N-Acyl Acrylimidates 3a-3d.

Entry	N-Acyl Acrylimidate	Diels-Alder Conditions (time; solvent; temp. °C)	Isolated Yield (%)	Isomer Distribution[a] 4c : 4t
1	3a	1 h; benzene; 80	78-82	8 : 1
2	3b	12 h; benzene; 80	80-83	5.5 : 1
3	3c	9 h; toluene; 110	72-83[b]	3.5 : 1
4	3d	12 h; toluene; 110	78	4 : 1

a) Isomer distributions determined by VPC or PMR; b) A yield of 83% was obtained by a Kugelrohr distillation (130-135°C/0.015 mm) of the crude isomer mixture. A lower yield was obtained when the mixture was purified by flash chromatography (SiO_2, 1:1 hexanes/ethyl acetate).

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