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ON THE SYNTHETIC UTILITY OF THERMALLY GENERATED IMINES: THE RETRO-ENE IMINO DIELS-ALDER REACTION

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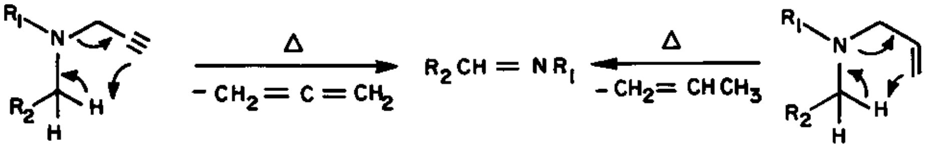
Abstract - The flash vacuum pyrolysis of several allyl and propargyl amines provides a preparatively useful synthesis of imines by retro-ene fragmentation. Their synthetic potential is indicated by intramolecular Diels-Alder trapping to give indolizidines in a novel ring-expansion sequence.

The imine function is a potentially very useful synthon in heterocycle synthesis, particularly when employed as one of the cycloaddends in the Diels-Alder reaction.[1] It has been known for some time that imines may be generated by the thermolysis of allylic and propargylic amines via retro-ene reaction (Scheme 1), but this method has not seen much preparative use.[2]

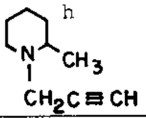
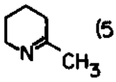
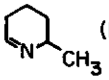
Scheme 1



We report here a facile synthesis of imines using flash vacuum thermolysis (FVP) techniques and some examples of a novel retro-ene-Diels-Alder sequence under these conditions.

We initially surveyed the potential of the approach by carrying out a number of model pyrolyses (Table 1) at 650-680° and 10^{-3} to 10^{-4} torr.[3]

TABLE 1. FVP Data on Allylic and Propargylic Amines

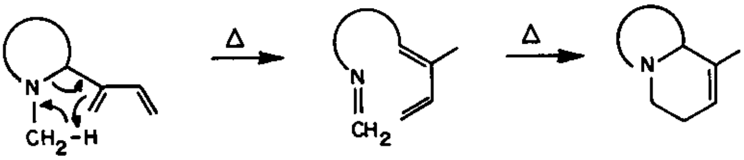
Entry	Amine	Products[a]	% Yield[b,j]
1	$(HC{\equiv}CCH_2)_2NH$[c]	$[HC{\equiv}CCH{=}NH]$ $CH_2{=}C{=}CH_2$	100
2	$(HC{\equiv}CCH_2)NH(CH_2CH{=}CH_2)$[d]	$CH_2{=}CHCH{=}NH$ $[HC{\equiv}CCH{=}NH]$ $CH_2{=}C{=}CH_2$ (5 parts) $CH_3CH{=}CH_2$ (1 part)	100
3	$(CH_2{=}CHCH_2)_2NH$[c]	$CH_2{=}CHCH{=}NH$ $CH_3CH{=}CH_2$	100
4	$(CH_3CH_2CH_2)_2NCH_2C{\equiv}CH$[e]	$CH_3CH_2CH{=}NCH_2CH_2CH_3$ $CH_2{=}C{=}CH_2$	100
5	$(CH_3CH_2CH_2)_2NCH_2CH{=}CH_2$[f]	$CH_3CH_2CH{=}NCH_2CH_2CH_3$ $CH_3CH{=}CH_2$	66
6	$C_6H_5CH_2NHCH_2C{\equiv}CH$[d]	$[C_6H_5CH{=}NH]$ $CH_2{=}C{=}CH_2$	100
7	$CH_2{=}CHCH_2NHC(CH_3)_2C{\equiv}CH$[g]	$CH_2{=}CHCH{=}NH$ $(CH_3)_2C{=}C{=}CH_2$	100
8	 [h]	 (5 parts) [i]  (1 part)	100

Footnotes to Table: [a] Products in square brackets were not observed due to rapid decomposition. [b] Determined by NMR spectroscopy. [c] Aldrich Chemical Company. [d] Reference 4. [e] Reference 5. [f] Reference 6. [g] Reference 7. [h] Prepared from 2-methylpiperidine and propargyl bromide in the presence of potassium carbonate. [i] Isolated by preparative g.l.c. in 54% yield. [j] Products were collected in liquid nitrogen traps and worked up directly or by vacuum transfer techniques.

Several observations are worthy of note: 1. At the same pyrolysis temperature (675°C) propargylic amines undergo the retro-ene reaction more efficiently than allylic amines (entries 4,5). This is in accord with similar findings in the FVP of the analogous ethers[8]; 2. The retro-ene reaction appears to be potentially regioselective (entry 8); 3. 2-Propene-1-imine, $CH_2=CHCH=NH$, a molecule of considerable theoretical interest[9], can be made by this method[2a] in excellent yields (entry 3), clearly superior to two previous preparations.[10]

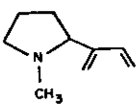
With these initial results in hand, systems were designed capable of generating α,ω-iminodienes, potential intramolecular Diels-Alder substrates (Scheme 2).

Scheme 2

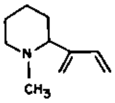


(stereochemistry uncertain)

Starting materials 1-3 were derived from the corresponding imminium salts [11] by treatment with 2-(1,3-butadienyl) magnesium chloride.[12] Surprisingly, FVP of 1 and 2 leads to secondary proton abstraction at C-4, presumably through a diaxial conformer of starting material providing the iminodienes 4 and 5 which could not be induced to undergo cycloaddition. Evidently, the lack of an electron withdrawing substituent on the imine function[1] precluded the intramolecular Diels-Alder reaction. The FVP of 3 was complicated by free radical formation leading to a complex mixture and only small amounts of both possible imines.



1



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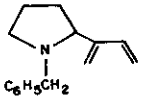

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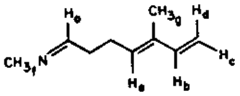

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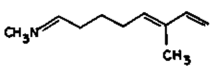

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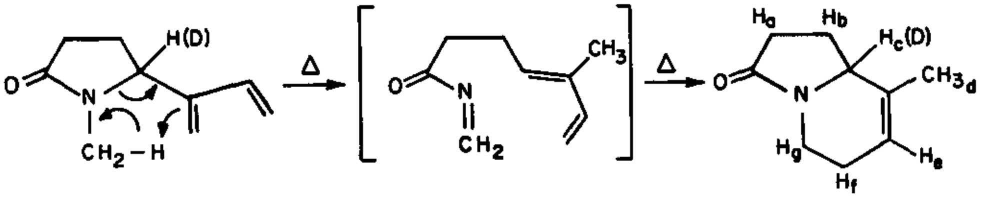
In order to block retro-ene proton cleavage at C-4 and to simultaneously activate the intermediate imine function for cycloaddition, a series of γ-lactams 6-8 were synthesized[3] by treatment [13]of the corresponding N-alkyl succinimides with 2-(1,3-butadienyl) magnesium chloride followed by reduction of the resulting alcohol with sodium cyanoborohydride.[14] FVP of these substrates required 800°C and quartz chip filled pyrolysis tubes to increase



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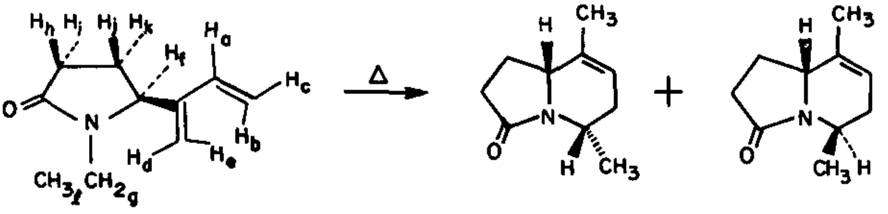
9



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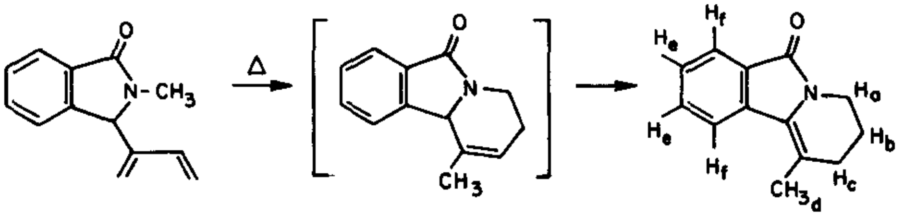
10a

10b



8

11

contact time. Under these conditions the indolizidinones 9-11[3]were obtained, however, only in low yield (<20%). The products were purified by p.g.l.c. or h.p.l.c. and identified by their spectral characteristics and comparison with literature data.[15] Additional confirmation of the identity of 9 was obtained by the FVP of monodeuterated 6 which led to deuterated 9 as shown. The relative stereochemical assignment of the two isomers of 10 was made by observation of a high field methyl doublet (δ=0.88 ppm) for 10b and a corresponding lower field absorption (δ=1.71 ppm) for 10a.[15] The ration of 10a: 10b was 1:2, diastereoselectivity arising either through control of the stereochemistry of the intermediate imine or the Diels-Alder transition state or both,[16] although the low yields make any speculation tenuous. Compound 11 is presumed to be a product of rearrangement of the initially formed retro-ene imino Diels-Alder adduct.

It was suspected that the reduced basicity of the nitrogen in 6-8 was responsible for the inefficacy of the retro-ene step.[2c,8] This was confirmed by competitive FVP of N,N-di-*n*-propyl-2-propynylamine and N-*n*-propyl-N-2-propynylpropionamide at 550°C, when the former is converted to the extent of 100%, whereas the latter is recovered almost unreacted (98%). Thus, the reported approach, the basic feasibility of which is being demonstrated here, suffers from an unusual dichotomy: the structural changes which improve the Diels-Alder cycloaddition occur to the detriment of the retro-ene step and vice versa. Current aims are directed at overcoming these difficulties by catalytic procedures.

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3. All compounds gave satisfactory analytical and/or spectral data. Selected examples: **1**, colorless oil; *m/e* (rel intensity) 137 (M^+, 2.84), 84 (base peak, 31.07), 42 (9.32); NMR (250 MHz, $CDCl_3$) δ 1.71 (m, 3H), 2.11 (m, 2H), 2.23 (s, 3H), 2.78 (t, J=8.3Hz, 1H), 3.14 (dt, J=8.2, 2Hz, 1H), 5.06 (bd, J=11Hz, 1H), 5.13 (d, J=2Hz, 1H), 5.20 (d, J=2Hz, 1H), 5.37 (dd, J=17.7, 1.2, 1H), 6.38 (dd, J=17.7,11Hz, 1H); IR (neat) 2967, 2841, 2778, 990, 901 cm.$^{-1}$ **4**, colorless oil; NMR (250 MHz, $CDCl_3$, assignments by decoupling) δ 1.72 (s, 3H, H_g), 2.35 (m,4H), 3.26 (d, J=1Hz, 3H, H_f), 4.94 (d, J=12Hz, 1H, H_c), 5.11 (d, J=18Hz, 1H, H_d), 5.48 (bt, J=9Hz, 1H, H_e) 6.35 (dd, J=18, 12Hz, 1H, H_b), 7.65 (m, 1H, H_a); IR (neat) $\nu_{C=N}$ 1675 cm.$^{-1}$ **7**, colorless oil; *m/e* (rel intensity) 165.1154 (M^+, 7.22, calcd. 165.1153), 112 (base peak, 21.2); ^{1}H NMR (250 MHz, C_6D_6, assignments by decoupling) δ 0.85 (t, J=7Hz, 3H, H_ℓ), 1.37 (m, 1H, H_k), 1.61 (m, 1H, H_j), 2.02 (m, 1H, $H_{h \text{ or } i}$), 2.15 (m, 1H, $H_{h \text{ or } i}$), 2.55 (apparent sex, J=7Hz, 1H, H_g), 3.79 (apparent sex, J=7Hz, 1H, H_g), 3.90 (dd, J=8.6, 3.6Hz, 1H, H_f), 4.70 (bs, 1H, H_e), 4.82 (bs, 1H, H_d), 4.88 (d, J=11Hz, 1H, H_c), 4.99 (d, J=18Hz, 1H, H_b), 6.05 (dd, J=18, 11Hz, 1H, H_a); ^{13}C NMR ($CDCl_3$) 12.51, 25.33, 29.83, 35.67, 58.72, 115.04, 135.81, 144.94, 175.13; IR (neat) 2980, 2960, 1690, 1465, 1425, 915 cm^{-1}. **9**, colorless oil; *m/e* (rel intensity) 151 (M^+, 11.55), 136 (base peak, 18.75); NMR (250 MHz, C_6D_6, assignments by decoupling) δ1.25 (bs, 3H, H_d), 1.48 (m, 2H, H_b), 1.99 (m, 4H, $H_{a,f}$), 2.34 (ddd, J=12, 12, 5Hz, 1H, H_g-axial), 3.36 (bt, J=8Hz, 1H, H_c), 4.38 (dd, J=12, 7Hz, 1H, H_g-equatorial), 5.06 (m, 1H, H_e); IR (neat) $\nu_{C=O}$ 1695 cm^{-1}. **11**, colorless oil; *m/e* (rel intensity) 199 (M^+, 7.75), 184 (base peak, 8.60); NMR (250 MHz, $CDCl_3$) δ 2.00 (q, J=6Hz, 1H, H_b), 2.26 (s, 3H, H_d), 2.41 (t, J=6Hz, 2H, H_c), 3.69 (t, J=5.9Hz, 2H, H_a), 7.43 (dd, J=7, 7Hz, 1H, H_e), 7.55 (dd, J=7, 7Hz, 1H, H_e), 7.85 (AA' m, 2H, H_f).

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