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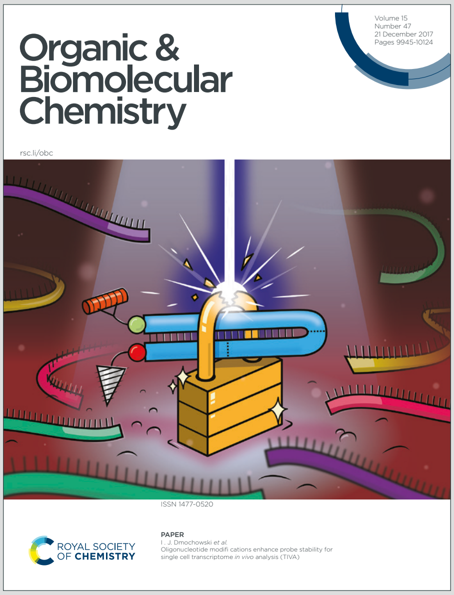

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ARTICLE

Direct synthesis of 2,3,5-trisubstituted pyrroles via copper-mediated one-pot multicomponent reaction

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We have developed a copper-mediated one-pot synthesis of 2,3,5-trisubstituted pyrroles from 1, 3-dicarbonyl compounds and acrylates using ammonium acetate as nitrogen source. The reaction achieves C-C and C-N bond formations and provides an efficient approach to access highly functionalized pyrroles without further raw material preparation. This method is operationally simple, compatible with a wide range of functional groups, and provides the target products in moderate to good yields.

Introduction

Pyrroles, as an important class of five-membered heterocyclic compounds, widely distribute in various natural products,[1] particularly in pharmaceutical drugs,[2] biologically active compounds,[3] and functional materials.[4] Among them, multisubstituted pyrrole derivatives have special significance because of their unique structural architecture, which are capable of building important lead compounds with diverse pharmacological effects (Figure 1).[5] Due to their remarkable properties, substantial attention has been worth to develop mild and efficient methods for synthesis of multisubstituted pyrroles.

Since Hantzsch first prepared pyrroles based on the reaction between a β-enaminone and a α-haloketone,[6] a variety of synthetic methods have been reported, including the Paal-Knorr reaction using 1,4-diketones with amines,[7] the Knorr reaction using α-amino ketones with β-dicarbonyl compounds,[8] and others.[9] Although plenty of approaches to synthesize multisubstituted pyrroles have been reported so far, it is structurally still significant to build various multisubstituted pyrroles from readily available building blocks.

In recent years, the cycloaddition reaction employed with various transition metals has been increasing in application to the construction of multisubstituted pyrroles. Amongst the transition metals used in the synthesis of that, Ag,[10] Au,[11] Rh[12] and Ir[13] were reported successively as catalysts, while copper and palladium metals have been extensively investigated. In this regard, Wang and co-workers reported a catalytic system for the synthesis of 2,3,5-trisubstituted pyrroles from enaminones with alkenes catalyzed by Pd(II) and Cu(Ⅱ) (Scheme 1, (1)).[14] In 2016, Yoshikai and co-worker have demonstrated the Cu(II) catalyzed synthesis of 2,3,5-trisubstituted pyrrole derivatives via the cyclization of 2-siloxy-2,3-dihydrofuran with 1,4-diketone surrogate (Scheme 1, (2)).[15] Recently, Kapur and Kumar has reported a Ru- and Cu-mediated method for the synthesis of 2,3,5-trisubstituted pyrrole derivatives via the reaction of substituted isoxazoles with acrylate esters (Scheme 1, (3)).[16]In spite of these advances, the development of an economical, mild and convenient methods for the synthesis of substituted pyrroles is promising. Multicomponent reactions (MCRs),[17] in which multiple reactions are combined into a one-pot synthetic method, can avoid the waste of time and energy for the preparation of various precursors. Considering previous work, we turned our attention to three-component synthesis of

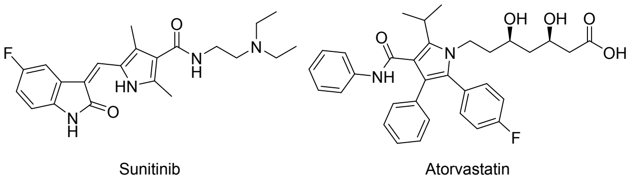

Figure 1. Pharmaceutical compounds with multisubstituted pyrroles.

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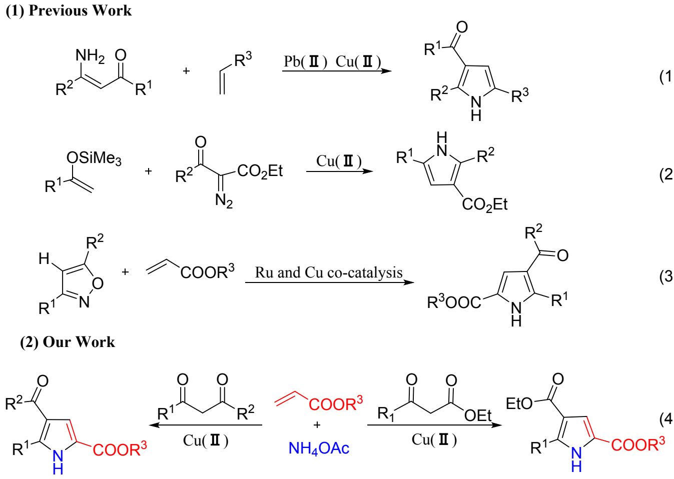


Scheme 1. Transition-metal-catalyzed synthesis of 2,3,5-trisubstituted pyrroles.

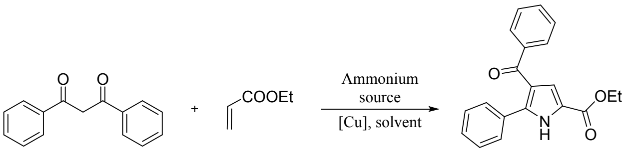
2,3,5-trisubstituted pyrroles. Herein, we reported a novel strategy to the synthesis of 2,3,5-trisubstituted pyrroles via a three-component coupled domino reaction of 1,3-dicarbonyl compounds, acrylate esters and ammonium salt in the presence of copper salt.

Results and discussion

In initial attempts, we commenced with the reaction of **1a**, ethyl acrylate (**2a**) and NH_4OAc for the exploration of the optimal reaction condition. Firstly, we used $Cu(OAc)_2$ (2.0 equiv.) as the additive and DCE (2 mL) as the solvent at 100 °C for 24 h, but did not obtain desired product. To our delight, after many trials to the solvent screening study, we found that HFIP remained as the most appropriate solvent to afford ethyl 5-benzoyl-4-phenyl-1H-pyrrole-2-carboxylate (**3a**), compared to DCE, MeCN and TFE (Table 1, entries 1-4). We further conducted the reaction with other kinds of copper salts as additives, and found that $Cu(OAc)_2•H_2O$ was the most efficient additive, among Cu_2O, CuI, CuO, $CuCl_2$, $Cu(OTf)_2$ and $Cu(NO_3)_2•3H_2O$, to give desired product (**3a**) in 46% yield (Table 1, entries 5-11). Encouraged by these results, other nitrogen sources such as $(NH_4)_2CO_3$, NH_4Cl, NH_4I, $(NH_4)_2SO_4$, $(NH_4)_2S_2O_8$ and NH_3 in water or methanol were explored. Unfortunately, the obtained results did not improve (Table 1, entries 12-18). Next, we screened different amounts of $Cu(OAc)_2•H_2O$, and found that the yield of the reaction decreased slightly when the concentration of $Cu(OAc)_2•H_2O$ was 1.5 or 2.5 equiv. (Table 1, entries 19-20). Furthermore, the reaction was screened at a temperature varying from 90°C to 120°C, and the obtained results revealed that 110 °C was the optimal reaction temperature (Table 1, entries 21-23). Meanwhile, we texted a sequence of conditions to explore a novel catalytic system, in which a catalytic amount of $Cu(OAc)_2•H_2O$ combined with a stoichiometric amount of oxidant such as TBHP, DTBP, DIPA and $K_2S_2O_8$, but we did not obtain target compound. Finally, the optimized reaction conditions for the synthesis of ethyl 5-benzoyl-4-phenyl-1H-pyrrole-2-carboxylate (**3a**) were **1a** (0.15 mmol), **2a** (0.30 mmol) and NH_4OAc (5.0 equiv.) as the reaction substrates, $Cu(OAc)_2•H_2O$ (2.0 equiv.) as the additive, and HFIP (2.0 mL) as the solvent at 110 °C for 24h.

With the optimized reaction conditions in hand (Table 1, entry 20), the scope of the reactions of a variety of 1, 3-dicarbonyl compounds **1**, ethyl acrylate **2a** and NH_4OAc were investigated (Table 2). Symmetrical 1,3-dicarbonyl compounds bearing a variety of electron-donating as well as electron-withdrawing substituents at the *para*-position on the phenyl ring could produce smoothly the corresponding pyrroles derivatives. With electron-donating groups $-CH_3$ and $-OCH_3$, the reaction provided the corresponding products **3b** and **3c** in admissible yields (62% and 60%, separately). Meanwhile, for substrates bearing electron-withdrawing substituents -F, the reaction provided the desired product **3d** in moderate yield (50%). In order to explore further the scope of the reactions, unsymmetrical 1,3-diketones containing an aryl group and a methyl group, could also be converted to the corresponding target products in good to moderate yields. As shown in Scheme

Table 1. Optimization of the Reaction Conditions [a]



1a 2a 3a

Entry	Additive (equiv.)	Ammonium salt (equiv.)	T (°C)	Solvent [b]	Yield[c] (%)
1	$Cu(OAc)_2$ (2.0)	NH_4OAc	100	DCE	N.R.[d]
2	$Cu(OAc)_2$ (2.0)	NH_4OAc	100	MeCN	N.R.
3	$Cu(OAc)_2$ (2.0)	NH_4OAc	100	TFE	20
4	$Cu(OAc)_2$ (2.0)	NH_4OAc	100	HFIP	42
5	Cu_2O (2.0)	NH_4OAc	100	HFIP	N.R.
6	CuI (2.0)	NH_4OAc	100	HFIP	N.R.
7	CuO (2.0)	NH_4OAc	100	HFIP	33
8	$CuCl_2$ (2.0)	NH_4OAc	100	HFIP	N.R.
9	$Cu(OTf)_2$ (2.0)	NH_4OAc	100	HFIP	Trace
10	$Cu(NO_3)_2$ (2.0)	NH_4OAc	100	HFIP	N.R.
11	$Cu(OAc)_2•H_2O$ (2.0)	NH_4OAc	100	HFIP	46
12	$Cu(OAc)_2•H_2O$ (2.0)	$(NH_4)_2CO_3$	100	HFIP	35
13	$Cu(OAc)_2•H_2O$ (2.0)	NH_4Cl	100	HFIP	20
14	$Cu(OAc)_2•H_2O$ (2.0)	NH_4I	100	HFIP	N.R.
15	$Cu(OAc)_2•H_2O$ (2.0)	$(NH_4)_2SO_4$	100	HFIP	N.R.
16	$Cu(OAc)_2•H_2O$ (2.0)	$(NH_4)_2S_2O_8$	100	HFIP	N.R.
17	$Cu(OAc)_2•H_2O$ (2.0)	NH_3 in water	100	HFIP	N.R.
18	$Cu(OAc)_2•H_2O$ (2.0)	NH_3 in MeOH	100	HFIP	N.R.
19	$Cu(OAc)_2•H_2O$	NH_4OAc	100	HFIP	38

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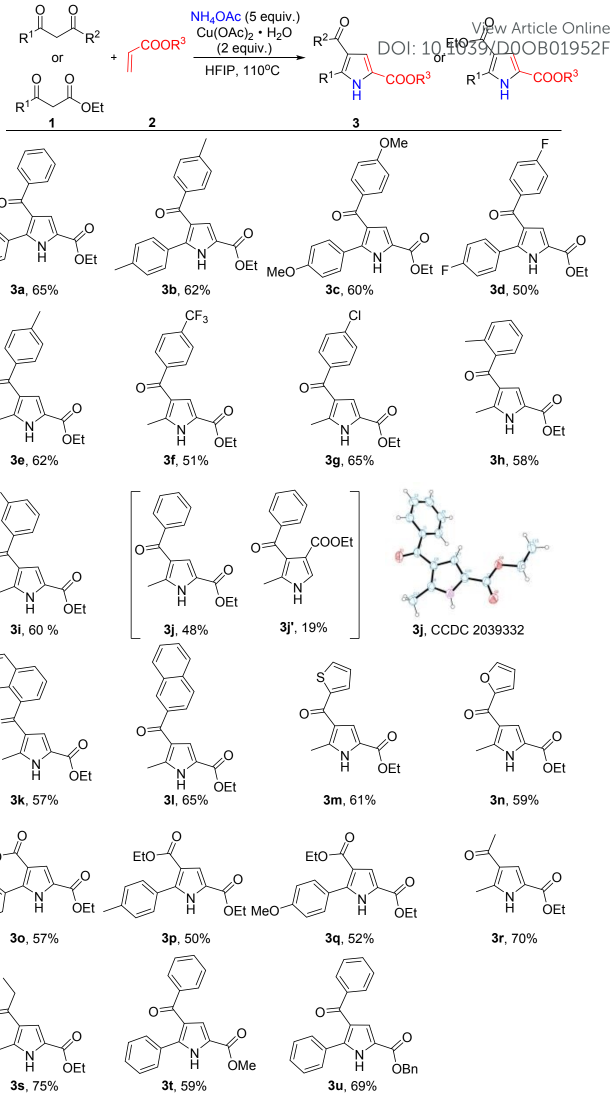
	(1.5)				
20	$Cu(OAc)_2{\bullet}H_2O$ (2.5)	NH_4OAc	100	HFIP	45
21	$Cu(OAc)_2{\bullet}H_2O$ (2.0)	NH_4OAc	90	HFIP	30
22	$Cu(OAc)_2{\bullet}H_2O$ (2.0)	NH_4OAc	110	HFIP	65
23	$Cu(OAc)_2{\bullet}H_2O$ (2.0)	NH_4OAc	120	HFIP	60
24 [e]	$Cu(OAc)_2{\bullet}H_2O$ (0.5)	NH_4OAc	110	HFIP	N.R.

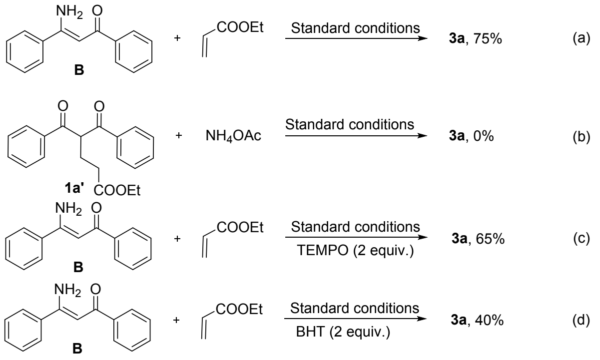
[a)] Reaction conditions: **1a** (0.15 mmol), **2a** (0.30mmol), additive, ammonium salt (5 equiv.), solvent (2.0 mL) in a sealed tube, 24 h. [b)] TFE = 2,2,2-Trifluoroethanol, HFIP = Hexafluoroisopropanol. [c)] Isolated yield. [d)] N.R. = no reaction. [e)] Oxidant (2 equiv.) was added, including TBHP, DTBP, DIPA and $K_2S_2O_8$; TBHP = ter-butyl hydroperoxide (5.0-6.0 M in decane), DTBP = di-t-butyl peroxide, PIDA = $PhI(OAc)_2$.

2, various substituents bearing electron-donating groups (-Me) or electron-withdrawing groups (-CF_3, -Cl) at the *para*-position of benzene were tolerated well, leading to the formation of desired pyrroles **3g-j** in yields varying from 51% to 65%. Nevertheless, electron-donating substituent (-CH_3) and electron-withdrawing substituent (-Cl) at the *ortho*- and *meta*-positions on the phenyl ring, gave a lower reactivity compared to *para*-substituted 1,3-diketones (**3h** vs **3e**, **3i** vs **3g**). Meanwhile, we found the regioselectivity of products in case of unsymmetrical 1,3-dicarbonyl compounds, such as **1j**. After separating two isomers which had very similar polarity, the desired product **3j** was obtained in 48% yields, the structure of which was further confirmed by single-crystal X-ray diffraction analysis.[18] What's more, 1- and 2-naphthalene 1,3-dicarbonyl compounds also provided the desired 2,3,5-trisubstitutedpyrroles in 57% and 65% yields, respectively (**3k**, **3l**). Besides, 1,3-dicarbonyl compounds containing a heterocycle, such as furan and thiophene, has also been tested, and the desired products were obtained in 61% and 59% yields (**3m**, **3n**). Moreover, several single-ester dicarbonyl compounds could be converted into the corresponding products in moderate yields (**3o**-**3q**). To our delight, 1,3-diketones containing two alkyl group were applied to the reaction, giving target products in 70% and 75% yields (**3r** and **3s**, respectively). Unfortunately, other substrates including 1,3-

Table 2. Substrate scope for the synthesis of trisubstituted pyrroles [a]



[a)] Reaction conditions: **1** (0.15 mmol), **2** (0.30 mmol), $Cu(OAc)_2{\bullet}H_2O$ (2 equiv.), NH_4OAc (5 equiv.), HFIP (2.0 mL) at 110 °C for 24 h, in a sealed tube.

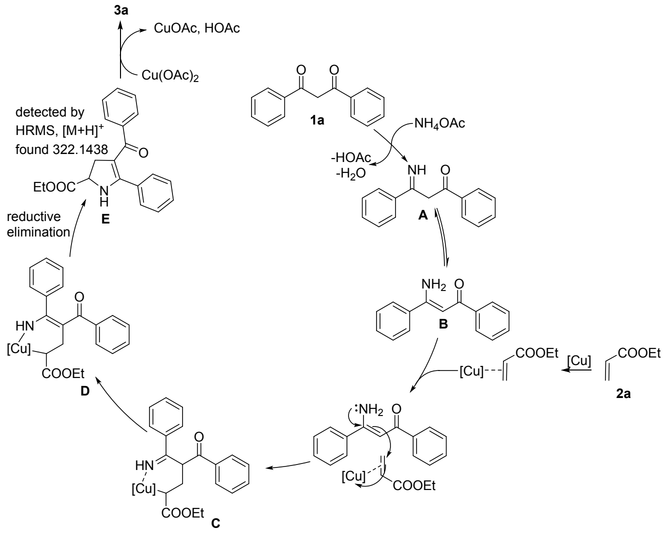


Scheme 2. Controlled experiments.

cyclohexanedione and β-cyano ketone did not result in the corresponding products. On the other hand, we extended the scope of the reaction with a variety of acrylate derivatives under the optimized reaction conditions. The reactions with methyl and benzyl acrylates also proceeded well, furnishing the corresponding products **3t** and **3u** in 59% and 69% yields, respectively. In the end, other activated olefins such as acrylonitrile, ethyl trans-2-butenoate and phenyl vinyl sulfone were used under standard conditions, but no corresponding products were observed, presumably because of the low reactivity of the functional groups.

In order to further understand the reaction mechanism of this three-component reaction process, some control experiments were conducted and shown in Scheme 2. When the reaction was carried out with prepared enamine **B** with ethyl acrylate under the standard conditions, it afforded the desired 2,3,5-trisubstituted pyrrole product **3a** in 75% yield (Scheme 2, (a)). However, when ethyl 4-benzoyl-5-oxo-5-phenylpentanoate **1a'** was used as the substrate to react with NH_4OAc under the standard conditions, the target product **3a** was not obtained (Scheme 2, (b)). It suggests that the enamine intermediate **B** might be the key intermediate in the reaction. We also performed the radical trap study with enamine **B** by using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT), and found no inhibition of the desired product **3a** in 65% and 40% yields (Scheme 2, (c), (d)).

Based on the above results and previous literature reports,[14, 16b, 19] a possible mechanism for the reaction is proposed in Scheme 3. Initially, the reaction of carbonyl group of 1,3-diphenyl-1,3- propanedione **1a** with ammonia from ammonium acetate would give the intermediate **A**. Next, the intermediate **A** would undergo an imine-enamine tautomerism reaction to give enamine **B**. On the other hand, the ethyl acrylate **2a** is activated by Cu(II), which undergoes an intermolecular C-C bond with enaminone to give the intermediate **C**. Furthermore, the intermediate **C** undergoes imine-enamine tautomerism to give intermediate **D**, which is followed by reductive elimination by Cu(II) to give the intermediate **E**. Finally, the intermediate **E** oxidized by Cu(II) to furnish the desired pyrrole product **3a**.



Scheme 3. Proposed reaction mechanism.

Conclusions

In conclusion, a series of 2,3,5-trisubstituted pyrroles were synthesized efficiently by one-pot condensation of 1, 3-dicarbonyl compounds, acrylates and ammonium salts in the presence of $Cu(OAc)_2•H_2O$ in HFIP. By the synergistic formation of new C-C, C-N bonds, we have synthesized highly functionalized pyrroles without further raw material preparation. This protocol, as it has readily available starting materials and a wide range of substrates, is expected to have the potential to apply in the pharmaceutical industry and material fields.

Conflicts of interest

There are no conflicts to declare.

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18 CCDC 2039332 contains the supplementary crystallo graphic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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- Wide scope and good group tolerance
- Construct C-C and C-N bond
- Convience operation
- Moderate to good yields