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An efficient synthesis of polysubstituted pyrroles *via* copper-catalyzed coupling of oxime acetates with dialkyl acetylenedicarboxylates under aerobic conditions<sup>†</sup>

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A Cu-catalyzed [3+2]-type condensation reaction of oxime acetates and dialkyl acetylenedicarboxylates that provides highly substituted pyrroles under aerobic conditions is described. The newly formed pyrroles are easily employed for further transformations to prepare pyrrolo[2,1-a]isoquinoline skeletons.

Pyrroles are important heterocyclic compounds and are present in many biologically active natural products,<sup>1</sup> agro-chemicals, functional materials,<sup>2</sup> and pharmaceutical compounds (Fig. 1).<sup>3</sup> Recently, they have been used as solar batteries and organic semiconductors.<sup>4</sup> Thus, many synthetic methods have been developed for constructing pyrroles,<sup>5</sup> including classical Knorr reaction,<sup>6</sup> cycloadditions,<sup>7</sup> and multicomponent<sup>8</sup> and tandem reactions.<sup>9</sup> However, they suffer from several drawbacks such as complicated operations, harsh reaction conditions, and poor availability of the starting materials and functional group tolerance. To overcome these limitations, new strategies, for example, metal catalyzed reactions,<sup>10</sup> have been developed.

Recently, the development of transition metal-catalyzed dehydrogenative coupling reactions to construct pyrroles has drawn much attention. Ag,<sup>10a</sup> Cu,<sup>10b</sup> and Ru<sup>10c,d</sup> catalysts have



Fig. 1 Selected examples for pyrrole-containing bioactive natural products and pharmaceutical compounds.

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enabled widely applicable oxidative alkyne annulations with enamines to provide pyrroles (Fig. 2A). Milstein's group<sup>10e</sup> and Saito's group<sup>10f</sup> have used various amino alcohols and secondary alcohols or ketones to synthesize pyrroles, catalyzed by a Ru complex (Fig. 2B). Very recently, Glorius<sup>10g</sup> and Yoshikai<sup>10h</sup> et al. independently developed a remarkably mild oxidative cyclization of imines to pyrroles with the use of molecular oxygen as the sole oxidant (Fig. 2C). Recently, oxime esters have been widely used as substrates for transition metal-catalyzed coupling reactions.<sup>11–14</sup> On the basis of our previous Cu-catalyzed synthesis of pyrroles<sup>10a</sup> and other heterocyclic compounds,<sup>15</sup> using oxime esters as substrates, herein, we disclose a novel and useful method to construct polysubstituted pyrroles *via* the Cu-catalyzed [3+2]-type condensation reaction of oxime acetates and dialkyl acetylenedicarboxylates (Fig. 2D).

We initially studied the reaction of oxime acetate (**1a**; 0.5 mmol) with dimethyl acetylenedicarboxylates (**2a**; 0.6 mmol), NaHSO<sub>3</sub> (0.6 mmol), CuCl (10 mol%) in DMSO at 120  $^{\circ}$ C under a pure O<sub>2</sub> atmosphere (Table 1, entry 1), and the desired pyrrole **3a** could be



Fig. 2 Synthesis of pyrroles via dehydrogenative coupling.

 Table 1
 Screening for optimal reaction conditions<sup>a</sup>

Ph	N_OAc + 1a	COOCH <sub>3</sub>	[M] , additive solvent, 120 °C	Ph N 3a	_СООСН₃ СООСН₃
Entry	[M]		Additive	Solvent	Yield <sup>b</sup> (%)
1	CuCl		NaHSO <sub>3</sub>	DMSO	71
2	CuCl		0	DMSO	53
3	CuCl		Na <sub>2</sub> SO <sub>3</sub>	DMSO	84 (80)
4	CuBr		$Na_2SO_3$	DMSO	73
5	CuI		$Na_2SO_3$	DMSO	57
6	Cu(O	$Ac)_2$	$Na_2SO_3$	DMSO	48
7	CuBr	2	$Na_2SO_3$	DMSO	41
8	PdCl <sub>2</sub>	-	$Na_2SO_3$	DMSO	0
9			$Na_2SO_3$	DMSO	0
10	CuCl		Na <sub>2</sub> SO <sub>3</sub>	DMF	48
11 <sup>c</sup>	CuCl		$Na_2SO_3$	DMSO	61
$12^d$	CuCl		Na <sub>2</sub> SO <sub>3</sub>	DMSO	25

<sup>*a*</sup> Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (10 mol%), additive (0.6 mmol) and DMSO (2 mL) at 120  $^{\circ}$ C under O<sub>2</sub> atmosphere for 12 h. <sup>*b*</sup> Determined using GC based on **1a**. <sup>*c*</sup> Under air. <sup>*d*</sup> Under N<sub>2</sub>.

detected in 71% GC yield. Low conversion was observed without additives (entry 2). To our delight, the addition of Na<sub>2</sub>SO<sub>3</sub> could increase the yield and 3a was formed in 80% isolated yield (entry 3). Encouraged by these results, different copper catalysts were evaluated for the reaction between 1a and 2a (entries 4-7). When CuBr, CuI, Cu(OAc)<sub>2</sub> and CuBr<sub>2</sub> were used, the yields were decreased. No reaction occurred in the presence of PdCl<sub>2</sub> (entry 8) and the absence of metal catalysts resulted in no product formation (entry 9). Changing the solvent to DMF was less effective (entry 10). The yield also became lower when the reaction was performed under an air atmosphere (entry 11). Under an atmosphere of N<sub>2</sub>, the yield sharply declined to 25% (entry 12). These observations suggested that copper species was necessary and O<sub>2</sub> played an important role in this process. Thus, the optimal reaction conditions were 1a (0.5 mmol), 2a (0.6 mmol), Na<sub>2</sub>SO<sub>3</sub> (0.6 mmol), CuCl (10 mol%) in 2 mL DMSO at 120 °C under a pure O<sub>2</sub> atmosphere.

Having identified our optimized reaction conditions, we then investigated the scope of this transformation, and the results are presented in Table 2. Generally, the reaction of oxime acetates with dimethyl acetylenedicarboxylate (DMAD) proceeded smoothly and gave the desired products 3 in moderate to good yields. para-Substituted acetophenone oxime acetates having electron-withdrawing groups gave lower yields than those with electron-donating groups (3a-3f). When 2'-methylacetophenone, 3'-methylacetophenone and 3',4'-dimethylacetophenone oxime acetates were used as the substrates, 3g-3i could be isolated in 80%, 73%, and 66% yields, respectively. In addition, 1-acetylnaphthalene oxime acetate also underwent the desired transformation to give the corresponding pyrrole 3j in 88% yield. A heteroaromatic substrate such as thiophene oxime acetate could give 3k in 62% yield. Propiophenone, substituted propiophenone, and *n*-butyrophenone oxime acetates gave good to excellent yields of the tetrasubstituted pyrroles 3l-3t. Tetrasubstituted pyrroles were obtained in higher yields than the corresponding trisubstituted pyrroles. It is worth mentioning





 $^a$  The reactions were carried out at 120 °C, using 1 (0.5 mmol), 2 (0.6 mmol), Na<sub>2</sub>SO<sub>3</sub> (0.6 mmol), CuCl (10 mol%) in DMSO (2 mL) at 120 °C under O<sub>2</sub> atmosphere for 12 h. Yields refer to the isolated yields.

that the alkyl oxime acetates could also be transformed into the desired pyrrole **3u**. However, cyclic ketone oxime acetates were not applicable to this system. When diethyl acetylenedicarboxylate was reacted with acetophenone oxime acetate and propiophenone oxime acetate, **3v** and **3w** were obtained in 79% and 89% yields, respectively. However, methyl propiolate, methyl but-2-ynoate and methyl 3-phenylpropiolate were not suitable substrates for this reaction.

The newly formed pyrroles bearing the free NH functionalities are easily transformed to more complicated organic architectures. We used ruthenium-catalyzed aerobic oxidative coupling of **3a** and **3l** with 3-hexyne to deliver the corresponding pyrrolo-[2,1-a]isoquinolines **4a** and **4l**, in excellent yields (Fig. 3).<sup>16</sup> Notably, pyrrolo[2,1-a]isoquinolines are indispensable structural motifs of *inter alia* bioactive lamellarine alkaloids.<sup>17</sup>

Based on the experimental results and previous reports,<sup>13,14</sup> a plausible mechanism for this transformation is proposed in Scheme 1. Firstly, in the presence of the Cu catalyst, the oxime acetate was easily transformed to copper enamide intermediate 2 and this process produced another Cu<sup>II</sup>. Intermediate 2 could react with dimethyl acetylenedicarboxylate to give intermediate 3. Then, a single-electron-transfer (SET) process occurred and intermediate 4 was formed, followed by a radical addition to afford intermediate 5. Finally, the dehydrogenation process of 5 gave



Fig. 3 Transformations of pyrroles.



the desired pyrrole product with the generation of  $H^+$ , while  $Cu^{II}$  was reduced to  $Cu^{I}$  that could enter into the next catalytic cycle. Theoretically, the reaction can be redox-neutral, but under an atmosphere of  $N_2$ , the yield was only 25%. Up until now the role of  $O_2$  was unknown, however, in this work it has been shown to promote the reaction significantly. Further mechanistic study is underway in our laboratory.

In conclusion, a novel and useful method has been developed to construct highly substituted pyrroles *via* a copper-catalyzed coupling reaction of dialkyl acetylenedicarboxylates with oxime acetates under aerobic conditions. This novel method tolerates a wide range of functionalities. The newly formed pyrroles bearing free NH functionalities are easily employed for further transformations to prepare useful pyrrolo[2,1-*a*]isoquinoline skeletons, which may find applications in natural product synthesis.

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