THE CHEMISTRY OF CYCLIC ENAMINOKETONES. II.
1,2- AND 1,4-ADDITION OF NUCLEOPHILES
LEADING TO SUBSTITUTED HETEROCYCLES

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The chemistry of the enaminoketone group ($>$N-C=C-C=O) is potentially an area
$\qquad$ a b c d e
of considerable scope when one considers that there are present in this moiety three nucleo-

philic sites (a, c, and e) and two electrophilic sites (b and d). When this group is present in a

cyclic molecule; i.e., 1, there is ample opportunity to provide a variety of substituted hete

cycles if the sites of attack could be controlled. We have recently described[2] the reactions of

enaminoketones and methyl iodide demonstrating the behavior of the nucleophilic sites and now

wish to report our preliminary findings on the behavior of the electrophilic sites with organo-

metallic and hydride reagents. The literature provides an early report[3] on the action of Grig-

nard reagents with acyclic enaminoketones which lead only to nitrogen-free products. These

types of enaminoketones have also been found to be rather sensitive to a variety of nucleophiles

(water,[4] amines[5]) resulting in cleavage to β-diketones and derivatives thereof. It is, there-

fore, rather apparent that the unstable nature of acyclic enaminoketones has deterred their

development as useful synthetic intermediates, whereas, systems of the type, 1 are extremely

resistant to cleavage. The latter was recovered unchanged after prolonged heating in acidic

or alkaline medium. The tricyclic enaminoketone, 1, prepared[2] from cycloheptanone and

ethyl-2-piperdylacetate in 60% yield [mp 58°; λ^{EtOH} 340 mμ] was treated with methyl lithium

in benzene and produced the 1,2-addition product, 2, in 85% yield [mp 144°; λ^{CHCl_3} 2.71,

2.86, 6.09 μ; nmr (CDCl$_3$), τ8.72 (CH$_3$), 8.33 (OH)] and a trace ($\sim$1%) of the 1,4-addition

product, 5 [mp 56°; λ^{CHCl_3} 5.81 μ; nmr (CDCl$_3$), τ9.13 (CH$_3$)]. The stereochemistry of

5 is tentatively assigned as a cis-quinolizidine (absence of Bohlmann bands[6]) containing a trans-

fused cycloheptane ring (β-methyl as seen from $CHCl_3$ to C_6H_6 upfield shift[7]). When $\underline{1}$ was similarly treated with methyl magnesium iodide only a small yield ($\sim 10\%$) of $\underline{5}$ was isolated along with unreacted $\underline{1}$ and considerable quantities of unidentified materials. Conversion of $\underline{1}$ to the acetylated iminium salt, $\underline{6}$ (hygroscopic, unstable salt, λ^{CH_3CN} 328 mμ, λ^{nujol} 5.65, 6.09 μ) was accomplished in 90% yield and was smoothly transformed with methyl magnesium iodide to $\underline{5}$ in 60% yield. Further evidence for the existence of the O-acetylated enaminoketone $\underline{6}$ was gathered by rapid treatment with ammonia in acetonitrile which resulted in the amino derivative, $\underline{7}$ [mp 215°; λ^{EtOH} 356 (20,360); λ^{CHCl_3} 6.04, 6.35 μ^2]. Furthermore, the addition of methyl lithium to $\underline{6}$ also produces only $\underline{5}$ in 60-65% yield. Thus, utilizing the O-acyl derivatives of enaminoketones, exclusive 1,4-addition can be expected.

The addition of phenyl lithium or phenyl magnesium iodide to $\underline{1}$ produced, in 80% yield, the enamine alcohol, $\underline{8}$ [mp 148°; λ^{CHCl_3} 2.75, 2.92, 6.10 μ; nmr (CDCl$_3$),τ2.32-2.75 (C_6H_5), 8.12 (OH)] and no trace of 1,4-addition products. Addition of phenyl metallics to the O-acylated salt, $\underline{6}$, gave no 1,4-addition (angular phenylation) but only a complex mixture which is still under investigation. The lithium aluminum hydride reduction of $\underline{1}$ was studied and found to give only the 1,4-addition product, $\underline{11}$ in 80% yield [bp 120° (1.1 torr); picrate, 176°; λ^{CCl_4} 3.61, 3.67 (Bohlmann bands, $\underline{trans}$-quinolizidine), 5.80 μ]. However, the products were found to be highly dependent upon order of hydride addition. The formation of $\underline{11}$ occurred in good yield only when a solution of $\underline{1}$ in tetrahydrofuran was added to two equivalents of the hydride. Reversal of this order resulted in over-reduction to an epimeric mixture of saturated alcohols.[8] No 1,2-addition products could be detected.

The enamine alcohols $\underline{2}$ and $\underline{8}$ proved to be rather useful precursors for pyridinium derivatives. When $\underline{2}$ is treated with cold perchloric acid, dehydration proceeds rapidly and the dihydropyridinium salt, $\underline{3}$, is obtained in 70% yield [hygroscopic solid, mp 74-80°; λ^{CHCl_3} 304 (6,064);[9] λ^{CHCl_3} 6.09, 6.32; nmr (CDCl$_3$),τ 7.94 (CH$_3$)]. However, if $\underline{2}$ is refluxed with ethanolic perchloric acid, the pyridinium salt, $\underline{4}$ is produced directly in 75% yield [mp 129°; λ^{CHCl_3} 282 (8,770); λ^{CHCl_3} 6.15, 6.40 μ; nmr (CDCl$_3$) τ 2.55, singlet, (aryl H), 7.51 (CH$_3$)]. Similarly, the phenyl alcohol, $\underline{8}$, was readily dehydrated with ethereal

perchloric acid producing $\underline{9}$ in 93% yield [mp 210°; λ^{CHCl_3} 330 (10,000)], and upon refluxing in ethanolic perchloric acid gave 70% of $\underline{10}$ [mp 220°; λ^{CHCl_3} 288 (12,900), nmr (CD$_3$CN) τ 2.39-2.65 (6 protons)].[10]

      It is clear that systems of the type, $\underline{1}$ exhibit rather extensive synthetic versatility and further studies should document the fact that enaminoketones can be useful vehicles for obtaining a variety of heterocyclic molecules.

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10.   All compounds (except $\underline{6}$, which was unstable) gave satisfactory elemental analyses. The addition of organometallic reagents to $\underline{1}$ were all performed in anhydrous benzene solution at 5-10°. The acetyl iminium salt ($\underline{6}$) was precipitated as a colorless solid when acetyl chloride was added to a benzene solution of $\underline{1}$. The excess acetyl chloride and benzene was removed in vacuo and anhydrous ether was added. The ethereal suspension of $\underline{6}$ was treated with methyl lithium or methyl magnesium iodide producing $\underline{5}$.