Iron mediated one pot three component synthesis of 3-substituted indoles via aerobic iminium ion formation

Vinay K. Singh, Laxmi Kant Sharma, Rana Krishna Pal Singh*

Electrochemical Laboratory of Green Synthesis, Department of Chemistry, University of Allahabad, Allahabad 211002, India

A R T I C L E   I N F O
Article history:
Received 31 October 2015
Revised 3 December 2015
Accepted 8 December 2015
Available online 9 December 2015

Keywords:
Multicomponent reaction
Atom economy
Indoles
Mannich reaction

A B S T R A C T
An efficient and economical method was developed for the synthesis of 3 substituted indoles by a highly efficient one-pot three component coupling reaction of substituted or unsubstituted benzyl alcohol, N-methyl aniline or pyrrolidine, and indoles or substituted indoles.

SYNTHETIC organic chemists have been continuously striving for improving the efficiency of organic synthesis, especially in terms of the atom economy and cost effectiveness. In this context, one-pot strategy involving the formation of multi component reactions is highly attractive. Multi component reactions (MCRs) play an important role in atom economy and green chemistry.1 These reactions are environmentally friendly, energy saving, and produce low wastage. Multi-component reactions2 (MCRs), which combine in one pot several simple building blocks, provide a most powerful platform to access diversity as well as complexity in a limited number of reaction steps. It is well utilized in the synthesis of medicinal compounds such as substituted indoles,3 decalhydroquinolin-4-ones,4 and 1,4 dihydropyridines. Strategy of multicomponent reactions has been playing a significant role in the preparation of structurally diverse chemical compounds. Indole is versatile synthetic intermediate for biologically active compounds which served as scaffolds in a number of natural and synthetic substituted indoles. Recently indole derivatives showing various pharmacological properties has been synthesized which contains natural and synthetic structural units responsible for activity.

Indole derivatives multi-component are one of the most abundant components of natural products as well as synthetic compounds possessing a variety of biological, medicinal and agrochemical importance. The biological activity of substituted indole has attracted researchers to explore different methods for the synthesis of indoles. Their biological properties5 have attracted many synthetic chemists to explore different methods suitable for the synthesis of substituted indoles, though there are several methods reported in the literature for the formation of three component reaction (Fig. 1). Despite several methods reported in the literature for the synthesis of substituted indoles, the development of simple, efficient, short, and environmentally benign approaches for the synthesis of indole derivatives is highly desirable (Scheme 1).

In the earlier methods three component compounds were prepared by the condensation method, which suffers the drawback of using the odorous3d and unstable aldehyde,3f and also requires in situ purification. Earlier methods also require large excess amounts of oxidants, which will also produce large amounts of undesired waste so developing efficient and greener methods is still an important need.

As a part of our ongoing effort towards the synthesis of medicinally important molecules using development of efficient the green methods in organic synthesis.6 We are demonstrating here...
We initiated our studies of the three-component reaction with N-methyl aniline (1a) (1 mmol) and benzyl alcohol (2a) (1.2 mmol), and indole (3a) (1 mmol) was taken as a model substrate to optimize the reaction condition. Treatment of benzyl alcohol (2a) (1.2 mmol) and N-methyl aniline (1a mmol) with 50 mol % of KOH in 0.5 mL of toluene in the presence 10/10 mol %

Previous work:

Present work:

Scheme 1. Synthesis of 3 substituted indoles.

Table 1
Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fe(NO₃)₃·9H₂O (mol %)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Base b (mol %)</th>
<th>Yield c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Toluene</td>
<td>rt</td>
<td>KOH (10)</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Toluene</td>
<td>50</td>
<td>KOH (10)</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>Toluene</td>
<td>80</td>
<td>KOH (10)</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Toluene</td>
<td>80</td>
<td>KOH (20)</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Toluene</td>
<td>80</td>
<td>KOH (50)</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Toluene</td>
<td>80</td>
<td>t-BuOK (10)</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>Benzene</td>
<td>80</td>
<td>t-BuOK (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>Benzene</td>
<td>80</td>
<td>Et₃N (10)</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>Benzene</td>
<td>80</td>
<td>t-BuOK (10)</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>Dioxane</td>
<td>80</td>
<td>KOH (10)</td>
<td>81</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>Dioxane</td>
<td>80</td>
<td>KOH (10)</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>Xylene</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>Xylene</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>DMF</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>CH₂CN</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>THF</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>DMSO</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>CH₂Cl₂</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
<tr>
<td>19</td>
<td>10</td>
<td>CH₂CN + H₂O (4:1)</td>
<td>80</td>
<td>KOH (10)</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Reaction was carried out in a sealed tube.

n.d. = not detected.

a All reactions were run with 1a (1.0 mmol), 2a (1.0 mmol), 3a (1.2 mmol) Fe(NO₃)₃·9H₂O (10 mol %), and the base in toluene (0.5 mL) and 10 mL of solvent (3 mL) was heated under air in a sealed tube for 24–30 h and then indole was added and monitored by TLC at room temperature.

b 0.1 mmol of TEMPO was used along with the base in all the cases.

c Isolated yield of 4a.
Table 2
Substrate scope for the preparation of 3 substituted indoles\textsuperscript{a,b,c}

\begin{align*}
\begin{array}{|c|c|c|}
\hline
\text{R}^\prime & \text{R}'' & \text{Yield} \\
\hline
\text{OH} & \text{CH}_3 & 38 \text{ h}, (80\%) \\
\text{MeO} & \text{Cl} & 36 \text{ h}, (84\%) \\
\text{Br} & \text{OMe} & 35 \text{ h}, (83\%) \\
\text{Cl} & \text{MeO} & 36 \text{ h}, (84\%) \\
\text{Cl} & \text{H} & 38 \text{ h}, (79\%) \\
\text{OH} & \text{H} & 35 \text{ h}, (80\%) \\
\text{MeO} & \text{H} & 36 \text{ h}, (84\%) \\
\text{Cl} & \text{Br} & 38 \text{ h}, (84\%) \\
\text{Br} & \text{Cl} & 36 \text{ h}, (87\%) \\
\text{Br} & \text{Cl} & 38 \text{ h}, (87\%) \\
\end{array}
\end{align*}

\textsuperscript{a} For the experimental procedure, see Supporting information.
\textsuperscript{b} All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.\textsuperscript{3d,m}
\textsuperscript{c} Yields of isolated pure compounds 4a.
of \((\text{Fe(NO}_3)_3 \cdot 9\text{H}_2\text{O/TMEDA})\) for 24–30 h yielded iminum ion which was again treated with indole, it gives the desired novel 3 substituted indole as a single product. It was found that the base played a crucial role in the reaction as shown in Table 1 (entry 1), the reaction was initially tested at room temperature with a catalytic amount of KOH added but only a low yield of 30% was detected. Reaction yield can be improved at higher temperature; at 80 °C the yield of 4a was 85% in the presence of KOH base (Table 1, entry 3).

During the course of the reaction we attempted a similar transformation in various solvents such as \(\text{CH}_2\text{Cl}_2\), DMSO, DMF, THF, acetonitrile, benzene, toluene, and dioxane and among these solvents benzene, toluene, dioxane and xylene (Table 1, entries 1–6 and 9–12) were found to be most efficient reaction media to give the product in good yield (76–85)%.

Furthermore catalyst conditions were optimized by using different variations of catalyst and catalyst loading, and the time period of the reaction screening showed that 10 mol % of \(\text{CsOH}\), and \(\text{rBuOK}\) was used in place of the potassium hydroxide reaction. The yield was very good when potassium hydroxide is used as base Table 1 (entries 1–3) to facilitate this reaction. After optimization of reaction condition it was concluded that benzylic alcohol gives corresponding product in good yield rather than other alcohols. Reaction proceeds well in both electron donating and electron withdrawing groups for the present protocol reaction. The result prompted us to test both electron donating and electron withdrawing groups and also for the present protocol reaction. The result prompted us to test both electron donating and electron withdrawing groups and also in situ iminium ion formation.

We developed a highly efficient, short, and green method for the synthesis of 3-amino-alkylated indole via one-pot three-component Mannich type reaction. Mannich-type reactions are very important carbon–carbon bond-forming reactions in organic synthesis. It is easy and safe to handle in large scale synthesis for the preparation of the final product making this an attractive protocol by using in situ iminium ion formation.

Acknowledgments

We sincerely thank Saif, Punjab University, Chandigarh, for providing microanalyses and spectra. V.K.S. is grateful to the University Grants Commission (UGC, India) for the award of Dr. D.S. Kothari post-doctoral fellowship and financial support.

Supplementary data

Supplementary data (detailed experimental procedures, product characterization, and NMR spectra of the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.086.