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A Facile Access to Pyrroles from Amino Acids via an Aza-Wacker Cyclization

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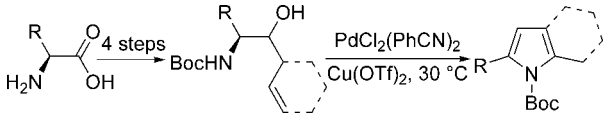


A facile and efficient synthesis of pyrroles from readily available amino acids is described. The key step in the method is an aza-Wacker oxidative cyclization catalyzed by palladium(II)/$Cu(OTf)_2$. A series of pyrroles were obtained by this method under mild conditions.

The pyrrole derivatives are widespread in numerous natural products, and many of them display diverse biological activities.[1] Besides, pyrrole is one common structural unit in many organic materials.[2] In the preparation of pyrrole derivatives, however, many disadvantages including harsh reaction conditions and poor yields limit the application of classical methods, such as Knorr reaction and Paal−Knorr reaction.[3,4] Although some novel strategies have been developed to synthesize pyrrole derivatives recently,[5,6] the preparation of pyrrole derivatives by more efficient and facile methods is still desired.

On the other hand, the palladium(II)-catalyzed Wacker-type oxidative cyclization is a well-known process for the formation of heterocycles.[7–9] Recently, we have focused our research on Wacker reactions and have developed some methods for the preparation of chromanones and quinolines.[10]

SCHEME 1. Synthesis of 2 by Aza-Wacker Oxidative Cyclization

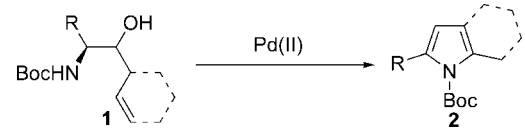
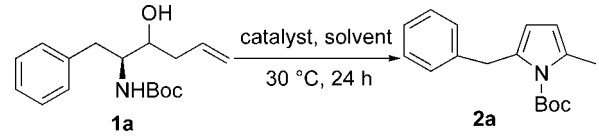


TABLE 1. Optimazation of Aza-Wacker Cyclization[a]



entry	solvent	catalyst (10 mol %)	oxidant	yield[b] (%)
1	MeOH	$Pd(OAc)_2$	air	23
2	EtOH	$Pd(OAc)_2$	air	25
3	*i*-PrOH	$Pd(OAc)_2$	air	trace
4	THF	$Pd(OAc)_2$	air	trace
5	Tol	$Pd(OAc)_2$	air	trace
6	DMF	$Pd(OAc)_2$	air	trace
7	DMSO	$Pd(OAc)_2$	air	trace
8	$CHCl_3$	$Pd(OAc)_2$	air	trace
9	EtOH	$PdCl_2$	air	41
10	EtOH	$PdCl_2(MeCN)_2$	air	44
11	EtOH	$PdCl_2(PhCN)_2$	air	45
12	EtOH	$PdCl_2(PhCN)_2$	O_2	50
13	EtOH	$PdCl_2(PhCN)_2$	$CuCl_2$ (10 mol %)	52
14	EtOH	$PdCl_2(PhCN)_2$	$Cu(OTf)_2$ (10 mol %)	69
15	EtOH	$PdCl_2(PhCN)_2$	$Cu(OTf)_2$ (50 mol %)	80
16	EtOH	$PdCl_2(PhCN)_2$	$Cu(OTf)_2$ (100 mol %)	88

[a] Reaction conditions: 0.2 M of **1a** in solvent. [b] Isolated yield.

Encouraged by these results, we envisioned that the Wacker reaction can be applied to the synthesis of pyrrole ring **2**, as shown in Scheme 1. The substrates **1** for the aza-Wacker oxidative reaction can be obtained from the natural amino acids. In 1996, the Cushman group[11] reported an interesting work on the application of amino acids for pyrrole synthesis via aldol condensation, but the yields were always 5−44%, which somewhat restricted its application.

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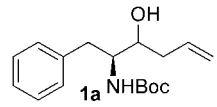
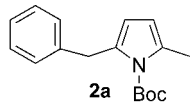
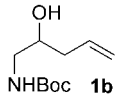
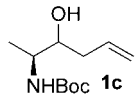
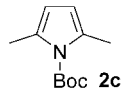
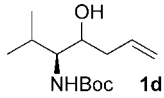
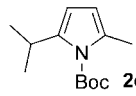
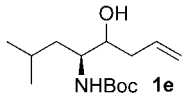
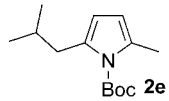
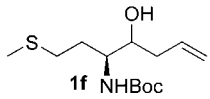
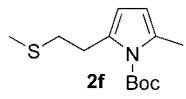
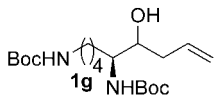
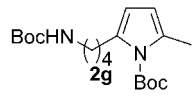
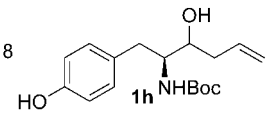
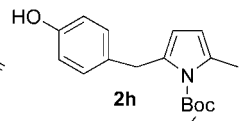
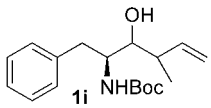
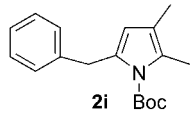
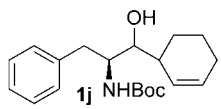
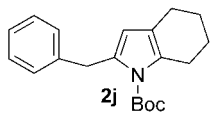
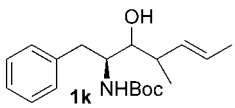
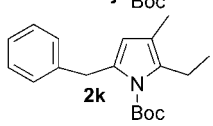
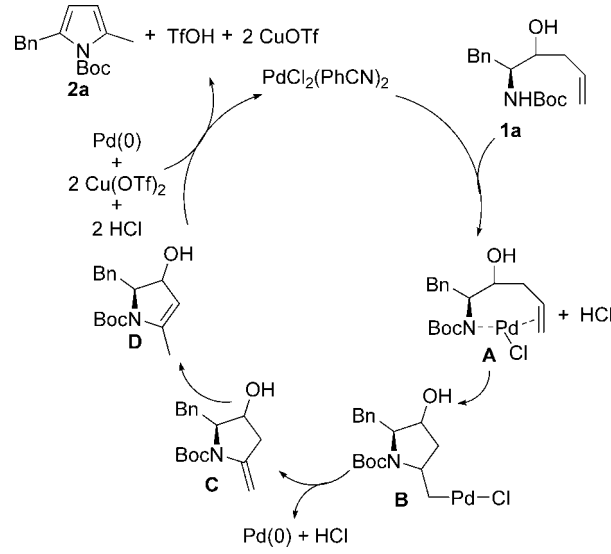
TABLE 2. Synthesis of Pyrrole by Aza-Wacker Cyclization[a]

entry	substrate	product	yield[b] (%)
1	 **1a**	 **2a**	88
2	 **1b**	 **2b**	86
3	 **1c**	 **2c**	89
4	 **1d**	 **2d**	87
5	 **1e**	 **2e**	92
6	 **1f**	 **2f**	85
7	 **1g**	 **2g**	62
8	 **1h**	 **2h**	79
9	 **1i**	 **2i**	76
10	 **1j**	 **2j**	70
11	 **1k**	 **2k**	26

[a] Reaction conditions: **1** (1 mmol), $PdCl_2(PhCN)_2$ (0.1 mmol), and $Cu(OTf)_2$ (1 mmol) in 5 mL of ethanol at 30 °C for 24 h. [b] Isolated yield.

Initially, $Pd(OAc)_2$ was employed as a catalyst, and various solvents were screened in the presence of air at 30 °C (Table 1, entries 1−8). The experimental results show that EtOH was a slightly better solvent (entry 2). Then different palladium sources were tested under the same conditions (entries 9−11). It was found that $PdCl_2(PhCN)_2$ and $PdCl_2(MeCN)_2$ had catalytic activities higher than those of $PdCl_2$ or $Pd(OAc)_2$ (entries 11 and 12). Nevertheless, the yield of **2a** (45%) needed to be enhanced, and the reaction conditions needed to be optimized further. In the reaction, it was observed that black palladium precipitation was formed, which perhaps resulted in the loss of the catalytic activity and the reduction of the reaction yield. Therefore, some oxidants other than air were added to the reaction in order to solve this problem (entries 12−16). $Cu(OTf)_2$ presented a higher activity than O_2 and $CuCl_2$, giving the product **2a** with a yield up to 88% (entry 16).

SCHEME 2. Proposed Mechanism of the Aza-Wacker Reaction for the Building of the Pyrrole Ring



The effect of ligands on the reaction was also investigated. Various ligands, such as pyridine (20 mol %), 2,2′-bipyridine (10 mol %), 1,10-phenanthroline (10 mol %), *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (10 mol %), ethane-1,2-diamine (10 mol %), and 1,4-diazabicyclo[2.2.2]octane (10 mol %), were used in the reaction. However, we hardly observed the effect of these ligands on the reaction.

Afterward, the scope of the reaction was extended to different substrates, which can be derived from different amino acids, including phenylalanine (**1a**), glycin (**1b**), alanine (**1c**), valine (**1d**), leucine (**1e**), methionine (**1f**), tyrosine (**1h**), and lysine (**1g**). Then these amino acid derivatives were employed in the reaction (Table 2). From Table 2, it was found that almost all the reactions can be carried out smoothly to afford the corresponding pyrrole derivatives with good yields, including 1,2,3-trisubstituted pyrrole **2i** and the annulated pyrrole **2j** (entries 9 and 10). When a methyl group is located at the end of the olefin, the desired product **2k** was obtained with a low yield (entry 11), perhaps due to the uncertain orientation of the β-hydride elimination because of the existence of the methyl group.

A possible mechanism for the reaction is shown in Scheme 2. Initially, aminopalladation of the complex **A** leads to intermediate **B**, which undergoes a β-hydride elimination to form

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(8) For a review, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

(9) For recent reports, see: (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257. (b) Tietze, L. F.; Stecker, F.; Zinngrebe, J.; Sommer, K. M. *Chem.—Eur. J.* **2006**, *12*, 8770.

(10) (a) Zhang, Z. H.; Pan, C. F.; Wang, Z. Y. *Chem. Commun.* **2007**, 4686. (b) Zhang, Z. H.; Tan, J. J.; Wang, Z. Y. *Org. Lett.* **2008**, *10*, 173.

(11) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999.

C.[12] After isomerization of **C**, the intermediate **D** is obtained, which is converted to pyrrole **2a** via a spontaneous dehydration. Pd(0) is eventually reoxidized by $Cu(OTf)_2$.

In conclusion, we have developed a new and facile method for the synthesis of pyrrole derivatives. The key step in this protocol is an aza-Wacker cyclization, which makes use of $Cu(OTf)_2$ as the oxidant. In particular, this strategy allows the natural amino acids to be the starting materials for the construction of differently substituted pyrroles.

Experimental Section

Typical Procedure for the Synthesis of Pyrrole. To a solution of **1a** (1 mmol, 291 mg) in 5 mL of EtOH were added $Cu(OTf)_2$ (1 mmol, 290 mg) and $PdCl_2(PhCN)_2$ (0.1 mmol, 38 mg) one by one. After the mixture was stirred at 30 °C for 24 h, the ethanol was removed by reduced pressure. Ten milliliters of water was then added to the residue, and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried using anhydrous Na_2SO_4 and evaporated under reduced pressure; the mixture was then purified by column chromatography over silica gel to afford product **2a** (248 mg, 88% yield) with high purity: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) $\delta = 7.27-7.11$ (m, 5H), 5.81 (d, $J = 2.7$ Hz, 1H), 5.66 (d, $J = 2.7$ Hz, 1H), 4.16 (s, 2H), 2.39 (s, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) $\delta = 150.4$, 140.4, 133.7, 132.1, 128.7, 128.3, 126.0, 111.7, 110.3, 83.5, 35.9, 28.0, 16.5; IR (liquid film, cm^{-1}) $\nu = 3028$, 2978, 2929, 1734, 1536, 1454, 1386, 1327, 1255, 1172, 1121, 1021, 851, 788, 698. HRMS (*m*/*z*): (M^+) calcd for $C_{17}H_{21}NO_2$, 271.1572; found, 271.1579.

(12) In aza-Wacker reaction, *cis*-stereochemistry was proposed in amino-palladium; see: Liu, G. S.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

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Supporting Information Available: Preparation of starting materials and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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