

Amines

2 - Synthesis

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Synthesis of Amines

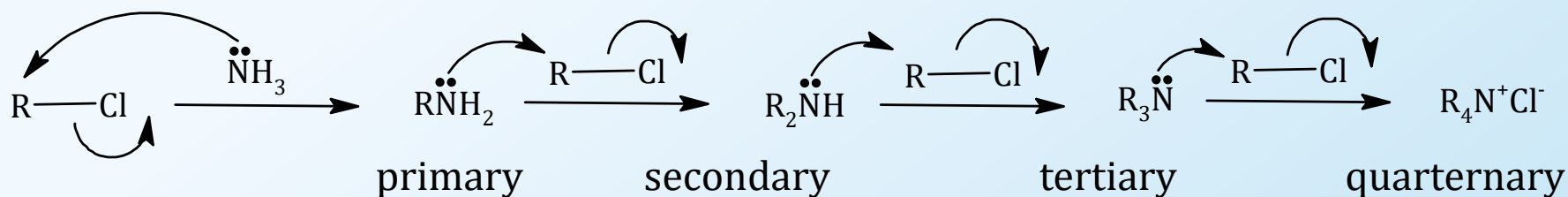
Amines can be synthesized in various ways, mostly by reduction reactions.

Primary, secondary and tertiary amines are synthesized in different ways. Some reactions from previous functional groups. They can be reduced to form amines.

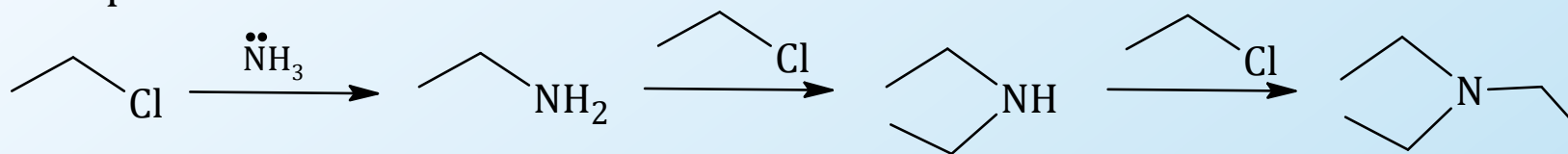
The next few slides cover many of the common ways to synthesize amines.

Synthesis of Amines – Substitution Reaction

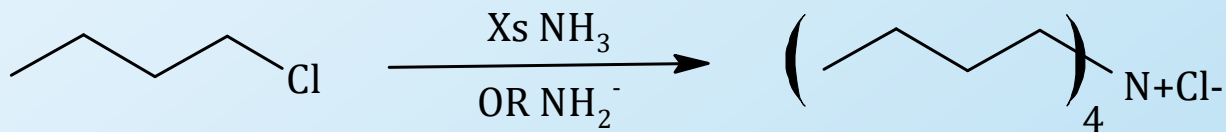
1) **From Alkyl halides and Ammonia Using Substitution (S_N2)**: Substitution reaction uses an alkyl halide as the substrate and ammonia as the nucleophile. The reaction works well except that multiple substitutions can occur as shown below. Each amine produced is a stronger nucleophile promoting the reaction.



Example:

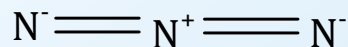


There is no control on the substitution and multiple alkylations can lead to formation of a quaternary ammonium salt.

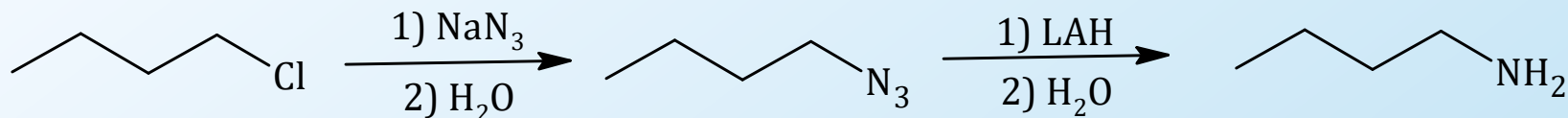


Synthesis of Amines– S_N2 Using Azide

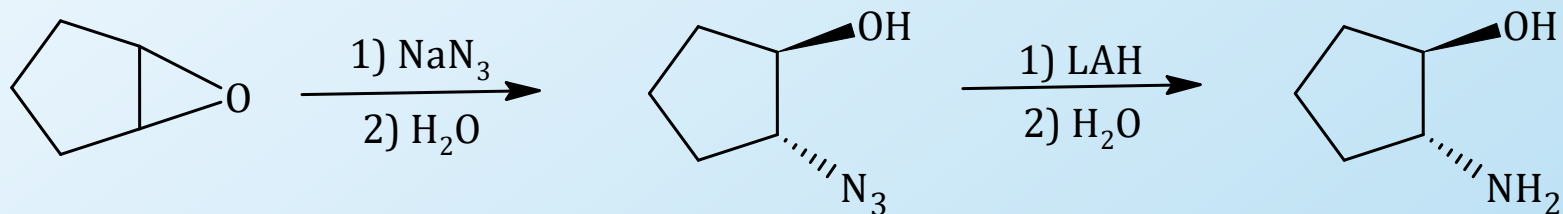
2) **From Alkyl halides and Azide Using Substitution (S_N2)**: To avoid the multiple substitution problem of the previous reaction, using a different nucleophile can help. Azides (N₃⁻) can be used as nucleophiles and then reduced with a strong reducing agent to make primary amines. Azides are available as alkali salts.



Example:



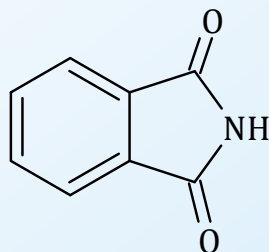
Example:



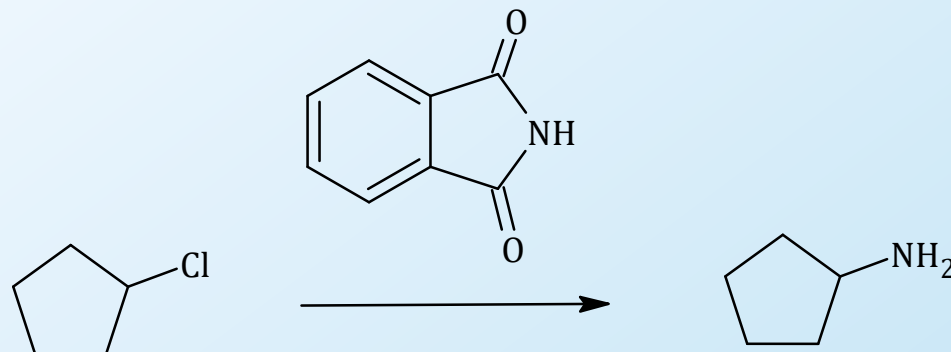
Synthesis of Amines - Gabriel Synthesis (for 1°)

3) **Gabriel synthesis using Phthalimide:** To ensure synthesis of primary amines, Gabriel's reagent, phthalimide, can be used with alkyl halides.

Phthalimide reagent



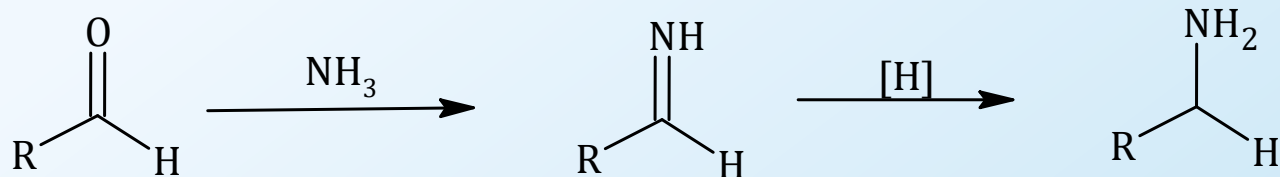
Example:



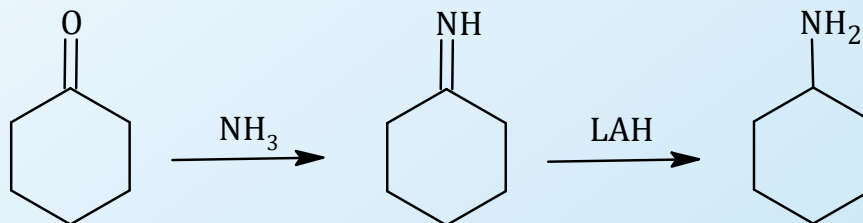
Synthesis of Amines - Reductive Amination - 1

4a) **Reduction of imines from aldehydes and ketones:** Aldehydes and ketones form imines when treated with ammonia or primary amines. Imines can be reduced using reducing agents to form primary or secondary amines.

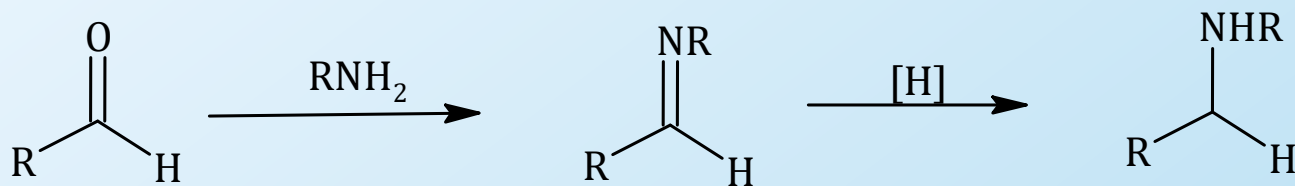
Carbonyl
and
ammonia



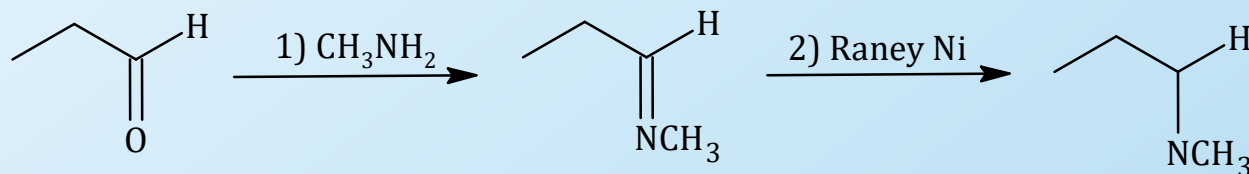
Example:



Carbonyl
and
 1° amine

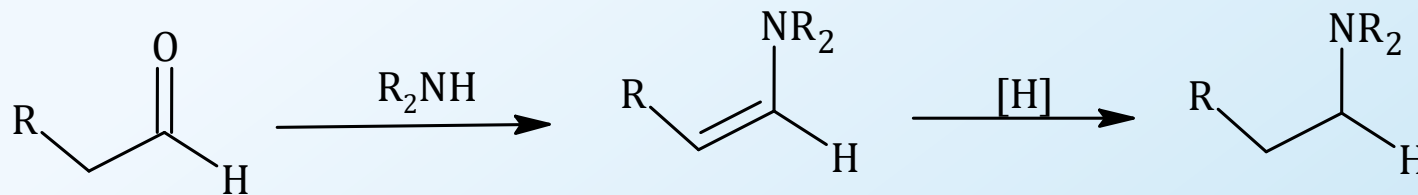


Example:

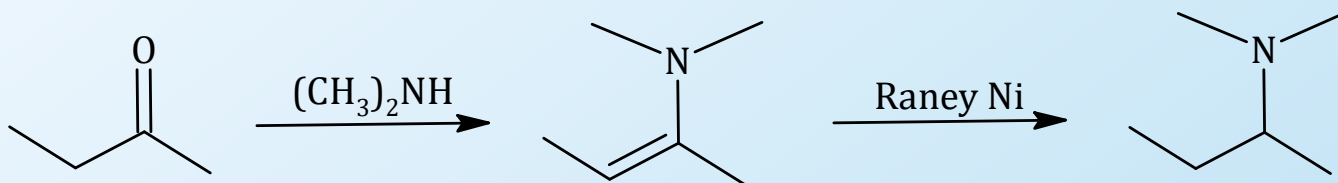


Synthesis of Amines - Reductive Amination -2

4b) Reduction of enamines from aldehydes and ketones: Enamines are formed by reaction of aldehydes and ketones with secondary amines. Enamines can be reduced using Raney Ni since this is reduction of alkene.



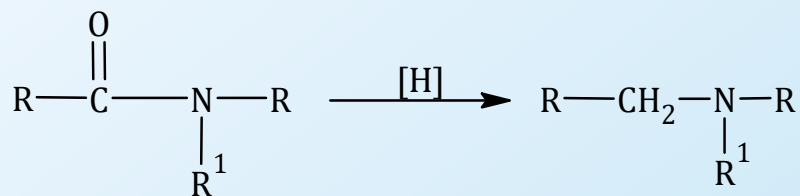
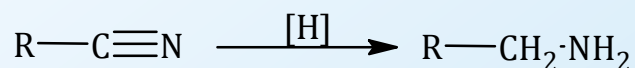
Example:



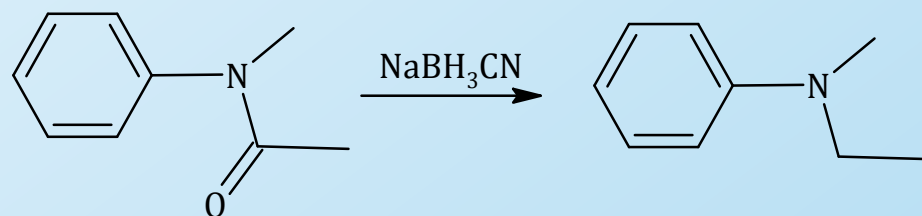
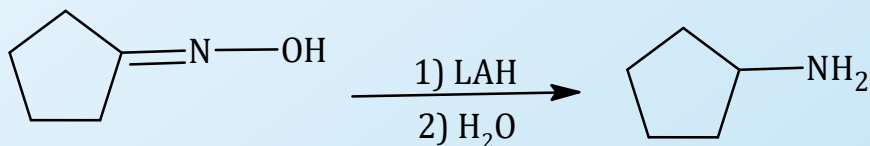
Synthesis of Amines– Reductions

5) **From reduction of nitriles, oximes and amides**: Other nitrogen derivatives formed by reactions of aldehydes and ketones are oximes. Nitriles and amides can also be reduced using strong reducing agents.

General Reactions

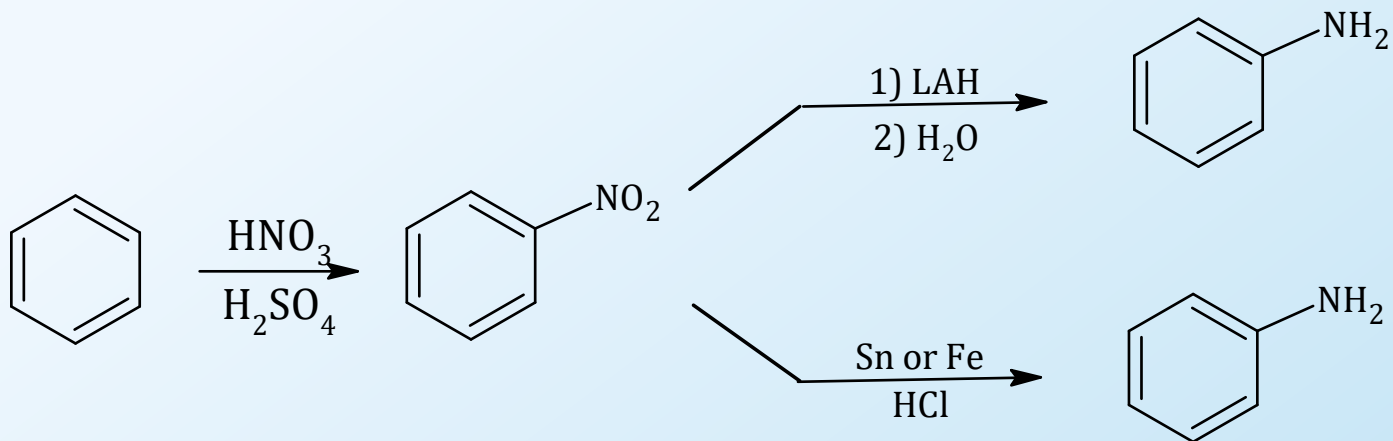


Examples



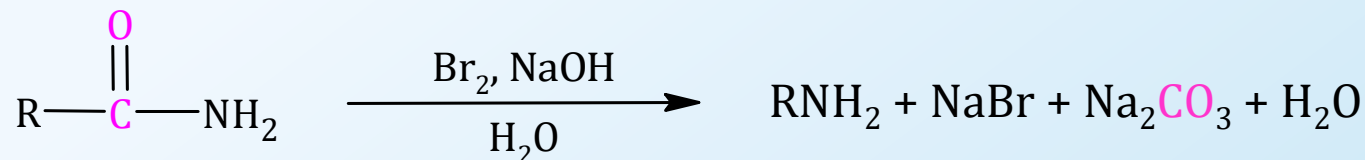
Reduction of Nitro Group

6) **From reduction of nitrobenzene**: Nitro groups formed during nitration can be reduced using lithium aluminum hydride or metals in acid to give an amino group.

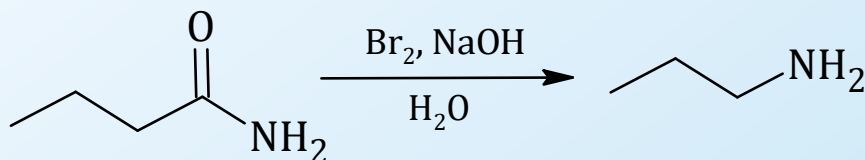


Hoffman Rearrangement - Mechanism

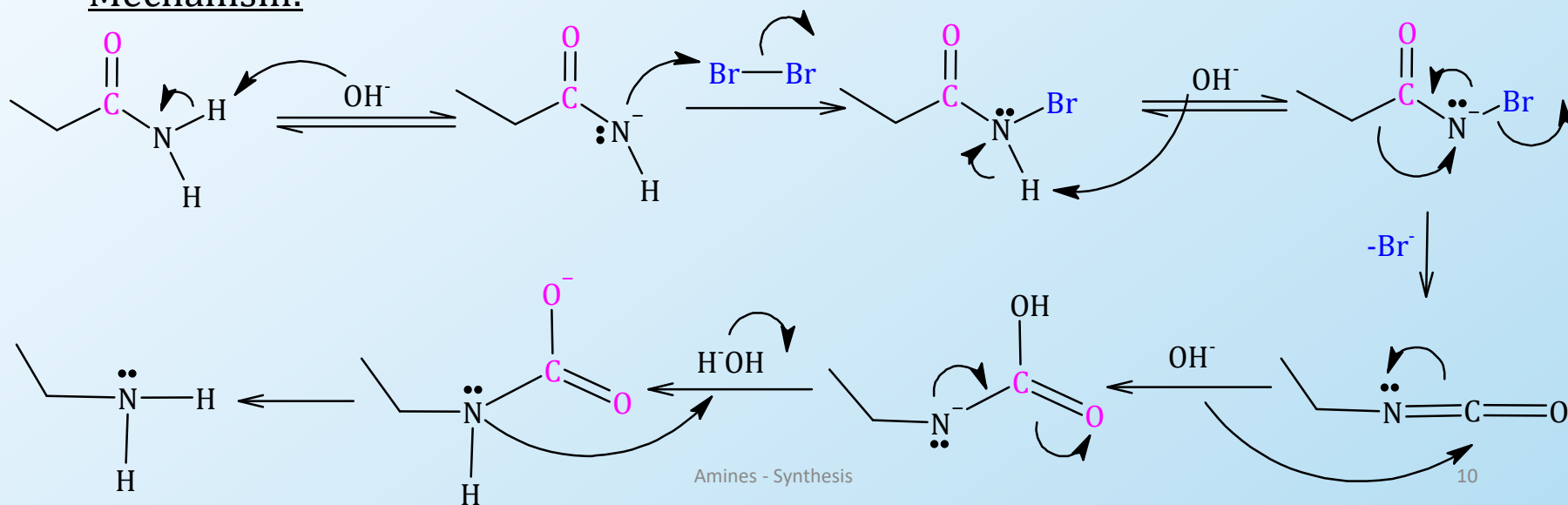
7) **Hoffman Rearrangement:** This is done by treating a primary amide with Br_2 and NaOH . The product of this reaction is a 1° amines. The mechanism of the reaction is given below the example.



Example:



Mechanism:



Reducing Agents

Almost all the reactions we have covered need reducing agents. Here is a list of all the reducing agents that can be used during those reductions.

LiAlH_4 – lithium aluminum hydride

NaBH_4 – sodium borohydride

NaBH_3CN – sodium cyanoborohydride

Raney Ni – Nickel with hydrogen

H_2/Pt – hydrogenation using heavy metals

Sn or Fe/HCl – metal with acids (for nitro group reduction)

Key Concepts

- Synthesis – almost all reductions
- Substitutions
- Gabriel synthesis
- Reductive amination
- Reduction of nitriles, amides and oximes
- Reduction of nitro group
- Hoffman rearrangement