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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†

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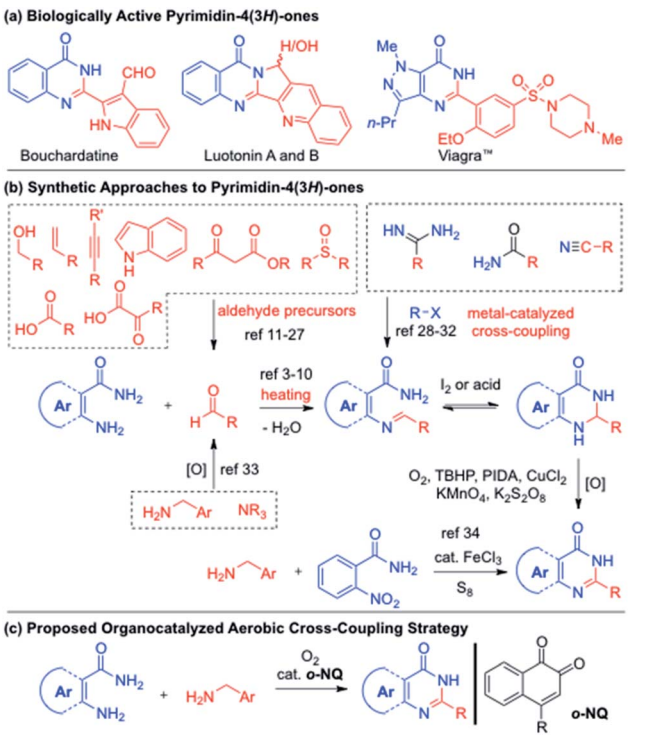
A facile access to fused pyrimidin-4(3*H*)-one derivatives has been established by using the metal-free *ortho*-naphthoquinone-catalyzed aerobic cross-coupling reactions of amines. The utilization of two readily available amines allowed a direct coupling strategy to quinazolinone natural product, bouchardatine, 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).[1] 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.[2] The synthetic approaches to the phenyl-fused pyrimidin-4(3*H*)-ones, quinazolinones, typically involve the condensation between anthranilamides and aldehydes to give aminal intermediates that in turn oxidized to quinazolinones under oxidation conditions (Scheme 1b). The oxidation catalysts include Cu,[3] Fe,[4] Ga,[5] Ir,[6] Mn,[7] iodine,[8] peroxide,[9] however the aerobic oxidation of aminal intermediates is also known at 150 °C.[10] The utilization of alcohols also effects the one-pot synthesis of quinazolinones through *in situ* oxidation to aldehydes in the presence of Fe,[11] Ir,[12] Mn,[13] Ni,[14] Pd,[15] Ru,[16] V,[17] Zn,[18] and iodine catalysts.[19] Other precursors to aldehydes have been also identified using alkynes,[20] benzoic acids,[21] indoles,[22] α-keto acid salts,[23] β-keto esters,[24] styrenes,[25] sulfoxides,[26] and toluenes.[27] Non-aldehyde approaches to quinazolinones have been also demonstrated in the cross coupling of amidines,[28] amines,[29] benzamides,[30] isocyanides,[31] and nitriles.[32] In 2013, the Nguyen group disclosed the synthesis of four quinazolinones, utilizing the autooxidation of benzylamines to imines that subsequently condensed with anthranilamides.[33] 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 $FeCl_3 \cdot 6H_2O$-catalyzed condensation of 2-nitroanilines and benzylamines in the presence of 20 mol% of S_8, where six quinazolinones were obtained in 68–75% yields.[34] 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.

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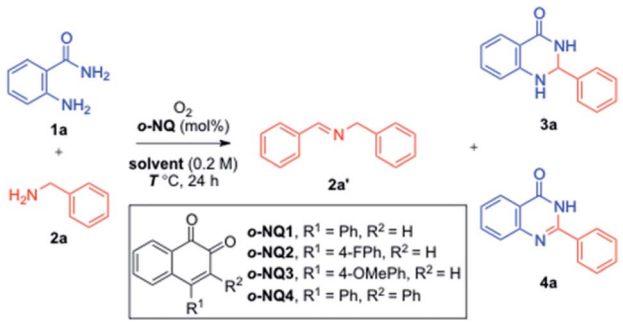
reaction temperature, closed system in neat conditions and excess use of amines). In addition, it is not entirely clear if the cross condensation of amide-containing amines and benzylamines would work for other fused pyrimidin-4(3*H*)-one derivatives.[35] To address such shortcomings in the cross condensation of amines, the *ortho*-naphthoquinone (***o*-NQ**)-catalyzed aerobic cross amination strategy was investigated (Scheme 1c).[36] 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,[37] 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).[38] 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.

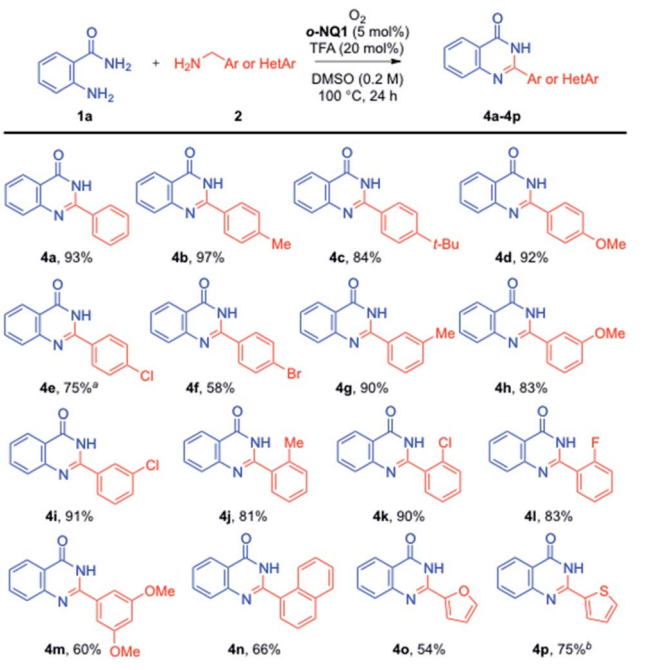
The optimized aerobic cross-coupling condition was applied to a variety of benzylamine derivatives (Scheme 2). In general, the electronic and steric characters of benzylamines did not significantly affect the formation of quinazolinones (**4a–4m**). However, the use of halogen-substituted and dimethoxy-substituted 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[a]



Entry	Cat. (mol%)	Solvent	*T* (°C)	Yield[b] (%)
1	***o*-NQ1** (10)	CH_3CN	80	**3a**, 11
2	***o*-NQ1** (10)/TFA (20)	CH_3CN	80	**3a**, 83
3	***o*-NQ2** (10)/TFA (20)	CH_3CN	80	**3a**, 13
4	***o*-NQ3** (10)/TFA (20)	CH_3CN	80	**3a**, 66
5	***o*-NQ4** (10)/TFA (20)	CH_3CN	80	**3a**, 32
6	***o*-NQ1** (10)/TFA (20)	MeOH	65	**3a**, 5
7	***o*-NQ1** (10)/TFA (20)	EtOH	78	**3a**, 31
8	***o*-NQ1** (10)/TFA (20)	DMF	150	**4a**, >95
9[c]	***o*-NQ1** (10)/TFA (20)	DMSO	150	**4a**, >95
10	***o*-NQ1** (10)/TFA (20)	DMSO	100	**4a**, >95
11	***o*-NQ1** (10)/TFA (20)	DMSO	80	**3a**, 30
12[d]	***o*-NQ1** (10)/TFA (20)	DMSO	100	**4a**, >95
13[d]	***o*-NQ1** (5)/TFA (20)	DMSO	100	**4a**, >95 (93)
14	***o*-NQ1** (5)/TFA (10)	DMSO	100	**3a**/**4a**, 45/50
15	—	DMSO	100	**3a**, 10
16	***o*-NQ1** (10)	DMSO	100	**3a**/**4a**, 34/51
17	TFA (20)	DMSO	100	NR
18	***o*-NQ1** (5)/AcOH (20)	DMSO	100	**3a**, 25
19[e]	***o*-NQ1** (5)/TFA (20)	DMSO	100	**3a**, 33
20[f]	***o*-NQ1** (5)/TFA (20)	DMSO	100	NR

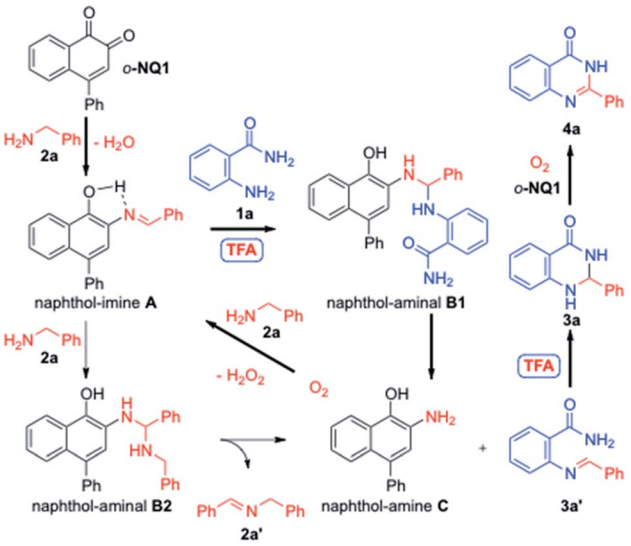
[a] Reaction using **1a** (0.20 mmol), **2a** (0.30 mmol), and ***o*-NQ** in solvent (0.2 M) under O_2 balloon for 24 h. [b] Yields based on internal standard and isolated yield in parentheses. [c] Reaction for 6 h. [d] Use of **2a** (0.24 mmol, 1.2 equiv.). [e] Reaction under air. [f] Reaction under argon. NR = no reaction.



Scheme 2 Substrate scope of aerobic oxidation to quinazolinones ([a]reaction for 36 h, [b]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.

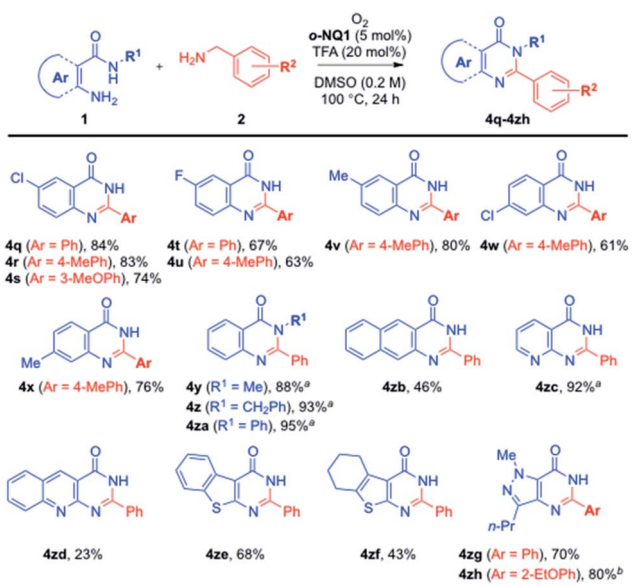
The mechanistic rationale of the aerobic cross-coupling reactions of amines is depicted in Scheme 4. Thus, the benzylamine **2a** is condensed with the ***o*-NQ1** catalyst to give the naphthol-imine species **A**.[37a] While the nucleophilic attack of **2a** to the naphthol-imine **A** is favored due 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.[38] The homocoupled imine **2a′** undergoes hydrolysis at >80 °C to the benzaldehyde and benzylamine **2a** that in turn re-enters the catalytic cycle.[37b] Our experimental observation of the homocoupled imine **2a′** by the ^{1}H NMR and TLC analysis during the



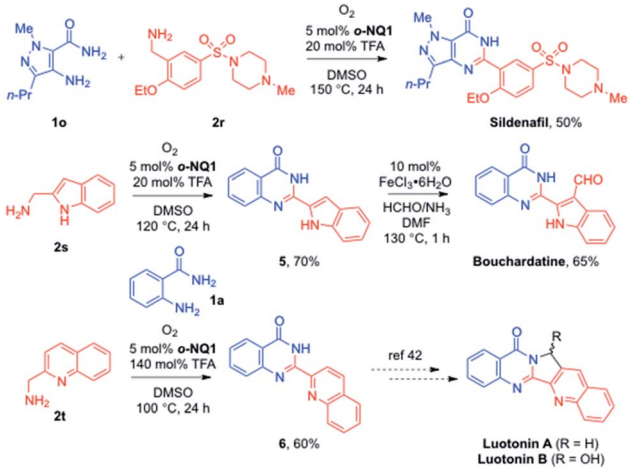
Scheme 4 Mechanistic rationale for aerobic cross coupling reaction of amines.

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.[39]

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 ([a]reaction at 120 °C, [b]reaction at 140 °C).



Scheme 5 Synthetic utilization to quinazolinone alkaloids and sildenafil.

a highly convergent synthetic approach to sildenafil.[40] 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[41] 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.[42]

Conclusions

In summary, we have developed the aerobic cross-coupling reactions of amines to fused pyrimidin-4(3*H*)-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(3*H*)-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 aminal **3a** to quinazolinone **4a** was investigated by using 20 mol% TFA/O_2 (86% conv. at 24 h), 5 mol% ***o*-NQ1**/O_2 (92% conv. at 10 h), and O_2 (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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