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ARTICLE TYPE

Copper-Catalyzed Homocoupling of Ketoxime Carboxylates for Synthesis of Symmetrical Pyrroles

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A novel and efficient copper-catalyzed homocoupling of ketoxime carboxylates has been developed for the synthesis of symmetrical pyrroles. This reaction tolerates a wide range of functional groups and provides a synthetically useful process to synthesize valuable symmetrical pyrroles under mild conditions.

Pyrroles are one of the most important heterocycles which prevlent in numerous natural products, pharmaceuticals, and functionalized materials.[1] Particularly, a lot of symmetrical pyrroles was recently discovered have remarkable bioactivity and fluorescence, such as COX-2 isoenzyme inhibitors (a), DNA minor groove recognition reagent DB884 (b), bio-antioxidant (c), fluorophores TPPy (d) and NPANPy (e) (Figure 1).[2] Over the past decades, tremendous efforts have been devoted to the synthesis of various substituted pyrroles.[3] Apart from the classical protocols,[4] many new strategies, such as cycloaddition reactions,[5] multicomponent reactions,[6] dehydrogenative cyclization reactions,[7] coupling of enamides with alkynes,[8] and oxidative cyclization of *N*-allylimines[9] have been developed for the synthesis of pyrroles. However, most of these methods are focused on versatile unsymmetrical substituted pyrroles, general protocols for the synthesis of valuable symmetrical pyrroles has rarely been developed.[10]

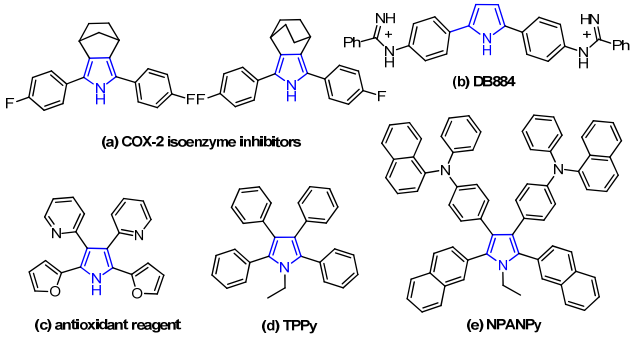
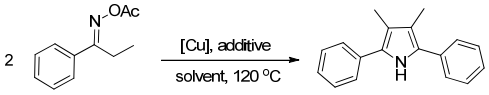


Figure 1 Bioactive or fluorescent symmetrical pyrroles

Oximes and their derivatives are versatile synthetic building blocks.[11] They are well-known fruitful candidates for the Beckmann rearrangement reactions to prepare amides,[12] and the dehydrations to produce nitriles.[13] Recently, reductive acylation of ketoximes have been developed as a practical method for the synthesis of enamides.[14] Meanwhile, much attention have been paid to the coupling reactions of the oxime carboxylates, because the N-O bond cleavage of the oxime carboxylates could be worked as an internal oxidant to make reactions proceed under redox-neutral conditions. Thus, transition-metal catalyzed coupling of oxime carboxylates with aldehydes, alkynes, and organoboronic acids have emerged for the synthesis of aza-heterocycles.[15] In connection with our interest in the oximes[14a-b,15a] and green synthesis of pyrroles,[5] we have developed a novel and efficient copper-catalyzed homocoupling of ketoxime carboxylates for the synthesis of valuable symmetric pyrroles.

Propiophenone oxime acetate **1a** was selected as a model substrate in the initial experiments to optimize the reaction conditions. Symmetrical pyrrole **2a** was obtained in 37% yield when CuBr was used as the catalyst in DMSO at 120 °C (Table 1, entry 1). Then, $NaHSO_3$ which we found good additive in our previous copper-catalyzed coupling of oxime

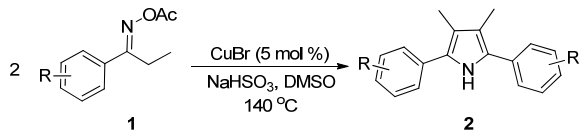
Table 1 Optimization of reaction conditions for homocoupling of propiophenone oxime acetate for synthesis of symmetrical pyrrole[a]

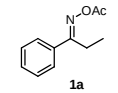
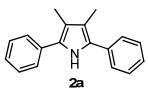
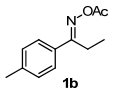
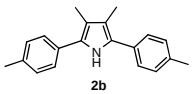
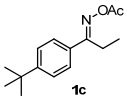
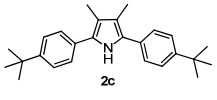
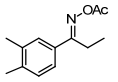
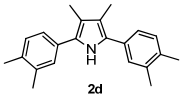
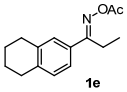
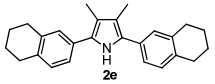
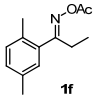
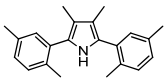
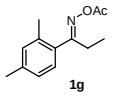
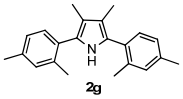
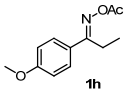
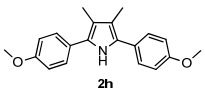
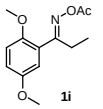
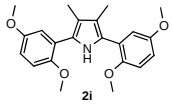
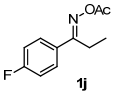
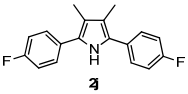
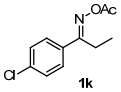
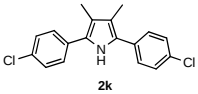
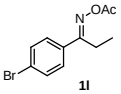
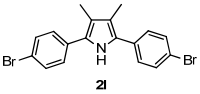


Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	CuBr	---	DMSO	37
2	CuBr	$NaHSO_3$	DMSO	68
3	CuBr	Na_2SO_3	DMSO	30
4	CuI	$NaHSO_3$	DMSO	35
5	CuCl	$NaHSO_3$	DMSO	64
6	$CuCl_2$	$NaHSO_3$	DMSO	62
7	$CuBr_2$	$NaHSO_3$	DMSO	59
8	$Cu(OAc)_2$	$NaHSO_3$	DMSO	31
9	CuBr	$NaHSO_3$	DMF	24
10	CuBr	$NaHSO_3$	CH_3CN	39
11	**CuBr**	**$NaHSO_3$**	**DMSO**	**72[c]**
12	---	$NaHSO_3$	DMSO	0

[a] Reaction conditions: propiophenone oxime acetate **1a** (0.3 mmol), catalyst (5 mol %), $NaHSO_3$ (1.2 equiv) in solvent (3 mL) under Ar at 120 °C for 2 h. [b] Isolated yields. [c] The reaction was run at 140 °C.

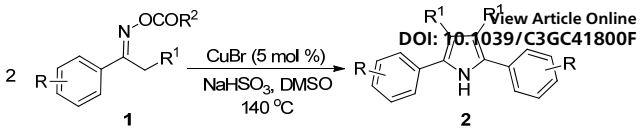
Table 2 Cu-catalyzed homocoupling of aryl ethyl ketoxime acetates[a]

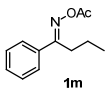
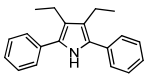
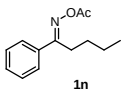
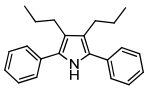
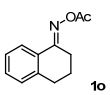
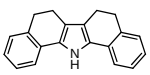
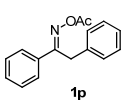
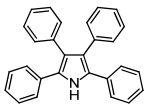
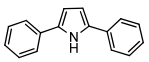
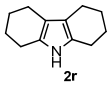
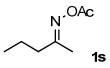
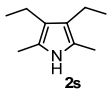


Entry	Substrate	Product	Yield (%)[b]
1	 1a	 2a	72
2	 1b	 2b	74
3	 1c	 2c	63
4	 1d	 2d	74
5	 1e	 2e	76
6	 1f	 2f	70
7	 1g	 2g	65
8	 1h	 2h	65
9	 1i	 2i	68
10	 1j	 2j	55
11	 1k	 2k	70
12	 1l	 2l	67

[a] Reaction conditions: **1** (0.3 mmol), CuBr (5 mol %), $NaHSO_3$ (1.2 equiv) in DMSO (3 mL) under Ar at 140 °C. [b] Isolated yields (averages of two experiments).

Table 3 Cu-catalyzed homocoupling of various ketoxime carboxylates[a]



Entry	Substrate	Product	Yield (%)[b]
1	 1m	 2m	56
2	 1n	 2n	66
3	 1o	 2o	68
4	 1p	 2p	52
5	 1q	 2q	10
6	 1r	 2r	0
7	 1s	 2s	0
8	1t	2a	62
9	1u	2a	56
10	1v	2a	45

[a] Reaction conditions: **1** (0.3 mmol), CuBr (5 mol %), $NaHSO_3$ (1.2 equiv) in DMSO (3 mL) under Ar at 140 °C for 2 h. [b] Isolated yields (averages of two experiments).

acetates with aldehydes was added to the reaction.[15a] The yield of pyrrole **2a** was dramatically improved to 68% (Table 1, entry 2). Na_2SO_3 shows inferior than $NaHSO_3$. Next, a series of copper catalysts, such as CuI, CuCl, $CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$ were screened to determine if they improved reaction efficiency (Table 1, entries 4-8). And various solvents, such as DMF and CH_3CN, were screened as well (Table 1, entries 9-10). However, we found that CuBr and DMSO are still the most effective catalyst and solvent respectively. Reaction temperature was also varied; the yield of **2a** was further increased to 72% when the reaction was conducted at 140 °C (Table 1, entry 11). Additionally, no reaction was observed in the absence of copper catalyst confirming that Cu species did indeed act as the catalyst in the reaction (Table 1, entry 12).

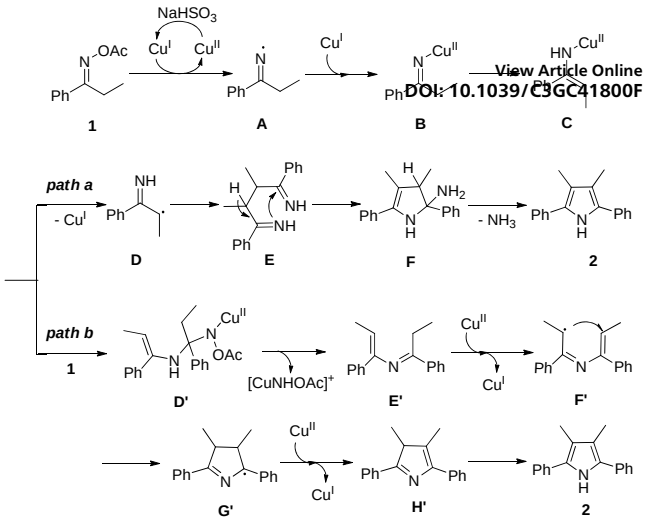
With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). The reaction showed good functional group tolerance and proved to be a general methodology for the preparation of symmetrical pyrroles. And the reaction was insensitive to the electronic effects of the substrates. Propiophenone oxime acetates with

methyl, alkyl, methoxyl, fluoro, and electron-withdrawing groups such as chloro and bromo groups on the aromatic rings all gave the corresponding symmetrical pyrroles **2b-2l** in good yields. In this manner, the resulting Cl or Br substituted products **2k-2l**, could be further expanded to a wider variety of functionalized symmetrical pyrroles by undergoing subsequent cross-coupling reactions. In addition, *ortho*-methyl and methoxyl substituted substrates reacted smoothly and resulted in the desired symmetrical pyrroles **2f-2g** and **2i** in 65-70% yields. These results indicated that steric hindrance on the aromatic rings of the substrates has little influence on the reaction (Table 2, entries 6-7, and 9).

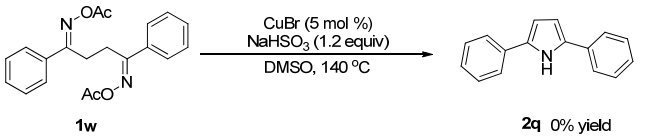
Furthermore, a series of phenyl alkyl ketoxime acetates were investigated for extension of the reaction scope (Table 3). Ketoxime acetates derived from butyrophenone, valerophenone and α-tetralone reacted smoothly to give the desired symmetrical pyrroles **2m-2o** in 56-68% yields (Table 3, entries 1-3). It should be noted that tetraphenyl pyrrole **2p**, which was fluorophores for glassy blue-light-emitting diodes,[2d] was obtained in 52% yield when 1, 2-diphenylethanone oxime acetate **1p** was used as the substrate (Table 3, entry 4). However, acetophenone oxime acetate **1q** gave only 10% yield of the corresponding 2,5-diphenyl pyrrole **2q** under the aforementioned conditions (Table 3, entry 5). And no desired pyrrole products were obtained when the alkyl alkyl ketoxime acetates, such as cyclohexanone oxime acetate **1r** and pentan-2-one oxime acetate **1s** were employed as the substrates under the standard conditions (Table 3, entries 6-7). Finally, different propiophenone oxime carboxylates were investigated to determine the reactivity of them. It was found that the reactivity of the different carboxylates follows the sequence: acetate > propionate > pentafluorobenzoate > benzoate (Table 3, entries 8-10).

On the basis of the above results and previous studies, the tentative mechanisms for this homocoupling reaction are proposed in Scheme 1. Firstly, the reaction starts from two-step single-electron-transfer reduction of ketoxime acetate **1** by Cu^{I} to generate imino-Cu^{II} complex **B**.[14a-b,15] Tautomerization of imino-Cu^{II} complex **B** gives the enamino-Cu^{II} intermediate **C**. Then, two pathways are possible for the following steps. In one case (path a), clevage of the N-Cu bond of the enamino-Cu^{II} intermediate **C** forms a radical intermediate **D**.[16] Radical coupling of intermediate **D** affords diimine intermediate **E**.[17] Intramolecular cyclization of intermediate **E** followed by elimination of NH_3 produces the pyrrole **2**. Alternatively, condensation of enamino-Cu^{II} intermediate **C** with a second ketoxime acetate **1** gives the intermediate **D'**.[15a,18] Elimination of intermediate **D** produces an enimine intermediate **E'**. Intramolecular radical cyclization of intermediate **E'** assisted by Cu^{II} sequence with tautomerization of intermediate **H'** produces the symmetrical pyrrole **2** (path b).[8d,15e,16]

To gain insight into the mechanism of the reaction, 1,4-diphenylbutane-1,4-dione dioxime diacetates **1w** was conducted under the standard conditions (Scheme 2). If the reaction is proceeded though path b, we will expect to observe the pyrrole **2q**. However, no pyrrole **2q** was observed in the reaction. This result indicated that the path b is less likely



Scheme 1 Proposed mechanism for the Cu-catalyzed homocoupling of ketoxime carboxylates



Scheme 2 Intramolecular homocoupling of diketoxime diacetates **1w**

In summary, we have developed a novel and efficient copper-catalyzed homocoupling of ketoxime carboxylates for the synthesis of symmetrical pyrroles. The reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available ketoxime carboxylates into a variety of valuable symmetrical pyrroles. Further scope and mechanistic studies of the reaction are underway and will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of products **2**.. See DOI: 10.1039/b000000x/

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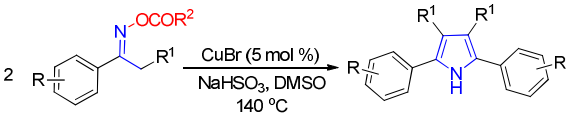
Table of contents entry:

Copper-Catalyzed Homocoupling of Ketoxime Carboxylates for Synthesis of Symmetrical Pyrroles

Longfei Ran, Zhi-Hui Ren, Yao-Yu Wang and Zheng-Hui Guan*



An efficient copper-catalyzed homocoupling of ketoxime carboxylates has been developed for the synthesis of symmetrical pyrroles.