**Introduction to Green chemistry:**

Organic chemicals are the feeders for various chemical industries such as polymers, pharmaceuticals, pesticides, paints, artificial fibers, food additives, etc. Organic synthesis involves the use of large amounts of energy, petrochemicals, and catalysts and at the end of the reaction, separation, purification, storage also requires large amounts of chemicals. During these syntheses these chemicals pose problems for the health and safety of workers. In addition, they contribute to the environmental problems caused by their use and disposition as waste is a major issue. Due to these factors chemical and allied industries, such as pharmaceuticals, are facing serious environmental problems. Many of the classical or conventional synthetic methodologies have broad scope but generate copious amounts of waste, and the chemical industry has been under pressure to minimize or eliminate this waste. Example: DDT, CFC’s, polymers, and soaps and detergents which are non-biodegradable.

At this point, Green Chemistry with its twelve principles aims at the replacement of conventional methods of synthesis that are being used for decades which are harmful to the environment by Green synthetic methods. This can be brought about by using less toxic starting materials, less toxic solvents; easily available catalysts reduce the number of steps and minimize waste generation as far as practically possible leading to sustainable development.\(^1\)\(^-\)\(^3\)

Green chemistry is being practiced in the research laboratories across the world. Considering the large magnitude of research going on for the industrial and academic purpose, this is essential to protect our environment. By changing
the methodologies of organic synthesis, health and safety will be advanced not only in the small scale laboratory level but this can also be achieved at the industrial level at large scale. Added benefit is the environmental protection through the use of less toxic reagents, minimization of waste and more biodegradable by-products.

International organizations, such as OECD (Organization of Economic Co-operation and Development), UNEP (United Nations Environment Programme) have complied with international standards on health and safety regulations, and on safer chemical products and materials. Most of the commercially available chemicals substances have been classified, regulated and tested for their toxicity and their rate of biodegradation under environmental conditions. Chemical industries all over the world are competing for innovation and generation of safer products. Practicing Green Chemistry has provided the alternative materials, and processes which have changed the sustainability of the production of chemical materials, as well as environmental impact by reducing toxicity and increasing recyclability.

The green chemistry revolution is providing an enormous number of challenges, wherein the classical methods are being replaced by green methods, to those who practice chemistry in industry and research. Green Chemistry has a key role to play in maintaining and improving our quality of life, along with sustainable development for achieving the economic and environmental objectives. This can be brought about by the development of new synthetic
pathways using alternative starting materials, reaction conditions, less toxic solvents and energy minimisation and designing of less toxic and safer chemicals.

Green methods are effective due to design of processes, starting at the molecular level which help us to design environmentally appropriate features.

The methods followed are,

a) Solvent –free reactions(solid state)

b) Microwave or ultrasound assisted reactions

c) Use of catalysts, ionic liquids, alternate media etc.

d) Multi-component reactions(MCRs)

Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic reactions should be conducted at ambient temperature and pressure as far as possible.

**Microwave-Assisted Synthesis:**

In the past two decades, heating and accelerating chemical reactions using microwave energy has gained popularity among the researchers. First reports using microwaves for the chemical reactions were published by Gedye ⁴ and Giguere ⁵ in 1986.

These experiments termed as microwave-assisted organic synthesis (MAOS) are carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. Due to uncontrolled heating of organic solvents leading to explosion in organic solvents, solvent free reactions are more popular. Now with the availability of
more sophisticated microwave reactors with temperature, pressure and power control large number of reports are being published in scientific literature. Advantages of Microwave synthesis include local heating, faster reactions, higher yields without any by products.

Examples of microwave assisted organic syntheses.

**Ultrasound-assisted organic synthesis:**

Ultrasound-assisted organic synthesis is another “green” methodology which is applied in many organic syntheses, having the advantages for short duration, high efficiency, and low energy requirements. Sonochemistry (in the region of 20 kHz to 1 MHz) has many applications due to its high energy and the ability to disperse reactants in small particles and accelerate reactions. Experimental results have shown that these bubbles have temperatures around
5000 K, pressures of roughly 1000 atm. These cavitations can create extreme physical and chemical conditions in otherwise cold liquids.

\[
R-\text{NH}_2 + \text{R-C}_2\text{H}_5\text{C} (\text{MeOH, r.t.} ) \xrightarrow{\text{UO}_2(\text{NO}_3)_2\cdot 6\text{H}_2\text{O}} \begin{array}{cc}
& \text{N} \\
\end{array} \text{R}
\]

Synthesis of 2,5-dimethyl-N-substituted pyroles catalyzed by uranyl nitrate hexahydrate.

Synthesis of 14-aryl-14H-dibenzo[\(a, j\)]xanthenes in the presence of poly(4-vinylpyridinium) hydrogen sulfate under normal heating and sonication conditions.

**Role of catalysts:**

The waste generated during the manufacture of organic compounds consists of inorganic salts, acids and other by-products in large quantities. This is a direct consequence of the use of stoichiometric amounts of inorganic reagents in organic synthesis. Ex: metals (Na, Mg, Zn, Fe) and metal hydride reagents (LiAlH\(_4\), NaBH\(_4\)) Lewis acids (AlCl\(_3\), ZnCl\(_2\), BF\(_3\)) etc. This can be prevented by substitution of classical stoichiometric methodologies with cleaner catalytic
alternatives. More and more reactions are being carried out in presence of catalysts such as Solid-Supported Reagents, zeolites, clays etc.\textsuperscript{12–14} These catalysts have the advantages as shown:

- Solid-supported reagents can be easily removed from reaction mixture by filtration.
- Excess reagents can be used to drive reactions to completion without introducing difficulties in purification.
- Recycling of recovered reagents is economical, environmentally-sound, and efficient.
- Ease of handling: Toxic, explosive, and noxious reagents are often more safely handled when contained on solid support.
- Finely tune the chemical properties by altering choice of support and its preparation.
- Reagents on solid-support react differently, mostly more selectively, than their unbound counterparts. Example: silica and alumina supported catalysts, zeolites etc.

\[ \text{Formation of pyrazoles using alumina.}^{15} \]
Examples of the reactions using solid supports or solid catalysts

Green solvents:

Use of a large amounts of conventional volatile organic compounds (VOC’s) required to carry out a chemical reaction created ecological and economic concerns. Chlorinated solvents are toxic and volatile, and are implicated in the destruction of the ozone layer. Simple alcohols (methanol, ethanol) or alkanes (heptane, hexane) are environmentally preferred solvents, whereas dioxane, acetonitrile, acids, formaldehyde, and tetrahydrofuran are not recommended from an environmental perspective. Solvent-free reactions are one solution to eliminate the use of VOC’s. But lack of reaction medium leads to overheating of the reaction mixture, yielding a mixture of by-products. Ionic liquids, aqueous systems and supercritical carbon dioxide etc are also finding use as replacement of VOC’s. They help in increasing reaction efficiency, helps in separation and catalyst recovery, reduce emissions to the environment. “Chemistry in Alternative Reaction Media” is gaining popularity among the researchers.
**Water as a solvent:**

Water is a desirable solvent for chemical reactions for reasons like easy availability, safe handling, cost, and environmental concerns. Many reactions have been studied in water. Many reactions like Diels–Alder cycloadditions and Claisen rearrangements have been found to work faster in water as medium. But most of the conventional reactions were carried out in VOCs due to solubility factor. In the recent past water is being explored as a desired medium due to insoluble nature of synthetic organic compounds. The use of water as the medium has advantage of easier product isolation and safety.

**Multi component reactions:**

Multi component reactions (MCRs) are the reactions in which two or more than starting materials react to form products incorporating all the starting materials. This is a one-pot conversion, efficient, gives 100% atom efficient. MCRs are offer an inexpensive and rapid way to generate libraries of compounds which are potentially bioactive. Example: Ugi reaction, Passerini reaction, Hantsch reaction, Biginelli reaction etc. MCRs have even been discovered by preparing libraries from 10 different starting materials. By analyzing the products of each combination (three-, four-, up to ten-component reactions), one is able to select those reactions that show a single main product and having the biological properties.
Hantzsch Dihydropyridine (Pyridine) Synthesis:

\[ R\text{-CHO} + 2 \text{R'}\text{OOCR''} + \text{NH}_3 \rightarrow \text{R'OOCR''} \]

Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones \(^2^3\):

\[ \text{EtO}_2\text{C} + \text{H}_2\text{N} + \text{NH}_2 \text{COO} \rightarrow \text{EtO}_2\text{C} + \text{NH} \]

Passerini reaction \(^2^4\):

\[ \text{R}_1\text{COOH} + \text{R}_2\text{CHO} + \text{R}^3\text{NC} \rightarrow \text{R}_1\text{OOCR}_2\text{N}^3 \]

Ugi reaction \(^2^5\):

\[ \text{R}_1\text{CHO} + \text{R}_2\text{NH}_2 + \text{R}_3\text{COOH} + \text{R}_4\text{NC} \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{R}_4 \]
Recent research papers on Green Chemistry synthetic organic routes.


\[
\begin{align*}
R\text{-OH} & \xrightarrow{0.1 \text{ eq. Bi}_2\text{O}_3, 5 \text{ eq. } t\text{BuOOH (70\% eq.)}} \xrightarrow{\text{EtOAc, r.t., 18 - 55 h}} R\text{-CO}_2\text{H, R\text{-CH(OH)}_2} \\
R & \text{: Ar, alkyl, vinyl}
\end{align*}
\]

Various aromatic, aliphatic and conjugated alcohols were transformed into the corresponding carboxylic acids and ketones in good yields with aq. 70% \( t\)-BuOOH in the presence of catalytic amounts of bismuth (III) oxide. This method possesses does not involve cumbersome work-up, exhibits chemoselectivity and proceeds under ambient conditions. The overall method is green.

2. Practical catalytic method for N-formylation 27:

\[
R\text{NH} + 2 \text{ eq. HCOODH} \xrightarrow{5 \text{ mol-% I}_2, \text{ neat, 70°C, 2 - 8 h}} R\text{N-CHO} \\
R\text{: Ar, alkyl, benzyl, CH}
\]

A simple, practical, and catalytic method for the N-formylation in the presence of molecular iodine as a catalyst under solvent-free conditions is applicable to a wide variety of amines. \( \alpha \)-Amino acid esters can be converted without epimerization.

3. Oxidation of sulfides with H\(_2\)O\(_2\) 28:

\[
R\text{S} \xrightarrow{4 \text{ mol-% NbC (diameter: 5 \( \mu \)m)}} \xrightarrow{\text{EtOH, 60°C, 1.75 - 22 h}} R\text{O} \xrightarrow{R\text{': Ar, Me, CH}_{3}, R\text{': Bn, allyl}} R\text{S} \\
R\text{': Bn, allyl}
\]

Oxidation of sulfides with 30% hydrogen peroxide catalyzed by tantalum carbide provides the corresponding sulfoxides in high yields, whereas niobium carbide as catalyst efficiently affords the corresponding sulfones. Both catalysts can easily be recovered and reused without losing their activity.
4. Mild method for N-formylation in the presence of Indium metal:\(^{29}\):

\[
\text{Reactions:} \quad R'NH + 3\text{eq. HCO}_2\text{H} \stackrel{0.1\text{eq. In}}{\underset{\text{neat}}{\text{100°C}, 15 - 24\text{ h}}}{\rightarrow} R'N-\text{CHO} \quad R': \text{Ar, alkyl, } H, \text{ alkyl}
\]

A simple, mild method for \(N\)-formylation in the presence of indium metal as a catalyst under solvent-free conditions is applicable to the chemoselective reaction of amines and \(\alpha\)-amino acid esters without epimerization.

**Conclusions:**

By Implementing the Green Chemistry Principle classical methods of preparation of organic compounds can be redesigned as well as new methodologies are developed. With the costs for energy, and chemicals increasing, development of greener procedures can be an investment for the future. With this background, the present study deals with the development of synthetic methods for some important bioactive organic molecules using green chemistry principles. Use of readily available, inexpensive reagents, water as green solvent, shorter reaction times and good yields of the products are the important features of the reactions investigated.

**References:**


Literature survey

A detailed literature survey was carried out before taking up the reactions. The library facilities at the Library in Smt. V. H. D. Central institute of home science, Library at Central College, Bangalore University and Tata memorial library, Indian Institute of Science, Bangalore, were used for the literature survey purpose. Online literature survey was carried out using electronic Journals through UGC-INFILIBNET to collect the available information in the area of research interest. Related information on the proposed schemes was collected using the online portals like sciﬁnder and other journals. The web pages surveyed were,

- www.wiley.com
- www.elsevier.org
- www.sciencedirect.com
- www.springerlink.com
- www.pubs.acs.org
- www.nature.com
- www.pubmed.com and other online web pages

The following journals were referred in finding the required information in the area of our research interest.

- Raman spectroscopy.
- Spectrochimica Acta Part A.
- Chemical Reviews.
➢ Journal of American Chemical Society.
➢ Synthetic communications.
➢ Organic Letters.
➢ Tetrahedron.
➢ Journal of heterocyclic chemistry
➢ Synlett
➢ Synthesis and various other journals.
Chapter 1: Synthesis of pyranopyrazole derivatives

Introduction:

Pyranopyrazoles are an important class of heterocyclic compounds, useful as biodegradable agrochemicals, pharmaceutical ingredients, analgesic and anti-inflammatory, anticancer agents. There has been considerable attention given to synthesize these heterocycles by new methodologies, using different catalysts. However, reported methods are associated with disadvantages such as preparation of starting materials by different methods, use of expensive and environmentally hazardous reagents. We herein report a method for the synthesis of these heterocyclics using a simple, inexpensive catalyst, and short reaction time as per the scheme given below.

![Scheme 1](image)

Results and Discussion

Initially, the reaction between p-anisaldehyde, ethylacetoacetate, malononitrile and hydrazine hydrate (1 m mol each) in the presence of Silica-NaHSO₄ was carried out. SiO₂-NaHSO₄ has been used as a heterogeneous
catalyst in the literature for the synthesis of compounds like quinazolinones
and the protection of aldehydes. The reaction was carried out in the absence of
catalyst, product was obtained in very low yield. For the optimization of catalyst
amount and solvent effect, the reaction was carried out in presence 0.025 mg,
0.05mg, 0.075 mg and 0.1mg of the catalyst and the solvents water, ethanol,
ethanol-water (1:1), and acetonitrile. From the reactions it was found that
maximum yield was obtained at 0.1mg of the catalyst and water as solvent.
Further increase in the amount of catalyst (more than 0.1mg) did not alter the
yields much. To establish the generality of the reaction, the catalyst and the
solvent were successfully applied to various araldehydes using ethylacetoacetate,
malononitrile and hydrazine hydrate and the results are presented in Table 1.1. It
was observed that the reaction gives good yields of the products in presence of
all aromatic aldehydes.

**Experimental:**

All chemicals used were commercial and without further purification. Progress
of the reaction was monitored using Silica gel-G TLC plates. The synthesized
compounds were characterized by $^1$H NMR spectral analysis, comparing the
products on TLC with products prepared by known methods. NMR spectra were
recorded on a Brucker AMX (400-MHz) spectrophotometer DMSO-$d_6$ as
solvent. FT-IR spectra were recorded on a Bruker Optics Alpha-P FT-IR
spectrophotometer with attenuated total reflectance (ATR) module and SH
IMADZU FT-IR-8400s spectrometer.
**General procedure for the preparation of pyranopyrazoles**

The aromatic aldehyde (1 m mol), malononitrile (1 m mol), ethyl acetoacetate (1 m mol) hydrazine hydrate (1 m mol) and Silica-NaHSO₄ (0.1 mg) were taken in water (~5 ml) and heated at 80 °C for 20–30 minutes. The solid product obtained was filtered, washed with water. Ethyl acetate (10 mL) was then added to dissolve the product and the solid catalyst was filtered, washed with chloroform and then recycled. The filtrate was evaporated to get the crude which was recrystallized from methanol to get the pure product.

**Recyclability of the catalyst:**

The catalyst can be recovered and reused for the synthesis of Pyranopyrazoles upto 5 cycles without much loss in the activity. (figure 1)

![Figure 1. Recyclability of the catalyst.](image)
Preparation of catalyst 11:

To a solution of NaHSO$_4$·H$_2$O (6.9 g, 50 mmol) in distilled water (100 mL), was added silica gel (15 g, 100-200 mesh) at 25 °C under magnetic stirring for 30 minutes, after allowing the sodium bisulphate to absorb on the surface of the silica gel (30 min). The powder obtained after removal of the water in a rotary evaporator under reduced pressure was dried in an oven at 120 °C for 2–3 hr.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde(1)</th>
<th>Product (5)</th>
<th>Time (min)</th>
<th>Yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Methoxy benzaldehyde</td>
<td>5a</td>
<td>20</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Benzaldehyde</td>
<td>5b</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>4-Chloro benzaldehyde</td>
<td>5c</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>4-N,N(Dimethyl)amino benzaldehyde</td>
<td>5d</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>4-Hydroxy, 3-Methoxy benzaldehyde</td>
<td>5e</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>2-Hydroxy benzaldehyde</td>
<td>5f</td>
<td>25</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>3-Methoxy benzaldehyde</td>
<td>5g</td>
<td>25</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$isolated yields.
Conclusions:
A convenient and efficient protocol has been developed for the synthesis of pyranopyrazoles in high yields using recyclable and inexpensive, Silica-NaHSO$_4$ as heterogeneous catalyst, short reaction time under mild conditions in water.

References:
Spectral data:

$^1$H NMR of pyranopyrazole derivatives:

Figure 1.1: $^1$H NMR spectrum of 3-methoxy, 4-hydroxy benzaldehyde pyranopyrazole

Figure 1.2: $^1$H NMR spectrum of 3-methoxy benzaldehyde pyranopyrazole
Figure 1.3: $^1$H NMR spectrum of benzaldehyde pyranopyrazole

Figure 1.4: $^1$H NMR spectrum of anisaldehyde pyranopyrazole
FT-IR spectra of pyranopyrazole derivatives:

Figure 1.5: FT-IR spectrum of 3-methoxy, 4-hydroxy benzadehyde pyranopyrazole

Figure 1.6: FT-IR spectrum of anisaldehyde pyranopyrazole
Figure 1.7: FT-IR spectrum of 3-methoxybenzaldehyde pyranopyrazole

Figure 1.8: FT-IR spectrum of N,N-dimethyl aminobenzaldehyde pyranopyrazole
Figure 1.9: FT-IR spectrum of 4-chloro benzaldehyde pyranopyrazole

Figure 1.10: FT-IR spectrum of benzaldehyde pyranopyrazole
Chapter 2: Synthesis of some novel dihydropyrano[2,3-c]pyrazol-6-amines

Introduction:

Dihydropyrano[2,3-c]pyrazole scaffold represents an interesting template in medicinal chemistry, and its derivatives possess useful biological and pharmacological properties. Only a few reports are available on the synthesis of dihydropyrano[2,3-c]pyrazol-6-amines. A Four-Component Domino Combinatorial Synthesis in presence of DIPEA is reported by Kanchithalaivan et al. We, herein, report an efficient and simple one-pot four-component synthesis of dihydropyrano [2, 3-c] pyrazol-6-amines using green chemistry principles.

In the present study, a series of new dihydropyrano[2,3-c]pyrazol-6-amines are synthesized by a one-pot four-component reaction of hydrazine hydrate, araldehydes, ethyl acetoacetate, and 4-fluoro phenylacetonitrile in water using sodium hydrogen sulphate as a catalyst in good yields as shown in the following scheme.

Results and Discussion

Initially, to identify the optimum reaction conditions, a representative reaction between 3-methoxy, 4-hydroxy benzaldehyde (vanillin),
ethylacetoacetate, 4-fluoro phenylacetonitrile and hydrazine hydrate (1 m mol each) was considered. To begin with, the reaction was carried out in the absence of any catalyst in ethanol, at room temperature, ultrasonic and microwave irradiation which did not afford desired product. This test reaction was then investigated using different catalysts (Table 2.1) in refluxing ethanol which gave different product yields. In the presence of NaHSO₄, the reaction afforded better yield of % after when compared to other catalysts (Table 2.1, entry 4). After selection of catalyst for the reaction, investigation for an appropriate solvent was performed. The representative reaction was carried out in solvents such as ethanol, water, acetonitrile and water: ethanol (1: 1) mixture (Table 2.1, entries 5-7). As seen from the data in Table 2.1, Water-ethanol(1:1) was found to be the ideal solvent for this reaction which afforded maximum yield of the product.

The reaction template, with NaHSO₄ as catalyst and Water-ethanol(1:1) as a solvent system, was applied to a various substituted araldehydes to prepare a library of compounds. The template works well for all the araldehydes to give corresponding products (Table 2.2) The template failed for aliphatic aldehydes (Table 2.2, entries 11-12) and the α,β-unsaturated aldehydes such as cinnamaldehyde (Table 2.2, entry 13) did not give any product even after the reaction was carried out for longer duration.

Experimental:

All chemicals used were commercial and without further purification. The progress of the reaction was monitored on TLC (eluent; 2 : 8 ethyl acetate–
petroleum ether). The melting points were measured in open capillary tubes and are uncorrected. Melting points were determined using Raaga, melting point apparatus, India. FT-IR spectra were recorded on SHIMADZU FT-IR-8400s spectrophotometer. \(^1\)H NMR and \(^{13}\)C NMR spectra of the products were recorded on Bruker AMX 400 MHz and 100 MHz respectively in DMSO-\(d_6\) as solvent and TMS as internal standard.

Table 2.1: Selection of suitable catalyst and solvent for the synthesis of 5d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imidazole</td>
<td>Ethanol</td>
<td>150</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>Ethanol</td>
<td>140</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Ba(OH)(_2)</td>
<td>Ethanol</td>
<td>180</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>NaHSO(_4)</td>
<td>Ethanol</td>
<td>120</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>NaHSO(_4)</td>
<td>Water</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>NaHSO(_4)</td>
<td>Water-ethanol(1:1)</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>NaHSO(_4)</td>
<td>Acetonitrile</td>
<td>120</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\) isolated yields

Table 2.2: Synthesis of novel dihydropyranо [2,3-c]pyrazol-6-amines from various aldehydes, hydrazine hydrate, ethyl acetoacetate, and 4-chloro phenylacetonitrile and NaHSO\(_4\) in water.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (1)</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield(^a) (%)</th>
<th>MP(^\circ)C found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-NO(_2)C(_6)H(_4)CHO</td>
<td>5a</td>
<td>120</td>
<td>85</td>
<td>185–187</td>
</tr>
<tr>
<td>2</td>
<td>4-HOC(_6)H(_4)CHO</td>
<td>5b</td>
<td>120</td>
<td>82</td>
<td>236–239</td>
</tr>
<tr>
<td>3</td>
<td>4-ClC(_6)H(_4)CHO</td>
<td>5c</td>
<td>120</td>
<td>80</td>
<td>199–200</td>
</tr>
</tbody>
</table>
General procedure for the preparation of dihydropyrido[2,3-c]pyrazol-6-amines:

The aromatic aldehyde (1 m mol), malononitrile (1 m mol), ethyl acetoacetate (1 m mol) hydrazine hydrate (1 m mol) and NaHSO₄ (0.5 m mol) were taken in ethanol-water (1:1) (~5 ml) and heated at 80 °C for 1-2 hrs. The progress of the reaction was monitored using Silica gel-G TLC plates with a mixture of petroleum ether (60–80°C) and ethyl acetate (20:80) as eluent. After the completion of the reaction, the mixture was cooled to room temperature and the precipitated solid was filtered, washed with water to get nearly pure product.

Conclusions:

To conclude, we have reported a simple, efficient one-pot multicomponent protocol for the expedient synthesis of dihydro-pyrido[2,3-c]pyrazol-6-amines.

---

4. 3-MeO, 4-HOC₆H₅CHO  5d  80  82  260–263
5. 3-MeOC₆H₄CHO  5e  80  89  195–197
6. 3,4,5-(MeO)₃C₆H₅CHO  5f  90  80  180–184
7. 4-NO₂C₆H₄CHO  5g  90  82  271–273
8. 2,4-Cl₂C₆H₃CHO  5h  120  80  205–207
9. 3,4-(MeO)₂C₆H₃CHO  5i  120  80  175–178
10. 2-HOC₆H₄CHO  5j  90  82  200–204
11. HCHO  5k  240  ND  -
12. CH₃CHO  5l  240  ND  -
13. C₆H₅CH=CHCHO  5m  240  ND  -

* isolated yields. ND: not detected
The noteworthy advantages of this protocol include easily available starting materials, simple procedure, and easier separation of products by filtration.

References:


Spectral data:

Figure 2.1: FT-IR Spectrum of 5a
Figure 2.2: $^1$H NMR Spectrum of 5a

Figure 2.3: $^{13}$C NMR Spectrum of 5a
Figure 2.4: FT-IR Spectrum of 5b

Figure 2.5: $^1$H NMR spectrum of 5b
Figure 2.6: FT-IR Spectrum of 5c

Figure 2.7: $^1$H NMR spectrum of 5c
Figure 2.8: $^{13}$C NMR spectrum of 5c

Figure 2.9: FT-IR Spectrum of 5d
Figure 2.10: $^1$H NMR spectrum of 5d

Figure 2.11: $^{13}$C NMR spectrum of 5d
Figure 2.12: FT-IR Spectrum of 5e

Figure 2.13: $^1$H NMR spectrum of 5e
Figure 2.14: $^{13}$C NMR spectrum of 5e
Chapter 3: Synthesis, antimicrobial and analgesic activity of some 5-arylmethylidene-pyrimidin-2,4,6 triones

Introduction:

Knöevenagel condensation is an important elemental reactions in organic chemistry through which aromatic aldehydes condense with acidic methylene compounds such as malononitrile, methyl cyanoacetate, cyanoacetamide, 5,5-dimethyl-1,3-cyclohexanedione, barbituric acid and 2-thiobarbituric acid to give products in quantitative yields. Several reports are available in the literature, reporting the condensation of one mole barbituric acid with one mole of carbonyl compound in presence of various catalysts 1–8.

The products of the condensation of aromatic aldehydes with barbituric acid (pyrimidinetrione) are important in pharmaceutical industry for their biological activities. Traditionally, they have been reported to show activity as anesthetics, sedatives, and hypnotics 9 and as anticancer 10. Recently, few methods have been reported in which aromatic aldehydes condense with one mole of barbituric acid to give bis-condensed heterocyclic systems with ring assemblies11, and salicylaldehydes condensing with barbituric acid to generate oxadeazaflavines 12.

Water as a reaction medium, is one of the most promising approaches in green chemistry. Breslow 13 rediscovered the use of water as a solvent in organic synthesis and showed that hydrophobic effects could strongly enhance the rate of several organic reactions. Previously, the incomplete solubility of the reactants
in water was the main reason that ruled out the use of this solvent in organic synthesis. But with the advent of Green chemistry, environmentally friendly solvents like water gained importance. Further reasons that make water unique among solvents are that it is cheap, not inflammable, and most important, nontoxic.

Amberlite has been explored as an effective heterogeneous and reusable catalyst. As heterogeneous catalyst it has many advantages in contrast to traditional catalysts. It is stable to air, water, relatively nontoxic, easy to handle, readily separable from the products. Reactions of organocatalysts in aqueous media are generally environmentally safe. The increasing attention during the last decade for the environmental protection has led both modern academicians and industrialists to develop chemical processes with maximum yield and minimum cost whilst using non-toxic reagents, solvents and catalysts. In our laboratory we have reported the synthesis of heterocyclic compounds. Continuing our research in developing new environmentally friendly methodologies for the preparation of organic compounds, we report an efficient condensation of aromatic aldehydes with barbituric acid in water using amberlite IR 120 as reusable catalyst (Scheme 1) and screening of the some of the synthesized compounds for the antimicrobial and analgesic activity.

![Scheme 1](image-url)
Results and discussion:

To investigate the feasibility of reaction, the reaction of Barbituric acid (1 mmol) and anisaldehyde (1 mmol) in 5mL of water in presence of amberlite IR 120 (0.1g) at 80°C on hot plate was taken up. The reaction proceeded efficiently, yielding product in excellent yield. To generalize the reaction, barbituric acid was treated with various structurally diverse aldehydes. Expected products were obtained in all the reactions giving products in good yields (Table 3.1).

General procedure for the synthesis of pyrimidinetrione:

Barbituric acid (1 mmol) was dissolved in boiling water; the aromatic aldehyde (1 mmol) was then added in presence of amberlite catalyst at 80°C. The reaction goes to completion in 1-2 minutes to give the product in good yield. Reactions were monitored using thin-layer chromatography (TLC, 2:8 ethyl acetate-petroleum ether). The product was separated just by filtration, the catalyst settles down, and easily separated. Product was washed with hot water. The catalyst was separated, washed with ethyl acetate, and reused for at least five times without the significant loss in its activity. The product after removal of solvent was re-crystallized product was obtained using glacial acetic acid.

Experimental:

All the chemicals were commercial products. IR spectra were recorded using a Shimadzu Fourier transform (FT)–IR-8400 s, and ^1^H NMR (dmso- d$_6$ as solvent and tetramethylsilane as an internal standard) spectra were recorded on a Bruker AMX (200-MHz) spectrophotometer.
Table 3. 1. Conversion of aromatic aldehydes to 5-arylmethylidene-pyrimidin-2,4,6-triones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (sec)</th>
<th>Yielda (%)</th>
<th>MP (ºC)</th>
<th>found</th>
<th>reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4-Methoxy</td>
<td>a</td>
<td>60</td>
<td>95</td>
<td>297</td>
<td>296-298[8a]</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>4-N, N (Dimethyl)amino</td>
<td>b</td>
<td>90</td>
<td>94</td>
<td>269</td>
<td>281-282[8a]</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>4-Chloro</td>
<td>c</td>
<td>90</td>
<td>94</td>
<td>296</td>
<td>296-298[8a]</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>4-Hydroxy 3-methoxy</td>
<td>d</td>
<td>60</td>
<td>90</td>
<td>294</td>
<td>293-297[8b]</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Benzaldehyde</td>
<td>e</td>
<td>60</td>
<td>90</td>
<td>264</td>
<td>264-266[8a]</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>4-hydroxy</td>
<td>f</td>
<td>90</td>
<td>89</td>
<td>324</td>
<td>&gt;320[8a]</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>2-Hydroxy</td>
<td>g</td>
<td>80</td>
<td>91</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

*a*isolated yield

**Pharmacological studies:**

Survey of literature revealed that, the antimicrobial study of the transition metal complexes of barbituric acid is reported by Ikotun et al 16. In view of this observation, investigation of the antimicrobial activity of few synthesized compounds was carried out. In this report, the assessment of the antimicrobial and analgesic activity of the compounds 3a, 3b, and 3c is reported.

**Evaluation of antimicrobial activity**

Synthesized compounds 3a, 3b, and 3c were screened for their antibacterial and antifungal activities. For preliminary screening, antimicrobial activity was carried out by the cup-plate method 17.
Screening of antibacterial activity

The compounds were screened against the common bacteria like *Staphylococcus aureus* (NCIM 2079) and *Klebsiella pneumoniae*, which are the representative type of gram positive and gram negative organisms using nutrient agar. Antifungal activities were screened against the common fungi like *Aspergillus niger* (NCIM 1196) and *Candida albicans* (NCIM 3471) using potato dextrose agar medium. Sub-cultures were prepared one day prior to the test for the antibacterial activity and two-days prior for the antifungal activity. The discs (8 mm in diameter), impregnated with 0.05ml of the test compounds at the concentration of 50 mg/ml and 100mg/ml impregnated with the test compound, prepared in dimethyl formamide were placed on the inoculated agar. Negative controls were prepared using the same solvent dimethyl formamide employed to dissolve the test compounds. Standard drugs, Ciclopirox olamine ($10^{-3}$ mole/lit) and Micanazole ($10^{-3}$ mole/lit) were used as positive reference standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37° C for 24 hr and 27° C for 72 hr for bacteria and fungi strains respectively. Antimicrobial activity was evaluated by measuring the diameter of zone of inhibition against test organisms. The antimicrobial activity results are summarized in Table 3. 2.
Table 3.2. Antimicrobial activities of 3a, 3b, 3c

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Diameter of Zone of inhibition in mm</th>
<th>0.5 (mg/ml)</th>
<th>0.75 (mg/ml)</th>
<th>0.50 (mg/ml)</th>
<th>0.75 (mg/ml)</th>
<th>0.50 (mg/ml)</th>
<th>0.75 (mg/ml)</th>
<th>A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong>&lt;sup&gt;a&lt;/sup&gt; (NCIM 2079)</td>
<td></td>
<td>08</td>
<td>09</td>
<td>08</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong>&lt;sup&gt;a&lt;/sup&gt; (NCIM 2957)</td>
<td></td>
<td>09</td>
<td>10</td>
<td>09</td>
<td>09</td>
<td>06</td>
<td>08</td>
<td>16</td>
</tr>
<tr>
<td><strong>Aspergillus niger</strong>&lt;sup&gt;b&lt;/sup&gt; (NCIM 1196)</td>
<td></td>
<td>09</td>
<td>10</td>
<td>06</td>
<td>07</td>
<td>09</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td><strong>Candida albicans</strong>&lt;sup&gt;b&lt;/sup&gt; (NCIM 3471)</td>
<td></td>
<td>08</td>
<td>11</td>
<td>08</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup>bacteria, <sup>b</sup>fungi, A- Ciclopirox olamine (standard used for the antibacterial activity), B- Micanazole (standard used for the antifungal activity)

Based on the results (Table 2), it is inferred that 5-arylmethyldene-pyrimidin-2,4,6-triones (3a, 3b, 3c) displayed have significant inhibition effect on the growth of bacteria and fungi. The potency of the compounds were found to be less at the concentration of 0.5mg/ml. Compound 3c registered good antimicrobial activity against bacteria and fungi tested at the concentration of 0.75 mg/ml. Compound 3a showed good antifungal activity at the same concentration.
Assessment of analgesic activity:

Colony bred albino mice (Swiss strain) of either sex weighing 22-35 g were used to evaluate analgesic activity\(^{18}\). Analgesic activity was determined with acetic acid induced writhing test in mice\(^{19}\). For this experiment 30 mice were used which were divided into 5 groups containing 6 animals in each group. Group I received 0.5 ml of Tween-80 (0.1%) and served as control, Group II received 50 mg/kg body weight of acetyl salicylic acid (aspirin) orally and served as standard. The remaining 3 groups received test compounds at a dose of 100 mg/kg body weight orally in the form of suspension in 0.1% Tween-80. After one hour, the animals received 0.6% of 10 ml/kg body weight of acetic acid intraperitoneally. The writhing movements were recorded for 15 min (between the 5th and 20th min after the injection of the irritant). The results are summarized in Table 3.3. The effect was expressed as the percentage of protection compared with the control group. The three compounds (3a, 3b and 3c) tested exhibited statistically significant anti-inflammatory activity.

Table 3.3. Analgesic activity \(^a\) of 3a, 3b, 3c

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg p.o)</th>
<th>Mean of writhing</th>
<th>% Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without the administration of drug± S.E.M.</td>
<td>With the administration of drug± S.E.M.</td>
</tr>
<tr>
<td>Standard</td>
<td>150</td>
<td>47.00±2.50</td>
<td>11.80±1.27</td>
</tr>
<tr>
<td>3a</td>
<td>100</td>
<td>39.80±3.74</td>
<td>18.00±2.13</td>
</tr>
<tr>
<td>3b</td>
<td>100</td>
<td>26.10±1.90</td>
<td>12.16±1.97</td>
</tr>
<tr>
<td>3c</td>
<td>100</td>
<td>37.16±2.40</td>
<td>22.18±2.27</td>
</tr>
</tbody>
</table>

\(^a\) Writhing test in mice.
Conclusions:

To conclude, we have developed an efficient method for the synthesis of condensed heterocyclics from barbituric acid and aromatic aldehydes. This method was found to be better with respect to handling, remarkable operational simplicity, product isolation, reaction time and temperature. Use of water as medium makes this a green method. In addition, three of the synthesized compounds were screened for antimicrobial and analgesic activity.

References:


Spectral Data:

Figure 3.1: FT-IR spectrum of 3a

Figure 3.2: $^1$H NMR spectrum of 3a
Figure 3.3: FT-IR Spectrum of 3b

Figure 3.4: $^1$H NMR spectrum of 3b
Figure 3.5: FT-IR spectrum of 3c

Figure 3.6: $^1$H NMR spectrum of 3c
Figure 3.7: FT-IR Spectrum of 3d

Figure 3.8: $^1$H NMR spectrum of 3d
Chapter 4: Synthesis of poly-substituted Quinolines and quinolino [1, 2-a]quinazolines

Introduction:

Quinolines and their derivatives are a class of important organic molecules which have been studied extensively in the recent years. These compounds have been conventionally prepared by Friedlander synthesis\(^1\) either from o-nitro or o-amino aryl carbonyl compounds in condensation with enolizable carbonyl compounds in presence of catalysts. (Scheme 1) Substituted Quinoline derivatives are found as substructures in natural products as well as in synthetic molecules. They find use in therapeutics because of their biological properties such as antimalarial, anti-inflammatory, antihypertensive and tyrosine kinase PDGF-RTK inhibiting agents\(^3\). These pharmacological properties have prompted the researchers to give significant importance for the construction of these compounds by new synthetic routes superior to Friedlander synthesis\(^4\).

Microwave assisted synthesis of 4-Methoxy-1-methyl-2-quinolinone and its analogs has been reported by Nadaraj et al.\(^5\) Multi component reactions are integral part of green chemistry. Atechiana et al have reported gold-catalyzed Friedlander reaction for the synthesis of trisubstituted quinolines \(^6\). One-pot, four component synthesis 2-amino- 7,7- dimethyl 4-substituted-5-oxo-1-(3,4,5-trimethoxy)-1,4,5,6,7,8 hexahydro quinoline -3-carbonitrile derivatives have been reported by Saleh I. et al \(^7\) Microwave-Assisted Combinatorial Synthesis of Quinolino[1,2- a]quinazoline Derivatives have been reported by Shujiang et al \(^8\). These quinoline derivatives have received significant attention due to their
wide range of biological activities and there is a need to explore simple experimental conditions for their synthesis. Continuing our efforts for the synthesis of bioactive molecules using MCRs, present work reports the synthesis of poly-substituted quinolines. (Scheme 2 and 3).

Scheme 1. Friedlander Synthesis.

Results and discussion:
Initially, a mixture of aniline, anisaldehyde, dimedone and malononitrile (1 mol each) taken in a beaker were subjected to microwave irradiation under neat conditions.
Scheme 2. Synthesis of poly substituted hexahydroquinoline

![Synthesis of poly substituted hexahydroquinoline](image)

Scheme 3. Synthesis of poly substituted quinolino[1,2-\(a\)]quinazolines

We failed to get the product under this condition, in the absence of catalyst and solvent. The reaction was repeated in presence of imidazole (0.1mg) as catalyst and 5 mL of water to get the product in low yield (45%). To check the feasibility of the reaction under other conditions, the reaction mixture was refluxed as well as irradiated under ultrasound in presence of catalyst and water as solvent. While ultrasound failed to induce the reaction, reflux in water improves the yield significantly. Water as a solvent offers many advantages of being non-toxic, environmentally compatible, low cost and safe handling. Encouraged by this result, the catalyst load was optimized by carrying the reaction at 0.1mg, 0.05 mg, 0.025 mg and different solvents like acetonitrile, and ethanol along with water were investigated. The best yields were obtained in water at 0.1mg catalyst. Further, this reaction was found to be compatible with aromatic
aldehydes as shown in the **Table 4.1**. With these same reaction conditions, a mixture of anthranilic acid, anisaldehyde, dimeredone and malononitrile (1 m mol each) were refluxed in water (5 mL) in a round bottomed flask. The reaction proceeds for a longer duration to give the desired product. The template was applied to a series of aldehydes to get the products in good yield as shown in **Table 4.2**.

**Table 4.1 : Synthesis of polysubstituted hexahydroquinolines various aromatic aldehydes, aniline, dimeredone and malononitrile**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (I)</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5a</td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>2.</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5b</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3.</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5c</td>
<td>60</td>
<td>82</td>
</tr>
<tr>
<td>4.</td>
<td>4-N,N(CH&lt;sub&gt;3&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5d</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>5.</td>
<td>4-OH,3-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;CHO</td>
<td>5e</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>6.</td>
<td>2-OHC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5f</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>7.</td>
<td>3-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5g</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yields
Table 4.2: Synthesis of quinolino[1,2-a]quinazolines from aromatic aldehydes, anthranilic acid, dimedone and malononitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (6)</th>
<th>Product</th>
<th>Time</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4-MeOC₆H₄CHO</td>
<td>10a</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>2.</td>
<td>4-ClC₆H₄CHO</td>
<td>10b</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>3.</td>
<td>4-NO₂C₆H₄CHO</td>
<td>10c</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>4.</td>
<td>4-N, N(CH₃)₂C₆H₄CHO</td>
<td>10d</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>5.</td>
<td>4-OH, 3-MeOC₆H₃CHO</td>
<td>10e</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>6.</td>
<td>2-OHC₆H₄CHO</td>
<td>10f</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>7.</td>
<td>3-MeOC₆H₄CHO</td>
<td>10g</td>
<td>4</td>
<td>78</td>
</tr>
</tbody>
</table>

a isolated yields

Experimental:

All chemicals used were commercial and without further purification. Progress of the reaction was monitored using Silica gel-G TLC plates. The synthesized compounds were characterized by ¹H NMR spectral analysis and FT-IR. NMR spectra were recorded on a Brucker AMX (400-MHz) spectrophotometer DMSO-d₆ as solvent. FT-IR spectra were recorded on a Bruker Optics Alpha-P FT-IR spectrophotometer with attenuated total reflectance (ATR) module. Elemental analysis was carried out using vario MICRO CHN analyser.

General procedure for the preparation of hexahydroquinoline (5a-g):

A mixture of aniline, anisaldehyde, dimedone, malononitrile (1 m mol each) water (5 mL) and imidazole catalyst (0.1 mg) were taken in a 50 mL
round-bottomed flask. The contents were refluxed for the time shown in Table 4.1. The reaction was monitored using TLC. The solid product obtained was filtered, washed with water repeatedly to remove the impurities and recrystallized from EtOH to give the pure products.

**General procedure for the preparation of quinolino[1,2-a]quinazolines (10a-g):** A mixture of anthranilic acid, anisaldehyde, dimedone, malononitrile (1 mmol each) water (5 mL) and imidazole catalyst (0.1 mg) were taken in a 50 mL round-bottomed flask. The contents were refluxed for the time shown in Table 4.2. The reaction was monitored using TLC. The solid product obtained was filtered, washed with water repeatedly to remove the impurities and recrystallized from EtOH to give the pure products.

**Conclusions:**

We have reported an efficient and mild protocol for the synthesis of polysubstituted quinolines and quinolino[1,2-a] quinazolines. Using a low cost catalyst, water as medium, mild reaction conditions are the advantages of this protocol.

**References:**

1. (a) Friedlander; *Chem. Ber.* **1882**, *15*, 2572; (b) McNaughton, B. R.; Miller, B. L.; *org. lett.*, **2003**, *5*, 4257.

3. (a) Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. 


   241.


8. Shujiang Tu, S.; Li, C.; Li, G.; Cao, L.; Qingqing Shao, Q.; Zhou,D.; Bo 

Spectral data:

Figure 4.1: FT-IR spectrum of 2-amino-4-(4′-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile

Figure 4.2: $^1$H NMR spectrum of 2-amino-4-(4′-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile

Elemental analysis: C$_{25}$H$_{25}$N$_3$O$_2$. C-75.16, H-6.31, N-10.52, O-8.01 (expected)
C-75.17, H-6.31, N-10.54 (found)
Figure 4.3: FT-IR spectrum of 2-amino-4-(4'-chlorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile

Figure 4.4: $^1$H NMR spectrum of 2-amino-4-(4'-chlorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile

Elemental analysis: C$_{24}$H$_{22}$ClN$_3$O. C-71.37, H-5.49, N-10.40, Cl-8.78, O-3.96(expected) C-71.39, H-5.47, N-10.43(found)
Figure 4.5: FT-IR spectrum of 2-amino-7,7-dimethyl-4-(4'-nitrophenyl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile

Figure 4.6: $^1$H NMR spectrum of 2-amino-7,7-dimethyl-4-(4'-nitrophenyl)-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile

Elemental analysis: C$_{26}$H$_{25}$N$_3$O$_3$. C-69.55, H-5.35, N-13.52, O-11.58 (expected)
C-69.55, H-5.37, N-13.53 (found)
Figure 4.7: FT-IR spectrum of 8-(4′-methoxyphenyl)-11,11-dimethyl-5,9-dioxo-6,8,9,10,11,12-hexahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile

Figure 4.8: 1H NMR spectrum of 8-(4′-methoxyphenyl)-11,11-dimethyl-5,9-dioxo-6,8,9,10,11,12-hexahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile

Elemental analysis: $C_{26}H_{25}N_3O_3$. C-73.05, H-5.89, N-9.83, O-11.23(expected)
C-73.059, H-5.85, N-9.87.(found)
Figure 4.9: FT-IR spectrum of 8-(4′-chlorophenyl)-11,11-dimethyl-5,9-dioxo-6,6a,7,8,9,10,11,12-octahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile

Figure 4.10: 1H NMR spectrum of 8-(4′-chlorophenyl)-11,11-dimethyl-5,9-dioxo-6,6a,7,8,9,10,11,12-octahydro-5H-quinolino[1,2-a]quinazoline-7-carbonitrile

Elemental analysis: C_{25}H_{22}ClN_{3}O_{2}. C-69.52, H-5.13, Cl-8.21, N-9.73 (expected)
C-69.55, H-5.10, N-9.76 (found)
<table>
<thead>
<tr>
<th>Weight [mg]</th>
<th>Name</th>
<th>N (%)</th>
<th>C (%)</th>
<th>H (%)</th>
<th>C/H ratio</th>
<th>C/N ratio</th>
<th>Date</th>
<th>Time</th>
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<td>36.80</td>
<td>4.004</td>
<td>9.1696</td>
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<td>12:00</td>
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<tr>
<td>4.4760</td>
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<td>51.49</td>
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Figure 4.11: Elemental analysis
Chapter 5: Synthesis of Benzopyrans

Introduction:

In recent years tetrahydrobenzo[b]pyrans and their derivatives show wide range of biological activities\(^1\), used as pigments, photoactive materials\(^2\). Tetrahydrobenzo[b]pyran and its derivatives are gaining considerable as anticoagulant, diuretic, spasmolytic, anticancer and anti-anaphylactin activities\(^3\). Tetrahydrobenzo[b]pyrans have been prepared by methods using, ultrasound\(^4\), microwave activation\(^5\), as well as heating\(^6\). Various catalysts like 1,1,3,3-\(N,\text{N},\text{N},\text{N}'\)-tetramethylguanidinium trifluoro acetate (TMGT, an ionic liquid)\(^7\), hexadecyldimethylbenzyl ammonium bromide\(^8\), as well as electrochemical synthesis\(^9\) have been reported for the synthesis of Tetrahydrobenzo[b]pyrans. These methods have their own demerits such as low yields, commercially unavailable catalysts, and long reaction times. We report an improved method for the multicomponent synthesis of tetrahydrobenzo[b]pyrans by using inexpensive and less toxic reagents such as imidazole, coupled with simple reaction conditions and easier work-up procedures.

![Scheme 1](image-url)
Results and discussion:

Synthesis of tetrahydrobenzo[b]pyrans by reacting dimedone, malononitrile and aromatic aldehydes (1 m mol each) in the presence of readily available organocatalyst imidazole was taken up under reflux and ultrasonication. Organic solvents like ethanol, methanol, acetonitrile, dichloromethane, chloroform as well as water were screened. Best yields were obtained when water was used as solvent under reflux condition.

Hence the reaction of anisaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol) and imidazole (0.5 mmol) was carried out in water (10 ml) at 80 °C to get the corresponding tetrahydrobenzo[b]pyran in 95% yield within 30 min. The reaction was extended to various aromatic aldehydes which gave good yields of the products as shown in Table 5.1.

Table 5.1. Synthesis of tetrahydrobenzo[b]pyran from various aromatic aldehydes, malononitrile and dimedone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (I)</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield° (%)</th>
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<tr>
<td>1.</td>
<td>C₆H₅CHO</td>
<td>4a</td>
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<tr>
<td>2.</td>
<td>4-MeO-C₆H₄CHO</td>
<td>4b</td>
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<td>3.</td>
<td>4-HO-C₆H₄CHO</td>
<td>4c</td>
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<td>4.</td>
<td>2-HO-C₆H₄CHO</td>
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<td>5.</td>
<td>4-N,N(CH₃)₂-C₆H₄CHO</td>
<td>4e</td>
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<tr>
<td>6.</td>
<td>3-Cl-C₆H₄CHO</td>
<td>4f</td>
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<td>95</td>
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<tr>
<td>8.</td>
<td>4-Cl-C₆H₄CHO</td>
<td>4g</td>
<td>30</td>
<td>89</td>
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</table>

°Yields refer to pure isolated products.
Experimental:

All chemicals used were commercial and without further purification. Progress of the reaction was monitored using Silica gel-G TLC plates. The synthesized compounds were characterized by $^1$H NMR spectral analysis, comparing the products on TLC or by the comparison of melting points (Raaga, Chennai, Indian make melting point apparatus) with products prepared by known methods. NMR spectra were recorded on a DSX-300(S) AV-III400L spectrophotometer DMSO-d$_6$ as solvent. FT-IR spectra were recorded on a Bruker Optics Alpha-P FT-IR spectrophotometer with attenuated total reflectance (ATR) module and SHIMADZU FT-IR-8400s spectrometer.

General Procedure for the synthesis of tetrahydrobenzo[b]pyrans in water:

A mixture of dimedone (0.14 g, 1 mmol), malononitrile (0.066 g, 1 mmol), corresponding aromatic aldehyde (1 mmol) and imidazole (0.5 mmol) in water (10 mL) was vigorously stirred at 80 °C for 30min, the solid thus separated was filtered, washed with ethyl acetate/light petrol (2:8, 2 ×10mL) to get nearly pure products. Recrystallization was carried out from ethanol.

Conclusions:

An efficient and environmentally friendly synthetic method for the synthesis of tetrahydrobenzo[b]pyrans using a simple organocatalyst imidazole in water as solvent is described. The remarkable advantage of this protocol is mild reaction condition, good yield of the products, experimental simplicity, cost effectiveness and solvent-free condition. We believe that, this methodology will be a valuable addition to the existing methods of synthesis of benzopyrans. This
work has been published in International Journal of Science Research Vol. 01, Issue 04, 2012.

References:


Spectral data:

Figure 5.1: FT-IR Spectra of anisaldehydebenezopyran

Figure 5.2: $^1$H NMR Spectra of anisaldehydebenezopyran
Figure 5.3: FT-IR Spectra of p-chlorobenzaldehydebenzopyran

Figure 5.4: $^1$H NMR Spectra of p-chlorobenzaldehydebenzopyran
Figure 5.5: $^1$H NMR Spectra of salicylaldehydebenzaldehydebenzopyran
Chapter 6: Conclusions

Past two decades the synthesis of organic compounds has undergone revolutionary changes. Most of the synthesized organic molecules have been explored to be potentially bioactive and pharmaceutically important ingredients. This has stimulated the development of cost-effective methods for the manufacture of these organic molecules. At the same time the growing environmental concern, has lead to a paradigm shift from the traditional methods of synthesis to the methods which are economical, and aim at conserving energy and raw materials, eliminating waste, and avoiding the use of toxic and/or hazardous chemicals. As a result there has been a remarkable progress in replacing traditional processes with greener, more sustainable alternative synthetic routes. The progress in drug discovery, Target molecules have become increasingly complex, and demand new green synthetic methodologies to be designed.

Chapter 1 deals with the synthesis of Pyranopyrazoles an important class of heterocyclic compounds, useful as biodegradable agrochemicals, pharmaceutical ingredients, analgesic and anti-inflammatory, anticancer agents. The protocol has Silica-NaHSO₄ as catalyst, water as a reaction medium as the highlights.

Chapter 2, reports the synthesis of Dihydropyrano[2,3-c]pyrazole scaffold and its derivatives. These molecules possess useful biological and
pharmacological properties. Easily available starting materials, simple procedure, and easier separation of products by filtration are the advantages of this synthesis.

Chapter 3 reports the Synthesis, antimicrobial and analgesic activity of some 5-arylmethylidene-pyrimidin-2, 4, 6 triones. These compounds have been reported to show activity as anaesthetics, sedatives, and hypnotics and as anticancer. This method was found to be better with respect to handling, recyclable catalyst, remarkable operational simplicity, product isolation, reaction time and temperature.

In chapter 4, Synthesis of poly-substituted Quinolines and quinolino[1,2-a]quinazolines has been reported. Quinoline derivatives are found as substructures in natural products, as well as therapeutics, antimalarial, anti-inflammatory, antihypertensive and tyrosine kinase PDGF-RTK inhibiting agents. These have been synthesized using a low cost catalyst, water as medium under mild reaction conditions.

In chapter 5, synthesis of tetra hydrobenzo[b]pyrans and their derivatives which show a wide range of biological activities such as anti-coagulant, diuretic, spasmylytic, anticancer and anti-anaphylactin activities, as well as these are used as pigments, photoactive materials. Mild reaction condition, good yield of the
products, experimental simplicity, and cost effectiveness are the highlights of this method.
Equipments used during the project:

Figure 1: Melting point apparatus

Figure 2: Ultra sonicator
Figure 3: Microwave oven

Figure 4: Hot plate and magnetic stirrers with heating.
Figure 5: UV chamber for TLC