[DBU][Ac]
Catalyzed One Pot Synthesis of Chromenes
4.1. INTRODUCTION

Heterocyclic compounds constitute the largest and diverse family of organic compounds [1]. A substantial number of them occur widely in nature and exhibit profound biological activity. As a consequence, many of the drug molecules used in therapy today are heterocycles [2]. Among the heterocyclic compounds, oxygen heterocycles are special because of their wide occurrence as a part structure of carbohydrates. The low molecular weight oxygen heterocycles find application as solvents and synthetic intermediates. Some of the fundamental small ring oxygen heterocycles are oxirane (3-member), oxetane (4-member), tetrahydrofuran (THF; 5-member) and tetrahydropyan (6-member). We were interested in the synthesis and structural studies of the six-member oxygen heterocycles fused to benzene ring. The compound in which benzene ring is fused to a 4H-pyran ring is known as 4H-chromene (4H-l-benzopyran) 1. Its dihydro-derivative, chroman 2 is a fragrance compound with peppermint like odor [3]. Figure 4.1 shows these two compounds.

Presence of chromene-based structure in a molecule is often associated with its capacity to prevent diseases [4]. Few naturally occurring chromenes exhibit antimicrobial [5], antitumor [6], antiviral [7], mutagenic [8], antiproliferative [9] and central nervous system (CNS) activities [10]. Some chromenes are sex pheromones [11]. Numerous synthetic derivatives of naturally occurring chromene have found use in pharmaceuticals [12], particularly as antifungal [13, 14] and antimicrobial agents [15]. Certain 2-aminochromeme derivatives are used in cosmetics and pigments industry [16]. Many bioactive molecules incorporate this key heterocycle eg, antioxidants [17], enzyme inhibitors [18].
Out of diverse array of chromenes, 4H-chromenes are of interest to present research workers. They are seldom encountered as a part of natural product structures. Few natural products, which possess 4H-chromene structural motifs are gathered in Figure 4.2.

6-Methoxy-4H-1-benzopyran-7-ol 3 and 6,7-dimethoxy-4H-1-benzopyran 4 are isolated from the flowers of *Wisteria sinensis* plant, they exhibit organoliptic property [19, 20]. Another 4H-chromene natural product uvafelelin 5 isolated from the stems of *Uvaria afzelii* showed significant antimicrobial activity against gram-positive and acid-fast bacteria [21].

The 4-aryl-4H-chromenes are potent apoptosis (controlled cell death) inducing agents [22]. Since cancer cells grow faster, apoptosis inducing agents act on cancer cells to restrict their abnormal cell division. Cai and coworkers discovered the use of the 4-aryl-4H-chromene 6 as a lead compound for the development of anticancer drugs [23]. By systematically changing substituents on the C4 aryl ring, they found that 4H-chromene is highly active against human lung tumor [24].

**4.1.1. General methods for the synthesis of 4H-chromenes**

Three component condensation of aromatic aldehydes and malononitrile along with active methylene heterocyclic compounds viz. 4-hydroxycoumarin [25, 26], 4-hydroxy-6-methylpyrone [26], 1,3-dimethylbarbituric acid [27] as well as carbocyclic compounds viz. cyclohexan-1,3-dione and dimedone [28], have fairly widened the scope of this reaction to generate 2-amino-3-cyano-4-aryl-4H-chromenes (Scheme 4.1.1) A variety of acidic and mildly basic reagents promote this highly atom-economic multi-component reaction (MCR) [29, 30]. The reaction goes through initially formed Knoevenagel condensation product from malononitrile and the aromatic
aldehydes. The reaction furnished by Michael addition involving active methylene compounds 7 and Knoevenagel product 8 provides 4H-chromenes 9.

Recently numerous reports are cited in literature in which the various catalysts have been employed for the synthesis of 4H-chromenes.

Khoobi, M. et al. [31] recently reported synthesis of 2-amino-5-oxo-4-aryl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile and 4H-benzo[b]pyran derivatives catalyzed by non-toxic and environmentally friendly inorganic–organic hybrid magnetic nano-catalyst. (2-aminomethyl)phenol moiety supported on HAp-encapsulated-γ-Fe₂O₃ [γ-Fe₂O₃@Hap-Si-(CH₂)₃ AMP] was employed as the novel catalyst in this process. The method has worthy advantages like excellent yields, operational simplicity, practicability, product purity, cost efficiency and environmental friendly benefits.

Nemouchi, S. et al. [32] reported an easy, convenient, inexpensive and environmental friendly synthetic approach for the preparation of tetrahydrobenzo[b]pyrans catalyzed by PhB(OH)₂ using a three-component condensation in aqueous ethanol. This procedure offered advantages like high yields, operational simplicity, non-toxic catalyst, short reaction time and minimum pollution of the environment.

Boumoud, B. et al. [33] carried out an efficient synthesis of tetrahydrobenzo[b]pyran catalyzed by nickel nitrate hexahydrate in aqueous media. The process gave high yield of targeted compounds by using catalytic amount of nickel nitrate hexahydrate.
Zhang, Z. et al. [34] recently developed an efficient and novel method for the one-pot tandem synthesis of pyran heterocyclic compounds via a Pd-catalyzed Suzuki reaction followed by using KF.\(2\text{H}_2\text{O}\) as the connecting bridge in three-component reaction. Khurana, J. et al. [35] devised efficient synthetic approaches for the synthesis of highly functionalized 4H-benzo[g]chromenes in water using \([\text{bmim}]\text{OH}\) as catalyst.

Khaksar, S. et al. [36] developed efficient synthesis of 2-amino- 4H-chromene and tetrahydrobenzo[b]pyran derivatives via one-pot condensation of aldehydes, malononitrile and resorcinol or dimedone in 2,2,2-trifluoroethanol (TFE) without using any catalyst or additives. Shekhar, A. et al. [37] demonstrated a facile and environmentally benign method for the synthesis of highly functionalized naphtho- and benzopyran compounds by a single-pot three-component condensation reaction of naphthalene-2-ol or a phenol, an aldehyde, and an active methylene compound in the presence of 5-Å molecular sieves as catalyst under solvent-free conditions.

Hasaninejad, A. et al. [38] carried out an efficient synthesis of benzo[b]pyran derivatives using catalytic amount of alumina supported KF in ethanol under reflux. Tabatabaeian, K. et al. [39] developed simple and convenient method for the synthesis of dihydropyrano[3,2-c]chromene and tetrahydrobenzo[b]pyran derivatives via one-pot three-component reaction in the presence of catalytic amount of Ru(II) as efficient, easily synthesized and reusable catalyst. Kharbangar, I. et al. [40] described an alternative and general method for the three component synthesis of functionalized 4H-pyran heterocycles using KF-Al\(_2\)O\(_3\) as the basic catalyst.

Valizadeh, H. et al. [41] introduced a three-component condensation reaction leading to a new class of 5-amino-6-cyano-3-hydroxybenzo[c]coumarin derivatives starting from simple and readily available precursors. This MCR approach includes some important aspects such as high yields, mild and solvent-free reaction conditions. Hasaninejad, A. et al. [42] carried out a synthesis of 4H-benzo[b]pyrans by one-pot, three-component condensation of cyclic ketones/1,3-diketones with aromatic aldehydes and alkyl nitriles using Silica
bonded n-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO) as catalyst.

Salvi, P. et al. [43] carried out an efficient synthesis of tetrahydrobenzo[b]pyrans catalyzed by amino functionalized ionic liquid. The heterocycles synthesized in this study were obtained in high regioselectivity, good yields and short reaction times. Shaterian, H. et al. [44] successfully developed a simple, facile and efficient method for the synthesis of benzylidenmalononitrile, 2-benzylidene-5,5-dimethylcyclohexane-1,3-dione, 2-amino-4-aryl-5-oxo-4,5-dihydropyran[3,2-c]chromene-3-carbonitrile, tetrahydrobenzo[b]pyran, spirooxindole using a catalytic amount of 2-hydroxyethylammonium formate under solvent-free and ambient conditions.

Zheng, J. et al. [45] prepared a series of new basic task-specific ionic liquids and used them as catalysts for the synthesis of pyranannulated heterocyclic systems. Davoodnia, A. et al. [46] reported a simple new catalytic method for the synthesis of tetrahydrobenzo[b]pyrans by a one-vessel cyclocondensation reaction of dimedone, aryl aldehydes, and malononitrile in water using PPA–SiO₂ as an efficient, reusable and environmentally acceptable heterogeneous catalyst.

Banerjee, S. et al. [47] synthesized a series of biologically and pharmacologically active 4H-pyran derivatives using SiO₂ NPs as catalyst via one-pot three component condensation of an aldehyde, malononitrile, and either 5,5-dimethyl-1,3-cyclohexanedione or ethyl acetoacetate in excellent yields (82–98%) within a practical reaction time (0.5–2 h). Katkar, S. et al. [48] have demonstrated a new and important catalytic activity of ZnO-beta zeolite as the catalyst for synthesis of tetrahydrobenzo[b]pyrans in high to excellent yields.


Khan, A. et al. [51] devised a simple and efficient protocol for the synthesis of pyran annulated heterocycles using DMAP as catalyst via one-
pot three-component condensation reaction of an aldehyde, ethyl cyanoacetate or malononitrile, and either 4-hydroxycoumarin or 1,3-cyclic ketones or 2-naphthol in excellent yields. Pratap, U. et al. [52] developed a novel baker’s yeast catalyzed methodology for the cyclocondensation of aryl/heteryl aldehydes, malononitrile, and ethyl acetoacetate/acetyl acetone in an organic solvent, dimethylacetamide.

Mobinikhaledi, A. et al. [53] developed an efficient and ecologically safe method for the synthesis of 4H-benzo[b]pyrans and pyrano[2,3-d]pyrimidinone derivatives using tetrabutyl ammonium bromide (TBAB) as catalyst. Reza, M. et al. [54] reported a new and effective methodology for the eco-compatible preparation of 2-amino-4H-chromenes via one-pot three component reaction of aromatic aldehydes, malononitrile, and active naphthols using catalytic amount of Na$_2$CO$_3$ under solvent-free conditions.

Mobinikhaledi, A. et al. [55] also developed an efficient method for the eco-compatible synthesis of 4H-benzo[b]pyrans and pyrano[2,3-d]pyrimidinone derivatives using a green media and catalyst. Fang, D. et al. [56] reported synthesis of acyclic TSILs and used as efficient catalysts for the synthesis of 5-oxo-5,6,7,8-tetrahydro-4H-benzo[b] pyrans in aqueous media.

Lu, G. et al. [57] developed an effective method for the synthesis of polysubstituted 4H-pyrans catalyzed by piperidine in aqueous medium. Li, M. et al. [58] developed a convenient and regioselective synthesis of functionalized tetrahydrobenzo[b]pyran and chromeno[2,3-b]quinoline frameworks containing a chromene moiety.


Kumar, D. et al. [61] developed a facile one-pot synthesis of 2-amino-4H-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes under solvent-free conditions using magnesium oxide as a recyclable catalyst in good yields. They also reported antibacterial activity of synthesised 4H-

Chen, L. et al. [63] described a practical and efficient procedure for the preparation of 4H-benzo[b]pyrans through the three-component reaction of aromatic aldehydes, malononitrile, and dimeredone by using catalytic amount of N,N-dimethylethanolbenzyldimethylammonium chloride as catalyst under solvent-free conditions. Khurana, J. et al. [64] reported 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed one-pot synthesis of 3,4-dihydro pyrano[3,2-c]chromenes, dihydropyrano[4,3-b]pyrans, 2-amino-4H-benzo-[h]chromenes and 2-amino-4H-benzo[g]chromenes from aldehydes, active methylene compounds malononitrile/ethyl cyanocacetate, and 4-hydroxycoumarin/4-hydroxy-6-methylpyrone/1-naphthol/2-hydroxy naphthalene-1,4-dione in water under reflux condition.

Wang R. et al. [65] successfully developed an unique approach to asymmetric synthesis of various optically pure pyranocoumarins and 2-amino-4H-chromenes catalyzed by a novel tertiary amine-thiourea with low ligand loading under one-pot, two-component and three-component intermolecular domino reactions with high yield (up to 95%) and enantioslectivities (up to 99% ee). Wang H. et al. [66] developed a simple, efficient approach for synthesis of dihydropyrano[3,2-c]chromene derivatives by one-pot, three-component reaction of aldehydes, malononitrile, and 4-hydroxycoumarin in the presence of a catalytic amount of hexamethylenetetramine.

Heravi M. et al. [67] developed a simple and rapid method for the synthesis of a variety of dihydropyrano[c]chromene derivatives catalyzed by small organic molecule. Heravi M. et al. [68] also reported reaction of 4-hydroxycoumarin, aldehydes and ethylcyanoacetate using various heteropolyacids.

From the literature review it becomes evident that the chemists all across the globe are continuously trying to achieve the simpler protocols for synthesizing the useful chromene derivatives. However, few reports are there to synthesize this important moiety using ILs. Much attention has not been paid to explore the advantage offered by IL in chromene synthesis.
This chapter deals with such an attempt using [DBU]Ac as the solvent and catalyst to find environmentally benign protocol for the synthesis of chromenes. The reaction are also performed under conventional as well non-conventional energy sources to proceed a step forward saving energy to make the protocol cost effective.

4.1.2. Objectives

The objectives of the present work are

- To synthesize variously substituted 4H-chromenes by using ionic liquid [DBU]Ac as a solvent or as a catalyst or both. Synthesis of two chromene derivatives tetrahydrobenzo[b]pyran and dihydropyrano[c]chromenes are covered in two different parts.
- To optimize the effect of ionic liquid under conventional and unconventional (Grinding) energy sources.
- Spectroscopic characterization of all synthesized 4H-chromenes.

The work carried out to encounter the said objective is described in the present chapter. The chapter is divided in two parts and each part is further divided into three different sections. The first part includes synthesis of tetrahydrobenzo[b]pyran. The second part contains synthesis of dihydropyrano[c]chromenes. The synthesis of 4H-chromenes using conventional energy source and grinding are respectively covered in section (a) and (b) of each part. The spectroscopic characterization is described in section 4c with the spectral data of all the synthesized 4H-chromenes and some selected spectra are also put on view in the same section.
Part - I

Synthesis of Tetrahydrobenzo [b]pyran by Conventional energy source
**4.1.4a.1. RESULT AND DISCUSSION**

**4.1.4a.1.1. Scheme**

The synthesis of tetrahydrobenzo[b]pyran derivatives 4 (Scheme 4.1.4a.1) was carried out by one-pot condensation reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) 1, various aromatic/heterocyclic aldehydes 2 and malononitrile 3 in presence of basic ionic liquid [DBU][Ac] by stirring at ambient temperature in methanol as co-solvent. The most optimum reaction condition and the role of ionic liquid to accelerate the reaction are discussed in detail in this section.

![Scheme 4.1.4a.1 Present protocol for the synthesis of tetrahydrobenzo[b]pyrans at ambient temperature](image)

**4.1.4a.1.2. Reaction Optimization**

Initially, the reaction of vanillin, dimedone and malononitrile was selected as a model reaction to optimize the reaction conditions in the presence of different amounts of ionic liquid [DBU][Ac] (0–8.82 mol%) in methanol as co-solvent at room temperature (Table 4.1.4a.1, entries 1-6). Upon examining the influence of the amount of ionic liquid on the reaction, it was found that without ionic liquid the reaction did not proceed effectively (Table 4.1.4a.1, entry1). It was observed that 6.06 mol% of ionic liquid was sufficient to promote the reaction efficiently. The yield is found to decrease significantly below 6.06 mol% of ionic liquid even after prolonging the duration. When the amount of ionic liquid was increased over 6.06 mol% equivalent, no significant improvement was observed in reaction yield as well as in duration of the reaction. A brief screening of solvents showed that water, THF, methylene dichloride, acetonitrile and toluene were less effective than methanol (Table 4.1.4a.1, entries 7-11).
The best result was achieved by carrying out the reaction with 1:1:1.2 molar ratio of vanillin: dinedone: malononitrile at 25°C in presence of ionic liquid (6.06 mole %) in methanol as co-solvent.

**Table 4.1.4a.1 The effect of reaction condition on the synthesis of 4a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic Liquid</th>
<th>Co-Solvent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mol%</th>
<th>Time /min</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>0</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>1.53</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>3.03</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>4.62</td>
<td>8</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>6.06</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>8.82</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>[DBU][Ac]</td>
<td>Water</td>
<td>6.06</td>
<td>25&lt;sup&gt;c&lt;/sup&gt;</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>[DBU][Ac]</td>
<td>THF</td>
<td>6.06</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>[DBU][Ac]</td>
<td>MDC</td>
<td>6.06</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>[DBU][Ac]</td>
<td>Acetonitrile</td>
<td>6.06</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>[DBU][Ac]</td>
<td>Toluene</td>
<td>6.06</td>
<td>45</td>
<td>68</td>
</tr>
<tr>
<td>12</td>
<td>DBU</td>
<td>Methanol</td>
<td>6.06</td>
<td>8</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were carried out of vanillin: dinedone: malononitrile 1:1:1.2 (molar ratio) at room temperature in ionic liquids

<sup>b</sup>yield refer to pure isolated products

<sup>c</sup>The reaction was conducted in water under reflux for 25 min
4.1.4a.1.3. Generalization of the method to synthesize other tetrahydrobenzo[b]pyrans derivatives

Under this optimized conditions, a variety of aromatic aldehydes undergo condensation with active methylene compound (malononitrile) and dimedone to provide the corresponding tetrahydrobenzo[b]pyrans derivatives. All the reactions were observed to be very fast (1-10 min) and good yielding (85-95%) compared to other existing procedures. The electronic nature of the substituents on the aromatic ring did not show a strong effect in terms of yields under these reaction conditions. Both aromatic aldehydes containing electron-withdrawing groups (such as nitro, halo) or electron-donating groups (such as alkoxy group) gave good to excellent yields of the corresponding tetrahydrobenzo[b]pyran (Table 4.1.4a.2). No side reactions were observed in any of the reactions.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4-OH-3-OMe-C₆H₃</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>4b</td>
<td>C₆H₅</td>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>4c</td>
<td>4-NO₂C₆H₄</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>4d</td>
<td>4-OCH₃C₆H₄</td>
<td>2.5</td>
<td>94</td>
</tr>
<tr>
<td>4e</td>
<td>2-furyl</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>4f</td>
<td>4-Cl C₆H₄</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>4g</td>
<td>3-NO₂C₆H₄</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>4h</td>
<td>2-NO₂C₆H₄</td>
<td>2</td>
<td>92</td>
</tr>
<tr>
<td>4i</td>
<td>2-Cl C₆H₄</td>
<td>1.5</td>
<td>90</td>
</tr>
<tr>
<td>4j</td>
<td>4-F C₆H₄</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>4k</td>
<td>3,4,5-(OCH₃)₃C₆H₂</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>4l</td>
<td>4-(CH₃)₂NC₆H₄</td>
<td>7</td>
<td>86</td>
</tr>
</tbody>
</table>
All the reactions were run till the completion as indicated by TLC.

Isolated yield

All the reactions were monitored by TLC and proceeded to completion. All the synthesized compounds were crystallized by using hot ethanol. All the compounds were characterized by melting point, $^1$H NMR, $^{13}$C NMR spectral techniques. Additional confirmation for the structures is also obtained by IR and Mass spectrometric studies for the representative samples from the series. The description is furnished in section 4c of this chapter.

**4.1.4a.1.4. Mechanism**

The mechanism of this reaction has not been unequivocally established, but a plausible explanation is proposed in Scheme 4.1.4a.2 using malononitrile as a substrate. According to the plausible mechanisms, in first step an aldehyde is condensed with malononitrile to afford the α-cyanocinnamonitrile derivative. In second step the active methylene of dime done $1a$ reacts with the electrophilic C=C double of α-cyanocinnamonitrile giving the Michael adduct intermediate $2b$ and then furnished the intermediate product, which upon intramolecular cyclization and rearrangement gave rise to $4$ (Scheme 4.1.4a.2). During such reaction, formation of many side products such as enaminonitrile, higher adducts and malononitrile self addition products have been noticed in earlier publications [69-70]. Increase in yield of the product may be due to higher basicity, and stability of [DBU][Ac]-H+ species generated in this reaction which may have suppressed the formation of these undesired side products.
4.1.4a.1.5. Recyclability of ionic liquid

We also investigated the possibility of recycling of the basic ionic liquid [DBU][Ac]. After completion of the reaction, the solid product was collected by filtration. To the filtrate vanilline, dimedone and malononitrile were added in the same molar ratio without any additional load of [DBU][Ac]. The reaction mixture was stirred at room temperature for the specified time. As it is shown in Fig. 4.1.4a.1, the activity of the catalyst did not show any significant decrease in the yields after five successive runs for the model reaction.
4.1.4a.2. CONCLUSION

The described procedure demonstrated an efficient protocol for multicomponent synthesis of tetrahydrobenzo[b]pyran derivatives at ambient temperature using 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate ([DBU][Ac]) ionic liquid as the catalyst. In addition, the procedure offers several advantages including high yields, operational simplicity, environment friendly and cleaner reaction, which is a practical alternative to the existing procedures to satisfy the need of academy as well as industry.

4.1.4a.3. EXPERIMENTAL

All Chemicals used were of commercial grade and they were used without any further purification. Melting points were measured in open capillaries and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F254 (Merck). 1H and 13C NMR spectra were recorded on Bruker Avance 400 MHz instrument with TMS as the internal standard. The reactions were performed in 25 ml round bottom flask equipped with magnetic stirrer.

![Figure 4.1.4a.1 Recyclability of [DBU][Ac] in model reaction](image-url)
4.1.4a.3.1. General procedure for the synthesis of Tetrahydrobenzo[b]pyran derivative

The ionic liquid, [DBU][Ac] (6.06 mol%) was added to a mixture containing dimedone 1 (10 mmol), aldehyde 2 (10 mmol), malononitrile 3 (10 mmol) in methanol (5 ml). The resulting mixture was stirred for the required time as shown in Table 4.1.4a.2. The reactions were carried out in a 25 mL capacity round bottom flask. After completion of the reaction (as indicated by TLC), a solid product gradually formed was filtered through small Buchner funnel under vacuum, washed with ethanol-water (1:2) to leave the crude product which was purified by crystallization in ethanol. The aqueous filtrate was heated at 60 °C under reduced pressure (10 mm Hg) for 2 h to leave behind the IL in near complete recovery, pure enough to use in next run without any further purification.
Part - I

4.1.4b.1. RESULT AND DISCUSSION

4.1.4b.1.1. Scheme

The efficient synthesis of Tetrahydrobenzo[b]pyran derivative 4 (Scheme 4.1.4b.1) was carried out by one-pot condensation reaction of dimedone 1, various aromatic aldehydes 2, and malononitrile 3 in presence of basic ionic liquid [DBU][Ac] using grindstone chemistry. The sole ionic liquid was found to be effective as a reaction media as well as promoter for the reaction. The detail report is given in the following section.

![Scheme 4.1.4b.1 Present protocol for the synthesis of tetrahydrobenzo[b]pyrans by grinding](image)

4.1.4b.1.2. Reaction Optimization

To optimize the reaction conditions, reaction of dimedone, vanillin and malononitrile in presence of [DBU][AC] was selected as the model reaction. To check the activity, different amounts of ionic liquid [DBU][Ac](0–4.62 mol%) were taken for the synthesis of tetrahydrobenzo[b]pyran by simple grinding method using mortar and pestle. The model reaction was attempted without ionic liquid. It was observed that the reaction mass became semi-solid and only Knoevenagel product was formed in the absence of IL. When 3.03 mol% of IL was used, amazingly complete conversion of reactants into the product (as confirmed by TLC) was observed within 4 min. The reaction time required for completion was observed to be very less with very high product yield as shown in Table 4.1.4b.1. The best result was achieved by carrying out the reaction with 1:1:1 molar ratio of vanillin: dimedone: malononitrile at 25°C in presence of ionic liquid (3.03 mol%), which indicated that the amount of ionic liquid played a key role in acceleration of reaction with higher yield.
Table 4.1.4b.1 Screening of amount of ionic liquid for synthesis 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic Liquid</th>
<th>Mol%</th>
<th>Time (min)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[DBU][Ac]</td>
<td>0</td>
<td>30</td>
<td>Knoevenagel product</td>
</tr>
<tr>
<td>2</td>
<td>[DBU][Ac]</td>
<td>1.53</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>[DBU][Ac]</td>
<td>3.03</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>[DBU][Ac]</td>
<td>4.62</td>
<td>4</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield

4.1.4b.1.3. Generalization of the protocol using 15 different aldehydes

The synthesis of tetrahydrobenzo[b]pyran derivatives using sole 3.03 mol % IL was observed the most optimum condition giving maximum yields. Hence, to delineate the scope of this approach, particularly with regard to library construction, this method was evaluated using fifteen variously substituted aldehydes, dimesone, and malononitrile. The corresponding tetrahydrobenzo[b]pyran derivatives were obtained in good yields under similar conditions (Table 4.1.4b.2). Aromatic aldehydes carrying either electron-donating or withdrawing substituents afforded high yields of products in high purity. Among the advantages of this protocol is that acid sensitive aldehydes such as furfural worked well without the formation of any side products. Another important feature of this procedure is the survival of a variety of functional groups such as ether, nitro, hydroxy, amino, halides, etc., under the reaction conditions. The reaction proceeds very cleanly under mild conditions.

Table 4.1.4b.2 Library of tetrahydrobenzo[b]pyran derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Time&lt;sup&gt;a&lt;/sup&gt; (min.)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4-OH-3-OMe-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>4b</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>4c</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>4d</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3</td>
<td>95</td>
</tr>
</tbody>
</table>
All the reactions were run till the completion as indicated by TLC.

Isolated yield

All the reactions were monitored by TLC and taken to completion. The time taken for the complete conversion and the isolated yields are recorded in Table 4.1.4b.2. All the synthesized compounds were crystallized by using ethanol. All the compounds were characterized by melting point, $^1$H NMR, $^{13}$C NMR spectral techniques. Additional confirmation for the structures is also obtained by IR and Mass spectrometric studies for the representative samples from the series.

4.1.4b.1.4. Mechanism

The IL [DBU][Ac] promotes the reaction due to its basicity. The higher basicity and stability of [DBU][Ac]-H$^+$ species generated in this reaction which may have suppressed the formation of side products and pushed the reaction in forward direction. The mechanistic pathway is expected to follows the same path as shown in section 4.1.4a.1.4.
4.1.4b.1.5. Recyclability of ionic liquid

To check the activity of the recovered ionic liquid, it was again used for the same reaction by charging with the same substrate. The recovered ionic liquid was found to be equally effective for at least five runs. The effectiveness of the recovered ionic liquid in terms of yield is shown in bar diagram (Figure 4.1.4b.1). It shows that the catalyst (ionic liquid) displayed very good reusability without losing its efficiency.

![Bar Diagram](image)

**Figure 4.1.4b.1** Recyclability of [DBU][Ac] in model reaction

4.1.4b.2. CONCLUSION

In conclusion, an efficient catalytic activity of [DBU][Ac] is demonstrated for the one-pot synthesis of tetrahydrobenzo[b]pyran derivatives by condensation of aldehydes, dimedone and malononitrile under organic solvent free conditions. The significant advantages offered by this methodology are: i) operational simplicity, ii) general applicability to all types of aldehydes, iii) mild reaction conditions, iv) excellent yields of products and v) green procedure avoiding hazardous organic solvents and providing reusability of ionic liquid as the catalyst. Moreover, this demonstrates the potential of this ionic liquid in organic synthesis and lots of promises for further useful applications.
4.1.4b.3. EXPERIMENTAL

All Chemicals used were of commercial grade and they were used without any further purification. Melting points were measured in open capillaries and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F\textsubscript{254} (Merck). \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Bruker Avance 400 MHz instrument with TMS as an internal standard.

4.1.4b.3.1. General procedure for the synthesis of tetrahydrobenzo[b]pyran derivatives by grinding

A mixture of aldehyde (10 mmol), malononitrile (10 mmol), dimedone (10 mmol) and 3.03 mol\% ionic liquid was thoroughly mixed in a mortar followed by grinding for appropriate time period till the completion of reaction as indicated by TLC (Table 4.1.4b.2). After completion of the reaction, water was added and the mixture was filtered to separate the ionic liquid. Water was evaporated under reduced pressure to recover the ionic liquid which was reused to perform subsequent model reaction. For the purification of the product, the precipitates were washed with cold aqueous ethanol and recrystallized from hot ethanol to give the purified product.
4.1.4c.1. CHARACTERIZATION

All the synthesized tetrahydrobenzo[b]pyran derivatives were characterized by $^1$H NMR and $^{13}$C NMR techniques. Additional confirmation was obtained by IR and mass spectrometry analysis of some representative compounds. $^1$H NMR and $^{13}$C NMR spectra were recorded on BRUKER AVANCE 400 MHz spectrometer using DMSO-$d_6$ as the solvent with TMS as an internal standard. Mass spectra were recorded on SHIMADZU GCMS QP 2010 instrument. FT IR spectra were recorded on FTIR Perkin Elmer Spectrum 100 spectrometer using KBr. The representative spectra are included at the end of the section for perusal. The $^1$H NMR data is interpreted in terms of number of protons, splitting pattern and their relative $\delta$ values. $^1$H NMR spectra for compounds 4a and 4b are given in Figures 4.1.4c.1 and 4.1.4c.5 respectively. $^{13}$C NMR spectra for the same compounds are described in Figures 4.1.4c.2 and 4.1.4c.6 respectively. The infrared spectra of these compounds are given in Figures 4.1.4c.3 and 4.1.4c.7 respectively. Mass spectra for the same compounds are described in Figures 4.1.4c.4 and 4.1.4c.8 respectively. The $^{13}$C NMR spectra of these compounds exhibited signals in the carbonyl, cyano, aromatic and aliphatic regions. For all the compounds, the spectra showed five quaternary carbon signals, one tertiary carbon signal and two secondary carbon signals. In $^{13}$C NMR spectra, two signals for C-2 and C-8a (Fig. 4.1.4c.1) are observed at higher $\delta$ values than expected for typical olefinic carbons. In contrast, carbons C-3 and C-4a appeared at unusually lower $\delta$ values. These findings could be accounted for the strong push–pull effect of the groups linked to the olefinic double bond. The carbonyl carbon in these systems resonates in the narrow range 195–197 ppm. The cyano carbon appears at 119–121 ppm. The signal at around $\delta$ 59.00 ppm is assigned to carbon attached with carbonitrile while signals around $\delta$ 127.03-145.21 ppm are attributed to all the aromatic carbons of the compounds. $^1$H NMR spectrum indicated the presence of one singlet in the range $\delta$ 4.032-4.389 ppm of -CH proton. Moreover, singlet in the range $\delta$ 6.949-7.263 ppm and multiplets in the range $\delta$ 6.522-7.346 ppm have appeared for amine and aromatic protons respectively. The molecular structures and characterization data for all synthesized tetrahydrobenzo[b]pyran derivatives are given below in tabular form.
Figure 4.1.4c.1 General structure of 4H-chromene derivatives
**2-Amino-3-cyano-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4a)**

<table>
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<th>Value</th>
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<td>Molecular Formula</td>
<td>C\textsubscript{19}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4}</td>
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<tr>
<td>Molecular Weight (gm·mol\textsuperscript{-1})</td>
<td>340.37</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>231-233</td>
</tr>
</tbody>
</table>

\[\text{H NMR} \ (400 \text{ MHz, DMSO}): \delta 8.805 \ (s, 1H), 6.906 \ (s, 2H), 6.522-6.697 \ (m, 3H), 4.092 \ (s, 1H), 3.724 \ (s, 3H), 2.539 \ (d, 1H, J 18.4 Hz), 2.475 \ (d, 1H, J 18.4 Hz), 2.264 \ (d, 1H / 16.0 Hz), 2.117 \ (d, 1H / 16.0 Hz), 1.046 \ (s, 3H), 0.981 \ (s, 3H)\]

\[\text{C NMR:} \ \delta 196.13, 162.61, 158.85, 147.72, 145.74, 136.29, 120.32, 119.87, 115.82, 113.53, 111.96, 59.26, 56.08, 50.53, 35.46, 32.21, 28.99, 27.11\]

\[\text{IR (KBr):} 3498 \ (\text{OH}), 3404, 3324 \ (\text{NH}_2), 2192 \ (\text{CN}), 169 \ (\text{C=O}), 1215 \ (\text{C-O}) \ \text{cm}^{-1}\]

\[\text{LC-MS data:} \ m/z = 341.0 \ (\text{M}^+ + 1)\]

**Elemental Analysis:** Calc.: C, 67.05; H, 5.92; N, 8.23%. Found: C, 67.29; H, 5.87; N, 8.38%

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**2-Amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4b)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
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<tr>
<td>Molecular Formula</td>
<td>C\textsubscript{18}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}</td>
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<tr>
<td>Molecular Weight (gm·mol\textsuperscript{-1})</td>
<td>294.35</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>230-232</td>
</tr>
</tbody>
</table>

\[\text{H NMR} \ (400 \text{ MHz, DMSO}): \delta 7.146-7.314 \ (m, 5H), 6.998 \ (s, 2H), 4.189 \ (s, 1H), 2.526 \ (s, 2H), 2.264 \ (d, 2H, J 16.0 Hz), 2.115 \ (d, J 16.0 Hz, 2H), 1.050 \ (s, 3H), 0.967 \ (s, 3H)\]

\[\text{C NMR:} \ \delta 196.08, 162.94, 158.98, 145.21, 128.79, 127.62, 127.03, 120.17, 113.25, 58.84, 50.47, 36.07, 32.27, 28.87, 27.29\]

\[\text{IR (KBr):} 3397, 3324 \ (\text{NH}_2), 2192 \ (\text{CN}), 1682 \ (\text{C=O}), 1215 \ (\text{C-O}) \ \text{cm}^{-1}\]

\[\text{LC-MS data:} \ m/z = 294.9 \ (\text{M}^+ + 1)\]

**Elemental Analysis:** Calc.: C, 73.45; H, 6.16; N, 9.52%. Found: C, 73.56; H, 6.22; N, 9.48%
### 2-Amino-3-cyano-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4c)

**Molecular Formula**  
C\textsubscript{18}H\textsubscript{17}N\textsubscript{3}O\textsubscript{4}

**Molecular Weight (gm·mol\textsuperscript{-1})**  
339.35

**Melting Point (\degree C)**  
180-181

\textsuperscript{1}H NMR (400 MHz, DMSO): δ 8.161 (d, 2H, J 8.0 Hz), 7.432 (d, 2H, J 8.0 Hz), 7.263 (s, 2H), 4.383 (s, 2H), 2.571 (s, 2H), 2.250 (d, 1H, J 16 Hz), 2.085 (d, 1H, J 16 Hz), 2.063 (s, 3H), 0.986 (s, 3H)

\textsuperscript{13}C NMR: δ 196.12, 162.90, 158.94, 145.17, 128.83, 127.58, 126.99, 120.21, 113.21, 58.88, 50.51, 36.11, 32.23, 28.83, 27.25

IR (KBr): 3418, 3375 (NH\textsubscript{2}), 2189 (CN), 1682 (C=O), 1221 (C=O) cm\textsuperscript{-1}

**Elemental Analysis:**  
Calc.: C, 63.71; H, 5.05; N, 12.38%. Found: C, 63.76; H, 5.11; N, 12.33%

### 2-Amino-3-cyano-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4d)

**Molecular Formula**  
C\textsubscript{19}H\textsubscript{20}N\textsubscript{2}O\textsubscript{3}

**Molecular Weight (gm·mol\textsuperscript{-1})**  
324.37

**Melting Point (\degree C)**  
200-201

\textsuperscript{1}H NMR (400 MHz, DMSO): δ 7.037 (d, 2H, J 8.6 Hz), 6.824 (d, 2H, J 8.6 Hz), 6.923 (s, 2H), 4.166 (s, 1H), 3.679 (s, 3H), 2.471 (s, 2H), 2.243 (d, 1H, J 16.4 Hz), 2.076 (d, 1H, J 16.4 Hz), 1.047 (s, 3H), 0.957 (s, 3H)

\textsuperscript{13}C NMR: δ 196.11, 162.97, 158.95, 145.24, 128.82, 127.65, 127.06, 120.20, 113.28, 58.87, 55.13, 50.59, 36.13, 32.33, 28.93, 27.33

IR (KBr): 3378, 3318 (NH\textsubscript{2}), 2198 (CN), 1683 (C=O), 1194, 1034 (C=O) cm\textsuperscript{-1}

**Elemental Analysis:**  
Calc.: C, 70.35; H, 6.21; N, 8.64%. Found: C, 70.39; H, 6.27; N, 8.68%
2-Amino-3-cyano-4-(2-furyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (4e)

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>C_{16}H_{16}N_{2}O_{3}</th>
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<tr>
<td>Molecular Weight (gm·mol(^{-1}))</td>
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<td>Melting Point (°C)</td>
<td>226-228</td>
</tr>
</tbody>
</table>

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 6 7.124 (s, 1H), 7.020 (s, 2H), 6.610 (s, 1H), 6.342 (s, 1H), 4.211 (s, 1H), 2.548 (s, 2H), 2.261 (d, 1H, J = 16.4 Hz), 2.192 (d, 1H, J = 16.4 Hz), 1.072 (s, 3H), 0.989 (s, 3H)

\(^1\)C NMR: 6 195.89, 162.75, 158.79, 156.12, 145.28, 120.01, 113.06, 111.91, 107.56, 58.65, 50.28, 35.88, 32.08, 28.68, 27.10

IR (KBr): 3327, 3213 (NH\(_2\)), 2187 (CN), 1678 (C=O), 1211 (C–O) cm\(^{-1}\)

Elemental Analysis: Calc.: C, 67.59; H, 5.67; N, 9.85%. Found: C, 67.81; H, 5.72; N, 9.63%

2-Amino-3-cyano-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (4f)

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>C_{18}H_{17}ClN_{2}O_{2}</th>
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<tbody>
<tr>
<td>Molecular Weight (gm·mol(^{-1}))</td>
<td>328.79</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>209-210</td>
</tr>
</tbody>
</table>

\(^1\)H NMR (400 MHz, DMSO): 6 7.241 (d, 2H, J = 8.4 Hz), 7.183 (d, 2H, J = 8.4 Hz), 7.078 (s, 2H), 4.210 (s, 1H), 2.495 (s, 2H), 2.241 (d, 1H, J = 16.0 Hz), 2.162 (d, 1H, J = 16.0 Hz), 1.048 (s, 3H), 0.952 (s, 3H)

\(^1\)C NMR: 6 196.15, 162.87, 158.91, 145.14, 128.72, 127.69, 127.11, 120.24, 113.18, 58.77, 50.40, 40.11, 36.14, 32.34, 28.94, 27.36

IR (KBr): 3379, 3325 (NH\(_2\)), 2189 (CN), 1674 (C=O), 1215 (C–O) cm\(^{-1}\)

Elemental Analysis: Calc.: C, 65.75; H, 5.21; N, 8.52%. Found: C, 65.93; H, 5.47; N, 8.46%
2-Amino-3-cyano-4-(3-nitrophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4g)

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<th>Value</th>
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<tr>
<td>Molecular Formula</td>
<td>C_{18}H_{17}N_{3}O_{4}</td>
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<tr>
<td>Molecular Weight (gm·mol⁻¹)</td>
<td>339.35</td>
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<tr>
<td>Melting Point (°C)</td>
<td>210-212</td>
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</tbody>
</table>

**¹H NMR** (400 MHz, DMSO): δ 7.174–7.342 (m, 4H), 7.026 (s, 2H), 4.217 (s, 1H), 2.554 (s, 2H), 2.224 (d, 1H, J 16.4 Hz), 2.146 (d, 1H, J 16.4 Hz), 1.120 (s, 3H), 0.978 (s, 3H)

**¹³C NMR:** δ 196.13, 162.97, 158.96, 145.25, 130.43, 128.81, 127.07, 120.22, 113.29, 58.86, 50.52, 40.12, 36.12, 32.33, 28.91, 27.33

**IR** (KBr): 3437, 3333 (NH₂), 2199 (CN), 1674 (C=O), 1221 (C–O) cm⁻¹

**Elemental Analysis:** Calc.: C, 63.71; H, 5.05; N, 12.38%. Found: C, 63.84; H, 5.01; N, 12.39%

2-Amino-3-cyano-4-(2-nitrophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4h)

<table>
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<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_{18}H_{17}N_{3}O_{4}</td>
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<td>Molecular Weight (gm·mol⁻¹)</td>
<td>339.35</td>
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<td>Melting Point (°C)</td>
<td>228-230</td>
</tr>
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</table>

**¹H NMR** (400 MHz, DMSO): δ 7.305–7.127 (m, 4H), 7.057 (s, 2H), 4.248 (s, 1H), 2.467 (dd, J=18.0, 2H), 2.231 (d, 1H, J 16.4 Hz), 2.130 (d, 1H, J 16.4 Hz), 1.011 (s, 3H), 0.991 (s, 3H)

**¹³C NMR:** 196.27, 162.75, 158.79, 145.02, 128.60, 127.43, 126.84, 119.98, 113.44, 59.03, 50.66, 36.26, 32.08, 28.68, 27.10

**IR** (KBr): 3471, 3334 (NH₂), 2193 (CN), 1687 (C=O), 1143 (C–O) cm⁻¹

**Elemental Analysis:** Calc.: C, 63.71; H, 5.05; N, 12.38%. Found: C, 63.80; H, 5.11; N, 12.43%
2-Amino-3-cyano-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (4i)

**Molecular Formula**  
C$_{18}$H$_{17}$ClN$_2$O$_2$

**Molecular Weight (gm·mol$^{-1}$)**  
328.79

**Melting Point (°C)**  
216-218

$^1$H NMR (400 MHz, DMSO): $\delta$ 7.158–7.326 (m, 4H), 7.010 (s, 2H), 4.201 (s, 1H), 2.538 (dd, $J$=18.4, 2H), 2.220 (d, 1H, $J$ 15.6 Hz), 2.132 (d, 1H, $J$ 15.6 Hz), 1.062 (s, 3H), 0.979 (s, 3H)

$^{13}$C NMR: $\delta$ 196.18, 162.86, 158.89, 145.12, 129.01, 128.70, 127.57, 127.12, 120.08, 113.16, 58.75, 50.38, 40.50, 36.16, 32.18, 28.78, 27.20

IR (KBr): 3396, 3330 (NH$_2$), 2196 (CN), 1674 (C=O), 1215 (C–O) cm$^{-1}$

**Elemental Analysis:** Calc.: C, 65.75; H, 5.21; N, 8.52%. Found: C, 65.71; H, 5.32; N, 8.58%

2-Amino-3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (4j)

**Molecular Formula**  
C$_{18}$H$_{17}$FN$_2$O$_2$

**Molecular Weight (gm·mol$^{-1}$)**  
312.34

**Melting Point (°C)**  
188-189

$^1$H NMR (400 MHz, DMSO): $\delta$ : 7.298 (d, 2H, $J$ 8.0 Hz), 7.153 (d, 2H, $J$ 8.0 Hz), 7.014 (s, 2H), 4.173 (s, 1H), 2.510 (s, 2H), 2.294 (d, 1H, $J$ 16.4 Hz), 2.126 (d, 1H, $J$ 16.4 Hz), 1.034 (s, 3H), 0.951 (s, 3H)

$^{13}$C NMR: $\delta$ 196.10, 162.96, 159.01, 154.23, 128.81, 127.84, 127.25, 120.19, 113.37, 58.86, 50.51, 37.09, 32.32, 28.89, 27.31

IR (KBr): 3390, 3285 (NH$_2$), 2198 (CN), 1690 (C=O), 1215 (C–O) cm$^{-1}$

**Elemental Analysis:** Calc.: C, 69.22; H, 5.49; N, 8.97%. Found: C, 69.35; H, 5.38; N, 8.88%
2-Amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-7,7-
dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4k)

<table>
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<td>Melting Point (°C)</td>
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\(^{1}\text{H NMR}\) (400 MHz, DMSO): δ 6.998 (s, 2H), 6.621 (s, 2H), 4.032 (s, 1H), 3.854 (s, 6H), 3.801 (s, 3H), 2.454 (s, 2H), 2.241 (d, 2H, J = 16.0 Hz), 2.171 (d, 2H, J = 16.0 Hz), 1.032 (s, 3H), 0.954 (s, 3H)

\(^{13}\text{C NMR}\): δ 195.92, 162.78, 158.82, 156.45, 145.05, 137.36, 120.17, 113.25, 106.98, 60.78, 58.84, 56.17, 50.31, 40.96, 36.23, 32.11, 28.71, 27.13

\(\text{IR (KBr)}\): 3382, 3150 (NH\(_2\)), 2205 (CN), 1670 (C=O), 1215 (C–O) cm\(^{-1}\)

\(\text{Elemental Analysis:}\) Calc.: C, 65.61; H, 6.29; N, 7.29%. Found: C, 65.42; H, 6.15; N, 7.50%

2-Amino-3-cyano-4-(4-dimethylaminophenyl)-7,7-
dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4l)

<table>
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<tr>
<th>Molecular Formula</th>
<th>C_{20}H_{23}N_{3}O_{2}</th>
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\(^{1}\text{H NMR}\) (400 MHz, DMSO): δ 6.981 (d, 2H, J = 8.4 Hz), 6.831 (d, 2H, J = 8.4 Hz), 6.874 (s, 2H), 4.119 (s, 1H), 2.911 (s, 6H), 2.536 (dd, J = 18.0, 2H), 2.237 (d, 2H, J = 16.4 Hz), 2.071 (d, 2H, J = 16.4 Hz), 1.064 (s, 3H), 0.977 (s, 3H)

\(^{13}\text{C NMR}\): δ 196.16, 162.86, 158.89, 145.29, 128.71, 127.74, 127.11, 120.25, 113.17, 58.76, 50.39, 42.10, 41.90, 40.38, 36.15, 32.19, 28.79, 27.21

\(\text{IR (KBr)}\): 3372, 3231 (NH\(_2\)), 2197 (CN), 1671 (C=O), 1218 (C–O) cm\(^{-1}\)

\(\text{Elemental Analysis:}\) Calc.: C, 71.19; H, 6.87; N, 12.45%. Found: C, 71.22; H, 6.82; N, 12.31%
2-Amino-3-cyano-4-(2-thienyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzo[b]pyran (4m)

Molecular Formula \( \text{C}_{16}\text{H}_{16}\text{N}_{2}\text{O}_{2}\text{S} \)
Molecular Weight (\( \text{gm}\cdot\text{mol}^{-1} \)) 300.38
Melting Point (\(^{\circ}\text{C} \)) 215-216

\(^1\text{H NMR}\) (400 MHz, DMSO): \( \delta \) 7.314 (d, 1H, J 5.2 Hz), 7.120 (s, 2H), 6.901 (dd, 1H, J 3.2 Hz), 6.852 (d, 1H, J 3.2 Hz), 4.536 (s, 1H), 2.498 (s, 2H), 2.273 (d, 1H, J 16.0 Hz), 2.202 (d, 1H, J 16.0 Hz), 1.042 (s, 3H), 0.979 (s, 3H)

\(^{13}\text{C NMR}\): \( \delta \) 196.08, 162.83, 159.47, 156.96, 147.58, 120.45, 113.76, 111.24, 107.88, 59.36, 50.95, 36.08, 31.97, 28.86, 27.22

IR (KBr): 3384, 3132 (NH\(_2\)), 2198 (C=O), 1676 (C=O), 1215 (C–O) cm\(^{-1}\)

Elemental Analysis: Calc.: C, 63.93; H, 5.37; N, 9.33%. Found: C, 64.12; H, 5.26; N, 9.55%

2-Amino-3-cyano-4-(5-methyl-2-furyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4n)

Molecular Formula \( \text{C}_{17}\text{H}_{18}\text{N}_{2}\text{O}_{3} \)
Molecular Weight (\( \text{gm}\cdot\text{mol}^{-1} \)) 298.34
Melting Point (\(^{\circ}\text{C} \)) 203-204

\(^1\text{H NMR}\) (400 MHz, DMSO): \( \delta \) 6.932 (s, 2H), 6.101 (m, 2H), 4.336 (s, 1H), 2.506 (s, 2H), 2.269 (d, 1H, J 16.0 Hz), 2.231 (d, 1H, J 16.0 Hz), 2.18 (s, 3H), 1.045 (s, 3H), 0.991 (s, 3H)

\(^{13}\text{C NMR}\): \( \delta \) 194.98, 162.57, 158.75, 156.67, 146.76, 119.96, 113.61, 110.68, 107.32, 58.19, 49.68, 35.32, 32.70, 28.59, 27.00, 13.26

IR (KBr): 3376, 3210 (NH\(_2\)), 2204 (CN), 1675 (C=O), 1218 (C–O) cm\(^{-1}\)

Elemental Analysis: Calc.: C, 68.44; H, 6.08; N, 9.39%. Found: C, 68.57; H, 6.17; N, 9.31%
2-Amino-3-cyano-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4o)

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>C_{19}H_{20}N_{2}O_{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight (gm·mol⁻¹)</td>
<td>308.37</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>225-226</td>
</tr>
</tbody>
</table>

\(^1H\) NMR (400 MHz, DMSO): δ 7.174 (d, 2H, J 8.4 Hz), 7.057 (d, 2H, J 8.4 Hz), 6.983 (s, 2H), 4.101 (s, 1H), 2.495 (s, 2H), 2.293 (s, 3H), 2.221 (d, 1H, J 16.0 Hz), 2.106 (d, 1H, J 16.0 Hz), 1.084 (s, 3H), 0.982 (s, 3H)

\(^13C\) NMR: δ 196.55, 163.21, 159.33, 142.75, 136.53, 129.80, 128.00, 127.21, 120.71, 113.77, 59.30, 50.89, 40.12, 36.09, 32.72, 29.36, 27.66, 21.52

IR (KBr): 3398, 3329 (NH\(_2\)), 2195 (CN), 1672 (C=O), 1213 (C–O) cm\(^{-1}\)

**Elemental Analysis:** Calc.: C, 74.00; H, 6.54; N, 9.08%. Found: C, 74.10; H, 6.57; N, 9.13%
Figure 4.1.4c.1 $^1$H NMR spectrum of compound 4a

Figure 4.1.4c.2 $^{13}$C NMR spectrum of compound 4a
Figure 4.1.4c.3 IR spectrum of compound 4a

Figure 4.1.4c.4 Mass spectrum of compound 4a
Figure 4.1.4c.5 $^1$H NMR spectrum of compound 4b

Figure 4.1.4c.6 $^{13}$C NMR spectrum of compound 4b
Figure 4.1.4c.7 IR spectrum of compound 4b

Figure 4.1.4c.8 Mass spectrum of compound 4b
Synthesis of dihydropyranoc[c] chromenes by Conventional energy source
4.2.4a.1. RESULT AND DISCUSSION

4.2.4a.1.1. Scheme

The synthesis of dihydropyranoc[chromen]es 4 (Scheme 4.2.4a.1) was carried out by one-pot multicomponent condensation reaction of 4-hydroxy coumarin 1, different aromatic/heterocyclic aldehydes 2 and malononitrile 3 in presence of basic ionic liquid [DBU][Ac] by stirring at ambient temperature in methanol as co-solvent. The most optimum reaction condition and the role of ionic liquid to accelerate the reaction are discussed in detail in this part.

![Scheme 4.2.4a.1 Present protocol for the synthesis of dihydropyranoc[chromen]es at ambient temperature](image)

4.2.4a.1.2. Reaction Optimization

Initially, the optimum reaction condition was derived for the typical reaction of 4-chlorobenzaldehyde, 4-hydroxycoumarin and malononitrile in the presence of different amounts of ionic liquid [DBU][Ac](0–8.82 mol%) in methanol as co-solvent at room temperature (Table 4.2.4a.1, entries 1-6). Upon examining the influence of the amount of ionic liquid on the reaction, it was found that without ionic liquid the reaction did not proceeded (Table 4.2.4a.1, entry1). It was observed that 6.06 mol% of ionic liquid was sufficient to promote the reaction efficiently. The yield was found to decrease significantly below 6.06 mol% of ionic liquid even after prolonging the duration. When the amount of ionic liquid was increased above 6.06 mol% equivalent, no significant improvement was observed in reaction yield as well as in duration of the reaction. A brief screening of solvents showed that water, THF, methylene dichloride, acetonitrile and toluene were less effective than methanol (Table 4.1.4a.1, entries 7-11).
The best result was achieved by carrying out the reaction with 1:1:1.2 molar ratio of 4-chlorobenzaldehyde: 4-hydroxycoumarin: malononitrile at 25°C in presence of ionic liquid (6.06 mole %) in methanol as co-solvent.

**Table 4.2.4a.1 The effect of reaction condition on the synthesis of 4a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic Liquid</th>
<th>Co-Solvent</th>
<th>Mol%</th>
<th>Time /min</th>
<th>Yieldb / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>0</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>1.53</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>3.03</td>
<td>20</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>4.62</td>
<td>10</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>6.06</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>[DBU][Ac]</td>
<td>Methanol</td>
<td>8.82</td>
<td>5</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>[DBU][Ac]</td>
<td>Water</td>
<td>6.06</td>
<td>30c</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>[DBU][Ac]</td>
<td>THF</td>
<td>6.06</td>
<td>30</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>[DBU][Ac]</td>
<td>MDC</td>
<td>6.06</td>
<td>20</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>[DBU][Ac]</td>
<td>Acetonitrile</td>
<td>6.06</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>[DBU][Ac]</td>
<td>Toluene</td>
<td>6.06</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>DBU</td>
<td>Methanol</td>
<td>6.06</td>
<td>10</td>
<td>68</td>
</tr>
</tbody>
</table>

a All reactions were carried out of 4-chlorobenzaldehyde: 4-hydroxycoumarin: malononitrile 1:1:1.2 (molar ratio) at room temperature in ionic liquids

b Yield refer to pure isolated products

c The reaction was conducted in water under reflux for 30 min
4.2.4a.1.3. Generalization for the protocol giving dihydropyrano[c]chromenes derivatives

Based on above optimization, a number of dihydropyrano[c]chromenes derivatives were successfully synthesized using 6.06 mol% of IL at RT from variety of aldehydes. All the reactions were observed to be very fast and good yielding compared to other existing procedures. Electronic effects and the nature of substituents on the aromatic ring showed strong obvious effects in terms of reaction time under these reaction conditions. The aromatic aldehydes with electron- withdrawing groups reacted faster as compared to those having electron- donating groups. (Table 4.2.4a.2). No side reactions were observed in any of the reactions performed.

Table 4.2.4a.2 Synthesis of dihydropyrano[c]chromenes derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Timea (min.)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4-Cl C₆H₄</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>4b</td>
<td>C₆H₅</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>4c</td>
<td>4-NO₂C₆H₄</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>4d</td>
<td>4-OCH₃C₆H₄</td>
<td>14</td>
<td>92</td>
</tr>
<tr>
<td>4e</td>
<td>3-NO₂C₆H₄</td>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>4f</td>
<td>2-NO₂C₆H₄</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>4g</td>
<td>2-Cl C₆H₄</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>4h</td>
<td>4-F C₆H₄</td>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>4i</td>
<td>4-Me-C₆H₄</td>
<td>7</td>
<td>91</td>
</tr>
<tr>
<td>4j</td>
<td>4-Br C₆H₄</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>4k</td>
<td>4-(CH₃)₂NC₆H₄</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>4l</td>
<td>3,4-(OCH₃)₂C₆H₃</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>4m</td>
<td>3,4,5-(OCH₃)₃C₆H₂</td>
<td>6</td>
<td>89</td>
</tr>
</tbody>
</table>
All the reactions were run till the completion as indicated by TLC.

Isolated yield

All the reactions were monitored by TLC and proceeded to completion. All the synthesized compounds were crystallized by using ethanol. All the compounds were characterized by melting point, $^1$H NMR, $^{13}$C NMR spectral techniques. Additional conformation for the structures is also obtained by IR and Mass spectrometric studies for the representative samples from the series.

### 4.2.4a.1.4. Mechanism

A plausible reaction mechanism is proposed in scheme 4.2.4a.2. In first step, aldehyde is condensed with malononitrile by Knoevenagel condensation to afford the $\alpha$-cyanocinnamanitrile derivative. In the second step, the active methylene of 4-hydroxycoumarin reacts with electrophilic $\beta$ carbon of C=C of $\alpha$-cyanocinnamanitrile giving the Michael adduct intermediate 5. The later is then cyclised by nucleophilic attack of the carbonyl group on cyano group giving intermediate 6. Finally, the expected product 4 is afforded by tautomerization. Increase in yield of the product may be due to higher basicity, and stability of [DBU][Ac]-H$^+$ species generated in this reaction which may have suppressed the formation of other side products.
4.2.4a.5. Recyclability of ionic liquid

In this study, the recycling of basic ionic liquid [DBU][Ac] has also been investigated by using reaction of 4-chlorobenzaldehyde, 4-hydroxycoumarin and malononitrile as the model substrates. Since the product is insoluble in the reaction media, it was easily separated by simple filtration. The filtrate containing EtOH:H₂O mixture used for washing the product was heated at 60 °C under reduced pressure (10 mm Hg) for 2 h to obtain IL in almost complete recovery. The recovered IL was subjected to subsequent run of the reaction by charging with the same reactants. As shown in the Fig. 4.2.4a.1, the reaction can be repeated for at least five times without any further purification of recovered ionic liquid.
Chapter 4 Part-II

For Chro

4.2.4a.1 Recyclability of [DBU][Ac] in model reaction

4.2.4a.2. CONCLUSION

In conclusion, there was a successful outcome of versatile and high yielding method for the synthesis of dihydropyrano[c]chromenes derivatives at ambient temperature using 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate ([DBU][Ac]) ionic liquid as catalyst. The procedure is a simple, environmentally friendly technique producing pure target compounds in high yields.

4.1.4a.3. EXPERIMENTAL

All the chemicals were of research grade and used as obtained without any further purification. The reactions were performed in 50 mL round bottom flask.

4.1.4a.3.1. General procedure for the synthesis of dihydropyrano[c]chromenes derivatives

A mixture of 4-hydroxycoumarin 1 (10 mmol), aldehyde 2 (10 mmol), malononitrile 3 (10 mmol) was added to a 50 mL capacity round bottom flask containing 6.06 mol% ionic liquid and 5 mL methanol. The reaction mixture was stirred for the required time as shown in Table 4.2.4a.2. After completion of the reaction (as indicated by TLC), a solid product gradually formed was filtered through small Buchner funnel under vacuum, washed with ethanol-water (1:2)
to leave the crude product which was purified by crystallization in ethanol. The aqueous filtrate containing IL was heated at 60 °C under reduced pressure (10 mm Hg) for 2 h to obtain IL in almost complete recovery. The recovered IL was used in next run without any further purification.
Part - II

Section - 46

Synthesis of dihydropyrano[c] chromenones by Grinding
4.2.4b.1. RESULT AND DISCUSSION

4.2.4b.1.1. Scheme

The synthesis of dihydropyrano[c]chromenes derivatives 4 (Scheme 4.2.4b.1) was carried out by one-pot condensation reaction of 4-hydroxycoumarin 1, various aromatic aldehydes 2, and malononitrile 3 in presence of basic ionic liquid [DBU][Ac] using grindstone chemistry. The sole ionic liquid was found to be effective as a reaction media as well as promoter for the reaction. The detail report is given in following section.

![Scheme 4.2.4b.1 Present protocol for the synthesis of dihydropyrano[c]chromenes by grinding](image)

4.2.4b.1.2. Reaction Optimization

To optimize the reaction conditions, reaction of 4-chlorobenzaldehyde, malononitrile and 4-hydroxycoumarin in presence of [DBU][AC] was selected as the model reaction. Initially the reaction mixture catalyzed by [DBU][AC] was ground in a mortar without solvent at room temperature for 4 min to give corresponding product in 93% yield. The amount of [DBU][AC] was gradually varied from 0 to 6.06 mol% (Table 4.2.4b.1). Reaction did not complete over a period of 30 min in absence of [DBU][AC] and only Knoevenagel product was formed. The best yield was attained by carrying out the reaction with 1:1:1 molar ratio of 4-chlorobenzaldehyde: 4-hydroxycoumarin: malononitrile at 25°C in presence of 3.03 mol% ionic liquid without using any organic solvent.
Table 4.2.4b.1 Screening of amount of ionic liquid for synthesis 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic Liquid</th>
<th>Mol%</th>
<th>Time (min)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[DBU][Ac]</td>
<td>0</td>
<td>30</td>
<td>Knoevenagel product</td>
</tr>
<tr>
<td>2</td>
<td>[DBU][Ac]</td>
<td>1.53</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>[DBU][Ac]</td>
<td>3.03</td>
<td>5</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>[DBU][Ac]</td>
<td>4.62</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>[DBU][Ac]</td>
<td>6.06</td>
<td>5</td>
<td>90</td>
</tr>
</tbody>
</table>

aIsolated yield

4.2.4b.1.3. Generalization of reaction yielding dihydropyrano[c]chromenes derivatives

The scope of the reaction was evaluated for various aldehydes with malononitrile and 4-hydroxycoumarin by applying the optimal conditions (Table 4.2.4b.2). All the reactions were observed to be very fast (2-15 min) and good yielding (89-95%) compared to other existing procedures. Electronic effects and the nature of substituents on the aromatic ring showed strong obvious effects in terms of reaction time under these reaction conditions. The aromatic aldehydes with electron- withdrawing groups reacted faster as compared to those having electron- donating groups.

Table 4.2.4b.2 Synthesis of dihydropyrano[c]chromenes derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Timea (min.)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4-Cl C6H4</td>
<td>3</td>
<td>93</td>
</tr>
<tr>
<td>4b</td>
<td>C6H5</td>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>4c</td>
<td>4-NO2C6H4</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>4d</td>
<td>4-OCH3C6H4</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>4e</td>
<td>3- NO2 C6H4</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>4f</td>
<td>2- NO2 C6H4</td>
<td>4</td>
<td>92</td>
</tr>
</tbody>
</table>
4g 2-Cl C₆H₄ 3 93
4h 4-F C₆H₄ 3 95
4i 4-Me-C₆H₄ 5 91
4j 4-Br C₆H₄ 3 93
4k 4-(CH₃)₂NC₆H₄ 13 91
4l 3,4-(OCH₃)₂C₆H₃ 7 89
4m 3,4,5-(OCH₃)₃C₆H₂ 4 90
4n 2-furyl 2 92
4o 5-Me-2-furyl 6 91

^aAll the reaction were run till the completion as indicated by TLC
^bIsolated yield

### 4.2.4b.1.4. Mechanism

The mechanism for the IL [DBU][Ac] catalysed protocol for the synthesis of dihydropyrano[c]chromenes derivatives follows the same path as shown in section 4.2.4a.1.4.

### 4.2.4b.1.5. Recyclability of ionic liquid

We also investigated the possibility of recycling the catalyst [DBU][Ac]. Catalytic activity of the recovered ionic liquid from the model reaction was checked in the subsequent runs (Figure 4.2.4b.1). The activity of the catalyst did not get much affected in terms of yields after five successive runs for the model reaction. It revealed that the catalyst displayed very good reusability.
In summary, an efficient catalytic activity of [DBU][Ac] is demonstrated for a one-pot synthesis of 3,4-dihydropyrano[c]chromenes derivatives under solvent free conditions at ambient temperature using grinding technique. The isolation procedure is very simple that entails the filtration of the precipitated product in aqueous workup with high yield of pure isolated product. The use of green, non toxic, economical and reusable catalyst [DBU][AC] has rendered this method eco-friendly being a solvent free protocol [71].

4.2.4b.3. EXPERIMENTAL

All Chemicals used were of commercial grade and they were used without any further purification. TLC was carried out using aluminium sheets precoated with silica gel 60 F254 (Merck).

4.1.4b.3.1. General procedure for the synthesis of dihydropyrano[c]chromene derivatives by grinding

A mixture of aldehyde (5 mmol), malononitrile (5 mmol), 4-hydroxycoumarin (5 mmol) and 3.03 mol% ionic liquid was thoroughly mixed in a mortar followed by grinding for appropriate time period till the completion of
reaction as indicated by TLC (Table 4.2.4b.2). After completion of the reaction, water was added and the mixture was filtered to separate the ionic liquid. Water was evaporated under reduced pressure to recover the ionic liquid which was reused to perform subsequent model reaction. For the purification of the product, the precipitates were washed with cold aqueous ethanol and recrystallized from hot ethanol to give the pure product.
Part - II

Spectroscopic Characterization of dihydropyrano[c]chromenes

Section - 4c
4.2.4c.1. CHARACTERIZATION

All the synthesized dihydropyrano[c]chromene derivatives were characterized by $^1$H NMR and $^{13}$C NMR techniques. Additional confirmation was obtained by IR and mass spectrometry analysis of some representative compounds. $^1$H NMR and $^{13}$C NMR spectra were recorded on BRUKER AVANCE 400 MHz spectrometer using DMSO-d$_6$ as the solvent with TMS as an internal standard. Mass spectra were recorded on SHIMADZU GCMS QP 2010 instrument. FT IR spectra were recorded on FTIR Perkin Elmer Spectrum 100 spectrometer using KBr. The representative spectra are included at the end of the section for perusal. The $^1$H NMR data is interpreted in terms of number of protons, splitting pattern and their relative δ values. $^1$H NMR spectra for compounds 4b and 4c are given in Figures 4.2.4c.1 and 4.2.4c.5 respectively. $^{13}$C NMR spectra for the same compounds are described in Figures 4.2.4c.2 and 4.2.4c.6 respectively. The infrared spectra of these compounds are given in Figures 4.2.4c.3 and 4.2.4c.7 respectively. Figures 4.2.4c.4 and 4.2.4c.8 respectively represent mass spectra of compound 4b and 4c. The other parameters like melting points were checked by the standard methods and compared with the reported one if available from the literature. The molecular structures and characterization data for all synthesized dihydropyrano[c]chromene derivatives are given below in tabular form.
### 2-Amino-4-(4-chlorophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4a)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_{19}H_{11}ClN_{2}O_{3}</td>
</tr>
<tr>
<td>Molecular Weight (gm·mol⁻¹)</td>
<td>350.76</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>259-260</td>
</tr>
</tbody>
</table>

**¹H NMR** (400 MHz, DMSO): δ 7.30–7.93 (m, 10H), 4.50 (s, 1H)

**¹³C NMR**: δ 160.0, 158.3, 154.0, 152.7, 142.6, 133.4, 132.1, 130.2, 128.8, 125.3, 123.1, 119.6, 117.0, 113.3, 103.6, 58.4, 36.7

**IR** (KBr): 3404, 3350 (NH₂), 2184 (CN), 1704 (C=O), 1668 (C=C), 1026 (C-O) cm⁻¹

**Elemental Analysis**: Calc.: C, 65.06; H, 3.16; N, 7.99%. Found: C, 65.17; H, 3.12; N, 7.82%

### 2-Amino-4-phenyl-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4b)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_{19}H_{12}N_{2}O_{3}</td>
</tr>
<tr>
<td>Molecular Weight (gm·mol⁻¹)</td>
<td>316.31</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>257-259</td>
</tr>
</tbody>
</table>

**¹H NMR** (400 MHz, DMSO): δ 7.23–7.91 (m, 11H), 4.46 (s, 1H)

**¹³C NMR**: δ 159.9, 158.4, 153.9, 152.6, 143.8, 133.4, 128.9, 128.1, 127.6, 125.1, 122.9, 119.6, 117.0, 113.4, 104.5, 58.5, 37.4

**IR** (KBr): 3369, 3333 (NH₂), 2195 (CN), 1717 (C=O), 1672 (C=C), 1054 (C-O) cm⁻¹

**LC-MS data**: m/z = 314.98 (M⁻ - 1)

**Elemental Analysis**: Calc.: C, 72.15; H, 3.82; N, 8.86%. Found: C, 72.19; H, 3.72; N, 8.83%
### 2-Amino-4-(4-nitrophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4c)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C(<em>{19})H(</em>{11})N(<em>{3})O(</em>{5})</td>
</tr>
<tr>
<td>Molecular Weight (gm·mol(^{-1}))</td>
<td>361.31</td>
</tr>
<tr>
<td>Melting Point ((^\circ)C)</td>
<td>260-261</td>
</tr>
</tbody>
</table>

**\(^1\)H NMR** (400 MHz, DMSO): δ 7.47–8.19 (m, 10H), 4.68 (s, 1H)

**\(^{13}\)C NMR:** δ 160.0, 158.5, 154.4, 152.7, 151.2, 147.0, 133.6, 129.7, 129.6, 125.1, 124.7, 124.1, 123.0, 119.3, 117.0, 113.3, 103.2, 57.2

**IR** (KBr): 3374, 3285 (NH\(_2\)), 2196 (CN), 1709 (C=O), 1674 (C=C), 1056 (C-O) cm\(^{-1}\)

**LC-MS data:** \(m/z = 361.9\) (M\(^+\) + 1)

**Elemental Analysis:** Calc.: C, 63.16; H, 3.07; N, 11.63%. Found: C, 63.19; H, 3.10; N, 11.67%

### 2-Amino-4-(4-methoxyphenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4d)

<table>
<thead>
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<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C(<em>{20})H(</em>{14})N(<em>{2})O(</em>{4})</td>
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<tr>
<td>Molecular Weight (gm·mol(^{-1}))</td>
<td>346.34</td>
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<td>Melting Point ((^\circ)C)</td>
<td>240-242</td>
</tr>
</tbody>
</table>

**\(^1\)H NMR** (400 MHz, DMSO): δ 6.87–7.90 (m, 10H), 4.40 (s, 1H), 3.72 (s, 3H)

**\(^{13}\)C NMR:** δ 160.0, 158.8, 158.4, 153.7, 152.6, 135.9, 133.3, 129.2, 125.1, 122.9, 119.8, 117.0, 114.3, 113.5, 104.7, 58.6, 55.5, 36.6

**IR** (KBr): 3426, 3380 (NH\(_2\)), 2199 (CN), 1710 (C=O), 1681 (C=C), 1040 (C-O) cm\(^{-1}\)

**Elemental Analysis:** Calc.: C, 69.36; H, 4.07; N, 8.09%. Found: C, 69.32; H, 4.03; N, 8.13%
### 2-Amino-4-(3-nitrophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4e)

<table>
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<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_{19}H_{11}N_{3}O_{5}</td>
</tr>
<tr>
<td>Molecular Weight (gm·mol⁻¹)</td>
<td>361.31</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>256-258</td>
</tr>
</tbody>
</table>

**1H NMR (400 MHz, DMSO):** δ 7.54–8.12 (m, 10H), 4.72 (s, 1H)

**13C NMR:** δ 160.5, 159.0, 154.8, 153.1, 148.7, 146.4, 135.6, 134.0, 130.9, 125.5, 123.5, 123.3, 123.1, 119.8, 117.4, 113.8, 103.7, 57.8

**IR (KBr):** 3383, 3314 (NH₂), 2194 (CN), 1715 (C=O), 1675 (C=C), 1058 (C-O) cm⁻¹

**Elemental Analysis:** Calc.: C, 63.16%; H, 3.07%; N, 11.63%. Found: C, 63.08%; H, 3.01%; N, 11.57%

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### 2-Amino-4-(2-nitrophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4f)

<table>
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<th>Property</th>
<th>Value</th>
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<td>Molecular Formula</td>
<td>C_{19}H_{11}N_{3}O_{5}</td>
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<tr>
<td>Molecular Weight (gm·mol⁻¹)</td>
<td>361.31</td>
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<tr>
<td>Melting Point (°C)</td>
<td>209-210</td>
</tr>
</tbody>
</table>

**1H NMR (400 MHz, DMSO):** δ 7.37–8.16 (m, 10H), 4.56 (s, 1H)

**13C NMR:** δ 160.4, 158.9, 154.4, 153.1, 143.1, 133.8, 132.6, 130.5, 129.3, 125.4, 123.4, 119.8, 117.3, 113.6, 104.4, 58.7

**IR (KBr):** 3378, 3296 (NH₂), 2196 (CN), 1709 (C=O), 1674 (C=C), 1046 (C-O) cm⁻¹

**Elemental Analysis:** Calc.: C, 63.16%; H, 3.07%; N, 11.63%. Found: C, 63.27%; H, 3.19%; N, 11.56%
**2-Amino-4-(2-chlorophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4g)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>$C_{19}H_{11}ClN_2O_3$</td>
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<tr>
<td>Molecular Weight (gm·mol$^{-1}$)</td>
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<td>Melting Point (°C)</td>
<td>245-246</td>
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</tbody>
</table>

$^1$H NMR (400 MHz, DMSO): δ 7.15–7.89 (m, 10H), 4.46 (s, 1H)

$^{13}$C NMR: δ 161.5, 157.7, 155.6, 152.1, 143.1, 135.8, 132.9, 131.8, 128.4, 126.4, 122.4, 119.6, 118.3, 112.8, 105.4, 57.6

IR (KBr): 3396, 3350 (NH$_2$), 2196 (CN), 1725 (C=O), 1672 (C=C), 1021 (C-O) cm$^{-1}$

**Elemental Analysis:** Calc.: C, 65.06; H, 3.16; N, 7.99%. Found: C, 65.19; H, 3.09; N, 8.02%

---

**2-Amino-4-(4-flourophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (4h)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>$C_{19}H_{11}FN_2O_3$</td>
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<tr>
<td>Molecular Weight (gm·mol$^{-1}$)</td>
<td>334.30</td>
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<tr>
<td>Melting Point (°C)</td>
<td>258-259</td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz, DMSO): δ 7.12–7.95 (m, 10H), 4.58 (s, 1H)

$^{13}$C NMR: δ 161.7, 159.3, 157.9, 153.4, 152.0, 139.2, 132.5, 129.4, 124.7, 122.5, 119.2, 116.8, 115.3, 112.8, 103.7, 57.1, 36.6

IR (KBr): 3378, 3316 (NH$_2$), 2191 (CN), 1714 (C=O), 1673 (C=C), 1025 (C-O) cm$^{-1}$

**Elemental Analysis:** Calc.: C, 68.26; H, 3.32; N, 8.38%. Found: C, 68.29; H, 3.37; N, 8.31%
**2-Amino-4-(4-methylphenyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one (4i)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_{20}H_{14}N_{2}O_{3}</td>
</tr>
<tr>
<td>Molecular Weight (g·mol(^{-1}))</td>
<td>330.34</td>
</tr>
<tr>
<td>Melting Point (°C)</td>
<td>253-255</td>
</tr>
</tbody>
</table>

\(^1\)H NMR (400 MHz, DMSO):  δ 7.12–7.93 (m, 10H), 4.40 (s, 1H), 2.25 (s, 3H)

\(^1^3\)C NMR:  δ 160.3, 158.9, 154.4, 153.1, 144.1, 133.8, 131.7, 130.5, 129.3, 125.4, 122.4, 119.9, 118.3, 115.8, 103.4, 59.7, 20.9

IR (KBr): 3402, 3359 (NH\(_2\)), 2196 (CN), 1722 (C=O), 1673 (C=C), 1029 (C-O) cm\(^{-1}\)

Elemental Analysis: Calc.: C, 72.72; H, 4.27; N, 8.48%. Found: C, 72.69; H, 4.27; N, 8.52%

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**2-Amino-4-(4-bromophenyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one (4j)**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_{19}H_{11}BrN_{2}O_{3}</td>
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<tr>
<td>Molecular Weight (g·mol(^{-1}))</td>
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<td>Melting Point (°C)</td>
<td>253-255</td>
</tr>
</tbody>
</table>

\(^1\)H NMR (400 MHz, DMSO):  δ 7.24–7.92 (m, 10H), 4.48 (s, 1H)

\(^1^3\)C NMR:  δ 160.1, 158.4, 154.0, 152.5, 143.3, 133.6, 131.7, 130.4, 125.2, 124.3, 122.9, 121.1, 116.8, 113.5, 104.0, 58.1, 35.9

IR (KBr): 3414, 3374 (NH\(_2\)), 2193 (CN), 1721 (C=O), 1673 (C=C), 1027 (C-O) cm\(^{-1}\)

Elemental Analysis: Calc.: C, 57.74; H, 2.81; N, 7.09%. Found: C, 57.88; H, 2.77; N, 7.21%
2-Amino-4-(4-dimethylaminophenyl)-3-cyano-4H,5H-pyran\[3,2-c\] chromene-5-one (4k)

Molecular Formula: C_{21}H_{17}N_{3}O_{3}

Molecular Weight (gm·mol^{-1}): 359.38

Melting Point (°C): 265-266

{\textsuperscript{1}H NMR} (400 MHz, DMSO): δ 7.35–8.17 (m, 10H), 4.54 (s, 1H), 2.83 (s, 6H)

{\textsuperscript{13}C NMR}: δ 161.4, 156.4, 154.6, 154.2, 149.7, 134.1, 130.9, 128.4, 124.4, 123.9, 117.6, 116.6, 112.6, 111.7, 100.1, 64.7, 43.0, 39.0

IR (KBr): 3378, 3293 (NH\textsubscript{2}), 2194 (C=O), 1716 (C=O), 1677 (C=C), 1051 (C-O) cm\textsuperscript{-1}

Elemental Analysis: Calc.: C, 70.18; H, 4.77; N, 11.69%. Found: C, 70.30; H, 4.70; N, 11.77%

2-Amino-4-(3,4-dimethoxyphenyl)-3-cyano-4H,5H-pyran\[3,2-c\] chromene-5-one (4l)

Molecular Formula: C_{21}H_{16}N_{2}O_{5}

Molecular Weight (gm·mol^{-1}): 376.36

Melting Point (°C): 227-229

{\textsuperscript{1}H NMR} (400 MHz, DMSO): δ 6.86–7.88 (m, 9H), 4.41 (s, 1H), 3.73 (s, 6H)

{\textsuperscript{13}C NMR}: δ 159.5, 157.9, 153.1, 152.1, 148.6, 148.0, 135.8, 132.7, 124.5, 122.4, 119.7, 119.2, 116.4, 112.9, 112.0, 111.8, 104.1, 58.3, 55.6, 55.5, 36.5

IR (KBr): 3406, 3326 (NH\textsubscript{2}), 2197 (CN), 1710 (C=O), 1671 (C=C), 1062 (C-O) cm\textsuperscript{-1}

Elemental Analysis: Calc.: C, 67.02; H, 4.28; N, 7.44%. Found: C, 67.17; H, 4.32; N, 7.51%
### 2-Amino-4-(3,4,5-trimethoxyphenyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one (4m)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C$<em>{22}$H$</em>{18}$N$_2$O$_6$</td>
</tr>
<tr>
<td>Molecular Weight (g·mol$^{-1}$)</td>
<td>406.39</td>
</tr>
<tr>
<td>Melting Point ($^\circ$C)</td>
<td>224-226</td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz, DMSO): δ 7.35–7.92 (m, 6H), 6.51 (s, 2H), 4.42 (s, 1H), 3.73 (s, 6H), 3.61 (s, 3H)

$^{13}$C NMR: δ 160.2, 158.6, 154.2, 152.5, 139.6, 137.2, 133.4, 125.7, 123.1, 119.6, 117.1, 113.5, 105.3, 104.0, 60.3, 58.2, 56.7, 37.7

IR (KBr): 3424, 3382 (NH$_2$), 2191 (CN), 1709 (C=O), 1672 (C=C), 1045 (C-O) cm$^{-1}$

Elemental Analysis: Calc.: C, 65.02; H, 4.46; N, 6.89%. Found: C, 65.00; H, 4.27; N, 6.93%

### 2-Amino-4-(2-furyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one (4n)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C$<em>{17}$H$</em>{10}$N$_2$O$_4$</td>
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<td>Molecular Weight (g·mol$^{-1}$)</td>
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<tr>
<td>Melting Point ($^\circ$C)</td>
<td>250-251</td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz, DMSO): δ 7.36–7.89 (m, 6H), 6.39 (t, 1H, J 3.0 Hz), 6.28 (d, 2H, J 3.0 Hz), 4.63 (s, 1H)

$^{13}$C NMR: δ 159.4, 158.8, 154.2, 154.0, 152.3, 142.6, 133.4, 125.1, 124.5, 122.2, 116.7, 112.9, 110.5, 106.7, 101.6, 55.1, 30.6

IR (KBr): 3410, 3380 (NH$_2$), 2200 (CN), 1704 (C=O), 1052 (C-O) cm$^{-1}$

Elemental Analysis: Calc.: C, 66.67; H, 3.29; N, 9.15%. Found: C, 66.76; H, 3.33; N, 9.19%
**2-Amino-4-(5-methyl-2-furyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one (4o)**

<table>
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<th>Property</th>
<th>Value</th>
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<tbody>
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<td><strong>Molecular Formula</strong></td>
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<td><strong>Molecular Weight (gm·mol⁻¹)</strong></td>
<td>320.30</td>
</tr>
<tr>
<td><strong>Melting Point (°C)</strong></td>
<td>225-226</td>
</tr>
</tbody>
</table>

**¹H NMR** (400 MHz, DMSO): δ 7.31-7.78 (m, 6H), 6.66 (s, 1H), 6.44 (s, 1H), 4.57 (s, 1H), 2.17 (s, 3H)

**¹³C NMR**: δ 160.4, 158.5, 159.5, 155.6, 154.5, 154.4, 147.8, 134.1, 124.2, 119.7, 118.9, 116.2, 111.3, 100.1, 98.1, 56.4, 29.7, 13.26

**IR (KBr)**: 3396, 3346 (NH₂), 2199 (CN), 1704 (C=O), 1674 (C=C), 1056 (C-O) cm⁻¹

**Elemental Analysis**: Calc.: C, 67.50; H, 3.78; N, 8.75%. Found: C, 67.45; H, 3.74; N, 8.81%
Figure 4.2.4c.1 $^1$H NMR spectrum of compound 4b

Figure 4.2.4c.2 $^{13}$C NMR spectrum of compound 4b
Figure 4.2.4c.3 IR spectrum of compound 4b

Figure 4.2.4c.4 Mass spectrum of compound 4b
Figure 4.2.4c.5 $^1$H NMR spectrum of compound 4c

Figure 4.2.4c.6 $^{13}$C NMR spectrum of compound 4c
Figure 4.2.4c.7 IR spectrum of compound 4c

Figure 4.2.4c.8 Mass spectrum of compound 4c
4.4. REFERENCES


(42) Hasaninejad, A.; Shekouhy, M.; Golzar, N.; Zare, A.; Doroodmand, M. M., Silica bonded n-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO):


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(60) Wen, L.-R.; Xie, H.-Y.; Li, M., A basic ionic liquid catalyzed reaction of benzothiazole, aldehydes, and 5,5-dimethyl-1,3-cyclohexanedione: Efficient


