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THE SYNTHESIS OF N-SUBSTITUTED TETRAHYDROPYRIDINES USING THE HETERO-COPE REARRANGEMENT.

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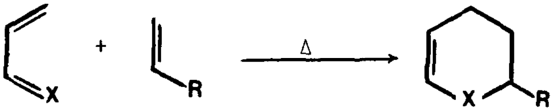
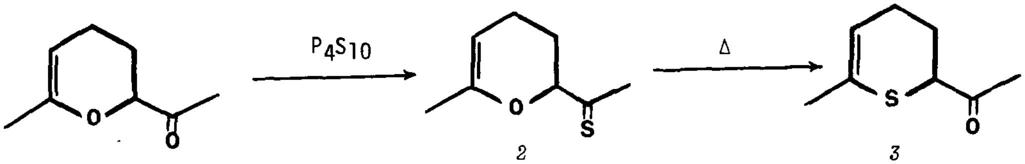
Summary: Several imines have been prepared from methacrolein dimer. Thermal rearrangement of these molecules resulted in the formation of N-substituted tetrahydropyridines.

Unsaturated six-membered heterocycles, *1*, are accessible via the 4+2 cycloaddition of heterodienes.[1] Often, a mixture of regioisomers along with heterodiene dimers contaminate the reaction. We and others[2] have found that regiospecific dimerization of α,β-unsaturated carbonyls followed by functional group modification and thermal rearrangement cleanly lead to *1*. For instance, thiomethylvinyl ketone (prepared *in-situ* from methylvinyl ketone) produced a mixture of four $C_8H_{12}OS$ isomers while thermal rearrangement of thiomethylvinyl ketone dimer, *2*, cleanly produces the desired thiapyran, *3*, exclusively.[2a,b]

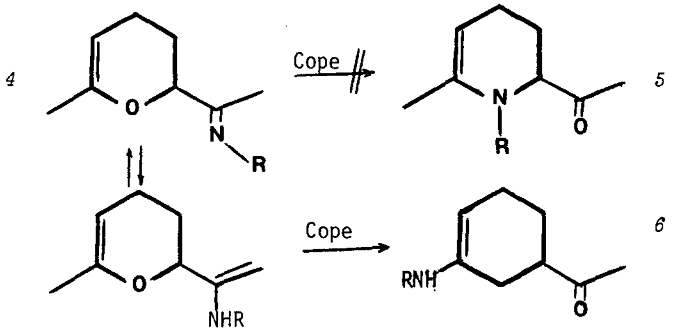


X = Heteroatom　　*1*

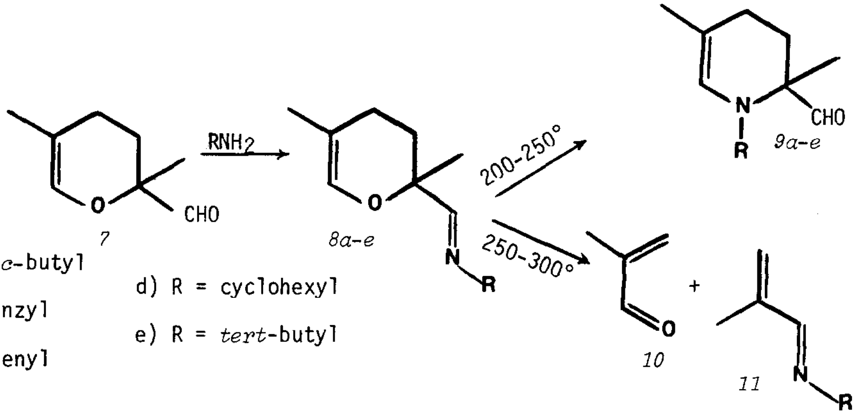


2　　*3*

Thermal rearrangement of the imines of methylvinyl ketone dimer, *4*, have been reported not to give the expected enamine, *5*, but rather the enamine, *6*.[2c,d] This is the result of an imine-enamine tautomerism prior to the sigmatropic shift. The question we ask is: if the imine-enamine tautomerism is eliminated, will the nitrogen migrate into the ring?



The answer is yes. The imines of methacrolein dimer, *8a-e*, can not tautomerize. They may rearrange or simply undergo a retro-Diels-Alder reaction when heated. We find that at low temperatures the system nicely rearranges but at higher temperatures the retro-Diels-Alder route is followed.



a) R = *sec*-butyl
b) R = benzyl
c) R = phenyl
d) R = cyclohexyl
e) R = *tert*-butyl

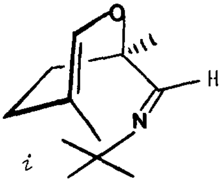
Whether the formation of *10* and *11* result from the retro-Diels-Alder reaction of imine *8* or enamine *9* or both is not yet known. Of interest is that very little methacrolein itself is found. At these high temperatures the dimer, *7*, is formed. In contrast we find no evidence for the dimerization of α,β-unsaturated imines, *11*. Table I contains the product distribution for the thermal rearrangement of *8*.[3]

Table I: The Products Obtained Upon Rearrangement of *8*.†

imine	Reaction Time (hours)	% Unreacted imine	% enamine	% Retro-Diels-Alder Products
8a	1.25	2	96	2
8b	0.33	0	75	25
8c	0.50	0	89	11
8d	1.15	24	59	11
8e	1.0	98	0	2

† glc yields

The rearranged products, *9*, even in the presence of various inhibitors polymerize within one hour. They appear to exist long enough for gas chromatographic purification and spectral analyses. Thermal rearrangement of the *tert*-butyl imine *8e* was not possible. Presumably the boat transition state *i* is too sterically encumbered for the imine pi bond to approach the vinyl ether pi bond.



i

We may conclude that the potential of this method for the synthesis of nitrogen heterocycles is limited by two factors. First, the dihydropyran that acts as the starting material can not be a ketone since an imine-enamine tautomerism gives rise to the undesired product, and second that the size of the substituent on the nitrogen is limited to primary, secondary and aromatic groups.

Acknowledgements: We wish to thank Eli Lilly and Company for financial support.

References and Footnotes:

1. For a review see G. Desimoni and G. Tacconi, Chem. Rev., **75**, 651 (1975).
2. a) K. B. Lipkowitz and B. P. Mundy, Tet. Lett., 3417 (1977).
   b) K. B. Lipkowitz, S. Scarpone, B. P. Mundy and W. Bornman, J. Org. Chem., xxx (1979).
   c) B. P. Mundy and W. Bornmann, Tet. Lett., 957 (1978).
   d) B. P. Mundy and W. Bornmann, Synthetic Commun., **8**, 227 (1978).

e) For the carbocyclic analog, see G. Buchi and J. Powell, J. Am. Chem. Soc., 92, 3126 (1970).

3. A typical experiment follows: Methacrolein dimer, *7*, a slight excess primary imine and Linde 4 Å molecular sieves are stirred in anhydrous ethyl ether overnight. The solution is decanted, reduced in volume and vacuum distilled to give imine *8* in 90-95% yield. The imine is stirred and refluxed neat under a nitrogen blanket to form a dark oil that rapidly polymerizes. It is advantageous to heat the imine gently since vigorous reflux results in bumping, frothing and rapid decomposition of product. Separation is achieved on a 5' x 1/4" 10% SE-30 on chromosorb-W vpc column. Rearrangements at elevated temperatures were attempted by passing the imine through a N_2 purged column of glass beads (approximately 15 second contact time). All products have been isolated by gas chromatography and characterized spectroscopically.

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