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Copper catalysis: One-pot simultaneous synthesis of quinolines and *gem*-diamine derivatives

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ABSTRACT

A copper(II)-catalyzed oxidative reaction for the one-pot simultaneous synthesis of quinolines and *gem*-diamine derivatives from *N*-arylglycine ethyl esters and enamides is described. In this reaction, the two fragments in an enamide substrate react with the same intermediate generated *in situ* from an *N*-arylglycine ethyl ester, respectively, producing two products simultaneously. This reaction has the advantages of high efficiency, simple operation and high atom economy.

Introduction

The quinoline framework is present in a quantity of biologically active natural products and synthetic drugs [1]. For example, cinchona alkaloid quinine and synthetic quinoline derivatives chloroquine and mefloquine are well-known antimalarials [2]. In addition, many compounds containing a quinoline backbone exhibit a variety of activities, including antibacterial, anticancer, anti-HIV, anti-inflammatory, and anti-tuberculosis [1]. Quinoline-2-carboxylate derivatives not only are potential as anti-Alzheimer's agents [3], but also can be used as important synthetic intermediates [4].

Enamides are an important class of synthons in organic chemistry and have been used to synthesize a variety of compounds, such as quinolines [5,6], β-keto-sulfones [7], 1,2,4-trisubstituted imidazoles [8], α-carbonyl selenocyanates [9], α-acetoxy ketones [10], and β-aryl 3-(3-indolyl)propanones [11]. However, in these reactions, the amide fragments cleaved from the enamides are not utilized, but only as by-products. If these amide fragments can be used, they would be a good source of amides. Therefore, we envision a reaction in which a substrate reacts with an enamide to produce a product, and then the substrate can also react with the amide fragment cleaved from the enamide during the first reaction to produce a second product. Thus, two valuable products can be obtained simultaneously in the same reaction system without discarding any fragments, which would be an ideal atomic economic reaction. Fortunately, we successfully achieved this idea through the reaction of *N*-arylglycine ethyl esters with enamides, obtaining quinolines and *gem*-diamine derivatives simultaneously. *gem*-Diamine derivatives are important scaffolds present in a number of biologically active molecules [12], such as certain HIV-1 Pr inhibitor [13], antimicrobial agent and *E. Coli* inhibitor [12b,14].

In this reaction, an *N*-arylglycine ethyl ester **1** is oxidized to a key intermediate iminium, which undergoes a Povarov reaction (aza-[4 + 2] cycloaddition) with the double bond moiety of an enamide **2**, and the resulting adduct is subjected to amide removal and oxidative aromatization to form a quinoline **3**. The amide then nucleophilically attacks another iminium intermediate to produce a *gem*-diamine derivative **4** (Scheme 1). To the best of our knowledge, this is the first example in which two fragments of an enamide react with the iminium generated *in situ* from an *N*-arylglycine ethyl ester, respectively, to produce quinoline and *gem*-diamine derivative simultaneously.

Results and discussion

To initiate our study, ethyl *p*-tolylglycinate **1a** and *N*-(1-phenylvinyl) acetamide **2a** were selected as model substrates. In order to oxidize **1a** to a key intermediate iminium under environmentally friendly conditions, we decided to use O_2 as a clean final oxidant. Therefore, a catalyst with variable oxidation states is required. From the perspective of green chemistry and practicality, copper is a good choice. Copper has very rich chemical properties because it can easily obtain the oxidation states of Cu^0, Cu^I, Cu^{II} and Cu^{III}, and it can undergo both one-electron and two-electron processes [15]. Moreover, compared with other transition metal catalysts, copper catalysts are cheaper, less toxic, easy to obtain, widely tolerant, insensitive to air and easy to handle [16]. Therefore, some copper salts were first screened as catalysts for this reaction (Table 1, entries 1–5). It was found that when 20 mol% of Cu $(OTf)_2$ was used, the reaction (in CH_3CN in air atmosphere at 30 °C for 24 h) produced quinoline **3aa** and *gem*-diamine derivative

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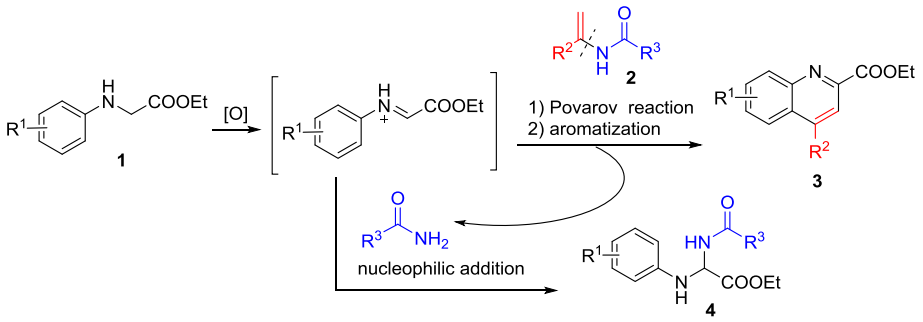
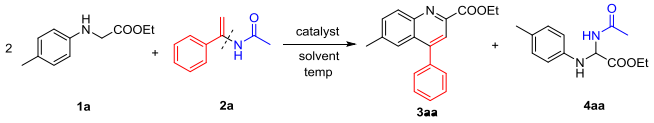


Scheme 1. Simultaneous synthesis of quinolines and *gem*-diamine derivatives.

4aa in isolated yields of 52% and 82%, respectively (Table 1, entry 1). In order to improve the yield of both products, other metal catalysts were screened (Table 1, entries 6–8), but no better results were obtained than using $Cu(OTf)_2$. Next, the effect of temperature on the reaction was investigated (Table 1, entries 1 and 9–12). It was found that as the temperature increased from 30 °C to 40 °C, the yield of both products increased. However, the continued increase in temperature resulted in a significant rapid decrease in yields. Various solvents were then evaluated, such as toluene, DMSO, 1,2-dichloroethane and chlorobenzene, but no better results were found than with acetonitrile (Table 1, entries 13–16). When the reaction was performed in oxygen, the yield of the products was increased compared to that in air (Table 1, entry 17). When the reaction was carried out under argon, the yield of both products was significantly reduced (Table 1, entry 18), indicating that oxygen is critical for the reaction. No desired product was observed in the absence of $Cu(OTf)_2$, revealing that $Cu(OTf)_2$ is essential for the reaction (Table 1, entry 19). In addition, the loading of $Cu(OTf)_2$ [For details, see the Supporting Information (SI), Table S1] and the molar ratio of the substrates (SI, Table S2) were optimized. Based on the above optimization, the optimal conditions for the reaction were determined as: **1a** (0.8 mmol, 4 equivalents), **2a** (0.2 mmol, 1 equivalent) and $Cu(OTf)_2$ (20 mol%) in CH_3CN (2.0 mL) under O_2 atmosphere (O_2 balloon) at 40 °C.

With the optimized conditions in hand (Table 1, entry 17), substrate scope of the reaction was studied (Table 2). Firstly, the scope of *N*-arylglycine ethyl esters **1** was investigated. various *N*-arylglycine ethyl esters bearing methyl, ethyl, isopropyl or *tert*-butyl at the *para*-position of the benzene rings worked smoothly to give the corresponding products **3** and **4** in satisfactory yields (Table 2, entries 1–4). Next, a variety of enamides **2** were investigated. Phenyl enamides with an electron-donating group (methyl or methoxy) (Table 2, entries 5 and 6) or an electron-withdrawing group (phenyl, fluoro, chloro, bromo or iodo) (Table 2, entries 7–12) on the benzene rings underwent smooth reactions with **1a** to

Table 1
Selected optimization experiments.[a]



Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]	
				3aa	**4aa**
1	$Cu(OTf)_2$	CH_3CN	30	52	82
2	$Cu(OAc)_2$	CH_3CN	30	n.d.	n.d.
3	$CuSO_4$	CH_3CN	30	trace	n.d.
4	CuCl	CH_3CN	30	trace	n.d.
5	CuBr	CH_3CN	30	7	trace
6	$Sn(OTf)_2$	CH_3CN	30	n.d.	n.d.
7	$Zn(OTf)_2$	CH_3CN	30	n.d.	n.d.
8	$FeCl_3$	CH_3CN	30	24	4
9	$Cu(OTf)_2$	CH_3CN	35	53	81
10	$Cu(OTf)_2$	CH_3CN	40	56	89
11	$Cu(OTf)_2$	CH_3CN	50	21	48
12	$Cu(OTf)_2$	CH_3CN	60	5	9
13	$Cu(OTf)_2$	toluene	40	27	59
14	$Cu(OTf)_2$	DMSO	40	9	15
15	$Cu(OTf)_2$	1,2-dichloroethane	40	20	70
16	$Cu(OTf)_2$	PhCl	40	41	54
17[c]	$Cu(OTf)_2$	CH_3CN	40	66	89
18[d]	$Cu(OTf)_2$	CH_3CN	40	26	13
19	—	CH_3CN	40	n.d.	n.d.

[a] Unless otherwise noted, reaction conditions: **1a** (0.8 mmol), **2a** (0.2 mmol), catalyst (20 mol%) and solvent (2.0 mL) in air atmosphere for 24 h.
[b] Yield of the isolated product.
[c] In O_2 atmosphere (O_2 balloon).
[d] In argon atmosphere (argon balloon). n.d. = not detected.

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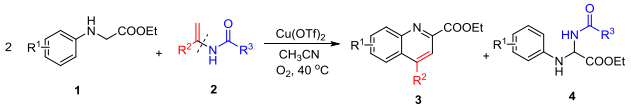
furnish the corresponding products in moderate to excellent yields, suggesting that the electronic nature of enamides **2** has no significant influence on this reaction. 2-Naphthyl enamide and thienyl enamide also performed well in this transformation (Table 2, entries 13 and 14). Aromatic acyl enamides were applicable to this protocol to provide the corresponding products in good yields (Table 2, entries 15 and 16).

In order to get an insight into the reaction mechanism, a series of control experiments were conducted (Scheme 2). When radical scavengers 2,6-*di*-*tert*-*butyl*-4-methylphenol (BHT) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added to the model reaction, respectively, no desired product was obtained (Scheme 2, a). The results revealed that this reaction may proceed via a radical process. Since imino ester **A** could be detected from the model reaction mixture by high-resolution mass spectrometry (HRMS) analysis (SI, page 36), we synthesized imino ester **A** and allowed it to react with **2a** under standard conditions, which smoothly provided the desired products **3aa** and **4aa** (Scheme 2, b). This result indicated that imino ester **A** may be a key intermediate in this reaction. In addition, acetophenone **9** was isolated from the model reaction (in approximately 10% yield), and when exploring the substrate scope, a small amount of the corresponding acetyl aromatic compound was also observed in each reaction. Therefore, we speculated that *N*-(1-phenylvinyl)acetamide **2a** may be tautomerized to *N*-(1-phenylethylidene)acetamide **2a'** with the assistance of Cu $(OTf)_2$ [17], and then a small amount of water in the reaction system may hydrolyze **2a'** to deliver acetamide **8** and acetophenone **9** (Scheme 2, c). Further control experiments showed that under standard conditions, ethyl *p*-tolylglycinate **1a** can react with acetamide **8** to deliver *gem*-diamine derivative **4aa**, suggesting that **8** may be an intermediate in the formation of **4aa** (Scheme 2, d). However, **1a** cannot react with acetophenone **9**, indicating that the formation of **3aa** does not involve **9** (Scheme 2, e). To verify whether there is a hydrolysis process in the reaction, 3 Å molecular sieves were added to the model reaction carried out in dry CH_3CN (dried with 3 Å molecular sieves for 24 h) to inhibit hydrolysis, and

Table 2
Substrate scope.[a,b]



Entry	**3** and **4**	Entry	**3** and **4**
1	**3aa** 66% **4aa** 89%	9	**3af** 73% **4aa** 95%
2	**3ba** 68% **4ba** 80%	10	**3ag** 69% **4aa** 89%
3	**3ca** 84% **4ca** 98%	11	**3ah** 81% **4aa** 85%
4	**3da** 70% **4da** 73%	12	**3ai** 70% **4aa** 94%
5	**3ab** 64% **4aa** 93%	13	**3aj** 48% **4aa** 93%
6	**3ac** 51% **4aa** 84%	14	**3ak** 79% **4aa** 88%
7	**3ad** 69% **4aa** 91%	15	**3aa** 76% **4al** 79%
8	**3ae** 82% **4aa** 96%	16	**3aa** 84% **4am** 87%

[a] Reaction conditions: a mixture of **1** (0.8 mmol), **2** (0.2 mmol) and $Cu(OTf)_2$ (20 mol%) in CH_3CN (2.0 mL) was stirred in O_2 atmosphere (O_2 balloon) at 40 °C.
[b] Yield of the isolated product.

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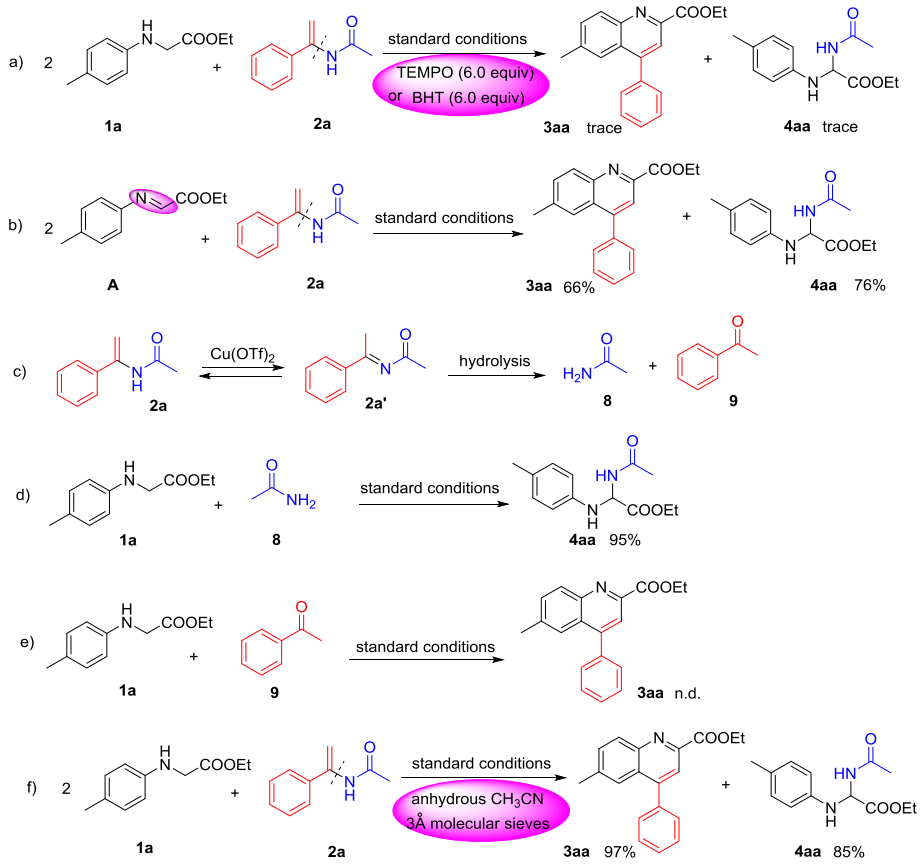
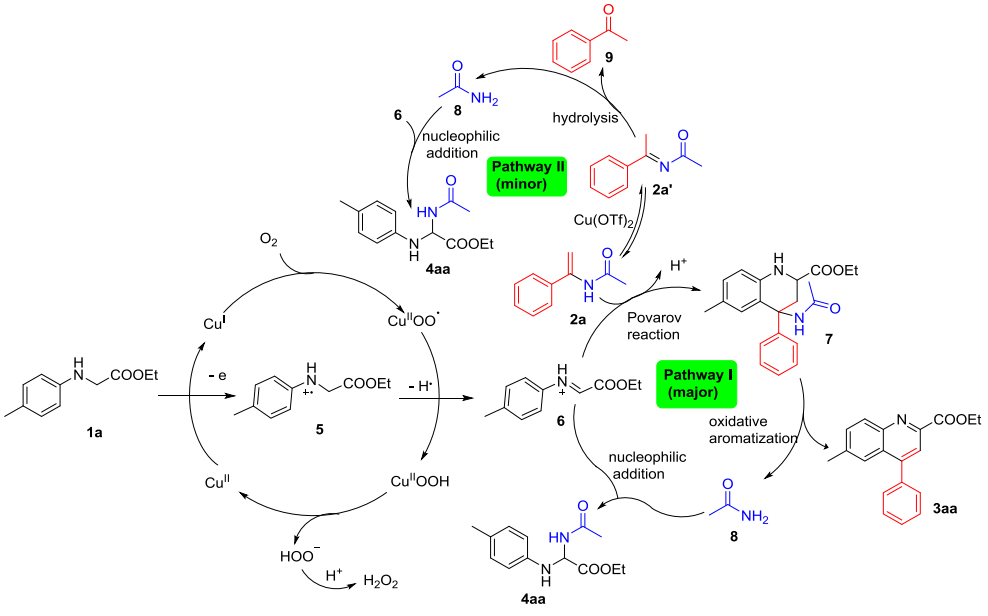


Scheme 2. Control experiments.

it was found that the anhydrous conditions favor the quinoline product **3aa** but have minor effect in forming *gem*-diamine derivative **4aa** (Scheme 2, f). The results of the above experiments (Scheme 2, d-f) indicated that a small amount of **2a** is hydrolyzed during the reaction, and the resulting acetamide **8** is a key intermediate in the formation of **4aa**, but the hydrolysis is not the main source of **8**. This may be the reason why the yield of **4** is always higher than the yield of **3**.

Based on the above control experiments and previous reports [5,6,18], a plausible mechanism was proposed for this reaction (Scheme 3). First, Ethyl *p*-tolylglycinate **1a** is oxidized to N-center radical cation **5** by a single-electron oxidation of Cu^{II}. The resulting



Scheme 3. Proposed reaction mechanism.

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Cu^{I} is then oxidized back to Cu^{II} by O_2. The $Cu^{II}OO^{\cdot}$ generated in this oxidation process abstracts a hydrogen atom from **5** to deliver the iminium **6**. The *gem*-diamine derivative **4aa** can be formed by two pathways, and the pathway **I** is dominant. Pathway **I** (major): The Povarov reaction (aza-[4 + 2] cycloaddition) between **6** and *N*-(1-phenylvinyl)acetamide **2a** forms the corresponding tetrahydroquinoline intermediate **7**, which removes the amide **8** and is oxidatively aromatized to deliver the desired product **3aa**. A nucleophilic addition of **8** to another molecular iminium **6** affords the desired product **4aa**. Pathway **II** (minor): In the presence of Cu $(OTf)_2$, *N*-(1-phenylvinyl)acetamide **2a** can be tautomerized to *N*-(1-phenylethylidene)acetamide **2a'**, and then a small amount of water in the reaction system hydrolyzes **2a'** to form acetamide **8** and acetophenone **9**. **8** nucleophilically attacks iminium **6** to afford the desired product **4aa**.

Conclusion

In summary, we have successfully developed a practical and operationally simple method for the simultaneous synthesis of quinolines and *gem*-diamine derivatives from *N*-arylglycine ethyl esters and enamides. This mild transformation employs ligand-free Cu(II) salt as a cheap and low-toxic catalyst and O_2 as a clean final oxidant without any other oxidants, thus making the protocol environmentally friendly. In this reaction, two fragments of one reactant each react with the same intermediate generated *in situ* by another reactant, simultaneously producing two valuable products, which is extremely efficient and highly atomically economic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152346.

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