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A Facile Construction of Quinoline-2-carboxylate Esters through An Aerobic Oxidation of Alkyl 4-Anilinocrotonates Induced by Radical Cation Salt

Xiaodong Jia*[a], Pengfei Li, [b] Yu Shao, [c] Yu Yuan, [a] Wentao Hou, [b] Xiaofei Liu, [b] Xuewen Zhang, [a] and Honghe Ji [b]

Abstract: A facile construction of quinoline-2-carboxylate esters through an aerobic oxidation of alkyl 4-anilinocrotonates was described. In the presence of dioxygen, sp^3 C-H bonds in 4-anilinocrotonates can easily be oxidized by catalytic radical cation salt, providing a radical intermediate. After further oxidation and domino cyclization, the desired quinoline derivatives were afforded in high yields. This reaction provided a new way to construct the pharmaceutically relevant quinoline skeleton, avoiding harsh reaction conditions and tedious starting material synthesis.

The quinoline skeleton, as substructures in a broad range of bioactive molecules, plays an important role in organic and pharmaceutical chemistry, exhibiting various biological activities, such as antimalarial, [1] anti-inflammatory, [2] antibacterial [3] and others. [4] In these huge compound libraries, quinoline-2-carboxylates possess an indispensable position, and exist in a number of natural products (Figure 1). [5] For example, Kynurenic acid derivatives were reported to possess glycine/NMDA antagonist activity. [5b, c] *Ascidiathiazones* **A** and **B**, which were isolated from the New Zealand ascidian Aplidium species, can inhibit the production of superoxide by PMA stimulated human neutrophils in a dose-dependent manner. [5d]

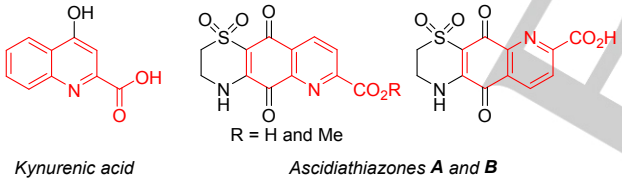

Figure 1. Some natural quinoline-2-carboxylate structures

Due to the great importance of quinoline derivatives, considerable efforts were devoted to synthesizing them, such as the Conrad_Limpach_Knorr synthesis, [6] the Skraup-Doebner-Von Miller synthesis, [7] the Friedländer synthesis, [8] and other methods. [9] However, the methods to quinoline-2-carboxylates remained limited (Figure 2). [10] In 2016, Chen and Yin reported an efficient copper-catalyzed aerobic oxidative esterification of 2-methylquinoline with alcohols, avoiding the use of SeO_2 as the stoichiometric oxidant. [10a] Miller developed a domino reduction--condensation process to quinoline formation, in which only one example of quinoline-2-carboxylate ester was provided. [10c] Based on a copper-promoted N=N bond cleavage of azobenzenes, Yi and Xi reported an elegant synthesis of quinoline derivatives, albeit harsh reaction conditions (120 °C in sealed tube) were necessary to achieve high yields of the desired products. [10d] A copper-catalyzed [5+1] annulation of 2-ethynylanilines with an *N,O*-acetal as a C1 unit were also utilized to preparation of quinoline-2-carboxylate esters. [10e] Although these methods provided different routes to quinoline-2-carboxylate esters, some shortcomings such as harsh reaction conditions, tedious starting material synthesis and narrow substrate scope still restricted their broader applications in synthesis of quinoline-2-carboxylate esters. Consequently, use of lower functionalized substrates, which avoided inaccessible substrate preparation and incompatibility between functional groups and harsh reaction conditions, is highly desirable to construct this structure.

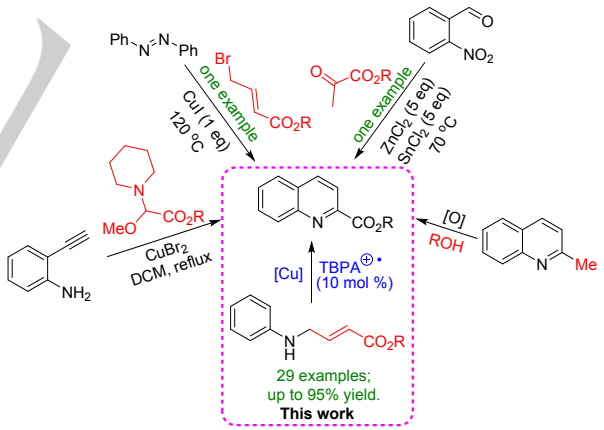

Figure 2. Different approaches to quinoline-2-carboxylates

In the past decades, free radical mediated transformations have become a powerful method to construct complex molecules. [11] Inspired by these elegant methodologies, our group has developed several related methodologies to build a series of heterocyclic structures based on oxidative Povarov reaction and its variants. [12] In these investigations, the sp^3 C-H bonds in N-aryl glycines were found to be reactive and easily oxidized to the corresponding radicals due to the captodative effect. [13] Since the captodative effect can be delivered by the C=C double bond through π-conjugation, we questioned whether alkyl 4-anilinocrotonates could also be employed to achieve the C-H

[a] Prof. X. Jia, Prof. Y. Yuan and Mr. X. Zhang
School of Chemistry & Chemical Engineering
Yangzhou University
Yangzhou, Jiangsu 225002, China
E-mail: jiaxd1975@163.com
[b] Mr. P. Li, Mr. W. Hou, Ms. X. Liu and Mr. H. Ji
College of Chemistry & Chemical Engineering
Northwest Normal University
Lanzhou, Gansu 730070, China
[c] Ms. Y. Shao
School of Information Engineering
Yangzhou University
Yangzhou, Jiangsu 225127, China

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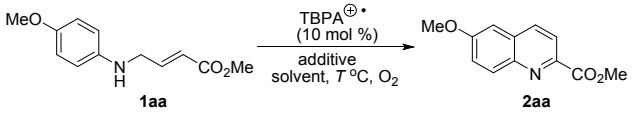
bond functionalization (Figure 2). Herein, we reported a facile construction of quinoline-2-carbloxylate esters through radical cation salt induced aerobic oxidation of sp^3 C-H bonds in alkyl 4-anilinocrotonates.

Table 1. Optimization of Reaction Conditions [a]



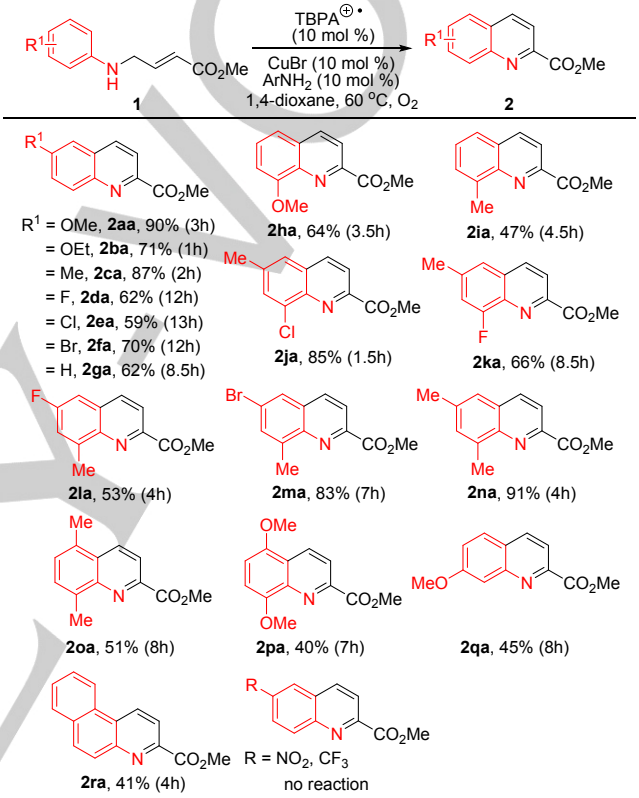
1aa 2aa

entry	additive	solvent	time (h)	yield (%) [b]
1	none	MeCN	72	38
2	none	THF	48	29
3	none	PhOMe	72	30
4	none	DCE	120	43
5	none	CCl_4	120	48
6	none	$CHCl_3$	160	41
7	none	1,4-dioxane	48	51
8	TfOH	1,4-dioxane	160	55
9	TFA	1,4-dioxane	8	56
10	CuOAc	1,4-dioxane	4	60
11 [c]	CuOAc	1,4-dioxane	4	74
12 [c]	$CuCl_2$	1,4-dioxane	3	83
13 [c]	$CuBr_2$	1,4-dioxane	3	78
14 [c]	CuBr	1,4-dioxane	3	90
15 [c]	CuCl	1,4-dioxane	3	84

[a] Unless otherwise specified, the reaction was carried out with **1aa** (0.1 mmol) in the presence of $TBPA^{+\cdot}$, and anhydrous solvent (1.0 mL) at 60 °C. [b] Yield of crude product ^{1}HNMR using 1,3,5-trimethoxylbenzene as internal standard. [c] 4-Anisidine (10 mol %) was added.

To find the best conditions to achieve the efficient synthesis of quinoline-2-carboxylate esters, we started our study on alkyl 4-anilinocrotonate **1aa** in the presence of 10 mol % $TBPA^{+\cdot}$ (tris(4-bromophenyl)aminium hexachloroantimonate) in MeCN (Table 1). To our delight, the reaction occurred smoothly, and the desired quinoline **2aa** was detected in 38% yield (entry 1). Then the solvent screen was performed to increase the reaction efficiency (entries 1-7), and the results show that halogenated solvents gave higher yields with elongated reaction time (entries 4-6), and when 1,4-dioxane used, the best result was obtained, providing the expected product in 51% yield (entry 7). We found that these aerobic oxidative conditions are sufficient to promote the full conversion of the starting material, however, the yields of the desired product remain unsatisfied. The reasons were attributed to decomposition of the generated iminium intermediate, which implied that the cyclization process to quinoline ring should be accelerated. Then some additives were added to increase the reaction efficiency (entries 8-15). In the presence of 10 mol % CuOAc, the yield of the quinoline was improved to 60%. Taking the mechanism into account (vide infra), addition of a catalytic amount of aniline (10 mol %) was then examined under similar conditions to initiate the Michael-type attack to the generated iminium intermediate (entries 11-15). To our delight, not only the reaction efficiency was increased to 74% yield, but also the reaction time was greatly shortened. Further copper catalysts examination revealed that CuBr gave the best result, and the corresponding quinoline derivative was observed in a 90% yield (entry 14).

Scheme 1. Scope of Anilines [a]



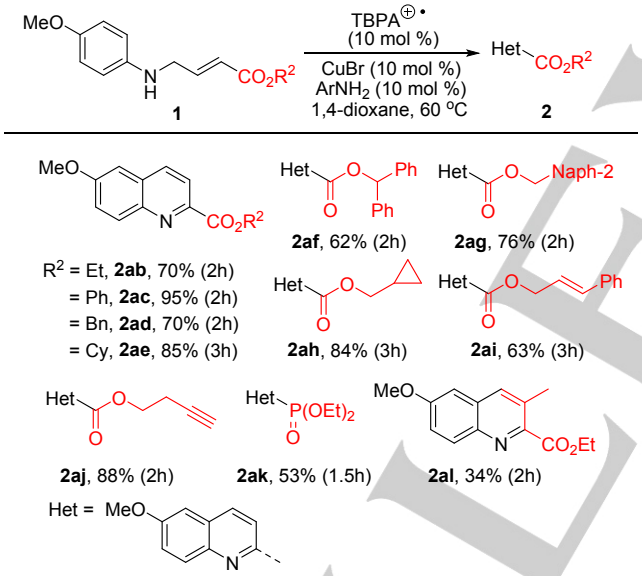
[a] Reaction conditions: **1** (1 mmol), $TBPA^{+\cdot}$ (10 mol %), CuBr (10 mol %), the corresponding anilines (10 mol %), 1,4-dioxane (5 mL), 60 °C under O_2, isolated yield.

With optimized reaction conditions in hand, the scope and limitations of the title procedure were explored. Firstly, the scope of anilines was investigated, and the results were compiled in Scheme 1. Aniline derivatives bearing electron-donating groups such as MeO, EtO and Me at the para-position of the aromatic ring underwent this transformation smoothly to produce the desired quinoline products in good yields (**2aa-2ca**). Slightly lower yields were obtained for the halogenated and unsubstituted systems with elongated reaction time (**2da-2ga**), for the conjugated effect between the lone pair on nitrogen and the generated radical center was weakened. *Ortho*-substituted analogues provided similar results (**2ha** and **2ia**). Various 2,4-disubstituted anilines were then tested, and the substrates with electron-donating groups still gave higher yields (**2ja-2na**). The reaction efficiency was reduced by 2,5-disubstituted substrates (**2oa-2pa**), probably due to the higher steric hindrance. When *meta*-group existed, the cyclization occurred selectively on *para*-position probably due to steric reasons, and the corresponding

product **2qa** was isolated in a moderate yield. Naphthylamine was shown to be compatible under the current oxidative conditions, affording the desired product **2ra** in 41% yield. The oxidation of *sp*^{3} C-H bonds was totally inhibited in the presence of strong electron-withdrawing groups such as NO_2, CF_3, and the corresponding starting materials were fully recovered.

We next examined various ester groups to test the reaction scope and functional group tolerance. Ethyl and phenyl esters performed well with good yields, giving the desired products **2ab** and **2ac** in 70% and 95% respectively. Then, esters with another relatively active benzyl C-H bond were employed to test the selectivity of the C-H bond oxidation (**2ad**-**2ag**), and the results showed that the reaction process was not disturbed, providing the expected quinolines in high yields. Other sensitive groups such as cyclopropyl ring (**2ah**), C-C double bond (**2ai**) and triple bonds (**2aj**) were completely tolerated in these mild oxidative conditions. It is worth noting that the congener of diethyl phosphate was also suitable for construction of quinolin-2-yl phosphonates **2ak**, which furnished desired quinolin-2-yl phosphonates in satisfactory yield. However, the reaction efficiency of methyl substituted crotonate was decreased (**2al**) probably due to steric reasons.

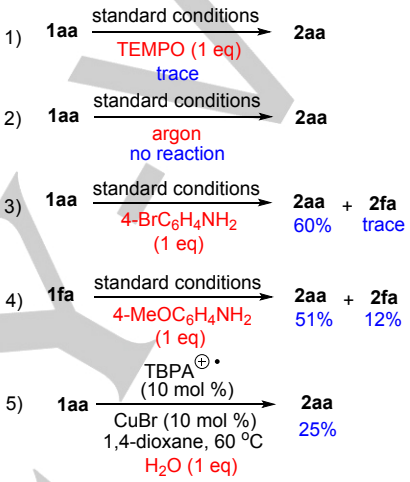
Scheme 2. Scope of Esters [a]



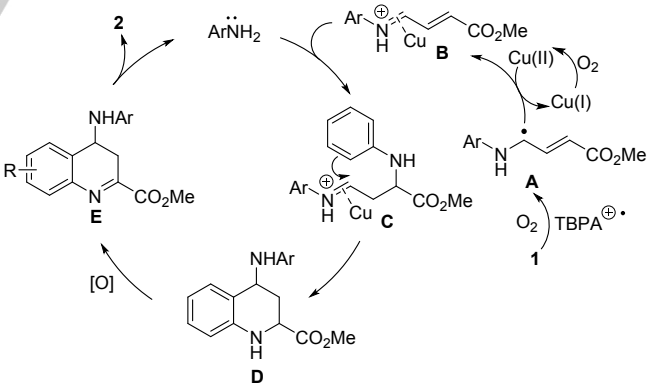
[a] Reaction conditions: **1** (1 mmol), TBPA$^{+\cdot}$ (10 mol %), CuBr (10 mol %), the corresponding anilines (10 mol %), 1,4-dioxane (5 mL), 60 °C under O_2, isolated yield.

Some control experiments were then performed to probe the mechanism (Scheme 3). In the presence of 1 equivalent of radical inhibitor TEMPO, the reaction was totally inhibited, and only trace amount of the desired product was detected by crude product ^{1}H NMR (eq 1), implying that a radical intermediate might be involved in this reaction. When the reaction was conducted under argon atmosphere, no reaction occurred, and the starting material was fully recovered (eq 2). So dioxygen is crucial to facilitate the C-H bond oxidation. To reveal the role of the additive, anilines, we performed this reaction in the presence of 1 equivalent of another aniline (4-bromoaniline), and the corresponding product **2aa** was isolated in 60% yield with trace amount of **2fa** (eq 3). On the other hand, when the reaction of **1fa** was conducted in the presence of more nucleophilic anisidine (1 equivalent), the quinoline product **2aa** and **2fa** were detected in 51% and 12% yields, respectively (eq 4). [14] These results suggested that the cyclization step is a Friedel-Crafts-type reaction, and the more electron-rich aniline is preferred. Since hydrolysis of the generated iminium intermediate could release an aniline to initiate the Michael addition, we added 1 equivalent of water to the reaction mixture, and the yield was decreased to 25% (eq 5), which means that the C-N bond cleavage does not mainly occur at the iminium intermediate formation step, and the extra aniline is necessary to promote the initial Michael addition. These results are also supported by the reaction condition optimization (see Table 1, entries 11-15).

Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



Based on these results, a radical mediated mechanism was proposed to rationalize this radical cation-initiated *sp*^{3} C-H oxidation (Scheme 4). In the presence of dioxygen and TBPA$^{+\cdot}$, the *sp*^{3} C-H bond adjacent to nitrogen was oxidized to a radical intermediate **A**. [15] The radical intermediated was further oxidized by the generated Cu(II) species, providing a an iminium intermediate **B**. The Cu(II) catalyst was reduced to Cu (I), which was further oxidized by dioxygen to participate next catalytic cycle. Then the corresponding aniline added to the iminium intermediate via a copper accelerated Michael-type addition, [16]

affording the adduct **C**. After an intramolecular Friedel-Crafts-type cyclization, an aniline substituted tetrahydroquinoline **D** was generated. The C-H bond adjacent to nitrogen is more active and was further oxidized, affording a dihydroquinoline intermediate **E**. Enabled by aromatization, the desired quinoline-2-carboxylate ester **2** was formed, together with aniline extrusion to initiate the second Michael-type addition.

In summary, a facile construction of quinoline-2-carboxylate esters was achieved under a radical cation promoted aerobic oxidation of sp^3 C-H bonds. Compared with other methods to this pharmaceutically relevant skeleton, this approach is superior in high reaction efficiency, accessible starting materials and mild reaction conditions. Further studies and applications in quinoline derivative preparation are still in progress in our laboratory.

Experimental Section

A solution of **1** (1 mmol), CuBr (10 mol %) and the corresponding aniline (10 mol %) in 1,4-dioxane (5 mL) was mixed fully and flushed with O_2, then $TBPA^{+\cdot}$ (10 mol %) was added dropwise under oxygen atmosphere. The reaction solution was stirred under 60°C. After completion monitored by TLC (by UV visualization), the reaction was quenched by addition of saturated Na_2CO_3 in MeOH (10 mL) solution. The mixture was poured into a separator funnel with the addition of excess DCM (10 mL), and then the crude organic solution was extracted three times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The products were separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 20:1) to afford the products.

Acknowledgements ((optional))

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Keywords: C-H functionalization • Quinoline-2-carboxylate esters • Radical cation salt • Radical • Aerobic oxidation

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[14] The lower yield of product **2aa** (compared with Scheme 1) is attributed to the presence of 1 equivalent of 4-bromoaniline, for anilines with high concentration will partly decompose the radical cation salt, resulting in decreased reaction efficiency.

[15] For the detailed mechanism of the catalytic oxidation and regeneration of $TBPA^{+\cdot}$, see ref 12a.

[16] For coordination between Cu and C=N bond, see: a) O. Baslé, C.-J. Li *Org. Lett.*, **2008**, *10*, 3661; b) M. Ghobrial, M. Schnürch, M. D. Mihovilovic *J. Org. Chem.* **2011**, *76*, 8781; c) Z. Xie, X. Liu, L. Liu *Org. Lett.* **2016**, *18*, 2982.

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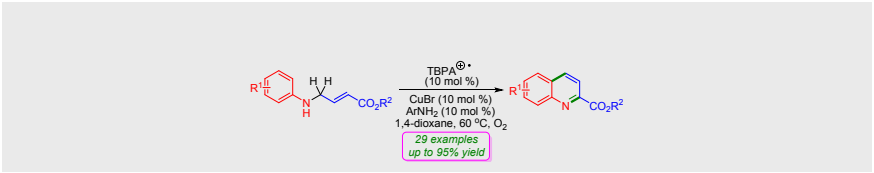

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