Organic Chemistry III

Mohammad Jafarzadeh

Faculty of Chemistry, Razi University

Organic Chemistry, *Structure and Function* **(7th edition)**

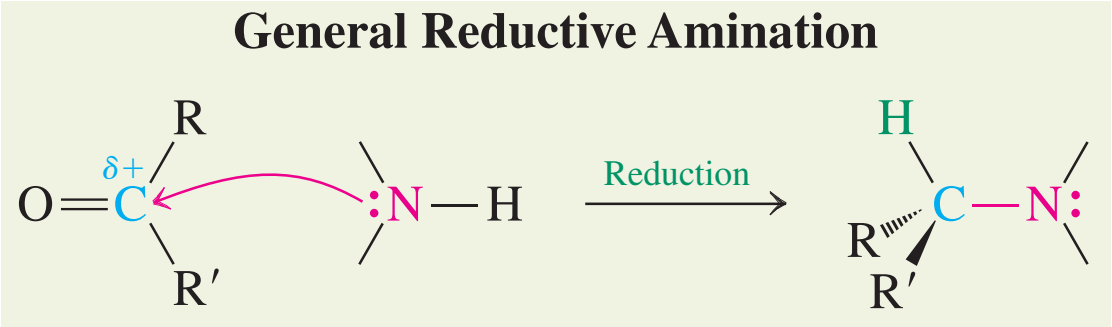
By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

21-6 SYNTHESIS OF AMINES BY REDUCTIVE AMINATION

Reductive amination of aldehydes and ketones, allows the construction of primary, secondary, and tertiary amines.

In this process, the carbonyl compound is exposed to an amine containing at least one N–H bond (NH_3, primary, secondary amines) and a reducing agent to furnish a new alkylated amine directly (a primary, secondary, or tertiary amine, respectively).

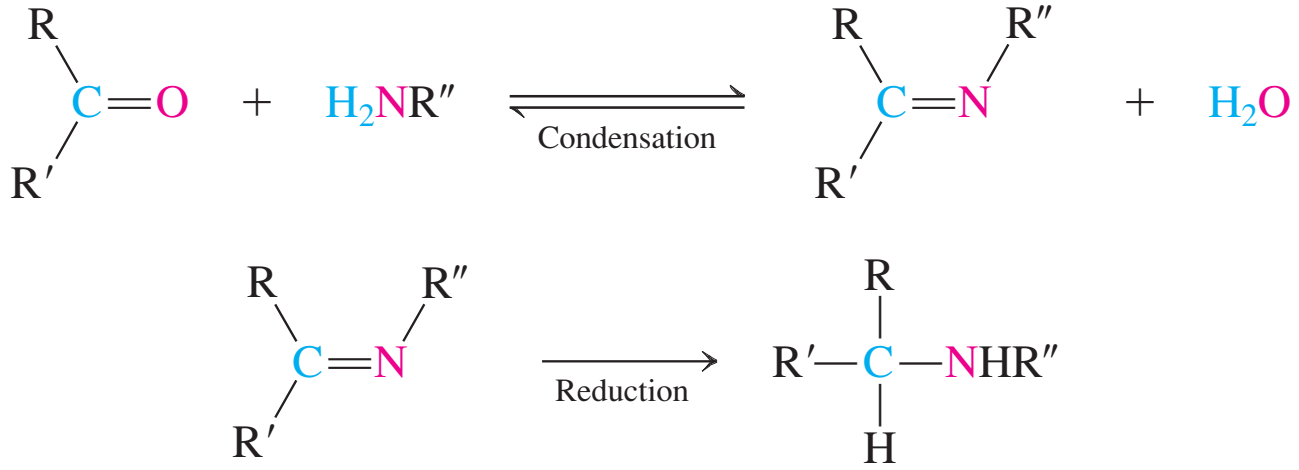
The new C–N bond is formed to the carbonyl carbon of the aldehyde or ketone.



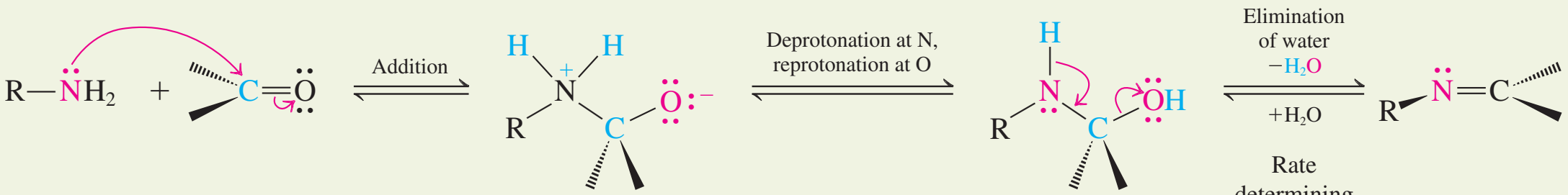
The sequence begins by the initial condensation of the amine with the carbonyl component to produce the corresponding imine (for NH_3 and primary amines) or iminium ion (secondary amines).

Similar to the carbon–oxygen double bond in aldehydes and ketones, the carbon–nitrogen double bond in these intermediates is then reduced by simultaneous catalytic hydrogenation or by added special hydride reagents.

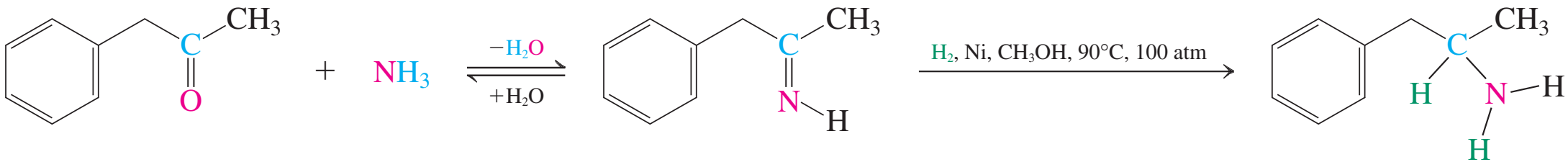
Reductive Amination of a Ketone with a Primary Amine



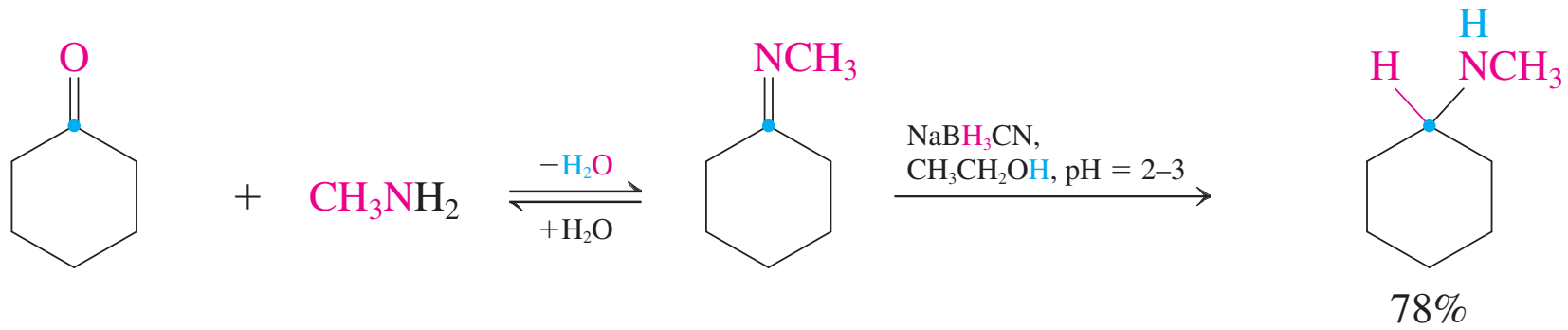
Imine Formation from Amines and Aldehydes or Ketones



Amine Synthesis by Reductive Amination



Phenyl-2-propanone — **Not isolated** — **Amphetamine (Industrial production)**



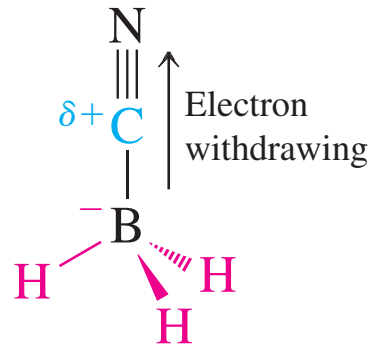
Cyclohexanone — **Not isolated** — ***N*-Methylcyclohexanamine**

This reaction succeeds because of the selectivity of the reducing agents: either hydrogen gas in the presence of a catalyst or sodium cyanoborohydride, $Na^+ {}^-BH_3CN$.

Both react faster with the imine double bond than with the carbonyl group under the conditions employed. With $Na^+ {}^-BH_3CN$, the conditions are relatively acidic (pH = 2–3), activating the imine double bond by protonation on nitrogen and thus facilitating hydride attack at carbon.

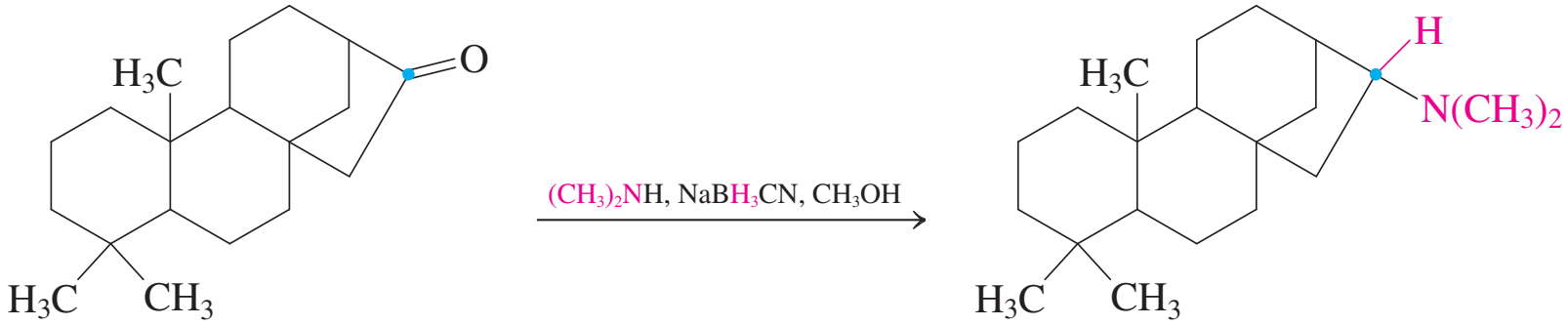
The relative stability of the modified borohydride reagent at such low pH (at which $NaBH_4$ hydrolyzes) is due to the presence of the electron-withdrawing cyano group, which renders the hydrogens less basic (hydridic).

In a typical procedure, the carbonyl component and the amine are allowed to equilibrate with the imine and water in the presence of the reducing agent. In this way, ammonia furnishes primary amines, and primary amines result in secondary amines.

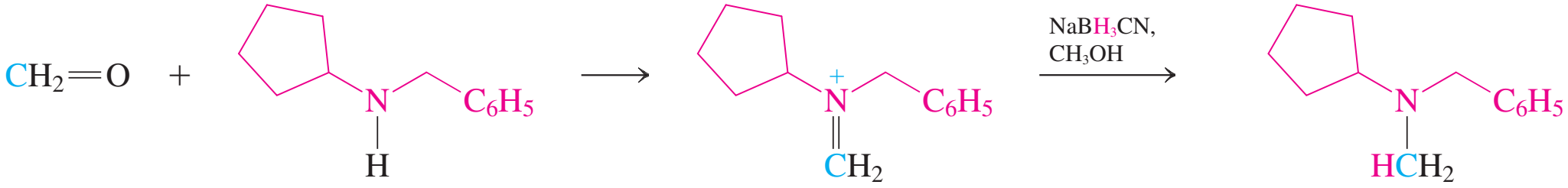


Diminished ability of H to leave as $:H^-$, hence reagent is less sensitive to H^+

Similarly, reductive aminations with secondary amines give tertiary amines.



Secondary amines cannot form imines with aldehydes and ketones, but are in equilibrium with the corresponding *N*,*N*-dialkyliminium ions, which are reduced by addition of H^- from cyanoborohydride.

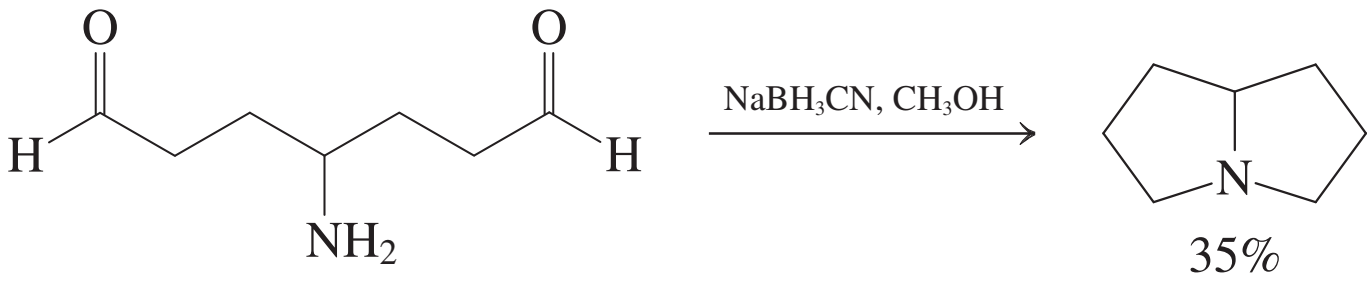


***N*-(Phenylmethyl)-cyclopentanamine (Benzylcyclopentylamine)**

Iminium ion

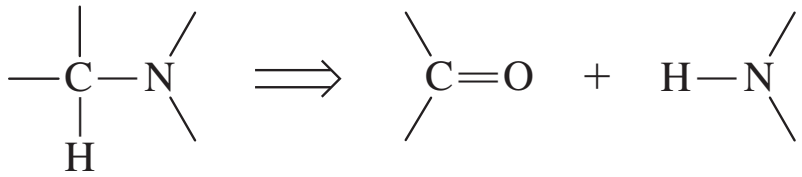
***N*-Methyl-*N*-(phenylmethyl)-cyclopentanamine (Benzylcyclopentylmethylamine)**

Solved Exercise 21-12 Explain the following transformation by a mechanism.

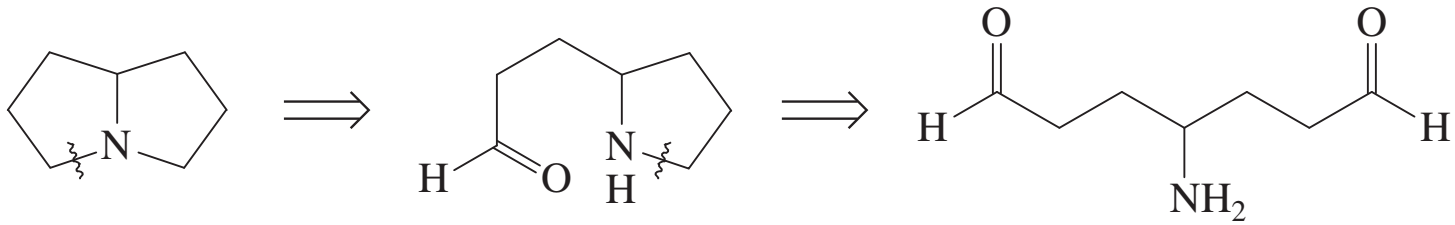


Solution

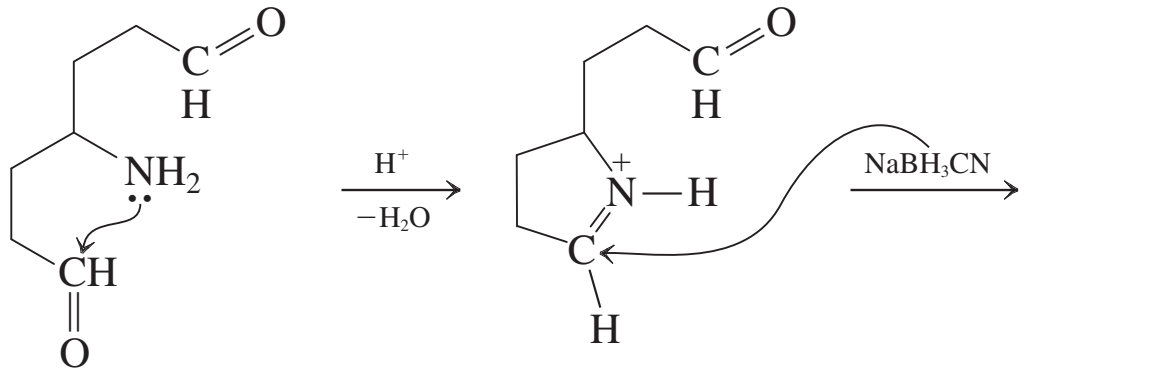
- First, write down the generic process retrosynthetically:

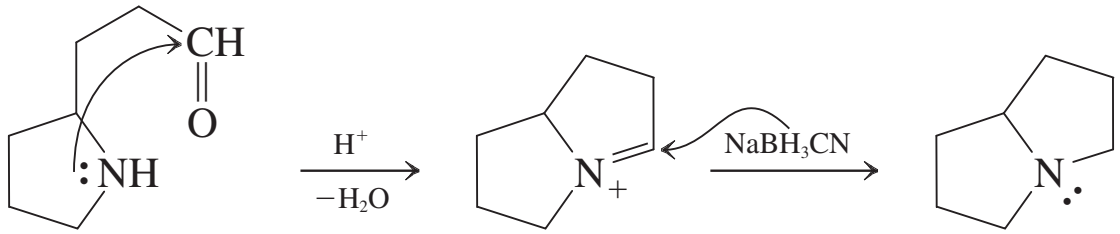


- Thus, the retrosynthetic disconnection from the product is



- The mechanism of the forward reaction follows accordingly (not all intermediates are shown):





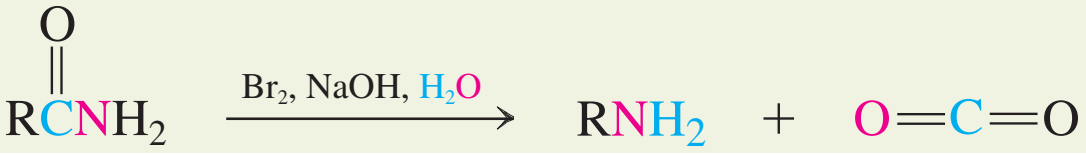
21-7 SYNTHESIS OF AMINES FROM CARBOXYLIC AMIDES

Carboxylic amides can be versatile precursors of amines by reduction of the carbonyl unit. Since amides are in turn readily available by reaction of acyl halides with amines, the sequence acylation–reduction constitutes a controlled mono-alkylation of amines.

Utility of Amides in Amine Synthesis

Primary amides can also be turned into amines by oxidation with bromine or chlorine in the presence of sodium hydroxide (**Hofmann rearrangement**). Recall that in this transformation the carbonyl group is extruded as carbon dioxide, so the resulting amine bears one carbon less than the starting material.

Amines by Hofmann Rearrangement

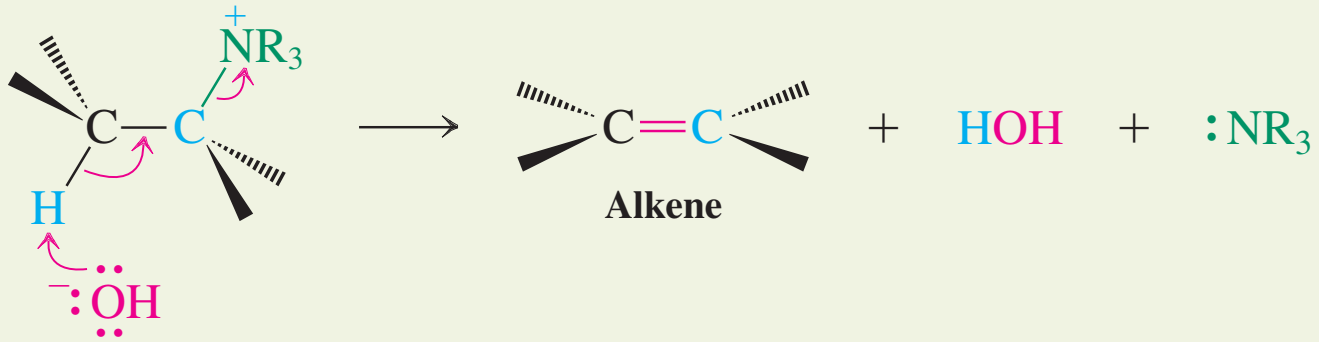


21-8 REACTIONS OF QUATERNARY AMMONIUM SALTS: HOFMANN ELIMINATION

Much like the protonation of alcohols, which turns the –OH into the better leaving group $^{+}OH_2$, protonation of amines might render the resulting ammonium salts subject to nucleophilic attack.

In practice, amines are not sufficiently good leaving groups (they are more basic than water) to partake in substitution reactions. In the **Hofmann elimination,** tetraalkylammonium salt is converted to an alkene by a strong base.

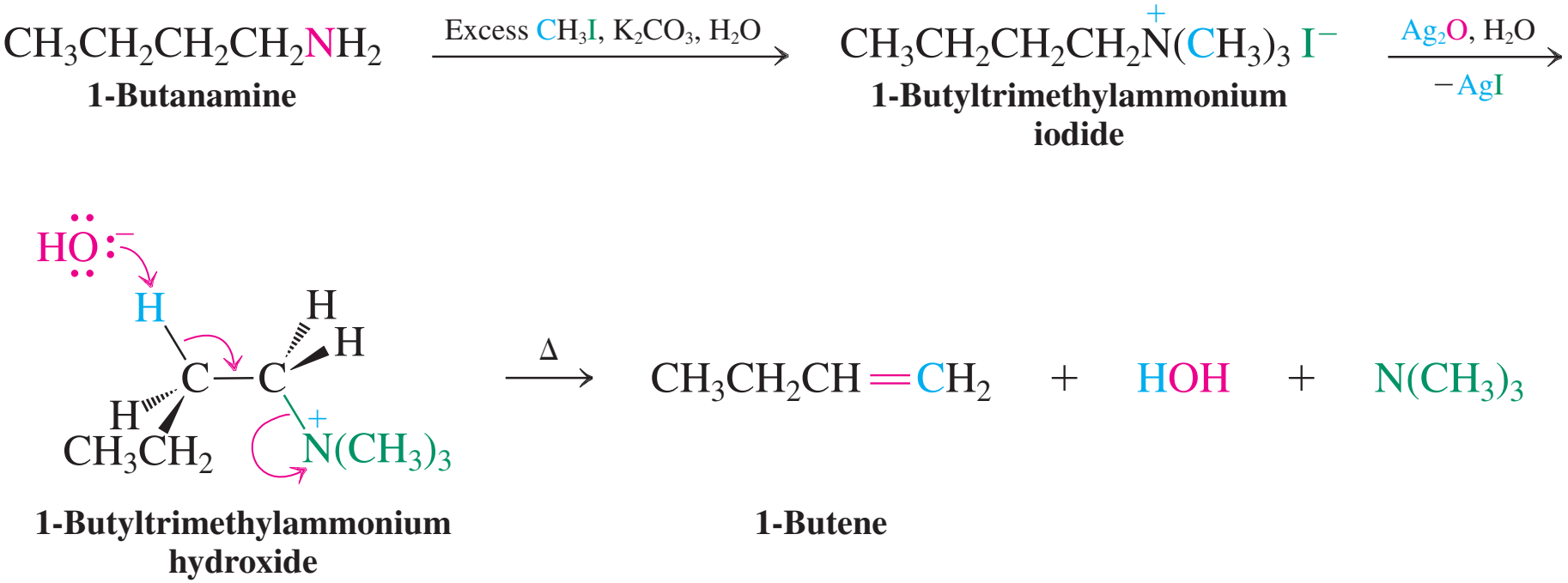
Bimolecular Elimination of Quaternary Ammonium Ions



The quaternary alkylammonium salts are unstable in the presence of strong base, because of a bimolecular elimination reaction that furnishes alkenes. The base attacks the hydrogen in the **β**-position with respect to the nitrogen, and a trialkylamine departs as a neutral leaving group.

In the procedure of Hofmann elimination, the amine is first completely methylated with excess iodomethane **(exhaustive methylation)** and then treated with wet silver oxide (a source of HO^-) to produce the ammonium hydroxide. Heating degrades this salt to the alkene.

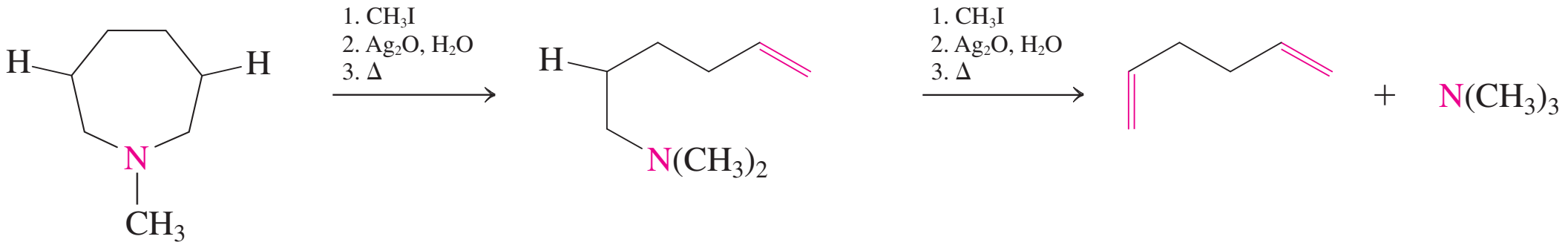
When more than one regioisomer is possible, Hofmann elimination, in contrast to most E2 processes, tends to give less substituted alkenes as the major products (the less hindered protons in the molecule).



The Hofmann elimination of amines has been used to elucidate the structure of nitrogen-containing natural products, such as alkaloids.

Each sequence of exhaustive methylation and Hofmann elimination cleaves one C–N bond.

Repeated cycles allow the heteroatom to be precisely located, particularly if it is part of a ring. In this case, the first carbon–nitrogen bond cleavage opens the ring.



***N*-Methylazacycloheptane** **N,*N*-Dimethyl-5-hexenamine** **1,5-Hexadiene**

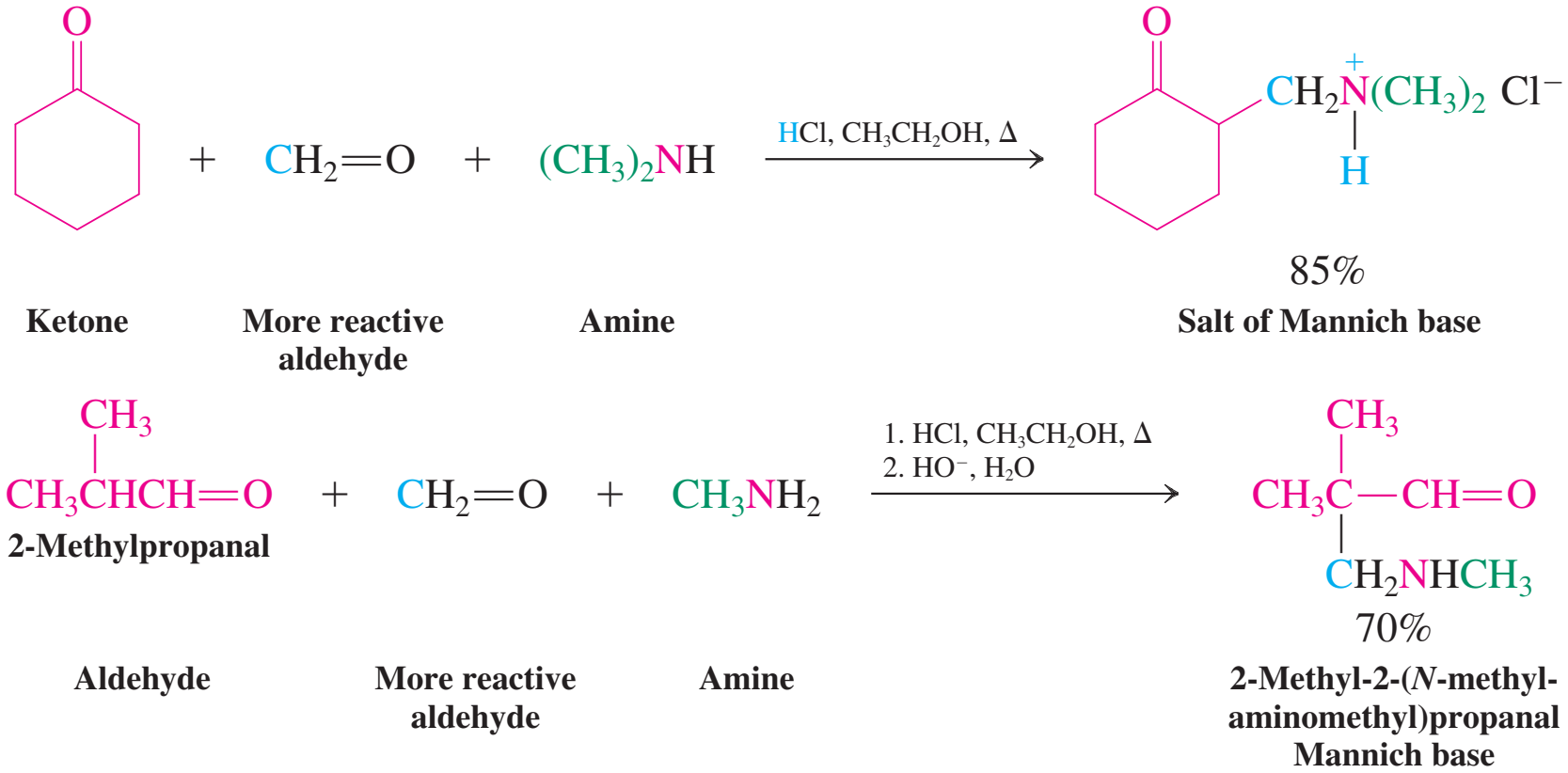
21-9 MANNICH REACTION: ALKYLATION OF ENOLS BY IMINIUM IONS

In the aldol reaction, an enolate ion attacks the carbonyl group of an aldehyde or ketone to furnish a **β**-hydroxycarbonyl product. A process that is quite analogous is the **Mannich reaction.**

Here, it is an enol that functions as the nucleophile and an iminium ion, derived by condensation of a second carbonyl component with an amine, as the substrate. The outcome is a **β**-aminocarbonyl product.

To differentiate the reactivity of the three components of the Mannich reaction, it is usually carried out with (1) a ketone or aldehyde; (2) a relatively more reactive aldehyde (often formaldehyde, CH_2=O); and (3) the amine, all in an alcohol solvent containing HCl.

These conditions give the hydrochloride salt of the product. The free amine, called a **Mannich base,** can be obtained upon treatment with base.

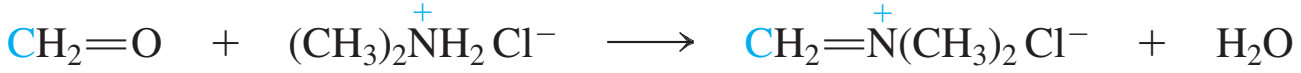


The mechanism of this process starts with iminium ion formation between the aldehyde (e.g., formaldehyde) and the amine, and enolization of the ketone.

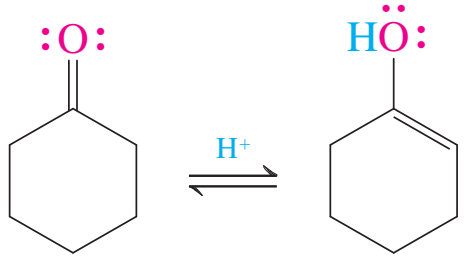
As soon as the enol is formed, it undergoes nucleophilic attack on the electrophilic iminium carbon, and the resulting species converts to the Mannich salt by proton transfer from the carbonyl oxygen to the amino group.

Mechanism of the Mannich Reaction

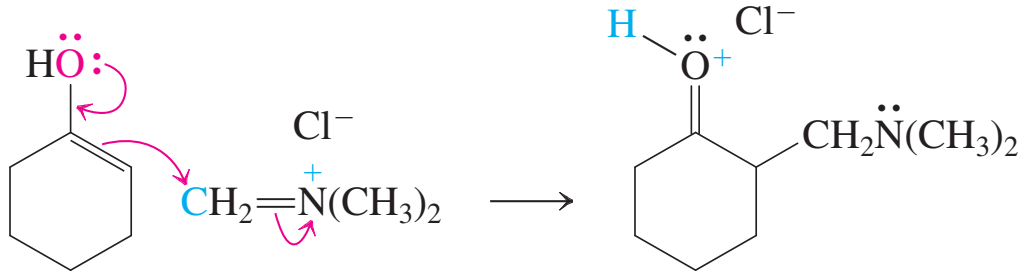
Step 1. Iminium ion formation



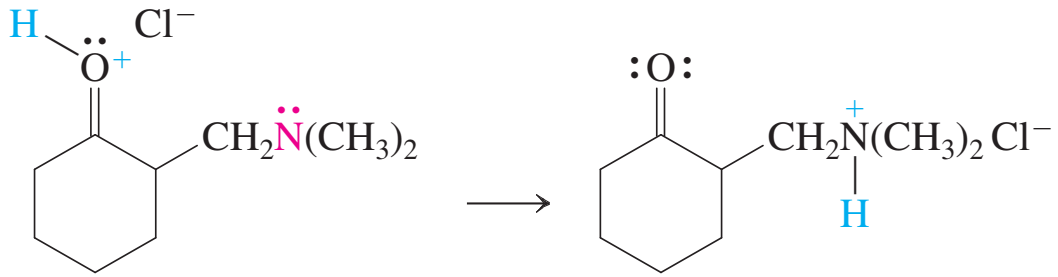
Step 2. Enolization



Step 3. Carbon–carbon bond formation



Step 4. Proton transfer

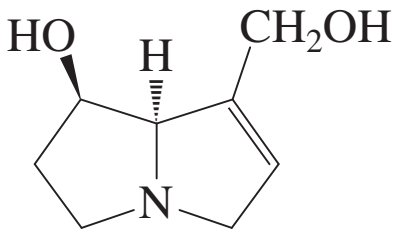


Salt of Mannich base

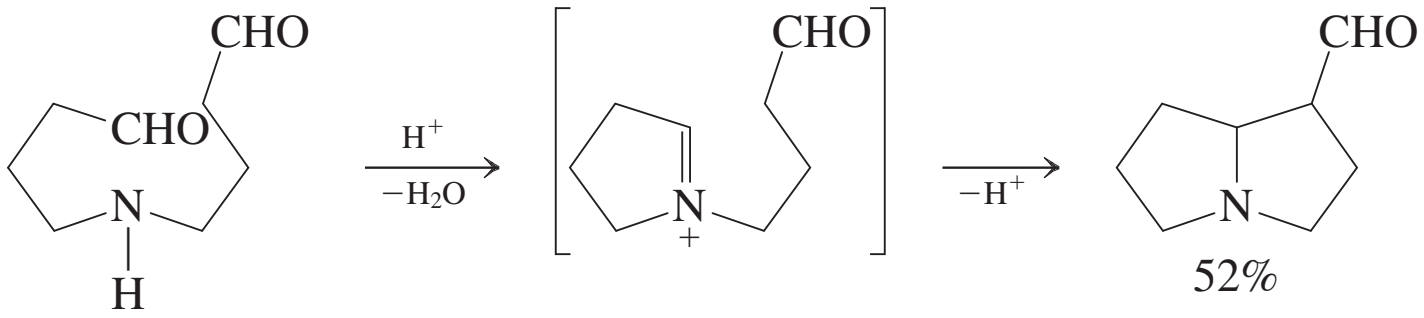
The following example shows the Mannich reaction in natural product synthesis. In this instance, one ring is formed by condensation of the amino group with one of the two carbonyl functions.

Mannich reaction of the resulting iminium salt with the enol form of the other carbonyl function follows.

The product has the framework of retronecine, an alkaloid that is present in many shrubs and is hepatotoxic (causes liver damage) to grazing livestock.



Mannich Reaction in Synthesis

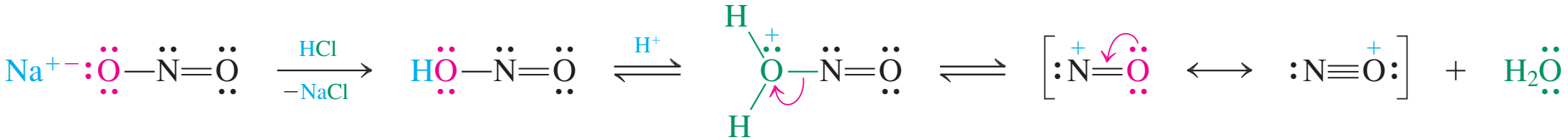


21-10 NITROSATION OF AMINES

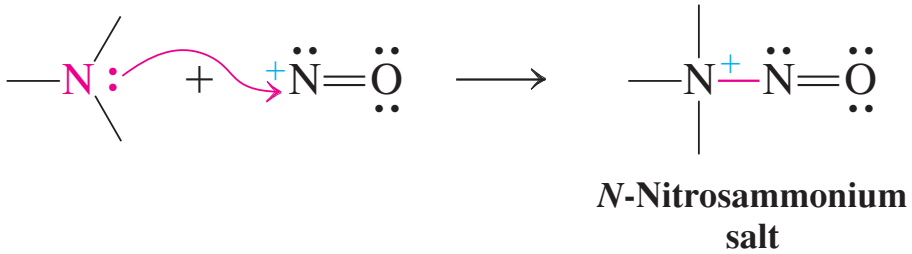
Amines react with nitrous acid, through nucleophilic attack on the **nitrosyl cation,** NO^+. The product depends very much on whether the reactant is an alkanamine or a benzenamine (aniline) and on whether it is primary, secondary, or tertiary.

To generate NO^+, the unstable nitrous acid prepares by the treatment of sodium nitrite with aqueous HCl.

Nitrosyl Cation from Nitrous Acid

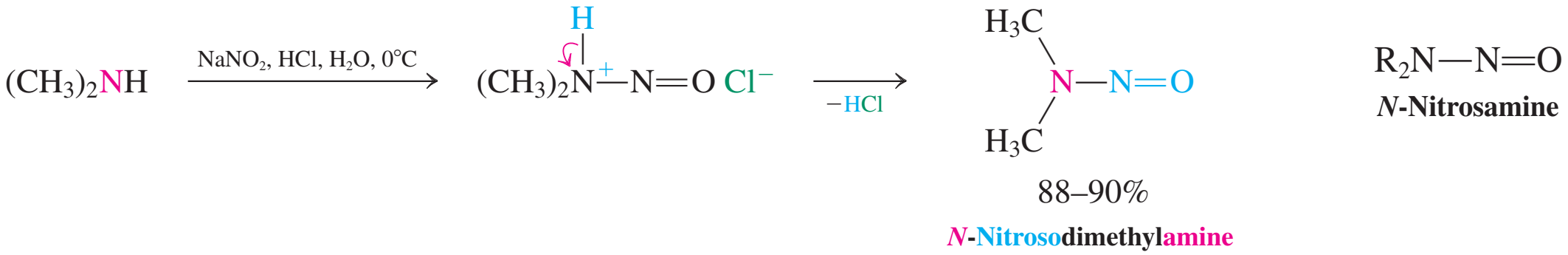


The nitrosyl cation is electrophilic and is attacked by amines to form an *N*-nitrosammonium salt.



The course of the reaction now depends on whether the amine nitrogen bears zero, one, or two hydrogens. *Tertiary N*-nitrosammonium salts are stable only at low temperatures and decompose upon heating to give a mixture of compounds.

Secondary N-nitrosammonium salts are simply deprotonated to furnish the relatively stable ***N*-nitrosamines** as the major products.

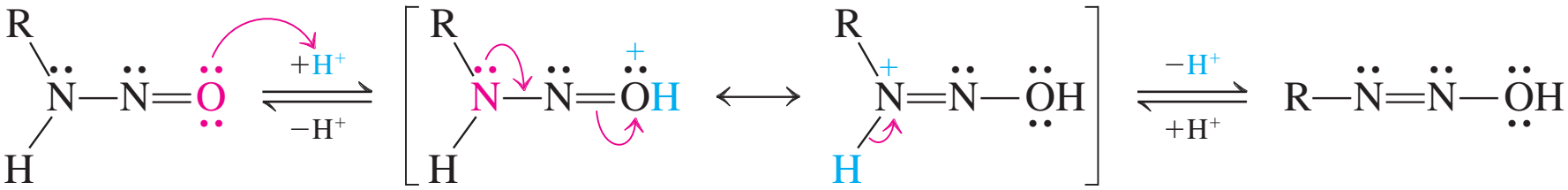


Similar treatment of *primary* amines initially gives the analogous monoalkyl-*N*-nitrosamines. However, these products are unstable because of the remaining proton on the nitrogen.

By a series of hydrogen shifts, they first rearrange to the corresponding diazohydroxides. Then protonation, followed by loss of water, gives highly reactive **diazonium ions,** $R–N_2^+$.

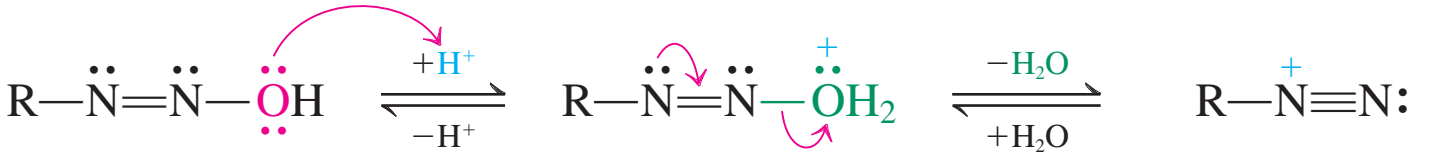
Mechanism of Decomposition of Primary *N*-Nitrosamines

Step 1. Rearrangement to a diazohydroxide



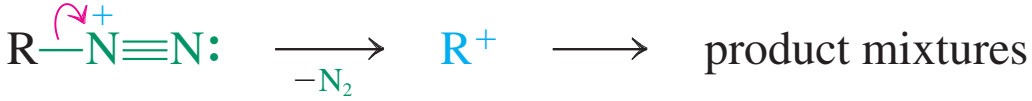
Diazohydroxide

Step 2. Loss of water to give a diazonium ion



Diazonium cation

Step 3. Nitrogen loss to give a carbocation

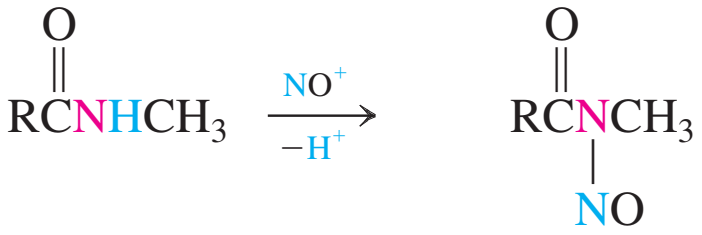


When R is a secondary or a tertiary alkyl group, these ions lose molecular nitrogen, N_2, and form the corresponding carbocations, which may rearrange, deprotonate, or undergo nucleophilic trapping to yield the observed mixtures of compounds.

The nitrosyl cation also attacks the nitrogen of *N*-methylamides. The products, *N*-methyl-*N*-nitrosamides, are precursors to useful synthetic intermediates.

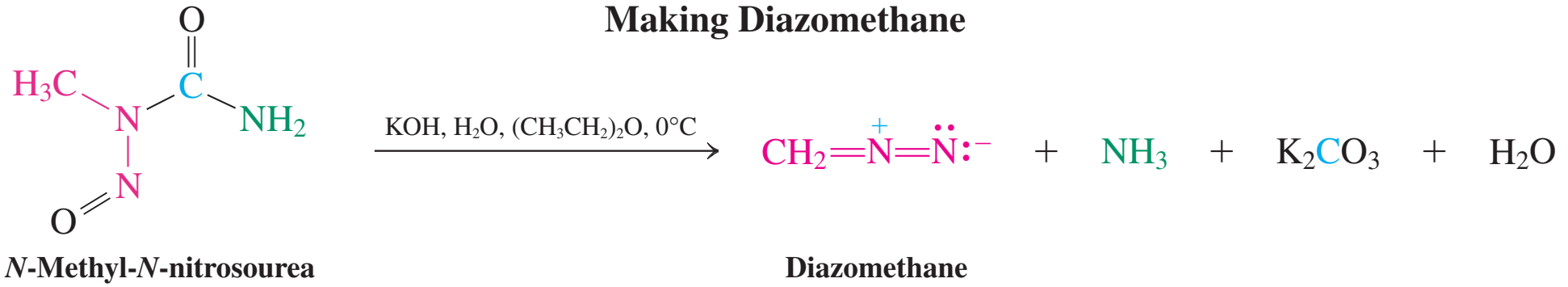
N-Methyl-*N*-nitrosamides are converted into **diazomethane,** CH_2N_2, upon treatment with aqueous base.

Nitrosation of an *N*-Methylamide



***N*-Methylamide** ***N*-Methyl-*N*-nitrosamide**

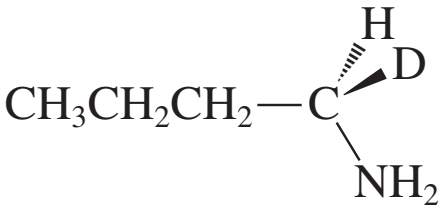
Making Diazomethane



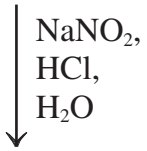
***N*-Methyl-*N*-nitrosourea** **Diazomethane**

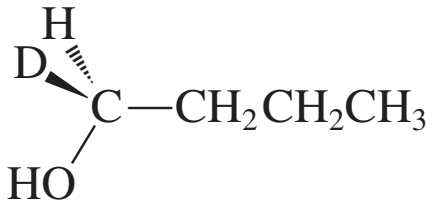
Exercise 21-21

The mechanism just shown pertains to the decomposition of diazonium ions in which the alkyl groups R are secondary or tertiary. The result depicted in the margin was reported in 1991 and addresses the pathway chosen in the case of R = *primary* alkyl. Is the mechanism the same?



Pure *R* enantiomer





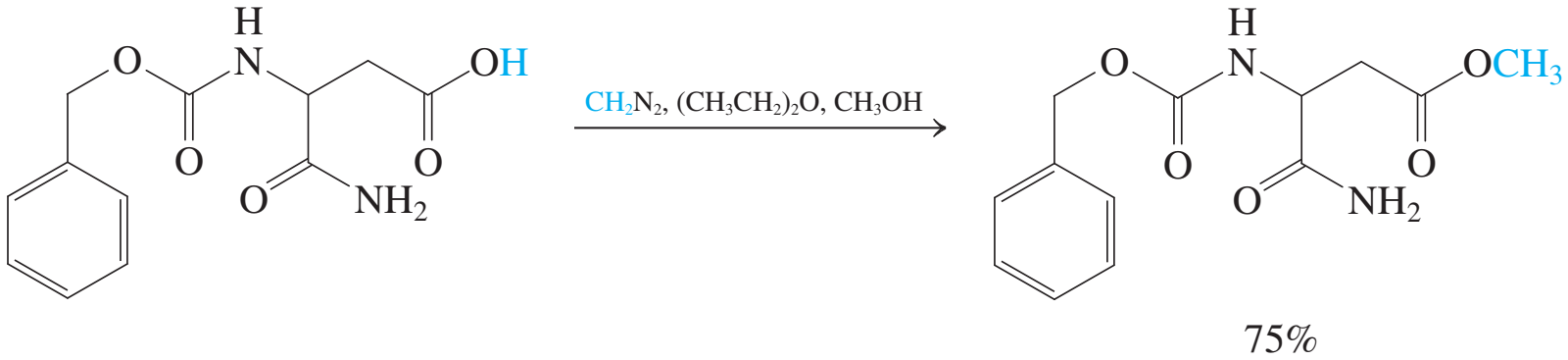
100%

Pure *S* enantiomer

Diazomethane is used in the synthesis of methyl esters from carboxylic acids. However, it is exceedingly toxic and highly explosive in the gaseous state (b.p. –24 °C) and in concentrated solutions.

It is therefore usually generated in dilute ether solution and immediately allowed to react with the acid.

This method is very mild and permits esterification of molecules possessing acid- and base-sensitive functional groups, as shown in the following example.



75%

When it is irradiated or exposed to catalytic amounts of copper, diazomethane evolves nitrogen to generate the reactive carbene methylene, H_2C: Methylene reacts with alkenes by addition to form cyclopropanes stereospecifically.