

Lecture 10 Carbon-Nitrogen Bonds Formation I

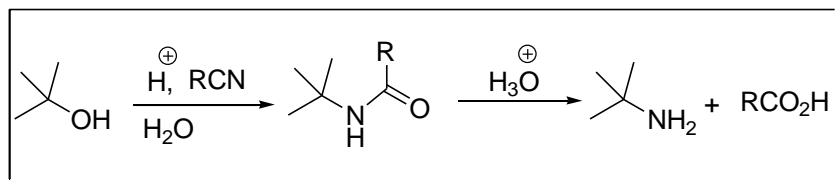
4.1 Principles

The methods for the formation of bonds between nitrogen and aliphatic carbon can be broadly divided into two categories: (i) reaction of nucleophilic nitrogen with electrophilic carbon, and (ii) reaction of electrophilic nitrogen with nucleophilic carbon. In this section, we will try to cover some of the important reactions.

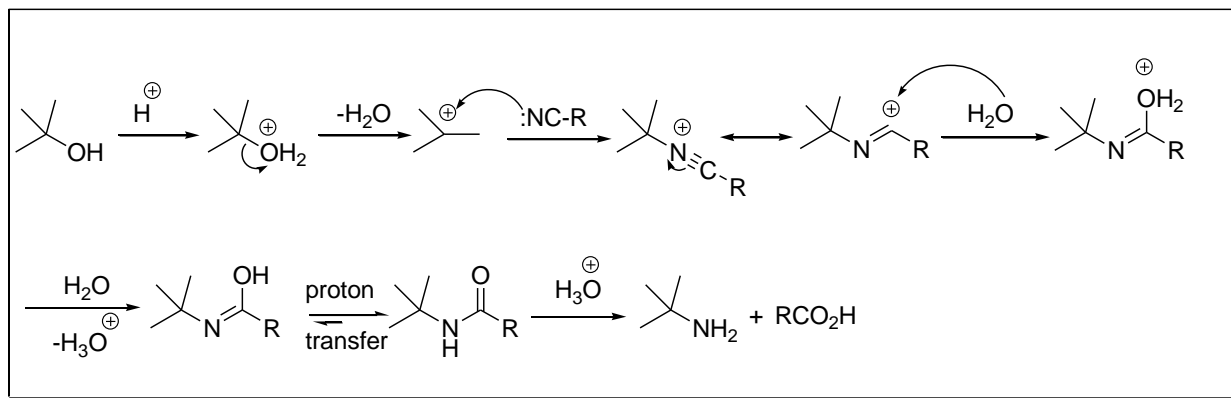
4.2 Substitution of Nitrogen Nucleophiles at Saturated Carbon

4.2.1 Ritter Reaction

Treatment of a tertiary alcohol or the corresponding alkene with concentrated sulphuric acid and a nitrile affords an amide that in acidic conditions undergoes hydrolysis to give amine. First, a

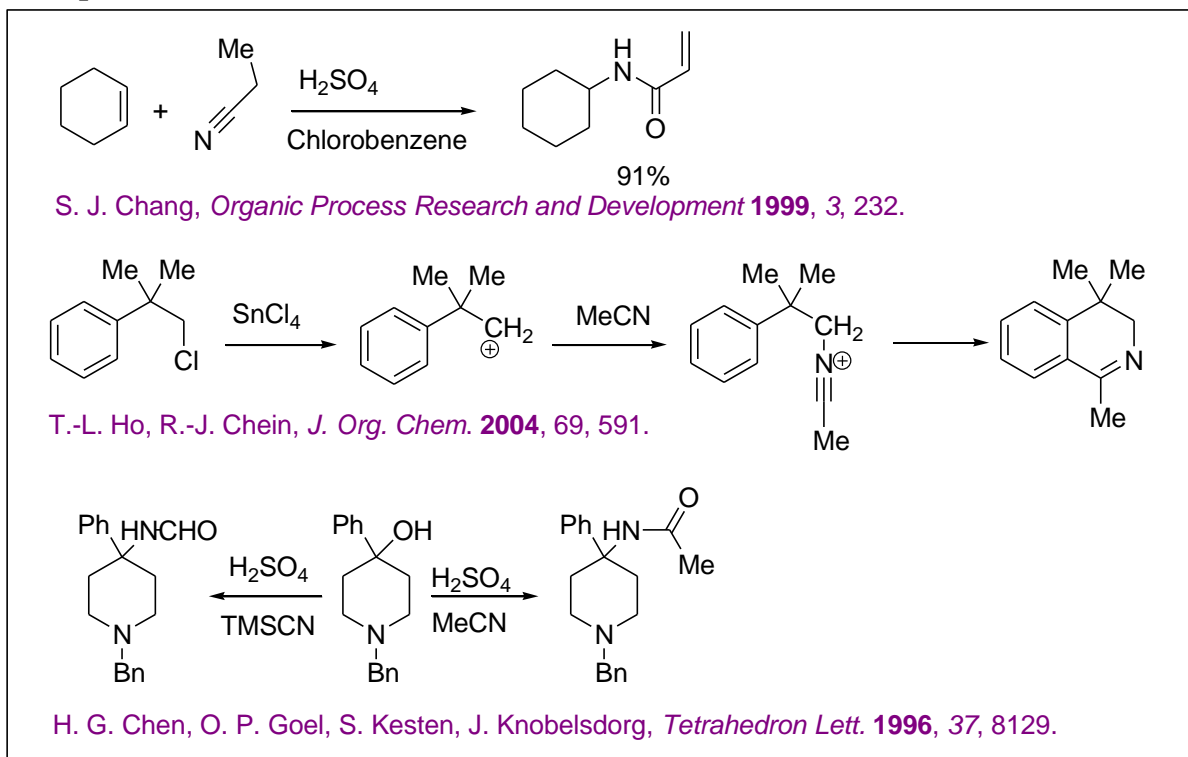


Mechanism

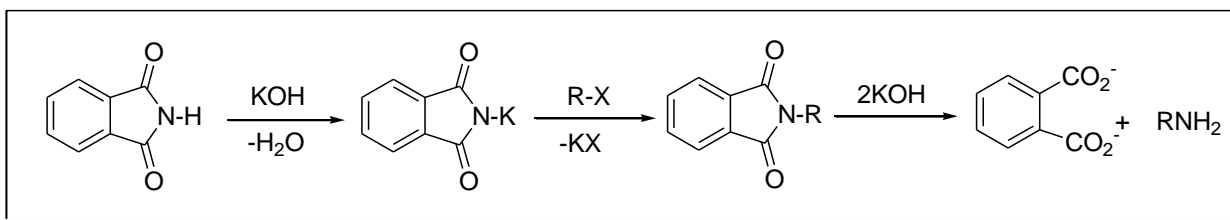


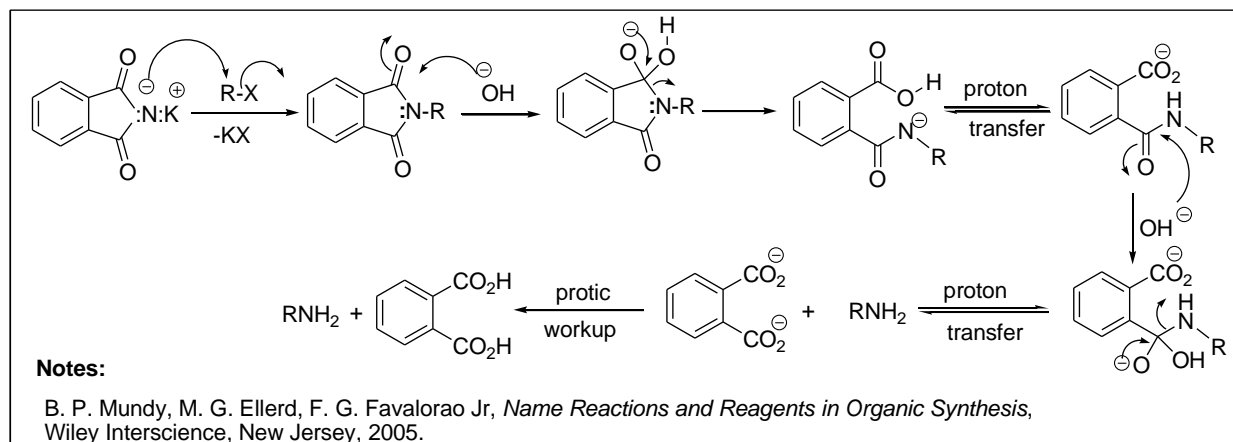
Scheme 1

tertiary carbocation is formed which is attacked by the nitrile to give a quaternary ion. The latter is decomposed by water to provide an amide which, in acidic conditions, is hydrolyzed to give an amine (Scheme 1).

Examples:**4.2.2 Gabriel Synthesis**

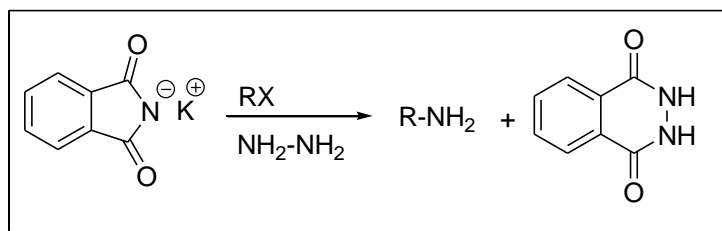
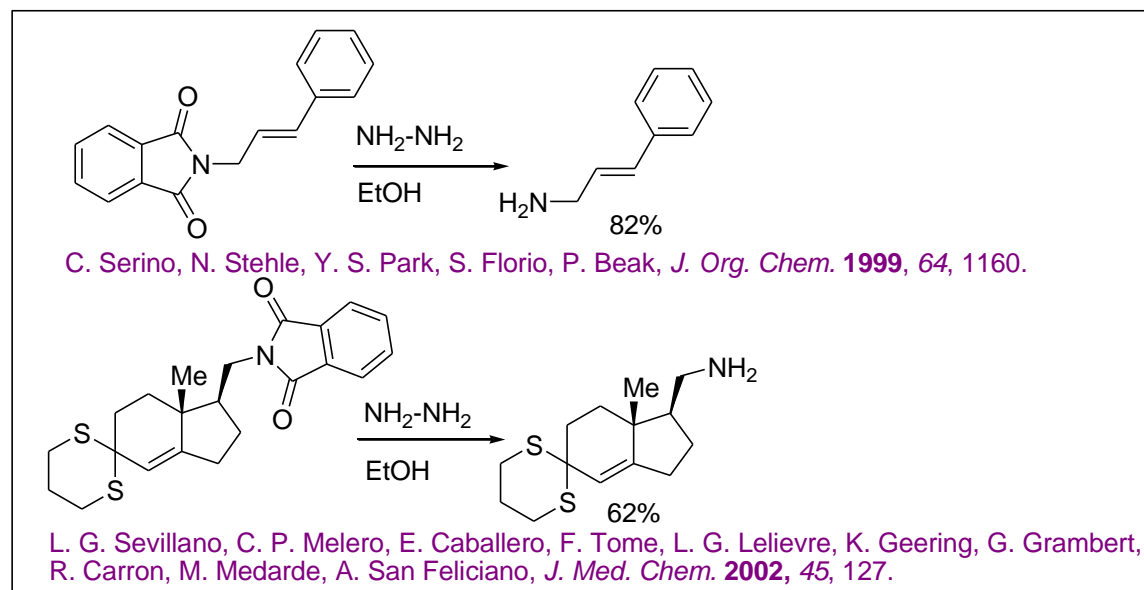
Gabriel method provides an effective route for the synthesis primary amine. In this reaction, phthalimide, having an acidic N-H group, reacts with base to afford a nitrogen containing anion that, as a nucleophile, undergoes substitution on alkyl halides. The resulting compound on hydrolysis with alkali gives the primary amine (Scheme 2).



Mechanism


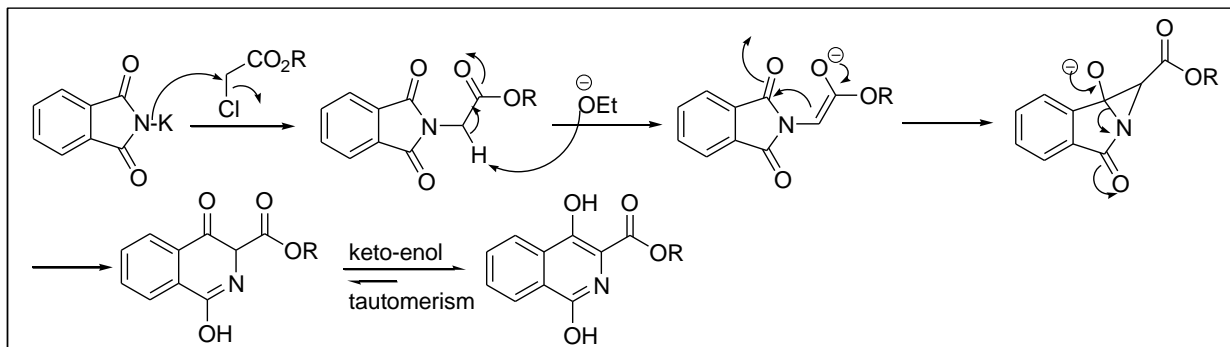
Scheme 2

The use of hydrazine to release the primary amine has been subsequently accomplished. This procedure is called **Manske modification** which finds more useful because it is gentle to other functional groups.


Examples:


4.2.3 Gabriel-Colman Rearrangement

Potassium phthalimide proceeds nucleophilic substitution with α -halo acetate and the resulting product in the presence of base undergoes rearrangement to afford isoquinoline derivatives (Scheme 3).

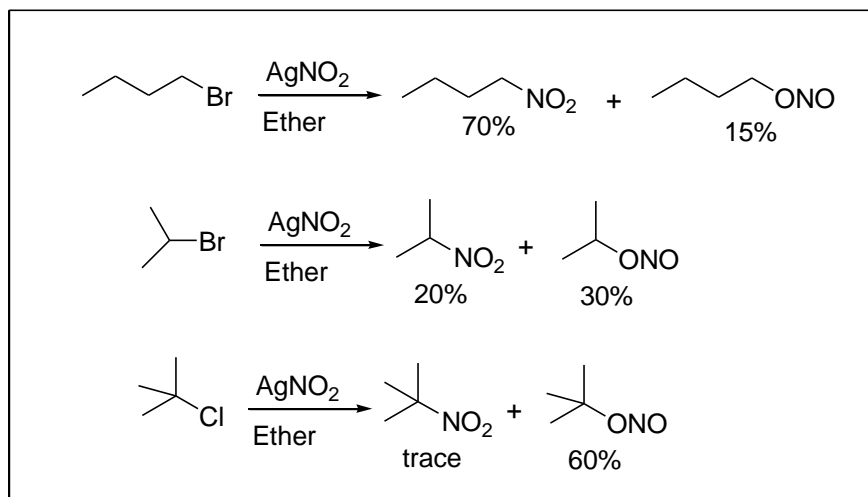


Scheme 3

4.2.4. Reactions of other Nitrogen Nucleophiles

4.2.4.1 Nitrite

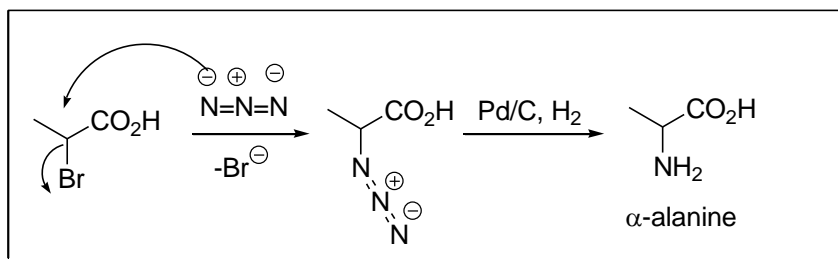
Metal nitrites can react with alkyl halides at both nitrogen and oxygen to give nitro compounds and nitrites, respectively, whose proportions depend on the structure of the reactants and reaction conditions. For example, silver nitrite suspended in ether reacts with alkyl halides to give a mixture of nitro-compounds and nitrites whose proportions depend on the nature of alkyl halides (Scheme 4).



Scheme 4

4.2.4.2 Azide

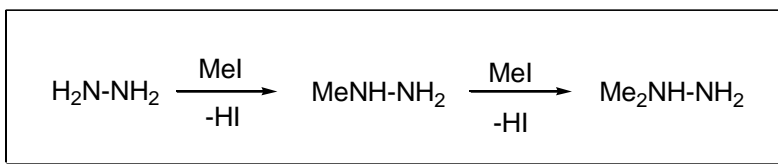
Azides react with halides to give alkyl azides that could be reduced to afford primary amines (Scheme 5).



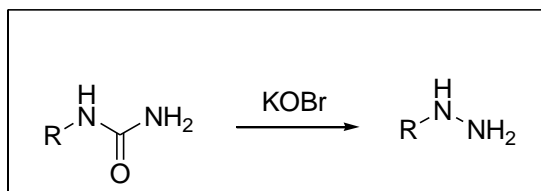
Scheme 5

4.2.4.2 Hydrazine

The reaction of hydrazine with alkyl halides generally gives dialkylated products. This is because the introduction of the first alkyl group increases the nucleophilicity of the alkylated nitrogen, so that further alkylation tends to take place.



Hofmann bromination of alkylurea can give monoalkylated hydrazines in good yield (Scheme 6).

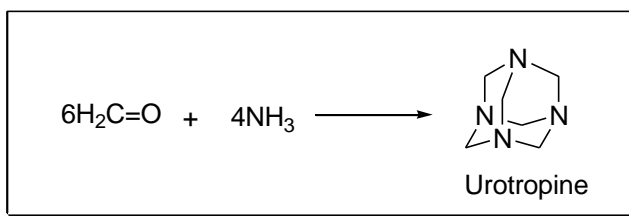


Scheme 6

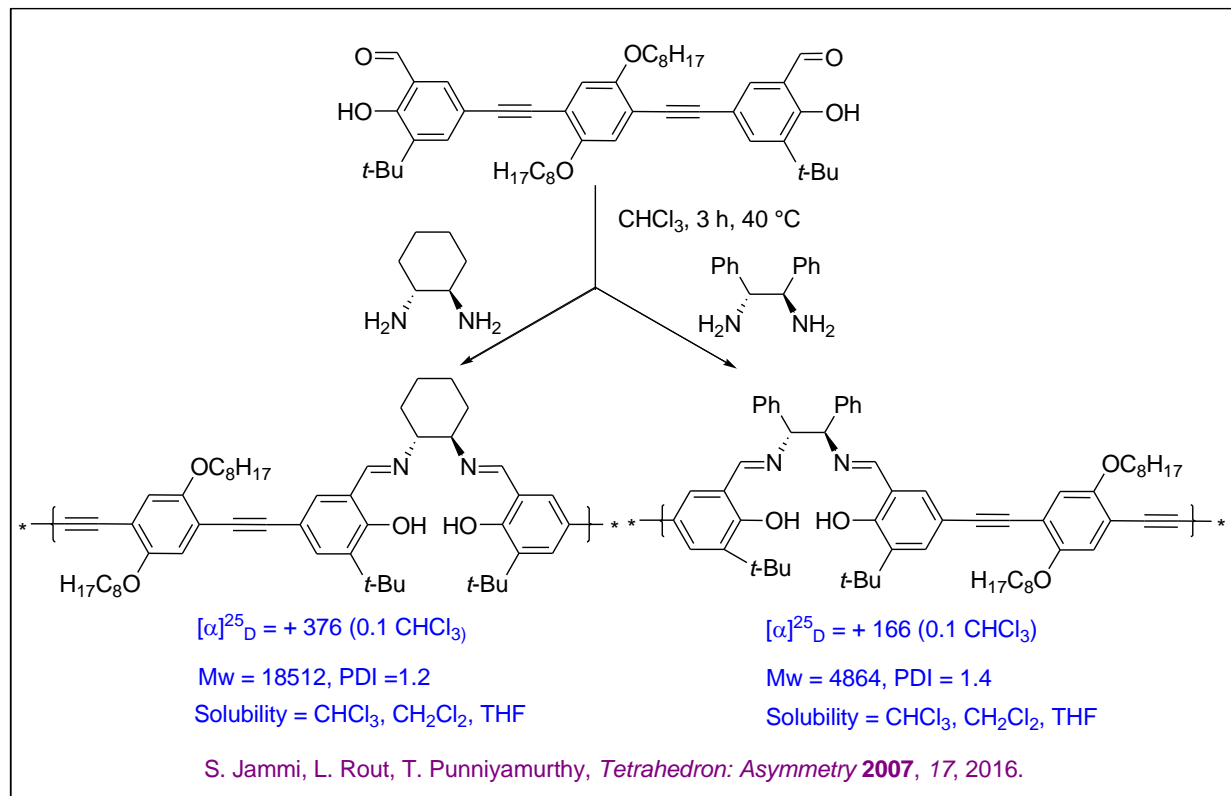
4.3 Addition of Nitrogen Nucleophiles to Unsaturated Carbon

4.3.1 Reactions with Aldehydes and Ketones

The condensation of aldehydes with amines finds wide applications. The fate of the adduct depends on the structure of the aldehydes, amine, and the reaction conditions. For examples, formaldehyde reacts with ammonia to give urotropine (hexamethylenetetramine).



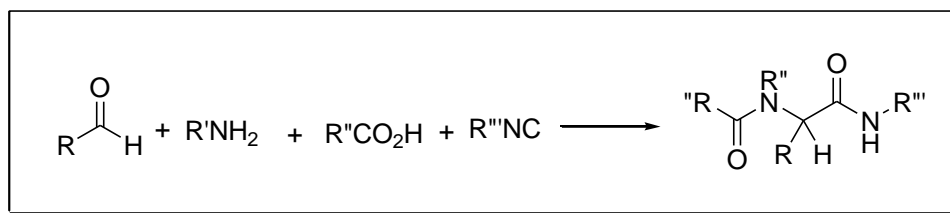
Aromatic aldehydes generally provide condensation products. This strategy has been used to construct stereoregular chiral main chain polymers from optically active diamines and dialdehydes with excellent yield which are otherwise difficult to access by other methods (Scheme 7).



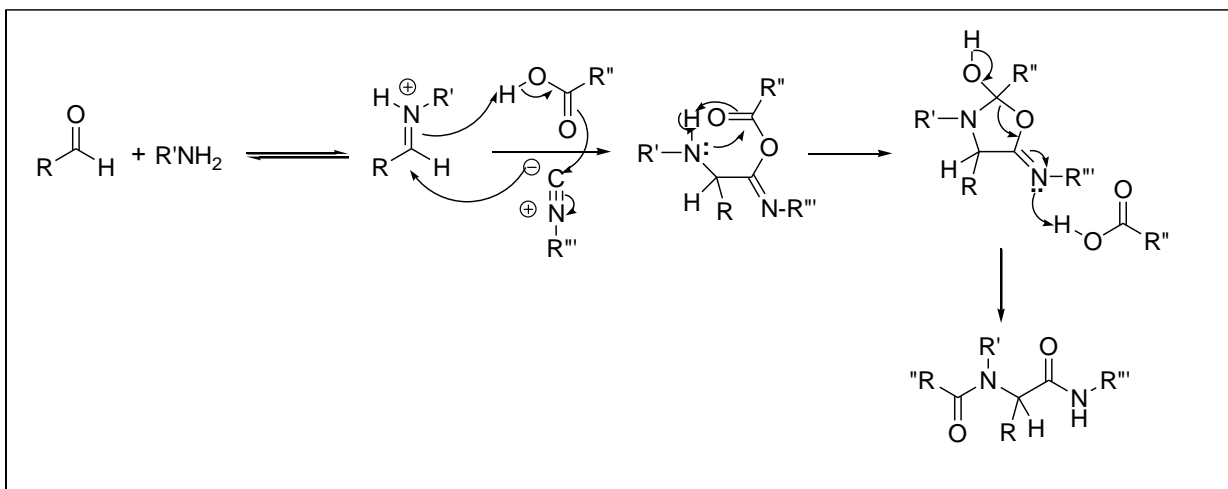
Scheme 7

4.3.1.1 Ugi Reaction

The four-component condensation of isocyanide, a carboxylic acid, an aldehydes or ketone and ammonia or amine gives bisamide (Scheme 8). The product formation probably takes place from a reaction between carboxylic acid, the isocyanide, and the imine formed from the aldehydes or ketone and ammonia or the primary amine. The use of N-protected amino acids allows the reaction to be used for peptide synthesis.

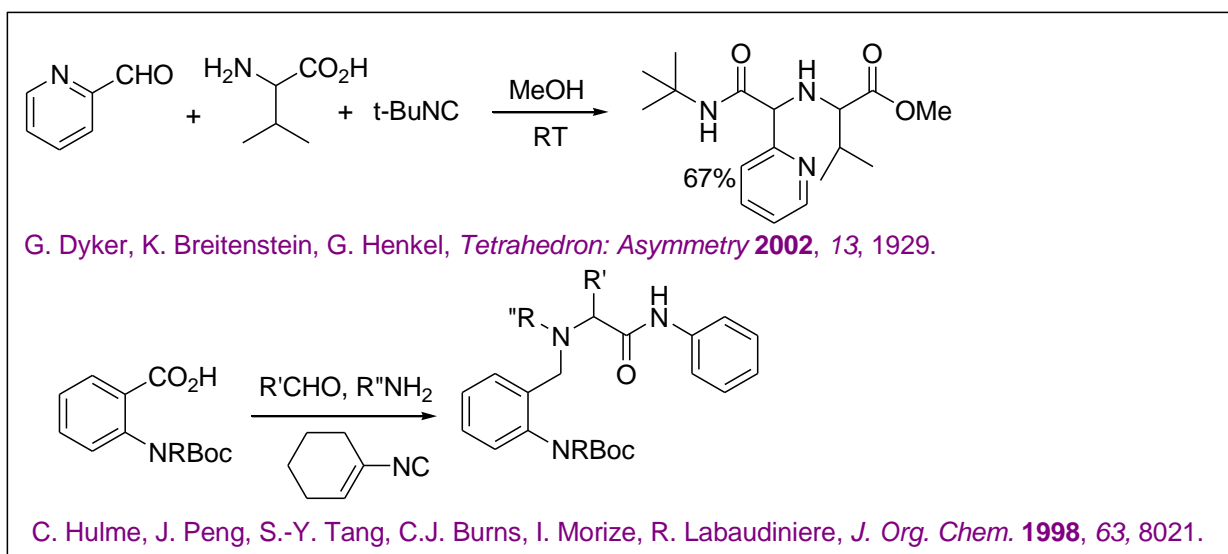


Mechanism



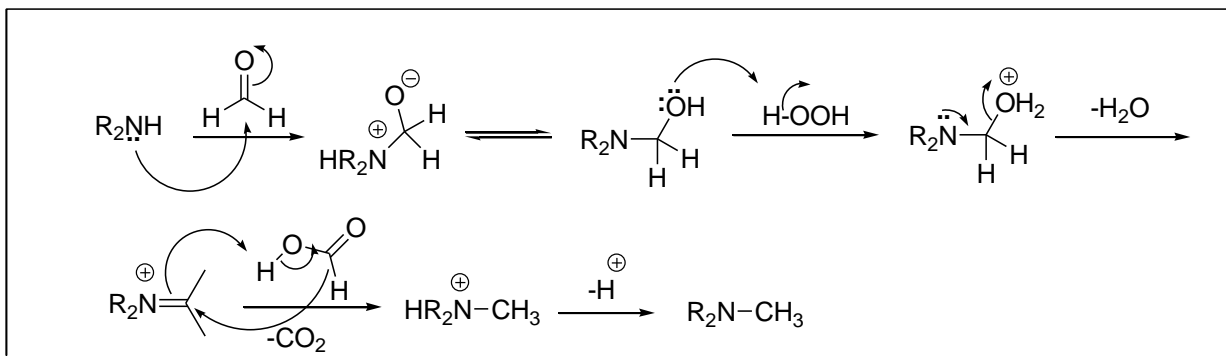
Scheme 8

Examples:



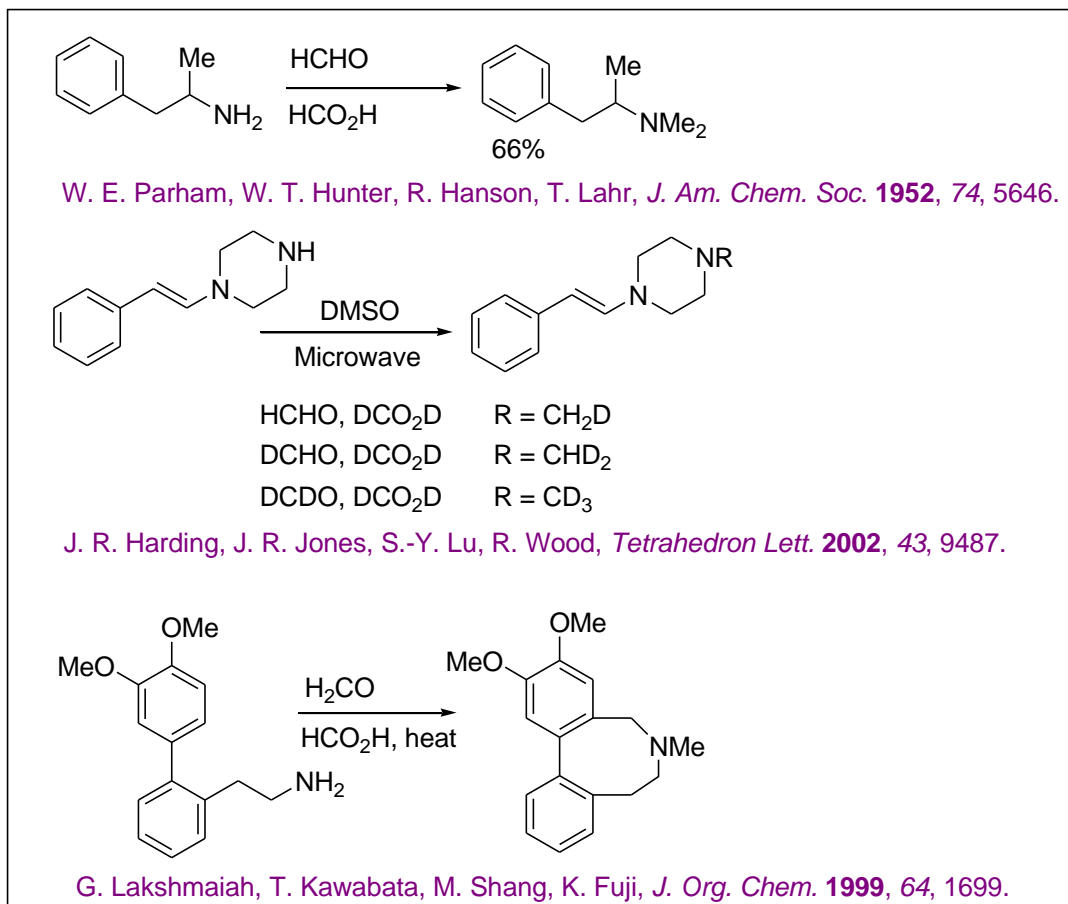
4.3.1.2 Eschweiler-Clarke (Clark) Methylation

Secondary amines could be readily methylated using the combination of formaldehyde and formic acid under heating. This process has been extensively used in total synthesis (Scheme 9).



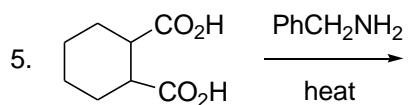
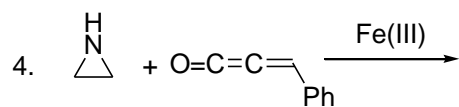
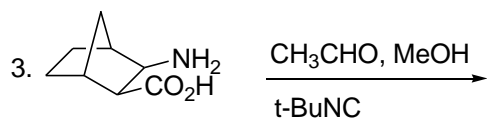
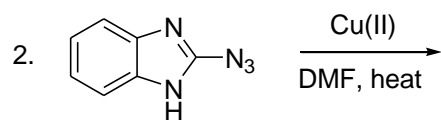
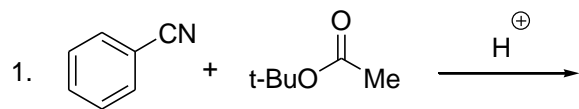
Scheme 9

Examples:

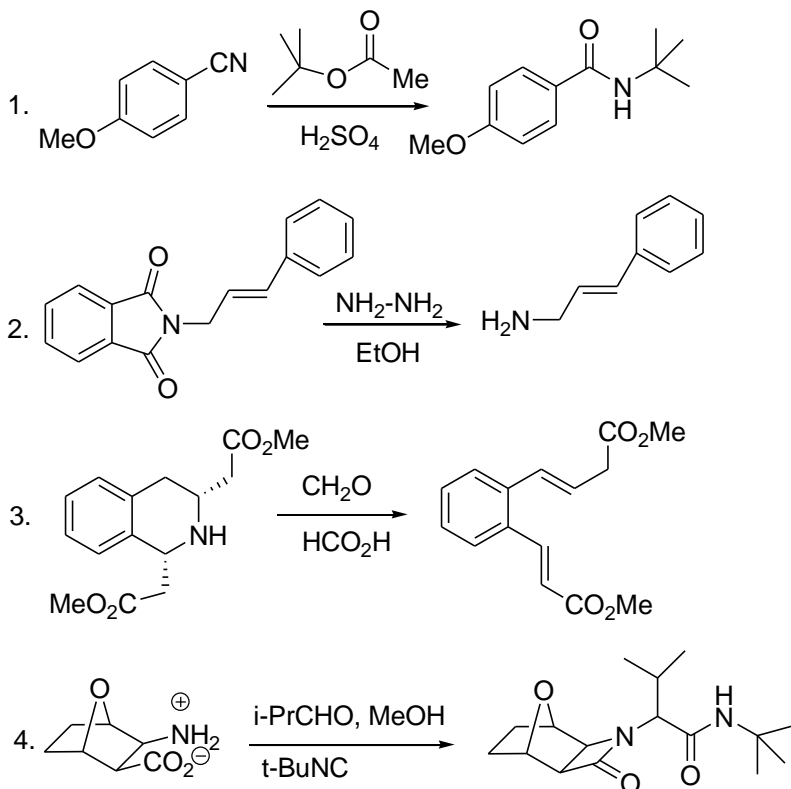


Problems:

A. Complete the following.



B. Formulate mechanisms for the following reactions.



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

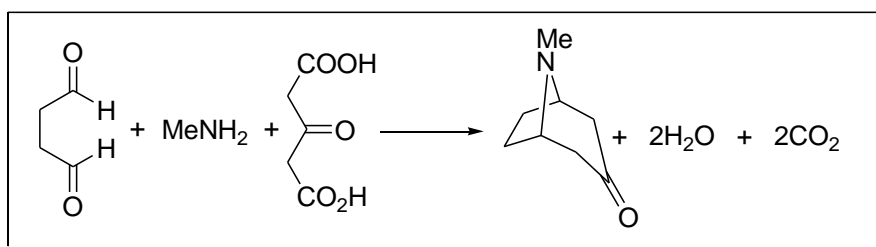
B. P. Mundy, M. G. Ellerd, F. G. Favalaro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.

J. March, *Advanced Organic Chemistry*, 4th ed, Wiley Interscience, New York, 1992.

Lecture 11 Carbon-Nitrogen Bonds Formation II

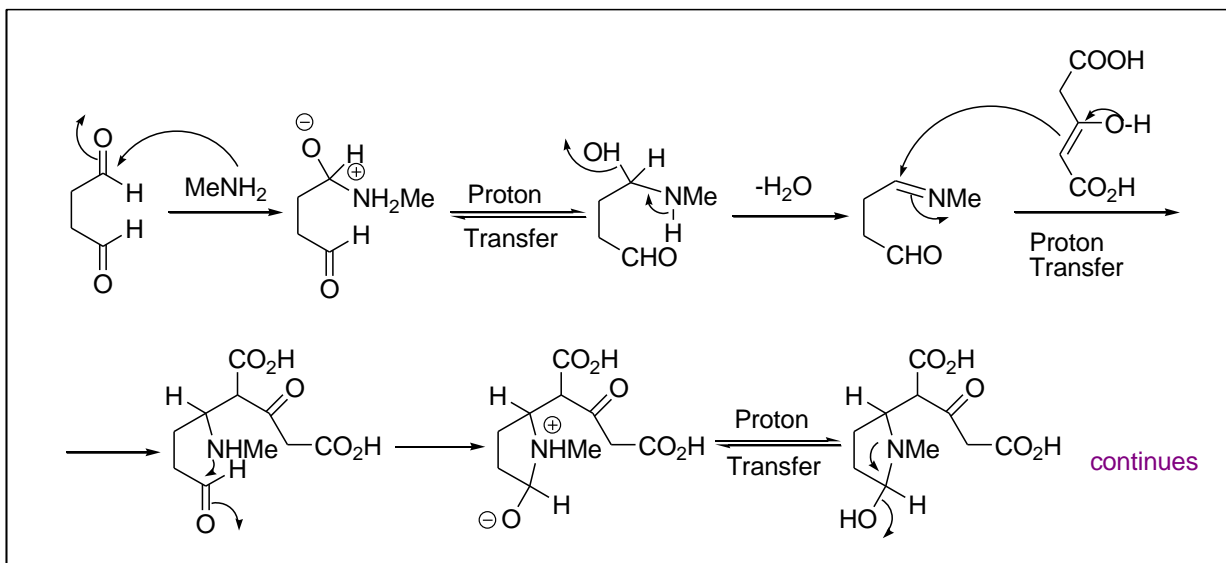
4.3.1.3 Robinson-Schopf Reaction

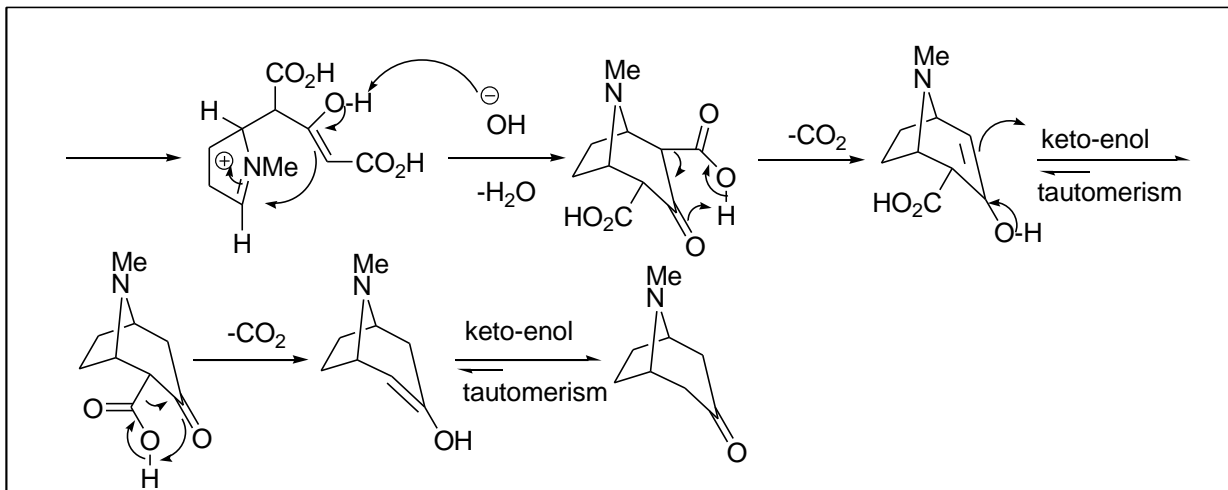
Compounds that are enolic or potentially enolic react with a mixture of aldehydes and primary or secondary amine in the presence of an acid to afford amine salt which, after basification, gives an aminomethyl derivative. The reaction has found wide applications in organic synthesis. For example, the synthesis of tropinone can be accomplished in 90% yield. This reaction follows biomimetic approach to forming alkaloids.



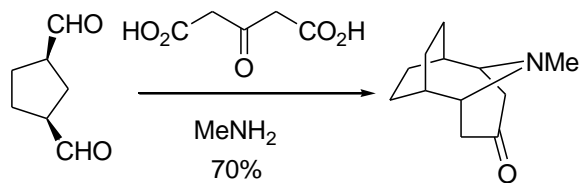
Mechanism

The synthesis involves two Mannich reactions followed by spontaneous decarboxylation of the dibasic β -keto acid.

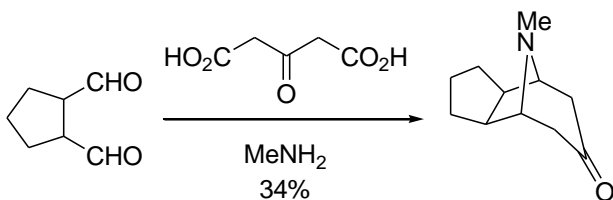




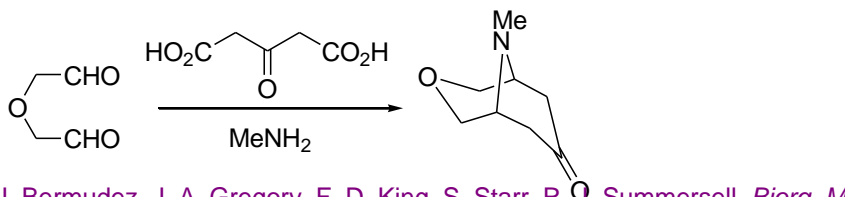
Examples:



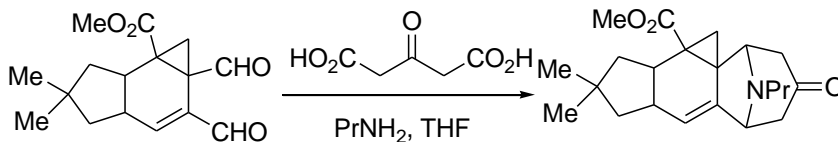
L. A. Paquette, J. W. Heimaster, *J. Am. Chem. Soc.* **1966**, 88, 763.



O. L. Chapman, T. H. Koch, *J. Am. Chem. Soc.* **1966**, 88, 763.



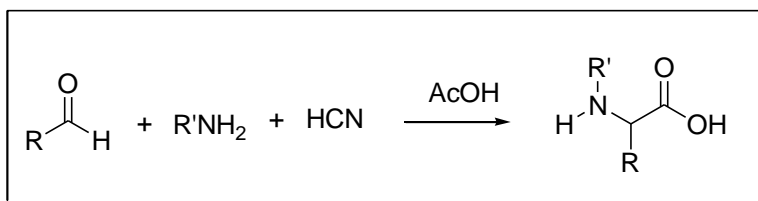
J. Bermudez, J. A. Gregory, F. D. King, S. Starr, R. G. Summersell, *Biorg. Med. Chem. Lett.* **1992**, 2, 519



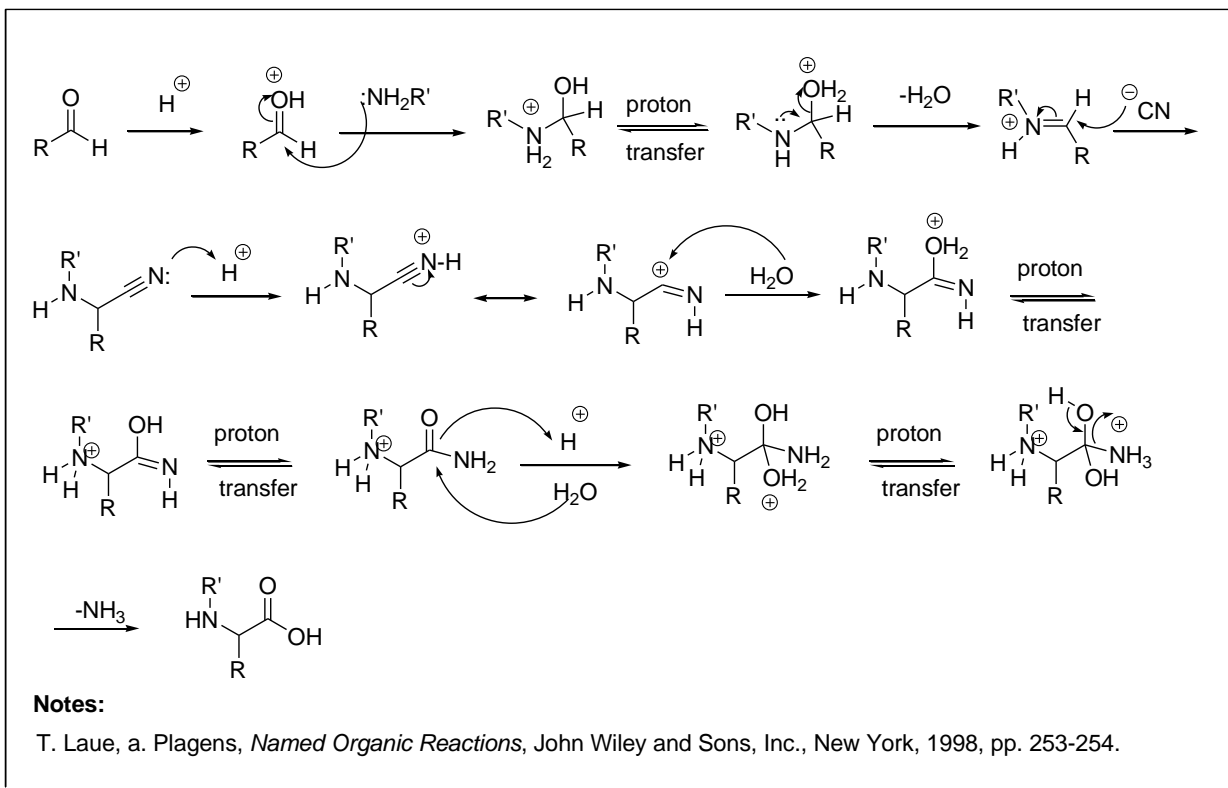
T. Jarevang, H. Anke, T. Anke, G. Erkel, O. Sterner, *Acta Chemica Scandinavia* **1998**, 52, 1350.

4.3.1.4 The Strecker Synthesis

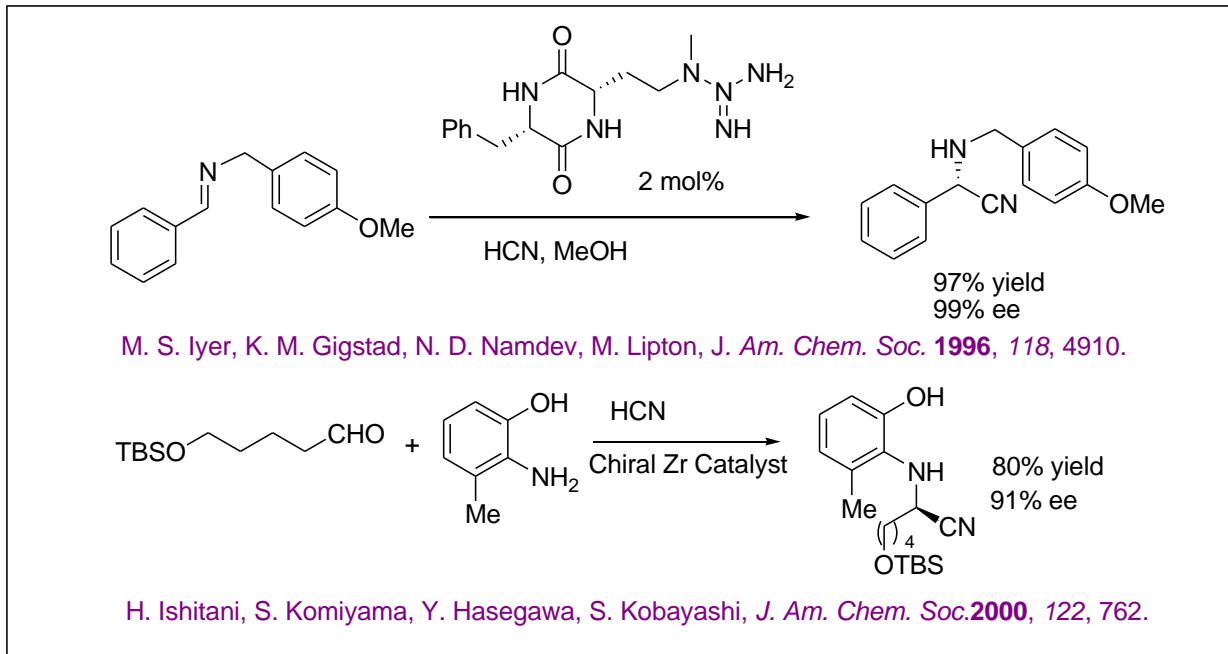
The condensation of an aldehyde with amine gives imine that can undergo reaction with cyanide ion *in situ* to give an α -aminonitrile which on hydrolysis gives α -amino acid. This process constitutes a useful method for α -amino acid synthesis. Asymmetric version has also been explored.



Mechanism

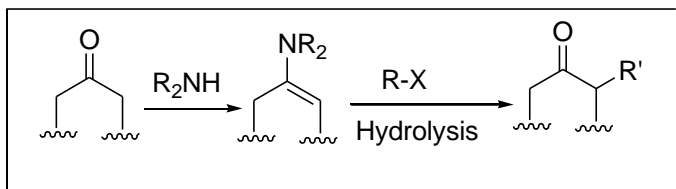


Examples:



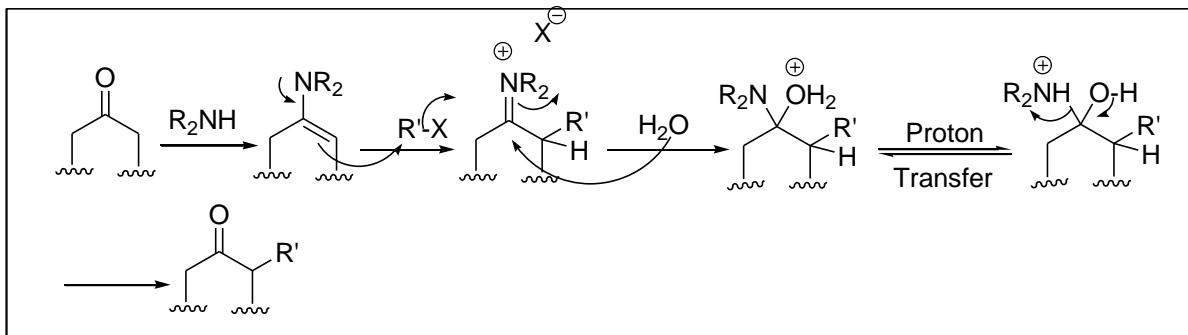
4.3.1.4 Stork Enamine Synthesis

Enamines are specific enol equivalents to alkylate aldehydes and ketones. They are formed when aldehydes or ketones react with secondary amines.



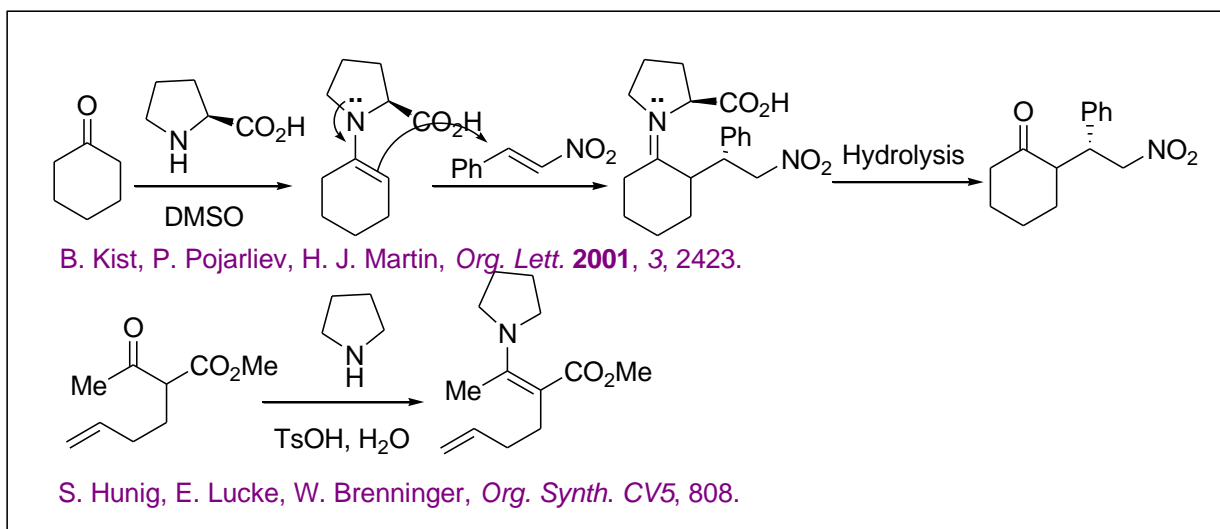
Mechanism

The mechanism shows how they react with alkylating agent to form a new carbon-carbon bond.



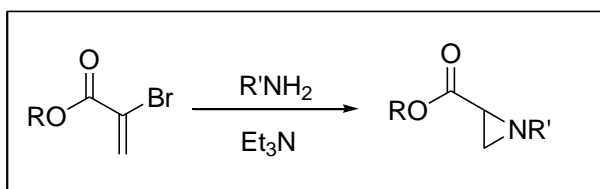
The overall process amounts to an enolate alkylation. The reaction conditions are mild and no self-condensation is observed.

Examples:

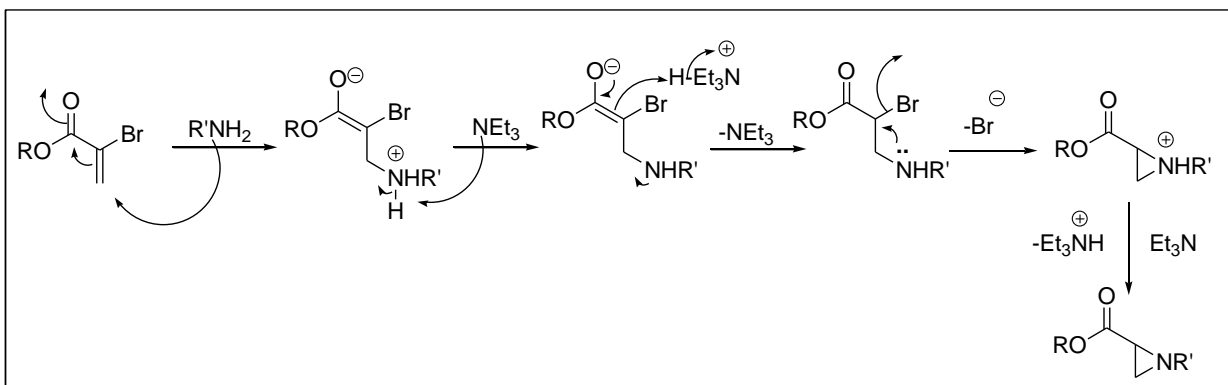


4.3.1.5 Gabriel-Cromwell Reaction

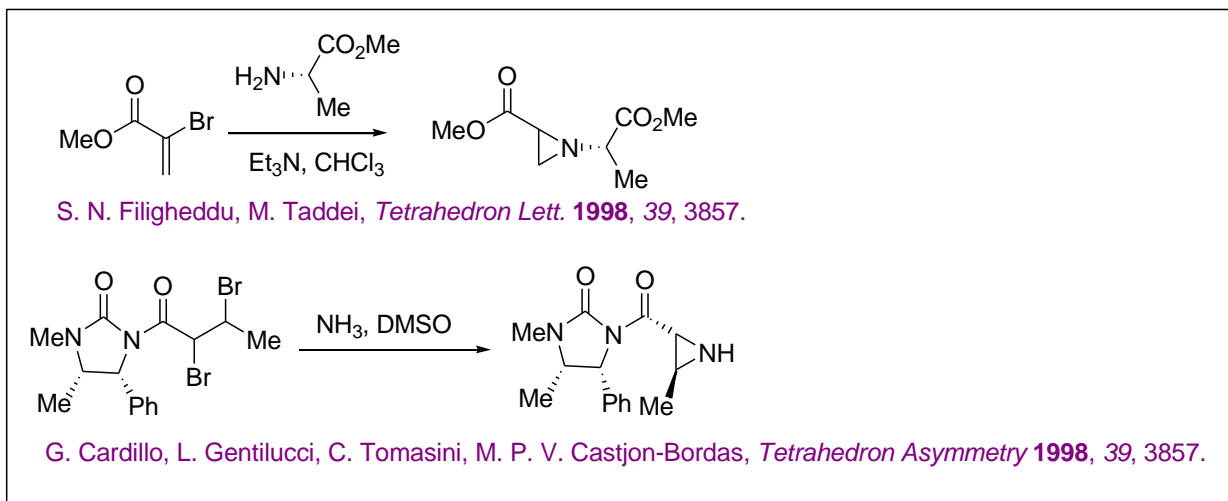
Amines react with α -bromoacrylates to give aziridines in the presence of base.



Mechanism

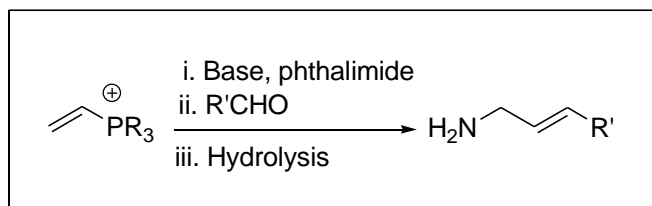
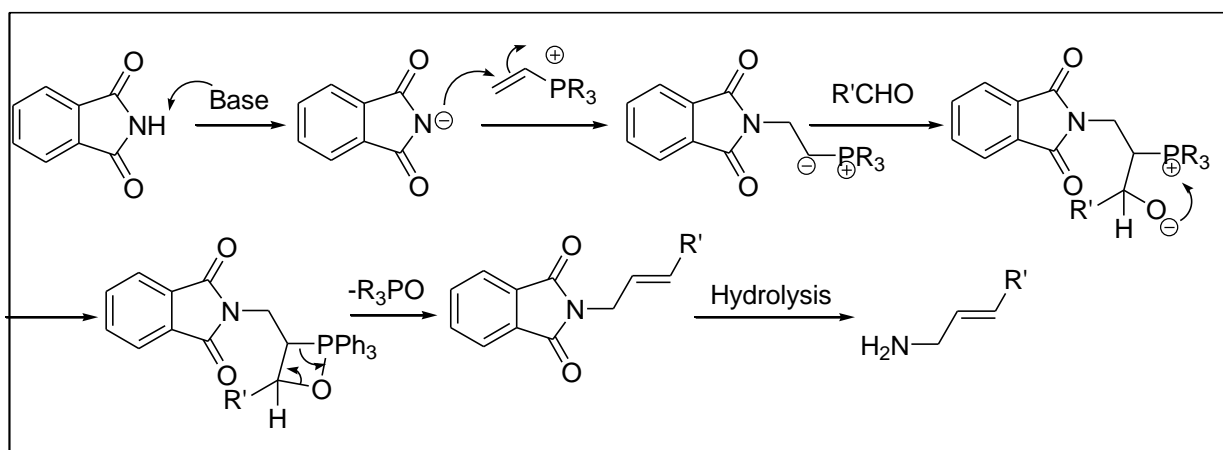


Examples:



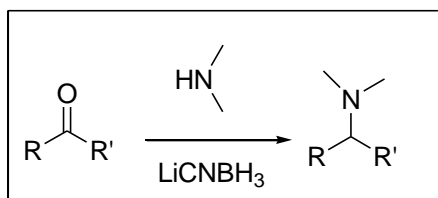
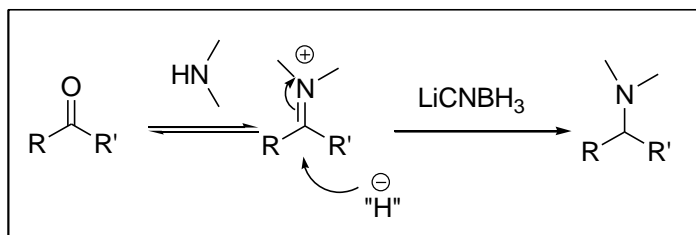
4.3.1.6 Schweizer Allyl Amine Synthesis

This reaction involves the combined use of Gabriel and Wittig chemistry for the synthesis of allyl amines from phthalimide, vinyl phosphonium salt and aldehyde in the presence of base.

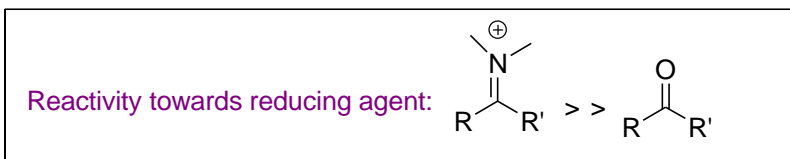
**Mechanism**

4.3.1.7 Borche Reduction

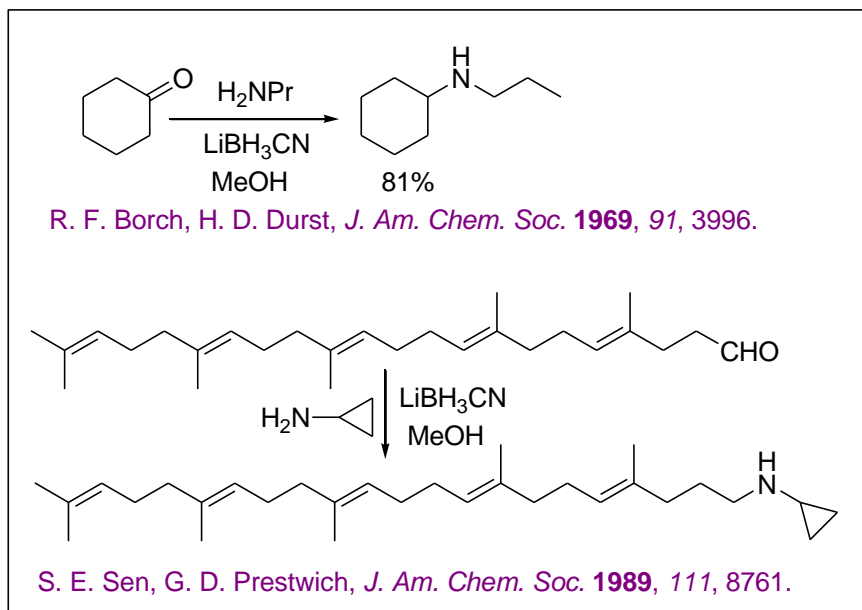
Aldehydes and ketones react with amines to give imine that could be reduced using LiCNBH_3 ($\text{M} = \text{Li, Na}$) to amines.

**Mechanism**

The success of this method rests on the much greater reactivity of imine salt compared to carbonyl group of aldehydes and ketone to the reducing agent.

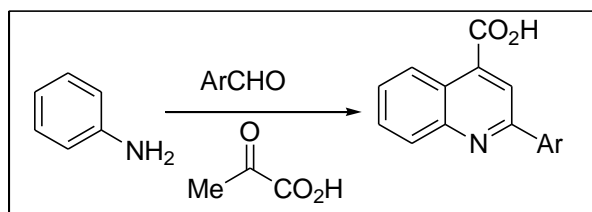


Examples:

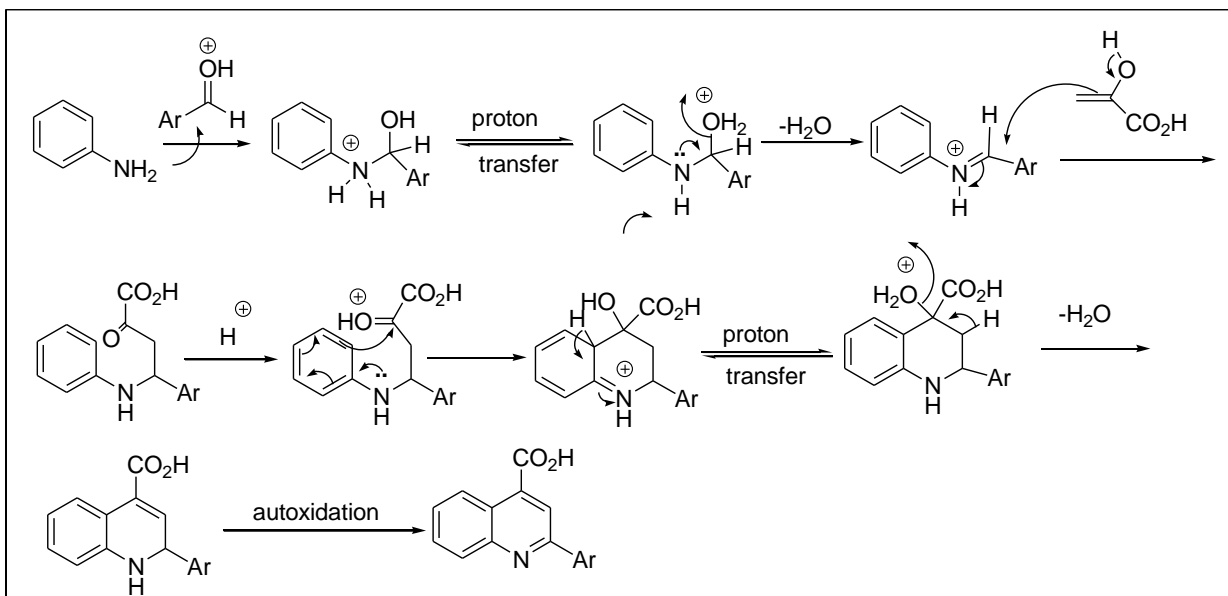


4.3.1.8 Doebner Reaction (Beyer Synthesis)

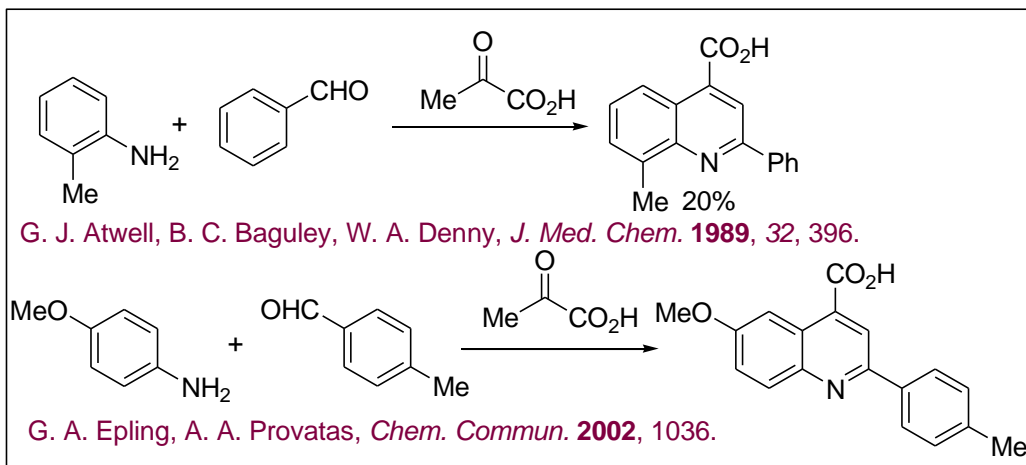
Aryl amine reacts with aldehydes and enolizable carbonyl compounds via condensation followed by aromatic electrophilic substitution and autoxidation to give quinolines.



Mechanism

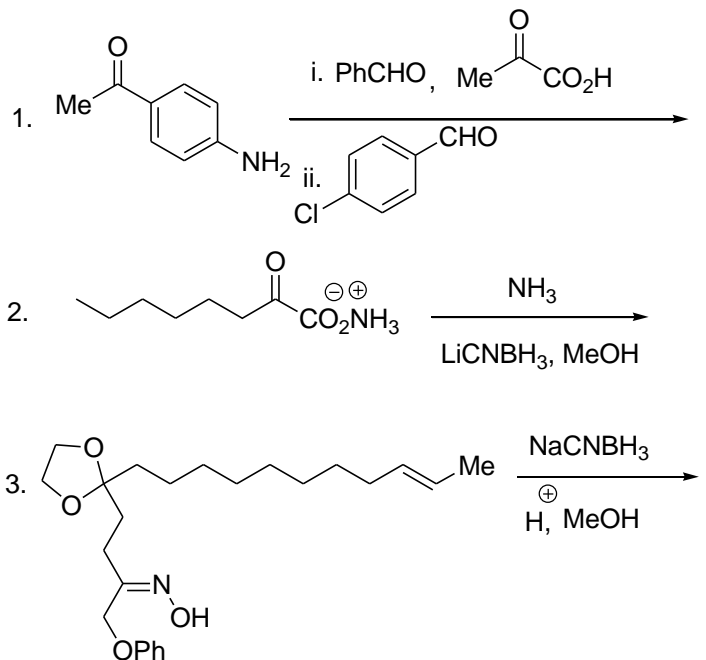


Examples:

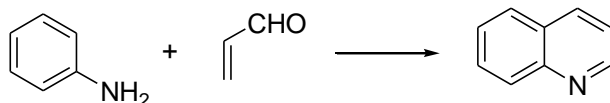


Problems:

A. What major products would you expect from the following reactions?



B. How will you carry out the following conversion? Explain with mechanism.



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

B. P. Mundy, M. G. Eller, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.

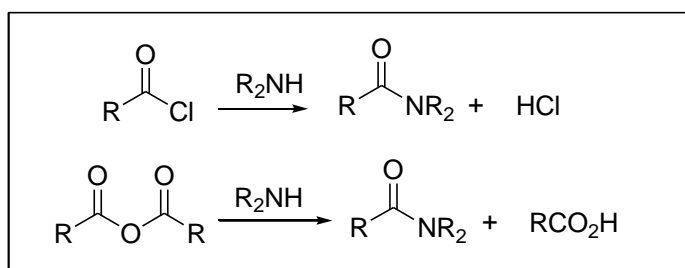
Lecture 12 Carbon-Nitrogen Bonds Formation III

4.4 Substitution by Nucleophilic Nitrogen at Unsaturated Carbon

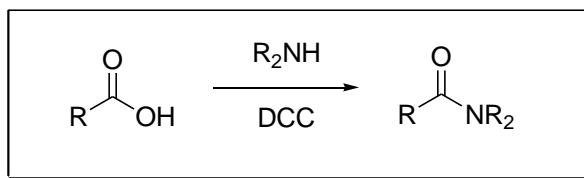
These reactions are analogous to the base-catalyzed hydrolysis of the carbonyl compounds. The order of reactivity of the compounds having different leaving groups is: acid halide > anhydride > ester > amide.

4.4.1 Reactions of Ammonia and Amines

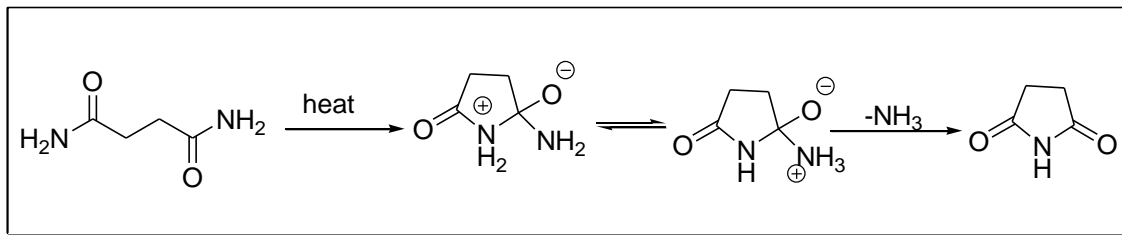
- Amines readily react with acylating agents such as acid chlorides and acid anhydrides in the presence of base to give amides. These are the general practical methods used for the acylation reactions.



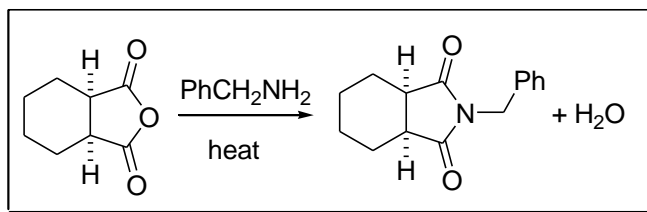
- The condensation of carboxylic acid with amines using DCC is also a popular route for the amide formation which will be discussed in the section on peptide synthesis. DCC is converted into urea which can be separated by filtration.



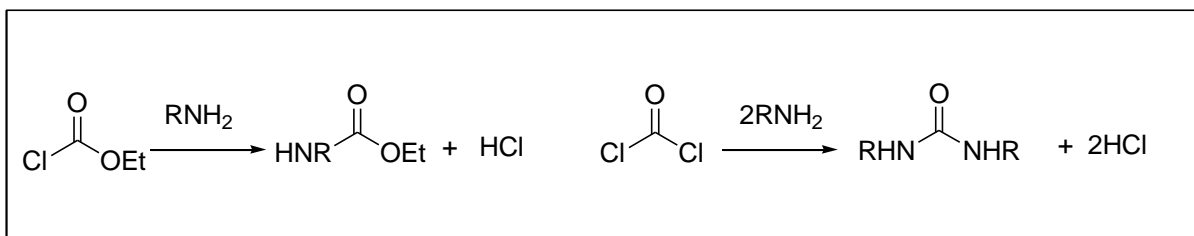
- Amides are weak nucleophiles and the further acylation occurs very slowly that leads to isolation of the monoacylated product. However, intramolecular displacement can take place if a five or six membered ring formation is possible. For example, heating of the acyclic diamide of succinic acid affords succinimide in good yield.



- Cyclic imides can be easily prepared (practical method) by heating a mixture of acid anhydride and amine.

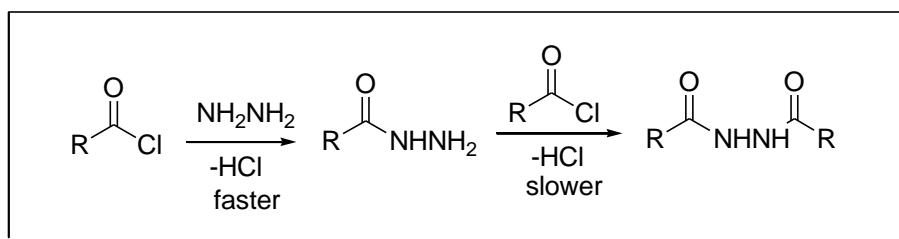


- The reaction of amines with ethyl chloroformate and carbonyl chloride affords urethanes and ureas, respectively.

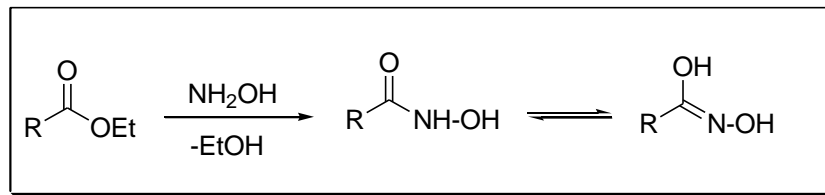


4.4.1 Reactions of other Nitrogen Nucleophiles

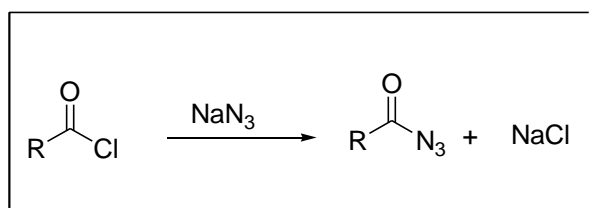
- Acid chloride, anhydrides and esters react with hydrazine to provide acid hydrazides which are less nucleophilic and the further acylation requires a more vigorous conditions. Thus, monoacylated product can be obtained in high yield.



- Hydroxylamine reacts with carboxylic acid derivatives giving hydroxyamic acids.



- Reaction of acid chloride with sodium azide gives acid azide which is the substrate precursor for Curtius rearrangement.

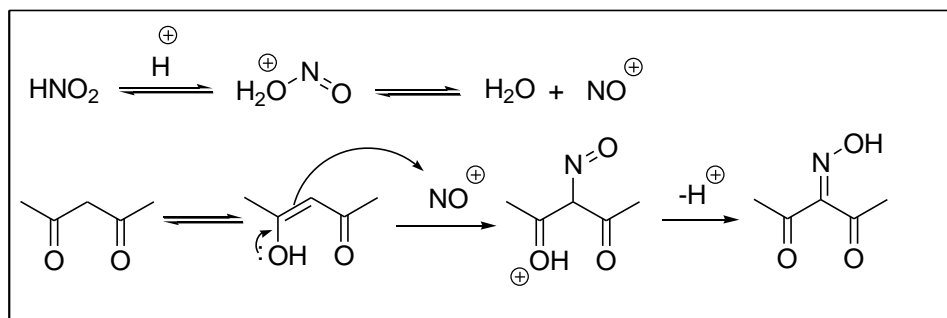


4.5 Reactions of Electrophilic Nitrogen

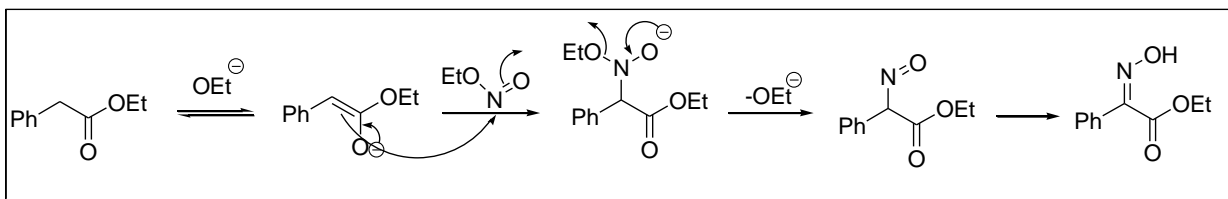
Four electrophilic nitrogen containing groups, nitroso (-NO), nitro (-NO₂), arylazo (-N=NAr), and arylimino (=NAr), could be bonded to aliphatic carbon *via* C-N bond formation.

4.5.1 Nitrosation

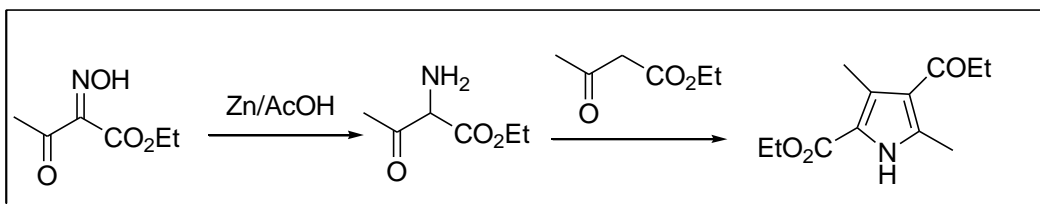
The reactions of nitroso group may be done by two ways. In first, enols react with nitrous acid or an organic nitrite by an acid-catalyzed process. The electrophile is to be the nitrosonium ion, NO⁺.



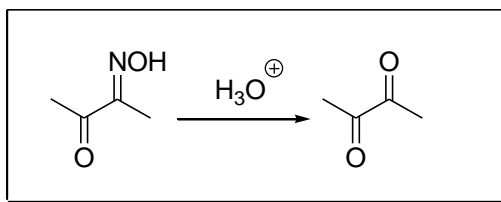
In the second, enolate reacts with the nitrite in a manner similar to the Claisen condensation.



The products have two main synthetic applications. First, several heterocyclic syntheses are performed by reducing α -keto oximes in the presence of compounds with which the products can proceed reaction to give cyclized products such as pyrroles.

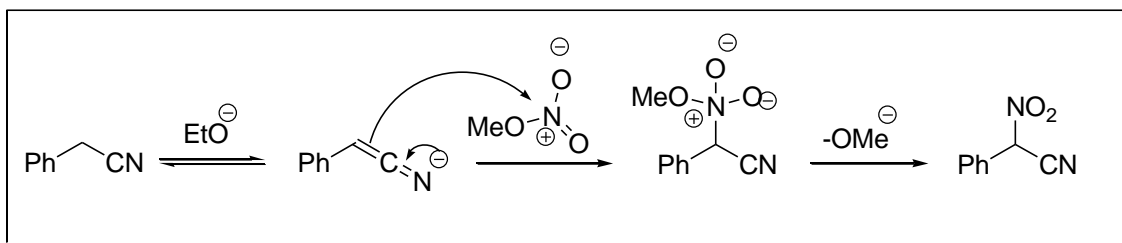


Second, the oxime is hydrolyzed into a carbonyl group.



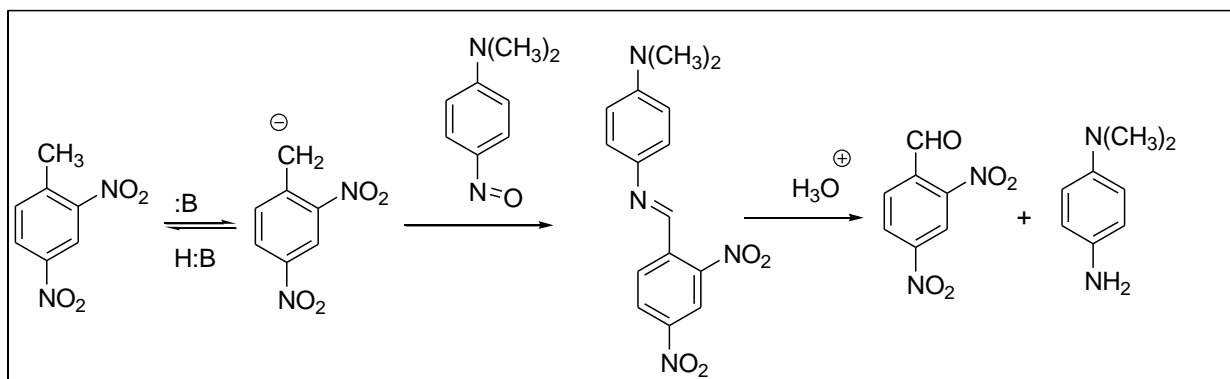
4.5.2 Nitration

Compounds generate enolate react with alkyl nitrate by base-catalyzed procedure. The reaction pathway is similar to that of the base-catalyzed nitrosation process.



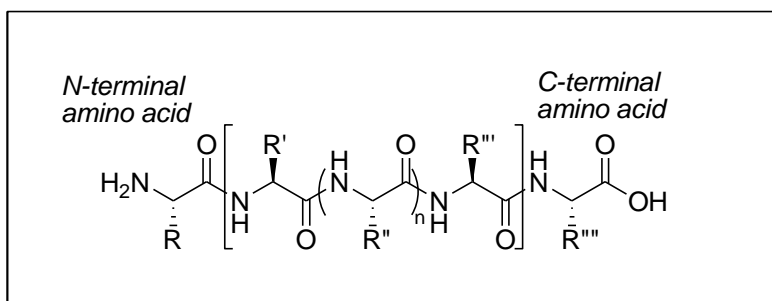
4.5.2 Imine Formation

Compounds that can generate enolates react with aromatic nitroso compounds to give imine which on hydrolysis affords carbonyl group. For example, 2,4-nitrotoluene can be converted into 2,4-dinitrobenzaldehyde by this process.



4.6 α -Amino Acids, Peptides and Proteins

Peptides and proteins are naturally occurring polymers in living systems. They are derived from α -amino acids linked together by amide bonds. The distinction between peptides and proteins is that the polymers with molecular weights less than 10000 are termed peptides and those with higher molecular weights are termed proteins.



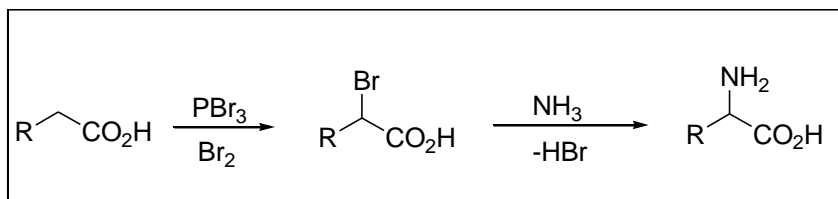
The acid-catalyzed hydrolysis of peptides and proteins provides the constituent α -amino acids which are, except glycine, chiral having L-configuration. The syntheses of peptides followed to date have been based on the reverse of this process. Therefore α -amino acids are of significant importance.

4.6.1 The Synthesis of α -Amino Acids

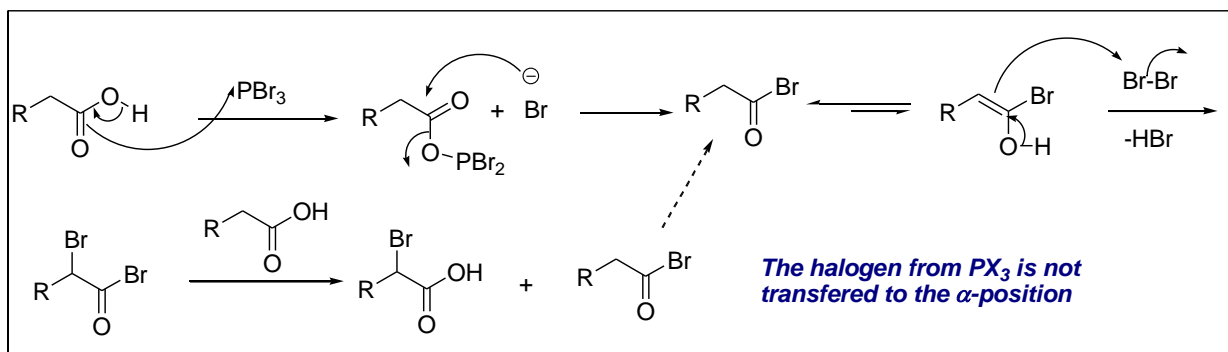
The following are some of the common methods used for the synthesis of α -amino acids.

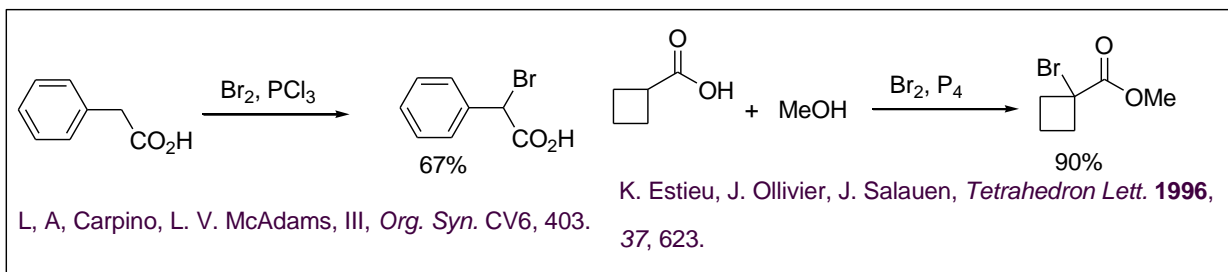
4.6.1.1 From α -Halo acids

The simplest method consists of the conversion of carboxylic acid into its α -bromo-derivative which could be reacted with ammonia to give α -amino acid.

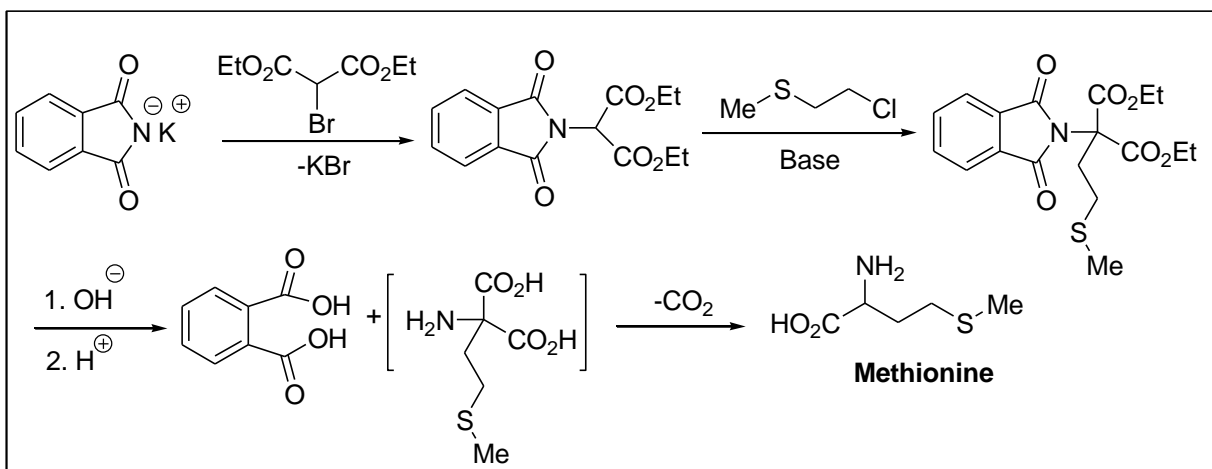


Hell-Volhard-Zelinski reaction is generally employed for the preparation of α -bromo acid. It involves the treatment of the acid with bromine in the presence of a small amount of phosphorus to give acid bromide which undergoes (electrophilic) bromination at the α -position *via* its enol tautomer. The resulting product exchanges with more of the acid to afford α -bromo acid together with more acid bromide for the further bromination.

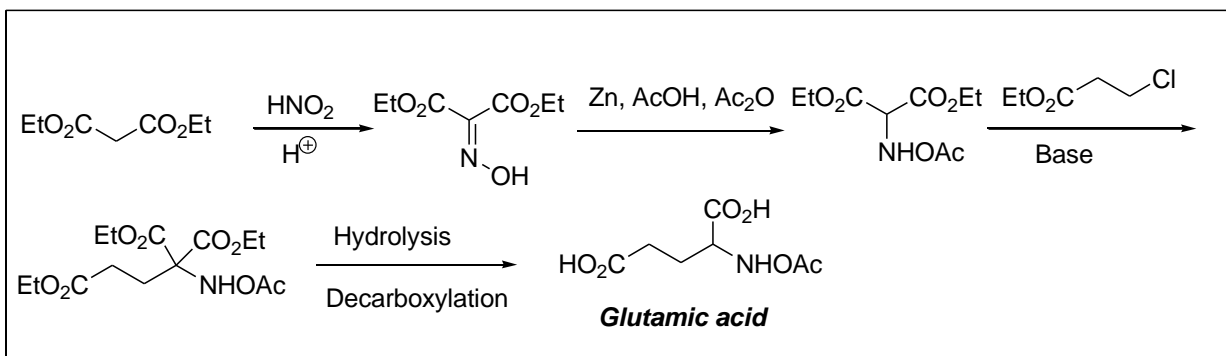




The amino group may also be introduced by **Gabriel procedure** (4.2.2) which gives better yield compared to that of the above described reaction with ammonia as an aminating agent.

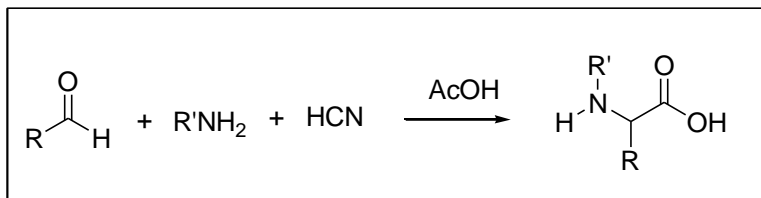


The amino group can also be introduced *via nitrosation* (4.5.1) followed by reduction and hydrolysis processes.



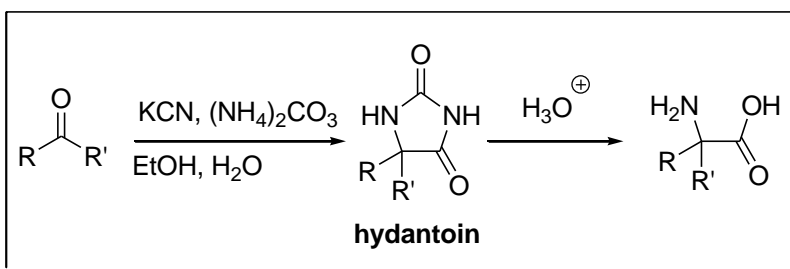
4.6.1.2 The Strecker Synthesis

The condensation of aldehydes with amine gives imine that can undergo reaction with cyanide ion *in situ* to give an α -aminonitrile which on hydrolysis gives α -amino acid. For mechanism see 4.3.1.4.

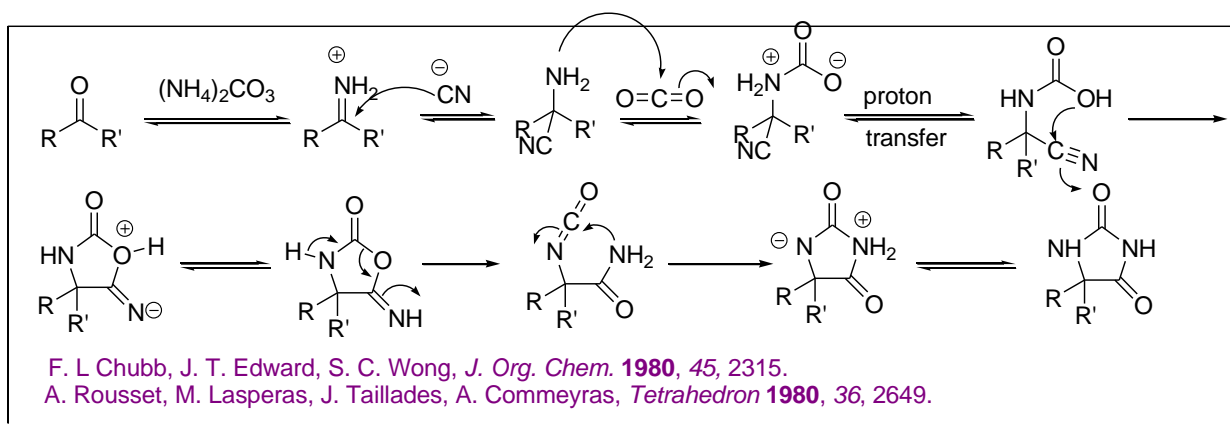


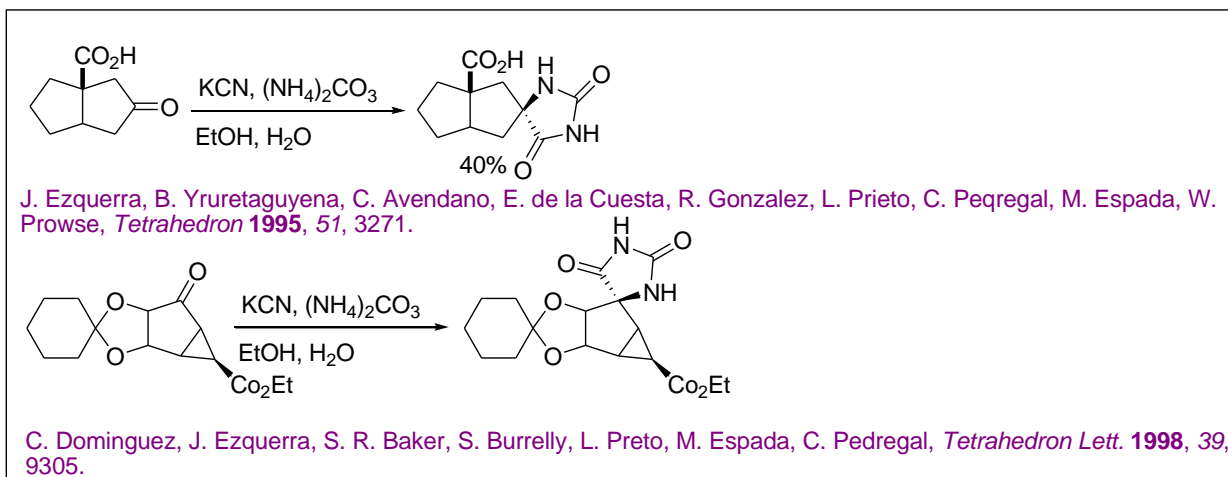
4.6.1.3 Bucherer-Bergs Reaction

Ketones proceed reaction with ammonium carbonate in presence of cyanide ion to afford hydantoin that could be hydrolyzed to α -amino acid.



Mechanism

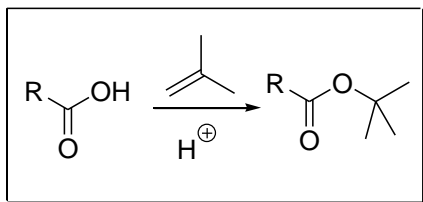


Examples:**4.6.2 The Synthesis of Peptides**

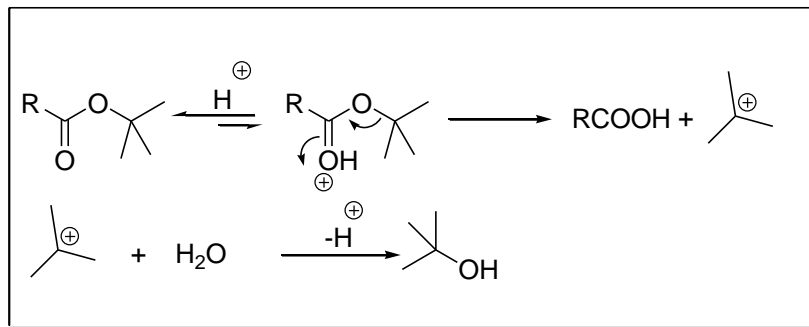
In the synthesis of peptides one amino acid is protected at its amino end with group Y and the second is protected at its carboxyl end with a group Z. The condensation of these protected amino acid derivatives is then carried out using dehydrating agent such as DCC to generate peptide bond. As per the requirement, one of the protecting groups is now removed and a third protected amino acid is introduced to the second peptide bond. Repetition of the procedure affords the desired peptide.

Protection and Deprotection of Carboxyl Group

- The carboxyl group is normally protected by converting it into its *t*-butyl ester using isobutylene in the presence of sulfuric acid.

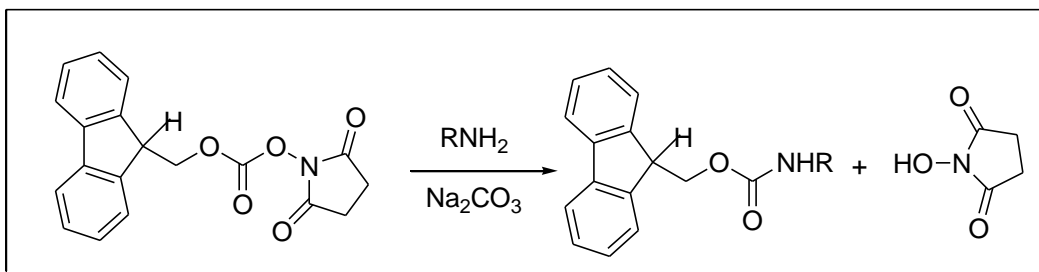


- The protecting group could also be easily removed using mild acid hydrolysis via the formation of a *t*-butyl carbocation.

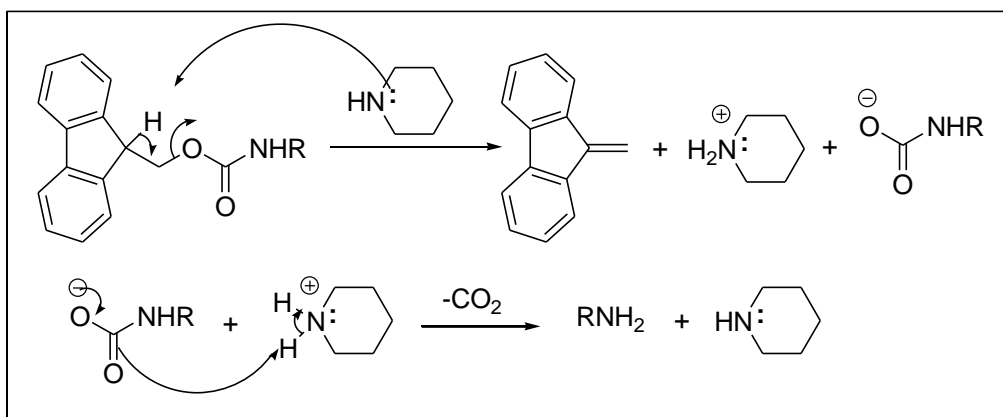


Protection and Deprotection of Amino Group

- (9-Fluorenyl)methoxycarbonyl group (Fmoc) is commonly used as protecting group for the protection of the amino group of amino acid which can be facilitated using Na_2CO_3 in a mixture of DME and water.

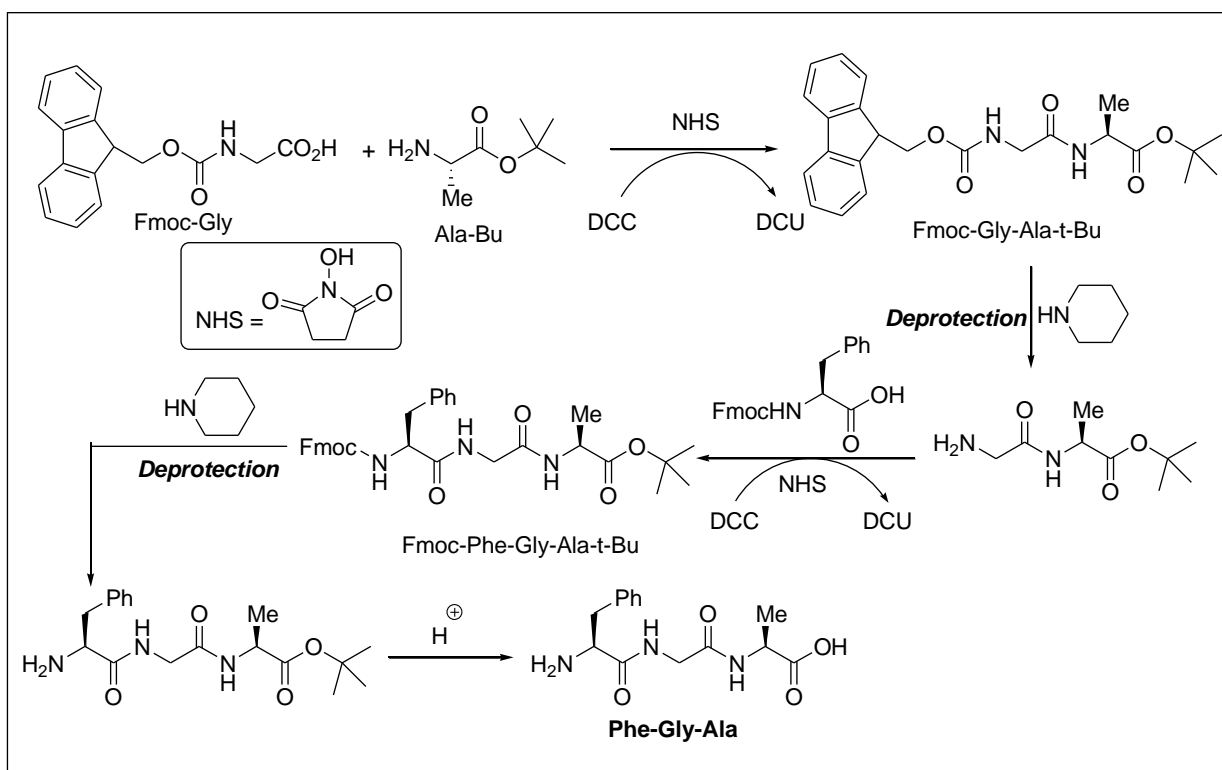


- The important characteristic of this protecting group is that it can be easily removed by treatment with amine base, such as piperidine.

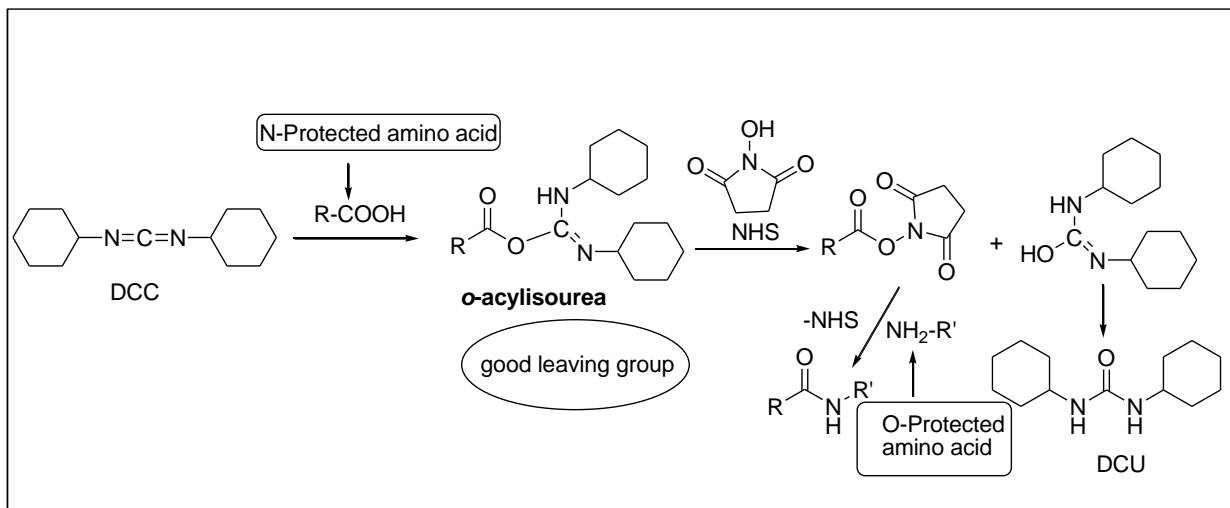


Synthesis of Tripeptide

Let us try the synthesis a tripeptide having Phe-Gly-Ala sequence. Coupling of Fmoc-glycine to the free amino group of t-butyl protected alanine could be effected by the reagent 1,3-dicyclohexylcarbodiimide (DCC) in the presence of N-hydroxysuccinimide (NHS). DCC is converted into DCU. The resulting protected dipetide could be deprotected using piperidine and coupled with Fmoc-phenylalanine to give the protected tripeptide Fmoc-Phe-Gly-Ala^tBu. The protecting groups could be deprotected using weak base (Fmoc) and mild acid (^tBu) to afford the target peptide, Phe-Gly-Ala.

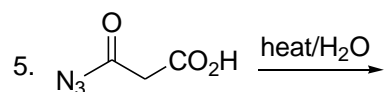
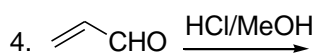
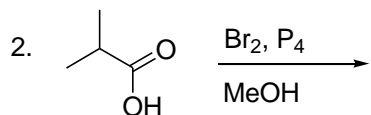
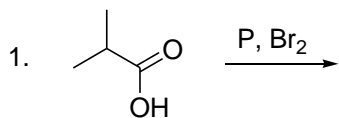


The Role of DCC and NHS in Peptide Synthesis

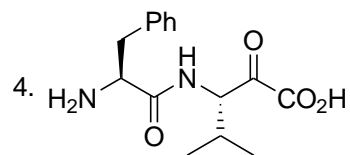
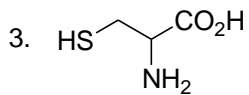
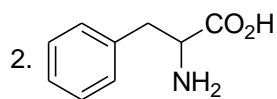
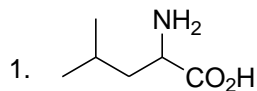


Problems:

A. Complete the following.



B. Outline synthetic routes to the following compounds.



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

J. March, *Advanced Organic Chemistry*, 4th ed, Wiley Interscience, New York, 1992.