CHAPTER 6

Greener Approach towards the Facile Synthesis of 1,4-Dihydropyrano[2,3-c]pyrazoles by Using GELA

6.1 Introduction

Synthesis of heterocyclic compounds is potentially important due to its pharmaceutical and agricultural fields. One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules [1]. Dihydropyrano[2,3-c]pyrazoles (Fig. 6.1) play an essential role as biologically active compounds and represent an interesting template for medicinal chemistry. Condensed pyrazoles are also biologically interesting compounds and their chemistry has recently received considerable attention [2, 3]. Moreover, the biological activity of fused azoles has led to intensive research on their synthesis [4-6].

![Fig. 6.1 1,4-Dihydropyrano[2,3-c]pyrazoles](image)

The polyfunctionalized benzopyrans and their derivatives are a kind of very useful compounds. Some 1,4-dihydropyrano[2,3-c]pyrazoles can be employed as photoactive materials [7]. Furthermore, multi-substituted 4H-pyrans also constitute a structural unit of a series of natural products [8, 9].

Synthesis of 4H-benzo-pyran has considerable interest as an important intermediate of many heterocycles [10-12]. Recently, these derivatives have
attracted strong interest because of their useful biological and pharmacological activities, such as anticoagulant, spasmylytic, diuretic, anticancer and antianaphylactin [13]. The versatile dihydropyrano[2,3-c]pyrazole derivatives have very important biological activities, such as anticancer, antimicrobial, anti-inflammatory, insecticidal, and molluscicidal activities (Fig. 6.2). They are also potential inhibitors of human Chk1 kinase (Fig. 6.3) [14].

One-pot, multi-component reactions (MCRs) permit rapid access to combinatorial libraries of complex molecules especially in drug discovery [15]. Synthesis of 4H-pyran unit bearing heterocyclic compounds has been given much attention to drugs in the field of medicinal chemistry [16].

The various methods are reported for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole in the literature.
B. Myrboh et al. [17] investigated synthesis of pyrano[2,3-d]pyrazole derivatives using ethyl acetoacetate, hydrazine hydrate, malononitrile and various aldehydes using L-proline (10 mol %) in water under mild reaction condition (Scheme 6.1).

Scheme 6.1

H. Sheibani and co-workers [18] synthesized a four-component reaction of hydrazine hydrate or phenyl hydrazine, ethyl 3-alkyl-3-oxo propanoate, aldehydes and malononitrile in the presence of nanosized magnesium oxide as a heterogeneous base catalyst to produce of 6-amino-3-alkyl-4-aryl-5-cyano-1,4-dihydropyrano[2,3-c]pyrazole derivatives (Scheme 6.2).

Scheme 6.2

B. P. Bandgar and group [19] investigated a series of pyranopyrazoles, in the presence of catalytic amount silicotungstic acid (Heteropolyacid) under solvent free condition (Scheme 6.2).
Proposed mechanism for synthesis of dihydropyrano[2,3-c]pyrazole:

Mechanistically, the reaction occurs via initial formation of arylidenemalononitrile 7 by the Knoevenagel condensation between 3 and 4, and pyrazolone 6 by the reaction between 1 and 2. Finally, Michael addition of pyrazolone 6 to arylidenemalononitrile 7, followed by cyclization and tautomerization to yield pyranopyrazole 5 (Fig. 6.4).

M. P. Patel et al. [20] used conventional and microwave irradiation approach for pyrano[2,3-c]pyrazole derivatives by multi-component reaction (Scheme 6.3).
M. M. Heravia and group [21] developed a new route for the synthesis of dihydropyrano[2,3-c]pyrazole using heteropolyacid $H_{14}[NaPW_{12}O_{40}]$ as a catalyst for three-component one-pot synthesis (Scheme 6.4).

Scheme 6.4

Proposed mechanism for synthesis of dihydropyrano[2,3-c]pyrazole by using heteropolyacids $H_{14}[NaPW_{12}O_{40}]$ as a catalyst (Fig. 6.5).

Fig. 6.5

K. Pitchumani and co-workers [22] synthesized a series of pyranopyrazole derivatives by using hydrazine hydrate, ethyl acetoacetate, aldehyde/ ketone and malononitrile in presence of Per-6-amino-β-cyclodextrine (per-6-ABCD) catalyst (Scheme 6.5).
D. V. Mane et al. [23] reported a synthesis of 1,4-dihydropyrano[2,3-c]pyrazole-5-yl by reaction of aromatic aldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one at room temperature using triethylammonium acetate (TEAA) ionic liquid as catalyst (Scheme 6.6).

M. M. Heravi et al. [24] investigated one-pot synthesis of 1, 4-dihydropyrano[2,3-c]pyrazole derivatives by using p-toluenesulfonic acid as a catalyst in aqueous medium (Scheme 6.6).

T. S. Jin and co-workers [25] reported a three-component reaction of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazoles from 3-methyl-1-phenyl-2-pyrazolin-5-one, aromatic aldehydes and malononitrile using p-dodecylbenzenesulfonic acid (DBSA) as catalyst (10 mol %) in aqueous medium (Scheme 6.6).

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Scheme 6.7

P. J. Steel and group [27] synthesized 6-amino-3,3’-dimethyl-5’-oxo-1,1’diphenylspiro-[pyrano[2,3-c]pyrazole-4(1H),4’-2-pyrazoline]-5-carbonitrile 4, by using tetracyanoethylene (TCNE) which reacts with 3-methyl-1-phenyl-2-pyrazolin-5-one in ethanol (Scheme 6.8).

Scheme 6.8

H. M. F. Madkour and co-workers [28] reported effect of some active methylene containing heterocyclic compounds viz. barbituric, thiobarbituric acids and 3-methyl-1-phenylpyrazol-5-one on α-cyano-3,4,5-trimethoxycinnaminitrile and ethyl-cyano-3,4,5-trimethoxycinnamate (Scheme 6.9).
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Scheme 6.9

Although the literature on 1,4-dihydropyrano[2,3-c]pyrazole synthesis enjoys a rich array of the versatile methodologies, new convergent approach for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole scaffold and novel methodologies is still a vibrant area of research in organic synthesis.

6.2 Present Work

Most of the synthetic reactions are performed in organic solvents. The use of water as the reaction medium is usually avoided since a large number of reactants decompose when brought into contact with water. Furthermore, many organic reactants are sparsely soluble in water. Traditional methods generally employ more than stoichiometric amounts of hazardous water soluble Lewis acids such as AlCl₃ or BF₃, which are destroyed during the workup leading to large volumes of waste [29]. Moreover, these Lewis acids are moisture sensitive and cannot be recovered and reused after the reactions are complete. The loss of inorganic reagents as waste products is undesirable.

Thus alternative reaction conditions are sought to minimize or eliminate the waste problem. In this regard, we envisioned that the entrapment of Lewis acids in matrix of agar-agar, the concept acronyemed as gel entrapped Lewis acids (GELAs), can prove to be highly attractive strategy to alleviate the problems associated with Lewis acids.

A model reaction of benzaldehyde, malononitrile ethyl acetoacetate and hydrazine hydrate was carried out to yield corresponding product (B) by using ZnCl₂-GELA and ethanol at ambient temperature with excellent yield within
very short time. When the same strategy was used for the reaction between benzaldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one, we obtained good to excellent yield (A) (Scheme 6.10).

Scheme 6.10

6.3 Results and Discussion

In our continued interest in the development of a highly expedient methodology for the synthesis of 1,4-dihydropyran[2,3-c]pyrazole, we employed a new method for the preparation of gel entrapped Lewis acid catalyst. ZnCl₂ and AlCl₃ were used as the prototype Lewis acid in these studies. In the present work we took different concentrations of ZnCl₂ (5-25 %) were dissolved in a varying amount of agar-agar in water. We found that 20 % w/w of agar-agar aqua gel containing 10 % Lewis acids resulted in the formation of soft gel that served as GELAs. The changes in physical nature of GELAs were studied in different solvents. The nature of gel remained intact in organic solvents like ethanol, acetone, dichloromethane, toluene and isopropanol. The GELAs swelled in water and became soft.

In order to delineate the role of GELAs, a control experiment was carried out in which the model reaction was performed without catalyst. No reaction was observed even after prolonged reaction time. As better results were obtained for ZnCl₂-GELA, instead of AlCl₃-GELA, we employed this particular catalyst for further studies. The generality of the protocol was validated by reacting commercially available benzaldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate (Scheme 6.10).
Table 6.1: Synthesis of pyrano[2,3-d]pyrazole catalyzed by ZnCl₂-GELA and AlCl₃-GELA

<table>
<thead>
<tr>
<th>Entry</th>
<th>GELA</th>
<th>Time [min]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnCl₂-GELA</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃-GELA</td>
<td>10</td>
<td>81</td>
</tr>
</tbody>
</table>

¹The reaction of benzaldehyde malononitrile, ethyl acetoacetate and hydrazinehydrate.
²Isolated yield.

GELA is used in the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole (Scheme 6.10). Typically, reactions were carried out at ambient temperature in open air using 1 g of GELAs with 5 mmol of substrates in ethanol. The reaction proceeded efficiently yielding the corresponding pyrano[2,3-d]pyrazole derivatives in excellent yields within very short time (Table 6.2).
Table 6.2: Synthesis of Dihydropyrano[2,3-c]pyrazole by ZnCl₂-GEAC

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Products</th>
<th>Time [min]</th>
<th>Yield [%]</th>
<th>M. P.[°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td><img src="image1" alt="Image" /></td>
<td>15</td>
<td>86</td>
<td>243 [244-246]</td>
</tr>
<tr>
<td>2</td>
<td>CHO⁻NO₂</td>
<td><img src="image2" alt="Image" /></td>
<td>18</td>
<td>87</td>
<td>214 [214-216]</td>
</tr>
<tr>
<td>3</td>
<td>CHO⁻Cl</td>
<td><img src="image3" alt="Image" /></td>
<td>15</td>
<td>86</td>
<td>235 [233-235]</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td><img src="image4" alt="Image" /></td>
<td>15</td>
<td>91</td>
<td>170 [170-171]</td>
</tr>
<tr>
<td>5</td>
<td>CHO⁻OMe</td>
<td><img src="image5" alt="Image" /></td>
<td>20</td>
<td>90</td>
<td>171 [170-172]</td>
</tr>
<tr>
<td>6</td>
<td>CHO⁻NO₂</td>
<td><img src="image6" alt="Image" /></td>
<td>16</td>
<td>88</td>
<td>195 [194-196]</td>
</tr>
<tr>
<td>7</td>
<td>CHO⁻NO₂</td>
<td><img src="image7" alt="Image" /></td>
<td>15</td>
<td>87</td>
<td>189 [188-190]</td>
</tr>
</tbody>
</table>
To check the possibility of recovery and reusability of catalyst is an important factor from a green chemistry point of view and for industrial applications.
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We carried out the model reaction using ZnCl₂-GELA in ethanol. After completion of the reaction, the catalyst was recovered by simple filtration, washed with ethanol and reused in another reaction with identical substrates. The catalyst could be recycled seven times without the considerable decrease of activity (Fig. 6.6).

Characterization of Products

The identification of all the products ascertained on the basis of IR, \(^1\)H NMR, \(^{13}\)C NMR and Mass spectroscopy. The spectroscopic data is in full agreement with the proposed structure.

6-amino-3-methyl-4-[3-nitrophenyl]-2,4-dihydropyran[2,3-c]pyrazole-5-carbonitrile (Entry 2)

IR spectrum (Fig. 6.7) exhibited stretching frequency at 3474 cm\(^{-1}\) for N-H stretching whereas amino group observed at 3223, 3118 cm\(^{-1}\). An intense peak at 2195 cm\(^{-1}\) was due to the presence of C-N. The nitro group absorbed at 1492 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig. 6.8) displayed a singlet at \(\delta 1.78\) for three
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protons of methyl group. Singlet at \( \delta 4.86 \) was due to methine proton, whereas a triplet and multiplet at \( \delta 7.65 \) and 8.13 indicated aromatic protons. A broad singlet observed at \( \delta 7.04 \) for amino group protons and a sharp singlet at \( \delta 12.20 \) ppm for N-H proton. \(^{13}\)C NMR spectrum (Fig. 6.9) showed the peaks at \( \delta 10.1 \) (CH\(_3\)), 36.0, 56.5 (chiral carbon), 97.1, 122.2, 122.4, 130.7, 134.8, 136.3, 147.2, 148.3 (Ar) and 161.5 ppm. The mass spectrum (Fig. 6.10) showed molecular ion peak at (m/z) 298 (M\(^+\)).

6-amino-3-methyl-4-[4-chlorophenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 3)

IR Spectrum (Fig. 6.11) exhibited a stretching frequencies at 3373, 3311 cm\(^{-1}\) for NH\(_2\) group. The sharp peak observed at 2193 cm\(^{-1}\) for C-N group. In \(^1\)H NMR spectrum (Fig. 6.12), methyl protons resonated at \( \delta 1.776 \) whereas a singlet encountered at \( \delta 4.61 \) for methine proton. Two doublets observed at \( \delta 7.19 \) (\( J =8.4 \text{ Hz} \)) and 7.37 (\( J=8.4 \text{ Hz} \)) for aromatic protons. Amino protons appeared as broad singlet at \( \delta 6.92 \) and N-H proton appeared at \( \delta 12.18 \) ppm. In \(^{13}\)C NMR spectrum (Fig. 6.13), the peaks appeared at \( \delta 10.1 \), 36.0, 57.2 (chiral carbon), 97.6, 121.1, 128.9, 129.8, 131.6, 136.1, 143.9, 155.1 and 161.3 ppm. In mass spectrum (Fig. 6.14), molecular ion peak observed at (m/z) 286 (M\(^+\)).

6-amino-5-cyano-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (Entry 4)

In IR spectrum (Fig. 6.15), stretching frequencies at 3471, 3324 cm\(^{-1}\) were due
to primary amino group and a band at 2198 cm\(^{-1}\) due to C-N stretching. \(^1\)H NMR spectrum (Fig. 6.16) exhibited a singlet at \(\delta\) 1.74 for methyl protons linked to pyrazole ring and a sharp singlet for one methine proton appeared at \(\delta\) 4.56. A broad singlet for amino protons observed at \(\delta\) 6.95, while aromatic protons showed downfield shift in form of multiplet between \(\delta\) 7.01-7.42 ppm.

In \(^{13}\)C NMR (Fig. 6.17), peaks observed at \(\delta\) 12.9, 37.3, 58.7 (chiral carbon), 98.8, 120.3, 126.4, 127.4, 128.0, 128.8, 129.6, 137.8, 143.7, 144.2, 145.7 and 159.8 ppm.

**6.4 Conclusion**

We have reported ZnCl\(_2\) catalyzed one pot multi-component reaction of benzaldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one or instead of 3-methyl-1-phenyl-2-pyrazolin-5-one we used ethyl acetoacetate and hydrazine hydrate for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole. The present protocol is efficient providing higher yield of the reaction product. This procedure offers several significant advantages including mild reaction condition, cleaner reaction, moisture-insensitive, cost effective, high yield of the product as well as a simple experimental procedure, which make it an attractive process.

**6.5 Experimental Section**

Melting points were determined in an open capillary and are uncorrected. Infrared spectra were recorded on a PerkinElmer FT-IR spectrometer. The samples were examined as KBr discs ~5 % w/w. \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on a Bruker Avon 300 spectrometer using DMSO-d\(_6\) as solvent and TMS as internal reference. The mass spectrum was recorded on Thermo, LCQ Tune spectrometer. TGA-DTA analysis was recorded on SDS Q600 N20.9 in nitrogen. All the chemicals were obtained from s. d. FiNE CHEM, SPECTROCHEM and used without further purification.
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**General Procedure**

**Preparation of Gel Entrapped ZnCl₂**

Gel Entrapped ZnCl₂ i.e GELA was prepared by using procedure as described in chapter 5 section I.

**Multi-Component Synthesis of 1,4-Dihydropyrano[2,3-c]pyrazole**

A mixture of benzaldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one (5 mmol each) path-A and benzaldehyde, malononitrile ethyl acetoacetate and hydrazine hydrate (5 mmol each) path-B was stirred in the presence of ZnCl₂-GELA in 5 mL ethanol till completion of the reaction as monitored by TLC. The resulting crude product was filtered and recrystallized from ethanol to give the desired product.

**Spectral Data of Representative Compounds**

6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (Table 6.1, Entry 1)

**IR (KBr):** ν 3371, 3248, 2192, 1613, 1445 cm⁻¹;

**¹H NMR (300 MHz, DMSO-d₆):** δ 1.79 (s, 3H), 4.85 (s, 1H), 6.91 (s, 2H), 7.18-7.35 (m, 5H), 12.13 (s, 1H) ppm;

**¹³C NMR (75 MHz, DMSO-d₆):** δ 10.1, 36.8, 58.1, 121.0, 126.9, 127.9, 128.7, 136.5, 146.5 ppm.

6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 6.1, Entry 12)

**IR (KBr):** ν 3485, 3258, 2185, 1608, 1442 cm⁻¹;

**¹H NMR (300 MHz, DMSO-d₆):** δ 1.77 (s, 3H), 3.82 (s, 3H), 4.62 (s, 1H), 6.88 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 7.15 (s, 2H), 12.10 (s, 1H) ppm;

**¹³C NMR (75 MHz, DMSO-d₆):** δ 10.0, 36.2, 55.1, 57.9, 107.4, 113.4, 114.2, 118.5, 136.8, 144.2, 155.8, 156.3 and 160.5 ppm.
Fig. 6.7: IR spectrum of 6-Amino-3-methyl-4-[3-nitrophenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Fig. 6.8: $^1$H NMR spectrum of 6-Amino-3-methyl-4-[3-nitrophenyl]-2,4-dihydropyran[2,3-c]pyrazole-5-carbonitrile
Fig. 6.9: $^{13}$C NMR spectrum of 6-Amino-3-methyl-4-[3-nitrophenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Fig. 6.10: Mass spectrum of 6-Amino-3-methyl-4-[3-nitrophenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Fig. 6.11: IR spectrum of 6-Amino-3-methyl-4-[4-chlorophenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Fig. 6.12: $^1$H NMR spectrum of 6-Amino-3-methyl-4-[4-chlorophenyl]-2,4-dihydropyran[2,3-c]pyrazole-5-carbonitrile
Fig. 6.13: $^{13}$C NMR spectrum of 6-Amino-3-methyl-4-[4-chlorophenyl]-2,4-dihydropyran[2,3-c]pyrazole-5-carbonitrile
Fig. 6.14: Mass spectrum of 6-Amino-3-methyl-4-[4-chlorophenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Fig. 6.15: IR spectrum of 6-Amino-4-(phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyran[2,3-c]pyrazole
Fig. 6.16: $^1$H NMR spectrum of Amino-4-(phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole
Fig. 6.17: $^{13}$C NMR spectrum of 6-Amino-4-(phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole
6.6 References


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