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Transition-Metal-Free Synthesis of Phenanthridinones from Biaryl-2-oxamic Acid under Radical Conditions

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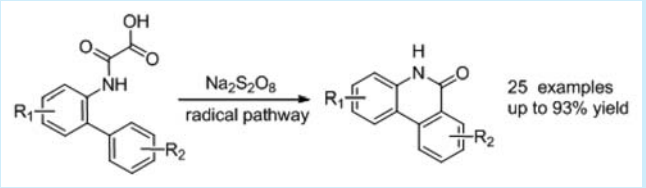
Supporting Information

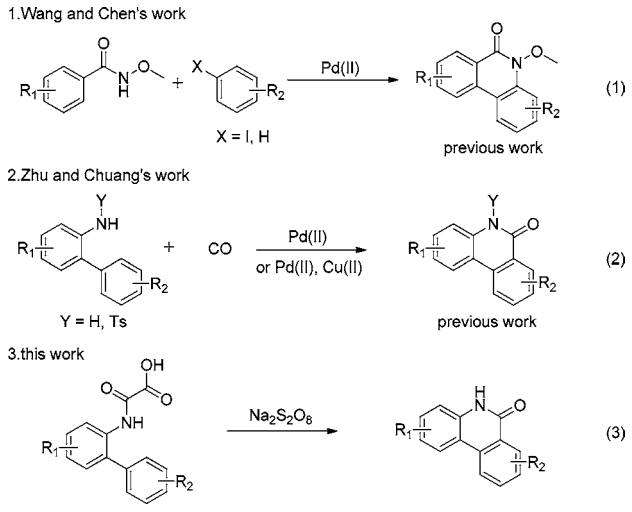
ABSTRACT: $Na_2S_2O_8$-promoted decarboxylative cyclization of biaryl-2-oxamic acid for phenanthridinones has been developed. This work illustrates the first example of intramolecular decarboxylative amidation of unactivated arene under transition-metal-free conditions. Additionally, this approach provides an efficient and economical method to access biologically interesting phenanthridinones, an important structure motif in many natural products.



Transition-metal-catalyzed decarboxylative coupling reactions are of great importance for the formation of C−C, C−N, C−S, and C−P bonds in modern organic synthesis.[1] In comparison to classical organometallic coupling reagents, the simple and readily available carboxylic acids can be directly used as reactants, and their transformations have some advantages such as releasing nontoxic CO_2 and avoiding highly basic reaction conditions. Since Myers[2] reported the first palladium-catalyzed decarboxylative Heck-type olefination, there has been a great deal of work[3] focused on decarboxylative coupling of carboxylic acids or their salts, such as the Pd-catalyzed decarboxylative arylation of aryl halide with benzoic acid by Goossen.[4] Recently, the combination[5] of decarboxylative coupling with C−H activation has attracted considerable interest due to its atom- and step-economical features. Acylation of unactivated arenes using α-oxocarboxylic acid via C−H activation and C−C coupling has also been demonstrated.[5p,6] However, most of the reactions still require transition-metal catalysts and release metal waste in the process. In addition, decarboxylic amidation of oxamic acid especially under transition-metal-free conditions has been rarely explored.[7]

Phenanthridinone nuclei are important organic structural motifs found in natural products and biologically active molecules. This has led to the search for a convenient approach to construct phenanthridinones.[8] Recently, Wang and Chen's research group[8j,k] has developed an efficient palladium-catalyzed coupling of *N*-methoxy benzamides with aryl iodides or benzene via dual C−H bond activations, respectively (Scheme 1, eq 1). Later on, independent reports by Zhu and Chuang's group[8g,h,o] showed palladium-catalyzed synthesis of phenanthridinones via C−H activation and oxidative insertion of carbon monoxide (Scheme 1, eq 2). For these approaches, a palladium catalyst is still necessary for most of the reactions. In view of this, we present a sodium persulfate ($Na_2S_2O_8$) mediated intramolecular decarboxylative cyclization for phenanthridinones (Scheme 1, eq 3). To the best of our knowledge, this is the first example of intramolecular decarboxylative amidation of an unactivated arene under transition-metal-free conditions.

Scheme 1. Approaches for the Synthesis of Phenanthridinones



Initially, biphenyl-2-oxamic acid (**1a**) was chosen as the model substrate to investigate the reaction conditions. Inspired

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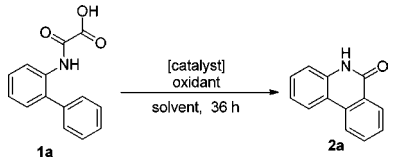
by Ge's work[5l,6b,c,7] on decarboxylative coupling reactions, $Pd(OAc)_2$ as the catalyst and potassium persulfate ($K_2S_2O_8$) as the oxidant were used in the reaction. To our delight, the reaction afforded the desired phenanthridinone **2a**, albeit in low yield (26%; Table 1, entry 1). Varying the palladium catalysts

Table 1. Optimization of Reaction Conditions[a]



1a 2a

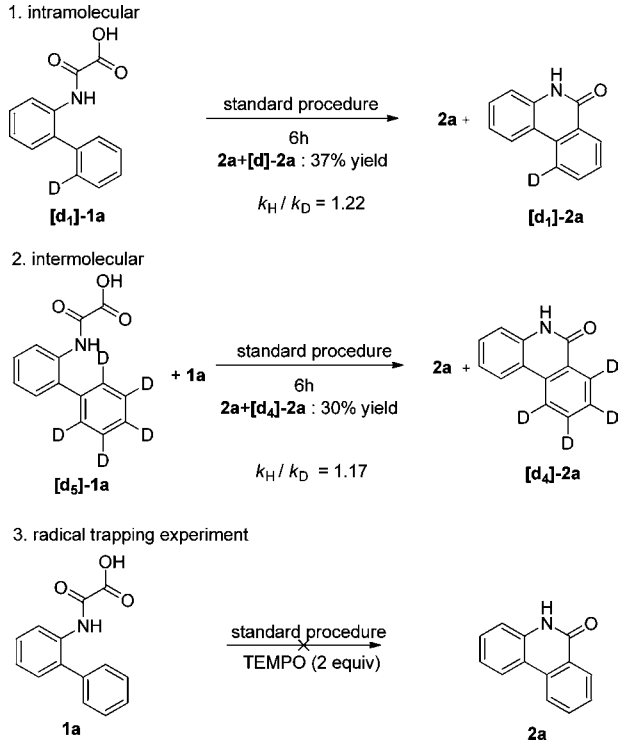
entry	catalyst	oxidant (amt (equiv))	solvent	yield[b] (%)
1	$Pd(OAc)_2$	$K_2S_2O_8$ (2)	DMSO	26
2	$AgNO_3$	$K_2S_2O_8$ (2)	DMSO	42
3	Ag_2O	$K_2S_2O_8$ (2)	DMSO	45
4	AgOAc	$K_2S_2O_8$ (2)	DMSO	41
5	Ag_2CO_3	$K_2S_2O_8$ (2)	DMSO	47
6		$K_2S_2O_8$ (2)	DMSO	72
7		$Na_2S_2O_8$ (2)	DMSO	79
8		$(NH_4)_2S_2O_8$ (2)	DMSO	70
9		$Na_2S_2O_8$ (2)	1,4-dioxane	0
10		$Na_2S_2O_8$ (2)	DMF	56
11		**$Na_2S_2O_8$ (2)**	**DMSO**	**80**[c]
12			DMSO	0
13		H_2SO_4 (2)	DMSO	0

[a]Conditions: **1a** (0.2 mmol), catalyst (10 mol %), solvent (5.0 mL), 110 °C, 36 h, under Ar. [b]Yield of isolated products. [c]In air.

could not improve the yield. Very recently, $AgNO_3$ in combination with $K_2S_2O_8$ has been widely utilized as an efficient and inexpensive system in decarboxylative coupling reactions by Greaney and co-workers.[5o,9] On the basis of these reports, we tried to use use $AgNO_3$ as a catalyst instead of $Pd(OAc)_2$; interestingly, the yield was increased to 42% (Table 1, entry 2). Unfortunately, further examination of silver salts such as Ag_2O, AgOAc, and Ag_2CO_3 (Table 1, entries 3−5) did not result in significant improvement. Surprisingly, the reaction could also occur in the absence of the silver catalyst (Table 1, entry 6). Under these tranistion-metal-free conditions an even higher yield (72%) was achieved. Among the different oxidants (Table 1, entries 7 and 8), $Na_2S_2O_8$ gave the best result. Moreover, screening of different solvents revealed that DMSO gave the best results (Table 1, entries 9 and 10). At this stage, it was found that the reaction could be conducted in air (Table 1, entry 11). Furthermore, control experiments proved that $Na_2S_2O_8$ was indispensable for this transformation (Table 1, entries 12 and 13). Finally, optimization of the reaction conditions demonstrated that the reaction was most productive using $Na_2S_2O_8$ as oxidant and DMSO as solvent, providing **2a** in 80% yield at 110 °C within 36 h in air (Table 1, entry 11).

To gain insight into the mechanism of the decarboxylative cyclization reaction, inter- and intramolecular kinetic isotopic effect (KIE) experiments of the arene C−H bond were carried out (Scheme 2, parts 1 and 2). The k_H/k_D values were found to be 1.22 and 1.17, respectively. The results imply that the rate-determining step does not involve the cleavage of the arene C−H bond,[10] and this transformation may be via a radical aromatic substitution pathway. Then, the reaction was conducted with the addition of 2.0 equiv of TEMPO by standard procedures (Scheme 2, part 3); in this case, the reaction was completely

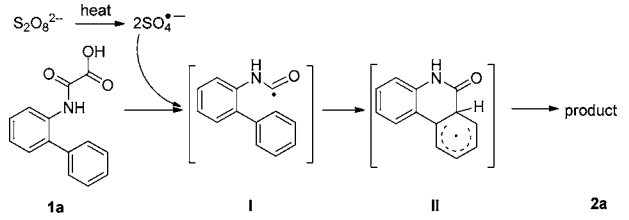
Scheme 2. Preliminary Mechanism Studies



inhibited, which suggested that this reaction involves radical intermediates.

On the basis of the mechanistic studies described above, a plausible reaction mechanism is depicted in Scheme 3. Initially,

Scheme 3. Proposed Reaction Mechanism



sulfate anion radical is generated through homolytic cleavage of the peroxydisulfate dianion. The radical could react with **1a** through a hydrogen abstraction and decarboxylation process, providing carbamoyl radical **I**. Subsequently, the intramolecular radical cyclization of radical **I** takes place to form intermediate **II**. Finally, another sulfate radical abstracts one H from intermediate **II** to give the annulation product **2a**.

At the same time, the byproduct **2as** was isolated from the TEMPO radical trapping experiment. After its single crystal was cultured (see the Supporting Information), compound **2as** was elucidated as biphenyl 2-formamide. Recently, a similar reaction was developed to synthesize fluorenones through intramolecular dehydrogenative arylation of aldehydes by Glorius.[11] Upon this work, we conceived that **2as** may be applied to synthesize phenanthridinones as well. To verify the hypothesis, our optimized reaction conditions were applied to compound **2as** and a 46% yield of the desired product was actually obtained (Scheme 4, eq 1), we also subjected compounds **1a** and **2as** to the same reaction conditions as reported by Glorius (Scheme 4, eqs 2 and 4). However, worse results were observed

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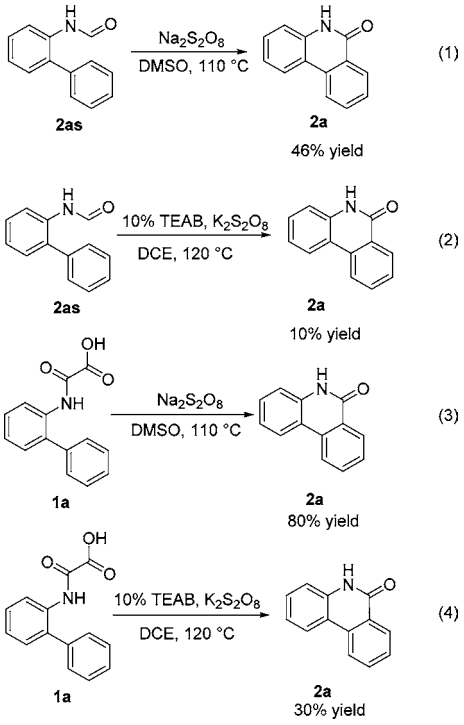
Scheme 4. Comparison of Two Methods for Phenanthridinones



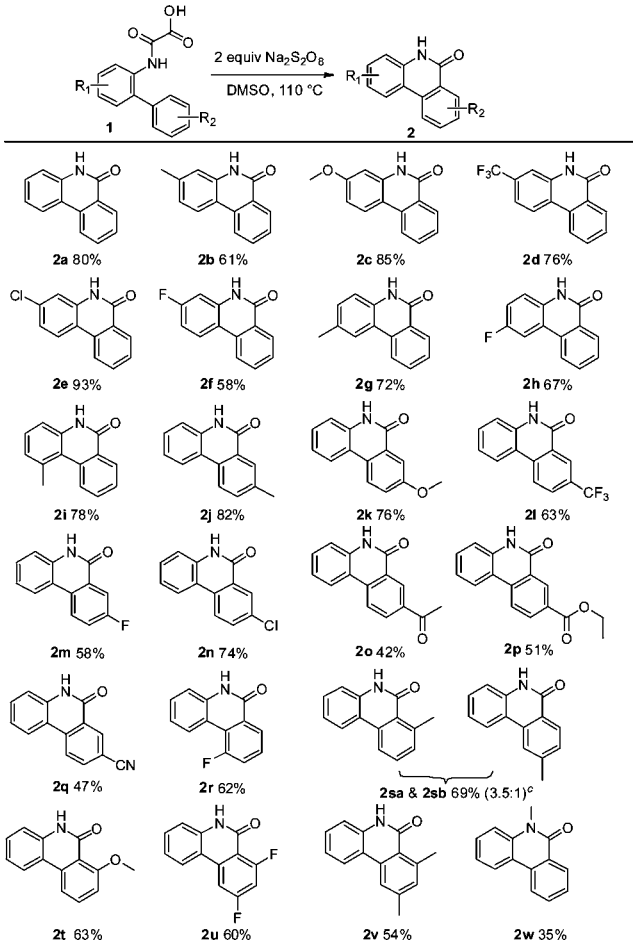
for both cases, possibly due to the instablility of the formamide structure at high temperature.

With a set of optimized conditions in hand, the substrate scope of biaryl 2-oxamic acid was investigated (Scheme 5). Substituents on the aromatic ring with different electronic properties, including methyl, methoxyl, halogen, and trifluoromethyl, were probed. It was found that all substrates ran smoothly in this reaction, giving the desired products (**2a**−**w**) in good to excellent yields. Electron-withdrawing groups on the aromatic ring did not lower the reaction efficiency. This may be because a radical pathway was involved in the procedure. For the meta-substituted substrate, to our surprise, the reaction preferably delivered the product with greater steric hindrance,[12] which is usually not easy to obtain in transition-metal-catalyzed reactions, such as **2sa**. Moreover, the product **2t** was generated as a single isomer. Multiply substituted products (**2u,v**) can also be easily obtained in good yields from the corresponding substrates.

The system was further applied to isoindolinone and isoquinolinone (Scheme 6), which are bioactive skeletons and are widespread in natural products. In these two cases, the substrates depicted as aliphatic amines (**3** and **4**) and the neighboring disubstituted species proved extremely important. Under the optimized reactions, the desired isoindolinone and isoquinolinone were obtained in moderate yields.

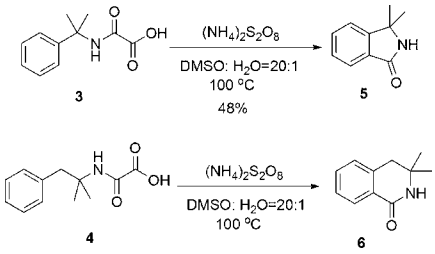
In summary, an efficient and economical approach for the synthesis of phenanthridinones by decarboxylative cyclization of biaryl 2-oxamic acid has been developed. This novel method, with an inexpensive system ($Na_2S_2O_8$ only) and good tolerance to air, obviates the use of expensive transition-metal catalysts and produces CO_2 as the waste.

Scheme 5. $Na_2S_2O_8$-Mediated Synthesis of Phenanthridinones[a,b]



[a]Reaction conditions: compound **1** (200 mg), $Na_2S_2O_8$ (2 equiv), DMSO (20 mL), 110 °C, 36 h, in air. [b]Yield of isolated products. [c]Isomer ratio determined by ^1H NMR.

Scheme 6. Further Applications



■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental procedures, characterizations data, and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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