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STEREOSELECTIVITY DURING INTRAMOLECULAR NITRILE OXIDE OLEFIN CYCLOADDITIONS. SYNTHESIS OF FUSED AZETIDINES[1].

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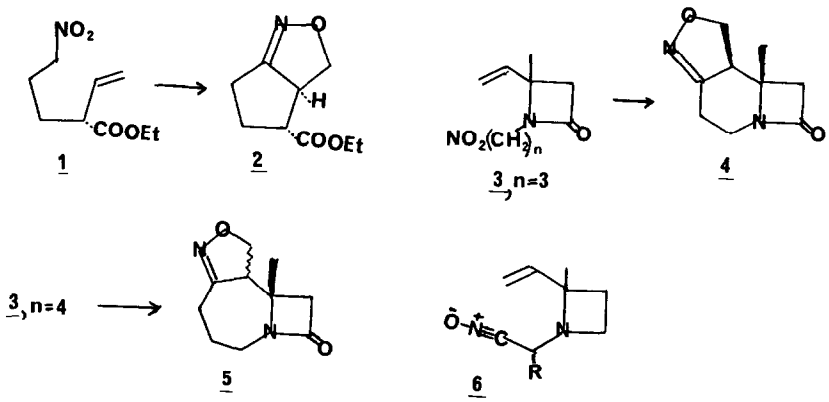
Summary: Vinyl azetidines 7 can be converted to nitro olefins 8,9 or to unsaturated aldoximes 21-23, which are useful precursors for intramolecular nitrile oxide - olefin cycloadditions (INOC). Such INOC reactions proceed with a fair degree of stereoselectivity producing novel heterocycles.

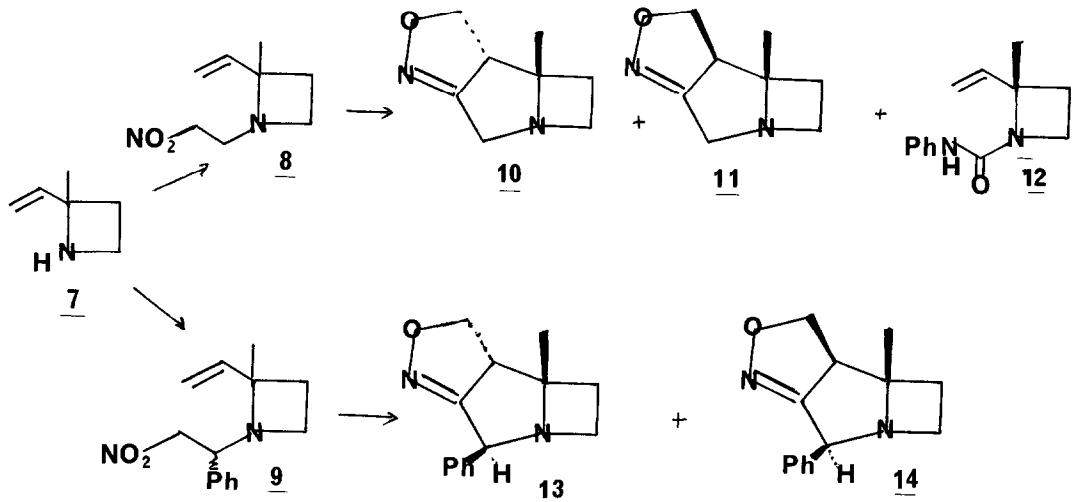
Intramolecular nitrile oxide-olefin cycloaddition (INOC) reactions have been shown to be of considerable synthetic interest, yet little is known about the factors influencing stereoselectivity of substituents during cyclization[1]. In some elegant synthetic studies Kozikowsky and coworkers[2], obtained a high degree of stereoselectivity during the INOC with formation of a 5-membered ring. This occurred when the substituents involved were on or adjacent to the olefinic double bond undergoing cyclization[3], for instance, 1 gave exclusively 2. Our own studies[4], with INOC involving β-lactams indicated that ring closure to 6-membered rings during INOC as well as during IAOC (azide-olefin cycloadditions) proceeded with much greater stereoselectivity than closure to a 7- or 8-membered ring (e.g. 3, n=3 ring closed to a single product 4, while 3, n=4 led to a mixture of stereoisomers, see for instance 5).



In order to assess the stereochemical influence of a substituent further removed from the double bond, we decided to study the nitrile oxide

vinyl azetidine system 6. The route previously employed (reaction of a vinyl azetidinone with an ω-dibromoalkane leading ultimately to 3)[4] was not applicable for vinyl azetidine 7. Hence, we investigated two other pathways to 6: (a) Michael addition of 7 to a vinyl nitro compound and (b) nucleophilic displacement of an α-bromoaldoxime with 7; both nitro and aldoxime functions can be readily converted to nitrile oxides[5].

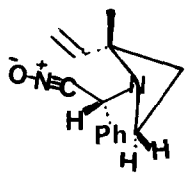
Reaction of 7 (available from isoprene and chlorosulfonyl isocyanate, followed by AlH_4 reduction)[6], with nitroethene proceeded readily at 0°C to give 8 in 80% yield. In an analogous manner, Michael addition of 7 to β-nitrostyrene produced 9 in quantitative yield as a 1:1 mixture of diastereomers. Treatment of 8 with phenyl isocyanate and Et_3N led via 6 (R:H) to a mixture of cis and trans tricyclic azetidines 10 and 11 in a ratio of 2:1 and in 50% yield, the remainder being the phenylurea 12. Possibly 12 resulted from 7 formed in a competitive retro Michael addition from 8. Similar results were obtained in the ring closure of 6 (R:Ph) derived from 9.



Interestingly, both stereoisomers 13 and 14 isolated from the intramolecular cycloaddition of 6(R=Ph) had only the cis Ph:Me configuration in spite of the fact that the starting nitro olefin 9 was a 1:1 mixture of diastereomers. From this we surmise that ring closure to the trans Ph:Me isomers was unfavorable. Indeed this is born out by an examination of models, which indicate steric interactions between the alpha oriented Ph and the hydrogen at C-4, at least in the transition state 15 leading to 16.

It is noteworthy, that while ring closure of 3 to the 6-membered ring gave exclusively the cis product 4, the preferred product during 5-membered ring formation from 6 was the trans product 10. This can again be explained by preferred conformation 17 over 18, leading to more favorable orbital overlap between the dipole and the olefin in 17. The geometry of the reacting

olefin and nitrile oxide dipole control the intramolecular dipolar cycloaddition which proceeds smoothly at room temperature in spite of the fact that the regiochemistry of the cycloaddition is in the opposite sense as that expected from a HOMO-LUMO controlled reaction.



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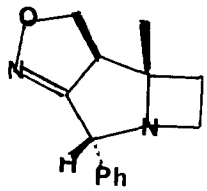

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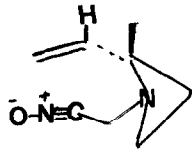

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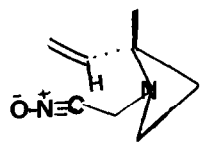

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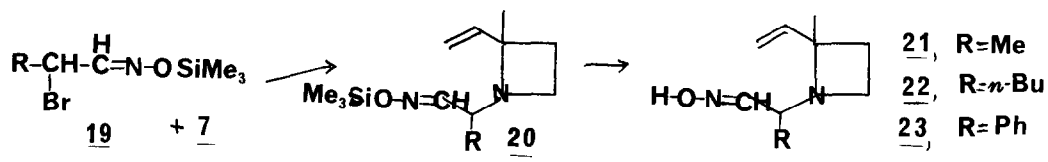
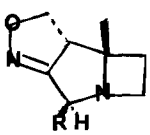
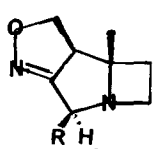
The second pathway to nitrile oxides 6 is based on our recent discovery that α-bromination of oximes can be carried out on their silyl derivatives to produce 19.[7] Nucleophilic displacement of the halogen in these O-silyl-α-bromoaldoximes 19 by the azetidine 7 led to the silylated oxime products 20. The latter were smoothly desilylated on chromatography over silicagel or in the presence of fluoride ions to produce 21-23 as a 1:1 mixture of diastereo-



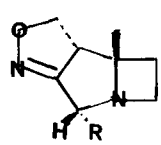
mers. Oximes 21-23 were converted via 6 to the INOC products by treatment with NaOCl. The major products were the stereoisomers possessing R and Me in a cis configuration. Conspicously absent in all three cases (R:Me, Bu, Ph) was the trans isomer corresponding to 16, indicating again the unfavorable interactions described above (see 15). In the case of R:Me and R=Bu, a third



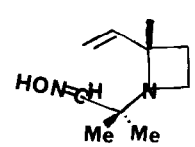
24, R=Me
25, R=n-Bu



26, R=Me
27, R=n-Bu



28=R Me
29, R=n-Bu



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isomer 28 or 29 was also present but it was absent when R was a larger substituent i.e. Ph. Again there was observed an overall preference for CH..:Me trans products with the ratio of (24 + 28) to 26 = 3:1 and the ratio of (25 + 29) to 27 = 2.5:1. Consistent with these observations is the fact that the dimethyl derivative 30 failed to undergo the INOC reaction since in this

case one of the methyl groups would necessarily interfere in the transition state for cyclization. The configurations of 10 ,11, 13, 14, 24-29 were established by ^{1}H- and ^{13}C-NMR and NOE experiments.

The above results make it easier to predict the stereochemical outcome of such intramolecular dipolar cycloadditions. Initial application of molecular orbital calculations to these systems bears out these results. We are currently studying the possibilty of using this strategy for the construction of the skeleton of necine and indolizidine alkaloids.

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