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Copper-Catalyzed Oxidative Cyclization of Enynes for the Synthesis of 4-Carbonyl-quinolines with O_2

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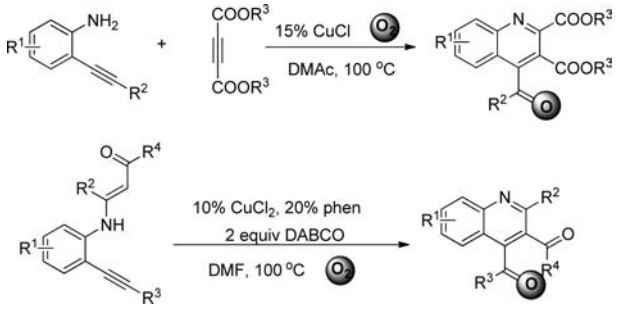
ABSTRACT



A novel copper-catalyzed oxidative cyclization of enynes and in situ formed enynes leading to 4-carbonyl-quinolines by using dioxygen as an oxygen source has been developed.

The synthesis of diverse oxygen-containing organic frameworks is one of the most fundamental and significant subjects in organic chemistry. From the viewpoint of green and sustainable chemistry, the direct utilization of molecular oxygen (O_2) for the construction of valuable oxygen-containing organic compounds has been of long-standing interest to organic chemists due to its tremendous importance in synthetic chemistry.[1] As is known, the transition-metal-catalyzed cyclization of 1,n-enynes has emerged as a useful tool for the synthesis of heterocyclic compounds due to the intriguing selectivity, atom economy, and exceptional ability to activate π-systems.[2] Despite considerable progress in this field, studies focusing on the development of mild 1,n-enyne cyclization routes using inexpensive catalysts to construct new and complex compounds need to be pursued. In recent years, copper-catalyzed reactions have received considerable attention because of their efficiencies

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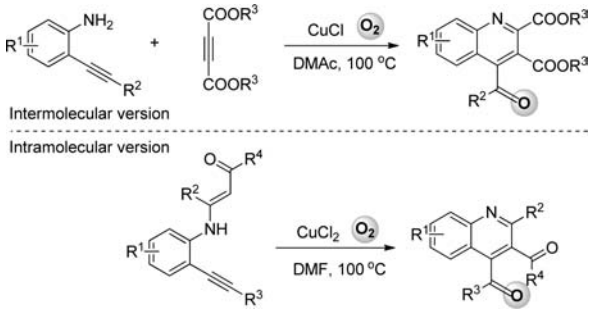
and low costs.[1b,3] However, examples of copper-catalyzed 1,n-enyne cyclization are rare,[4] especially in the synthesis of oxygen-containing quinolines.

The oxygen-containing quinoline unit represents an important structural motif found in a variety of biologically active compounds.[5] For instance, the 4-carbonyl-quinoline moiety is contained in the design of pharmaceuticals and related compounds, which has been synthesized *via* many steps in traditional synthetic routes.[6] Since the substituents on the quinoline rings have a great influence on the properties of these compounds, effective methods for the preparation of a diverse range of substituted 4-carbonyl-quinolines are highly desirable. The classical route to these compounds proceeded from the condensation of substituted anilines with α,β-unsaturated carbonyl compounds under strongly acidic conditions.[7] Although the improvement of these harsh conditions has recently been addressed by metal-catalyzed approaches, these new methodologies are confined for the lack of generality and limited functional-group tolerance.[8] Therefore, there remains a demand for versatile and effective methodologies to construct substituted quinoline derivatives with selective control of substitution patterns from readily accessible building blocks. The present report is the first on a novel and efficient copper-catalyzed oxidative cyclization of enynes or in situ formed enynes, in which the atmospheric molecular oxygen as the most sustainable oxidant available was incorporated into various functionalized quinoline derivatives (Scheme 1).

Scheme 1. Designed Route to Substituted 4-Carbonyl-quinolines



Our investigation began with the reaction of 2-(phenylethynyl)aniline **1a** with dimethyl but-2-ynedioate catalyzed by $CuCl_2$ in air at 80 °C. To our delight, the target cyclization product **2a** was obtained (Table 1, entry 1).

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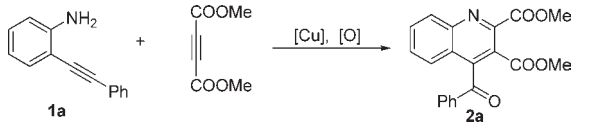
Consequently, a series of other copper salts (e.g., $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, CuCl, CuBr, and CuI) were evaluated, wherein CuCl displayed high catalytic activity (see Table S1 in the Supporting Information (SI)). It is noteworthy that the yield can be improved to 57% using O_2 instead of air (entry 3). Lower yields were obtained when 1,10-phenanthroline (Phen) or 2,2′-bipyridine were added as ligands (entries 4 and 5). The cylization reaction did not take place when DABCO was added as a base (entries 6 and 7). In addition, we found that the increasing amount of CuCl has a positive effect on the reaction yield (entries 8 and 9), in which the yield of **2a** was increased to 61% using 15 mol % CuCl. Then the amount of dimethyl but-2-ynedioate was also examined, and 2 equiv of dimethyl but-2-ynedioate were found to give a better result (entry 10). When the solvent was changed from DMF to DMAc, the yield of 83% was obtained (entry 12). Notably, performing the reaction in the absence of CuCl led to the complete recovery of **1a**.

Using these optimized conditions, the oxidative cyclization scope of the transformation was investigated.

Table 1. Screening Optimal Conditions[a]

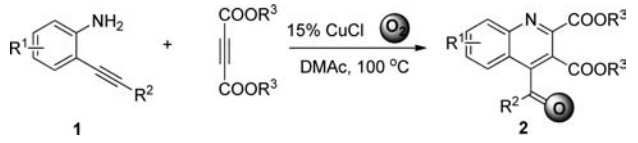


entry	[Cu] (mol %)	oxidant	additive	*t* (°C)	solvent	yield (%)[b]
1	$CuCl_2$ (10)	air	–	80	DMF	40
2	CuCl (10)	air	–	80	DMF	50
3	CuCl (10)	O_2	–	100	DMF	57
4	CuCl (10)	O_2	Phen (20%)	100	DMF	30
5	CuCl (10)	O_2	2,2′-bipyridine (20%)	100	DMF	25
6	CuCl (10)	O_2	Phen (20%), DABCO (2 equiv)	100	DMF	trace
7	CuCl (10)	O_2	DABCO (2 equiv)	100	DMF	trace
8	CuCl (15)	O_2	–	100	DMF	61
9	CuCl (5)	O_2	–	100	DMF	50
10[c]	CuCl (15)	O_2	–	100	DMF	75
11[d]	CuCl (15)	O_2	–	100	DMF	53
12	*CuCl (15)*	*O_2*	–	*100*	*DMAc*	*83*
13	CuCl (15)	air	–	100	DMAc	46

[a] Reaction conditions: **1a** (0.2 mmol), dimethyl but-2-ynedioate (1.5 equiv), [Cu], oxidant (1 atm), additive, and solvent (2 mL) for 8 h. [b] Yield of isolated product. [c] 2 equiv of dimethyl but-2-ynedioate was used. [d] 1.2 equiv of dimethyl but-2-ynedioate was used.

As shown in Table 2, a great variety of aminoalkynes were converted to the corresponding 4-carbonyl-quinolines. Several useful functional groups were tolerated, including chloride, nitro, acetyl, and ether substituents. The presence of electron-withdrawing or -donating groups in $\mathbf{R^2}$ was well tolerated. An electron-donating substituent in $\mathbf{R^2}$ favored product formation (Table 2, entries 2−5), whereas an electron-withdrawing group slightly hindered the reaction (entries 6−9). When a sterically demanding *ortho* substituent was used in $\mathbf{R^2}$, a lower yield was obtained (entry 10). When there were substituents *para* to the nitrogen atom regardless if they were electron-donating or -withdrawing, the oxidative cyclization products were achieved (entries 11 and 13). However, the presence of the substituent at the *ortho* position of the aniline fragment

Table 2. CuCl-Catalyzed Synthesis of 4-Carbonyl-quinolines[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	H	Ph	Me	**2a**	83
2	H	4-Me-C_6H_4-	Me	**2b**	74
3	H	4-MeO-C_6H_4-	Me	**2c**	73
4	H	4-PhCH_2O-C_6H_4-	Me	**2d**	68
5	H	3,4-di-Me-C_6H_3-	Me	**2e**	80
6	H	4-Cl-C_6H_4-	Me	**2f**	60
7	H	3-Cl-C_6H_4-	Me	**2g**	57
8	H	4-MeCO-C_6H_4-	Me	**2h**	45
9	H	4-NO_2-C_6H_4-	Me	**2i**	42
10	H	2-MeO-C_6H_4-	Me	**2j**	40
11	4-Me	Ph	Me	**2k**	75
12	4,6-di-Me	Ph	Me	**2l**	40
13	4-Cl	Ph	Me	**2m**	52
14	H	Ph	Et	**2n**	65
15	H	4-HO-C_6H_4-	Me	**2o**	60
16	H	*n*-propyl	Me	**2p**	32

[a] Reaction conditions: **1** (0.2 mmol), but-2-ynedioate (0.4 mmol), CuCl (15%), O_2 (1 atm), and DMAc (2.0 mL) at 100 °C for 10 h. [b] Yield of isolated product.

hampered the reaction (entry 12). Importantly, the aryl group $\mathbf{R^2}$ with an unprotected hydroxyl group was also compatible, and the desired product was isolated in 60% yield (entry 15). To our delight, when $\mathbf{R^2}$ was an alkyl substituent, the desired oxidative cyclization product was obtained in acceptable yield. To confirm further the structural assignment of products in the present oxidative cyclization, the structure of the product **2b** was unambiguously assigned by X-ray crystallography (see the SI).

In view of these results, we turned our attention to investigate the intramolecular oxidative cyclization. As described in Table 3, a variety of 4-carbonyl-quinolines were produced in the presence of catalytic amounts of $CuCl_2$ (10 mol %), 1,10-phenanthroline (phen; 20 mol %), and DABCO (2 equiv) at 100 °C under 1 atm of O_2 (see Table S2 in the SI). Table 3 reveals that the electronic property of alkyne substitutions did not show obvious influences on the reaction efficiency. However, when strong electron-withdrawing groups such as acetyl, nitro, and cyano were embedded in the arylic $\mathbf{R^3}$, lower yields were observed (entries 8, 9, and 11). Notably, several functional groups such as methoxy, chloro, and bromo were compatible with this reaction. In addition, heterocycle-derived substrates also appeared to be excellent in the reaction, and the product **4l** was isolated in 93% yield (entry 12). Enaminones could also participate in this reaction, giving moderate to good yields (entries 15 and 16). Surprisingly, unlike in the intermolecular oxidative cyclization, the substrate with an alkyl group in $\mathbf{R^3}$ cannot participate in the reaction (entry 17).

Some control experiments were carried out to elucidate the mechanism (see the SI). The reaction of substrate **3a** with $H_2{}^{18}O$ under the optimal reaction conditions afforded the 4-carbonyl-quinoline product without any ^{18}O atoms, as determined by MS. When the reaction was conducted under a $^{18}O_2$ atmosphere, the 4-carbonyl-quinoline product [^{18}O]-**4m** containing an ^{18}O atom in ketone was afforded. These results indicated that the oxygen atom in ketone was originated from molecular oxygen (O_2). When the reaction was carried out under an Ar atmosphere, only a trace amount of product was detected. The use of a stoichiometric amount of copper catalyst did not give any product under an Ar atmosphere. These results indicated that the molecular oxygen was essential to the reaction.

Based on the above results, EPR studies,[9] and ESI/MS analysis (see the SI), a plausible mechanism for the copper-catalyzed aerobic oxidative cyclization[4a] is illustrated in Scheme 2. First, Cu(III)[10] and a superoxide radical ($O_2{}^{\bullet-}$) are formed through the reaction of $CuCl_2$ and O_2 in the presence of an organic base (DABCO) and Phen, which could be detected by EPR (see the SI).[1c,d,f] Then, Cu(III) can combine with **3a** to form Cu(III) complex **A**. Successive carbocupration to the alkyne moiety gives vinyl copper peroxy intermediate **B** (ESI/MS analysis, SI). Then, intermediate **B** underwent deprotonative O−O bond cleavage to give 4-carbonyl-quinoline along with the generation of Cu(II).

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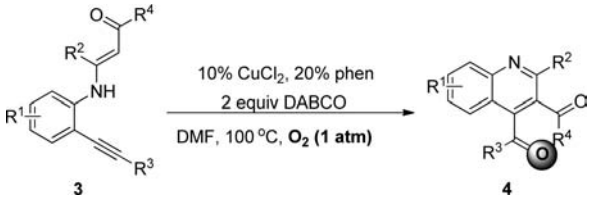
Table 3. $CuCl_2$-Catalyzed Synthesis of 4-Carbonyl-quinolines[a]



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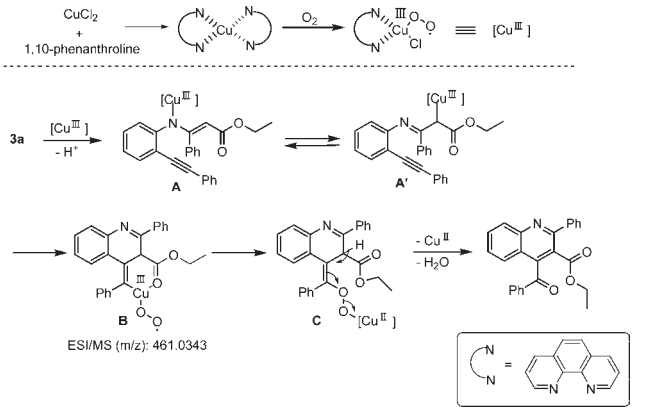
entry	R^1	R^2	R^3	R^4	product	yield (%)[b]
1	H	Ph	Ph	EtO	**4a**[c]	89
2	H	Ph	4-Me-C_6H_4-	EtO	**4b**	88
3	H	Ph	4-MeO-C_6H_4-	EtO	**4c**	88
4	H	Ph	3,4-di-Me-C_6H_3-	EtO	**4d**	89
5	H	Ph	3-Me-C_6H_4-	EtO	**4e**	93
6	H	Ph	4-Cl-C_6H_4-	EtO	**4f**	94
7	H	Ph	4-Br-C_6H_4-	EtO	**4g**	90
8	H	Ph	4-MeCO-C_6H_4-	EtO	**4h**	56
9	H	Ph	4-NO_2-C_6H_4-	EtO	**4i**	63
10	H	Ph	2-Cl-C_6H_4-	EtO	**4j**	82
11	H	Ph	2-CN-C_6H_4-	EtO	**4k**	50
12	H	Ph	thienyl	EtO	**4l**	93
13	4-Me	Ph	Ph	EtO	**4m**	95
14	4-Cl	Ph	Ph	EtO	**4n**	93
15	H	Ph	Ph	Ph	**4o**	79
16	H	Me	Ph	Ph	**4p**	53
17	H	Ph	*n*-propyl	EtO	–	–[d]

[a] Reaction conditions: **3** (0.2 mmol), $CuCl_2$ (10%), Phen (20%), DABCO (2.0 equiv), O_2 (1 atm), and DMF (2.0 mL) at 100 °C for 5 h. [b] Yield of isolated product. [c] The structure was determined by X-ray crystallographic analysis. [d] Decomposed.

In conclusion, we demonstrated a novel copper-catalyzed aerobic oxidative cyclization of enynes and in situ formed enynes leading to 4-carbonyl-quinolines.

Scheme 2. Proposed Mechanism for the Direct Transformation



The proposed method proceeded using inexpensive copper as the catalyst and molecular oxygen as the oxygen source, making this transformation sustainable and practical. The mechanism was also discussed according to the labeling experiments, EPR studies, and ESI/MS analysis. Studies on the applications of this copper-catalyzed oxidative cyclization in organic syntheses are currently underway in our laboratory.

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Supporting Information Available. Representative experimental procedures, X-ray crystallographic data of **2b** and **4a**, and ^1H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.