CYCLIZATION OF α- AND β-AMINO KETONES. (REVIEW)

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In this review data on the synthesis of three-, four-, five-, and six-membered heterocycles, as well as of condensed heterocyclic compounds from α-amino ketones and Mannich bases are classified for the first time.

The chemistry of α- and β-amino ketones is one of the most interesting areas of organic chemistry due to the wide spectrum of biological activity and also the high reactivity of these compounds. Their effect on the cardiovascular and central nervous systems as well as their antiviral activity have been considered in detail in the monograph by A. N. Kudrin [1]. The α- and β-amino ketones are widely used for the synthesis of compounds of various classes such as amino alcohols, β-enamino ketones, nitrosoamino ketones, etc. The chemistry of β-amino ketones has been illuminated in detail in other reviews [2,3]. No correlation of literature material on the synthesis and chemical properties of α-amino ketones and on the cyclization of α- and β-amino ketones has been published up to the present time. The literature data of the past 40 years on the preparation of heterocyclic compounds from α- and β-amino ketones are reviewed systematically below.

1. SYNTHESIS OF THREE-, FOUR-, AND FIVE-MEMBERED HETEROCYCLES

Only one study is known devoted to the synthesis of three-membered heterocycles, viz. 3-fluoroalkyl-2-aziridinyl ketones I by the cyclization of the corresponding β-amino ketones by the action of iodine [4]:

\[
\begin{align*}
&\text{RCHCH}_2\text{CR}^1 \\
&\text{NH}_2 \\
&\text{O} \\
&\text{I}_2 \\
&\text{R} = \text{H(CF}_2)_6, \text{H(CF}_2)_4; \text{R}^1 = \text{t-Bu, Ph}
\end{align*}
\]

It was established that the N-phenyl-substituted β-amino ketone \([R = \text{H(CF}_2)_6, \text{R}^1 = \text{Ph}]\) did not undergo this reaction.

Four-membered heterocycles, azetidines, are obtained by the photolysis of α-amino ketones in ether or in tetrahydrofuran [5-9]. For example, the formation of azetidines II according to the following scheme was described in [6]:

\[
\begin{align*}
&\text{RCHCH}_2\text{CR}^1 \\
&\text{NH}_2 \\
&\text{O} \\
&\text{R} = \text{H(CF}_2)_6, \text{H(CF}_2)_4; \text{R}^1 = \text{t-Bu, Ph}
\end{align*}
\]
Photolysis of \(\alpha\)-N-alkylamidoacetophenones also leads to N-substituted 3-azetidinols of type II [8]:

\[
\begin{align*}
\text{Ph} - \text{CCH}_2\text{N}(...) & = \text{R}^1 \\
\text{Ts} & \quad \text{II}
\end{align*}
\]

A significantly larger number of studies has been devoted to the synthesis of five-membered heterocycles containing one and especially two heteroatoms. The Knorr pyrrole synthesis has been extended not only to \(\alpha\)-halo ketones but also to \(\alpha\)-amino ketones. In the reaction of the latter with acetoacetic ester and its derivatives pyrrole-3-carboxylic acids III are formed [10-15]:

\[
\begin{align*}
\text{O} + \text{MeCOCH}_2\text{COOR}^3 \\
\text{RCHNH}_2\text{CHR}^1 \\
\text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{R} = 2\text{-NO}_2\text{-3-ClC}_6\text{H}_3, \ 	ext{R}^1 = \text{R}^2 = \text{H}, \ 	ext{R}^3 = \text{Et} \ [10];
\text{R} = 4\text{-O}_2\text{NC}_6\text{H}_4, \ 	ext{R}^1 = \text{H}, \ 	ext{R}^2 = 4\text{-MeC}_6\text{H}_4,
\text{4-MeOC}_6\text{H}_4, \ 	ext{4-ClC}_6\text{H}_4 \ [11];
\text{R} = 4\text{-O}_2\text{NC}_6\text{H}_4, \ 	ext{R}^1 = \text{H}, \ 	ext{R}^2 = \text{Ph}, \ 	ext{R}^3 = \text{Et} \ [12];
\text{R} = \text{R}^1 = 4\text{-MeOC}_6\text{H}_4, \ 	ext{R}^2 = \text{R}^3 = \text{H} \ [13];
\text{R} = 3\text{-ClC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4, 2\text{-O}_2\text{NC}_6\text{H}_4,
\text{R}^1 = 4\text{-ClC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, \text{R}^2 = \text{R}^3 = \text{H} \ [14];
\text{R} = \text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Alk} \ [15]
\end{align*}
\]

The one-step synthesis of 3-(acylamino)pyrroles from \(\alpha\)-N-acylamino ketones [16] has been proposed as one of the simplest methods of constructing the pyrrole ring. Under the action of \(\text{Ba(OH)}_2\) in aqueous medium selfcondensation of N-acetyl- and N-benzoylamino acetone to 3-acetylamino- and 3-benzoylamino-2,4-dimethylpyrroles (IV) occurs. In the authors' opinion the conversion occurs through an intermediate stage of a crotonic condensation and is accompanied by partial deacylation.

\[
\begin{align*}
\text{O} + \text{EtNH}CO\text{~~~\text{EtNH}CO} \\
\text{2 RCHNH}CH_2\text{C} \text{Et} \\
\text{R}
\end{align*}
\]

\[
\begin{align*}
\text{Et} \text{NHCOR} \\
\text{COEt}
\end{align*}
\]

\[
\begin{align*}
\text{Et} \text{NHCOR} \\
\text{N}
\end{align*}
\]

\[
\begin{align*}
\text{Et} \text{H} \\
\text{IV}
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{Me, Ph}
\end{align*}
\]

On heating N-acylated \(\alpha\)-amino ketones with malonic acid dinitrile in alcohol in the presence of \(\text{NaOH}\) 1-acyl-2-amino-3-cyanopyrroles (V) are obtained which are of interest as potential antimicrobial agents [17-19].