‘One Pot’ Synthesis of 2-Amino-3-cyano-4,6-diarylpyridines under Ultrasonic Irradiation and Grindstone Technology

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Received August 10, 2010, Accepted September 4, 2010

A simple facile ‘one pot’ synthesis of 2-amino-3-cyano-4,6-diarylpyridine derivatives via three component reaction of chalcone, malanonitrile and ammonium acetate under ultrasonic irradiation and grindstone technology. All the synthesized compounds have been characterized on the basis of their elemental analyses and spectral data (IR, 'H NMR, 13C NMR and Mass).

Key Words: 2-Amino-3-cyano-4,6-diarylpyridines, Chalcones, Ultrasonic irradiation, Grindstone technology

Introduction

Pyridine functionalities have been widely studied 1,2 and widely used 3-6 but still generate much interest due to their wide range of application in medicinal chemistry.7-11 The naturally occurring B6-vitamins pyridoxine, pyrodoxal, pyridoxamine and codecarbaxylase contain a pyridine nucleus. 12 Pyridine derivatives have been used as herbicides,13 for enrichment of cereals,14 for regulation of arterial pressure,15 and cholesterol levels in blood.16 Some pyridines constitute an important class of antitumor compounds.17,18 They also show antibacterial,19 antifungal,20 antiviral21 and antidepressant22 activities.

Some bifunctional pyridines are used as non linear optical materials,23 electrical materials,24 chelating agents in metal-ligand chemistry,25 and as fluorescent liquid crystals.26 Among them, 2-amino-3-cyanopyridines have been identified as IKK-β inhibitors.27 Besides this, they are important and useful intermediates in preparing variety of heterocyclic compounds.28-30 Therefore, the synthesis of 2-amino-3-cyano-4,6-diarylpyridines attract much interest in organic chemistry. There are a variety of methods described in literature 31-33 to synthesize similar skeleton. Many precedent methods, however have inevitable drawbacks, for eg., conventional methods used in synthesis of substituted pyridines involve volatile organic solvents and display only moderate to low yields with low atom efficiency.34 In developing a more versatile route for synthesis of such compounds, and adopting principles of green chemistry, we have extended our studies with new green procedures (ultrasonic irradiation and grindstone technology). A survey of literature shows that various organic reactions could be accelerated by ultrasonic irradiation with a higher yield, shorter reaction time and milder conditions.35-36 The pioneering work of Toda et al. has shown that many exothermic reactions can be accomplished in high yields by just grinding solids together using mortar and pestle, a technique known as ‘Grindstone Chemistry’. Reactions are initiated by grinding, with the transfer of very small amounts of energy through friction. It is not only advantageous from the environmental point of view but also offers rate enhancement, less waste products and higher yields.37

Results and Discussion

Synthesis. Chalcone, malanonitrile and ammonium acetate were ground together with pestle and mortar without using any solvent for 15 - 20 minutes. The reaction mixture was left at room temperature overnight which yielded a yellow solid product. But, in ultrasonic irradiation requisite amount of ethanol was used (Scheme 1). Both the above said procedures provided products in good to excellent yields with simple and mild reaction conditions.

The comparative data of both the procedures are tabulated in Table 1. Structures of synthesized compounds were established on the basis of elemental and spectral analyses (IR, 'H NMR, 13C NMR and Mass).

In the IR spectra of chalcone, characteristic absorption band at 1660 cm⁻¹ (> C=O) is observed which disappears in the IR spectra of 2-amino-3-cyano-4,6-diarylpyridine derivatives 2. Besides this, the stretching vibration of -CN group in the region 2250 - 2200 cm⁻¹ confirms the formation of desired compounds (2a-h).

In the 1H NMR spectra of 2-amino-3-cyano-4,6-diarylpyridine derivatives 2, a singlet is observed in the region δ 5.60 - 5.94 ppm due to presence of NH₂ group. Aromatic protons are obtained as multiplets in the region δ 6.79 - 8.01 ppm* (*The 5-C-H proton of pyridyl ring is also merged in this region). Aromatic protons are obtained as multiplets in the region δ 6.79 - 8.01 ppm. In the 13C NMR of 2-amino-3-cyano-4,6-diarylpyridine derivatives 2, various characteristic peaks at δ 154.06, 157.86, 160.36 ppm are observed. Aromatic region is obtained from δ

![Scheme 1](image_url)
109.77 - 135.79 ppm.

Final confirmation was obtained from FAB Mass spectra which showed an accurate M'/M+2 peaks at m/z 287 (2a), 306/308 (2b, 2c), 380/382 (2d), 350/352 (2e), 336/338 (2f), 368/370 (2g), 324 (2h) that agreed well with their corresponding molecular formulae.

**Conclusion**

In summary, we have developed two simple, novel and eco-friendly synthetic protocols for the synthesis of 2-amino-3-cyano-4,6-diarylpyridines (2a-h) using ultrasonic irradiation and grindstone technology which provides higher yields in shorter reaction time with the simplicity of the procedures.

**Experimental**

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra (νmax in cm⁻¹) were recorded on FT-IR SHIMADZU-8400S Spectrophotometer using KBr pellets. ¹H NMR spectra were recorded on JEOL-AL 300 spectrometer using CDCl₃/DMSO-d₆ as solvents. TMS was taken as internal standard. FAB mass spectra were recorded on JEOL SX-102/DA-6000 (FAB) mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the matrix. ¹³C NMR (75.45 MHz, CDCl₃) δ 109.77, 115.64, 115.92, 128.68, 128.82, 130.31, 135.77, 154.05, 157.85, 160.62.

**Table 1. Synthesis of 2-amino-3-cyano-4,6-diarylpyridines (2a-h)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>Y</th>
<th>Ultrasonic irradiation</th>
<th>Grinding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>22</td>
<td>85</td>
</tr>
<tr>
<td>2b</td>
<td>4-Cl</td>
<td>H</td>
<td>23</td>
<td>86</td>
</tr>
<tr>
<td>2c</td>
<td>H</td>
<td>4-Cl</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>2d</td>
<td>4-OCH₃</td>
<td>4-Br</td>
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<tr>
<td>2e</td>
<td>H</td>
<td>4-Br</td>
<td>25</td>
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<tr>
<td>2f</td>
<td>4-OCH₃</td>
<td>4-Cl</td>
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<tr>
<td>2g</td>
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<tr>
<td>2h</td>
<td>4-F</td>
<td>4-Cl</td>
<td>24</td>
<td>86</td>
</tr>
</tbody>
</table>

Method (i): Chalcone (1) (0.05 mol), malanonitrile (0.05 mol), and ammonium acetate (0.04 mol) were grinded together in a mortar and pestle for 13 - 18 mins. The color of the reaction mixture turned light yellow from colorless starting reactants. The progress of the reaction was monitored by TLC using C₆H₆ : EtOAC : 95:5 as solvent system.

Method (ii): Chalcone (1) (0.05 mol), malanonitrile (0.05 mol), and ammonium acetate (0.04 mol) were grinded together in a mortar with pestle for 13 - 18 mins. The color of the reaction mixture turned light yellow from colorless starting reactants.

In summary, we have developed two simple, novel and eco-friendly synthetic protocols for the synthesis of 2-amino-3-cyano-4,6-diarylpyridines (2a-h) using ultrasonic irradiation and grindstone technology which provides higher yields in shorter reaction time with the simplicity of the procedures.
2-Amino-3-cyano-6-(4-chlorophenyl)-4-(4-methoxyphenyl)pyridine (2f). Yellow solid, Yield: (i) 80%, (ii) 86%, mp 177 °C. IR (cm⁻¹): 3455 and 3380 (NH₂), 3200 (ArH), 2970 (OCH₃), 2200 (CN), 1625, 1575, 1550, 1510, 1250, 1175, 1025, 820. MS (m/z): 336/338. ¹H NMR (300 MHz, CDCl₃) δ 3.93 (s, OCH₃, 3H), 5.37 (s, NH₂, 2H), 7.02-8.01 (m, ArH, 9H). ¹³C NMR (75.45 MHz, CDCl₃) δ 61.17, 109.57, 113.34, 115.12, 127.68, 128.86, 130.33, 135.75, 154.05, 157.84, 161.62.

2-Amino-3-cyano-6-(4-bromophenyl)-4-(4-fluorophenyl)pyridine (2g). Yellow solid, Yield: (i) 82%, (ii) 82%, mp 172 °C. IR (cm⁻¹): 3470 and 3375 (NH₂), 3260 (ArH), 2200 (CN), 1620, 1575, 1555, 1505, 1260, 1175, 1030, 830. MS (m/z): 368/370. ¹H NMR (300 MHz, CDCl₃) δ 5.77 (s, NH₂, 2H), 7.17-7.97 (m, ArH, 9H). ¹³C NMR (75.45 MHz, CDCl₃) δ 109.87, 115.44, 115.82, 128.68, 128.80, 130.34, 135.65, 154.00, 157.83, 160.61.

2-Amino-3-cyano-6-(4-fluorophenyl)pyridine (2h). Yellow solid, Yield: (i) 86%, (ii) 81%, mp 181 °C. IR (cm⁻¹): 3475 and 3380 (NH₂), 3250 (ArH), 2210 (CN), 1625, 1575, 1555, 1511, 1250, 1170, 1025, 825. MS (m/z): 324/326. ¹H NMR (300 MHz, CDCl₃) δ 5.46 (s, NH₂, 2H), 7.17-7.97 (m, ArH, 9H). ¹³C NMR (75.45 MHz, CDCl₃) δ 109.87, 115.64, 115.92, 128.68, 128.82, 130.31, 135.79, 154.06, 157.86, 160.63.

Acknowledgments. One of the authors (Anshu Jain) is thankful to Malaviya National Institute of Technology for providing financial assistantship, University of Rajasthan for providing necessary spectral facilities, CDRI, Lucknow for CHN analyses, mass spectrometry.

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