

Organic Synthesis

102721

Dr. Pichaya Nakkiew

School of Chemistry

Institute of Science

Suranaree University of Technology

Organic Synthesis

- Retrosynthesis (Disconnection Approach)
- Asymmetric synthesis (will be included in stereoselective synthesis part)
- Special Topics: Combinatorial Chemistry

Routine for Designing a Synthesis

- Analysis
 - Recognize functional groups of target molecules
 - Disconnection by a known and reliable reaction
 - Repeat above processes as necessary
- Synthesis
 - Write out a plan according to the analysis
 - Modify as necessary from the result in the laboratory

Essential Background Knowledge

- Understanding reaction mechanism
- Working knowledge of reliable reactions
- Knowing availability of some compounds
- Understanding the stereochemistry

Disconnection Approach

- Disconnection:
Reverse of synthetic steps or reactions
- Functional group interconversion (FGI):
Change of functional groups into other which can be disconnected
- Synthons:
Idealized fragments which help to design the reaction to be used. They may or may not be involved in the reaction.

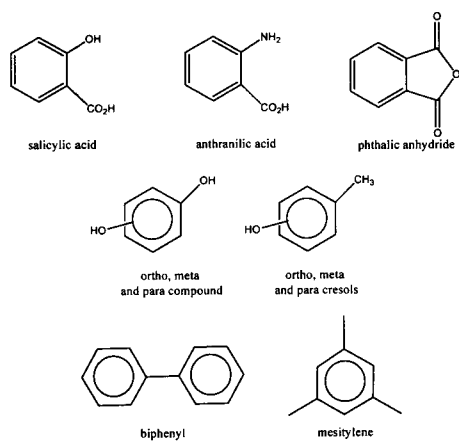
The Order of Events

- Looking for a group that direct to the right direction
- The group first to be disconnected is the most electron withdrawing group
- Remember FGI might change the directing effect of some substituents
- When using nucleophilic substitution on diazonium salt, it is a good idea to add at the amine stage

Guideline (continued)

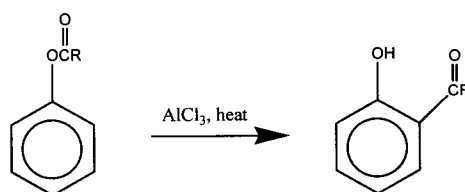
- Sometimes, an extra group has to be added and then removed later
- Look for substituents that are difficult to add => Don't disconnect them but to use starting materials containing those groups
- Look for a combination of substituents in a readily available starting materials
- Avoid sequence that may lead to unwanted reaction
- If o,p-substitution is involved, block the other position

Some Readily Available Compounds

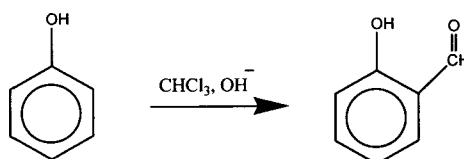


Ortho-favored Reactions (for phenolic aromatic compounds)

- Fries Rearrangement



- Reimer-Tiemann Reaction



To Select A Good Route

Judgement

Laboratory Trial And Error

One-Group C-X Disconnections

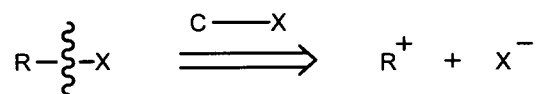
Ether, Amides and Sulfides

- Disconnect a bond joining carbon to the heteroatom (X)

Nucleophilic Heteroatoms

- alcohol (ROH), amines (RNH₂) or thiols (RSH)

Disconnection scheme



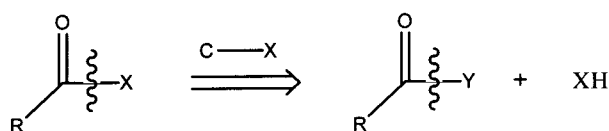
RY; Y = Br, OTs

Carbonyl Derivatives

Disconnect the bond between carbonyl group and heteroatom

- Reactivity of acid derivative is as followed (from the most reactive to less)

acid chloride > acid anhydride > esters > amides

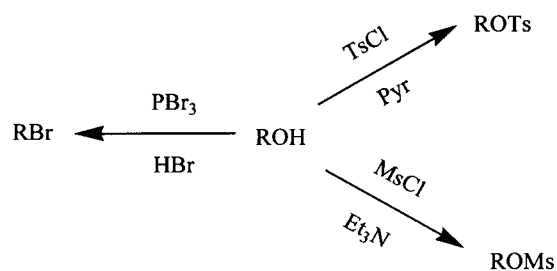


Alcohols, Ethers, Alkylhalides and Sulfides

In Aliphatic compounds RX

=> nucleophiles XH

=> electrophilic carbon species R⁺ (Reagents are RBr, ROTs or ROMs)



Aliphatic Compounds Derived from Alcohols

ROH can be converted to RX ; X = halide, OTs, OMs

Then

$RX + R^1OH, \text{ base} \longrightarrow$ Ethers ROR^1

$RX + R^1SH, \text{ base} \longrightarrow$ Sulfides RSR^1

$RX + (NH_2)_2CS, HO^-/H_2O \longrightarrow$ Thiols RSH

$RX + Hal^- \longrightarrow$ Alkyl halides $RHal$

$RX + Nu \longrightarrow$ Other derivatives

Considerations

*Conditions used must suit the structure of the molecules

S_N1

- Tertiary compounds
- Via carbocation intermediate
- Polar solvent medium, and acid catalysis

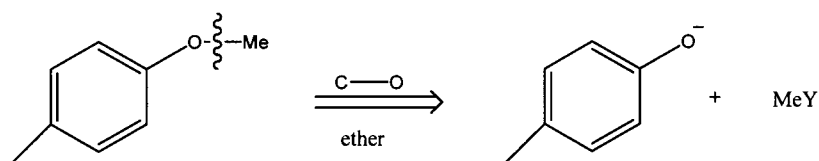
S_N2

- Methyl and primary alkyl derivatives
- No intermediate involved
- Non polar solvent and powerful nucleophiles condition

Ethers and Sulphides

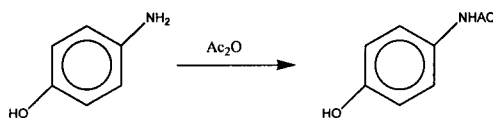
The bond to be disconnected is between C-O bond (for ethers) and C-S bonds (for sulphides)

- Dimethylsulphate $(\text{MeO})_2\text{SO}_2$ is used for methylation (in alkaline solution - NaOH)

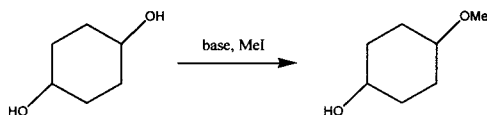


Chemoselectivity

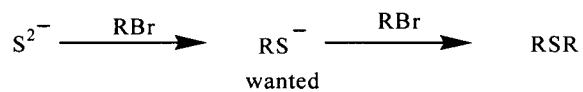
- Relative reactivity of two different functional groups



- Reaction of one of the two functional groups



- Reaction of a group once when it may react again



Guidelines to Chemoselectivity

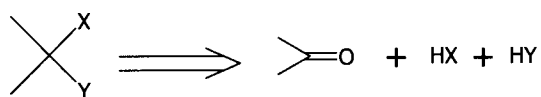
- With two functional groups of unequal reactivity, the more reactive one can always be made to react alone e.g. hydroxy acid
- If one functional group can react twice, make sure the first product is less reactive than the starting material
- To solve above problems, use protecting groups
- One of the two identical groups can react if the product is less reactive than reactant
- Stoichiometric method can be used to control the two identical reaction site
- Use a derivative that can react once only
- When two groups are nearly but not quite identical, avoid to make one of them react

Two-Group C-X Disconnections

- 1,1-Difunctionalized Compounds
- 1,2-Difunctionalized Compounds
- 1,3-Difunctionalized Compounds

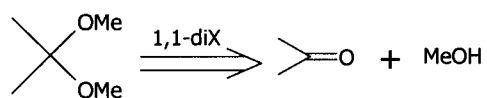
1,1-Difunctionalized Compounds

Two functional groups to be disconnected are at the same
carbon atom: 1,1-diX



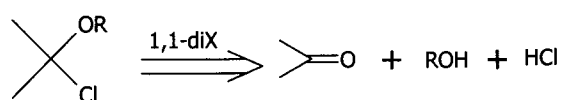
Synthesis of Acetals

One carbon atom has two C-O bonds: one oxygen atom
can help to disconnect the other



Synthesis of α -Halo Ethers

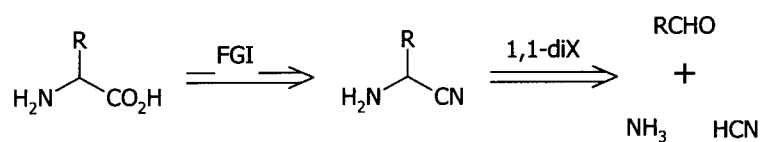
Reaction is similar to that of preparing acetals but the acid has nucleophilic counter ion (Cl^-), and proportions of the reagents are changed



Synthesis of α -Amino Acids

Both oxygen atoms have been replaced by other groups

Strecker synthesis via amino cyanide



1,2-Difunctionalized Compound

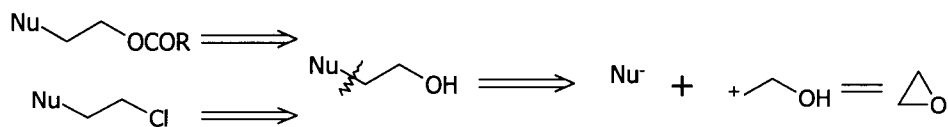
Two functional groups to be disconnected are on adjacent

carbon atoms : 1,2-diX

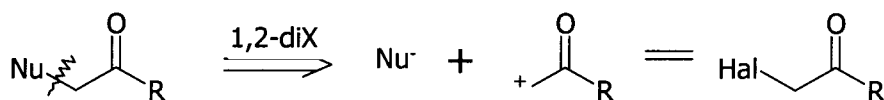
- alcohol derivatives
- carbonyl compounds

Synthesis of alcohol derivatives

Reagent: Epoxides



Synthesis of carbonyl compounds

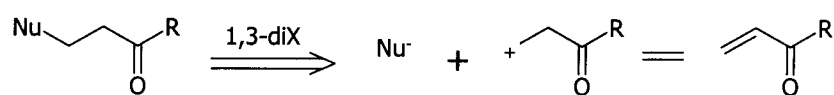


1,3-Difunctionalized Compounds

These compounds can be disconnected only at carbonyl

oxidation level: 1,3-diX

Reagent: Unsaturated compounds



Reversal of Polarity

Nucleophilic attack on a heteroatom reverse the
polarity of the atom

e.g., synthesis of

- Epoxides
- α -Haloketones
- α -Haloacids

Cyclization Reaction

Preferred Condition for Ring Formation:

- bimolecular reaction to form an open-chain compound then cyclize, giving three-, five-, six-, or seven-membered rings

e.g., five-membered cyclic acetal and N-methylmorpholine

Summary of Strategy

Analysis:

1. Recognize the functional group
2. Disconnect by known reliable methods
 - Ar-C or Ar-X;
 - Any C-X bond; RCO-X and 1,1-, 1,2-, or 1,3-diX
3. Repeat as necessary to reach available starting materials

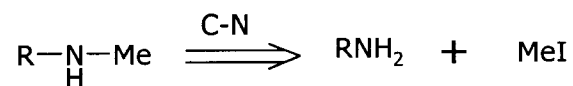
Summary of Strategy

Synthesis:

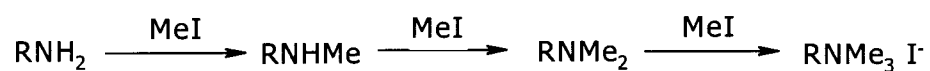
1. Write out plan according to analysis, adding reagents and conditions
2. Check for reasonable order of events
3. Check aspect of chemoselectivity
4. Modify the plan according to above and to unexpected failures or success

Amine Synthesis

Problem of synthesis amine by disconnect C-X

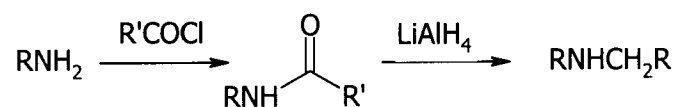


- The first product is at least as active as the starting material so it reacts further to give over alkylation product

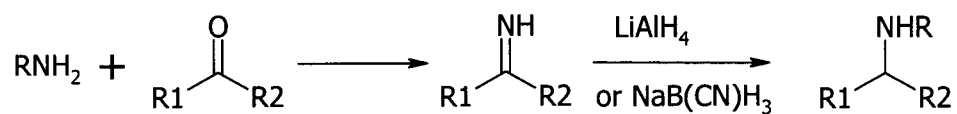


Alternative Methods

- The Amide method



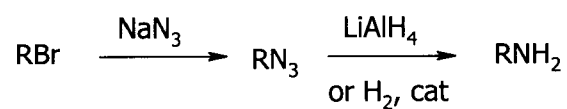
- The Imine Method (good for branch substrates)



Alternative Methods

(continued)

- The Azide Method (Reduction)



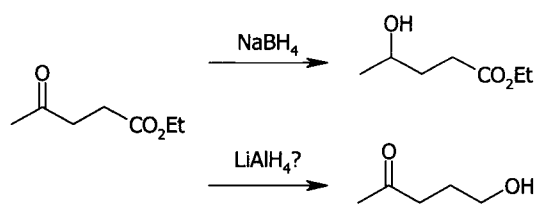
- * NaNH_2 is available commercially but it is very basic so leads elimination instead of substitution

Synthesis of Primary Amines

- Imines (not give a very good yield)
- Oxime method use NH_2OH and reducing agents (LiAlH_4)
- Alkylation and reduction of aliphatic nitro compounds
- Ritter reaction followed by hydrolysis of amides

Protecting Groups

Why we have to use protecting group?



Chemoselectivity

Characteristics of Protecting Groups

1. Easy to put in and remove
2. Resistant to reagents which would react with unprotected groups
3. Resistant to other reagents

Some Useful Protecting Groups

- Alcohol and diols protecting groups
 - acetals
 - THP (tetrahydropyranyl ether)
 - MOM (methoxymethyl), and MEM
(β -methoxyethoxymethyl)
- Amino protecting groups
 - CBz (carbobenzyloxy)
 - TBoc (t-butoxycarbonyl)

Some Useful Protecting Groups

- Carbonyl protecting groups
 - acetals and ketals
 - 1,3-oxathiolane derivatives (nonacidic condition required for deprotection)
- Carboxylic acid protecting groups
 - esters e.g. methyl, ethyl, or benzyl esters
 - oxazoline derivatives (e.g. 4,4-dimethyl derivative)

One-Group C-C Disconnection

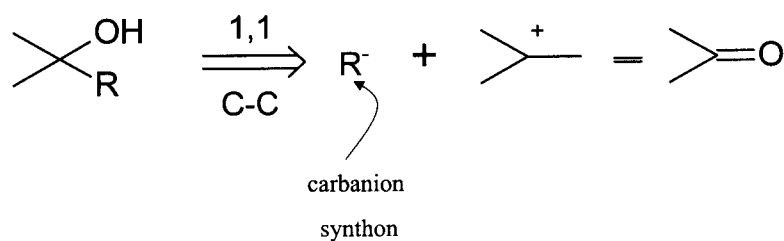
- 1,1 C-C Disconnections
- 1,2 C-C Disconnections
- 1,3 C-C Disconnections

Application: alcohol synthesis

- Electrophilic reagents; e.g., RBr
- Nucleophilic reagents; e.g., RMgBr

1,1 C-C Disconnections

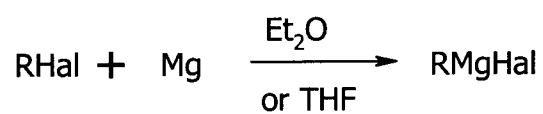
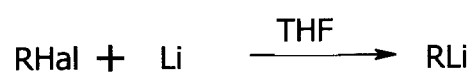
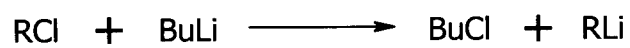
Alcohols can be disconnected at the C-C bond next to oxygen



Reagents for Carbanion Synthons

Carbanion R^-

- Reagents: carbon joining to a more electropositive atom such as a metal e.g., Li or Mg

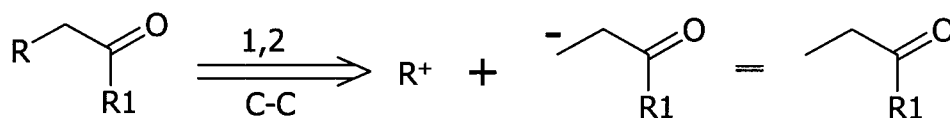
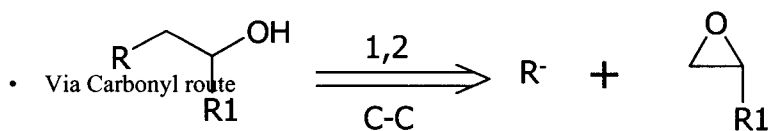


Compounds Derived from Alcohols

- Aldehydes and Ketones
 - oxidation of alcohols
- * Popular oxidizing agents are chromium(VI), PCC and PDC
- Carboxylic Acids
 - addition of CO_2 to Grignard reagents or RLi and the cyanide method (works well with allylic and benzylic halides)

1,2 C-C Disconnections

- Via Epoxides route (substrates with not too many substituents)



Carbonyl Compounds

2 step synthesis via epoxides:

- making alcohols
- oxidation
- * Other approaches will be discussed later

Choosing A Disconnections for C-C

- Greatest Simplification:
 - disconnect in the middle of molecule
 - disconnect at a branch point
 - disconnect rings from chains
- Symmetry
- Approach with highest yield
- Recognizable starting materials

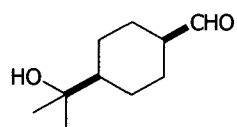
Guidelines to Good Disconnections

1. Make the synthesis as short as possible
2. Consider disconnections only with known reliable reactions
3. Disconnect C-X bonds and C-C bonds
4. Choose approach with highest yield
5. Use available starting materials or compounds which are easily to make

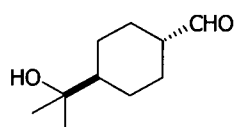
Stereoselectivity

Why important?

- Biological activity of organic molecules such as drugs, perfumes, or insecticides depend on stereochemistry



cis
strong pleasant smell



trans
odorless

Enantiomeric Excess and Optical Purity

- Enantiomeric excess (ee)

$$= \frac{(\text{amount of major} - \text{minor})}{(\text{amount of major} + \text{minor})} \times 100$$

- Optical Purity

$$= \frac{\text{observed specific rotation}}{\text{specific rotation of a pure enantiomer}} \times 100$$

To Obtain Optically Active Compounds

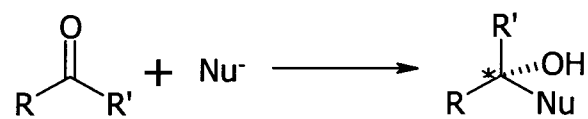
- Resolution
- Asymmetric Synthesis
 - Substrate Control
 - Auxiliary Control
 - Reagent Control
 - stereospecific or stereoselective mechanism
 - stoichiometric
 - catalysis

Resolution Methods

- Crystallization - entainment process
- Formation of diastereomers
- Kinetic resolution
- Use chiral column

Asymmetric Synthesis

- Most widely used method for producing chiral compounds; for example, adding nucleophile to carbonyl generating a new asymmetric center (,)



Prochiral Center

A Nucleophile can attack either face of
carbonyl (trigonal planar)

- Re face - in the clockwise direction
- Si face - in the counterclockwise direction

(priority according to Cahn-Ingold-Prelog - CIP
system)

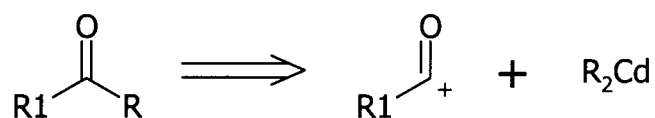
*Addition of a ligand can generate a new chiral center

Synthesis of Carbonyl Compounds

- 1,1 C-C Disconnections
- Alkylation of Enols
- Michael Addition

1,1 C-C Disconnections

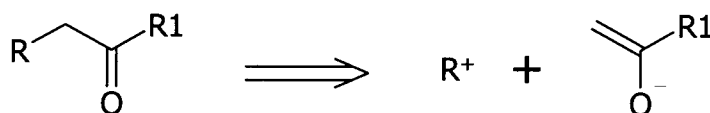
- Less reactive organometallic reagents such as cadmium will be used instead of Grignard reagent
- Use cyanides



Grignard reagent will react with ketones and give alcohols

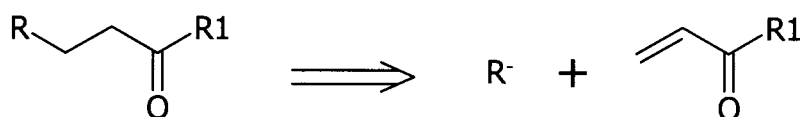
Alkylation of Enols

- 1,2 C-C disconnection requires the alkylation of an enol or enolate anion by an alkyl halide
- * CO₂Et must be present on the α-carbon atom



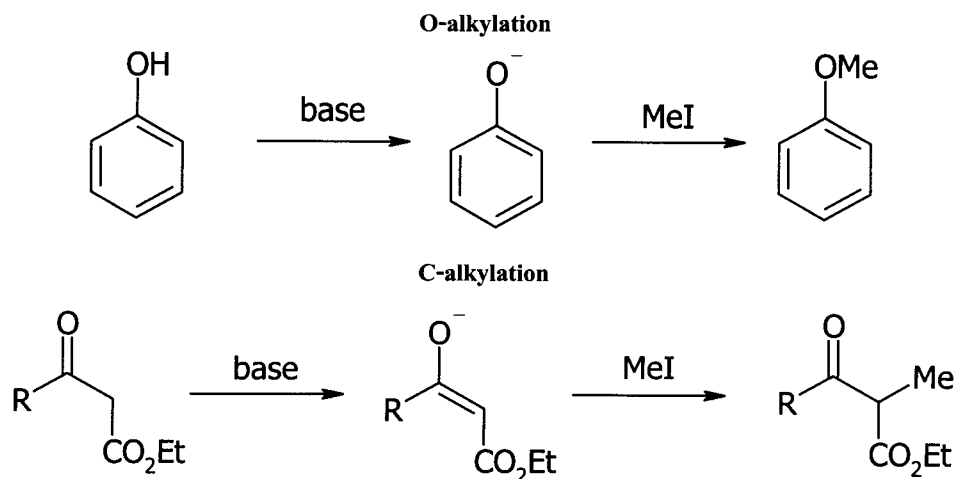
Michael Addition

- 1,3-disconnection should look for a branch point at the β or γ carbon atoms, and particularly when it joins a ring to a chain



Regioselectivity

- Reaction on one specific part of a single functional group



Regioselective Alkylation of Ketones

- Alkylation can add an alkyl group to either side of a ketone
- To solve the problem use ester e.g. malonate ester as the substrate

Regioselective Michael Addition

Direct 1,2 addition at the carbonyl, giving alcohol

V.S. Michael addition or 1,4 addition

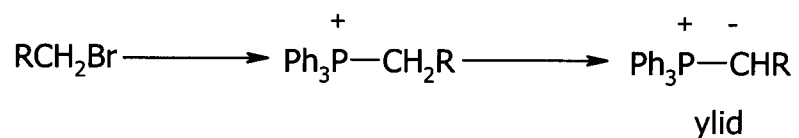
- Michael addition product is the thermodynamic product
- More stable nucleophiles give more Michael addition product
- C=O is harder than C=C; weaker basic nucleophiles favor Michael addition

Alkene Synthesis

- Elimination of Alcohols and Derivatives
 - dehydration of alcohols under acidic condition; acids used are such as KHSO_4 , phosphoric acid and POCl_3
 - dehydrohalogenation of alkyl halides with bases
- The Wittig Reaction
 - widely used for olefin synthesis

The Wittig Reaction

- Stabilized ylids ($\text{R} = \text{Ar}, \text{COR}, \text{C}=\text{C}$ etc.) react with aldehyde to give mainly E (trans)
- Unstabilized ylids ($\text{R} = \text{alkyl}$) give mainly Z (cis)



Use of Acetylenes

- Form an anion (carbanions) by treating with NaNH_2 in NH_3 (l)
 - react with alkyl halides, carbonyl and epoxides etc.
- Use in diene synthesis
- Use in hydration with $\text{Hg}(\text{II})$; terminal acetylenes always give methyl ketones

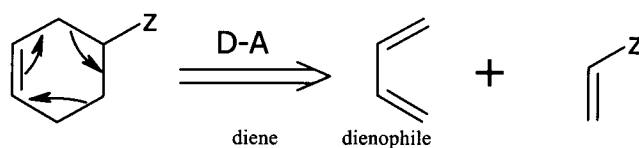
Two-Group Disconnections: Diels-Alder Reactions

Pericyclic cycloaddition reaction

- all new bonds are created simultaneously and electrons are moving in circle

Target for trying Diels-Alder (D-A) reaction

- cyclohexene and electron withdrawing groups



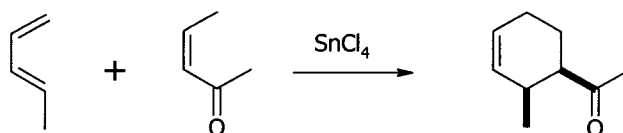
Stereospecificity and Stereoselectivity

- Stereospecificity aspect:
 - cis dienophiles give cis products and trans dienophiles give trans products
 - same to that of dienes
- Stereoselectivity aspect:
 - endo* selectivity (kinetic product)

*refers to the relationship between Z groups in the dienophile and the double bond in a new cyclohexene ring

Regioselectivity of D-A Reactions

- Ortho-Para directing under Lewis acid catalyst (no meta product observed)



Introduction to Carbonyl Condensations

- 1,3-Difunctionalized compounds and α, β unsaturated carbonyl compounds
- 1,5- Dicarbonyl compounds
- 1,2- Difunctionalized compounds
- 1,4- Difunctionalized compounds
- 1,6- Difunctionalized compounds

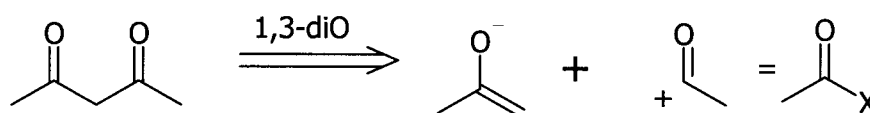
Two-Group Disconnections: 1,3 Difunctionalized and α, β -unsaturated Carbonyl Compounds

1. 1,3 Dicarbonyl Compounds
2. β -Hydroxy Carbonyl Compounds
3. α, β -Unsaturated Carbonyl Compounds

1,3-Dicarbonyl Compounds

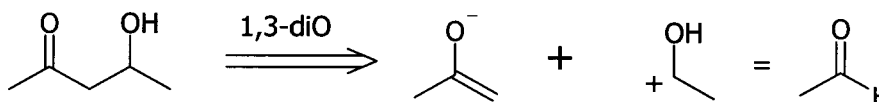
- Disconnection where it requires acylation reaction of enolate anion

X = OR or Cl



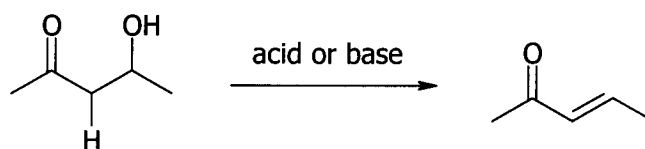
β -Hydroxy Carbonyl Compounds

- Disconnection at lower oxidation level, the ester is being replaced by aldehyde or ketone



α,β -unsaturated Carbonyl Compounds

- Dehydration of β -hydroxy carbonyl compounds: removing of enolic proton and producing conjugated system



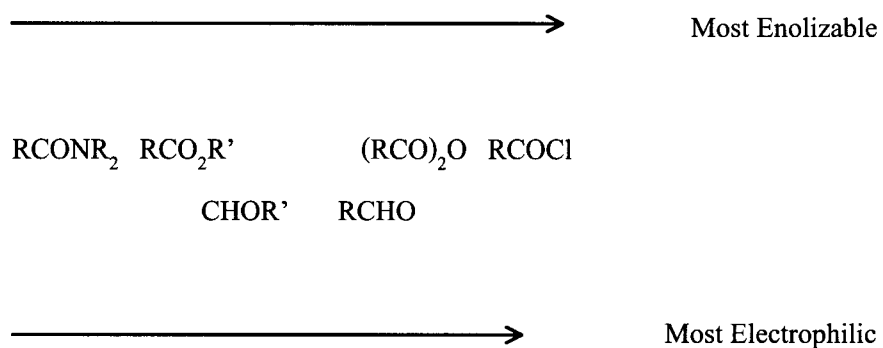
Control in Carbonyl Condensations

Considerations for carbonyl condensations

Chemo- or Regioselectivity Problems

- Which compound enolized?
- Which side does it enolize?
- Which compound acts as the electrophile?

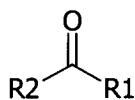
Reactivity of Carbonyl Compounds



Strategy in Controlling Carbonyl Condensations

- Self condensations: use symmetrical ketones or aldehydes
- Varying the conditions
- Intramolecular reaction: stable 5- and 6-membered ring are the most favored
- Use compounds which cannot enolize e.g. formaldehyde (the Mannich reaction)

R1,R2 = H, OEt, Cl, Ar, t-Alk, CO₂Et



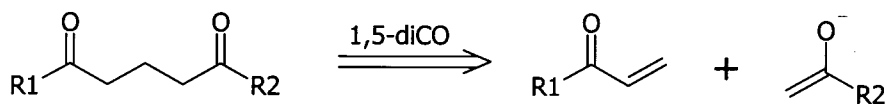
Strategy in Controlling Carbonyl Condensations (continued)

- Use specific enol equivalents
 - activating groups, usually CO_2Et
 - Wittig and Reformatsky reagents
 - enamines
- Removal of one product
 - dehydration to give enones
 - product ionization to give β -dicarbonyl anions
 - decarboxylation

Two-Group Disconnections: 1,5 Difunctionalized Compounds

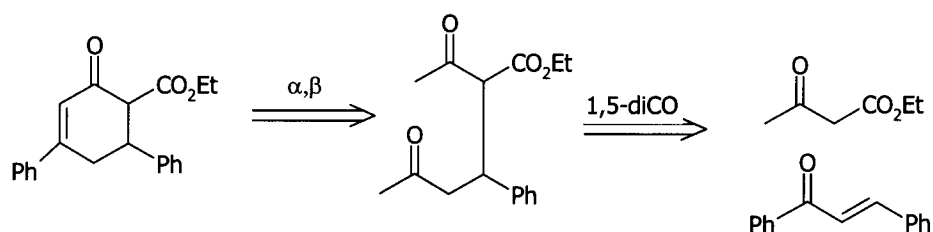
Michael Addition

- 1,5 Dicarbonyl compounds can be disconnected at either α,β bond in a reverse michael addition
 - Activating groups are such as CO_2Et and enamines



The Robinson Annulation

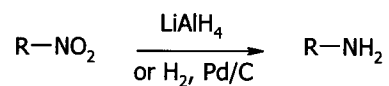
- One important extension of Michael addition to make six-membered rings and 1,3-diketones
- Disconnection at the α,β bond



Use of Aliphatic Nitro Compounds in Synthesis

Nitro group is a very powerful anion-stabilizing group
(one nitro group is at least as anion-stabilizing as two
carbonyl groups)

- converts to amines

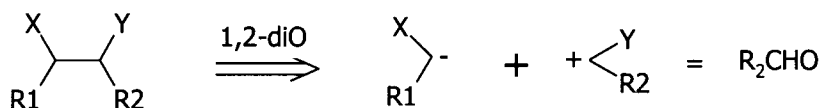


- converts to carbonyl by TiCl_3 catalyzed hydrolysis



Two-Group Disconnections

1,2-Difunctionalized Compounds



Sources of nucleophilic synthons

1. Acyl anion equivalents
 - alkynes
 - cyanide for -COOH and Benzoin condensation
2. Methods from alkenes e.g. epoxidation, halogenation
or hydroxylation

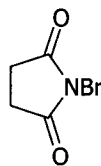
Sources for nucleophilic synthons (continued)

3. α -functionalization of carbonyl compounds
 - α -halo compounds
 - conversion of ketones to α -diketones
 - oxidation with SeO_2
 - nitroization followed by hydrolysis
4. Use of available starting materials

1,2-Difunctionalized Compounds

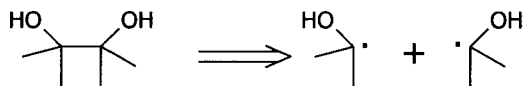
Radical Reactions

- Functionalization of Allylic and Benzylic Positions
 - Bromination
 - Br₂, light
 - allylic, α to carbonyl, and alkynes brominations- NBS (N-bromosuccinimide) or Wohl-Ziegler bromination (usually in nonpolar solvent medium e.g, CCl₄)



Radical Reactions (continued)

- C-C bond formation
 - radical dimerization e.g. synthesis of 1,2-diol or pinacol



- acyloin reaction (α-hydroxy carbonyl compounds)
 - use electron donors to give diradicals e.g. Na metal

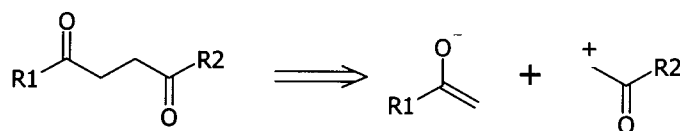
Functional Group Addition (FGA)

- Use in syntheses of hydrocarbons (no functional group)
- The functional groups are added then removed to give desired products
 - FGA alcohols; removed by dehydration
 - FGA carbonyl; removed by Clemmensen method (Zn, Hg in conc HCl)
 - FGA of double bonds; removed by hydrogenation

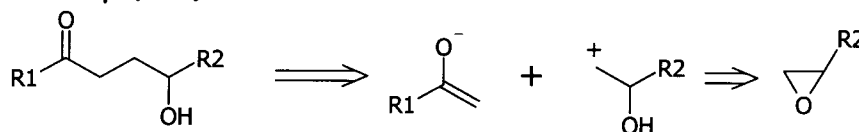
Two-Group Disconnections

1,4-Difunctionalized Compounds

- 1,4-diketones
 - unnatural electrophilic synthons can be from α -halo carbonyl compounds reacts with specific enol equivalents



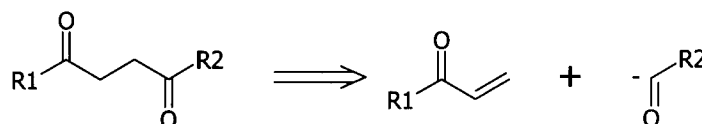
- δ - or γ -hydroxyketones



1,4-Difunctionalized Compounds

(continued)

- unnatural nucleophilic synthons; use cyanide method or nitroalkanes

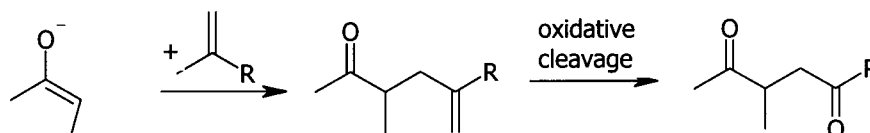


- Use of available starting materials
- FGA of a triple bond

Reconnections

- Join a bond which will be broken during the synthesis of a molecule
- Cleavage of C=C bond
 - ozonolysis with Me_2S or H_2O_2 work-up (depends of types of product wanted)
 - hydroxylation and cleavage of diol and hydroxylation and cleavage combined

Oxidative Cleavage of Double Bonds



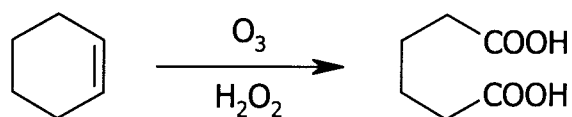
Synthesis with Reconnection Approach

- Synthesis of 1,2- and 1,4*-difunctionalized compounds by C=C cleavage
 - Synthesis of 1,2-dicarbonyl compounds
- and
- Synthesis of 1,6-difunctionalized compounds

* 1,4-difunctionalized compounds can be synthesized without reconnection, e.g. by using propargyl halides and by adding of HBr to allyl groups

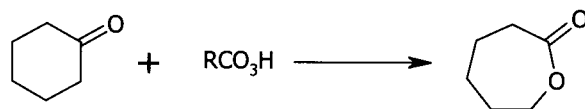
1,6-Difunctionalized Compounds

- Reconnection approach is normally used for the synthesis of these compounds
 - one of the important key step is to use cyclohexene in the synthesis
 - cyclohexenes can be obtained from dehydration or Diels-Alder



Baeyer-Villiger Reaction

- Insertion of an oxygen atom to the ring giving lactones
- Reagents are peracids such as perbenzoic or peracetic acids



Strategy of Carbonyl Disconnections

- Look at target molecules and recognize FGs
- Consider all possible disconnections
- Choose the best possible route

Summary of Approach

- Convert all FGs based on oxygen (OH, CO, etc.) by FGI or C-X disconnections
- Identify 1,n-relationships
- Adjust oxidation level by oxidation or reduction (if necessary)
- Look for the best possible disconnection
- Add extra FGs (FGA) or activating groups (if necessary)
- If a bad step must be included, put it as early as possible

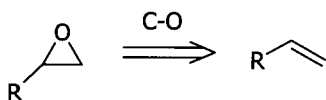
Introduction to Ring Synthesis (Saturated Heterocycles)

- Cyclization
 - usually kinetically favored intramolecular over intermolecular reaction
 - five, six and seven-membered rings are easy to make
 - three-membered rings are easy to make but not thermodynamically favored (usually break down)
 - four-membered rings are not easy to make

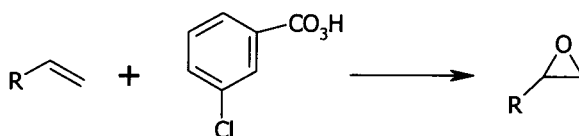
Three-Membered Rings

- e.g. epoxides can be synthesized from alkenes and peracids; often used MCPBA

Analysis



Synthesis

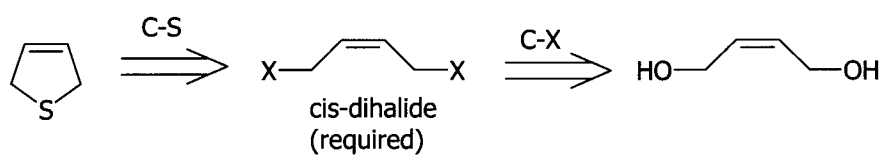


Five-Membered Rings

Cyclization (favorable)

- Tactics
 - disconnect both C-X bonds
 - identify electrophilic carbon fragment needed to be added to nucleophilic heteroatom

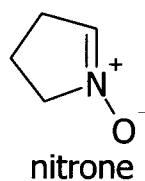
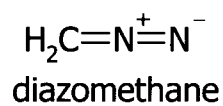
Analysis



Five-Membered Rings

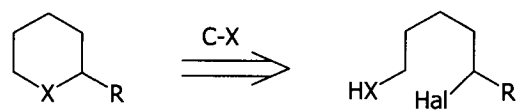
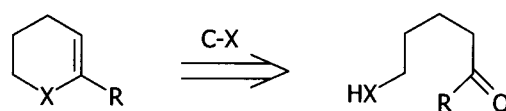
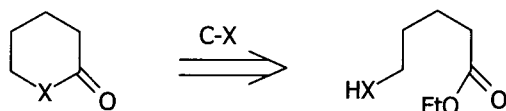
(continued)

- 1,3-Dipolar cycloaddition (pericyclic reaction)
 - conjugated alkenes react best by using this method
 - using 3 atom, 4 electron reagents such as diazomethane and nitrene



Six-Membered Rings

- Order of disconnections (from first to last)

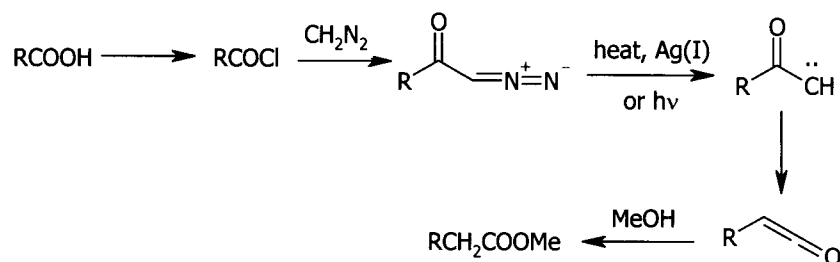


Three-Membered Ring Synthesis

- Cyclization reactions
 - kinetically favorable but thermodynamically unfavorable
- Insertion reactions
 - epoxides; peracid and Darzens reaction
 - cyclopropylketones
 - cyclopropanes; Simmons-Smith reaction (CH_2I_2 with Zn/Cu)
 - use of halocarbenes

Rearrangement in Ring Syntheses

- To construct a slightly different framework by using conventional reactions and rearrange it to the target molecule, e.g. Arndt-Eistert procedure



Some Useful Rearrangement Techniques

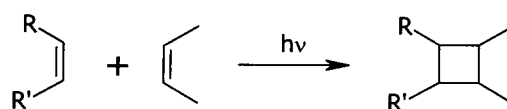
- Arndt-Eistert procedure; chain extension by diazomethane (increase by one CH_2 group)
- Ring expansion using diazoalkanes and ketones
- Pinacol rearrangement; useful method for making of t-alkyl ketones
- Epoxide rearrangements in the synthesis of carbonyl compounds
- Anionic rearrangement - Favorskii (Faworskii) rearrangement

Guideline of Rearrangement Techniques

- Compounds with a carbonyl group one atom away from a position where it would be helpful
- Compounds with t-alkyl group next to the carbonyl group

Four-Membered Ring Synthesis

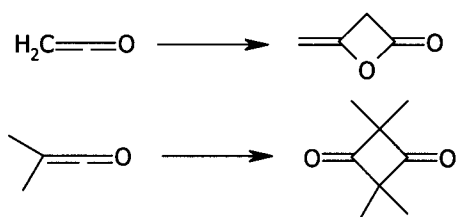
- Photochemical [2+2] Cycloadditions



- Ionic Reactions : ring expansion or contraction techniques

Ketenes

- Highly electrophilic at sp carbon atom
 - Nucleophiles can attack and give acyl derivatives
 - ketenes can dimerize to give esters or cyclobutadiones (for disubstituted ketenes)



Use of Ketenes in Cyclobutanes Synthesis

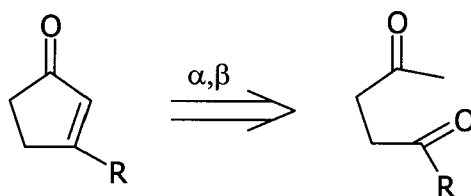
- [2+2] Thermal Cycloadditions
- Ketene dimerization reaction

Five-Membered Ring

- Five-membered ring compounds can be made by:
 - standard carbonyl chemistry
 - 1,4-dicarbonyl compounds
 - 1,5- dicarbonyl compounds
 - and
 - 1,6- dicarbonyl compounds
- Pericyclic rearrangement

Synthesis of Five-Membered Rings

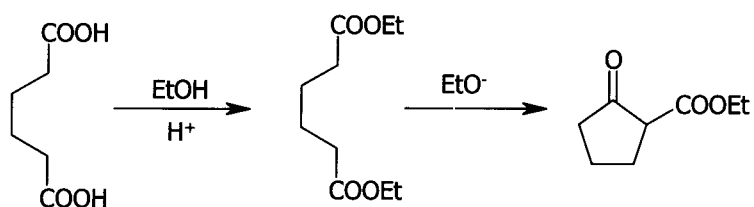
- From 1,4-dicarbonyl compounds



Synthesis of Five-membered Rings

(continued)

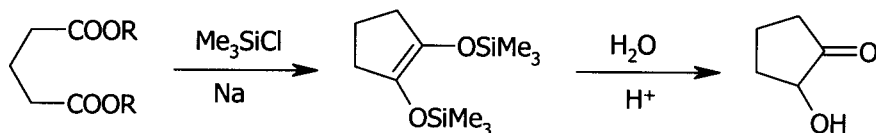
- From 1,6-dicarbonyl compounds



Synthesis of Five-membered Rings

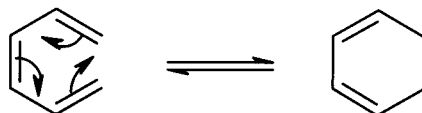
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- From 1,5-dicarbonyl compounds
 - silicon modified acyloin reaction

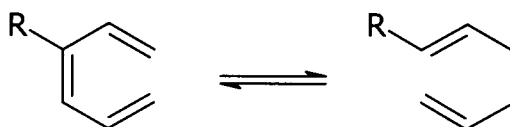


Pericyclic Rearrangement for Five-membered Ring Synthesis

- Electrocyclic reaction



- Sigmatropic rearrangement



[3,3] Sigmatropic Shifts

- Claisen-Cope rearrangement
 - converts C-O bond in an ether into C-C bond in the product
 - highly stereoselective
- Carroll rearrangement
 - important industrial process of making vitamin A, and many perfume and flavoring compounds

Six-Membered Ring

- Methods of making six-membered rings :

- Carbonyl condensation - Robinson Annulation



- Diels-Alder reaction



- Reduction of aromatic compounds

- total reduction



- partial reduction: Birch reduction



Strategies of Ring Synthesis

- Cyclization to control selectivity
 - If a difficult step has to be involved, cyclization is a good idea
- Small ring considerations
 - disconnect a small ring at an early stage
 - consider how a small ring could be made before doing other disconnections
- Developing reagents for a given synthon

Strategies of Ring Synthesis

(continued)

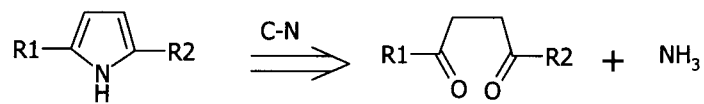
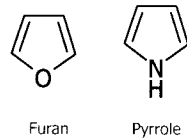
- Use alternative strategies, e.g. carbenes or other disconnection strategies
- Polycyclic compounds syntheses
 - disconnect in the middle of molecules
 - Common atom approach
 - disconnections of bonds to atoms that are common to two or more rings

Aromatic Heterocycles

- convey a biologically active substituents into the living cell
- Same disconnection techniques as the saturated heterocycles can be used but aromaticity makes it easier to make

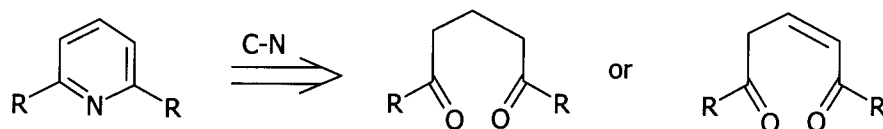
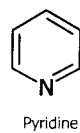
Five-Membered Ring

- Furans and Pyrroles



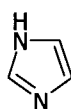
Six-Membered Ring

- Pyridines



Aromatic Heterocycles with Two Heteroatoms

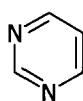
- oxazole (five-membered ring)
- diazepine (seven-membered ring)
- pyridazine, pyrazine and pyrimidine
- imidazoles



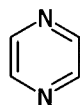
Imidazole



Oxazole



Pyrimidine



Pyrazine



pyridazine

Stereoselectivity

- Analysis of target molecules with many chiral centers
 - set up one to set the next chiral center nearby
- Synthesis to establish stereochemistry of natural products
- To control stereochemistry
 - one useful strategy of open-chain compounds syntheses is to use a rigid structure which can be broken down to give open-chain compounds later

Advanced Strategy

- Convergent plan of synthesis
 - usually provide higher yield than linear synthesis plan
 - disconnection in the middle of molecule or at a branch point
- Key reaction strategy
- Available of starting materials strategy

Molecular Diversity

- Differences in physical properties that exist among different molecules
- Sources of molecular diversity
 - biological sources
 - chemical syntheses
 - parallel synthesis: simultaneous synthesis of multiple products
 - combinatorial synthesis: perform multiple reactions in one reaction vessel at the same time

Combinatorial Chemistry

Intelligently planned => Collections of molecular
diversity compounds

Without Planning => GIGO

Logic of Combinatorial Chemistry

Historically

- Biological assays from natural products screening were carried out on mixtures

Combinatorial Chemistry Ideas

- Intentionally making mixtures for the purpose of testing
- If a mixture showed no activity, all compounds could be assumed to be inactive
- provide more rapid screening

Combinatorial Chemistry Approach

- making the library - a large collection of synthetic compounds for biological testing
- finding the active compound

History

Beginning in 1980s

- Bruce Merrifield (Nobel prize 1984) : solid phase peptide synthesis
- Richard Houghten (1985) : tea bag method for rapid multiple peptide synthesis
- Mario Geysen (1984) : first report describing combinatorial chemistry

From 1992, combinatorial library field has been the domain of peptides and oligonucleotides in pharmaceutical industry

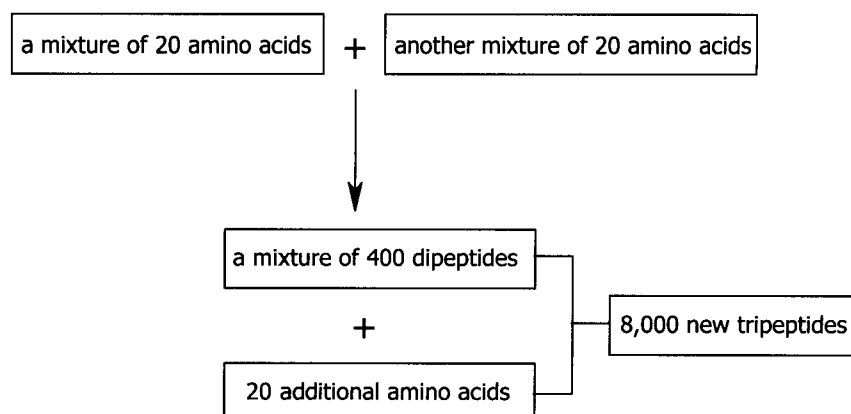
Comprehensive bibliography references: <http://vesta.pd.com>

Combinatorial Chemistry

Multidisciplinary Integration:

- new analytical methods
- new computer modeling
- database-related challenges
- new synthetic approach
- new types of reagents
- new types of assays

Example of Peptide Synthesis



Problems-Solutions

- What if one or more of the amino acid would not react or react sluggish?

Answer: Always difficult to solve

- How to find a single active peptides in a mixture of 7,999 inactive ones?

Answer: Deconvolution method- omit one

position after another to find the best residue

Requirements for Combinatorial Chemistry

Synthesis must be fast and efficient

Testing must be fast and easy



Automation and Robotics

Solid-Phase Organic Synthesis

- 1963, Merrifield : introducing of solid phase peptide synthesis

Ealier Days Problems

- solid-phase synthesis often produced only small quantities
- In pre 1980, NMR required a large amount of compounds for characterization

Solid-Phase Organic Synthesis (continued)

- 1992, Bunin and Ellman: preparation of combinatorial libraries of organic molecules

Analytical Techniques for Solid-Phase Synthesis

- Elemental analysis
- Titration of reactive groups
- weight gain
- Spectroscopic methods, e.g. IR, NMR, or MS

Encoding of Beads

- Each compound is attached to a separated bead
=> **bead encoding**
- Each bead can be derivatized with a 'Tag'

Positionally Addressable

Spatial Arrays

- Another approach to separation/identification of combinatorial library collections
- each compounds immobilized on a separate spot on a surface
- solid-phase synthesis s carried out on surface derivatized glass substrate using photolabile protecting groups and photolithographic techniques

Robotic Instrumentation

- Zymark Corporation introduced its sample handling robot (1981)
- Zymark robot (1992) Robotic combinatorial library synthesizer (split-mix procedure)

Computational Chemistry in Combinatorial Chemistry

Structure-activity relationship study and drug design

- molecular spread sheet methods
- databases
- software

Combinatorial library usually represented by generic structures with a small variation in R group positions

Commercial Sources

- Chemical Design (Oxon, England)
- Tripos (St. Louis, MO)
- MDL (San Leandro, CA)
- Daylight (Irvine, CA)
- Synopsys (Leeds, England)

Other Approaches and Applications

- Solution-phase can be used
 - Carell and co-workers use of central core molecule with many reactive groups
e.g. cubane tetracarboxylic acid chloride and xanthane tetracarboxylic chloride

Building Blocks (BBs)

- small reactive molecules that may be intercombined with each other or with members of other building blocks families (amines, carboxylic, aldehydes)

Difference Between Combinatorial Chemistry and Traditionally Chemistry

- Traditional synthesis goal is to produce a single product of previously specified structure
- Combinatorial chemistry goal is to create searchable populations of molecules

Strategies in The Design And Synthesis of Chemical Libraries

What is Chemical libraries?

- Intentionally created collections of differing molecules that may be screened for sets of preselected criteria, e.g. molecular recognition or biological activity

Library Design

- Strategic Considerations
- Building Blocks (small and reactive)
 - random screening or lead development
- Design and Synthesis of Library
 - direct the preparation of a group than an individual molecule

Format for Molecular Diversity

- Spatially addressable
- Split-pool
- Encoded Library

Strategies for Identification of Members in Library

- Microanalysis
 - microsequencing
 - mass spectrometry: off-bead and on-bead
- Iterative deconvolution
- Encoding
 - chemical encoding
 - radio frequency method

Chemical Encoding

- Oligonucleotide Tags
- Peptide tags
- Molecular Tags or Binary Encoding
- Isotope Encoding

Radiofrequency Encoding

- use of small electronic semiconductors
 - chemically inert porous enclosure
 - solid-phase synthesis resin
 - Single or Multiple Addressable Radiofrequency Tag (SMART)

Solid-Phase Method in Combinatorial Chemistry

- solid support
- linker
- scaffold or target molecule

Resin for Solid-Phase Synthesis

- Crosslinked polystyrene (Merrifield-type resin)
 - most common
- TentaGel- a polystyrene core with polyethylene glycol spacer arms,
PS-PEG
 - attached reacting group out in solution rather than close to polymer backbone;
increase reactivity

Examples of Solid-Phase Synthesis of Biphenyl library

- Biphenyls; commonly found in many important natural products that have antitumor and antiviral activities
- Synthesis method: Pd-catalyzed cross-coupling reaction between aryl electrophiles and stannanes

Multiple-Component Condensation

Multiple-component condensation (MCC)

- three or more reactants combine in a single event to yield a product that feature aspects of all the inputs
- Examples; Passerini Reaction and application to the synthesis of azinomycin analogues

