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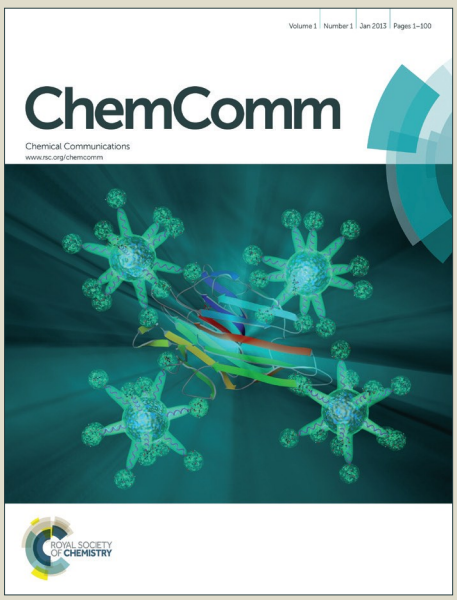

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Copper-Catalyzed Aerobic Oxidative Amidation of Tertiary Amines

Hui-Cheng Cheng, Wen-Jun Hou, Zeng-Wen Li, Ming-Yu Liu and Bing-Tao Guan*

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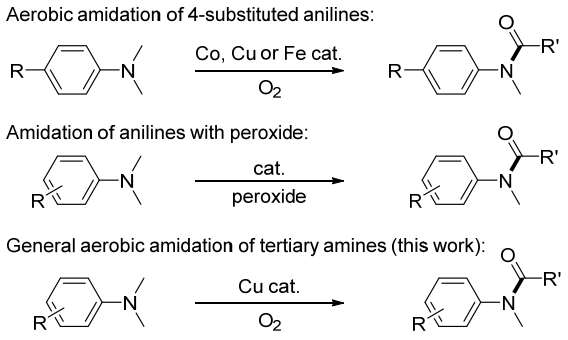
A general and efficient method for the tertiary amide synthesis has been developed via copper-catalyzed aerobic oxidative amidation of tertiary amines. Due to the use of O_2 oxidant, various functional groups were well tolerated under present conditions. Extensive substrates studies demonstrated its potential as a practical approach for the tertiary amide synthesis.

Amides as an important structure unit exist widely in natural products, biological compounds, pharmaceuticals and synthetic materials.[1] Therefore, the development of amides synthesis has attracted much attention and has been extensively studied.[2] Traditionally, amide is synthesized by the amidation of primary and secondary amines. Due to the reactivity of the amines and amides, the protection and deprotection processes are always necessary in a multistep synthesis, which would undoubtedly compromise their synthetic efficiency. Generally, tertiary amines are easily available and stable enough to survive under many conditions. So the amides synthesis via tertiary amines amidation could provide an ideal late stage synthetic approach.[3]

The easy oxidative reactivity[4] enables tertiary amines to undergo efficient amidation reactions in the presence of oxidants such as peroxides [Scheme 1, eqn (2)].[5, 6] The use of those oxidants would definitely lead to poor function group tolerance from a synthetic point of view. The aerobic oxidative amidation of tertiary amines was reported in 1990s by Miura and coworkers with Co or Cu catalysts.[7] However, the substrates were greatly limited to 4-substituted anilines [Scheme 1, eqn (1)]. The aerobic amidation of tertiary amines were further developed with various catalysts in conjugation with various acylation reagents.[8] Those methods reported so far suffered from limited substrate scope and poor selectivity. The use of molecular oxygen as an ideal oxidant for organic synthesis has drawn much attention.[9] The copper catalysts had recently proved their powerful ability in the aerobic oxidativ transformations.[10] Herein, we report a general and efficien protocol for the aerobic amidation of tertiary amines. The good efficiency, selectivity and function group tolerance m it a possible candidate as an ideal late stage amidation reaction.



Scheme 1. Catalytic Oxidative Amidation of Tertiary Amines.

Initially, we investigated the catalytic efficiency of sever catalysts using *N,N*-dimethylaniline and acetic anhydride substrates in refluxing acetonitrile under O_2 atmosphere. Th Cu, Co and Fe salts which successfully catalyzed the aerob amidation of 4-substituted anilines[7, 8e] failed to drive th amidation of *N,N*-dimethylaniline efficiently (Table 1, entries 3). $Cu(OAc)_2$ was found to be a suitable catalyst and N-methyl-N-phenylacetamide **3a** was obtained in the yield of 88% aft refluxing in MeCN for 36 hours (Table 1, entry 6). Shorter reaction time or lower temperature would lead to the dro of the yields (Table 1, entries 7-8). Blank experiments w carried out, and the reaction could not take place witho either $Cu(OAc)_2$ catalyst or O_2 atmosphere (Table 1, entries 10). The catalytic aerobic amidation could even take place air, and a comparable yield was obtained with longer time (Table 1, entries 11-12). The efficiency of the catalytic aerob amidation reaction was related much to the amount of the acetic anhydride: 3 equivalent of acetic anhydride or mo would give comfortable yields, while less amount of the acetic

State Key Laboratory and Institute of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071 (China). E-mail: guan@nankai.edu.cn

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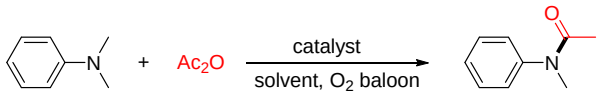
Table 1. Catalytic Aerobic Oxidative Acetylamination of *N,N*-Dimethylaniline.



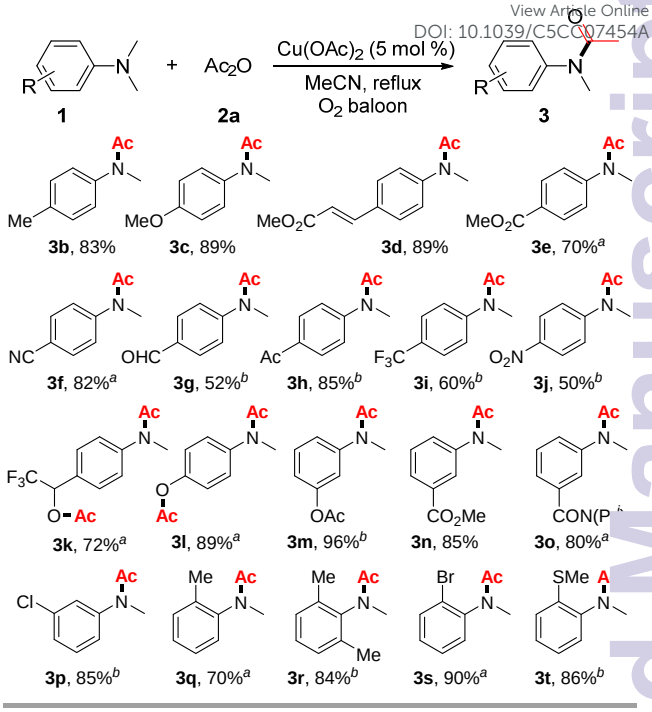
1a **2a** **3a**

Entry[a]	Catalyst	Solvent	Temp.	Time	Yield 3a[b]
1	CuCl	CH_3CN	reflux	36	40%
2	$CoCl_2$	CH_3CN	reflux	36	7%
3	$FeCl_3$	CH_3CN	reflux	36	5%
4	$CuCl_2$	CH_3CN	reflux	36	25%
5	$CuBr_2$	CH_3CN	reflux	36	57%
6	$Cu(OAc)_2$	CH_3CN	reflux	36	88%
7	$Cu(OAc)_2$	CH_3CN	reflux	24	76%
8	$Cu(OAc)_2$	CH_3CN	60 °C	36	32%
9	--	CH_3CN	reflux	36	<5%
10[c]	$Cu(OAc)_2$	CH_3CN	reflux	36	<5%
11[d]	$Cu(OAc)_2$	CH_3CN	reflux	36	45%
12[d]	$Cu(OAc)_2$	CH_3CN	reflux	72	86%
13[e]	$Cu(OAc)_2$	CH_3CN	reflux	36	60%
14[f]	$Cu(OAc)_2$	CH_3CN	reflux	36	94% (90%)
15	$Cu(OAc)_2$	toluene	100 °C	36	14%
16	$Cu(OAc)_2$	DMSO	100 °C	36	11%

[a] Conditions: *N,N*-dimethylaniline 1a (0.5 mmol), Ac_2O (3.0 equiv), catalyst (5 mol %), MeCN (1 mL), O_2 balloon, reflux, 36 hours; unless otherwise noted; [b] GC yields with tridecane as internal standard and isolated yield in parenthesis. [c] Under argon. [d] Under air. [e] 2.0 equiv. [f] Ac_2O: 5.0 equiv.

anhydride gave a lower yield (Table 1, entries 13-14). Several solvents were tested in the reaction, and MeCN proved to be the solvent of choice (Table 1, entries 15-16).

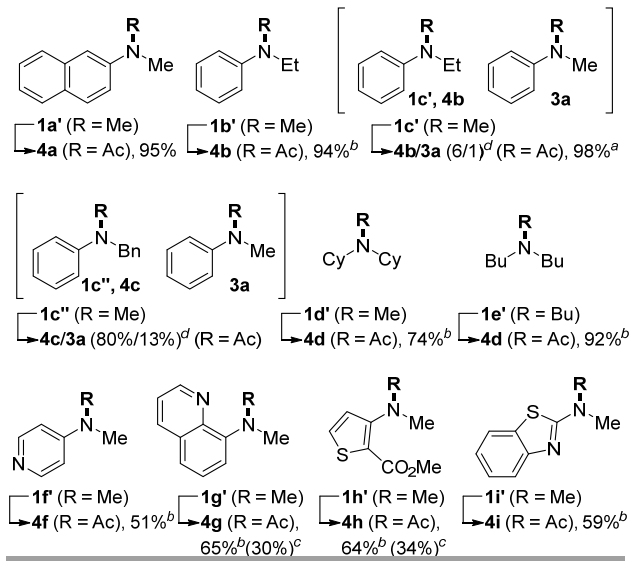
Under these optimized conditions, various substituted tertiary anilines were subjected to the catalytic aerobic acetylamination reaction (Scheme 2). *para*-Methyl and methoxy-*N,N*-dimethylaniline gave amidation products in good yields under present conditions (**3b**-**c**). Methyl 4-dimethylaminocinnamate smoothly reacted with acetic anhydride to afford desired amidation product with the methyl cinnamate part intact (**3d**). Electron-withdrawing groups on anilines would reduce the electron density and suppress the oxidative reactions. Hence, the anilines with electron-withdrawing groups were seldom reported to undergo the aerobic oxidative amidation reaction. For the efficiency of the present method, the anilines bearing electron-withdrawing groups such as cyano, methoxycarbonyl, formyl, acyl, trifluoromethyl and even nitro group could afford amidation



Scheme 2 Scope of substituted N,N-dimethylanilines. Conditions: Aniline (0.5 mmol), Ac_2O (3.0 equiv), $Cu(OAc)_2$ (5 mol %), MeCN (1 mL), O_2 balloon, reflux, 36 hours, isolated yields reported. [a] Ac_2O: 10 equiv. [b] 2 mL of Ac_2O, no MeCN, 100℃.

products in fair to good yields if only under more concentrated acetic anhydride conditions (**3e**-**j**). 4-(Dimethylamino)-phenol and 2,2,2-trifluoro-1-(4-(dimethylamino)phenyl)ethanol could also undergo the amidation reaction with the hydroxyl group acetylized at the same time (**3k**-**l**). *N,N*-Dimethylanilines with substituted group at *meta*- or *ortho*-position were reacted with acetic anhydride, and the corresponding products were obtained in good to excellent yields (**3m**-**t**). It is interesting to note that the steric hindered substrates smoothly underwent the aerobic amidation reaction (**3q**-**t**). Moreover, the methylthio group well survived the oxidative condition (**3t**).

N,N-Dimethyl-2-naphthylamine smoothly reacted with acetic anhydride, and gave the amidation product in excellent yield (Scheme 3, **4a**). Not only the N-Me bonds containing anilines but also the other *N*-alkyl compounds could serve as substrates for the aerobic oxidative amidation reaction. The reaction between *N,N*-diethylaniline and acetic anhydride gave *N*-ethyl-*N*-phenylacetamide (**4b**) in yield of 94%. The unsymmetrical anilines such as *N*-ethyl-*N*-methylaniline and *N*-benzyl-*N*-methylaniline gave a mixture of *N*-phenylacetamides with nice selectivity (**4b** and **3a**, **4c** and **3a**). Compared with ethyl and benzyl group, methyl group showed much better reactivity.[11] Beside anilines, alkyl amines could also undergo the aerobic oxidative amidation reaction: either N-Me bond of dicyclohexylmethylamine or N-Bu bond of tributylamine were converted to acetamide groups (**4d**-**e**). Notably, a wide range of heterocycles were also compatible with this protocol. Tertiary amines bearing heterocycles such as pyridine,

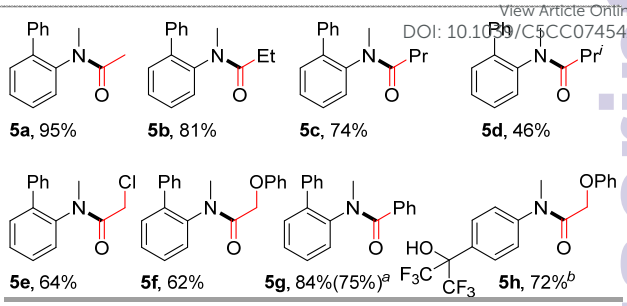


Scheme 3. Scope of tertiary amines. Conditions: tertiary amine (0.5 mmol), Acetic anhydride (3.0 equiv), $Cu(OAc)_2$ (5 mol%), MeCN (1 mL), O_2 balloon, reflux, 36 hours, isolated yields reported; unless otherwise noted. [a] Ac_2O: 10 equiv. [b] 2 mL of Ac_2O, no MeCN, 85℃. [c] Formyl amide byproduct. [d] NMR ratio.

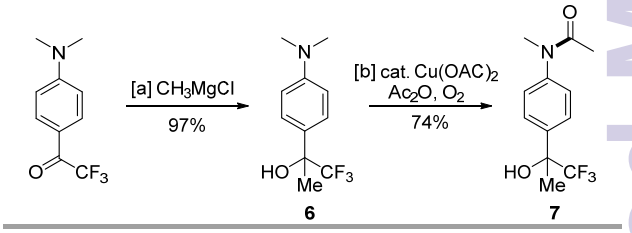
quinoline, thiophene and benzothiazol underwent the aerobic oxidative amidation reaction smoothly, and gave desired products in moderate yields (**4f-i**).

To examine the scope of anhydrides further, *N,N*-dimethyl-2-phenylaniline was allowed to react with various anhydrides (Scheme 4). With the increase of the steric hindrance of the anhydrides, the yields of the amidation products tended to decline under similar conditions (**5a-d**). The pivalic anhydride completely failed to drive the aerobic amidation reaction. Chloride or a phenoxy group substituted acetic anhydride reacted with *N,N*-dimethyl-2-phenylaniline smoothly, and the amidation products were obtained in moderate yields (**5e-f**). Moreover, benzoic anhydride was subjected to the aerobic oxidative amidation, and the benzamide product (**5g**) was produced in 84% yield. Instead of benzoic anhydride, the mixture of benzoic acid and pivalic anhydride could also serve as the benzoylation reagent to afford **5g** in 75% yield.

As an important small-molecule MCD inhibitor, compound **5h** was synthesized by the amidation of the secondary aniline.[12] Starting from its tertiary analogue, the aerobic oxidative amidation could give compound **5h** in yield of 72%. The hexafluoroisopropanol moiety well survived under present conditions. To further demonstrate the generality and practicality of the aerobic oxidative amidation, we proposed to synthesize another MCD inhibitor candidate **7** (Scheme 5), which was prepared via multiple-step reactions such as amidation, alkylation, oxidation and addition reactions.[12b] The easily available starting material trifluoroacetyl aniline could undergo the addition reaction with methyl magnesium chloride under mild condition to give compound **6** in a high yield. Then the aerobic oxidative amidation was carried out to afford the desired product **7** in 74% yield.



Scheme 4. Scope of anhydrides. Conditions: 2-Phenylaniline (0.5 mmol), anhydride (3.0 equiv), $Cu(OAc)_2$ (5 mol %), MeCN (1 mL), O_2 balloon, reflux, 36 hours, isolated yields reported. [a] Benzoic acid (3.0 equiv) and pivalic anhydride (3.0 equiv) instead of benzoic anhydride. [b] 2-phenoxyacetic anhydride: 5.0 equiv.



Scheme 5. Synthetic application. Conditions: [a] CH_3MgCl (2.0 equiv), THF, rt, 2 hours; [b] Compound **6** (0.5 mmol), anhydride (10.0 equiv), $Cu(OAc)_2$ (5 mol %), MeCN (1 mL), O_2 balloon, reflux, 36 hours.

In summary, we have developed a general and practic l method for the tertiary amide synthesis via copper-catalyzed aerobic oxidative amidation of tertiary amines. For the easi available substrates, mild conditions, and good functional group compatibility, this process could potentially offer a practical approach for the tertiary amide synthesis.

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