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Three-Component Synthesis of Polysubstituted Pyrroles from α-Diazoketones, Nitroalkenes, and Amines

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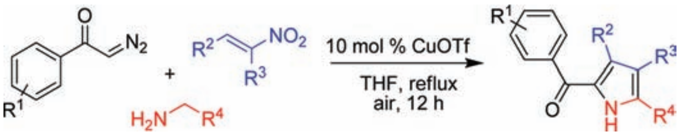
ABSTRACT



Polysubstituted pyrroles are regiospecifically synthesized via the copper-catalyzed three-component reaction of α-diazoketones, nitroalkenes, and amines under aerobic conditions. The cascade process involves an N−H insertion of carbene, a copper-catalyzed oxidative dehydrogenation of amine, and a [3 + 2] cycloaddition of azomethine ylide.

Pyrroles represent an important class of heterocycles in organic chemistry. They are structural units in many natural products and pharmaceuticals and are key intermediates for the synthesis of a variety of biologically active molecules and functional materials.[1] As the world's leading cholesterol-lowering drug, atorvastatin calcium (Lipitor) is a prime example.[2] The conventional methods for the construction of a pyrrole ring include the Hantzsch reaction,[3] the Paal−Knorr synthesis,[4] and various cycloaddition methods.[5] A number of metal-catalyzed approaches were also developed.[6] Still, general and efficient strategies for the synthesis of pyrroles from simple and readily available precursors are of great value due to the continued importance of the pyrrole core in both biological and chemical fields.

Multicomponent reactions (MCRs) have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry for their facileness and efficiency as well as their economy and ecology in organic synthesis.[7] These features make MCRs well suited

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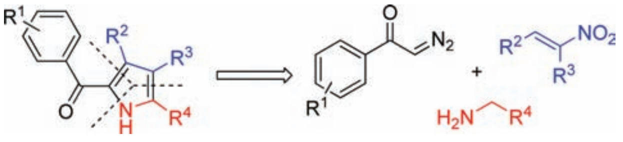
for the construction of diversified heterocyclic scaffolds from readily available materials.[8] Recently, this strategy has found its applications in the synthesis of pyrroles.[9]

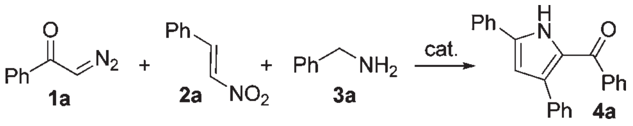
As a part of our ongoing research on development of multicomponent approaches to heterocycles,[10] we were interested in the rapid construction of a polysubstituted pyrrole ring via the copper-catalyzed three-component reaction of α-diazoketones, nitroalkenes and amines under aerobic conditions. The reaction involves the assembling of the pyrrole core from [1 + 2 + 2] atom fragments (Scheme 1).

Scheme 1. Synthesis of Pyrroles via MCRs



We began our studies by evaluating the reaction of 2-diazo-1-phenylethanone (**1a**), (2-nitrovinyl)benzene (**2a**), and phenylmethanamine (**3a**) using $Cu(OTf)_2$ as catalyst. Simple heating of a mixture of the three components and $Cu(OTf)_2$ in THF under atmosphere led to the formation of the desired product **4a**, albeit in only 44% yield (Table 1, entry 1). We then examined other triflates, such as AgOTf (Table 1, entry 2), $Zn(OTf)_2$ (Table 1, entry 3), $Sc(OTf)_3$ (Table 1, entry 4), $Yb(OTf)_3$ (Table 1, entry 5), and $In(OTf)_3$ (Table 1, entry 6), but found that they did not work for this one-pot reaction. By altering $Cu(OTf)_2$ to CuOTf (Table 1, entry 7), the reaction proceeded well and gave a better yield (50%). It meant that either Cu (II) or Cu (I) would be essential for this reaction. Thus, we tested copper sources. $CuBr_2$ (Table 1, entry 8), $Cu(OAc)_2$ (Table 1, entry 9), and CuO (Table 1, entry 10) were found to be able to promote the reaction but in relatively lower yields. CuBr (Table 1, entry 11) or CuI (Table 1, entry 12) worked for this reaction with comparative yields. Increasing the amount of catalyst to 20 mol % only slightly raised the yield (Table 1, entry 13). Further screening of reaction conditions revealed that the yields largely depended on the reaction temperature (Table 1, entry 14). When the reaction was carried out at 25 °C, it did not occur at all (Table 1, entry 15). Solvent also highly affected the reaction (Table 1, entries 16−18). Since this reaction involved an oxidation process, we examined the other oxidant instead of air. When *t*-BuOOH was added, yield was slightly improved (Table 1, entry 19), similar with the case of bubbling the reaction with oxygen (Table 1, entry 20). Finally, we selected CuOTf (10 mol %) as catalyst and THF as solvent to perform the reaction under atmosphere for 12 h.

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp	Lewis acid	yield (%)[b]
1	THF	reflux	$Cu(OTf)_2$	44
2	THF	reflux	AgOTf	0
3	THF	reflux	$Zn(OTf)_2$	NR
4	THF	reflux	$Sc(OTf)_3$	NR
5	THF	reflux	$Yb(OTf)_3$	NR
6	THF	reflux	$In(OTf)_3$	NR
7	THF	reflux	CuOTf	50
8	THF	reflux	$CuBr_2$	30
9	THF	reflux	$Cu(OAc)_2 \cdot H_2O$	10
10	THF	reflux	CuO	<5
11	THF	reflux	CuBr	46
12	THF	reflux	CuI	48
13	THF	reflux	CuOTf	52[c]
14	THF	50 °C	CuOTf	20
15	THF	25 °C	CuOTf	0
16	DCE	refluex	CuOTf	0
17	toluene	80 °C	CuOTf	40
18	1.4-dioxane	reflux	CuOTf	41
19	THF	reflux	CuOTf	52[d]
20	THF	reflux	CuOTf	53[e]

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), **3a** (0.75 mmol), catalyst (0.05 mmol), solvent (8 mL), air, 12 h. [b] Yield of the isolated product. [c] Catalyst (0.10 mmol). [d] *t*-BuOOH (0.75 mmol) was added. [e] Reaction was under oxygen (1 atm).

With the optimized reaction conditions in hand, we tested the substrate diversity. A steady increment of yields could be seen by varying the substituent on **1** from electron donating group to electron withdrawing group (Table 2, entries 1−5 and 16−18). When the nitro group occupied on the *para* position (**1e**), the highest yield was reached (Table 2, entry 5). Structure of **4b** was confirmed by X- ray analysis (Figure 1). When ethyl α-diazoacetate was used instead of α-Diazoketone, reaction occurred, but without isolable products. Then, we examined the substitute effect on Michael acceptor **2** (Table 2, entries 6−13). The yields varied from 49% to 70% without significant trends.

Aliphatic nitroalkenes also afforded the corresponding products, but with relatively lower yields (Table 2, entries 14 and 15). With substituents occupied α-position of

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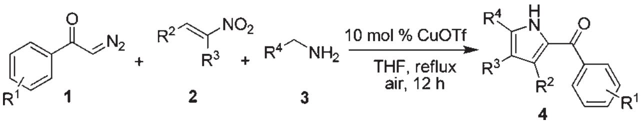
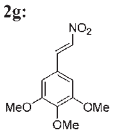
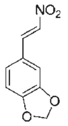
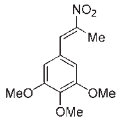
nitroalkenes (**2l**–**2o**), reactions performed smoothly and the desired products were obtained (Table 2, entries 16–21). Substituent effect on the benzyl amine was not significant (Table 2, entries 22–26). When *n*-butyl amine or *n*-octyl amine was used instead of **3a**, no desired product was detected. Similar result was observed for 2-phenylethanamine. When allyl amine was used, the desired **4A** was obtained in 46% yield (Table 2, entry 27). Altering the primary amine into secondary amine, neither *N*-methylbenzylamine nor *N*-sulfonylbenzylamine worked for the reaction and **2** was recovered quantitatively.

Table 2. Copper-Catalyzed Multicomponent Synthesis of Pyrrole **4** [a]



entry	**1** (R^1)	**2** (R^2/R^3)	**3** (R^4)	yield(%)[b]
1	**1a** (H)	**2a** (Ph/H)	**3a** (Ph)	**4a**/50
2	**1b** (4-Me)	**2a**	**3a**	**4b**/48
3	**1c** (4-MeO)	**2a**	**3a**	**4c**/43
4	**1d** (4-Br)	**2a**	**3a**	**4d**/58
5	**1e** (4-NO$_2$)	**2a**	**3a**	**4e**/65
6	**1a**	**2b** (2-ClC$_6$H$_4$/H)	**3a**	**4f**/56
7	**1a**	**2c** (2-BrC$_6$H$_4$/H)	**3a**	**4g**/49
8	**1a**	**2d** (3-MeOC$_6$H$_4$/H)	**3a**	**4h**/53
9	**1a**	**2e** (4-MeOC$_6$H$_4$/H)	**3a**	**4i**/50
10	**1a**	**2f** (4-BrC$_6$H$_4$/H)	**3a**	**4j**/67
11	**1a**	**2g:** 	**3a**	**4k**/57
12	**1a**	**2h** (2-furanyl /H)	**3a**	**4l**/65
13	**1a**	**2i:** 	**3a**	**4m**/70
14	**1a**	**2j** (Et/H)	**3a**	**4n**/49
15	**1a**	**2k** (CH$_3$(CH$_2$)$_5$/H)	**3a**	**4o**/45
16	**1a**	**2l** (Ph/Me)	**3a**	**4p**/57
17	**1c**	**2l**	**3a**	**4q**/52
18	**1e**	**2l**	**3a**	**4r**/60
19	**1a**	**2m:** 	**3a**	**4s**/56
20	**1a**	**2n** (2-BrC$_6$H$_4$/Me)	**3a**	**4t**/45
21	**1a**	**2o** (Ph/Et)	**3a**	**4u**/55
22	**1a**	**2a**	**3b** (2-ClC$_6$H$_4$)	**4v**/43
23	**1a**	**2a**	**3c** (3-MeOC$_6$H$_4$)	**4w**/61
24	**1a**	**2a**	**3d** (4-ClC$_6$H$_4$)	**4x**/55
25	**1a**	**2a**	**3e** (2-furanyl)	**4y**/48
26	**1a**	**2a**	**3f** (2-Py)	**4z**/50
27	**1a**	**2a**	**3g** (vinyl)	**4A**/46

[a] Reaction conditions: **1** (1.5 mmol), **2** (1 mmol), **3** (1.5 mmol), Cu(OTf) (0.1 mmol), THF (8 mL), air, 12 h. [b] Yield of the isolated product.

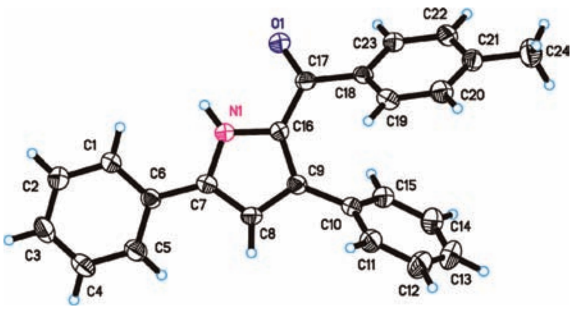


Figure 1. X-ray crystal structure of **4b**.

On the basis of these results, a tentative mechanism for this three-component reaction is postulated in Scheme 2. In the presence of copper catalyst, α-ketocarbene generated from α-diazoketone **1a** is traped by benzylamine (**3a**) to form **A** through N–H insertion.[11] Then, amine **A** undergoes a copper-catalyzed oxidative dehydrogenation to form imine **B** through activation of sp^3 C–H adjacent to nitrogen.[12] **B** then generates azomethine ylide **C**, which is trapped by the *trans* nitroalkene **2a** to produce the pyrrolidine **5** via a copper-catalyzed *exo*-selective [3 + 2] cycloaddition.[13] Finally, **4a** is obtained by the thermal extrusion of HNO$_2$ accompanying the

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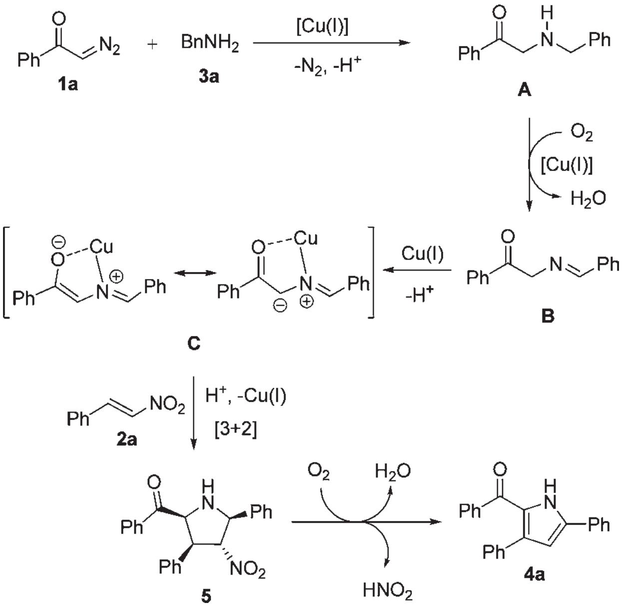
Scheme 2. Possible Mechanism for the Formation of **4a**



dehydrogenative aromatization. The pyrrolidine **5** could be separated before the reaction was completed and its structure was unambiguously confirmed by single-crystal X-ray analysis (Figure 2).

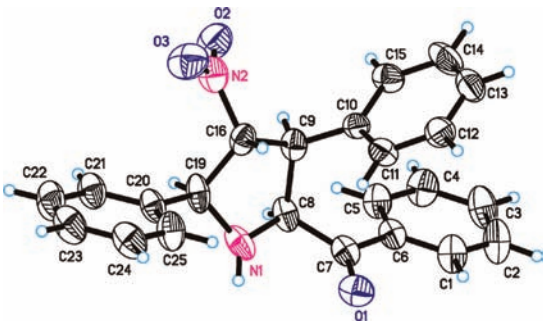
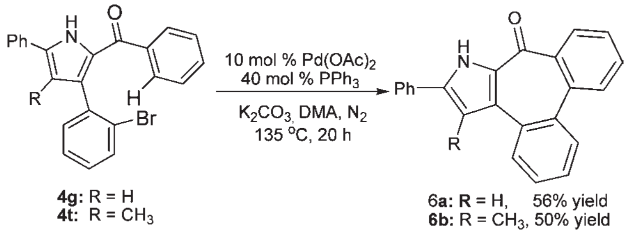


Figure 2. X-ray crystal structure of **5**.

Scheme 3. Concise Synthesis of Polycyclic Compounds **6**



A demonstration of the interesting synthetic utility of this method is shown in Scheme 3. The resulting products **4g** and **4t** could be easily transformed to the polycyclic compounds **6a** and **6b** via the Pd-catalyzed intramolecular C–C coupling reaction, and the products are potentially useful scaffolds for the synthesis of biologically active compounds and photophysical materials. The structure of compound **6b** was unambiguously confirmed by single crystal X-ray analysis (Figure 3).

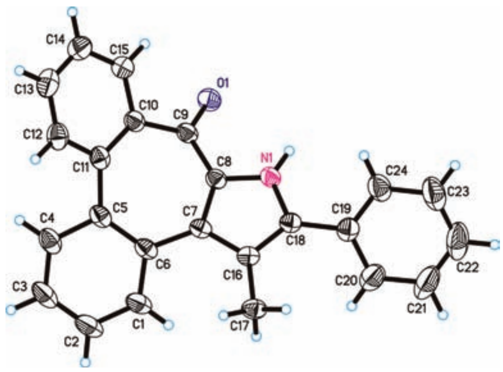


Figure 3. X-ray crystal structure of **6b**.

In summary, we have developed an efficient approach to polysubstituted pyrroles via a copper-catalyzed three-component reaction of α-diazoketones, nitroalkenes, and amines under aerobic conditions. The cascade process involves an N–H insertion of carbene, a copper-catalyzed oxidative dehydrogenation of amine, and a [3 + 2] cycloaddition of azomethine ylide. Due to the easy availability of the starting materials and potential utilities of products, this method might be useful in organic synthesis and medicinal chemistry.

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Supporting Information Available. Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C spectra, and crystallographic information files (CIF) for compounds **4b**, **5** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.