A ONE POT THREE-COMPONENT SYNTHESIS OF SPIROOXINDOLES USING Cu-NANOPARTICLES GRAFTED ON CARBON MICROSPHERES AS CATALYST

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The copper nanoparticles grafted on carbon microsphere is employed for an efficient one-pot three-component synthesis of spirooxindole derivatives involving isatin, malononitrile and enolizable ketones such as 3-methyl-1-phenyl-2-pyrazolin-5-one, 3-methyl-1-(2-chlorophenyl)-2-pyrazoline 5-one, 4-hydroxy-6-methyl-2-pyrene and 1-methyl-4-hydroxyquinoline-2-one. The cheap starting material, easy separation, high catalytic efficiency and reusability of the catalyst for several times without loss of its efficiency, good yield of products, and simple workup are promising features of the reaction in 1:1 (v/v) aqueous-alcoholic medium.

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Introduction

Multicomponent reactions (MCRs) involve an effective combination of three or sometimes more reactants simultaneously in a one-pot synthesis and do not require the separation of intermediates. MCR can be widely used for the synthesis of most of the heterocyclic compounds to form new C-C bonds. These reactions are highly selective, energy efficient, environmentally-friendly, involves simple purification techniques, and requires low cost with short reaction time. Some examples which involve MCRs are the Biginelli, Mannich, and Robinson reactions. Heterocycles containing the indole moiety exhibit antifungal and antibacterial activities, and pyrazole ring derivatives are useful in the development of insecticides, fungicides and herbicides. The spirooxindole moiety is an essential unit of natural products and pharmaceuticals, for example the cytostatic alkaloids Spirotryprostatins A and B. The structural characteristics of these compounds are the spiro ring fused at the C3 position of the oxindole unit with various heterocyclic motifs.

A large number of bioactive natural products containing the indole moiety exhibit antifungal and antibacterial activities. In the structure of spirooxindoles, the indole 3-carbon is shared in the formation of spiroindolines and it is a carbonyl group at the C-2 position. Compounds containing spirooxindole as the structural unit exhibit different biological activities like antimicrobial, antioxidant, antitubercular, anticancer, anti-HIV and anti-inflammatory activities. Some representative examples of spirooxindoles are provided in Figure 1.

Figure 1. Some bioactive spirooxindole derivatives.

Synthesis of various spirooxindole derivatives involves the one-pot condensation reaction of isatin, activated methylene and a 1,3-dicarbonyl compound. This reaction can be achieved using different catalysts and conditions such as SnCl4, triethylamine, basic alumina under microwave irradiation, triethylbenzylammonium chloride (TEBA), β-cyclodextrin, NaCl under sonication, ZnS nanoparticles, piperidine under ultrasound irradiation, CaCl2 under ultrasound irradiation, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), ethylenediammonium diformate (EDDF), mesoporous silica (SBA-15)-PrNH2, L-prolin, silica bound ionic liquids, tris(hydroxymethyl)aminomethane (THAM), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-Ac, cerium oxide, microwaves, 1,4-diazabicyclo[2.2.2]octane (DABCO), sodium acetate or potassium fluoride, and 1-(carboxymethyl) pyridinium iodide.

Heterogeneous catalysts are always superior to their homogeneous counterparts in many aspects such as operational simplicity, reusability, and high selectivity. The use of low cost and readily available heterogeneous catalyst plays a significant role in chemical processes. Recently, most of the attention is made towards the synthesis and application of metallic nanoparticles (NPs) due to their unique properties compared to bulk materials.
Nanoparticles have high specific surface areas, various shapes and sizes, and high reactivity. Handling of nanoparticles is not easy because they lead to self-aggregation and it is also difficult to separate them from the reaction medium. To overcome these limitations, nanoparticles are used by some supports. Such developed catalytic metallic nanoparticles that are inexpensive, non- or minimally poisonous, highly active, stable and easily separable from reaction mixture are highly useful. Copper nanoparticles are one of the alternatives to heavy metal nanoparticle catalysis. Therefore, copper nanoparticles grafted on carbon microsphere find alternatives to these problems. 35,36

In the present work, an effective, copper nanoparticle grafted on carbon microsphere catalysed method for the one-pot synthesis of spirooxindole derivatives in aqueous ethanol is reported herein (Scheme 1).

### Experimental

Chemicals were purchased from Sigma Aldrich, Alpha Caesar, TCS and Spectochem, and used as such without further purification. Products were characterized by 1H and 13C NMR and Mass spectra. 1H and 13C NMR spectra were recorded on a Bruker (400 MHz) spectrometer using DMSO-d6 as deuterated solvent and tetramethylsilane (TMS) as an internal standard. Reactions were monitored by TLC using TLC Silica gel 60 F254 aluminium sheet (Merck). The Cu-NP/C catalyst was prepared as described in our previous papers. 35,37

### General procedure for the synthesis of spirooxindole derivatives

A mixture of isatin (1 mmol), malononitrile (1 mmol) and enolisable ketone (1 mmol) were refluxed with stirring in 1:1 aqueous ethanol (2 mL) in oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the remaining was washed with warm ethanol to separate the Cu-NP/C catalyst. After cooling the filtrate, the precipitated solid was filtered off. The crude products were purified by recrystallization from 95% ethanol.

6'-Amino-5-methoxy-3'-methyl-1'-phenyl-2'-chloro-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c][pyrazole]-5'-carbonitrile (4m)

Mp. 222-224 °C, 1H NMR (400 MHz, DMSO-d6): δ (ppm) 1.546 (s, 3H, CH3), 2.260 (s, 3H, CH3), 3.799 (d, 1H, Ar), 7.516 (s, 1H, Ar), 7.540-7.560 (d, 1H, Ar), 7.583 (s, 2H, NH2), 7.634-7.642 (m, 2H, Ar), 7.656-7.665 (d, 1H, Ar), 7.715-7.742 (d, 1H, Ar), 10.632 (s, 1H, NH), 13C NMR: 11.65, 20.55, 47.39, 55.40, 57.02, 97.92, 98.32, 112.30, 128.26, 129.44, 130.25, 133.81, 144.20, 146.04, 149.99, 156.95, 177.25.

6'-Amino-5-methoxy-3'-methyl-1'-phenyl-2'-chloro-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c][pyrazole]-5'-carbonitrile (4n)

Mp. 250-252 °C, 1H NMR (400 MHz, DMSO-d6): δ (ppm) 1.536 (s, 3H, CH3), 6.940-6.955 (d, 1H, Ar), 7.033-7.050 (t, 1H, Ar), 7.108-7.123 (d, 1H, Ar), 7.277-7.307 (t, 1H, Ar), 7.409 (s, 2H, NH2), 7.530-7.644 (m, 2H, Ar), 7.655-7.659(d, 1H, Ar), 7.715-7.731(d, 1H, Ar), 10.731 (s, 1H, NH), 13C NMR: 94.91, 109.75, 117.86, 122.56, 124.61, 128.27, 129.44, 130.25, 133.81, 135.02, 144.24, 145.99, 160.91, 177.32.

6'-Amino-5-chloro-3'-methyl-1'-phenyl-2'-chloro-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c][pyrazole]-5'-carbonitrile (4p)

Mp. 250-252 °C, 1H NMR (400 MHz, DMSO-d6): δ (ppm) 1.536 (s, 3H, CH3), 6.940-6.955 (d, 1H, Ar), 7.033-7.050 (t, 1H, Ar), 7.108-7.123 (d, 1H, Ar), 7.277-7.307 (t, 1H, Ar), 7.409 (s, 2H, NH2), 7.530-7.644 (m, 2H, Ar), 7.655-7.659(d, 1H, Ar), 7.715-7.731(d, 1H, Ar), 10.731 (s, 1H, NH), 13C NMR: 94.91, 109.75, 117.86, 122.56, 124.61, 128.27, 129.44, 130.25, 133.81, 144.24, 145.99, 160.91, 177.32.

6'-Amino-5-chloro-3'-methyl-1'-phenyl-2'-chloro-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c][pyrazole]-5'-carbonitrile (4q)

Mp. 266-268 °C, 1H NMR (400 MHz, DMSO-d6): δ (ppm) 1.578 (s, 3H, CH3), 6.799-6.818 (d, 1H, Ar), 7.463 (s, 1H, Ar), 7.481 (s, 2H, NH2), 7.541-7.565 (m, 2H, Ar), 7.581-7.646(m, 2H, Ar), 7.659-7.732(d, 1H, Ar), 10.875 (s, 1H, NH), 13C NMR 11.72, 47.85, 55.57, 85.44, 94.31, 112.30, 117.81, 128.22, 129.87, 130.67, 131.26, 132.87, 133.75, 134.78, 137.82, 141.27, 144.06, 146.07, 161.00, 176.76.
2'-Amino-5-chloro-6'-'N-methyl-2',5'-dioxo-5',6'-dihydrospiro-[pyrano[2,3-c]quinoline-3',4-indoline]-3'-carbonitrile (4s)

Mp. > 280 °C, 25 1H NMR (400 MHz, DMSO-d6); δ (ppm) 3.495 (s, 3H, CH3), 3.486 (s, 3H, CH3), 6.838-6.854 (d, 1H, Ar), 7.197-7.231 (t, 1H, Ar), 7.760-7.778 (t, 1H, Ar), 8.061-8.077 (d, 1H, Ar), 10.663 (s, 1H, NH); 13C NMR: 20.50, 48.16, 57.39, 106.54, 108.94, 112.24, 114.98, 117.46, 122.33, 123.31, 128.54, 130.49, 132.18, 134.30, 138.59, 139.97, 151.39, 158.76, 177.76.

Table 1. Optimization of reaction between 1 mmol of isatin, 1 mmol of malononitrile and 1 mmol of 3-methyl-1-phenyl-2-pyrazoline-5-one under reflux.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time, h</th>
<th>Catalyst, mg</th>
<th>Isolated yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>3.5</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>3.0</td>
<td>5</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>1.0</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>55</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>EtOH:H2O (1:1)</td>
<td>50</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>EtOH:H2O (1:1)</td>
<td>40</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>EtOH:H2O (1:1)</td>
<td>40</td>
<td>15</td>
<td>90</td>
</tr>
</tbody>
</table>

The set of reactions were examined in various solvents and different amounts of catalyst under reflux (Table 1). Firstly, reactions were conducted in five different solvents (entries 1-5, Table 1). The best deal was obtained in EtOH:H2O (1:1) (entry 5, Table 1) using 5 mg of catalyst. The reactions using other solvents gave moderate to low yield of the product (entries 1-4, Table 1). Different catalytic conditions were also applied in EtOH:H2O (1:1), high yield was found when 10 mg of the catalyst was used (entry 6, Table 1). The workup of reaction involves only filtration and washing with hot ethanol. The catalyst was separated from the product by filtering it with hot ethanol and reused with washing with ethanol and then with acetone.

The following series of compounds have been prepared:

6'-Amino-3'-methyl-1'-phenyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (entry 1-6, Table 2),

2'-Amino-7-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[4,3-b]pyran]-3'-carbonitrile (entry 7-12, Table 2)

6'-Amino-3'-methyl-1'-phenyl-2'-chloro-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (entry 13-18, Table 2) and

2-Amino-6-methyl-2,5-dioxo-5,6-dihydrospiro[pyrano[3,2-c]quinoline-4,3'-indoline]-3-carbonitrile (entry 19-23, Table 2).

The reactions were conducted under reflux for 40-63 min in 1:1 aqueous ethanol in the presence of 10 mg of Cu-NP/C catalyst. The products were obtained in good yields. The molecular structures of the products were characterized by 1H NMR, ESI-MS and 13C NMR spectroscopic data.

Herein, an efficient and straightforward method for the synthesis of spiro[indoline3,4'-pyrano[2,3-c]pyrazole]-derivative was developed via one-pot three-component reaction of isatins, malononitrile and enolizable 1,3-dicarbonyl compounds under reflux in 1:1 aqueous ethanol. The procedure offers several advantages like high yields, fast reactions, and convenient and straightforward procedure.
Table 2. One pot synthesis of spiro-oxoindole derivatives in 1:1 aqueous ethanol using Cu-NP/C catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time</th>
<th>Yield, %</th>
<th>MP, °C</th>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>3a</td>
<td>40 min</td>
<td>92</td>
<td>237-238 °C</td>
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<tr>
<td>2</td>
<td>Br</td>
<td>3a</td>
<td>50 min</td>
<td>88</td>
<td>242-244 °C</td>
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<tr>
<td>3</td>
<td>Cl</td>
<td>3a</td>
<td>54 min</td>
<td>87</td>
<td>232-234 °C</td>
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<tr>
<td>4</td>
<td>CH₃</td>
<td>3a</td>
<td>48 min</td>
<td>91</td>
<td>288-290 °C</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>3a</td>
<td>52 min</td>
<td>86</td>
<td>&gt;300 °C</td>
</tr>
<tr>
<td>6</td>
<td>OCH₃</td>
<td>3a</td>
<td>45 min</td>
<td>90</td>
<td>213-215 °C</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>3b</td>
<td>62 min</td>
<td>86</td>
<td>&gt;280</td>
</tr>
<tr>
<td>8</td>
<td>OCH₃</td>
<td>3b</td>
<td>60 min</td>
<td>90</td>
<td>262-265</td>
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<tr>
<td>9</td>
<td>Cl</td>
<td>3b</td>
<td>64 min</td>
<td>88</td>
<td>&gt;300 °C</td>
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<tr>
<td><strong>10</strong></td>
<td>H</td>
<td><strong>3b</strong></td>
<td>58 min</td>
<td>87</td>
<td>283-28531</td>
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<tr>
<td><strong>11</strong></td>
<td>Br</td>
<td><strong>3b</strong></td>
<td>63 min</td>
<td>90</td>
<td>&gt;300&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>12</strong></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td><strong>3b</strong></td>
<td>60 min</td>
<td>91</td>
<td>&gt;270&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>13</strong></td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td><strong>3c</strong></td>
<td>45 min</td>
<td>92</td>
<td>222-224</td>
</tr>
<tr>
<td><strong>14</strong></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td><strong>3c</strong></td>
<td>50 min</td>
<td>90</td>
<td>251-254</td>
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<tr>
<td><strong>15</strong></td>
<td>Cl</td>
<td><strong>3c</strong></td>
<td>52 min</td>
<td>89</td>
<td>247-248&lt;sup&gt;29&lt;/sup&gt;</td>
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<tr>
<td><strong>16</strong></td>
<td>H</td>
<td><strong>3c</strong></td>
<td>48 min</td>
<td>91</td>
<td>250-252&lt;sup&gt;28&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>17</strong></td>
<td>Br</td>
<td><strong>3c</strong></td>
<td>53 min</td>
<td>90</td>
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## References


Synthesis of spirooxindoles with Cu/C catalyst

Section A-Research paper


23 Liu, W., Ablajian, K., Jun, F., Ultrason. Sonochem. 2015, 22, 113–118. https://doi.org/10.1016/j.ultsonch.2014.05.013


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