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Cu (I)-Catalyzed Synthesis of Polysubstituted Pyrroles from Dialkyl Ethylenedicarboxylates and *β*-Enamino Ketones or Esters in the Presence of O_2

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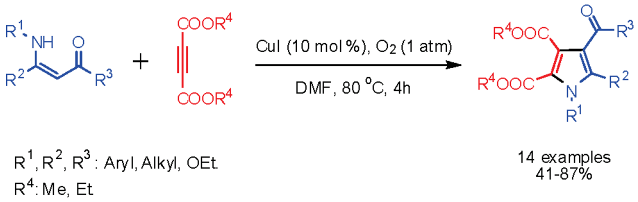
Received May 25, 2010



A straightforward method for the synthesis of polysubstituted pyrroles was achieved easily from oxidative cyclization of *β*-enamino ketones or esters and alkynoates catalyzed by CuI in the presence of O_2.

As the most prevalent heterocyclic compounds,[1] polysubstituted pyrroles are playing increasingly important roles as synthetic building blocks,[2] pharmacophores,[3] and various kinds of functional materials.[4] Consequently, they have drawn considerable interest for synthetic chemists. Classical methods for the synthesis of polysubstituted pyrroles included the classical Knorr reaction,[5] Hantzsch reaction,[6] and Paal–Knorr condensation reaction.[7] Recently, new approaches based on the multicomponent coupling[8] and cycloisomerization of alkyne- and allene-containing substrates catalyzed by a transition metal[9] have been developed and have drawn extensive and enduring attention. Despite numerous diverse approaches toward the synthesis of polysubstituted pyrroles have been developed,[10] a easy and efficient synthetic method still remains an attractive goal.

Oxygen is a very ideal oxidant and in attractive to chemists in terms of its numerous advantages in industry.[11] With the development of the C–H activation[12] and in view of the increased attention to environmental problems, new methods of using oxygen to construct heterocycles with simple and readily accessible substrates are highly desirable and urgent because of its economic, sustainable, and environmentally friendly features.[13] As a part of our continuing study on the utilization of oxygen in organic chemistry,[14]

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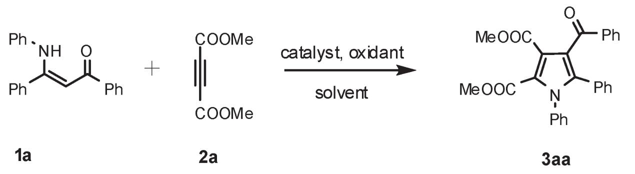
DOI: 10.1021/jo101022k

herein we wish to report an efficient method to synthesize polysubstituted pyrroles in thepresence of O_2.

Initially, we examined the reaction of (*Z*)-1,3-diphenyl-3-(phenylamino)prop-2-en-1-one (**1a**) and dimethyl but-2-ynedioate (**2**a) using air as the oxidant in DMF at 80 °C (Table 1, entry 1). Gratifyingly, the desired dimethyl 4-benzoyl-1,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (**3aa**) was obtained in 75% yield in the reaction catalyzed by CuI after 4 h. When O_2 was employed as the oxidant, to our delight, 83% of **3aa** was isolated (Table 1, entry 2). By increasing the temperature to 110 °C, the yield had a slight change (Table 1, entry 3). When the reaction was carried out at 60 °C, compound **3aa** was isolated in only 52% yield (Table 1, entry 4). Among the metal salts we examined, CuI showed the highest activity for this reaction (Table 1, entries 5−9). In addition, without metal salts as catalyst, no desired product was obtained (Table 1, entry 10). Other organic and inorganic oxidants such as ^{t}BuOOH, H_2O_2, $PhI(OAc)_2$, and *m*CPBA were also evaluated, and no improved result was obtained (Table 1, entries 11−14). Therefore, oxygen was proved to be the most efficient oxidant in this reaction. Furthermore, changing the solvent to toluene, THF, or CH_3CN failed to improve the yields (Table 1, entries 15−17). The results indicated that the choice of DMF as solvent was crucial for the reaction. Ultimately, optimized conditions were identified, which provided **3aa** in good yield (Table 1, entry 2).

TABLE 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	temp (°C)	yield (%)
1	CuI	air	DMF	80	75
2	CuI	O_2	DMF	80	83
3	CuI	O_2	DMF	110	82
4	CuI	O_2	DMF	60	52
5	CuBr	O_2	DMF	80	80
6	CuCl	O_2	DMF	80	70
7	$Cu(OTf)_2$	O_2	DMF	80	51
8	$Cu(OAc)_2$	O_2	DMF	80	66
9	$FeCl_2$	O_2	DMF	80	27
10		O_2	DMF	80	
11[b]	CuI	^{t}BuOOH	DMF	80	tr
12[b]	CuI	H_2O_2	DMF	80	15
13[b]	CuI	$PhI(OAc)_2$	DMF	80	
14[b]	CuI	*m*CPBA	DMF	80	11
15	CuI	O_2	toluene	80	tr
16	CuI	O_2	THF	80	17
17	CuI	O_2	CH_3CN	80	13

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), catalysts (0.03 mmol) in 2 mL of solvent for 4 h under oxygen (1 atm). [b] Reactions were carried out with oxidant (2.0 equiv) under nitrogen.

SCHEME 1. Reaction of the Substrates of 1k and 2b

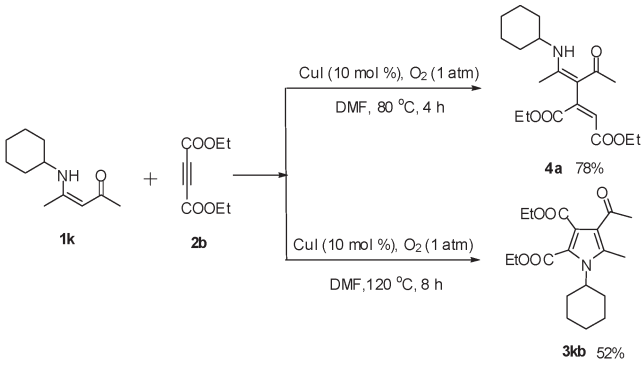
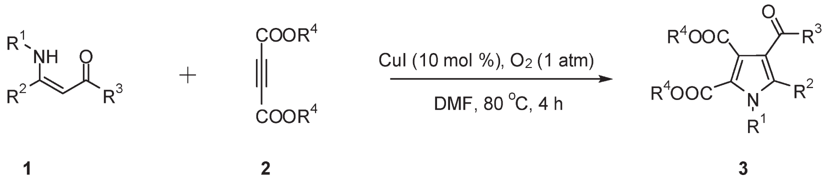


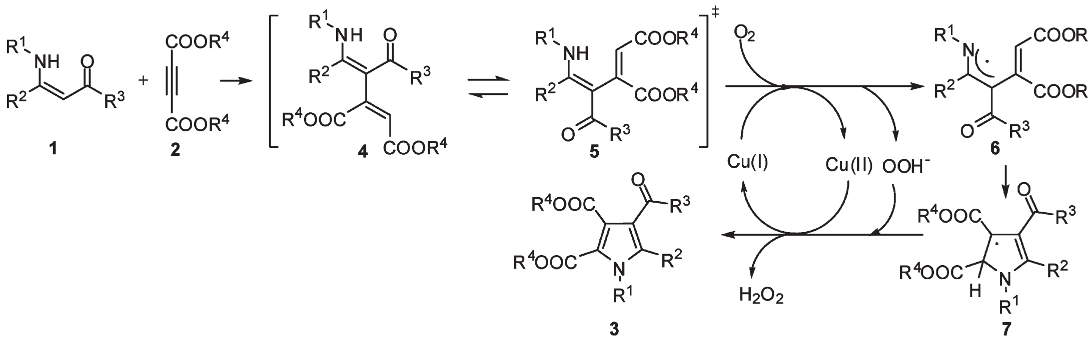
TABLE 2. Synthesis of Polysubstituted Pyrroles from Dialkyl Ethylenecarboxylates and *β*-Enamino Ketones or Esters[a]



entry	1				2		product	yield (%)
		R^1	R^2	R^3		R^4		
1	**1a**	Ph	Ph	Ph	**2a**	Me	**3aa**	83
2	**1b**	Ph	Ph	*m*-Me-Ph	**2a**	Me	**3ba**	80
3	**1c**	Ph	Me	Ph	**2a**	Me	**3ca**	81
4	**1d**	Ph	Me	Me	**2a**	Me	**3da**	46
5	**1e**	Ph	Ph	OEt	**2a**	Me	**3ea**	56
6	**1a**	Ph	Ph	Ph	**2b**	Et	**3ab**	85
7	**1c**	Ph	Me	Ph	**2b**	Et	**3cb**	87
8	**1f**	*p*-MeO-Ph	Ph	Ph	**2b**	Et	**3fb**	85
9	**1f**	*p*-MeO-Ph	Ph	Ph	**2a**	Me	**3fa**	82
10	**1g**	*p*-Me-Ph	Ph	Ph	**2b**	Et	**3gb**	87
11	**1h**	*p*-Cl-Ph	Ph	Ph	**2a**	Me	**3ha**	75
12	**1i**	*m*-Cl-Ph	Ph	Ph	**2a**	Me	**3ia**	64
13[b]	**1j**	*n*-Bu	Me	Me	**2b**	Et	**3jb**	41
14[b]	**1k**	cyclohexanyl	Me	Me	**2b**	Et	**3kb**	52

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), CuI (0.03 mmol), O_2 (1 atm), 2 mL DMF, 80 °C, 4 h. [b] The reactions were carried out at 120 °C for 8 h.

SCHEME 2. Plausible Reaction Mechanism



Having the optimized condition, we then extended the scope of this reaction, and the results are illustrated in Table 2. Generally, the reaction of β-enamino ketones or esters with dialkyl ethylenecarboxylates proceeded smoothly and led to the desired product **3** in moderate to good yields. To our delight, this reaction can also tolerate a broad substituents range of β-enamino ketones or esters (Table 2, entries 1−5). Remarkably, the electron density on the β-enamino ketones or esters drastically affects the yields of this reaction. For example, the reaction of **1a** with alkynoate afforded **3ab** in 87% yield, whereas **1d** was converted to **3da** only in 45% yield (Table 2, entries 4 and 6). Moreover, a wide range of N-substituents were also compatible with the process, which include functionalized groups, phenyl, and simple alkyl groups, and the electron-rich N-substituents also can improve the yields of the reaction (Table 2, entries 8−14). Satisfactorily, when the *N*-phenyl groups were replaced with *N*-alkyl groups, the desired pyrroles could be obtained in moderate yields at the expense of a higher reaction temperature and a longer reaction time (Table 2, entries 13 and 14). Further investigations demonstrated that the *meta* positions of the aromatic group of β-enamino ketones can slightly decrease the yields, which was presumablely caused by electron effection. The substrates **1b** and **1i** reacted with **2a** to form the products **3ba** and **3ia** in 80% and 64% yields, respectively (Table 2, entries 2 and 12).

It is worth mentioning that when (*Z*)-4-(cyclohexylamino)-pent-3-en-2-one **1k** and diethyl but-2-ynedioate **2b** were subjected to the optimized reaction conditions, an unexpected compound **4a** was isolated in 78% yield,[15] and the desired pyrroles **3kb** could be successfully obtained in 52% yield at the 120 °C for 8 h (Scheme 1). So the compound **4a** would be the intermediate of the transformation.

On the basis of the results obtained above, a plausible mechanism of this reaction is illustrated in Scheme 2. The first step involved a coupling of the substrates **1** and **2** to produce the Michael additional intermediate **4**. Conversion configurations existed between the intermediate **4** and **5** due to high temperature. Then, the intermediate **6** was generated by the hydride abstraction with oxidant from the intermediate **5**. Meanwhile, Cu(I) was oxidized to Cu(II), and oxygen was transformed to OOH$^-$. Sequently, the intermediate **7** is formed from the intermediate **6** through radical addition. Finally, the pyrrole **3** results from the dehydrogenation process with the generation of hydrogen peroxide. In addition, Cu(II) was reduced to Cu(I) which entered to the next catalytic cycle.

In conclusion, we have developed a direct method for the construction of polysubstituted pyrroles. Variation of N-substituents, aromatic ring, alkyl, and ester was proven possible, and this reaction can proceed smoothly in moderate to good yields. In this procedure, molecular oxygen was used as the oxidant in the synthesis of polysubstituted pyrroles.

Experimental Section

Typical Procedure for the Synthesis of Dimethyl 4-Benzoyl-1,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3aa). An oven-dried Schlenk tube was charged with CuI (5.7 mg, 0.03 mmol), (*Z*)-1,3-diphenyl-3-(phenylamino)prop-2-en-1-one (**1a**, 90 mg, 0.30 mmol), and dimethyl but-2-ynedioate (**2a**, 43 mg, 0.30 mmol). The Schlenk tube was sealed and then evacuated and backfilled with oxygen (3 cycles). Then 2 mL of DMF was added to the reaction system. The reaction was stirred at 80 °C under O_2 (1 atm) for 4 h. After cooling to room temperature, the solvent diluted with 10 mL of ethyl acetate, washed with 5 mL of brine, and dried over anhydrous Na_2SO_4. After the solvent was evaporated in vacuo, the residues were purified by column chromatography, eluting with petroleum ether/EtOAc (5:1) to afford 109 mg (83%) of dimethyl 4-benzoyl-1,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (**3aa**) as a yellow solid, mp 38−40 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 2 H), 7.39−7.22 (m, 6 H), 7.15−7.13 (m, 2 H), 7.05−6.95 (m, 5 H), 3.70 (s, 3 H), 3.63 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 164.5, 160.5, 139.2, 138.1, 137.1, 132.3, 130.6, 129.2, 129.0, 128.76, 128.72, 128.3, 128.0, 127.9, 127.7, 125.3, 122.5, 121.6, 52.3, 52.0; IR (neat, cm^{-1}) 2951, 1725, 1661, 1443, 1278, 1220, 1080, 917, 696; HRMS calcd for $C_{27}H_{22}NO_5$ [M + H]$^+$ 440.1492, found 440.1489.

Acknowledgment. We thank the National Science Foundation (NSF-20732002, NSF-20090443, and NSF-20872052) for financial support.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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