



# An atom-economic synthesis of functionalized pyrroles via a sequential metal-catalyzed three-component reaction



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## ABSTRACT

A three-component reaction of one molecule of imine and two molecules of alkynoates is realized with the catalysis of Cu(I)–Fe(III) in a sequential manner to allow the direct synthesis of functionalized pyrroles, during which, one C–N bond and two C–C bonds are formed with high atom economy. This method benefits from easily available starting materials, low-cost catalysts, and convenient operations.

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## 1. Introduction

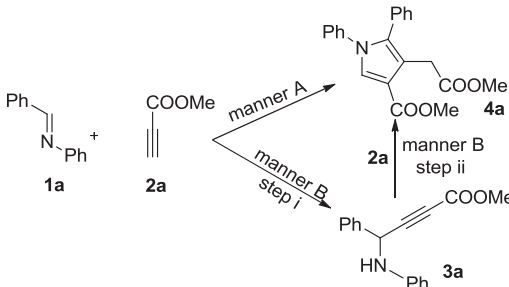
Pyrroles represent one of the most important five-membered heterocycles that constitute the vast majority of drugs and biologically relevant molecules, such as antiviral, antibacterial, chlorophyll, and so on.<sup>1</sup> Besides, they are very important intermediates in synthetic chemistry<sup>2</sup> and widely used in the field of material design.<sup>3</sup> As such, a variety of well-documented methods have been dedicated to the construction of pyrroles and their derivatives in the past.<sup>4</sup> The Hantzsch reaction<sup>5</sup> based on condensation of  $\alpha$ -haloketones with 1,3-dicarbonyl compounds and amines, the Paal–Knorr reaction<sup>6</sup> involving cyclocondensation of 1,4-diketones with amines, and the Knorr reaction<sup>7</sup> by condensation of  $\alpha$ -aminoketones with  $\beta$ -keto esters or  $\beta$ -diketones are good conventional examples for pyrroles synthesis. Recently, modern methods including transition metal-catalyzed self-assembly reactions,<sup>8,9</sup> microwave-assisted approaches,<sup>10</sup> and multibond-forming strategies<sup>4a,11</sup> have been increasingly applied in the construction of substituted pyrroles. Indeed, in order to achieve higher efficiency as well as good eco-compatibility, the adoption of modern thoughts and technologies for building complex molecules from relatively simple materials has become a favoring trend in the field of synthetic chemistry.<sup>12</sup>

In this context, we wish to describe our recent research on a metal-catalyzed three-component reaction of an aldimine with two alkynoates for the synthesis of functionalized pyrroles. The process was performed in a sequential manner including a Cu(I)-catalyzed addition of methyl propionate to an aldimine giving **3a** and a following Fe(III)-catalyzed cyclization of **3a** with another alkynoate. One C–N bond and two C–C bonds are formed with excellent atom economy in the reaction. And as far as we know, cuprum and iron are both abundant and low-cost metals on Earth, and the catalysts we used are easily recyclable by filtration.

## 2. Results and discussion

The reaction of one portion of aldimine (**1a**) with two portions of methyl propionate (**2a**) was performed initially for catalyst screening as well as condition optimization. As the manner A (shown in Table 1), using CuCl (10 mol %) as the catalyst, only a propargylamine type adduct (**3a**) was isolated in heated dichloroethane (50 °C) for 5 h.<sup>13</sup> When the reaction time was prolonged to 50 h under 80 °C, functionalized pyrrole (**4a**) was obtained in a lowered yield (Table 1, entry 2). The structure of **4a** was determined by NMR analysis. Increasing CuCl to 100 mol %, the yield of **4a** was not distinctly enhanced (Table 1, entry 3). CuCl<sub>2</sub>, FeCl<sub>3</sub>, FeCl<sub>2</sub>, ZnCl<sub>2</sub>, PdCl<sub>2</sub>, and AgNO<sub>3</sub> were screened for the reaction and all of them gave neither **3a** nor **4a**. Fortunately, when adding FeCl<sub>2</sub> (10 mol %) to the CuCl-mediated system (after heated for 5 h), **4a** was obtained in 64% yield (Table 1, entry 4). Increasing the amount of FeCl<sub>2</sub> (15 mol %) seemed to be little beneficial to the

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**Table 1**  
Reaction condition—optimization


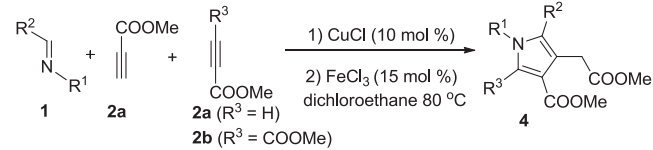
Entry	Substrates, mole ratio	Conducting manner, conditions	Product, yield <sup>a</sup> (%)
1	<b>1a/2a</b> =1:2	A, CuCl (10 mol %), DCE, 50 °C, 5 h	<b>3a</b> , 95
2	<b>1a/2a</b> =1:2	A, CuCl (10 mol %), DCE, 50 °C, 50 h	<b>3a</b> , 81; <b>4a</b> , 12
3	<b>1a/2a</b> =1:2	A, CuCl (100 mol %), DCE, 50 °C, 50 h	<b>3a</b> , 77; <b>4a</b> , 14
4	<b>1a/2a</b> =1:2	A, CuCl (10 mol %), FeCl <sub>2</sub> (10 mol %), DCE, 80 °C, 24 h	<b>4a</b> , 64
5	<b>1a/2a</b> =1:2	A, CuCl (10 mol %), FeCl <sub>2</sub> (15 mol %), DCE, 80 °C, 24 h	<b>4a</b> , 66
6	<b>1a/2a</b> =1:2	A, CuCl (10 mol %), FeCl <sub>3</sub> (15 mol %), DCE, 80 °C, 24 h	<b>4a</b> , 82
7	<b>1a/2a</b> =1:2	A, CuCl (10 mol %), FeCl <sub>3</sub> ·6H <sub>2</sub> O (15 mol %), DCE, 80 °C, 24 h	<b>4a</b> , 78
8	<b>3a/2a</b> =1:1	B (step ii), FeCl <sub>3</sub> (10 mol %), DCE, 80 °C, 19 h	<b>4a</b> , 83
9	<b>3a/2a</b> =1:1	B (step ii), FeCl <sub>2</sub> (10 mol %), DCE, 80 °C, 19 h	<b>4a</b> , 64
10	<b>3a/2a</b> =1:1	B (step ii), ZnCl <sub>2</sub> (10 mol %), DCE, 80 °C, 19 h	<b>4a</b> , 19
11	<b>3a/2a</b> =1:1	B (step ii), CuCl <sub>2</sub> (10 mol %), DCE, 80 °C, 19 h	<b>4a</b> , 11
12	<b>3a/2a</b> =1:1	B (step ii), PdCl <sub>2</sub> (10 mol %), DCE, 80 °C, 19 h	<b>4a</b> , 0 <sup>b</sup>
13	<b>3a/2a</b> =1:1	B (step ii), AgNO <sub>3</sub> (10 mol %), DCE, 80 °C, 19 h	<b>4a</b> , 0
14	<b>3a/2a</b> =1:1	B (step ii), FeCl <sub>3</sub> (10 mol %), toluene, 100 °C, 19 h	<b>4a</b> , 52
15	<b>3a/2a</b> =1:1	B (step ii), FeCl <sub>3</sub> (10 mol %), DMF, 100 °C, 19 h	<b>4a</b> , 40
16	<b>3a/2a</b> =1:1	B (step ii), FeCl <sub>3</sub> (10 mol %), dioxane, 100 °C, 19 h	<b>4a</b> , 31
17	<b>3a/2a</b> =1:1	B (step ii), FeCl <sub>3</sub> (10 mol %), ethanol, 80 °C, 19 h	<b>4a</b> , 21

<sup>a</sup> Isolated yield after purification by silica gel chromatography.<sup>b</sup> Compound **4a** was observable in TLC but inseparable due to its low content.

reaction (Table 1, entry 5). Alternatively, when anhydrous FeCl<sub>3</sub> (15 mol %, considering the practical reduction of FeCl<sub>3</sub> with CuCl) was adopted instead of FeCl<sub>2</sub>, the yield of **4a** was enhanced to 82% (Table 1, entry 6). Comparing to FeCl<sub>3</sub>, FeCl<sub>3</sub>·6H<sub>2</sub>O also worked well and gave **4a** in a good yield (Table 1, entry 7).

Next, the sequential process was divided into two steps to check the exact action of the two catalysts (shown as conducting manner B). A mixture of **1a** and **2a** in a ratio of 1:1 (mol) was treated, respectively, with CuCl, CuCl<sub>2</sub>, FeCl<sub>2</sub>, FeCl<sub>3</sub>, ZnCl<sub>2</sub>, PdCl<sub>2</sub>, and AgNO<sub>3</sub> in dichloroethane at 50 °C, and it was found that only CuCl exhibited good activation giving a good yield of **3a**. Then **3a** was isolated and treated with one portion of **2a** in the presence of FeCl<sub>3</sub>, FeCl<sub>2</sub>, ZnCl<sub>2</sub>, CuCl<sub>2</sub>, PdCl<sub>2</sub>, and AgNO<sub>3</sub>, respectively. After heated at 80 °C for 19 h, only FeCl<sub>3</sub> and FeCl<sub>2</sub> gave inspiring results (Table 1, entries 8 and 9). When ZnCl<sub>2</sub> and CuCl<sub>2</sub> were used, both the reactions gave lowered yields of **4a** (Table 1, entries 10 and 11). While PdCl<sub>2</sub> was employed in the step ii, no **4a** was isolated for its low contents (Table 1, entry 12). AgNO<sub>3</sub> showed no activation on the reaction (Table 2, entry 13). Furthermore, other solvents, such as toluene, *N,N*-dimethyl formamide, 1,4-dioxane, and ethanol, were proved to be unsuitable for the step ii (Table 1, entries 14–17).

Following the manner B, the other alkyne substrates were then examined for their possible adaption in pursuing for molecular diversity. With the second alkyne motif fixed as **2a**, phenylacetylene, trimethylsilylacetylene, 1-propyn-3-ol, and propargyl benzoate were, respectively, tested as the first alkyne motif. Phenylacetylene's reaction gave a high yield of 1,4-diphenylbuta-1,3-diene in accordance with a reported Cu(I)-catalyzed coupling.<sup>14</sup> Both trimethylsilylacetylene<sup>15</sup> and propargyl benzoate reactions indeed gave good yields of the relevant adducts in Cu(I) catalyzed addition, but the following Fe(III)-catalyzed cyclization couldn't take place. 1-Propyn-3-ol showed a bad selectivity in the Cu(I)-

**Table 2**  
Scope of aldimines and alkyneates<sup>a</sup>


Entry	Substrates	Product	Yield <sup>b</sup> (%)
1	<b>1a</b> (R <sup>1</sup> =Ph, R <sup>2</sup> =Ph); <b>2a</b> (R <sup>3</sup> =H)	<b>4a</b>	82
2	<b>1b</b> (R <sup>1</sup> =4-MeC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> =Ph); <b>2a</b> (R <sup>3</sup> =H)	<b>4b</b>	85
3	<b>1c</b> (R <sup>1</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> =Ph); <b>2a</b> (R <sup>3</sup> =H)	<b>4c</b>	84

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