POLYETHYLENE GLYCOL-400 USED AS PHASE TRANSFER CATALYST FOR ONE-POT SYNTHESIS OF 2-AMINO-3-CYANOPYRIDINE DERIVATIVES UNDER AQUEOUS CONDITIONS

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ABSTRACT
A green, multicomponent reaction method for the synthesis of 2-amino-3-cyanopyridine derivatives is developed by using Poly Ethylene Glycol (PEG-400) as phase transfer catalyst under aqueous conditions. Utilizing this protocol, 2-amino-3-cyanopyridines (5a-l) are synthesized by condensation followed by reactions of benzaldehyde, malononitrile, acetophenone and ammonium acetate. The prominent points for the present methodology are the use of a green solvent, cleaner reaction profile, efficiency, simplicity, easy work-up, excellent yields and recyclability of the solvent and final agreement with green chemistry protocols.

Keywords: PEG-400, Phase transfer catalyst, 2-amino-3-cyanopyridines, aqueous condition.

INTRODUCTION
The discovery of new methodologies for the synthesis of Nitrogen heterocyclics are thrust area in the field of organic, bioorganic and medicinal chemistry. One approach to fulfill this challenge involves the development of one-pot multicomponent reactions. The multicomponent reactions (MCRs) are prominent as an efficient and powerful technique in modern synthetic organic chemistry due to their important features.1-3 MCRs are an important in the synthesis of interesting heterocyclic scaffolds, particularly in complex molecules such as natural products and many other drugs.4 Pyridine and pyridine derivatives are heterocyclic compounds which are present in many natural and medicinal compounds. Therefore, the synthesis of pyridine derivatives is important in heterocyclic chemistry.5,6 This motivated us to synthesize 2-amino-3-cyano pyridines in the presence of PEG-400 as reaction medium and works as phase transfer catalyst (PTC) under aqueous conditions. 2-amino-3-cyano pyridine derivatives have attracted considerable interest as bioactive agents,7,8 such as A2A Adenosine receptor antagonists,9 IKK-β inhibitors,10 a potent inhibitors of HIV-1 integrase,11 modulate androgen receptor function12 and anticancer agents.13 The focal point of research in organic chemistry is to investigate newer recyclable solvents, catalysts and environmentally friendly approaches. Various eco-hardships can be satisfied by using green catalyst and green solvents.14 The prime focus of our concern in the selection of solvent and catalyst was their unique properties such as inexpensive, immiscible with organic solvents and biodegradable water and PEG-400 as phase transfer catalyst.15-19 PEG-400 emerged as a powerful phase transfer catalyst and also a reaction medium for many organic transformations under mild reaction conditions. Moreover, PEG-400 is inexpensive, easy to handle, thermally stable, non-toxic and recyclable in various organic transformations, such as synthesis of thiadiazoles,20 quinazolines,21 α-amino acids22 and many transformations.23,24

EXPERIMENTAL

Materials and methods
Pre-coated silica-gel plates (E. Merck-60 F254, 0.2mm layer) for TLC and Column chromatography packed with Silica gel (60-120 mesh) were used. Fischer-John apparatus was used for melting point
detection. Thermo Nicolet Nexus 670 FT-IR spectrometer was used to record IR spectrum. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker-Avance 400 MHz and 75 MHz instruments using CDCl$_3$ and TMS were used as internal standard. ESI-HRMS spectra recorded on Finnigan MAT 1020 mass spectrometer.

**General Procedure for synthesis of the 2-amino-3-cyano pyridine derivatives**

In a 50 ml round bottom flask, aldehyde (1.0 mmol), malononitrile (1.0 mmol), acetophenone (1.0 mmol) and ammonium acetate (1.0 mmol) were dissolved in 30% (v/v) polyethylene glycol in water, stirred with heating at 80°C for the 6h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mass was extracted with ethyl acetate. The organic portion was removed under reduced pressure and crude was purified by column chromatography. The PEG-400 was recovered and reused for four cycles without loss of significant activity.

**Spectral data of representative examples**

### 2-Amino-4, 6-diphenylnicotinonitrile (5a): Yield: 85%; White solid; m.p. 181-183°C; $^1$H NMR (400MHz, CDCl$_3$, ppm): δ 8.10 (s, 1H), 7.48-7.20 (m, 6H), 6.90 (s, 7H), 6.83 (s, 1H), 5.45 (s, 2H); $^{13}$CNMR (75 MHz CDCl$_3$, ppm): 155, 154.66, 147.32, 147, 139, 136.23, 132.23, 129, 128, 126, 124, 118, 111, 98, 77, 76; FT-IR (KBr, cm$^{-1}$): 3129, 2991, 2914, 2264, 1751, 1627, 1573, 1476, 1403, 1342, 1243, 1233, 1178, 1102, 1037, 978, 747, 522; ESI-HRMS [M+H]$^+$m/z: Found: 271.1156; C$_{18}$H$_{13}$N$_3$; Calculated: 271.1142.

### 2-Amino-4-(4-hydroxyphenyl) 6-phenyl nicotinonitrile (5b): Yield: 80%; White solid; m.p. 226-228°C; $^1$HNMR (400MHz, CDCl$_3$, ppm) δ 8.10-7.90 (m, 3H), 7.75 (d, 1H), 7.61-7.39 (m, 7H), 5.40 (s, 1H, OH); $^{13}$CNMR (75MHz CDCl$_3$, ppm): 164.52, 164, 158.23, 158, 141, 139.11, 134.21, 133, 132, 130, 120, 114, 106, 80; FT-IR (KBr, cm$^{-1}$): 3389, 3168, 3056, 2264, 1723, 1620, 1598, 1540, 1481, 1340, 1245, 1098, 842, 741, 610, 551; ESI-HRMS [M+H]$^+$m/z: Found: 287.1148; C$_{18}$H$_{13}$N$_3$O; Calculated: 287.1156.

### 2-Amino-4-(4-bromophenyl) 6-phenyl nicotinonitrile (5c): Yield: 82%; Yellow solid; m.p. 191-193°C; $^1$HNMR (400MHz, CDCl$_3$, ppm) δ 8.20 (d, 2H), 8.01 (s, 1H), 7.71-7.30 (m, 10H); $^{13}$CNMR (75MHz CDCl$_3$, ppm): 165, 159, 143, 141, 137, 135, 134, 133, 129, 121, 115, 92, 81; FT-IR (KBr, cm$^{-1}$): 3448, 2924, 2853, 2243, 1613, 1578, 1508, 1495, 1458, 1381, 1265, 1109, 842, 741, 610, 551; ESI-HRMS [M+H]$^+$m/z: Found: 350.2156; C$_{18}$H$_{12}$BrN$_3$; Calculated: 349.0216.

### 2-Amino 6-phenyl -4-p-tolylnicotinonitrile (5d): Yield: 85%; White solid; m.p. 170-173°C; $^1$HNMR (400MHz, CDCl$_3$, ppm) δ 7.70-7.27 (m, 10H), 4.15 (m, 1H), 3.85 (m, 1H), 1.25 (m, 3H); $^{13}$C NMR (75MHz CDCl$_3$, ppm): 159, 154, 153, 150, 139, 137, 135, 134, 133, 129, 121, 115, 92, 81; FT-IR (KBr, cm$^{-1}$): 3462, 3305, 2967, 2924, 2832, 2203, 1723, 1620, 1598, 1481, 1304, 1246, 1098, 1250, 1176, 1109, 1025, 821, 767, 701, 520; ESI-HRMS [M+H]$^+$m/z: Found: 285.1386; C$_{19}$H$_{15}$N$_3$; Calculated: 285.1362.

### 2-Amino -4-(naphthalene1-yl)6-phenyl nicotinonitrile (5e): Yield: 75%; White solid; m.p. 175-177°C; $^1$HNMR (400MHz, CDCl$_3$, ppm) δ 7.70-7.27 (m, 10H), 4.15 (m, 1H), 3.85 (m, 1H), 1.25 (m, 3H); $^{13}$CNMR (75MHz CDCl$_3$, ppm): 159, 154, 153, 150, 139, 137, 135, 134, 133, 129, 121, 115, 113, 105, 89, 79, 36; FT-IR (KBr, cm$^{-1}$): 3462, 3305, 2967, 2924, 2832, 2203, 1751, 1638, 1577, 1509, 1452, 1368, 1296, 1250, 1176, 1109, 1025, 821, 767, 701, 520; ESI-HRMS [M+H]$^+$m/z: Found: 285.1386; C$_{19}$H$_{13}$N$_3$; Calculated: 285.1362.

### 2-Amino-4-(4-methoxyphenyl)-6-phenyl nicotinonitrile (5f): Yield: 78%; White solid; m.p. 178-180°C; $^1$H NMR (400MHz, CDCl$_3$, ppm) δ 8.10 (d, 1H), 7.64-7.31 (m, 8H), 5.42 (s, 1H), 2.15 (s, 3H); $^{13}$C NMR (75MHz CDCl$_3$, ppm): 163, 162.5, 162, 161.5, 160, 154, 139, 131.5, 131, 130.5, 130, 129, 128, 114, 111, 77, 76.5; FT-IR (KBr, cm$^{-1}$): 3463, 3306, 3182, 2967, 2924, 2632, 2204, 1639, 1577, 1509, 1452, 1215,
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Employing the reaction using various aromatic aldehydes, malononitrile, acetophenone, ammonium acetate in presence of PEG-400 and aqueous media refluxed for 6h, obtained the products in excellent yields (Scheme -1).

RESULTS AND DISCUSSION

Employing the reaction using various aromatic aldehydes, malononitrile, acetophenone, ammonium acetate in presence of PEG-400 and aqueous media refluxed for 6h, obtained the products in excellent yields (Scheme -1).

Optimization

We studied different methods for synthesis of 2-amino-3-cyano pyridine derivatives, in various solvents and catalysts at different proportion conditions. It was observed that trace amount of product (10% yield) formed in solvent-free and aqueous conditions (Entry 1 in Table. 1). In organic solvents such as DCM and DMF, media product was afforded in 30, 35% yield after 6h reaction (Entry 2 and 3 in Table. 1). A
moderate yield was obtained in polyethylene glycol and good yield was observed in PEG-400, water mixtures at 80 °C (Entry 4, 5, 6 and 7 in Table-1). However, it was found that 30% of PEG-400 in water to be an essential promoter for this reaction, as can be seen from the Table-1. It seems that PEG-400 in water at different proportions given a different range of yields.

Table-1: Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. °C</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neat/Water</td>
<td>80</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>80</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>80</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>PEG-400</td>
<td>80</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>PEG (10%) in Water</td>
<td>80</td>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>PEG (20%) in Water</td>
<td>80</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>PEG (30%) in Water</td>
<td>80</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>PEG (50%) in water</td>
<td>80</td>
<td>6</td>
<td>75</td>
</tr>
</tbody>
</table>

The PEG-400 in water acts as PTC which promotes the reaction by interfering with reactants and facilitates to transfer from one phase to another phase of all intermediates in the reaction. The reaction mechanism involves addition followed by aromatization through the enamine intermediate formation, which is shown in Fig.-1. The phase transfer catalyst mechanism is shown in Fig.-2.

PEG-400 was recollected from the reaction mixture and reused four with same reaction conditions for four to five times and observed that PEG-400 has shown good phase transfer catalytic activity with 5% loss of its activity.

Table-2: Recycling of PEG-400/H₂O.

<table>
<thead>
<tr>
<th>No. of Cycles</th>
<th>Fresh Yield (%)</th>
<th>Run1</th>
<th>Run2</th>
<th>Run3</th>
<th>Run4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

The reaction was established by synthesis of various 2-Amino-3-cyano pyridine derivatives using simple starting materials. In general, all the obtained products were clean and structures were confirmed by ¹H NMR, ¹³C NMR, IR and Mass Spectral Analysis.

Table-3: Synthesis of various 2-Amino-3-Cyanopyridine derivatives by MCR.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-CHO</th>
<th>ArCO CH₃</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>5b</td>
<td>4-OH- Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>5c</td>
<td>4-Br- Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>82</td>
</tr>
<tr>
<td>5d</td>
<td>4-CH₃- Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>5e</td>
<td>1-Naphtha- Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>5f</td>
<td>4-OCH₃- Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>5g</td>
<td>Thiophene-2- Ph-</td>
<td>Ph-</td>
<td>6</td>
<td>75</td>
</tr>
</tbody>
</table>
CONCLUSION

In summary, we have developed an efficient and facile method to synthesize 2-Amino-3-cyanopyridine derivatives using aldehyde, acetophenone, malononitrile and ammonium acetate in aqueous medium and PEG-400 as phase transfer catalyst. The advantage of this method is utilizing of green chemistry protocols such as multicomponent reaction with high yields and mild reaction conditions. PEG-400 was used as PTC and reaction medium in various reactions, it may be applicable for development of new synthetic methods.

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REFERENCES


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