Lecture 21 Agenda...

Hofmann & Curtius rearrangements (24.6)
Amine Reactions (24.7)

Group Question 11

Suggested Ch 24 Problems:
24.13 – 24.15, 24.37, 24.38(a,b),
24.41, 24.44(a,b,c), 24.45,
24.47, 24.50, 24.51, 24.53,
24.54, 24.60, 24.63 – 24.65,
24.70, 24.75

Exam 3
Tuesday, July 1
Covers Lectures 15 to 21!
Two rearrangements can afford amine products: (1) Hofmann rearrangement and (2) the Curtius rearrangement.

**Hofmann rearrangement**

\[
\text{RC(O)NH}_2 + \text{NaOH, Br}_2 \rightarrow R\text{-NH}_2 + \text{CO}_2
\]

**Curtius rearrangement**

\[
\text{RC(O)N}_2 + \text{H}_2\text{O} \rightarrow R\text{-NH}_2 + \text{CO}_2 + \text{N}_2
\]
The Hofmann rearrangement converts an amide functionality into an amine with one less carbon (a formal loss of C=O from the amide). The mechanism involves the formation of an isocyanate intermediate.

\[ \text{2,2-Dimethyl-3-phenyl-propanamide} \xrightarrow{\text{NaOH, Cl}_2, \text{H}_2\text{O}} \text{Phetermine} + \text{CO}_2 \]
The Curtius rearrangement converts an acyl azide functionality into an amine with one less carbon (a formal loss of C=O). Like the Hofmann rearrangement, this mechanism involves the formation of an isocyanate intermediate.

\[ \text{trans-2-Phenylcyclopropanecarbonyl chloride} \rightarrow \text{Tranylcypromine} \]

Used to treat moderate to severe depression.
You have already seen several reactions where amines serve as nucleophiles. These include:

1. Alkylation and acylation of amines
2. Imine and enamine formation

Another reaction to know is the Hofmann elimination. It is an extension of amine alkylation.
As seen previously, the alkylation of amines...

Ammonia: \( \text{NH}_3 + \text{R}-\text{X} \xrightarrow{\text{S}_\text{N}2} \text{RNH}_3\text{X}^- \xrightarrow{\text{NaOH}} \text{RNH}_2 \) Primary

Primary: \( \text{RNH}_2 + \text{R}-\text{X} \xrightarrow{\text{S}_\text{N}2} \text{R}_2\text{NH}_2\text{X}^- \xrightarrow{\text{NaOH}} \text{R}_2\text{NH} \) Secondary

Secondary: \( \text{R}_2\text{NH} + \text{R}-\text{X} \xrightarrow{\text{S}_\text{N}2} \text{R}_3\text{NH}\text{X}^- \xrightarrow{\text{NaOH}} \text{R}_3\text{N} \) Tertiary

Tertiary: \( \text{R}_3\text{N} + \text{R}-\text{X} \xrightarrow{\text{S}_\text{N}2} \text{R}_4\text{N}\text{X}^- \) Quaternary ammonium
As seen previously, the acylation of amines. Note, any carboxylic acid derivative can be used as the electrophile.
As seen previously, aldehydes or ketones can react with amines to make imines or enamines.

Primary amines yield imines.

Secondary amines yield enamines.
The Hofmann elimination converts an amine to an alkene. The steps include:

1. *(Multi)-Alkylation of the amine to form an ammonium salt.*

2. *Elimination of the amine via an E2 mechanism. The major alkene formed is the less substituted alkene.*

\[
\begin{align*}
\text{1-Methylpentyamine} & \quad \xrightarrow{\text{Excess } \text{CH}_3\text{I}} \quad \text{(1-Methylpentyl)trimethylammonium iodide} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \quad \xrightarrow{+\text{N(CH}_3)_3\text{I}^-} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{Ag}_2\text{O} & \quad \xrightarrow{\text{H}_2\text{O}, \text{heat}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2=\text{CH}_2 \\
\end{align*}
\]

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The Hofmann elimination yields the less substituted alkene as the major product.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{H} & \quad \text{N} \quad \text{CH}_3 \\
\text{CH}_3\text{CH}_2 & \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{H} & \quad \text{H} \quad \text{H} \quad \text{H} \\
(1\text{-Methylbutyl})\text{trimethylammonium} & \\
\text{hydroxide} & \\
& \\
\downarrow & \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH} &= \text{CH}_2 & + & \text{CH}_3\text{CH}_2\text{CH} &= \text{CHCH}_3 \\
\text{1-Pentene} & \quad (94\%) & \quad \text{2-Pentene} & \quad (6\%) & \\
\end{align*}
\]
Group Question 11
Design a synthesis of the following transformation.