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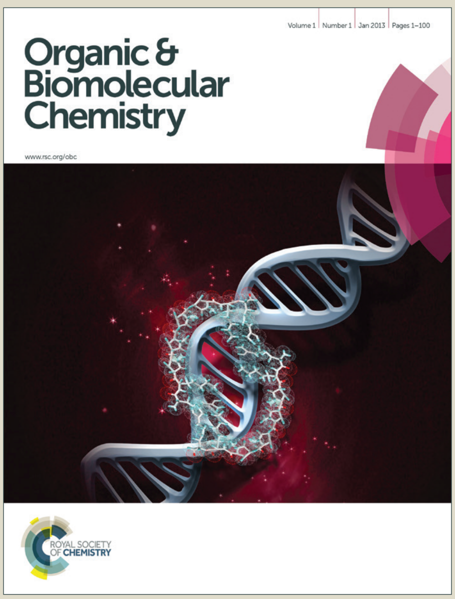

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ARTICLE TYPE

Metal-Free Aerobic Oxidative C-N Bond Cleavage of Tertiary Amines for the Synthesis of *N*-Heterocycles with High Atom Efficiency

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An efficient metal-free aerobic oxidative C−N bond cleavage of tertiary amines has been developed to construct *N*-heterocycles using molecular oxygen as the sole oxidant with high atom efficiency, in which all of the three alkyl groups in tertiary amines can be utilized and transformed into *N*-heterocycles.

Quinazolinone derivatives (Figure 1), one kind of important *N*-heterocyclic compounds, are key components in a variety of synthetic drugs and natural products.[1,2] They are widely used as hypnotic,[2a] sedative,[2b] *anti*-convulsant,[2c] *anti*-bacterial,[2d] *anti*-diabetic,[2e] *anti*-inflammatory[2f] and *anti*-tumor agents.[2g] Although many methods for the synthesis of quinazolinone derivatives have been developed,[3-8] transition metals are generally required. Metal-free condition is highly desirable especially for drug and pharmaceutical industry, because transition metal catalysts are toxic and their contamination must be carefully removed from the products. Besides, O_2 is the ideal oxidant due to its abundance and low cost. Thus, metal-free aerobic oxidative synthesis of *N*-heterocyclic compounds would be a preferable choice.

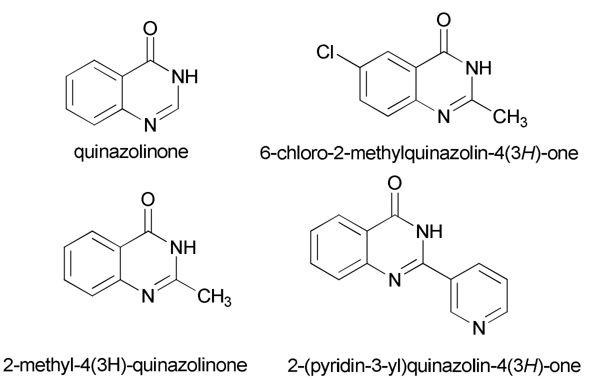
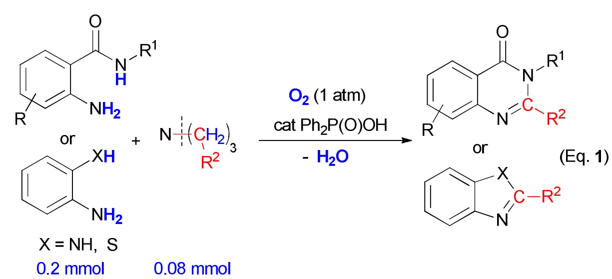


Figure 1 Structure of natural and synthetic biological quinazolinones.

The cleavage of C−N bonds is of significant synthetic interest since such bonds are common in numerous molecules.[9] Given that tertiary amines contain three C−N bonds and are easily prepared, efficient cleavage of the C−N bonds and further synthetic applications in organic synthesis are very attractive.[8] In the reported work, transition metals and their complexes are generally required as the catalysts for the cleavage of C-N bonds[9]. Herein, we report a metal-free aerobic oxidative C-N bond cleavage of tertiary amines for the synthesis of quinazolinone derivatives in high yield (eq. 1). *Worth noting is that all of the three alkyl groups in tertiary amines can be utilized and transformed into quinazolinone derivatives under the present conditions*. In addition, this strategy can also be applied to efficient synthesis of benzimidazoles and benzothiazoles via similar oxidation-cyclization of tertiary amines with *o*-phenylenediamine or *o*-aminothiophenol, respectively. To the best of our knowledge, there is no precedent on transition-metal-free C-N bond cleavage of tertiary amines for the synthesis of *N*-heterocycles employing molecular oxygen as the sole oxidant.



Initially, 0.2 mmol *o*-aminobenzamide **1a** and 0.08 mmol triethylamine **2a** were used to synthesize quinazolinone **3a** in the presence of 10 mol% $Cu(OAc)_2$ and 20 mol% $Ph_2P(O)OH$ in dioxane at 130 °C. After 13 h, 2-methylquinazolin-4(3*H*)-one **3a** was produced in 82% yield (Table 1, entry 1). By extending reaction time to 18 h, 88% yield of **3a** was achieved (Table 1, entry 2). Interestingly, in the absence of the copper salt, the reaction also proceeded to give 76% yield of **3a** and 13% yield of 2-methyl-2,3-dihydroquinazolin-4(1*H*)-one **3a**[1] (Table 1, entry 3). Compound **3a**[1] could be further converted to **3a** via oxidative dehydrogenation after a prolonged reaction time (Table 1, entry 4). It was noted that the reaction catalyzed by $Cu(OAc)_2$ gave only 25% yield of **3a** (Table 1, entry 5), almost equivalent to that under metal-free and acid-free conditions (Table 1, entry 6),

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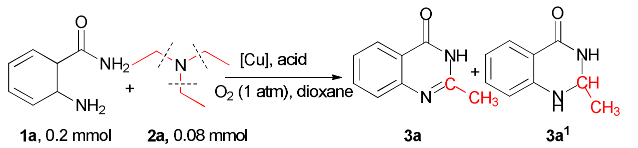
indicating that copper catalyst was not necessary in the present system (for details, see SI). Then, the effect of $Ph_2P(O)OH$ loading was investigated. Obviously, increase of $Ph_2P(O)OH$ to 50 mol% amount did not improve the yield of **3a** (Table 1, entry 7), whereas decrease of $Ph_2P(O)OH$ to 10 mol% amount resulted in much lower yield (Table 1, entry 8). Oxygen was essential for this reaction. For example, lower yield of **3a** was obtained under air (Table 1, entry 9), while this reaction did not take place at all under inert atmosphere (Table 1, entry 10).

Table 1 Optimization of the reaction conditions[a]

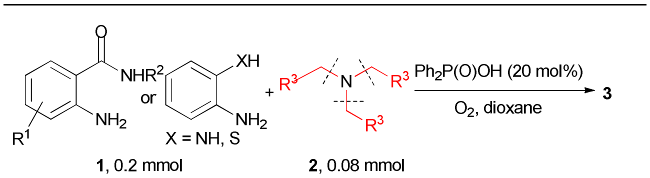


Entry	Catalyst	Additive	Time (h)	Yield **3a**/**3a**^{1}(%)[b]
1	$Cu(OAc)_2$	$Ph_2P(O)OH$	13	82/2
2	$Cu(OAc)_2$	$Ph_2P(O)OH$	18	88/-
3	-	$Ph_2P(O)OH$	13	76/13
4	-	$Ph_2P(O)OH$	18	90/0
5	$Cu(OAc)_2$	-	18	25/5
6	-	-	18	27/4
7[c]	-	$Ph_2P(O)OH$	18	91/-
8[d]	-	$Ph_2P(O)OH$	18	61/8
9[e]	-	$Ph_2P(O)OH$	18	15/6
10[f]	-	$Ph_2P(O)OH$	18	-/-

[a] Reaction conditions: *o*-aminobenzamide **1a** (0.2 mmol), NEt_3 **2a** (0.08 mmol), catalyst (For [Cu], 10 mol%; for acid, 20 mol%) based on **1a**, dioxane (1.0 mL), O_2 (1 atm) in a Schlenk tube (10 mL), 130 ºC, 13-18 h, recharging oxygen after 9 h. [b] GC yield based on **1a**, **3a**/**3a**^{1} based on GC. [c] $Ph_2P(O)OH$ (50 mol%). [d] $Ph_2P(O)OH$ (10 mol%). [e] Under air. [f] Under N_2.

Under the optimized reaction conditions, substrate scope of this reaction was investigated. As shown in Table 2, *o*-substituted anilines could readily react with aliphatic tertiary amines to produce the corresponding quinazolinone derivatives. It should be noted that the reactivity of the oxidative cyclocondensation was independent of the alkyl chain length, and different aliphatic tertiary amines could efficiently undergo oxidative cyclocondensation with *o*-substituted anilines, giving the quinazolinone derivatives **3** in high yields with high atom efficiency (Table 2, entries 1-4). Especially, tribenzylamine **2e** was used as the substrate, the aryl-substituted quinazolinone **3e** was afforded in 86% yield

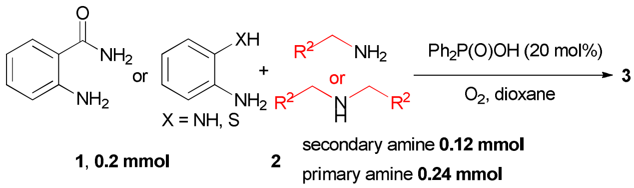
Table 2 Substrate scope of *o*-substituted anilines **1** and amines **2**[a]



Entry	Aniline **1**	Amine **2**	Product	Yield[b] (%)
1	**1a**	$N(C_2H_5)_3$ **2a**	**3a**	87
2	**1a**	$N(n\text{-}C_3H_7)_3$ **2b**	**3b**	80
3	**1a**	$N(n\text{-}C_4H_9)_3$ **2c**	**3c**	79
4	**1a**	$N(n\text{-}C_8H_{17})_3$ **2d**	**3d**	81
5	**1a**	$N(CH_2Ph)_3$ **2e**	**3e**	86
6	**1a**	**2f**	**3f**	82
7	**1a**	**2g, 0.04 mmol**	**3g**	95
8	**1a**	**2h**	**3g** / **3e**	65 / 26
9	**1b**	**2a**	**3h**	91
10	**1b**	**2e**	**3i**	87
11	**1c**	**2b**	**3j**	83
12	**1c**	**2e**	**3k**	85
13	**1d**	**2b**	**3l**	81
14	**1d**	**2e**	**3m**	82
15[c]	**1e**	**2b**	**3n**	85
16[c]	**1e**	**2d**	**3o**	88
17[c]	**1f**	**2d**	**3p**	82
18[c]	**1f**	**2e**	**3q**	86

[a] Reaction conditions: **1a-1f** (0.2 mmol), tertiary amine **2a-2h** (0.08 mmol), $Ph_2P(O)OH$ (20 mol%) based on **1**, dioxane (1.0 mL), O_2 (1 atm) in a Schlenk tube (10 mL), 130 ºC, 18 h, recharging oxygen after 9 h. [b] Isolated yield. [c] 115 ºC, 12 h.

Table 3 Substrate scope of *o*-substituted anilines **1** with primary amines or secondary amines[a]



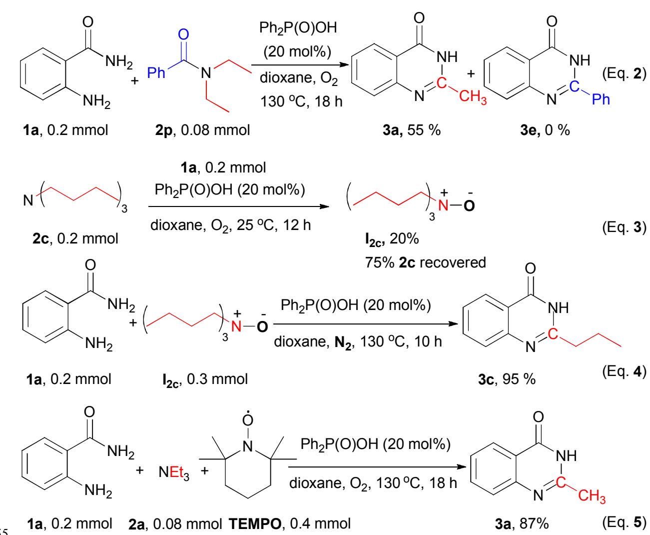
Entry	Aniline **1**	Amine **2**	Product	Yield[b] (%)
1	**1a**	**2i**	**3f**	74
2	**1a**	*t*-BuNH2 **2j**	—	—
3	**1a**	**2k**	**3r**	92
4[c]	**1e**	NH(*n*-C4H9)2 **2l**	**3s**	80
5[c]	**1e**	**2m**	**3t**	90
6[c]	**1f**	NH(*n*-C3H7)2 **2n**	**3u**	78
7[c]	**1f**	**2o**	**3v**	93

[a] Reaction conditions: *o*-substituted aniline **1a-1f** (0.2 mmol), primary amine (0.24 mmol), secondary amine (0.12 mmol), $Ph_2P(O)OH$ (20 mol%) based on 1, dioxane (1.0 mL), O_2 (1 atm) in a Schlenk tube (10 mL), 130 °C, 18 h, recharging oxygen after 9 h. [b] Isolated yield. [c] 115 °C, 12 h.

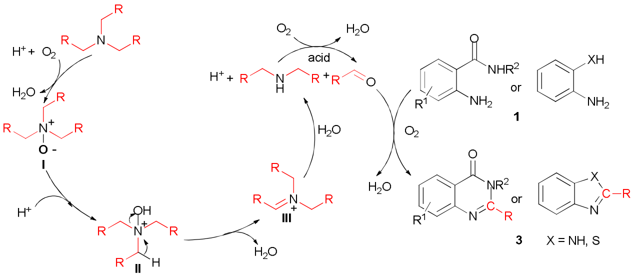
(Table 2, entry 5). When triisopropanolamine **2f** bearing only one α-H was used as substrate, product **3f** was obtained (Table 2, entry 6). Promoted by $Ph_2P(O)OH$, hexamethylenetetramine also served as efficient substrate, furnishing natural product **3g** in 95% yield (Table 2, entry 7). Using *N,N*-dimethyl-1-phenylmethanamine **2h** with two kinds of N-C bonds as the substrate, two types of products, **3g** and **3e** with an almost 2:1 ratio were formed (Table 2, entry 8). Under the present reaction conditions, substituted *o*-aminobenzamides **1b**, **1c** and **1d** bearing methyl and chloro functionalities also reacted with tertiary amines to give the corresponding quinazolinone derivatives **3** in good yields (Table 2, entries 9-14). The protocol can also be applied to synthesis of the bioactive benzimidazoles and benzothiazoles. For example, similar oxidative cyclization of *o*-phenylenediamine and *o*-aminothiophenol with tertiary amines readily took place, giving the corresponding benzimidazoles **3n-3o** and benzothiazoles **3p-3q** in high yields (Table 2, entries 15-18).

Besides tertiary amines, primary and secondary amines are also efficient substrates to afford the corresponding *N*-heterocyclic compounds in high yields (Table 3, entries 1-7). It is noted that NC-H bond in tertiary amine is essential for this catalytic oxidative system. For example, there was no product detected using *t*-butylamine **2j** as substrate, which has no NC-H unit (Table 3, entry 2).

To get insights into the reaction mechanism, several control experiments were carried out. Firstly, the reaction of *o*-aminobenzamide **1a** with *N,N*-diethylbenzamide **2p** was performed under similar reaction conditions, **3a** was obtained in 55% yield, whereas **3e** was not detected at all, showing that amide was not the efficient substrate (eq. 2). When *o*-aminobenzamide **1a** and 1.0 equiv tri-*n*-butylamine **2c** were used as substrates at 25 °C, tri-*n*-butylamine *N*-oxide $\mathbf{I_{2c}}$ was obtained (eq. 3) and the resulting tri-*n*-butylamine *N*-oxide $\mathbf{I_{2c}}$ was found to react with *o*-aminobenzamide **1a** under N_2 atmosphere, producing the corresponding quinazolinone derivatives **3c** (eq. 4). Thus, *N*-oxide was probably an intermediate of this reaction.[10] During the reaction of *o*-aminobenzamide with 1.2 equiv tri-*n*-octylamine, secondary amine and aldehyde were detected by GC-MS (see SI). When radical scavenger TEMPO was loaded under the standard reaction conditions, the desired product **3a** was still obtained in 87% yield, indicating that a free radical perhaps was not involved in the present reaction process (eq. 5).



Based on above results and the reported literatures,[11] the reaction possibly takes place as shown below (Scheme 1). Initially, in the presence of molecular oxygen, tertiary amine is oxidized to *N*-oxide **I**, followed by protonation to form **II** under suitable pH condition. Dehydration of **II** affords the immonium ion **III**, which is readily hydrolyzed to produce secondary amine and aldehyde.[12] Finally, *N*-heterocyclic compound **3** is produced by condensation/oxidative dehydrogenation of *in situ* aldehyde[13] with *o*-substituted aniline. The resulting secondary amine and primary amine can react with *o*-substituted aniline readily and be further converted to *N*-heterocyclic compound **3**.[7] The fact that the amine bearing no α-H can not be converted to **3** also supports this mechanism, in which the immonium salt **III** can not be formed.



Scheme 1. Possible mechanism for aerobic oxidative C-N bond cleavage and cyclization reaction.

In summary, a metal-free aerobic oxidative C-N bond cleavage of tertiary amines with *o*-substituted anilines for the preparation of *N*-heterocyclic derivatives has been developed. We believe this environmentally benign and highly atom-efficiency protocol will find wide potential application in organic synthesis.

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12 Aldehydes were formed in the absence of the substrate **1** under similar reaction condition. For examples, in the presence of 20 mol% $Ph_2P(O)OH$, tri-*n*-octylamine and tribenzylamine could be readily oxidized by dioxygen and the corresponding aldehydes were provided in 56% and 50% yields, respectively.

13 In the absence of $Ph_2P(O)OH$, the reaction of benzaldehyde with *o*-aminobenzamide **1a** took place smoothly under similar reaction condition and the product 2-phenylquinazolin-4(3*H*)-one was produced in 97% yield.