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Syntheses of Acridones via Copper(II)-Mediated Relay Reactions from *o*-Aminoacetophenones and Arylboronic Acids

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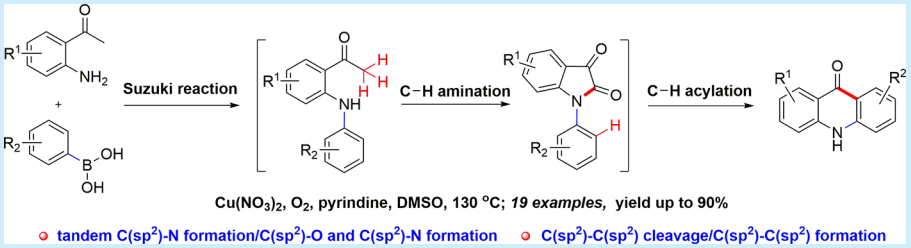
Supporting Information



ABSTRACT: The reaction of *o*-aminoacetophenones and arylboronic acids catalyzed by copper(II) salts in the presence of pyridine under an O_2 atmosphere provides a general and efficient one-pot preparation of biologically interesting acridones. This relay reaction comprises an intermolecular Suzuki cross-coupling, intramolecular oxidative C(sp^3)−H amination, and C(sp^2)−H activation with simultaneous rearrangement of the generated isatin intermediates. This strategy tolerates both electron-donating and -withdrawing functionalities to afford various acridones in good to excellent yields.

Acridones are important core scaffolds in many natural products, pigments, dyes, bioactive molecules, fluorescent labels, and functional materials. For example, acridone derivatives have been broadly used as important antimalarial, antifungal, antileishmanial, antitumor, and antiviral agents,[1] and as fluorescent labels.[2] Furthermore, acridones with extended conjugated systems are promising candidates for organic semiconductors due to their unusual electronic and photophysical properties.[3] Acridones are also fascinating potential catalyst backbones owing to their rigid structure and dentate N atom.[4] Therefore, the development of an efficient and facile method for acridone synthesis is needed.

Generally, syntheses of acridones rely on intramolecular ring-closure pathways (Scheme 1a). Acridones have been prepared by C−C bond formation from the corresponding *N*-aryl-substituted acids,[1b,d] amides,[5] and ketones,[6] or by C−N bond formation from 2-aminobenzophenones.[7] As the substrates in the above methods require prior preparation, their applications are limited. Relative to these methods, a one-pot intermolecular synthetic approach from readily available starting materials would exhibit advantages of step economy and high reaction efficiency. A one-pot strategy is more attractive than current methods, but remains challenging and has, therefore, received little research attention.[8] Recently, Lei developed a route proceeding via the palladium/copper cocatalyzed oxidative carbonylation of diphenylamines (Scheme 1b).[8a] Other routes proceeding via one-pot intermolecular annulation reactions have been reported, including the tandem arylation/Friedel−Crafts reactions of anthranilic acid esters with aryliodonium salts under a N_2 atmosphere in a sealed tube,[8b] and the tandem intermolecular nucleophilic coupling of anthranilic acid esters with an aryne generated *in situ* by treatment of *o*-(trimethylsilyl)aryl triflates with CsF and subsequent intramolecular electrophilic cyclization[8c] (Scheme 1c). Although these strategies provide access to substituted acridones, they have some drawbacks, such as relatively harsh and strict reaction conditions and the use of inaccessible or expensive substrates. Therefore, the design of a general and practical strategy for acridone preparation, particularly in a one-pot manner from readily available substrates, would be highly interesting. Herein, we report a practical and facile method for the efficient construction of acridones from commercially available phenylboronic acids and *o*-aminoacetophenones in a relay reaction comprising an intermolecular Suzuki cross-coupling of *o*-aminoacetophenones with phenylboronic acids, aerobic oxidative C(sp^3)−H amination of 1-(2-(arylamino)-aryl)-ethanone intermediates, and Ar−H activation with simultaneous rearrangement and C(sp^2)−C(sp^2) bond cleavage of the *in situ* generated isatin intermediates. This new method realizes these three reaction steps using a copper salt catalyst in a one-pot manner. These reactions of *o*-aminoacetophenones with phenylboronic acids produced various acridones in good to excellent yields that were similar or superior to those of previously reported copper-catalyzed intramolecular annulations of precursor 1-(2-(arylamino)aryl)ethanones[6a,9] and 2-aminobenzophenones.[7]

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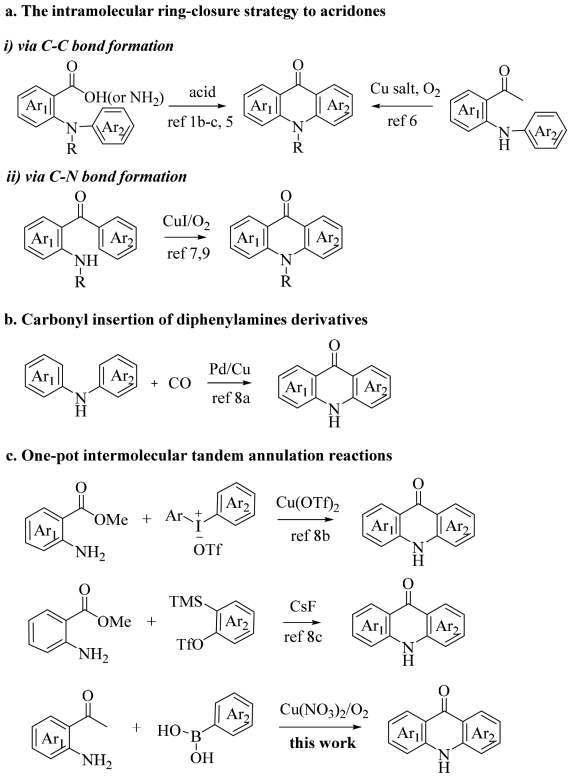
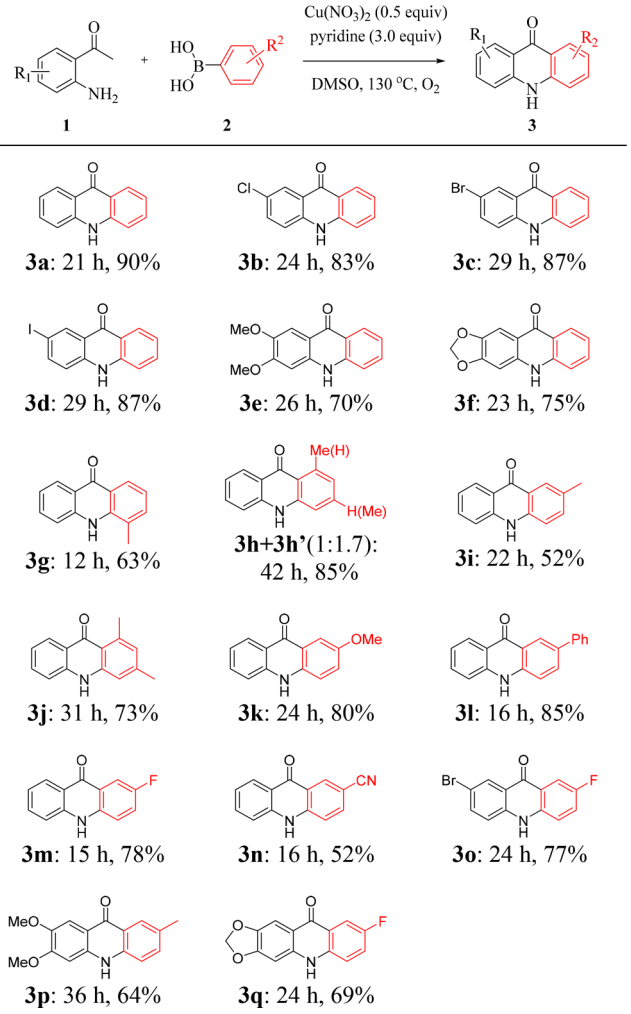
Scheme 1. Synthetic Routes for Acridones



Recently, we achieved the one-pot synthesis of various furo[3,2-*b*]indoles via a silver(I)-mediated [3 + 2] cycloaddition of *o*-propargylaminoacetophenones prepared from readily available *o*-aminoacetophenones.[10] We have an ongoing interest in the construction of medicinally important nitrogen-containing heterocycles from *o*-aminoacetophenones. Considering the reaction possibilities of intermolecular couplings of arylamines with arylboronic acids catalyzed by transition metal catalysts under basic conditions,[11] we speculated that the fused tricycle of acridones could be synthesized by reacting *o*-aminoacetophenones with arylboronic acids (or esters) via an intermolecular tandem strategy of C(sp^2)−N bond formation/C(sp^2)−C(sp^3) bond cleavage/C(sp^2)−C(sp^2) bond formation in the presence of an appropriate metal catalyst system. Arylboronic acids are widely applied in organic synthesis owing to their stability, structural diversity, ready availability, and low toxicity, which indicated that the proposed strategy might be simple and practical. After extensive screening of different reaction parameters (see Supporting Information (SI), Table S1), optimum conditions were identified to be $Cu(NO_3)_2$ (0.5 equiv) as the catalyst, pyridine (3 equiv) as an additive, and DMSO as the solvent at 130 °C under an oxygen atmosphere (Table S1, entry 7).

With the optimized conditions in hand, we proceeded to investigate the scope of this new domino reaction, with the results summarized in Scheme 2. This procedure tolerated both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) on the benzene rings of both aminoacetophenones **1** and phenylboronic acids **2** to give various acridones in good to excellent yields. *o*-Acetylanilines (**1b**−**1d**) bearing EWGs showed higher reactivities and afforded higher yields than those bearing strong EDGs (such as **1e** and **1f**). The electronic nature of substituents on arylboronic acids **2** had no evident influence on the reactions (**3k** vs **3m** and **3n**, **3p** vs **3q**).

Scheme 2. Extension of Reaction Scope[a]



[a]Unless otherwise indicated, all reactions were conducted with **1** (0.3 mmol), **2** (1.2 equiv), $Cu(NO_3)_2$ (0.5 equiv), and pyridine (3.0 equiv) in DMSO (3 mL) at 130 °C under oxygen (1 atm).

The reaction of phenylboronic acid **2** bearing an *ortho*-substituent gave a lower yield compared with those bearing *meta*- and *para*-substituents (**3g** vs **3h+3h′** and **3i**), owing to steric hindrance in the Suzuki coupling reaction caused by *ortho*-substituents. Notably, the *meta*-Me-substituted substrate (**2h**) showed interesting regioselectivity, affording a product mixture with a 1:1.7 ratio in 85% yield (**3h**/**3h′**), which indicated that cyclization at the *para*-position relative to R^2 was preferable to that at the *ortho*-position, based on the ratio of the isolated regioisomers. Notably, the reaction of 3,5-dimethylphenylboronic acid **2j** afforded product **3j** in an unexpectedly high yield of 73%, despite significant hindrance between 1,3-disubstitutents in the intramolecular annulation of intermediate **4j**. This result suggested that steric hindrance might not affect the final cyclization step. Pleasingly, the reaction of phenylboronic acid pinacol ester and 2,2-dimethyl-1,3-propanediol ester under the same conditions afforded **3a** in 93% and 83% yields, respectively (Scheme 3).

To investigate the mechanism of the relay reaction, we performed several controlled experiments (Scheme 4).

The reaction of **1r** with **2a** did not proceed under the standard conditions, with 92% of **1r** recovered and desired product **3a** and coupling intermediate **4r** not detected (as

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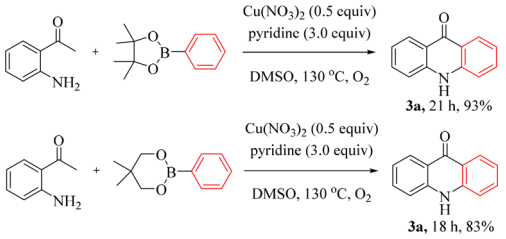
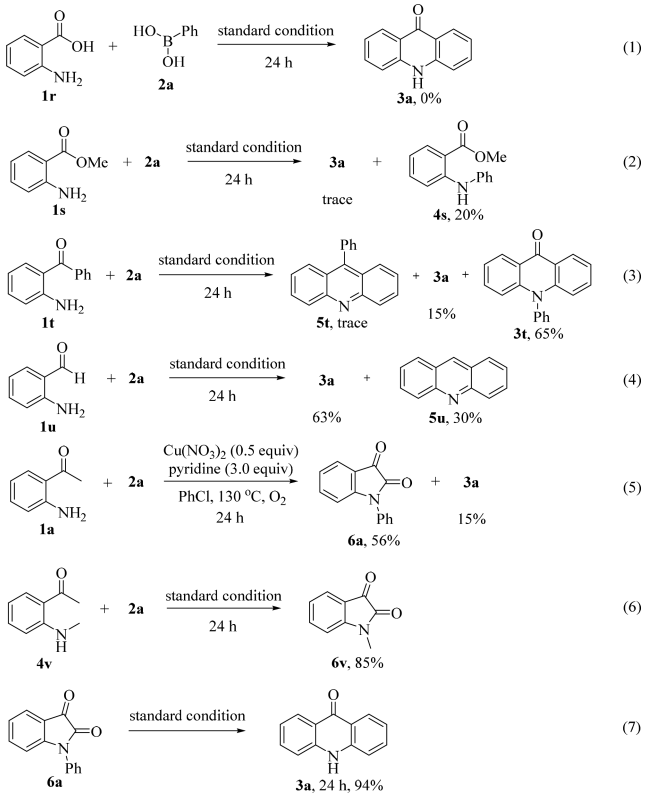
Scheme 3. Reactions with Phenylboronic Acid Esters

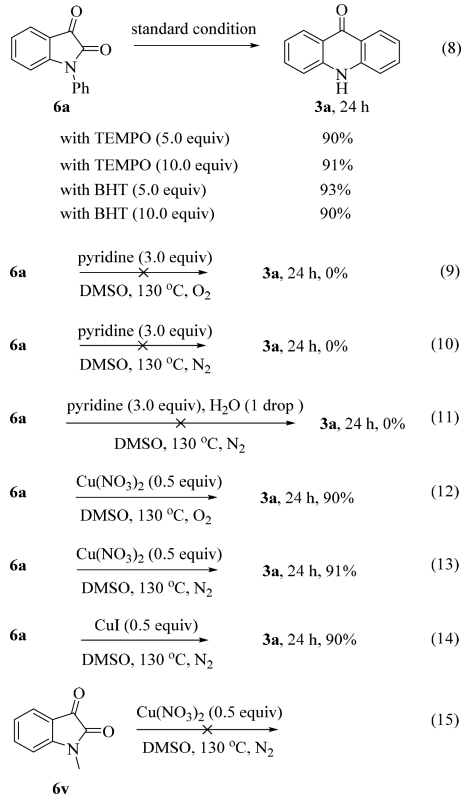


Scheme 4. Mechanism-Probing Experiments



monitored by TLC) (eq 1). This result suggests that $-CO_2H$ influenced the formation of coupling intermediate **4r** and affected the efficiency of pyridine.[11] When methyl *o*-aminobenzoate **1s** and **2a** were reacted, a 20% yield of coupling intermediate **4s** was afforded, with only a trace amount of desired product **3a** detected and 50% of **1s** recovered (eq 2). This indicated that intermediate **4s** could not undergo the intramolecular Friedel–Crafts-type reaction to produce **3a** under the present reaction conditions.[8b] The control reaction of **1t** with **2a** was also conducted using the optimized procedure, with **3a** and **3t** obtained in 15% and 65% yields, respectively, while only a trace amount of Friedel–Crafts-type product **5t** was detected (eq 3). The formation of **3a** likely began with **1t** through a Cu-catalyzed intramolecular aromatic C–H amination process,[9,12] with intermediate **4t** similarly undergoing aromatic C–H amination to generate **3t** rather than Friedel–Crafts-type product **5t**. Although desired **3a** was afforded in 63% yield when **1u** was reacted with **2a** under the optimized conditions, a 30% yield of acridine **5u** was also obtained (eq 4).[6a,13] These results implied that 2-(arylamino)-benzaldehydes were key intermediates in these chemical processes (Scheme 2).[6a,13c] Isatins **6** were detected during the reactions, as shown in Scheme 2. The conversion of *o*-(aminophenyl)-ethan-1-ones (**4**) to isatins **6** catalyzed by copper salts has been reported.[6a,9,11] This indicated that isatins **6** might be involved in these present reactions. To confirm this, three additional reactions were conducted (eqs 5–7). The reaction of **1a** with **2a** gave a 15% yield of desired **3a** and a 56% yield of isatin **6a** when chlorobenzene (PhCl) was used as the solvent instead of DMSO (eq 5). When *o*-(methylamino)-phenylethan-1-one (**4v**) was reacted with **2a** under the optimized conditions, isatin **6v** was obtained in 85% yield (eq 6). When isatin **6a** was subjected to the optimized conditions, **3a** was afforded in 94% yield (eq 7). Finally, isatins **6** were shown to be key intermediates in the new cascade reactions. To probe the transformation mechanism of intermediates **6** to products **3**, indoline-2,3-dione **6a** was synthesized and subjected to control experiments (Scheme 5).

Scheme 5. Reactions of Isatins under Different Conditions



Radical mechanism studies indicated that a radical pathway might not be involved in this transformation (eq 8). The reaction of isatin **6a** did not occur in the presence of pyridine under O_2 and N_2 atmospheres, with most of **6a** recovered (eqs 9–11). These results ruled out that **6a** was ring-opened in the presence of pyridine and water under heating to give an α-keto acid pyridine salt with a subsequent intramolecular Friedel–Crafts-type reaction to give product **3a**.[6b] Copper salts were shown to be necessary for the transformations, while pyridine and O_2 were not necessary (eqs 13 and 14). To gain further insight into the mechanism, the black powders obtained by filtration at the end of the reactions (eqs 12–14), were analyzed by powder X-ray diffraction (XRD; see SI, Figure S1). XRD showed that the black powders were Cu(II) salts (no Cu(I) and Cu(0) detected, eqs 12 and 13) and Cu(I) salts (no Cu(II) and Cu(0) detected, eq 14), respectively. 1-Methyl

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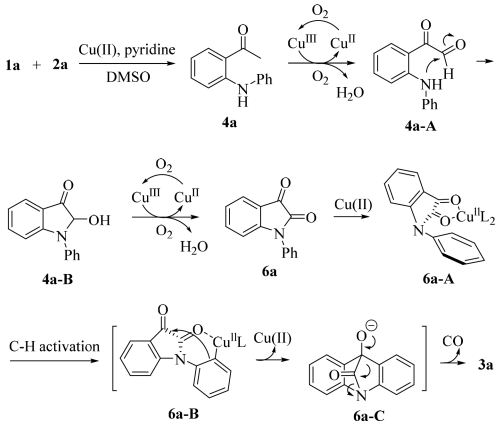
isatin **6v** (eq 15) tolerated Cu(II) salts in DMSO under heating,[14] which ruled out a mechanism via the Cu(II)-mediated cleavage of the C_2-C_3 bond of **6** and subsequent annulation to **3**.

Based on previous literature and all controlled results described above, a possible mechanism for the copper-mediated cascade reactions is proposed in Scheme 6. Initially, **1a** and **2a**

Scheme 6. Proposed Mechanism



react to afford **4a** through a cross-coupling process with copper as the catalyst under basic conditions (provided by pyridine).[11] Then, **4a-A** is expected to be formed by **4a** in the presence of Cu(II) and oxygen under heat.[14a,15] Subsequently, intramolecular addition of the amino group to the aldehyde group of glyoxal **4a-A** results in the formation of 2-hydroxyindolin-3-one derivative **4a-B**, which is further oxidized to form key intermediate isatin **6a**.[9,14a,15c,16] Product **3a** is finally formed by rearrangement of **6a**.[17] The transformation from **6a** to **3a** might occur via three processes, as follows: C−H activation of **6a** by Cu complex **6a-A** to afford metallacycle **6a-B** via S_EAr,[17a−c] direct intramolecular nucleophilic attack at the ketone to form tricyclic intermediate **6a-C**, and then conversion of **6a-C** to **3a** after carbon monoxide extrusion.[17d,e]

In summary, we have developed a convenient and mild method for the construction of acridones in one step from commercially available *o*-aminoacetophenones and phenylboronic acids. This Cu(II)-mediated cascade reaction involves the following steps: Intermolecular Suzuki cross-coupling, intramolecular oxidative C−H amination, and C−C bond cleavage with recyclization. In general, this strategy tolerates both electron-donating and -withdrawing functional groups on benzene rings of both the aminoacetophenones and phenylboronic acids to give various acridones in good to excellent yields. The advantages of this method include relatively mild reaction conditions, high reaction efficiency, the use of commercially available reaction substrates and a cheap metal catalyst (copper), and the tolerance of various functional groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00957.

Screening of reaction conditions, experimental procedures, X-ray diffraction data, ^1H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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