2.2.1 General Introduction & Literature Review

4H-benzopyran derivatives have attracted much attention during the past decade, because of their broad spectrum of biological and pharmaceutical activities. In addition, they can be used as synthetic intermediates in organic synthesis. Conventional synthetic methods for the synthesis of 4H-benzopyran derivatives involves bi-component condensation of dimesone (5,5-dimethylcyclohexane-1,3-dione) with 2-cyano cinnamomitrile by piperidine in acetic acid solution[1] or in ethanolic piperidine/morpholine[2].

![Chemical Reaction](image)

In the recent years synthesis of 4H-benzopyran derivatives has been extensively studied. This includes one-pot reaction of dimesone, aldehydes and malononitrile in ethanolic piperidine (or by using of ammonium acetate as catalyst instead of piperidine) [3]. Hassanien et al. synthesized 4H-benzopyrans using ammonium acetate as a catalyst [4]. T-S Jin et al. performed the preparation of chromenes in aqueous medium by stirring the reaction mixture at 85-90°C for 3hrs., using hexadecyltrimethyl ammonium bromide (HTMAB) as a catalyst [5]. T-S Li et al synthesized 4H-benzopyran derivatives catalyzed by KF/Basic Al₂O₃ under ultrasound irradiation [6]. In addition, microwave irradiation was also used to promote the condensation of 5,5-dimethyl-1,3-cyclohexanedione and β-amino- β-carbethoxy styrene [7]. Xiamin reported microwave-assisted one-pot synthesis of 2-amino-3-cyano-4-aryl-4H-pyrans[8]. Tu et al [9 (a)] and Pulak et al [9 (b)] also reported the preparation of 4H-benzopyran derivatives under microwave irradiation where as Wang et al reported it in DMF catalyzed by KF-alumina [10].
A series of pyrano[3,2-c]pyran derivatives have been synthesized by X-S Wang et al [11] by the reaction of aromatic aldehyde, malononitrile or cyanoacetate and 4-hydroxy-5-methylpyran-2-one in EtOH at room temperature catalyzed by KF/Al₂O₃ (reaction time 5-10hrs / yield 75 – 98%).

T-S Li et al also synthesized 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin from aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexadione and Meldrum’s acid catalysed by hexadecyltrimethylammonium bromide in water. [12] This group also synthesized 1,8-dioxdecahydroacridines from aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione and p-toluidine in water in the presence of p-dodecylbenzenesulfonic acid (DBSA) as a Bronsted acid-surfactant-combined catalyst.[13]

Gonghua Song et al reported synthesis of 4H-benzopyran derivatives through the one-pot condensation of aromatic aldehyde, malononitrile, and β-dicarbonyl compounds, using tetramethylguanidine in [bmim][BF₄] ionic liquid as a recyclable catalytic system [14] and Jiang et al also reported synthesis of 4H-pyrans using various ionic liquids[15].
Shi Da-Qing et al synthesised 7,7- Dimethyl-2-amino-3-cyano-4-(3,4-methylenedioxylphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]pyran from by the reaction of 2-cyano-3-(3,4-methylenedioxylphenyl) acrylonitrile and 5,5-dimethyl-1,3-cyclohexanedione in DMF at room temperature catalyzed by KF-Al₂O₃ [16].

From literature review it is quite clear that 4H-benzopyran ring is one of the extensively studied molecules and still there is scope for the development of improved methodology for its synthesis.
2.2.2 Present work

In continuation of our work described in section 2.1, herein we wish to report use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst for one-pot synthesis of 4H-benzopyran derivatives under solvent free condition. Present work deals with an efficient and mild procedure for the synthesis of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyrans-3-carbonitrile derivatives via one-pot condensation of aromatic aldehydes with malononitrile and 5,5-dimethylcyclohexane-1,3-dione catalyzed by DBU under solvent free conditions.

![Scheme 2.2.1]

2.2.2.1 General Experimental Procedure

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (1 mmol) was mixed thoroughly with a pestle in a mortar and the DBU (0.1 mmol) was added. The reaction mixture was vigorously ground and the progress of reaction was monitored by TLC. On completion, the reaction mixture was treated with cold water. The product was filtered, dried, recrystallized from ethanol (95%), and characterized by comparison of melting point, 1H NMR and IR spectra with those reported in the literature.

2.2.2.2 Result and Discussion

As a model reaction equimolar quantities of 4-methoxybenzaldehyde, malononitrile, and 5,5-dimethylcyclohexane-1,3-dione were taken in a mortar, mixed thoroughly with the pestle and then 10 mol % DBU was added. The reaction mixture was vigorously ground
in with pestle. With the progress of the reaction, the reaction mixture turned into yellowish viscous liquid, then into thick yellowish mass and finally to free flowing powder. Slight heat was generated after addition of the catalyst. Surprisingly the reaction mixture turned into the desired product within a short period of 5 min. (Table 2.2.2, entry-4a). To investigate role of catalyst and effect of grinding, the model reaction was performed under various reaction conditions as summarized in Table 2.2.1. In the absence of DBU, the reaction does not proceed under similar conditions even after grinding for 30 min (entry 1). In the absence of grinding, the reaction was performed by stirring the reactants and catalyst at room temperature (entry 2) and the result was formation of viscous liquid, showing approximately 65% conversion of reactants into the product. Model reaction was also performed using ethanol as a solvent and stirring at room temperature (entry 3). Reaction performed using 0.1 mmol of DBU followed by grinding was found to be most effective.

**Table 2.2.1 Optimization of reaction Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Grinding without DBU</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2.</td>
<td>Stirring with DBU for 3 hrs</td>
<td>65% conversion</td>
</tr>
<tr>
<td>3.</td>
<td>Stirring with DBU in EtOH for 3Hrs</td>
<td>75 % conversion</td>
</tr>
<tr>
<td>4.</td>
<td>Grinding using DBU</td>
<td>100% conversion</td>
</tr>
</tbody>
</table>

Miscibility of DBU with water makes the workup process quite easy as the catalyst can be easily removed from product simply by washing the product with water.

The nature of substituents on the aromatic ring did not show strongly obvious effect in terms of yield and reaction time under these reaction conditions. Benzaldehyde, Thiophene-2-carbaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro or chloro group) or electron-donating groups (such as alkoxy or dimethylamine group) were employed and reacted well to give the
corresponding 4H-benzopyrans in excellent yields (Table 2.2.1). The proposed mechanism for this reaction is as given in Scheme 2.2.2. As observed during reaction monitoring, aromatic aldehyde 1 first condenses with malononitrile 2 to afford α-cyanocinnamonomitrile derivative 5, a low melting compound as compared with the final product 4. The active methylene moiety of 3 attacks the electrophilic C=C double bond of 5, giving intermediate 6, which isomerizes to 7. Intramolecular condensation of 7 results into intermediate 8, which isomerizes to give the expected product 4.

\[
\text{ArCHO} + \text{H}_2\text{C} = \text{CN} \rightarrow \text{ArCH} = \text{CN}
\]

Scheme 2.2.2

2.2.2.3 Conclusion

In conclusion, we have successfully demonstrated the use of DBU as novel and efficient catalyst, for the synthesis of 4H-benzopyran derivatives. The attractive features of this procedure are the mild reaction conditions, high conversions, cleaner reaction profiles, solvent-free reaction conditions and operational simplicity, all of which make it a useful and attractive strategy for the preparation of 4H-benzopyrans derivatives at room temperature.
2.2.2.4 Spectral Data

2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(2-thienyl)-4H-benzopyran-3-carbonitrile (4c).

**IR (KBr):** $v_{\text{max}}$

3385, 3205, 2960, 2195, 1675, 1650, 1600 cm$^{-1}$.

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$

1.07 (s, 3H, CH$_3$), 1.12 (s, 3H, CH$_3$), 2.27 (s, 2H, 6-H), 2.43 (s, 2H, 6-H), 4.60 (s, 2H, NH$_2$), 4.72 (s, 1H, 4-H), 6.88–7.12 (m, 3H, 2-Thienyl) ppm.

**$^{13}$C NMR (400 MHz, CDCl$_3$):** $\delta$

27.6, 29.1, 30.5, 32.3, 40.7, 50.6, 63.2, 113.9, 118.4, 124.4, 124.8, 126.9, 147.5, 157.7, 161.4, 195.5.

**LCMS:** $m/z = 301$ (M-H)$^+$. 
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (Ar)</th>
<th>Time (Min)</th>
<th>Yield(^a) (%)</th>
<th>Melting Point (°C)</th>
<th>Observed</th>
<th>Literature(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4-Methoxybenzaldehyde</td>
<td>5</td>
<td>94</td>
<td>198-200</td>
<td>199-201</td>
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<tr>
<td>4b</td>
<td>Benzaldehyde</td>
<td>8</td>
<td>89</td>
<td>228-230</td>
<td>229-231</td>
<td></td>
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<tr>
<td>4c</td>
<td>2-Thiophenecarbaldehyde</td>
<td>7</td>
<td>92</td>
<td>228-230</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>4-Methylbenzaldehyde</td>
<td>5</td>
<td>92</td>
<td>216-218</td>
<td>214-216</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>2-Chlorobenzaldehyde</td>
<td>8</td>
<td>91</td>
<td>204-206</td>
<td>200-202</td>
<td></td>
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<tr>
<td>4f</td>
<td>3-Chlorobenzaldehyde</td>
<td>5</td>
<td>95</td>
<td>228-230</td>
<td>224-225</td>
<td></td>
</tr>
<tr>
<td>4g</td>
<td>4-Chlorobenzaldehyde</td>
<td>5</td>
<td>92</td>
<td>210-212</td>
<td>208-210</td>
<td></td>
</tr>
<tr>
<td>4h</td>
<td>3-Nitrobenzaldehyde</td>
<td>5</td>
<td>90</td>
<td>208-210</td>
<td>208-211</td>
<td></td>
</tr>
<tr>
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<td>4-Nitrobenzaldehyde</td>
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<tr>
<td>4j</td>
<td>4-(N,N)-Dimethylamino (N)-benzaldehyde</td>
<td>7</td>
<td>95</td>
<td>216-218</td>
<td>220-222</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Yield of isolated product.
2.2.3 References