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Cu(TFA)$_2$-Catalyzed Oxidative Tandem Cyclization/1,2-Alkyl Migration of Enamino Amides for Synthesis of Pyrrolin-4-ones

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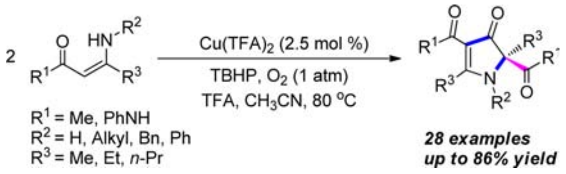
ABSTRACT



A novel Cu(TFA)$_2$-catalyzed oxidative tandem cyclization/1,2-alkyl migration of readily available enamino amides for the synthesis of pyrrolin-4-ones has been developed. The reaction tolerates a wide range of functional groups and is a reliable method for the rapid synthesis of substituted pyrrolin-4-ones in high yields under mild conditions.

The tandem reaction is an active area of research in organic chemistry and is a powerful and versatile synthetic tool for the construction of complex molecules from simple starting materials.[1] Over the past decades, transition-metal catalyzed tandem reactions have been developed for the efficient synthesis of many heterocycles, polycycles, and natural products;[2] however, most of these reactions proceeded under redox-neutral conditions.[3] Oxidative coupling has recently emerged as an atom-economical and high-efficiency protocol for organic synthesis.[4] Accordingly, the oxidative tandem reaction is a promising avenue for the further extension of traditional tandem reactions.[5]

1,2-Alkyl migration is one of the most fundamental reactions. Classic 1,2-alkyl migration reactions, such as pinacol rearrangement and α-ketol rearrangement, are well established in organic synthesis.[6] Recently, transition-metal catalyzed tandem reactions along with 1,2-alkyl migration have been found to be a powerful strategy for the rapid construction of complex molecules.[7] Our interest in the cyclization of enamines or enamides for the synthesis

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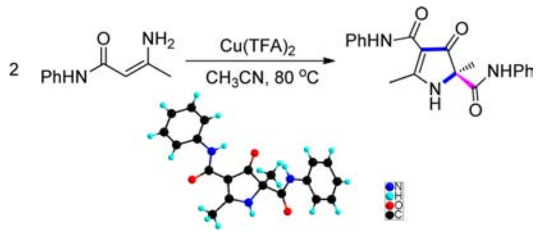
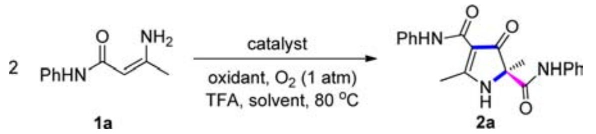
Scheme 1. Oxidative Tandem Cyclization/1,2-Alkyl Migration of Enamino Amide



of azaheterocycles[8] prompted us to study the oxidative cyclization of enamines. Unexpectedly, pyrrolin-4-one was observed when the cyclization of enamino amides was conducted in the presence of a $Cu(TFA)_2$ catalyst (Scheme 1). We assumed that it was generated from the intermolecular oxidative cyclization of enamino amide **1a** subsequent to 1,2-methyl migration. The pyrrolin-4-one scaffold is a class of valuable azaheterocycles that is prevalent in many pharmaceuticals and biologically active compounds.[9] Despite a few synthetic methods that have been recently developed for the synthesis of pyrrolin-4-ones,[10] versatile and efficient methods for the direct construction of pyrrolin-4-one scaffolds that are compatible with various functional groups and use readily available starting materials are rare. In this paper, we report a $Cu(TFA)_2$-catalyzed oxidative tandem cyclization/1,2-alkyl migration of enamino amides that we developed for the synthesis of pyrrolin-4-ones.

We began our study by investigating the copper-catalyzed oxdative cyclization of 3-amino-*N*-phenylbut-2-enamide **1a** in the presence of AgOAc under a balloon pressure of O_2.[11] Unexpectedly, pyrrolin-4-one, which may be from intermolecular oxidative cyclization of enamino amide **1a** subsequent to 1,2-methyl migration, was obtained at a yield of 12%.[10c] The structure of product **2a** was confirmed by X-ray diffraction analysis (Scheme 1). This result promoted us to optimize reaction conditions in order to develop a synthetically useful process for the synthesis of substituted pyrrolin-4-ones.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant	additive	solvent	yield (%)
1	$Cu(TFA)_2$	AgOAc		CH_3CN	12
2	$Cu(TFA)_2$	Ag_2CO_3		CH_3CN	0
3	$Cu(TFA)_2$	BQ		CH_3CN	0
4	$Cu(TFA)_2$	DDQ		CH_3CN	0
5	$Cu(TFA)_2$	DTBP		CH_3CN	23
6	$Cu(TFA)_2$	TBHP		CH_3CN	36
7	$Cu(TFA)_2$	TBHP		1,4-dioxane	31
8	$Cu(TFA)_2$	TBHP		toluene	29
9	$Cu(TFA)_2$	TBHP		CH_3OH	11
10	$Cu(TFA)_2$	TBHP		DCE	26
11	$Cu(OAc)_2$	TBHP		CH_3CN	8
12	$Cu(OTf)_2$	TBHP		CH_3CN	0
13	$Cu(TFA)_2$	TBHP	AcOH	CH_3CN	35
14	$Cu(TFA)_2$	TBHP	PivOH	CH_3CN	33
15	$Cu(TFA)_2$	TBHP	TFA	CH_3CN	49
16[b]	$Cu(TFA)_2$	TBHP	TFA	CH_3CN	57
17[b,c]	$Cu(TFA)_2$	TBHP	TFA	CH_3CN	65
18[c,d]	**$Cu(TFA)_2$**	**TBHP**	**TFA**	**CH_3CN**	**71**
19[c]	$Cu(TFA)_2$	TBHP	TFA	CH_3CN	52,[e] (39)[f]
20	–	TBHP	TFA	CH_3CN	0

[a] Reaction conditions: (*Z*)-3-amino-*N*-phenylbut-2-enamide **1a** (0.4 mmol), [Cu] (10 mol %), oxidant (0.5 equiv), additive (0.5 equiv) in solvent (3 mL) at 80 °C for 2 h; isolated yields. [b] $Cu(TFA)_2$ (5 mol %). [c] TBHP (0.25 equiv) (70% in water). [d] $Cu(TFA)_2$ (2.5 mol %). [e] $Cu(TFA)_2$ (1.0 mol %). [f] $Cu(TFA)_2$ (0.5 mol %).

Then, a series of oxidants, such as Ag_2CO_3, BQ, DDQ, DTBP, and TBHP, were screened to determine if they improved the reaction efficiency (Table 1, entries 2–6). TBHP was found to be the most effective of the screened oxidants. By screening various solvents, such as 1, 4-dioxane, toluene, CH_3OH, and DCE, we found that CH_3CN is the most effective at increasing the reaction yield (Table 1, entries 7–10). In contrast, no reaction was observed in the presence of the $Cu(OTf)_2$ catalyst, and only an 8% yield of **2a** was obtained when $Cu(OAc)_2$ was used as the catalyst (Table 1, entries 11–12). To further improve the reaction outcome, acid additives were screened. TFA proved to be an active additive in the reaction and resulted in a 49% yield of **2a** (Table 1, entries 13–15). Finally, we found that the catalyst loading as well as TBHP loading play an important role in the reaction (Table 1, entries 16–18). 2.5 mol % of $Cu(TFA)_2$ and 0.25 equiv of TBHP give the highest yields of **2a** (Table 1, entry 18). However, further decreasing of the catalyst loading resulted in a long

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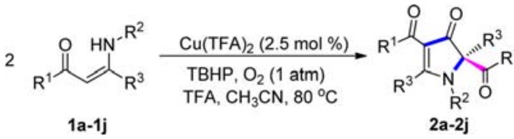
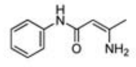
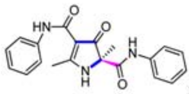
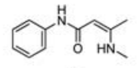
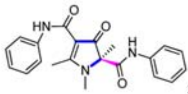
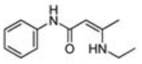
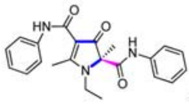
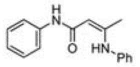
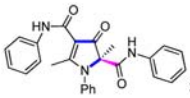
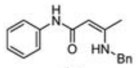
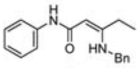
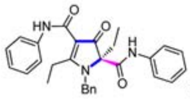
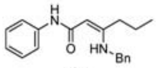
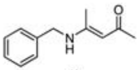
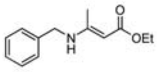
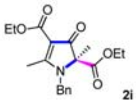
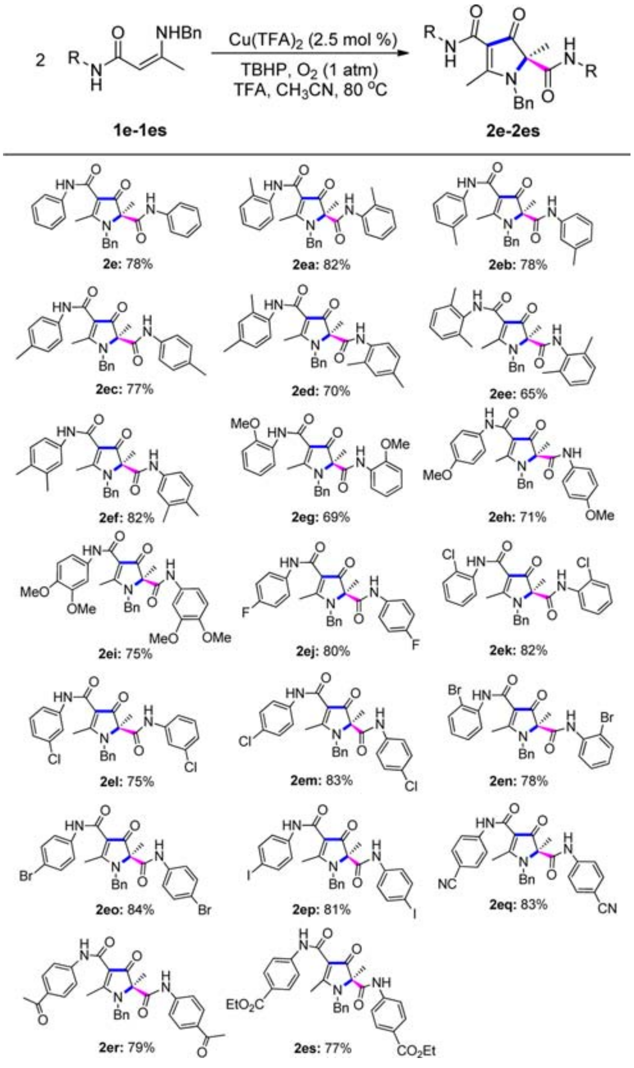
Table 2. Cu(TFA)$_2$-Catalyzed Oxidative Tandem Cyclization/1,2-Alkyl Migration of Enamines[a]



entry	enamino amides **1**	pyrrolin-4-ones **2**	yield (%)[b]
1	 1a	 2a	71
2	 1b	 2b	86
3	 1c	 2c	83
4	 1d	 2d	77
5	 1e	 2e	78
6	 1f	 2f	68
7	 1g	 2g	63
8	 1h	 2h	62
9	 1i	 2i	NR

[a] Reaction conditions: **2** (0.4 mmol), Cu(TFA)$_2$ (2.5 mol %), TBHP (0.25 equiv), and TFA (0.5 equiv) in CH$_3$CN (3 mL) at 80 °C for 2 h. [b] Isolated yields.

Scheme 2. Cu(TFA)$_2$-Catalyzed Oxidative Tandem Cyclization/1,2-Alkyl Migration of Enamino Amides for Synthesis of Pyrrolin-4-ones[a,b]



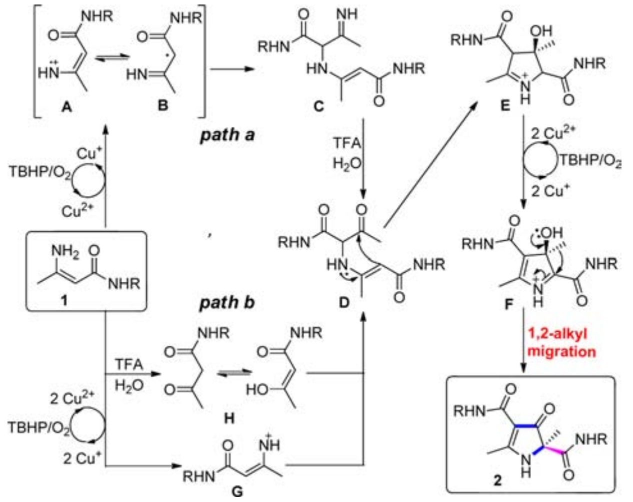
[a] Reaction conditions: 1 (0.4 mmol), Cu(TFA)$_2$ (2.5 mol %), TBHP (0.25 equiv), TFA (0.5 equiv) in CH$_3$CN (3 mL) at 80 °C for 2 h. [b] Isolated yields.

reaction time and low yield (Table 1, entry 19). And no reaction occurred in the absence of the copper catalyst (Table 1, entry 20).

With the optimized conditions in hand, we investigated the scope of the reaction (Table 2). This new cyclization reaction displayed high functional-group tolerance and proved to be a general protocol for the synthesis of substituted pyrrolin-4-ones. Enamino amides with methyl, ethyl, phenyl, and benzyl substitutents on the *nitrogen* atom (**1b**–**1e**) were well tolerated and exhibited slightly higher reactivity compared to *N*-unsubstituted enamino amide **1a** and gave the corresponding pyrrolin-4-ones **2b**–**2e** in 77–86% yields (Table 2, entries 2–5). We also examined alkyl substituents on the olefin skeleton of the enamino amides. Ethyl- and propyl-substituted enamino amides **1f**–**1g** proceeded smoothly and resulted in the corresponding pyrrolin-4-ones **2f**–**2g** in 63–68% yields (Table 2, entries 6–7). Enaminone **1h** tolerated the conditions as well. Acetyl-substituted pyrrolin-4-one **2h** was obtained at a yield of 62% (Table 2, entry 8); however, enaminoester **1i** was unable to induce the reaction.

Encouraged by the above results, further extension of the reaction scope of the enamino amides was conducted (Scheme 2). Enamino amides with a series of substituents, such as methyl, methoxyl, fluoro, chloro, bromo, sensitive functional groups such as iodo, and strong electron-withdrawing groups such as cyano, acetyl, and ester, all gave the corresponding substituted pyrrolin-4-ones in good to high yields. These results indicate that the reaction was unaffected by the electronic effects of the substituents on the

Scheme 3. Plausible Mechanisms of the Reaction

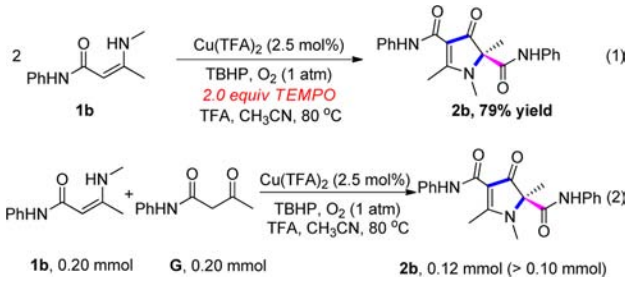


aryl ring of the amide group. Meanwhile, *ortho*-Me-, MeO-, Cl-, and Br- substituted substrates reacted smoothly and resulted in the desired pyrrolin-4-ones (**2ea**, **2ed**, **2ee**, **2eg**, **2ek**, **2en**) in 65−82% yields, implying that steric hindrance of the substrates has little influence on the reaction.

The tentative mechanisms are proposed in Scheme 3 on the basis of the aforementioned observations. One proposed mechanism is that the reaction starts from a single-electron-transfer oxidation of enamino amide **1** by Cu^{2+} to generate amino radical **A** and alkyl radical **B**.[12] Then, radical coupling of **A** and **B** leads to the intermediate **C**. Hydrolysis of **C** gives intermediate **D**. Intramolecular cyclization of intermediate **D** leads to intermediate **E**.[8d] Tautomerization followed by oxidation by Cu^{2+} then generates the 3*H*-pyrrol-1-ium intermediate **F**. Finally, α-hydroxy imine rearrangement of the intermediate **F** produces pyrrolin-4-one **2** (pathway a).[6,13] Alternatively, two steps of a single-electron-transfer oxidation of enamino amide **1** by Cu^{2+} to generate nitrenium ion **G** could occur.[10c] Meanwhile, hydrolysis of enamino amide **1** would generate acetoacetyl aniline **H**. Then, the nucleophilic attack of **H** to nitrenium ion **G** produces the intermediate **D** (pathway b).[14]

To gain more insight into the reaction mechanism, a radical-trapping reagent, (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), was added to the reaction. However, the reaction was not influenced by TEMPO (Scheme 4, eq 1), indicating that the radical pathway (pathway a) is less likely. To confirm that the mechanism follows pathway b, acetoacetyl aniline **G** (1.0 equiv) was added to the reaction under the aforementioned conditions. Pyrrolin-4-one **2b** was obtained in 0.12 mmol (> 0.10 mmol), implying that acetoacetyl aniline **G** was a reactant in the reaction (Scheme 4, eq 2). Therefore, the reaction probably proceeds through pathway b.

Scheme 4. Experiments To Elucidate the Reaction Mechanism



In summary, we have developed a novel and highly efficient copper-catalyzed oxidative tandem cyclization/1,2-alkyl migration of readily available enamino amides for the synthesis of pyrrolin-4-ones. This general reaction tolerates a wide range of functional groups and is a reliable method for the rapid synthesis of substituted pyrrolin-4-ones in high yields under mild conditions. Our preliminary mechanistic studies indicate that the mechanism of the reaction likely proceeds through nucleophilic attack of an acetoacetyl aniline intermediate to a nitrenium ion. Further investigation of the reaction scope and mechanistic studies are underway.

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Supporting Information Available. Experimental procedures, spectral data for all products, and X-ray data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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