



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.¹ Besides, they are very important intermediates in synthetic chemistry² and widely used in the field of material design.³ As such, a variety of well-documented methods have been dedicated to the construction of pyrroles and their derivatives in the past.⁴ The Hantzsch reaction⁵ based on condensation of α -haloketones with 1,3-dicarbonyl compounds and amines, the Paal–Knorr reaction⁶ involving cyclocondensation of 1,4-diketones with amines, and the Knorr reaction⁷ by condensation of α -aminoketones with β -keto esters or β -diketones are good conventional examples for pyrroles synthesis. Recently, modern methods including transition metal-catalyzed self-assembly reactions,^{8,9} microwave-assisted approaches,¹⁰ and multibond-forming strategies^{4a,11} 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.¹²

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.¹³ 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). CuCl₂, FeCl₃, FeCl₂, ZnCl₂, PdCl₂, and AgNO₃ were screened for the reaction and all of them gave neither **3a** nor **4a**. Fortunately, when adding FeCl₂ (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 FeCl₂ (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 ^a (%)
1	1a / 2a =1:2	A, CuCl (10 mol %), DCE, 50 °C, 5 h	3a , 95
2	1a / 2a =1:2	A, CuCl (10 mol %), DCE, 50 °C, 50 h	3a , 81; 4a , 12
3	1a / 2a =1:2	A, CuCl (100 mol %), DCE, 50 °C, 50 h	3a , 77; 4a , 14
4	1a / 2a =1:2	A, CuCl (10 mol %), FeCl ₂ (10 mol %), DCE, 80 °C, 24 h	4a , 64
5	1a / 2a =1:2	A, CuCl (10 mol %), FeCl ₂ (15 mol %), DCE, 80 °C, 24 h	4a , 66
6	1a / 2a =1:2	A, CuCl (10 mol %), FeCl ₃ (15 mol %), DCE, 80 °C, 24 h	4a , 82
7	1a / 2a =1:2	A, CuCl (10 mol %), FeCl ₃ ·6H ₂ O (15 mol %), DCE, 80 °C, 24 h	4a , 78
8	3a / 2a =1:1	B (step ii), FeCl ₃ (10 mol %), DCE, 80 °C, 19 h	4a , 83
9	3a / 2a =1:1	B (step ii), FeCl ₂ (10 mol %), DCE, 80 °C, 19 h	4a , 64
10	3a / 2a =1:1	B (step ii), ZnCl ₂ (10 mol %), DCE, 80 °C, 19 h	4a , 19
11	3a / 2a =1:1	B (step ii), CuCl ₂ (10 mol %), DCE, 80 °C, 19 h	4a , 11
12	3a / 2a =1:1	B (step ii), PdCl ₂ (10 mol %), DCE, 80 °C, 19 h	4a , 0 ^b
13	3a / 2a =1:1	B (step ii), AgNO ₃ (10 mol %), DCE, 80 °C, 19 h	4a , 0
14	3a / 2a =1:1	B (step ii), FeCl ₃ (10 mol %), toluene, 100 °C, 19 h	4a , 52
15	3a / 2a =1:1	B (step ii), FeCl ₃ (10 mol %), DMF, 100 °C, 19 h	4a , 40
16	3a / 2a =1:1	B (step ii), FeCl ₃ (10 mol %), dioxane, 100 °C, 19 h	4a , 31
17	3a / 2a =1:1	B (step ii), FeCl ₃ (10 mol %), ethanol, 80 °C, 19 h	4a , 21

^a Isolated yield after purification by silica gel chromatography.

^b Compound **4a** was observable in TLC but inseparable due to its low content.

reaction (Table 1, entry 5). Alternatively, when anhydrous FeCl₃ (15 mol %, considering the practical reduction of FeCl₃ with CuCl) was adopted instead of FeCl₂, the yield of **4a** was enhanced to 82% (Table 1, entry 6). Comparing to FeCl₃, FeCl₃·6H₂O 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, CuCl₂, FeCl₂, FeCl₃, ZnCl₂, PdCl₂, and AgNO₃ 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 FeCl₃, FeCl₂, ZnCl₂, CuCl₂, PdCl₂, and AgNO₃, respectively. After heated at 80 °C for 19 h, only FeCl₃ and FeCl₂ gave inspiring results (Table 1, entries 8 and 9). When ZnCl₂ and CuCl₂ were used, both the reactions gave lowered yields of **4a** (Table 1, entries 10 and 11). While PdCl₂ was employed in the step ii, no **4a** was isolated for its low contents (Table 1, entry 12). AgNO₃ 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.¹⁴ Both trimethylsilylacetylene¹⁵ 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 alkynoates^a

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

Table 2 (continued)

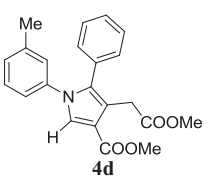
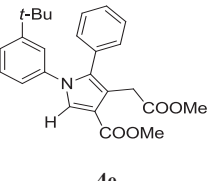
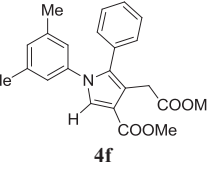
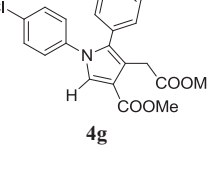
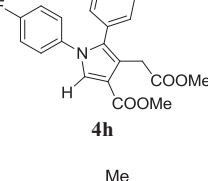
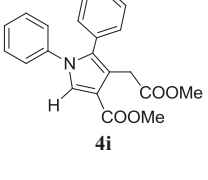
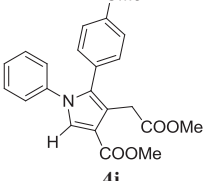
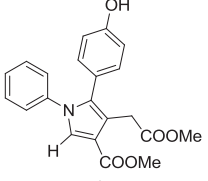
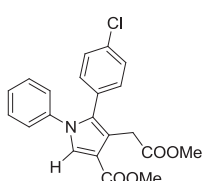
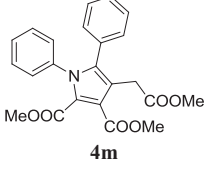
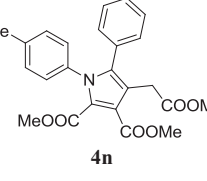
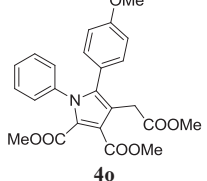
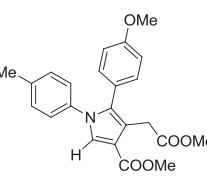
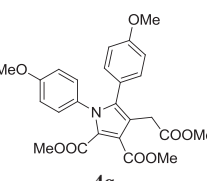
Entry	Substrates	Product	Yield ^b (%)
4	1d (R ¹ =3-MeC ₆ H ₄ , R ² =Ph); 2a (R ³ =H)		83
5	1e (R ¹ =3- <i>t</i> -Bu-C ₆ H ₄ , R ² =Ph); 2a (R ³ =H)		80
6	1f (R ¹ =3,5-(Me) ₂ C ₆ H ₃ , R ² =Ph); 2a (R ³ =H)		81
7	1g (R ¹ =4-ClC ₆ H ₄ , R ² =Ph); 2a (R ³ =H)		62
8	1h (R ¹ =4-FC ₆ H ₄ , R ² =Ph); 2a (R ³ =H)		60
9	1i (R ¹ =Ph, R ² =4-MeC ₆ H ₄); 2a (R ³ =H)		84
10	1j (R ¹ =Ph, R ² =4-MeOC ₆ H ₄); 2a (R ³ =H)		82
11	1k (R ¹ =Ph, R ² =4-OHC ₆ H ₄); 2a (R ³ =H)		85

Table 2 (continued)

Entry	Substrates	Product	Yield ^b (%)
12	1l (R ¹ =Ph, R ² =4-ClC ₆ H ₄); 2a (R ³ =H)		79
13	1a (R ¹ =Ph, R ² =Ph); 2b (R ³ =COOMe)		70
14	1b (R ¹ =4-MeC ₆ H ₄ , R ² =Ph); 2b (R ³ =COOMe)		72
15	1j (R ¹ =Ph, R ² =4-MeOC ₆ H ₄); 2b (R ³ =COOMe)		71
16	1p (R ¹ =4-MeC ₆ H ₄ , R ² =4-MeOC ₆ H ₄); 2b (R ³ =COOMe)		74
17	1q (R ¹ =4-MeOC ₆ H ₄ , R ² =4-MeOC ₆ H ₄); 2b (R ³ =COOMe)		78
18	1r (R ¹ =4-NO ₂ C ₆ H ₄ , R ² =Ph); 2a — ^c (R ³ =H)		0
19	1s (R ¹ =3-NO ₂ C ₆ H ₄ , R ² =Ph); 2a — ^c (R ³ =H)		0
20	1t (R ¹ =2-NO ₂ C ₆ H ₄ , R ² =Ph); 2a — ^c (R ³ =H)		0

^a All reactions were conducted as the manner A with dichloroethane as the solvent.

^b Isolated yield of **4** after purification by silica gel chromatography.

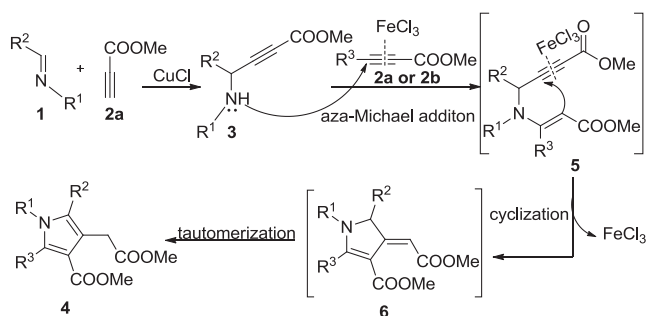
^c No reaction.

catalyzed step, and the following step only gave an inseparable mixture. Next, with the first alkyne fixed as **2a**, the above mentioned acetylene compounds as well as dimethyl acetylenedicarboxylate (**2b**) were, respectively, examined for their behavior in

the addition–cyclization step. Only **2b** gave a satisfactory result (Table 2, entries 13–17), and other substrates all exhibited too lowered reactivity to provide the desirable products.

With the optimized reaction conditions in hand, we turned to explore the scope of aldimines. Two typical aliphatic aldimines, benzylidenecyclohexanamine and benzylidenebenzylamine, were, respectively, treated at first with **2a** in the presence of CuCl, and both the two reactions gave inseparable products. Further treatment of the above mixtures with FeCl₃ was also fruitless. Compared with aliphatic aldimines, *N*-arylbenzalimines' reactivities were good and the corresponding pyrroles were obtained with satisfactory yields (Table 2, entries 1–17), except that aldimines bearing strong electron-withdrawing groups (–NO₂) on the side of amines gave no desirable products (Table 2, entries 18–20).

On the basis of the above experimental results, a possible Cu(I)–Fe(III)-catalyzed mechanism for the sequential procedure was depicted in Scheme 1. Cu(I)-promoted addition of **1** to **2a** generates propargylamine intermediate **3** as the literature presented.^{13a} Under the help of FeCl₃, the aza-Michael addition occurs to form **5**.¹⁶ This is well testified by that the direct treatment of **3a** with **2a** in the absence of FeCl₃ gives no any detectable intermediate or the desired product. As soon as the intermediate **5** is formed, the intramolecular 5-*exo-dig* cyclization takes place immediately to give **6** under the activation of triple bond via the coordination of FeCl₃.¹⁷ Compound **6** transforms quickly into **4** as the tautomerized product through a 1,3-hydrogen migration procedure.¹⁸



Scheme 1. The plausible mechanism of the reaction.

3. Conclusion

In conclusion, we have developed an eco-friendly method for the direct synthesis of substituted pyrroles. Although the scope of aldimine and acetylene substrates is some limited, the mild reaction conditions, inexpensive catalyst, operational simplicity, good yields, and high atomic economy make the method valuable for pyrroles synthesis. And, how to inhibit the coupling of phenyl-acetylene and trimethylsilylacetylene to acquire pyrroles based on this method is a further project of us.

4. Experimental section

4.1. General

All the reagents were purchased from commercial suppliers, and were used without further purification. The ¹H NMR and ¹³C NMR spectra were performed with a Varian Unity Plus 400 MHz spectrometer in CDCl₃. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for ¹H, δ 77.0 for ¹³C). Coupling constants (*J*) are reported in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet). Melting points were measured on

microscopic melting point apparatus. HPLC was PGENERAL (chromatographic column, pgandsil-STC-C18, 5 μm, 100 Å, 4.6×250 mm; CH₃OH/H₂O (volume)=9:1).

4.2. General synthesis of pyrroles 4

To a solution of methyl propionate (**2a**, 5.0 mmol) in dichloroethane (30 mL), CuCl (0.5 mmol) and aldimine (**1**, 5.0 mmol) were added. The mixture was stirred at 50 °C for 5 h. After the step completed according to TLC analysis, another portion of alkynoate (**2a** or **2b**, 5.0 mmol) and FeCl₃ (0.75 mmol) were added at room temperature. The mixture was further stirred at 80 °C for 19 h. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by flash chromatography on silica gel to give desired pyrroles **4**.

4.3. Characterization

4.3.1. Methyl 4-(2-methoxy-2-oxoethyl)-1,5-diphenyl-1H-pyrrole-3-carboxylate (4a). A pale yellow viscous liquid, 82% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.29–7.27 (m, 3H), 7.17 (s, 5H), 7.06 (dd, *J*=6.6, 3.0 Hz, 2H), 6.73 (s, 1H), 3.69 (s, 3H), 3.59 (s, 3H), 3.50 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.04, 165.20, 139.28, 133.84, 130.57, 129.26, 129.01, 128.28, 127.95, 127.73, 127.26, 126.75, 125.54, 116.82, 115.03, 51.91, 50.98, 31.55 ppm.

4.3.2. Methyl 4-(2-methoxy-2-oxoethyl)-5-phenyl-1-(*p*-tolyl)-1H-pyrrole-3-carboxylate (4b). A pale yellow viscous liquid, 85% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.54 (s, 1H), 7.24 (d, *J*=2.3 Hz, 2H), 7.12–7.09 (m, 3H), 7.04 (d, *J*=8.2 Hz, 2H), 6.94 (d, *J*=8.3 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 5H), 2.29 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.07, 165.24, 137.13, 136.82, 133.86, 130.59, 129.80, 129.59, 128.26, 128.14, 127.98, 127.67, 126.49, 125.33, 116.66, 114.79, 51.88, 50.93, 31.57, 20.98 ppm.

4.3.3. Methyl 4-(2-methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-3-carboxylate (4c). A yellow viscous liquid, 84% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.42 (s, 1H), 7.15 (dd, *J*=5.1, 1.7 Hz, 3H), 7.03–7.01 (m, 2H), 6.91–6.88 (m, 2H), 6.67 (d, *J*=8.9 Hz, 2H), 3.73 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 3.62 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.07, 165.23, 158.57, 134.01, 132.35, 130.58, 128.25, 128.15, 128.04, 127.95, 127.65, 126.77, 126.14, 116.43, 114.27, 114.10, 55.39, 51.86, 50.91, 31.58 ppm.

4.3.4. Methyl 4-(2-methoxy-2-oxoethyl)-5-phenyl-1-(*m*-tolyl)-1H-pyrrole-3-carboxylate (4d). A pale yellow viscous liquid, 83% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.56 (s, 1H), 7.26–7.22 (m, 5H), 7.11 (dd, *J*=6.6, 2.4 Hz, 4H), 3.80 (s, 3H), 3.72 (s, 5H), 2.25 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.02, 165.21, 139.07, 133.82, 130.55, 128.68, 128.22, 127.98, 127.94, 127.68, 126.05, 125.70, 123.67, 122.70, 116.75, 114.88, 51.86, 50.93, 31.55, 21.23 ppm.

4.3.5. Methyl 1-(3-(*tert*-butyl)phenyl)-4-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (4e). A yellow viscous liquid, 80% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.61 (s, 1H), 7.28 (d, *J*=2.6 Hz, 1H), 7.25–7.23 (m, 4H), 7.12–7.09 (m, 4H), 3.81 (s, 3H), 3.74 (s, 2H), 3.73 (s, 3H), 1.08 (s, 9H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.07, 165.24, 152.11, 138.81, 133.85, 130.64, 128.73, 128.27, 128.08, 127.68, 127.64, 123.92, 123.47, 121.85, 116.72, 114.86, 51.89, 50.96, 34.54, 31.04, 30.94 ppm.

4.3.6. Methyl 1-(3,5-dimethylphenyl)-4-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (4f). A pale yellow viscous liquid, 81% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.55 (s, 1H), 7.25 (d, *J*=2.1 Hz, 2H), 7.11 (dd, *J*=6.5, 3.1 Hz, 2H), 6.90–6.85 (m, 2H), 6.67 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.72 (s, 2H), 2.19 (s, 6H) ppm. ¹³C NMR

(101 MHz, CDCl₃): δ 173.09, 165.27, 139.11, 138.66, 133.79, 130.80, 130.53, 128.81, 128.16, 127.93, 127.61, 123.25, 116.58, 114.69, 51.88, 50.93, 31.57, 21.13 ppm.

4.3.7. Methyl 1-(4-chlorophenyl)-4-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (4g). A yellow viscous liquid, 62% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.54 (s, 1H), 7.29–7.27 (m, 3H), 7.25–7.22 (m, 2H), 7.11–7.08 (m, 2H), 7.02–6.99 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.71 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.94, 165.04, 137.81, 133.81, 133.07, 130.55, 130.28, 129.23, 128.47, 127.97, 127.72, 126.66, 117.13, 115.40, 51.94, 51.05, 31.48 ppm.

4.3.8. Methyl 1-(4-fluorophenyl)-4-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (4h). A yellow viscous liquid, 60% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.53 (s, 1H), 7.27–7.25 (m, 3H), 7.09 (dd, J =6.5, 3.0 Hz, 2H), 7.07–7.03 (m, 2H), 6.98–6.95 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.71 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.93, 165.08, 160.22, 135.41, 134.01, 130.59, 130.40, 128.36, 127.87, 127.30, 127.22, 116.84, 116.05, 115.82, 115.15, 51.86, 50.96, 31.48 ppm.

4.3.9. Methyl 4-(2-methoxy-2-oxoethyl)-1-phenyl-5-(p-tolyl)-1H-pyrrole-3-carboxylate (4i). A pale yellow viscous liquid, 84% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.55 (s, 1H), 7.24 (d, J =8.3 Hz, 3H), 7.06–7.03 (m, 4H), 6.98 (d, J =8.1 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 5H), 2.29 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.05, 165.22, 139.39, 137.52, 130.43, 129.02, 128.97, 127.97, 127.77, 127.67, 127.19, 126.73, 125.55, 116.64, 114.98, 51.82, 50.90, 31.57, 21.22 ppm.

4.3.10. Methyl 4-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-1-phenyl-1H-pyrrole-3-carboxylate (4j). A yellow viscous liquid, 82% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 1H), 7.19–7.16 (m, 3H), 6.99 (dd, J =7.9, 1.5 Hz, 2H), 6.96–6.93 (m, 2H), 6.70 (d, J =8.7 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.62 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 173.11, 165.24, 159.12, 139.36, 133.71, 131.82, 128.99, 127.57, 127.17, 125.55, 122.90, 116.45, 114.86, 113.76, 55.18, 51.88, 50.93, 31.57 ppm.

4.3.11. Methyl 5-(4-hydroxyphenyl)-4-(2-methoxy-2-oxoethyl)-1-phenyl-1H-pyrrole-3-carboxylate (4k). A pale yellow solid, mp: 164–169 °C, 85% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.50–7.43 (m, 4H), 7.36–7.33 (m, 2H), 7.19 (d, J =8.5 Hz, 2H), 6.78 (d, J =8.5 Hz, 2H), 6.29 (s, 1H), 3.72 (s, 3H), 3.51 (s, 3H), 3.46 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 171.29, 165.39, 155.20, 138.83, 131.37, 129.46, 128.62, 128.16, 126.40, 126.33, 126.02, 125.26, 115.00, 113.93, 52.09, 51.07, 30.93 ppm.

4.3.12. Methyl 5-(4-chlorophenyl)-4-(2-methoxy-2-oxoethyl)-1-phenyl-1H-pyrrole-3-carboxylate (4l). A pale yellow viscous liquid, 79% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (s, 1H), 7.28 (s, 2H), 7.25–7.22 (m, 2H), 7.08–7.03 (m, 5H), 3.81 (s, 3H), 3.74 (s, 3H), 3.70 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.87, 165.04, 139.01, 133.86, 131.76, 129.50, 129.37, 129.18, 128.61, 128.36, 128.20, 127.51, 126.70, 125.57, 117.21, 115.16, 51.96, 51.02, 31.45 ppm.

4.3.13. Dimethyl 4-(2-methoxy-2-oxoethyl)-1,5-diphenyl-1H-pyrrole-2,3-dicarboxylate (4m). A yellow viscous liquid, 70% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.15 (dd, J =3.3, 2.8 Hz, 3H), 7.11 (dd, J =5.1, 1.3 Hz, 3H), 7.03 (dd, J =6.5, 3.2 Hz, 2H), 6.99 (dd, J =6.5, 3.2 Hz, 2H), 3.74 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 3.54 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.26, 164.86, 162.00, 137.53, 136.56, 130.75, 129.73, 128.60, 128.35, 128.18, 128.17, 127.93, 127.88, 117.47, 115.75, 52.28, 51.91, 51.61, 31.29 ppm.

4.3.14. Dimethyl 4-(2-methoxy-2-oxoethyl)-5-phenyl-1-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate (4n). A yellow viscous liquid, 72%

yield. ¹H NMR (400 MHz, CDCl₃): δ 7.22 (dd, J =5.0, 1.9 Hz, 3H), 7.08 (dd, J =6.5, 3.2 Hz, 2H), 7.04 (d, J =8.3 Hz, 2H), 7.01–6.98 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.62 (s, 2H), 2.29 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.33, 164.95, 162.13, 138.23, 136.61, 134.91, 130.78, 129.87, 129.23, 128.13, 128.10, 127.58, 117.30, 115.61, 52.29, 51.91, 51.59, 31.33, 21.13 ppm.

4.3.15. Dimethyl 4-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-1-phenyl-1H-pyrrole-2,3-dicarboxylate (4o). A yellow viscous liquid, 71% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.27 (d, J =3.8 Hz, 3H), 7.13–7.10 (m, 2H), 7.01–6.98 (m, 2H), 6.75–6.72 (m, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.61 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.37, 165.01, 162.00, 159.37, 137.67, 136.61, 132.02, 128.59, 128.27, 127.94, 121.91, 117.59, 115.52, 113.64, 55.14, 52.24, 51.93, 51.62, 31.34 ppm.

4.3.16. Dimethyl 4-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-1-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate (4p). A yellow viscous liquid, 74% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.05 (d, J =8.3 Hz, 2H), 7.02–6.98 (m, 4H), 6.75–6.72 (m, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.60 (s, 2H), 2.29 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.37, 164.99, 162.10, 159.33, 138.12, 136.59, 135.02, 132.01, 129.22, 127.61, 122.00, 117.28, 115.38, 113.61, 55.09, 52.22, 51.87, 51.54, 31.33, 21.11 ppm.

4.3.17. Dimethyl 4-(2-methoxy-2-oxoethyl)-1,5-bis(4-methoxyphenyl)-1H-pyrrole-2,3-dicarboxylate (4q). A yellow viscous liquid, 78%. ¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, J =8.9 Hz, 2H), 7.00 (d, J =8.8 Hz, 2H), 6.77–6.75 (m, 2H), 6.74 (d, J =4.7 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.59 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 172.42, 165.05, 162.12, 159.32, 159.11, 136.84, 132.04, 130.38, 129.05, 127.61, 122.03, 117.29, 115.27, 113.70, 113.66, 55.31, 55.14, 52.26, 51.91, 51.59, 31.37 ppm.

Supplementary data

Experimental procedures, characterization data, and copies of the ¹H NMR and ¹³C NMR spectra for the products. Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.tet.2014.01.037>.

References and notes

- (a) Fesenko, A. A.; Shutalev, A. D. *J. Org. Chem.* **2013**, *78*, 1190–1207; (b) Herath, A.; Cosford, N. D. *P. Org. Lett.* **2010**, *12*, 5182–5185; (c) Jacobi, P. A.; Coutts, L. D.; Guo, J. S.; Hauck, S. I.; Leung, S. H. *J. Org. Chem.* **2000**, *65*, 205–213; (d) Unverferth, K.; Engel, J.; Hoefgen, N.; Rostock, A.; Guenther, R.; Lankau, H. J.; Menzer, M.; Rolf, A.; Liebscher, J.; Mueller, B.; Hofmann, H. *J. Med. Chem.* **1998**, *41*, 63–73; (e) Khana, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619–1633; (f) Andreani, A.; Cavalli, A.; Granaola, M.; Guardigli, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Recanatini, M.; Roda, A. *J. Med. Chem.* **2001**, *44*, 4011–4014.
- (a) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62; (b) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhailova, A. I. *Chem. Rev.* **2004**, *104*, 2481–2506; (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256.
- (a) Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2001**, *66*, 4058–4061; (b) Pu, S. Z.; Liu, G.; Shen, L.; Xu, J. K. *Org. Lett.* **2007**, *9*, 2139–2142; (c) Facchetti, A.; Abboto, A.; Beverina, L.; Dutta, P.; Evmenenko, G.; Pagani, G. A.; Marks, T. J. *Chem. Mater.* **2003**, *15*, 1064–1072; (d) Cooper, J. M.; Glidle, A.; Hillman, A. R.; Ingram, M. D.; Ryder, C.; Ryder, K. S. *Phys. Chem. Chem. Phys.* **2004**, *6*, 2403–2408.
- (a) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421; (b) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110; (c) Xin, X. Y.; Wang, D. P.; Li, X. C.; Wan, B. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693–1697; (d) Shafi, S.; Kedziorek, M.; Grela, K. *Synlett* **2011**, 124–128; (e) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674–1683; (f) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16626–16627; (g) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811–1813.
- Hantzsch, A. *Chem. Ber.* **1890**, *23*, 1474–1476.
- (a) Knorr, L. *Chem. Ber.* **1884**, *17*, 2863–2870; (b) Paal, C. *Chem. Ber.* **1884**, *17*, 2756–2767.

7. Knorr, L. *Liebigs Ann. Chem.* **1886**, 236, 290–332.
8. (a) Ciez, D. *Org. Lett.* **2009**, *11*, 4282–4285; (b) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005; (c) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372–374.
9. (a) Gabriele, B.; Salerno, G.; Fazio, A. J. *Org. Chem.* **2003**, *68*, 7853–7861; (b) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261.
10. (a) Bianchi, I.; Forlani, R.; Minetto, G.; Peretto, I.; Regalia, N.; Taddei, M.; Ravaglia, L. F. *J. Comb. Chem.* **2006**, *8*, 491–499; (b) Kim, Y. J.; Kim, J. H.; Park, S. B. *Org. Lett.* **2009**, *11*, 17–20.
11. Lv, L. Y.; Zheng, S. C.; Cai, X. T.; Chen, Z. P.; Zhu, Q. H.; Liu, S. W. *ACS Comb. Sci.* **2013**, *15*, 183–192.
12. (a) Chen, W. L.; Jin, L.; Zhu, Y. H.; Mo, W. M. *ARKIVOC* **2012**, *viii*, 295–307; (b) Li, Q. J.; Fan, A.; Lu, Z. Y.; Cui, Y. X.; Lin, W. H.; Jia, Y. X. *Org. Lett.* **2010**, *12*, 4066–4069.
13. (a) Colombo, F.; Benaglia, M.; Orlandi, S.; Uselli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064–2070; (b) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107–1110; (c) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405–2408; (d) Lu, Y. D.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284–11285.
14. Susanto, W.; Chu, C. Y.; Ang, W. J.; Chou, T. C.; Lo, L. C.; Lam, Y. L. *J. Org. Chem.* **2012**, *77*, 2729–2742.
15. Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319–4321.
16. Attanasi, O. A.; Berretta, S.; Crescentini, L. D.; Favi, G.; Giorgi, G.; Mantellini, F. *Adv. Synth. Catal.* **2009**, *351*, 715–719.
17. (a) Bera, K.; Sarkar, S.; Jalal, S.; Jana, U. *J. Org. Chem.* **2012**, *77*, 8780–8786; (b) Yang, Q.; Wang, L. D.; Guo, T. L.; Yu, Z. K. *J. Org. Chem.* **2012**, *77*, 8355–8361.
18. (a) Wang, Y. M.; Bi, X. H.; Li, D. H.; Liao, P. Q.; Wang, Y. D.; Yang, J.; Zhang, Q.; Liu, Q. *Chem. Commun.* **2011**, 809–811; (b) Trost, B. M.; Lumb, J. P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740–743.