M. Sc. Thesis

One Pot Synthesis of Some Substituted Naphthoic Acid Catalyzed by Bismuth(III) Nitrate in Excess Sulfuric Acid

One Pot Synthesis of Some Substituted Naphthoic Acid Catalyzed by Bismuth(III) Nitrate in Excess Sulfuric Acid

M. Sc. Thesis

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By

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Affectionately Dedicated

to

My Beloved Parents

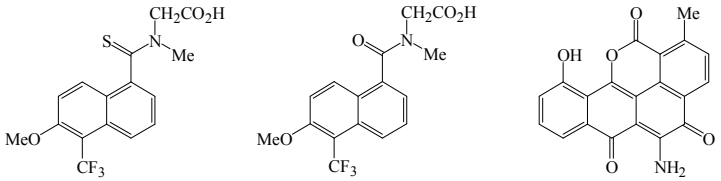
and

Uzzal Hossain

Abstract:

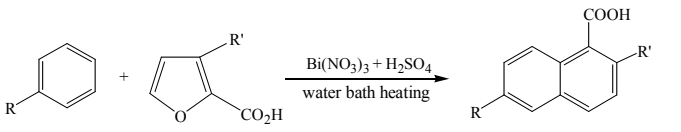
6-Substituted naphthoic acid and its derivatives are popularly used as the valuable precursors to some life controlling drugs. Tolrestat **1, 2** are orally effective aldose reductase inhibitors generally synthesised from 6-substituted naphthalene derivatives. During the synthesis of chrymutin **3** a potent antitumor agent, 2-methyl-6-methoxy naphthoic acid derivatives was used as the effective Michael acceptor for the annulation with cyanophthalide. Fluorine contains at the metabolic site in aromatic and heteroaromatic rings is an important criteria of activity enhancement of some pharmaceuticals and acts as essential part in medicinal chemistry which convincingly increases the activity of the compounds.

Figure: 1.



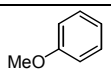
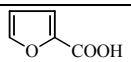
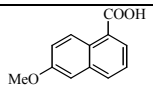
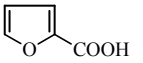
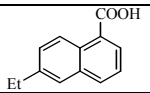
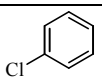
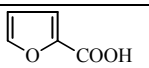
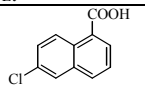
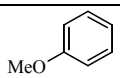
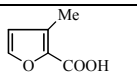
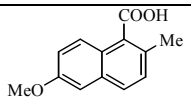
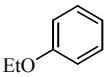
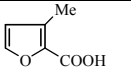
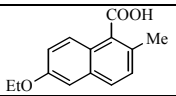
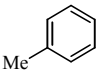
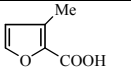
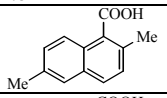
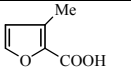
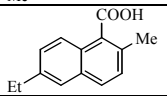
Tolrestat **1** Oxo-tolrestat **2** Chrymutin **3**

Synthetic route via tetralones is an unambiguous and established way to achieve 6- or 7-substituted-1-naphthoic acid derivatives. But, the route is not general to all kind of naphthalene derivatives and particularly the method is lengthy and cumbersome. Direct conversion of 1-naphthoic acid from benzene derivatives, 2-furoic acid and in the presence of excess $AlCl_3$ has been described. Nevertheless, this method could satisfy the huge current demand of naphthoic acid owing to its lower yields (7~10%) and clumsy separation procedure of some unwanted sticky materials create during this techniques. Recently, a new method has been designed for the synthesis of 6-fluoro-1-naphthoic acid using excess anhyd. $AlCl_3$ but it has some disadvantages as described and in few cases bromine was not found in C_6 of the naphthalene ring. Therefore, to overcome these difficulties we, herein, reported a very simple, one pot method using anhydrous $Bi(NO_3)_3$ and H_2SO_4 (Concd.) as mixed catalyst under solvent free conditions synthesize different substituted naphthoic acid.



This strategy has brought an improved transformation of the reactants into methoxy naphthoicacid derivatives. Some of our synthesized products are tabulated below:

Table-1

Entry	Reactant	Acids	Products	m.p.(°C)	Yield (%)
(i)				180 (Lit.[171] 180)	45
(ii)				167-170	45
(iii)				188 (Lit.[171] 188-189)	50
(iv)				161 (Lit.[23] 160-162)	45
(v)				165	40
(vi)				169	35
(vii)				187	40

All of the products were characterized by IR and NMR spectroscopic methods. Some of the products are known in the literature, so the melting points were matched with the literature values.

This is an elegant method to synthesise some naphthoic acid with high yields. $Bi(NO_3)_3$ is an inexpensive, available and less toxic catalyst. So, with the present method one can readily synthesize the given naphthoic acids avoiding the unwanted cumbersome of the earlier methods.

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In the Name of Allah, the Most Beneficent, the Most Merciful

All praise to Almighty Allah for his infinite mercy and the blessings to complete my thesis works. It is my great pleasure to expressmy sincere gratitude to all who furnished immeasurable memories and who offered perspicacity support during this endeavor.

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Iqubal Hossain

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ABBREVIATIONS

b.p.	=	Boiling point
bm	=	Broad multiplete
br s	=	Broad singlet
cm^{-1}	=	Per-centimeter
Concd.	=	Concentrated
^{13}C NMR	=	^{13}C Nuclear magnetic resonance
d	=	Doublet
dd	=	Doublet of doublet
DCM	=	Dichloromethane
DMSO	=	Dimethyl sulphoxide
EtOAc	=	Ethyl acetate
Fig.	=	Figure
g	=	Gram
h	=	Hour
Hz	=	Hertz
^{1}H NMR	=	^{1}H Nuclear magnetic resonance
Hz	=	Hertz
HRMS	=	High resolution mass spectroscopy
IR	=	Infrared spectroscopy
J	=	Coupling constant
m	=	Multiplete
mg	=	Miligram
mL	=	Mililiter
m.p.	=	Melting point
MHz	=	Mega-Hertz
MS	=	Mass Spectroscopy

MeOH = Methanol

MIRC = Michael Initiated Ring Closure Reaction.

NMP = N-methyl Pyrrolidene

NMR = Nuclear Magnetic Resonance

ppm = parts per million

PTP = Protein tyrosine phosphate

PIDA = Phenyliodonium diacetate

q = Quartet

rt = Room temperature

R.B = Round bottomed flask

s = Singlet

TLC = Thin Layer Chromatography

THF = Tetrahydrofuran

t = Triplet

TMS = Tetramethyl silane

TBDMS = Tertiary butyldimethyl silane

wt = Weight

δ = Chemical shift in ppm

Chapter 1

Introduction and Overview

1.1 One-pot Synthesis:

One pot synthesis is a strategy with the aim to improve the efficiency of a chemical reaction whereby reactants are subjected to successive chemical treatments in one and the same reactor. This is much desirable by the chemists because of lengthy reaction processes and purification of the intermediates could be avoided by saving resources, time and thereby chemical yields could be increased.[1, 2]

1.1.1 How to Control One-pot Reaction:

One pot method could be tamed under two major controlling parameters:

I. By employing effective homologates to a particular reaction

II. By exploiting catalyst in the reactions.[3]

1.1.2 Usefulness of One-pot Synthesis:

(i) By one pot synthesis we can avoid lengthy preparation steps for the reaction precursors. Thus one step protocol can technically obviate the successive purification steps of the precursors.

(ii) By this short-cut technique yield of the products obviously would be higher than that of any other conventional techniques.

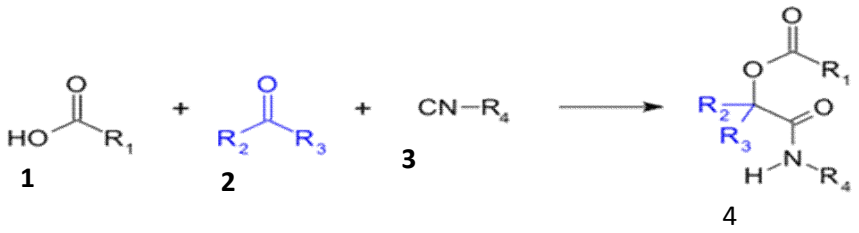
(iii) One pot method save huge solvent spoilages that is the most important advantage of this straight forward method.

(iv) Exposure of the huge solvent smog in the air currently is a serious concern to the environment. So, only by this technique we can minimize the injury of this fresh planet.

1.1.3 Examples of some One-pot Reactions :

(i) Passerini reaction.[4]

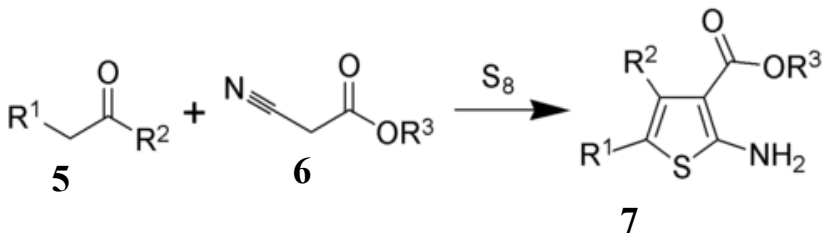
Passerini reaction is a chemical reaction involving an isocyanide **4**, an aldehyde (R_3=H) / ketone **2**, and a carboxylic acid **1** to form a α-acyloxy amide **4**, in an one-pot.



This above organic reaction was discovered by Mario Passerini in 1921 in Florence, Italy. It is the first isocyanide based multi-component reaction developed, and currently plays a central role in combinatorial chemistry.

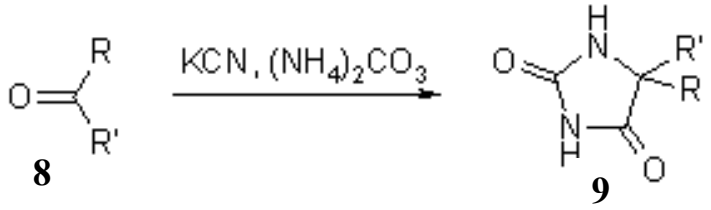
(ii) Gewald Reaction.[5]

Gewald reaction is a multicomponent organic reaction involving the condensation of a ketone **5** (or aldehyde when R^2 = H) with a α-cyanoester **6** in the presence of elemental sulfur and a base to give a poly-substituted 2-amino-thiophene **7**.



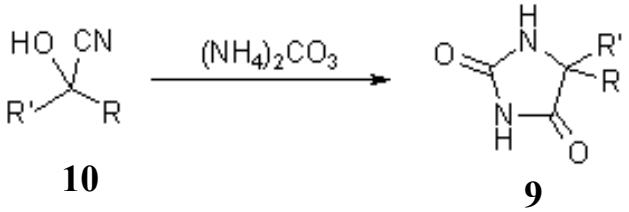
(iii) Bucherer-Bergs Reaction.[6]

It is another multicomponent chemical reaction of carbonyl compounds **8** (aldehydes or ketones) or cyanohydrins **10** with ammonium carbonate and potassium cyanide to give hydantoins **9**. The reaction is named after Hans Theodor Bucherer.



8 **9**

A pre-formed cyanohydrin can react with ammonium carbonate to give the same product:

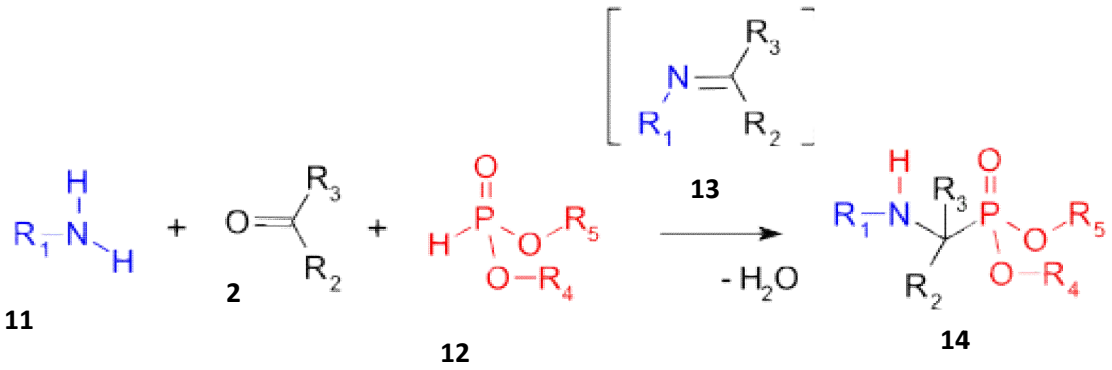


10 **9**

iv) Kabachnik–Fields Reaction.[7]

Kabachnik–Fields reaction is a convenient, one-pot three-component synthesis of an α-amino phosphonate **14** from an amine **11**, a carbonyl compound **2** and a

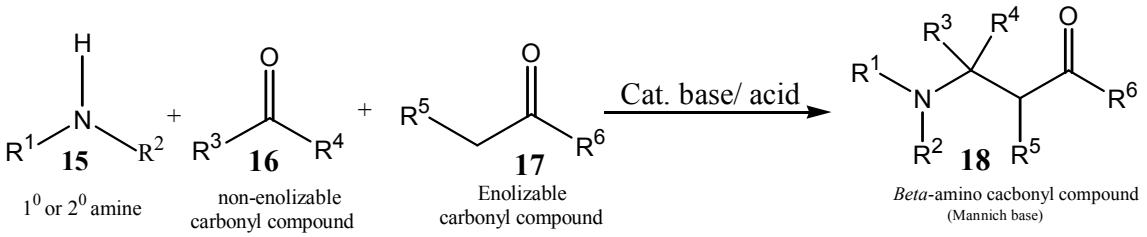
dialkyl phosphonate **12**. Aminophosphonates were the synthetic target of biologically important as phosphorus analogues of *α*-amino acids, a bioisosteric. This multicomponent reaction was independently discovered by Martin Izrailevich Kabachnik and Ellis K. Fields in 1952.



(v) Mannich Reaction.[8]

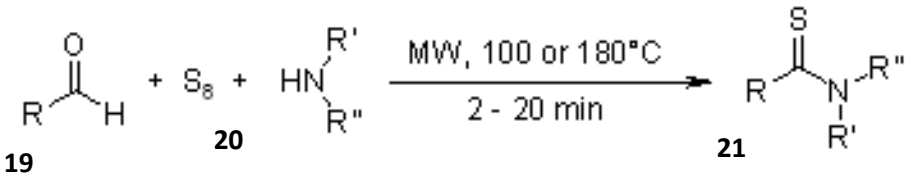
Mannich reaction is an important organic reaction used to convert a primary or secondary amine **15** and two carbonyl compound (one non-enolizable **16** and one enolizable **17**) to a *β*-amino carbonyl compound, in the presence of acid or base catalysts. In the acid catalyzed mechanism both carbonyl compounds get protonated at the oxygen. The enolizable carbonyl compound, which has an *α*-hydrogen, then gets deprotonated to form an enol intermediate. The non-enolizable carbonyl compound reacts with the amine to form an iminium ion. The enol

intermediate then attacks the iminium ion which after deprotonation provides the final Mannich base product.



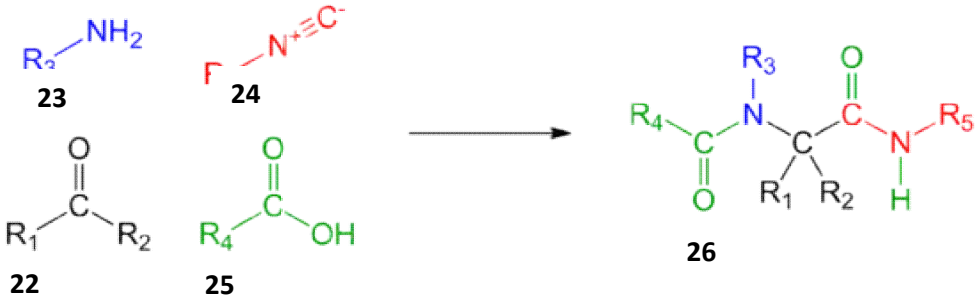
(vi) Kindler Reaction.[9]

A microwave-assisted three-component condensations of aldehydes **19**, amines **20**, and elemental sulfur were carried out using N-methyl-2-pyrrolidone (NMP) as solvent employing microwave flash heating at 110-180°C for 2-20 min. to obtain some of synthetically valuable thioamide building blocks **21** in good yields.



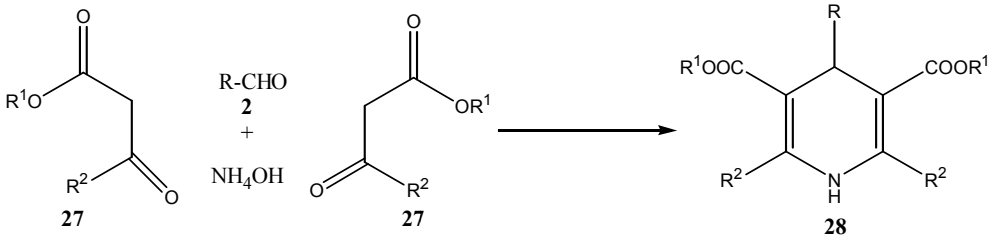
(vii) Ugi Reaction.[10]

Ugi reaction is a well known one-pot multi-component reaction in organic chemistry involving a ketone or aldehyde **22**, an amine **23**, an isocyanide **24** and a carboxylic acid **25** to form a bis-amide **26**. The reaction is also carried out in one pot as multicomponent scaffold.



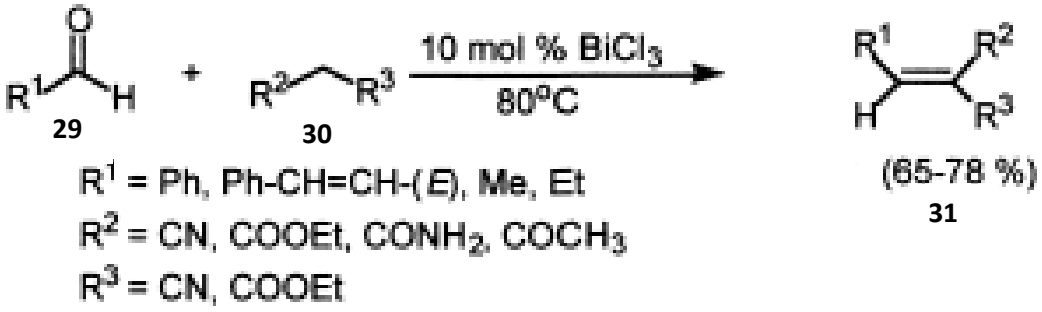
(viii) **Hantzsch Dihydropyridine Synthesis**[11]

This is a fantastic pure chemical reaction envolving an aldehyde **2**, *β*-keto ester **27** and ammonium hydroxide to form a dihydropyridine **28**.



(ix) Knoevenagel condensation.[12]

The condensation of an aldehyde or ketone **29** with an active methylene compound **30**, is an important method to synthesize *α, β*-unsaturated carboxylic acids **31**, and is typically catalyzed by organic amines. A solvent free procedure for the Knoevenagel reaction, catalyzed by $BiCl_3$ has shown below.

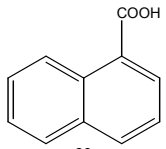


29 30 31

R^1 = Ph, Ph-CH=CH-(*E*), Me, Et
R^2 = CN, COOEt, $CONH_2$, $COCH_3$
R^3 = CN, COOEt

1.2 Naphthoic Acid :

Naphthoic acid is an aromatic mono-carboxylic acid of naphthalene, consisting of two fused benzene ring.



32

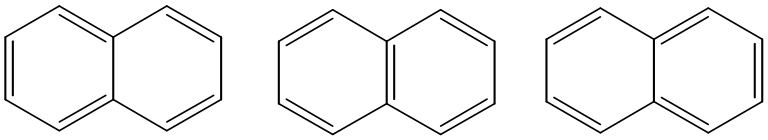
Naphthoic acid contains naphthalene ring to its core structure

1.2.1 Physical Properties of Naphthalene:

Naphthalene in naphthoic acid is classified as aromatic because its properties resemble to those of benzene. Its molecular formula $C_{10}H_{8,}$ might lead one to expect a high degree of unsaturation; yet naphthalene is resistant to the addition reactions characteristics of unsaturated compounds. Instead, the typical reactions of naphthalene are electrophilic substitution reactions, in which hydrogen is displaced as hydrogen ions and naphthalene ring system is preserved. Like benzene, naphthalene is unusually stable because of lower value of heat (61 Kcal/mol).

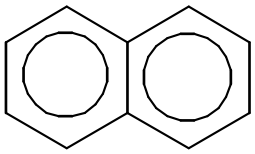
From the theoretical standpoint, naphthalene has the structure required of an aromatic compound. It contains flat six-member rings, and condensation of

aromatic orbital shows that the structure can provide π electron clouds containing six electron , the sextet. Ten carbons lie at the corners of two fused hexagons. Each carbon is attached to three other atoms by σ bonds, since these σ bonds result from the overlap of trigonal sp^2 orbitals and all carbons and hydrogen atom lie in a single plane. Above and below this plane there is a cloud of π electrons formed by the continuous overlap of *p* orbitals. We can consider this cloud as two partially overlapping sextets that have a pair of π electron in common. In terms of valence bonds, naphthalene is considered to be a resonance hybrid of three structures I, II and III. Its resonance energy, as shown by the heat of combustion, is 61Kcal/mole.



I II III

X-ray analysis shows that, in contrast to benzene, all carbon-carbon bonds in naphthalene are not the same; in particular, the C_1-C_2 bond is considerably shorter (1.365 Å) than the C_2-C_3 bonds (1.404 Å). Examining the structures I, II and III we can readily understood the difference of bond lengths in naphthalene ring. For convenience, we can represent naphthalene as the single structure **33**, in which the circles stand for partially overlapping aromatic sextets.

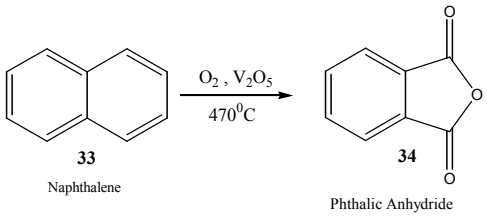


33

The resonance energy of naphthalene is about 61 Kcal/mole. Which is less than twice the amount of a single benzene ring (36 Kcal/ mol). As a result naphthalene is somewhat less aromatic and more reactive than the benzene.

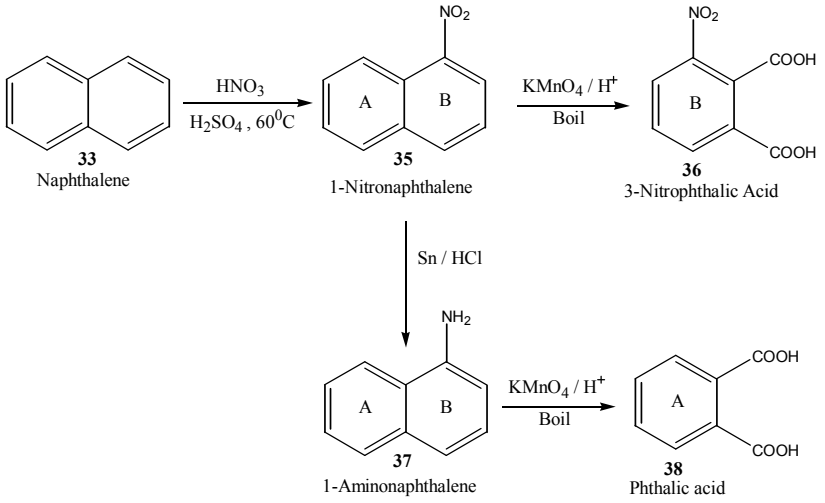
1.2.2 Naphthalene Contains two fused Benzene ring .

Oxidation of naphthalene **33** with oxygen and vanadium pentoxide at 470^0C yields phthalic anhydride **34**. This indicates the presence of a benzene ring with ortho side-chains in the molecule.



Nitration of naphthalene **33** produces a nitronaphthalene **35** which when oxidized gives 3-nitrophthalic acid **36**. Reduction of nitronaphthalene gives an aminonaphthalene **37** which when oxidized yields only phthalic acid **38**.

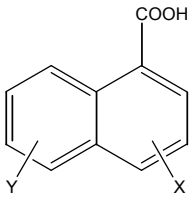
Scheme 1



The electrophilic nitro group stabilizes the benzene ring to which it is attached (ring B), and the other benzene ring is preferentially oxidized. On the other hand, the nucleophilic amino group makes the benzene ring to which it is attached (ring B) more susceptible to oxidation. These results clearly indicate that naphthalene consists of two fused benzene rings.

1.3 Substituted Naphthoic Acid

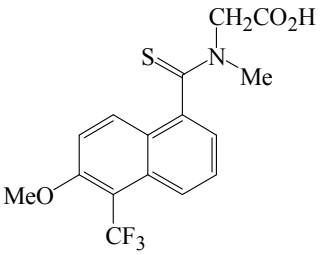
Naphthalene ring contains a –COOH group to any position is called naphthoic acid. Whenever substituent present in any position of the naphthoic acid leaving position C-1 is called substituted naphthoic acid.



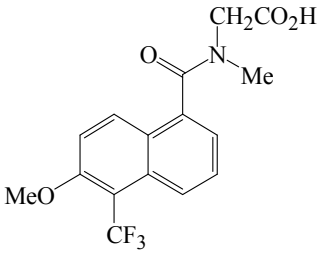
1.4 Application of Substituted Naphthoic Acid :

Substituted naphthoic acid is very important in various plant and animal growth activities. Among them 6-substituted acids and its derivatives are popularly used as valuable precursors to some life controlling drougs[13]. Tolrestat[14] **39, 40** are orally effective aldose reductase inhibitors on urinary albumin excretion rate and Glomerular filtration rate in IDDM subjects with Nephropathy, that are generally synthesized from 6-substituted naphthalene derivative.

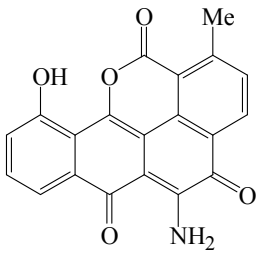
During the synthesis of chrymutin[15] **41** a potent antitumor agent, 2-methyl-6-methoxynaphthoic acid derivatives was used as the effective Michael acceptor for the annulation with cyanophthalide.[16] Fluorine contains at the metabolic site in aromatic and heteroaromatic rings is an important criteria of activity enhancement of some pharmaceuticals and acts as essential part in medicinal chemistry[17] which to convincingly increases the activity of the compounds.



Tolrestat **39**



Oxo-tolrestat **40**



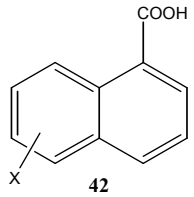
Chrymutin **41**

1.4.1 Anti-Cancer and anti-Dermatological activities[18]:

Naphthoic acids are identified as a potent RAR (Retionic Acid Receptor). Retinoic acid, a metabolite of retinol (vitamin A), is known to be involved in many essential life processes. A series of 6-substituted 2-naphthoic acid retinoids evaluated in vitro in a trans activation assay and a competition binding assay for all RARs. Particularly, because of its functions in cell proliferation and differentiation, retinoic acid and its derivatives (retinoids) have been extensively studied and show excellent beneficial effects in the treatment of cancers and several dermatological diseases.

1.4.2 Plant Growth Activity of Substituted 1-Naphthoic Acid Derivatives[19]:

1-Naphthoic acid derivatives **42** substituted with chlorine, bromine, methyl or nitro groups at various positions of the ring were assayed for their activities in the pea straight-growth and found appreciable results in regulating different plant growth.



42

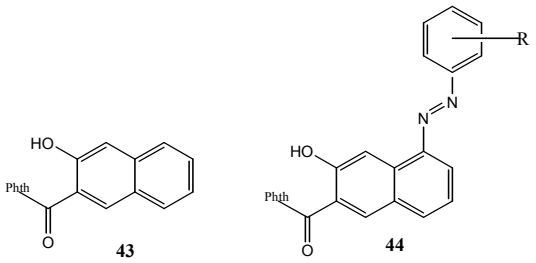
X= Cl, Br, OMe or NO_2

1.4.3 Substituted Naphthoic Acid Derivatives in the Treatment of Insulin Resistance and Hyperglycemia[20]:

This invention relates to substituted naphthoic acid derivatives as inhibitors of protein-tyrosine phosphatases (PTPases) and therapeutic compositions containing such compounds useful in the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic heart diseases of the large and small blood vessels.

1.4.4 Antibacterial Activity of Naphthalene Derivative[21]:

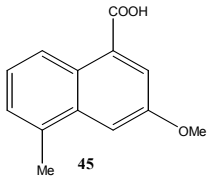
These given compounds are evaluated as antibacterial agents. The screening results showed that the compounds (given below) exhibited interestingly high activities compared with references drugs. Also, the mentioned compounds were applied to polyester as disperse dyes in which there color measurement and fastness properties were evaluated.



43(a) R=H
(b) R= m-CH_3
(c) R= o-CH_3
(d) R= o-OCH_3
(e) R= m-OCH_3
(g) R= m-Cl

1.4.5 Antitumor Activity of 3-Methoxy-5-Methyl-2-Naphthoic Acid: [22]

Azinomycin B is a potent antitumor antibiotic that features a set of unusual, densely assembled functionalities. Among them, the 3-methoxy-5-methylnaphthoic acid **45** moiety provides an important non-covalent association with DNA, and may, therefore, contribute to the specificity of DNA alkylation for biological activity exhibition.

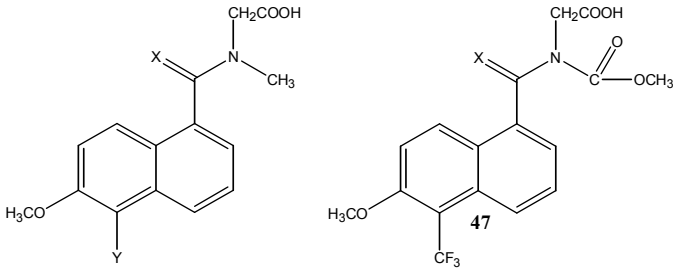


45

1.4.6 Uses of 6-Substituted Naphthoic Acids: [23]

Tolrestat **39** is currently marketed under the trade name alredase for the treatment of diabetic complications. The naphthoilamide analogue of Tolrestat **40** and the 5-bromo-bioisostere **46**, were also shown to be potent aldose reductase inhibitors, although both compounds were somewhat less effective in *vivo* than Tolrestat. In addition, the N-carboxymethoxy derivative **47**, was recently shown to have similar potency to **40 .** Tolrestat and its analogues belong to the carboxylic acid class of aldose reductase inhibitors. It is demonstrated that the intrinsic and oral activities of analogues of **39** are strongly influenced by the functionalities and the position of the substituents on the naphthalene ring. The carboxylic acid moity in **39, 40, 46, 47** is the key pharmacophore. Alteration of this group (for instance, esterification or amidation) resulted intrinsically

inactive compounds. The metabolic disposition and pharmacokinetics of Tolrestat were studied in rats, dogs, assamese, capuchin and found good results in each for Tolrestat. In addition, the ocular penetration of Tolrestat was examined in rabbits.



47

X=S, Y=CF_3, Tolrestat **39**; X=O, Y=CF_3 , Oxo-tolrestat **40**; X=S, Y=Br ,**46**

1.4.7 Use of Naphthoic Acid Derivatives in Polyneuropathy: [24]

Polyneuropathy , a common complication of diabetes mellitus, cause pain and sensory and motor deficits in the limbs, and is also an important independent predictor of foot ulceration. Inhibiting the metabolism of glucose by polyol pathway using aldose reductase inhibitors, is a potential mechanism to slow or reverse the neuropathys progression.

Diabetic mellitus is a serious threat to our helth and life. Specially in Bangladesh, Diabetic is spreading dramatically, not maintaining even ages and obesity. So, it is an urgent need to develop aldose reductase and other potential sugar reductases so that we can relief the pains and pangs of thousands lives. As far we know, Aldose reductase contains 6- or 5- methoxy / substituents in the naphthalene derivatives.

So, improvement of this general core unit is very crucial. In the little sphere we have tried to develop a procedure where 6- or 5-substituted naphthalene derivatives could be synthesized.

1.5. Organocatalyst :

Organocatalyst is a low molecular weight simple organic compounds containing S, N, or both that can accelerates a chemical reaction with substoichiometric amount and does not contain any metal atom.[25]

The advantages of organocatalysts include their lack of sensitivity towards moisture and oxygen, their ready availability, low cost and low toxicity, which confer a huge direct benefit in the production of pharmaceutical intermediates in comparison with metal / transition metal catalysts.

1.5.1 Organocatalysis :

The vast majority of organocatalytic reactions are amine based reactions. The scope of organocatalytic reactions has been expanded considerably. Typical transition-metal-mediated coupling reactions, such as Suzuki,[26] Sonogashira,[27] Ullmann, [28] and Heck-type coupling reactions,[29] as well as the Tsuji–Trost reaction,[30] can now be performed under organocatalysts.

1.5.2 Primary Attractions of Organocatalysis:

- Usually robust.
- Inexpensive
- Readily available
- Non - toxic
- Can carry unusual transformations that were not known earlier
- Insensitive towards moisture and oxygen
- Demanding reaction conditions (inert atmospheres, low temperatures, absolute solvent etc.) are usually not required
- Absence of transition metals especially attractive for the synthesis of pharmaceutical products &
- All organocatalysts are able to form temporary covalent bonds, with the substrates molecule and other catalysts can form H-bonds, or can engage pi-stacking or ion pair interactions (phase transfer catalysts).

1.5.3 Comparison with Conventional Analysis:

Type	Advantages	Disadvantages
Organometallic Catalysis	Wide substrate scope and high catalytic activity	Tedious process & potential heavy metal pollution
Enzyme catalysis.	High selectivity & limited Catalytic activity, usually single enantiomer.	Limited substrate scope
Organocatalysis	Simple structure, inexpensive . natural molecules & nontoxic.	Robust in organic synthesis

1.5.4 Organocatalyst in Modern Aspects:

An increasing number of asymmetric organic reactions can be accelerated by a catalytic amount of some chiral organic molecule. This novel type of catalysis has emerged as a major concept in organic chemistry in the last few years and is currently experiencing its golden age. The number of organocatalytic (non-asymmetric) reactions is steadily increasing, which provides a solid basis for the development of novel enantioselective reactions.[31] The increasing use of automatization and computational techniques may facilitate both the discovery of

novel catalyst structures and the screening of reactions by those catalysts for the next generations. Some of the advanced organocatalysts are highlighted below :

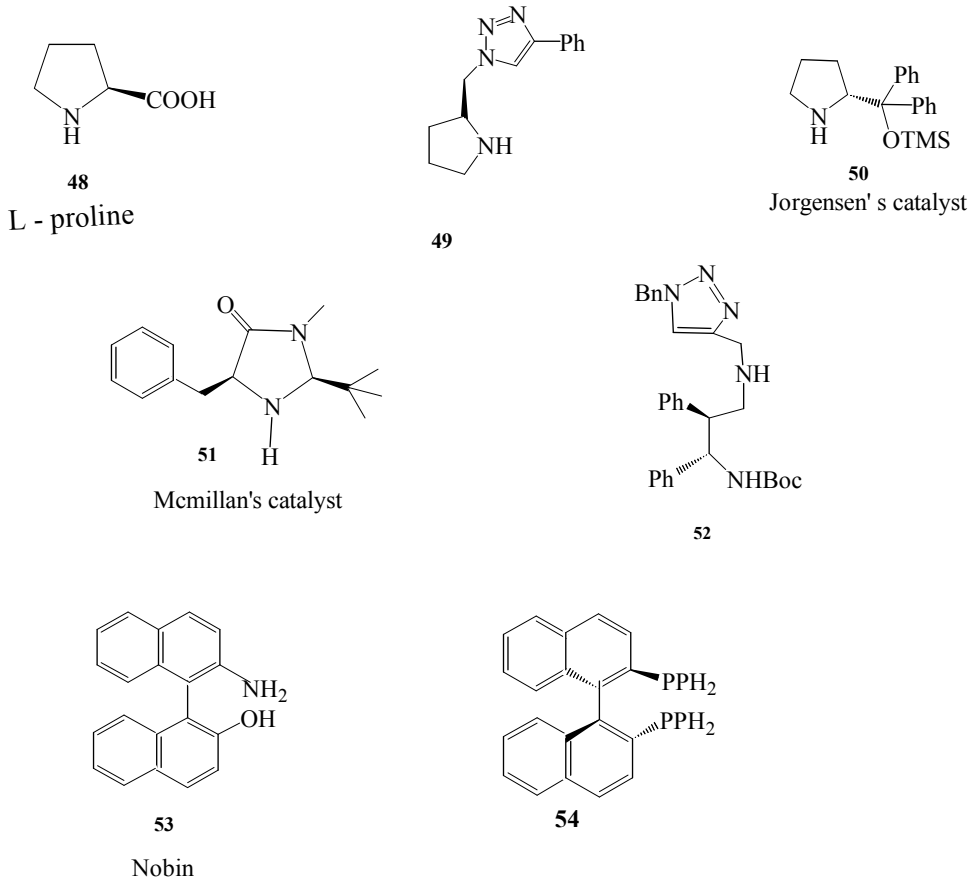


Figure 1: Some important organocatalyst

1.6 Heterogeneous Catalysis:

Whenever a catalyst perform its catalyzation reaction without being soluble in the solvent or can experience its catalytic activity in a biphasic reaction.[32] As for example, Pd-C in hydrogenation reaction can beautifully perform its catalytic activity without undergoing solubilization in the necessary solvent.[33]

1.7 Homogeneous Catalysis:

Whenever a catalyst present in a reaction as the soluble counterpart and can carry out its catalytic activity by mixing with the reactants intimately. Wilkinson, Noyori and today popularly known organocatalysts are the best examples of homogeneous catalyst. Metabolic reaction are carrying out by enzymes also known as organocatalytic reaction.[33]

1.8 Efficiency of Bismuth as Catalyst.

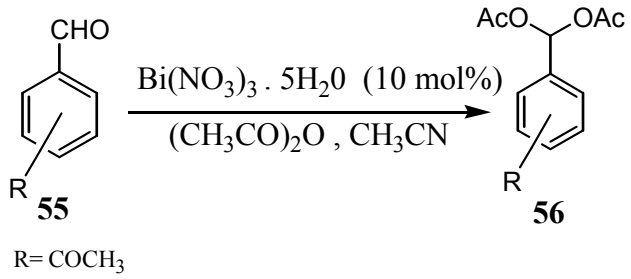
The bismuth is the heaviest stable element on the periodic table. In spite of its heavy metal status, bismuth is considered to be safe, as it is non-toxic and non-carcinogenic. Several bismuth compounds have application as treatment for gastric disorders. With increasing environmental concerns and necessity of 'green

reagents', the interest of bismuth and its compounds has increased tremendously in the last decade, since most of the bismuth compounds are non-toxic. Several review articles and a monograph has focused on the applications of bismuth and its compounds in organic synthesis. Some bismuth nitrate catalyzed reactions has been shown below:

1.8.1 Bismuth Nitrate in acetal formation[34]:

Chemoselective conversion of aromatic aldehydes into acetals :

This has report proved that bismuth nitrate, $Bi(N0_3)_3 \cdot 5H_20$ is an efficient catalyst for the chemoselective conversion of aromatic aldehydes **55** to a variety of acylals **56**.



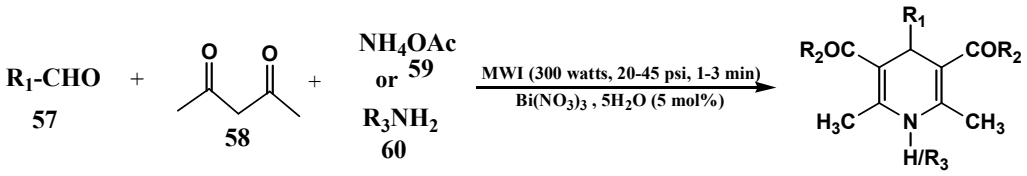
55 **56**

R= $COCH_3$

It is a new catalytic method where bismuth nitrate catalysis has been developed for the conversion of aromatic aldehydes (not ketones) to acelals with a variety of anhydrides.

1.8.2 Hantz Reaction effected by $Bi(NO_3)_3$:[35]

The classical **Hantzsch** reaction is one of the simplest and most economical methods for the synthesis of biologically important and pharmacologically useful 1, 4-dihydropyridine derivatives. Bismuth nitrate pentahydrate under microwave irradiation has proven its potentiality to synthesize of 1, 4-dihydropyridines in excellent yields.



R_1 = aryl, alkyl, heteroaryl

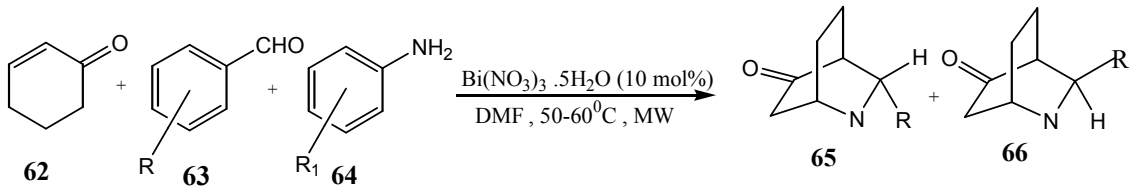
R_2= Me, OEt, OMe

R_3 = aryl, heteroaryl

1.8.3 Bismuth Nitrate-Catalyzed Aza-Diels-Alder Reaction [36]:

Bismuth nitrate-catalyzed microwave-assisted one-pot three components Aza-Diels-Alder reaction has been investigated. Attempt has taken to optimize the conditions for the Aza-Diels-Alder reaction using aromatic aldehydes **63**, amines **64** and cyclohexenone **62** in various solvents under conventional heating and

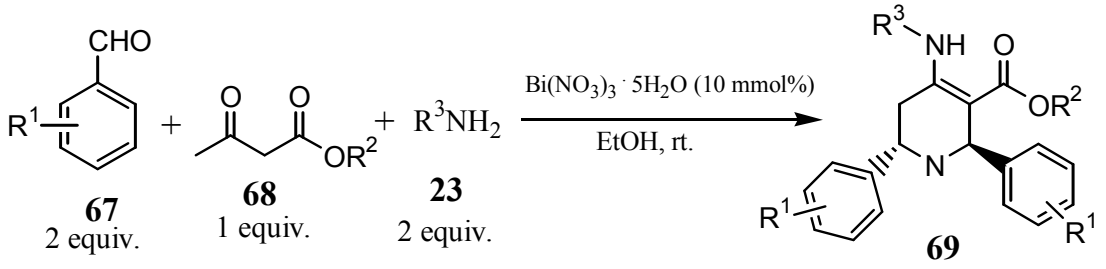
obtained the following bicyclic compounds **65, 66.**



If the above reaction was carried out without bismuth nitrate, no desired product was obtained. So the trivalent bismuth (III) has a strong tendency to coordinate with the oxygen atoms of the cyclic enones and enhances the keto-enol tautomerization. This helped to shift the equilibrium toward the enol form (cyclohexadienolate) which can act as the diene counterpart in the cyclization**.**

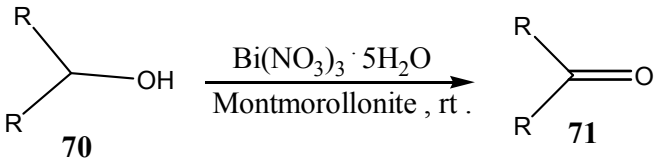
1.8.4 $Bi(NO_3)_3$ in Diasterioselective Synthesis[37]:

A simple, straightforward, and highly efficient diastereoselective multicomponent one-pot synthesis of a series of pharmaceutically interesting functionalized piperidine derivatives **69** were prepared via a low-cost and environmentally benign $Bi(NO_3)_3 \cdot 5H_2O$ catalyst.

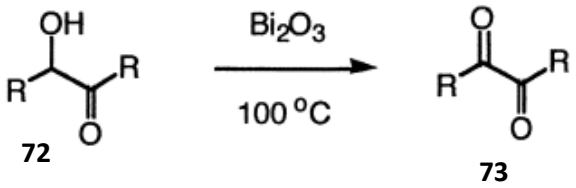


1.8.5 Oxidation Carried out by $Bi(NO_3)_3$:

(i). Oxidation of 2^0 alcohols **70** to ketones **71** using bismuth nitrate, $Bi(NO_3)_3$, impregnated on montmorillonite has been reported.[38] The oxidation is very rapid at room temperature and proceeds well without the need for any pre-treatment of the catalyst or microwave irradiation.

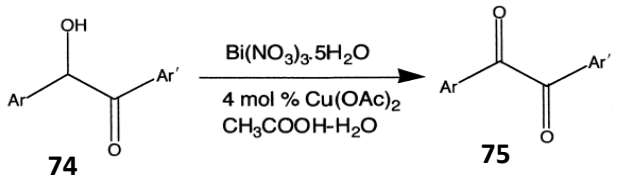


(ii). Bismuth(III) oxide, Bi_2O_3 is also used for the oxidation of acyloins **72** to diketones[39] **73** in acidic or ethanolic solvent in high yields.



Entry	R	Time	Solvent	Yield (%)
1	Ph	1 h	AcOH-$HOCH_2CH_2OCH_2CH_3$	95
2	Ph	30 min	AcOH	93
3	*p*-$MeOC_6H_4$	1 h	AcOH-$HOCH_2CH_2O\ CH_2CH_3$	95
4	*p*-$MeOC_6H_4$	20 min	AcOH	91
5		1.25 h	AcOH-$HOCH_2CH_2OCH_2CH_3$	97
6		45 min	AcOH-$HOCH_2CH_2OCH_2CH_3$	92
7		10 min	AcOH-H_2O	88
8	$CH_3CH_2CH_2$–	15 min	AcOH	64

(iii) Oxidation of benzoins **74** into benzils **75** using bismuth nitrate in aqueous acetic acid has given below, just to give an idea about the conversion rate and yields.[40]

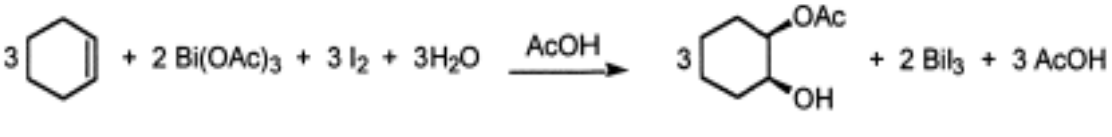


74 **75**

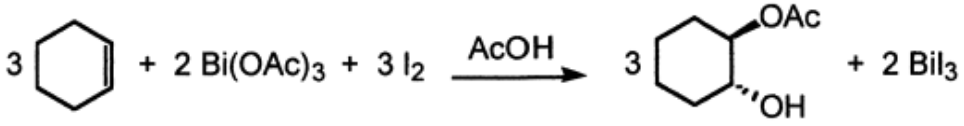
Entry	Ar	Ar'	Yield (%)
1	Ph	Ph	99
2	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	99
3	*p*-MeC_6H_4	*p*-MeC_6H_4	95
4	Ph	*p*-$MeOC_6H_4$	95
5			58
6			10

1.8.6 Woodward[42] and Prevost [41] oxidation by $Bi(NO_3)_3$:

The Prevost (dry) and the Woodward–Prevost (wet) reactions for the conversion of alkenes into diols were typically carried out with silver(I) salts. Modification of these reaction with bishmuth(III) acetate in 'wet' and 'dry' acetic acid, respectively gives cis- and trans-diol derivatives from alkenes.



76 **77**

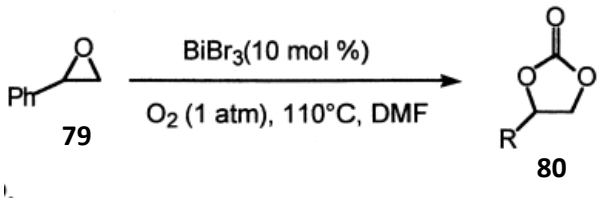


78

76

1.8.7 Formation of Cyclic Carbonates by $BiBr_3$ [43]:

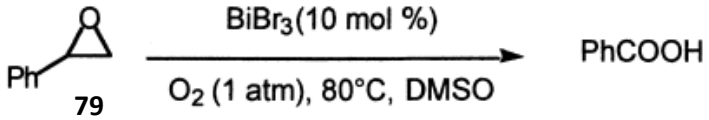
Oxidation of epoxides **79** into cyclic carbonates **80** using molecular oxygen also carried out by the oxidant and a catalyst $BiBr_3$.



79 **80**

1.8.8 Convertion of Epoxide into Benzoic acid :

Oxidation of the epoxides can also be carried out in the presence of DMSO and $BiBr_3$ which afforded carboxylic acids **81** from an epoxide **79**

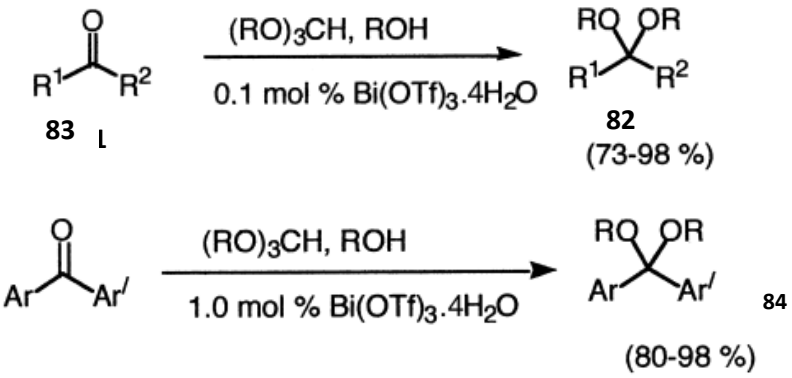


79 **81**

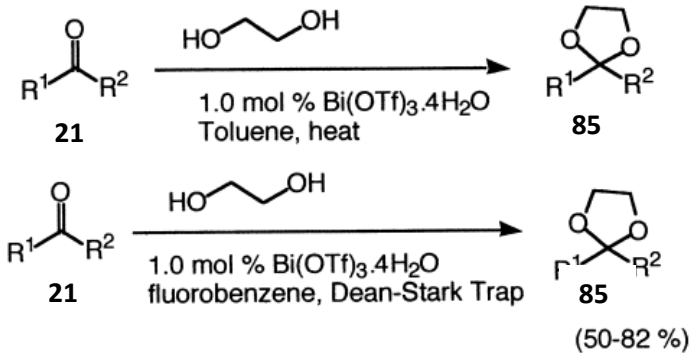
1.8.9 Protection of Carbonyl Functionality:

In the past, acetals **82**[44] were obtained by the treatment of aldehydes and ketones **21** with trialkyl orthformate and the corresponding alcohol in the presence of 0.1 mol% $Bi(OTf)_3 \cdot 4H_2O$. Synthesis of dialkyl acetals from diaryl ketones is more difficult, and the standard acetalization conditions generally do not work with

diaryl ketones. Now a days Triflic acid (20 mol%) found to be a superior catalyst for the synthesis of diaryl ketones. But, Bismuth triflate (1.0 mol%) was found to be more effective[45] for the acetalization of diaryl ketones **83**.

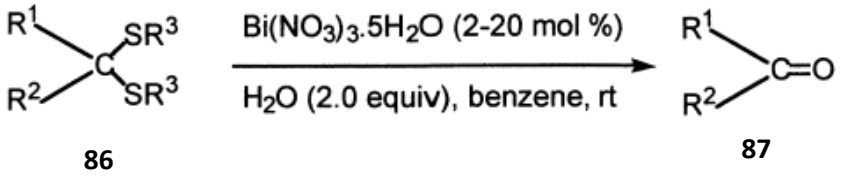


Bismuth triflate also an effective catalyst for the protection of aldehydes and ketones **21** as 1, 3-dioxalanes **85**.



1.8.10 Deprotection of S, S-acetals into carbonyl compounds[46] :

The oxidative deprotection of S, S-acetals **86** using $Bi(NO_{3)3}\cdot 5H_2O$ as a catalyst proceeds smoothly at room temperature to give the corresponding carbonyl compounds **87** in good yields**.**



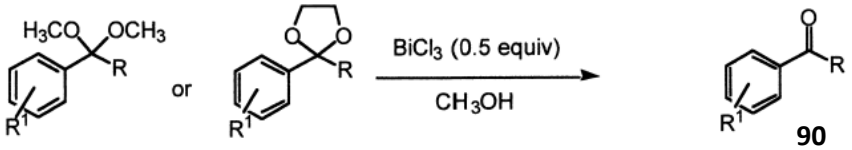
86 **87**

R^1 = *p*-$MeOC_6H_4$, Ph, $Me(CH_2)_6$, $Me(CH_2)_5$, $Me(CH_2)_4$,

R^2 = H, Me, Et R^3 = $(CH_2)_2$, $(CH_2)_3$, Ph, Et, $(CH_2)_3$,

1.8.11 Deprotection of O, O-acetals[47]:

Several bismuth(III) compounds have been used to deprotect O, O-acetals. One chemoselective method for deprotection of acetals **88, 89** makes use of the catalytic activity of $BiCl_3$ in CH_3OH as the solvent**.**

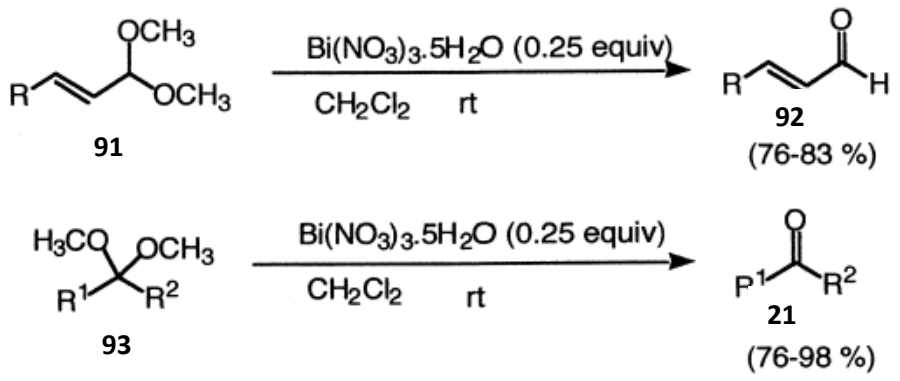


88 **89** **90**

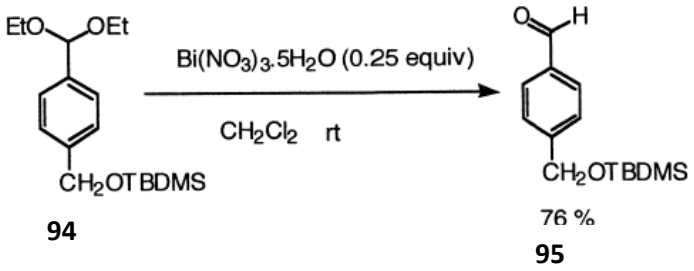
(70-92 %)

1.8.12 Chemoselective removal of –OMe[48]:

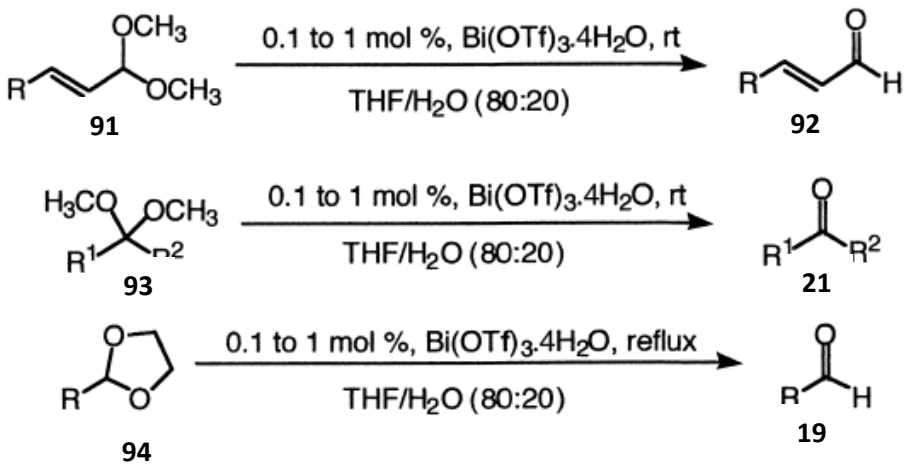
Another mild and chemoselective method has utilized $Bi(NO_3)_3 \cdot 5H_2O$ inCH_2Cl_2 for the deprotection of acetals **91, 93.**



The chemoselectivity of the same method has been demonstrated to selective deprotection of a bi-functional compound **94** given below:



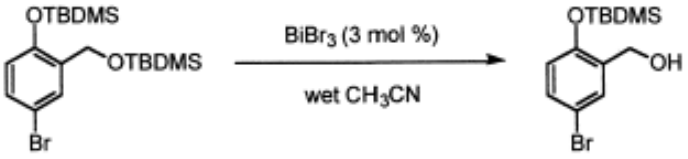
A highly catalytic, mild and efficient method[49] for the deprotection of acetals **91, 93**, which takes advantage of the catalytic activity of bismuth(III) triflate has recently been reported



91 92 93 21 94 19

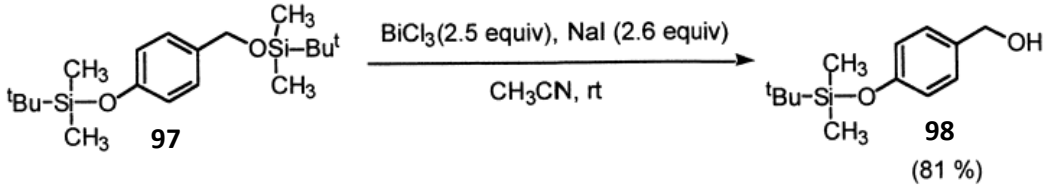
1.8.13 Deprotection of a tert-butyldimethylsilyl (TBDMS)[50] group:

A highly efficient procedure for the selective cleavage of alkyl TBDMS **95** groups in the presence of aryl TBDMS groups using $BiBr_3$ in wet CH_3CN has shown below:



95 96

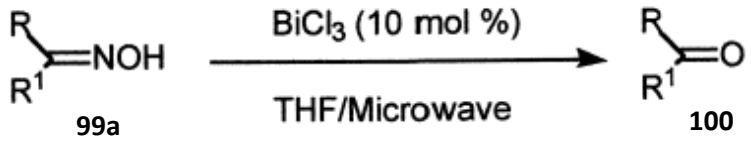
Another method that utilized excess $BiCl_3$ / NaI in CH_3CN, has also an effective method[51] for TBDMS expulsion.



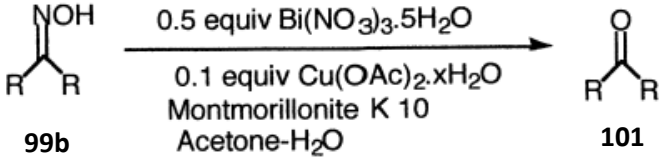
97 98

1.8.14 Deprotection of oximes to Carbonyl compounds :

The regeneration of carbonyl compounds **100** from oximes is an important synthetic transformation, especially in light of the fact that oximes **99a** can be synthesized from non-carbonyl compounds. An efficient method that utilizes $BiCl_3$ and microwave irradiation has been used for oxime deprotection.[52] The selective deprotection of ketoximes **99b** has been achieved using $Bi(NO_3)_3 \cdot 5H_2O$ in a relatively non-toxic solvent system acetone-H_2O.[53]

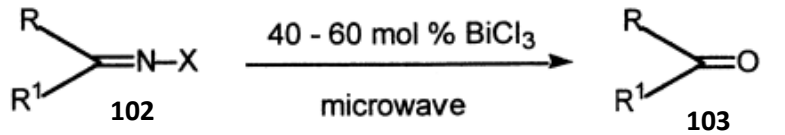


99a **100**



99b **101**

An efficient method for the hydrolytic cleavage of C=N bond of dimethyl and tosylhydrazones **102** to yield the corresponding carbonyl compounds **103** using $BiCl_3$ in wet THF under microwave irradiation has been reported.[54]

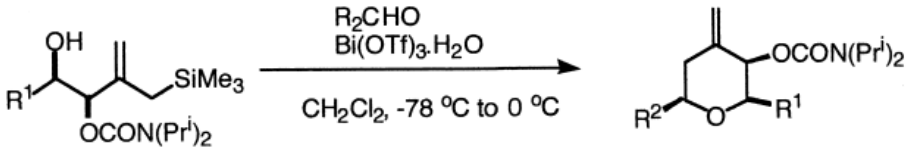


102 **103**

X = -NMe_2, -NHTs (75 - 98 %)

1.8.15 Cyclization carried out by Bismuth Salt:

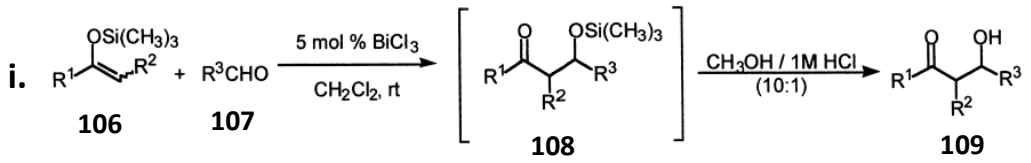
The intramolecular Sakurai cyclization[55] of homoallylic alcohols **104** to yield polysubstituted tetrahydropyrans **105** were efficiently catalyzed by $Bi(OTf)_3 \cdot H_2O$**.** Target products were obtained in good yields but no desilylated by-products were obtained.

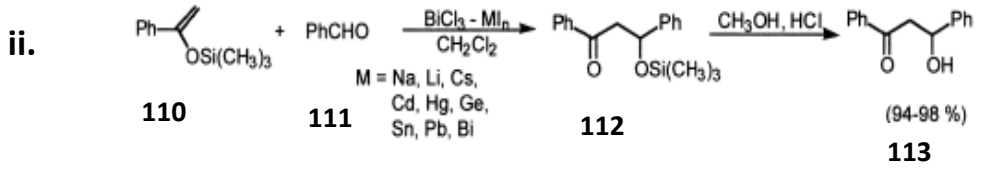


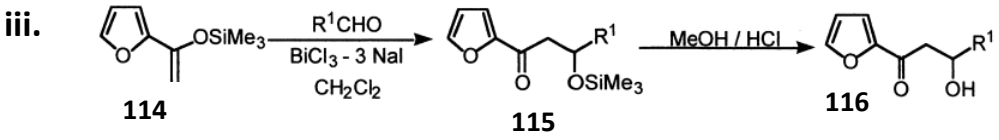
104 (84-98 %) **105**

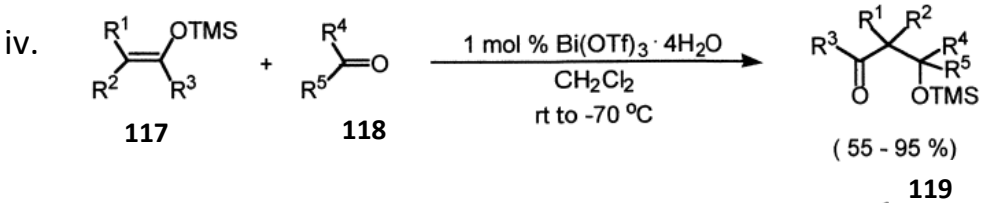
1.8.16 Aldol condensations by Bismuth Salt [56-58]:

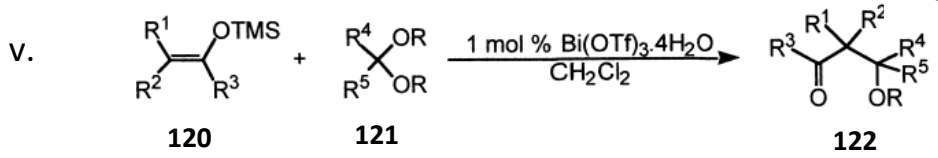
One of the most important carbon– carbon bond forming reactions in organic chemistry is the Mukaiyama-aldol condensation.[56] Bismuth(III) chloride has been well studied as a catalyst for carbon–carbon forming reactions by Wada and co-workers[57] as well as Dubac and co-workers[58] and has proven to be an efficient and mild catalyst for such reactions were Bismuth(III) chloride (5 mol%). Both aliphatic and aromatic aldehydes gave good results.





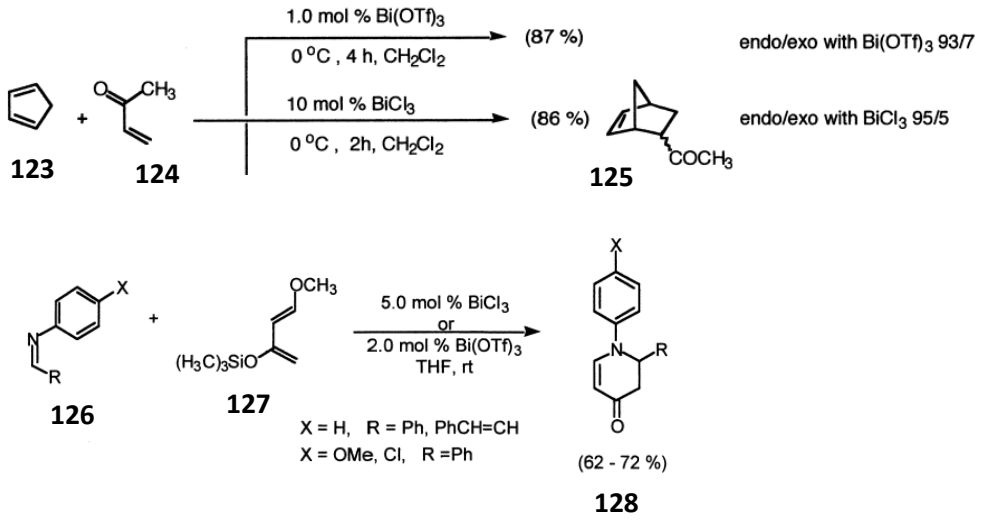






1.8.17 Diels–Alder and Aza-Diels–Alder reaction by Bismuth Triflate:

Dubac and co-workers discovered that $BiCl_3$ and $Bi(OTf)_3$ are mild and efficient catalysts for the Diels–Alder reaction.[59] Both bismuth(III) chloride, $BiCl_3$ and bismuth triflate, $Bi(CF_3SO_3)_3$, are very efficient catalysts for the hetero Diels–Alder reactions of imines **124, 126** with Danishefsky's diene[60] **123, 127**.



So, From the literature reports, Bismuth(III) salt has proved to be an effective catalyst to many reactions. From this literature reviews it has well established that Bismuth(III) salt could be used to other newer reactions where other metal toxic salts were successfully used.

1.9 Green Chemistry

A proverb says, "Prevention is better than cure." As the voices against pollution become louder and louder in the later part of the twentieth century, the USA went for the prevention of pollution by passing the pollution prevention act of the 1990, which established a national policy to prevent or reduce pollutions at its source whenever possible. Scientists came forward to accept the challenge and in no time the newest branch of chemistry called green chemistry emerged, which is defined by the IUPAC as the "invention, design and application of chemical products and processing to reduce or eliminate the use and generation of hazardous substance". Green chemistry aims at tackling problems before they happen.

1.9.1 Principle of Green Chemistry: P. Anastas and J.C. Warner[61] formulated in 1998 twelve Principle of green chemistry those are as follows

1. **Prevent waste:** Design chemical synthesis to prevent waste, leaving no waste to treat or clean up.
2. **Design safer chemicals and products:** Design chemical products to fully effective, yet have little or no toxicity.
3. **Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or toxicity to humans' and the environment.

4. **Use renewable feedstocks:** Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fassil fuel (petroleum, natural gas or coal) or are mined.
5. **Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are use small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. **Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
7. **Maximize atom economy:** Design synthesis so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
8. **Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.
9. **Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.

10. **Design chemicals and products to degrade after use:** Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.
11. **Analyze in real time to prevent pollution:** Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
12. **Minimize the potential for accidents:** Design chemicals and their forms (solid, liquid or gas) to minimize the potential for chemical accidents including explosions, fires and releases to the environment.

1.9.2 Scope of Green Chemistry: The scope of green chemistry is so vast that it is almost impossible to bring all the areas within the purview of this short article. The principle of green chemistry can be applied broadly to areas like synthesis, catalyst, reaction conditions, analysis and monitoring, extraction, separation, etc. an emerging area of increasing importance in green chemistry is that of analytical chemistry and all its associated activities. Green chemistry should find its greatest use in all sectors chemical industry, ranging from pharmaceuticals and specialty chemicals to high volume manufacture of bulk chemicals. Waste treatment being the Achilles heel of the industries, the focus of the industries is now no minimizing

the production of waste by reducing or eliminating water or organic solvents. If solvent use is unavoidable, they are trying to recycle it; in other cases they are either going for “solvent free” or “solvent alternatives”.

1.9.3 Some Achievements of Green Chemistry: Achievements of Green Chemistry include amongst many others the following-

1. Bristol-Myers Squibb Co. has developed a green way of producing their anti-cancer drug, Taxol, which would protect the environment from an estimated 6.5 tons of hazardous substances per annum.
2. Development of a green process eliminated millions of pounds of wastes annually in Monsanto’s production of herbicide, “Round-up”.
3. Dow chemical company’s substitution of 100% CO_2 for ozone depleting CFCs in the making of polystyrene.
4. Development of economical processes to substitute biodegradable thermal polyasperate for polyacrylic acid, a key component of such products as disposable diapers and contact lenses, by the Donald Company.

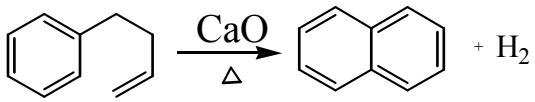
Chapter 2

Review of the Synthetic Approaches:

So far we know, naphthalene ring contains two benzene rings fused each in ortho sense. Therefore, to synthesize naphthalene or naphthalene derivatives we have to start either from benzene ring or from naphthalene ring. To start from naphthalene ring and to impose substituents to a particular position on the ring specially to a particular position is tough, because settlement of substituents onto a particular position is not a manual job for the tiny entity molecule. Therefore, Chemists are thinking newer strategies / schemes to synthesize naphthalene derivatives. Some of them are highlighted below :

2.1.1 From 4-phenyl-1-butene[62]:

When 4-pheny-l-butene **129** is passed over red hot calcium oxide, it will give naphthalene **32**. But this theoretical method require to synthesize the precursor **129,** which is an additive difficult iob in the synthesis.

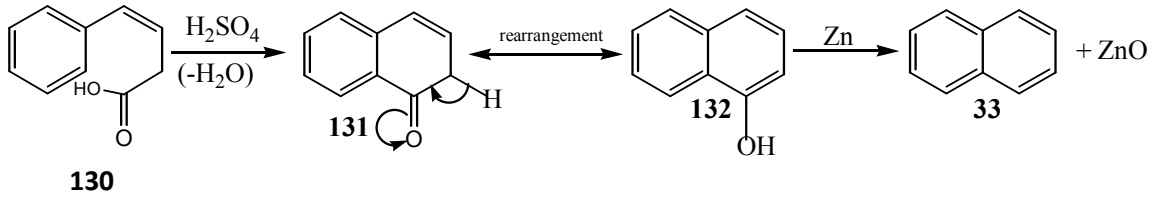


129 **32**

2.1.2 From 4-phenyl-3-butanoic acid : [63]

When 4-phenyl-3-butenoic acid is heated with Concd. sulfuric acid, 1-naphthol is formed which on distillation with zinc dust gives naphthalene. But making the precursors **130** needed needed a few steps to synthesize.

Scheme : 2



2.1.3 Haworth Synthesis[64]: Haworth had focused a long route to synthesize naphthalene which is consisting of the following regular routes :

Step 1: Benzene **33** and succinic anhydride **134** are heated in the presence of anhydrous aluminum chloride to form *β*-benzoylpropionic acid **135** which is Friedel Crafts acylation.

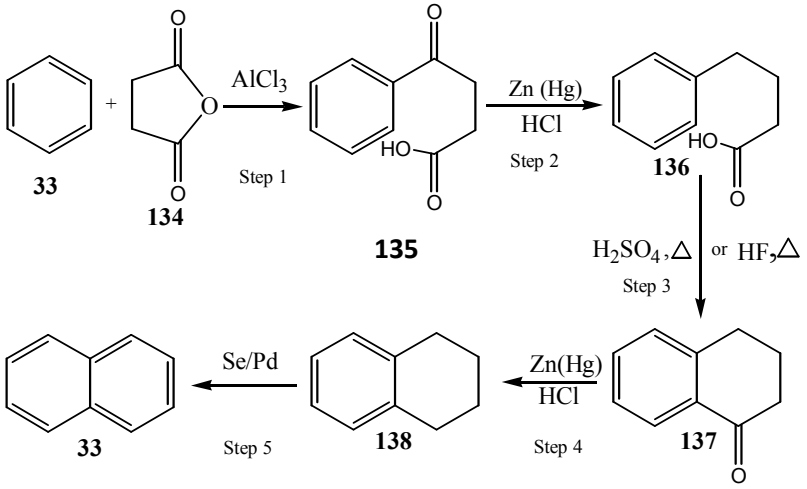
Step 2: *β*-Benzoylpropionic acid **135** is treated with amalgamated Zinc in the presence of hydrochloric acid to give *γ*-phenylbutyric acid **136** by Clemmensen method.

Step 3: γ-Phenylbutiyric acid **136** is heated with concentrated sulfuric acid or HF or Phosphoric acid to form α-tetralone **137** briefly known 'Ring Closure Reaction'.

Step 4: Further Clemmension reduction to α-Tetralone with amalgamated zinc and hydrochloric acid to give tetralin **138** a hydrocarbon**.**

Step 5: Tetralin is heated with selenium or palladium to make tetralin into aromatic naphthalene **33**.

Scheme: 3

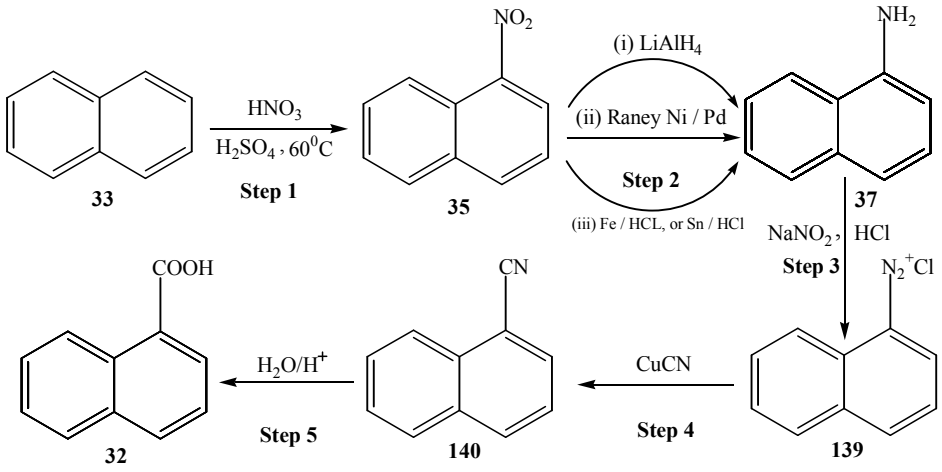


Substituted naphthalenes coud be obtained by using toluene, bromobenzene or anisole instead of benzene from the same scheme **3**.

2.1.4 Preparation of 1-Naphthoic Acid from Naphthalene:[65]

Naphthalene undergoes nitration at 40~60^{0}C afforded 1-nitronaphthalene **35** which on reduction gives 1-aminonaphthalene **37**. 1-Naphthylamine reacted with sodium nitrite in excess dilute hydrochloric acid at 0-5^0 C yielded 1-naphthalene diazonium chloride **139**. Treatment of diazonium salt with $Cu_2(CN)_2$ gives 1-cyanonaphthalene **140** which on hydrolysis in concentrated HCl gives 1-naphthoic acid **32**.

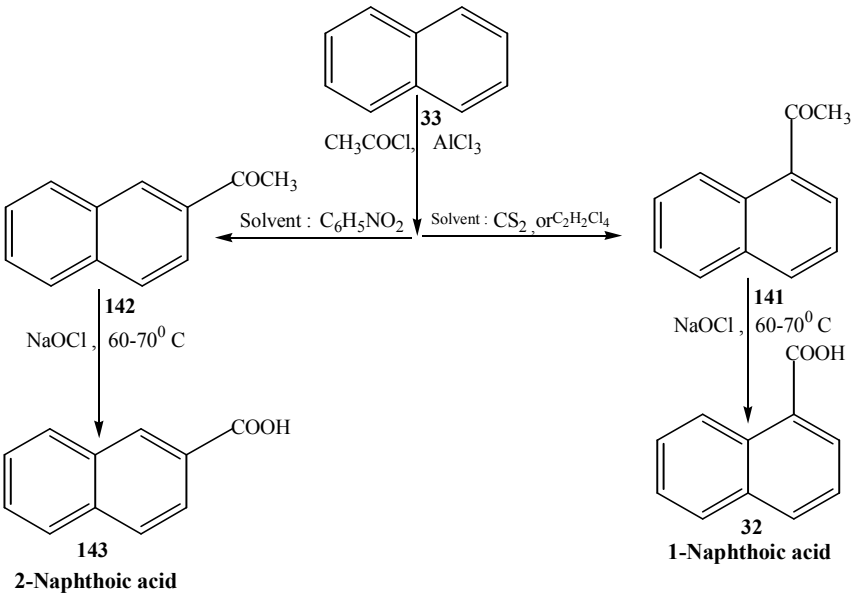
Scheme : 4



This is undoubtedly a longer reaction routes to accomplish 1-naphthoic acid. But, today people seeking short cut ways to reach the targets.

2.1.5 Preparation of Naphthoic Acid by Friedel-Crafts Acylation of Naphthalene: [66]

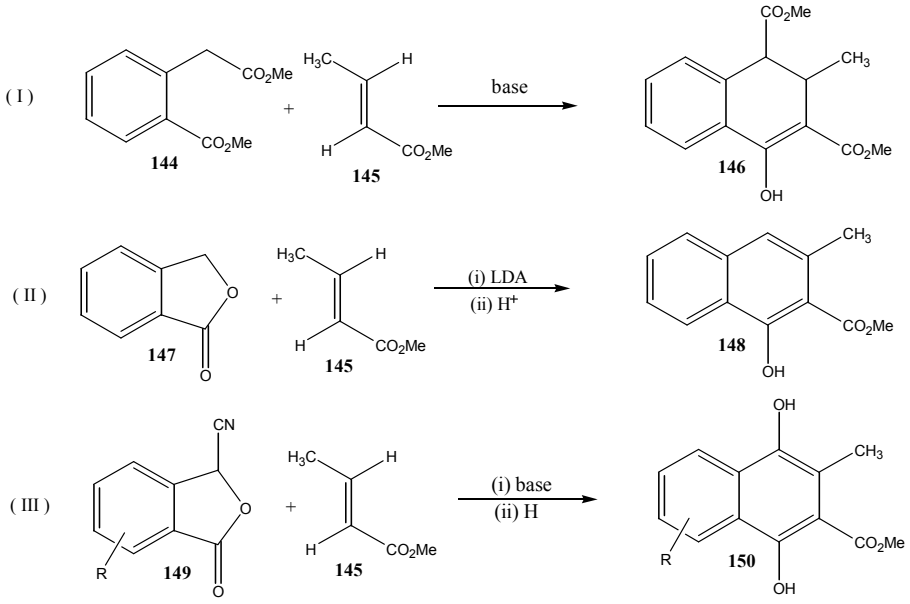
Naphthalene can be acetylated by acetyl chloride in the presence of anhydrous aluminum chloride. The orientation of substitution is determined by using special solvents. α-Substituents **141** are generally obtained in carbon disulfide or solvents like tetrachloroethane and predominantly gives β-substituents in naphthalene **143**. Treatment of these acetonaphthalene with NaOCl provides the following naphthoic acid, **32 or 143.** **Scheme: 5**



But by this procedure, substituents at the other position are not readily to be impossed, because, Friedel-Crafts alkylation or acylation sometimes removes the –OMe, -OEt or CH_3CO- substituents by excess anhydrous $AlCl_3$.

2.2 Michael Initiated Ring Closure Reaction: [67]

The Michael initiated ring closure reactions (MIRC) of phthalides have been introduced by different groups almost simultaneously for generation of naphthalene moiety. A variety of reagent serving the purpose of 1,4- dipolar synthons has been developed. The important feature of these methodologies are convergence and regiosfecific with respect to peripheral positions of the ring skeleton. This methodology has been effectively exploited in synthesizing different polycyclic ring skeletons with fixed regiochemistry by mere choice of suitable 1,4-dipolar synthons and Michael acceptors. Some of the important 1,4-dipolar synthons and Michael acceptors are given below

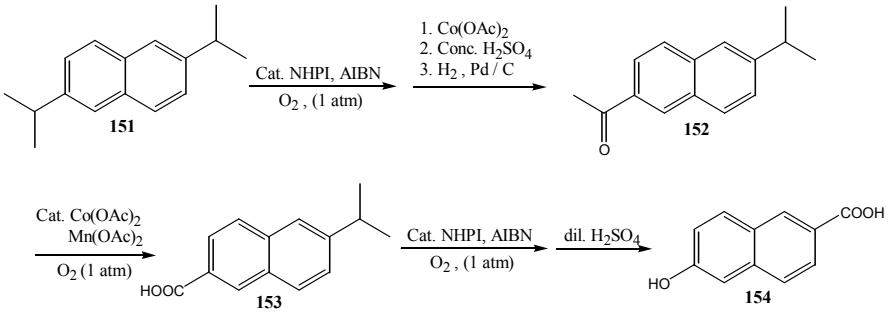


All of these reactions were carried out in the presence of base, thus acid sensitive functionalities of the products will remain intact. Although the reactions are quite general but their success depends on the reaction conditions e.g., nature of base, solvent and temperature.

2.3 Synthesis of 6-Hydoxy Naphthoic Acid

A new strategy to synthesize 6-hydroxy-2-naphthoic acid (HNPA) **154** from 2,6-diisopropyl- naphthalene **151**, was developed by using the NHPI-catalyzed and aerobic oxidation as a principal reaction route. 2, 6-Diisopropylnaphthalene was oxidized by the aerial oxidation (1 atm) under NHPI (10 mol %) combined with $Co(OAc)_2$ (0.5 mol %) to give 6-acetyl-2-isopropylnaphthalene **152**, which was then converted to 6-isopropyl-2-naphthoic acid **153** under O_2 (1 atm) in the presence of $Co(OAc)_2$ (0.5 mol %) and $Mn(OAc)_2$ (0.5 mol %). Esterification of the resulting acid followed by aerobic oxidation produced methyl 6-hydroxy-2-naphthoate whose hydrolysis led to the desired HNPA **154**. An alternative route involves the oxidation of 6-acetyl-2-isopropylnaphthalene to 6-acetyl-2-naphthol on which subsequent oxida **Scheme : 6** cetylation gave HNPA. This method was successfully extended to the synthesis of 4-hydroxybenzoic acid from *p*-cymene.

Scheme: 6

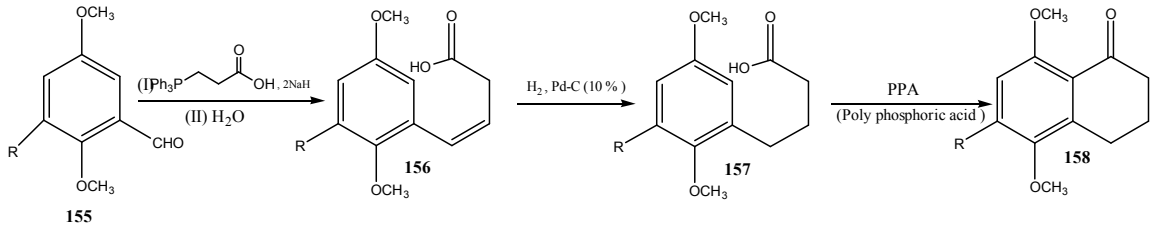


This above method exploited two metal acetate which are restrictly prohibited for the environment. Today, chemists are seeking metal free method to reach the targets.

2.4 Synthesis of Naphthalene Moiety Via Tetralones: [68]

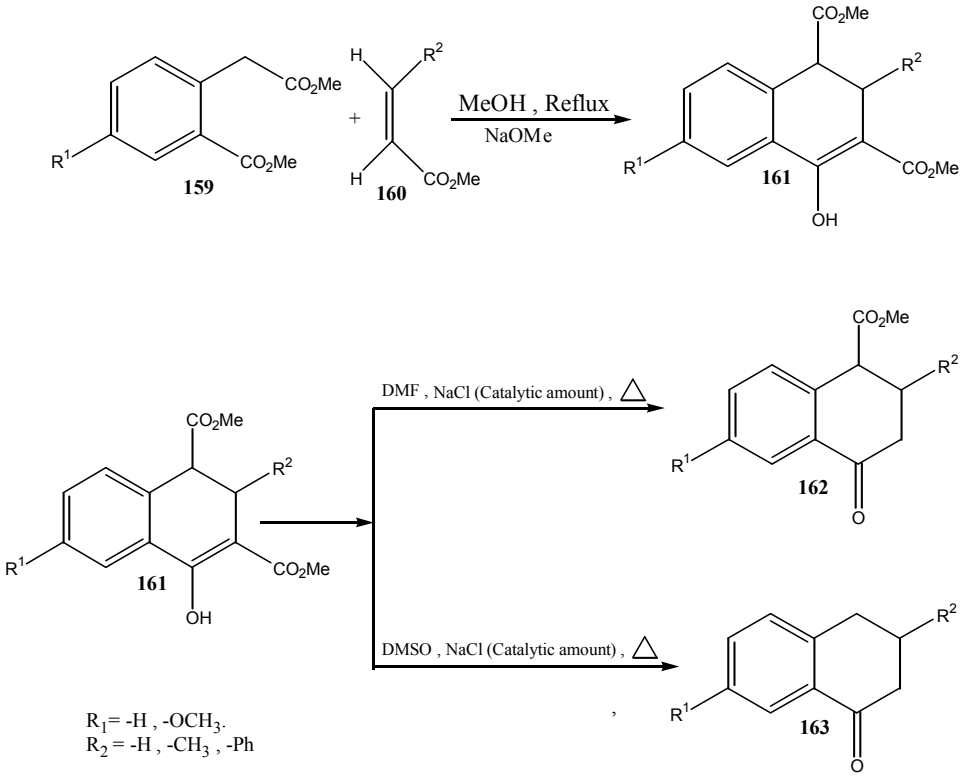
The usual method to prepare α-tetralone is a lengthy procedure. The following given scheme has shortened the longer the reaction path for the tetralone synthesis.

Scheme : 7



In consonance with the previous work an attempt was initiated in Roy's laboratory[69] to synthesis α-tetralones by a simple condensation procedure with homophthalates **159** and acrylates **160**. The condensation was eventually formed an enolic product , which on subsequent treatment with DMF and DMSO, afforded different α-tetralones **162, 163**. But in this method yield of the enolic product **161** was not satisfactory.

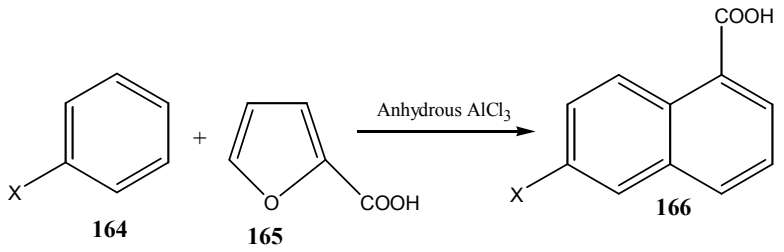
Scheme: 8



All these α-tetralones would be the precursors of different naphthoic acid derivatives. But the method to synthesize naphthoic acid via tetralones [70] is not general to all kinds of naphthalene derivatives, and particularly this method is lengthy and cumbersome.

2.5 Reaction of Furoic Acid with other Aromatic Substrates :[71]

C. C. Price et al [71] in 1958 has utilized anhydrous aluminum chloride to react furoic acid with benzene to fabricate α-naphthoic acid. They have isolated the pure 6-methoxy naphthoic acid with poor yield (11~12%). Later, McCorcle and Turck[72], isolated methyl α-Naphthoate (56%) from the aluminum chloride catalysed reaction of methyl furoate with benzene. They also reported that toluene, anisole and chlorobenzene reacted similarly and afforded the corresponding 6-substituted-1-naphthoic acids, With other important impurities having naphthalene ring.



164 **165** **166**

X= H, CH_3 , OCH_3 or Cl

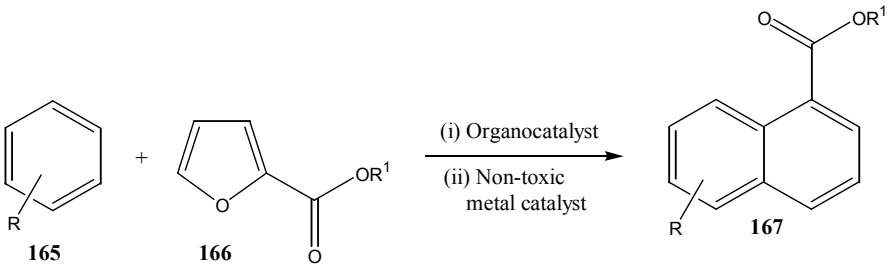
This method afforded naphthoic acid with lower yield. So the present requirements demanded another new method.

Although several methods has already been emerged out to serve the purpose of naphthalene synthesis, but they are all not free from restraints. So, today, chemists are seeking newer methodologies to synthesize naphthoic acid derivatives that can satisfy the current requirements like yields, economy, shortcut ways and above all a green process.

Chapter 3

3. Aim of the Work:

C. C. Price's method[71] is an elegant method to synthesize naphthoic acid to a very short-cut way with furoic acid and anisole in exess anhydrous $AlCl_3$. Unfortunately, this method afforded only 11~12 % yield. In this dissertation we would like to take an initiative to develop the yield of naphthoic acid derivatives with varying substituent at different position of naphthalene ring. Therefore, herein, we wish to select a non pollutant catalyst to improve the yields and to remove the difficulties either by an organocatalyst or any non-toxic metal catalyst.



165 **166** **167**

R = H, CH_3, OCH_3, Cl, OH

R^1 = H, CH_3

If, anyway, our strategy becomes successful then we can afford huge naphthoic acids with different substituent.

Chapter 4

4. PRESENT WORK (Results and Discussion):

After rigorous studies from various literatures it is perceived that substituted naphthoic acids are the essential core units to several biologically active compounds. Due to immense antibacterial activities of various naphthoic acid derivatives and today, all are mostly used as aldose reductase inhibitors and the valuable precursors of some life controlling drugs, it is very crucial to find a short-cut way to synthesize them. Unfortunately, up till now, there are no suitable methods available to synthesize naphthoic acid derivatives in a one-pot strategy. Some of the conventional methods are available but they are not free from restraints, specially, lengthy, clumsy preparation & purification procedures. In view to eliminate those difficulties, we were searching an appropriate and advantageous technique to synthesize naphthoic acid derivatives.

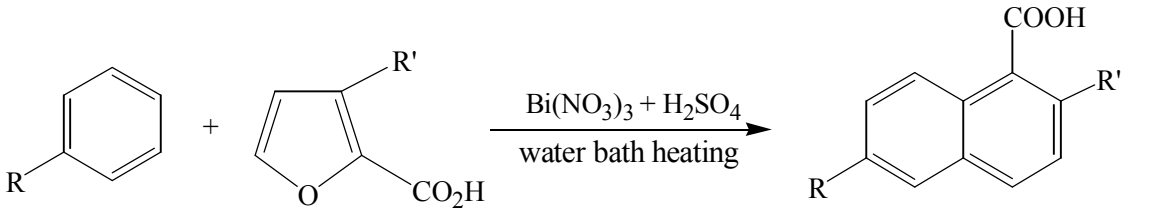
Considering huge demands of this biologically active precursors we herein, have tried to standardize and modify an old, conventional method,[71, 72] where the mentioned yields were very poor (10~12%). The investigation was first started in view to prepare 6-methoxynaphthoic acid **170** by the condensation technique of furoic acid with excess anisole in the presence of excess anhydrous $AlCl_3$ at about 70°C. After 24 hour, a tan color product was isolated from the water through a

clumsy separation of huge sticky materials developed in this reaction. Overall isolated yield of 6-methoxynaphthoic acid **170** was poor (only 7-11%). Therefore, to overcome these difficulties we have attempted different tricks to make the reaction clean and high yielding. In one such effort, catalytic amount of mixed Lewis acid ($ZnCl_2$ and $AlCl_3$) were employed to three equivalent of anisole and one equivalent of furoic acid. By this tricky way, we have avoided the sticky materials, but the yield was not satisfactory. After reaction, the starting furoic acid was recovered which was the symptom of the anisole lacks in the reaction medium. Later, we also employed $ZnCl_2$ with anhydrous $CuSO_4$ in view to remove H_2O from the reaction media. But in this case, the resulting sticky product did not show any naphthoic acid in TLC detection. It was suspected that with this reagent furoic acid ring did not opened and not involved in the reaction. Exploitation of $ZnCl_2$ with few drops of (Concd.) H_2SO_4 to the same reaction mixture did not bring about any improvement of the yield.

Today, Bismuth compounds have drawn much attraction due to their remarkably low toxicity, low cost and ease of handling in many reactions. Specially Bismuth(III) nitrate pentahydrate, $Bi(NO_3)_3 \cdot 5H_2O$, is notable because it is inexpensive, easy to handle, commercially available solid and it were exploited to many reactions for the chemoselective formation of different aromatic aldehydes,[38] acids[59] and heterocycles.[34.36,37] One drawback of using bismuth compounds is that

it is not yet commercially available and so it must be synthesized in the laboratory prior to use.

The trivalent bismuth (III) has a strong tendency to coordinate with the oxygen atoms of the cyclic enones and thereby, enhances the keto-enol tautomerization. This extra benefit helped to shift the equilibrium toward the enol form (cyclohexadienolate) which can act as the diene counterpart in cyclization**.** Taking the advantages of Bi(III)NO_3 salt, finally, under solvent free condition over water bath heating and addition of 20 mol% $Bi(NO_3)_3$ with few drops of Concd. H_2SO_4 has brought an improved transformation of anisole with furoic acids into 6-methoxy naphthoic acids **170** at greater ease.

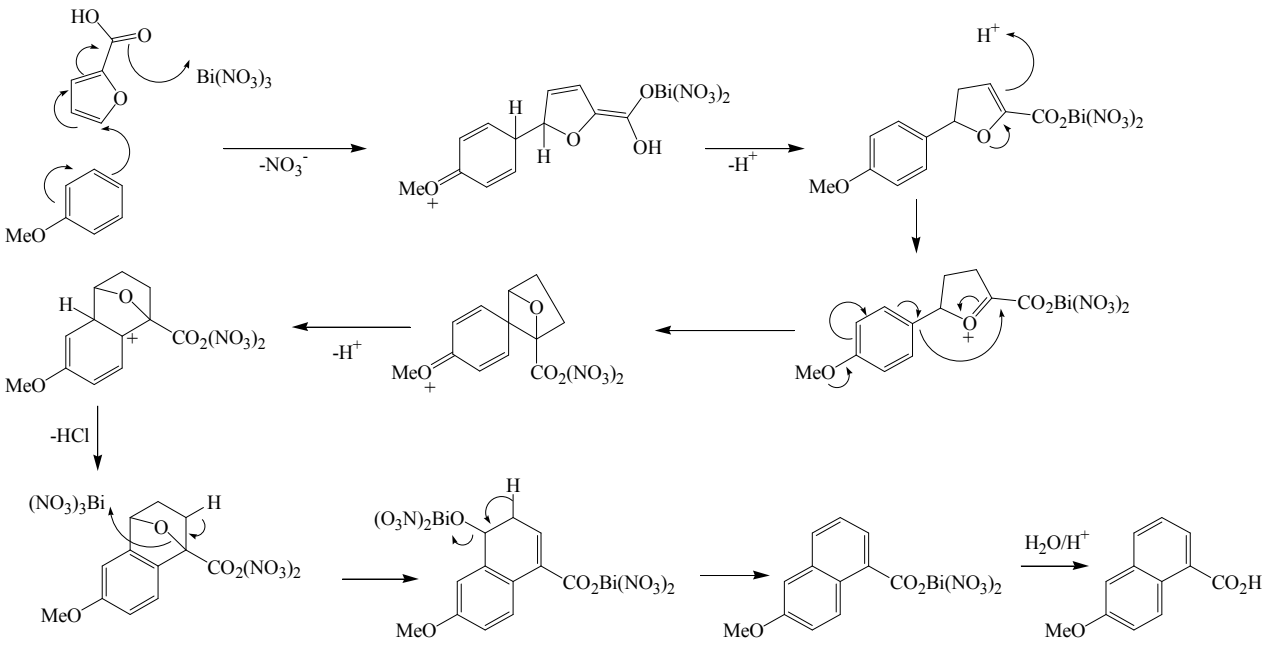


R = OMe, OH, OEt, Me, Et, Cl
R' = H, Me

This compound **170** is known in the literature, so its melting point was matched with the literature[71] value. Moreover, we have taken ^{1}H NMR spectrum of this compound which is indicating 6-aromatic protons in the aromatic regions (δ =8.99~7.14 ppm) and 3H at δ = 3.95 ppm for the –OMe group. So, 6-methoxy

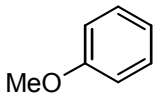
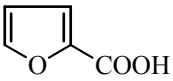
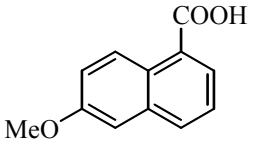
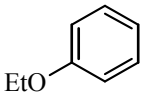
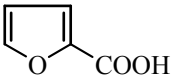
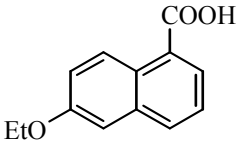
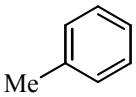
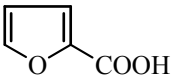
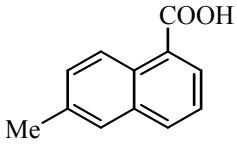
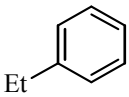
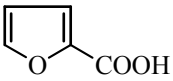
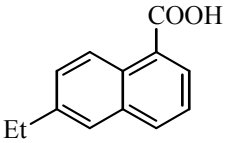
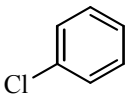
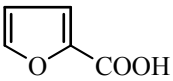
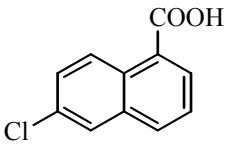
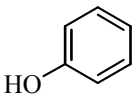
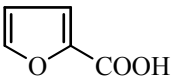
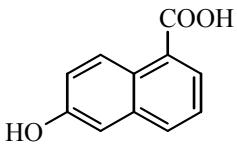
naphthoic acid was formed without any doubt. Plausible mechanism for the formation of **170** by $Bi(NO_3)_3$ catalyst has shown by the scheme:

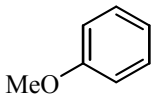
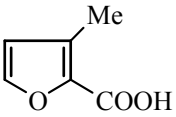
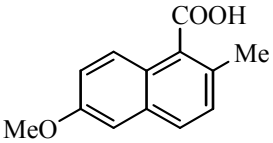
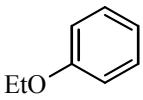
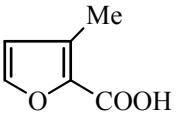
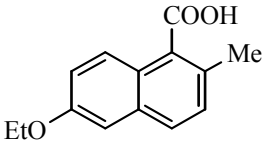
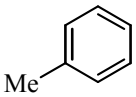
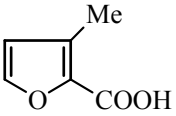
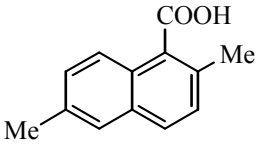
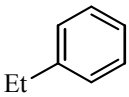
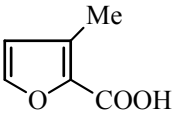
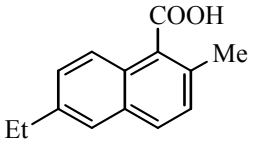
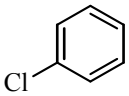
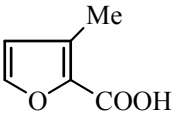
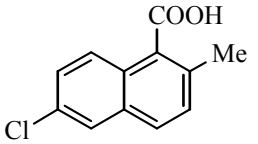
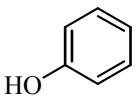
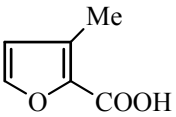
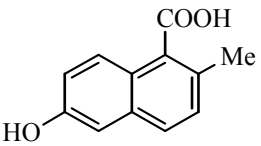
Scheme: 9



Several other derivatives were synthesized by the same procedure using phenol, phenetol, toluene, ethylbenzene and chlorobenzene with furoic acid and methyl furoic acid. In brief, all of these products are focused in table **1**.

Table 1: Reactant, condition, product, yield and characterization

Entry	Reactant	Acids	Products	m. p. (°C)	Yield (%)
(i)			 **170**	180 (Lit.[71] 180)	45
(ii)			 **171**	187	49
(iii)			 **172**	176 (Lit.[71] 176.-177)	40
(iv)			 **173**	167-170	45
(v)			 **174**	188 (Lit.[71] 188-189)	50
(vi)			 **175**	211 (Lit.[71] 210-211)	40

(vii)			 **176**	161 (Lit.[23] 160-162)	45
(viii)			 **177**	165	40
(ix)			 **178**	169	35
(x)			 **179**	187	40
(xi)			 **180**	180	45
(xii)			 **181**	167	35

In another attempt, bromo-benzene was reacted with furoic acid or its ester derivative but we obtained low yield of 6-bromonaphthoic acid. Probably the 'Br'

atom in position C_6 was replaced by $Bi(NO_3)_3$ during the reaction. In the case of phenol, yield is quite discouraging and this may be caused by the participation of the reactive -OH to some unwanted oxidation reactions during condensation. Most of our synthesized naphthoic acids are known in the literature[71] and therefore the melting points were matched by the literature values. In a few cases, ^{1}H & ^{13}C NMR and HRMS data were taken to ensure the substituent at position C-6 in naphthoic acid.

$Bi(NO_3)_3$ is an effective, inexpensive catalyst. In the present reaction, $Bi(NO_3)_3$ again proved its efficacy towards cyclization reaction. Comparatively an easier way we have tackled the clumsy separation of unwanted filthy materials developed in the earlier reaction. $Bi(NO_3)_3$ with its effective cyclization ability, has made the reaction clean and high yielding. By this way using of excess anisole or other benzene derivatives were avoided and interestingly 03 equivalents of benzene derivatives were sufficient in this reaction. We think this is an elegant method of naphthoic acid synthesis. So, this improved method could be used as a contending one to other existing methodologies.

Chapter 5

5. Summary and Future Plan:

In the middle of the twentieth century synthetic organic chemists have concentrated their target to synthesize bigger molecules only. Because up to that period people were thinking that only the bigger molecules are the key factors in controlling our biological events. But, today, after the discovery of organocatalysts and their tiny presence in the reaction media made the chemists to rethink about the small molecules. So, in order to join the work-fair of synthetic organic chemistry, we have taken initiative to synthesis small biologically active molecules with the cheap and nontoxic metal catalyst to meet the present challenge of environment pollution. Fortunately, in this short time span we have successfully synthesized several naphthoic acid moiety by an environmentally benign protocol. All this achievements are given below :

- Eleven 6-substituted naphthoic acids were synthesized throughing one pot reaction by using benzene derivatives and 3-substituted furoic acid.
- According to green chemistry protocol we have exploited catalytic amount of environmentally benign, inexpensive $Bi(NO_3)_3$ and concentrated H_2SO_4.
- From this protocol eleven different substituted Naphthoic acid have been synthesized with moderate to good yields.

- All the **6-substituted Naphthoic acids** are characterized by ^{1}H NMR and Mass spectroscopic analyses.
- Purification of the products was accomplished by some simple techniques. No expensive column chromatographic methods were adopted during the purification of all compounds.
- ^{1}H NMR, and Mass spectroscopic analyses are firmly agreed with the given structures of 6-substituted naphthoic acid.

In future, yields of the products would be extensively verified, their number of examples will be increased and all the prepared compounds will be verified as insulin resistance, antibacterial and anti-cancer and anti-dermatological activities.

Part 2: Chapter 6

Experimental

6.1 General :

The melting ponts of the compound were recorted on electrothermal melting point apparatus and also on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellets for solids and neat for liquids on FT-IR 8400 Perkin-Elmer 883 grating spectrometer. ^{1}H NMR spectra were taken on AC-Bruker 300 MHz spectrometer in D_6-DMSO or $CDCl_3$, containing TMS as internal standard. All *J* values are given in Hz, chemical shifts in δ-units. Reactions were monitored by tlc and column chromatography were carried out on (60-120 mesh E. Merck) silica gel. 2-Methylfuroic acids were purchased from Fluka Chemicals.

All the solvent for chromatography were distilled prior to use. Ethyl acetate, diethyl ether, and petroleum ether were used as eluent in the column chromatographic separations. Columns were prepared with silica gel (60-120 msh ; E. Merck). Thin layer chromatographic plates (.25 mm thickness) were prepared by spreading a layer of silica gel (60 GF_{254}. E. Merck) over glass plates.

The phrase “usual work-up” or “worked up in usual manner” refers to washing of organic phase with water, drying(Na_2SO_4) and evaporation under reduced pressure.

6.2 Solvent Purification and Drying :

1. Methanol :

To 500 mL of methanol about 50 gm CaO were added and it was kept overnight. Then methanol was decanted from CaO and refluxed the bulk solvent for 5-6 hrs usingan efficient $CaCl_2$ Guard tube. After reflux, distillation was carried out and distlled methanol was collected to a round bottom flax. A white cake of Mg-turning was formed in an another round bottom flask, by taking small amount of above methanol with some cleaned and dried Mg tunnings, and whole mass of methanol was poured into it. Again, it was refluxed for 4 hr, distilled out and collected it into an air tight container.

2. Chloroform ($CHCl_3$) :

About 250 mL of chloroform was taken in a round bottom flask and CaH_2 was added to it. Then the whole amount of chloroform was stirred with an efficient magnetic stirrer at about 4-6 hr. After that , Chloroform was decanted from CaH_2 and distilled it out. This Distilled $CHCl_3$ was collected and kept into an air tight container.

3. Petroleum ether

To 500 mL of petroleum ether it was added anhydrous $CaCl_2$ (20 gm) and it was kept overnight. Then petroleum ether was decanted from $CaCl_2$ and distilled out . The given pure petroleum ether was then collected into an air tight container.

4. Ethyl acetate :

About 500 mL ethyl acetate was taken into a separating funnel and it was washed with 1N $NaHCO_3$ (3×100 mL) to remove trace amount of acetic acid from it. Later it was washed with water (3×100 mL) and dried over anhydrous $CaCl_2$. Finally, This ethyl acetate was distilled out and collected into an air tight container.

5. Diethyl ether :

About 100mL diethyl ether was added over about 50 gm KOH pellets. and it was kept overnight. Then diethyl ether was decanted to another round bottom flux and it was refluxed for 5-6 hr under N_2 prior and ice water was passes through the condenser. After Reflux , it was distilled and collected into another airtight container. Addition of Na-metal with little benzophenone tested the presence of water. Deep blue coloration ensured the absence of any water molecule in diethyl ether.

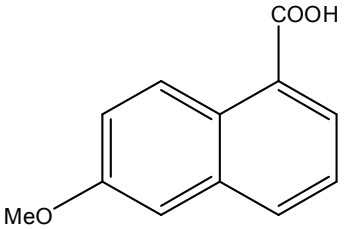
6. Tetrahydrofuran (THF) :

About 50 mg KOH pellets were added to 50 mL of THF (tetrahydrofuran) and it was kept overnight. Then THF was decanted to another R.B and was refluxed for 5-6 hr under N_2 prior. ice water was passes through the condenser. After Reflux, it was distilled and collected into another airtight container. Addition of Na-metal with little benzophenone tested the presence of water. Deep blue coloration ensured the absence of any water molecule inTHF.

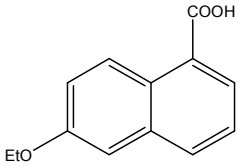
5.3 General Procedure for the preparation of Substituted Naphthoic acid :

To a well stirred mixture of anisole (7.8g, 75 mmol) and 2-furoic acid (3.36g, 30 mmol) anhydrous $Bi(NO_3)_3$ (1.185g, 3 mmol%) and 2 mL H_2SO_4 were added slowly. Then the reaction mixture was heated over water bath (80^0C) at about 24 hour with occasional mechanical shaking. After completion, this hot mixture was poured onto crushed ice (100 g) and it was scratched efficiently with a glass rod. The resulting acidic mixture was extracted with Et_2O (3 x 25 ml), dried over Na_2SO_4 and then concentrated in *vacuo*. A gummy tan color mass was appeared from which after column chromatographic separation (eluent: Pet. Ether / EtOAc 5:1) the pure product (**170)** was obtained in yield 45% (2.72g).

IR (KBr); 1687, 1505, 1029, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$); 8.99 (d, 1H, *J* = 8, Ar-H), 8.26 (dd, 1H, *J* = 1.24,; 1698, Ar-H), 7.99 (d, 1H, *J* = 8, Ar-H), 7.50 (t, 1H, *J* = 8, Ar-H), 7.35-7.14 (m, 2H, Ar-H), 3.95 (s, 3H, OMe); ^{13}C NMR.8, 157.2, 135.1, 133.7, 127.9, 127.5, 127.0, 126.7, 124.9, 119.8, 106.5.



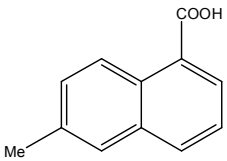
170



171

Data for Compound **171 :**

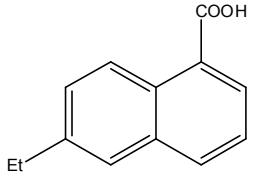
IR (KBr); 1686, 1506, 1028 cm^{-1}; ^{1}H NMR($CDCl_3$); 8.93 (d, 1H, *J* = 8, Ar-H), 8.21 (dd, 1H, *J* = 1.25, 8, Ar-H), 7.94 (d, 1H, *J* = 8, Ar-H), 7.42 (t, 1H, *J* = 8, Ar-H), 7.28-7.09 (m, 2H, Ar-H), 3.73 (q, 2H, *J* = 6.7, OCH_2), 1.91 (t, 3H, *J* = 6.7, $-CH_3$).



172

Data for Compound **172**

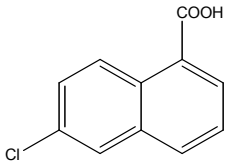
IR (KBr); 1667, 1505, 1261 cm^{-1}; ^{1}H NMR($CDCl_3$); 7.85 (d, 1H, *J* = 8, Ar-H), 7.64 (dd, 1H, *J* = 1.24, 8, Ar-H), 7.49 (d, 1H, *J* = 8, Ar-H), 7.35 (t, 1H, *J* = 8, Ar-H), 7.22-7.01 (m, 2H, Ar-H), 2.43 (s, 3H, Me).



173

Data for Compound **173**

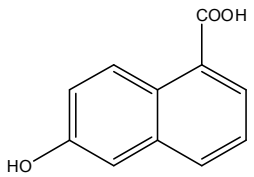
IR (KBr); 1667, 1506, 1261 cm^{-1}; ^1H NMR($CDCl_3$); 7.83 (d, 1H, J = 8, Ar-H), 7.51 (dd, 1H, J = 1.25, 8, Ar-H), 7.48 (d, 1H, J = 8, Ar-H), 7.36 (t, 1H, J = 8, Ar-H), 7.28-7.09 (m, 2H, Ar-H), 2.71 (q, 2H, J = 6.6, CH_2), 1.28 (t, 3H, J = 6.6, CH_3).



174

Data for Compound **174**

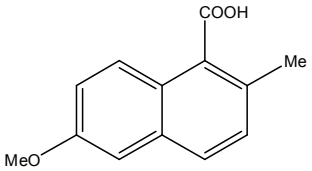
IR (KBr); 1668, 1507, 1263 cm^{-1}; ^1H NMR ($CDCl_3$); 8.91 (d, 1H, J = 8, Ar-H), 8.24 (dd, 1H, J = 1.24, 8, Ar-H), 7.93 (d, 1H, J = 8, Ar-H), 7.51 (t, 1H, J = 8, Ar-H), 7.31-7.19 (m, 2H, Ar-H); HRMS calcd. for $C_{11}H_7O_2Cl$, 206.46761; found 206.46760.



175

Data for Compound **175**

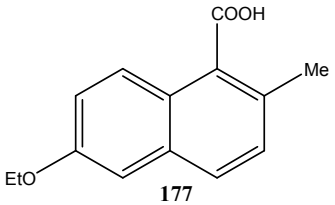
IR; 3063, 1668, 1506, 1262, 767 cm^{-1}; ^1H NMR ($CDCl_3$); 8.68 (d, 1H, J = 10, Ar-H), 7.89-7.77 (m, 2H, Ar-H), 7.33 (t, 1H, J = 8, Ar-H), 7.11-7.02 (m, 2H, Ar-H), 5.90(s, 1H, Ph-OH); HRMS calcd. for $C_{11}H_8O_3$, 188.04734; found 188.04737.



176

Data for Compound **176**

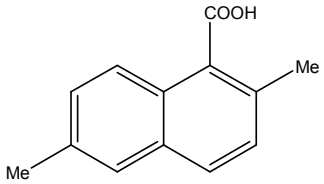
IR; 3431, 2943, 2605, 1687, 1117, 1495, 1441, 1361, 1266, 1151, 1036, 923, 836 cm^{-1}; ^1H NMR($CDCl_3$); 8.04 (d, 1H, *J* = 9, Ar-H), 7.75 (d, 1H, *J* = 9, Ar-H) 7.40-7.21 (m, 3H, Ar-H,), 3.90 (s, 3H, OMe), 2.43 (s, 3H, Ar-CH_3).



177

Data for Compound **177** :

IR (KBr); 1667, 1508, 1265 cm^{-1}; ^1H NMR($CDCl_3$); 8.02 (d, 1H, *J* = 9, Ar-H), 7.71 (d, 1H, *J* = 9, Ar-H) 7.37-7.20 (m, 3H, Ar-H,), 4.01 (q, 2H, *J* = 6.7, OCH_2), 2.41 (s, 3H, Ar-CH_3), 1.97 (t, 3H, *J* = 6.7, -CH_3).

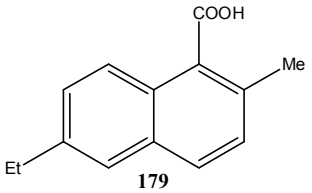


178

Data for Compound **178**

IR (KBr); 1667, 1507, 1263 cm^{-1}; ^1H NMR ($CDCl_3$); 7.91 (d, 1H, *J* = 9, Ar-H), 7.73 (d, 1H, *J* = 9, Ar-H) 7.21-7.08 (m, 3H, Ar-H), 2.44 (s, 3H, CH_3), 2.23 (s, 3H, CH_3).

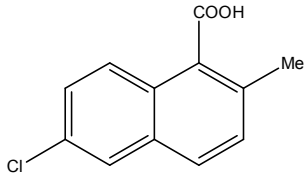
Data for Compound **179**:



179

IR (KBr); 1669, 1509, 1267 cm^{-1}; ^1H NMR ($CDCl_3$); 8.85 (d, 1H, J = 9, Ar-H), 7.68 (d, 1H, J = 9, Ar-H) 7.17-7.01 (m, 3H, Ar-H,), 3.01 (q, 2H, J = 6.7, CH_2), 2.41 (s, 3H, Ar-CH_3), 1.31 (t, 3H, J = 6.7, CH_3).

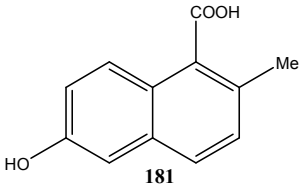
Data for Compound **180**



180

IR (KBr); 1668, 1506, 1261 cm^{-1}; ^1H NMR ($CDCl_3$); 7.79 (d, 1H, J = 8.9, Ar-H), 7.58 (d, 1H, J = 8.4, Ar-H), 7.20 (d, 1H, J = 8.4, Ar-H), 7.16-6.98 (m, 2H, Ar-H), 2.41 (s, 3H, CH_3); HRMS Calcd. for $C_{12}H_9O_2Cl$, 220.51327; found 220.51330.

Data for Compound **181**



181

IR (KBr); 3063, 1667, 1506, 1262 cm^{-1}; ^1H NMR ($CDCl_3$); 7.78 (d, 1H, J = 8.9, Ar-H), 7.56 (d, 1H, J = 8.4, Ar-H), 7.17 (d, 1H, J = 8.4, Ar-H), 7.16-6.99 (m, 2H, Ar-H), 5.78(s, 1H, Ph-OH) 2.47(s, 3H, CH_3)

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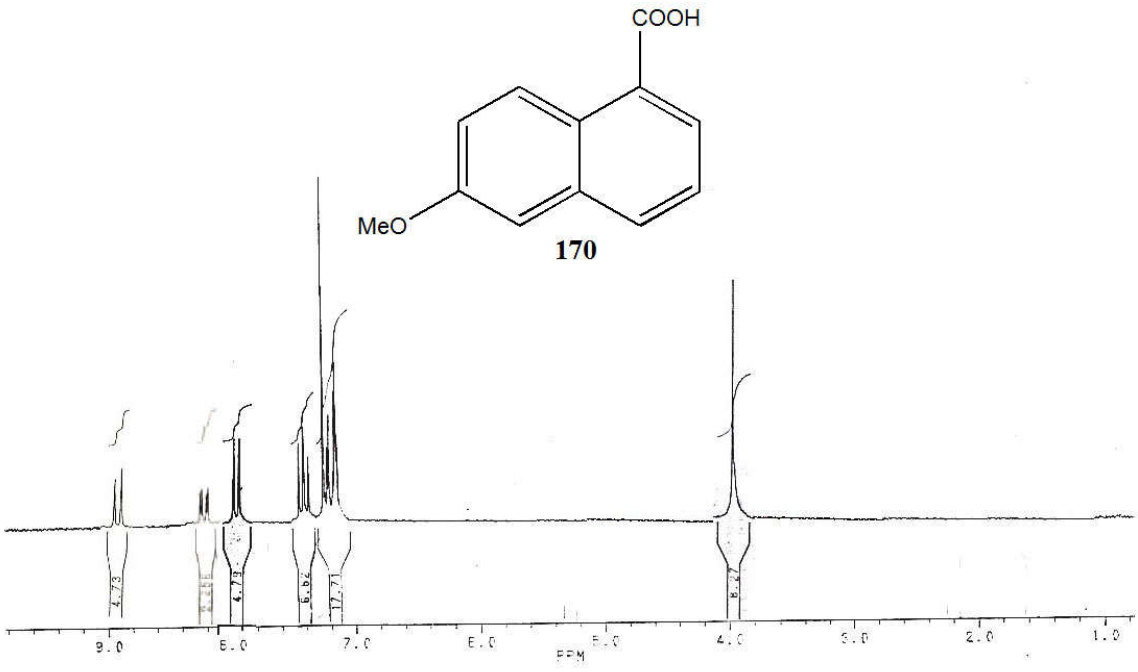
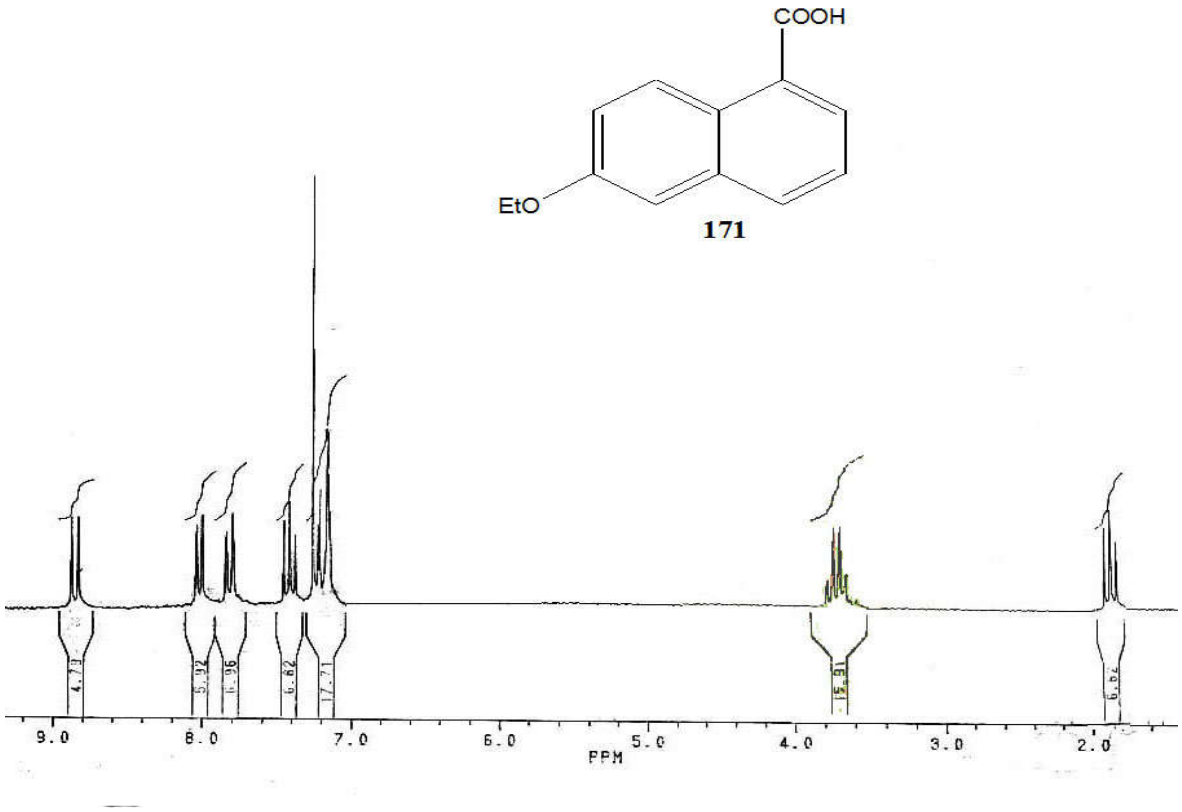
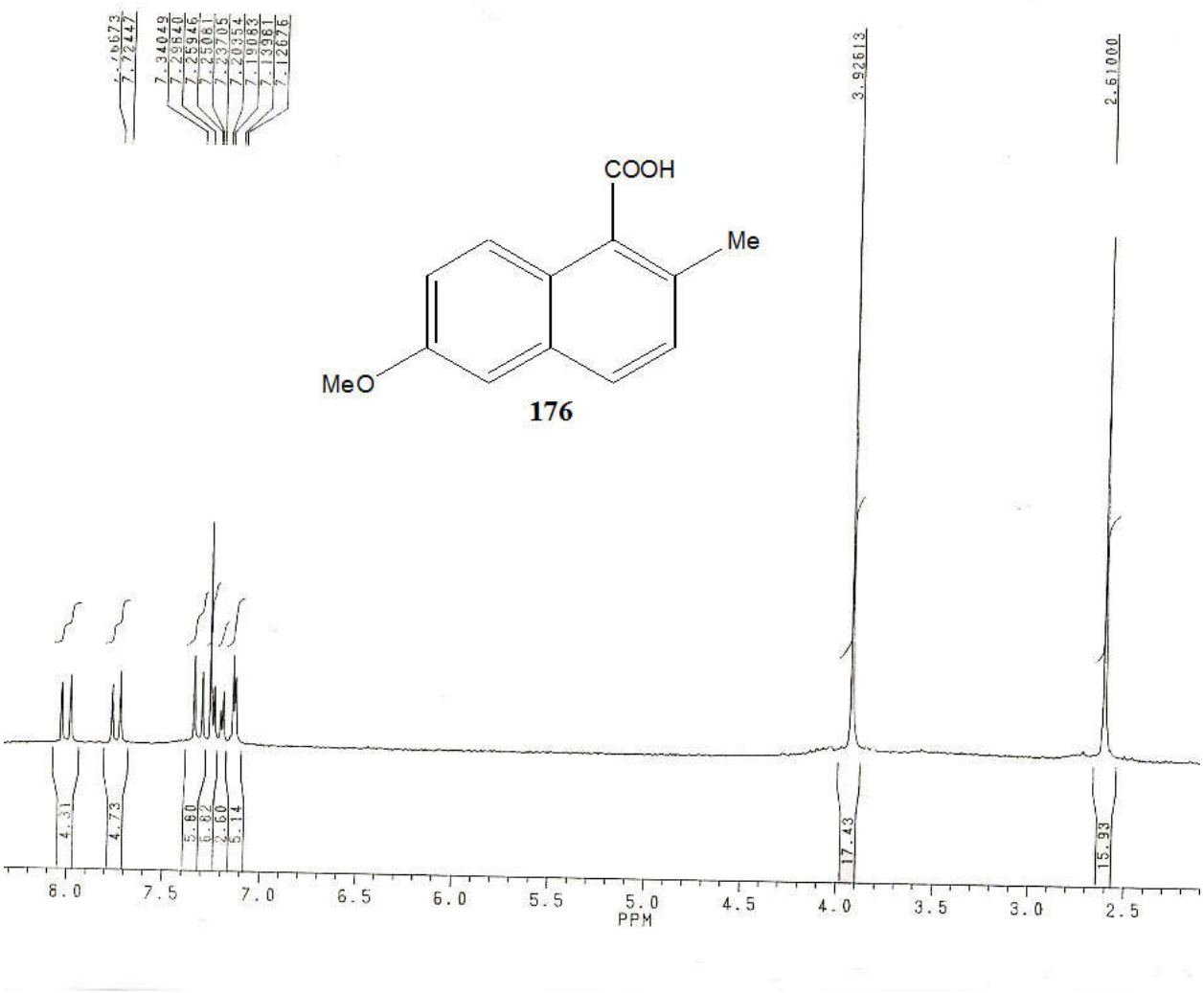
Appendix-1

Experimental Proof





171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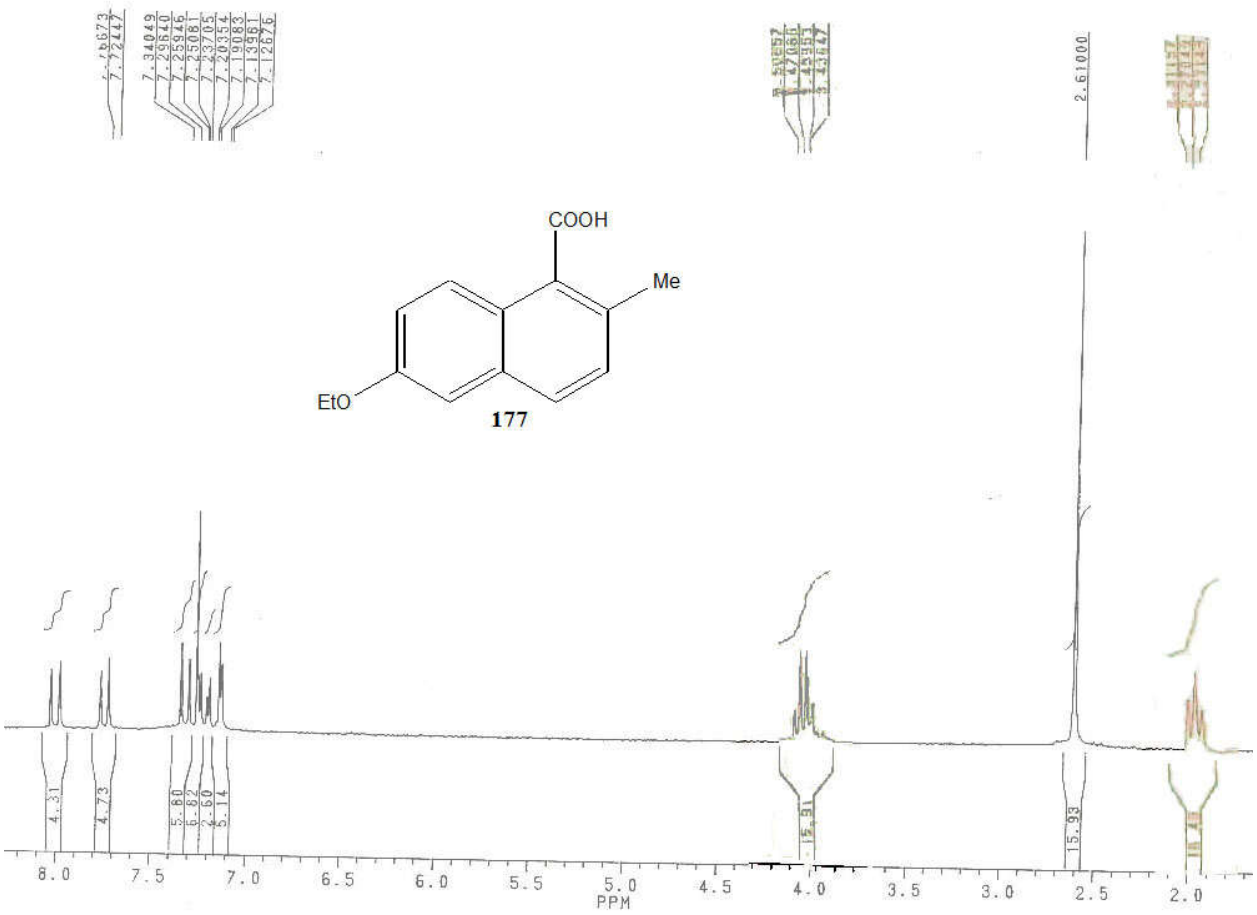
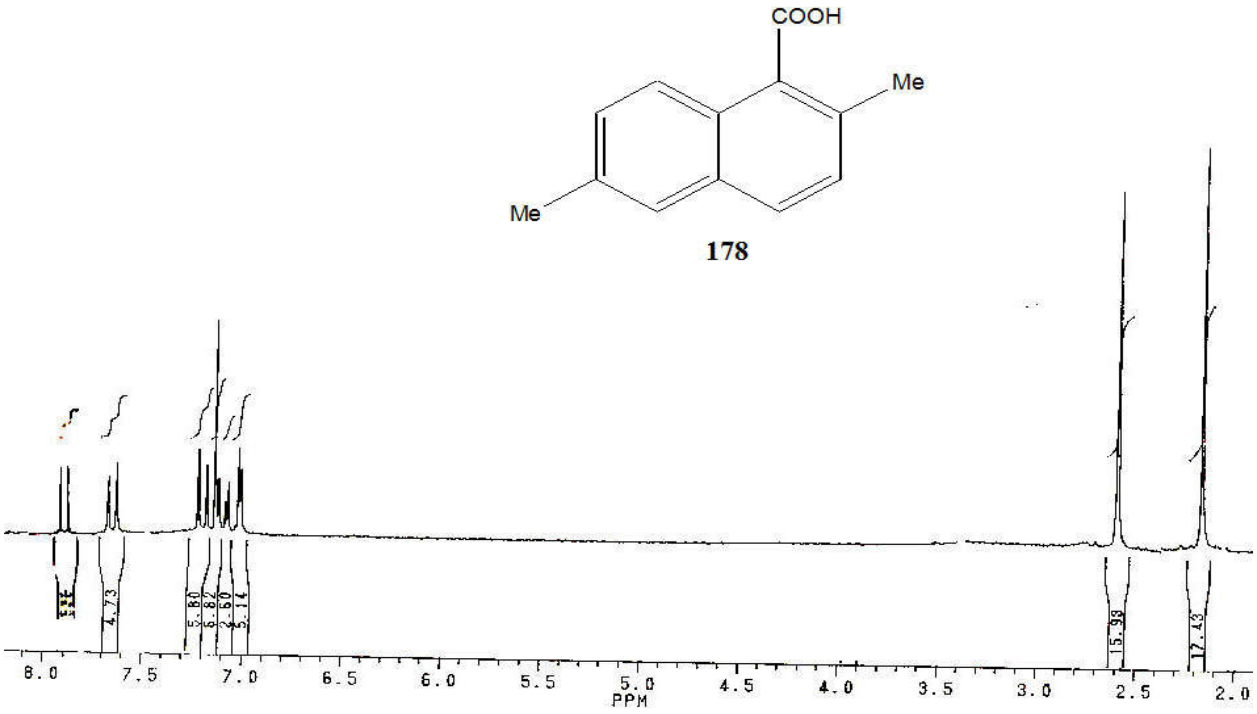
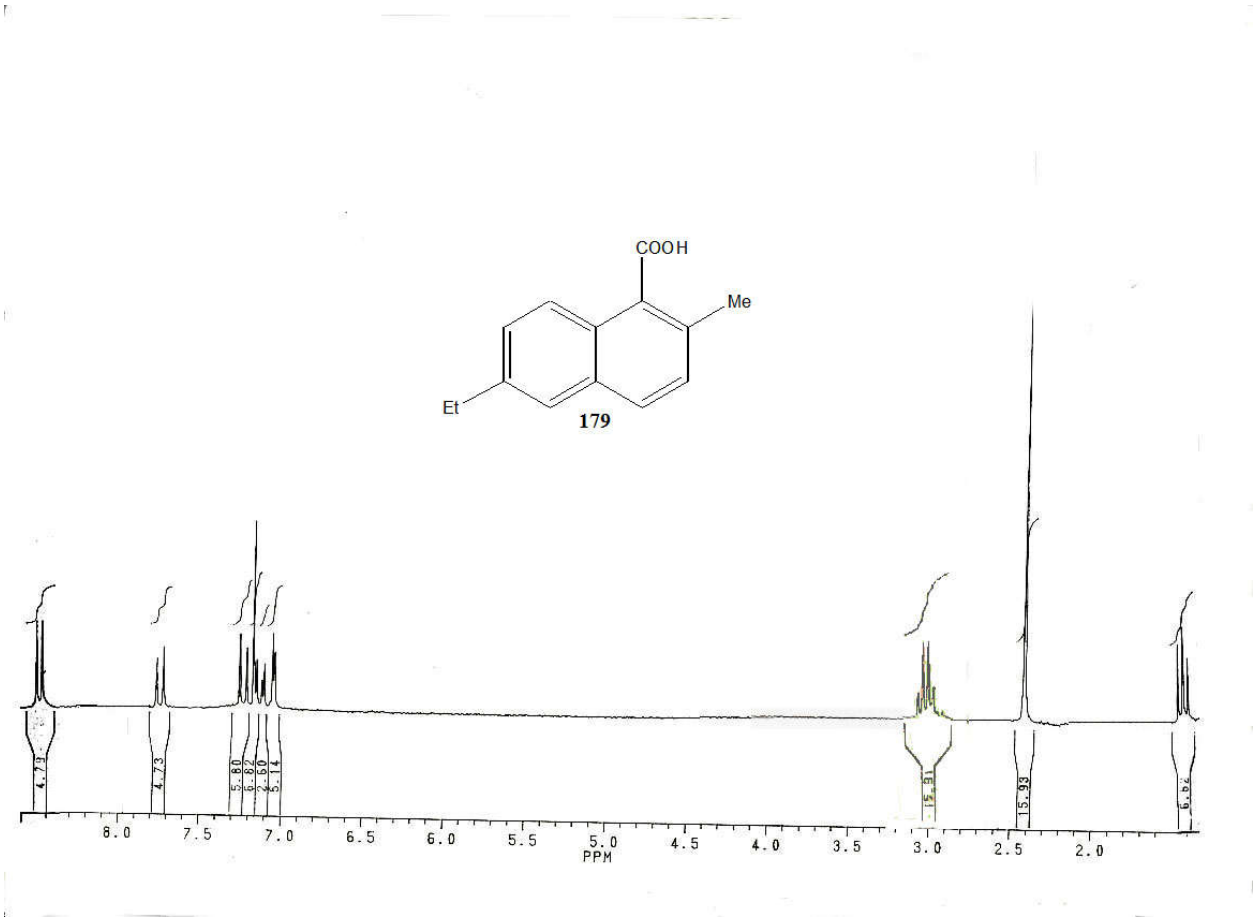
7.12447
7.34049
7.29640
7.25946
7.24308
7.23705
7.20354
7.19083
7.13961
7.12676
3.92613
2.61000
COOH
Me
MeO
4.31
4.73
5.60
5.82
6.60
5.14
17.43
15.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM

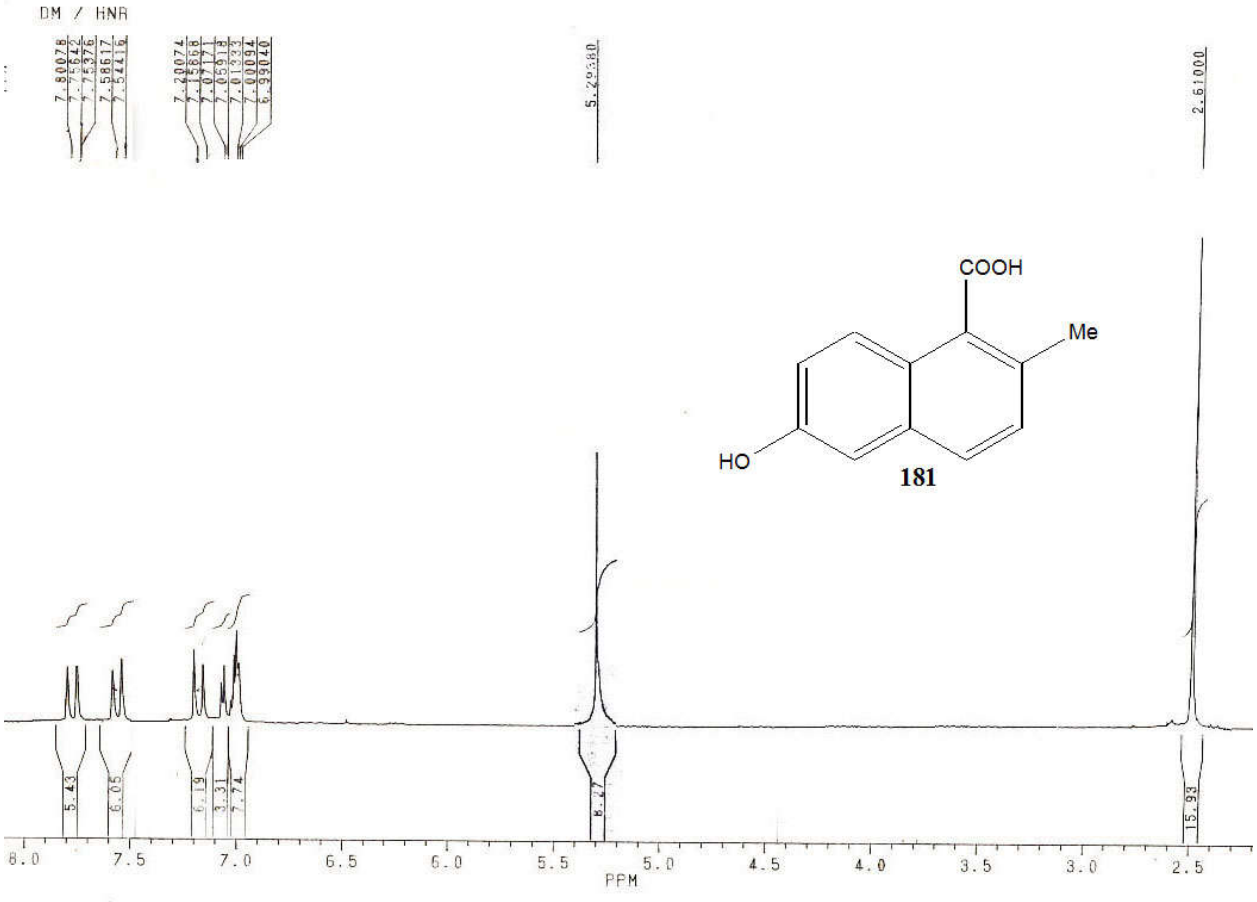
176


COOH
Me
EtO
177
2.61000
4.31
4.73
5.80
6.82
2.60
5.14
15.93
PPM


COOH
Me
Me
4.73
5.80
6.82
2.60
3.14
15.98
17.43
8.0
7.5
7.0
6.5
6.0
5.5
5.0
PPM
4.5
4.0
3.5
3.0
2.5
2.0

178


COOH
Me
Et
179
4.73
4.73
5.80
6.82
2.60
5.14
15.91
15.93
6.84
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM


DM / HNR
COOH
Me
HO
181
5.43
6.05
6.19
3.31
7.74
8.47
15.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM

Publications:

I. *One Pot Synthesis of Some Substituted Naphthoic Acid Catalyzed by $Bi(NO_3)_3$ in Excess H_2SO_4.* **H. N. Roy, *Iqubal Hossain, Mahbub Alam, Masud Rana, Abu Jafar and P. G. Karmaker**. J. of Bangladesh Chem. Soc. (Accepted)

II. *Four Component Synthesis of '1H-Pyrazol [1,2-b] phthalazine-5,10-dione Derivatives by L-Proline Catalysis.* **H. N. Roy*, M. Alam, Iqubal Hossain and M. Masud.** (Communicated to Ind. J. Chem. Sec. B)