PART-III
Triethylammonium acetate catalyzed organic transformations
SECTION A

TRIETHYLAMMONIUM ACETATE CATALYZED SYNTHESIS OF TETRAHYROBENZO[|B|]PYRAN DERIVATIVES
3A.1 INTRODUCTION

Ionic liquids have attracted considerable interest as environmentally friendly or “green” alternatives to conventional molecular organic solvents because they have very low vapor pressure and are non-explosive and thermally stable in a wide temperature range.1,2 Furthermore, they are often immiscible with organic solvents because of their polar nature and may therefore be used in biphasic systems. Now, ionic liquids have been used as environmentally benign solvents or catalysts for a number of chemical processes3 such as separations,4 reactions,5 homogeneous two-phase catalysis6 and polymerizations.7

The current emphasis on alternative reaction media is motivated by the need for efficient methods for replacing toxic or hazardous solvents and catalysts. The use of ionic liquids as alternative reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem.8 Although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of non-volatility, non-flammability, thermal stability, and controlled miscibility, today they have marched far beyond this boundary, showing their significant role in controlling reactions as solvent or catalysts.9 Another feature of ionic liquids is their ability to be reused many times.

In past several years a great deal of attention has been given towards imidazolium based ionic liquids viz [bmim]Br,10 [bmim]BF₄,11 [bmim]NTf₂,12 [hmim]PF₆,13 [mim-t-OH][OMs],14 [Hbim]BF₄.15 Although as the unique advantage of ionic liquid as reaction media and catalyst they were not been applied in industries probably due to high cost of ionic liquids, difficulty in separation or recycling.16 Low-cost ionic liquids, such as ammonium ionic liquids have drawn much attention in the recent time for their use in synthesis methodology.

Weng Li et al. reported17 novel quaternary ammonium ionic liquids both as a catalyst and environmentally benign solvent for the hydrolytic reaction of 1,1,1,3-tetrachloro-3-phenylpropane, eliminating the need for a volatile organic solvent and additional catalyst (Scheme 1).
Scheme 1

Wang and co-worker\textsuperscript{18} have simple ammonium ionic liquids used as catalysts and environmentally benign solvents for the cracking reactions of dialkoxypropanes, eliminating the need for volatile organic solvents and additional catalysts (Scheme 2).

\[ R=\text{C}_2\text{H}_5, \text{R', R''}=\text{H} \]

Scheme 2

Jiang \textit{et al.} also performed\textsuperscript{19} preparation of dialkoxypropanes by the use of simple ammonium ionic liquids as a dual catalyst and environmentally benign reaction medium for, eliminating the need for volatile organic solvents and poisonous hydrogen chloride catalysts (Scheme 3).

\[ R=\text{CH}_3, \text{CH}_2\text{CH}_3 \]

Scheme 3

Verma \textit{et al.} performed\textsuperscript{20} chemoselective aza/thia-Michael addition reactions of amines/thiols to $\alpha,\beta$-unsaturated compounds using triethylammonium acetate [TEAA] ionic liquid (Scheme 4).

\[ \text{R, S, B, A, M, U, N, V, E, I, R, Y} \]
Tetrahydrobenzo[b]pyrans have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals. Among the different types of chromene systems (Figure 1), tetrahydrobenzo[b]pyrans (I) are of considerable interest because of their wide range of biological properties, such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactia activities.

They can also be used as cognitive enhancers not only for the treatment of schizophrenia and myoclonus but also for the treatment of neurodegenerative disease, including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS associated dementia, and Down’s syndrome.

Similar compounds (II), as the first class of compounds, have shown fully selective inhibition of the human excitatory amino acid transporter subtype 1 (EAAT 1).

Based on the chromene based heterocycles framework, a typical example of an approved drug is amlexanox (III), which is a commonly prescribed antiallergic and...
typical antiulcer agent,\textsuperscript{25} and many other compounds such as compound IV, V, and VI exemplify the wide therapeutic spectrum and active interest.\textsuperscript{26}

Other than their biological importance, some 2-aminoo-4\textit{H}-pyrans have been widely used as photoactive materials.\textsuperscript{27} In addition, the tetrahydrobenzo[b]pyran nucleus is an important structural motif of a series of natural products\textsuperscript{28, 29} and can be converted into pyridine systems which relate to pharmacologically important calcium antagonists of the dihydropyridine(DHP)\textsuperscript{30, 31} type. The importance of these compounds has led the scientific community to synthesize them using the bicomponent condensation\textsuperscript{32, 33} of dimedone with \(\alpha\)-cyanocinnamionitriles or multicomponent condensation\textsuperscript{34-39} of dimedone with aromatic aldehydes and malononitrile.

### 3A.2. Literature Review

Pore \textit{et al.} achieved\textsuperscript{40} synthesis of tetrahydrobenzo[b]pyran via a three-component reaction of aldehydes, 1,3-diketone, malononitrile in 20\% ethanol using anhydrous potassium phosphate as a catalyst and the reaction was stirred at room temperature (Scheme 5).

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{CN} & \quad + \quad \text{O} & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
\end{align*}
\]

\[\text{K}_2\text{PO}_4 \quad \text{EtOH} : \text{H}_2\text{O} \quad \text{r.t.}\]

\[\text{Scheme 5}\]

Lian \textit{et al.} \textsuperscript{41} synthesized tetrahydrobenzo[b]pyran derivatives using N-methylimidazole as the organocatalyst in 10\textsuperscript{cm\textsuperscript{3}} 95\% of EtOH (Method A) or in 10 \textsuperscript{cm\textsuperscript{3}} \text{H}_2\text{O} (Method B) was vigorously stirred at room temperature (Scheme 6).

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{CN} & \quad + \quad \text{O} & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
\end{align*}
\]

\[\text{N-methylimidazole} \quad \text{EtOH, H}_2\text{O} \quad \text{r.t.}\]

\[\text{Scheme 6}\]
Fotouhi and co-workers\textsuperscript{42} introduced Electrogenerated base-promoted synthesis of tetrahydrobenzo[b]pyran derivatives and the reaction was carried out at room temperature in acetonitrile with the use of a sacrificial magnesium anode in a single-compartment cell (Scheme 7).

\textbf{Scheme 7}

Hekmatshoar \textit{et al.} performed\textsuperscript{43} the synthesis of tetrahydrobenzo[b]pyran derivatives using sodium selenate as a catalyst by refluxing the reaction in aqueous media (Scheme 8).

\textbf{Scheme 8}

Balalaie \textit{et al.}\textsuperscript{44} used tetra-methyl ammonium hydroxide for the synthesis of tetrahydrobenzo[b]pyran via three component one pot by refluxing the reaction mixture in aqueous ethanol at 50 °C (Scheme 9).

\textbf{Scheme 9}

Mobinikhaledi \textit{et al.} introduced\textsuperscript{45} synthesis of tetrahydrobenzo[b]pyran derivatives in the presence of KAl(SO\textsubscript{4})\textsubscript{2}.12H\textsubscript{2}O (alum) by refluxing in aqueous media at 80 °C (Scheme 10).
Sun et al. reported\textsuperscript{46} synthesis of tetrahydro-4H-chromene derivatives by concurrent refluxing the reaction of aryl aldehydes, active methylene compounds, and 1,3-cyclohexanedins using a catalytic amount of lithium bromide in aqueous media (Scheme 11).

Seifi and Sheibani reported\textsuperscript{37} MgO as a heterogeneous base catalyst for three-component synthesis of tetrahydrobenzo[b]pyran (Scheme 12). The reaction was carried out by refluxing the reaction mixture in ethanol.

Luo and coworkers reported\textsuperscript{47} PEG-1000-based dicationic ionic liquid exhibiting temperature-dependent phase behavior with toluene and its application in one-pot synthesis of benzopyrans under reflux condition (Scheme 13).
Bhosale et al. introduced molecular iodine catalyzed synthesis of tetrahydrobenzo[b]pyran derivatives using DMSO as solvent and heated at 120 °C for 3-4 hrs (Scheme 14).

Scheme 14

Shingare et al. introduced Sodium hypochlorite (NaOCl) as a catalyst for the synthesis of 4H-benzo[b]pyran derivatives from one-pot three component condensation of aldehydes, dimeredone and malononitrile by using grinding method.
3A.3. Present Work

As part of our ongoing research work to reduce toxic waste and byproducts arising from chemical processes by using mild, cheap and environmentally compatible materials in the design of new synthetic methods, we have implemented triethylammonium acetate [TEAA] as catalyst and greener reaction media for the one pot three component synthesis of tetrahydro-4H-chromene derivatives (Scheme 15).

In this section we have discussed the synthesis of tetrahydrobenzo[b]pyrans under simple ammonium ionic liquid i.e. triethylammonium acetate [TEAA] are air and water stable, easy to prepare from amine and acid, and relatively cheap compared with the imidazolium ionic liquids.

\[
\begin{align*}
\text{R} \quad \text{CHO} & \quad \text{CN} & \quad \text{O} & \quad \text{O} \\
+ & + & \quad \text{[TEAA]} & \quad \text{Stirring, r.t.} \\
\text{1(a-n)} & \quad \text{2} & \quad \text{3} & \quad \text{4(a-n)}
\end{align*}
\]

Scheme 15

3A.4. Results and Discussion

Initially, choosing an appropriate solvent is of crucial importance for the successful organic synthesis. Therefore, screening of solvents in three component reaction of 4-Cl-benzaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) in the presence of triethylammonium acetate (40 mol%) as a model reaction was investigated for the synthesis of 2-Amino-7,7-dimethyl-5-oxo-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 1). In each case, the substrate was mixed together with [TEAA] (40 mol%) agitated with 5 mL of solvent. When H₂O, DCM and THF was used as solvent there is a retard in the rate of reaction which ultimately resulted into decrease in the product yield (Table 1, entry 1, 2 and 3). The results obtained for CH₃CN and EtOH were also not satisfactory. After complete optimization [TEAA] was found to be appropriate reaction media and catalyst for this reaction (Table 1, entry 4 and 5). There is dramatic acceleration in the rate of the
reaction and the yields were also found to be improved as we introduce triethylammonium acetate as reaction media and catalyst (Table 1, entry 6). Therefore, [TEAA] found to be a better catalyst and a reaction media for proceed the reaction forward with improved yield.

Table 1: Solvent effect on the synthesis of tetrahydrobenzo[b]pyran using [TEAA] as catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent : Catalyst</th>
<th>Time</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O : [TEAA]</td>
<td>4 h</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>DCM : [TEAA]</td>
<td>3 h</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>THF : [TEAA]</td>
<td>3 h</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN: [TEAA]</td>
<td>1 h</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>EtOH : [TEAA]</td>
<td>1 h</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>[TEAA]</td>
<td>&lt;20 min&gt;</td>
<td>97</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction condition: 4-Cl-benzaldehyde (1mmol), malononitrile (1mmol), dimedone (1mmol), Solvent (5 mL) with triethylammonium acetate (40 mol%) was stirred at r.t., <sup>b</sup>Yields were isolated.

After brief screening of solvent we also optimized the quantity of catalyst required for reaction to proceed further. From fig 1 it is noteworthy that without any solvent and catalyst the reaction did not proceed further. As the amount of [TEAA] was increased from 10 mol% to 40 mol% there was dramatically continuous improvement in the reaction with respect to time and yield of the product. Increasing the amount of catalyst did not show any improvement in the reaction rate and yield of the product. Finally, 40 mol% of the catalyst showed the better optimistic condition to forward the reaction.
Figure 1: Optimization of quantity of catalyst considering (Table 2, entry 4f) as model reaction.

![Optimization of catalyst](image)

Table 2: Characterization of tetrahydrobenzo[b]pyran derivatives†

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (min.)</th>
<th>Yield$^a$(%)</th>
<th>M.P.$^b$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C₆H₅</td>
<td>10</td>
<td>95</td>
<td>227-229</td>
</tr>
<tr>
<td>4b</td>
<td>4-ClC₆H₄</td>
<td>20</td>
<td>97</td>
<td>208-210</td>
</tr>
<tr>
<td>4c</td>
<td>3-ClC₆H₄</td>
<td>15</td>
<td>95</td>
<td>230-232</td>
</tr>
<tr>
<td>4d</td>
<td>4-NO₂C₆H₄</td>
<td>25</td>
<td>94</td>
<td>180-182</td>
</tr>
<tr>
<td>4e</td>
<td>4-BrC₆H₄</td>
<td>20</td>
<td>96</td>
<td>200-202</td>
</tr>
<tr>
<td>4f</td>
<td>2,4-Cl₂C₆H₃</td>
<td>15</td>
<td>95</td>
<td>195-197</td>
</tr>
<tr>
<td>4g</td>
<td>4-FC₆H₄</td>
<td>25</td>
<td>94</td>
<td>193-195</td>
</tr>
<tr>
<td>4h</td>
<td>4-MeC₆H₄</td>
<td>35</td>
<td>92</td>
<td>218-220</td>
</tr>
<tr>
<td>4i</td>
<td>4-OHC₆H₄</td>
<td>30</td>
<td>93</td>
<td>207-209</td>
</tr>
<tr>
<td>4j</td>
<td>3-OHC₆H₄</td>
<td>40</td>
<td>89</td>
<td>237-239</td>
</tr>
<tr>
<td>4k</td>
<td>4-OMeC₆H₄</td>
<td>35</td>
<td>91</td>
<td>197-199</td>
</tr>
<tr>
<td>4l</td>
<td>3-OH,4-OMeC₆H₃</td>
<td>45</td>
<td>88</td>
<td>230-232</td>
</tr>
<tr>
<td>4m</td>
<td>2-Thienyl</td>
<td>30</td>
<td>93</td>
<td>211-213</td>
</tr>
<tr>
<td>4n</td>
<td>2-Furyl</td>
<td>35</td>
<td>92</td>
<td>197-199</td>
</tr>
</tbody>
</table>

†Reaction condition: aldehydes (1 mmol), malononitrile (1 mmol) and dimedone (5,5-dimethylcyclohexane-1,3-dione) (1 mmol) in the presence of [TEAA] triethylammonium acetate (40 mol%) stirred at room temperature. $^a$Isolated yields of product are obtained before crystallization and $^b$Melting points were compared with literature data.⁴⁻⁸
In order to explore the scope of the methodology a wide range of structurally diverse and functionalized aromatic and heteroaromatic aldehydes were examined, which underwent cyclocondensation with excellent yields (Table 2, entries 4a-4n). Various aldehyde bearing electron-withdrawing groups (-Cl, -Br, -NO$_2$, -F) and electron-donating groups (-OCH$_3$, -CH$_3$, -OH) were employed and it is indeed gratifying to note that substituents in the aromatic ring of aldehydes did not show any obvious effect on the rate of the reaction and yield of the product. The heteroaryl aldehydes, such as 2-thiophenealdehyde and 2-furaldehyde reacted very smoothly to obtain the corresponding derivatives in good yields.

The recovery and reuse of solvent and catalyst are highly preferable in terms of green synthetic process. Therefore, with the success of these above reactions, we continued our research by studying reusability and recycling of [TEAA] by choosing (Table 2, entry 4e) as model reaction. After completion of reaction, the aqueous layer consisting of the IL was subjected to distillation at temperature of 40°C and Vacuum Pressure upto 72 mbar for 2h to remove water and remaining IL was reused. The recovery yield was 96-98% which does not show any significant decrease up to 8 runs. Purity was measured on the basis of recovery yield of the IL and product yield. From results there was no any major changes observed in the yield of the product even after six runs (Figure 2).

![Figure 2: Reusability of [TEAA] considering](image)
3A.5. CONCLUSIONS

It can be concluded that, introduction of triethylammonium acetate [TEAA] can be considered as an interesting new alternate route for synthesis of tetrahydro-4H-chromene derivatives and the merit of this method includes highly inexpensive, ease of handling, easily recycling and reuse of the catalyst. Therefore with increasing “green” concern, the conditions employed in the present method will make it environment friendly and useful for industrial applications.

3A.6. EXPERIMENTAL SECTION

General procedure: Synthesis of Tetrahydrobenzo[b]pyran derivatives(4a-n)

A mixture of benzaldehyde (1 mmol), malononitrile (1 mmol) and dimesdone (1 mmol) in the presence of triethylammonium acetate (40 mol%) was stirred at room temperature for appropriate time (Table2). Course of the reaction was monitored by TLC. After completion of reaction, mixture was poured on ice cold water (15-20 ml) and obtained solid product was collected by filtration. Further purification was accomplished by recrystallization from ethanol to afford final product which was in full agreement with the spectral data.

Spectral analysis:

\[
\text{IR (KBr, cm}^{-1}\text{)} = 1241, 1606, 2243, 2956, 3243.
\]

\[
^1H \text{ NMR (CDCl}_3, 200 \text{ MHz) } \delta \text{ ppm } = 1.06 \text{ (s, 3H, -CH}_3\text{), 1.13 } \text{ (s, 3H, -CH}_3\text{), 2.22 } \text{ (s, 2H, -CH}_2\text{), 2.45 } \text{ (s, 2H, -CH}_2\text{), 4.32 } \text{ (s, 1H, -CH), 4.53 } \text{ (s, 2H, -NH}_2\text{), 7.19-7.30 (m, 5H, Ar-H)}
\]

MASS : 295 [M+1]
\(^1\)H NMR Spectra

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)
Mass Spectra

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)
IR Spectra

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)
3A.7. REFERENCES


SECTION B

TRIETHYLAMMONIUM ACETATE CATALYZED SYNTHESIS OF

PYRANO[2,3-c] PYRAZOLE DERIVATIVES
3B.1. INTRODUCTION

Dihydropyran[2,3-c]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. Many of those compounds are known as antimicrobial, insecticidal, and anti-inflammatory. Furthermore dihydropyran[2,3-c]pyrazoles showed molluscicidal activity and was identified as a screening hit for Chk1 kinase inhibitor. Over the last years, the chemistry of dihydropyran[2,3-c]pyrazoles has received great interest. Edaravone inhibits the disease activity in rheumatoid arthritis. 4-Acetamidoantipyrine was a metabolism of Metamizol in early stages of the incubated hen’s egg. Rimonabant Hydrochloride is a brain cannabinoid receptor (CB1) antagonist which is an antiobesity agent. Pyrazole N-Demethyl Sildenafil is a novel pyrazolopyrimidine derivative, useful as cardiovascular agent.

The first approach to synthesize these substances was undertaken by Otto, in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-arylidene-5-pyrazolone. In a further report, the same group showed that weak bases can also be used for a Michael-type cyclization. Extension the work of Otto, Klokol and coworkers performed the direct conversion of 3-methyl-3-pyrazolin-5-
one with malononitrile in the presence of a weak base.\textsuperscript{13} Recent methods for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles include synthesis in aqueous media\textsuperscript{14,15} under microwave irradiation\textsuperscript{[16]}, and under solvent-free conditions.\textsuperscript{17,18} Herein, we report a general, facile, and efficient method based on the procedure of Klokol \textit{et al.},\textsuperscript{13} to generate wide variety in the substitution pattern of novel 1,4-dihydropyrano[2,3-c]pyrazoles. Also there are some reports available for the synthesis of pyrano[2,3-c]pyrazole derivatives.

### 3B.2. Literature Survey

Sheibani and Babaie\textsuperscript{19} performed three-component reactions of 3-alkyl-1-phenyl-2-pyrazolin-5-ones, aryl aldehydes, and malononitrile in the presence of base catalysts such as sodium acetate, triethylamine, and magnesium oxide (MgO) to form 1,4-dihydropyrano[2,3-c]pyrazole derivatives (Scheme 1).

![Scheme 1](image1)

\textbf{Scheme 1}

Jin \textit{et al.}\textsuperscript{15} introduced hexadecyltrimethylammonium bromide (HTMAB) Phase transfer catalyst for the synthesis of Pyrano[2,3-c]pyrazole derivatives (Scheme 2).

![Scheme 2](image2)

\textbf{Scheme 2}

Wang \textit{et al.}\textsuperscript{17} used \textit{D,L}-Proline-catalyzed one pot synthesis of Pyrans and Pyrano[2,3-c]pyrazole derivatives (Scheme 3).
Ren et al.\textsuperscript{18} achieved one-pot process for the preparation of 4\textit{H}-pyrans in the presence of potassium fluoride dihydrate (KF.2H\textsubscript{2}O) by grinding (Scheme 4).

Laufer\textsuperscript{20} and co-workers reported different base catalyzed three component combinatorial synthesis of novel 4\textit{H}-pyrans (Scheme 5).

Song et al. performed\textsuperscript{21} the Synthesis of 4\textit{H}-pyrano[2,3-c]pyrazoles by the reaction of hydrazine monohydrate and a catalytic amount of piperazine (Scheme 6).
Pitchumani and Kanagaraj developed\textsuperscript{22} syntheses of various dihydropyrano[2,3-c]pyrazole derivatives involving a four-component reaction by using per-6-amino-\(\beta\)-cyclodextrin (per-6-ABCD) which acts simultaneously as a supramolecular host and as an solid base catalyst (Scheme 7).

Al-Hazimi\textsuperscript{23} synthesized derivatives of spiropiperidine-4,40-pyano[2,3-c]pyrazole, dihydropyrano[2,3-c]pyrazole, pyrazole-4-carbothioamide, 4-(2-oxo-1,2-diphenylethylidene)-1\(H\)-pyrazol-5(4\(H\))-one, azopyrazole, arylmethylenebis-1\(H\)-pyrazol-5-ol and arylidene-1\(H\)-pyrazol-5(4\(H\))-one via reactions with different reagents applying the ultrasound method in some cases (Scheme 8).

Shostoplov \textit{et al.}\textsuperscript{24} synthesized 6-amino-2\(H\),4\(H\)-pyrano[2,3-c]pyrazole-5-carbonitriles, namely, four component condensation of carbonyl compounds (aromatic aldehydes, heterocyclic ketones), malononitrile, \(\beta\)-keto esters, and
hydrazine hydrate in ethanol in the presence of triethylamine as a catalyst (Scheme 9).

\[
\text{H}_2\text{N} - \text{NH}_2 + \text{R}^2 \text{C} = \text{O} + \text{CN} - \text{CN} \rightarrow \text{EtOH} \rightarrow \text{Et}_2\text{N} \rightarrow \text{R}^2 \text{R}^1 \text{N} - \text{NH}_2
\]

**Scheme 9**

### 3B.3. PRESENT WORK

Each of the reported methods has its own merit, with at least one of the limitations of low yields, long reaction time, effluent pollution, harsh reaction conditions, and tedious workup procedures. Our interest in organic reaction is to carry out exclusively simple routes for the synthesis of different organic compound.

In this section we have synthesized 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles via multicomponent reaction of aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one using triethylammonium acetate [TEAA] both as a catalyst and reaction media at room temperature (Scheme 10).

\[
\text{CHO} + \text{CN} - \text{CN} + \text{N} - \text{CN} \rightarrow \text{Stirring, RT} \rightarrow \text{Stirring, RT}
\]

**Scheme 10**

### 3B.4. RESULTS AND DISCUSSION

Initially, choosing an appropriate solvent is of crucial importance for the successful organic synthesis. For optimization, the reaction of 4-Cl-benzaldehyde (1 mmol), malononitrile (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1
mmol) was examined in various solvent using TEAA as catalyst (Table 1) at room temperature. The reaction does not proceed when it was carried out without solvent and catalyst (Table 1, entry 1). The use of solvents retards the rate of reaction which ultimately resulted into decrease in the product yield with prolonged reaction time (Table 1, entry 2-6). After complete optimization TEAA was found to be appropriate reaction media and catalyst for this reaction (Table 1, entry 7). From the results it is noticeable that triethylammonium acetate (TEAA) plays a crucial role in the success of reaction and proved to be most effective.

![Fig. 1. Optimization of quantity of catalyst.](image)

**Table 1: Optimization of solvent effect**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent : Catalyst</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>6 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Water : TEAA</td>
<td>6 h</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>DCM : TEAA</td>
<td>6 h</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>THF : TEAA</td>
<td>6 h</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>EtOH : TEAA</td>
<td>6 h</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>CH₃CN: TEAA</td>
<td>6 h</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td><strong>TEAA</strong></td>
<td><strong>25 min</strong></td>
<td><strong>96</strong></td>
</tr>
</tbody>
</table>

a Reaction condition: 4-Cl-benzaldehyde (1 mmol), malononitrile (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) and triethylammonium acetate (40 mol %) stirred at RT. b Yields were isolated.

The catalyst plays, a crucial role in the success of the reaction in terms rate of the reaction and yield. We have also optimized the quantity of catalyst for the reaction of 4-Cl-benzaldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one stirring at room temperature (Fig. 1.) When the reaction was carried out in presence of 10 mol% of catalyst (TEAA) gives 52% of the yield. As we increase the percentage of the catalyst as 20 mol%, 30 mol%, 40 mol% the yields were also
found to be increased up to 68%, 82%, 96% respectively. Higher amount of the catalyst did not improve the result to greater extent. Thus, 40 mol% of catalyst was chosen as maximum quantity of the catalyst for the reaction.

**Table 2**: Synthesis of pyrano[2,3-c]pyrazoles by stirring at room temperature.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>20</td>
<td>97</td>
<td>167-169</td>
</tr>
<tr>
<td>4b</td>
<td>2-Cl</td>
<td>25</td>
<td>98</td>
<td>145-147</td>
</tr>
<tr>
<td>4c</td>
<td>4-Cl</td>
<td>25</td>
<td>96</td>
<td>175-177</td>
</tr>
<tr>
<td>4d</td>
<td>4-Br</td>
<td>30</td>
<td>97</td>
<td>180-182</td>
</tr>
<tr>
<td>4e</td>
<td>2,4-Cl₂</td>
<td>30</td>
<td>96</td>
<td>183-185</td>
</tr>
<tr>
<td>4f</td>
<td>4-NO₂</td>
<td>35</td>
<td>94</td>
<td>191-193</td>
</tr>
<tr>
<td>4g</td>
<td>3-NO₂</td>
<td>35</td>
<td>95</td>
<td>189-191</td>
</tr>
<tr>
<td>4h</td>
<td>4-OH</td>
<td>45</td>
<td>90</td>
<td>209-210</td>
</tr>
<tr>
<td>4i</td>
<td>4-CH₃O</td>
<td>45</td>
<td>92</td>
<td>172-174</td>
</tr>
<tr>
<td>4j</td>
<td>4-CH₃</td>
<td>50</td>
<td>91</td>
<td>175-177</td>
</tr>
<tr>
<td>4k</td>
<td>2,4-(CH₃O)₂</td>
<td>55</td>
<td>89</td>
<td>176-178</td>
</tr>
<tr>
<td>4l</td>
<td>3,4-OCH₂O</td>
<td>55</td>
<td>87</td>
<td>173-175</td>
</tr>
</tbody>
</table>

*Isolated yields. Reaction condition: benzaldehyde (0.10 g, 1 mmol), malononitrile (0.06 g, 1 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (0.17 g, 1 mmol) in presence of triethylammonium acetate (40 mol%) [TEAA] stirred at room temperature. * Melting points were matched literature data.²⁵-²⁸

In order to explore the scope of the methodology wide range of structurally diverse and functionalized aromatic aldehydes were examined, which underwent cyclocondensation with excellent yields (Table 2). When mixture of benzaldehyde (0.10 g, 1 mmol), malononitrile (0.06 g, 1 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (0.17 g, 1 mmol) in presence of triethylammonium acetate (40 mol%) was stirred at room temperature (Scheme 11), the reaction proceeds smoothly to afford corresponding products (Table 2, Entry 4a-4l). When aromatic aldehydes containing electron-withdrawing groups (such as -Cl, -Br, -NO₂) and electron-donating groups (such as -OCH₃, -CH₃, -OH) were employed the reaction proceeds smoothly with improved reaction time and excellent yields were observed. There is no any obvious effect observed due to electronic effect and nature of the substituents during the reaction.
Table 3: Reusability of TEAA considering (Table 2, compound 4c) as reaction model.

<table>
<thead>
<tr>
<th>Runs</th>
<th>Time (min)</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^b\)Yields were isolated.

The recovery and reuse of solvent and catalyst are highly preferable in terms of green synthetic process. Therefore, with the success of these above reactions, we continued our research by studying reusability and recycling of TEAA. After completion of reaction, the reaction mixture was poured on ice cold water and filtered off. The filtrate was distilled under reduced pressure and obtained IL was reused for the same reaction. From results catalytic activity of catalyst did not show any significant decrease even after four runs (Table 3).

3B.5. CONCLUSIONS

It can be concluded that, introduction of triethylammonium acetate (TEAA) can be considered as an interesting new alternate route for synthesis of 1,4-dihydropyran[2,3-c]pyrazol-5-yl Cyanides derivatives and the merit of this method includes solvent-free, highly inexpensive, ease of handling, easily recycling and reuse of the catalyst. Therefore with increasing “green” concern, the solvent-free conditions employed in the present method will make it environment friendly and useful for industrial applications.

3B.6. EXPERIMENTAL SECTION

General procedure: A mixture of benzaldehyde (1 mmol), malononitrile (1 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) in presence of triethylammonium acetate (40 mol%) was stirred at room temperature for appropriate time. Course of the reaction was monitored by TLC. After completion of reaction, mixture was poured on ice cold water and obtained solid product was collected by filtration. Further purification was accomplished by recrystallization.
from ethanol to afford final product which was in full agreement with the spectral data.

**Spectral analysis:** 6-Amino-4-(2-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyran[2,3-c]pyrazole (4c)

IR: IR (KBr, cm⁻¹) = 3062, 2228, 1201, 755.

¹H NMR (CDCl₃, 200 MHz) δ (ppm) = 1.89 (s, 3H, CH₃), 4.66 (s, 1H, -CH), 4.69 (s, 2H, -NH₂), 7.27-7.68 (m, 9H, Ar-H)

MASS : 363 [M+1]
§H NMR Spectra

6-Amino-4-(2-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (4c)
MASS Spectra

6-Amino-4-(2-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (4c)
IR Spectra

6-Amino-4-(2-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (4c)
3B.7. REFERENCES


SECTION C

TRIETHYLAMMONIUM ACETATE CATALYZED SYNTHESIS OF
PYRANO[3,2-c]COUMARIN DERIVATIVES
3C.1. **INTRODUCTION**

Pyrano [3,2-c]chromene derivatives are a class of important heterocycles with a wide range of biological properties\(^1\) such as spasmolytic, diuretic, anticoagulant, anticancer, and anti-anaphylactic activity.\(^2\) Moreover they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer’s disease, amyotrophic lateral sclerosis, Parkinson’s disease, Huntington’s disease, AIDS associated dementia and Down’s syndrome as well as for the treatment of schizophrenia and myoclonus.\(^3\) In addition, aminochromene derivatives exhibit a wide spectrum of biological activities including antihypertensive and anti-ischemic behavior.\(^4\)\(^-\)\(^6\) Also, a number of 2-amino- 4H-pyrans are useful as photoactive materials.\(^7\)

![Chemical Structures](image)

**Figure 1.**

Most of the coagulants are made up of coumarin derivatives such as Warfarin, 4-hydroxycoumarin, Umbelliferone. Also some of coumarin derivatives such as \(+\)-calanolide A, \(+\)-12-oxocalanolide, Suksdorfin possesses anti-HIV activity\(^8\) (Figure 1).
3C.2. LITERATURE REVIEW

Balalaie et al. introduced Diammonium hydrogen phosphate, \((NH_4)_2HPO_4\) as a catalyzed one-pot three-component reaction of an aromatic aldehyde, malononitrile and 4-hydroxycoumarin to afford the corresponding dihydropyrano[c]chromenes (Scheme 1). (S)-Proline has also been used as another neutral catalyst for this reaction at reflux.

![Scheme 1](image)

Al-Haiza and co-workers synthesized coumarin derivatives by the condensation of 4-hydroxycoumarin (4-hydroxy-2H-1-benzopyran-2-one) with \(\alpha\)-cyano-\(p\)-bromocinnamnonitrile in ethanol containing a catalytic amount of piperidine in ethanol to afforded a product (Scheme 2).

![Scheme 2](image)

Xia and co-workers synthesized pyrano[3,2-c]chromenes derived from 4-hydroxycoumarin and Baylis–Hillman bromides using DABCO (1,4-diazabicyclo[2.2.2]octane) as a catalyst and acetone as a solvent under reflux condition (Scheme 3).

![Scheme 3](image)
Zhang et al. performed\textsuperscript{12} synthesis of dihydropyrano[3,2-c]chromene derivatives by one pot three-component reaction of aldehydes, malononitrile, and 4-hydroxycoumarin in the presence of hexamethylenetetramine (Scheme 4).

\begin{center}
\begin{tikzpicture}
\node[anchor=west] at (0,0) \text{R};
\node[anchor=west] at (2,0) \text{CH}O;
\node[anchor=west] at (4,0) \text{CN};
\node[anchor=west] at (8,0) \text{OH};
\node[anchor=west] at (10,0) \text{NH}_2;
\node[anchor=west] at (12,0) \text{CN};
\node[anchor=west] at (14,0) \text{R};
\node[anchor=west] at (16,0) \text{EtOH};
\node[anchor=west] at (18,0) \text{(CH}_2\text{)}_3\text{N}_4;
\end{tikzpicture}
\end{center}

\textbf{Scheme 4}

Naliapara et al. studied\textsuperscript{13} the three component reaction between 4-hydroxycoumarin, malononitrile and carbonyl compounds in ethanol in the presence of morpholine as a catalyst for the synthesis of pyrano[3,2-c]chromenes (Scheme 5).

\begin{center}
\begin{tikzpicture}
\node[anchor=west] at (0,0) \text{R};
\node[anchor=west] at (2,0) \text{CN};
\node[anchor=west] at (4,0) \text{CN};
\node[anchor=west] at (8,0) \text{OH};
\node[anchor=west] at (10,0) \text{NH}_2;
\node[anchor=west] at (12,0) \text{CN};
\node[anchor=west] at (14,0) \text{R};
\node[anchor=west] at (16,0) \text{EtOH, reflux};
\node[anchor=west] at (18,0) \text{Morpholine};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5}

Heravi et al. introduced\textsuperscript{14} three-component one-pot synthesis of 2-amino-5-oxo-dihydropyrano[3,2-c]chromene derivatives by condensing 4-hydroxycoumarin, aldehydes and alkynitriles using $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$ $18\text{H}_2\text{O}$ in aqueous ethanol under heating conditions (Scheme 6).

\begin{center}
\begin{tikzpicture}
\node[anchor=west] at (0,0) \text{R};
\node[anchor=west] at (2,0) \text{CH}O;
\node[anchor=west] at (4,0) \text{CN};
\node[anchor=west] at (8,0) \text{OH};
\node[anchor=west] at (10,0) \text{NH}_2;
\node[anchor=west] at (12,0) \text{CN};
\node[anchor=west] at (14,0) \text{R};
\node[anchor=west] at (16,0) \text{EtOH};
\node[anchor=west] at (18,0) \text{H}_2\text{O};
\node[anchor=west] at (20,0) \text{EtOH};
\node[anchor=west] at (22,0) \text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$ $18\text{H}_2\text{O}$;
\end{tikzpicture}
\end{center}

\textbf{Scheme 6}

Khurana and Kumar\textsuperscript{15} reported a procedure using tetrabutylammonium bromide as catalyst for the synthesis of biscoumarin and dihydropyrano[c]chromene derivatives in water and solvent-free neat conditions (Scheme 7).
Scheme 7

Shestopalov et al. developed\textsuperscript{16} synthesis of dihydropyrano[c]chromene derivatives using triethylamine as catalyst in ethanol under reflux condition (Scheme 8).

Scheme 8

Khurana and co-workers reported\textsuperscript{17} DBU as catalyst for one-pot synthesis of 3,4-dihydropyrano[3,2-c]chromenes, from aldehydes, active methylene compounds and 4-hydroxycoumarin (Scheme 9).

Scheme 9

3C.3. PRESENT WORK

Some of the reported procedures require the use of toxic organic solvents, expensive catalysts and tedious workup. Thus, in view of the importance of chromenes for diverse therapeutic activity we considered it necessary to develop a general rapid, high yielding, environmentally benign and easy synthetic protocol for a variety of chromene derivatives.

In the present section we have synthesized pyrano[3,2-c]coumarin derivatives via one pot three component reaction of aldehyde, malononitrile, and 4-hydroxycoumarin using triethylammonium acetate [TEAA] as both catalyst as well as reaction media at room temperature (Scheme 10).
3C.4. RESULTS AND DISCUSSION

At first, amount of catalyst required to synthesize dihydropyrano[c]chromenes was investigated. Therefore initially, 10 mol % of catalyst was added to the reaction choosing synthesis of 2-amino-4-(4-chlorophenyl)-4H-benzo[h]chromene-3-carbonitrile (compound 4c) as a model reaction. By increasing the amount of catalyst by 20 mol%, 30 mol%, 40 mol%, 50 mol%, 60 mol% there is also increase in the yield of the product. But the result obtained with the use of 40 mol% was better as compared to others. Therefore, after complete optimization 40 mol % of the catalyst was found to be appropriate to carry the reaction forward (Figure 3).

![Figure 3. Optimization of catalyst](image)
Table 1: Optimization of solvent effect

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent : Catalyst</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water : TEAA</td>
<td>4 h</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>DCM : [TEAA]</td>
<td>4 h</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>THF : [TEAA]</td>
<td>4 h</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>EtOH : [TEAA]</td>
<td>4 h</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN : [TEAA]</td>
<td>4 h</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>[TEAA]</td>
<td>40 min</td>
<td>98</td>
</tr>
</tbody>
</table>

*Reaction condition: 4-Cl-benzaldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarin (1 mmol) and triethylammonium acetate (40 mol %) stirred at RT. *Yields were isolated.

Using optimized reaction condition of catalyst we also investigated the solvent effect on the present reaction. Reaction of 4-Cl-benzaldehyde, malononitrile and 4-hydroxycoumarin (Comp. c) was chosen as model reaction for optimization of solvent effect (Table 1). From result, H₂O, DCM, THF gives moderate amount of yield after 4h of reaction (Table 1, Entry 1, 2 & 3). EtOH and acetonitrile gives average amount of yield (Table, Entry 4 & 5). Finally, the better results were obtained when [TEAA] was used as solvent as well as catalyst (Table 1, Entry 6).

Table 2: Synthesis of pyrano[3,2-c]coumarin derivatives by stirring at room temperature.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>30</td>
<td>97</td>
<td>256-258</td>
</tr>
<tr>
<td>4b</td>
<td>2-Cl</td>
<td>35</td>
<td>96</td>
<td>267-269</td>
</tr>
<tr>
<td>4c</td>
<td>4-Cl</td>
<td>40</td>
<td>98</td>
<td>262-264</td>
</tr>
<tr>
<td>4d</td>
<td>4-Br</td>
<td>35</td>
<td>96</td>
<td>252-254</td>
</tr>
<tr>
<td>4e</td>
<td>2,4-Cl₂</td>
<td>40</td>
<td>95</td>
<td>257-259</td>
</tr>
<tr>
<td>4f</td>
<td>4-NO₂</td>
<td>45</td>
<td>94</td>
<td>260-262</td>
</tr>
<tr>
<td>4g</td>
<td>3-NO₂</td>
<td>50</td>
<td>94</td>
<td>261-263</td>
</tr>
<tr>
<td>4h</td>
<td>4-OH</td>
<td>55</td>
<td>93</td>
<td>265-267</td>
</tr>
<tr>
<td>4i</td>
<td>4-CH₃O</td>
<td>50</td>
<td>91</td>
<td>242-244</td>
</tr>
<tr>
<td>4j</td>
<td>4-CH₃</td>
<td>45</td>
<td>92</td>
<td>251-252</td>
</tr>
<tr>
<td>4k</td>
<td>Vanillin</td>
<td>55</td>
<td>89</td>
<td>252-254</td>
</tr>
<tr>
<td>4l</td>
<td>2-thiopene</td>
<td>60</td>
<td>87</td>
<td>228-230</td>
</tr>
</tbody>
</table>

*Isolated yields, *Melting points were matched with literature data. 12, 14, 15
With the help of optimization of catalyst and solvent effect the scope and efficiency of the catalyst approach was explored for the synthesis of a wide variety of substituted pyrano[3,2-c]chromene-5-ones and the obtained results are summarized in Table 2. Series of differently substituted 2-amino-4-aryl-4H-benzo[h]chromene derivatives were prepared from different aromatic aldehydes bearing electron-withdrawing and electron-donating groups which underwent condensation with good to better yields (Table 2, entries 4a-l). Heteroaromatic aldehydes was also examined such as 2-thiophenecarbaldehyde which undergoes condensation with good yield (Table 2, Entry 1). We do not observe any obvious effect due to the nature of electronic effect on the aromatic ring. All the products were obtained were isolated smoothly to afford the desired product.

3C.5. Conclusions

In conclusion we have developed a new and effective methodology for the eco-compatible preparation of pyrano[3,2-c]coumarin derivatives via one-pot three component reaction. The use of triethylammonium acetate as inexpensive catalyst, avoiding use of hazardous organic bases and organic solvents, easy workup, short reaction times, and mild reaction conditions make this method very attractive and practical.
3C.6. EXPERIMENTAL SECTION

General procedure for the synthesis of Pyrano[3,2-c]coumarin derivatives (4a-l):

A mixture benzaldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarin (1 mmol) and triethylammonium acetate (40 mol%) was taken in a 25 ml RBF and stirred at room temperature for appropriate time. Course of the reaction was monitored by TLC. After completion of reaction, mixture was poured on ice cold water and obtained solid product was collected by filtration. Further purification was accomplished by recrystallization from ethanol to afford final product which was in full agreement with the spectral data.

Spectral analysis:

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (DMSO-\textit{d}_6, 300 MHz)} & \quad \delta \text{ ppm } = \\
& \quad 5.37 (s, 1H, -CH), 7.47 (s, 2H, NH_2), 8.10-8.77 (m, 8H, Ar-H).
\end{align*}
\]

MASS : 351 [M+1].
$^1$H NMR Spectra

2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4c)
MASS Spectra

2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4c)
3C.7. REFERENCES


SECTION D

TRIETHYLAMMONIUM ACETATE CATALYZED SYNTHESIS OF

ARYLIDENE-2-THIOHYDANTOIN DERIVATIVES
3D.1. INTRODUCTION

Thiohydantoins and their derivatives represent an important class of biologically active molecules having broad medicinal as anticancer, antidiabetic, antimicrobial, antiarrhythmic, hypolipidemic, and hypotensive, and agrochemical (herbicidal and fungicidal) applications. Furthermore, many thiohydantoins are responsible for inhibition of fatty acid hydrolases, glycogen phosphorylases, amylases, serine proteases, antimycobacterial, antiviral, and anticonvulsant indications, and for the treatment of schistosomiasis infections (Figure 1).

They are also useful synthons in natural product synthesis. Complex natural products such as the tetracyclic core of styloguanidine (a) and hymenialdisine (b), and
bioactive heterocycles possessing a glycociamidine ring are commonly synthesized from their corresponding thiohydantoins.

Additionally, 2-thiohydantoins have been used as reference standards for the development of C-terminal protein sequencing as reagents for the development of dyes and in textile printing, metal cation complexation and polymerization catalysis.

3D.2. LITERATURE REVIEW

Chauhan et al. synthesized multicomponent reaction producing arylmethylene-2-thiohydantoins (Scheme 1).

\[
\text{Scheme 1}
\]

Vatsadze et al. synthesized first organic-inorganic hybrid material based on AgNO\textsubscript{3} and 3-pyridine containing 2-thiohydantoin (Scheme 2).

\[
\text{Scheme 2}
\]

Perrissin et al. introduced synthesis and physic-chemical properties of new 3-benzyl-4-thioxo-5-arylideneimidazolidine-2-ones. It was synthesized by the reaction of aldehyde and 4-thioxoimidazolidine-2-ones in presence of glacial acetic acid and sodium acetate at 150 °C (Scheme 3).

\[
\text{Scheme 3}
\]

Sádor et al. prepared 5-substituted hydantoins and thiohydantoins by condensing with aldehydes in presence of ethanolamine at 80 °C (Scheme 4).
Abdelaziz et al. synthesized\textsuperscript{23} 5-substituted arylidene-2-thiohydantoin derivatives using catalytical amount of triethylamine and ethanol as a solvent by refluxing (Scheme 5).

Gašparová and Lácová\textsuperscript{24} present a survey of condensation of 3-formyl chromone with active methylene eg thiohydantoin in presence of sodium acetate and acetic anhydride as acylating reagent (Scheme 6).

Lesyk et al.\textsuperscript{25} synthesized 5-arylidene-2-amino-4-azolones and evaluation of their anticancer activity. In this report 5-arylidene-2-thiohydantoin has been synthesized by the reaction of aldehyde and 2-thiohydantoin using acetic acid and sodium acetate under reflux condition (Scheme 7).

Greeg and co-worker performed\textsuperscript{26} Lewis Acid Catalyzed Synthesis of a 3-Substituted 5-Arylidene-1-methyl-2-thiohydantoin Library (Scheme 8).
Khodair and Ibrahim\textsuperscript{27} synthesized arylidene thiohydantoin at 5-position using piperidine in ethanol with reflux at 60-70 °C (Scheme 9).

In the present work we have synthesized one pot three component benzylidene-2-thiohydantoin (BTH) derivatives in presence of triethylammonium acetate [TEAA] as a catalyst as well as reaction media. Synthesis of BTH was carried out by multicomponent one pot reaction of substituted aldehydes, glycine and potassium thiocyanate in presence of triethylammonium acetate (Scheme 10).
3D.4. RESULTS AND DISCUSSION

Initially, amount of catalyst required for the synthesis of 5-arylidene-2-thiohydantoins was investigated. Therefore, by choosing 4-chloro-benzaldehyde, glycine and potassium thiocyanate as model reaction we examined the required amount of catalyst to forward the reaction. At first, 5 mol% of the [TEAA] was added to the model reaction mixture and heated at 60 °C, the reaction proceeds by giving 68% of the yield. As we increase the quantity of catalyst the obtained yields were also found to be increased. But 20 mol% of [TEAA] was found to be appropriate and minimum amount of catalyst which also increase the rate of the reaction and gives maximum yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>94</td>
</tr>
</tbody>
</table>

*Reaction was heated for 30 mins*  
*Isolated Yield.*

In order to explore the scope of the methodology several other substituted aldehydes were investigated with this protocol. The results are summarized in Table 1. The effect of electron and the nature of substituents on the aromatic ring did not show strongly obvious effects in terms of yield under the reaction conditions. The three component reaction proceeded smoothly in [TEAA] to give the corresponding products 4 in high yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl, alkyl, alkoxy) were employed and reacted well to give the corresponding aryldene-2-thiohydantoins in good to excellent yields (Table 2).

<p>| Table 2: Synthesis of benzylidene-2-thiohydantoin (BTH) derivatives in presence of triethylammonium acetate [TEAA]. |</p>
<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M.P. (°C)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>30</td>
<td>96</td>
<td>268-269</td>
</tr>
<tr>
<td>3b</td>
<td>4-Cl</td>
<td>30</td>
<td>95</td>
<td>281-280</td>
</tr>
<tr>
<td>3c</td>
<td>2,4-Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>30</td>
<td>94</td>
<td>271-273</td>
</tr>
<tr>
<td>3d</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>92</td>
<td>294-296</td>
</tr>
<tr>
<td>3e</td>
<td>4-Me</td>
<td>35</td>
<td>91</td>
<td>279-280</td>
</tr>
<tr>
<td>3f</td>
<td>4-OMe</td>
<td>35</td>
<td>93</td>
<td>264-265</td>
</tr>
<tr>
<td>3g</td>
<td>4-OH</td>
<td>40</td>
<td>90</td>
<td>303-304</td>
</tr>
<tr>
<td>3h</td>
<td>2,4-(OMe)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>45</td>
<td>92</td>
<td>218-219</td>
</tr>
<tr>
<td>3I</td>
<td>2-OMe</td>
<td>40</td>
<td>91</td>
<td>239-241</td>
</tr>
<tr>
<td>3j</td>
<td>4-NMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>50</td>
<td>89</td>
<td>249-251</td>
</tr>
<tr>
<td>3k</td>
<td>2-furan</td>
<td>55</td>
<td>87</td>
<td>259-261</td>
</tr>
<tr>
<td>3l</td>
<td>2-thiophene</td>
<td>60</td>
<td>85</td>
<td>252-253</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields, <sup>b</sup>Recorded melting points and compared with literature data.<sup>28,29</sup>

### 3D.5. Conclusions

It can be concluded that, introduction of [TEAA] can be considered as an interesting new alternate route for synthesis of arylidene-2-thiohydantoin derivatives. The merit of this method includes solvent-free, highly inexpensive, ease of handling, easily recycling and reuse of the catalyst. Therefore with increasing “green” concern, the solvent-free conditions employed in the present method will make it environment friendly and useful for industrial applications. Further application of [TEAA] for other reaction systems are under investigation.
3D.6. EXPERIMENTAL SECTION

General procedure for synthesis of arylidene2-thiohydantoin derivatives

A mixture of 4-OMe-benzaldehyde (10 mmol), potassium thiocyanate (10 mmol), glycine (10 mmol) and triethyl ammonium acetate (20 mol%) was taken in 25ml RBF and heated at 60°C for 30 mins. The progress of the reaction was monitored on TLC plates. After completion of reaction the mixture was extracted with diethyl ether for separation of catalyst. The extracted mass was evaporated under reduced pressure to obtain the solid product. The obtained product was again recrystallized from ethanol to afford pure product. The final product was in full agreement with the spectral analysis.

Spectral analysis: 5-(4-methoxybenzylidene)-2-thioxoimidazolidin-4-one (3f)

IR: IR (KBr, cm⁻¹)= 2869, 1688, 1593, 1206, 755.

¹H NMR (CDCl₃, 200 MHz): δ ppm = 3.21 (s, 1H, -NH), 3.24 (s, 1H, -NH), 3.90 (s, 3H, -OCH₃), 6.78 (s 1H, Vinylic proton), 6.93-7.00 (m- 2H, Ar-H), 7.30-7.37 (m, 1H, Ar-H), 7.67-7.71 (d, 1H, Ar-H).

MASS : 235 [M+1].
$^1$H NMR

5-(4-methoxybenzylidene)-2-thioximidazolidin-4-one (3f)
MASS Spectra

5-(4-methoxybenzylidene)-2-thioximidazolidin-4-one (3f)
5-(4-methoxybenzylidene)-2-thioxoimidazolidin-4-one (3f)
3D.7. REFERENCES


