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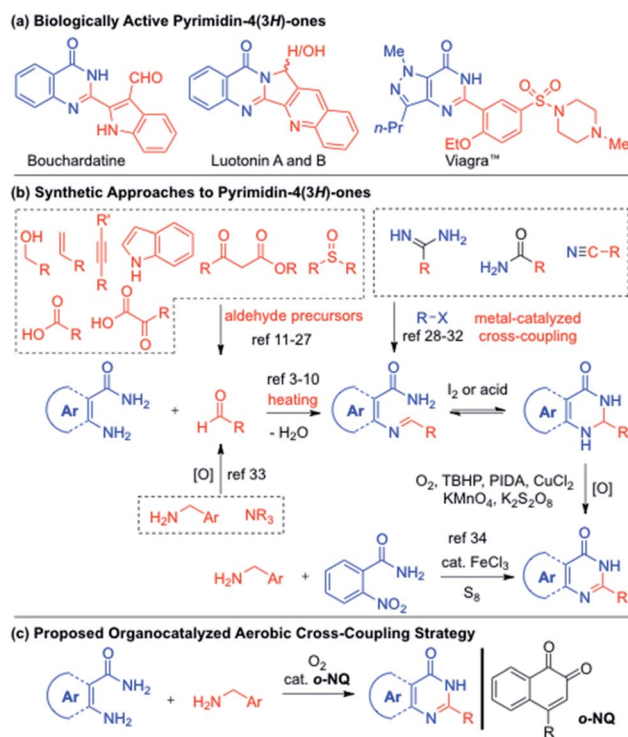
# *ortho*-Naphthoquinone-catalyzed aerobic oxidation of amines to fused pyrimidin-4(3*H*)-ones: a convergent synthetic route to bouchardatine and sildenafil†

 Kyeongha Kim, Hun Young Kim  and Kyungsoo Oh \*

A facile access to fused pyrimidin-4(3*H*)-one derivatives has been established by using the metal-free *ortho*-naphthoquinone-catalyzed aerobic cross-coupling reactions of amines. The utilization of two readily available amines allowed a direct coupling strategy to quinazolinone natural product, bouchardatine, as well as sildenafil (Viagra™) in a highly convergent manner.

N-Heterocyclic compounds with a pyrimidin-4(3*H*)-one core constitute a large number of natural products and biologically active molecules. For example, quinazolinone alkaloids possess a phenyl-fused pyrimidin-4(3*H*)-one structure and display a wide spectrum of pharmacological activities (Scheme 1a).<sup>1</sup> Sildenafil (Viagra™), a potent and selective inhibitor of type 5 phosphodiesterases on smooth muscle cell, is based on the pyrazole-fused pyrimidin-4(3*H*)-one structure and marketed for erectile dysfunction.<sup>2</sup> The synthetic approaches to the phenyl-fused pyrimidin-4(3*H*)-ones, quinazolinones, typically involve the condensation between anthranilamides and aldehydes to give amination intermediates that in turn oxidized to quinazolinones under oxidation conditions (Scheme 1b). The oxidation catalysts include Cu,<sup>3</sup> Fe,<sup>4</sup> Ga,<sup>5</sup> Ir,<sup>6</sup> Mn,<sup>7</sup> iodine,<sup>8</sup> peroxide,<sup>9</sup> however the aerobic oxidation of amination intermediates is also known at 150 °C.<sup>10</sup> The utilization of alcohols also effects the one-pot synthesis of quinazolinones through *in situ* oxidation to aldehydes in the presence of Fe,<sup>11</sup> Ir,<sup>12</sup> Mn,<sup>13</sup> Ni,<sup>14</sup> Pd,<sup>15</sup> Ru,<sup>16</sup> V,<sup>17</sup> Zn,<sup>18</sup> and iodine catalysts.<sup>19</sup> Other precursors to aldehydes have been also identified using alkynes,<sup>20</sup> benzoic acids,<sup>21</sup> indoles,<sup>22</sup>  $\alpha$ -keto acid salts,<sup>23</sup>  $\beta$ -keto esters,<sup>24</sup> styrenes,<sup>25</sup> sulfoxides,<sup>26</sup> and toluenes.<sup>27</sup> Non-aldehyde approaches to quinazolinones have been also demonstrated in the cross coupling of amidines,<sup>28</sup> amines,<sup>29</sup> benzamides,<sup>30</sup> isocyanides,<sup>31</sup> and nitriles.<sup>32</sup> In 2013, the Nguyen group disclosed the synthesis of four quinazolinones, utilizing the autooxidation of benzylamines to imines that subsequently condensed with anthranilamides.<sup>33</sup> While a closed system at 150 °C was necessary, the use of 40 mol% AcOH without solvent provided the quinazolinones in 46–75%

yields. The Nguyen group also developed the FeCl<sub>3</sub>·6H<sub>2</sub>O-catalyzed condensation of 2-nitroanilines and benzylamines in the presence of 20 mol% of S<sub>8</sub>, where six quinazolinones were obtained in 68–75% yields.<sup>34</sup> While the cross condensation of anthranilamides and benzylamines was accomplished, there exists a significant knowledge gap due to the limited substrate scope combined with less optimal reaction conditions (*i.e.* high



Scheme 1 Biologically active fused pyrimidin-4(3*H*)-one derivatives and their synthetic methods.

Center for Metareceptome Research, Graduate School of Pharmaceutical Sciences, Chung-Ang University, 84 Heukseok-ro, Dongjak, Seoul 06974, Republic of Korea.  
 E-mail: [kyungsooh@cau.ac.kr](mailto:kyungsooh@cau.ac.kr)

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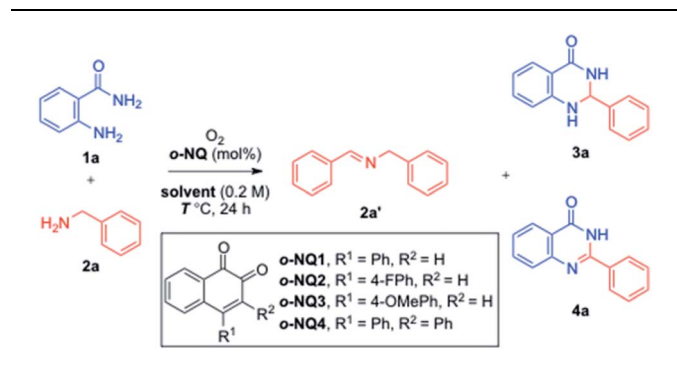
reaction temperature, closed system in neat conditions and excess use of amines). In addition, it is not entirely clear if the cross condensation of amide-containing amines and benzylamines would work for other fused pyrimidin-4(3*H*)-one derivatives.<sup>35</sup> To address such shortcomings in the cross condensation of amines, the *ortho*-naphthoquinone (*o*-NQ)-catalyzed aerobic cross amination strategy was investigated (Scheme 1c).<sup>36</sup> Herein, we report a highly general approach to fused pyrimidin-4(3*H*)-one derivatives in the presence of *o*-NQ catalyst, culminating to the direct aerobic coupling of two amines to bouchardatine and sildenafil.

Given that the *o*-NQ-catalyzed aerobic cross coupling of benzylamines and aniline derivatives such as *o*-phenylenediamines provided a facile approach to heterocyclic compounds including benzoimidazoles,<sup>37</sup> the use of anthranilamide **1a** and benzylamine **2a** was examined as a model study (Table 1). The catalytic use of *o*-NQ1 smoothly converted benzylamine **2a** to

the corresponding homocoupled imine **2a'** under aerobic conditions. However, the subsequent *in situ* condensation reaction of **2a'** with anthranilamide **1a** only provided the aminal product **3a** in 11% yield (entry 1). To facilitate the cross coupling between the amine **2a** and anthranilamide **1a**, a catalytic amount of TFA was utilized where a significant improvement in yield was observed for **3a** (entry 2). Faced with the inability to oxidize the aminal **3a** to the corresponding product, quinazolinone **4a**, other *ortho*-naphthoquinone catalysts were screened without much success (entries 3–5). To our delight, the examination of solvents revealed that the reaction temperature of 100 °C was needed for the formation of **4a** (entries 6–11).<sup>38</sup> The reaction in DMSO lowered down the ratio of **1a** and **2a** from 1.0 : 1.5 to 1.0 : 1.2 (entry 12) and the catalyst loading to 5 mol% without affecting the overall reaction efficiency (entry 13). The control experiments confirmed the critical roles of both *o*-NQ1 and TFA (entries 15–18), and the reaction utilized molecular oxygen as a terminal oxidant (entries 19 and 20). Piecing together the experimental data, the employment of 5 mol% *o*-NQ1 and 20 mol% TFA in DMSO at 100 °C was selected for further studies.

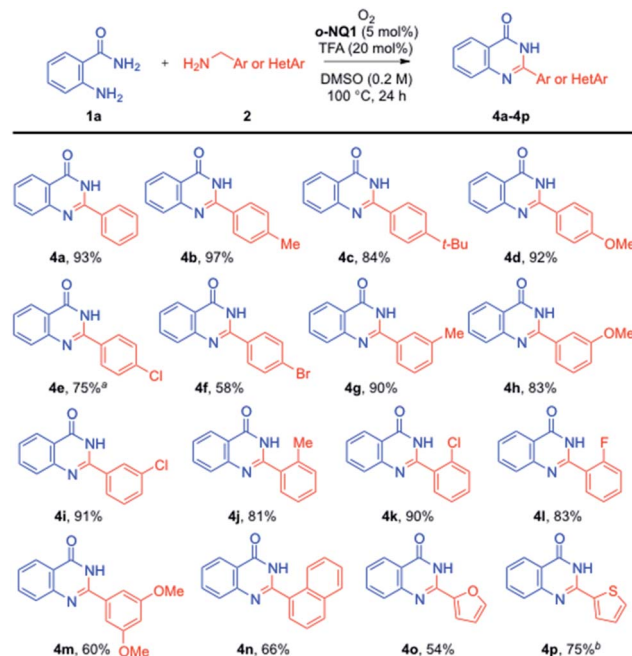
The optimized aerobic cross-coupling condition was applied to a variety of benzylamine derivatives (Scheme 2). In general, the electronic and steric characters of benzylamines did not significantly affect the formation of quinazolinones (**4a–4m**). However, the use of halogen-substituted and dimethoxy-substituted benzylamines led to the slightly lower yields of quinazolinones (**4e**, **4f** and **4m**) in 58–75% yields. In addition, the current aerobic cross-coupling reaction tolerated the furanyl and thiophenyl moieties, where the corresponding quinazolinones (**4o** and **4p**) were obtained in 54% and 75% yields, respectively.

Table 1 Optimization of *o*-NQ-catalyzed aerobic cross-coupling of amines to quinazolinone<sup>a</sup>



Entry	Cat. (mol%)	Solvent	T (°C)	Yield <sup>b</sup> (%)
1	<i>o</i> -NQ1 (10)	CH <sub>3</sub> CN	80	<b>3a</b> , 11
2	<i>o</i> -NQ1 (10)/TFA (20)	CH <sub>3</sub> CN	80	<b>3a</b> , 83
3	<i>o</i> -NQ2 (10)/TFA (20)	CH <sub>3</sub> CN	80	<b>3a</b> , 13
4	<i>o</i> -NQ3 (10)/TFA (20)	CH <sub>3</sub> CN	80	<b>3a</b> , 66
5	<i>o</i> -NQ4 (10)/TFA (20)	CH <sub>3</sub> CN	80	<b>3a</b> , 32
6	<i>o</i> -NQ1 (10)/TFA (20)	MeOH	65	<b>3a</b> , 5
7	<i>o</i> -NQ1 (10)/TFA (20)	EtOH	78	<b>3a</b> , 31
8	<i>o</i> -NQ1 (10)/TFA (20)	DMF	150	<b>4a</b> , >95
9 <sup>c</sup>	<i>o</i> -NQ1 (10)/TFA (20)	DMSO	150	<b>4a</b> , >95
10	<i>o</i> -NQ1 (10)/TFA (20)	DMSO	100	<b>4a</b> , >95
11	<i>o</i> -NQ1 (10)/TFA (20)	DMSO	80	<b>3a</b> , 30
12 <sup>d</sup>	<i>o</i> -NQ1 (10)/TFA (20)	DMSO	100	<b>4a</b> , >95
13 <sup>d</sup>	<i>o</i> -NQ1 (5)/TFA (20)	DMSO	100	<b>4a</b> , >95 (93)
14	<i>o</i> -NQ1 (5)/TFA (10)	DMSO	100	<b>3a/4a</b> , 45/50
15	—	DMSO	100	<b>3a</b> , 10
16	<i>o</i> -NQ1 (10)	DMSO	100	<b>3a/4a</b> , 34/51
17	TFA (20)	DMSO	100	NR
18	<i>o</i> -NQ1 (5)/AcOH (20)	DMSO	100	<b>3a</b> , 25
19 <sup>e</sup>	<i>o</i> -NQ1 (5)/TFA (20)	DMSO	100	<b>3a</b> , 33
20 <sup>f</sup>	<i>o</i> -NQ1 (5)/TFA (20)	DMSO	100	NR

<sup>a</sup> Reaction using **1a** (0.20 mmol), **2a** (0.30 mmol), and *o*-NQ in solvent (0.2 M) under O<sub>2</sub> balloon for 24 h. <sup>b</sup> Yields based on internal standard and isolated yield in parentheses. <sup>c</sup> Reaction for 6 h. <sup>d</sup> Use of **2a** (0.24 mmol, 1.2 equiv.). <sup>e</sup> Reaction under air. <sup>f</sup> Reaction under argon. NR = no reaction.

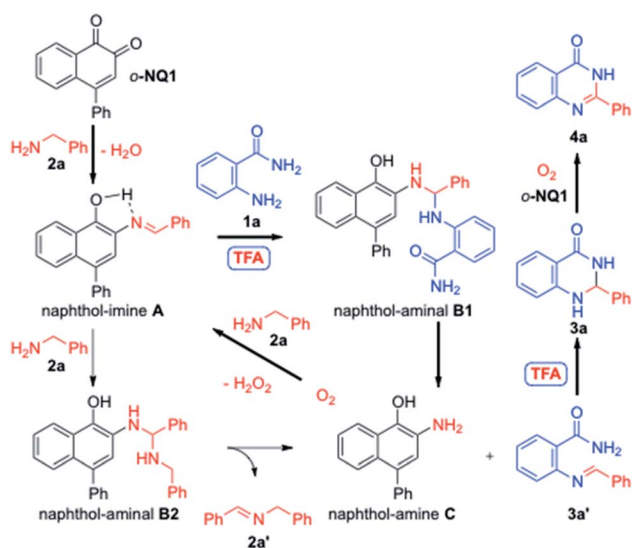


Scheme 2 Substrate scope of aerobic oxidation to quinazolinones (<sup>a</sup>reaction for 36 h, <sup>b</sup>reaction for 12 h).



Further extension of the current aerobic cross-coupling reactions of amines is illustrated in Scheme 3. Thus, an array of substituted anthranilamides was readily employed to give the fused pyrimidin-4(3*H*)-one derivatives (**4q–4x**) in 61–84% yields. In particular, the *N*-substituted anthranilamides also participated in the current aerobic cross-coupling reaction in excellent yields (**4y–4za**). While the use of 3-amino-2-naphthamide led to the corresponding quinazolinone **4zb** in 46% yield, the synthetic advantage of the current method was well demonstrated in the preparation of heteroaryl fused pyrimidin-4(3*H*)-one derivatives (**4zc–4zh**), where a variety of heterocyclic amines were successfully utilized in a tandem sequence of aerobic oxidation processes.

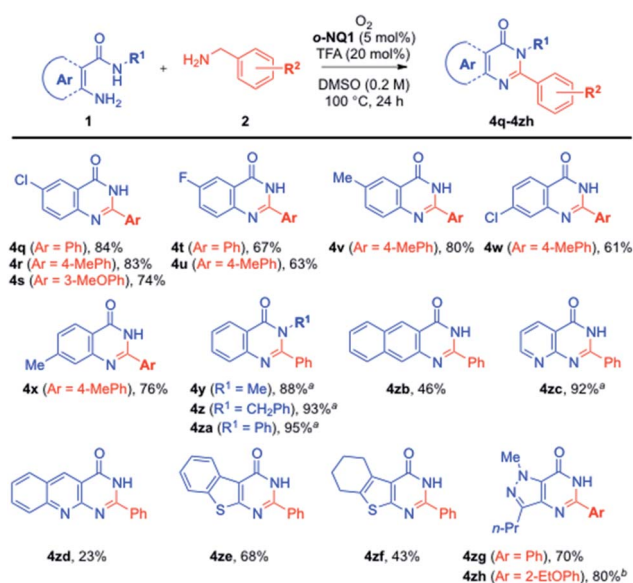
The mechanistic rationale of the aerobic cross-coupling reactions of amines is depicted in Scheme 4. Thus, the benzylamine **2a** is condensed with the *o*-NQ1 catalyst to give the naphthol-imine species **A**.<sup>37a</sup> While the nucleophilic attack of **2a** to the naphthol-imine **A** is favored due to the low nucleophilicity of the anthranilamide **1a**, the presence of TFA promotes the cross-coupling between naphthol-imine **A** and anthranilamide **1a** to give the naphthol-aminal **B1**. This process releases the hetero-coupled imine **3a'** and naphthol-amine **C**. The use of TFA promotes the intramolecular Mannich cyclization of imine **3a'**, leading to the aminal **3a** that in turn converts to the desired fused pyrimidin-4(3*H*)-one **4a** with the help of *o*-NQ1 catalyst and molecular oxygen. Alternatively, the naphthol-imine **A** can produce the homocoupled imine **2a'** and the naphthol-amine **C** *via* the naphthol-aminal **B2** through the nucleophilic attack of benzylamine **2a**. The conversion of the naphthol-amine **C** to *o*-NQ1 catalyst is effected upon exposure to oxygen atmosphere.<sup>38</sup> The homocoupled imine **2a'** undergoes hydrolysis at >80 °C to the benzaldehyde and benzylamine **2a** that in turn re-enters the catalytic cycle.<sup>37b</sup> Our experimental observation of the homocoupled imine **2a'** by the <sup>1</sup>H NMR and TLC analysis during the



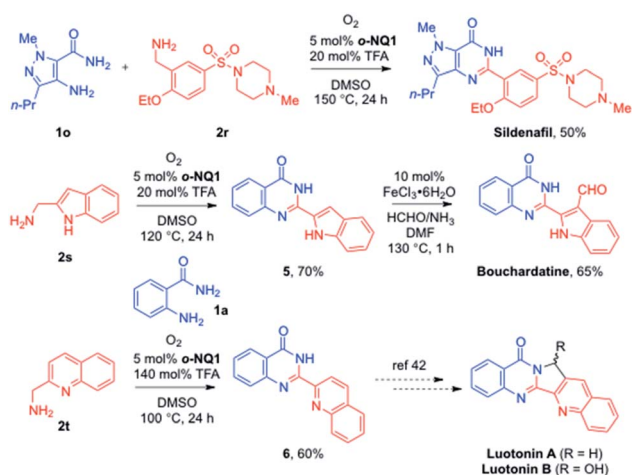
Scheme 4 Mechanistic rationale for aerobic cross coupling reaction of amines.

reaction supports the involvement of **2a'**. However, the major pathway to the fused pyrimidin-4(3*H*)-one **4a** appears to involve the naphthol-aminal **B1** since the use of benzaldehyde instead of benzylamine **2a** under the optimized conditions only led to the 80% conversion. The *o*-NQ1 catalyst without added TFA provided a mixture of aminal **3a** and quinazolinone **4a** in 34% and 51% yields, respectively (Table 1, entry 16). Thus, it is likely that the role of TFA is the catalyst for the cross-coupling of two amines to give the naphthol-aminal **B1** and the cyclization of the imine **3a'** to aminal **3a**. Our control experiments also revealed that TFA alone slowly oxidize **3a** to **4a**, but rapidly oxidized by the action of *o*-NQ1 within 10 h.<sup>39</sup>

The synthetic utility of the aerobic cross-coupling strategy is demonstrated in the synthesis of quinazolinone alkaloids and sildenafil (Scheme 5). The direct cross coupling of a commercially available pyrazole amine **1o** and benzylamine **2r** afforded



Scheme 3 Further substrate scope for fused pyrimidin-4(3*H*)-one derivatives (<sup>a</sup>reaction at 120 °C, <sup>b</sup>reaction at 140 °C).



Scheme 5 Synthetic utilization to quinazolinone alkaloids and sildenafil.



a highly convergent synthetic approach to sildenafil.<sup>40</sup> Likewise, the employment of anthranilamide **1a** and 2-(aminomethyl) indole **2s** provided the desired quinazolinone **5** in 70% yield, and the subsequent formylation under the Zeng's conditions<sup>41</sup> paved a way to the total synthesis of bouchardatine. In addition, while the basicity of quinolin-2-ylmethanamine **2t** required an excess of TFA, the corresponding quinazolinone **6** was obtained in 60% yield under the optimized conditions. The conversion of **6** to the luotonin natural products has been reported by the Argade group and others.<sup>42</sup>

## Conclusions

In summary, we have developed the aerobic cross-coupling reactions of amines to fused pyrimidin-4(3H)-one derivatives. This metal-free tandem aerobic oxidation sequence utilizes 5 mol% of **o**-NQ catalyst and 20 mol% of TFA as co-catalyst. The developed aerobic oxidation protocol allows a highly convergent approach to quinazolinone alkaloids and sildenafil. Given that the fused pyrimidin-4(3H)-one derivatives possess a diverse array of biological activities, the **o**-NQ-catalyzed tandem aerobic cross-coupling reactions should find their synthetic utility in the medicinal chemistry projects. We are current extending the **o**-NQ-catalyzed aerobic oxidation protocols to other heterocycles of medicinal interest, and our results will be reported in due course.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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- 39 The conversion of amination **3a** to quinazolinone **4a** was investigated by using 20 mol% TFA/O<sub>2</sub> (86% conv. at 24 h), 5 mol% *o*-NQ1/O<sub>2</sub> (92% conv. at 10 h), and O<sub>2</sub> (81% conv. at 24 h) at 100 °C in DMSO (0.2 M).
- 40 The commercial synthesis of sildenafil involves the amide coupling strategy, rather than the condensation of aldehyde and aminopyrazole route, possibly due to the two-step procedure (the formation of dihydrosildenafil by condensation and the following oxidation step to sildenafil), see: ref. 2*b*.
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