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Copper(II)-Catalyzed Cleavage of Carbon-Carbon Triple Bond to Synthesize 1,2,3-Triesterindolizines

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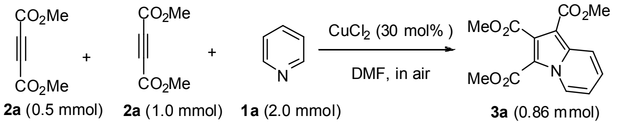
An efficient Cu(II)-catalyzed carbon-carbon triple bond cleavage protocol for the synthesis of 1,2,3-triesterindolizines via the reaction of pyridines with butynedioates has been developed. This reaction has perfect atom economy and both fragments from the cleaved alkyne are successively incorporated into the products.

Cleavage of carbon-carbon bond is a useful transformation in organic synthesis.[1] In sharp contrast to carbon-carbon single and double bonds cleavage reactions,[2-3] the cleavage of carbon-carbon triple bond is particularly difficult owing to its high bond dissociation energy.[4] Apart from alkyne metathesis,[5] early works on carbon−carbon triple bond cleavage mainly relied on stoichiometric organometallic reactions.[6] Later on, some metal-catalyzed cleavage of C−C triple bonds was reported,[7] however, the limited examples usually used expensive and toxic metals such as rhodium,[7a] ruthenium,[7b,7c] gold,[7d] or palladium.[7e-7g] Therefore, there have great demands for carbon-carbon triple bond cleavage using eco-friendly and cheap metal as the catalyst.

On the other hand, as an important class of *N*-heterocycles, indolizines have found various pharmaceutical applications as anti-HIV,[8] anti-inflammatory,[9] H3 receptor antagonist,[10] and MPtpA/ MPtpB phosphatases inhibitors.[11] Moreover, the indolizines constitute the core structure of many naturally occurring alkaloids.[12] Consequently, synthesis of indolizines continues to attract the attention of chemists.[13] Recently, a domino synthesis of 1,2,3-triaryolindolizines from methyl ketones and pyridines in the presence of iodine had been reported.[14] Following our interest in copper-catalyzed reaction[15] and as a complementary to the synthesis of 1,2,3-trisubstituted indolizines, we reported herein copper(II)-catalyzed carbon-carbon triple bond cleavage reaction to synthesize 1,2,3-triesterindolizines.

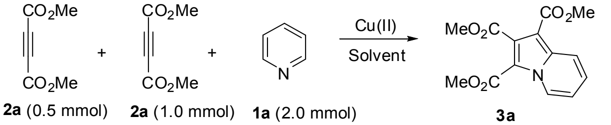
Recently, we have reported the first example of copper(II)-catalyzed carbon-carbon triple bond cleavage via the reaction of naphthoquinone, butynedioates, and pyridines.[15a] On the basis of this, we tried to use open chain unsaturated compounds in place of naphthoquinone to undergo this reaction. To our delight, we found that an additional amount of butynedioate itself may serve as an electrophile to take part in the reaction with butynedioate and pyridine under copper(II)-catalysis, leading to the efficient carbon-carbon triple bond cleavage (Scheme 1).



Scheme 1 Cleavage of carbon-carbon triple bond

Encouraged by this result, we optimized the reaction conditions using dimethyl butynedioate **2a** and pyridine **1a** as the model compounds. Solvents were first screened and acetonitrile was confirmed to be most promising (entry 1–5, Table 1). Regarding the copper(II) salts, copper(II) chloride led to higher yield than other copper(II) salts (entry 5–9, Table 1). Subsequently, we screened the amount of copper(II) chloride in this reaction. Without copper(II) salt but in the air, only small amount of target product **3a** was formed **(**entry 10, Table 1**)**.[16] When the reaction was carried out in oxygen atmosphere, the amount of copper(II) chloride can be decreased to 0.1 mmol (entry 11, Table 1). Finally, we optimized the reaction temperature under 1 atm O_2, and found refluxing was the best choice (entry 12, Table 1). Therefore, the optimized reaction condition was refluxing the reaction mixture in acetonitrile for 12 h under 1 atm O_2 using 10 mol% copper(II) chloride as catalyst.

Table 1 Optimization of the Reaction Condition[a]



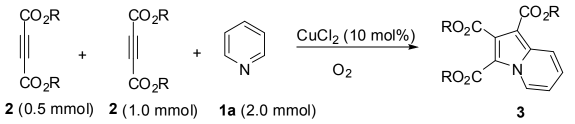
entry	Solvent	Copper (mmol)	Temp (^{o}C)	Yield (%)[b]
1	DMF	$CuCl_2$ (0.3)	80	86
2	C_2H_5OH	$CuCl_2$ (0.3)	reflux	22
3	C_6H_6	$CuCl_2$ (0.3)	reflux	75
4	Toluene	$CuCl_2$ (0.3)	80	78
5	CH_3CN	$CuCl_2$ (0.3)	reflux	89

6	CH_3CN	$CuBr_2$ (0.3)	reflux	83
7	CH_3CN	$Cu(OAc)_2$ (0.3)	reflux	87
8	CH_3CN	$CuSO_4$ (0.3)	reflux	80
9	CH_3CN	$Cu(OTf)_2$ (0.3)	reflux	82
10	CH_3CN	None	reflux	15
11	**CH_3CN**	**$CuCl_2$ (0.1)**[c]	**reflux**	**89**
12	CH_3CN	$CuCl_2$ (0.1)[c]	60	52

[a] Reaction condition: the mixture of pyridine **1a** (2.0 mmol), dimethyl butyndioate **2a** (1.5 mmol) and copper(II) salt was heated in the solvent for 12 h in the air. [b] Isolated yield. [c] Heated in oxygen atmosphere.

With the optimized reaction conditions in hand, the substrate scope for this transformation was investigated. Firstly, we used butyndioates **2a**–**2f** to react with pyridine **1a** under the optimal reaction condition, and found various butynedioates possessing different ester groups underwent this reaction smoothly, leading to corresponding indolizines **3a**–**3f** in good to excellent yields.

Table 2 Reactions of **1a** with **2**[a]

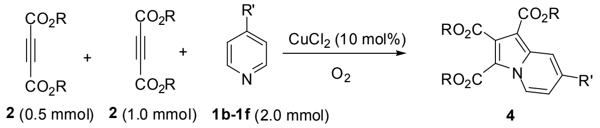


entry	2 R	3	Yield (%)[b]
1	**2a** R = Me	**3a**	89
2	**2b** R = Et	**3b**	86
3	**2c** R = *n*-Pr	**3c**	85
4	**2d** R = *i*-Pr	**3d**	85
5	**2e** R = *n*-Bu	**3e**	83
6	**2f** R = *t*-Bu	**3f**	82

[a] The mixture of pyridine **1a** (2.0 mmol), butynedioates **2a**–**2f** (1.5 mmol) and copper(II) chloride (0.1 mmol) was refluxed in acetonitrile for 12 h in oxygen atmosphere. [b] Isolated yield.

The generality of this reaction was further examined by employing *p*-substituted pyridines as the substrates. As we expected, pyridines including either electron-withdrawing groups (CO_2Me, CO_2Et, CN) or electron-donating group (phenyl, *tert*-butyl) could be converted to the desired products **4a**–**4o** well, in 72% to 93% yield. All products are fully characterized by analytical and spectral data and the structure of **4d** was unambiguously established by X-ray crystallography (see supporting information).

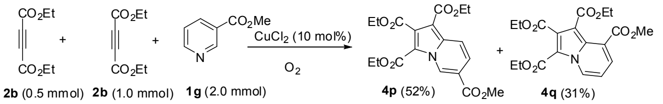
Table 3 Reactions of **1b-1f** with **2**[a]



entry	1 R'	2 R	4	Yield (%)[b]
1	**1b** R' = CO_2Me	**2a** R = Me	**4a**	91
2	**1b** R' = CO_2Me	**2b** R = Et	**4b**	88
3	**1b** R' = CO_2Me	**2c** R = *n*-Pr	**4c**	86
4	**1c** R' = CO_2Et	**2a** R = Me	**4d**	92
5	**1c** R' = CO_2Et	**2b** R = Et	**4e**	90
6	**1c** R' = CO_2Et	**2c** R = *n*-Pr	**4f**	87
7	**1c** R' = CO_2Et	**2d** R = *i*-Pr	**4g**	88
8	**1d** R' = CN	**2a** R = Me	**4h**	76
9	**1d** R' = CN	**2b** R = Et	**4i**	72
10	**1e** R' = Ph	**2a** R = Me	**4j**	93
11	**1e** R' = Ph	**2b** R = Et	**4k**	90
12	**1f** R' = *t*-Bu	**2a** R = Me	**4l**	88
13	**1f** R' = *t*-Bu	**2b** R = Et	**4m**	86
14	**1f** R' = *t*-Bu	**2c** R = *n*-Pr	**4n**	85
15	**1f** R' = *t*-Bu	**2d** R = *i*-Pr	**4o**	85

[a] Refluxing the mixture of pyridine **1b**–**1f** (2.0 mmol), butynedioates **2** (1.5 mmol), and copper(II) chloride (0.1 mmol) in acetonitrile for 12 h in oxygen atmosphere. [b] Isolated yield.

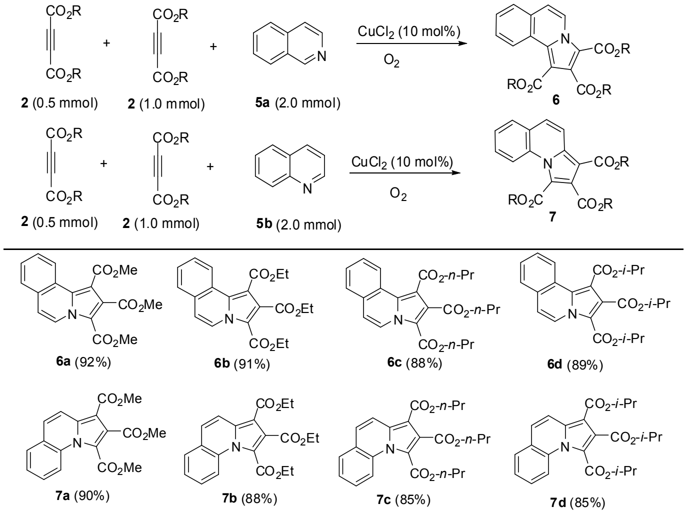
The regioselectivity in the reaction of 3-substituted pyridines **1g** with butynedioates **2** was then studied (Scheme 2). After refluxing methyl nicotinate **1g** (2.0 mmol) with diethyl butynedioate **2b** (1.5 mmol) and copper(II) chloride (0.1 mmol) in CH_3CN for 12 h under 1 atm O_2, two regioisomers **4p** and **4q** were generated simultaneously.



Scheme 2 Reaction of 3-Susbstituted Pyridine

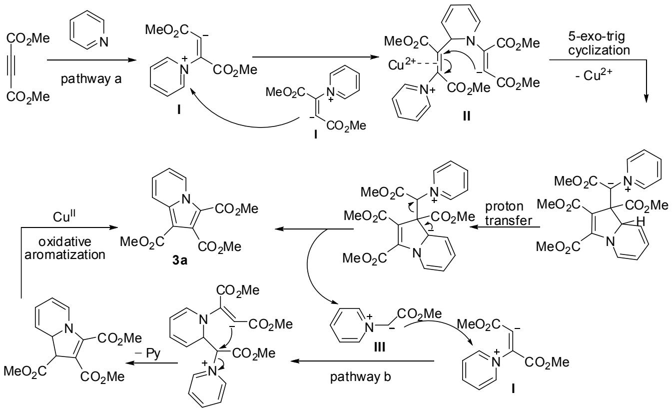
In order to expand the substrate scope further, we used isoquinoline **5a** or quinoline **5b** to carry out this reaction for the synthesis of annulated indolizines. It is found that isoquinoline **5a** could react with butynedioates **2a**–**2d** under the optimal condition to generate the desire products **6a**–**6d** in 88% to 92% yields. Noteworthy, quinoline **5b** could also react with butynedioates **2a**–**2d** to give **7a**–**7d** with excellent yields, which indicated the steric hindrance caused by the C(8)–H bond in quinoline has very little effect in this reaction.

Table 4 The reaction condition of **5** with **2**[a]



[a] Refluxing the mixture of isoquinoline **5a** or quinoline **5b** (2.0 mmol), butynedioates **2** (1.5 mmol), and copper(II) chloride (0.1 mmol) in acetonitrile for 12 h in oxygen atmosphere.

On the basis of the above experimental results, a possible reaction mechanism was proposed. Initially, the reaction of pyridine with dimethyl butyndioate **2a** generated intermediate **I**,[17] which dimerized to form intermediate **II**. Intramolecular 5-exo-trig cyclization of **II** followed by proton transfer and loss of pyridinium ylide **III** led to product **3a** (pathway a, Scheme 3). The eliminated pyridinium ylide **III** could then take part in reaction with the intermediate **I**, via nucleophilic addition, subsequent intramolecular cyclization and oxidative aromatization, also leading to **3a** (path b, Scheme 3). According to the proposed mechanism, it is seen that both fragments of cleaved butynedioate eventually go into the products via pathway a and b, resulting in a perfect atom economy.



Scheme 3 Proposed Mechanism

Conclusions

In summary, an effective copper(II)-catalyzed cleavage of carbon-carbon triple bond for the synthesis of 1,2,3-triesterindolizines has been developed. This reaction has perfect atom economy and both fragments from the cleaved alkyne are successively incorporated into the products.

Experimental

General Procedure: Pyridine **1a** (2.0 mmol), butynedioates **2** (1.5 mmol), and hydrated copper(II) chloride (0.1 mmol) were mixed in 15 mL acetonitrile and refluxed for 12 h under 1 atm of oxygen. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. Chromatographic separation of the reaction mixture (ethyl acetate/petroleum ether, 1:6) after removal of the solvent gave product **3**.

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Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds. See DOI: 10.1039/c000000x/

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