

**Final Report Summary**  
**Minor Research Project**  
(2009-2011)

Submitted to  
**University Grants Commission**  
**Western Regional Office, Pune**

In the subject of  
**Chemistry**

On the topic  
**NEW METHODS IN HETEROCYCLIC**  
**SYNTHESIS USING REUSABLE CATALYST**

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## **SUMMARY OF THE PROJECT**

### **Final Report (2009-2011)**

#### **1. INTRODUCTION**

Heterocycles forms the largest class of compounds. These heterocycles are widely distributed in nature. They are essential for life and play a vital role in metabolism of living cells. A large number of heterocyclic compounds are in clinical use due to their pharmacological activity. Nodought the chemistry of heterocyclic to continue to develop new drugs agrobases chemicals and different novel materials.

The synthesis of heterocyclic compounds is always challenge to the scientist community due to the high cost raw materials, longer reaction time, low yield and waste form in the reaction. In proposed work we will try to carry out various heterocyclic syntheses using non-hazardous and low cost recyclable catalyst.

Several heterocyclic compounds are used in various drug synthesis hence the demand of these heterocycles is high. The need of these drug intermediate molecules can be fulfill by reducing the cost of material. Considering this facts we are plan to use recyclable catalyst to carry out the several heterocyclic compounds synthesis. The reaction using conventional methods and high cost catalyst increases the cost of the products. Herein the proposed work is carried out using recyclable catalyst and green methodology, which may reduce the cost of forming products.

## **02. OBJECTIVES OF THE PROJECT:**

Following are the objectives of the research project;

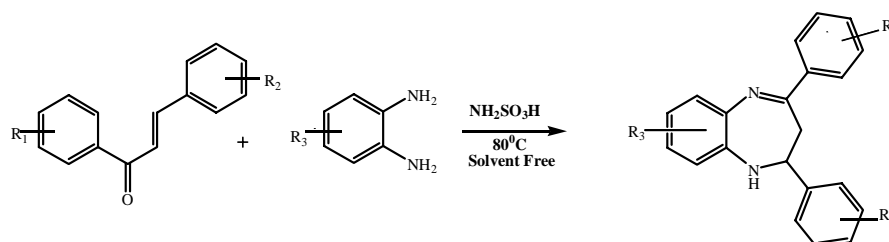
1. In proposed work we are try to reduce the cost of raw material used in the synthesis of several heterocycles.
2. The work will be carried out using cheaper non-conventional green methodology.
3. The reaction conditions will be environment safety.
4. Reusable and non-hazardous catalyst will be use for above mention synthesis process.
5. These catalysts enhance the rate of reactions and reduce the reaction time also.

### 03. RESEARCH ACHIEVEMENTS:

#### [A] Sulfamic Acid Catalyzed Synthesis of Benzo-[b]-1,4-diazepines:

Benzodiazepines are interesting compounds because of their pharmacological properties. Many members of this family are widely used as tranquilizing and anticonvulsant agents. Although, the first benzodiazepine was introduced as a drug nearly 30 years ago. In this section synthesis of 1,4-benzodiazepine derivatives using sulfamic acid catalyst under solvent free condition has been described. The method afforded several advantages including easy workup, operational simplicity, solvent free, excellent yields of the products and catalyst was recycled and reused for several times.

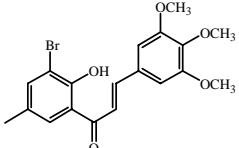
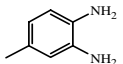
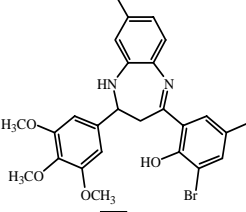
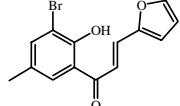
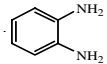
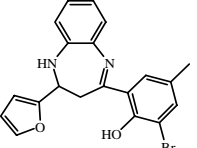
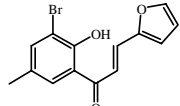
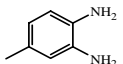
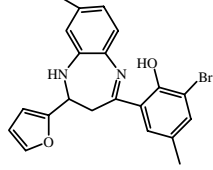
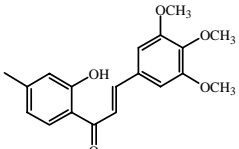
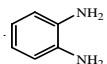
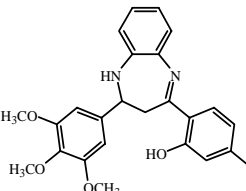
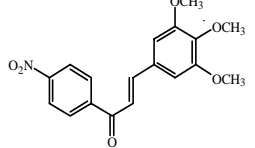
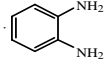
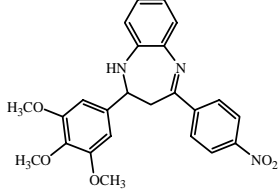
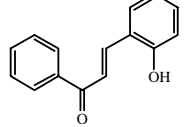
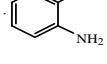
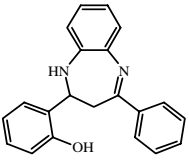
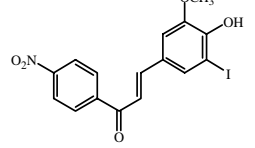
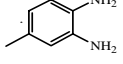
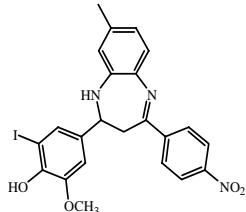
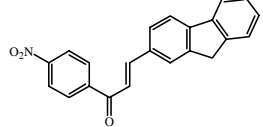
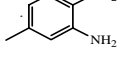
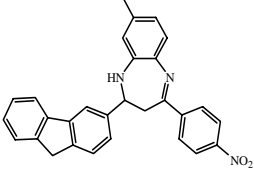
**Synthesis of 2,4-Diphenyl-2,3-dihydro-1H-benzo-[b]-[1,4]-diazepine:** A mixture of  $\alpha,\beta$ -unsaturated carbonyl compound (10 mmol), *o*-phenylenediamine (10 mmol), and sulfamic acid (10 mol%) was heated at 80 °C without any organic solvent for the appropriate time (Table 1). After completion of reaction as indicated by TLC, the reaction mixture was cooled at room temperature and extracted with diethyl ether (3 × 10 ml). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the residue was column chromatographed using petroleum ether: ethyl acetate (2:3) as the eluent, to obtain pure compound. The recovered sulfamic acid catalyst was washed with diethyl ether, activated at 70 °C temperatures and reused. Similarly the other derivatives were also synthesized.

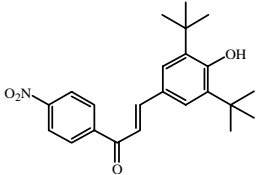
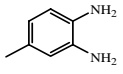
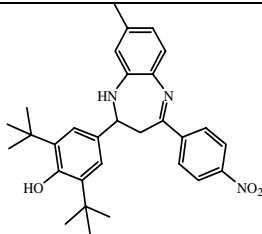
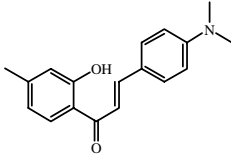
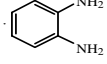
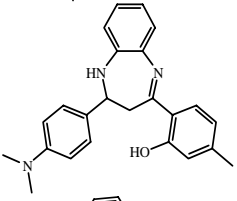
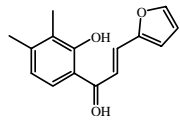
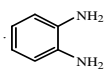
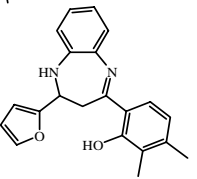
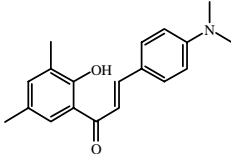
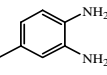
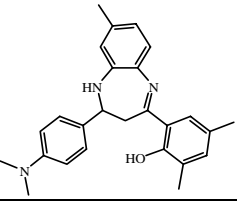


**Scheme-1** [J. Iranian Chem. Society, 2009, 6(3), 477-482]

**Table-1:** Synthesis of benzo-[b]-1,4-diazepines using sulfamic acid catalyst.

Entry	Chalcones	OPD	Product	Time (min.)	M.P. (°C)	Yield <sup>a</sup> (%)
A <sub>1</sub>				110	110	85

A <sub>2</sub>				120	145	95
A <sub>3</sub>				105	90	85
A <sub>4</sub>				110	96	85
A <sub>5</sub>				95	101	85
A <sub>6</sub>				120	140	85
A <sub>7</sub>				85	221	86
A <sub>8</sub>				130	114	82
A <sub>9</sub>				120	229	80

<b>A<sub>10</sub></b>				115	240	80
<b>A<sub>11</sub></b>				90	283	85
<b>A<sub>12</sub></b>				90	107	90
<b>A<sub>13</sub></b>				100	120	90

<sup>a</sup>Isolated and unoptimized yield.

**Table-2:** Recovery of sulfamic acid catalyst:

Entry	Products	Yield (%)		
		<i>Cycle-1</i>	<i>Recycle-2</i>	<i>Recycle-3</i>
1	<b>A-1</b>	85	81	77
2	<b>A-9</b>	86	80	75

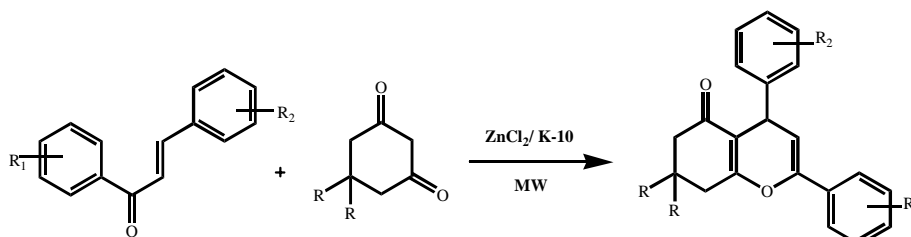
### [B] Synthesis of 2,4-diphenyl-4,6,7,8-tetrahydro chromen-5-one:

Microwave heating has been used for a variety of organic reactions and has found application in rapid and efficient syntheses of organic compounds. Recently, the emphasis has shifted in favour of microwaves-assisted methods under solvent-free conditions, Microwave assisted heterogeneous reactions with various solid inorganic supports have attracted research interest because of the simplicity, greater stability and rapid synthesis of a variety of organic compounds. Synthesis of 2,4-diphenyl-4*H*-chromen-5-one using ZnCl<sub>2</sub>/montmorillonite K-10 as a recyclable heterogeneous catalyst. The procedure is simple, ecofriendly and solvent free with excellent yield of products.

**1) Catalyst preparation:** Zinc chloride is dissolved in water at room temperature. Impregnate the solid support as montmorillonite K-10 so that the aqueous solution of zinc chloride is

adsorbed on the surface of or in porous portion of the solid montmorillonite K-10. Excess water was evaporated by heating, to load zinc chloride on montmorillonite K- 10. Since zinc chloride has a high deliquescence, it deteriorates during storage before or after the preparation of catalyst. Therefore the prepared catalyst should be stored in sealed bottle or in dry room.

**2) Synthesis of 2,4-diphenyl-4,6,7,8-tetrahydro chromen-5-one:** A mixture of chalcones (10 mmol), dimethylcyclohexane-1,3-dione (10 mmol) and ZnCl<sub>2</sub>/montmorillonite K-10 catalyst (10 mmol%) in a 100 ml beaker was irradiated in a domestic microwave oven for a specified time period. The progress of reaction is monitored on TLC. After completion of reaction, the reaction mixture was cooled and diluted with ethyl acetate (5 ml). The catalyst was filtered and washed with ethyl acetate (2×5 ml). The catalyst activated at 120 oC for one hour and reused for other reactions with slight decrease in its efficiency. Combined filtrates were concentrated under reduced pressure to afford the crude 4-diphenyl-4,6,7,8-tetrahydrochromen-5-one. The obtained crude product was further purified by column chromatography using chloroform: ethyl acetate (3:1) as an eluent. Similarly the other 4-diphenyl-4,6,7,8-tetrahydro chromen-5-one synthesized using same method. The obtained products were identified by comparison with IR, <sup>1</sup>HNMR and melting points of authentic samples (**Table-3**).



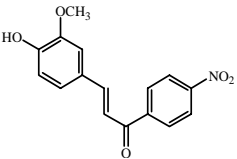
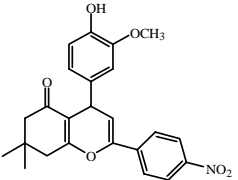
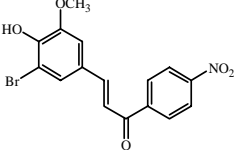
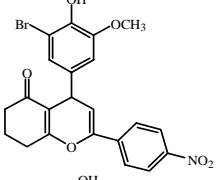
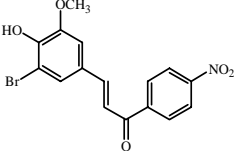
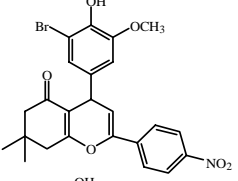
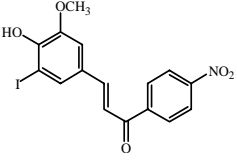
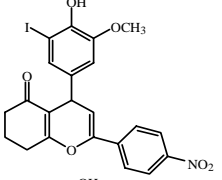
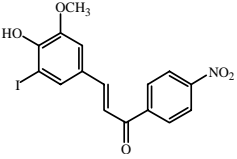
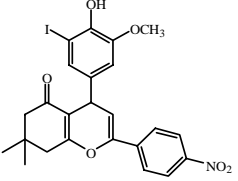
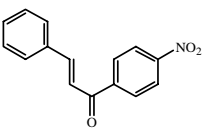
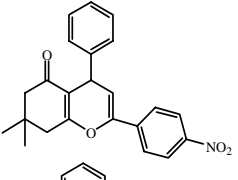
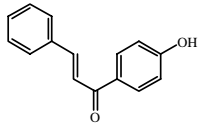
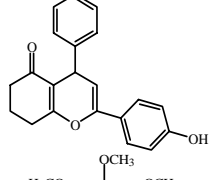
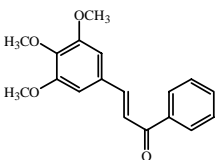
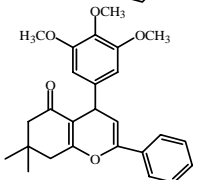
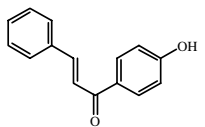
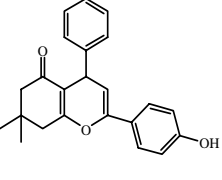
Scheme-2

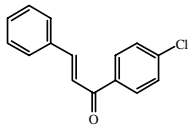
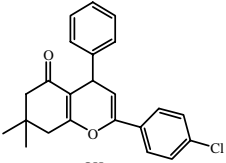
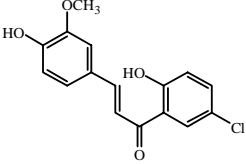
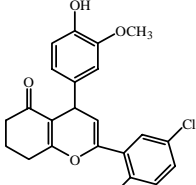
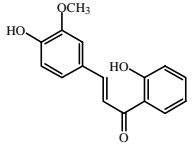
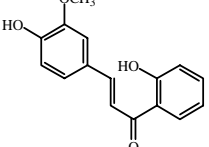
[*E-Journal of Chemistry, 2009, 6(1), 151-155*]

**Table-3:** Synthesis of 2,4-Diphenyl-4,6,7,8-tetrahydro chromen-5-one catalyzed by ZnCl<sub>2</sub>/montmorillonite K-10.

Entry	Chalcone (1)	Products (3)	Time (min)	M.P. ( <sup>o</sup> C) (Reported)	Yield (%) <sup>b</sup>
B <sub>1</sub>			7.0	200-201	82



<b>B<sub>2</sub></b>			7.5	182-183	80
<b>B<sub>3</sub></b>			7.0	129-130	78
<b>B<sub>4</sub></b>			7.5	147-149	84
<b>B<sub>5</sub></b>			8.0	108-109	80
<b>B<sub>6</sub></b>			8.0	160-162	82
<b>B<sub>7</sub></b>			9	184	88
<b>B<sub>8</sub></b>			8.5	195	80
<b>B<sub>9</sub></b>			7.5	72-74	85
<b>B<sub>10</sub></b>			8	209	84

<b>B<sub>11</sub></b>			8.5	178	88
<b>B<sub>12</sub></b>			8.0	142-143	78
<b>B<sub>13</sub></b>			7.5	156-158	75

<sup>b</sup>Isolated and unoptimized yield.

**Table-4:** Solvent and catalyst effect on reaction process <sup>a</sup>.

Entry	Catalyst	Solvent	Reaction condition	Time	Yield(%) <sup>b</sup>
1	ZnCl <sub>2</sub>	Toluene/n-heptane	Reflux	28 hr	70
2	ZnCl <sub>2</sub>	Benzene/n-heptane	Reflux	28-30 hr	75
4	Et <sub>3</sub> N	methanol	Reflux	14-15 hr	72
5	ZnCl <sub>2</sub>	Solvent free	MW	14 min.	80
6	ZnCl <sub>2</sub> /K-10	Solvent free	MW	8 min	85

<sup>a</sup>Reaction conditions:- 5,5-dimethyl-cyclohexane-1,3,dione (10 mmol), 1-Phenyl-3-(3,4,5- trimethoxy- phenyl)-propenone (10 mmol)[B<sub>9</sub>].

<sup>b</sup>Isolated and unoptimized yield.

**Table-5:** Recovery of catalyst.

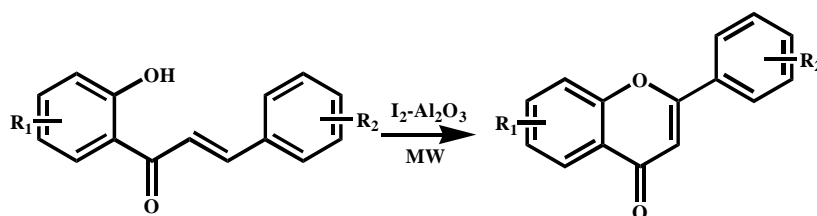
Entry	Products	Yield (%)		
		Recycle-1	Recycle-2	Recycle-3
1	B <sub>9</sub>	88	82	75
2	B <sub>10</sub>	85	80	76

### [C] Synthesis of flavones using I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> under microwave irradiation:

A simple and solvent free method for the synthesis flavones using I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> catalyst under microwave irradiation with excellent yields has been described.

**1) Synthesis of heterogeneous catalyst I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>:** Iodine (2.538 g, 10 mmol) was dissolve in minimum quantity of solvent dichloro methane. This iodine solution was adsorbed on 25 g neutral alumina and stirred. The mixture was air dried and stored in glass bottle until use.

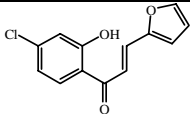
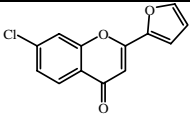
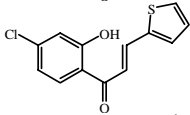
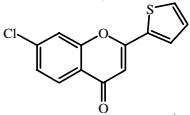
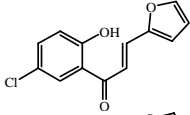
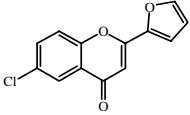
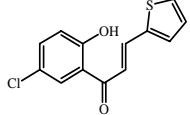
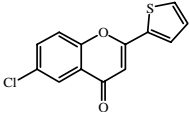
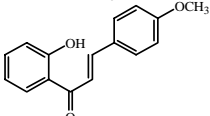
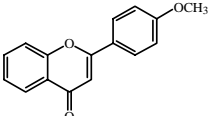
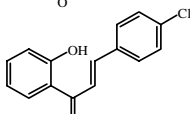
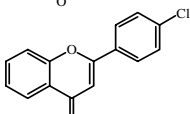
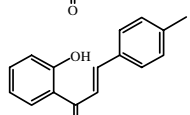
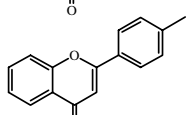
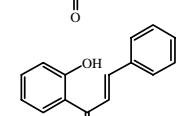
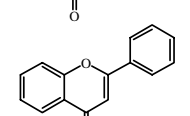
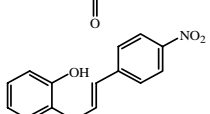
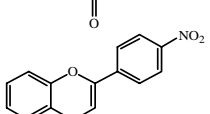
**2) Synthesis of 2-phenyl-4-H-chromen-4-one using I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>:** A mixture of chalcone (1mmol) and of I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> (0.25 g) catalyst was irradiated in a microwave oven (400W) for appropriate time (3 to 5 min). After completion of reaction as monitored by TLC, the mixture was cooled, diluted with ethyl acetate and filtered to separate insoluble Al<sub>2</sub>O<sub>3</sub>. The filtrate was washed with a dilute solution of sodium thiosulfate to remove iodine and subsequently with water. After evaporation of ethyl acetate, the crude was purified by column chromatography using hexane: ethyl acetate (9:1) eluent to afford pure 2-phenyl-4-H-chromen-4-one (flavones). The products obtained were characterized by comparison of IR, <sup>1</sup>H NMR and melting point with literature values (**Table-6**).



Scheme 3

[*International J. Chem. Tech. Res.* 2009, 1(3), 539-543]**Table-6:** I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> catalyzed synthesis of flavones under microwave irradiation

Entry	Chalcone	Product	Time (min)	Yield(%) <sup>a</sup>	M. P. (°C)
C <sub>1</sub>			4	80	136-138
C <sub>2</sub>			3.5	90	155-156
C <sub>3</sub>			4.5	85	140-142
C <sub>4</sub>			3.5	82	119-120
C <sub>5</sub>			4	85	126-128
C <sub>6</sub>			4.5	78	146-148

C <sub>7</sub>			3.5	90	130-132
C <sub>8</sub>			3.5	85	149
C <sub>9</sub>			4	85	148-149
C <sub>10</sub>			4	90	152-154
C <sub>11</sub>			4.5	85	155-156
C <sub>12</sub>			4	90	187-188
C <sub>13</sub>			4	88	78-80
C <sub>14</sub>			3.5	92	100
C <sub>15</sub>			5	85	276-278

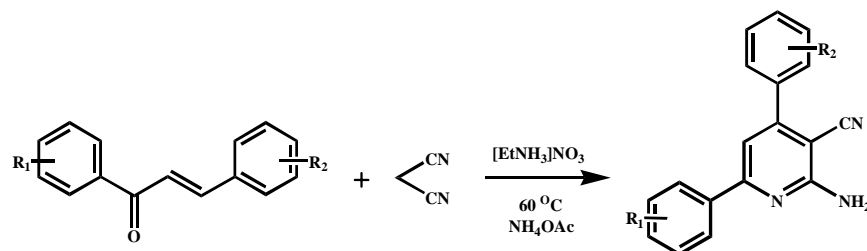
<sup>a</sup> Isolated and unoptimized yield

#### [D] Synthesis of 2-amino-3-cyanopyridine:

**1) Preparation of ethyl ammonium nitrate:** In a cooled aqueous solution of ethylamine (70%, 100 ml), nitric acid (30%, 330 ml) was added drop-wise with vigorous stirring, maintaining the temperature below 10 °C. As soon as the pH of the mixture attained the value of 7.3, the addition was stopped and the mixture stirred further for 0.5 hr. Water was removed first with a rotary evaporator, the traces of water were removed at 100 °C, affording the colorless or faint yellow IL ethyl ammonium nitrate.

**2) Synthesis of 2-amino-3-cyanopyridine:** Ionic liquid EAN (2 ml) was added to a mixture of 1,3-diaryl-2-propene-1-ones (1 mmol), malononitrile (1 mmol), ammonium acetate (8 mmol) and stirred at 60 °C for the appropriate time. After reaction completion as monitored by TLC, the reaction mixture was poured on 50 ml ice-cold water. The separated solid was filtered, washed

with cold water and recrystallized in ethyl alcohol. The aqueous layer was distilled at 80 °C under vacuum to remove water, leaving behind the ionic liquid (about 90%), which was recycled for several times. The crude was purified by column chromatography using hexane-ethyl acetate (9:1) as eluent and characterized by comparison of IR, <sup>1</sup>H NMR and melting point with literature values (**Table-7**).

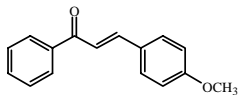
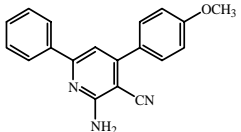
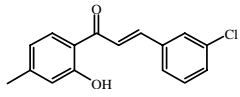
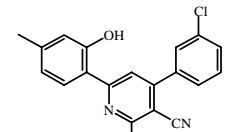
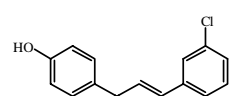
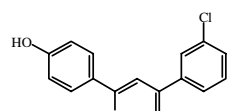
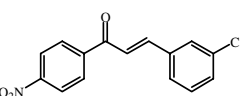
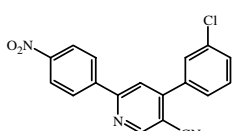


Scheme-4

[*Molecular Diversity*, 2009, 13, 545-549]**Table-7:** Synthesis of 2-amino-3-cyanopyridine:

Entry	Chalcone (1)	Product (4)	Time (hr)	M. P. (°C)	Yield (%) <sup>b</sup>
D <sub>1</sub>			3	88-90	80
D <sub>2</sub>			3.15	150-151	85
D <sub>3</sub>			3	164-165	82
D <sub>4</sub>			3	135-136	80
D <sub>5</sub>			2.75	125-127	78
D <sub>6</sub>			3.5	130-131	85

<b>D7</b>			<b>3</b>	191-192	88
<b>D8</b>			<b>2.75</b>	25-27	82
<b>D9</b>			<b>2.5</b>	82-84	80
<b>D10</b>			<b>2.5</b>	95-96	90
<b>D11</b>			<b>3</b>	154-155	84
<b>D12</b>			<b>3.5</b>	165-166	82
<b>D13</b>			<b>3</b>	208	82
<b>D14</b>			<b>3</b>	215	80
<b>D15</b>			<b>2.75</b>	122-125	88
<b>D16</b>			<b>2.5</b>	98-100	85
<b>D17</b>			<b>2.5</b>	153-154	80

<b>D<sub>18</sub></b>			<b>2</b>	183-184	88
<b>D<sub>19</sub></b>			<b>2.5</b>	217-219	90
<b>D<sub>20</sub></b>			<b>2</b>	200-201	82
<b>D<sub>21</sub></b>			<b>3</b>	273-280	85

<sup>b</sup> Isolated and unoptimized yield.

**Table-8:** Recovery of ethyl ammonium nitrate (EAN)

Entry	Products	Yield (%)		
		<i>Recycle-1</i>	<i>Recycle-2</i>	<i>Recycle-3</i>
1	<b>D<sub>15</sub></b>	88	85	80
2	<b>D<sub>16</sub></b>	85	80	77

#### 4. RESULT AND DISCUSSION

A synthesis of benzodiazepines using sulfamic acid catalyst was completed in 2 to 3 h giving 90 to 95% of the desired product (Table-1). The results showed the efficiency and yield of the reaction was high as compared with other conventional methods. Recovery of catalyst was very easy so that the sulfamic acid was recovered and reused for consecutive reactions without any significant loss of catalyst efficiency (Table-2). The use of 10-mol% of the catalyst was quite sufficient to promote the reaction; higher amount of the catalyst did not improve the yield. The reaction proceeded cleanly at 80 °C without any undesirable side-product formation. The yield of isolated products after purification was found to be excellent. However, in the absence of sulfamic acid, the reaction did not proceed following long reaction times (15-20 hr.). The reaction did not proceed with aliphatic diamines, even after heating at higher temperatures for a long time as compared with the reported methods (Table-2). This method offers several advantages in terms of simple procedure and workup, cheap and reusable catalyst, short reaction time, mild reaction conditions, excellent yield and solvent free condition. One more advantage of this process is the possibility of formation of hetero disubstituted benzodiazepines ring.

Synthesis of 2,4-diphenyl-4,6,7,8-tetrahydro chromen-5-one derivatives using  $ZnCl_2$ /montmorillonite-K-10 catalysts under microwave irradiations is rapid and ecofriendly process. Chalcones and 1, 3-cyclohexanedione (1:1) with  $ZnCl_2$ / montmorillonite K-10 catalysts was irradiated in microwave oven for a specific time offered corresponding 2,4-diphenyl-4,6,7,8-tetrahydro chromen-5-one. The reaction takes place in two steps, in first step Michael addition of cyclic 1,3-diketone on chalcone followed by cyclization of resultant diketo intermediate. Most of the reaction was completed within 8-9 minutes in microwave irradiation giving 90-95% yield of products (Table-3). However, the reported method required strong acidic conditions and longer reaction time.

Synthesis of flavones using the heterogeneous catalyst  $I_2-Al_2O_3$  under microwave irradiation offered excellent yield of products in shorter reaction time (**Scheme-3**). As these reactions were carried out under microwave irradiation, it reduces the cost and time period of reaction.

Ionic liquid ethyl ammonium nitrate was prepared as per literature method. The ethyl ammonium nitrate was found to be a more suitable solvent and catalyst for these reactions. In presence of EAN the reactions proceed in a shorter time, under milder condition and with



excellent yield of products. Ethyl ammonium nitrate is liquid at room temperature and is miscible with water, thus the separation and isolation of the product becomes easier. In a typical reaction, a mixture of 1,3-diaryl-2-propene-1-ones, malononitrile, and ammonium acetate in EAN was refluxed at 60 °C temperatures for the appropriate time. After reaction completion as monitored by TLC, the usual work-up affords pure 2-amino-4,6-diphenylpyridine-3-carbonitrile in excellent yield (Table-7). The reaction proceeds cleanly at 60 °C temperatures. However, at room temperature the reaction required longer time (12-15 hr) and at higher temperature the yield of the product decreases. Ionic liquid is water-soluble, thus goes to the aqueous layer, which was distilled at 80 °C under vacuum to remove water, leaving behind the ionic liquid. The recovered EAN was recycled and reused several times to carry out the same experiment (Table-8). No undesirable byproduct formation takes place. Most of the reactions were completed within 2-3 hours affording the product in 80-90% yield. However at room temperature the reaction time increases with a decrease in the yield of the product. The reported methods required much longer reaction time and harsh reaction conditions.

## 5 PUBLICATIONS FROM THIS PROJECT:

1. Solvent-Free One Pot Synthesis of Benzo-[b]-1,4-diazepines Using Reusable Sulfamic Acid Catalyst; *J. Iran. Chem. Soc.*, 2009, 6(3), 477-482.
2. Microwave Assisted Synthesis of 2,4-Diphenyl-4Hchromen-5-one using ZnCl<sub>2</sub>/Montmorillonite K-10; *E-J. Chem.* 2009, 6(1), 151-155.
3. I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>: A suitable heterogeneous catalyst for the synthesis of flavones under microwave irradiation; *Internat. J. Chem. Tech. Res.* 2009, 1(3), 539-543.
4. An efficient protocol for the synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile using ionic liquid ethylammonium nitrate; *Mol. Diver.*, 2009, 13, 545-549.