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A NOVEL ENTRY INTO 3-ACETYLCYCLOHEXANONE VIA A COPE REARRANGEMENT

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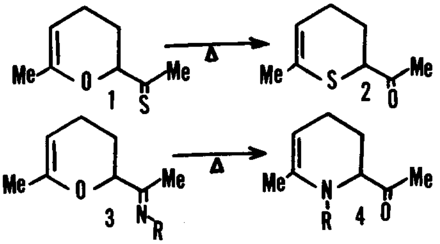
We recently reported an interesting approach to a thiapyran derivative [2], via Cope rearrangement of [1][1](equation 1). This work prompted us to attempt replacing the pyran oxygen with nitrogen according to the scheme delineated in equation 2.



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Various imines [3] (R = Me, Et, n-Pr, and n-Bu) were prepared by mixing a slight excess of the appropriate amine with the dimer of methylvinyl ketone in diethyl ether over molecular sieves. The imines were obtained in good yield and could be purified by distillation. However, because of rapid deterioration they had to be used within a short time of purification. Passing the imines through a heated column (250° C) resulted in an efficient conversion to an enamine product (R = Me(62%); Et(58%); n-Pr(74%); n-Bu(70%))[2]. Spectral analyses of the products were not consistant with structure [4] (see tables 1 and 2); and, hydrolysis of the rearrangement products yielded 3-acetylcyclohexanone [7][3]. This observation is best rationalized by the scheme presented in equation 3.

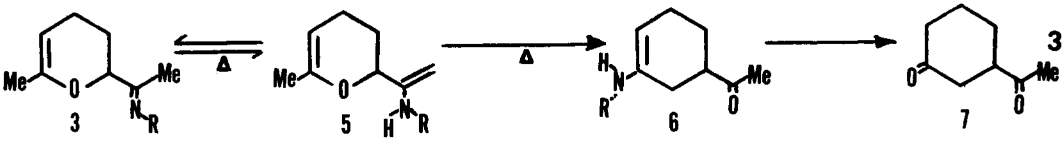

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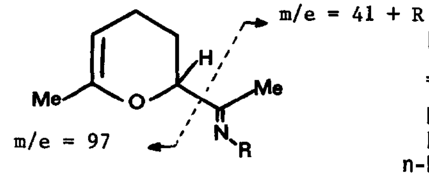
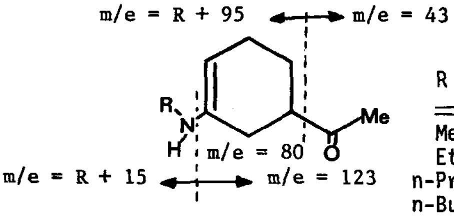
Table 1: MASS SPECTRAL FRAGMENTATIONS

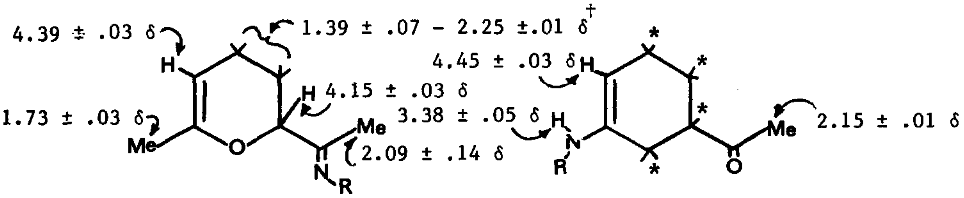


R	Molecular Ion	*(Rel. Abundance)* m/e = 97	m/e = R+41
Me	153*(28)*	*(100)*	56*(32)*
Et	167*(29)*	*(100)*	70*(56)*
n-Pr	181*(31)*	*(100)*	84*(40)*
n-Bu	195*(28)*	*(100)*	98*(51)*



R	Mol. Ion	m/e=R+15	m/e=80	m/e=43	m/e=123	m/e=R+95
Me	153*(28)*	---	*(98)*	*(27)*	*(16)*	110*(100)*
Et	167*(42)*	44*(33)*	*(100)*	---	*(27)*	---
n-Pr	181*(31)*	58*(21)*	*(100)*	*(39)*	*(22)*	138*(17)*
n-Bu	195*(36)*	72*(21)*	*(100)*	*(33)*	*(21)*	152*(17)*

Table 2: NMR AND IR DATA



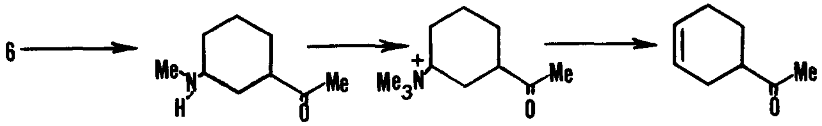
† This multiplet contains the methylene protons <u>not adjacent</u> to the nitrogen for R = n-Pr and n-Bu.

* = 1.01 ± .12 - 2.50 ± .06 δ
An unresolved multiplet which also contains the methylene protons of the n-Pr and n-Bu groups.

IR: Imine $>C=N'$ 1674 ± 5 cm^{-1}

Enamine $>C=C\langle^{N}$ 1643.5 ± 5 cm^{-1}

Additional evidence supporting the rearrangement to [6] was provided by the following reaction sequence. Hydrogenation of [6] (R = Me) yielded [8], which when treated with methyl iodide gave the ammonium salt [9]. Elimination of the trimethyl amine group of [9] with t-butoxide in t-butyl alcohol gave [10], which is readily accessible by other synthetic methods.



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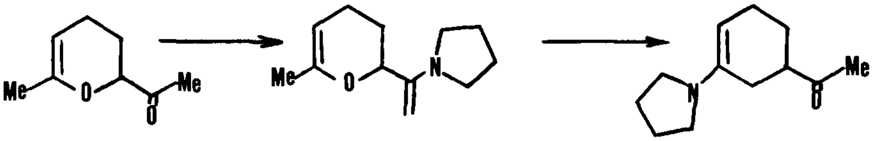
This interesting and operationally simple entry into 3-acetylcyclohexanone encouraged us to investigate a modification of the procedure. Methylvinyl ketone dimer [11] and pyrrolidine were stirred over molecular sieves to yield [12]. Subjecting this enamine to the conditions of the rearrangement gave [13], which could be hydrolzed to [7]. Spectral data for [12] and [13] are presented in table 3.



11 12 13

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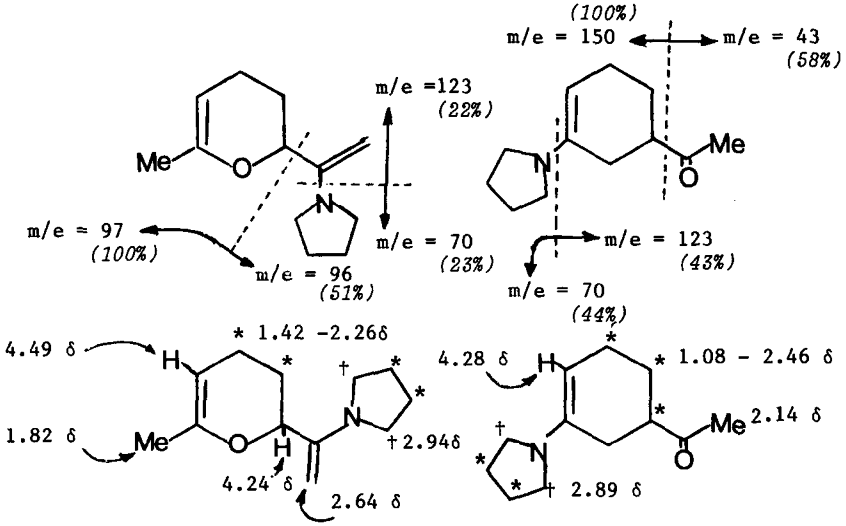
Table 3: MASS SPECTRAL AND NMR DATA



Of particular interest in this approach is the direct preparation of [13], which is properly funtionalized for selective alkylation, direct annelation, or serves as a protecting group while additional chemical modification of the acetyl group is carried out. The potential applications of this methodology , with modifications of the starting enamine, to terpene synthesis is obvious.

REFERENCES

1. K.B. Lipkowitz and B.P. Mundy, Tet. Lett.,3417 (1977).

2. The rapid deterioration of both [3] and [4] precluded combustion analyses for these compounds. An acceptable combustion analysis of [13] was obtained and buttresses the wealth of spectral evidences available for this compound.

3. This product has been previously prepared:
    a. E.J. Corey and D. Crouse, J. Org. Chem., 33, 298 (1968).
    b. A. McCoubrey, J. Chem. Soc., 2931 (1951).
    c. E.J. Corey and L.S. Hegedus, J. Am. Chem. Soc., 91, 4926 (1969).