New Synthetic Applications of Enaminoketones

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NEW SYNTHETIC APPLICATIONS OF ENAMINOKETONES

BY

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ABSTRACT

This report discusses research concerning synthetic applications of enaminoketones. The work may be divided into four parts as follows: a) replacement of the dimethylamino group of certain enaminones by other amine groups through a simple procedure; b) formation of 3-alkylpyrazoles; c) formation of 2-amino-4-alkyl-pyrimidines; d) synthesis and subsequent reduction of iminium salts. The starting materials (E-1-(N,N-dimethylamino)-1-alkene-3-ones) have been condensed with hydrazine and guanidine to form pyrazoles and pyrimidines, respectively. The same starting materials have been reacted with POCl₃ in CH₂Cl₂ to produce chlorovinyliminium salts. These have then been reacted in situ with reducing agents to produce chlorovinyl amines. Additionally, the experimental procedures used to produce these products are revealed, and the physical properties of the products are given. Recommendations for future research are made.
ACKNOWLEDGEMENTS

A great deal is owed to Dr. John T. Gupton for his wisdom, encouragement, and patience. These proved to be indispensable during the completion of the work presented here. I would like to thank the other members of my research committee, Drs. Graeme Baker and Guy Mattson, for their time and effort. I would also like to thank the faculty and staff of the Department of Chemistry of the University of Central Florida for their teachings, friendship and good humor. Finally, I would like to thank my family for their love and support over the years.
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LIST OF ABBREVIATIONS

Δ  heat sufficient to cause reflux
amu atomic mass units
bp boiling point
ca circa
cm⁻¹ wavenumber
d doublet
EtOH ethanol
g grams
GC gas chromatograph
hrs hours
Hz hertz
IR infrared
i-PrOH iso-propanol
J coupling constant (NMR spectrum)
lit. literature value
m multiplet (NMR spectrum)
m/e mass to charge ratio
\( M^+ \) molecular ion peak
MeOH methanol
MHz megahertz
ml milliliter
min minutes
<table>
<thead>
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<th>Symbol</th>
<th>Definition</th>
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<tr>
<td>mm</td>
<td>millimeters</td>
</tr>
<tr>
<td>mol</td>
<td>gram-moles</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>n-</td>
<td>normal, e.g. n-butane</td>
</tr>
<tr>
<td>NMR</td>
<td>$^1$H nuclear magnetic resonance</td>
</tr>
<tr>
<td>O.N.</td>
<td>overnight</td>
</tr>
<tr>
<td>p-</td>
<td>para, e.g. para-toluidine</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-toluene sulfonic acid</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectrum)</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectrum)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectrum)</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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</table>
INTRODUCTION

The synthetic importance of enaminoketones (also known as enaminones, or vinylogous amides) has increased in recent years.\textsuperscript{1-3}

In some of this recent work it was shown that enaminones of form (1) are regiospecifically accessible through reaction of a methyl ketone of form (2) with an azavinamidinium salt \[((3\text{-dimethylamino})\text{-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (3)}\], as depicted in Fig. 1. Not only are these enaminones available in anywhere from 50-90% purified yield, but the azavinamidinium salt itself is available in quantitative yield from cyanuric chloride and N,N-dimethylformamide,\textsuperscript{4} as shown in Fig. 2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Producing N,N-dimethylamino ketones from methylketones and Gold's reagent.}
\end{figure}
Enaminones of form (1) are a specialized form of this general group of fairly reactive molecules. Traditionally the enaminone is any molecule containing the conjugated system $N-C=C-C=O$. The chemistry of this system is not well established and is under current investigation.\(^3\)

In the past, synthesis of the enaminone system was most easily carried out by reaction of ammonia, a primary, or a secondary amine with a $1,3$-diketone, $3$-keto-ester, or $\beta$-halo-$\alpha,\beta$-unsaturated ketone as shown in Fig. 3.\(^3\) It can be seen from Fig. 1 that reaction of a methyl ketone with Gold's reagent is conceptually rather different from such processes.

![Figure 2](image-url)

**Figure 2.** Producing Gold's reagent from cyanuric chloride and dimethylformamide.

![Figure 3](image-url)

**Figure 3.** Preparation of enaminoketones by standard methods.
The process depicted in Fig. 1 has been called -dimethylamino methylenation. To date, the standard reagents used to carry out this transformation have been the formamide acetals. These function well, but are expensive and sensitive to heat. Gold's reagent, on the other hand, is made in almost quantitative yield from inexpensive starting materials, and reacts at relatively low temperatures (65-90°C) over moderate reaction times of 12-24 hr. It functions well in replacement of the aforementioned formamide acetals, reacting with amines to give amidines, with amides to give acylamidines, and regiospecifically with ketones (Fig. 1) to give enaminoketones.

In early work, it was found that enaminones derived from 3-keto-1-butanal and pentane-2,4-dione underwent C-alkylation with methyl iodide, and O-alkylation with ethyl iodide as shown in Fig. 4. Solvent dependency was found for the same reaction using a different substrate, the tricyclic enaminoketone (4). When reacted with methyl iodide in non-polar solvents, the C-methyl derivative was formed, but the same reaction performed in alcoholic solvent gave the O-methyl product shown in Fig. 5.

![Figure 4. Alkylation of enaminones by methyl or ethyl iodide.](image)
Figure 5. C- or O- methylation by methyl iodide in different solvents.

Grignard reagents add to acyclic enaminones in 1,4- fashion, eliminating dimethylamine to give $\alpha,\beta$-unsaturated ketones (Fig. 6). Enaminones featuring a methyl substituent at the $\beta$-position have been condensed with aldehydes by first deprotonating the substrate with butyl-lithium (Fig. 7). Ketones react in the same manner.

Figure 6. Grignard addition to enaminones.

Figure 7. Reaction of an enaminone with base and aldehyde.
Reductions attempted have in some cases either failed or forced nitrogen or oxygen out of the molecule. Catalytic hydrogenation has been more successful. Hydrogenation of simple open-chain enaminoles over Pt or Pd has reduced them to the saturated ketone. The same reaction run over rhodium or ruthenium, however, gives the saturated amino alcohol, and reduction with lithium aluminum hydride gives the amino-ketone seen in Fig. 8.  

\[ \text{Me} \text{C=CH}_2 \text{NMe}_2 \xrightarrow{\text{H}_2/\text{Pt}} \text{Me} \text{C}=-\text{CMe}_2 \]

\[ \text{Me} \text{C}=\text{NMe}_2 \xrightarrow{\text{LiAlH}_4} \text{Me} \text{C}=\text{NMe}_2 \xrightarrow{\text{H}_2/\text{Pd}} \text{Me} \text{C}=-\text{CMe}_2 \]

Enaminones have also been reacted with their corresponding chlorovinyl ketones at room temperature to give pyridine derivatives in good yield (Fig. 9). For further information concerning enamino synthesis of lactones and some fused heterocyclic systems, see reference number 3.
With this past heterocycle synthesis in mind, it is proposed to react both hydrazine (5) and guanidine (6) with a series of regiospecifically produced enaminones (1, R=n-pentyl, i-Bu, i-Pr, Et, Me) in an effort to produce 3-alkyl-pyrazoles and 2-amino-4-alkyl-pyrimidines, respectively.
Iminium salt chemistry has also gained importance in recent years. In work reported by Liebscher,7 compounds similar to enaminones of form (1) have been converted to 3-chloropropeniminium salts by the action of reagents such as POC13 and PCl5. In work which would parallel this, it is proposed to attempt to convert members of the enaminone series mentioned earlier into 3-chloro-propeniminium salts by reaction with POC13. If this is successful, an attempt will be made to reduce these salts, made in situ, with NaBH4 and NaCNBH3, yielding amines.

In work which would broaden the scope of these reduction reactions, it is further proposed to attempt to exchange amines (pyrrolidine, piperidine, diethylamine, etc.) for the N,N-dimethylamino group of enaminones (1) through a simple reflux operation. If successful, this would render the procedure of iminium salt production/subsequent reduction all the more useful.

\[ \begin{align*}
\text{Me}_2\text{N} & \text{R} = \text{alkyl} \\
\text{O} & \\
\text{R} & \text{an enaminoketone}
\end{align*} \]
A. Preparation of Enaminoketones

$$\text{Cl}^\ominus \xrightarrow{\text{Me}_2\text{N} = \text{N} = \text{NMe}_2} \xrightarrow{\text{NaH}, \text{i-PrOH}, \text{N}_2, \Delta, \text{O.N.}} \text{CH}_3\text{C}_\text{CH}_2\text{-R}$$

Table I

Experimental data for the preparation of alkyl enaminones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yielda</th>
<th>bp (°C)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CH$_3$</td>
<td>65.4)$_c$</td>
<td>lit.$^8$ 118 (11)</td>
</tr>
<tr>
<td>2</td>
<td>-CH$_2$-CH$_3$</td>
<td>lit.$^1$ 100 (75)$^d$</td>
<td>lit.$^1$ 73-95 (0.5)</td>
</tr>
<tr>
<td>3</td>
<td>-C-H</td>
<td>100 (88.5)$^e$</td>
<td>lit.$^1$ 75-88 (0.3)</td>
</tr>
<tr>
<td>4</td>
<td>-CH$_2$-C-H</td>
<td>100 (92.8)$^f$</td>
<td>lit.$^1$ 81-101 (0.4)</td>
</tr>
<tr>
<td>5</td>
<td>-(CH$_2$)$_4$-CH$_3$</td>
<td>100 (88.2)$^g$</td>
<td>lit.$^1$ 91-98 (0.4)</td>
</tr>
</tbody>
</table>
(a) Distilled yields are presented in parentheses.
(b) Boiling points are in degrees centigrade; pressures are presented in millimeters of Hg.

(c) NMR (CDCl₃) δ 1.10 (t, J=8Hz, 3H), 2.36 (q, J=8Hz, 2H), 2.93 (s, 6H), 5.04 (d, J=12Hz, 1H), 7.53 (d, J=12Hz, 1H); IR (thin film) 1660 and 1580 cm⁻¹; mass spectrum m/e 127 (M⁺).

(d) None of this compound was prepared for the present work. It was obtained from a previously prepared sample. NMR (CDCl₃) δ 0.92 (t, J=6Hz, 3H), 1.61 (t of q, J=6Hz, 2H), 2.31 (t, J=6Hz, 2H), 2.92 (s, 6H), 5.04 (d, J=12Hz, 1H), 7.46 (d, J=12Hz, 1H); IR (thin film) 1660 and 1580 cm⁻¹; mass spectrum m/e 141 (M⁺).

(e) NMR (CDCl₃) δ 0.94 (d, J=6Hz, 6H), 1.50 (m, 1H), 2.18 (d, J=2Hz, 2H), 2.92 (s, 6H), 5.05 (d, J=12Hz, 1H), 7.52 (d, J=12Hz, 1H); IR (thin film) 1660, 1580 cm⁻¹; mass spectrum m/e 155 (M⁺).

(f) NMR (CDCl₃) δ 0.90 (d, J=6Hz, 6H), 1.50 (m, 3H), 2.31 (t, J=6Hz, 2H), 2.91 (s, 6H), 5.02 (d, J=12Hz, 1H), 7.47 (d, J=12Hz, 1H); IR (thin film) 1660, 1580 cm⁻¹; mass spectrum m/e 169 (M⁺).

(g) NMR (CDCl₃) δ 0.90 (t, J=4Hz, 3H), 1.20 (m, 8H), 2.36 (t, J=6Hz, 2H), 2.98 (s, 6H), 5.08 (d, J=12Hz, 1H), 7.52 (d, J=12Hz, 1H); IR (thin film) 1660, 1580 cm⁻¹; mass spectrum m/e 183 (M⁺).

Preparation of E-1-(N,N-dimethylamino)-6-methyl-1-heptene-3-one

A 500 ml three-neck round bottom flask was swept with nitrogen and equipped with magnetic stirring and a reflux condenser. To this was added 5.25 g (0.131 mol) of a 60% mineral oil dispersion of sodium hydride and 25 ml of hexane. After stirring this for a few minutes the hexane was removed and 100 ml of anhydrous isopropanol was slowly added. This mixture was refluxed for 5 min to react all of the sodium
hydride (or until no more hydrogen evolved), then cooled to room temperature.

The starting ketone (5-methyl-2-hexanone, 15.0 g, 0.131 mol) and 3-(dimethylamino)-2-azaprop-2-en-1-ylidene dimethylammonium chloride (21.5 g, 0.131 mol) were then added. The flask was stoppered and heated to reflux overnight while stirring. After the reaction mixture was cooled to room temperature, the solvent was removed under vacuum and the residue partitioned between 80 ml of water and 3 x 75 ml of CHCl₃. The CHCl₃ phases were combined, dried (MgSO₄), and distilled under reduced pressure (0.1-0.5 torr) via Kugelrohr apparatus to yield 20.6 g (92.8%) of a dark yellow liquid. The purity was found to be 95% by GC, and the structure was verified by taking NMR and IR spectra. All other compounds in Table I were prepared in this manner.

B. Preparation of N-alkyl-substituted enaminoketones

\[
\text{R-H} + \xrightarrow{\Delta, \text{O.N.}} \text{R-CH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_3
\]
Table II  
Experimental data for the preparation of N-alkyl substituted enamionones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield$^a$</th>
<th>bp/mp (°C)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>65 (43)$^c$</td>
<td>95 (0.5)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>100 (97)$^d$</td>
<td>95 (0.5)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>100 (86)$^e$</td>
<td>98-103 (0.2)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>100 (86)$^f$</td>
<td>70-80 (0.2)</td>
</tr>
<tr>
<td>5</td>
<td>$\text{H}_3\text{C}-\text{CH}_2\text{N-CH}_2\text{CH}_3$</td>
<td>100 (90)$^g$</td>
<td>80-83 (0.2)</td>
</tr>
<tr>
<td>6</td>
<td>$\text{H-N-(CH}_2\text{)}_3\text{-CH}_3$</td>
<td>65 (43)$^h$</td>
<td>95 (0.5)</td>
</tr>
<tr>
<td>7</td>
<td>$\text{H}_3\text{C-CH-CH}_2\text{-CH}_3$</td>
<td>100 (66)$^i$</td>
<td>65-70 (0.3)</td>
</tr>
<tr>
<td>8</td>
<td>$\text{H-N-CH}_2\text{-CH}_2\text{CH}_3$</td>
<td>100 (86)$^j$</td>
<td>40-95 (0.07)</td>
</tr>
<tr>
<td>9</td>
<td>$\text{H-N-}[\text{CH}_3]$</td>
<td>96 (15)$^k$</td>
<td>71-75</td>
</tr>
</tbody>
</table>

(a) Purified yields are presented in parentheses.

(b) Pressures are given in torr.
(c) NMR (CDCl₃) δ 0.90 (broad t, 3H), 1.33 (m, 8H), 1.97 (m, 4H), 2.33 (t, J=7Hz, 2H), 3.35 (broad m, 4H), 5.03 (d, J=13Hz, 1H), 7.78 (d, J=13Hz, 1H); IR (thin film) 1650, 1605 1570 cm⁻¹.

(d) This sample exhibited the same spectral characteristics as the previous sample.

(e) NMR (CDCl₃) δ 0.87 (broad t, 3H), 1.27 (m, 8H), 1.60 (broad m, 6H), 2.27 (t, J=7Hz, 2H), 3.15 (broad m, 4H), 5.00 (d, J=12Hz, 1H), 7.27 (d, J=12Hz, 1H); IR (thin film) 1645, 1600, 1550 cm⁻¹.

(f) NMR (CDCl₃) δ 0.85 (broad t, 3H), 1.27 (m, 8H), 2.28 (t, J=7Hz, 2H), 3.17 (t, J=5Hz, 4H), 3.63 (t, J=5Hz, 4H), 5.07 (d, J=13Hz, 1H), 7.25 (d, J=13Hz, 1H); IR (thin film) 1650, 1600, 1560 cm⁻¹.

(g) NMR (CDCl₃) δ 0.87 (broad t, 3H), 1.15 (m, 14H), 2.28 (t, J=7Hz, 2H), 3.17 (q, J=7Hz, 4H), 4.97 (d, J=12Hz, 1H), 7.32 (d, J=12Hz, 1H); IR (thin film) 1650, 1605, 1565 cm⁻¹.

(h) NMR (CDCl₃) δ 0.70-2.00 (m, 18H), 2.22 (t, J=7Hz, 2H), 3.10 (m, 2H), 4.84 (d, J=7Hz, 1H), 6.50 (d of d, J=7Hz, J=14Hz, 1H), 9.77 (broad s, 1H); IR (thin film) 3260, 1635, 1565 cm⁻¹.

(i) NMR (CDCl₃) δ 0.60-1.90 (m, 19H), 2.25 (t, J=7Hz, 2H), 3.07 (m, 1H), 4.82 (d, J=7Hz, 1H), 6.53 (d of d, J=7Hz, J=14Hz, 1H), 9.77 (broad s, 1H); IR (thin film) 3260, 1630, 1565 cm⁻¹.

(j) NMR (CDCl₃) δ 0.50-1.90 (m, 16H), 2.27 (t, J=7Hz, 2H), 3.10 (d of t, J=6Hz, 2H), 4.90 (d, J=7Hz, 1H), 6.57 (d of d, J=7Hz, J=14Hz, 1H), 9.77 (broad s, 1H); IR (thin film) 3260, 1635, 1565 cm⁻¹.

(k) NMR (CDCl₃) δ 0.72 (broad t, 3H), 1.17 (broad m, 8H), 1.90 (s, 3H), 2.30 (t, J=7Hz, 2H), 5.15 (d, J=8Hz, 1H), 6.55-7.20 (m, 5H); IR (thin film) 3025, 1635, 1595, 1560, 1520, 810 cm⁻¹.
Preparation of E-1-(pyrrolidinyl)-non-1-ene-3-one

In order to show the effectiveness of one method over another, both methods (a) and (b) were used to prepare the same compound, as shown below. Method (b), however was used to prepare entries 2-8 in Table II; entry 9 was prepared by method (c), as explained below.

(a) A 250 ml three-neck round bottom flask was placed under a nitrogen atmosphere and equipped with magnetic stirring, a thermometer and reflux condenser. To this was added E-1-(N,N-dimethylamino)-non-1-ene-3-one (2.0 g, 0.011 mol), PTSA (100 mg), pyrrolidine (1.6 g, 0.022 mol) and 50 ml of anhydrous methanol. The reaction flask was then stoppered and heated to reflux.

After 48 hr, the reaction vessel was cooled and solid Na₂CO₃ was added until visible reaction ceased. The liquid was decanted away from residual solid, the methanol was removed using a rotary evaporator, and the residue was partitioned between 70 ml of saturated aqueous NaHCO₃ and 3 x 70 ml of CHCl₃.

The CHCl₃ phases were combined, dried (MgSO₄), and gravity filtered. The CHCl₃ was then removed using a rotary evaporator to give 1.5 g (65% yield) of a yellow oil which was then distilled at reduced pressure (0.5 mm Hg) using a Kugelrohr apparatus to yield 0.98 g (43% yield) of product. Purity was assured by TLC, and an IR and NMR spectrum were obtained to provide positive structural identification.

(b) A 250 ml three-neck round bottom flask was placed under a nitrogen atmosphere and equipped with magnetic stirring, a thermometer and reflux condenser. To this was added E-1-(N,N-dimethylamino)-non-1-ene-3-one (1.0 g, 0.0055 mol), and 15 ml of pyrrolidine. The flask was stoppered and heated to reflux overnight.
After 24 hr the reaction vessel was cooled, excess pyrrolidine was removed by evaporation in vacuo, and the residue (100% yield) was distilled at reduced pressure (0.1 mm Hg) using a Kugelrohr apparatus to yield 1.1 g (97% yield) of product. Purity was assured by TLC and IR and NMR spectra were taken to provide positive structural identification.

**Preparation of Z-1-(N-(p-methyl)-phenyl)-non-1-ene-3-one**

(c) The fact that p-toluidine is a solid at room temperature made it incompatible with the procedure used with the other seven amines in method (b). This necessitated the use of a solvent. It was found that a mixture of 5 ml dioxane/5 ml i-PrOH dissolved 1.17 g (0.0109 mol) of p-toluidine well enough to adapt the former procedure.

A 250 ml three-neck round bottom flask equipped with magnetic stirring, reflux condenser and thermometer was placed in a nitrogen atmosphere. To this was added the mixture previously described as well as 2.0 g (0.011 mol) E-1-(N,N-dimethylamino)-non-1-ene-3-one. This reaction mixture was heated and allowed to reflux. After 48 hr, the reaction mixture was cooled to room temperature, the solvent was removed in vacuo, and the residue (2.5 g, 96% yield) was collected on a Buchner funnel. This product was then recrystallized by the mixed solvent method using 95% hexane:5% ethyl acetate, v/v. The recrystallized yield was 0.396 g (15.0% yield), and the physical properties of this recrystallized product were determined.
C. Preparation of 3-alkyl-pyrazoles

\[
\begin{align*}
\text{Me}_2\text{N} \quad \text{O} & \quad \text{EtOH} \\
\text{CH}_2\text{R} & \quad \text{H}_2\text{O} \quad \text{O.N.} \\
\text{EtOH} & \quad \text{N} \\
\text{CH}_2\text{R} & \\
\end{align*}
\]

**Table III**

Experimental data for the preparation of 3-alkyl-pyrazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield %\text{a,b}</th>
<th>bp (°C)\text{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CH\text{3}</td>
<td>65\text{d}</td>
<td>56 (0.1)</td>
</tr>
<tr>
<td>2</td>
<td>-CH\text{2CH}_{3}</td>
<td>75\text{e}</td>
<td>62 (0.1)</td>
</tr>
<tr>
<td>3</td>
<td>-CH\text{3}</td>
<td>68\text{f}</td>
<td>63-98 (0.3)</td>
</tr>
<tr>
<td>4</td>
<td>-CH\text{2CH}-H</td>
<td>59\text{g}</td>
<td>150-160 (124)</td>
</tr>
<tr>
<td>5</td>
<td>-(CH\text{2})\text{4-CH}_{3}</td>
<td>71\text{h}</td>
<td>70-90 (0.3)</td>
</tr>
</tbody>
</table>

\text{a) All yields are distilled yields.}
(b) The purity of each compound was assured by GC.

**Instrument Conditions**

Column dimensions and packing 1/8" x 6', 3% SP-2401-DB
Injection temperature 200°C
Column temperature 150°C
Flow rate 50 ml/min

(c) Pressures shown are in millimeters of Hg.

(d) NMR (CDCl₃) δ 1.23 (t, J=8Hz, 3H), 2.63 (q, J=8Hz, 2H), 5.90 (d, J=2Hz, 1H), 7.28 (d, J=2Hz, 1H), 12.17 (broad s, 1H); IR (thin film) 3175, 3130, 3100, 2400-3600, 3070, 3030, 2670-3010, 1660, 1575, 1470, 1365, 1205, 1190, 1025, 1000, 935, 790 cm⁻¹.

(e) NMR (CDCl₃) δ 0.97 (t, J=8Hz, 3H), 1.37-1.97 (m, 2H), 2.67 (t, J=8Hz, 2H), 6.05 (d, J=2Hz, 1H), 7.48 (d, J=2Hz, 1H), 12.13 (s, 1H); IR (thin film) 3180, 3125, 3100, 2440-3660, 3060, 3040, 2770-3010, 1575, 1465, 1370, 1205, 1185, 1010, 1000, 935, 805 cm⁻¹; mass spectrum m/e 110 (M⁺).

(f) NMR (CDCl₃) δ 0.93 (d, J=6Hz, 6H), 1.60-2.17 (m, 1H), 2.58 (d, J=6Hz, 2H), 6.05 (d, J=2Hz, 1H), 7.52 (d, J=2Hz, 1H); IR (thin film) 3180, 3130, 3100, 2300-3680, 3080, 3040, 2780-3020, 1635, 1575, 1465, 1385, 1365, 1205, 1180, 1020, 995, 820 cm⁻¹; mass spectrum m/e 124 (M⁺).

(g) NMR (CDCl₃) δ 0.95 (d, J=6Hz, 6H), 1.60 (m, 3H), 2.70 (t, J=7Hz, 2H), 6.12 (broad s, 1H), 7.53 (broad s, 1H), 12.17 (broad s, 1H); IR (thin film) 3180, 3130, 3100, 2400-3700, 3060, 3050, 2760-3010, 1660, 1575, 1465, 1380, 1365, 1200, 1185, 1030, 1010, 935, 820 cm⁻¹; mass spectrum m/e 138 (M⁺).

(h) NMR (CDCl₃) δ 0.97 (t, J=5Hz, 3H), 1.16-2.07 (broad m, 8H), 2.83 (t, J=7Hz, 2H), 6.27 (d, J=2Hz, 1H), 7.73 (d, J=2Hz, 1H), 12.17 (broad s, 1H); IR (thin film) 3180, 3130, 3100, 2400-3500, 3060, 2700-3010, 1575, 1465, 1370, 1200, 1170, 1015, 990, 935, 820 cm⁻¹; mass spectrum m/e 152 (M⁺).
Preparation of 3-propyl-pyrazole

To a 250 ml three-neck flask equipped with magnetic stirring, drying tube and thermometer was added 2.04 g (0.0144 mol) of E-1-(N,N-dimethylamino)-hex-1-ene-3-one and 75 ml anhydrous ethanol. To this mixture was added 2.10 g (0.0419 mol) of hydrazine hydrate via pipet. The flask was then stoppered and allowed to stir at room temperature overnight.

After 24 hr, the reaction mixture was quenched with 10 ml of water, and the solvent was removed using a rotary evaporator. To the residue was added 50 ml water, and the mixture was extracted with 3 x 50 ml CHCl$_3$. The CHCl$_3$ extracts were combined, dried (MgSO$_4$), and the CHCl$_3$ was removed under vacuum to give a yellow oil. This was then distilled under reduced pressure (0.3 mm Hg) using a Kugelrohr apparatus to yield 1.2 g (75% yield) of purified product. All other entries in Table III were prepared in this manner.

D. Preparation of 2-amino-4-alkyl-pyrimidines

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{CH}_2\text{R} \\
\text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{HCl} & \quad \text{H}
\end{align*}
\]
Table IV

Experimental data for the preparation of 2-amino-4-alkyl-pyrimidines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield^a</th>
<th>mp^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CH2-CH3</td>
<td>100 (86)^c</td>
<td>111-116</td>
</tr>
<tr>
<td>2</td>
<td>-CH3</td>
<td>100 (64)^d</td>
<td>112-115</td>
</tr>
<tr>
<td>3</td>
<td>-CH2-C-H</td>
<td>100 (73)^e</td>
<td>93-97</td>
</tr>
<tr>
<td>4</td>
<td>-(CH2)4-CH3</td>
<td>100 (57)^f</td>
<td>95-97</td>
</tr>
</tbody>
</table>

(a) Purified yields are represented in parentheses.

(b) Melting points are given in degrees centigrade, and were taken using a Fischer-Johns melting point apparatus.

(c) NMR (CDCl3) δ 1.00 (t, J=7Hz, 3H), 1.70 (m, 2H), 2.58 (t, J=6Hz, 2H), 5.48 (broad s, 2H), 6.52 (d, J=5Hz, 1H), 8.22 (d, J=5Hz, 1H); IR (CHCl3) 3200-3600, 1580, 1560, 1460, 820 cm⁻¹; mass spectrum m/e 137 (M⁺).

(d) NMR (CDCl3) δ 0.91 (d, J=7Hz, 6H), 1.55-2.30 (m, 1H), 2.42 (d, J=7Hz, 2H), 5.55 (broad s, 2H), 6.45 (d, J=5Hz, 1H), 8.17 (d, J=5Hz, 1H); IR (CHCl3) 3200-3600, 1580, 1560, 1450, 1435, 800 cm⁻¹; mass spectrum m/e 151 (M⁺).
(e) NMR (CDCl₃) δ 0.98 (d, J=6Hz, 6H), 1.40-1.80 (m, 3H), 2.57 (t, J=7Hz, 2H), 5.28 (broad s, 2H), 6.50 (d, J=5Hz, 1H), 8.20 (d, J=5Hz, 1H); IR (CHCl₃) 3200-3600, 1580, 1560, 1455, 1440, 810 cm⁻¹; mass spectrum m/e 165 (M⁺).

(f) NMR (CDCl₃) δ 0.88 (t, J=5Hz, 3H), 1.05-1.97 (m, 8H), 2.54 (t, J=7Hz, 2H), 5.65 (broad s, 2H), 6.43 (d, J=5Hz, 1H), 8.13 (d, J=5Hz, 1H); IR (CHCl₃) 3200-3600, 1580, 1555, 1455, 1435, 820 cm⁻¹; mass spectrum m/e 179 (M⁺).

**Preparation of 2-amino-4-propyl-pyrimidine**

Sodium hydride (0.57 g of a 60% mineral oil dispersion, 0.014 mol) was placed under nitrogen in a 250 ml three-neck round bottom flask equipped with magnetic stirring, a reflux condenser and thermometer. This was washed with 25 ml of hexane and stirred for a few minutes. After removing the hexane, 75 ml of anhydrous ethanol was added dropwise via an addition funnel. The reaction flask was stoppered, heated until all of the sodium hydride had reacted, and cooled to room temperature.

Guanidine hydrochloride (1.4 g, 0.014 mol) was then added and allowed to react with the sodium ethoxide solution previously formed. After ten min, 1.0 g (0.0071 mol) of E-1-(N,N-dimethylamino)-hex-1-ene-3-one was added. The reaction vessel was stoppered and heated to reflux for two hr.

After this period, the reaction mixture was filtered hot through a sintered glass funnel. After removing the ethanol using a rotary evaporator, the crude product was then collected on a Buchner funnel, washed with ice cold water, and dried under vacuum. A small analytical sample was recrystallized from ethanol, and its physical properties were determined. All other entries in Table IV were prepared in this manner.
E. Preparation of chlorovinyl amines

\[
\begin{align*}
&\text{Me}_2N\text{CH}_2\text{Cl} \quad \text{R} \\
&\text{POCl}_3, \quad \text{CH}_2\text{Cl}_2, \quad \text{N}_2, \\
&\text{0}^\circ \text{C} \text{ to RT, 30 min.} \\
&\text{NaBH}_4/\text{NaCNBH}_3, \quad \text{THF*} \\
&\text{0}^\circ \text{C} \text{ to RT overnight.} \\
\end{align*}
\]

Table V

Experimental data concerning the preparation and reduction of iminium salts

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reducing Agent</th>
<th>Method$^a$</th>
<th>% Yield$^b$</th>
<th>bp$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1#</td>
<td>n-hexyle$^e$</td>
<td>NaBH$_4$</td>
<td>A</td>
<td>86 (54)</td>
<td>45-50 (0.3)</td>
</tr>
<tr>
<td>2#</td>
<td>sec-butyl$^f$</td>
<td>NaBH$_4$</td>
<td>A</td>
<td>74 (39)</td>
<td>115-125 (114)</td>
</tr>
<tr>
<td>3</td>
<td>propyl$^g$</td>
<td>NaBH$_4$</td>
<td>A</td>
<td>96 (56)</td>
<td>86 (115)</td>
</tr>
<tr>
<td>4</td>
<td>i-pentyl$^h$</td>
<td>NaBH$_4$</td>
<td>A</td>
<td>64 (18)</td>
<td>100-110 (122)</td>
</tr>
<tr>
<td>5</td>
<td>i-pentyl$^i$</td>
<td>NaBH$_4$</td>
<td>B</td>
<td>100 (37)</td>
<td>110-130 (117)</td>
</tr>
<tr>
<td>6#</td>
<td>i-pentyl$^j$</td>
<td>NaCNBH$_3$</td>
<td>B</td>
<td>80 (48)</td>
<td>d</td>
</tr>
</tbody>
</table>

$^a$-A second solvent was not always used—see (a) below.

$^b$-Combustion analyses were performed on the compounds so marked.
(a) Method A involved the use of two solvents, and consequently, two reaction vessels. Method B was a one-solvent, one-pot method. An example of each method follows.

(b) Purified yields are in parentheses. Purity was assured by GC.
Instrument Conditions
Column dimensions and packing (1/8) x 6', 3% SP-2401-DB
Injection temperature 200°
Column temperature 100°
Flow rate 50 ml/min

(c) Boiling points are given in degrees centigrade, pressures are given in mm Hg.

(d) Purified by acid extraction, not distillation, thus no boiling point was obtained on this occasion.

(e) NMR (CDCl₃) δ 0.90 (t, J=5Hz, 3H), 1.08-1.87 (m, 8H), 2.20-2.52 (m, 2H), 2.72 (s, 6H), 3.10 (d, J=6Hz, 2H), 5.63 (t, J=6Hz, 1H); IR (thin film) 2680-2960, 1660, 1460, 1360, 1260, 1175, 1155, 855, 725 cm⁻¹; mass spectrum m/e 203, 205 (M⁺); calcd. for C₁₁H₂₂NCl: C, 64.83; H, 10.90; N, 6.87. Found: C, 64.55; H, 11.01; N, 7.07.

(f) NMR (CDCl₃) δ 0.90 (d, J=6Hz, 6H), 1.67-2.00 (m, 1H), 2.10-2.35 (m, 2H), 2.72 (s, 6H), 3.10 (d, J=6Hz, 2H), 5.55 (t, J=6Hz, 1H); IR (thin film) 2660-2960, 1650, 1460, 1385, 1370, 1260, 1175, 1165, cm⁻¹; mass spectrum m/e 175, 177 (M⁺); calcd. for C₉H₁₈NCl: C, 61.51; H, 10.35; N, 7.97. Found: C, 61.53; H, 10.41; N, 7.98.

(g) NMR (CDCl₃) δ 0.92 (t, J=7Hz, 3H), 1.30-1.93 (m, 2H), 2.22-2.40 (m, 2H), 2.27 (s, 6H), 3.08 (d, J=6Hz, 2H), 5.57 (t, J=6Hz, 1H); IR (thin film) 2640-2960, 1650, 1450, 1360, 1255, 1175, 1160, cm⁻¹; mass spectrum m/e 161, 163 (M⁺).
(h) NMR (CDCl$_3$) $\delta$ 0.92 (d, J=6Hz, 6H), 1.33-1.73 (m~3H), 2.22-2.46 (m, 2H), 2.28 (s, 6H), 3.02 (d, J=16Hz, 2H), 5.58 (t, J=6Hz, 1H); IR (thin film) 2660-2960, 1655, 1465, 1455, 1380, 1365, 1260, 1175, 1155, 1095, 1070, cm$^{-1}$; mass spectrum m/e 189, 191 (M$^+$).

(i) This compound showed the same spectral properties as compound (h).

(j) This compound exhibited the same spectral properties as compound (h); calcd. for C$_{10}$H$_{20}$NCl: C, 63.29; H, 10.65; N, 7.38. Found: C, 63.45; H, 10.82; N, 7.61.

**Method A (using NaBH$_4$): Z-1-(N,N-dimethylamino)-3-chloro-2-hexene**

A 250 ml three-neck round bottom flask was placed under a nitrogen atmosphere and equipped with a thermometer and magnetic stirring. To this was added 50 ml CH$_2$Cl$_2$ and 2.0 g (0.014 mol) E-1-(N,N-dimethylamino)-1-hexene-3-one. This was cooled to 0°C by the use of an ice/salt water bath.

To this cooled mixture was added 2.2 g (0.014 mol) POC$_3$ and the ice bath was removed. The contents of the reaction vessel were allowed to stir while warming to room temperature (25°C). After half an hour, the reaction mixture was transferred to a one-neck round bottom flask and the solvent was removed by the use of a rotary evaporator. The residue was taken up in 50 ml THF, placed in the original reaction vessel, and again cooled to 0°C. Two equivalents of NaBH$_4$ (1.1 g, 0.028 mol) were then added, the reaction vessel was stopped and the contents allowed to stir while warming to room temperature.

After 24 hr had elapsed, 10 ml of water was carefully added to the reaction mixture, then 20 ml of 10% HCl was added, and the mixture was heated to reflux for 2 hr. The mixture was then cooled, made basic
(pH 10) with 30 ml 10% NaOH, and extracted with 3 x 50 ml CHCl₃. The CHCl₃ phases were combined, dried (MgSO₄), and concentrated using a rotary evaporator to yield 2.2 g crude material. This was subsequently distilled at reduced pressure (113 torr) using a Kugelrohr apparatus to yield 1.3 g (56% yield) of purified material. Purity was checked by GC, and NMR and IR spectra were obtained for structural verification. Entries 1-4 in Table V were produced in this manner.

Method B (using NaBH₄): Z-1-(N,N-dimethylamino)-3-chloro-6-methyl-2-heptene.

A 250 ml three-neck round bottom flask was placed under a nitrogen atmosphere and equipped with a thermometer and magnetic stirring. To this was added 50 ml CH₂Cl₂ and 2.0 g (0.012 mol) E-1-(N,N-dimethylamino)-6-methyl-1-heptene-3-one. This was cooled to 0°C by the use of an ice/salt water bath. To this cooled reaction mixture was added 1.8 g (0.012 mol) POCl₃, and the ice bath was removed. The contents of the vessel were allowed to stir while warming to room temperature. After half an hour, the vessel was again cooled to 0°C by the use of an ice/salt water bath, and 2 equivalents (0.89 g, 0.024 mol) of NaBH₄ were added. The vessel was then stoppered and allowed to warm to RT overnight.

After 24 hrs had elapsed, 10 ml of water was added, and the reaction mixture was partitioned between 50 ml of water and 3 x 50 ml CHCl₃. The CHCl₃ phases were combined, dried (MgSO₄), and evaporated to give 2.9 g crude material which was then distilled to yield 0.81 g (37% yield) of purified product. Purity was assured by GC, and NMR and IR spectra were obtained to provide structural verification.
Method B (using NaCNBH₃): Z-1-(N,N-dimethylamino)-3-chloro-6-methyl-2-heptene.

A 250 ml three-neck round bottom flask was placed under a nitrogen atmosphere and equipped with a thermometer and magnetic stirring. To this was added 80 ml CH₂Cl₂ and 5.0 g (0.030 mol) of E-1-(N,N-dimethylamino)-6-methyl-1-heptene-3-one. This was cooled to 0°C by the use of an ice/salt water bath.

To this cooled reaction mixture was added 4.5 g (0.030 mol) POC1₃, and the ice bath was removed. The contents of the vessel were allowed to stir while warming to room temperature (25°C). After a half hour, the reaction vessel was again cooled to 0°C and 2 equivalents (3.7 g, 0.060 mol) of NaCNBH₃ were added. The vessel was then stoppered and allowed to warm to room temperature.

After 24 hrs had elapsed, the reaction mixture was partitioned between 50 ml water and 3 x 50 ml CHCl₃. This crude product showed a characteristic B-N stretch around 2300 cm⁻¹ in its IR spectrum, and so was taken up in 75 ml THF, added to 20 ml 5% HCl in a 250 ml one-neck round bottom flask, and refluxed for 2 hr. The mixture was cooled, made basic (pH 10) with 10% NaOH, saturated with NaCl, and extracted with 3 x 70 ml CHCl₃. The extracts were combined, dried (MgSO₄), and evaporated to yield 4.5 g of product (80% yield). Since the IR spectrum still showed a significant B-N stretch, the product was taken up in ethyl ether, extracted with 3 x 50 ml 5% HCl, made basic (pH 13) with solid NaOH pellets, saturated with NaCl, and extracted with 3 x 70 ml CHCl₃. Again the phases were combined, dried and evaporated to yield 2.7 g (48% yield) of relatively pure product. Purity was checked by GC, and NMR
and IR spectra were obtained to provide structural verification. The peak at 2300 cm\(^{-1}\) was not visible in the IR spectrum of this product.
DISCUSSION OF RESULTS

Formation of all enaminoketone starting materials proceeded smoothly and in reasonably high yield. This was no surprise, being a reflection of work previously done by Gupton, et al.\textsuperscript{1}

Enaminoketones containing the N,N-dimethylamino group appear to be versatile synthons, in that primary or secondary amines which are liquids at room temperature are capable of being exchanged with the N,N-dimethylamino group. These amines all have boiling points which are not so high as to decompose the substrate enaminone. The procedure consists of simply refluxing the substrate enaminone in approximately 15 ml of the amine. The reaction does not work very well, however, when the amine/solvent boils at a relatively low temperature. The convenience of this procedure stems from the fact that the N,N-dimethylamino group, when displaced by the 'new' amino group, simply leaves the reaction vessel, dimethylamine being a gas at room temperature. A proposed mechanism for this amine exchange process is presented in Fig. 10.

A notable exception to this reasonably high reactivity is t-butyl amine. More work needs to be done with low-boiling solvents to determine the temperature range that corresponds to the minimum activation energy for this reaction, but one obvious factor contributing to this unreactivity is steric crowding. Another, of course, is the lower (46°C) boiling point of t-butyl amine.
All eight amines studied were reacted with one compound, E-1-(N,N-dimethylamino)-non-1-ene-3-one. It is believed that these amines would react as well with an enamino possessing an alkyl or aryl moiety of different character in place of the six carbon chain of the enamino studied. Pyrrolidine was reacted with the substrate enamino in two different ways. The first, which resulted in low conversion and yield, involved the substrate enamino and attacking amine in roughly equal concentrations in a large amount (50 ml) of solvent (MeOH). The second method resulted in a much higher yield (100% crude, 97% distilled). This improvement is due to the much greater ratio of amine:enaminone by the use of the amine as the solvent.

The relative efficiency of the second method was proven during the reactions with pyrrolidine, so this method was used to react the substrate enamino with seven more amines. In each case, relatively high reactivity was shown, with yields close to or exceeding 90% in five of eight cases.
Entry 9 in Table V, however, presented a problem, in that p-toluidine is a solid at room temperature, and therefore boils at a high temperature. The solution was to dissolve this amine in a minimum amount of solvent with the substrate enaminone. The reaction worked well, giving 96% crude yield, but a great deal of the product was lost on recrystallization, and no attempt was made to recover more of the product from the filtrate.

The conformation of the groups attached to the pi bond in the molecule depicted in Fig. 11 can easily be determined by proton NMR. The coupling constants given by vinylic protons in 'trans' relationship is always greater than the coupling constants given by vinylic protons in a 'cis' relationship. The configuration about the double bond in enaminones produced from Gold's reagent and methyl ketones is 'trans', as shown by the value of the vinylic protons' coupling constant, $'J'$, at approximately 12 Hz.

![Figure 11. Two possible conformations of an enaminone.](image-url)
The configuration of enaminoketones made by the amine exchange procedure from other enaminones may be cis or trans, depending on whether they are made using a primary or secondary amine. In the 'primary amine' case, the product has a proton on the amine nitrogen atom which may force the structure into the cis form by hydrogen bonding with the carbonyl oxygen (Fig. 12). Hydrogen bonding would thus force the molecule into the cis-s-cis orientation shown in Fig. 13. Enaminones made using a secondary amine prefer a trans orientation.

Figure 12. H-Bonded 'cis' orientation of an enaminone.

trans-s-trans

 cis-s-trans

trans-s-cis

 cis-s-cis

Figure 13. Four possible orientations of the enaminone skeleton.
The $^1$H NMR spectra of the eight separate products presented in Table II exhibited exactly what was expected. All spectra obtained possessed a pair of vinylic doublets, at ca. 5 ppm and 6.5-7.8 ppm. In some cases the downfield pair of peaks was split into an additional pair of peaks by an N-H proton. In cases where a simple pair of doublets was found, the coupling constants were found to be 12-13 Hz. In those cases where the downfield pair was split into a companion pair, coupling constants were found to be of the order of 7 Hz. These values indicate 'trans' and 'cis' configurations respectively. The driving force for a change in configuration from trans to cis is believed to be hydrogen bonding.

As an example of a typical proton NMR spectrum obtained for enaminones, please refer to Fig. 14.

<table>
<thead>
<tr>
<th>Peak assignments</th>
<th>Chemical shift, Protons ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1.97 (m,4H)</td>
</tr>
<tr>
<td>b</td>
<td>3.35 (broad s,4H)</td>
</tr>
<tr>
<td>c</td>
<td>7.78 (d,J=13Hz,1H)</td>
</tr>
<tr>
<td>d</td>
<td>5.03 (d,J=13Hz,1H)</td>
</tr>
<tr>
<td>e</td>
<td>2.33 (t,2H)</td>
</tr>
<tr>
<td>f</td>
<td>1.33 (m,8H)</td>
</tr>
<tr>
<td>g</td>
<td>0.90 (t,3H)</td>
</tr>
</tbody>
</table>

Figure 14. Protons responsible for peaks in the $^1$H NMR spectrum of an enaminone
In the infrared spectrum of enaminones of this form (Fig. 14), there appear three peaks, at 1650, 1605, and 1570 cm\(^{-1}\). These are characteristics of coupled vibrations of the carbonyl and vinyl systems found in these compounds.\(^{10}\)

The formation of 3-alkyl-pyrazoles from \(\beta\)-dimethylamino-methylene-alkyl ketones and hydrazine hydrate proceeded smoothly and in good yields (see Table III). The procedure is quite simple, involving only stirring a solution of the substrate enaminone and three equivalents of hydrazine hydrate in ethanol at room temperature for 24 hrs. The product 3-alkyl-pyrazoles are easily isolated using a simple water:chloroform workup, and then they are distilled at reduced pressure using a Kugelrohr apparatus.

The mechanism presented in Fig. 15 is proposed to explain the addition of hydrazine hydrate to an enaminone. As an example of an NMR spectrum obtained for the product pyrazoles, consider 3-propyl-pyrazole (Fig. 16).

Figure 15. Suggested mechanism of hydrazine addition to an enaminone.
The IR spectrum of the same compound showed absorption bands consistent with the literature. All other compounds in Table III showed similar IR absorptions, the only difference between them being the strength of the bands at 1465 and 1370 cm⁻¹. The typical spectrum of an alkyl pyrazole exhibited the following absorption bands: 3180, 3125 and 3100 cm⁻¹, N-H stretches; 3660-2440 cm⁻¹, a broad band absorption due to the presence of dimer and trimer caused by hydrogen bonding in a concentrated sample (neat); 3060 and 3040 cm⁻¹, C-H stretches due to protons 'b' and 'c' (refer to Fig. 16); 3010-2770 cm⁻¹, aliphatic C-H stretching; 1660 and 1575 cm⁻¹, coupled -C=C-C=N-stretches; 1465 cm⁻¹, CH₃ and CH₂ bending; 1370 cm⁻¹, CH₃ bending; in 'iso' compounds, coupled H₃C-CH₃ bending causes a pair of peaks at 1385 and 1365 cm⁻¹; 1205 and 1185 cm⁻¹, due to in-plane C-H bending; 1010 and 1000 cm⁻¹ are both ring 'breathing' modes; 935 cm⁻¹, due to a C-H out of plane bend; 800 cm⁻¹, due to an N-H in plane bend.  

Peak assignments

<table>
<thead>
<tr>
<th>Chemical shift,</th>
<th>Protons</th>
<th>Chemical shift,</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>a 12.13 (broad s,1H)</td>
<td>a</td>
<td>b 7.48 (d,J=2Hz,1H)</td>
<td>b</td>
</tr>
<tr>
<td>b 7.48 (d,J=2Hz,1H)</td>
<td>b</td>
<td>c 6.05 (d,J=2Hz,1H)</td>
<td>c</td>
</tr>
<tr>
<td>c 6.05 (d,J=2Hz,1H)</td>
<td>c</td>
<td>d 2.67 (t,2H)</td>
<td>d</td>
</tr>
<tr>
<td>d 2.67 (t,2H)</td>
<td>d</td>
<td>e 1.36-1.97 (m,2H)</td>
<td>e</td>
</tr>
<tr>
<td>e 1.36-1.97 (m,2H)</td>
<td>e</td>
<td>f 0.97 (t,3H)</td>
<td>f</td>
</tr>
<tr>
<td>f 0.97 (t,3H)</td>
<td>f</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 16. Protons responsible for peaks in the NMR spectrum of 3-propyl-pyrazole.

Mass spectra were obtained for four of the five pyrazoles synthesized. In each of these four cases molecular ion peaks m/e, (M⁺), were found that equalled the molecular weight predicted for the compounds (see Experimental section).
Preparation of 2-amino-4-alkyl-pyrimidines from alkyl enaminones and guanidine was successful in every case attempted. The crude products were found to be pure by TLC. The analytical samples prepared by recrystallization were pure by $^1$H NMR.

A proposed mechanism for the attack of guanidine on a typical enaminone is presented in Fig. 17. All pyrimidines were isolated from the crude reaction mixture by filtering the mixture hot through a sintered glass filter, then removing the solvent from the filtrate with a rotary evaporator. The product was then collected on a Buchner funnel, and washed with cold water. The NMR spectra of these compounds detailed an aromatic system attached to a saturated alkyl group. As an example of an NMR spectrum, refer to Fig. 18 for designation of protons responsible for peaks in the NMR spectrum of 2-amino-4-propyl-pyrimidine.

Figure 17. Suggested mechanism for guanidine attack on an enaminone.
Peak assignments

Chemical shifts,

Protons           ppm
a                  5.48 (broad s, 2H)
b                  8.22 (d, J=5Hz, 1H)
c                  6.52 (d, J=5Hz, 1H)
d                  2.58 (t, 2H)
e                  1.70 (m, 2H)
f                  1.00 (t, 3H)

Figure 18. Designation of protons in 2-amino-4-propyl-pyrimidine.

The IR spectrum of the same compound exhibited four bands between 1600-1400 cm⁻¹ and one at 820 which Katritzky described as "usual" and "characteristic" for such systems. All four compounds synthesized showed similar IR characteristics. The mass spectra of each of the four pyrimidines produced showed a molecular ion peak m/e (M⁺) at the predicted molecular weight for the compound.

In procedures reported by Liebscher, compounds possessing the structure of enaminones have been converted into chlorovinyl iminium salts by reagents such as PCl₅ or POCl₃ (Fig. 19). These compounds have been characterized as useful synthons and have been precipitated as the perchlorate salt from a solution of the iminium dichlorophosphate. This was achieved by addition of perchloric acid to such a solution. (An attempt was made during the course of the work being reported to precipitate the iminium dichlorophosphate of alkyl compounds, but this failed.)

Reaction of these useful intermediates with reducing agents had not been reported in the literature, so it was sought to investigate this reaction with chloropropeniminium salts made in situ by the reaction of enaminoketones and POCl₃ in CH₂Cl₂.
Figure 19. Conversion of enaminones into iminium salts by POC\textsubscript{3}/PCl\textsubscript{5}.

In general, conditions were not optimized, but the reaction was found to proceed well in fair yields, giving 1-chloro-1-alkyl-3-(N,N-dimethylamino)-1-propenes.

One interesting feature of this reaction is the stereochemistry of the products. Moebus\textsuperscript{12} reported similar work using aryl-enaminones (compared to alkyl enaminones in the present work) as starting materials. His products were of the 'E' configuration, whereas products isolated in the present work have been found to favor the 'Z' configuration (see Fig. 19). Product having the 'E' configuration was also produced, but the ratio of Z to E was approximately 3:1, as determined by NMR.

Chemical shift values of vinyl protons may be calculated according to an equation given in reference 13. For instance, the chemical shift of a vinyl proton which is geminal, cis and trans to three groups may be calculated:

$$\delta H = 5.28 + Z_{\text{gem}} + Z_{\text{cis}} + Z_{\text{trans}}$$

The $Z$ values for this 'additivity rule' are given in tabular form. Using this calculation, a value of 5.84 ppm is calculated for the 'E' configuration, and 5.71 ppm for the 'Z' configuration.
Table VI
Chemical shift values found for the proton in chlorovinyl amines (major product)

<table>
<thead>
<tr>
<th>R</th>
<th>$\delta$ H, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-pentyl</td>
<td>5.63</td>
</tr>
<tr>
<td>i-propyl</td>
<td>5.57</td>
</tr>
<tr>
<td>ethyl</td>
<td>5.57</td>
</tr>
<tr>
<td>i-butyl</td>
<td>5.58</td>
</tr>
</tbody>
</table>

As can be seen from Table VI, the values found for the chemical shift of the vinylic proton of chlorovinyl amines are closer to that calculated for the 'Z' configuration. The inescapable conclusion is that the major product occupies the 'Z' configuration. This may be explained on steric grounds if the mechanism in Fig. 20 is proposed. The bond connecting the PO$_2$Cl$_2$ group to the carbon atom must become coplanar with the pi system, in order that a reaction may take place, and the group can leave. This 'leaving' configuration occurs with the dichlorophosphate group in one of two possible positions, 180° apart. In one of the positions, the steric bulk of the alkyl group near the proton alpha to the nitrogen atom raises the energy level to such an extent that the opposite position is favored, leading to the 'Z' configuration.

As can be seen from Table V, several methods were used to prepare, isolate, and purify the four chlorovinylamines produced. It is thought that the enaminoketones prepared by amine exchange will undergo the same two reactions required to produce the chlorovinylamines reported. All entries in Table V were purified by distillation at reduced pressure (Kugelrohr), except entry 6. This was purified by acid extraction, but
was later distilled in the same manner as the other entries. All chlorovinyl amines prepared were subjected to NMR, IR and mass spectroscopy. Three of them were additionally subjected to combustion analysis.

![Diagram of proposed mechanism for iminium salt formation](image)

<table>
<thead>
<tr>
<th>Protons</th>
<th>ppm</th>
<th>Chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2.27 (S,6H)</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>3.08 (d,2H)</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>5.57 (t,1H)</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>2.22 (t,2H)</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>1.30-1.93 (m,2H)</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>0.92 (t,3H)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 20. Proposed mechanism for iminium salt formation; designation of protons in a chlorovinylamine.
In an example of an NMR spectrum obtained for the chlorovinylamines produced, refer to Fig. 20 for designation of peaks in the NMR spectrum of Z-1-(N,N-dimethylamino)-3-chloro-2-hexene.

A sample IR spectrum for the same compound showed the following peaks: 3040-2640 cm\(^{-1}\), due to saturated C-H alkyl stretching and a vinyl C-H stretch; 1650 cm\(^{-1}\), due to C=C stretching; 1450 cm\(^{-1}\), due to CH\(_2\) and CH\(_3\) bending; 1360 cm\(^{-1}\), due to CH\(_3\) bending; 1255, 1175 and 1160 cm\(^{-1}\), due to C-N stretching.

Mass spectra obtained for the four compounds prepared exhibited both a peak at the predicted molecular weight, and a companion peak of approximately 1/3 the intensity of the first at 2 amu higher in mass. This indicates the natural isotopic ratio of chlorine atoms.\(^9\)

Combustion analyses were performed on the compounds appearing as entries 1, 2, and 6 in Table 5. The weight percentages of carbon, hydrogen and nitrogen found in these analyses were satisfactory.
CONCLUSIONS

This research has been successful in showing that 3-alkyl-pyrazoles may be produced by reaction of certain enaminoketones with hydrazine hydrate in anhydrous ethanol at room temperature. It has also shown that 2-amino-4-alkyl-pyrimidines may be produced by reaction of the same enaminones with guanidine in refluxing ethanol.

The work done has shown that the aforementioned enaminoketones may be transformed into chlorovinyliminium salts by the action of phosphorous oxychloride, and reduced in situ by sodium borohydride and sodium cyanoborohydride to the amines. The amine group of enaminoketones has been shown to be readily replaceable by an amine group of higher molecular weight by simply heating the enaminone substrate in the presence of an excess of primary or secondary amine.
RECOMMENDATIONS

These are recommendations for future research.

1. Reduce chlorovinyliminium salts made from enaminoles prepared by the amine exchange procedure. This will widen the scope of this amine exchange reaction and justify its inclusion in this report as a useful synthetic method rather than merely a curiosity.

2. Optimize conditions for reduction of iminium salts with NaBH₄ and NaCNBH₃. Purified yields will be improved, possibly a great deal, by optimizing reaction conditions and minimizing physical losses during the workup procedure.
INSTRUMENTATION AND EQUIPMENT

Infrared spectra were recorded on a Perkin-Elmer Model 1420 infrared spectrophotometer. Samples were run as thin films or as CHCl₃ solutions. NMR spectra were obtained with a Varian Model EM-360 NMR spectrometer. Samples were run as CDCl₃ solutions at 60 MHz. Gas chromatograms were obtained with a Shimadzu GC-7A gas chromatograph using a Shimadzu model C-R1B recorder. Melting points were determined using a Fischer-Johns melting point apparatus. Solvents were evaporated using a Buchi Rotovapor-R rotary evaporator.
BIBLIOGRAPHY


