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Original article

Synthesis of quinazolinones from *o*-aminobenzamides and benzyl amines under metal-free conditions

Xin-Xin Qi [a], Zhen-Zhen Song [a], Jin-Long Gong [a], Zheng-Yu Fang [b], Xiao-Feng Wu [a,c,*]

[a] Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campous, Hangzhou 310018, China
[b] Department of Anal-colorectal Surgery, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, China
[c] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, 18059 Rostock, Germany

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ABSTRACT

A convenient and transition-metal free protocol for quinazolinones synthesis with *o*-aminobenzamides and benzyl amines as substrates has been developed. Using H_2O_2 as the oxidant, various quinazolinones were obtained in moderate to good yields under metal- and additive-free conditions.

1. Introduction

Quinazolinones represent a high value class of compounds in organic chemistry, which has a wide range of biological and pharmacological activities [1], including anti-bacterial [2], anti-cancer [3], anti-inflammatory [4], anti-microbial [5], anti-tubercular [6], anti-ulcer [7], and so on [8]. Additionally, they are important intermediates in natural products preparation [9] and applied as structural scaffold in drug discovery [1c].

Owing to their diverse bioactivity and privileged sub-structure for drug design, the synthetic methodologies development becomes attractive and many synthetic routes have been developed [10a]. For example, copper-catalyzed Ullmann-type coupling reactions [10b], redox condensation between *o*-substituted nitrobenzenes with amines in the presence of iron and cobalt as catalysts [11], one-pot synthesis of quinazolinones from benzyl alcohols by iridium or ruthenium catalysts [12]. In these reactions, metal-salts turned out to be indispensable, and many metal wastes were generated. Besides, condensation between *o*-aminobenzamides and aldehydes with additional oxidants is also a typical method to prepare quinazolinones [13]. Recently, a procedure on autoxidation of benzyl amines and applied in heterocycles synthesis was developed as well [14a]. Five examples of quinazolinones were prepared in moderate yields under 150 °C with 40% AcOH as the additive. Meanwhile, we reported a procedure for the transformation of benzyl amines to the corresponding imines [15]. Various imines were produced in good to excellent yields under metal-free conditions and with H_2O_2 as the green oxidant. From mechanistic point of view, the oxidation of benzyl amines to the corresponding benzaldehydes should be the first step and then followed by condensation to give the imines. Hence, we believe a procedure for quinazolinones preparation with *o*-aminobenzamides and benzylamines as the substrates without metal catalysts and using H_2O_2 as the green oxidant should be highly realizable. Under this context, we developed this interesting metal-free and additive-free procedure for the synthesis of quinazolinones from *o*-aminobenzamides and benzyl amines.

2. Experimental

A 15 mL tube was added 2-aminobenzamide (1 mmol), benzyl amine (1.5 mmol), and a stir bar. Then H_2O_2 (30 wt% in H_2O, 5 equiv.) was added by a syringe at room temperature under open air. The tube was closed and kept at 120 °C for 20 h. The conversion and yield were determined by GC and GC–MS using hexadecane (0.1 mmol) as the internal standard.

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[*] Corresponding author at: Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campous, Hangzhou 310018, China.
E-mail address: xiao-feng.wu@catalysis.de (X.-F. Wu).

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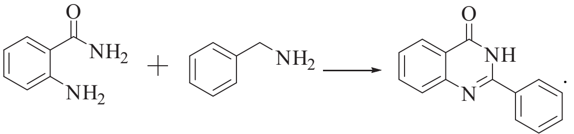
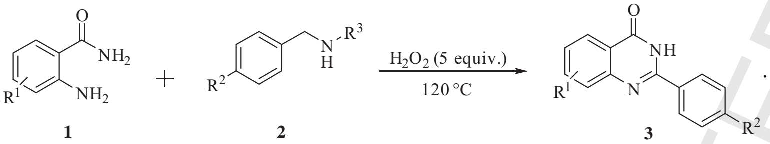
Table 1
Screening of the reaction conditions.[a]


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

Entry	Oxidant (equiv.)	Solvent (2 mL)	Temp. (°C)	Yield (%)[b]
1	H_2O_2 (5)	DMSO	100	25
2	H_2O_2 (5)	DMF	100	0
3	H_2O_2 (5)	DMA	100	0
4	H_2O_2 (5)	dioxane	100	<5
5	H_2O_2 (5)	THF	100	<5
6	H_2O_2 (5)	H_2O	100	<5
7	H_2O_2 (5)	C_2H_5OH	100	20
8	H_2O_2 (5)	CH_3CN	100	20
9	H_2O_2 (5)	CH_3NO_2	100	0
10	H_2O_2 (5)	DCE	100	35
11	H_2O_2 (5)	–	100	50
12	H_2O_2 (3)	–	100	30
13	H_2O_2 (8)	–	100	<10
14	H_2O_2 (5)	–	120	71
15	H_2O_2 (5)	–	80	46

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), oxidant, solvent (2 mL), 20 h.
[b] GC yield, with hexadecane as the internal standard.

Table 2
Synthesis of quinazolinones: substrates testing.[a]



1 **2** **3**

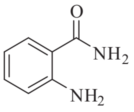
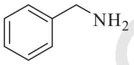
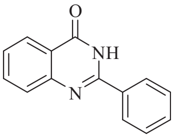
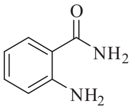
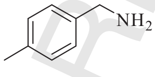
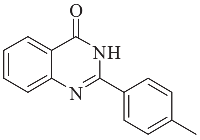
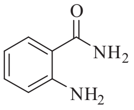
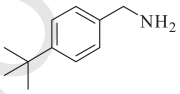
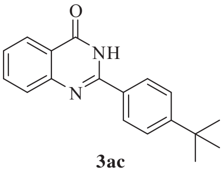
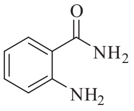
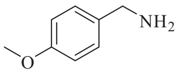
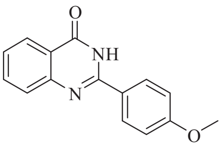
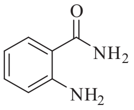
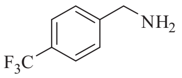
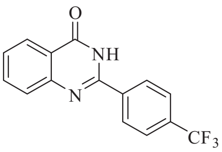
Entry	1	2	3	Yield **3** (%)[b]
1	 **1a**	 **2a**	 **3aa**	71
2	 **1a**	 **2b**	 **3ab**	59
3	 **1a**	 **2c**	 **3ac**	69
4	 **1a**	 **2d**	 **3ad**	44
5	 **1a**	 **2e**	 **3ae**	50

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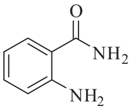
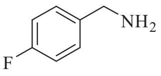
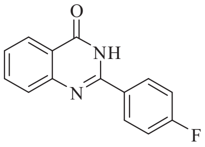
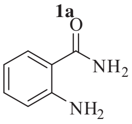
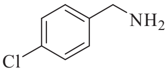
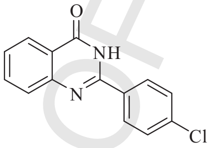
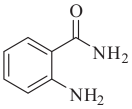
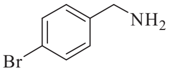
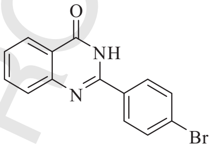
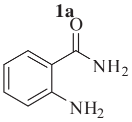
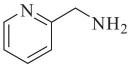
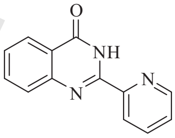
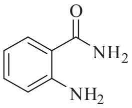
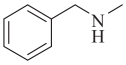
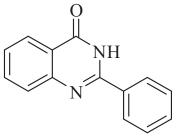
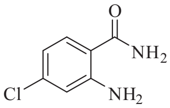
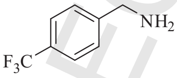
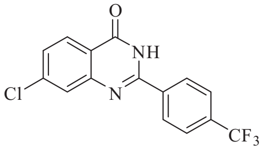
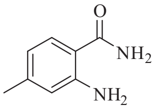
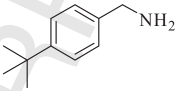
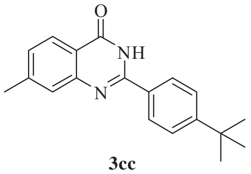
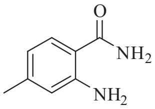
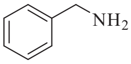
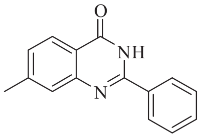
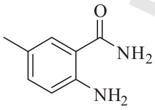
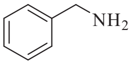
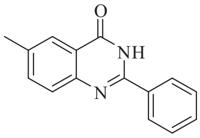
Table 2 (*Continued*)

Entry	**1**	**2**	**3**	Yield **3** (%)[b]
6	 **1a**	 **2f**	 **3af**	45
7	 **1a**	 **2g**	 **3ag**	40
8	 **1a**	 **2h**	 **3ah**	44
9	 **1a**	 **2i**	 **3ai**	65
10	 **1a**	 **2j**	 **3aa**	45
11	 **1b**	 **2k**	 **3bk**	40
12	 **1c**	 **2c**	 **3cc**	40
13	 **1c**	 **2a**	 **3ca**	50
14	 **1d**	 **2a**	 **3da**	65

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), H_2O_2 (5 equiv.), 120 °C, 20 h.
[b] GC yield.

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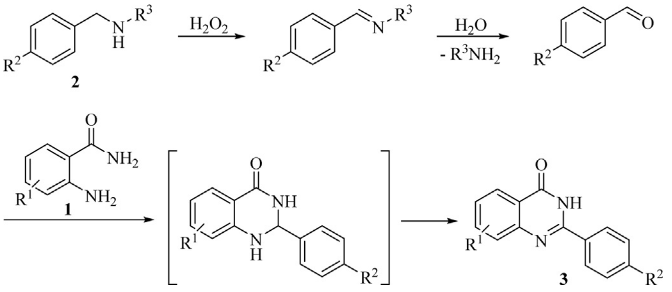

Scheme 1. Proposed reaction mechanism.

3. Results and discussion

At the beginning, substrates **1a** and **2a** were chosen as the starting materials. The reaction was conducted with 5 equiv. of H_2O_2 (30 wt% in H_2O) at 100 °C in DMSO, fortunately, 25% yield of the target product **3aa** was obtained (Table 1, entry 1). Encouraged by this result, we continued with the studies of different solvents which did not improve the yield significantly (Table 1, entries 2–10). However, when we tried the reaction without solvent, the yield raised to 50% (Table 1, entry 11). Furthermore, the amount of H_2O_2 was examined, less and more H_2O_2 all decreased the yield (Table 1, entries 12 and 13). Notably, reaction temperature was found hold great influence for this transformation. 80 °C resulted in 46% yield (Table 1, entry 15), while 120 °C resulted in 71% yield (Table 1, entry 14). No better yield can be obtained under higher reaction temperature.

Inspired by this result, we next investigated the substrates scope. First, *o*-aminobenzamide and a variety of *para*-substituted benzyl amines were studied (Table 2, entries 1–10). The substrates with electron-donating group, such as methyl, *tert*-butyl group smoothly afford the quinazolinones in 59% and 69% yield (Table 2, entries 2 and 3). However, as an electron-rich group, *para*-methoxybenzylamine decreased the yield of the desired product to 44% (Table 2, entry 4). A moderate product yield was generated when the substrate decorated with electron-deficient group, such as trifluoromethyl moiety (Table 2, entry 5). Moreover, benzyl amines bearing fluoro, chloro, and bromo provided the desired products with slightly lower yields (Table 2, entries 6–8). It is noteworthy that heteroaromatic substrate can also be tolerated under the standard condition, resulted the corresponding product in 65% yield (Table 2, entry 9). In addition, *N*-substituted benzylamine was also examined, affording the product **3aa** in 45% yield (Table 2, entry 10). However, aliphatic amines such as butylamine and 2-phenylethanamine failed in our system. Additionally, no desired product was observed with *N,N*-dimethylbenzyl amine.

Next, a series of *o*-aminobenzamides were then subjected to the optimized reaction conditions, and the results were summarized (Table 2, entries 11–14). We were delighted to find that all the *o*-aminobenzamides examined worked well and succeeded to give the target products in moderate yields.

Regarding the reaction pathway, a possible reaction mechanism has been proposed in Scheme 1. First, benzyl amine **1** was oxidized to benzaldehyde in the presence of H_2O_2. Then, the condensation of the *in situ* formed aldehyde with *o*-aminobenzamide **2** occurred. The condensed intermediate can provide the final quinazolinone **3** after further oxidation step.

4. Conclusion

In conclusion, we have developed an environmental friendly strategy for the quinazolinones preparation. With *o*-aminobenzamides and benzyl amines as the substrates and H_2O_2 as the green oxidants under metal-free and solvent-free conditions, a variety of quinazolinones were generated in moderate to good yields.

Acknowledgments

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