

Objective 14. Apply acid-base, substitution, and elimination principles to amines.

Skills: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu⁻ and E⁺, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.

Key ideas: amines are bases and nucleophiles

Amines can be LG – see substitution and elimination

Practice problems solutions:

Amine types: 1^o, 2^o, 3^o amine.

Acid-base and pK_a.

Reaction types: substitution (and elim)

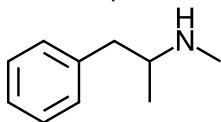
Imine and enamine

Amide

Oxidation to nitro

Reduction of nitrile

1. Methamphetamine is a stimulant.



methamphetamine

a. Draw the conjugate acid of methamphetamine.

b. Estimate the pK_a of the conjugate acid of methamphetamine.

c. At physiological pH of 7.4, does methamphetamine have a charge of 0 or +1? Give reasons.

Answers:

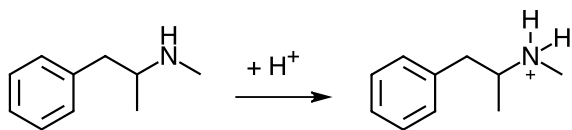
At low pH, methamphetamine has a +1 charge (acid form). At pH = pK_a = 11, 50% +1 charge (acid form) and 50% 0 charge (base form).

At pH 7.4 (below pK_a 11), mostly +1 charge. See Henderson-Hasselbach equation (from Chem 1B).

$$\text{pH} = \text{pK}_a + \log \left(\frac{[\text{base}]}{[\text{acid}]} \right)$$

$$7.4 = 11 + \log \left(\frac{[\text{base}]}{[\text{acid}]} \right)$$

Solve for [base]/[acid] = 10^{-3.6} = 0.00025. For every 1 acid (+1 charge), there is 0.00025 base (0 charge).



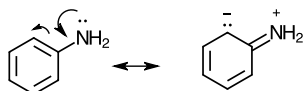
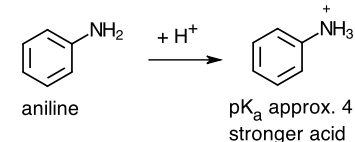
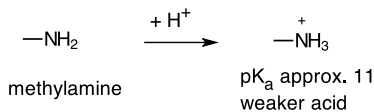
methamphetamine

pK_a approx. 11

At pH 7.4 (physiological pH), charge is mostly +1.

2. Methyl amine is a stronger base than aniline (C₆H₅NH₂). Remember from Objective 11 that “A weak base is more stable and less reactive (does not want to donate its H⁺) than a strong base.” Explain why aniline is more stable than methyl amine.

Answers: Lone pair on N in aniline is delocalized around benzene ring. One resonance structure is shown.

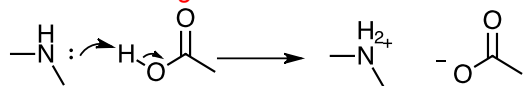


3. Dimethyl amine smells like fish. Why is lemon juice used on fish? Could you use vinegar to do the same thing? Show what happens with a chemical reaction. Identify the reaction type.

Answers:

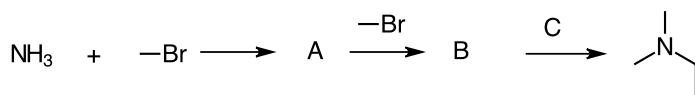
Dimethyl amine is a base and reacts with Lemon juice, which is an acid, in an acid-base reaction.

You could use vinegar to do the same neutralize the basic dimethyl amine.



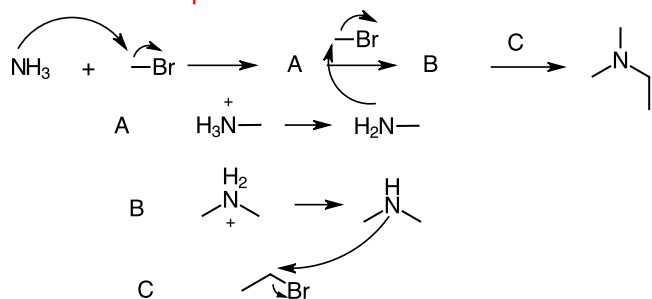
dimethylamine

4. Draw the structures of A, B, and C. Use curved arrows to show how A, B, and the 3° amine form.



Answers:

This is a nucleophilic substitution reaction.



5. Methamphetamine has two alpha carbons.

a. Circle each alpha carbon.

b. Identify Reagent A.

c. (i) Methamphetamine reacts with glycine. Draw the structure of B.

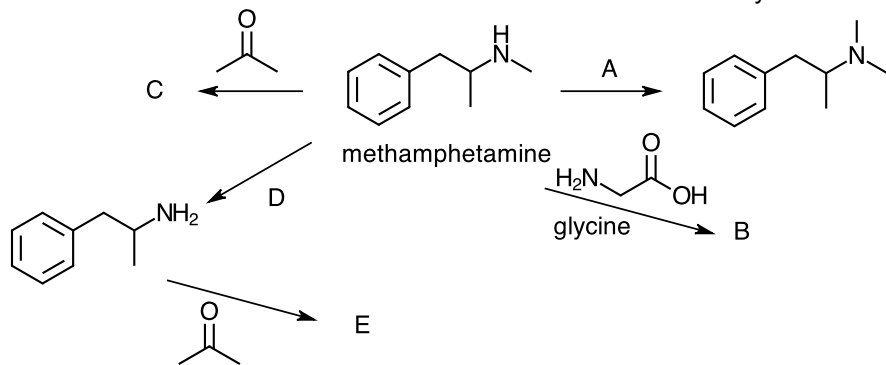
(ii) This reaction is faster with an acid catalyst. Use curved arrows to show how the acid catalyst participates in this reaction.

d. (i) Methamphetamine reacts with acetone. Draw the structure of C.

(ii) This reaction is faster with an acid catalyst. Use curved arrows to show how the acid catalyst participates in this reaction.

e. Methamphetamine is a 2° amine. Show how you would convert this 2° amine to a 1° amine (D). Hint: make a better leaving group and then do a substitution reaction.

f. Show how the 1° amine reacts with acetone and an acid catalyst to form E.

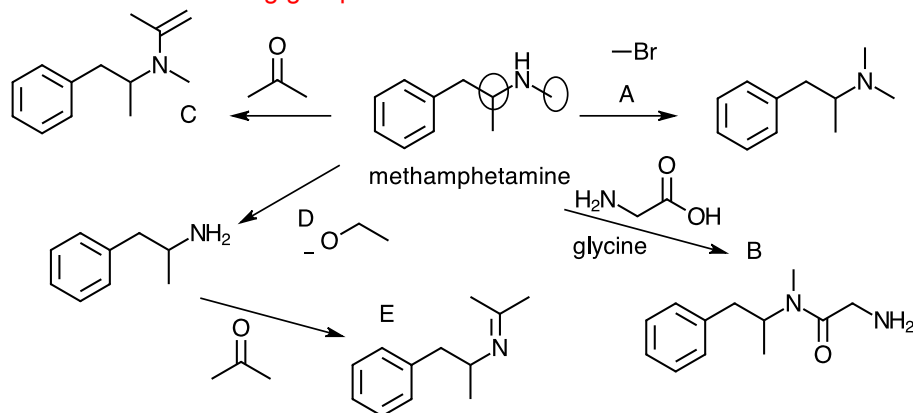


Answers:

a. Alpha carbon to left of N ==> leaving group is CH₃NH₂.

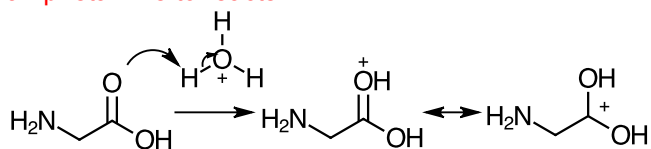
Alpha carbon to right of N ==> leaving group is C₆H₅CH₂CH(CH₃)NH₂.

b. A = CH₃X where X = Br or Cl or I. Nucleophile is lone pair on N that reacts with CH₃X in nucleophilic substitution reaction with X⁻ leaving group.



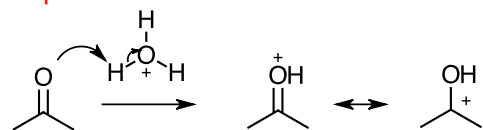
c. (i) Methamphetamine reacts with glycine in nucleophilic acyl substitution reaction.

(ii) Acid catalyst reacts with carbonyl O in acetone to make carbonyl C a better electrophile for nucleophilic N in amphetamine to react.

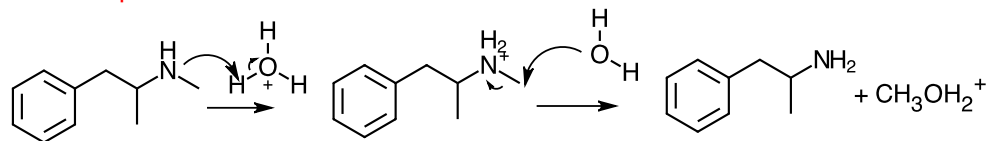


d. (i) Methamphetamine reacts with acetone in a nucleophilic addition reaction. C is an enamine.

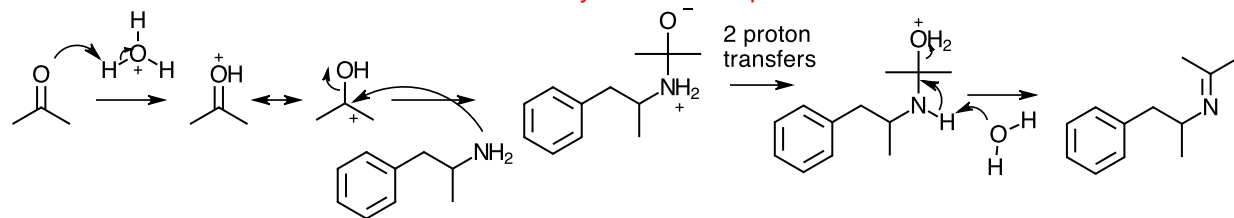
(ii) Acid catalyst reacts with carbonyl O in acetone to make carbonyl C a better electrophile for nucleophilic N in amphetamine to react.



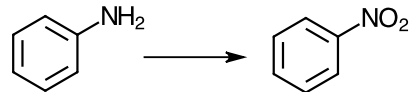
e. Nucleophilic substitution reaction.



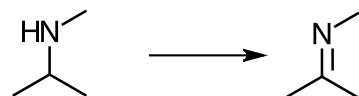
f. 1° amine reacts with acetone and an acid catalyst in a nucleophilic addition reaction. E is an imine.



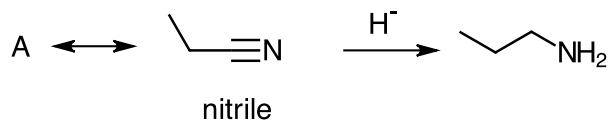
6. a. Is this reaction an oxidation or reduction? Suggest a reagent for this reaction.



b. Is this reaction an oxidation or reduction? Determine the number of H's and O's gained/lost to support your answer.



c. Nitriles (RCN) can be reduced with LiAlH_4 (but not the weaker reducing agent NaBH_4) to an amine. If you have used nitrile gloves, you've used a nitrile.

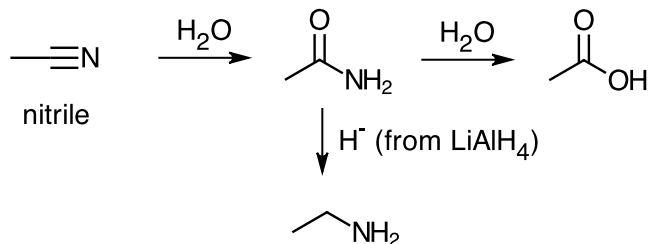


(i) The C triple bonded to N is like a carbonyl carbon and acts like a _____. This means nitriles undergo nucleophilic _____ reactions.

(ii) Draw resonance structure A to support your answer to part a.

(iii) The hydride part (H^-) of LiAlH_4 is the reducing agent part of this reducing agent. Use curved arrows to show how hydride reacts with the nitrile shown to form the amine.

(iv) Use curved arrows to show how each compound forms. Use H_3O^+ as needed. What is the leaving group in each reaction?



Answers:

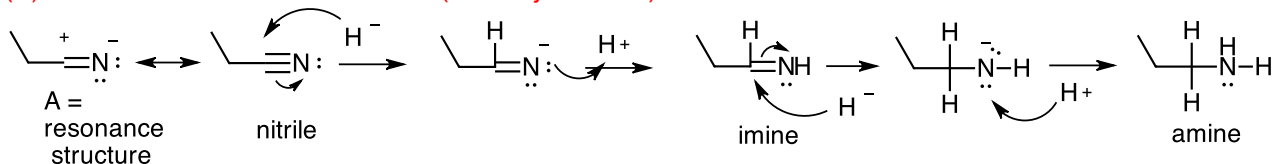
a. oxidation. N loses 2 H's and gains 2 O's. Can use KMnO_4 , H_2O_2 , bleach.

b. oxidation. N and C lose 1 H each.

c. (i) C triple bonded to N is like a carbonyl carbon and acts like an **electrophile**. This means nitriles undergo nucleophilic **addition** reactions.

(ii) A = resonance structure

(iii) The nitrile is reduced to an imine (see Objective 10). The imine is reduced to an amine.

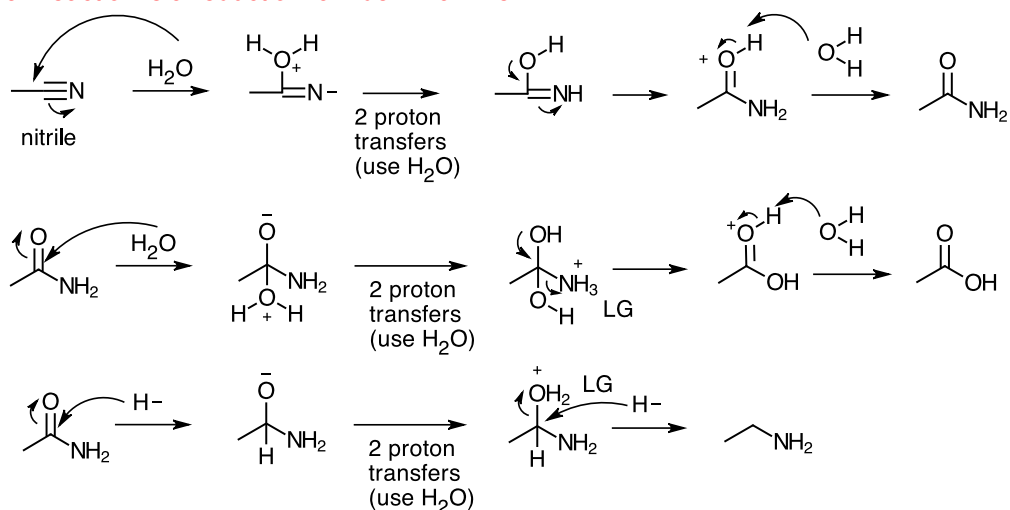


(iv)

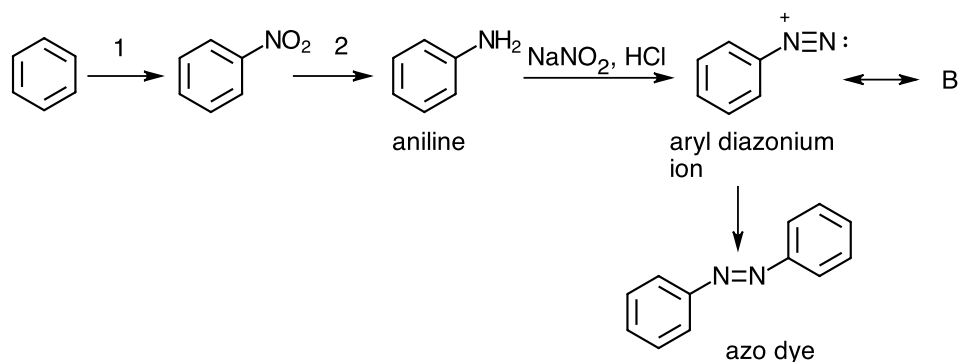
1st reaction is a nucleophilic addition. Nitrile behaves like carbonyl carbon.

2nd reaction is a nucleophilic acyl substitution: amide \rightarrow acid.

3rd reaction is a reduction: amide \rightarrow amine.



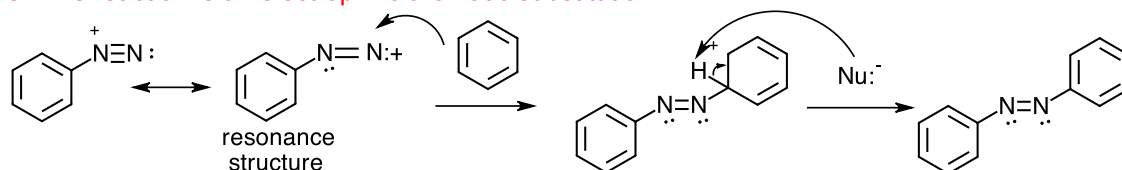
7. See Objective 14 Lecture Slides 15 and 16 on aromatics and the aryl diazonium ion.



- Determine Reagent 1.
- Determine Reagent 2.
- What reaction type is aniline → aryl diazonium ion? What type of reagent is NaNO₂?
- Draw resonance structure B. (This structure will help you with 7e.)
- The aryl diazonium ion reacts with benzene to form an azo dye. Use curved arrows to show how benzene reacts with the aryl diazonium ion to form the azo dye.

Answers:

- HNO₃/H₂SO₄
- use a reducing agent, e.g., NaBH₄ or LiAlH₄.
- oxidation reaction. N loses 2 H's.
-
- This reaction is an electrophilic aromatic substitution.



8. The aryl diazonium ion is an intermediate to make phenol, C₆H₅OH.

- Starting from benzene, propose a synthesis of phenol.
- Starting from phenol, propose a synthesis of salicylic acid.



Answers: See Objective 14 Lecture slide 17.

a. benzene + HNO₃/H₂SO₄ → nitrobenzene -- NaBH₄ → aniline – NaNO₂, HCl → aryl diazonium ion -- H₂O → phenol
NaNO₂ (sodium nitrite) is an oxidizing agent. Nitrites are used to cure pork, e.g., ham, to give it a red color.

b. In phenol, the OH group is an activating group and ortho, para director.

You can increase the yield by “protecting” or “blocking” the para position with a SO₃H group and then “unprotecting” or “unblocking” it after substituting the acid group. See Objective 8 Lecture slide 18 and 19.

