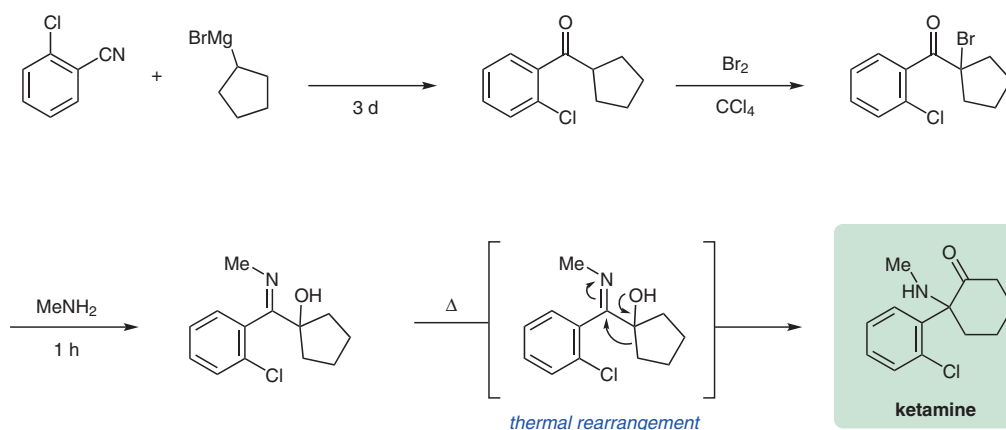


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Amino Ketone Rearrangements. IV. Thermal Rearrangements of α -Amino Methyl Ketones

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Synthesis of Anesthetic Ketamine



Significance: Ketamine is an anesthetic drug used both in human and veterinary medicine. It acts primarily as a noncompetitive antagonist of the NMDA receptor, but also shows an activating effect on AMPA receptors. Besides its use as a sedative or pain management drug, ketamine has been shown to be a potent short-acting antidepressant. It induces effects similar to phencyclidine (PCP) with reduced behavioral toxicity.

Comment: The key methodology for the synthesis of ketamine is a thermal rearrangement of α -hydroxy imines to α -amino ketones. This was developed by Stevens and co-workers, who also reported on a series of analogs in a patent (US patent 3254124), which included ketamine. Although synthesized as a racemic mixture, the two enantiomers have remarkably different pharmacologies, with (*S*)-ketamine being a more potent anesthetic and (*R*)-ketamine being a more potent antidepressant.