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Synthesis of Phenanthridine and Quinoxaline Derivatives via Copper-Catalyzed Radical Cyanoalkylation of Cyclobutanone Oxime Esters and Vinyl Azides

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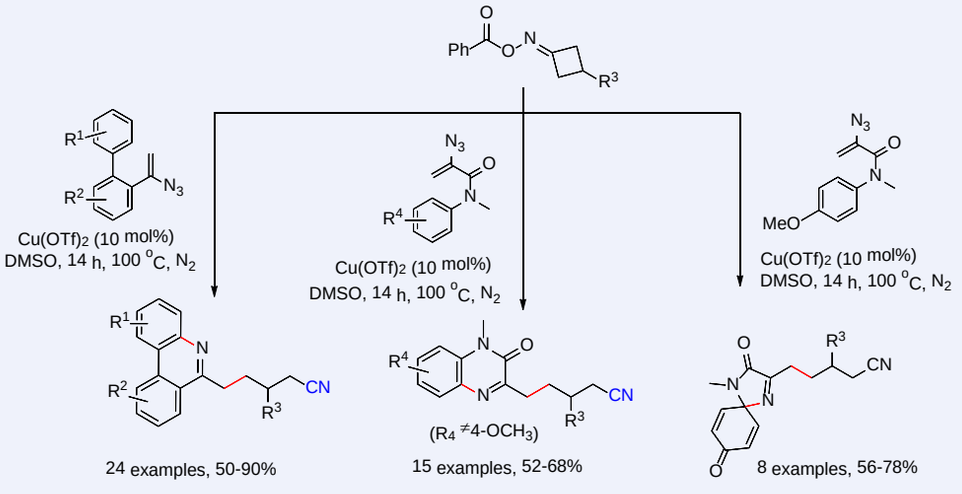
Keywords

Copper | Radical | Cyanoalkylation | Vinyl Azides | phenanthridine

Main observation and conclusion

A copper-catalyzed radical cyclization of cyclobutanone oxime esters and vinyl azide is described. This method provides facile access to the cyanoalkyl-substituted phenanthridines and quinoxalines with excellent isolated yields. Moreover, these reactions proceed under mild conditions with a board substrate scope and excellent functional group tolerance.

Comprehensive Graphic Content



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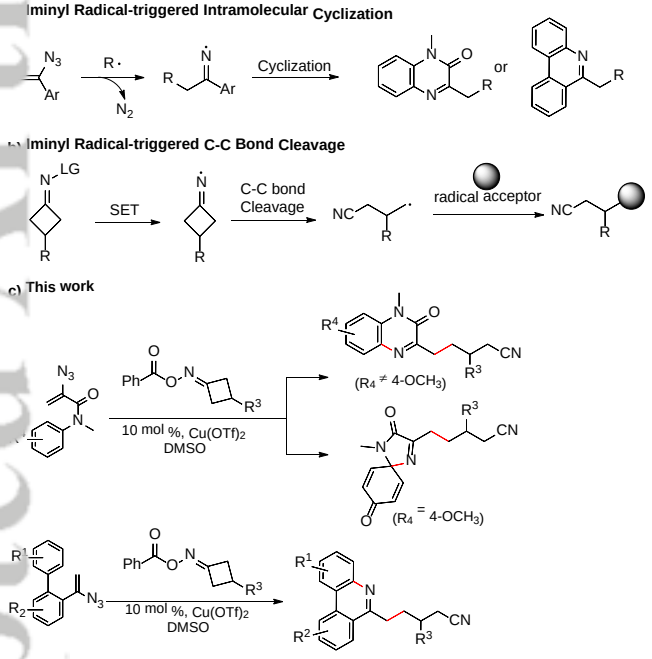
Background and Originality Content

Nitrogen-containing heterocycles, especially phenanthridine and quinoxaline derivatives, had been applied extensively in pharmaceuticals, materials, and organic synthesis.[1-6] Therefore, the exploration of efficient and selective preparation methods for phenanthridine and quinoxaline derivatives is of great significance.[7] Dating from 1896, Pictet and Hubert have already found that N-([1,1'-biphenyl]-2-yl)acetamide can transform into 6-substituted phenanthridine with high temperature and low yield.[8] Since then, many researchers have begun to explore the efficient and selective preparation of phenanthridine[9-14] and quinoxaline[15-19] derivatives. Recently, vinyl azides have become a class of versatile synthon for organic synthesis.[20-25] And cyclization of vinyl azides utilizing radical addition reaction provides a new method to prepare the phenanthridine and quinoxaline derivatives (**Scheme 1a**).[26-33]

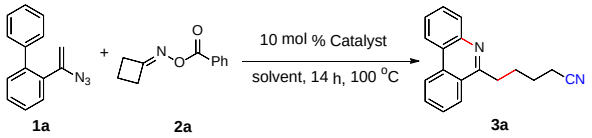


Scheme 1. Literature background.

Cyanoalkyl moieties are of wide appearance in modern pharmaceuticals and bioactive compounds.[34-38] Cyano groups could also be converted to many other common functional groups conveniently.[39-41] Therefore, a wide variety of methods have been developed for cyanoalkylation.[42,43] Traditionally, cyanoalkyl is usually prepared using inorganic cyanides and alkyl halides. Inorganic cyanides are highly toxic, and the preparation of alkyl halides may also need extra steps. Recently, the C-C bond cleavage of cyclic iminyl radicals has been successfully applied to synthesizing alkyl nitriles (**Scheme 1b**).[44-53]And cyclobutanone oxime esters have become important raw materials for organic synthesis. [54-59] Especially, cyanoalkyl can be introduced to the nitrogen-containing heterocycles by using cyclo ketone oxime esters.[60,61] For example, the group of Guo has reported a metal-catalyzed radical cyclization of cyclobutanone oxime esters and vinyl azides to synthesize cyanoalkyl-substituted phenanthridines.[62,63] Besides, the group of Li[64] and our group[65] have described visible-light-driven cyanoalkylation of quinoxalinones. Herein, we are glad to report radical cyclization of cyclobutanone oxime esters and vinyl azides to synthesize cyanoalkyl-substituted phenanthridine and quinoxaline derivatives by using inexpensive Cu(II) as the catalysts (**Scheme 1c**).

Results and Discussion

Table 1. Optimization for synthesis 6-substituted phenanthridines[a]



1a **2a** **3a**

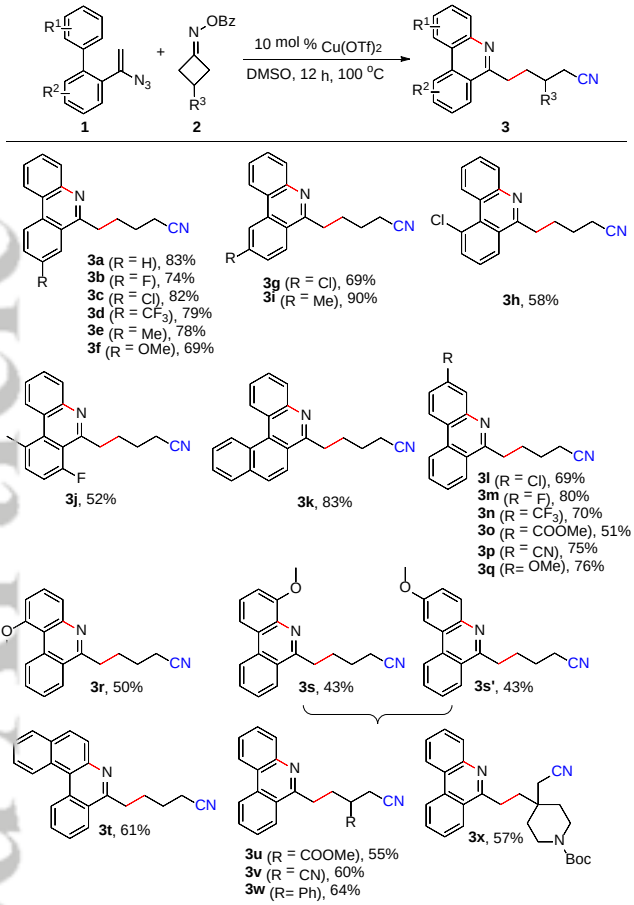
Entry	Solvent	**2a**	Catalyst	Yield
1	1,4-dioxane	1.2	$Cu(OTf)_2$	65
2	Toluene	1.2	$Cu(OTf)_2$	51
3	Diethyl Ether	1.2	Cu(OTf)2	42
4	THF	1.2	$Cu(OTf)_2$	48
5	DMF	1.2	$Cu(OTf)_2$	39
6	CH_3CN	1.2	$Cu(OTf)_2$	46
7	DMSO	1.2	$Cu(OTf)_2$	72
8	DMSO	1.2	$CuBr_2$	54
9	DMSO	1.2	CuI_2	49
10	DMSO	1.2	$Cu(OAc)_2$	62
11	DMSO	1.2	$Cu(CF_3SO_3)_2$	67
12	**DMSO**	**2.0**	**$Cu(OTf)_2$**	**87 (83[c])**
13[d]	DMSO	2.0	$Cu(OTf)_2$	54
14[e]	DMSO	2.0	$Cu(OTf)_2$	75
15[f]	DMSO	2.0	$Cu(OTf)_2$	79
16	DMSO	2.0	-	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a**, 10% mmol catalyst, N_2, solvent (2 mL) at 100 °C, 14 h. [b] Yields were determined by ^{1}H-NMR. [c] Isolated yield. [d] Temperature: 60 °C. [e] Temperature: 80 °C. [f] Temperature: 120 °C.

Vinyl azide **1a** and cyclobutanone O-benzoyl oxime **2a** were chosen as model substrates to optimize the reaction conditions (Table 1). Initially, $Cu(OTf)_2$ was evaluated as the catalyst. As expected, **1a** can be successfully transformed to **3a** with 65% yield at 100 °C using 1,4-dioxane as the solvent (Table 1, entry 1). Different solvents were examined (Table 1, entries 2-7), and DMSO was the optimal solvent (72% yield). A variety of Cu^{II} catalysts was investigated as well (Table 1, entries 8-11). However, they were less effective. The use of a larger amount of cyclobutanone O-benzoyl oxime (**2a**) led to a higher chemical yield (83%) (Table 1, entry 12). Modification of temperature (60 °C, 80 °C, 120 °C) could not improve the reaction (Table 1, entries 13-15). Finally, a control experiment revealed that only a trace amount of **3a** was formed in the absence of Cu^{II} catalyst.

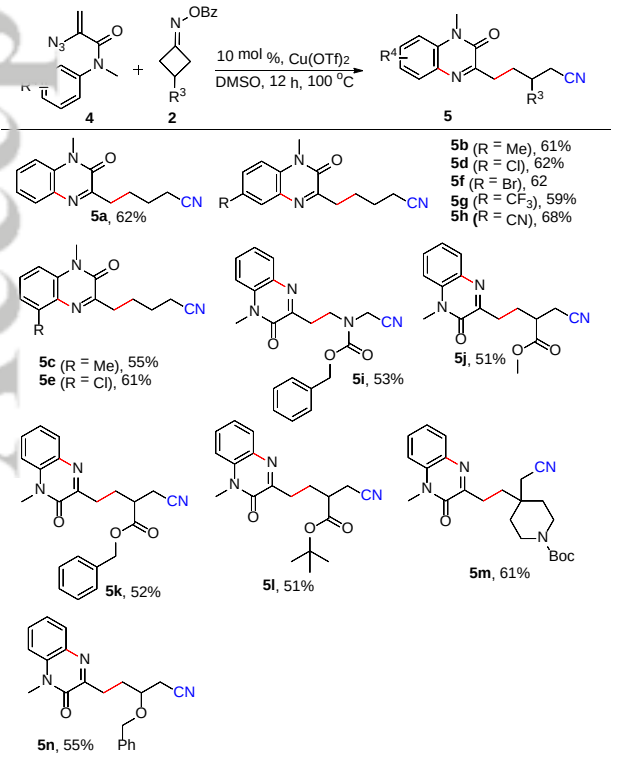
With the optimized reaction conditions in hand (Table 1, entry 12), we then explored the scope and functional group tolerance of the phenanthridine synthesis (Table 2). First, we evaluated the effects of R^2 functional group. The substitution pattern (*meta*, *para*) and electronic properties of aromatic substituents (electron deficient or rich) of R^2 played a small role; good yields were obtained regardless (Table 2, **3b-3d**, **3e-3f**). The halogen (Table 2, **3g, 3h, 3j**), alkyl (Table 2, **3i, 3j**), even naphthalene (Table 2, **3k**) groups were well-tolerated. Then, the effect of R^1 functional groups was also investigated: a very wide range of substituents were all suitable for this transformation (Table 2, **3m-3r, 3t**), furnishing the corresponding products in good yields. Also, 3-substituted substrates were also converted into the desired products (Table 2, **3u–3x**) in 55–64% yields.

Table 2. Synthesis of phenanthridine derivatives.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OTf)_2$ (10 mol%), N_2, solvent (2 mL) at 100 °C, 14 h. All yields are isolated yields.

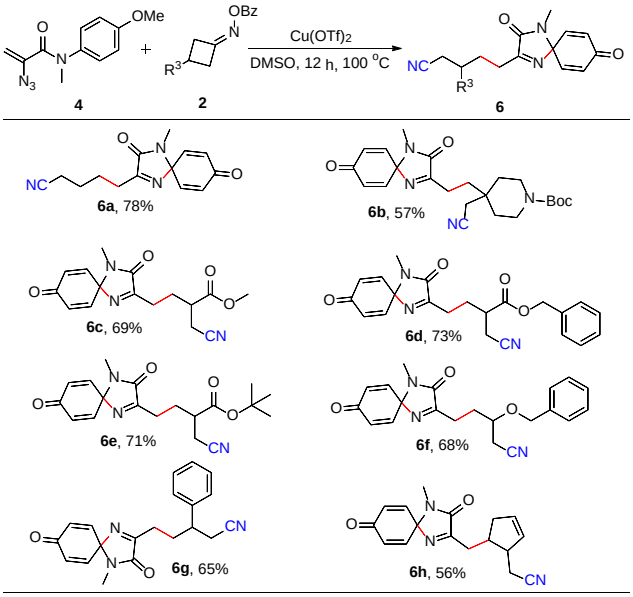
Table 3. Synthesis of quinoxalinone derivatives.[a]



[a] Reaction conditions: **4** (0.2 mmol), **2** (0.24 mmol), $Cu(OTf)_2$ (10 mol%), N_2, solvent (2 mL) at 100 °C, 14 h. All yields are isolated yields.

After completion of phenanthridine synthesis, we turned our attention to the quinoxalinone synthesis (Table 3). When we exposed 2-azido-N-methyl-N-phenylacrylamide **4a** as our radical acceptor to our standard conditions, the quinoxaline product **5a** was isolated in a slightly lower yield (62%), possibly due to the fact that 2-azido-N-methyl-N-phenylacrylamide **4a** is an electron-poorer alkene than 2-(1-azidovinyl)-1,1'-biphenyl **1a**. Subsequently, the substrate scope was explored by using various quinoxalinones and different 3-substituted cyclobutanone oxime esters. Methyl, chloro, bromo, trifluoromethyl, and cyano groups on the benzene ring were well-tolerated under the standard conditions, and the corresponding products were isolated in good yields (Table 3, **5b**–**5h**). We found that cyclobutanone oxime esters bearing the bulky groups (Table 3, **5i**-**5o**), even the 3-N-substituted cyclobutanone oxime ester (Table 3, **5i**), and the cyclobutanone oxime ester substituted with ester group, all were suitable substrates.

Table 4. Synthesis of spiro-cyclic compound **6**[a]

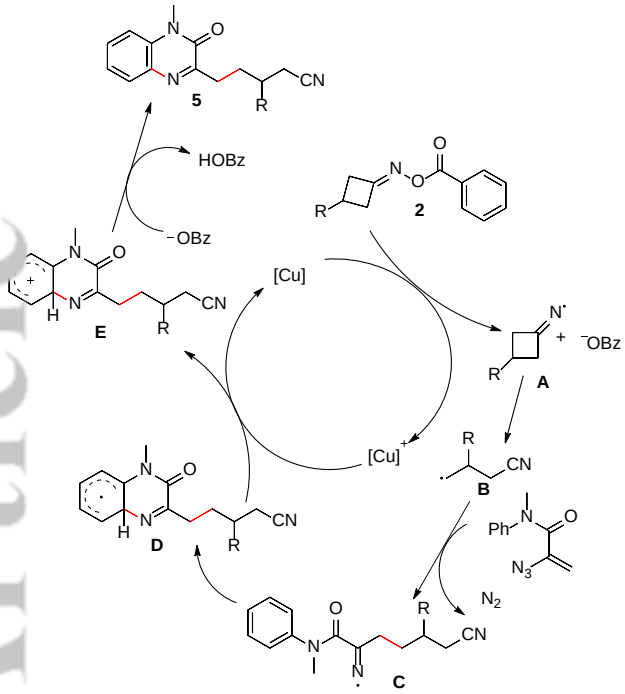


[a] Reaction conditions: **4** (0.2 mmol), **2** (0.24 mmol), $Cu(OTf)_2$ (10 mol%), N_2, solvent (2 mL) at 100 °C, 14 h. All yields are isolated yields.

We found that spiro-cyclic compound **6** was isolated synthesized with the starting material 2-azido-N-(4-methoxyphenyl)-N-methylacrylamide (Table 4). 3-Ester-, 3-oxybenzyl-, and 3-phenyl substituted cyclobutanone oxime esters were suitable substrates, affording the corresponding products good yields (65−73%)(Table 4, **6d**–**6g**). The 3,3-disubstituted substrates were also converted into the desired products **6c** in 57% yields. Surprisingly, the 2,3-disubstituted substrates were well-tolerated in this transformation (Table 4, **6h**).

Based on the previous reports, a possible mechanism is proposed (Scheme 2). Initially, iminyl radical **A** is generated from the decomposition of cyclobutanone oxime ester catalyzed by copper catalysts and rearranges to cyanoalkyl radical **B** by C–C bond cleavage. The addition of radical **B** to the double bond in starting material **1** to give iminyl radical **C** with the generation of N_2 gas. Cyclization of iminyl radical **C** to generate radical **D,** which is re-oxidized by the copper to give cation **E**. After deprotonation, cation **E** is converted to final product **5**.

Scheme 2. Plausible reaction mechanism.



Conclusions

In summary, we have developed an efficient method of radical cyclization of cyclobutanone oxime esters and vinyl azides using an accessible and inexpensive Cu(II) catalyst. Using this uncomplicated method, we were able to synthesize cyanoalkyl-substituted phenanthridine and quinoxaline derivatives from readily available and safe starting materials under mild conditions.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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