A facile and efficient synthesis of multisubstituted pyrroles from enaminoesters and nitroolefins†

Zheng-Hui Guan,* Liang Li, Zhi-Hui Ren, Jianli Li and Mi-Na Zhao

Received 14th March 2011, Accepted 1st April 2011
DOI: 10.1039/c1gc15278e

A facile and efficient method for the synthesis of substituted pyrroles from enaminoesters and nitroolefins is reported. This general procedure provides a wide variety of multisubstituted pyrroles in good to excellent yields under mild reaction conditions.

As one of the most important heterocycles, substituted pyrroles are not only found in many natural products and pharmaceuticals but are also widely used in material science, bioorganic chemistry, and supramolecular chemistry. A variety of elegant methods for the synthesis of pyrroles have been developed in the past decades, however, a facile and efficient procedure for the synthesis of multisubstituted pyrroles remains highly desirable.

Apart from the well-documented traditional methods, such as the Knorr, Paal–Knorr, and Hantzsch reactions, the modern approaches to the synthesis of substituted pyrroles are mainly based on the transition-metal catalyzed cyclizations and multicomponent coupling reactions. However, the high catalyst loading in some of these processes results in not only high cost but also potential contamination of the products, particularly in the pharmaceutical industry. Recently, a metal-free synthesis of substituted pyrroles by the domino reaction of cyclic enamiones with halogenated nitroolefins has emerged. However, the procedure was not environmentally benign due to using halogenated nitroolefins. We envision that the Michael-type addition and cyclization of enamiones or enaminoesters to nitroolefins would be a direct approach to construct the pyrrole rings in accordance with the principles of green chemistry (Scheme 1). There is limited precedent for these transformations, but the reaction is still limited in substrate scope and low yields. In this communication, we have improved the synthetic method and developed an environmentally benign, facile and efficient synthetic method for the synthesis of multisubstituted pyrroles from readily available enaminoesters and nitroolefins.

To begin our study, 1-(2-nitroprop-1-enyl)benzene 1a and methyl 3-(phenylamino)but-2-enooate 2a were chosen as model substrates to optimize the reaction conditions. Screening of various solvents revealed that CH₃OH was the most efficient one for the transformation (Table 1, entries 1–6). Various additives, such as NaOAc, pyridine, CAN (ammonium cerium(IV) nitrate), and Zn powder were tested and failed to improve the efficiency of the transformation (Table 1, entries 7–10). Therefore, the combination of the nitroolefins 1a (0.3 mmol) and enaminoesters 2a (0.45 mmol), in solvent (2 mL) at 120 °C gave the best result.

Under the optimized reaction conditions, we have explored the substrate scope. The reaction results of enaminoester 2a with various nitroolefins are summarized in Table 2. These
Table 2 Reactions of enaminoester 2a with various nitroolefins 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitroolefin 1</th>
<th>Pyrrole 3</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>3aa</td>
<td>14</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>3ba</td>
<td>22</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>3ca</td>
<td>22</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3da</td>
<td>23</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>3ea</td>
<td>35</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>3fa</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>3ga</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>3ha</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>3ia</td>
<td>35</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>3ja</td>
<td>12</td>
<td>78</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1 (0.3 mmol), 2a (0.45 mmol), in CH₃OH (2 mL) at 120 °C.

transformations displayed high functional group tolerance. Nitroolefins with methyl, methoxyl, amino, fluoro and chloro groups on the arene all gave the corresponding pyroles in good yields (Table 2, entries 2–8). For the electronic effects of the transformation, we found that electron-rich nitroolefins showed better reactivity and gave higher yields than electron-deficient ones (Table 2, entries 2–8). In addition, the nitroolefin possessing a furanyl group also underwent the desired reaction to give the corresponding pyrole product 3ia in good yield (Table 2, entry 9). An extensive investigation of the reaction shows that the
Table 3  Reactions of various enaminoesters 2 with nitroolefin 1a<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminoester 2</th>
<th>Pyrrole 3</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>3ab</td>
<td>12</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>3ac</td>
<td>13</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>3ad</td>
<td>24</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>3ae</td>
<td>13</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>3af</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>3ag</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>3ah</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>3ai</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td>3aj</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td>3ak</td>
<td>24</td>
<td>30(54)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>2l</td>
<td>3al</td>
<td>29</td>
<td>60(68)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>2m</td>
<td>3am</td>
<td>27</td>
<td>82</td>
</tr>
</tbody>
</table>

*<sup>a</sup>Green Chem., 2011, 13, 1664–1668 This journal is © The Royal Society of Chemistry 2011*

<sup>b</sup>Reactions were carried out in methanol at 120 °C.
Table 3 (Contd.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminoester</th>
<th>Pyrrole</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 13    | \[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\cdot \\
\text{H} \\
\text{N}
\end{array}
\] | \[
\begin{array}{c}
\text{MeO} - \\
\text{C} \\
\text{N}
\end{array}
\] | 7    | 92   |
| 14    | \[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\cdot \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{EtO} - \\
\text{C} \\
\text{N}
\end{array}
\] | 6    | 89   |
| 15    | \[
\begin{array}{c}
\text{C}_6\text{H}_{11} \\
\cdot \\
\text{C}_6\text{H}_{11}
\end{array}
\] | \[
\begin{array}{c}
\text{MeO} - \\
\text{C} \\
\text{N}
\end{array}
\] | 12   | 86   |
| 16    | \[
\begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{N}
\end{array}
\] | 24   | 58   |

* Reaction conditions: 1a (0.3 mmol), 2 (0.45 mmol), in CH₃OH (2 mL) at 120 °C. NaOAc (0.6 mmol) was added.

nitroolefin 1j also worked well, and a 78% yield of the desired pyrrole 3ja was obtained (Table 2, entry 10).

For extending the substrate scope, we have investigated the reactions of various enaminoesters 2b–2q with nitroolefin 1a as well, and the results are illustrated in Table 3. Satisfactorily, the reactions displayed high functional group tolerance and afforded the corresponding pyroles with great efficiency. In general, the electron-rich enaminoesters show better reactivity and gave higher yields than electron-deficient ones, and the reactions were insensitive to the steric hindrance of the substitutes on the aromatic rings (Table 3, entries 1–9). Pyrrole 3ak was only obtained in low yield because NO₂ substituted enaminoester 2k was partially decomposed in the reaction. This issue has been resolved by using NaOAc as an additive (Table 3, entry 10). The reaction of enaminoesters 2l and 2m, which derived from naphthalen-1-amine and naphthalen-2-amine respectively, also gave the corresponding pyrrole products 3al and 3am in good yields (Table 3, entries 11–12). It is worth noting that N-benzyl substituted pyrroles were obtained in excellent yields in the transformations (Table 3, entries 13–14). Similarly, N-cyclohexanyl substituted pyrrole 3ap was achieved in 86% yield (Table 3, entry 15). Moreover, the reaction of nitroolefin 1a with enamino 2q also gave the pyrrole product 3aq in good yield (Table 3, entry 16). In conclusion, we have demonstrated a facile and efficient procedure for the synthesis of multisubstituted pyroles. This general protocol employs readily available starting materials and shows good functional group tolerance. Under the transition metal-free and non-halogenation conditions, a wide variety of multisubstituted pyroles were synthesized in good to excellent yields in an environmentally benign manner.

Acknowledgements

This research was supported by National Natural Science Foundation of China (NSFC-21002077), Northwest University (PR09037, NF0913), and Education Department of Shaanxi Provincial Government (2010JK869).

Notes and references
