Chapter 3

Creating skeletal diversity through multi-component reactions: Applying principles of folding pathways and developing reagent controlled multi-component reactions

3.1 Introduction

Chapter 2 discussed in detail the scope, possible mechanism of the reaction and limitations of a 4CR between hydrazine hydrate $A_1$ as 1,2-dinucleophile $A$, $\beta$-keto esters $B_1$ as 1,3-dielectrophile $B$, carbonyl compounds $C$ and malononitrile $D_1$ as active methylene compound $D$ in water to obtain the specific scaffold, pyranopyrazole derivatives. Investigation of reaction mechanism provided an insight to understand the role of each building block in the 4CR. The 4CR is suggested to result in the specific scaffold through (i) heterocyclization and aromatization to give reactive heterocycle, (reaction between $A_1$ and $B_1$ to give product $P_1$), (ii) reaction of $P_1$ with carbonyl building block $C$ to give $P_2$ and (iii) reaction of $P_2$ through ionic intermediate with malononitrile $D_1$. Therefore, scope of this protocol for creating skeletal diversity was explored by applying the principles of folding pathways and reagent control to this MCR and the results are discussed in this chapter.

3.1.1 Principles of folding pathways

The term folding pathways\(^1\) refers to the substrate controlled approach to DOS\(^2\) where substrates having suitable reaction centers, known as the ‘$\sigma$-elements’ were transformed into a collection of distinct molecular skeletons by a common reaction condition. The position of the reaction centers in the substrate dictates the skeletal outcome of the reaction. This approach is referred as folding pathways due to similarity with the natural process of protein folding.\(^3\) This approach has been used in classical two-component reactions to obtain skeletal diversity (Chapter 1, section 1.2.2). However, a multi-component reaction incorporating ‘$\sigma$-elements’ in the building blocks to achieve skeletal diversity is not much explored. For example, S. Santra and P. R. Andreana achieved skeletal diversity 5–8 through U–4CR by incorporating ‘$\sigma$-elements’ in the building blocks.\(^4\) Steric effects and solvent play significant role in the skeletal
outcome of the U-4CR. DOS is achieved by introducing ‘σ-element’ either in aldehyde component 1 or in amine component 2 (Scheme 3.1).

Scheme 3.1

3.1.2 Reagent controlled MCRs

Diversity in skeletal outcome can be achieved through MCR by using same set of building blocks under different reaction conditions. This strategy can be considered to be analogous to reagent controlled method of DOS (Chapter 1, section 1.2.1). For example, S.-J. Tu and co-workers achieved scaffold switching from thiazolidinenones 12 to potential therapeutic benzothiazepinones 13 through 3CR using same set of building blocks viz., aromatic amines 9, aldehydes 10 and mercaptoacetic acid 11 by different reaction conditions. When the reaction was carried out in aprotic solvent such as benzene, DCM, DMF and THF it afforded the thiazolidinenones 12 with excellent yield. Interestingly, use of protic solvents such as glycol, ethanol, glacial acetic acid and water afforded biologically important benzothiazepinones 13 (Scheme 3.2).
Only a few examples have been reported in literature where this strategy is being used to achieve DOS through MCR. Rational design of new MCRs integrating this principle are not much explored. Analysis of the role of building blocks in the 4CR developed in the present research work reveal that building blocks 1,2-dinucleophiles A and 1,3-dielectrophiles B offer scope for creating skeletal diversity while carbonyl compounds C and active methylene compounds D can be explored for creating diversity in substitution pattern. Therefore, it was proposed to investigate the outcome of the 4CR by systematically changing components A and B with appropriate ‘σ-elements’ to get desired scaffold.

Changing the building block hydrazine hydrate $A_1$ by hydroxylamine $A_4$ is hoped to result in the formation of isoxazolone moiety $P_{1b}$ in the 4CR and subsequent reactions might result in $4H$-pyrano[3,2-$d$]isoxazole 14 scaffold. Any other skeletal outcome might also help in understanding the course of the 4CR facilitating rational design of MCRs (Scheme 3.3).
Similarly, the functionality generated by reaction between hydrazine hydrate $A_1$ and ethyl acetoacetate $B_{1a}$ leads to pyran ring in the 4CR. If reaction between 1,2-dinucleophile $A$ and 1,3-dielectrophile $B$ could lead to generation of an intermediate $P_{1c}$ with amine functionality, subsequent reactions would result in a scaffold with a pyridine ring (Fig. 3.1).

Folding pathways & Reagent controlled 4CRs

Replacement of ketone/ester functionality in $\beta$-keto ester $B_1$ by a nitrile group may result in such scaffold and therefore, it was proposed to replace ethyl acetoacetate $B_1$ to ethyl cyanoacetate $B_2$. Heterocyclization of ethyl cyanoacetate $B_2$ with hydrazine hydrate $A_1$ might result in 3-amino-1H-pyrazol-5-one $P_{1d}$ which may result in a 3-hydroxy-2H-pyrazolo[3,4-b]pyridine 15 or 3-amino-2H,4H-dihydropyran-2,3-cpyrazole 16 scaffold. Pyrazolopyridine scaffold 15 is expected if the reaction follows classical mechanism and pyranopyrazole 16 is expected if reaction follows the proposed inoic mechanism (Scheme 3.4).

The results of the investigations with these aims are discussed in this chapter.
3.2 Results and discussion

3.2.1 Creating diversity by introducing ‘σ-element’in building block A

A 4CR between hydroxylamine A₄, ethyl acetoacetate B₁₄, benzaldehyde C₁₄ and malononitrile D₁ with catalytic amount of piperidine was performed under an open atmosphere with vigorous stirring for 15–20 min in water at ambient temperature. The precipitated solid was filtered, washed with water and then ethyl acetate/hexane (30:70) mixture. The product was further purified by recrystallization from acetonitrile. Product of this 4CR was characterized to be 2-((3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malononitrile¹¹ S₆₄ by spectral techniques (Scheme 3.5). The NMR spectra of this compound are shown in Fig. 3.2 & 3.3. Single crystal XRD study of the compound confirms the structure (Fig. 3.4).

![Scheme 3.5](image)

Fig. 3.4 ORTEP diagram of 2-((isoxazol-4-yl)methyl)malononitrile S₆₄
Fig. 3.2 $^1$H NMR spectrum of 2-((isoxazol-4-yl)methyl)malononitrile $S_{6a}$

Fig. 3.3 $^{13}$C NMR spectrum of 2-((isoxazol-4-yl)methyl)malononitrile $S_{6a}$
The 4CR for 2-((isoxazol-4-yl)methyl)malononitrile derivative $S_6$ was found to be slow compared to the reaction with hydrazine hydrate $A_1$ and therefore suggested to follow classical mechanism. Reaction might follow either path I or path II (Scheme 3.6). Nature of the product formed indicates that reaction between hydroxylamine $A_4$ and ethyl acetoacetate $B_{1a}$ results in the formation of isoxazolone $P_{1a}$ moiety as one of the intermediates. Lack of cyclization to form pyran ring may be attributed to the reluctance of oxygen to delocalize electron to generate 1,3 dipole.

![Scheme 3.6](image)

Moreover, a 3CR between hydroxylamine $A_4$, ethyl acetoacetate $B_{1a}$ and benzaldehyde $C_{1a}$ did not yield bis(isoxazolone) derivative $19$ indicating that path II is the probable mechanism (Scheme 3.7).

![Scheme 3.7](image)

It is pertinent to note that similar 3CR with hydrazine hydrate $A_1$ as 1,2-dinucleophilic building block $A$ resulted in bispyrazole derivative $13$ $S_{10a}$ indicating that pyrazolone $P_{1a}$ is more reactive and reacts with carbonyl building block $C$ forming
benzylidene pyrazolone $\text{P}_{2a}$. But changing the 1,2-dinucleophile $\text{A}_1$ to hydroxylamine $\text{A}_4$ changes the reaction mechanism.

To verify the proposal that the reaction follows path $\text{II}$, this 4CR was performed using ethyl cyanoacetate $\text{B}_2$ as active methylene component $\text{D}$. A semisolid product was formed which was purified by column chromatographic technique. The product was characterized to be an ethyl 2-cyano-3-(3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)-3-phenylpropanoate $\text{S}_{7a}$ single crystal X-ray studies (Scheme 3.8 & Fig. 3.5).

![Scheme 3.8](image)

**Scheme 3.8**

![Fig. 3.5 ORTEP diagram of ethyl-3-(isoxazol-4-yl)propanoate derivative $\text{S}_{7a}$](image)

The compatibility of this reaction for different carbonyl compounds as building block $\text{C}$ was tested and the results are presented in Table 3.1. It was interesting to notice that while the 4CR in water discussed in chapter 2 was compatible to an array of substituted aldehydes and ketones, the 4CR with hydroxylamine $\text{A}_2$ as building block $\text{A}$
was sensitive to substituents on component C. This observation again support that this reaction might follow path II.

Table 3.1  Synthesis of 2-((isoxazol-4-yl)methyl)malononitrile S₆

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>C₁a</td>
<td>S₆a</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>4'-Me-C₆H₄</td>
<td>C₁b</td>
<td>S₆b</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>4'-MeO-C₆H₄</td>
<td>C₁c</td>
<td>S₆c</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>4'-Cl-C₆H₄</td>
<td>C₁e</td>
<td>S₆e</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>4'-O₂N-C₆H₄</td>
<td>C₁f</td>
<td>S₆f</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>4'-HO-C₆H₄</td>
<td>C₁g</td>
<td>S₆g</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>4'-Pyridinyl</td>
<td>C₁s</td>
<td>S₆s</td>
<td>4</td>
</tr>
</tbody>
</table>

a isolated pure product.
b formation of arylidene malononitrile

Fig. 3.6 ORTEP diagram of 2-((isoxazol-4-yl)methyl)malononitrile S₆b

Thus, the results of 4CR integrating ‘σ-element’ in the building block A, besides offering scope for achieving skeletal diversity, support the mechanism proposed in the previous chapter for the 4CR in water.
3.2.2 Creating diversity by introducing ‘σ-element’in building block B

It was pointed out that part of the pyran ring in 4CR is derived from building block B, the β-keto ester $B_1$. Therefore to achieve skeletal diversity, ‘σ-element’ was then incorporated in building block B. A base catalyzed 4CR was performed with hyrazine hydrate $A_1$, ethyl cyanoacetate $B_2$ as 1,3-dielectrophilic building block B, 4-methylbenzaldehyde $C_{1b}$ and malononitrile $D_2$ in water at ambient temperature (Scheme 3.9). Product of this 4CR was characterized to be a 2-cyano-$N'$-(4-methylbenzylidene)-acetohydrazide$^{14} S_{8b}$ by spectral techniques (Fig. 3.7–3.9)

![Scheme 3.9](image)

**Fig. 3.7 HRMS of 2-cyano-$N'$-(4-methylbenzylidene)acetohydrazide $S_{8b}$**
Fig. 3.8 $^1$H NMR spectrum of 2-cyano-$N'$-(4-methylbenzylidene)acetohydrazide $S_{8b}$

Fig. 3.9 $^{13}$C NMR spectrum of 2-cyano-$N'$-(4-methylbenzylidene)acetohydrazide $S_{8b}$
Reaction with different aldehydes and ketones resulted in the same scaffold (Fig. 3.10) and the results are presented in Table 3.2.

**Table 3.2** Synthesis of 2-cyano-\(N^1\)-arylidene/alkyldeneacetohydrazide \(S_{10}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde/Ketone</th>
<th>Product</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(C_6H_5)</td>
<td>(C_{1a})</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>4'-Me-(C_6H_4)</td>
<td>(C_{1b})</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>4'-MeO-(C_6H_4)</td>
<td>(C_{1c})</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>4'-Cl-(C_6H_4)</td>
<td>(C_{1e})</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>4'- Pyridinyl</td>
<td>(CH_3)</td>
<td>63</td>
</tr>
</tbody>
</table>

\(^a\) isolated pure product

**Fig. 3.10** ORTEP diagram of 2-cyano-\(N^1\)-(1-(pyridin-4-yl)ethylidene)acetohydrazide \(S_{8e}\)

Reaction between building blocks \(A\) and \(B\), did not lead to expected heterocyclization under the reaction conditions. Survey of literature revealed that reaction between hydrazine hydrate \(A_1\) and ethyl cyanoacetate \(B_2\) readily produce cyanoacetohydrazide which can be manipulated to obtain several heterocyclic scaffolds.\(^{15}\) Cyclization to 3-amino-\(1H\)-pyrazol-5-one \(P_{1d}\) is achieved only under strongly basic condition.\(^{16}\)
3.2.3 Creating diversity through reagent controlled 4CR

To explore the possibility of obtaining a heterocyclic scaffold in 4CR where \( \sigma \)-element’ has been incorporated in building block B, the base catalyzed reaction was performed between hyrazine hydrate \( A_1 \), ethyl cyanoacetate \( B_2 \), benzaldehyde \( C_{1a} \) and malononitrile \( D_2 \) in various water/alcohol mixtures at ambient temperature. The reaction resulted in a product as white solid within 30 minutes. The solid separated out was filtered and then washed with cold ethanol. From spectral data (Fig. 3.11 & 3.12) the product was characterized to be 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile\(^{17} \) S\(_{9a}\) (Scheme 3.10).

![Scheme 3.10]

But the yield of reaction was low. Yield of the product could not be improved in repeated investigations with different bases and reaction conditions (Table 3.3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction medium</th>
<th>Base</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( H_2O : EtOH ) (50:50)</td>
<td>Piperidine</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>( H_2O : EtOH ) (50:50)</td>
<td>Ba(OH)(_2)</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>( H_2O : EtOH ) (50:50)</td>
<td>( K_2CO_3 )</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>( H_2O : EtOH ) (60:40)</td>
<td>( K_2CO_3 )</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>( H_2O : EtOH ) (70:30)</td>
<td>( K_2CO_3 )</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>( H_2O : Acetonitrile ) (50:50)</td>
<td>( K_2CO_3 )</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>( K_2CO_3 )</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>Ba(OH)(_2)</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>EtOH</td>
<td>Piperidine</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>EtOH</td>
<td>Morpholine</td>
<td>14</td>
</tr>
</tbody>
</table>
Fig. 3.11 $^1$H NMR spectrum of 1,2-dihydropyridin-2-one $S_{9a}$

Fig. 3.12 $^{13}$C NMR spectrum of 1,2-dihydropyridin-2-one $S_{9a}$
Therefore, other compound present in the aqueous filtrate of the reaction was extracted with DCM and purified by column chromatography. From the spectral data the compound was characterized to be benzylmalononitrile 18a (Fig. 3.13 & 3.14). From these observations, formation of heterocyclic scaffold in the 4CR in water/alcohol mixture is proposed to follow the following mechanism (Scheme 3.11).

Scheme 3.11
Fig. 3.13 $^1$H NMR spectrum of benzylmalononitrile 18a

Fig. 3.14 $^{13}$C NMR spectrum of benzylmalononitrile 18a
The reaction was compatible with several aldehydes as component C (Table 3.4).
The single crystal X-ray structure of S_{9k} and S_{9n} are shown in Fig 3.15. But 2,6-
disubstituted aldehyde (entry 22) resulted in hydrazone derivative S_{8v} only.

Table 3.4  Synthesis of 4-aryl/heteroaryl/alkyl-1,2-dihydropyridin-2-one S_9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Pyridin-2-one</th>
<th>Yield (^a), (XX) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C_6H_5</td>
<td>C_{1a}</td>
<td>S_{9a} 49, (22)</td>
</tr>
<tr>
<td>2</td>
<td>4’-Me-C_6H_4</td>
<td>C_{1b}</td>
<td>S_{9b} 48, (26)</td>
</tr>
<tr>
<td>3</td>
<td>4’-MeO-C_6H_4</td>
<td>C_{1c}</td>
<td>S_{9c} 46, (35)</td>
</tr>
<tr>
<td>4</td>
<td>4’-F-C_6H_4</td>
<td>C_{1d}</td>
<td>S_{9d} 41</td>
</tr>
<tr>
<td>5</td>
<td>4’-Cl-C_6H_4</td>
<td>C_{1e}</td>
<td>S_{9e} 44</td>
</tr>
<tr>
<td>6</td>
<td>4’-O_2N-C_6H_4</td>
<td>C_{1f}</td>
<td>S_{9f} 50</td>
</tr>
<tr>
<td>7</td>
<td>4’-HO-C_6H_4</td>
<td>C_{1g}</td>
<td>S_{9g} 46</td>
</tr>
<tr>
<td>8</td>
<td>3’-MeO-C_6H_4</td>
<td>C_{1h}</td>
<td>S_{9h} 46</td>
</tr>
<tr>
<td>9</td>
<td>3’-Br-C_6H_4</td>
<td>C_{1i}</td>
<td>S_{9i} 41</td>
</tr>
<tr>
<td>10</td>
<td>3’-O_2N-C_6H_4</td>
<td>C_{1j}</td>
<td>S_{9j} 50</td>
</tr>
<tr>
<td>11</td>
<td>2’-MeO-C_6H_4</td>
<td>C_{1k}</td>
<td>S_{9k} 44, (27)</td>
</tr>
<tr>
<td>12</td>
<td>3’-MeO,5’-MeO-C_6H_4</td>
<td>C_{1l}</td>
<td>S_{9l} 44</td>
</tr>
<tr>
<td>13</td>
<td>2’-Cl,4’-Cl-C_6H_3</td>
<td>C_{1m}</td>
<td>S_{9m} 41</td>
</tr>
<tr>
<td>14</td>
<td>3’-MeO,4’-MeO,5’-MeO-C_6H_3</td>
<td>C_{1n}</td>
<td>S_{9n} 31</td>
</tr>
<tr>
<td>15</td>
<td>2’-MeO,3’-MeO,4’-MeO-C_6H_3</td>
<td>C_{1o}</td>
<td>S_{9o} 39</td>
</tr>
<tr>
<td>16</td>
<td>3’-Pyridinyl</td>
<td>C_{1p}</td>
<td>S_{9p} 47</td>
</tr>
<tr>
<td>17</td>
<td>4’-Pyridinyl</td>
<td>C_{1q}</td>
<td>S_{9q} 44</td>
</tr>
<tr>
<td>18</td>
<td>2’-Furanyl</td>
<td>C_{1r}</td>
<td>S_{9r} 44</td>
</tr>
<tr>
<td>19</td>
<td>2’-Thiophenyl</td>
<td>C_{1s}</td>
<td>S_{9s} 47, (34)</td>
</tr>
<tr>
<td>20</td>
<td>2’-chloroquinolinyl</td>
<td>C_{1t}</td>
<td>S_{9t} 42, (19)</td>
</tr>
<tr>
<td>21</td>
<td>isopropyl</td>
<td>C_{1u}</td>
<td>S_{9u} 40, (22)</td>
</tr>
<tr>
<td>22</td>
<td>2’-Cl,6’-Cl-C_6H_3</td>
<td>C_{1v}</td>
<td>S_{9v} -^c, ^-c</td>
</tr>
</tbody>
</table>

\(^a\) isolated pure product, \(^b\) byproduct, alkylmalononitrile 18v
\(^c\) aryldiene acetohydradize S_{8v}
When ketones were used as building block C corresponding hydrazones $S_8$ were formed except with acetone which resulted in 4,4-dimethyl-1,2,3,4-tetrahydropyridin-2-one derivative (Fig. 3.16).

Fig. 3.15 ORTEP digram of 1,2-dihydropyridin-2-one $S_{9k}$ & $S_{9u}$

Fig. 3.16 ORTEP digram of 4,4-dimethyl-1,2,3,4-tetrahydropyridin-2-one
From the results of 4CR performed in different reaction medium it may be inferred that solvent significantly influences the path of the reaction. While aldehyde readily reacts with hydrazine derivative, 2-cyanoacetohydrazide 19 to give hydrazone, 2-cyano-\textit{N}'-(4-arylidene)acetohydrazide \textit{S}_8 as product in water, it reacts with malononitrile \textit{D}_1 to form arylidenemalononitrile 17 which undergoes further reaction with 2-cyanoacetohydrazide 19 to give 1,2-dihydropyridin-2-one derivative \textit{S}_9 in water/alcohol mixture. This observation again supports the mechanism proposed for the 4CR discussed in chapter 2.

Thus introducing ‘σ-element’ in building block \textit{B} resulted in two different skeletons by changing the reaction condition. Under the reaction condition used in the present study, reaction between \textit{A}_1 and \textit{B}_2 did not lead to cyclization to yield 3-aminopyrazolin-5-one \textit{P}_{1d}. If heterocyclization between \textit{A}_1 and \textit{B}_2 is achieved by tuning the reaction condition this protocol might lead to either scaffold 15 or 16. It might be possible to obtain both scaffolds by tuning the reaction medium.

To verify this hypothesis a 3CR using 5-methyl-1\textit{H}-pyrazol-5-amine \textit{P}_{1c}, benzaldehyde \textit{C}_{1a} and malononitrile \textit{D}_1 with catalytic amount of piperidine was performed in water at ambient temperature. The reaction mixture after several hours was found to contain benzylidenemalononitrile 17 and 3-methyl-5-aminopyrazole \textit{P}_{1c} (Scheme 3.12). But, survey of literature revealed that the two/three-component reaction has resulted in pyrazolopyridine scaffold in organic solvents under reflux.\textsuperscript{18}

\begin{center}
\textbf{Scheme 3.12}
\end{center}
It may be suggested that C-4 position of 5-methyl-1H-pyrazol-5-amine $P_{1c}$ is not activated in water to the extent of the activation present in 5-methyl-1H-pyrazol-5-one $P_{1a}$. Probably phenolic form might be present as phenolate in water in presence of base and subsequent resonance stabilization might activate C-4 position. At the same time the amino group is also not reactive to react with benzaldehyde to form imine. Probably delocalization of lone pair on nitrogen to the hetero aromatic system might make it less reactive. Moreover, this observation supports the proposed mechanism in the previous chapter that the 4CR in water occurs through formation of charged/inoic intermediate. Therefore, it may suggest that one of the building blocks might posses a functionality which can readily generate an ion/dipole in the reaction medium.

### 3.2.4 Creating diversity by changing dimensionality of MCRs

After exploring the feasibility of four-component reaction to create scaffold diversity, it was proposed to explore the efficiency of the multi-component reaction in water to obtain skeletal diversity for different combinations of the building blocks.

Initially a *pseudo* five-component reaction of the type $A^2B^2C$ was performed with two equivalents of each of the building block *viz.*, 1,2-dinucleophile $A$ and 1,3-dielectrophile $B$ and one equivalent of carbonyl compound $C$ in water. The product was formed within five minutes and then recrystallized from ethanol. The product was characterized to be bispyrazole derivatives $^{13}S_{10}$ by spectral methods (Scheme 3.13). The reaction occurred very fast similar to the four-component reaction in water.

![Scheme 3.13](image-url)
Next, a 3CR between β-keto ester $B_1$, aldehyde $C_1$ and malononitrile $D_1$ was performed in water at ambient temperature. The product was characterized to be 4H-pyran derivative $S_{11}$ from spectral data (Fig. 3.17 & 3.18) and single crystal X-ray analysis (Fig. 3.19). The reaction was also performed using acetylacetone $B_3$ as 1,3-dielectrophile $B$. The reaction was found to be suitable for introducing substituents at 4, 5 & 6 positions (Scheme 3.14).

Scheme 3.14

**Fig. 3.19** ORTEP diagram of 4H-pyran derivatives $S_{11a}$ & $S_{11c}$
**Fig. 3.17** $^1$H NMR spectrum of 4-(thiophen-2-yl)-4$H$-pyran $S_{11b}$

**Fig. 3.18** $^{13}$C NMR spectrum of 4-(thiophen-2-yl)-4$H$-pyran $S_{11b}$
3.3 Conclusion

1. Skeletal diversity was achieved by integrating the principles of folding pathways into the four-component reaction in water discussed chapter 2 by introducing ‘σ-element’ in building blocks and using reagent controlled strategy.

2. Introducing ‘σ-element’ in component A, besides offering opportunity for achieving diversity supports the proposed mechanism of 4CR.

3. Scaffold switching was achieved in 4CR using ethyl cyanoacetate B₂ as 1,3-dinucleophilic building block B by changing reaction medium.

4. Skeletal diversity through MCR in water was achieved by changing the dimensionality of the multi-component reaction.
3.4 Experimental methods

3.4.1 General procedure for four-component synthesis of 2-((2,5-dihydroisoxazol-4-yl)methyl)malononitriles S₆:

To a stirred aqueous mixture of hydroxylamine 50% A₁ (122 mg, 2 mmol), and ethyl acetoacetate B₁ (260 mg, 2 mmol) respective aldehyde C₁, (2 mmol) malononitrile D₁ (132 mg, 2 mmol) or ethyl cyanoacetate B₂ (226 mg, 2 mmol) as active methylene component D and catalyst, piperidine (5 mol%) were added successively at room temperature under open atmosphere with vigorous stirring for 15-20 min. The solid thrown out from the reaction mixture was filtered, washed with water and then with mixture of ethyl acetate/hexane (1:4). The products were further purified by recrystallization from ethanol or acetonitrile. The products obtained were pure by TLC and spectral techniques.

2-((3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)malononitrile S₆a:
White solid, yield 62%; mp 149–152 °C; IR (KBr): \( \nu_{\text{max}} = 3697, 2662, 2527, 2365, 1668, 1649, 1558, 1454, 1439, 1394, 1348, 1261, 1059 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta = 7.44 \) (d, 2H, \( J = 7.6 \) Hz), 7.31 (t, 2H, \( J = 7.6 \) Hz), 7.27–7.25 (m, 1H), 5.61 (d, 1H, \( J = 11.2 \) Hz), 4.65 (d, 2H, \( J = 11.6 \) Hz), 2.11 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta = 170.0, 161.3, 138.3, 129.5, 128.8, 128.1, 127.5, 113.7, 92.7, 26.4, 10.02 \) ppm.

2-((3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(p-tolyl)methyl)malononitrile S₆b:
White solid, yield 76%; mp 132–135 °C; IR (KBr): \( \nu_{\text{max}} = 3107, 2669, 2257, 1649, 1554, 1514, 1456, 1257, 1045 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta = 12.5 \) (br s, 1H), 7.36 (d, 2H, \( J = 7.6 \) Hz), 7.16 (d, 2H, \( J = 7.6 \) Hz), 5.62 (d, 1H, \( J = 11.2 \) Hz), 4.64 (d, 2H, \( J = 11.2 \) Hz), 2.27 (s, 3H), 2.11 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta = 170.0, 161.3, 137.4, 135.3, 129.3, 127.4, 113.7, 113.6, 92.8, 26.4, 20.6, 10.0 \) ppm.

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3.4.2 General procedures for 4CR in water: ethyl cyanoacetate B₂ used as 1,3-dielectrophile B  

3.4.2a General procedure for synthesis of \textit{N}'-arylidene-2-cyanoacetohydrazide S₈  

To a stirred aqueous mixture of hydrazine hydrate 96% \textit{A₁} (107 mg, 2 mmol), and ethyl cyanoacetate \textit{B₂} (226 mg, 2 mmol) respective aldehyde \textit{C₁}, (2 mmol) malononitrile \textit{D₁} (132 mg, 2 mmol) and catalyst, piperidine (5 mol%) were added successively at room temperature under open atmosphere with vigorous stirring for 20-30 min. The solid thrown out from the reaction mixture was filtered, washed with water and then with mixture of ethyl acetate/hexane (1:4). The products were further purified by recrystallization from ethanol or acetonitrile. The products obtained were pure by TLC and spectral techniques.  

(E)-\textit{N}'-Benzylidene-2-cyanoacetohydrazide S₈ₐ: White solid, yield 78%; mp 162–165 °C; IR (KBr): \(v_{\text{max}}\) = 3392, 3267, 2215, 1682, 1586, 1372, 1305, 1208, 1092 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃-d): \(\delta = 10.00\) (s, 1H), 7.898 (s, 1H), 7.67–7.65 (m, 2H), 7.42–7.31 (m, 3H), 3.929 (s, 2H) ppm; LC-MS \(m/z\) (ESI) Calcd. for \textit{C}_{10}\textit{H}_{10}\textit{N}_{3}\textit{O}⁺ (M⁺)⁺: 188.1, found: 188.2; HRMS (ESI-TOF) Calcd. for \textit{C}_{10}\textit{H}_{9}\textit{N}_{3}\textit{NaO}⁺ (M⁺Na⁺): 210.064, found: 210.097.  

(E)-2-Cyano-\textit{N}'-(4-methylbenzylidene)acetohydrazide \(S₈₉b:\) White solid, yield 71%; mp 189–193 °C; IR (KBr): \(v_{\text{max}}\) = 3210, 3074, 1674, 1611, 1558, 1377, 1337, 1234, 1064 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃-d): \(\delta = 9.29\) (s, 1H), 7.798 (s, 1H), 7.55 (d, 2H, \(J = 8\) Hz), 7.23 (d, 2H, \(J = 8\) Hz), 3.91 (s, 2H), 2.397 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl₃-d): \(\delta = 163.9, 146.1, 141.6, 129.96, 129.7, 127.4, 113.8, 24.5, 21.6\) ppm; LC-MS \(m/z\) (ESI) Calcd. for \textit{C}_{11}\textit{H}_{12}\textit{N}_{3}\textit{O}⁺ (M⁺)⁺: 202.1, found: 202.2; HRMS (ESI-TOF) Calcd. for \textit{C}_{11}\textit{H}_{11}\textit{N}_{3}\textit{NaO}⁺ (M⁺Na⁺): 224.079, found: 224.096.
(E)-2-Cyano-N’-(4-methoxybenzylidene)acetohydrazide S8c:
White solid, yield 54%; mp 199–201 °C; IR (KBr): \( \nu_{\text{max}} = 3214, 3080, 1674, 1605, 1511, 1381, 1313, 1249, 1024 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)-d): \( \delta = 8.59 \) (s, 1H), 7.71 (s, 1H), 7.65 (d, 2H, \( J = 8.4 \text{ Hz} \)), 6.94 (d, 2H, \( J = 8.4 \text{ Hz} \)), 3.88 (s, 2H), 3.86 (s, 3H) ppm.

(E)-2-Cyano-N’-(4-methoxybenzylidene)acetohydrazide S8d:
White solid, yield 56%; mp 188–192 °C; IR (KBr): \( \nu_{\text{max}} = 3087, 1672, 1488, 1397, 1251, 1088 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)-d): \( \delta = 8.798 \) (s, 1H), 7.75 (s, 1H), 7.59 (d, 2H, \( J = 8.8 \text{ Hz} \)), 7.41 (d, 2H, \( J = 8.4 \text{ Hz} \)), 3.88 (s, 2H) ppm.

(E)-2-Cyano-N’-(1-(pyridin-4-yl)ethylidene)acetohydrazide S8e:
White solid, yield 63%; IR (KBr): \( \nu_{\text{max}} = 3342, 3282, 3225, 3170, 2180, 1679, 1635, 1571, 1437, 1346, 1224 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)-d): \( \delta = 9.30 \) (s, 1H), 8.70 (d, 2H, \( J = 5.6 \text{ Hz} \)), 7.596 (dd, 2H, \( J = 8.4 \& 5.6 \text{ Hz} \)), 3.90 (s, 2H), 2.28 (s, 3H) ppm.

3.4.2b General procedure for reagent controlled four-component reaction:

**Synthesis of 1,2 dihydropyridin-2-one S9**

To a stirred aqueous ethanol solution (70:30) of hydrazine hydrate 96% \( A_1 \) (107 mg, 2 mmol), and ethyl acetoacetate \( B_2 \) (226 mg, 2 mmol) respective aldehyde \( C_{1a-aa} \) (2 mmol) malononitrile \( D_1 \) (132 mg, 2 mmol) and catalyst, potassium carbonate (5 mol%) were added successively at room temperature under open atmosphere. The vigorous stirring was continued until appearance of white solid (around 30 min.). The solid was filtered and then washed with cold ethyl acetate or ethanol. To isolate the byproduct, the filtrate was extracted with ethyl acetate/DCM. The organic phase was evaporated in vacuum and purified by chromatographic techniques.
1,6-Diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile S9a:
White solid, yield 49%; IR (KBr): $v_{\text{max}} = 3346, 3246, 2220, 1642, 1600, 1551, 1526, 1468, 1439, 1299, 1227$ cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.47$ (br s, 2H), 7.56–7.54 (m, 3H), 7.49–7.47 (m, 2H), 5.66 (s, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 159.5, 159.2, 156.6, 134.5, 130.1, 128.5, 127.9, 1116.3, 115.4, 86.5, 74.3$ ppm; LC-MS $m/z$ (ESI) Calcd. for C$_{13}$H$_{10}$N$_5$O$^+$ (M+2)$^+$: 253.1, found: 253.0.

2-Benzylmalononitrile 18a:
White solid, yield 22%; IR (KBr): $v_{\text{max}} = 3027, 2980, 2915, 1597, 1489, 1446, 1070, 1019$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$-$d$): $\delta = 7.44–7.38$ (m, 3H), 7.34–7.31 (m, 2H), 3.91 (t, 1H, $J = 6.8$ Hz), 3.29 (d, 2H, $J = 6.8$ Hz) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$-$d$): $\delta = 132.9, 129.3, 129.1, 128.8, 112.2, 36.7, 24.99$ ppm.

1,6-Diamino-2-oxo-4-(p-tolyl)-1,2-dihydropyridine-3,5-dicarbonitrile S9b:
White solid, yield 48%; IR (KBr): $v_{\text{max}} = 3453, 3400, 3298, 3253, 2215, 1637, 1606, 1521, 1466, 1297, 1228$ cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.35$ (br s, 2H), 7.29 (dd, 4H, $J = 13.6$ & 8.4 Hz), 5.58 (s, 2H), 2.32 (s, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 159.98, 159.2, 156.6, 140.0, 131.6, 129.1, 127.9, 116.4, 115.3, 86.3, 74.2, 20.9$ ppm.

2-(4-methylbenzyl)malononitrile 18b:
White solid, yield 26%; IR (KBr): $v_{\text{max}} = 3028, 2929, 2253, 1604, 1505, 1444, 1255, 1024$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$-$d$): $\delta = 7.20$ (s, 4H), 3.87 (t, 1H, $J = 6.8$ Hz), 3.24 (d, 2H, $J = 6.8$ Hz), 2.36 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$-$d$): $\delta = 138.7, 129.9, 129.5, 128.9, 112.3, 36.4, 25.1, 21.1$ ppm.
1,6-Diamino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S\(_{4c}\):
White solid, yield 46%; IR (KBr): \(\nu_{\text{max}} = 3456, 3392, 3273, 3220, 3084, 2123, 2169, 1652, 1602, 1514, 1466, 1302, 1256 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 8.37\) (br s, 2H), 7.44 (dd, 2H, \(J = 6.8 \text{ & } 2 \text{ Hz}\)), 7.08 (dd, 2H, \(J = 6.8 \text{ & } 2 \text{ Hz}\)), 5.61 (s, 2H), 3.82 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 160.7, 159.3, 159.2, 156.6, 129.8, 126.4, 116.6, 115.7, 113.9, 88.2, 74.2, 55.3\) ppm.

2-(4-methoxybenzyl)malononitrile 18c:
White solid, yield 35%; IR (KBr): \(\nu_{\text{max}} = 2918, 2831, 2253, 1606, 1504, 14447, 1288, 1168, 1025 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)-\(d_2\)): \(\delta = 7.24\) (d, 2H, \(J = 8.4 \text{ Hz}\)), 6.92 (d, 2H, \(J = 8.4 \text{ Hz}\)), 3.81 (s, 2H), 3.22 (d, 2H, \(J = 6.8 \text{ Hz}\)), 2.36 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)-\(d_2\)): \(\delta = 159.9, 130.4, 124.9, 114.6, 112.3, 55.3, 36.0, 25.3\) ppm.

1,6-Diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S\(_{2a}\):
White solid, yield 41%; IR (KBr): \(\nu_{\text{max}} = 3292, 3201, 2213, 1666, 1631, 1520, 1467, 1292, 1229, 1159 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 8.53\) (br s, 2H), 7.63–7.59 (m, 2H), 7.47–7.42 (m, 2H), 5.71 (s, 2H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 162.98\) (\(\delta J_{CF} = 246 \text{ Hz}\)), 159.1, 158.6, 156.5, 130.9, 130.88, 130.6 (\(\delta J_{CF} = 9 \text{ Hz}\)), 116.3, 115.7 (\(\delta J_{CF} = 22 \text{ Hz}\)), 115.4, 86.5, 74.4 ppm.

1,6-Diamino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S\(_{2c}\):
White solid, yield 44%; IR (KBr): \(\nu_{\text{max}} = 3456, 3392, 3273, 3220, 3084, 2204, 1652, 1602, 1514, 1466, 1302, 1256 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 8.48\) (br s, 2H), 7.62 (d, 2H, \(J = 8.4 \text{ Hz}\)), 7.51 (d, 2H, \(J = 8.4 \text{ Hz}\)), 5.64 (s, 2H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 159.1, 158.4, 156.6, 135.1, 133.3, 129.9, 128.7, 116.2, 115.3, 86.4, 74.3\) ppm.
White solid, yield 50%; IR (KBr): $\nu_{\text{max}} = 3465, 3299, 3201, 3057, 2198, 1648, 1599, 1514, 1466, 1319, 1256 \text{ cm}^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.58$ (br s, 2H), 8.41 (d, 2H, $J = 8.4$ Hz), 7.81 (d, 2H, $J = 8.4$ Hz), 5.68 (s, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta =$ 158.6, 157.5, 156.6, 148.4, 140.8, 129.7, 123.8, 115.9, 115.0, 86.2, 74.1 ppm.

**1,6-Diamino-4-(3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S$_{9b}$:**

White solid, yield 46%; IR (KBr): $\nu_{\text{max}} = 3439, 3318, 3198, 2209, 1649, 1601, 1514, 1463, 1289, 1248 \text{ cm}^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.50$ (br s, 2H), 7.50 (t, 1H, $J = 8.4$ Hz), 7.17–7.14 (m, 1H), 7.08–7.06 (m, 1H), 5.70 (s, 2H), 3.85 (s, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta =$ 159.2, 159.17, 158.9, 156.8, 156.6, 135.8, 129.9 120.0, 116.2, 115.4, 86.3, 74.3, 55.3 ppm.

**1,6-Diamino-4-(3-bromophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S$_{9f}$:**

White solid, yield 41%; IR (KBr): $\nu_{\text{max}} = 3369, 3277, 3219, 3084, 2218, 1652, 1597, 1510, 1468, 1302, 1248 \text{ cm}^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.51$ (br s, 2H), 7.78–7.72 (m, 2H), 7.55–7.49 (m, 2H), 5.67 (s, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta =$ 159.1, 157.8, 156.6, 136.7, 132.98, 130.8, 130.4, 127.1, 121.5, 116.1, 115.2, 86.4, 74.3 ppm.
1,6-Diamino-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉j:
White solid, yield 50%; IR (KBr): \( \nu_{\text{max}} = 346, 3327, 3704, 2213, 1675, 1613, 1522, 1471, 1348, 1259 \ \text{cm}^{-1}; \) \( ^1\text{H} \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.68 \) (br s, 2H), 8.45 (d, 2H, \( J = 6.8 \) Hz), 8.04 (d, 2H, \( J = 8 \) Hz), 7.92 (dd, 1H, \( J = 8.8 \) & 7.6 Hz), 7.57 (s, 2H) ppm; \( ^{13}\text{C} \) NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 158.9, 157.1, 156.6, 147.8, 136.0, 134.8, 130.6, 124.97, 123.2, 123.0, 116.0, 115.2, 86.6, 74.4 \) ppm.

1,6-Diamino-4-(2-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉k:
White solid, yield 44%; IR (KBr): \( \nu_{\text{max}} = 3429, 3311, 3198, 2219, 1669, 1608, 1514, 1463, 1289, 1250 \ \text{cm}^{-1}; \) \( ^1\text{H} \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.44 \) (br s, 2H), 7.56–7.52 (m, 1H), 7.31 (dd, 1H, \( J = 7.6 \) & 2 Hz), 7.24, (d, 1H, \( J = 8.4 \) Hz), 7.13 (t, 1H, \( J = 7.2 \) Hz) 5.68 (s, 2H), 3.85 (s, 3H) ppm; \( ^{13}\text{C} \) NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 159.2, 157.5, 156.4, 155.5, 131.6, 79.1, 123.4, 120.5, 116.1, 115.2, 111.9, 87.3, 75.1, 55.7 \) ppm.

1,6-Diamino-4-(3,5-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉₉:
White solid, yield 44%; IR (KBr): \( \nu_{\text{max}} = 3452, 3370, 3194, 2217, 1673, 1627, 1527, 1466, 1418, 1308, 1203 \ \text{cm}^{-1}; \) \( ^1\text{H} \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.46 \) (br s, 2H), 6.67 (d, 1H, \( J = 2 \) Hz), 6.62 (d, 2H, \( J = 2 \) Hz), 5.67 (s, 2H), 3.80 (s, 6H) ppm; \( ^{13}\text{C} \) NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 159.2, 158.2, 158.0, 155.5, 135.2, 115.1, 114.2, 105.0, 100.3, 85.2, 73.1, 54.3 \) ppm.

1,6-Diamino-4-(2,4-dichlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉₉₉:
White solid, yield 41%; IR (KBr): \( \nu_{\text{max}} = 3413, 3301, 3192, 2220, 1667, 1609, 1524, 1476, 1242 \ \text{cm}^{-1}; \) \( ^1\text{H} \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.65 \) (br s, 2H), 7.90 (d, 1H, \( J = 2 \) Hz), 7.61 (dd, 1H, \( J = 8.4 \) & 2 Hz), 7.56, (d, 1H, \( J = 8.4 \) Hz), 5.69 (s, 2H), 3.85 (s, 3H) ppm; \( ^{13}\text{C} \) NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 158.8, 156.5, 156.2, 135.3, 132.7, 131.8, 131.1, 129.4, 128.1, 115.4, 114.5, 87.0, 74.8 \) ppm.
1,6-Diamino-2-oxo-(3,4,5-trimethoxyphenyl)-1,2-dihydropyridine-3,5-dicarbonitrile \( S_{0n} \): White solid, yield 31%; IR (KBr): \( \upsilon_{\text{max}} = 3323, 3201, 2215, 1670, 1634, 1518, 1466, 1413, 1362, 1322, 1249 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.43 \) (br s, 2H), 6.84 (s, 2H), 5.68 (s, 2H), 3.81 (s, 6H), 3.75 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 158.1, 158.0, 155.5, 151.5, 137.6, 128.5, 115.4, 114.5, 104.9, 85.1, 73.2, 58.98, 55.0 \text{ ppm}.\)

1,6-Diamino-2-oxo-(2,3,4-trimethoxyphenyl)-1,2-dihydropyridine-3,5-dicarbonitrile \( S_{0b} \): White solid, yield 39%; IR (KBr): \( \upsilon_{\text{max}} = 3379, 3324, 3188, 2984, 2942, 2214, 1673, 1620, 1522, 1460, 1412, 1293, 1099 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.41 \) (br s, 2H), 6.99 (d, 1H, \( J = 8.4 \text{ Hz} \)), 6.93 (d, 1H, \( J = 8.8 \text{ Hz} \)), 5.64 (s, 2H), 3.87 (s, 3H), 3.793 (s, 3H), 3.789 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 159.1, 157.4, 156.3, 154.8, 149.9, 141.3, 132.6, 121.2, 116.2, 115.3, 87.6, 7.5, 61.2, 60.5, 55.9 \text{ ppm}.\)

1,6-Diamino-2-oxo-1,2-dihydro-[3',4-bipyridine]-3,5-dicarbonitrile \( S_{0p} \):

White solid, yield 47%; IR (KBr): \( \upsilon_{\text{max}} = 3427, 3382, 3273, 3217, 2207, 1671, 1598, 1512, 1469, 1327, 1287 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.73 \) (dd, 1H, \( J = 5.2 \text{ & 1.6 Hz} \)), 8.68 (d, 1H, \( J = 2 \text{ Hz} \)), 8.53 (br s 2H), 7.98–7.95 (m, 2H), 7.61–7.58 (m, 2H), 5.66 (s, 2H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 159.0, 156.6, 156.3, 151.1, 147.97, 136.0, 130.7, 123.5, 116.1, 115.3, 86.6, 74.5 \text{ ppm}.\)

1,6-Diamino-2-oxo-1,2-dihydro-[4,4'-bipyridine]-3,5-dicarbonitrile \( S_{0q} \):

White solid, yield 44%; IR (KBr): \( \upsilon_{\text{max}} = 3419, 3387, 3273, 3217, 2215, 1678, 1600, 1514, 1469, 1327, 1287 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.77 \) (dd, 1H, \( J = 4.4 \text{ & 2 Hz} \)), 8.67 (br s 2H), 7.51 (dd, 1H, \( J = 4.4 \text{ & 2 Hz} \)), 5.67 (s, 2H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 158.98, 156.9, 156.7, 150.1, 142.3, 122.5, 115.8, 114.96, 85.9, 73.8 \text{ ppm}.\)
1,6-Diamino-4-(furan-2-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉:
White solid, yield 44%; IR (KBr): \( \nu_{\text{max}} = 3394, 3273, 3211, 2208, 1632, 1609, 1520, 1455, 1253 \text{ cm}^{-1}; 1^H \text{NMR (}400 \text{ MHz, DMSO-}d_6\text{): } \delta = 8.38 \text{ (br s 2H), } 8.04 \text{ (d, 1H, } J = 3.6 \text{ Hz), } 7.32 \text{ (d, 1H, } J = 3.6 \text{ Hz), } 5.61 \text{ (s, 2H) ppm; } ^{13}C \text{NMR (}100 \text{ MHz, DMSO-}d_6\text{): } \delta = 159.5, 157.2, 146.2, 145.1, 144.8, 116.6, 116.3, 115.8, 112.6, 82.6, 70.4 \text{ ppm.}

1,6-Diamino-2-oxo-4-(thiophen-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile S₉₈:
White solid, yield 47%; IR (KBr): \( \nu_{\text{max}} = 3452, 3396, 3294, 3252, 2209, 1657, 1605, 1520, 1462, 1407, 1230 \text{ cm}^{-1}; 1^H \text{NMR (}400 \text{ MHz, DMSO-}d_6\text{): } \delta = 8.43 \text{ (br s 2H), } 7.89 \text{ (d, 1H, } J = 4.8 \text{ Hz), } 7.50 \text{ (d, 1H, } J = 3.6 \text{ Hz), } 5.61 \text{ (s, 2H) ppm; } ^{13}C \text{NMR (}100 \text{ MHz, DMSO-}d_6\text{): } \delta = 159.2, 156.7, 151.6, 133.2, 130.7, 130.2, 127.9, 116.4, 115.5, 86.4, 74.2 \text{ ppm.}

1,6-Diamino-4-(2-chloroquinolin-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉₁
White solid, yield 42%; IR (KBr): \( \nu_{\text{max}} = 3456, 3392, 3273, 3220, 3084, 2123, 2169, 1652, 1602, 1514, 1466, 1302, 1256 \text{ cm}^{-1}; 1^H \text{NMR (}400 \text{ MHz, DMSO-}d_6\text{): } \delta = 8.74 \text{ (br s 3H), } 8.17 \text{ (d, 1H, } J = 6 \text{ Hz), } 8.09 \text{ (d, 1H, } J = 6.4 \text{ Hz), } 7.99–7.98 \text{ (m, 1H), } 7.81–7.79 \text{ (m, 2H), } 5.74 \text{ (s, 2H) ppm; } ^{13}C \text{NMR (}100 \text{ MHz, DMSO-}d_6\text{): } \delta = 159.3, 157.0, 155.9, 147.7, 146.5, 140.2, 132.9, 129.0, 128.8, 128.4, 128.3, 126.6, 116.1, 115.2, 87.98, 75.7 \text{ ppm.}

1,6-Diamino-4-isopropyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile S₉₄:
White solid, yield 40%; IR (KBr): \( \nu_{\text{max}} = 3449, 3366, 3291, 3252, 2998, 2217, 1652, 1605, 1518, 1449, 1407, 1230 \text{ cm}^{-1}; 1^H \text{NMR (}400 \text{ MHz, DMSO-}d_6\text{): } \delta = 8.32 \text{ (br s 2H), } 5.59 \text{ (s, 2H), } 3.22 \text{ (q, 1H, } J = 14.4 \text{ & } 7.2 \text{ Hz), } 1.40 \text{ (d, 6H, } J = 7.2 \text{ Hz) ppm; } ^{13}C \text{NMR (}100 \text{ MHz, DMSO-}d_6\text{): } \delta = 166.4, 159.6, 157.0, 116.3, 115.5, 84.8, 72.4, 33.3, 19.4 \text{ ppm.}

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(E)-2-Cyano-N’-(2,6-dichlorobenzylidene)acetohydrazide 18v:
White solid, yield 63%; mp 224–225 °C; IR (KBr): \( \nu_{\text{max}} \) = 3194, 3082, 2917, 2873, 1684, 1607, 1409, 1262, 1194 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.90 \) (s, 1H), 8.08 (s, 1H), 7.39–7.26 (m, 3H), 3.90 (s, 2H) ppm.

3.4.3 General procedure for A\(^2\)B\(^2\)C type *pseudo* five-component reaction:

**Synthesis of bis(3-methyl-1H-pyrazol-5-ol) S\(_{10}\)**

To a stirred aqueous mixture of 1,2 dinucleophiles A\(_{1,2}\) (4 mmol), and ethyl acetoacetate B\(_{1a}\) (520 mg, 4 mmol) respective aldehyde C\(_1\) (2 mmol) and catalyst, piperidine (5 mol\%) were added successively at room temperature under open atmosphere. The solid separated out within 2–5 minutes. The solid was filtered by simple filtration and then purified from ethanol by recrystallization.

**4,4’-(phenylmethylene)bis(3-methyl-1H-pyrazol-5-ol) S\(_{10a}\):**
White solid, yield 83%; IR (KBr): \( \nu_{\text{max}} \) = 2955, 1599, 1519, 1477, 1393, 1279, 1213, 1146, 1027 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta = 11.30 \) (br s, \( \approx 4\)H), 7.20–7.11 (m, 5H), 4.82 (s, 1H), 2.07 (s, 6H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta = 161.0, 143.3, 139.7, 127.6, 127.4, 125.3, 104.2, 32.7, 10.3 \) ppm.

**4,4’-(2-hydroxyphenyl)methylene)bis(3-methyl-1H-pyrazol-5-ol) S\(_{10b}\):**
White solid, yield 79%; IR (KBr): \( \nu_{\text{max}} \) = 3391, 3329, 3193, 1571, 1451, 1375, 1276, 1146, 1093 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta = 11.48 \) (br s, \( \approx 4\)H), 9.38 (br s, \( \approx 1\)H), 7.47 (dd, 1H, \( J = 7.6 \& 1.2 \) Hz), 6.91 (dd, 1H, \( J = 7.6 \& 1.6 \) Hz), 6.68–6.62 (m, 2H), 5.06 (s, 1H), 2.05 (s, 6H) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta = 166.7, 159.1, 145.2, 135.6, 131.5, 123.4, 119.7, 109.4, 32.0, 15.8 \) ppm.
4,4′-(phenylmethylene)bis(1,3-dimethyl-1H-pyrazol-5-ol) S\textsubscript{10c}:

White solid, yield 41%; IR (KBr): \( \nu_{\text{max}} = 3247, 1590, 1491, 1410, 1280, 1070, 1025 \text{ cm}^{-1} \); \(^1\text{H} \text{ NMR} (400 \text{ MHz, DMSO}-d_6): \delta = 14.00 \) (br s, \( \approx 2 \text{H} \)), 7.23–7.16 (m, 5H), 4.73 (s, 1H), 3.36 (s, 6H), 3.33 (s, 1.25H), 2.17 (s, 1.2H), 2.15 (s, 6H) ppm.

3.4.3 General procedure for three-component reaction: Synthesis of 4\(H\)-pyran derivatives S\textsubscript{11}:

To a stirred aqueous solution of malononitrile \( \text{D}_1 \) (132 mg, 2 mmol) respective \( \beta \)-ketoester \( \text{B}_1,2 \) (520 mg, 4 mmol) respective aldehyde \( \text{C}_1 \), (2 mmol) and catalyst, piperidine (5 mol\%) were added successively at room temperature under open atmosphere. The vigorous stirring was continued until appearance of solid (around 30 min.). The solid was isolated by simple filtration and then purified from ethanol by recrystallization.

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-3,4-dihydro-4\(H\)-pyran-3-carboxylate S\textsubscript{11a}:

White solid, yield 83%; mp 189–190 °C; IR (KBr): \( \nu_{\text{max}} = 3403, 3331, 3211, 2974, 2191, 1689, 1605, 1489, 1407, 1379, 1331, 1258, 1212 \text{ cm}^{-1} \); \(^1\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3-d_2): \delta = 7.31–7.27 \) (m, 2H), 7.23–7.19 (m, 3H), 4.49 (s, 2H), 4.44 (s, 1H), 4.09–3.98 (m, 2H), 2.37 (s, 3H), 1.08 (t, 3H, \( J = 7.2 \) Hz) ppm; \(^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3-d_2): \delta = 165.9, 157.5, 156.8, 143.8, 128.6, 127.5, 118.9, 107.99, 62.4, 60.7, 38.8, 18.4, 13.9 \) ppm.

Ethyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4\(H\)-pyran-3-carboxylate S\textsubscript{11b}:

White solid, yield 79%; IR (KBr): \( \nu_{\text{max}} = 3397, 3324, 3209, 2986, 2199, 1700, 1605, 1489, 1407, 1379, 1331, 1258, 1212 \text{ cm}^{-1} \); \(^1\text{H} \text{ NMR} (400 \text{ MHz, DMSO}-d_6): \delta = 7.35 \) (d, 1H \( J = 8 \) Hz), 7.04 (s, 2H), 6.93 (d, 1H \( J = 8 \) Hz), 6.84–6.85 (m, 3H), 4.64 (s, 1H), 4.11–4.04 (m, 2H), 2.28 (s, 3H), 1.15 (t, 3H, \( J = 8 \) Hz) ppm; \(^{13}\text{C} \text{ NMR} (100 \text{ MHz, DMSO}-d_6): \delta = 165.1, 159.0, 156.7, 149.3, 126.8, 124.7, 119.5, 107.6, 60.4, 56.9, 33.8, 18.1, 13.8 \) ppm.

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Ethyl 6-amino-5-cyano-2,4-di-p-tolyl-3,4-dihydro-4H-pyran-3-carboxylate S11c:
White solid, yield 62%; mp 212–214 °C; IR (KBr): $V_{\text{max}} = 3415, 3326, 3196, 2983, 2921, 2200, 1684, 1606, 1511, 1408, 1371, 1340, 1250 \text{ cm}^{-1}; ^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta = 7.31–7.21$ (m, 4H), 7.12–7.11 (m, 4H), 6.95 (s, 2H), 4.36 (s, 1H), 3.85–3.65 (m, 2H), 2.32 (s, 3H), 2.25 (s, 3H), 0.76 (t, 3H, $J = 7.2$ Hz) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta = 166.2, 159.6, 154.2, 141.6, 140.1, 136.6, 130.6, 57.5, 21.4, 21.1, 13.8$ ppm.

3-acetyl-6-amino-2-methyl-4-phenyl-3,4-dihydro-4H-pyran-5-carbonitrile S11d:
White solid, yield 70%; mp 154 °C; $^{1}H$ NMR (400 MHz, CDCl$_3$-$d$): $\delta = 7.35–7.22$ (m, 3H), 7.20–7.18 (m, 2H), 4.52 (s, 2H), 4.43 (s, 1H), 2.29 (s, 3H), 2.09 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, CDCl$_3$-$d$): $\delta = 198.8, 157.2, 155.1, 142.9, 129.1, 127.6, 127.4, 118.9, 114.8, 62.3, 39.5, 29.7$ ppm.
3.5 References


