Efficient Synthesis of N-amino Pyridine-2,6-diones via a Novel One-pot, the Three-component Reaction between 2-Cyanoacetohydrazide, Meldrum's Acid, and Aryl Aldehyde

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(Received 3 March 2020, Accepted 5 September 2020)

A new and efficient approach has been developed for the synthesis of N-amino pyridine-2,6-dione derivatives by a one-pot, three-component reaction of 2-cyanoacetohydrazide, Meldrum's acid, and aryl aldehyde in the presence of piperidine in DMF. All the products were obtained in excellent yields and their structures were established using their spectroscopic data.

Keywords: 2-Cyanoacetohydrazide, Meldrum's acid, Aryl aldehyde, N-amino pyridine-2,6-dione

INTRODUCTION

The pyridone cores are one of the most important six-membered heterocyclic compounds containing-nitrogen, found in a large number of pharmacological activities [1-3]. Among pyridones, N-amino pyridone derivatives have attracted organic and medicinal chemists’ attention due to their broad range of biological pharmacological activities such as antitumor A [4], anti-measles virus B [5], anticonvulsant C [6], antitubercular D [7], antimicrobial E [8], antibacterial F [9] and antifungal activity G [10] (Fig. 1). Moreover, N-amino pyridone cores can be appeared in the structure of different drugs, for example, amifloxacin [11], cytadren, and orimeten [12]. Also, some of these N-amino pyridine derivatives are used as antiplasmodial falcipain-2 inhibitors (FP-2) [13].

Thus, studies on methods for the synthesis of N-amino pyridone derivatives have received high importance in organic synthesis. Some synthetic approaches were reported in the literature for the synthesis of the N-amino pyridones and their derivatives, such as metal-catalyzed approaches [14], cyclization method [15-17], multistep approaches [18], synthesis via ANORC rearrangement [19], reductive reactions [20,21] and various other methods [22-25]. Also, the reaction between β-ketoester, and 2-cyanoacetohydrazide has been reported for preparation of N-amino 2-pyridone derivatives [26,27].

In recent years, multicomponent reactions (MCRs) have attracted much attraction due to their efficiency for the preparation of complex biologically important compounds from readily-accessible starting materials [28]. Also, many strategies are available based on the multicomponent reactions for the synthesis of N-amino pyridones and their derivatives [29-32]. The development of multicomponent reactions for the synthesis of the N-amino pyridone skeleton is still highly essential. Continuing our research on multicomponent reactions [33,34], in this paper, we describe a simple and highly efficient benign strategy is introduced for the synthesis of N-amino pyridine-2,6-dione derivatives by a one-pot, the three-component reaction of 2-cyanoacetohydrazide, Meldrum's acid, and aryl aldehyde.

EXPERIMENTAL

General Methods

All chemicals were purchased from Aldrich and Merck with high-grade quality, and used without any purification. All melting points were obtained by Barnstead Electrothermal 9200 apparatus and are uncorrected. The reactions were monitored by TLC and all yields were
referred to isolated products. NMR spectra were obtained on a Varian 500 MHz spectrometer (1H NMR at 500 MHz, 13C NMR at 125 MHz) in DMSO using TMS as an internal standard. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in cm⁻¹. Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectral and physical data.

**General Procedure for the Preparation of Compounds 6a-k**

A mixture of Meldrum's acid 4 (1.0 mmol) and aryl aldehyde 5 (1.0 mmol), in the presence of four drops of piperidine, was stirred in DMF (5.0 ml) at reflux for 2 h to give the arylidene Meldrum’s acid. Then, 2-cyanoaceto- hydrazide 3 (1.0 mmol) was added, and the resulting mixture was stirred at reflux for 2 h. After completion of the reaction, determined by TLC, the solvent was removed under reduced pressure and the viscous residue was purified by chromatography silica gel plate (20 × 20 cm) using n-hexane-EtOAc (2:1) as eluent to give the pure compounds 6a-k (73-92%).

**1-Amino-2,6-dioxo-4-(p-tolyl)-1,2,3,6-tetrahydro-pyridine-3-carbonitrile (6a).** Yellow solid; (yield: 80%); m. p.: 153-156 °C; IR (KBr) (νmax, cm⁻¹): 3349, 2260, 1675; 1H NMR (500 MHz, DMSO-d₆): δ 11.71 (2H, bs, NH₂), 7.96 (1H, s, CH), 7.57 (2H, d, 3JHH = 7.5 Hz, ArH), 7.23 (2H, d, 3JHH = 7.5 Hz, ArH), 4.18 (1H, s, CH), 2.32 (3H, s, CH₃) ppm. 13C NMR (125 MHz, DMSO-d₆): δ 165.1, 156.1, 144.8, 140.4, 131.5, 129.8, 129.7, 127.4, 116.5, 24.7, 21.5 ppm. Anal. Calcd for C₁₁H₁₀N₂O₂ (241.25): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.81; H, 4.63; N, 17.37.

**Fig. 1.** Selected bioactive molecules containing N-amino pyridine derivatives.
NH₂), 7.95 (1H, s, CH), 7.62 (2H, d, 3JHH = 8.5 Hz, ArH), 6.98 (2H, d, 3JHH = 8.5 Hz, ArH), 4.16 (1H, s, CH), 3.78 (3H, s, OCH₃) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 164.9, 161.3, 144.7, 129.0, 126.8, 116.5, 114.7, 114.6, 111.9, 55.7, 18.7 ppm. Anal. Calcd. for C₁₂H₁₀N₂O₃ (257.25): C, 60.70; H, 4.31; N, 16.33. Found: C, 60.75; H, 4.33; N, 16.28.

1-Amino-2,6-dioxo-4-(o-toly)-1,2,3,6-tetrahydropyridine-3-carbonitrile (6d). Yellow solid; (yield: 79%); m.p.: 161-164 °C; IR (KBr) (υmax, cm⁻¹): 3307, 2210, 1660; ¹H NMR (500 MHz, DMSO-d₆): δ 11.98 (2H, bs, NH₂), 7.98 (1H, s, CH), 7.51 (1H, d, 3JHH = 6.0 Hz, ArH), 7.47 (1H, d, 3JHH = 7.5 Hz, ArH), 7.31 (1H, t, 3JHH = 7.5 Hz, ArH), 7.23 (1H, t, 3JHH = 7.0 Hz, ArH), 4.20 (1H, s, CH), 2.32 (3H, s, CH₃) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.2, 159.2, 144.9, 138.4, 134.1, 132.2, 129.0, 127.8, 127.7, 124.8, 116.5, 24.7, 21.3 ppm.

1-Amino-4-(4-bromophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (6e). Yellow solid; (yield: 84%); m.p.: 169-172 °C; IR (KBr) (υmax, cm⁻¹): 3421, 2263, 1672; ¹H NMR (500 MHz DMSO-d₆): δ 11.12 (2H, bs, NH₂), 7.69 (1H, s, CH), 7.34-7.64 (4H, m, ArH), 4.21 (1H, s, CH) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.3, 156.0, 154.0, 147.7, 143.6, 139.4, 133.5, 132.2, 129.3, 23.2 ppm. Anal. Calcd. for C₁₃H₁₀BrN₂O₃ (306.12): C, 47.08; H, 2.63; N, 13.73. Found: C, 47.19; H, 2.65; N, 13.68.

1-Amino-4-(3-bromophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (6f). Yellow solid; (yield: 82%); m.p.: 157-160 °C; IR (KBr) (υmax, cm⁻¹): 3295, 2257, 1669; ¹H NMR (500 MHz DMSO-d₆): δ 11.98 (2H, bs, NH₂), 7.97 (1H, s, CH), 7.92 (1H, s, ArH), 7.66 (1H, d, 3JHH = 7.5 Hz, ArH), 7.59 (1H, d, 3JHH = 7.5 Hz, ArH), 7.38 (1H, t, 3JHH = 8.0 Hz, ArH), 4.24 (1H, s, CH) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.5, 159.6, 146.4, 143.1, 136.7, 133.0, 131.3, 129.4, 126.8, 122.6, 116.5, 24.8 ppm.

1-Amino-4-(3-chlorophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (6g). Yellow solid; (yield: 85%); m.p.: 167-170 °C; IR (KBr) (υmax, cm⁻¹): 3450, 2259, 1677; ¹H NMR (500 MHz, DMSO-d₆): δ 11.96 (2H, bs, NH₂), 7.97 (1H, s, CH), 7.79 (1H, s, ArH), 7.42-7.67 (3H, m, ArH), 4.25 (1H, s, CH) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.5, 159.6, 146.4, 143.1, 136.4, 134.1, 131.0, 130.1, 127.0, 126.5, 116.5, 24.8 ppm.

1-Amino-4-(4-chlorophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (6h). Yellow solid; (yield: 87%); m.p.: 168-171 °C; IR (KBr) (υmax, cm⁻¹): 3449, 2244, 1670; ¹H NMR (500 MHz, DMSO-d₆): δ 11.90 (2H, bs, NH₂), 8.01 (1H, s, CH), 7.70 (2H, d, 3JHH = 8.5 Hz, ArH), 7.48 (2H, d, 3JHH = 8.5 Hz, ArH), 4.20 (1H, s, CH) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.4, 154.1, 143.4, 135.0, 133.2, 129.2, 129.1, 122.8, 116.5, 24.8 ppm. Anal. Calcd. for C₁₂H₁₀ClN₂O₃ (261.67): C, 55.08; H, 3.08; N, 16.06. Found: C, 55.12; H, 3.09; N, 16.02.

1-Amino-4-(2-methoxyphenyl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (6i). Yellow solid; (yield: 73%); m.p.: 126-129 °C; IR (KBr) (υmax, cm⁻¹): 3449, 2260, 1691; ¹H NMR (500 MHz, DMSO-d₆): δ 11.76 (2H, bs, NH₂), 8.33 (1H, s, CH), 7.81 (1H, d, 3JHH = 7.0 Hz, ArH), 7.40 (1H, t, 3JHH = 8.5 Hz, ArH), 7.08 (1H, d, 3JHH = 8.0 Hz, ArH), 6.99 (1H, t, 3JHH = 7.5 Hz, ArH), 4.18 (1H, s, CH), 3.83 (3H, s, OCH₃) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.1, 158.1, 148.9, 140.3, 132.0, 126.0, 122.2, 121.1, 118.6, 116.6, 112.2, 56.1, 24.7 ppm. Anal. Calcd. for C₁₃H₁₂ClN₃O₃ (306.11): C, 48.68; H, 2.38; N, 14.19. Found: C, 48.79; H, 2.40; N, 14.16.

1-Amino-4-(2-chlorophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (6k). Yellow solid; (yield: 92%); m.p.: 174-176 °C; IR (KBr) (υmax, cm⁻¹): 3449, 2265, 1694; ¹H NMR (500 MHz, DMSO-d₆): δ 12.01 (2H, bs, NH₂), 8.40 (1H, s, CH), 7.97 (1H, d, 3JHH = 6.5 Hz, ArH), 7.35-7.57 (3H, m, ArH), 4.21 (1H, s, CH) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 165.4, 159.6, 140.9, 133.5, 132.0, 131.5, 130.2, 128.0, 127.9, 127.4, 116.4, 24.8 ppm.

RESULTS AND DISCUSSION

Our study began with the reaction of hydrazine hydrate 1
with ethyl 2-cyanoacetate 2 in ethanol to give 2-cyanoacetohydrazide 3 was achieved following a literature procedure (Scheme 1) [28].

Then, the reaction of 2-cyanoacetohydrazide 3 (1.0 mmol), Meldrum's acid 4 (1.0 mmol), and aryl aldehyde 5 (1.0 mmol) was performed in the presence of four drops of piperidine under various reaction conditions for the synthesis of 1-amino-2,6-dioxo-4-(p-tolyl)-1,2,3,6-tetrahydropyridine-3-carbonitrile 6a as a model reaction to establish the best reaction conditions (Table 1).

Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>Reflux</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>Reflux</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>CH₃CN</td>
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<tr>
<td>9</td>
<td>THF</td>
<td>Reflux</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>DMF</td>
<td>Reflux</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>DMF</td>
<td>Reflux</td>
<td>80</td>
</tr>
</tbody>
</table>

*aReaction conditions: 3 (1.0 mmol), 4 (1.0 mmol), 5a (1.0 mmol), with four drops of piperidine, the solvent was 5.0 ml and the reaction time was 4 h.*

*bIsolated yields.*

*cReaction time was 12 h.*
Efficient Synthesis of N-amino Pyridine-2,6-diones

Scheme 2. The proposed mechanism

Table 2. Synthesis of N-amino Pyridine-2,6-dione Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ar</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>4-CH₃C₆H₄</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>3-CH₃C₆H₄</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>4-OCH₃C₆H₄</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td>2-CH₂C₆H₄</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>6e</td>
<td>4-BrC₆H₄</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>6f</td>
<td>3-BrC₆H₄</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>6g</td>
<td>3-ClC₆H₄</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>6h</td>
<td>4-ClC₆H₄</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>6i</td>
<td>2-OCH₂C₆H₄</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>6j</td>
<td>2,6-(Cl)₂C₆H₃</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>6k</td>
<td>2-ClC₆H₄</td>
<td>92</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields. <sup>b</sup>Reaction time was 4 h.
When the reaction was carried out in a variety of solvents; ethanol, methanol, acetonitrile, tetrahydrofuran (THF), and N,N-dimethylformamide (DMF) (Table 1, entries 1-5) at room temperature, the yield of product was trace but when the reaction was carried out in ethanol, methanol, acetonitrile, tetrahydrofuran (THF), and N,N-dimethylformamide (DMF) at reflux conditions the product was obtained in yields of 58%, 47%, 65%, 51% and 80%, respectively (Table 1, entries 6-10). Of course, more time of the reaction in N,N-dimethylformamide (DMF) at reflux conditions did not improve the yield (Table 1, entry 11).

After having optimized conditions in hand, such as 2-cyanoacetohydrazide 3 (1.0 mmol), Meldrum’s acid 4 (1.0 mmol), and aryl aldehyde 5 (1.0 mmol), in N,N-dimethylformamide (DMF) as a solvent under the reflux conditions for 4 h. (entry 10, Table 1), explored the scope of this novel transformation for various aryl aldehydes under the optimized reaction conditions; the summarized results are in Table 2.

As seen in Table 2, substituted aryl aldehydes with electron-withdrawing and electron-donating groups under the same reaction condition also resulted in good to the excellent yield of the products. The nature of the aryl aldehyde was important. When the aldehyde derivatives, especially with electron-withdrawing groups, such as halide, were employed, a higher yield was achieved as a consequence of effective.

All the synthesized compounds were unknown to the best of our knowledge and were characterized by $^1$H and $^{13}$C NMR, IR, and elemental analysis. For instance, the $^1$H NMR spectrum of the compound 6a consisted of one singlet at δ = 2.32 ppm for the three hydrogens of the methyl group, and a singlet for one hydrogen was observed at δ = 4.18 ppm for the methine proton. Two doublet signals at δ 7.23 and 7.57 ppm for the aromatic protons of the phenyl ring and a singlet for one hydrogen were observed at δ = 7.96 ppm for the alkenic proton. Also, a broad singlet for two hydrogens was observed at δ = 11.71 ppm for the NH$_2$ protons. The $^{13}$C NMR spectrum of compound 6a exhibited 11 distinct signals in agreement with the proposed structure. In the IR spectrum, the amide carbonyl and nitrile group absorption were observed at 1675 and 2260 cm$^{-1}$.

According to previous reports [27-30], a plausible reaction mechanism for the synthesis of compound 6 is shown in Scheme 2. Firstly, arylidene Meldrum’s acid A is formed by means of a Knoevenagel condensation between Meldrum’s acid 4 and aryl aldehyde 5 in the presence of piperidine. Then, intermediate A is used through in situ, the Michael addition of 2-cyanoacetohydrazide 3 to arylidene Meldrum’s acid A afforded intermediate B. In the last step, N-amino pyridine-2,6-dione 6 is formed by the intramolecular cyclization intermediate B and loss of one molecule of acetone and carbon dioxide and oxidative dehydrogenation in DMF under reflux conditions.

**CONCLUSIONS**

In conclusion, we have successfully described a simple and highly efficient procedure for the synthesis of N-amino pyridine-2,6-dione derivatives via one-pot, the three-component reaction between 2-cyanoacetohydrazide, Meldrum’s acid, and aromatic aldehyde by using piperidine as a base. High yields, availability of starting compounds, low reaction times, and atom economy are some of the significant advantages of the present method.

**REFERENCES**
