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### Efficient synthesis of substituted pyrroles through

# Pd(OCOCF<sub>3</sub>)<sub>2</sub>-catalyzed reaction of 5-hexen-2-one with

## primary amines

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#### **Abstract Graphic**



#### Abstract

An efficient and facile  $Pd(OCOCF_3)_2$ -catalyzed one-pot cascade protocol has been developed for the synthesis of multiple substituted pyrroles in good to excellent yields. Unlike the reported method starting from the 2-alkenal-1,3-carbonyl compounds, the process utilizes the less reactive 5-hexen-2-one and the method has great potential as an complement to the current developed methods.

Keywords: pyrroles, palladium, intermolecular, 5-hexen-2-one

#### Introduction

Pyrroles are the privileged nitrogen-containing heterocycles and are widely encountered in the scaffolds of bioactive natural products<sup>1</sup> and pharmaceutical agents, <sup>2</sup> exhibiting pronounced bioactivities such as antitumor,<sup>3</sup> anti-inflammatory,<sup>4</sup> antibacterial<sup>5</sup> and antifungal effects<sup>6</sup>. Moreover, they are also employed as building blocks in organic synthesis to construct the more structurally complicated scaffolds.<sup>7</sup> Therefore, there has been a long interest in developing novel synthetic methods for the efficient construction of pyrroles. Traditional synthetic methods include the Knorr,<sup>8</sup> Pall-Knorr,<sup>9</sup> and Hantzsch reactions.<sup>10</sup> which have been used for more than a century. While, the increasing applications of this highly important class of compounds demand novel and more efficient synthetic approaches from the readily available starting materials under mild reaction conditions with good to excellent yields. Among these novel reported approaches, the convenient access of hydroamination of functionalized alkynes or alkenes catalyzed by the transition-metal catalysts such as Pd,<sup>11</sup> Fe,<sup>12</sup> Ag,<sup>13</sup> Au,<sup>14</sup> Cu<sup>15</sup> to pyrroles is a very common strategy and highly attractive from the atom- and step-economical points of view. For example, Li's group has disclosed  $Pd(OCOCF_3)_2$ -catalyzed cascade Aza-Wacker type reaction of 2-alkenal-1,3-dicarbonyl compounds with primary amines to synthesize highly substituted pyrroles in moderate to excellent yields (Scheme 1A).<sup>11b</sup> Additionally, Liu's group has reported the formation of tetrasubstituted pyrroles via FeCl<sub>3</sub>-mediated sequential amination/annulation reaction of 2-propynyl-1,3-dicarbonly compounds with primary amine.<sup>12</sup> Within these two exemplified reactions, the involved 1.3-dicarbonly compounds facilitated the formation of the enamine and made the subsequent attack of nitrogen on the alkene or alkyne proceed smoothly to generate the pyrroles products. To the best of our knowledge, Pd(II)-catalyzed intermolecular Wacker-type reaction of 5-hexen-2-one with primary amines, leading to the formation of functionalized pyrroles has not been reported, which is more challenging due to the less reactivity of mono-ketone compared to the 1,3-diketone. Toward this end, we wish to report a highly efficient Pd(II)-catalyzed

cascade Wacker-type reaction of 5-hexen-2-one with primary amines for the synthesis of multiple substituted pyrroles in moderate to excellent yields. This protocol not only provides a complement to the currently available methods, but also broadens the application of Wacker-type reaction to synthesize heterocyclic compounds.

#### SCHEME 1. Palladium-catalyzed intermolecular annulation to pyrroles



#### **Results and Discussion**

Initially, 5-Hexen-2-one 1a and aniline 2a were chosen as model substrates to explore the optimal reaction conditions for the synthesis of multiple substituted pyrrole 3a. As shown in Table 1, We were pleased to found that the most promising reaction yield was obtained when the reaction was performed in toluene in the presence of  $Pd(OAc)_2$  as catalyst under an atmosphere of ambient air (entry 6), whereas the other solvents such as DMF,  $CH_3CN$ , DMSO, THF, DCE gave the desired products in poor to moderate yields (entries 1-5). Screening different of а varietv of palladium catalysts revealed that  $Pd(OCOCF_3)_2$ -catalyzed reaction of **1a** with **2a** under air atmosphere afforded the desired product **3a** in 75% yield (entry 7), which was dramatically higher than those reactions catalyzed by PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> (entries 8-10). Subsequently, we turned our attentions to the effects of oxidants on the reaction yields. The reaction yield was increased to 85% when the O<sub>2</sub> was involved to replace air (entry 11). While compared to the reaction done with  $O_2$ , the reaction yields dropped significantly

upon employing K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, Cu(OAc)<sub>2</sub>.H<sub>2</sub>O, CuCl<sub>2</sub>, AgNO<sub>3</sub>, Ag<sub>2</sub>CO<sub>3</sub> as

#### Table 1. Optimization of reaction conditions

	1	1a O	+ H <sub>2</sub> o solv	cat xidant ent, 12 h		~
	Entry <sup>a</sup>	Solvent	Catalyst	Oxidant	Yield <sup><math>b</math></sup> (%)	
	1	DMF	Pd(OAc) <sub>2</sub>	air	13	
	2	CH <sub>3</sub> CN	Pd(OAc) <sub>2</sub>	air	18	
	3	DMSO	Pd(OAc) <sub>2</sub>	air	5	
	4	THF	Pd(OAc) <sub>2</sub>	air	35	
	5	DCE	Pd(OAc) <sub>2</sub>	air	46	
	6	Toluene	Pd(OAc) <sub>2</sub>	air	60	
	7	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	air	75	
	8	Toluene	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	air	56	
	9	Toluene	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	air	48	
	10	Toluene	Pd(PPh <sub>3</sub> ) <sub>4</sub>	air	20	
	11	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	$O_2$	85	
	12	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	$K_2S_2O_8$	40	
	13	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	Cu(OAc) <sub>2</sub> .H <sub>2</sub> O	54	
	14	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	CuCl <sub>2</sub>	50	
	15	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	AgNO <sub>3</sub>	40	
1	16	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	Ag <sub>2</sub> CO <sub>3</sub>	35	
	17	Toluene	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	$N_2$	trace	
	18	Toluene	-	$O_2$	$NP^{c}$	

<sup>*a*</sup> A solution of **1a** (0.6 mmol, 1.2 eq) and **2a** (0.5 mmol, 1 eq) with catalyst (0.05 mmol, 0.1 eq) and oxidant (0.6 mmol 1.2 eq) in solvent (2 mL) was stirred at 100 °C for 12 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> NP indicated no desired product **3a** was obtained.

oxidants respectively (entries 12-16). These results demonstrated the O2 was a highly

effective oxidant for this transformation. If the reaction was carried out under nitrogen, only a trace of amount of the product **3a** was obtained (entry 17), indicating that the  $O_2$  was essential for the catalyst recycling. Moreover, no targeting product **3a** was obtained when the reaction was conducted in the absence of Pd(OCOCF<sub>3</sub>)<sub>2</sub> (entry 18).

With the optimal conditions in hand, we next surveyed the generality of this process to the synthesis of structurally diverse pyrroles **3**. As shown in Table 2, this method was compatible with significant structural variations both in the amines and 5-hexen-2-one substrates. Only limited impact on the reaction yields imposed by the substitution patterns on the phenyl ring was observed (**3a-g**). The anilines possessing electron-donating groups on the phenyl ring such as the phenoxyl, acetamido gave the higher yields under the same conditions (**3h-i**). However, the electron-withdrawing groups (EWG) on the phenyl ring such as the ester, nitro, fluorine resulted in the significant drop on the yields (**3j-n**). It was believed that the EWG significantly reduced the nucleophilic activities of the amines. It was well worth mentioning that this process was tolerated with a wide range of functional groups on the phenyl ring such as bromine, chlorine, ester, amide and nitro to generate the corresponding products in 40-92% yields (**3i-q**). These products had great potential as building blocks to construct structurally more complicated compounds. We noted that in addition to the aromatic amines, the aliphatic amines could smoothly involve in the process to afford the corresponding

#### Table 2. Scope of Pd(OCOCF<sub>3</sub>)<sub>2</sub>-catalyzed synthesis of Pyrroles 3





pyrroles in excellent yields. For example, over 90% yields were observed when the primary amines such as benzyl, cyclohexanemethyl, propyl, 2-methoxyethyl, 2-phenylethyl, isobutyl, 2,2-diphenylethyl amines participated in this transformation (**3r**,

**3u-3z**). The *N*-Boc-protected diamines could also perform well in the reaction and afforded the corresponding products in excellent yields (**3s**, **3aa**). While, the more sterically hindered isopropylamine caused a decrease in the yield (**3ab**), furthermore the tert-butylamine couldn't afford the desired product due to the steric hindrance of the tert-butyl group (**3ac**). Probing the 5-hexen-2-one substrates implied that the more hindered  $R_2$ = isopropyl appeared to be a good candidate for this process (**3ad**), while switch  $R_2$  on **1** from methyl to phenyl resulted in a significant drop in the yield (**3ae**). Additionally, we examined the challenging non-terminal alkene substrates, and found the process proceeded with high regioselectivity. Only pyrrole **3af** was afforded in acceptable yield.

It was attractive that the protocol was sufficiently efficient to afford the bipyrroles products in 88-94% yields when the diamines such as 1,4-phenylenediamine, ethylenediamine, 4-aminobenzylamine were involved (Table 3, **3ag-ai**).

**Table 3. The bipyrroles products** 



A plausible mechanism for the reaction of 5-Hexen-2-one **1a** with primary amine **2** is illustrated in Scheme 2, in which neutral ligands are omitted. Coordination of enamine **A** generated from 5-hexen-2-one **1**and primary amine **2** to  $Pd^{II}$  center and subsequent nucleophilic attack on the resulting intermediate A by the nitrogen take place to form Pd-alkyl intermediate **B** with the loss of HX. The intermediate **B** undergoes a  $\beta$ -hydride elimination to release intermediate **C**, which can undergo acid-catalyzed isomerization to give the pyrroles **3**. Alternatively, Pd(H) can reinsert into the alkene **C** to form the Pd-alkyl

intermediate **D** again. The intermediate **D** undergoes the second  $\beta$ -hydride elimination to aromatize the system to generate the pyrroles **3**. Catalyst  $Pd^{II}$  is regenerated through Pd(0)oxidized by O<sub>2</sub>.



#### Scheme 2. A proposed mechanism for the reaction

#### Conclusions

In summary, we have disclosed an efficient palladium-catalyzed cascade Wacker-type process of the less reactive 5-hexen-2-one with primary amines for the synthesis of the synthetically and biologically meaningful pyrroles. It represents a facile access to multiple substituted pyrroles from the readily available reagents in moderate to excellent yields for a diverse range of substrates and an excellent complement to the currently available synthetic methods.

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#### Highlights

- A palladium-catalyzed cascade access to multiple substitute pyrroles was explored. •
- The less reactive 5-hexen-2-one was involved as the substrate
- The method broadens the application of Wacker reaction to construct pyrroles.
- This method is complementary to the current synthetic approaches to pyrroles.

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