CHAPTER-I

Functional group transformations under reflux condition

PART A

Introduction to functional group transformations
IA. 1. FUNCTIONAL GROUP TRANSFORMATIONS

Functional group transformation are very essential and most important in organic chemistry. The selective functional group transformation of either simple or complex molecules to target molecules is a very important requirement in the organic synthesis. Functional group transformation or interconversion is a process wherein one functional group is converted into another by substitution, addition, elimination, reduction, oxidation or by a rearrangement reaction by the use of different reagents, reagent systems under different reaction conditions. In the last decade there has been tremendous development in the field of functional group transformations and “Comprehensive Organic Functional Group Transformations I” and “Comprehensive Organic Functional Group Transformations II” are two excellent editions which present the vast subject of organic synthesis in terms of the introduction and interconversion of all known functional groups, thus providing a unique information source documenting on all the methods of efficiently performing a particular transformation of all known functional groups, providing a unique information.[1, 2]

Functional group interconversions have also become an important tool in order to make the important alteration or modifications to the intermediate molecules which help in establishing the required functionality in the target molecules. This is very much evident at almost every stage of a multi step or total synthesis.[3]

There are a number of functional group interconversions and only challenge lies in how to practically bring about these conversions effectively. A few functional group transformations are presented below.

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Introduction to Functional Group Transformations
IA. 2. SOME INTERESTING AND USEFUL EXAMPLES OF FUNCTIONAL GROUP TRANSFORMATIONS USING VARIOUS REAGENTS UNDER DIFFERENT REACTION CONDITIONS

A well established conversion of alcohols to iodides using $I_2$/Ph$_3$P/imidazole sytem is presented in Scheme IA.1.[4, 5]

![Scheme IA.1.](image)

1-Tosyl-$1H$-imidazole/NaN$_3$/TBAI reagent system for effecting the transformation of alcohols to azides is given in Scheme IA.2.[6]

![Scheme IA.2.](image)

Both hydrogenation (Rosenmund) and hydride transfer have been used to reduce acid chlorides to aldehydes. Sm metal also effects this transformation. Nitro groups and alkenes were stable to the conditions (Scheme IA.3).[7]

![Scheme IA.3.](image)

C-H amination to convert the ether into sulfonamide using TsNH$_2$/Cu is achieved. Further reduction with NaBH$_4$ gives hydroxy sulfonamides as shown in Scheme IA.4.\[8\]

![Scheme IA.4.](image)

Conversion of an aldehyde to a primary amide would usually take three steps (acid, activation, amide). The method using Ir catalyst, in the presence of hydroxylamine, can effect this transformation in a single step (Scheme IA.5).\[9\]

![Scheme IA.5.](image)

A simple procedure for amide metathesis is reported. Use of excess of $N$-phenylacetamide would be expected to drive the conversion to completion (Scheme IA.7).\[10\]

![Scheme IA.6.](image)

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*Introduction to Functional Group Transformations*
Anti-Markovnikov hydration of a terminal alkyne yields the corresponding carboxylic acid. Cul is an effective catalyst for the combination of a terminal alkyne with a sulfonyl azide to give the amide. Internal alkynes are stable to the reaction conditions (Scheme IA.7).[11]

Scheme IA.7.


Introduction to Functional Group Transformations
Few functional group transformations from our lab.

Aralkyl and aryl oximes are easily converted into the corresponding hydrazones by hydrazine hydrate (Scheme IA.8).[12]

![Scheme IA.8](image)

Direct one-pot novel transformation of oximes to the corresponding hydrocarbons without converting them back into the carbonyl function and then into hydrocarbon using hydrazine/KOH is achieved (Scheme IA.9).[13]

![Scheme IA.9](image)

A simple, rapid, efficient and selective method for the preparation of aromatic compounds with benzoyl chloride and acetyl chloride in presence of TiO$_2$ under the influence of microwaves using conventional microwave (Scheme IA.10). [14]

![Scheme IA.10](image)

One-pot solvent-free conversion of araldehyde into corresponding nitriles using ZnO as catalyst under microwave irradiation is presented in Scheme IA.11.[15]

\[
\begin{align*}
\text{O} & + \text{NH}_{2}\text{OH} \cdot \text{HCl} \xrightarrow{\text{ZnO}} \text{R} \xrightarrow{\text{MW/320 W, 20-60 sec, Neat}} \text{R} = \text{C} \equiv \text{N}
\end{align*}
\]

**Scheme IA.11.**

Simple, efficient and rapid oxidation of primary alcohols to aldehydes and secondary alcohols into ketones by a Ni(NO\(_3\))\(_2\).6H\(_2\)O/I\(_2\)/water system under ultrasonic irradiation is reported by us (Schemes IA.12, 13, 14).[16]

\[
\text{CH}_2\text{OH} \xrightarrow{\text{Ni(NO}_3\text{)}_2\cdot6\text{H}_2\text{O/I}_2/\text{Water}} \text{CHO}
\]

**Scheme IA.12.**

\[
\text{CH}_2\text{OH} \xrightarrow{\text{Ni(NO}_3\text{)}_2\cdot6\text{H}_2\text{O/I}_2/\text{Water}} \text{CHO}
\]

**Scheme IA.13.**

\[
\text{n = 0, 1, 2}
\]

**Scheme IA.14.**

\[
\text{n = 0, 1, 6}
\]


*Introduction to Functional Group Transformations*
IA. 3. REACTIONS AT REFLUX[17]

Reflux to apply energy to chemical reactions.

Generally organic chemical reactions take a very long time to go to completion without some external energy. In order to speed up these reactions, heat is applied. It is the energy supply that proppogates the reaction. The application of heat must be achieved in a specific way in order to overcome the issue of evaporating too much of solvent which leads to drying the reaction vessel, as often organic compounds are volatile with high vapour pressures and low boiling points. When heated after certain temperature, they will become flammable which results in explosion. Reflux is continuously cooling the vapours generated back into the liquid form returning to the flask as condensate, using a condenser which is caused by heating the chemical reaction for a specific amount of time. This technique guarantees the temperature of the reaction to remain constant. The reactants for reflux experiments can be solid and liquid, or both liquids. The temperature at which the reaction is heated depends on the boiling points of the solvents and also the reflux ring (Fig. IA.1). As the reaction proceeds, a part of the solvent travels up the condenser tube before condensing back into the flask. Above this point, the inner jacket of the condenser will appear dry. Below this point, the solvent flows back into the flask. The boundary between these two portions is the reflux ring.

![Diagram of a reflux system](image-url)

Fig. IA.1.

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*Introduction to Functional Group Transformations*
If the reactants are not too viscous, a magnetic stirrer can be employed to prevent violent bumping of the boiling liquid and ensure uniform heating (Fig. IA.2).

The condenser is always filled with water to ensure efficient cooling. There is a change from gas phase back to liquid phase of vapours generated from the reaction mixture due to loss of heat. This results in the liquid mixture falling back to the round bottom flask. The temperature of the reaction must be set so that the reflux ring should only be one-third to half way up the condenser. It is said that boiling point has been reached when there are bubbles of vapours produced inside the liquid. At this point, if the heating is increased, there will be no change in the temperature of the reactants but there will be increase in the rate at which boiling liquid changes into vapour. This is caused by the increased energy supply which will facilitates more and more liquid molecules to overcome their intramolecular interactions and entre the gas phase. When there is heating of two or more volatile compounds, the total vapour pressure of the mixture \((P_t)\) is equal to the sum of the vapour pressures of the compound 1 and 2 \((P_1 \text{ and } P_2)\) in the reaction mixture. The magnitude of the vapour pressure exerted by each compound is determined by the vapour pressure of the compound \((P_0)\) and the mole fractions of both the compounds present in the mixture \((X_1 \text{ and } X_2)\).

For an ideal two-compound solution, the solution vapour pressure is expressed by Raoult’s Law.

*Introduction to Functional Group Transformations*
CHAPTER-I

Depending on the mixtures the mixture boils at variable temperatures. Homogenous mixtures boil at a temperature between the boiling points of the pure compounds, but the exact value depends on the amount (mass or volume) of each compounds. In a mixture of cyclohexane and toluene, cyclohexane is more volatile between the two and a liquid composed of 50 percent cyclohexane and 50 percent toluene would boil at 90°C and yield a vapour composed of 70 percent cyclohexane and 30 percent toluene. A liquid mixture when boiled will yield a vapour that will contain a larger percent of the more volatile compound (Fig. IA.3).

![Diagram showing the boiling point of a mixture of cyclohexane and toluene.](image)

\[ PT = X_{1}P_{10} + X_{2}P_{20} \] [1]

**Fig. IA.3.**

**IA.4. SOME INTERESTING AND USEFUL EXAMPLES OF REACTIONS UNDER REFLUX**

A convinent protocol for the catalytic dehydration of aromatic and aliphatic amides using silanes in the presence of catalytic amounts of fluoride under reflux allows the synthesis of a wide range of aliphatic and aromatic nitriles with high selectivity under mild conditions (Scheme IA.15). [18]

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*Introduction to Functional Group Transformations*
Scheme IA.15.
Kikuchi et al. have reported the formation of 1,4-dihydropyridine derivatives starting from imines and ethylpropionate in the presence of Sc(OTf)$_3$ (Scheme IA.16).[19]

Scheme IA.16.
Regioselective one step synthesis of naturally occurring phenyl coumarin balsamiferone under reflux condition is described using Wittig reaction (Scheme IA.17).[20]

Scheme IA.17.
Holmberg and Hansen have reported the synthesis of acylals by treating dichloromethane with selected tetrabutylammonium carboxylates under reflux (Scheme IA.18).[21]


Introduction to Functional Group Transformations
Scheme IA.18.

α,β- Unsaturated esters were obtained with full control of stereoselectivity utilizing a reaction of dichloroesters with a variety of aldehydes. The reaction is promoted by active manganese under reflux. This method is usually applicable where C–C double bond can be di- or trisubstituted (Scheme IA.19).[22]

Mn*:  

a) 1 eq. MnCl₂, 2 eq. LiCl, THF, r.t, 0.5 h  
b) 2 eq. Li, 0.3 eq. 2-Ph-pyridine, THF, r.t, 1 h  
c) a) + b) r.t, 4 h

Scheme IA.19.

Simple and highly selective system for the reductive fission of azoarenes to aminoarenes under reflux is reported. The reactions proceed smoothly without affecting the substituents (Scheme IA.20).[23]

Scheme IA.20.

\[ \text{R, } R^1 = H, -\text{CH}_3, -\text{OH}, -\text{COOH}, -\text{OCH}_3, -\text{Cl, -Br} \]

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*Introduction to Functional Group Transformations*
A convenient and efficient procedure for the Friedel–Crafts acylation of aromatic compounds with carboxylic acids in the presence of P$_2$O$_5$/SiO$_2$ under reflux condition is described. Both aromatic and aliphatic carboxylic acids were found to react easily to afford the corresponding ketones (Scheme IA.21).[24]

\[
\text{R-COOH} + \text{ArH} \xrightarrow{\text{P}_2\text{O}_5/\text{SiO}_2, \text{Reflux, 1-5 h}} \text{R}^\prime \text{Ar}
\]

\[\text{R} = \text{Aryl, Alkyl, Alkenyl}\]

Scheme IA.21.


*Introduction to Functional Group Transformations*