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Heterocycles

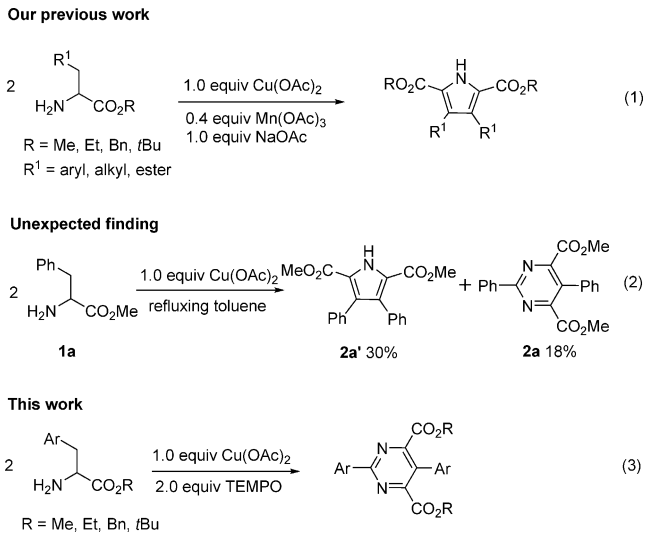
Cu^{II}/TEMPO-Promoted One-Pot Synthesis of Highly Substituted Pyrimidines from Amino Acid Esters

Nini Zhou, Tao Xie, Zhongle Li, and Zhixiang Xie*[a]

Abstract: A novel, $Cu(OAc)_2$/TEMPO promoted one-step approach for the preparation of fully substituted pyrimidines from readily available amino acid esters has been described. In this reaction, the amino acid esters act as the only N–C sources for the construction of corresponding pyrimidines. The mechanism of this process includes oxidative dehydrogenation, the generation of an imine radical, and a formal [3+3] cycloaddition. This methodology proves to be a high atom-economic and straightforward strategy for the synthesis of pyrimidines and diverse substrates which are substituted by various functional groups have been afforded in moderate to good yield.

Pyrimidine derivatives are a very important class of azaheterocycle compounds and an integral part of many bioactive natural products.[1] Moreover, they have been widely used as important carriers of pharmacophore,[2] prospective candidates for light-materials,[3] and crucial ligands in transition metal catalysis.[4] Therefore, the synthesis of pyrimidine derivatives has long attracted much attention. Based on the classical condensation reaction of the N–C–N fragment and the cross-coupling reaction, methodologies for the synthesis of pyrimidines have recently proliferated.[5] In addition, tandem inverse-electron-demand hetero-/retro-Diels–Alder reactions of triazines,[6] the activation of carbonyl moieties,[5a] and the activation of N-vinyl amides[5a] have each contributed to the development of the synthesis of pyrimidine derivatives. Although, to date, the synthesis of pyrimidines developed rapidly, it is significant to explore a straightforward and amenable approach to fully substituted pyrimidines in organic chemistry. Moreover, to our knowledge, the synthesis of pyrimidine derivatives directly from only one N–C source, with high atom economy, would be a new phenomenon in the development of approaches to prepare pyrimidines.

We recently reported a method for the preparation of pyrroles from readily available amino acid esters [Scheme 1, Eq. (1)].[7] During the study, we discovered that some amino acid esters were also transformed into pyrimidines. When phenylalanine methyl ester **1a** was treated with 1.0 equivalents of $Cu(OAc)_2$ in refluxing toluene, the corresponding pyrrole **2a′** was obtained as a major product in 30% yield, along with another product **2a** in 18% yield [Scheme 1, Eq. (2)]. On the basis of spectroscopic data and X-ray crystallography (see the Supporting Information), the structure of **2a** was established to be a symmetrically substituted pyrimidine.[8] Therefore, exploration of our unexpected finding led to the development of a novel protocol for the preparation of symmetrically substituted pyrimidines from amino acid esters, promoted by $Cu(OAc)_2$/TEMPO [Scheme 1, Eq. (3)], which combines oxidative dehydrogenation, the formation of an imine radical, and a formal [3+3] cycloaddition.



Scheme 1. $Cu(OAc)_2$-promoted conversion of amino acid esters.

Optimization of the reaction conditions was carried out with **1a** to improve the yield of pyrimidine **2a** (Table 1). After several metal reagents had been examined, we found that $Cu(OAc)_2$ was better than others to promote the conversion of **1a** to **2a** (Table 1, entry 1). As TEMPO (2,2,6,6-tetramethyl-piperidinooxy) could inhibit the transformation of **1a** to pyrrole,[7] we screened several radical scavengers. The results showed that TEMPO successfully increased the yield of pyrimidine **2a** (Table 1, entry 2). With the help of 2.0 equivalents of TEMPO, the yield of **2a** was further improved to 41% in refluxing toluene. However, 2.5 equivalents of TEMPO led to a decrease in yield (Table 1, entries 3, 4). It was subsequently found that the yield of **2a** was enhanced to 56% when the reaction was performed in refluxing xylene (Table 1, entry 5). A decrease in the amount of $Cu(OAc)_2$ to 0.8 equivalents led to a decrease in

[a] Dr. N. Zhou, T. Xie, Z. Li, Prof. Dr. Z. Xie
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (P. R. China)
E-mail: xiezx@lzu.edu.cn

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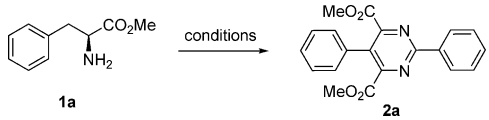
Table 1. Optimization of the reaction conditions.[a]



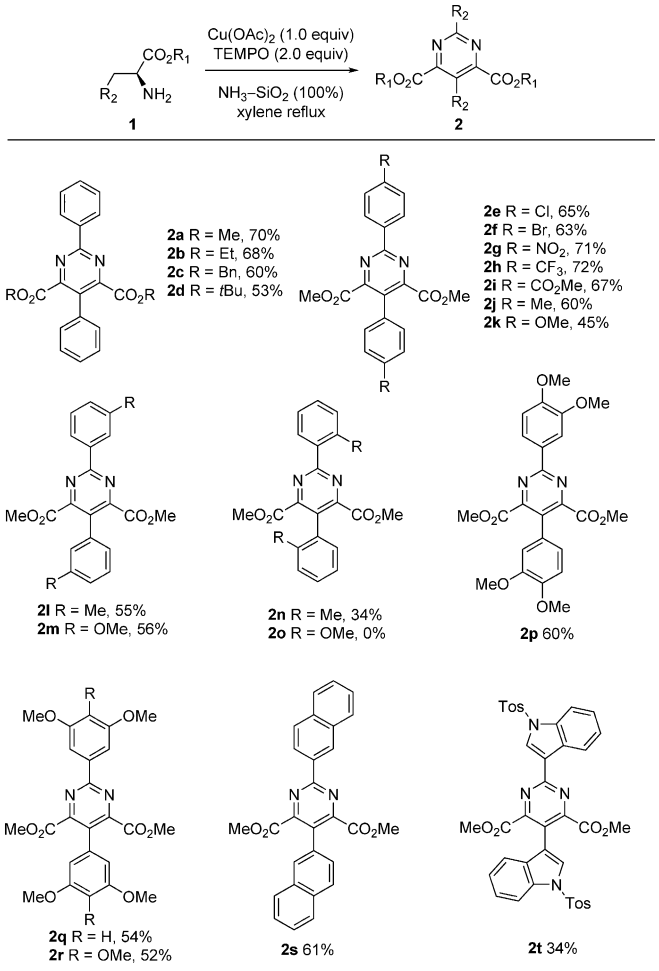
1a 2a

Entry	TEMPO [equiv]	Additive	Yield [%][b]
1[c]	–	–	18
2[c]	1.0	–	31
3[c]	2.0	–	41
4[c]	2.5	–	36
5	2.0	–	56
6[d]	2.0	–	35
7	2.0	NaOAc[e]	58
8	2.0	Et_3N[e]	61
9	2.0	4 Å MS[f]	43
10	2.0	Al_2O_3[f]	56
11	2.0	SiO_2[f]	62
12	2.0	Et_3N–SiO_2[f]	66
13	2.0	NH_3–SiO_2[f]	70

[a] All reactions were carried out under the following conditions, unless otherwise noted, 0.28 mmol of **1a** and 1.0 equivalents of $Cu(OAc)_2$ in refluxing xylene under argon; [b] yield of isolated product; [c] the reaction proceeded in refluxing toluene; [d] 0.8 equivalents of $Cu(OAc)_2$ was used; [e] 1.0 equivalents; [f] 100% mass fraction of **1a**.

yield of **2a** to 35% (Table 1, entry 6). We then tested the effect of various additives. The presence of NaOAc or Et_3N (1.0 equiv) both led to slight increases in the yield of pyrimidine (Table 1, entries 7, 8). In contrast, 4 Å molecular sieves and Al_2O_3 (100% mass fraction of **1a**) both failed to enhance the yield (Table 1, entries 9, 10), although SiO_2 (silica gel) could increase the yield of **2a** to 62% (Table 1, entry 11). Notably, when the additive was silica gel basified with Et_3N or NH_3, the yield of **2a** was further improved to 66% and 70%, respectively (Table 1, entries 12, 13). Therefore, after carefully examining the different conditions, we found that the reaction proceeded most efficiently in the presence of $Cu(OAc)_2$ (1.0 equiv), TEMPO (2.0 equiv), and NH_3–SiO_2 (100% mass fraction of **1a**) in refluxing xylene under argon.

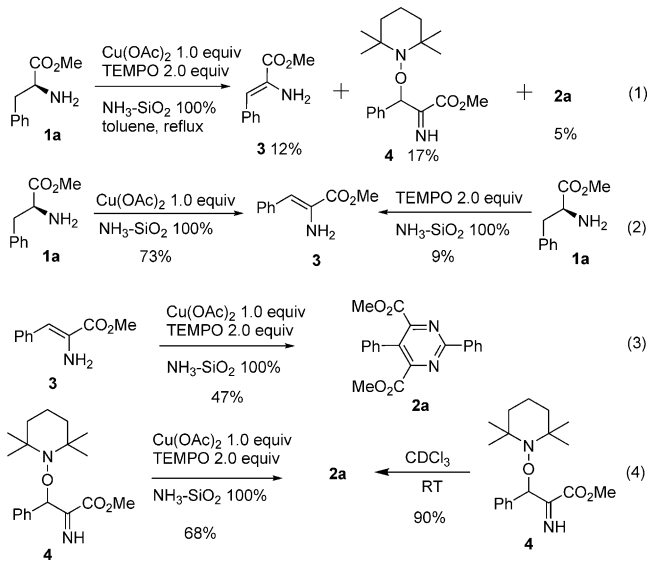
We subsequently explored the scope and limitation of this conversion with the optimized reaction conditions (Scheme 2). Firstly, we investigated the influence of ester groups. The desired pyrimidines (**2a**–**c**) were obtained in good yield with methyl, ethyl, or benzyl substituents (R in Scheme 2), and that, by switching R to *tert*-butyl, the yield of **2d** was reduced to 53%, as a result of steric effects. The influence from electronic and steric effects of the benzene ring was then examined. Notably, for substrates bearing electron-withdrawing or weakly electron-donating *para*-substituents on the benzene ring, the reaction could proceed smoothly and the desired products were afforded in good yield (**2e**–**j**). The product **2f**, with Br as *para*-substituents on the benzene ring, would allow further functionalization. Moving to strongly electron-donating *para*-substituents (OMe) on the benzene ring, the yield of **2k** drastically decreased to 45%, which might be attributed to the increased tendency of their enamine intermediates to condense with primary amines[9] or the reduced stability of the α-imine radical intermediate. As *meta*-substituents on benzene ring,



Scheme 2. Reaction substrate scope of amino acid ester conversion. Reaction conditions: Amino acid ester **1** (0.28 mmol), $Cu(OAc)_2$ (1.0 equiv), TEMPO (2.0 equiv), NH_3–SiO_2 (100% mass fraction of **1**) in refluxing xylene under argon. Yields of isolated products are given.

Me and OMe showed similar effects, effecting conversion to the desired pyrimidines in moderate yield (**2l**, **2m**). With Me as *ortho*-substituents on the benzene ring (**2n**), pyrimidine yields were much lower and with ortho OMe substituents (**2o**), no conversion to the desired pyrimidine was detected. With two to three OMe *meta*- and *para*-substituents on benzene ring, the desired pyrimidines were produced in moderate yield (**2p**–**r**), which indicated that OMe as a *meta*-substituent on the benzene ring might be helpful to produce the desired pyrimidines. When the benzene ring was replaced by a naphthalene group, **2s** was obtained in 61% yield. Furthermore, heteroaromatics with steric hindrance, such as an *N*-tosyl indole group, were also tolerated in this reaction (**2t**), albeit with reduced yield.

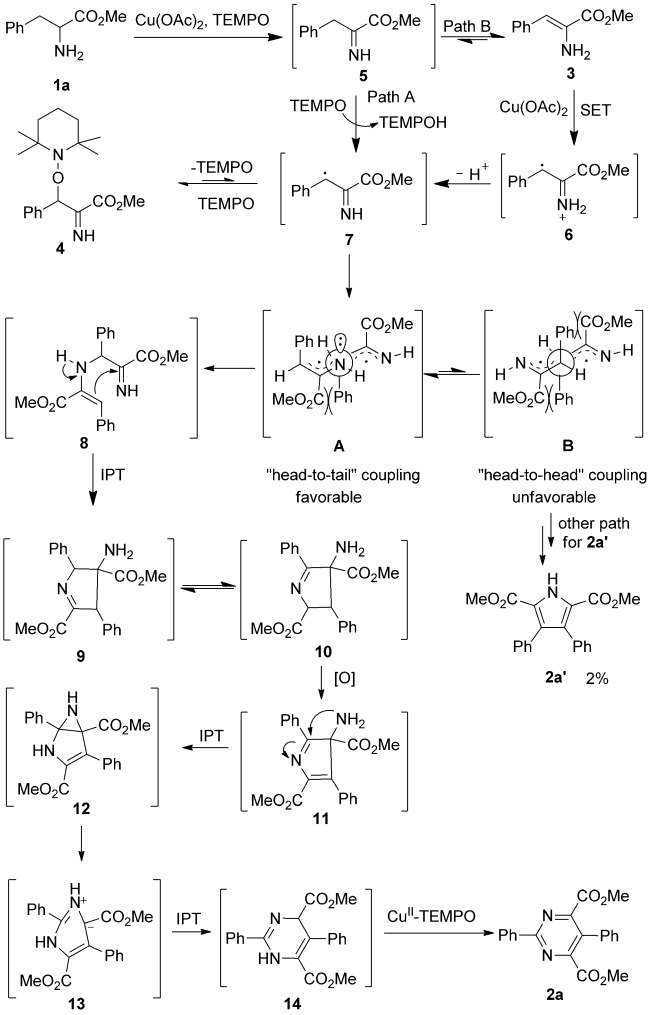
To illuminate the mechanism of the conversion, further exploration on the reaction was conducted and the intermediate was obtained in the early stage of the process when the reaction was slowed down in refluxing toluene (Scheme 3). **1a** was treated with 1.0 equivalent of $Cu(OAc)_2$, 2.0 equivalents of TEMPO, and 100% NH_3–SiO_2 in refluxing toluene under argon for 60 min. The mixture was purified by flash column chroma-



Scheme 3. Investigation of the reaction mechanism.

tography on silica gel, which was pre-saturated with NH_3 (NH_3–SiO_2) to give compounds **3** in 12% yield, **4** in 17% yield, and **2a** in 5% yield [Scheme 3, Eq. (1)]. However, **4** could not be obtained when the mixture was purified by flash column chromatography on silica gel that had not been pre-saturated with NH_3, demonstrating that NH_3–SiO_2 was a helpful contributor to preventing the decomposition of **4** and extending the lifespan of the imine radical. Compound **3** could be formed not only without TEMPO but also without $Cu(OAc)_2$ [Scheme 3, Eq. (2)], which showed that TEMPO might be helpful for the oxidation of **1a** to **5** or **3**.[10] We also found that **3** could smoothly convert to **2a** [Scheme 3, Eq. (3)] under the standard reaction conditions, which showed that compound **3** stood out as a key intermediate for the preparation of pyrimidine **2a**, as did **4**; **4** could also transform to **2a** in $CDCl_3$ at room temperature [Scheme 3, Eq. (4)].

Scheme 4 outlines a possible mechanism for the synthesis of **2a** from **1a** on the basis of the above experimental results. Firstly, the oxidative dehydrogenation of the amine **1a** by $Cu(OAc)_2$ provides imine **5**, in tautomeric equilibrium with enamine **3**,[7] and TEMPO might facilitate this process.[10] Subsequently, there are two pathways for the construction of α-imine radical intermediate **7**. One is the oxidation of **5** by TEMPO to give **7** (path A),[11] and the other is the transformation of enamine **3** into **6** through single-electron transfer (SET) and the departure of a proton from **6** to form **7** (path B).[12] Then, the α-imine radical intermediate **7** would be quickly captured by TEMPO to give the key intermediate **4** which, under the standard reaction conditions, could gradually transform into the α-imine radical for the subsequent transformation in turn[13] and effectively prolong the life of the α-imine radical. Therefore, the fact that NH_3–SiO_2 could improve the yield of the **2a** by its contribution to preventing the decomposition of **4** was understandable. Two α-imine radicals then undergo intermolecular C–N coupling (transition state **A**) to give **8** or intermolecular C–C coupling (transition state **B**) to finally give



Scheme 4. Proposed mechanism for the conversion of **1a** to **2a**.

2a′, in another reaction pathway[12b] that is different from the one we previously reported.[7] The coupling selectivity of the radical intermediate **7** is the result of both transition-state and electronic effects. Two molecules of α-imine radical intermediate **7** preferentially adopt the favorable transition state **A** ("head-to-tail" C–N coupling) over the sterically congested transition state **B** ("head-to-head" C–C coupling). The transition-state energies for "head-to-tail" C–N coupling are reduced by favorable polarizations in reactions of "polarity matched" radicals, for the reason that an N-centered radical with lone pair electrons is electron-rich whereas a C-centered radical with an electron-withdrawing group is electron-deficient.[14] The effect of electron–electron repulsion between two aminyl radicals rules out "tail-to-tail" N–N coupling. Therefore, under standard reaction conditions, **2a** was obtained as a major product in 70% yield via transition state **A**, whereas **2a**′, which might form from transition state **B**, was detected as byproduct in 2% yield.[11b]

Intermediate **8** from transition state **A** would transform to five-membered heterocycle **9**, in equilibrium with **10** through electrophilic cyclization and intramolecular proton transfer (IPT; Scheme 4). **10** would then be further oxidized to generate **11**

which is converted to **12** via intramolecular electrophilic cyclization. Then, **12** smoothly converts to dipolarophile **13**[15] which undergoes IPT to give six-membered heterocycle **14**. Finally, fully substituted pyrimidine **2a** is afforded from **14** by efficient aromatization, which could also be enhanced by the Cu^{II}–TEMPO complex.[16]

In conclusion, we have developed a novel methodology for the synthesis of fully substituted pyrimidines from commercially available amino acid esters, promoted by Cu^{II}/TEMPO. We investigated the mechanism with the acquisition of the key intermediate. The process is simple, efficient, atom-economic, and with great practical worth. The reactions could be tolerated a broad substrate scope to prepare corresponding pyrimidines in reasonable to good yield. To our knowledge, this is the first example of pyrimidine preparation from amino acid esters acting as the only N–C source, through an imine radical process in which a formal [3+3] cycloaddition is included. Research on the course of imine radical pathway is underway in our laboratory.

Experimental Section

General procedure for the preparation of pyrimidines from corresponding amino acid esters: To a solution of the amino acid ester **1** (0.28 mmol) in anhydrous xylene (10 mL) was added the $Cu(OAc)_2$ (0.28 mmol, 1.0 equiv), TEMPO (0.56 mmol, 2.0 equiv), and NH_3–SiO_2 (100% mass fraction of **1**) under argon. After stirring in refluxing xylene for 2.0 h, the mixture was cooled to room temperature and the solvent removed by evaporation under reduced pressure. The resulting residue was purified by flash column chromatography to give the pure pyrimidine product.

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Keywords: amino acid esters · copper · pyrimidines · radical reactions · reaction mechanisms

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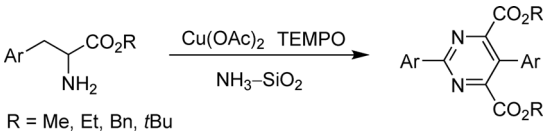

R = Me, Et, Bn, *t*Bu

Heterocycles

*N. Zhou, T. Xie, Z. Li, Z. Xie**

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Cu^{II}/TEMPO-Promoted One-Pot Synthesis of Highly Substituted Pyrimidines from Amino Acid Esters

A Cu(OAc)$_2$/TEMPO-promoted approach to prepare symmetrically substituted pyrimidines from readily available amino acid esters is described, the mechanism of which consists of oxidative dehydrogenation, generation of an imine radical, and a formal [3+3] cycloaddition. This methodology proves to be an atom-economic and straightforward strategy for the synthesis of pyrimidines and diverse substrates that are substituted by various functional groups are afforded in moderate to good yield.