Today: Amines (Ch 25)
- Properties of amines
- Preparation of amines
- Mannich reaction

There are 2 handouts!

Friday Nov 18
Midterm 2 in class (noon-12:50)
Seating chart will be on website.

Office hours this week:
Monday (Eric) 2pm DBH 1423
Wednesday (ERJ) 10-11am NS1 4114
Thursday (ERJ) 3-4pm RH 517
Thursday (Erika) 4-6pm RH 550

TRY midterm 2-f14 before discussion

Mannich Reaction

via:

Cationic 2-aza-Cope rearrangement

Overman lab (UCI) developed the aza-
Mannich reaction for natural product synthesis
Mannich reaction

Mechanism: 6,50,12–14

The mechanism of the Mannich reaction has been extensively investigated. The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions the first step is the reaction of the amine component with the protonated non-enolizable carbonyl compound to give a hemiaminal, which after proton transfer loses a molecule of water to give the electrophilic iminium ion.50 This iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its α-carbon in an aldol-type reaction to give rise to the Mannich base.

Taken from: Strategic applications of name reactions in organic synthesis (Kurti and Czako)
http://books.google.com/books?id=MdxkSyzhcCc&printsec=frontcover#v=onepage&q=mannich&f=false
Application of Mannich reaction: Pioneering chemistry at UCI

One of the most well-known applications of the Mannich reaction is its use in a tandem fashion with the aza-Cope rearrangement to form heterocycles. This reaction was the cornerstone of the strategy in the research group of L.E. Overman during the total synthesis of (±)-didehydrostemandolone (asparagamine A). The bicyclic amine hydrogen iodide salt was exposed to excess paraformaldehyde, which led to the formation of the first iminium ion intermediate that underwent a facile [3,3]-sigmatropic rearrangement. The resulting isomeric iminium ion spontaneously reacted with the enol in an intramolecular Mannich cyclization.

Taken from: Strategic applications of name reactions in organic synthesis (Kurti and Czako)
http://books.google.com/books?id=MdxkSyzhcC&printsec=frontcover#v=onepage&q=mannich&f=false
Mannich reactions:

Recall reductive amination:

H-N=Me + H₂ → H-NH₂

Nucleophile attack by H₂CN⁻ to form imine is electrophilic.

Ph + H₂CN⁻ → Imine

Recall reductive amination:

NaBH₃CN

Ph + H₂CN⁻ → Imine

Lactone or aldehyde

Recall reductive amination:

Ph + H₂CN⁻ → Imine

Recall reductive amination:
So, Mannich: nucleophile is an enol! Therefore, nucleophile attack by nucleophile enol is nucleophile.
Nucleophile

Imine (or iminium) electrophile

1. make imine
2. make react with each other
3. make "mild" acid

Mechanism:

1. make imine
2. H₂NMe + H⁺
Back to the order in Ch 25

- properties of amines
- preparation of amines
  - alkylation
  - Gabriel Synthesis
- amines as bases
  (amines versus anilines)

Skip:
- Hoffmann elimination 25.12
- with nitrous acid 25.13
- aryl diazoniums 25.14, 25.15
Amines: Key components of bioactive compounds

Beneficial natural products

Synthetic medicinal agents

Infamous natural products

Lysergic acid (psilocybin)
Alkaloids: Nitrogen-containing Natural Products

- Dark chocolate
- Theobromine
- Caffeine
- Cocaine
- Morphine
- Serotonin
- Nicotine

Often target our receptors... and have a bitter taste
Natural Product: Quinine
chemical defense systems

Isolated from *cinchona tree* (South America):

“Quina-Quina”
Muscle relaxant used by Quechuas

1st used to treat malaria
In Rome, 1631:
Quinine: the active ingredient isolated in early 1800's current treatment for malaria
Tonic Water: Contains Quinine

black
light

bitter
Tonic Water: Contains Quinine
Atropine

- Antagonist of acetylcholine receptor
- Antidote for nerve gas
- Dilates pupils
- Overdose: increased heart rate, nausea, hallucinations

Deadly nightshade (Atropa belladonna)
Pharmaceutical agents containing amines

Amines provide great properties: bind enzymes and exhibit good pharmacokinetics

Most pharmaceutical agents contain N

ventolin

amoxicillin

http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster
### Top 5 name-brand drugs 2012 (by US sales)

1. **NexIUM**  
   *Esomeprazole*  
   ![Chemical structure of NexIUM](image1)  
   *AstraZeneca*  
   **$5,989 Million**  
   **ANTIULCERANTS**

2. **Abilify**  
   *Aripiprazole*  
   ![Chemical structure of Abilify](image2)  
   *Otsuka*  
   **$5,870 Million**  
   **ANTIPSYCHOTICS**

3. **Crestor**  
   *Rosuvastatin*  
   ![Chemical structure of Crestor](image3)  
   *AstraZeneca*  
   **$5,092 Million**  
   **CHOLEST&TRIGLY.REGULATOR**

4. **Advair Diskus**  
   *Fluticasone Propionate*  
   ![Chemical structure of Advair Diskus](image4)  
   **$4,889 Million**  
   **CORTICOIDS**

5. **Cymbalta**  
   *Duloxetine*  
   ![Chemical structure of Cymbalta](image5)  
   **Lilly**  
   **$4,720 Million**  
   **ANTIDEPRESS.& MOOD STAB.**
Dopamine: for Parkinson's

Figure 25.6  Dopamine—A neurotransmitter

Dopamine is released by one nerve cell, and then binds to a receptor site in a target cell.

Parkinson's disease is characterized by degeneration of dopamine nerve pathways in the basal ganglia.

See the movie: Awakenings (starring Robin Williams and Robert DeNiro)

Dr. Oliver Sacks. Patient
Preparation of amines: By Reduction

Amides

Amine \( \rightarrow \text{R} \text{-CH}_2 \text{-NH}_2 \rightarrow \text{NH}_2 \text{C}=\text{N} \)

Nitrides

Amine \( \rightarrow \text{R} \text{-CH}_2 \text{-NH}_2 \rightarrow \text{NH}_2 \text{H}^+ \text{Pd}\text{-C} \)

Nitro compounds

Amine \( \rightarrow \text{R} \text{-CH}_2 \text{-NH}_2 \rightarrow \text{NO}_2 \)
Reductive amination

The C=O is replaced by C-H and C-N bonds.

1º amine
CH₃NH₂ → CH₃CN

2º amine

Mannich reaction

via:

O
CH₃

H₂N-CH₃
Preparation of amines

1. Reductions
2. Addition to imines (reductive amination Mamish)
3. $S_N2$ substitution

Simple $S_N2$ reactions of amines with allyl bromides are not efficient.
\[ \text{H}_3\text{C}-\text{N}^+\text{CH}_3 \Rightarrow \text{Br} + \text{H}_2\text{NCH}_3 \]

Unfortunately can't just mix.

\[ \text{Br} + \text{H}_2\text{NCH}_3 \xrightarrow{\text{SN2}} \text{good nucleophile} \]

\[ \text{quaternary ammonium salt} \]

\[ \text{better nucleophile (more electron-rich)} \]

\[ \text{even better nuc!} \]
Doesn't work! Therefore, use a reductive amination.

Gabriel synthesis

Protecting group strategy

Phthalimide

More alkylation

Imide
Synthesis problem:

TARGET:

\[ \text{amide (need an oxidation)} \]

\[ \text{aldehyde} \]

\[ \text{Br} + \text{CH}_3\text{COCH}_3 \rightarrow \text{CH}_3\text{CONHCH}_3 \]