Chapter II: Section A
Newer Convenient Synthetic Protocols for Some Diverse Heterocyclic Scaffolds

Development of new protocols for some Diverse range of substituted Pyridines

Tetrahydropyridines

Thiopyridines

Dihydropyridines

An efficient synthesis of functionalized tetrahydropyridines catalyzed by glycolic acid
2.1.1. Introduction and literature survey

The tetrahydropyridine (piperidine) ring is a constitutive structural feature of many natural products [1], preclinical and clinically trial drugs [2] and a number of bioactive molecules [3]. Some of the molecules having tetrahydropyridine (piperidine) scaffold are useful established drugs in the world market. [4] The tetrahydropyridine (piperidine) motif exhibit anti-inflammatory & anticonvulsant [5], antihypertensive [6] and antibacterial [7] properties. Moreover, a few of them found to be inhibitors for enzymes of farnesyl tranferase [8] or dihydroorate dehydrogase(DHODH)[9] and also useful in Parkinson’s disease[10]. Some of the established drugs which constituents’ piperdine frameworks are shown in Fig: 2.1.1.

![Fig: 2.1.1. Established drugs containing tetrahydropyridine motif](image)

Consequently, the design and development of numerous methods for the synthesis of highly functionalized tetrahydropyridine (piperidines) has evoked considerable interests among synthetic chemists and still deserved attention.

Rong-Gang Han and coworkers [11] have developed synthesis of tetrahydropyridines catalyzed by proline in a cascade Mannich-type intramolecular
cyclization reaction from N–PMP aldi-mines and aqueous tetrahydro-2H-pyran-2, 6-diol. 2, 3-disubstituted tetrahydropyridines were produced in diastereo- and enantioselective reaction (Scheme: 2.1.1).

Scheme: 2.1.1
Hirokazu Tsukamoto and Yoshinori Kondo [12] developed palladium catalyzed synthesis of 1, 4-disubstituted 1,2,3,6-tetrahydropyridines via allenyl and alkynyl iminium ion cyclization reaction. The mild reaction conditions, wide substrates tolerance, easy availability of the reagents and good regioselectivity make this protocol interesting in term of combinatorial synthesis (Scheme: 2.1.2).

Scheme: 2.1.2
Hyun Seung Lee and coworkers [13] developed synthesis of poly-substituted tetrahydropyridine and its derivatives by radical cyclization strategy which involve consecutive 1,5-hydrogen transfer and double bond isomerization starting from Baylis–Hillman adducts (Scheme: 2.1.3).

Scheme: 2.1.3
J. S. Yadav and coworkers [14] developed synthesis of trans-2, 4-disubstituted piperidine and its analogues by using different N-protected homoallyl amines and epoxides via aza-Prins cyclization catalyzed by BiCl₃ (Scheme: 2.1.4).
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Scheme: 2.1.4

Terry P. Lebold and coworkers [15] developed synthesis of piperidines from propargyl amines and cyclopropanes diesters catalyzed by Zn (NTf₂)₂. The corresponding piperidines were achieved in excellent yields via a tandem cyclopropane ring-opening/Conia-ene cyclization (Scheme: 2.1.5).

Scheme: 2.1.5

Santos Fustero and his team [16] developed synthesis of piperidines alkaloids and other heterocycles by carbamates having α, β-unsaturated aldehydes under organocatalytic conditions via intramolecular aza-Michael reaction.

Nowadays multicomponent reactions have gained much attention over their multistep alternatives for reasons of environmental friendliness, energy efficiency and atom economy [17]. Owing to the importance of piperidine chemistry, some multicomponent reactions are also developed.

Marcus Blumel and coworkers [18] synthesized tetrahydropyridines through one-Pot multicomponent reaction of 1,3-dicarbonyl compounds, β-nitroolefins, and aldmines via Michael/Aza-Henry/Cyclization triple domino reaction in excellent enantiomeric excesses, and up to high diastereomeric ratios (Scheme: 2.1.6).

Scheme: 2.1.6
Nikolas G and coworkers [19] developed synthesis of 3, 5-dispirosubstituted piperidines by three component, one-pot reaction of aniline, dimedone and formaldehyde. The protocol offers good to excellent yields of the corresponding piperidines in a catalyst free reaction conditions (Scheme: 2.1.7).

\[ \text{Aniline} + \text{Dimedone} + \text{Formaldehyde} \rightarrow \text{Piperidine} \]

\( R = \text{Me, OMe, OEt, Ph,OPh, Br, NH}_2 \)

Scheme: 2.1.7

Yan Li, Zhiheng Xue and coworkers [20] developed synthesis of highly functionalized piperidines from the multicomponent reaction of ammonium acetate, aromatic aldehydes, substituted \( \beta \)-nitrostyrenes and Meldrum’s acid. The reaction involves sequential Michael addition, formation of acyclic imines and intermolecular nitro-Mannich reaction (Scheme: 2.1.8).

\[ \text{Ammonium Acetate} + \text{Aromatic Aldehyde} + \text{Active Nitrostyrene} \rightarrow \text{Piperidine} \]

\( R = \text{EtOH, 45}^\circ \text{C} \)

Scheme: 2.1.8

Recently, few methods [21-26] have been reported for the multicomponent synthesis of functionalized piperidines by a five component reaction of aldehyde, ethyl acetoacetate and anilines (Scheme: 2.1.9)
2.1.2. Objectives and present work

Most of the developed routes and strategies for the synthesis of tetrahydropyridine associated with low yielding multistep reactions and advanced and expensive starting materials. Later on an efficient synthesis of tetrahydropyridine by five-component reaction of aldehyde, ethyl acetoacetate and anilines was developed (Scheme 2.1.10).

\[
\text{R}_1\text{CHO} + \text{NH}_2 + 2\text{R}_2\text{CHO} + \text{H}_2\text{C} - \text{CO} - \text{OR}^2 \xrightarrow{\text{Varied Conditions}} \text{R}_1\text{R}_2\text{NH} - \text{O} - \text{OR}^2
\]

Scheme 2.1.10

Different reagents and catalysts are used to carry out this one-pot reaction such as InCl$_3$ [21], CAN [22], L-proline/TFA [23], tetrabutylammonium tribromide (TBATB) [24], ZrOCl$_2$$\cdot$8H$_2$O [25], bromodimethyl sulfonium bromide (BDMS) [26], molecular iodine [27], picric acid [28], bismuth nitrate [29], boric acid[30], PPA–ZrP [31], B(C$_6$F$_5$)$_3$ [32] and Nano-TiCl$_4$/SiO$_2$ [33]. Due to the importance of tetrahydropyridine (piperidine) chemistry a simple, high-yielding and more eco-friendly methods is needed. The use of environmentally friendly organo-catalysts for the synthesis of pharmaceuticals and fine chemicals is becoming an area of interest among synthetic chemists.

In continuation of our ongoing attempt for the development of newer and convenient synthetic methodologies for some privileged diverse heterocyclic scaffolds, we decided to explore the efficiency of glycolic acid as a catalyst for the synthesis of highly substituted tetrahydropyridine. So herein we wish to report for the first time the multicomponent reaction for the synthesis of tetrahydropyridine (piperidines) from various aldehydes, ethyl acetoacetate and aromatic amines using glycolic acid as a safe, cheap, non-toxic organo-catalyst in quantitative yield (Scheme: 2.1.10). Glycolic acid is a well-known skin care agents used in pharmaceuticals [34]. It has received considerable attention as a tanning and dyeing agent in textile industries and also in plastics and adhesives. There is no any report on the use of glycolic acid as a catalyst in any organic transformation; it’s a novel organo-catalyst.
2.1.3. Results and discussion

Initially in search of the best catalytic system for the multicomponent synthesis of 1,4 tetrahydro pyridine in a more efficient way, optimization of various reaction parameters like different acid catalysts, solvents and temperature was carried out with the model reaction of 4-chloro benzaldehyde (2mmol), 4-chloro aniline (2mmol) and ethyl acetoacetate (1mmol) as representative reactants (Table 1). It was found that no 1, 4 tetrahydropyridine was obtained even after 20 hr when the reaction performed under catalyst free conditions in ethanol solvent (Table 1, entry 1). In search of convenient and efficient catalytic system for this reaction, same model reaction was performed with different acid catalysts such as FeCl$_3$, NiCl$_2$, Amberlite-IR120, PMA-SiO$_2$, Zn (L-proline) and glycolic acid in ethanol at reflux temperature (Table 1, entry 2-6). Among all screened catalysts glycolic acid in ethanol gave the best result in view of reaction time and yield (Table 1, entry 6).

**Table 1:** Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (20 mol%)</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>EtOH</td>
<td>reflux</td>
<td>20</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_3$</td>
<td>EtOH</td>
<td>reflux</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>NiCl$_2$</td>
<td>EtOH</td>
<td>reflux</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Amberlite-IR120</td>
<td>EtOH</td>
<td>reflux</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>PMA-SiO$_2$</td>
<td>EtOH</td>
<td>reflux</td>
<td>16</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>Glycolic acid</td>
<td>EtOH</td>
<td>reflux</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>Glycolic acid</td>
<td>Acetonitrile</td>
<td>reflux</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>Glycolic acid</td>
<td>water</td>
<td>reflux</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>Glycolic acid</td>
<td>DCM</td>
<td>reflux</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>Glycolic acid</td>
<td>MeOH</td>
<td>reflux</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>Glycolic acid</td>
<td>MeOH</td>
<td>R.T</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>12</td>
<td>Glycolic acid (10 mol %)</td>
<td>MeOH</td>
<td>reflux</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>Glycolic acid (25 mol %)</td>
<td>MeOH</td>
<td>reflux</td>
<td>4</td>
<td>90</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields.

The selection of a proper reaction medium is of crucial importance for successful organic synthesis. To establish the ideal solvent for the transformation, we
investigated this model reaction by replacing ethanol with different solvents with different polarity such as methanol, acetonitrile, water and dichloromethane (Table 1, entry 6-10). The desired product 4b was achieved in all the tested solvents, but methanol gave the best isolated yield (90 %) (Table 1, entry 10). To investigate the optimum quantity of catalyst, the model reaction was carried out using 10 %, 20 mol % and 25 mol % of glycolic acid in methanol at reflux temperature. It was found that 20 mol % of catalyst gave maximum yield in minimum time (Table 1, entry 10). Increment in amount of catalyst loading to 25 mol % neither increases the product yield nor shortens the conversion time (Table 1, entry 13).

**Table 2: Synthesis of Functionalized Tetrahydropyridines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>P</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M. p (°C)</th>
<th>Observed</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>4a</td>
<td>4.5</td>
<td>86</td>
<td>172-174</td>
<td>174-175[22]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>4-Cl</td>
<td>4b</td>
<td>4</td>
<td>90</td>
<td>210-212</td>
<td>214-215[33]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>4c</td>
<td>4</td>
<td>90</td>
<td>230-232</td>
<td>227-230[26]</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4d</td>
<td>4.5</td>
<td>91</td>
<td>173-175</td>
<td>170-172[33]</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4e</td>
<td>3.5</td>
<td>88</td>
<td>170-172</td>
<td>172-174[29]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4f</td>
<td>4</td>
<td>88</td>
<td>194-196</td>
<td>196-198[29]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>4-Cl</td>
<td>4g</td>
<td>4</td>
<td>86</td>
<td>202-204</td>
<td>200-202[23]</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4-Cl</td>
<td>4h</td>
<td>3.5</td>
<td>80</td>
<td>178-180</td>
<td>180-181[29]</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields.

Once the reaction conditions were optimized, the efficiency of the procedure was tested using a variety of aldehydes and anilines containing electron withdrawing and releasing groups in the aromatic ring. In all cases, the reactions were completed at specified time and afforded the corresponding products in excellent yields (Table 2, entries 1-8). When α-naphthyl amine was used, the reaction even after stirring for several hours did not give the corresponding tetrahydropyridine product; the reason may be the steric factor.
To rationalize the synthesis of tetrahydropyridine a plausible mechanism of glycolic acid catalyzed process (Scheme: 2.1.11) was suggested in which glycolic acid can serve as a Bronsted acidic catalyst for the one-pot multicomponent reaction of aldehyde and amine with ethylacetoacetate to give the imine A and β-enaminone B respectively. The β-enaminone B reacts with imine A through intermolecular Mannich reaction affords butanoate intermediate C. Subsequently, the reaction of aldehyde with the butanoate intermediate C takes place to afford the intermediate D. Next, tautomerization of D intermediate generates intermediate E, which after intramolecular Mannich-type reaction affords intermediate F. Intermediate F after tautomerization generates the desired tetrahydropyridine structure due to conjugation with the ester group.

Scheme: 2.1.11. Plausible mechanism for the synthesis of tetrahydropyridine catalyzed by glycolic acid.
2.1.4. Conclusion

In conclusion, we have developed a simple, convenient, highly efficient one-pot five-component method for the synthesis of various tetrahydropyridine derivatives by reaction of aldehydes, aromatic amines and ethyl acetoacetate catalyzed by glycolic acid. This protocol has many attractive features, such as high product yield, operational simplicity, easy work-up and purification. Furthermore glycolic acid is inexpensive, safe and non-toxic making the protocol eco-friendly and economically acceptable.

2.1.5. Experimental Section

*General procedures for the synthesis of tetrahydropyridine (4a-4h)*

To a 20mL flask sequentially added ethyl acetoacetate (0.5mmol) and amine (1mmol), glycolic acid (20mol%) in 4mL of methanol and the reaction was stirred for 15min at room temperature, followed by addition of aldehyde (1 mmol). The reaction mixture was stirred at reflux temperature for an appropriate time (Table 2, entries 1-8), upon completion of the reaction as indicated by TLC (ethyl acetate-hexane, 2: 8), a thick precipitate was obtained which was filtered off and washed with cold ethanol to afford the desired pure product.

**Spectral Data**

Ethyl 4-(4-chlorophenylamino)-1,2,6-tris(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4b): M. p. 210-212 °C; $^1$HNMR: (CDCl$_3$, 400MHz) /δ (ppm): 10.24 (s,1H), 7.26-7.00 (m, 12H), 6.28-6.20 (m, 5H), 5.05 (s, 1H), 4.45 (brs, 1H), 4.22(brs, 1H), 2.79(brS, 1H), 2.69 (brS, 1H), 1.45 (brcs, 3H); $^{13}$C NMR (CDCl$_3$, 400MHz) /δ (ppm): 168.18, 156.44, 145.53, 143.29, 142.27, 136.44, 131.36, 129.02, 128.83, 128.74, 126.57, 121.26, 114.06, 98.75, 77.06, 59.94, 58.33, 34.50, 14.78.; Mass (m/z) =611.2 [M-1].
$^1$HNMR of compound 4b
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$^{13}$CNMR of compound 4b
Mass spectrum of compound 4b
2.1.6. References


Chapter II: Section B

Newer Convenient Synthetic Protocols for Some Diverse Heterocyclic Scaffolds

Pot, atom and step economic (PASE) synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines in aqueous PEG-400 promoted by sodium benzoate

![Reaction Diagram]

R+ \text{CN} + \text{SH} \xrightarrow{\text{PEG-400: H}_2\text{O}} \text{Sodium Benzoate} \xrightarrow{70^\circ \text{C}} \text{R} \text{NC} \text{CN} \text{H}_2\text{N} \text{S-aryl}
2.2.1. Introduction and literature survey

The pyridine-3, 5-dicarbonitrile is a “privileged medicinal scaffolds” has established a varied range of biological activities. The molecule A-C having the pyridine framework exhibits several significant medicinal utilities. One of them is antiprion agent A [1], molecule B is recognized as a effective inhibitor of HIV-1 integrase [2], type C molecule acts as antitumor agent against numerous human cancer cells [3] (Fig: 2.2.1).

![Molecular structures]

Furthermore, some of the molecular structures having pyridine-3, 5-dicarbonitrile motif were found to be capable of providing selective ligands for adenosine receptors, kidney disease, Parkinson’s disease, epilepsy, hypoxia and asthma [4]. The huge applications in medicinal field attracted medicinal chemists to design and develop new synthetic strategies for pyridine scaffolds.

E. R. Anabha and coworkers [5] developed cyclization of 2-aroyl-3, 3 bis (alkylsulfanyl) acrylaldehydes and malononitrile in the presence of diisopropylamine to gave 5-aroyl-2,6-bis (methylsulfanyl) nicotinonitriles (Scheme:2.2.1).

![Scheme: 2.2.1]

Adam R. Renslo and Rick L. Danheiser [6] developed synthesis of substituted tetrahydropyridines via Diels−Alder cycloadditions of oximinosulfonate with a different 1, 3-dienes. The oximinosulfonate is synthesized from Meldrum's acid and
reacts with conjugated dienes in the presence of dimethyl aluminum chloride to afford [4+2] cycloadducts i.e substituted pyridines in good to excellent yield (Scheme: 2.2.2).

Ajith Dain Thomas and C. V. Asokan [7] developed a facile synthesis of substituted pyridines from hydroxy ketene dithioacetals by Vilsmeier- Haack reaction. The reaction starts with dehydration to give sulphur substituted 1, 3-butadienes, catalyzed by acid followed by iminoalkylations. The iminium salts formed in the presence of ammonium acetate transformed in to 2-methylsulfanyl substituted 4-aryl pyridines (Scheme: 2.2.3).

Matthew D. Fletcher and coworkers [8] developed synthesis of highly-functionalized pyridines by the reaction between 1-aza-3-siloxy-1, 3-butadienes and electron deficient acetylenes proceed through hetero-Diels–Alder reaction. The reaction prompted by the use of microwave, which reduced the reaction time and improved products yields from poor to moderate (Scheme: 2.2.4).

Mohammad Movassaghi and Matthew D. Hill [9] designed synthesis of substituted pyridine derivatives by cycloisomerization of 3-Azadienynes from a two-step conversion of various N-vinyl and N-aryl amides (Scheme: 2.2.5).
Katsunori Tanaka [11] developed a new method for the synthesis of substituted pyridines by utilizing 6π-Azaelectrocyclization reaction [10]. Tilman Lechel and coworkers synthesized perfluoroalkyl or perfluoroaryl-substituted 4-hydroxypyridine derivatives by the multicomponent reaction of nitriles, lithiated alkoxyallenes and perfluorinated carboxylic acids. These pyridines compounds were transformed into 4-pyridyl nonaflates via palladium-catalyzed couplings (Scheme: 2.2.6).

Mohammad Ali Ghasemzadeh and coworkers [13] developed chromeno [2, 3-b] pyridine derivatives through multicomponent reactions of salicylaldehydes, malononitrile and thiol catalyzed by Fe₃O₄@SiO₂–NH₂ nanocatalyst. The protocol offers several merits such as green approach, maximum yields, short reaction times and recyclability of the catalyst (Scheme: 2.2.8).
Mehdi Daryabari and coworkers [14] synthesized highly substituted \(5H\)-indeno [1, 2-\(b\)] pyridin-5-one derivatives by a four component one-pot reaction in trifluoroethanol medium. Simple operation, maximum yields, easy workup and reusability of the solvent are the merits of the method (Scheme: 2.2.9).

Jianjun Li and coworkers [15] developed regioselective synthesis of polysubstituted pyridines catalyzed by diphenylammonium triflate (DPAT) from a multicomponent reaction of aldehydes, ketones and amines under solvent-free conditions. For the formation of pyridine nucleus different source of nitrogen like ammonium acetate, urea, thiourea and organic amines were used (Scheme: 2.2.10).

Wang, H.-Y and coworkers [16] reported synthesis of tricyclic pyridines in excellent yields from a multicomponent reaction of 5-aminopyrazole, dimesone, aromatic aldehydes catalyzed by sodium dodecyl sulfate (SDS) in water (Scheme: 2.2.11).
2.2.2. Objectives and present work

The above mentioned synthetic routes, most of them involve multistep synthesis, use of expensive and toxic catalysts, low yields and tedious procedures. Recently synthesis of pyridine-3, 5-dicarbonitrile through multicomponent reaction (MCR) of thiols, malonitrile and various aldehydes due to its efficiency and step economy have gain much more attention (Scheme: 2.2.12).

This multicomponent reaction has been carried out by using different reagents and catalyst such as Et₃N [17], DBU [18], KF/Alumina [19], ZnCl₂ [20], TBAH and [bmim]OH [21], boric acid [22], microporous molecular sieves [23], silica nanoparticles [24]. CaO nanoparticles [25] and sodium chloride [26] and diethyl amine[27]. In spite of potential efficacy of these protocols, some of them bear limitations such as long reaction times, forcing conditions, low yields and long reaction times. Some of these protocols involve use of corrosive solvents and corrosive strong acids or bases. Some of the nano-particles catalyzed protocol provides better yields but their preparations require some difficult and tedious procedure. Thus the development and design of a newer readily available method that avoids many of these demerits is highly desirable therefore to overcome these demerits, we report a new procedure for more efficient and cleaner synthesis of pyridine-3, 5-dicarbonitrile derivatives. Recently, the use of PEG in organic transformations has drawn great attention as it is being used in food and cosmetic products, easy to handle, inexpensive, thermally stable, recyclable, non-toxic and non volatile reaction media [28-31]. Thus, great attention has been focused on its application in organic reactions [32-36]. PEG and its aqueous solutions represent interesting solvent system for solvent substitution.

Organo-catalysts have attracted scientific community due to their immense importance as they are non-toxic, less expensive, and insensitive to moisture and air
and provide a large chiral pool. Sodium benzoate is a common, low cost, commercially available safe food preservative and antimicrobial agent [37-39]. Not much work has been reported, which explored the activity of sodium benzoate as an organo-catalyst. We report here for the first time an efficient multicomponent synthesis of 2-amino pyridine-3, 5-dicarbonitriles catalyzed by sodium benzoate in PEG-400 in water as a green solvent system.

### 2.2.3. Results and discussion

In order to determine the real efficiency of sodium benzoate for the synthesis of pyridine-3, 5-dicarbonitrile, a test reaction was carried out without catalyst using malonitrile, 4-methoxybenzaldehyde and thiophenol in ethanol (4b). It was observed that no product was obtained in the absence of catalyst after several hours at room temperature or at reflux conditions (Table 1, entry 1). 10 mole % of sodium benzoate gave 60% of yield in ethanol at reflux conditions (Table 1, entry 3), whereas at room temperature low yield was obtained (Table, entry 2). Once we found sodium benzoate as a good catalyst for the reaction, we focused on the solvent and temperature screening in order to increase the yields. We optimized different solvents such as ethanol, acetonitrile, water, THF, toluene and PEG-400 at room temperature to 100 °C (Table 1, entry 3-8). Among tested various solvents, EtOH, water, toluene and PEG-400 found to give better yields (Table 1, entries 3, 4, 6, and 8). To our surprise, when mixture of PEG-400/Water (1:1) was used at 70 °C, the reaction gave maximum yield (Table 1, entry 9). Here also, the reaction is highly effected by the temperature as the yield was only 30% after stirring at room temperature for several hours in PEG-400/Water(1:1) medium (Table 1, entry 11), whereas when the temperature was increased to 90 °C , no improvement in the yield was observed (Table 1, entry 10).

Once found best solvent and temperature condition, we examined the influence of varying amounts of sodium benzoate for this multicomponent reaction. In order to estimate the appropriate catalyst concentration, reactions were carried out using 5 to 20 mol% of the sodium benzoate. It was observed that 10 mol % of the catalyst gave maximum yield in minimum duration (Table 1, entry 9). 20 mol% of catalyst loading neither shortens the conversion duration nor increases the yield (Table 1, entry 12). However, a lower amount of the catalyst (5mol %) resulted in lower yields (Table 1, entry 13). So, optimal quantity of 10 mol % of the catalyst was sufficient to promote the reaction (Table 1, entry 9).
Table 1: Optimization of reaction conditions (4b)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst (mol %)</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)^a</th>
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<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>---</td>
<td>R.T/70</td>
<td>120</td>
<td>No product</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>10</td>
<td>R.T</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>10</td>
<td>70</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Water</td>
<td>10</td>
<td>100</td>
<td>130</td>
<td>40</td>
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<tr>
<td>5</td>
<td>Acetonitrile</td>
<td>10</td>
<td>80</td>
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<td>Toulene</td>
<td>10</td>
<td>100</td>
<td>120</td>
<td>50</td>
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<td>7</td>
<td>THF</td>
<td>10</td>
<td>70</td>
<td>160</td>
<td>20</td>
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<td>PEG-400</td>
<td>10</td>
<td>70</td>
<td>120</td>
<td>60</td>
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<tr>
<td>9</td>
<td>PEG:Water (1:1)</td>
<td>10</td>
<td>70</td>
<td>90</td>
<td>88</td>
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<tr>
<td>10</td>
<td>PEG:Water (1:1)</td>
<td>10</td>
<td>90</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>11</td>
<td>PEG:Water (1:1)</td>
<td>10</td>
<td>R.T</td>
<td>120</td>
<td>30</td>
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<tr>
<td>12</td>
<td>PEG:Water (1:1)</td>
<td>20</td>
<td>70</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>13</td>
<td>PEG:Water (1:1)</td>
<td>5</td>
<td>70</td>
<td>120</td>
<td>70</td>
</tr>
</tbody>
</table>

^a Isolated yields.

To explore the extent and general applicability of this protocol, different substituted aldehydes were then tested and the results are mentioned in Table 2. All the reactions regardless the positions of substituent’s and their electronic nature or steric hindrance, afforded the corresponding products in excellent yields (Table 2, entries 1-8).
**Scheme: 2.2.12** Multicomponent synthesis of thio-pyridine derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>M. p (°C)</th>
<th>Observed</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4a</td>
<td>100</td>
<td>85</td>
<td>215-217</td>
<td>216-218[20]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-MeO</td>
<td>4b</td>
<td>90</td>
<td>88</td>
<td>240-242</td>
<td>242-244[27]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-Cl</td>
<td>4c</td>
<td>90</td>
<td>87</td>
<td>220-222</td>
<td>223-224[26]</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3-NO₂</td>
<td>4d</td>
<td>110</td>
<td>82</td>
<td>214-216</td>
<td>216-218[27]</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3-OH</td>
<td>4e</td>
<td>90</td>
<td>86</td>
<td>262-264</td>
<td>265-267[25]</td>
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</tr>
<tr>
<td>6</td>
<td>4-Me</td>
<td>4f</td>
<td>90</td>
<td>88</td>
<td>207-209</td>
<td>208-211[20]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-OH</td>
<td>4g</td>
<td>100</td>
<td>85</td>
<td>322-324</td>
<td>318-320[27]</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-Br</td>
<td>4h</td>
<td>90</td>
<td>86</td>
<td>257-259</td>
<td>256-258[27]</td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yields.*

A recyclability study was performed for scale up batch of 5mmol of model reaction (4b) in 20 mL of PEG-400: Water (1:1). The aqueous filtrate/layer containing PEG-400 was washed with Et₂O to remove any organic impurity dissolved in the aqueous phase. The aqueous phase after separation of water by vacuum evaporation at 80 °C gives pure PEG-400 which was reused for the next similar reaction. It was found that it can be reused for at least four additional times with no significant loss of activity (88-80% of 4b).

Mechanistically, sodium benzoate acting as a base, thereby promoting the reaction through in situ-generated benzylidenemalononitrile intermediate via Knoevenagel condensation between aldehyde and malonitrile followed by Michael addition of second molecule of malonitrile to benzylidenemalononitrile adduct. This then reacts with thiophenol produces dihydropyridine which undergoes air oxidation to afford the final product (Scheme: 2.2.13). The catalytic activity of sodium benzoate has been increased in aqueous polyethylene glycol medium at 70 °C.
as compared to other conditions (Table 1, entries 1-14) and accelerates the synthesis of 2-amino pyridine-3,5-dicarbonitriles more effectively.

Scheme: 2.2.13 Proposed mechanism for the sodium benzoate catalyzed synthesis of thio-pyridine derivatives

2.2.4. Conclusion

We have described an efficient one-pot reaction of aldehyde, malonitrile and thiophenol for the synthesis of 2-amino pyridine-3, 5-dicarbonitriles catalyzed by sodium benzoate as a cheap, non-toxic and readily available organocatalyst. PEG-400: water also offers a convenient, inexpensive, non-toxic and very efficient reaction medium. Moreover, this method offers several other merits such as environmental friendliness, convenient procedure higher yields and shorter reaction time.
2.2.5. Experimental

*General Procedure for the synthesis of 2-amino pyridine-3, 5 dicarbonitriles (4a-4h)*

To a solution of a selected aldehyde (1mmol) and malononitrile (2 mmol) in 4 mL of PEG-400: Water (1:1), was added sodium benzoate (0.1 mmol). The resulting mixture was heated to 40-50 °C for 15 min then thiophenol (1mmol) was added. The reaction mixture was heated at 70 °C for an appropriate time (Table 2, entries 1-8) as monitored by TLC. In workup procedure, for some products, the reaction mixture was cooled to room temperature and poured in to ice cold water. The obtained solid product was filtered and washed with cyclohexane: CHCl₃ (7:3) and dried to afford the pure product. To some products after completion, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous and organic layers were then separated and the aqueous layer was extracted by ethyl acetate twice. The combined ethyl acetate extracts were dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford the crude compound which after washing with cyclohexane: CHCl₃ (7:3) gave pure product.

*Spectral data*

2-Amino-4-(4-methoxyphenyl)-6-(phenylsulfanyl)-3, 5-pyridinedicarbonitrile (4b): M.p. 240-242°C; ¹HNMR (DMSO, 500MHz)/δ (ppm): 7.57-7.60 (m, 4H), 7.50 (brs, 2H), 7.47-7.49(m, 3H), 7.12 (d, 2H), 3.87 (s, 3H), ¹³C NMR (DMSO d6, 75MHz) δ/(ppm) 166.3, 160.8, 159.76, 157.96,153.3, 130.0, 129.3, 129.17, 127.30, 125.65, 115.31, 115.18, 113.95, 93.35, 86.82, 55.15; Mass (m/z)= 359.2 (M+1).
$^1$HNMR of compound 4b
Chapter II: Section B
Newer Convenient Synthetic Protocols for Some Diverse Heterocyclic Scaffolds

^13 CNMR of compound 4b
Mass spectrum of compound 4b
2.2.6. References


An efficient synthesis of 1, 4 dihydropyridines (polyhydroquinolines) catalyzed by SiO$_2$-I
2.3.1. Introduction and literature survey

Synthesis of 1, 4 dihydropyridines (Hydroquinolines) through the Hantzsch reaction [1] is one of the earliest and well-known multicomponent reactions (MCRs) (Scheme: 2.3.1).

Scheme: 2.3.1. Classical Hantzsch reaction

Some of the most popular pharmaceutical drugs involving 1, 4 DHPS, are prescribed calcium channel blockers, such as Nimodipine A, Nicardipine B, Nifedipine C and Felodipine D (Fig: 2.3.1). Moreover 1,4-DHPs exhibits other biological activities such as sirtuin activation and inhibition [2], radio protective activity [3], selective denosine-A3 receptor antagonism [4] and anticonvulsant activity [5] etc. Therefore 1, 4-DHPs are very significant and interesting synthetic targets.

Figure: 2.3.1. Some pharmaceutical drugs containing 1, 4 DHP scaffolds

Even though a vast number of applications are reported for the synthesis of 1, 4-DHPs by the traditional Hantzsch reaction there are some limitations are also associated with this classical reaction. The main limit for the Hantzsch reaction is that all the 1,4-DHPs synthesize by the reactions are symmetrical because two same molecules of 1,3 dicarbonyl compounds are involve in the reaction. In terms of
biological evaluation, synthesis of diverse derivatives of a known 1, 4-DHP pharmacophore is a main target for designing new bio-active compounds [6]. To synthesize diverse symmetrical 1, 4-DHPs was not the only necessity of biological receptors. Later on synthesis of structurally diverse unsymmetrical 1, 4-DHPs by the improved Hantzsch reaction were developed in search of new and improved biologically potent target molecules. Therefore, in recent years, new modified MCRs for the designing and development of novel 1, 4-DHPs have drawn significant attention.

Renaud [7] and coworkers developed two step syntheses of 1, 4-DHPs by the reaction of amines, 1, 3-dicarbonyl compounds and α, β-unsaturated aldehydes catalyzed by Lewis acids. The protocol afforded moderate to excellent yields of 1, 4-DHPs (Scheme: 2.3.2).

Later on Menendez et al [8] have designed three component one-pot synthesis of 1,4-DHPs by the reaction of primary amine, 1,3-dicarbonyl compound and α, β-unsaturated accelerated by ceric ammonium nitrate(CAN) as an efficient Lewis acid catalyst. Their method was established by employing cerium ammonium nitrate (CAN) as a Lewis acid catalyst. They have used β–keto-thioesters as the 1,3 dicarbonyl compound for the synthesis of 1,4-DHPs. Tolerance of varied substrates, maximum yields and ambient conditions are the key features of developed methodology to synthesized corresponding 1,4-DHPs involving thioester as a reactive group (Scheme: 2.3.3).

Jiang and coworkers [9] designed synthesis of 1, 4-DHPs from multicomponent reaction of 1, 3-dicarbonyl compounds, acetylenedicarboxylates and
aldehydes catalyzed by L-proline as an efficient organo-catalyst. Room temperature reaction condition, wide substrate tolerance, cheap and non-toxic organo-catalyst are the merits of the developed protocol (Scheme: 2.3.4).

Scheme: 2.3.4

J. Sun and group [10] worked on the synthesis of 1,4-DHPs by the reaction of cyclic1,3-dicarbonyl compounds, dimethyl acetylenedi-carboxylate, aromatic amines and aromatic aldehydes promoted by acetic acid (Scheme: 2.3.5).

Scheme: 2.3.5

Kumar and his team [11] designed solvent free, on grinding multicomponent synthesis of 1,4-DHPs by the four component reaction of malonitrile/ethyl cyanoacetate, diethyl acetylene-dicarboxylate, aromatic amines and aldehydes in catalyst-free protocol gave 79-98% of the corresponding products (Scheme: 2.3.6).

Scheme: 2.3.6

A. M. Zonouz and D. Moghani [12] reported that benzylidenemalononitriles on reaction with ethyl acetoacetate and ammonia acetate gives corresponding 1, 4-DHPs under solvent-free conditions (Scheme: 2.3.7).
Safari and group [13] synthesized 1, 4-DHPs by a high yielding process through a new three-component one-pot reaction of chalcones, ethyl acetoacetate and ammonia in water at reflux conditions catalyzed by cellulose sulfuric acid as biodegradable catalyst (Scheme: 2.3.8).

A. Feiz and coworkers [14] developed a four component one-pot synthesis of 1,4-DHPs by the reaction of acylc 1,3-dicarbonyl compounds, cyclic 1,3-diketone ammonium acetate and isatin. The reaction provides unsymmetrical sipro and fused cyclic 1, 4-DHPs in good to excellent yield catalyzed by pyridine in refluxing toluene (Scheme: 2.3.9).
2.3.2. Objectives and present work

This broad range of applications has elicited numerous methods for the preparation of these compounds.

\[
\begin{array}{c}
\text{R}^1 \text{H} + \text{R}^2 \text{R}^3 + \text{MeO} \text{COR}^4 + \text{NH}_4 \text{OAc} \rightarrow \text{R}^2 \text{R}^3 \text{MeO} \text{COR}^4 \text{O} \text{N} \text{Me}
\end{array}
\]

Scheme: 2.3.10

The four-component condensation of aldehydes, a diketone, a β-keto ester and ammonium acetate (Scheme: 2.3.10) is one of the simplest, most common and straightforward approaches under a variety of conditions such as traditional heating [15] use of microwave [16] of ultrasound [17] and of catalysts and reagents such as ceric ammonium nitrate [18] TMSCl [19] organocatalysts [20] sulfamic acid [21] \(\text{Al}_2(\text{SO}_4)_3\) [22] Baker’s yeast [23] ZnO-beta zeolite [24] thiourea dioxide [25] \(\text{HClO}_4–\text{SiO}_2\) [26] heteropoly acids [27] \(\text{FeF}_3\) [28] molecular iodine [29] \(\text{ZrCl}_4\) [30] PPA-SIO2 [31] nano particles [32-34] metal triflates [35-36] thiazolium ion [37] and ceric ammonium nitrate [38]. However, several of these procedures suffer from some disadvantages such as hazardous catalysts or solvents, formation of by-products, prolonged reaction times, use of expensive metal precursors and high temperature conditions and in some cases, the need to use microwave or ultrasonic irradiation.

However, some of the nano particles and heterogeneous acids catalyzed procedures provide better yields, but they are not only expensive, their preparation requires tedious procedure and results in low yields. Thus the development of a new convenient and efficient protocol that avoids many of these drawbacks is highly desirable. The present work reports the use of silica iodide (SiO2-I) as a highly efficient and inexpensive heterogeneous catalyst for the preparation of 1, 4 dihydropyridine (hydroquinolines). In comparison with mineral acids, metal trifaltes, nano particles and other heterogeneous catalysts, SiO2-I is non-corrosive, economical, provide ease of preparation and handling, cleaner reaction profile; can be separated easily with high recovery and reusability. These features lead to decreasing environment pollution and equipment cauterization, as the hallmarks of green chemistry are atom efficiency, elimination of toxic reagents, safe and cleaner aspects,
reduction in the generation of waste and re-usability of the reagents [39-43]. To our knowledge, there is only one report on the application of silica iodide (SiO$_2$-I) as a catalyst in organic transformations [44].

### 2.3.3. Results and discussion

We initiated our study with one equivalent (1mmol) of 4-chlorobenzaldehyde (1mmol), ethyl acetoacetate (1mmol), dimedone (1mmol) and ammonium acetate (1mmol) in ethanol at room temperature as a model reaction (5b). Various amounts of the catalyst (SiO$_2$-I) ranging from 0.05 g to 0.15 g were attempted and it was found that the use of 0.1g of the catalyst for a one mmol scale proved to be best to lead to the highest yield of 5b (70%) (Table 1, entry 3).

![Scheme: 2.3.11](image)

**Table 1** Optimization of the Reaction to 5b

<table>
<thead>
<tr>
<th>Entry</th>
<th>SiO$_2$-I (mmol)</th>
<th>Dimedone (mmol)</th>
<th>Compound</th>
<th>Side-product</th>
<th>Yield (%)$^a$</th>
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<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>1</td>
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<td>55</td>
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<td>2</td>
<td>0.08</td>
<td>1</td>
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<td>Yes</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>1</td>
<td>5b</td>
<td>Yes</td>
<td>70</td>
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<tr>
<td>4</td>
<td>0.15</td>
<td>1</td>
<td>5b</td>
<td>Yes</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>1.2</td>
<td>5b</td>
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<td>77</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>1.5</td>
<td>5b</td>
<td>No</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields

Although a better yield of product 5b (70 % in ethanol) was obtained, some amount of the symmetrical diethyl 4-(4-chlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-dicarboxylate (Scheme: 2.3.11) was also formed as a side-product of reaction of ethyl acetoacetate, 4-chlorobenzaldehyde and ammonium acetate (Table 1, entry 3), it was isolated by column chromatography. To minimize its generation, the concentration of dimedone was progressively increased (Table 1, entry 5-6) and it was
found that the use of a 1.5 mmol of dimedone completely minimize the formation of this by-product (Table 1, entry 6), therefore, 1.5 mmol of dimedone or 1,3-cyclohexanedione were utilized for all the reactions (5a-5q).

Once the reaction conditions were optimized, the generality and efficiency of the procedure was explore for the synthesis of a wide variety of substituted corresponding 1, 4 dihydropyridine derivatives (Table 2, entries 1-17). The reaction conditions are sufficiently mild to tolerate a variety of groups such as OCH$_3$, NO$_2$, OH, Cl, Br on the benzene ring of aldehydes (Table 2, entries 1-10 & 14-17). Moreover amino (NH$_2$) group substituted benzaldehydes were also utilized in this reaction; unfortunately, only sticky materials of dark colored were obtained and none of the desired products could be formed. The reactions of aliphatic aldehydes such as propionaldehyde and butyraldehyde proceeded more slowly and gave the corresponding quinolines in somewhat lower yields (Table 2, entries 12-13) while cinnamaldehyde reacted more rapidly and gave an excellent yield of the expected product (Table 2, entry 11). The cyclic ketone, dimedone was then replaced with 1, 3-cyclohexanedione and the reaction with different aldehydes were performed. The resulting hydroquinolines were produced in equally high yields (Table 2, entries 14-16). We then focused our attention on replacing ethyl acetoacetate by acetyl acetone in a reaction, here also the corresponding 1, 4 dihydropyridines (polyhydroquinoline) was synthesized in quantitative yields (Table 2, entry 17).

The reactions carried out under solvent-free conditions in an agate mortar at room temperature proceeded successfully in less time with increased yields (Table 2, entries 1-17). All the products (5a-q) are known compounds and their structures were confirmed by comparison of their physical and spectral data with those reported previously. [29-38, 16, 20, 23]. The catalyst SIO$_2$-I was prepared by the reported method with some minor modifications [44].
### Table 2: SiO$_2$-I Catalyzed Synthesis of Hydroquinolines (5) at RT

<table>
<thead>
<tr>
<th>Entry</th>
<th>P</th>
<th>EtOH</th>
<th>Solvent-free</th>
<th>Mp °C</th>
<th>Literature</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5a</td>
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<td>30</td>
<td>90</td>
<td>207-209</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>80</td>
<td>30</td>
<td>92</td>
<td>241-243</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>90</td>
<td>40</td>
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<td>5d</td>
<td>90</td>
<td>30</td>
<td>88</td>
<td>202-204</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>80</td>
<td>30</td>
<td>92</td>
<td>258-260</td>
</tr>
<tr>
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<td>5f</td>
<td>80</td>
<td>30</td>
<td>94</td>
<td>260-262</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>80</td>
<td>30</td>
<td>90</td>
<td>234-236</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>90</td>
<td>40</td>
<td>85</td>
<td>220-222</td>
</tr>
<tr>
<td>9</td>
<td>5i</td>
<td>90</td>
<td>40</td>
<td>88</td>
<td>256-258</td>
</tr>
<tr>
<td>10</td>
<td>5j</td>
<td>90</td>
<td>40</td>
<td>80</td>
<td>228-230</td>
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<tr>
<td>11</td>
<td>5k</td>
<td>80</td>
<td>30</td>
<td>90</td>
<td>202-204</td>
</tr>
<tr>
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<td>5l</td>
<td>90</td>
<td>40</td>
<td>68</td>
<td>144-145</td>
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<tr>
<td>13</td>
<td>5m</td>
<td>90</td>
<td>40</td>
<td>72</td>
<td>142-144</td>
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<tr>
<td>14</td>
<td>5n</td>
<td>80</td>
<td>30</td>
<td>91</td>
<td>238-240</td>
</tr>
</tbody>
</table>
From a mechanistic point of view, one can envisage that the interaction of the Si-I bond with the carbonyl group of the aldehyde would enhance the susceptibility of the aldehydes to nucleophilic attack by the α-carbon of the keto ester (Scheme: 2.3.12).

One of the advantages of using heterogeneous catalysts is their re-cyclability and re-usability. After completion of the reaction, SiO$_2$-I can be easily separated from the reaction mixture and after drying at 100°C for two hours, it was re-used at least four additional times with no significant loss of activity (92-85% of 5b)(Fig 2.3.2).

**Figure: 2.3.2:** Reusability of the SiO$_2$-I catalyst (compound-5b)
2.3.4. Conclusion

In conclusion, to the best of our knowledge, this is the first report of the use of silica iodide as a catalyst in the four-component synthesis of 1, 4 dihydropyridines (polyhydrohydroquinolines). The mild reaction conditions, excellent yields obtained at room temperature coupled with the simple work-up procedure, shorter reaction times, cost effectiveness and re-usability of the catalyst are the key advantages of our protocol over those previously reported.

2.3.5. Experimental Section

Preparation of Silica Iodide

Silica gel (10 g) was dispersed in dichloromethane (25 ml), and thionyl chloride (10 ml) was added dropwise (addition funnel) with stirring (stir bar) at 20-30°C. After 1 hr, the solvent was removed by rotary evaporation in vacuo to give 13.0 g of silica chloride (SiO₂-Cl) as a dry solid. It was washed with water and dried at 80°C under vacuo (2 mm Hg, 1 hr). Then a solution of sodium iodide (1.5 g) in a mixture of EtOH-H₂O (4:1, 5 mL) was added to 3.0 g of the solid SiO₂-Cl and the suspension was stirred for 30 min. The solid obtained was collected, washed with water and dried at 80°C under vacuo (2 mm Hg, 1 hr) to afford 3.5 g of SiO₂-I as a colorless solid. In order to confirm the presence of iodide in SiO₂-I, chemical tests of sodium fusion extract (SFE) were performed. Silver nitrate test gave a very positive result, formed a yellow precipitate, which confirmed the presence of iodine in the catalyst.

General Procedures for the Synthesis of Hydroquinolines (5a-5q)

a) In Ethanol

To a stirred (spin bar) mixture of the aldehyde (1 mmol), ethyl acetoacetate (0.130 g, 1 mmol), dimedone (or 1,3-cyclohexanediones) (1.5 mmol), and ammonium acetate (0.077 g, 1 mmol) in 5 mL of ethanol was added 0.1 g of SiO₂-I and the mixture was stirred at room temperature for an appropriate time (Table 2, entries 1-17). Upon completion of the reaction as indicated by TLC (ethyl acetate-hexane, 3:7), the reaction mixture was poured onto 5 ml ice water and the precipitated solid mixture was collected. The solid mixture of the product and catalyst was washed with diethyl ether (20 mL) and the insoluble solid (catalyst) was separated and kept aside for re-use. Evaporation of the ethereal solution gave the crude product which after recrystallization from ethanol-water (4:1), afforded the pure products.
b) Under Solvent-free Conditions

A mixture of aldehyde (1 mmol), ethyl acetoacetate (0.130g, 1 mmol), dimedone (or 1,3-cyclohexanediones) (1.5 mmol), ammonium acetate (0.077g, 1mmol) and SiO$_2$-I (0.1g) was thoroughly mixed in an agate mortar and ground using a pestle manually at room temperature for an appropriate time (Table 2, entries 1-17). Upon completion of the reaction as indicated by TLC (ethyl acetate-hexane, 3:7), work-up and recrystallization procedures were same as described above.

Spectral data

2, 7, 7-Trimethyl-5-oxo-4-phenyl-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxilic acid ethyl ester (5a): M.p. 207-209 °C. $^1$H NMR (CDCl$_3$, 300 MHz)/$\delta$ (ppm): 7.28-7.32 (m, 2H), 7.17-7.23 (m, 2H), 7.07-7.13 (m, 1H), 6.63 (s, 1H), 5.06 (s, 1H), 4.08 (q, 2H), 2.35 (s, 3H), 2.12-2.28 (m, 4H), 1.22 (t, 3H), 1.07 (s, 3H), 0.94 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz)/$\delta$ (ppm): 194.42, 166.23, 147.45, 142.41, 145.81, 126.73, 126.57, 124.72, 110.70, 104.71, 58.51, 49.50, 39.63, 35.32, 31.36, 28.15, 25.83, 17.95, 12.91; Mass (m/z) = 340.2 (M+1).

2,7,7-Trimethyl-5-oxo-(3-nitrophenyl)-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxilic acid ethyl ester (5c): M. p. 173-175 °C; $^1$H NMR (CDCl$_3$, 300 MHz)/$\delta$ (ppm): 7.71 (d, 1H), 8.00 (m, 1H), 7.97 (m, 1H), 7.33 (t, 1H), 6.86 (s, 1H), 5.17 (s, 1H), 4.03 (q, 2H), 2.11-2.42 (m, 7H), 1.22 (t, 3H), 1.08 (s, 3H), 0.94 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz)/$\delta$ (ppm): 194.36, 143.41, 148.02, 165.71, 146.93, 133.50, 127.32, 121.57, 119.97, 109.76, 103.71, 58.78, 49.31, 39.53, 35.71, 31.43, 28.07, 25.77, 18.03, 12.90; Mass (m/z) = 385.2 (M+1).
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$^1$HNMR of compound 5a
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\[13\text{CNMR of compound 5a}\]
Mass spectrum of compound 5a
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\(^1\)HNMR of compound 5c

[Chemical structure and NMR spectrum of compound 5c]
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\[ 13 \text{CNMR of compound 5c} \]
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Mass spectrum of compound 5c
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2.3.6. References


