



## A facile vanadium-catalyzed aerobic oxidative synthesis of quinazolinones from 2-aminobenzamides with aldehydes or alcohols



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### ABSTRACT

An efficient and simple VO(acac)<sub>2</sub>-catalyzed approach to the synthesis of quinazolinones has been developed. Various substituted quinazolinones have been synthesized from 2-aminobenzamides with alcohols or aldehydes in good to excellent yields with molecular oxygen as the oxidant. The process can also be scaled up.

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### Introduction

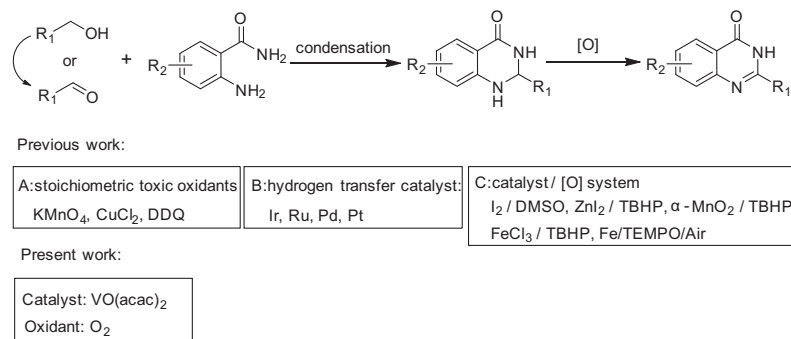
As an important class of fused heterocycles, quinazolinones are widely present in natural products and play a significant role in the synthesis of pharmaceutical compounds for their excellent biological and therapeutic activities.<sup>1</sup> The quinazolinone derivatives are efficient antitumor, antihistamine, anti-inflammatory, and antihypertensive.<sup>2</sup> Moreover, they are used as ligands in the central nervous system, including CNS stimulant, analgesic, tranquilizer, and antianxiotic.<sup>3</sup>

Regarding the variety of uses of quinazolinone skeleton in medicinal chemistry, a number of different substituted quinazolinones have been synthesized.<sup>2c,4</sup> A lot of different substrates have been utilized for their preparation, such as 2-nitrobenzamides,<sup>5</sup> 2-aminobenzamides,<sup>6</sup> 2-halobenzamides,<sup>7</sup> 2-aminobenzophenones,<sup>8</sup> 2-aminobenzonitriles,<sup>9</sup> and 2-halobenzoic acids.<sup>10</sup> Among those synthetic methods, the reactions of 2-aminobenzamide with alcohols have received more and more attention. As shown in Scheme 1, a classical synthetic method is the condensation of 2-aminobenzamide with aldehydes to give the amination intermediate, followed by oxidation to quinazolinones. For this oxidation, stoichiometric and large excess amounts of toxic oxidants, e.g., KMnO<sub>4</sub>, CuCl<sub>2</sub>, DDQ, were required.<sup>11</sup> In 2013, Wei and co-workers reported a two-step oxidative system using I<sub>2</sub> as a catalyst and using DMSO as an oxidant for the synthesis of quinazolinones.<sup>12</sup> In 2014, Wu

and co-workers reported a ZnI<sub>2</sub>-catalyzed oxidative cyclization to quinazolinones by using *tert*-butyl hydroperoxide (TBHP) as the oxidant.<sup>13</sup> Cheon and co-workers developed a metal-free protocol for the synthesis of quinazolinones in DMSO at relatively high temperature, but this system is limited to aldehydes as substrates.<sup>14</sup> Recent reports gave improved catalytic methods using transition metal catalysts, such as α-MnO<sub>2</sub>, FeCl<sub>3</sub>, and using TBHP as an oxidant.<sup>15</sup> Very recently, an iron nitrate/TEMPO-catalyzed approach for the synthesis of quinazolinones has been developed.<sup>16</sup> Some noble metals, for example Ir, Ru, Pd, Pt, were also used in the synthesis of quinazolinones.<sup>17</sup> But these methods are suffering from drawbacks such as harsh reaction conditions and longer reaction time. Sometimes low yields were observed due to the complicated reaction process. In an effort to address some of these limitations and based on our group continuing interest in developing more efficient and facile synthetic methodologies using environmentally friendly molecular oxygen as terminal oxidant,<sup>18</sup> we intend to develop a new and efficient catalytic system for the synthesis of quinazolinones by utilizing dioxygen as an oxidant.

Vanadium compounds have been known as important oxidation catalysts and applied in organic synthesis.<sup>19</sup> Quite recently, we discovered that vanadium complex (HQ)<sub>2</sub>V(O)(O<sup>i</sup>Pr) as catalyst can realize the aerobic oxidative synthesis of imines directly from the oxidative reactions of coupling of primary amines and alcohols with amines without any additional additive or promoter.<sup>20</sup> In an attempt to extend this chemistry, we can make a reasonable conjecture that the in situ generated aldehyde from alcohol can

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**Scheme 1.** Synthesis of quinazolinones from aldehydes and alcohols.

react with *o*-aminobenzamide to form an imine intermediate, then the imine intermediate cyclized to form a iminal and subsequent oxidative dehydrogenation in the presence of vanadium catalyst. Herein, we report the vanadium-catalyzed aerobic oxidative synthesis of quinazolinones from 2-aminobenzamides with alcohols or aldehydes under mild conditions with dioxygen as the oxidant. Without the addition of any ligand and additive, various substituted quinazolinones have been synthesized in excellent yields. These very mild reaction conditions make the present catalysts useful, particularly for practical applications in organic synthesis.

## Results and discussion

In order to optimize the catalytic conditions, we chose the reaction of equimolar amounts of 2-aminobenzamide (**1a**) and benzaldehyde (**2a**) as a model system. To begin with, 2-aminobenzamide was reacted with benzaldehyde in the presence of 5 mol % VO(acac)<sub>2</sub> at 80 °C under 1 atm of oxygen atmosphere for 17 h, 99% of dehydrogenated product (**3a**) was obtained (Table 1, entry 1). Further, when the reaction time was shortened to 2 h, dehydro-

**Table 1**  
Optimization of the reaction conditions for the synthesis of quinazolinones<sup>a</sup>

Entry	Catalyst	Solvent	Time [h]	Yield <sup>b</sup> [%]
1	VO(acac) <sub>2</sub>	DCE	17	>99
2	VO(acac) <sub>2</sub>	DCE	12	>99
3	VO(acac) <sub>2</sub>	DCE	8	>99
4	VO(acac) <sub>2</sub>	DCE	4	>99
5	VO(acac) <sub>2</sub>	DCE	2	99
6	V <sub>2</sub> O <sub>5</sub>	DCE	2	55
7	VOSO <sub>4</sub>	DCE	2	64
8	(HQ) <sub>2</sub> V(O)(O <sup>i</sup> Pr)	DCE	2	55
9	VO(acac) <sub>2</sub>	Toluene	2	61
10	VO(acac) <sub>2</sub>	MeOH	2	95
11	VO(acac) <sub>2</sub>	MeCN	2	86
12	VO(acac) <sub>2</sub>	THF	2	54
13	VO(acac) <sub>2</sub>	DMF	2	34
14 <sup>c</sup>	VO(acac) <sub>2</sub>	DCE	2	52
15 <sup>d</sup>	VO(acac) <sub>2</sub>	DCE	2	80
16 <sup>e</sup>	VO(acac) <sub>2</sub>	DCE	2	0
17 <sup>f</sup>	—	DCE	2	0

<sup>a</sup> Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), catalyst (5 mol %), solvent (2 mL), 80 °C, 1 atm O<sub>2</sub>.

<sup>b</sup> Determined by GC using internal standard.

<sup>c</sup> 60 °C.

<sup>d</sup> Under air.

<sup>e</sup> Under argon. Determined by NMR.

<sup>f</sup> Without catalyst. Determined by NMR.

**Table 2**  
Reaction of 2-aminobenzamide with different aldehydes<sup>a</sup>

Entry	Aldehyde	Product	Yield <sup>b</sup> [%]
1	<b>2a</b> (benzaldehyde)	<b>3a</b> (2-phenylquinazolinone)	89
2	<b>2b</b> (4-methylbenzaldehyde)	<b>3b</b> (2-(4-methylphenyl)quinazolinone)	90
3	<b>2c</b> (4-methoxybenzaldehyde)	<b>3c</b> (2-(4-methoxyphenyl)quinazolinone)	85
4	<b>2d</b> (4-fluorobenzaldehyde)	<b>3d</b> (2-(4-fluorophenyl)quinazolinone)	79
5	<b>2e</b> (4-chlorobenzaldehyde)	<b>3e</b> (2-(4-chlorophenyl)quinazolinone)	84
6	<b>2f</b> (4-bromobenzaldehyde)	<b>3f</b> (2-(4-bromophenyl)quinazolinone)	82
7	<b>2g</b> (4-(trifluoromethyl)benzaldehyde)	<b>3g</b> (2-(4-(trifluoromethyl)phenyl)quinazolinone)	82
8	<b>2h</b> (3-fluorobenzaldehyde)	<b>3h</b> (2-(3-fluorophenyl)quinazolinone)	81

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