SYNTHESIS OF SUBSTITUTED HETEROCYCLIC SCAFFOLDS USING ORGANO CATALYST IN AQUEOUS MEDIUM

Mohsin Abdul Aziz and Maqdoom Farooqui*

Post Graduate and Research Center, Maulana Azad College, Aurangabad 431001 (MS) India.

Graphical Abstract

ABSTRACT

A competent simple and green method has been developed for the synthesis of pyridine using catalytic amount of L-Arginine as a reusable catalyst. The method includes the reaction between aldehyde, dicyanomethane and thiol. The advantage of this protocol is excellent yield, short reaction time, no column chromatography, water as a green solvent and L-Arginine a reusable organo catalyst in catalytic amount.

KEYWORDS: Multicomponent Reactions (MCRs), Pyridines, L-Arginine, Organocatalyst, Green process.

1. INTRODUCTION

In recent years sustainability has bring eyes towards green synthesis[1-5] that has become an integral part of the scientific community. The rising merits of the green protocols have given birth to many article and reviews. Last decades have witnessed the discovery of many organo-catalytic reactions[6-8] as a replacement of the metal catalyzed reactions. Multicomponent reactions (MCRs)[9-15] have engrossed significant attention due to its advantages such as step, atom and pot economy. MCRs have become a proficient synthetic tool for the construction of useful heterocycles in contemporary organic synthesis. [16-17]
Amongst the heterocyclic compounds, the synthesis or modifications of pyridine core has always fascinated synthetic chemists due to its large spread over the biologically active compounds, functional materials, natural products and active pharmaceutical ingredients.\textsuperscript{[18]}

Taking into consideration the broad range applications of functionalized pyridines, it has attracted enormous attention both from the medicinal and synthetic chemist.\textsuperscript{[19]} Literature survey reveals that this well functionalized penta substituted pyridine has various medicinal uses such as antibacterial\textsuperscript{[20]}, anticancer\textsuperscript{[21]}, anti hepatitis B virus (HBV) infection\textsuperscript{[22]}, potassium channel openers for the treatment of urinary incontinence\textsuperscript{[23]}, Parkinson’s disease, asthma, hypoxia, and kidney disease etc.\textsuperscript{[24-26]} Florescence properties of this type of pyridine and their analogue have been explored.\textsuperscript{[27]} Substituted 2-amino pyridines tethered with nitrile and amino functionality as shown in Figure 1 is considered as privileged medicinal scaffolds.\textsuperscript{[28]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Examples of biologically active 2-amino-6-(arylthio) pyridine-3, 5-dicarbonitriles}
\end{figure}

Examples of biologically dynamic 2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles\textsuperscript{[29]}, has disclose the synthesis of 2-amino-3, 5-dicarbonitrile-6 sulfanylpyridines by reacting one equivalent of aldehydes, two equivalents of malononitrile and one equivalent of thiophenol by multicomponent reactions by means of Et\textsubscript{3}N or DABCO as a catalyst. Due to the formation of “enaminonitriles” the yield changes in the range of (20–48%) which is
Farooqui et al. considerably low and requires further improvement in process. As this moiety has a extensive pharmacological applications that encourages for further development and a some improved methods came into existence using diverse catalysts such as basic ionic liquid [bmIm]OH$^{[30]}$, ZnCl$_2$$^{[31]}$, silica nanoparticle$^{[32]}$, boric acid$^{[33]}$, ZrOCl$_2$.8H$_2$O/NaNH$_2$ in [bmim]BF$_4$ under acoustic cavitating irradiation$^{[34]}$, Zn(II) and Cd(II) metal-organic frameworks (MOFs)$^{[35]}$, etc. Ref.$^{[36-44]}$

The appeared literature methods experience typically from one or the other draw back such as low yields, noxious or expensive catalyst, organic solvents or the prolonged reaction time. Therefore development of a better and green process for the synthesis of these privileged molecules with readily accessible and low-cost catalyst has great scope. We have observed that one-pot multicomponent reaction of aldehyde with malononitrile and thiophenol in presence of catalytic amount of L-Arginine in aqueous solvent produce 2-amino-3, 5-dicarbonitrile-6-thio-pyridines in good yield (Scheme 1). Amino acids has been used as a Reagent for the organic transformation.$^{[45-47]}

![Scheme 1 Synthesis of highly substituted pyridine](image)

L-Arginine amino acid (Figure 2) containing guanidine functional group as a nitrogenous moiety of the carbonate functional group. Guanidine based catalysis are considered as an useful catalyst.$^{[48-51]}$ Due to the presence of this nitrogenous component L-Arginine shows strong basic character as a protonated structure in aqueous medium.$^{[52]}$ This may attribute effectiveness of L-Arginine towards the condensation reaction of aldehyde, malononitrile and thiol for bringing out the reaction successfully compare to the analogue of other amino acids. We have also tested cystein but it gave inseparable mixture of products.
2. Experimental

2.1 Chemistry

Solvents and reagents are procured from commercially sources and used without further purification. IR spectra were recorded in a Shimadzu FTIR spectrophotometer. Melting points were determined in an open capillary. $^1$H NMR spectra and $^{13}$C NMR spectra were recorded on a Jeol 500, and Bruker 400 MHz spectrometer in CDCl$_3$ and DMSO-d$_6$ using TMS as the internal reference. Elemental analyses were conceded out in a Perkin Elmer 2400 automatic CHN analyzer. All new compounds were characterized by recording melting point, $^1$H NMR, $^{13}$C NMR and elemental analysis.

General procedure for synthesis of pyridine (1k) and dihydropyridine (2c-2d)

2.2 General Procedure

A mixture of aldehyde (3.0 mmol), malononitrile (6.0 mmol), L-Arginine (20 mmol %), thiol (3.0 mmol) and water (10 ml) at reflux temperature was taken in 25 ml round bottom flask fitted with reflux condenser. The reaction mixture was refluxed in open air. The progress of the reaction was monitored by TLC (Hexane/Ethyl acetate, 8:2). After completion of the reaction, the reaction mixture was slowly cooled to room temperature. The solid product was collected by simple filtration and washed with ethanol and dried. The crude solid was purified by recrystallization in acetonitrile as a solvent.

$2$-amino-$6$-(2-aminophenylthio)-4-(3,4-dimethoxyphenyl) pyridine-$3,5$-dicarbonitrile (1k, $C_{21}H_{17}N_5O_2S$)

Yield 94 %. Yellow solid. M.p: 257-259$^0$C; IR (KBr): 3337, 3221, 3072, 2933, 2831, 2772, 2211, 2191, 1632, 1541, 1492, 1432, 1317, 1261, 1157, 1068, 1011, 832, 806, 773, 752, 683 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$ + DMSO-d$_6$): $\delta$ = 7.60 (bs, 2H, NH$_2$), 7.26-7.12 (m, 4H+1H, Ar-H), 6.82 (d, J = 7.1 Hz, 1H, Ar-H), 6.58 (bs, 1H, Ar-H), 5.38 (bs, 2H, NH$_2$),
3.84 (s, 3H, -OCH3), 3.82(s, 3H, -OCH3). $^{13}$C NMR (100 MHz, CDCl3 + DMSO-d6): δ = 166.6, 159.6, 158.1, 151.1, 150.3, 148.3, 137.2, 131.6, 125.9, 121.5, 116.3, 115.9, 115.5, 115.2, 112.1, 111.5, 107.6, 93.6, 86.3, 55.4, 55.5. Elemental analysis; Calculated: C, 62.52; H, 4.25; N, 17.36; Found: C, 62.53; H, 4.27; N, 17.35.

2-amino-6-(cyclohexylthio)-4-(2, 6-dichlorophenyl)-1, 4-dihydropyridine-3, 5-dicarbonitrile ($^{2c}$, $C_{19}H_{18}Cl_{2}N_{4}S$)

Yield: 90 %, Yellow solid, M.p.: 252-253 °C. IR νmax (KBr): 3432, 3346, 3232, 3091, 3001, 2968, 2911, 2822, 2742, 2212, 2188, 1667, 1659, 1608, 1493, 1343, 1252, 1118, 1047, 788, 747, 672, 578; $^1$H NMR (DMSO-d6, 500 MHz): δ = 9.23 (bs, 1H, NH), 7.49-7.46 (d, J = 7.8 Hz, 2H, Ar-H), 7.32 (t, J = 8.1 Hz, Hz, 1H, Ar-H), 5.91 (bs, 2H, NH2), 5.42 (s, 1H, CH), 2.46 (bs, 2H, CH2), 1.91-1.90 (bm, 2H, CH2), 1.68 (bs, 2H, CH2), 1.52-1.51 (bm, 1H, CH), 1.38-1.19 (m, 4H, 2CH2); $^{13}$C NMR (DMSO-d6, 125 MHz): δ = 151.9, 144.4, 135.9, 130.7, 120.4, 118.3, 87.4, 52.7, 46.4, 39.2, 33.3, 33.1, 25.5, 25.4; Elemental analysis; Calculated: C, 56.30; H, 4.48; N, 13.82. Found: C, 56.32; H, 4.47; N, 13.81.

2-amino-4-(2,6-dimethoxyphenyl)-6-(o-tolylthio)-1,4-dihydropyridine-3,5-dicarbonitrile ($^{2d}$, $C_{22}H_{20}N_{4}O_{2}S$)

Yield: 96 %, White solid, M.p.: 231-233 °C. IR νmax (KBr): 3431, 3348, 3238, 3091, 3001, 2971, 2918, 2822, 2211, 21932, 1671, 1664, 1602, 1490, 1347, 1256, 1118, 1042, 782, 745, 674, 577; $^1$H NMR (DMSO-d6, 500 MHz): δ = 8.76 (bs, 1H, NH), 7.37-7.19 (m, 4H + 1H, Ar-H), 6.67 (d, J = 8.5 Hz, 2H, Ar-H), 5.64 (bs, 2H, NH2), 5.03 (s, 1H, CH), 3.71 (s, 6H, 2-OCH3), 2.32 (s, 3H, CH3); $^{13}$C NMR (DMSO-d6, 125 MHz): δ = 158.9, 152.1, 141.1, 138.3, 131.4, 130.5, 130.2, 129.6, 128.7, 127.8, 121.6, 119.0, 105.3, 91.4, 56.7, 56.6, 54.1, 31.8, 20.4, 19.0; Elemental analysis; Calculated: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.35; H, 4.99; N, 13.87.

3. RESULTS AND DISCUSSION

As a representative reaction, 4-Bromobenzaldehyde (1.0 equiv.), malononitrile (2.0 equiv.) and thiophenol (1.0 equiv.) was reacted in the presence of 20 mol% L-Arginine organo catalysts in water (5 ml) at high temperature. Amongst the various readily accessible amino acids, we have tested this reaction with L-Proline, L-Arginine, Histidine, L-Alanine, (Table 1, entries 2-6). L-Arginine is found to be the most efficient catalyst of choice for this
conversion in terms of reaction time and yields obtained. In absence of any catalyst product is not formed even after 20h (Entry-1). Similarly different solvents like ethanol, acetonitrile, Tetrahydrofuran, dichloromethane and water are also screened for the same reaction maintaining the substrate ratio unchanged (Table1, entries 7-11). Among all these solvents, water is found to be the choice of solvent for this transformation. This may be due to the high solubility of amino acids in water compare to the other solvents.

Table 1 Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time/(h)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>------</td>
<td>H₂O</td>
<td>20</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>Cystein</td>
<td>H₂O</td>
<td>2.0</td>
<td>IMd</td>
</tr>
<tr>
<td>3</td>
<td>L-Arginine</td>
<td>H₂O</td>
<td>1.0</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Histidine</td>
<td>H₂O</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>L-Alanine</td>
<td>H₂O</td>
<td>3.0</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>Lucine</td>
<td>H₂O</td>
<td>2.5</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>L-Arginine</td>
<td>CH₃CN</td>
<td>7.0</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>L-Arginine</td>
<td>THF</td>
<td>8.0</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>L-Arginine</td>
<td>CH₂Cl₂</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>L-Arginine</td>
<td>EtOH</td>
<td>6.0</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>L-Arginine</td>
<td>H₂O</td>
<td>4.0</td>
<td>71c</td>
</tr>
</tbody>
</table>

Table 2 Optimization of catalyst amount

<table>
<thead>
<tr>
<th>Entry</th>
<th>L-Arginine (mol %)</th>
<th>Time (min/h)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>5</td>
<td>5.0 h</td>
<td>73</td>
</tr>
<tr>
<td>2.</td>
<td>10</td>
<td>3.0 h</td>
<td>82</td>
</tr>
<tr>
<td>3.</td>
<td>20</td>
<td>1.0 h</td>
<td>91</td>
</tr>
<tr>
<td>4.</td>
<td>30</td>
<td>45 min</td>
<td>87</td>
</tr>
</tbody>
</table>

To optimize the reaction parameters, the same model reaction was carried out in presence of different amounts of L-Arginine (Table 2). The variations of the quantity of L-Arginine from 5 mol% to 30 mol% give different yields of 1a in 73, 82, 91 and 87 % respectively. Higher mole percent of the catalyst minimises the reaction time but did not effect on the reaction yield. 20 mol% is found to be the best concentration for excellent yield of the product.

Table 2 Optimization of catalyst amount

<table>
<thead>
<tr>
<th>Entry</th>
<th>L-Arginine (mol %)</th>
<th>Time (min/h)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>5</td>
<td>5.0 h</td>
<td>73</td>
</tr>
<tr>
<td>2.</td>
<td>10</td>
<td>3.0 h</td>
<td>82</td>
</tr>
<tr>
<td>3.</td>
<td>20</td>
<td>1.0 h</td>
<td>91</td>
</tr>
<tr>
<td>4.</td>
<td>30</td>
<td>45 min</td>
<td>87</td>
</tr>
</tbody>
</table>

Reaction conditions: 4-Bromobenzaldehyde (3.0 mmol), malononitrile (6.0) , thiophenol (3.0 mmol), catalyst (20 mol %) in water (10 cm³) at reflux temperature. Isolated yields. Reaction performed at room temperature, Not isolated inseparable mixtures (IM).
With the optimum parameters in hand, we moved our thought to study the scope and general diversity of this method by carrying out the synthesis of pyridines using various aldehydes and thiols (Table 3). We have observed that a number of various substituted aromatic aldehydes tethered with both electron- withdrawing and electron-donating substances give 2-amino-3, 5-dicarbonitrile-6-sulfanylpyridines in good to excellent yields (Table 3, entries 1-8). In the same way aliphatic aldehyde such as cyclohexyl carbaldehyde also undergo this multicomponent reaction easily to provide the corresponding pyridine derivative (1h) in good yields.

Table 3 Synthesis of 2-amino-3, 5-dicarbonitrile -6-thio-pyridines (1a-1k)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes (R1)</th>
<th>Thiols (R2)</th>
<th>Product a</th>
<th>Time min/hour</th>
<th>Yield b (%)</th>
<th>M.p./oC</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO Br</td>
<td>SH</td>
<td><img src="image" alt="" /></td>
<td>1.0 h</td>
<td>91</td>
<td>231-233</td>
<td>232-234 [37]</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>SH</td>
<td><img src="image" alt="" /></td>
<td>1.0 h</td>
<td>84</td>
<td>215-217</td>
<td>216-218 [30]</td>
</tr>
<tr>
<td>3</td>
<td>CHO Me</td>
<td>SH</td>
<td><img src="image" alt="" /></td>
<td>1.0 h</td>
<td>86</td>
<td>205-207</td>
<td>208-211 [30]</td>
</tr>
<tr>
<td>4</td>
<td>CHO Cl</td>
<td>SH</td>
<td><img src="image" alt="" /></td>
<td>1.0 h</td>
<td>88</td>
<td>223-225</td>
<td>222-224 [30]</td>
</tr>
<tr>
<td>5</td>
<td><img src="" alt="Chemical Structure 5" /></td>
<td><img src="" alt="Chemical Structure 6" /></td>
<td>30 min</td>
<td>89</td>
<td>236-238</td>
<td>238-240 [30]</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="" alt="Chemical Structure 7" /></td>
<td><img src="" alt="Chemical Structure 8" /></td>
<td>30 min</td>
<td>89</td>
<td>208-210</td>
<td>209-211 [27]</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="" alt="Chemical Structure 9" /></td>
<td><img src="" alt="Chemical Structure 10" /></td>
<td>1.0 h</td>
<td>83</td>
<td>220-222</td>
<td>219-220 [38]</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="" alt="Chemical Structure 11" /></td>
<td><img src="" alt="Chemical Structure 12" /></td>
<td>1.5 h</td>
<td>81</td>
<td>218-220</td>
<td>219-220 [31]</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="" alt="Chemical Structure 13" /></td>
<td><img src="" alt="Chemical Structure 14" /></td>
<td>30 min</td>
<td>82</td>
<td>232-234</td>
<td>230-231 [29]</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="" alt="Chemical Structure 15" /></td>
<td><img src="" alt="Chemical Structure 16" /></td>
<td>30 min</td>
<td>93</td>
<td>213-215</td>
<td>214-216 [27]</td>
<td></td>
</tr>
</tbody>
</table>
Likewise, 2-naphthaldehyde as a bulky aldehyde is also screened and observed to be appropriate in this process to obtain its pyridine derivatives (1j). Interestingly, in case of 2-amino thiophenol, the corresponding normal pyridine derivative (1k) was found in very good yield and we do not found any 2, 6 diamino pyridine derivative.

It is to our astonish, in this process we have also obtained dihydropyridine (Table 4, 2a-2c) for o,o’-headed aldehyde related to the former reported literatures (27,28,29, and 53). All the synthesized molecules are totally characterized using common spectroscopic techniques.

Table 4 Synthesis of 2-amino-3,5-dicarbonitrile -6-thio-dihydropyridines (2a-2d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes</th>
<th>Thiols</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time ( min )</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>M.p./o&lt;sup&gt;c&lt;/sup&gt;</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>1k</td>
<td>2a</td>
<td>30 min</td>
<td>93</td>
<td>315-317</td>
<td>317-318 [28]</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>1k</td>
<td>2b</td>
<td>30 min</td>
<td>94</td>
<td>204-206</td>
<td>203-205 [27]</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>1k</td>
<td>2c</td>
<td>45 min</td>
<td>90</td>
<td>251-253</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>1k</td>
<td>2d</td>
<td>30 min</td>
<td>96</td>
<td>230-232</td>
<td>----</td>
</tr>
</tbody>
</table>
After the first reaction, to the mother liquor methylenedichloride was added and the aqueous layer was collected. The second reaction was performed to this aqueous solution and in this way this recycling was performed five times. The ability of the catalyst after recycling five times is shown as in the Figure 3.

![Figure 3 Recyclability of the catalyst](image)

The proposed mechanism for the synthesis of the required pyridine is shown as in <Scheme 2>. In the first stage the formation of Knoevenagel adducts observes in between aldehyde and malononitrile. The second step mainly the Michael addition of second molecule of malononitrile and simultaneous thiolate addition to C≡N that gives to a cyclic adduct dihydropyridine. Finally, dihydropyridine, undergo oxidative aromatization to give highly substituted pyridine.

![Scheme 2 Proposed mechanism for the L-Arginine mediated synthesis of thio-pyridine derivatives](image)
4. CONCLUSION

In review, we have developed a green and an proficient method for the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines via multicomponent reactions (MCRs) from aldehydes, malononitrile and thiols by means of a cost effective, environmentally benign L-Argnine as an organo catalyst in water as a green solvent. This method has advantages over wide scope of substrates, operational simplicity, and no need of column chromatographic separation, shorter reaction times, and excellent yields, readily available and low cost catalyst.

ACKNOWLEDGEMENT

The authors are grateful to Maulana azad college Post Graduate and Research Center, Dr Rafiq Zakaria Campus, Aurangabad MS.

REFERENCES