Module 5  Reactions with Miscellaneous Reagents

Lecture 36

5.1 N-Bromosuccinimide (NBS)

N-Bromosuccinimide (NBS) is a convenient source of bromine for radical substitution as well as electrophilic addition reaction. It is prepared from succinimide and bromine in the presence of NaOH solution. The colourless solid obtained is washed with water and recrystallized from hot water, and stored in a refrigerator and protected from moisture to avoid decomposition. NBS is easier and safer to handle compared to bromine.

\[
\text{\text{NH}}_2\text{CO}_2\text{H} + \text{Br}_2 \xrightarrow{\text{NaOH}} \text{\text{NH}}_2\text{CO}_2\text{Br} + \text{HBr}
\]

5.1.1 Substitution Reactions

Allylic and Benzylic Brominations

Alkenes react with NBS in dry CCl₄ under reflux conditions to give allyl bromide. The reaction is initiated by light or peroxide. Although a number of reagents are available for bromination of allylic C-H bond of alkenes, NBS is most commonly used. The reaction is called Wohl-Zigler bromination. For example, cyclohexene reacts with NBS to give 3-bromocyclohexene in the presence of catalytic amount AIBN (radical initiator).
Allylic methylene groups are prone to undergo reaction more readily than allylic methyl group due to stabilization of the radical (2 >1). For example, 2-heptene can be selectively brominated at the secondary allylic carbon compared to the primary carbon.

![Chemical structure of NBS, CCl4, and Br reaction](image)

The reaction conditions are compatible for the bromination of benzylic C-H bonds, which are important from synthetic and mechanistic standpoint. For examples, diphenylmethane reacts with NBS to give bromodiphenylmethane in 81% yield.

![Chemical structure of NBS, CCl4, heat, and Br reaction](image)

Similarly, 1-phenylbutane, 1-methylnaphthalene and 3-methylthiophene could be reacted with NBS to give the corresponding brominated products (Scheme 1).

![Chemical structures of Scheme 1](image)
Mechanism

The reaction involves a free radical process (Scheme 2). The reaction is initiated by small amounts of Br radical. The role of NBS is to afford a constant low concentration of molecular bromine. Abstraction of an allylic or benzylic hydrogen by Br radical gives a resonance stabilized allyl or benzyl radical. The selective bromination occurs because the intermediate leading to the product is stabilized by resonance.

α-Bromination of Carbonyl Derivatives

Ketones having enolizable hydrogen can be brominated at the α-position. The reaction probably involves an addition of Br₂ to the enol form of the carbonyl derivatives, and elimination of HBr generates the α-bromoketone (Scheme 3).
**Allylic Bromination of Unsaturated Acids, Esters, Aldehydes and Ketones**

$\alpha,\beta$-Unsaturated carbonyl compounds undergo reaction with NBS at the allylic C-H bond to give allylic brominated $\alpha,\beta$-unsaturated carbonyl compound that can be used in the Reformatsky reaction. For example, ethyl crotonate can be transformed into ethyl 4-bromocrotonate using NBS

\[\text{OEt}\]
\[\text{OEt}\]
\[\text{O}\]
\[\text{O}\]
\[\text{O}\]
\[\text{O}\]
\[\text{NBS/AIBN}\]
\[\text{CCl}_4\]
\[\text{Br}\]
\[\text{OEt}\]
\[\text{OEt}\]
\[\text{Scheme 4}\]

in the presence of catalytic amount of AIBN in CCl$_4$ under reflux conditions (Scheme 4). Under similar conditions, testosterone acetate can be converted into 6-bromotestosterone acetate in good yield (Scheme 5)

\[\text{OAc}\]
\[\text{OAc}\]
\[\text{O}\]
\[\text{O}\]
\[\text{O}\]
\[\text{NBS/CCl}_4\]
\[\text{heat}\]
\[\text{Br}\]
\[\text{Scheme 5}\]

**Bromination of Aromatic Rings**

Aromatic compounds react with NBS under ionic conditions to undergo bromination in the aromatic ring by substitution. In these reactions, the brominating agent could probably be the protonated NBS. Benzene when treated with NBS and a 1:1 mixture of conc. H$_2$SO$_4$ and water gives bromobenzene in 95% yield. Under these conditions, aromatic compounds having highly branched chains also appears to undergo bromination in the aromatic ring with selectivity.
5.1.2 Addition Reactions

NBS is often used as the source of electrophilic bromine in polar solvents. For an example, cyclohexene reacts with NBS in the presence of tetraethylammonium bromide to give trans-1,2-dibromocyclohexane in good yield (Scheme 6).

\[
\text{NBS} \quad \text{(C}_2\text{H}_5\text{)}_4\text{NBr} \quad \text{Br} \quad \text{Br} \quad 75\%
\]

Scheme 6

A possible mechanism is represented in Scheme 7.

\[
\text{NBS} \quad \text{Br} \quad \text{Br} \quad \text{NS}^- \quad \text{NS}^+ \quad \text{H donor} \quad 2\text{HNS}
\]

Scheme 7

In the presence of excess of water, alkenes undergo reaction with NBS to give bromohydrins that could be converted into epoxides in the presence of base (Scheme 8).

\[
\text{NBS} \quad \text{H}_2\text{O} \quad \text{base} \quad \text{C}_3\text{O}
\]

Scheme 8

5.1.3 Oxidation

Secondary alcohols undergo oxidation to give ketones in the presence of NBS in water. This method has found wide applications in the oxidation of steroidal alcohols. For an example, cholic acid can be selectively oxidized at C-7 using NBS in the presence of water (Scheme 9).
In hot aqueous solution, \( \alpha \)-hydroxy acids can be oxidized to give aldehydes or ketones with loss of one carbon atom (Scheme 10). For example, glycolic acid, lactic acid and mandelic acid are converted into formaldehyde, acetaldehyde and benzaldehyde. Under these conditions \( \alpha \)-amino acids proceed decarboxylation to give aldehydes.
Examples:

\[
\begin{array}{c}
\text{MeO}_2\text{C} - \text{Me} - \text{O} \quad \text{NBS/light} \quad \text{AIBN} \\
\text{MeO}_2\text{C} - \text{Me} - \text{O} \\
\end{array}
\]


\[
\begin{array}{c}
\text{CO}_2\text{Me} \\ \text{O} \quad \text{NBS} \\
\text{CH}_3 \quad \text{Benzoyl peroxide} \\
\end{array}
\]


\[
\begin{array}{c}
\text{O} \\ \text{O} \\ \text{MeO} \\ \text{MeO} \\
\text{NBS, MeOH} \\
\text{O} \\ \text{O} \\ \text{MeO} \\ \text{MeO} \\
\end{array}
\]

Problems:

A. Find out the major products in the following reactions.

1. \[ \text{NBS} \quad \text{Benzoyl peroxide} \quad \text{CCl}_4, \text{reflux} \]

2. \[ \text{NBS, HBr} \quad \text{CCl}_4 \]

3. \[ \text{β-Cyclodextrin} \quad \text{NBS} \quad \text{Aq. Acetone} \]

4. \[ \text{2 equiv LiBr, 2 equiv NBS} \]

5. \[ \text{2 equiv LiBr, 2 equiv NBS} \]

6. \[ \text{NBS, TBAB} \]

7. \[ + \text{TsNH}_2 \quad \text{NBS} \]
Text Books


Lecture 37

5.2 N,N-Dicyclohexylcarbodiimide (DCC)

*N,N*-Dicyclohexylcarbodiimide (DCC) is a dehydrating agent often used to form esters, amides or anhydrides. It is commercially available as a waxy low-melting solid (34-35 °C). It can also be prepared by oxidation of dicyclohexylurea with $p$-toluenesulfonyl chloride in hot pyridine or by heating dicyclohexylthiourea with yellow mercuric oxide (Scheme 1). The section covers some important applications in organic synthesis.

\[ \text{Scheme 1} \]

\[ \text{DCC} \quad \text{Me} \quad \text{SO}_2\text{Cl} \quad \text{Me} \quad \text{N} = \text{C} = \text{N} \quad + \quad \text{H}_2\text{O} \]

\[ \text{DCC} \quad \text{Hg}_2\text{O} \quad \text{N} = \text{C} = \text{N} \quad + \quad \text{H}_2\text{O} \quad + \quad \text{Hg}_2\text{S} \]
5.2.1 Synthesis of Peptides

DCC is useful for the coupling of amino acids via amide C-N bonds. The amino acid monomers should be such that the ends to be available and other reactive groups protected. For example, for the synthesis of dipeptide between to two \( \alpha \)-amino acids, the amino group of one of the amino acids and the carboxylic group of the other must be protected before the two amino acids are brought together in the presence of DCC (Scheme 2).

\[
\begin{align*}
\text{O} & \text{N} \quad \text{Ph} \quad \text{H} \\
\text{O} & \text{N} \quad \text{C} \quad \text{H} \quad \text{O} \\
\text{Me} & \text{O} \quad \text{DCC} \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

Scheme 2

Mechanism

DCC reacts with the carboxyl group of amino protected acid to give activated acylating agent that undergoes reaction with amino group of other amino acid to form of a new amide bond (Scheme 3).
5.2.2 Synthesis of Esters

The synthesis of esters from carboxylic acids and alcohols can be accomplished in the presence of DCC in \( \text{CH}_2\text{Cl}_2 \) solvent at ambient conditions. This reaction is called Steglich esterification and usually for the sterically hindered substrates (Scheme 4).
**Mechanism**

The carboxylic acid proceeds reaction with DCC to afford activated acylating agent that undergoes reaction with the alcohol (Scheme 5).
5.2.3 Synthesis of Ethers and Thioethers

Phenols and thiophenols can be reacted with alcohols to give ethers in the presence of DCC (Scheme 5).

\[
\text{ArOH} + \text{MeOH} \xrightarrow{\text{DCC}} \text{ArOMe} \\
\text{ArSH} + \text{MeOH} \xrightarrow{\text{DCC}} \text{ArSMe}
\]

Scheme 5

5.2.4 Synthesis of Nitrile

The readily accessible oximes from aldehydes and hydroxyl amine readily undergo dehydration in the presence of DCC to nitriles in quantitative yields (Scheme 6).

\[
\text{ArOH} + \text{MeOH} \xrightarrow{\text{DCC}} \text{ArOMe} \\
\text{ArSH} + \text{MeOH} \xrightarrow{\text{DCC}} \text{ArSMe}
\]


Scheme 6

5.2.5 Synthesis of \(\alpha,\beta\)-Unsaturated Esters

The dehydration of \(\beta\)-hydroxy esters can be efficiently carried out using DCC to give \(\alpha,\beta\)-unsaturated ester (Scheme 7).
5.2.6 Heterocyclization Reactions

DCC is used as reactant as well as reagent in heterocyclization reactions. For an example, barbituric acid and its derivatives can be prepared by the reaction of malonic acid with DCC (Scheme 8).

\[
\text{CH}_2(\text{COOH})_2 + 2 \text{DCC} \rightarrow \text{N-}C_6\text{H}_{11} + \text{C}_6\text{H}_{11}\text{N} = \text{C}_6\text{H}_{11}
\]

Scheme 8

5.2.7 Heterocyclization Reactions

A mixture of DCC and DMSO catalyzes the oxidation of alcohols to aldehydes or ketones in the presence of acid catalyst. The reaction is called Pfitzner-Moffatt oxidation. A sulfur ylide is formed with base abstracts the \(\alpha\)-proton, generating dimethyl sulfide and the aldehyde or ketone (Scheme 9).
Scheme 9

Examples:


**Problems:**

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

1. ![Reaction 1](image1)

2. ![Reaction 2](image2)

3. ![Reaction 3](image3)

4. ![Reaction 4](image4)

B. Rationalize the following reaction.
5.3 Diazomethane (CH$_2$N$_2$)

Diazomethane is yellow, toxic and reactive gas which is soluble in ether. Liquid diazomethane is explosive but may be handled safely in ethereal solution. It is prepared immediately prior to use and represented by the following resonance hybrid structures.

\[ \text{CH}_2\text{N}≡\text{N} \leftrightarrow \text{H}_2\text{C}≡\text{N}≡\text{N} \]

Major sources for the preparation of diazomethane are the basic hydrolysis of $N$-methyl-$N$-nitrosocompounds (Scheme 1-3).
N-Methyl-N-nitrosourethane

\[
\text{Me} - \text{N} \rightarrow \text{CO}_2\text{Et} + \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{CO}_2 + \text{C}_2\text{H}_5\text{OH}
\]

\[\text{Me-N-CO}_2\text{Et} \rightarrow \text{Me-N-CO}_2\text{Et} + \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{CO}_2 + \text{C}_2\text{H}_5\text{OH}\]

N-Methyl-N-nitrosourea

\[
\text{Me} - \text{N} - \text{CO}_2\text{Et} \rightarrow \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{CO}_2 + \text{C}_2\text{H}_5\text{OH}
\]

Scheme 1

N-Methyl-N-nitroso-\(p\)-toluenesulfonamide

\[
\text{Me} - \text{N} - \text{SO}_2\text{Me} \rightarrow \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{H}_2\text{O} + \text{Me} - \text{N} - \text{SO}_2\text{Me}
\]

Scheme 2

\[\text{Me} - \text{N} - \text{SO}_2\text{Me} \rightarrow \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{H}_2\text{O} + \text{Me} - \text{N} - \text{SO}_2\text{Me}\]

\[\text{Me} - \text{N} - \text{CO}_2\text{Et} \rightarrow \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{CO}_2 + \text{C}_2\text{H}_5\text{OH}\]

N-Methyl-N-nitrosourea

\[
\text{Me} - \text{N} - \text{CO}_2\text{Et} \rightarrow \text{KOH} \rightarrow \text{CH}_2\text{N}_2 + \text{CO}_2 + \text{C}_2\text{H}_5\text{OH}
\]

Scheme 1
Mechanism

The key step is base-catalyzed elimination.

![Scheme 3]

5.3.1 Methylation

Diazomethane methlates acidic hydroxyl groups, carboxylic acids, sulfonic acids, phenols and enols. Conditions are mild and the products are obtained in high yield (Scheme 5).

![Scheme 5]
Mechanism

Diazomethane is a powerful methylating agent, particularly useful for mild preparation of methyl esters of acids (Scheme 6).

\[
\begin{align*}
\text{N}_2\text{-CH}_2 + \text{HOOCR} & \rightarrow \text{N}_2\text{-CH}_3 + \text{OOOCR} \\
\rightarrow & \text{H}_3\text{COOCR}
\end{align*}
\]

Scheme 6

The reactions aliphatic alcohols require catalyst because of the low acidity of the hydroxyl hydrogen. AlCl\textsubscript{3} and BF\textsubscript{3}∙OEt\textsubscript{2} are generally employed for this purpose (Scheme 7).

Similarly, the reactions of aliphatic amines with diazomethane are also effective in the presence of catalysts such as BF\textsubscript{3}∙OEt\textsubscript{2} and cuprous cyanide. However, the methylation of aromatic amines can be accomplished without the Lewis acid catalyst.

Example:

\[
\begin{align*}
\text{O}_2\text{N} & \text{N} & \text{H} & \text{N} & \text{CO}_2\text{Me} \\
\text{CH}_2\text{N}_2 & \rightarrow & \text{O}_2\text{N} & \text{N} & \text{H} & \text{N} & \text{CO}_2\text{Me}
\end{align*}
\]

5.3.2 Homologations

Diazomethane reacts with aldehydes to afford methyl ketones and ketones can be converted into higher homologues (Scheme 8). In both the cases the yields are moderate due to the formation of epoxides as by-product.

![Scheme 8]

**Mechanism**

The addition of diazomethane to the carbonyl group of the aldehydes or ketone can give betain, which could lose nitrogen and lead rearrangement to yield higher ketone or can cyclize to afford epoxides (Scheme 9).

![Scheme 9]
**Example:**

![Example Reaction Diagram]


**Arndt-Eistert Homologation Reaction**

The reaction of acid chloride with diazomethane gives $\alpha$-diazoketone, which rearranges with loss of nitrogen to provide ketene in the presence of colloidal silver. The ketene is subsequently transformed into carboxylic acid (Scheme 10). It is called Arndt-Eistert Homologation reaction.

![Arndt-Eistert Reaction Scheme]

Scheme 10
Example:

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{(COCl)}_2, \text{CH}_2\text{N}_2 \\
\text{Ag}_2\text{O}, \text{Na}_2\text{CO}_3, \text{Na}_3\text{S}_2\text{O}_3 & \quad \text{CO}_2\text{H}
\end{align*}
\]


\[
\begin{align*}
\text{Cl} & \quad \text{NH}_{\text{Cbz}} \\
\text{CO}_2\text{Et} & \quad \text{CH}_2\text{N}_2 \\
\text{light, MeOH} & \quad \text{MeO} \quad \text{NH}_{\text{Cbz}} \\
65\% & \quad \text{CO}_2\text{Et}
\end{align*}
\]


5.3.3 Addition Reactions

The 1,3-dipolar addition of reaction of diazomethane with a variety of compounds having ethylenic and acetylenic bonds afford heterocyclic compounds (Scheme 11).
5.3.4 Cycloaddition

Heat as well as light produces carbene from diazomethane through loss of nitrogen that can add to alkenes to give cyclopropane derivatives (Scheme 12). If the reaction is diluted with a large amount of an inert solvent, the carbene undergoes more collisions before it reacts and so the chances of flipping singlet to triplet carbene are increased. Addition to alkenes is then less stereospecific.
Problems:

A. Complete the following reactions.

1. $\text{OCl} + \text{CH}_2\text{N}_2 \xrightarrow{1.1 \text{ eq CaO}}$

2. $\text{EtOOCl} + \text{CH}_2\text{N}_2 \xrightarrow{1.1 \text{ eq CaO}}$

3. $\text{PhOCONHCONH} \xrightarrow{1. \text{ ClCO}_2\text{Et}, \text{NEt}_3} \xrightarrow{2. \text{ CH}_2\text{N}_2}$

4. $\text{PhOCONHNCONN}_2 + \text{H}_2\text{NOMe} \xrightarrow{10 \text{ mol\% PhCO}_2\text{Ag}} \xrightarrow{3 \text{ equiv NEt}_3}$

5. $\text{PhOCONHNCONN}_2 \xrightarrow{10 \text{ mol\% PhCO}_2\text{Ag}} \xrightarrow{\text{H}_2\text{O}}$

B. Rationalize the following reaction.

[Cyclic structure with Cl, CO$_2$Et, light, MeOH] $\xrightarrow{\text{CH}_2\text{N}_2}$ [Another cyclic structure with CO$_2$Et, MeO$_2$C$\text{C}_\text{C}_\text{C}_\text{C}_\text{O}_2$Et]

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Lecture 39

5.4 Phosphorus Reagents

Phosphorus based compounds are extensively used in organic synthesis as reagents as well as ligands for metal-catalyzed reactions. This section covers some of the important applications as reagents.

5.4.1 Wittig Reaction

The reactions of alkyl halides with aldehydes or ketones in the presence of triphenylphosphine and base give alkenes in high yield (Scheme 1). The reaction is known as Wittig reaction and was awarded Nobel prize in 1979. The reaction is versatile and affords powerful tool for the construction of alkenes with excellent stereoselectivity.

\[
PPh_3 + R'X \xrightarrow{\text{base}} \xleftarrow{\text{O}} \xrightarrow{\text{R"R'"}} \xleftarrow{\text{R"R'"}} \xrightarrow{\text{Ph}_3\text{P}=\text{O}}
\]

Mechanism

\(\text{PPh}_3\) reacts with alkyl halide to give phosphonium salt via the nucleophilic displacement (\(S_N2\)) of halide by the nucleophilic phosphorus atom of triphenylphosphine (Scheme 2). The acidic hydrogen of the phosphonium salt can be removed by strong base to give phosphorus ylides (commonly known as Wittig reagent). These phosphorus ylides carry a positive and a negative charge on adjacent atoms can be represented as double bonded species, called phosphoranes. Phosphorus ylides are strong nucleophiles and add to aldehydes or ketones to form betain that collapses to a four membered ring called oxaphosphetatne, which can decompose to give the alkene and triphenylphosphine oxide.
Other phosphines may be used for the reaction. But they should not contain a proton that could be abstracted as is the proton on the halide coupling partner, as a mixture of desired and undesired ylides would be formed.

If the halide contains an electron withdrawing group, the negative charges in the ylide is delocalized, decreasing its nucleophilicity and reactivity. Aldehydes may still react, but ketones likely will not.
Examples:


### 5.4.2 Wittig Indole Synthesis

Indoles are important structural unit and found in numerous natural product and biologically important compounds. Thus, the construction of the indole structural framework remains in organic synthesis. Anilides having memthylphosphonium
salt at their *ortho* position can be converted into indoles in the presence of base (Scheme 3). The reaction is called Wittig indole synthesis.

![Scheme 3](image)

**Mechanism**

An intramolecular nucleophilic addition of phosphorus yield to carbonyl group of amide can give four membered ring oxaphosphetatne that can decompose to give the target heterocycle (Scheme 4).

![Scheme 4](image)
### Examples:

\[
\text{PPh}_3^+ \xrightarrow{\text{t-BuOK}} \begin{array}{c}
\text{O} \\
\text{CF}_2\text{CF}_3
\end{array}
\]


\[
\text{PPh}_3^+ \xrightarrow{\text{t-BuOK}} \begin{array}{c}
\text{O} \\
\text{CO}_2\text{Et}
\end{array}
\]


\[
\text{PPh}_3^+ \xrightarrow{\text{t-BuOK}} \begin{array}{c}
\text{O} \\
\text{Me}
\end{array}
\]


### 5.4.3 Michaelis-Arbuzov Reaction

Several modifications of the Wittig reaction have been made to improve the reactivity of the ylides. The reaction of alkyl halides with triethylphosphite gives phosphonate esters (Scheme 7). This reaction is called Michaelis-Arbuzov reaction. The phosphonate esters are the precursor for the synthesis of more reactive ylides.
**Mechanism**

The rearrangement takes place via $S_{N}2$ reaction (Scheme 8).

**Michaelis-Becker Reaction**

Hydrogen phophonate reacts with alkyl halide in the presence of base to give an alkyl phosphonate. However, the yield is often lower than the corresponding Michaelis-Arbuzov reaction.

**Kabachnik-Fields Reaction**

The three-component coupling of a carbonyl compound, an amine and a hydrogen phosphonate leads to $\alpha$-aminophosphonates. This has been an important method in drug discovery research for generating peptidomimetic compounds.
The Photo-Arbuzov Reaction

Irradiation of benzyl phosphate leads to rearrangement to give benzyl phosphonate.

\[
\text{Ar} \begin{array}{c}
\text{P} \\
\text{O} \\
\text{R'}
\end{array} + \text{light} \rightarrow \text{Ar} \begin{array}{c}
\text{P} \\
\text{O} \\
\text{R''}
\end{array}
\]

Examples:

\[
\begin{array}{c}
\text{Ph} \begin{array}{c}
\text{P} \\
\text{O} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \begin{array}{c}
\text{P} \\
\text{O} \\
\text{Me}
\end{array}
\end{array}
\]

40%


\[
\text{Ph} \begin{array}{c}
\text{P} \\
\text{O} \\
\text{Ph}
\end{array} \text{Br} \rightarrow \text{Ph} \begin{array}{c}
\text{P} \\
\text{Me}
\end{array}
\]

80 °C, sealed tube


\[
\begin{array}{c}
\text{EtO} \\
\text{P} \\
\text{Na}
\end{array} + \begin{array}{c}
\text{Br} \\
\text{CH}_2\text{CH}_2
\end{array} \rightarrow \begin{array}{c}
\text{EtO} \\
\text{P} \\
\text{Et}
\end{array}
\]


\[
\begin{array}{c}
\text{MeO}_2\text{S} \\
\text{Cl}
\end{array} \rightarrow \begin{array}{c}
\text{MeO}_2\text{S} \\
\text{P} \begin{array}{c}
\text{Et} \\
\text{O}
\end{array}
\end{array}
\]

92%

5.4.4 Vilsmeier-Haack Reaction

Activated alkenes as well as aromatic compounds react with disubstituted formamides and POCl$_3$ to give aldehydes (Scheme 7). The reaction is called Vilsmeier reaction.

$$
\text{Ar-H or } \text{R=R'} \xrightarrow{\text{POCl}_3/\text{DMF}} \text{ArCHO or } \text{R=R'}
$$

Scheme 7
Mechanism

\(N,N\)-Dimethylformamide reacts with POCl\(_3\) to afford the reactive species that reacts with organic substrates to give the aldehydes (Scheme 8).

\[
\text{Me}_2\text{NCH} = \text{H} + \text{Cl}_2\text{POCl}_3 \rightarrow \text{Me}_2\text{NCH} = \text{H} + \text{POCl}_3
\]

\[
\text{Me}_2\text{NCH} = \text{H} + \text{HCl} \rightarrow \text{Me}_2\text{NCH} = \text{H} + \text{HCl}
\]

\[
\text{H}_2\text{O} \rightarrow \text{Me}_2\text{NH}
\]

\[
\text{CHO}
\]

Scheme 8

**Examples:**

\[
\text{Benzyl chloride} \xrightarrow{\text{POCl}_3/\text{DMF}} \text{Benzaldehyde} \quad \text{90%}
\]


\[
\text{EST} \xrightarrow{\text{POBr}_2/\text{DMF}} \text{2-Bromo-3-methyl-3-buten-2-one} \quad \text{64%}
\]

5.4.5 Appel Reaction

Alcohols react with CCl₄ or CBr₄ in the presence of PPh₃ to give alkyl halide (Scheme 9). The process is known as Appel reaction. The method is straightforward and the products are obtained in moderate to good yield.

\[
\begin{align*}
R\text{-OH} & \xrightarrow{\text{PPh₃}} R\text{-X} + \text{Ph₃P=O} + \text{HCX₃} \\
X & = \text{Cl or Br}
\end{align*}
\]

Scheme 9

Mechanism

The reaction takes place via S₅₂ process (Scheme 10).

\[
\begin{align*}
\text{Ph₃P+} + \text{X} &= \text{Ph₃P-X} + \text{CX₃} \\
R\text{-OH} + \text{CX₃} & \xrightarrow{\text{Ph₃P}} R\text{-O⁻} + \text{Ph₃P=X} + \text{X⁻} \\
R\text{-O⁻} + \text{Ph₃P=X} & \xrightarrow{\text{X⁻}} R\text{-X} + \text{Ph₃P=O}
\end{align*}
\]

Scheme 10
**Examples:**


Problems:

Write the major products for the following reactions.

1. \[
\begin{align*}
 & \text{CHO} \\
 & \text{OMe}
\end{align*}
\]
\[
\text{Ph}_3\text{P} \xrightarrow{} \text{Br} \xrightarrow{} \text{COEt} \\
\text{THF} \xrightarrow{} \text{Base}
\]

2. \[
\begin{align*}
 & \text{CHO} \\
 & \text{Ph}_3\text{P}
\end{align*}
\]
\[
\text{Br} \xrightarrow{} \text{Base}
\]

3. \[
\begin{align*}
 & \text{Ph} \\
 & \text{N}
\end{align*}
\]
\[
\text{(COCl)}_2/\text{DMF} \xrightarrow{} \text{NaOAc}
\]

4. \[
\begin{align*}
 & \text{OMe} \\
 & \text{Ph}
\end{align*}
\]
\[
1. \text{POCl}_3, \text{DMF} \\
2. \text{I}_2, \text{aq. NH}_3
\]

5. \[
\begin{align*}
 & \text{Ph} \\
 & \text{Ph}
\end{align*}
\]
\[
\text{OH} \xrightarrow{} \text{P(OEt)}_3 \xrightarrow{} \text{ZnBr}_2
\]

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Lecture 40

5.5 Sulfur, Selenium and Tellurium Compounds

5.5.1 Sulfur Compounds
Organosulfur compounds find wide applications in organic synthesis. Following are the some of the important applications.

5.5.1.1 Sulfur Ylides
Sulfur ylides have numerous applications in organic synthesis. Among them, diethylsulfonium methylide (unstabilized) and dimethyloxosulfonium methylide (stabilized) are extensively used in organic synthesis. These reagents are called Corey-Chaykovsky reagents.

They exhibit different reactions with $\alpha,\beta$-unsaturated carbonyl compounds. The former afford epoxides and the latter give cyclopropanes (Scheme 1). In the absence of double bond, both give epoxides. The epoxide formation is kinetically favourable while the formation of cyclopropane is the thermodynamic product.

Sulfur ylides undergo rearrangements to give valuable products (Scheme 2).

\[
\text{Scheme 2}
\]

### Examples:


### 5.5.1.2 Oxidation
N-Chlorosuccinimide-dimethyl sulfide, prepared \textit{in situ} from NCS and DMS, is used as mild oxidizing reagent in organic synthesis (Scheme 3). This reagent is called Corey-Kim reagent.

![Scheme 3]

\[
\text{N-Cl} \quad \text{+ Me}_2\text{S} \quad \xrightarrow{\text{solvent}} \quad \text{Me}_2\text{S-Cl}
\]


**Examples:**

\[
\text{OH} \quad \xrightarrow{\text{NCS, DMS, toluene, Et}_3\text{N}} \quad \text{CO} \quad \text{93%}
\]


\[
\text{O} \quad \xrightarrow{\text{NCS, DMS, CH}_2\text{Cl}_2, \text{Et}_3\text{N}} \quad \text{O} \quad \text{O} \quad \text{N}_3
\]


**5.5.1.3 C-C Bond Formation**
2-Lithio-1,3-dithiane is widely used in organic synthesis as “umpolung” reagent (Scheme 4). It is also called Corey-Seebach reagent.

2-Lithio-1,3-dithiane

**Scheme 4**


**Examples:**


**5.5.2 Selenium Compounds**

The study of organoselenium compounds has received considerable attention because of their interesting properties. In this section, we will cover some of the important applications of Se and SeO₂ in organic synthesis.

**5.5.2.1 Selenium**
Selenium reacts with organolithium, -sodium and -magnesium to provide metal selenolates that afford selenides by the reaction with electrophiles (Scheme 1), diselenides by oxidation, and selenols by acidification.

Scheme 1

Selenium is reduced to metal salts of hydrogen selenide or diselenide that are useful precursor of selenides and diselenides, respectively. For example, NaBH₄ reduces Se into NaSeH or Na₂Se₂ depending on the reaction conditions that could be readily reactive with benzyl chloride to give dibenzyl diselenide in high yield (Scheme 2).

Scheme 2

Reaction of Se with hydrazones, sulfonium or phosphonium ylides and ρ-halo carbonions gives selones. Sterically hindered selones can be isolated, whereas the less hindered selones can be reacted in situ with ylides (Scheme 3).

Scheme 3

Reaction of Se with diaminoalkyne and isocyanide gives a diselenoamide and isoselenocyanate, respectively (Scheme 4).
5.5.2.2 Selenium Dioxide

Selenium dioxide (SeO$_2$) is useful for the oxidation of allylic and benzylic C-H bonds to give alcohols or ketones (Scheme 5). The order of ease of oxidation is CH$_2$ > CH$_3$ > CH. The oxidation takes place at the more substituted end of the double bond.


Mechanism
The reaction takes place via ene reaction. In the absence of hydrolysis, alkenes can be converted into carbonyl compounds (Scheme 6).

SeO$_2$ oxidizes alkynes into 1,2-dicarbonyl compounds in the presence of small amount of H$_2$SO$_4$ with high yield (Scheme 7).

SeO$_2$ is useful reagent for the oxidation of methyl or methylene group adjacent to the carbonyl group to give 1,2-dicarbonyl compounds (Scheme 8). The reaction is called Riley oxidation.
The reaction takes place via the intermediate $\beta$-ketoseleninic acid.

![Reaction Mechanism Diagram]

**Scheme 8**

**Examples:**

\[
\]

\[
\text{H. Rapopart, U. T. Bhalerao, J. Am. Chem. Soc. 1971, 93, 4835.}
\]
5.5.3 Tellurium Compounds

Organotellurium compounds have been used in a number of organic transformations. The following are some of the important applications.

Synthesis of Biaryls

\[
\begin{align*}
\text{MeO-} & \text{TeCl}_4 \xrightarrow{\text{heat}} \text{MeO-TeCl}_3 \\
\text{MeO-TeCl}_3 & \xrightarrow{\text{heat}} \text{MeO-TeCl-OMe} \\
\text{MeO-TeCl-OMe} & \xrightarrow{\text{Raney- Ni}} \text{MeO-TeOMe}
\end{align*}
\]

Deoxygenation of Epoxides

\[
\begin{align*}
\text{EtO-P} & \text{TeNa} \xrightarrow{\text{heat}} \text{EtO-Te-OMe} \\
\text{EtO-Te-OMe} & \xrightarrow{\text{heat}} \text{EtO}
\end{align*}
\]

Vicinal Dibromination

\[
\begin{align*}
\text{PhBrPh} & \xrightarrow{\text{heat}} \text{Ph-Ph} + \text{Ph}_2\text{TeBr}_2
\end{align*}
\]
Problems:

A. What product would you expect from the following reactions?

1. \( \text{Me}_3\text{S}=\text{O} \) \( \overset{\ominus}{\underset{\ominus}{\text{I}}} \) \( \longrightarrow \) \( \text{KOH} \)

2. \( \text{Me} \) \( \overset{\ominus}{\underset{\ominus}{\text{I}}} \) \( \longrightarrow \) \( \text{Me}_3\text{S} \) \( \text{KOH} \)

3. \( \text{SeO}_2 \)

4. \( \text{SeO}_2 \) \( \longrightarrow \) \( \text{H}_2\text{O}_2 \)

5. \( \text{RCO}_3\text{H} \) \( \overset{\text{Base}}{\rightarrow} \)

B. Rationalize the following reaction.

\( \text{SeO}_2 \) \( \longrightarrow \) \( \text{OH} \) \( \overset{\text{Oxidation}}{\longrightarrow} \)

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