CHAPTER VI

Synthesis of 6-Amino-4-(4-substituted phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles
Abstract

Chapter VI gives the details of an efficient and ecofriendly one-pot multi-component cyclocondensation of aromatic aldehydes, malononitrile, hydrazine hydrate and ethylaceto acetate in deep eutectic solvent (choline chloride:urea), carried for obtaining 6-Amino-4-(4-substituted phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (5a-j). The synthetic sequences is presented in Scheme 6.2.
Introduction

Polyfunctionalized pyran and their derivatives are very important heterocyclic compounds, which frequently exhibit a variety of biological activities.\(^{1,2}\) 4H-Pyran is an important and common structural unit both in natural and synthetic heterocyclic molecules.\(^{3,4}\)

A number of 2-amino-4\(H\)-pyran derivatives are useful as photoactive materials.\(^{5}\) 4H-Pyran derivatives are potential calcium channel antagonists.\(^{6}\) They can be used in the treatment of neurodegenerative disease, including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS associated dementia, down syndrome, schizophrenia and myoclonus.\(^{7}\) 4H-Pyrans are also useful intermediates for the synthesis of various potentially active compounds, such as pyranopyrimidines,\(^{8}\) polyanzapthalenes,\(^{9}\) pyrano[2,3-d]pyrazoles,\(^{10}\) pyrano[2]pyrimidines\(^{11}\) and pyridin-2-ones.\(^{12}\) Moreover, 4H-pyrans can be transformed into the corresponding pyridines, related to important DHP type calcium antagonists.\(^{13}\)

The significance of pyrazoles has been well reviewed in the earlier sections. Pyrazole and pyrazolonyl ring systems represent an important class of compounds not only for their theoretical interest but also for their anti-inflammatory, postmenopausal osteophoresis, angiotensin antagonists, antibacterial, sedative and anticoagulant activities.\(^{14-16}\) The pharmacophoric moiety, 3,5-dimethylpyrazole was reported by Gerritsen et al. Based on this pharmacophoric system numerous compounds have been synthesized e.g. 1-(2,4-dinitrophenyl)-3,5-dimethyl-4-arylazopyrazoles and evaluated their antidiabetic activity. Later, a series of 4-arylhydrazono-N-guanynaminate-3-methyl-2-pyrazoline-5-ones have also been synthesized and evaluated their hypoglycemic activity.\(^{17}\)

Bertrand et al.\(^{18}\) synthesized pyrazole-4-carboxylic acids (6.1) as potent hypoglycemic agents. Maekawa et al.\(^{19}\) synthesized benzyl pyrazole phenylacetic acid (6.2) as a potent PPAR\(\gamma\) agonist with a half-maximal effective concentration.
Potential pharmacologically active compounds have been generated by exploring a wide variety of pyrazoles fused with different biodynamic heterocycles and have displayed various chemotherapeutic activities like antileukemic,\textsuperscript{20} antitumor,\textsuperscript{21} antimicrobial\textsuperscript{22} and antiviral\textsuperscript{23} agents. Substituted pyrazoles and condensed pyrazoles are gaining importance as pharmaceuticals and biodegradable agrochemicals.\textsuperscript{24} Hohn \textit{et al.}\textsuperscript{25} synthesized Pyrazolo[3,4-b]pyridines (6.3) and evaluated its antidiabetic activity. Das \textit{et al.}\textsuperscript{26} synthesized pyrazol-3-one derivative (6.4) as potential hypoglycemic agent.

Pyranopyrazoles are an important class of biologically active heterocycles. They are reported to possess a multiplicity of pharmacological properties including anticancer,\textsuperscript{27} antimicrobial,\textsuperscript{28} antinflammatory,\textsuperscript{29} insecticidal and molluscicidal.\textsuperscript{30} Pyrazolyl derivatives are also potential inhibitors of human Chk1 kinase.\textsuperscript{31} They also find applications as pharmaceutical ingredients and biodegradable agrochemicals.\textsuperscript{32} Michael \textit{et al.}\textsuperscript{33} synthesized fused pyrazolines (6.5) a PDE9 inhibitor having potential antidiabetic activity. Phosphodiesterase 9 (PDE9) is one of three cGMP specific enzymes out of the nineteen known PDE isoforms. There activity was investigated in patients with Type I and Type II diabetes. Om Prakash \textit{et al.}\textsuperscript{34} synthesized some new pyranopyrazole derivative (6.6) with a view to explore its potency as good analgesic and anti-inflammatory agents. Foloppe N\textsuperscript{35} synthesized pyranopyrazole (6.7) as an inhibitor of Chk 1 kinase.
Objectives of the Work

Pyranes and their fused derivatives have attracted a great deal of interest due to their wide range of biological activities. The incorporation of another heterocyclic moiety in pyranes either in the form of a substituent or as a fused component often leads to incredible diverse biological activities. In addition, pyrazoles act as core nucleus in various drugs due to the activities viz antidiabetic, anti-tumour, antipyretic, anti-inflammatory, anti-hypertensive and antidepressant. Literature survey reveals that there is scanty information on the pyranopyrazoles possessing antidiabetic activity.

Considering the pharmacological importance of 4H-pyrans and multifunctional fused pyrazoles here it was decided to design and synthesize some pyranopyrazoles having amino and cyano functionalities by novel one pot multicomponent synthesis and evaluate their antidiabetic activity.

Synthetic Plan

In view of the pharmacological significance of the pyranopyrazoles more attention has been found to develop better synthetic routes for pyranopyrazoles. Junek and co-worker first time established the synthesis of pyrano[2,3-c]pyrazoles, by condensing 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine. Later on, a number of synthetic approaches have also been attempted for obtaining 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazoles, employing triethylamine, piperazine and piperidine as prominent catalysts.

Various methods have been developed for the synthesis of these compounds using arylidene malononitriles, 3-methyl-5-pyrazolones or 4-arylidene-3-methyl-5-methyl-5-pyrazolones. The three component condensation of aromatic aldehydes, malononitrile and 3-methyl-5-pyrazolone has also been performed for obtaining the fused pyranopyrazoles. Shestopalov and coworkers have developed a chemical as well as an electrochemical methods for the synthesis of pyranopyrazoles via a three component condensation of N-methylpiperidone, pyrazoline-5-one and malononitrile. Recently pyranopyrazoles are synthesized by a two component reaction involving pyran derivatives and hydrazine hydrate and by four component reaction involving ethylacetoacetate, hydrazine hydrate, aldehydes and malononitrile.

Recently, some methods involving the use of cupreine, per-6-amino-β-cyclodextrin, glycine, γ-alumina, L-proline, nanosized magnesium oxide, and Mg/Al hydrotalcite are reported for obtaining the titled heterocycles.
The reported methods are effective but have one or other kind of limitations. Therefore, though having many reported methods for synthesizing 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles, the quest to provide new synthetic strategies using easily accessible catalysts is still continuing.

Nowadays, more focus is directed to perform sustainable chemistry, particularly the syntheses of value-added materials, in order to minimize the great amount of waste and consecutive treatments. One of the key principles of green chemistry is the elimination of solvents in chemical processes or the replacement of volatile/hazardous solvents with environmentally benign solvents. In performing the majority of organic transformations, solvents play a critical role in making the reaction homogeneous and hence facilitating molecular interactions.

In this connection, in this decade, chemists are paying more attention to the use of deep eutectic solvents (DESs) for carrying out various chemical transformations safely and rapidly. A DES is generally composed of two or three cheap and safe components which are capable of keeping association with each other through hydrogen bond interactions to form a eutectic mixture. The resulting DES is characterized by its melting point which is lower than that of individual components. Generally, DESs are characterized by a very large depression of freezing point and mostly are liquid at room temperature. In most cases, a DES is obtained by mixing a quaternary ammonium salt with metal salts (e.g., ZnCl$_2$) as hydrogen bond donors, having the ability to form a complex with the halide anion of the quaternary ammonium salt.

Owing to its low cost, biodegradability, and low toxicity, Choline chloride, 2-hydroxy-$N,N,N$-trimethylethanaminium chloride has been widely used as an organic salt to produce eutectic mixtures generally with cheap and safe hydrogen bond donors such as urea, polyols, and carboxylic acids. These DESs are attracting the researchers since they exhibit similar physicochemical properties to traditional imidazolium-based ionic liquids and thus, are found to be more advantageous in organic syntheses. Therefore, they are replacing the traditional ionic liquids while carrying value-added organic transformations. DESs are chemically tolerable solvents and there by find applications as nonvolatile, recyclable, and cost-effective media for carrying the organic transformations 

$viz.$ Knoevenagel condensation, Diels–Alder reactions, Fischer indole annulations, Perkin reaction, selective acylation of primary
hydroxyl groups in cellulose,\textsuperscript{64} flourination of acetophenone\textsuperscript{65} and bromination of substituted 1-aminoanthra-9,10-quinone.\textsuperscript{66}

Considering the advantages of deep eutectic solvents and drawbacks associated with the existing protocols, used for synthesizing pyranopyrazoles here an attempt has been made to develop a modified protocol by optimizing the reaction conditions for carrying the cyclocondensation of aromatic aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate in DES for obtaining poly functional pyranopyrazoles by cost effective and rapid way. The details of the synthetic sequences is depicted in Scheme 6.1.

**Present Work**

One-pot multi component cyclocondensation protocol has been developed for pyranopyrazoles, (5a-j) by carrying the condensation of aromatic aldehydes, (1a-j) malononitrile, (2) ethyl acetoacetate (3) and hydrazine hydrate (4) in freshly prepared deep eutectic solvent (Choline chloride:Urea Scheme 6.1) at 80°C (Scheme 6.2).

![Scheme 6.1 Schematic presentation of synthesis of DES based on Choline chloride and urea](image)

![Scheme 6.2 6-Amino-4-(4-substituted phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (5a-j)](image)

To examine the choice of solvents, investigation was initiated with the optimization of four component one pot condensation of 4-methoxy benzaldehyde (1a), malononitrile (2), hydrazine hydrate (3) and ethyl acetoacetate (4) to afford
pyranopyrazole (5a) as a model reaction. Initially the reaction was run in the absence of a catalyst and a solvent by varying temperature (30-100 °C). It was observed that after prolonged heating also the cyclocondensation did not run. Considering the significance of green chemistry concept, efforts were directed towards the use of green reaction media. When the above model reaction was performed separately in various green solvents like PEG-400 and ionic liquids at 80 °C were found to gave the desired pyranopyrazole with moderate to better yields (Table 6.1, entries 1-3).

Therefore considering the above results and having importance of DES, model reaction was carried in DES, derived from a mixture with 1:2 composition of Choline chloride and obtained 91% yield of the pyranopyrazole (5a).

In preliminary studies, the model reaction was performed by the condensing 2-(4-methoxybenzylidene)malononitrile (obtained by Knoevenagel condensation of 4-methoxy benzaldehyde and malononitrile) and pyrazolin-5-one (prepared by condensation of hydrazine hydrate and ethyl acetoacetate) in DES at 80 °C obtained successfully the expected product pyranopyrazole (5a) with 82% yield. After having these results one pot four component reaction of 4-methoxy benzaldehyde (1a), malononitrile (2), hydrazine hydrate (3) and ethyl acetoacetate (4) was carried at 80 °C. It successfully yields pyranopyrazole (5a) with high yields without the need of prior isolation of the intermediates. From these results, it was confirmed that DES has been promoting the formation of the intermediates and their successive condensation to the desired titled product.

During the study, the model reaction was performed using DES as a reaction medium at different temperatures. Model reaction in DES at 80 °C was found to precede with excellent yield (91 %) of the pyranopyrazole (5a) in 20min (Table 6.1). It was also noted that there was no condensation at room temperature. As temperature increases (40, 60, 80, 100) the yields of the product also increased (78, 85, 91, 92,). There was no significant change in the product yield when reaction was run above 80 °C.

The recyclability/reuse of the DES has also been confirmed for the model reaction and it was noticed that even for successive three cycles, DES was found to be effectively working as medium and catalyst. The details of recovery and reuse of DES is given in experimental section.

The generality of this protocol was tested using various aldehydes with electron donating and withdrawing groups in order to determine the scope of the DES,
ChCl:urea as medium and catalyst. A variety of aldehydes have been found to undergo cyclocondensation smoothly to offer the respective pyranopyrazoles in good to excellent yields at 80 °C within 20 min (Table 6.2).

The rate acceleration of this one pot multistep cyclocondensation leading to pyranopyrazoles is attributed to unique solubility behavior of DES for various organic/inorganic solutes. This might be responsible to maintain high concentration of the reactants at commencing stage of the reaction and even in the progression of the reaction. Hence high to saturated solution of reaction mass would be responsible for rate acceleration of the cyclocondensation. There is an even possibility that DES might be assisting to enhance electrophilic character of carbonyl carbon of carbonyl reactants, thereby causing rate acceleration and high yields of the desired pyranopyrazoles.
Table 6.1 Screening of reaction medium for the synthesis of compound 5a\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG-400</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Dicationic ionic liquid</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>Ionic liquid</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>DES</td>
<td>91</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: All the reactions were carried at 80 °C for 20 min.

\textsuperscript{b}Isolated Yields

Table 6.2 Synthesis of 6-Amino-4-(4-substituted phenyl)-3-methyl-1,4-dihydropyran\textsubscript{2,3-c} pyrazole-5-carbonitriles (5a-j).\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Yield\textsuperscript{b} (%)</th>
<th>M.P.\textsuperscript{c} (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>4-methoxy phenyl</td>
<td>91</td>
<td>243-244</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>phenyl</td>
<td>92</td>
<td>210-211</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>4-chloro phenyl</td>
<td>89</td>
<td>230-232</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>4-touyl</td>
<td>91</td>
<td>207-209</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>4-fluro phenyl</td>
<td>87</td>
<td>230-231</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>4-nitro phenyl</td>
<td>85</td>
<td>252-253</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>4-hydroxy phenyl</td>
<td>90</td>
<td>219-221</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>2-furyl</td>
<td>70</td>
<td>171-172</td>
</tr>
<tr>
<td>9</td>
<td>5i</td>
<td>2-thiophenyl</td>
<td>72</td>
<td>185-186</td>
</tr>
<tr>
<td>10</td>
<td>5j</td>
<td>4-pyridyl</td>
<td>71</td>
<td>214-216</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: benzaldehyde (1a-j) (3 mmol), malononitrile (2) (3 mmol), hydrazine hydrate (3) (3 mmol) and ethyl acetoacetate (4) (3 mmol) in DES (5 mL) was stirred at 80 °C for 20 min\textsuperscript{b}Isolated Yields; \textsuperscript{c}Melting point matches with literature values.
Experimental

Synthesis of deep eutectic solvent:
A mixture of choline chloride (70 mmol) and urea (140 mmol) i.e. in the ratio of 1:2 was heated at 80 °C with stirring for 30 min. The resulting eutectic solvent, the liquid was then allowed to cool to room temperature and was used for the synthesis of pyranopyrazoles (5a-j) without further purification. The procedure adopted to get DES has been already reported.\textsuperscript{67}

Recycling of DES, Choline chloride:Urea:
A mixture of 4-methoxy benzaldehyde (1a) (3 mmol), malononitrile (2) (3 mmol), hydrazine hydrate (3) (3 mmol) and ethyl acetoacetate (4) (3 mmol) in DES (5 mL) was stirred at 80 °C for 20 min. Progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was poured on crushed ice. The DES remained in water layer as being highly soluble in water. The solid product was separated by filtration. The deep eutectic solvent was recovered from the filtrate by evaporation, removing water of the filtrate under vacuum. The recovered DES was reused for running the next batch of the cyclocondensation.
Synthesis of 6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-pyrano[2,3-c]pyrazole-5-carbonitrile (5a)

A mixture of 4-methoxy benzaldehyde (1a) (3 mmol), malononitrile (2) (3 mmol), hydrazine hydrate (3) (3 mmol) and ethyl acetoacetate (4) (3 mmol) was added in DES (5 mL) and then the reaction mass was stirred at 80 °C. Progress of the reaction was monitored by TLC (ethyl acetate:n-hexane 1:9). After 20 min of stirring, reaction mixture was poured on crushed ice. Thus obtained solid was filtered and dried. This crude product (5a) was purified by crystallization from ethanol.

Similarly the other compounds, (5b-j) of the series were prepared. The melting points and the yields of the derivatives are recorded in Table 6.2.

Spectral analysis:

Following is a spectral analysis of one of the representative products from the series, 6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-pyrano[2,3-c]pyrazole-5-carbonitrile (5a).

**IR (KBr, ν cm⁻¹)** Characteristic absorptions:
3425 (N-H stretching), 3128 (Ar-H stretching), 2928 (C-H stretching), 2200 (CN stretching), 1597 (C=N stretching), 1153 and 1203 (C-O-C stretching)

**MS (Scanning mode, ESI⁺)**: m/z (% intensity):
283.2 (M⁺, 15), 269 (100), 243 (4), 242 (39), 217 (3), 130 (3) and 102 (10).

**¹H-NMR (400 MHz, DMSO-d₆, δ ppm):**
1.76 (s, 3H, -CH₃), 3.71 (s, 3H, -OCH₃), 4.51 (s, 1H, -CH-), 6.79 (s, 2H, -NH₂), 6.84 (d, 2H, J = 8.0 Hz), 7.04 (d, 2H, J = 8.0 Hz) and 12.04 (s, 1H, -NH).

**¹³C NMR (75 MHz, DMSO-d₆, δ ppm):**
8.8, 34.7, 53.8, 57.7, 94.7, 96.5, 112.5, 119.7, 127.4, 134.7, 134.8, 153.8, 157.0 and 159.5.

**Elemental Analysis:**
Anal. Calcd for C₁₅H₁₄N₄: C, 63.82; H, 5.00; N, 19.85; found C, 63.37; H, 5.67; and N, 19.65
Mass spectrum of compound (5a)

\[ \text{Scan ES}^+ \]

\[ 5.74 \text{eV} \]

\[ \text{OMe} \]

\[ \text{CH} \]

\[ \text{NH}_2 \]

\[ 102.1 \]

\[ 130.1 \]

\[ 217.0 \]

\[ 243.3 \]

\[ 324.1 \]

\[ 347.1 \]

\[ 412.3 \]

\[ 500 \]

\[ 50 \]

\[ 75 \]

\[ 100 \]

\[ 125 \]

\[ 150 \]

\[ 175 \]

\[ 200 \]

\[ 225 \]

\[ 250 \]

\[ 275 \]

\[ 300 \]

\[ 325 \]

\[ 350 \]

\[ 375 \]

\[ 400 \]

\[ 425 \]

\[ 450 \]

\[ 475 \]

\[ 500 \]

\[ \text{ppm} \]

\[ 13 \]

\[ 12 \]

\[ 8 \]

\[ 7 \]

\[ 5 \]

\[ 4 \]

\[ 3 \]

\[ 2 \]

\[ 1 \]

\[ -0 \]

\[ \text{ppm} \]

\[ \text{H-NMR of compound (5a)} \]

\[ \text{OMe} \]

\[ \text{CH} \]

\[ \text{NH}_2 \]

\[ 1 \]

\[ 2 \]

\[ 3 \]

\[ 4 \]

\[ 5 \]

\[ 6 \]

\[ 7 \]

\[ 8 \]

\[ 9 \]

\[ 10 \]

\[ 11 \]

\[ 12 \]

\[ 13 \]

\[ 0 \]

\[ \text{ppm} \]
$^{13}$C NMR of compound (5a)
References


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