Efficient Construction of 4-aryl-5,8-epiminobenz[7]annulenes based on a Cascade Michael/Cyclization Reaction

Dao-Cai Wang*, Yi Luo, Jian-Jun Li, Chi Zhang and Xiao-Peng Liu**

Hubei Key Laboratory of Biologic Resources Protection and Utilization, School of Biological Science and Technology, Hubei Minzu University, Enshi, 445000, P. R. China
daocaiwang@yeah.net*, Liuxp999@163.com**

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Summary: A practical method was developed for the gain of potentially biologically active 4-aryl-5,8-epiminobenz[7]annulenes using tropinone as starting material with an azabicyclo[3.2.1]octan skeleton. In an effort to improve product yield, reaction process conditions were optimized and the cascade Michael/cyclization reaction went most smoothly using tetrahydrofuran as solvent in the presence of DBU at 60°C for 10 hours. More diverse 4-aryl-5,8-epiminobenz[7]annulenes were synthesized in good yields and structurally identified by NMR, FTIR and mass spectrometry analysis. The assembly of the heterocyclic core proceeds by a cascade Knovenagel condensation, Michael addition and cyclocondensation sequence with a broad substrate applicability and good functional group tolerance.

Keywords: Tropinone; 5,8-epiminobenz[7]annulenes; DBU; Michael addition; Cyclization

Introduction

The 5,8-epiminobenz[7]annulene skeleton is widely distributed in natural products as well as synthetic compounds with various valuable biological activity, such as anticonvulsant [1-2], N-methyl-D-aspartate (NMDA) antagonist [3-5], phenylethanolamine N-methyltransferase (PNMT) inhibitor [6], antitumor [7-8] and treatment of type 2 diabetes [9]. Simultaneously, the compound contains a 5,8-epiminobenz[7]annulene skeleton can be used as a raw material for the synthesis of other useful compounds [10-12]. The medicinal relevance and other important applications of 5,8-epiminobenz[7]annulene derivatives have attracted more and more attention among synthetic chemists, and a lot of different synthesis methods were explored and proposed for the gain of 5,8-epiminobenz[7]annulene frameworks. In its characteristic molecular structure, a pyrrolidine ring was essentially contained. As an efficient way for the assembly of pyrrolidine ring, 1,3-dipolar cycloaddition with azomethine ylides can be employed for the design of 5,8-epiminobenz[7]annulenes, such as asymmetric [3+2]-dipolar cycloaddition [13-14], cycloisomerization/dipolar cycloaddition [15-16], dehydrogenative [3+2] cycloaddition [17] and intramolecular cross [3+2] cycloaddition [18]. In addition, a few different synthesis strategies, including radical translocation/cyclization [19], cyclization [20], intramolecular alkene carboamination [21], intramolecular ring closure [22], tandem C-H amination [23], hydroamination [24], and formal carbene insertion into the C–N bond in amide [25], have been developed for the construction of 5,8-epiminobenz[7]annulene skeleton. Although rich and diverse synthetic strategies have been explored, it is still a great challenge for the proposal of more novel methods with high efficiency and operability.

Recently, tropinone has been taken as a structural core for the gain of various tropinone derivatives. Some of these compounds were obtained through the reaction of tropinone and aromatic aldehydes, such as 2,4-di((E)-aryliden)-8-azabicyclo[3.2.1]octan-3-ones [26-28], 2-((E)-aryliden)-8-azabicyclo[3.2.1]octan-3-ones [29-30], and 2-(hydroxy(aryl)methyl)-8-azabicyclo[3.2.1]octan-3-ones [31-33]. Moreover, these compounds can be further converted to other heterocyclic compounds [34-36]. In addition, 2-(8-azabicyclo[3.2.1]octan-3-ylidene)malononitriles can be synthesized by the reaction between tropinone analogs and malononitrile, and can be used as a raw material in many other reactions [37]. However, there was few research about the direct synthesis of 4-aryl-5,8-epiminobenz[7]annulenes through one-pot reaction of tropinone, malononitrile and aldehydes. As a classical methodology, the Michael addition was a powerful tool for constructing new carbon–carbon bond playing a key role in many multicomponent reactions (MCR) especially in the construction of novel ring, which converted at least three different and
easily accessible starting materials to the expected products in only one step with reduced consumption, increased output and simplified operation [38-40]. Therefore, we try hard to supplement a different and effective method for the preparation of a series of 4-aryl-5,8-epiminobenzo[7]annulenes by a tandem Michael addition−Cyclization reaction with acceptable results.

Experimental

All chemical reagents needed in the experiment were purchased from some reliable reagent companies and used as received. Thin layer chromatography (TLC) was used for the analysis of all reaction process, and column chromatography was applied to separate target compounds. The NMR spectra with the reported chemical shifts in ppm were applied for the structure characterization of all target compounds, and sample test was carried out on a Bruker AM400 NMR spectrometer utilizing tetramethylsilane (TMS) as the internal standard. The IR spectra of all products were determined by a Thermo Fisher FTIR spectrometer. Negative ion TOF-MS data of all compounds were acquired from an Agilent mass spectrometer.

General experiment process and operation steps for the one-pot synthesis of 4-aryl-5,8-epiminobenzo[7]annulenes 4: Tropinone 1 (0.3 mmol), malononitrile 2 (1.2 mmol), aromatic aldehydes 3 (0.3 mmol) and DBU (0.6 mmol) were taken and added to dry glass tube equipped with a stirring bar, and then 3 mL tetrahydrofuran was added to dissolve the reactants. All reaction tubes were placed in a constant-temperature oil bath, the reaction temperature was set at 60 °C, and the reaction solution was stirred for 10 hours. Subsequently, the desired product was isolated by column chromatography utilizing petroleum ether/ethyl acetate (1:1, v/v) as eluent. Finally, target product was concentrated making the use of a rotary evaporator and the residual organic solvent was removed by a vacuum drying oven. The spectral data of pure compounds is listed as follows.

Compound 4a: Yellow solid; mp: 272-273°C. 1H NMR (CDCl3): δ = 7.69-7.08 (m, 4H, Ar-H), 7.10 (s, 2H, NH2), 3.52-3.37 (m, 4H), 3.53-3.50 (m, 1H), 3.61-3.27 (m, 1H), 2.69-2.64 (m, 1H), 2.27 (s, 3H, CH3), 2.18-2.09 (m, 2H, CH2), 1.74-1.57 (m, 2H, CH2).

IR (KBr): 3382, 3117, 2922, 2849, 2796, 2213, 1566, 1490, 1449, 1296, 1266, 1254, 1236, 1159, 1140, 1071, 1011, 826, 787, 754 cm⁻¹. MS-ESI: m/z 391.06 [M-H].

Compound 4b: Yellow solid; mp: 296-298°C. 1H NMR (CDCl3): δ = 7.16-7.10 (m, 4H, Ar-H), 4.99 (s, 2H, NH2), 3.51-3.49 (m, 1H), 3.43-3.41 (m, 1H), 3.26-3.20 (m, 1H), 2.60-2.55 (m, 1H), 2.18 (s, 3H, CH3), 2.15-2.03 (m, 2H, CH2), 1.66-1.61 (m, 2H, CH2).

IR (KBr): 3387, 3238, 2923, 2849, 2797, 2217, 1606, 1564, 1512, 1484, 1454, 1296, 1258, 1231, 1158, 834, 787, 752 cm⁻¹. MS-ESI: m/z 331.14 [M-H].

Compound 4c: Yellow solid; mp: 275-277°C. 1H NMR (CDCl3): δ = 7.44-7.05 (m, 4H, Ar-H), 5.02 (s, 2H, NH2), 3.49-3.48 (m, 1H), 3.43-3.40 (m, 1H), 3.26-3.20 (m, 1H), 2.59-2.55 (m, 1H), 2.17 (s, 3H, CH3), 2.14-2.01 (m, 2H, CH2), 1.70-1.48 (m, 2H, CH2).

IR (KBr): 3382, 3237, 3124, 2919, 2848, 2797, 2214, 1567, 1494, 1451, 1296, 1255, 1237, 1159, 1141, 1092, 1014, 829, 791, 756 cm⁻¹. MS-ESI: m/z 347.11 [M-H].

Compound 4d: Pale yellow solid; mp: 278-280°C. 1H NMR (CDCl3): δ = 7.47-7.07 (m, 4H, Ar-H), 5.05 (s, 2H, NH2), 3.57-3.47 (m, 2H), 3.33-3.28 (m, 1H), 2.67-2.61 (m, 1H), 2.25 (3H, CH3), 2.22-2.07 (m, 2H, CH2), 1.73-1.63 (m, 2H, CH2). IR (KBr): 3387, 3312, 3122, 2924, 2849, 2794, 2211, 1564, 1452, 1354, 1296, 1255, 1237, 1162, 1140, 1079, 927, 887, 780, 751, 717 cm⁻¹. MS-ESI: m/z 347.11 [M-H].

Compound 4e: Black solid; mp: 288-290°C. 1H NMR (CDCl3): δ = 8.05-7.33 (m, 4H, Ar-H), 5.03 (s, 2H, NH2), 3.45-3.37 (m, 2H), 3.28-3.22 (m, 1H), 3.09 (s, 3H, CH3), 2.63-2.58 (m, 1H), 2.18 (s, 3H, CH3), 2.15-2.02 (m, 2H, CH2), 1.65-1.61 (m, 2H, CH2).

IR (KBr): 3359, 3252, 3065, 2923, 2870, 2211, 1568, 1493, 1450, 1400, 1303, 1150, 1087, 1062, 960, 766, 545 cm⁻¹. MS-ESI: m/z 391.13 [M-H].

Compound 4f: Tawny solid; mp: 270-272°C. 1H NMR (CDCl3): δ = 7.73-7.25 (m, 4H, Ar-H), 5.04 (s, 2H, NH2), 3.44-3.42 (m, 2H), 3.28-3.22 (m, 1H), 2.61-2.57 (m, 1H), 2.18 (s, 3H, CH3), 2.08-1.97 (m, 2H, CH2), 1.66-1.61 (m, 2H, CH2).

IR (KBr): 3342, 3233, 3061, 2953, 2920, 2850, 2801, 2223, 1570, 1467, 1406, 1331, 1287, 1270, 1167, 1124, 1106, 1068, 864, 840 cm⁻¹. MS-ESI: m/z 381.14 [M-H].

Compound 4g: Pale yellow solid; mp: 191-193°C. 1H NMR (CDCl3): δ = 7.77-7.39 (m, 4H, Ar-H), 5.09 (s, 2H, NH2), 3.52-3.46 (m, 2H), 3.35-3.29 (m, 1H), 2.69-2.63 (m, 1H), 2.25 (3H, CH3), 2.20-2.02 (m, 2H, CH2), 1.79-1.70 (m, 2H, CH2).

IR (KBr): 3373, 3226, 2925, 2853, 2216, 1571, 1449, 1354, 1326, 1308, 1270, 1168, 1122, 1073, 809, 703 cm⁻¹. MS-ESI: m/z 381.14 [M-H].
Compound 4h: Yellow solid; mp: 249-250°C. H NMR (CDCl3): δ = 7.84-7.32 (m, 4H, Ar-H), 5.11 (s, 2H, NH2), 3.52-3.45 (m, 2H), 3.34-3.30 (m, 1H), 2.68-2.64 (m, 1H), 2.25 (s, 3H, CH3), 2.22-2.08 (m, 2H, CH2), 1.69-1.56 (m, 2H, CH2). IR (KBr): 3340, 3233, 2921, 2852, 2230, 1568, 1511, 1455, 1351, 1287, 1263, 1167, 1136, 1107, 1071, 868, 845cm⁻¹. MS-ESI: m/z 338.15 [M-H]⁻.

Compound 4i: Yellow solid; mp: 297-298°C. H NMR (CDCl3): δ = 8.33-7.32 (m, 4H, Ar-H), 5.05 (s, 2H, NH2), 3.45-3.39 (m, 2H), 3.28-3.23 (m, 1H), 2.63-2.58 (m, 1H), 2.18 (s, 3H, CH3), 2.15-2.03 (m, 2H, CH2), 1.64-1.57 (m, 2H, CH2). IR (KBr): 3352, 3241, 2922, 2850, 2218, 1565, 1517, 1454, 1344, 1264, 1104, 1016, 850, 733, 702cm⁻¹. MS-ESI: m/z 358.14 [M-H]⁻.

Compound 4j: Tawny fawn solid; mp: 261-262°C. H NMR (CDCl3): δ = 8.30-7.46 (m, 4H, Ar-H), 5.07 (s, 2H, NH2), 3.45-3.38 (m, 2H), 3.28-3.23 (m, 1H), 2.64-2.56 (m, 1H), 2.19 (3H, CH3), 2.12-1.99 (m, 2H, CH2), 1.73-1.63 (m, 2H, CH2). IR (KBr): 3384, 3181, 2924, 2825, 2215, 1566, 1528, 1452, 1350, 1296, 1258, 1233, 1163, 1140, 927, 860, 795, 732, 702cm⁻¹. MS-ESI: m/z 342.90 [M-H]⁻.

Compound 4k: Yellowish-brown solid; mp: 250-251°C. H NMR (CDCl3): δ = 7.16-6.92 (m, 4H, Ar-H), 4.96 (s, 2H, NH2), 3.80 (s, 3H, OCH3), 3.59-3.58 (m, 1H), 3.43-3.40 (m, 1H), 3.26-3.20 (m, 1H), 2.59-2.54 (m, 1H), 2.18 (s, 3H, CH3), 2.15-2.05 (m, 2H, CH2), 1.67-1.52 (m, 2H, CH2). IR (KBr): 3382, 3136, 2921, 2849, 2214, 1610, 1565, 1516, 1450, 1348, 1292, 1252, 1173, 1034, 831, 786cm⁻¹. MS-ESI: m/z 373.17 [M-H]⁻.

Results and Discussion

Initially, we explored the three-component reaction of tropinone 1 (0.3 mmol), malononitrile 2 (0.6 mmol) and 4-bromobenzaldehyde 3a (0.3 mmol) in the presence of 2 equiv DBU in toluene at 100°C for 10 hours. The product 4a was isolated in 30% yield (Table-1, entry 1). Subsequently, other organic bases including pyrrolidine, piperidine, morpholine, triethylamine, triethylenediamine and sodium methanolate, were used in model reaction to find out the ideal organic base with the most extraordinary performance. To our disappointment, the model reaction with other organic bases did not show better results in the perspective of product yield (Table-1, entries 2-7). Therefore, DBU was the most prominent organic base and used in the next optimization of process conditions. Then, the reaction solvent was replaced with other organic solvents including ethylene glycol, DMF, DMSO, tetrahydrofuran, acetonitrile and methanol, and the experimental results were shown in Table-1 (entries 8-13). Experimental results indicated that product yield has been significantly improved when tetrahydrofuran was used as a solvent. Finally, we turned our attention to study the influences of different amounts of malononitrile, expecting that product yield may increase along with the addition of more malononitrile (Table-1, entry 11 and entries 14–16). When the amount of malononitrile was doubled, the reaction can proceed smoothly with highest yield. Through systematic screening, we have
established a direct and effective means for the preparation of 4-aryl-5,8-epiminobenzo[7]annulene derivative 4a in 70% yield (Table-1, entry 15).

Table-1: Optimization of process conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Equiv. of malononitrile</th>
<th>Temp (°C)</th>
<th>Yield of 4a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>DBU</td>
<td>2</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>Pyrrolidine</td>
<td>2</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>Piperidine</td>
<td>2</td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>Morpholine</td>
<td>2</td>
<td>100</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>Triethylamine</td>
<td>2</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>Triethylenediamine</td>
<td>2</td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Methanol</td>
<td>Sodium methanol</td>
<td>2</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>Ethylene glycol</td>
<td>DBU</td>
<td>2</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>DBU</td>
<td>2</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>DBU</td>
<td>2</td>
<td>100</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>Tetrahydrofuran</td>
<td>DBU</td>
<td>2</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>Acetonitrile</td>
<td>DBU</td>
<td>2</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>13</td>
<td>Methanol</td>
<td>DBU</td>
<td>2</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>14</td>
<td>Tetrahydrofuran</td>
<td>DBU</td>
<td>3</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>15</td>
<td>Tetrahydrofuran</td>
<td>DBU</td>
<td>4</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>16</td>
<td>Tetrahydrofuran</td>
<td>DBU</td>
<td>5</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

*Isolated yield after purification by silica gel column chromatography.


<table>
<thead>
<tr>
<th>Entry</th>
<th>R (3)</th>
<th>Compound</th>
<th>Yield (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-BrC₆H₄ (3a)</td>
<td>4a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>4-FC₆H₄ (3b)</td>
<td>4b</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>4-ClC₆H₄ (3c)</td>
<td>4c</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>3-ClC₆H₄ (3d)</td>
<td>4d</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>4-CH₂SO₂C₂H₄ (3e)</td>
<td>4e</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>4-CF₃C₆H₄ (3f)</td>
<td>4f</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>3-ClC₆H₄ (3g)</td>
<td>4g</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>4-CNC₆H₄ (3h)</td>
<td>4h</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>4-NO₂C₆H₄ (3i)</td>
<td>4i</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>3-NO₂C₆H₄ (3j)</td>
<td>4j</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>4-CH₂OC₂H₄ (3k)</td>
<td>4k</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>3,4-(CH₂O)₂C₆H₄ (3l)</td>
<td>4l</td>
<td>41</td>
</tr>
<tr>
<td>13</td>
<td>4-iPrC₆H₄ (3m)</td>
<td>4m</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>2-Naphthyl (3n)</td>
<td>4n</td>
<td>34</td>
</tr>
<tr>
<td>15</td>
<td>2-Thienyl (3o)</td>
<td>4o</td>
<td>35</td>
</tr>
</tbody>
</table>

*Isolated yield after purification by column chromatography.
Scheme-1: Reasonable mechanism for the tandem reactions.

With the optimum process conditions at hand, the exploration of substrate scope with regard to the above-mentioned reaction has become the next most pressing matter (Table-2). Firstly, different aromatic aldehydes containing halogen substituent 3a-d were used for the reaction, and barely satisfying yields were obtained (Table-2, entries 1-4). Then, various aromatic aldehydes with an electron-withdrawing group 3e-j were selected as the substrate for this reaction, and the corresponding final products 4e-j have also been successfully synthesized (Table-2, entries 5-10). Afterwards, the substituent group in aromatic aldehydes were replaced by diversified electron-donating groups as substrate (Table-2, entries 11-13), and the reactions proceeded well, affording the target products 4k-m with acceptable isolated yields (up to 70%). Furthermore, 2-naphthaldehyde 3n, as a member of fused-ring compounds, was also transformed to the product 4n smoothly (Table-2, entry 14). To further extend the application of the model reaction, heterocyclic analogue 3o was employed in this procedure, and the desired target product 4o was separated successfully (Table-2, entry 15).

A plausible mechanism for the one-pot reaction was outlined in Scheme-1. The reaction started from the Knoevenagel condensation of aromatic aldehydes and malononitrile, and the formed 2-arylidemalononitrile was then reacted with tropinone through a Michael addition reaction. Subsequently, the keto group in the intermediate product was nucleophilically attacked by another activated malononitrile. Finally, a new benzene ring was successfully constructed by successive domino reactions, including dehydration, intramolecular nucleophilic addition and cyclization reaction.

Conclusion

On balance, we have explored a candidate synthesis means for the preparation of potentially biologically active 4-aryl-5,8-epiminobenzo[7]annulenes through one-pot Michael/cyclization reaction of tropinone, malononitrile and aromatic aldehydes. Under optimized reaction process conditions, various 4-aryl-5,8-epiminobenzo[7]annulenes with different substituents were synthesized in good yield. The tandem domino reaction has broad industrial application prospect in organic and medicinal chemistry due to its notable advantages, such as extensive substrate scope, high atomic utilization efficiency, diminished costs as well as simple and practical operation process.

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