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THERMAL REARRANGEMENT OF AMINOMETHYL CYCLOPROPYL KETONES

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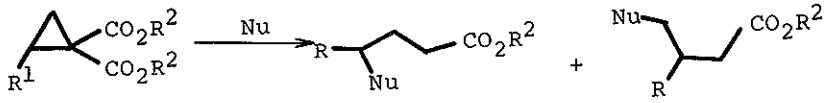
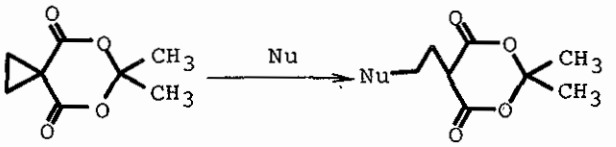
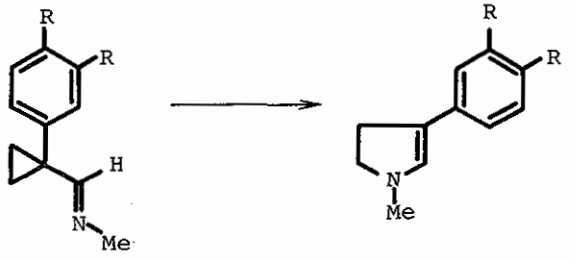
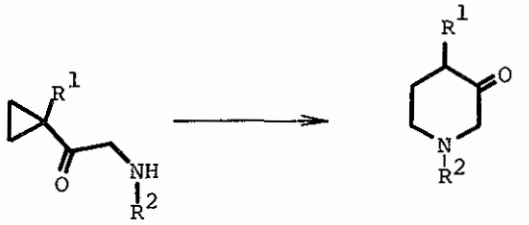
The susceptibility of cyclopropane rings with suitable activating groups to several kinds of nucleophiles has been well documented[1] since the studies of Bone and Perkin.[2] Recently, Danishefsky reported[3] the nucleophilic homoconjugate reactions of cyclopropanes with two geminal activating groups and an enhanced activation of cyclopropanes with cyclic acylal. On the other hand, the acid catalyzed thermal rearrangement of cyclopropylimines, which was originally reported by Cloke,[4] has been shown to be a useful reaction for the synthesis of Δ^1- or Δ^2-pyrrolines,[5] and aminomethyl cyclopropyl ketones have been transformed to 3-ketopiperidine rings.[6]







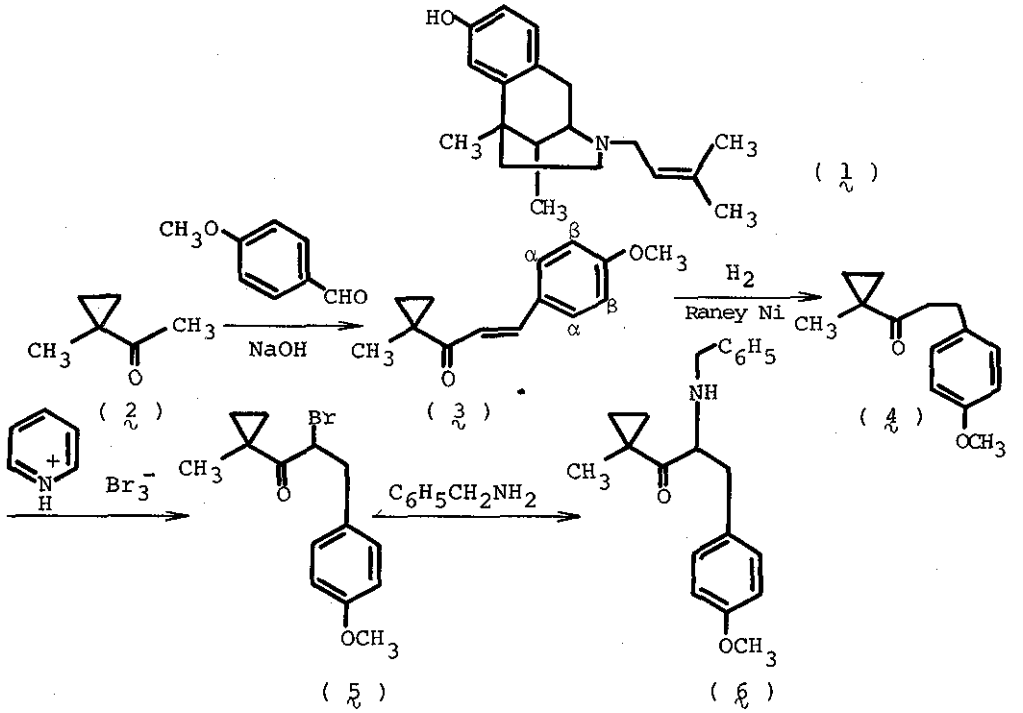


In contrast to the well studied thermal rearrangement of cyclopropylimines, there have been very limited studies regarding the thermal rearrangement of aminomethyl cyclopropyl ketones and this prompted us to examine its possible use for the synthesis of pentazocine (1).

Since pentazocine (1), 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine, was first synthesized by Archer, et al.,[7] many kinds of synthetic methods[8] for this compound 1 have been reported because of its non-narcotic analgesic activity. Herein we wish to discuss a

simple and novel synthesis of pentazocine (1) by using the thermal rearrangement of aminomethyl cyclopropyl ketone 6 as a key reaction.

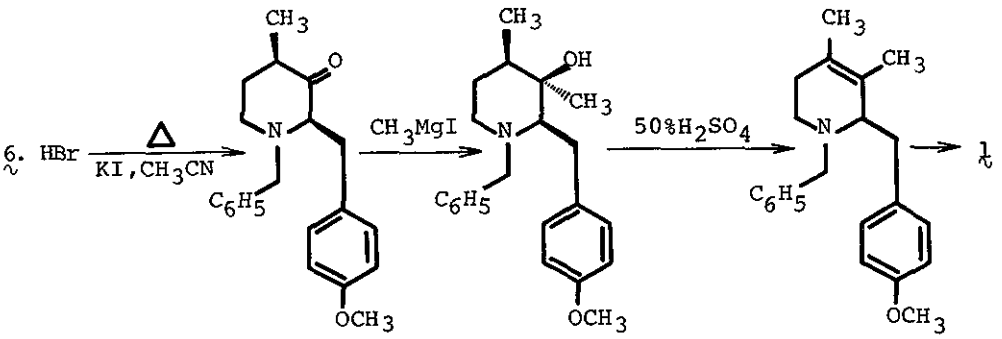
The key compound 6 in our synthesis was prepared as follows. Condensation of 1-acetyl-1-methylcyclopropane (2)[9] with p-methoxybenzaldehyde in the presence of sodium hydroxide, followed by the catalytic hydrogenation of the resulting styril ketone 3, afforded the cyclopropylpropanone 4 in 81.35 % overall yield. Bromination of the compound 4 with pyridinium hydrobromide perbromide in ether gave the bromide 5, which was subsequently treated with benzylamine in methanol to afford the key intermediate 6 in 75.6 % yield (based on the propanone 4).



Secondly, thermolysis of the compound 6 was carried out to proceed smoothly in high yield. A solution of hydrobromide of the compound 6 in acetonitrile was heated at 140 - 145°C in a sealed tube in the presence of potassium iodide to give the piperidone 7 in 71.2 % yield as a single product.

Finally, the piperidone 7 was treated with methylmagnesium iodide in ether to furnish the piperidin-3-ol 8 in 59 % yield.

The dehydration was effected by treating the piperidin-3-ol 8 with 50 % sulfuric acid to give the olefinic compound 10 as a single product in 81 % yield. Our product 9 was found to be identical with the authentic sample[10] in its ir ($CHCl_3$) and nmr ($CDCl_3$) spectra, and mixed melting point. Since this olefin 9 had been transformed to pentazocine (1),[10] this work constitutes a novel synthesis of pentazocine (1). Thus we could demonstrate the thermal rearrangement of aminomethyl cyclopropyl ketone as a useful reaction for the synthesis of the compounds which contain a piperidine ring.



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