# TOPIC 5. AMINES
# (Chapter 20)

## OBJECTIVES

1. Name aliphatic and aromatic amines
2. Describe the basicity of amines, predict base strength based on structure
3. Recognize nucleophilicity of amines
4. Develop methods to synthesize amines by nucleophilic substitution and reduction of other *N*-containing functional groups

# NOMENCLATURE

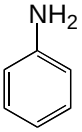
*S:20.1*
*Prob:20.21-23*

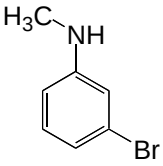
alkane

1° amine
alkylamine

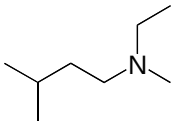
2° amine
*N*-alkylalkylamine

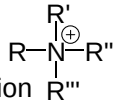
3° amine
*N*-alkyl-*N*-alkylalkylamine





aniline





Tetraalklyammonium cation

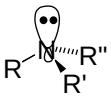
Section 20.1B: You do not need to know the names of all of these heterocycles. However, you should be able to describe the structure (hybridization of nitrogen, aromaticity) of these compounds

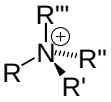
# PHYSICAL PROPERTIES, STRUCTURE AND BASICITY OF AMINES

*S:20.2-3*

## Structure

Trigonal pyramidal nitrogen ($sp^3$ hybridized).





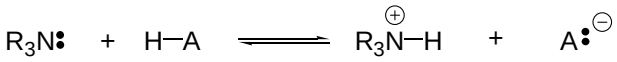
If R ≠ R' ≠ R'':

## Properties

Hydrogen bonding (present in 1º and 2º amines) increases the boiling point and solubility in $H_2O$.

| Compound | Boiling point |
|---|---|
| $CH_3CH_2CH_2NH_2$ | 50 °C |
| $CH_3CH_2NHCH_3$ | 34 °C |
| $(CH_3)_3N$ | 3 °C |
| $(CH_3)_3CH$ | -10 °C |

## Basicity



*Electron donating alkyl groups:*

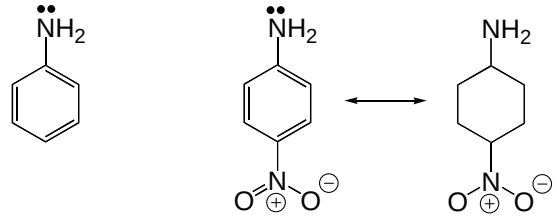
stabilize the conjugate acid

increase electron density on nitrogen

$\Rightarrow$ *stronger base*

| Base | Conjugate acid | p$K_a$(aq. soln) |
|---|---|---|
| $Me_3N$ | $Me_3\overset{\oplus}{N}H$ | 9.7 |
| $Me_2NH$ | $Me_2\overset{\oplus}{N}H_2$ | 10.7 |
| $MeNH_2$ | $Me\overset{\oplus}{N}H_3$ | 10.6 |
| $NH_3$ | $\overset{\oplus}{N}H_4$ | 9.3 |

## Basicity of Anilines

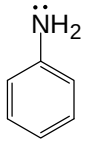
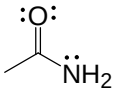


*Electron withdrawing groups*:

destabilize the conjugate acid

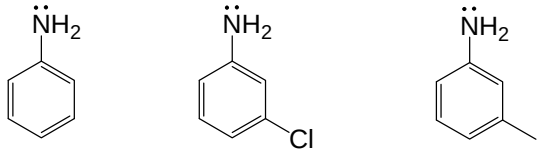
decrease electron density on nitrogen

$\Rightarrow$ *weaker base*

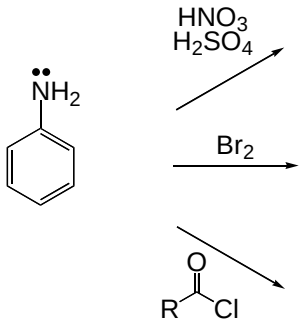
| | p$K_a$ of conjugate acid |
|---|---|
| $\dot{N}H_3$ | 9 |
| $CH_3\dot{N}H_2$ | 11 |
|  | 4.6 |
|  | 0.0 |

---

*Problem* – What is the order of relative basicity of the following compounds?



## Nucleophilicity of Anilines




? *Problems 20.21-23* ?

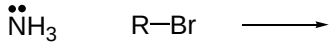
***Naming and Preparation***

# SYNTHESIS OF AMINES

*S:20.5*
*Prob:20.23-25,29*

## Alkylation of Nitrogen: Ammonia + alkyl halides

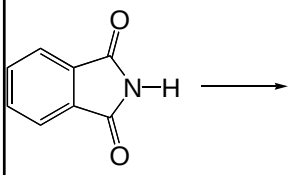
Ammonia undergoes polyalkylation



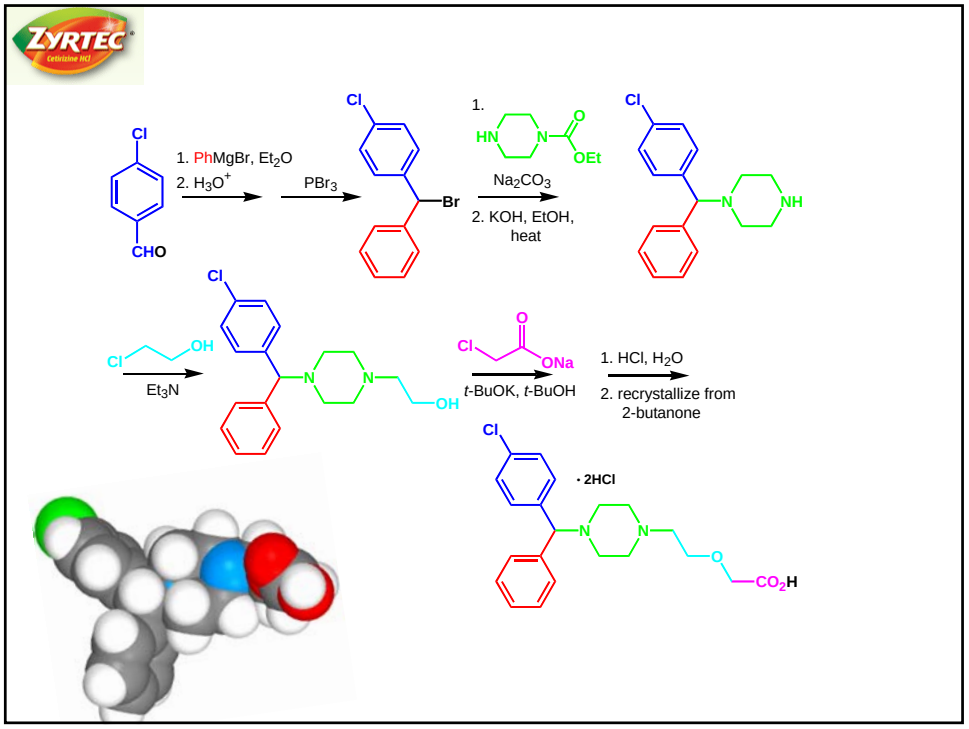

Avoiding polyalkylation: HOW? What if you want polyalkylation?

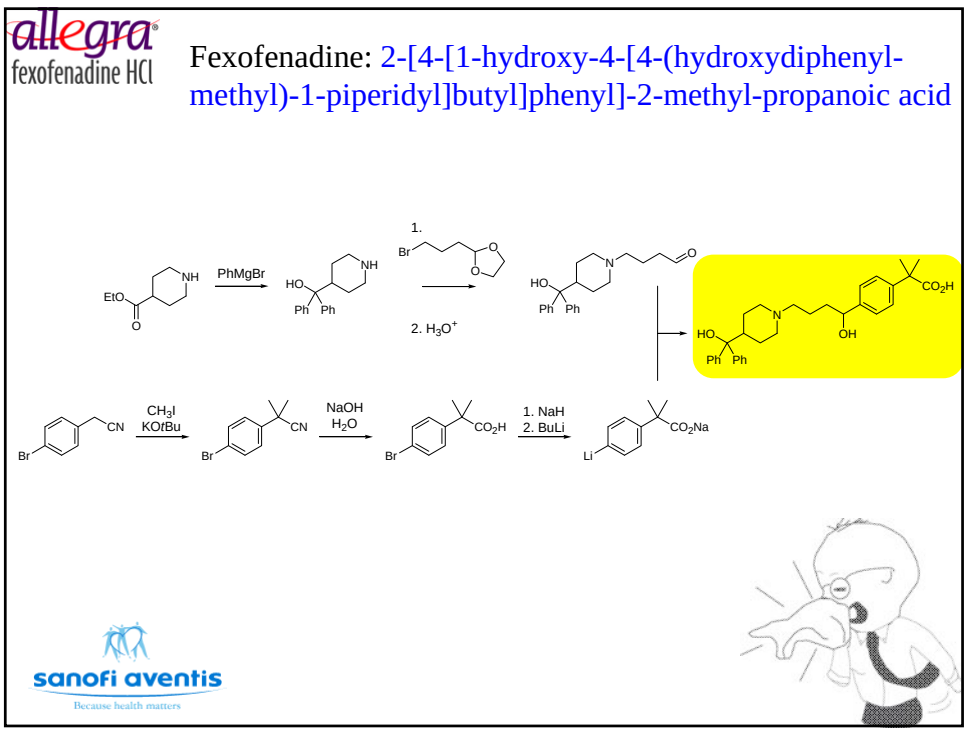
---

## Gabriel Synthesis: Alkylation of Phthalimide



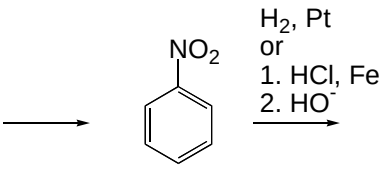

phthalimide


ZYRTEC
Cetirizine HCl
1. PhMgBr, Et2O
2. H3O+
PBr3
1.
Na2CO3
2. KOH, EtOH, heat
Et3N
t-BuOK, t-BuOH
1. HCl, H2O
2. recrystallize from 2-butanone
· 2HCl

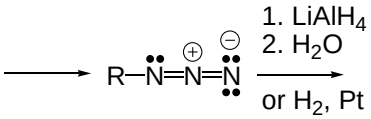

allegra
fexofenadine HCl
Fexofenadine: 2-[4-[1-hydroxy-4-[4-(hydroxydiphenyl-methyl)-1-piperidyl]butyl]phenyl]-2-methyl-propanoic acid
PhMgBr
1.
2. H3O+
CH3I
KOtBu
NaOH
H2O
1. NaH
2. BuLi
sanofi aventis
Because health matters

## Reduction of Nitrogen-containing Functional Groups

***Nitroarenes***

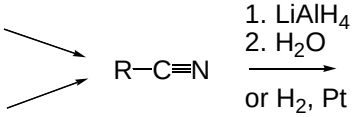



***Alkyl azides***

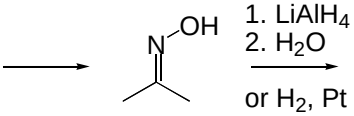



---

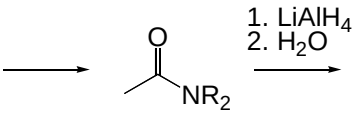
***Nitriles***



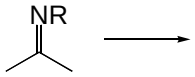

***Oximes***

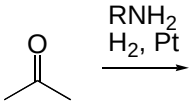



***Amides***



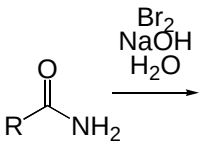
***Imines: Reductive amination of aldehydes and ketones***



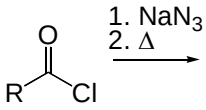




## Rearrangements Leading to Amines

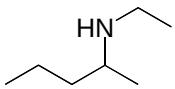
***Hoffman rearrangement (or Hoffman degradation)***

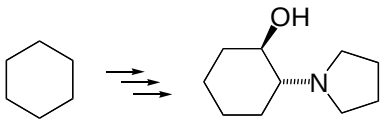


***Curtius Rearrangement***




## Planning Syntheses of Amines






## Summary of synthetic methods to prepare various amines

*1º amine on 1º C*

| | |
|---|---|
| RBr | Gabriel synthesis |
| | 1. $N_3^-$; 2. [H] |
| | 1. $^-CN$; 2. [H] |
| $RCONH_2$ | [H] |
| RCHO | $NH_3$ [H] |

*1º amine on 2º C*

| | |
|---|---|
| RCOR | $NH_3$ [H] |

*2º amine on 1º C*

| | |
|---|---|
| RCHO | $RNH_2$ [H] |
| RCONHR | [H] |

*2º amine on 2º C*

| | |
|---|---|
| RCOR | $RNH_2$ [H] |

*3º amine on 1º C*

| | |
|---|---|
| RCHO | $R_2NH$ [H] |
| $RCONR_2$ | [H] |

*3º amine on 2º C*

| | |
|---|---|
| RCOR | $R_2NH$ [H] |

α-amino alcohol

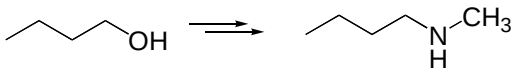
| | |
|---|---|
| RCHO | 1. $^-CN$; 2. [H] |
| RCOR | 1. $^-CN$; 2. [H] |

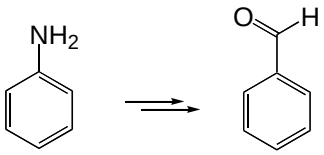
Aniline

| | |
|---|---|
| Ar-$NO_2$ | [H] |

[H] = reduction

*Problem [Solomons 20.15d,26k]* - How would you achieve the following transformations?




? *Problems 20.24,25,26,29* ?

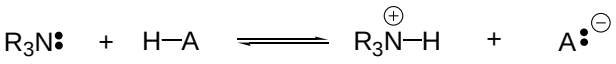
## *Preparation*

# REACTIONS OF AMINES

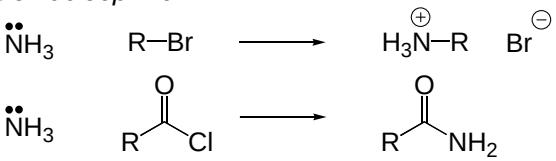
*S:20.5,6,9*
*Prob:20.30*

## Review/Overview

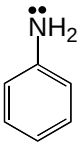
*Amines are basic*



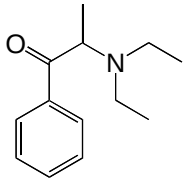
*Amines are nucleophilic*



*Rings of anilines are nucleophilic*



Diethylpropion is a stimulant, is marketed as Tenuate™ for appetite suppression. Propose a synthesis of diethtylpropion from benzene and any other starting materials.




?

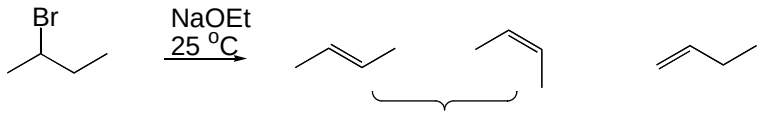
food NETWORK

## ELIMINATIONS INVOLVING AMMONIUM COMPOUNDS

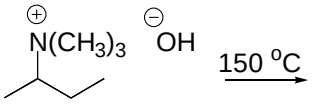
*S:20.11*

### Hofmann Elimination

*Standard (Zaitsev) elimination*




*Hofmann elimination*



# SPECTROSCOPIC ANALYSIS OF AMINES

*S.20.10*
*Prob: 20.38*

*Problem*

Elemental Analysis: C, 80.5; H, 10.1; N, 9.4

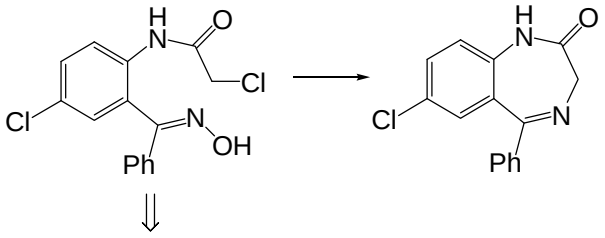
MS: $M^+$=149

IR: 3480, 3395, 3050, 2950, 1622 $cm^{-1}$

$^1H$ NMR: 1.3 (t, 6H), 2.6 (q, 4H), 3.7 (br. s, 2H), 6.8 (t, 1H), 7.1 (d, 2H)

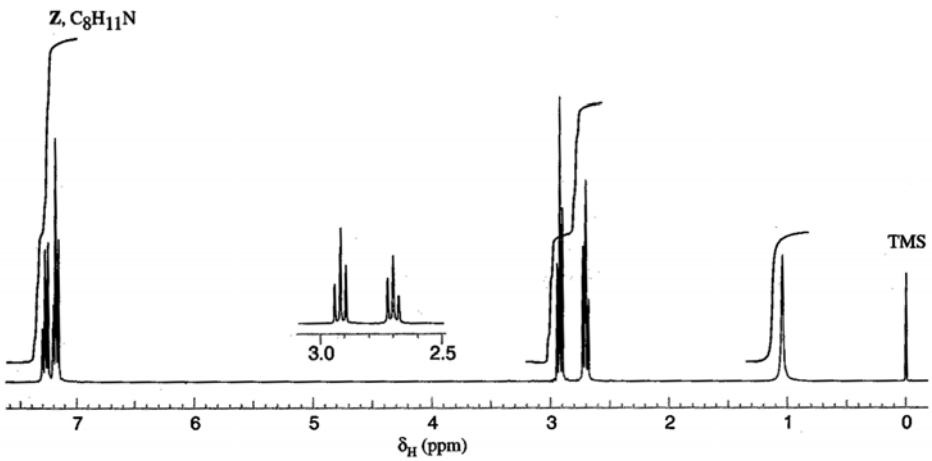
---

*Problem* – The final step in the synthesis of vallium is shown below. How would you prepare the precursor from benzene and any other starting materials.



? *Problems 20.30,38* ?

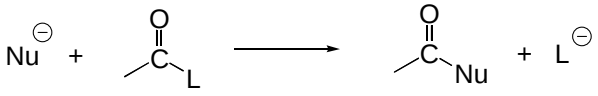

The $^1$H NMR spectrum of **X** gives two signals, a multiplet at $\delta$ 7.3 (5H) and a singlet at $\delta$ 4.25 (2H). The $^1$H NMR spectrum of **Y** is similar to that of **X**: multiplet at $\delta$ 7.3 (5H), singlet at $\delta$ 3.7 (2H). The $^1$H NMR spectrum of **Z** is shown below.



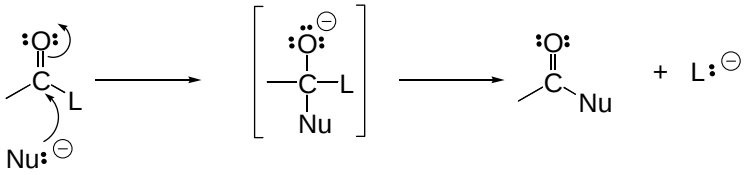

L

## REVIEW: NUCLEOPHILIC ADDITION-ELIMINATION REACTIONS AT ACYL CARBONS

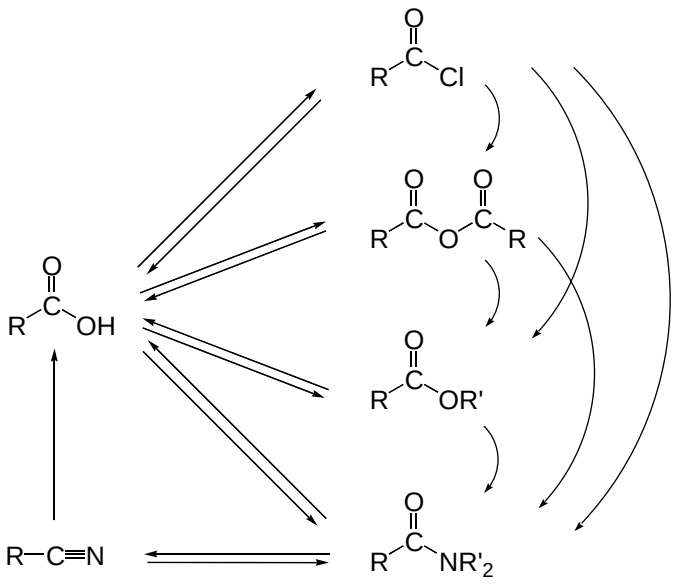
### Nucleophilic substitution at *sp*$^2$ carbons



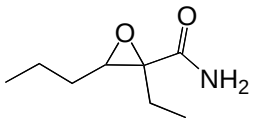

### Mechanism: Addition-Elimination



## Transformations of acids and acid derivatives



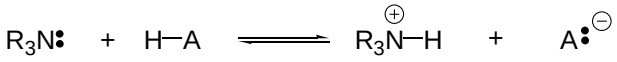

*Problem* - How would you prepare oxanamide, which is a mild sedative and is anxiolytic.



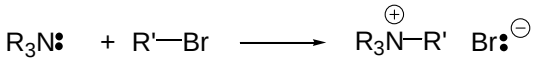

?

# REVIEW: AMINES

## Amines are Basic

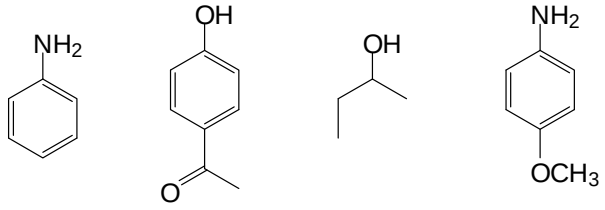


## Amines are Nucleophilic



---

What is the correct order of basicity of the following compounds? (more basic > less basic)



1 2 3 4

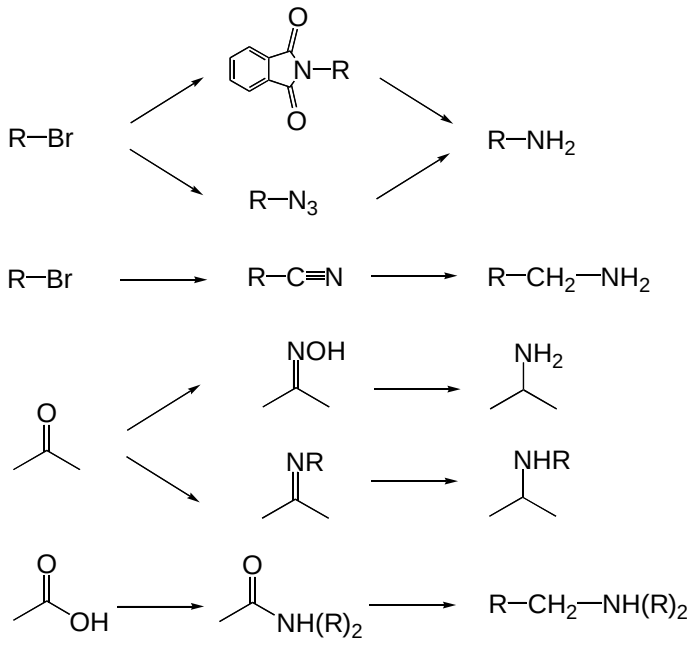
**1** 3 > 2 > 4 > 1

**2** 4 > 1 > 3 > 2

**3** 1 > 4 > 2 > 3

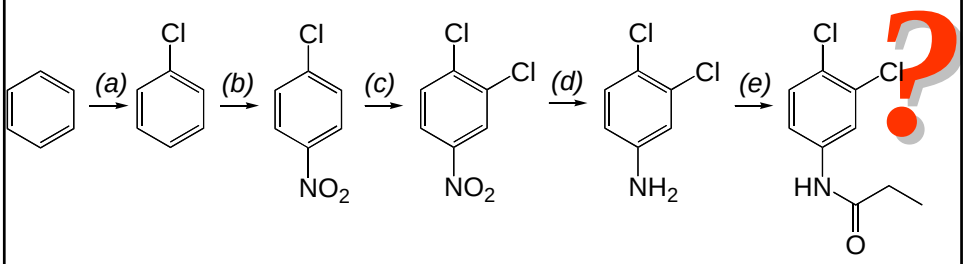
**4** 2 > 3 > 1 > 4

## Synthesis

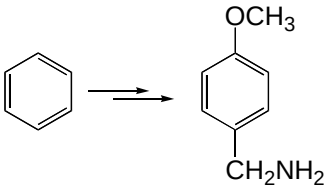



---

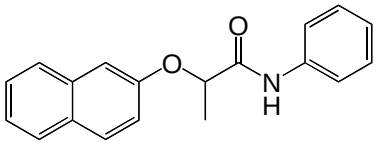
*Problem* – The herbicide Propranil is prepared in a five step synthesis from benzene. Identify reagents appropriate for each step.



*Problem* - How would you perform the following transformation?




*Problem* – Naproanilide is an herbicide used in rice paddies in Asia. How could this be prepared from naphthol, aniline and any other starting material with three or fewer carbon atoms?




# TOPIC 5 (CHAPTER 20) ON EXAM 4

## Types of Questions

- Nomenclature
- Predict products (or provide reagents or starting materials to complete a reaction),
- Design multistep syntheses
- Provide mechanistic rationales

*Do the problems in the book; they are great examples of the types of problems on the exam!*

## Preparing for Exam 4

- Get up-to-date *NOW!*
- Work as many problems as possible. Do the problems first, then consult the solutions manual.
- Work in groups, discuss chemistry, teach and test each other.
- Do the "Learning Group Problem" at the end of the chapter.