Ionic liquid [Et$_3$NH][HSO$_4$]-catalyzed Multicomponent Synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyran[2,3-c] pyrazole-5-carbonitrile

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Graphical Abstract:
Ionic liquid [Et₃NH][HSO₄]-catalyzed Multicomponent Synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

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Abstract: A series of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitriles(5a-5j) as a potent anticancer agent were synthesized via one-pot, four-component condensation reaction of aryl aldehydes, ethyl acetoacetate, malononitrile, and hydrazine hydrate in solvent-free conditions using ionic liquid[Et₃NH][HSO₄] as an efficient, eco-friendly and reusable catalyst. The Multicomponent coupling reactions (MCRs) indicate a highly appreciated synthetic tool for the establishment of novel and complex molecular scaffold with a minimum number of synthetic steps with the advantage like shorter reaction times, lower costs, high degrees of atom economy etc. With the literature survey it is found that dihydropyrano[2,3-c]pyrazole derivatives possess very important biological activities, including anticancer, antiinflammatory, antimicrobial, inhibitors of human Chk1 kinase, molluscicidal, and insecticidal activities. The solvent used in conventional organic synthesis are suffered by many disadvantage like environmental hazards, toxicity, volatile nature, expensive etc. A new term ‘designer solvents’ refers to Ionic liquids because of their adjustable physical and chemical properties with the change in selected cationic and anionic combination. Ionic liquids have become a promising alternative media for various chemical processes due to their properties including good solvating capability, negligible vapour pressure, non-inflammability, ease of recyclability, controlled miscibility and high thermal stability. Herein we are introducing first time the use of acidic Bronsted ionic liquid(ABILs)[Et₃NH][HSO₄] triethyl ammonium sulphate for the synthesis of biologically important scaffold 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, the synthesised derivatives subjected to anticancer activity. Compared to other methods, this new method consistently has advantages, including excellent yields, a short reaction time, mild reaction conditions and catalyst reusability.

Keywords: Ionic liquid, Solvent free, Multicomponent Synthesis, Dihydropyrano[2,3-c]pyrazoles.

Introduction:

In modern synthetic organic chemistry, Multi-component reactions have been established as efficient and prominent tool assisting the reaction of three or more components in one pot to give new “drug-like” molecules with the essential parts of all the initial reactants. Multi-component reactions contribute to the needs of an eco-friendly methods of synthesis of simple and complex building blocks offering significant advantages such as variety of convergent synthesis of complex organic compounds, facile mechanism, atom economy, low cost, shorter reaction and workup time, easy purification processes, and minimum wastage [1,2]. So Multicomponent reactions gain an outstanding position in medicinal and organic chemistry by implementation of principles of
green chemistry. In modern era, academicians and industrialist are looking for green protocols for the synthesis of chemical processes to conquer eco-friendliness [3]. To replace conventional media or solvents used for organic synthesis is very essential as they show some side effects including toxicity, flammable and volatile nature so research is progressing in finding alternative greener media for commonly used organic synthesis [4]. Research and development of room-temperature ionic liquids are acting as best replacement to conventional media with the advantages such as chemoselectivity and facile condensation reactions [5,6,7].

In organic synthesis green chemistry is now a days acting as boon with the use of deliberately important solvents so called a ‘designer solvents’ referring to Ionic liquids because of their adjustable physical and chemical properties with the change in selected cationic and anionic combination. Ionic liquids have become a promising alternative media for various chemical processes due to their properties including good solvating capability, negligible vapour pressure, non-inflammability, ease of recyclability, controlled miscibility and high thermal stability [8,9]. Hence acting as very excellent catalysts, as well as solvents, for many organic transformations [10]. Acidic Bronsted Ionic Liquids (ABILs) are of special importance, because they simultaneously possess proton acidity and the characteristic properties of ionic liquids. ABILs offer environmental friendly catalyst properties due to the combination of the advantages of liquid acids and solid acids, such as uniform acid sites, stability in water and air, easy separation and reusability [11]. In recent times, the value of Acidic Bronsted Ionic Liquid (ABIL), mainly [Et$_3$NH][HSO$_4$] has acknowledged as a catalyst and solvent of choice for organic transformation with excellent yield. [Et$_3$NH][HSO$_4$] ionic liquid posses advantages as non-toxic, inexpensive, easy preparation with readily available starting reactants [12,13].

Organic chemist are always looking for the synthesis of new moiety with some biological effect. Pyrano[2,3-c]pyrazoles are such recently synthesised scaffold with numerous biological activity [14] including anticancer–antitumor [15], antimicrobial [16], anti-inflammatory [17], analgesic [18] inhibitors of human chk1 kinase [19]. Molluscicidal and insecticidal activity [20] also acting as potent pharmaceutical constituents and biodegradable agrochemicals [21,22,23]. Due to the broad spectrum of important biological activity associated with Pyrano[2,3-c]pyrazoles we planned to synthesize this moiety by multicomponent, one pot cyclocondensation of aromatic substituted aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate.

Synthesis of dihydropyrano[2,3-F]pyrazoles can be achieved by various methodology with several catalyst are reported in literature including use of Piperazine [24], Piperidine [25], N-methylmorpholine [26], heteropolyacids [27], glycine [28], per-6-amino-b-cyclodextrin [29], Mg/Al hydrotalcite [30], nanosized magnesium oxide [31], L-proline [32], Y-alumina [33], sodium benzoate [34] and amberlyst A21 [35], CTACl [36].

Junek and Aigner [37] first time introduced the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine as a catalyst. Sharanin and sharanina [38] also reported synthesis of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazoles using triethylamine. The use of Triethyl amine for the synthesis of pyranopyrazole moiety in early period has given us an idea to work on the ionic liquid containing triethyl amine as catalyst therefore we selected very efficient Acidic Bronsted Ionic Liquid (ABIL), Triethyl ammonium Sulphate [Et$_3$NH][HSO$_4$] [39] as catalyst for present synthesis. This ionic liquid posses significant characteristics such as, cost effective, non-toxic, catalyst as well as solvent for many organic transformations giving excellent yield. Herein we are reporting synthesis of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (5a-j) with excellent yield at room temperature using Ionic liquid [Et$_3$NH][HSO$_4$] as catalyst as well as solvent and introducing one more
novel green chemistry protocol in the list of methods of synthesis for pyrano[2,3-c]pyrazole derivatives as important biologically active scaffold.

Results and discussion:

![Chemical structure and reactions](image)

**Scheme 1.** Synthesis of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (5a-5j)

**Table 1.** Physical characterization of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield(%)</th>
<th>Mp(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>-Ph</td>
<td>88</td>
<td>240-242</td>
</tr>
<tr>
<td>5b</td>
<td>4-Cl-Ph</td>
<td>94</td>
<td>228-230</td>
</tr>
<tr>
<td>5c</td>
<td>4-F-Ph</td>
<td>92</td>
<td>172-174</td>
</tr>
<tr>
<td>5d</td>
<td>4-OCH₃</td>
<td>94</td>
<td>205-207</td>
</tr>
<tr>
<td>5e</td>
<td>4-OH</td>
<td>88</td>
<td>219-221</td>
</tr>
<tr>
<td>5f</td>
<td>4-OH-3-OMe-Ph</td>
<td>85</td>
<td>232-234</td>
</tr>
<tr>
<td>5g</td>
<td>3,4-(OMe)₂-Ph</td>
<td>87</td>
<td>185-187</td>
</tr>
<tr>
<td>5h</td>
<td>3-NO₂</td>
<td>88</td>
<td>188-190</td>
</tr>
<tr>
<td>5i</td>
<td>2-thiophenyl</td>
<td>89</td>
<td>222-224</td>
</tr>
<tr>
<td>5j</td>
<td>4-benzylxoy-Ph</td>
<td>88</td>
<td>212-214</td>
</tr>
</tbody>
</table>

Herein we also compared the reported ionic liquid with other three solvent as comparison for the synthesis of dihydropyrano[2,3-c]pyrazole in which [Et₃NH][HSO₄] provided better results in terms of high yield and a solvent-free protocol, and the reaction was carried out at room temperature and so we find it most significant method of synthesis.
Table 2 Screening of reaction media for the synthesis of compound 5a-5j

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time in minutes</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Ionic liquid (N-methylpyridiniumtosylate)</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>DES(At 80°C)</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>[Et₃NH][HSO₄] (At RT)</td>
<td>15</td>
<td>94</td>
</tr>
</tbody>
</table>

All the final compounds (5a-5j) were synthesised following the procedure depicted in scheme I. Synthesis is carried out in one pot by adding all the reactant at a time with equimolar ratio as substituted aromatic aldehyde(1mmol), malononitrile(1mmol), hydrazine hydrate(1mmol) and ethyl acetoacetate(1mmol) initially, the reaction was carried out in the absence of the catalyst; no product is obtained so catalyst is added increasing amount to determine the appropriate concentration of the catalyst and solvent [Et₃NH][HSO₄], we investigated the model reaction at different concentrations of [Et₃NH][HSO₄], such as 0,5, 10, 15, 20 and 25 mol%. The dihydropyrano[2,3-c]pyrazole formed in 0,50,65,70,94 and 85 % yields, respectively(Table 2). The increase in concentration of catalyst from 20 to 25 mol% does not increase the yield of product. This indicates that 20 mol% of [Et₃NH][HSO₄] is sufficient for the reaction by considering the product yield.

Table 3 Effect of ionic liquid concentration on reaction time and yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Et₃NH][HSO₄] mol%</th>
<th>Time in minutes</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>60</td>
<td>00</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>10</td>
<td>85</td>
</tr>
</tbody>
</table>

We have also statistically reported the recyclability of the ionic liquid [Et₃NH][HSO₄] in Table 4. After the completion of the reaction, the reaction mixture was quenched with ice crystals and extracted with ethyl acetate. The residual ionic liquid was washed with diethyl ether, dried under vacuum at 60 and reused for subsequent reactions. The recovered ionic liquid could be used for four times without much loss of catalytic activity.

Table 4 Reusability of ionic liquid for model reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Run</th>
<th>Time in min</th>
<th>Yield in%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>15</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>15</td>
<td>75</td>
</tr>
</tbody>
</table>

With extreme high literature survey of all available method of multi component one pot cyclo condensation synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile herein as far as our genuine knowledge first time we are introducing the use of this green medium i.e. Acid Bronsted
Ionic Liquid [Et₃NH][HSO₄] as solvent and catalyst in 20mol% at room temperature in 10 to 15 minutes with excellent yield up to 94%.

Material & Methods:

General Information

All the chemicals used for synthesis were procured from Merck (Mumbai, Maharashtra, India), Sigma (Mumbai), HiMedia (Mumbai) or Qualigens (Mumbai) and used without further purification. The progress of each reaction was monitored by ascending thin layer chromatography (TLC) using pre-coated silica gel F254 aluminum TLC sheets (Merck) and the spots were visualized by UV light and iodine vapors. Elemental analyses (C, H, and N) were done with a FLASHEA 112 Shimadzu analyzer (Mumbai) and all analyses were consistent (within 0.4%) with theoretical values. Infrared (IR) spectra were recorded on a PS 4000 FTIR (JASCO, Tokyo, Japan) using KBr pellets. ¹H-(400MHz) and ¹³C-NMR (100 MHz) spectra were recorded on a BRUKER AVANCE 400NMR spectrometer (Bruker, Billerica, MA, USA) fitted with an Aspect 3000 computer and all the chemical shifts (δppm) were referred to internal TMS for ¹H and DMSO-d₆ for ¹³C-NMR. ¹H-NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; br s, broad singlet; m, multiplet and/or multiple resonance), number of protons. A Micro TOF-Q-II (Bruker Daltonics, Billerica, MA, USA) with electron spray ionization (ESI) was used to obtain the HRMS data.

Synthesis of [Et₃NH][HSO₄]: 98% solution of Sulphuric acid (1.96 g, 0.02 mol) in water was dropped into triethylamine (2.02 g, 0.02 mol) with stirring at 60°C for 1 h. After the addition, the reaction mixture was stirred for another 1 h at 70°C. The water molecule was removed by heating the residue at 80–90°C under a high vacuum until the weight of the residue remained constant.

Synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile:

A mixture of substituted aromatic benzaldehyde (1) (1 mmol), malononitrile (2) (1 mmol), hydrazine hydrate (3) (1 mmol), and ethyl acetoacetate (4) (1 mmol) was added in [Et₃NH][HSO₄] 20mol% and then the reaction mass was stirred at room temperature. Progress of the reaction was monitored by TLC (ethyl acetate: n-hexane 1:9). After 15 min of stirring, the reaction mixture was cooled to room temperature. It was extracted using ethyl acetate. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate.

The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were recrystallized using ethanol. An important feature of this method is that both electron-releasing and withdrawing groups give excellent yields.

5a) 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

Yield 88%, mp 240-242°C: IR (KBr, cm⁻¹): 329 (N–H), 3122 (Ar–H), 2936 (C–H), 2208 (C–N), 1598 (C=N), 1152 and 1215 (C–O–C); ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.86 (s, 3H, –CH₃), 4.51 (s, 1H, –CH–), 6.99–7.76 (m, 5H, Ar–H) 8.45 (s, 2H, –NH₂), 12.02 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d₆): δ ppm 8.85, 34.69, 150.57, 94.69, 96.48, 112.57, 119.69, 127.35, 134.73, 134.79, 153.84, 151.157.23 and 159.45; MS (ESI) m/z: 252.10 (100.0%), 253.10 (16.6%), 254.11 (1.3%)Elemental Analysis Calculated for C₁₄H₁₂N₄O: C, 66.65; H, 4.79; N, 22.21; Found C, 66.67; H, 4.75; N, 22.21

5b) 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile
Yield 94%, mp 228-230°C; IR(KBr, νmax, cm⁻¹): 3380 (N–H), 3281 (Ar–H), 2193 (C–H), 1598 (C=N), 1152 and 1215 (C–O–C), 744 (C–Cl); ¹H NMR (400 MHz, DMSO-d6): δ ppm 1.80 (s, 3H, –CH₃); 4.58 (s, 1H, –CH=); 7.68-7.73 (m, 4H, Ar–H); 8.2 (s, 2H, –NH₂); 12.06 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d6): δ ppm 9.72, 40.18, 56.82, 120.5, 129.1, 131.3, 135.4, 143.2, 154.6, 160.8; MS (ESI) m/z: 286.06 (100.0%), 288.06 (32.2%), 287.07 (15.3%), Elemental Analysis Calculated for: C₁₄H₁₂ClN₂O C, 58.65; H, 3.87; N, 19.54; Found: C, 58.61; H, 3.82; N, 19.50

5c) 6-amino-4-(4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Yield 92%, mp 172-174°C; IR(KBr, νmax, cm⁻¹): 3388 (N–H), 3280 (Ar–H), 3055 (C–H), 1640 (CN), 1160 and 1220 (C–O–C); ¹H NMR (400 MHz, DMSO-d6): δ ppm 1.92 (s, 3H, –CH₃); 4.60 (s, 1H, –CH=); 7.12-7.21 (m, 4H, Ar–H); 7.88 (s, 2H, –NH₂); 12.04 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d6): δ ppm 13.13, 25.5, 59.2, 113.4, 117.3, 115.4, 130.6, 139.1, 159.9, 163.7, 176.1; MS (ESI) m/z: 270.09 (100.0%), 271.10 (15.3%), 271.09 (1.5%), Elemental Analysis Calculated for: C₁₄H₁₂FNO; C, 62.22; H, 4.10; N, 20.73; Found: C, 62.22; H, 4.10; N, 20.73

5d) 6-amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Yield 92%, mp 203-207°C; IR(KBr, νmax, cm⁻¹): 3483 (N–H), 3280 (Ar–H), 2930 (C–H), 2208 (C–N), 1598 (C=N), 1450 (C=O–C), 1152 and 1215 (C–O–C); ¹H NMR (400 MHz, DMSO-d6): δ ppm 1.79 (s, 3H, –CH₃); 3.74 (s, 3H, –OCH₃); 4.51 (s, 1H, –CH=); 6.80-7.0 (m, 4H, Ar–H); 8.2 (s, 2H, –NH₂); 12.0 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d6): δ ppm 11.5; 24.5; 55.4; 70.4; 114.7; 115.2; 127.8; 129.2; 140.5; 143.8; 153.3; 159.9; 160.0; MS (ESI) m/z: 282.11 (100.0%), 283.12 (16.5%), 284.12 (1.7%), Elemental Analysis Calculated for: C₁₄H₁₂NO₂; C, 63.82; H, 5.00; N, 19.85; Found: C, 63.78; H, 5.05; N, 19.82

5e) 6-amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Yield 88%, mp 219 to 221°C; IR(KBr, νmax, cm⁻¹): 3470 (N–H), 3270 (Ar–H), 2940 (C–H), 2198 (C–N), 1600 (C=N), 1145 and 1200 (C–O–C); ¹H NMR (400 MHz, DMSO-d6): δ ppm 2.00 (s, 3H, –CH₃); 4.46 (s, 1H, –CH=); 5.44 (s, 1H, –OH); 6.33-7.06 (m, 4H, Ar–H); 8.52 (s, 2H, –NH₂); 11.90 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d6): δ ppm 12.0; 25.0; 59.0; 113.6; 119.5; 127.0; 130.2; 141.5; 143.8; 155.4; 163.5; 179.1; MS (ESI) m/z: 268.10 (100.0%), 269.10 (15.4%), 270.10 (1.7%), Elemental Analysis Calculated for: C₁₄H₁₂NO₂; C, 62.68; H, 4.51; N, 20.88; Found: C, 62.70; H, 4.48; N, 20.87; 5f) 6-amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Yield 85%, mp 232 to 234°C; IR(KBr, νmax, cm⁻¹): 3583 (N–H), 3180 (Ar–H), 2830 (C–H), 2308 (C–N), 1590 (C=N), 1440 (C=O–C), 1200 and 1222 (C–O–C); ¹H NMR (400 MHz, DMSO-d6): δ ppm 2.00 (s, 3H, –CH₃); 3.80 (s, 3H, –OCH₃); 4.46 (s, 1H, –CH=); 5.44 (s, 1H, –OH); 6.33-7.06 (m, 3H, Ar–H); 8.50 (s, 2H, –NH₂); 11.95 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d6): δ ppm 12.0; 25.0; 59.0; 113.6; 119.5; 127.0; 130.2; 141.5; 143.8; 155.4; 163.5; 179.1; MS (ESI) m/z: 298.11 (100.0%), 299.11 (16.5%), 300.11 (2.1%), Elemental Analysis Calculated for: C₁₄H₁₂NO₂; C, 60.40; H, 4.73; N, 18.78; Found: C, 60.38; H, 4.70; N, 18.75

5g) 6-amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Yield 87%, mp 185 to 187°C; IR(KBr, νmax, cm⁻¹): 3500 (N–H), 3190 (Ar–H), 2850 (C–H), 2318 (C–N), 1580 (C=N), 1400 (C=O–C), 1190 and 1225 (C–O–C); ¹H NMR (400 MHz, DMSO-d6): δ ppm 2.07 (s, 3H, –CH₃); 3.70 (s, 6H, –OCH₃); 4.61 (s, 1H, –CH=); 6.80-7.16 (m, 3H, Ar–H); 7.52 (s, 2H, –NH₂); 11.99 (s, 1H, –NH); ¹³C NMR (100 MHz, DMSO-d6): δ ppm 11.5; 24.5; 55.4; 70.4; 114.7; 115.2; 127.8; 129.2; 140.5; 143.8; 153.3; 159.9; 160.0;
MS (ESI) m/z: 312.12 (100.0%), 313.13 (17.6%), 314.13 (2.1%), Elemental Analysis Calculated for: C_{16}H_{16}N_{4}O_{3}: C, 61.53; H, 5.16; N, 17.94; Found: C, 61.50; H, 5.12; N, 17.92

5h) 6-amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyran[2,3-c]pyrazole-5-carbonitrile
Yield 88%, mp 188-190°C; IR (KBr, ν max, cm^{-1}): 3365 (N–H), 3222 (Ar–H), 2936 (C–H), 2208 (C–N), 1598 (C=N), 1345 (NO2), 1152 and 1215 (C–O–C); ^1H NMR (400 MHz, DMSO-d6): δ ppm 2.03 (s, 3H, CH3); 4.75 (s, 1H, -CH-); 7.54-8.65 (m, 4H, Ar-H); 8.45 (s, 2H, -NH2); 11.88 (s, 1H, -NH); ^13C NMR (100 MHz, DMSO-d6): δ ppm 11.9; 26.3; 71.4; 112.4; 121.3; 127.6; 129.6; 133.1; 135.2; 141.6; 147.2; 151.4; 154.0; 160.1; MS (ESI) m/z: 297.09 (100.0%), 298.09 (15.4%), 299.09 (2.0%), Elemental Analysis Calculated for: C_{14}H_{11}N_{5}O_{3}: C, 56.56; H, 3.73; N, 23.56; Found: C, 56.58; H, 3.70; N, 23.52

4. Conclusion: In conclusion we have tried to developed an efficient, greener and prompt synthetic protocol for substituted dihydropyran[2,3-F]pyrazoles via one pot cyclocondensation of various aromatic aldehydes, ethyl acetooacetate, hydrazine hydrate, and malononitrile by using [Et3NH][HSO4] catalyst. This technique overcomes some of the problems associated with excessive or wasteful refluxing procedure. Remarkable advantages of this synthetic strategy are reaction performs at ambient room temperature in very less reaction time with nontoxic and economically viable catalyst by avoiding the use of solvent and lastly shortened work-up procedure. As far our knowledge this is the first report on the use of [Et3NH][HSO4] catalyst for the syntheses of substituted dihydropyran[2,3-F]pyrazoles.

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Author Contributions: U.D.N. research student, A.P.G.N. research guide, J.A.S.V. and M.P.V. co-operated for spectral analysis.
References:


[33] H. Mecadon, M. R. Rohman, M. Rajbangshi, B. Myrboh, g-Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrido[2,3-c]pyrazole-5-carbonitriles


[38] (a) Sharanin, Y. A.; Sharanina, L. G.; Puzanova, V. V. Zh. Org. Khim. 1983, 19, 2609; (b) Sharanin, Y. A.; Sharanina, L. G.; Puzanova, V. V. J. Org. Chem. USSR 1983, 221;

**SUPPLEMENTARY DATA**

**Table 1** Physical characterization of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

<table>
<thead>
<tr>
<th>Derivatives</th>
<th>R</th>
<th>(Mol. wt)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Analysis (%) Found [calculated]</th>
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<td>a</td>
<td><img src="image" alt="image" /></td>
<td>252.10</td>
<td>88</td>
<td>240-242</td>
<td>C, 66.65; H, 4.79; N, 22.21</td>
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<td></td>
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<td>[C, 66.67; H, 4.75; N, 22.21]</td>
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<tr>
<td>b</td>
<td><img src="image" alt="image" /></td>
<td>286.06</td>
<td>94</td>
<td>228-230</td>
<td>C, 58.65; H, 3.87; N, 19.54</td>
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<td>[C, 58.61; H, 3.82; N, 19.50]</td>
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<tr>
<td>c</td>
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<td>270.09</td>
<td>92</td>
<td>172-174</td>
<td>C, 62.22; H, 4.10; N, 20.73</td>
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<td>[C, 62.22; H, 4.10; N, 20.73]</td>
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<td>d</td>
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<td>94</td>
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<td>C, 63.82; H, 5.00; N, 19.85</td>
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<td>[C, 63.78; H, 5.05; N, 19.82]</td>
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<td>85</td>
<td>232-234</td>
<td>C, 60.40; H, 4.73; N, 18.78</td>
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<td>[C, 60.38; H, 4.70; N, 18.75]</td>
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<td>g</td>
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<td>88</td>
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<td>[C, 70.40; H, 5.10; N, 15.70]</td>
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Mass Spectra: 5b) 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Mass Spectra: 5d) 6-amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile
Current Data Parameters
BMRR: April 25, 2016
EXPNO: 580
PROCNO: 1

F2 - Acquisition Parameters:
Date: 20160426
Time: 3.27
INSTRUM: spect
PROBHD: 5 mm PABBO BB-
PULPROG: zg30
TD: 65536
SOLVENT: DMSO
NS: 8
DS: 2
SH: 12019.230 Hz
FIDRES: 0.183399 Hz
AQ: 2.7263477 sec
RG: 322
DW: 41.600 usec
DE: 6.00 usec
TE: 294.7 K
D1: 1.00000000 sec
T0: 1

--- CHANNEL f1 ---
NUC1: 1H
PL1: -3.00 dB
SF1: 400.1324710 MHz

F2 - Processing parameters:
SF: 400.1299952 MHz
FDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.00

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

manishkumarmanu1986@gmail.com
Current Data Parameters
NAME: Apr25-2016
EXPO: 500
PROCNO: 1

F2 - Acquisition Parameters
Date: 2016-04-26
Time: 3.55
INSTRUM: spect
PROBHD: 5 mm PABBO BB-
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NS: 512
DS: 4
SWH: 29761.904 Hz
FIDRES: 0.454131 Hz
AQ: 1.1010548 sec
RG: 1030
DW: 16.800 usec
DE: 6.00 usec
TE: 295.0 K
D1: 2.00000000 sec
d11: 0.03000000 sec
DELTA: 1.89999998 sec

======== CHANNEL f1 ========
NUC1: 13C
P1: 9.60 usec
PL1: -2.00 dB
SFO1: 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2: waltz16
NUC2: 1H
PCPD2: 80.00 usec
PL2: -3.00 dB
PL12: 14.31 dB
PL13: 18.00 dB
SFO2: 400.1316005 MHz

F2 - Processing parameters
SI: 32768
SF: 100.6128193 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

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