



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

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**Keywords:** Heterogeneous catalyst; spirooxindoles; Enolisable ketones; copper nanoparticle/C.

The copper nanoparticles grafted on carbon microsphere is employed for an efficient one-pot three-component synthesis of spirooxindole derivatives involving isatin, malononitrile and enolisable ketones such as 3-methyl-1-phenyl-2-pyrazolin-5-one, 3-methyl-1-(2-chlorophenyl)-2-pyrazolin-5-one, 4-hydroxy-6-methyl-2-pyryone 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.

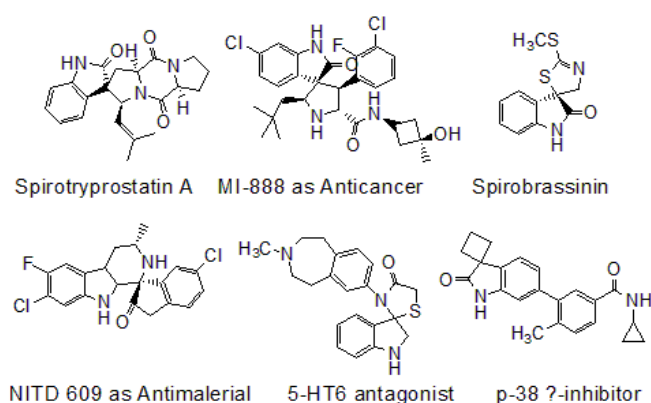
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## Introduction

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 in the synthesis of most of the heterocyclic compounds to form new C-C bonds. These reactions are highly selective, energy efficient, environmental-friendly, involves simple purification techniques, and requires low cost with short reaction time.<sup>1</sup> Some examples which involve MCRs are the Biginelli,<sup>2</sup> Mannich,<sup>3</sup> and Robinson<sup>4</sup> 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.<sup>5,6</sup> The spirooxindole moiety is an essential unit of natural products and pharmaceuticals,<sup>7</sup> for example the cytostatic alkaloids Spirotryprostatins A and B. The structural characteristics of these compounds are the spiro ring fused at the C<sub>3</sub> position of the oxindole unit with various heterocyclic motifs.<sup>8</sup>

A large number of bioactive natural products containing the indole moiety<sup>9</sup> 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.<sup>10</sup> 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 SnCl<sub>4</sub>,<sup>11</sup> triethylamine,<sup>12</sup> basic alumina under microwave irradiation,<sup>13</sup> triethylbenzylammonium chloride (TEBA),<sup>14</sup> β-cyclodextrin,<sup>15</sup> NaCl under sonication,<sup>16</sup> ZnS nanoparticles,<sup>1</sup> piperidine under ultrasound irradiation,<sup>18</sup> CaCl<sub>2</sub> under ultrasound irradiation,<sup>19</sup> 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),<sup>20</sup> ethylenediammonium diformate (EDDF),<sup>21</sup> mesoporous silica (SBA-15)-PrNH<sub>2</sub>,<sup>22</sup> L-prolin,<sup>23</sup> silica bound ionic liquids,<sup>24</sup> tris(hydroxymethyl)aminomethane (THAM),<sup>25,19</sup> 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-Ac,<sup>26</sup> ultrasound,<sup>27</sup> cerium oxide,<sup>28</sup> microwave irradiation,<sup>29</sup> 1,4-diazabicyclo[2.2.2]octane (DABCO),<sup>30</sup> sodium acetate or potassium fluoride,<sup>31</sup> and 1-(carboxymethyl) pyridinium iodide.<sup>32</sup>

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.<sup>33</sup>

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.<sup>34</sup> Therefore, copper nanoparticles grafted on carbon microsphere find alternatives to these problems.<sup>35,36</sup>

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 Spectrochem, and used as such without further purification. Products were characterized by <sup>1</sup>H and <sup>13</sup>C NMR and Mass spectra. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker (400 MHz) spectrometer using DMSO-d<sub>6</sub> as deuterated solvent and tetramethylsilane (TMS) as an internal standard. Reactions were monitored by TLC using TLC Silica gel 60 F<sub>254</sub> aluminium sheet (Merck). The Cu-NP/C catalyst was prepared as described in our previous papers.<sup>35,37</sup>

### 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 the presence of Cu-NP/C (10 mg) 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-3'-methyl-1'-phenyl-2'-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (4a)

Mp. 237-238 °C,<sup>16</sup> <sup>1</sup>H NMR (400 MHz, DMSO d<sub>6</sub>): δ (ppm) 1.545 (s, 3H, CH<sub>3</sub>), 6.94-7.054 (m, 2H, Ar), 7.174 (d, 1H, Ar), 7.273-7.504 (m, 2H, Ar), 7.525-7.544 (m, 2H, Ar), 7.590 (s, 2H, NH<sub>2</sub>), 7.780-7.802 (d, 2H, Ar), 10.756 (s, 1H, NH); ESI-MS: m/z = 370.

#### 2'-Amino-5-iodo-7'-methyl-2,5'-dioxo 5'H-spiro[indoline-3,4'-pyrano[4,3-b]pyran]-3'-carbonitrile (4g)

Mp. > 280 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 2.247 (s, 3H, CH<sub>3</sub>), 6.352-6.354 (m, 1H, Ar), 6.667-6.684 (d, 1H, Ar), 7.509 (s, 2H, NH<sub>2</sub>), 7.523-7.527 (d, 1H, Ar), 7.539-7.543 (d, 1H, Ar), 10.705 (s, 1H, NH), <sup>13</sup>C NMR: 19.21,

46.90, 56.25, 84.75, 97.99, 111.79, 116.96, 132.13, 135.57, 137.25, 141.91, 158.63, 159.76, 163.75, 176.65.

#### 2'-Amino-5-methoxy-7'-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[4,3-b]pyran]-3'-carbonitrile (4h)

Mp. 262-264 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 2.235 (s, 3H, CH<sub>3</sub>), 3.662 (s, 3H, OCH<sub>3</sub>), 6.339 (s, 1H, Ar), 6.728-6.768 (m, 3H, Ar), 7.427 (s, 2H, NH<sub>2</sub>), 10.396 (s, 1H, NH), <sup>13</sup>C NMR: 19.23, 47.39, 55.40, 57.02, 97.92, 98.32, 109.73, 110.66, 113.45, 117.09, 134.27, 135.40, 155.16, 158.53, 159.56, 159.96, 163.58, 177.09.

#### 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, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 1.560 (s, 3H, CH<sub>3</sub>), 3.702 (s, 3H, OCH<sub>3</sub>), 6.719 (m, 1H, Ar), 7.397-7.554 (d, 1H, Ar), 7.563-7.576 (m, 2H, Ar), 7.578-7.590 (m, 2H, Ar), 7.713 (s, 2H, NH<sub>2</sub>), 7.727 (d, 2H, Ar), 10.552 (s, 1H, NH); ESI-MS: m/z = 434; <sup>13</sup>C NMR: 11.66, 48.33, 54.82, 55.45, 94.95, 110.25, 113.88, 117.91, 128.24, 130.26, 133.51, 144.23, 146.04, 155.5, 160.95, 177.25.

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

Mp. 252-254 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 1.546 (s, 3H, CH<sub>3</sub>), 2.260 (s, 3H, CH<sub>3</sub>), 7.399 (d, 1H, Ar), 7.516 (s, 1H, Ar), 7.540-7.560 (d, 1H, Ar), 7.583 (s, 2H, NH<sub>2</sub>), 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), <sup>13</sup>C NMR: 11.65, 20.55, 47.89, 56.29, 95.01, 109.47, 117.91, 125.01, 128.26, 129.44, 130.25, 132.24, 133.81, 139.02, 144.24, 145.99, 160.91, 177.32.

#### 6'-Amino-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,<sup>28</sup> <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 1.536 (s, 3H, CH<sub>3</sub>), 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, NH<sub>2</sub>), 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); ESI-MS: m/z = 404; <sup>13</sup>C NMR 94.91, 109.75, 117.86, 122.56, 124.61, 128.27, 129.16, 129.79, 130.24, 131.25, 132.16, 133.81, 141.49, 144.20, 146.04, 160.96, 177.37.

#### 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 (4r)

Mp. 266-268 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 1.578 (s, 3H, CH<sub>3</sub>), 6.799-6.818 (d, 1H, Ar), 7.463 (s, 1H, Ar), 7.481 (s, 2H, NH<sub>2</sub>), 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); <sup>13</sup>C 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)**

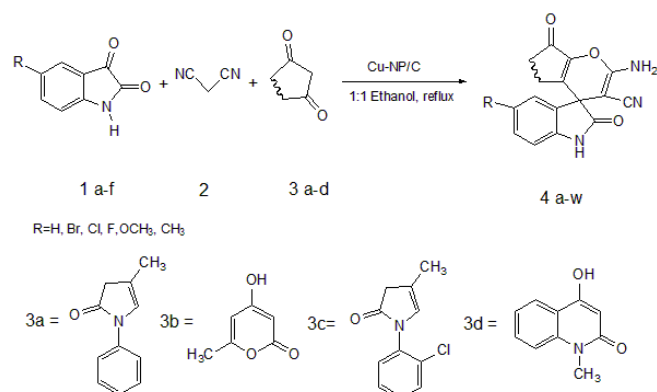
Mp. > 280 °C, <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>): δ (ppm) 3.495 (s, 3H, CH<sub>3</sub>), 6.838-6.854 (d, 1H, Ar), 7.197-7.231 (t, 2H, Ar), 7.433-7.466 (t, 1H, Ar), 7.541(s, 2H, NH<sub>2</sub>), 7.596-7.613 (d, 1H, Ar), 8.076(d, 1H, Ar), 10.663 (s, 1H, NH); <sup>13</sup>C NMR: 29.23, 48.36, 56.44, 105.71, 111.07, 112.32, 113.36, 115.00, 117.32, 122.44, 126.34, 130.99, 132.26, 136.62, 138.66, 141.79, 151.72, 158.96, 177.50.

**2'-Amino-5-methyl 6'-N-methyl-2,5'-dioxo-5',6'-dihydrospiro[pyrano[2,3-c]quinoline-3',4'-indoline]-3'-carbonitrile (4t)**

Mp. > 280 °C, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 2.166(s, 3H, CH<sub>3</sub>), 3.486 (s, 3H, CH<sub>3</sub>), 6.711-6.727 (d, 1H, Ar), 6.827 (s, 1H, Ar), 6.959-6.977 (d, 1H, Ar), 7.429-7.442(s, 2H, NH<sub>2</sub>), 7.442-7.458 (d, 1H, Ar), 7.743-7.760(d, 1H, Ar), 7.760-7.778(t, 1H, Ar), 8.061-8.077(d, 1H, Ar), 10.410 (s, 1H, NH); ESI-MS: m/z = 385; <sup>13</sup>C NMR: 20.50, 29.18, 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.

**Results and discussion**

A method for the synthesis of spirooxindole derivatives in 1:1 aqueous ethanol by a one-pot three-component reaction of isatin, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one, 4-hydroxy-6-methyl-2-pyrone or 1-methyl-4-hydroxyquinoline-2-one catalysed by copper nanoparticles grafted on carbon microsphere is presented in the present article (see Scheme 1).



**Scheme 1.** Synthesis of spirooxindole derivatives using Cu-NP/C catalyst under reflux for 40-63 min in 1:1 aq. ethanol.

To optimize the reaction conditions, the reaction between isatin (1 mmol), malononitrile (1 mmol) and 3-methyl-1-phenyl-2-pyrazoline-5-one (1 mmol) was chosen as a model reaction in 1:1 aqueous ethanol in order to optimize the

reaction conditions. Starting materials of this model reaction were converted to **4a** in high yield using 10 mg Cu-NP/C catalyst (Table 1).

**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.

Entry	Solvent	Time, h	Catalyst, mg	Isolated yield, %
1	DMF	3.5 h	5	52
2	THF	3.0 h	5	44
3	MeOH	1.0 h	5	78
4	EtOH	55 min	5	84
5	EtOH:H <sub>2</sub> O (1:1)	50 min	5	88
6	EtOH:H <sub>2</sub> O (1:1)	40 min	10	92
7	EtOH:H <sub>2</sub> O (1:1)	40 min	15	90

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:H<sub>2</sub>O (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:H<sub>2</sub>O (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 by 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)

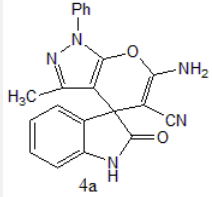
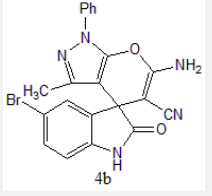
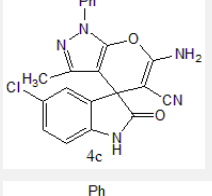
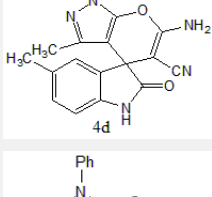
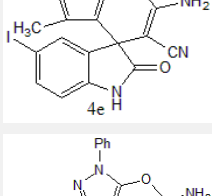
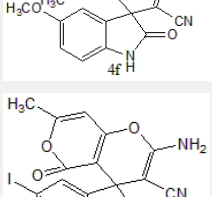
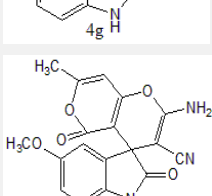
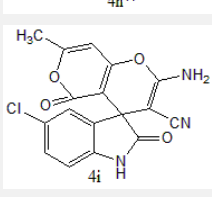

6'-Amino-3'-methyl-1'-phenyl-2'-chloro-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (entry 13-18, Table 2) and

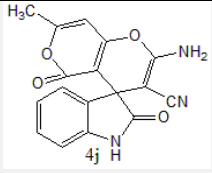
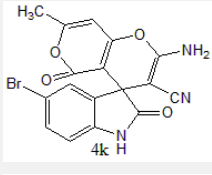
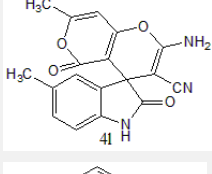
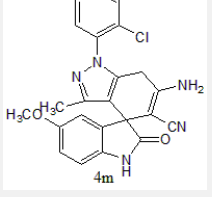
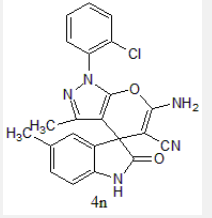
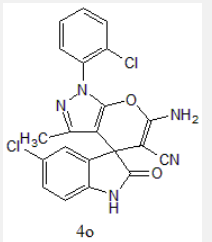
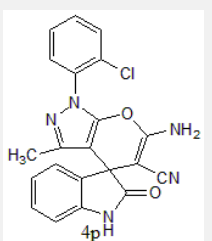
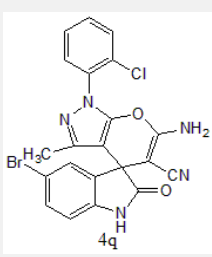
2-Amino 6-methyl-2,5-dioxo-5,6-dihydrospiro[pyrano-[3,2-c]quinoline-4,3'-indoline]-3-carbonitrile (entry 19-23, Table 2).

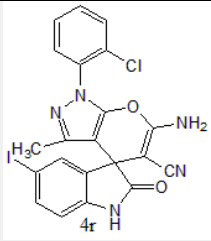
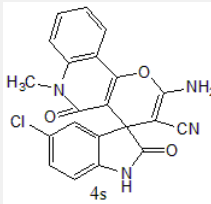
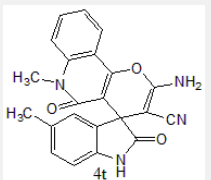
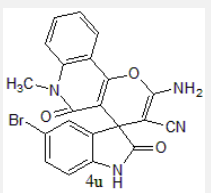
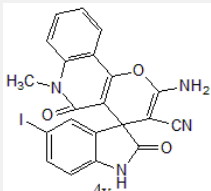
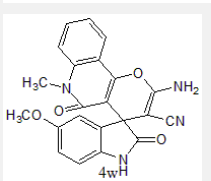
The reactions were conducted under reflux for 40-63 min in 1:1 aqueous ethanol in the presence of 10 mg of Cu-NP/C catalyst. The products were obtained in good yields. The molecular structures of the products were characterized by <sup>1</sup>H NMR, ESI-MS and <sup>13</sup>C NMR spectroscopic data.

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

**Table 2.** One pot synthesis of spiro-oxindole derivatives in 1:1 aqueous ethanol using Cu-NP/C catalyst.

Entry	R 1a-1f	Product 3a-3d	Product 4a-4w	Time	Yield, %	MP, °C
1	H	<b>3a</b>		40 min	92	237-238 <sup>16</sup>
2	Br	<b>3a</b>		50 min	88	242-244 <sup>16</sup>
3	Cl	<b>3a</b>		54 min	87	232-234 <sup>16</sup>
4	CH <sub>3</sub>	<b>3a</b>		48 min	91	288-290 <sup>16</sup>
5	I	<b>3a</b>		52 min	86	>300 <sup>32</sup>
6	OCH <sub>3</sub>	<b>3a</b>		45 min	90	213-215 <sup>28</sup>
7	I	<b>3b</b>		62 min	86	>280
8	OCH <sub>3</sub>	<b>3b</b>		60 min	90	262-265
9	Cl	<b>3b</b>		64 min	88	>300 <sup>31</sup>

10	H	<b>3b</b>		58 min	87	283-285 <sup>31</sup>
11	Br	<b>3b</b>		63 min	90	>300 <sup>31</sup>
12	CH <sub>3</sub>	<b>3b</b>		60 min	91	>270 <sup>30</sup>
13	OCH <sub>3</sub>	<b>3c</b>		45 min	92	222-224
14	CH <sub>3</sub>	<b>3c</b>		50 min	90	251-254
15	Cl	<b>3c</b>		52 min	89	247-248 <sup>29</sup>
16	H	<b>3c</b>		48 min	91	250-252 <sup>28</sup>
17	Br	<b>3c</b>		53 min	90	259-262

18	I	3c		50 min	91	266-269
19	Cl	3d		40 min	93	>280 <sup>25</sup>
20	CH <sub>3</sub>	3d		45 min	90	>280 <sup>25</sup>
21	Br	3d		50 min	92	>300 <sup>26</sup>
22	I	3d		48 min	90	>300 <sup>26</sup>
23	OCH <sub>3</sub>	3d		46 min	88	>300 <sup>27</sup>

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