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THE INTRAMOLECULAR ENE REACTION OF CARBON-NITROGEN DOUBLE BONDS

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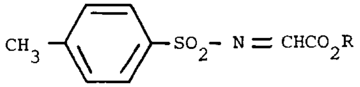
Abstract: Acyl imines, prepared from hydroxyl amine derivatives, have been observed to undergo the intramolecular ene reaction producing nitrogen heterocycles.

Although the ene reaction has been known for over forty years its scope and limitations continue to be explored. Recent advances include a more complete understanding of its mechanism[1], the role of Lewis acid catalysis[2] and the application of the intramolecular version of this reaction to natural product synthesis[3].

The carbon-nitrogen double bond is a potential enophile of both theoretical and synthetic interest. In contrast to carbon-carbon and carbon-oxygen double bonds[4] there is, to our knowledge, only one carbon-nitrogen double bond known to participate in the ene reaction[5,6].

It has recently been shown that alkyl N-(p-tolylsufonyl) iminoacetates react with a number of alkenes[5]. This reaction provides a novel synthesis of amino acids and a recent study on its stereochemistry suggests it may provide a useful synthesis of amino substituted natural products[6].



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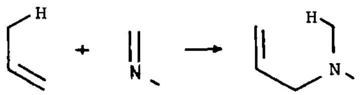
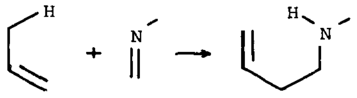
R= C_2H_5, n-Bu

The reluctance of simple carbon-nitrogen double bonds to participate in pericyclic reactions that involve forming carbon-nitrogen single bonds is a general phenomenon. Because of our interest[7] in exploring these reactions we have investigated the intramolecular ene reaction of N-acylimines.

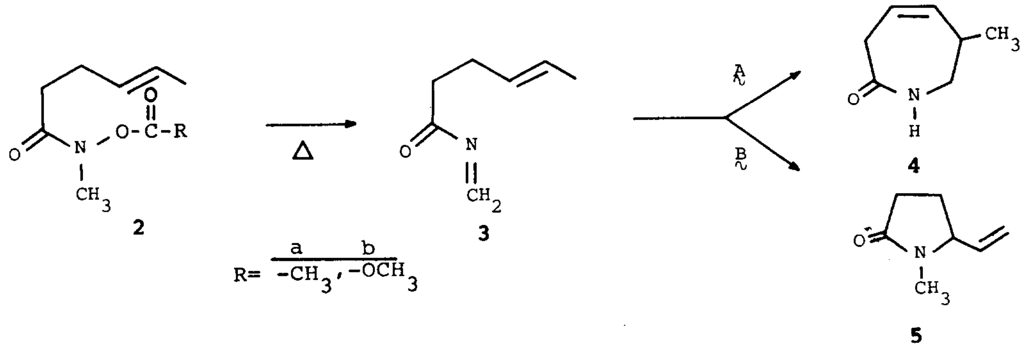
In principle, the intramolecular ene reaction of imines can be complicated. There is the question of regiochemistry about the ene and enophile as well as the question of stereochemistry about the atoms involved in the newly formed sigma bonds[6]. For example, when





an imine undergoes an ene reaction there is the possibility of forming either a carbon-carbon or carbon-nitrogen bond.

One of the simplest carbon-nitrogen double bonds capable of the intramolecular ene reaction is the N-hex-4-enoylimine 2. Two of the possible ene reactions (A and B) for 3 are shown in scheme 1. From thermodynamic considerations[8] and by analogy to the intermolecular



2 3 4 5 (1)

ene reaction of carbonyl compounds [4] pathway **A** would predicted to be more favorable. Also the single example, discussed above, of a carbon-nitrogen double bond behaving as an enophile follows regiochemical pathway **A**. However, previous studies on the intramolecular ene reaction show a clear preference for pathway B[3].

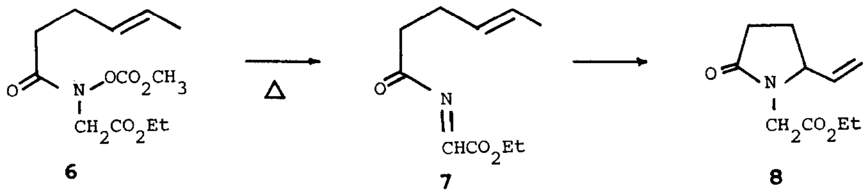
Because of our previous success[7] with hydroxyl amine derivatives for the preparation of activated carbon-nitrogen double bonds we chose **2a** as a potential precursor to the acyl imine 3.

Flash pyrolysis[9] of 2[10] induced loss of acetic acid produced the pyrrolidinone **5** as the major product (40%) in addition to 1-methyl-3,4-dihydro-2-pyridone (15%) and 1,5-dimethyl-pyrrolidone (15%).[11] The mechanistic pathways leading to these latter two products are not obvious. Since the ene product **4** was not detected any unfavorable thermodynamic considerations for pathway **B** appear to be more than met by the stereoelectronic requirements of the transition state.

Greater selectivity could result if the temperature of the reaction was lower. It is known that the preparation of alkenes from the pyrolysis of acetates requires a higher temperature than the pyrolysis of carbonates. For this reason we prepared carbonate **2b** and observe that its thermal reaction gave pyrrolidone 5 in higher yield (54%) with only the formation of trace amounts of side products.

Additional electron withdrawing groups on the imine should further facilitate the ene reaction. Therefore, we investigated the thermal behavior of 6[10] and the effect of the additional electron withdrawing ester group was dramatic. The thermal elimination of carbon dioxide and methanol as well as the ene reaction occurred at approximately 200°C lower than **2b** and produced pyrrolidine **8** in quantitative yield. The lower temperature required for the elimination of **6** compared to **2b** is understandable since the hydrogen being removed is activated by a carbonyl group and greater reactivity of imine 7 compared to 3 can be attributed to it possessing a lower energy LUMO.[13]

These preliminary results on the ene reaction of imines provide the first example of the intramolecular version of this reaction and the first example of forming a nitrogen-carbon



(2)

preferentially to a nitrogen-hydrogen bond. We are presently exploring the utility of this reaction for the synthesis of nitrogen heterocycles.

References and Footnotes

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8. Although accurate data for analogous compounds are not available, in general, the bond strengths for C-C and N-H are 2 to 9 kcal/mole stronger than C-N and C-H.

9. The apparatus we used in this work is similar to the one described previously (J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein, K. Zolo, and F. W. Fowler, J. Am. Chem. Soc., **1979**, 101, 6677). The main difference is the heating coil is wrapped inside rather than outside the reaction tube. The temperature of the reaction tube is controlled with a variac. The voltage required to induce the

reaction of **3b** to **5** corresponds to approximately 640^{o}C and the contact time is approximately 1 usec.

10. The acylimine precursors were prepared by acylation of the appropriate hydroxyl amine derivatives. Compound **2** was prepared by treatment of commercially available N-methyl hydroxyl amine with *trans*-hex-4-enoyl chloride followed by methyl chloroformate. The hydroxyl amines **5** and **8** were prepared from N-butoxycarbonyl-O-methoxycarbonyl hydroxyl amine (G. Zinner, G. Nebel and M. Hitze, Arch. Pharmaz., **1970**, *303*, 316) by alkylation with ethyl bromoacetate, acid hydrolysis, and acylation with *trans*-hex-4-enoyl chloride (for **6**).

11. These compounds were separated by preparative gas chromatography (SE-30 at 100^{o}). The 1,5-dimethyl-2-pyrrolidone was identical to a commerically available sample (Pfaltz and Bauer) and the spectral data for 1-methyl-3,4-dihydro-2-pyridone were consistent with those previously reported (J.C. Hubert, J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron, **1975**, *31*, 1437). The ene product **5** was a colorless liquid: ^{1}Hnmr(300 MHz, $CDCl_3$) δ 1.70-1.80(m,1H), 2.19-2.50(m,3H), 2.75(s3H), 3.88-4.00(m,1H), 5.20-5.30(m,2H), 5.60-5.77(m1H); IR(film) 1670cm^{-1}(C=O); MS(70ev)(*m/z*, rel intensity), 125(100), 124(23), 98(96), 96(21).

12. The crude ene product **8** product was greater than 90% pure. It was further purified by flash column chromatography (Hexane=EtOAc (3=1)) ^{1}H-NMR (300 MHz, $CDCl_3$), δ 1.28 (t, *J*=7 Hz, 3H), 1.74-1.86 (m, 1H), 2.26-2.48 (m, 3H), 3.64 (d, *J*=9 Hz, 1 H), 4.14-4.24 (m, 1H), 4.18 (q, *J*=7 Hz, 3H), 4.32 (d, *J*=9 Hz, 1H), 5.21-5.28 (m, 2H), 5.60-5.71 (m, 1H); IR(film) 1690 (C=O), 1740 cm^{-1} (C=O); ms (70 ev) (*m/z*, rel intensity).

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