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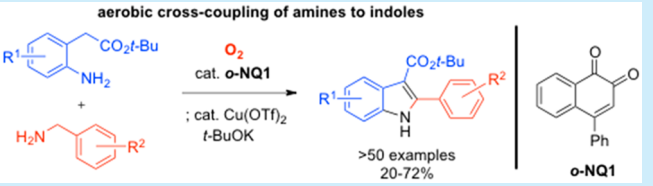
Aerobic Oxidation Approaches to Indole-3-carboxylates: A Tandem Cross Coupling of Amines−Intramolecular Mannich−Oxidation Sequence

Kyeongha Kim, Hun Young Kim,* and Kyungsoo Oh*

Center for Metareceptome Research, College of Pharmacy, Chung-Ang University, 84 Heukseok-ro, Dongjak, Seoul 06974, Republic of Korea

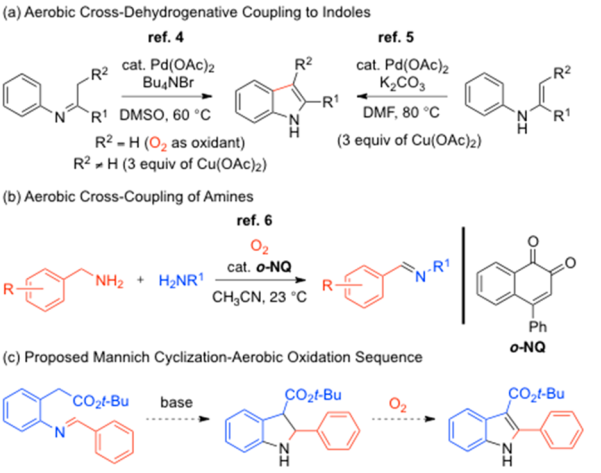
Supporting Information

ABSTRACT: A tandem aerobic oxidation protocol has been developed for the facile synthesis of indole-3-carboxylates. Two readily available starting materials, anilines and benzylamines, were efficiently cross-coupled under the *o*-naphthoquinone-catalyzed aerobic oxidation conditions to the corresponding 2-arylmethyleneaminophenylacetates that in turn smoothly underwent the Cu(II)-catalyzed intramolecular Mannich reaction. The resulting indoline derivatives were aerobically oxidized to indole-3-carboxylates, providing a ready access to indole derivatives from two simple amine derivatives.



A direct access to indole derivatives from readily available starting materials significantly improves the overall synthetic efficiency without having to isolate the synthetic intermediates.[1] The recent development of transition-metal-catalyzed C−H activation strategies has further strengthened the late-stage installation of an indole moiety in a target-oriented synthesis.[2] While numerous synthetic methods to indole derivatives boast diverse starting materials and rationally designed catalyst systems,[3] it is highly practical to develop the aerobic oxidation protocol to indole derivatives from two readily available starting materials given that the structural diversity of indoles can be achieved. In 2012, Yoshikai et al. disclosed the Pd(II)-catalyzed aerobic oxidative cross-dehydrogenative coupling of imines,[4] in contrast to the previous Pd(II)-catalyzed oxidative cyclization of *N*-aryl enamines with stoichiometric amounts of $Cu(OAc)_2$ as the oxidant (Scheme 1a).[5] Previously, we developed the *o*-naphthoquinone (*o*-NQ)-catalyzed deaminative cross-coupling of amines, where two different amines were condensed under aerobic conditions to give imines (Scheme 1b).[6] Since the access to *N*-benzylideneaniline derivatives could be secured under the aerobic oxidation conditions, we envisioned an intramolecular Mannich reaction to indolines that could be aerobically oxidized to indole derivatives (Scheme 1c). The reaction design was partially supported by the work of Hodges et al. where the intramolecular Mannich reaction did provide the desired indoline in 37% yield.[7] While this result contradicted the earlier works of Speckamp et al., who reported the failure of the reaction under a variety of solvent and base combinations,[8] the challenge poised by the precarious experimental results did not deter us from verifying our reaction design.[9] The use of *N*-benzylideneanilines as the cyclization precursor is clearly beneficial since the isomerization of substituted imines to *N*-aryl enamines does require a stoichiometric amount of oxidants, not suitable under Yoshikai's aerobic oxidation conditions.[4] In addition, the aerobic oxidation of indolines to indoles implies the dehydrogenative oxidation of amines, a valuable oxidation protocol from the viewpoint of green chemistry.[10]

Scheme 1. Aerobic Oxidation Approaches to Indole Derivatives



With the aim of developing a direct access to indole-3-carboxylates from simple two-amine starting materials, the *o*-**NQ**-catalyzed aerobic cross-coupling of *tert*-butyl 2-(2-aminophenyl)acetate **1a** and benzylamine **2a** was examined (Table 1). The use of *o*-**NQ1** in THF at ambient temperature provided the imine **3a**, a homocoupling product of **2a**, as a

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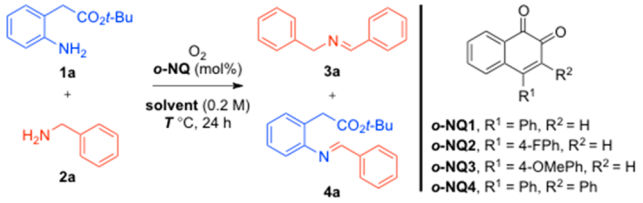
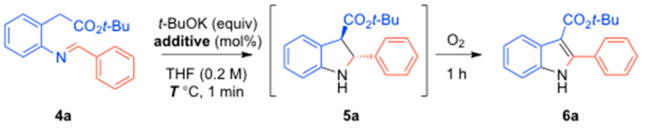
Table 1. Optimization of *o*-NQ-Catalyzed Aerobic Cross-Coupling of Amines[a]



entry	cat. (mol %)	solvent	T (°C)	yield[b] (%)
1	*o*-**NQ1** (10)	THF	23	27
2	*o*-**NQ1** (10)/TFA (20)	THF	23	45
3	*o*-**NQ2** (10)/TFA (20)	THF	23	40
4	*o*-**NQ3** (10)/TFA (20)	THF	23	45
5	*o*-**NQ4** (10)/TFA (20)	THF	23	4
6	*o*-**NQ1** (10)/TFA (20)	MeOH	23	46
7	*o*-**NQ1** (10)/TFA (20)	CH_3CN	23	66
8	*o*-**NQ1** (10)/TFA (20)	CH_3CN	80	73
9	*o*-**NQ1** (15)/TFA (20)	CH_3CN	80	70
10	*o*-**NQ1** (10)/TFA (30)	CH_3CN	80	79
11[c]	*o*-**NQ1** (10)/TFA (20)	CH_3CN	80	85
12[d]	*o*-**NQ1** (10)/TFA (20)	CH_3CN	80	87

[a]Reaction using **1a** (0.20 mmol), **2a** (0.24 mmol), *o*-**NQ** in solvent (0.2 M) under O_2 balloon for 24 h. [b]Yields of **4a** based on internal standard. [c]Use of **2a** (0.30 mmol, 1.5 equiv). [d]Use of **2a** (0.40 mmol, 2.0 equiv).

Table 2. Optimization of Intramolecular Mannich Reaction–Aerobic Oxidation[a]



entry	additive (mol %)	*t*-BuOK (equiv)	T (°C)	yield[b] (%)
1		0.1	23	20
2		0.5	23	48
3		1.0	23	60
4		1.0	0	60
5		1.0	−78	60
6	$Zn(OTf)_2$ (10)	1.0	23	70
7	$In(OTf)_2$ (10)	1.0	23	60
8	$Sc(OTf)_2$ (10)	1.0	23	66
9	$Ti(Oi\text{-}Pr)_2$ (10)	1.0	23	50
10	$Cu(OTf)_2$ (10)	1.0	23	78
11	$Cu(OAc)_2$ (10)	1.0	23	70
12	CuOTf (10)	1.0	23	66
13	CuI (10)	1.0	23	71
14	$Cu(OTf)_2$ (5)	1.0	23	56
15	$Cu(OTf)_2$ (15)	1.0	23	64

[a]Reaction using **4a** in THF (0.2 M) under Ar → O_2 balloon for 1 h. [b]Yields after column chromatography.

major product, along with the desired cross-coupled product **4a** in 27% yield (entry 1). The presence of cocatalyst TFA facilitated the formation of **4a** to 45% yield (entry 2). The structure–activity relationship of *o*-**NQ** catalysts revealed a minimal electronic effect of the phenyl moiety at the C-4 position of *o*-naphthoquinone (entries 3 and 4), while the steric hindrance was exerted by the substituent at the C-3 position of *o*-naphthoquinone (entry 5). A brief survey of solvents suggested that other solvents were comparable, but CH_3CN was the optimal solvent for the current cross-coupling of two amines (entry 7). Further improvement of the reaction was achieved by elevating the reaction temperature to 73% yield (entry 8). The final tuning of the reaction conditions involved the use of 2.0 equiv of benzylamine **2a**, where the formation of the cross-coupled imine **4a** was obtained in 87% yield (entry 12).

With the optimized cross-coupling reaction of amines, the projected intramolecular Mannich reaction of **4a** was investigated (Table 2). Our initial attempts using various bases such as Et_3N, DBU, NaOMe, and KOH failed to provide the desired cyclized product. These results were in line with the previous observation by Speckamp.[8] Upon use of *t*-BuOK, the formation of Mannich product **5a** was observed in 5–10% yields.[7,9] To our surprise, the indoline **5a** was not stable under the reaction conditions and thus rapidly decomposed to a mixture of unidentifiable products. Upon a close look at the reaction course, we found that the intramolecular Mannich cyclization of **4a** by *t*-BuOK happened instantaneously, and then the indoline **5a** immediately decomposed in the next few minutes. Thus, it was crucial to minimize the exposure of **5a** under the reaction conditions. After some experimentation, it was found that the in situ formed indoline **5a** could be oxidized to the corresponding indole **6a** under an oxygen balloon. Thus, while the *t*-BuOK addition stage of the reaction required an inert atmosphere of argon, the aerobic oxygen was directly introduced to the reaction mixture immediately after the addition of *t*-BuOK. In this way, the direct formation of indole **6a** was accomplished. The use of substoichiometric amounts of *t*-BuOK provided the indole **6a** in 20–48% yields after the aerobic oxidation (entries 1 and 2). While the use of 1 equiv of *t*-BuOK improved the yield of **6a** to 60% (entry 3), the reaction temperature did not exert any influence to the reaction efficiency (entries 4 and 5). Next, we screened various Lewis acids for the intramolecular Mannich reaction to further optimize the yields (entries 6–10).[11] Among them, $Cu(OTf)_2$ was identified as an optimal Lewis acid, providing the desired product **6a** in 78% yield (entry 10). The use of other copper salts was effective but less efficient compared to $Cu(OTf)_2$ (entries 11–13). The different amounts of $Cu(OTf)_2$ provided **6a** in 56–64% yields (entries 14 and 15), suggesting the optimal loading of $Cu(OTf)_2$ as 10 mol %.

Analyzing our experimental findings of the *o*-**NQ1**-catalyzed aerobic oxidation and the Mannich cyclization followed by the aerobic oxidation, it was necessary to switch the reaction solvent from CH_3CN to THF. Thus, after the *o*-**NQ1**-catalyzed aerobic oxidation, the reaction solvent, CH_3CN, was evaporated, and then THF was reintroduced into the reaction mixture. This simple solvent change did not affect the following Mannich cyclization–aerobic oxidation sequence, where the overall yields of indole-3-carboxylates were identical between the stepwise and tandem reactions. The substrate scope of thus combined tandem reaction procedure to indole-3-carboxylates from *tert*-butyl 2-(2-aminophenyl)acetate **1a** and substituted benzylamines **2** is presented in Scheme 2. A structurally diverse array of indole-3-carboxylates **6b–6q** was prepared in 20–67% yields. Considering the three reactions in a tandem sequence, the average chemical yield for each step is estimated around 80–85% yields. Of note, the electronic and steric features of benzylamines **2** did not have significant influence to the overall reaction sequence; however a furan moiety **6p** and other alkyl amines presented the substrate

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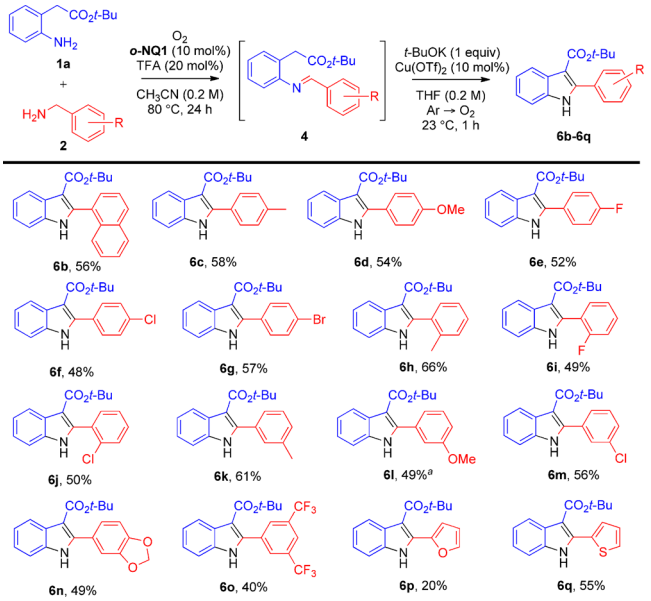
Scheme 2. Substrate Scope of Aerobic Oxidation to Indoles

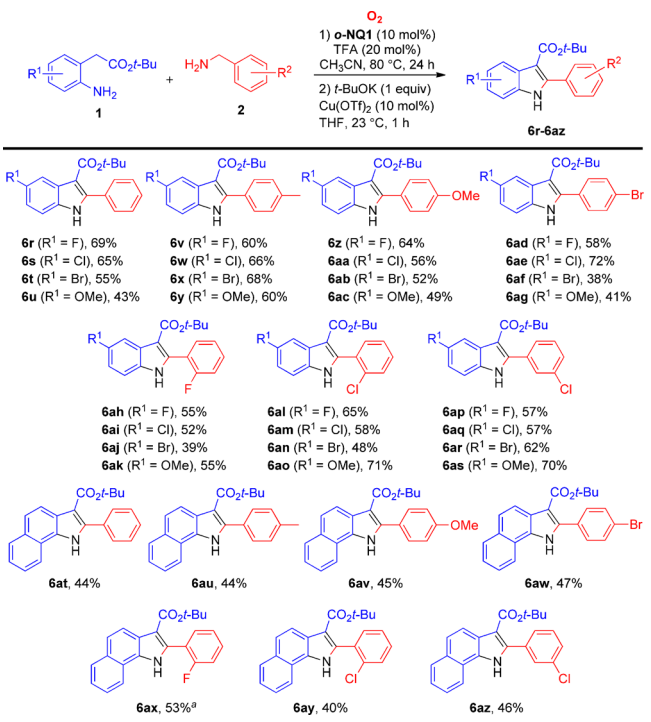


[a]Reaction using *o*-**NQ3** (10 mol %).

limitation during the *o*-**NQ**-catalyzed aerobic cross-coupling of amines (vide infra).

Further substrate scope was investigated using substituted anilines **1** and benzylamines **2** (Scheme 3). In general, the observed yields were slightly lower for bromide-substituted anilines (**6t**, **6ab**, **6af**, **6aj**, **6an**), some methoxy-substituted anilines (**6u**, **6ac**, **6ag**), and naphthyl amines (**6at**–**6az**). Nevertheless, the ready access to a large number of indole-3-

Scheme 3. Further Substrate Scope for Tandem Reactions to Indoles

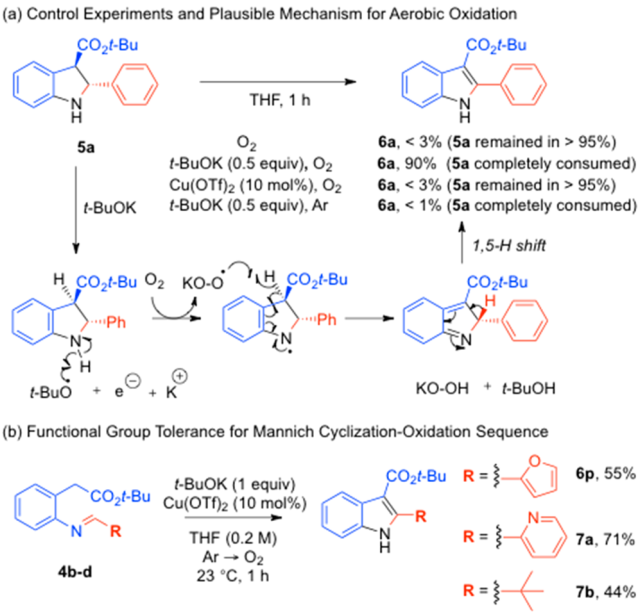


[a]Reaction using *o*-**NQ3** (10 mol %).

carboxylates was achieved from readily available amines in a tandem sequence of aerobic oxidation processes.

To provide mechanistic insight into the intramolecular Mannich process, we isolated the indoline intermediate **5a**.[12] Under our control experiments as shown in Scheme 4a, the

Scheme 4. Plausible Reaction Mechanism for Aerobic Oxidation and Access to Functionalized Indole-3-carboxylates



solid indoline **5a** as well as the indoline **5a** THF solution was stable under air and under inert atmosphere in the absence of *t*-BuOK. The use of *t*-BuOK and molecular oxygen was needed for the rapid oxidation of indoline **5a** to indole **6a**.[13] The addition of $Cu(OTf)_2$ did not have much effect to the oxidation of indoline **5a** to indole **6a**; thus, the role of $Cu(OTf)_2$ in the reaction could be assigned as a promoter for the intramolecular Mannich reaction.[11] The indoline **5a** was rapidly decomposed to unidentifiable products in the presence of *t*-BuOK, demonstrating the crucial role of molecular oxygen in the oxidation of **5a** to indole **6a**. While further studies are needed for the precise reaction mechanism for the observed aerobic oxidation of indolines to indoles, given the direct electron transfer capability of *t*-BuOK[14] one possible mechanistic explanation would be the abstraction of hydrogen radical from the indoline N–H bond, followed by the benzylic H radical abstraction and aromatization to indoles (Scheme 4a). The current aerobic oxidation method utilizes the imine intermediates from the *o*-**NQ**-catalyzed cross imination of two amines. While the imine intermediates can be obtained through the condensation reactions between aldehydes and anilines, the use of protic solvents[15] or acid catalysts[16] typically requires the purification of imines for the subsequent reactions. While the use of the unpurified imines in our control experiments could provide the comparable yields of products in 50–60% yields after the *t*-BuOK-promoted intramolecular Mannich–aerobic oxidation protocol, the aldehyde condensation approaches lacked the substrate generality due to the residual protic solvents and catalysts. Thus, the functional group tolerance for the Mannich cyclization followed by aerobic oxidation was further demonstrated using the purified

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imines **4b–d** for consistent reproducibility (Scheme 4b). In this way, the indole-3-carboxylates **6p**, **7a**, and **7b** could be accessed in synthetically useful yields, providing a convenient synthetic route to highly functionalized indole derivatives.

In summary, we have developed a tandem aerobic oxidation sequence to indole-3-carboxylates from readily available amine derivatives. The key finding of the current synthetic access to indole derivatives is the successful Mannich cyclization of 2-(2-aminophenyl)acetates by *t*-BuOK in the presence of a catalytic amount of $Cu(OTf)_2$. The subsequent aerobic oxidation of indolines to indoles is also noteworthy, where the stability and reactivity of indoline intermediates were thoroughly examined. The current tandem aerobic oxidation reactions should find wide synthetic utility in organic synthesis. Our current research efforts are directed to further broadening the tandem aerobic oxidation sequence to other heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02348.

Experimental procedures and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kyungsoooh@cau.ac.kr.
*E-mail: hunykim@cau.ac.kr.

ORCID

Hun Young Kim: 0000-0002-8461-8910
Kyungsoo Oh: 0000-0002-4566-6573

Notes

The authors declare no competing financial interest.

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