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Synthesis of 2-Quinolinones via a Hypervalent Iodine(III)-Mediated Intramolecular Decarboxylative Heck-Type Reaction at Room Temperature

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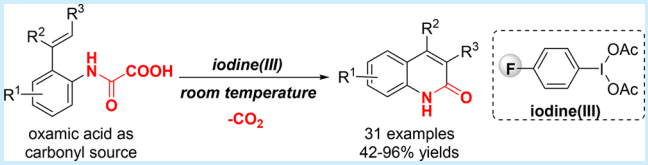
Supporting Information

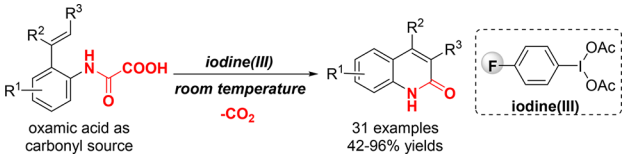
ABSTRACT: A hypervalent iodine(III)-mediated intramolecular decarboxylative Heck-type reaction of 2-vinyl-phenyl oxamic acids has been developed. The unique ring-strain-enabled radical decarboxylation mechanism is preliminarily revealed. This protocol features metal-free reaction conditions and operational simplicity, allowing the lactamization of 2-vinylanilines using a readily accessible carbonyl source and the synthesis of various 2-quinolinones with excellent chemoselectivity at room temperature.



2-Quinolinone is a common structural motif in numerous natural products and synthetic pharmaceuticals with a broad spectrum of biological activities (see the representative examples shown in Figure S1).[1] Not surprisingly, the preparation of this useful heterocyclic moiety has received considerable attention from medicinal and synthetic organic chemists. One of the most efficient and straightforward methods for the preparation of this motif is the lactamization of 2-vinylanilines using a suitable carbonyl source via direct alkenyl C−H bond transformation. Heck-type lactamization approaches using carbamoyl chloride or carbamoyl cyanide as carbonyl donors have been reported, but suffer from the use of transition metals or strong acids (30 mol % hydrobromic acid) as catalysts at high reaction temperatures (130−150 °C).[2] Furthermore, the intrinsic issue is that toxic phosgene or its derivatives were typically required in the synthesis of the starting materials. These drawbacks have significantly restricted the industrial application of these methods, especially in the pharmaceutical sector (Scheme 1a). In 2013, the Alper group reported an efficient Pd-catalyzed oxidative carbonylation reaction of 2-vinylanilines using CO as a carbonyl source and copper acetate/air as the terminal oxidant.[3a] However, the use of highly toxic CO and a large amount of high-valent transition metals as the oxidant or catalyst at high temperature (110 °C) caused safety issues, high costs, and risks of residual heavy metals (Scheme 1b). Recently, a green approach employing CO_2 as the carbonyl donor for the lactamization of 2-vinylaniline under transition-metal-free conditions was reported for the preparation of 2-quinolinones in moderate to excellent yields; however, a high reaction temperature (140 °C) and a large excess of strong base (NaO^{t}Bu, 4.5 equiv) were still required (Scheme 1b).[3b] Therefore, the development of a mild and green method for the lactamization of 2-vinylanilines using a suitable carbonyl donor to deliver more diverse 2-quinolinone structures remains a great challenge.

The decarboxylative Heck-type reaction, which utilizes readily available and structurally diverse carboxylic acids as coupling reagents, represents a powerful tool for constructing valuable olefin targets.[4] The advantages of these transformations also include simply releasing nontoxic CO_2 as a byproduct and avoiding the production of stoichiometric amounts of toxic metal halides. Since the pioneering work by the Myers group,[4a] transition-metal catalyzed decarboxylative Heck-type reactions employing aromatic carboxylic acids as coupling partners have been well developed. However, the corresponding metal-free version, which would be an important addition to this field owing to the particular purity requirements of the biological and medicinal chemistry fields, is notably absent. Furthermore, the extension of the substrate scope to other readily accessible carboxylic acids is also an important goal.[5] Hypervalent iodine(III) compounds are a class of readily available and environmentally benign reagents with comparable efficiencies to transition-metal catalysts in various oxidative coupling reactions.[6] Herein, we report the first metal-free intramolecular

Scheme 1. Synthesis of 2-Quinolinones via the Lactamization of 2-Vinylanilines



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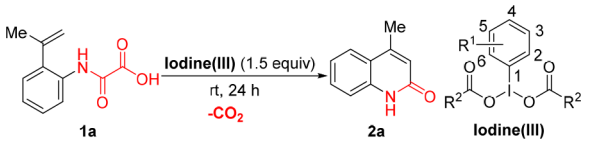
decarboxylative Heck-type reaction of oxamic acids (as the carbonyl source) with alkenes using hypervalent iodine(III) as the sole promoter to efficiently mediate the lactamization of 2-vinylanilines (Scheme 1c). This protocol features excellent chemoselectivity and a distinct ring-strain-enabled radical decarboxylation mechanism, which is operationally simple and allows the synthesis of various 2-quinolinones in moderate to excellent yields at room temperature.

The oxidative decarboxylative coupling reactions of oxamic acids, which involve the formation of carbamoyl radicals, served as a versatile platform for the synthesis of various amide-containing compounds.[7] We envisioned that this readily accessible acid might also participate in intramolecular decarboxylative Heck-type reactions, creating a novel method for the lactamization of 2-vinylanilines to deliver diverse 2-quinolinones. However, efficiently avoiding the formation of indoles (oxidative C−N bond formation) would be significantly challenging for successful implementation of this strategy (Scheme S1).[8] The initial investigation of the proposed reaction started with subjecting 2-(prop-1-en-2-yl)phenyloxamic acid (**1a**) to several reported photocatalytic conditions that can promote decarboxylation-induced radical formation under mild conditions.[7e,9] However, only the reaction system employing phenyliodine(III) diacetate (PIDA) as a co-oxidant resulted in the production of target compound **2a** in 20% yield (entry 3, Table S1). Interestingly, in the absence of a photocatalyst and light source, **2a** was generated in a higher yield (40% yield, entry 1 in Table 1 or entry 7 in Table S1). This fact, as well as the results of the control reactions (entries 4−7, Table S1), suggests that the hypervalent iodine(III) reagent (HIR) plays an essential role in this process, which occurs via a nonphotoredox engaged radial decarboxylation mechanism. Various HIRs were then screened (Table S1 and Table 1). The use of cyclic HIRs (acetoxybenziodoxole and hydroxybenziodoxole) and Koser reagent in place of PIDA led to a dramatic decrease in reaction efficiency (entries 8−10, Table S1). A further survey of PIDA analogues indicated that the replacement of the acetoxy group with better leaving groups, such as trifluoroacetoxy groups and benzoyloxy groups, was detrimental to the reaction outcome (entries 1−3, Table 1). In addition, the use of PIDA analogues with both electron-donating groups (4-Me and 4-OMe) and strong electron-withdrawing groups (4-CF_3) on the benzene resulted in a slight decrease in reaction efficiency (34−39% yields, entries 4−6, Table 1). The introduction of a fluorine atom at the 4 position of the benzene provided the product in an improved yield (58%, entry 7, Table 1). The yield could not be further increased by the introduction of another fluorine atom at the 2 or 3 positions of the benzene (44−47% yields, entries 8−9, Table 1). 4-$FC_6H_4I(OAc)_2$ was then identified as the most efficient promoter for further screening. The suitable oxidation capacity of this reagent, which enables the selective decarboxylation functionalization while avoiding other oxidative side reactions, might help to explain this result. Furthermore, 1.5 equiv proved to be the optimal amount of this reagent (entries 10−11, Table 1). It should be noted that this iodine(III) reagent was also identified as the most efficient promoter in the cross-coupling reaction of pyrroles with electron-rich arenes.[10] The solvent screening revealed that $CHCl_3$ was the most favorable solvent for this transformation (80% yield, entry 12 in Table 1, Table S2). Neither running the reaction under oxygen-free conditions nor extending the reaction time to 48 h further improved the reaction efficiency (68−80% yields, entries 13−14, Table 1). Hence, the optimized reaction conditions are shown in entry 12 (4-$FC_6H_4I(OAc)_2$, 1.5 equiv, $CHCl_3$, rt, 24 h). Under these reaction conditions, the reaction can be scaled up to 1.0 g and provide the product in 66% isolated yield (entry 15, Table 1). It should be noted that the formation of indole, which can be synthesized via a HIR-mediated oxidative C−N bond formation of Cbz-protected 2-vinylaniline,[8a] was not observed in this process, highlighting the excellent chemoselectivity of this reaction (Scheme S1).

Table 1. Investigation of the Hypervalent Iodine(III)-Mediated Intramolecular Decarboxylative Heck-Type Reaction[a]



entry	R^1	R^2	solvent	yield[b]
1	H	Me	DCE	40%
2	H	CF_3	DCE	trace
3	H	Ph	DCE	30%
4	4-OMe	Me	DCE	35%
5	4-Me	Me	DCE	39%
6	4-CF_3	Me	DCE	34%
7	4-F	Me	DCE	58%
8	3,4-diF	Me	DCE	44%
9	2,4-diF	Me	DCE	47%
10	4-F	Me	DCE	49%[c]
11	4-F	Me	DCE	45%[d]
12	4-F	Me	$CHCl_3$	80% (77%[e])
13	4-F	Me	$CHCl_3$	68%[f]
14	4-F	Me	$CHCl_3$	80%[g]
15	4-F	Me	$CHCl_3$	66%[e,h]

[a]Reaction conditions: **1a** (0.15 mmol, 1.0 equiv), iodine(III) (1.0−2.0 equiv), solvent (3.0 mL), rt, 24 h, unless otherwise noted. [b]Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [c]2.0 equiv of 4-$FC_6H_4I(OAc)_2$ was employed. [d]1.0 equiv of 4-$FC_6H_4I(OAc)_2$ was employed. [e]Isolated yields are shown. [f]N_2 was bubbled through the reaction solution for 30 min. [g]The reaction time was extended to 48 h. [h]Performed on 1.0 g scale.

Having established the optimal reaction conditions, we next sought to evaluate the substrate scope employing 2-(prop-1-en-2-yl)phenyloxamic acids with different substituents on the benzene ring (Scheme 2). The reactions proceeded well for the substrates with weak electron-donating groups at the 4 or 5 position of the benzene, providing the product in comparable yields (**2b−2f**, 60−77% yields). However, the introduction of strong electron-donating groups at these two positions was detrimental to the reaction efficiency (**2g−2i**, 46−60% yields), which can be attributed to the undesired oxidative side reactions of the highly electron-rich methoxyaniline structure. The introduction of electron-withdrawing groups at the 4 or 5 position, especially at the 4 position, slightly decreased the reactivity (**2j−2r**, 52−70% yields), and further elevation of the reaction temperature (80 °C) increases the yield (**2q**, 68% yield). It should be noted that chloride, alkynyl, nitro, and cyano groups were well tolerated, and these moieties provide handles for further functionalization. For example, a simple two-step procedure starting from **2p** can be used to generate a reported MAO-B inhibitor with anti-Alzheimer activity.[1f] Interestingly, the installation of a methyl group at the 6 position led to the generation of the corresponding products in excellent yields

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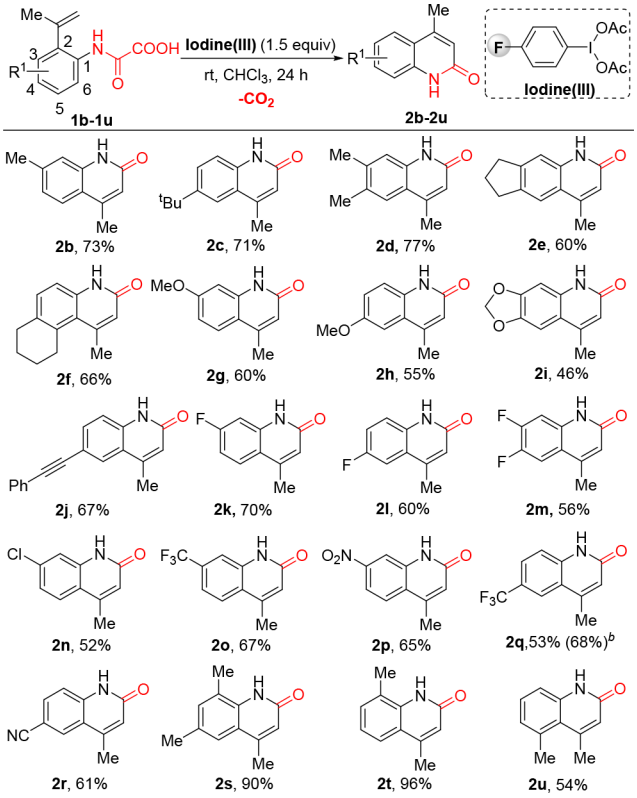
Scheme 2. Scope of the Hypervalent Iodine(III)-Mediated Intramolecular Decarboxylative Heck-Type Reaction[a]



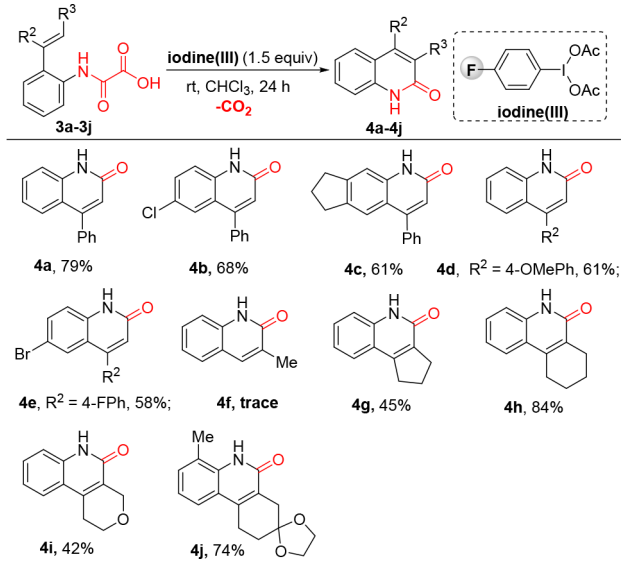
[a]See general procedure F for the experimental details. Isolated yields are reported unless otherwise noted. [b]Performed at 80 °C.

(**2s**–**2t**, 90–96% yields), while the introduction of a methyl group at the 3 position has little effect on the reaction outcome (**2u**, 54% yield). This is presumably caused by the increased torsional strain induced by the *ortho*-methyl group (6 position) strongly favoring this intramolecular organic transformation.

In light of the high importance of 4-aryl-2-quinolinones in drug discovery, we further tested the reactivities of various 2-(1-phenylvinyl)phenyl oxamic acids (Scheme 3). We found that this class of substrates could typically undergo the reaction to generate the corresponding 4-aryl-2-quinolinones in moderate to excellent yields (**4a**–**4e**, 58–79% yields). It should be noted that the important 4-aryl-2-quinolinones **4b** (HBV inhibitor)[1c] can be accessed in a facile manner in good yield with our method (68% yield), which provides an alternative approach for the synthesis of this medicinally valuable structure. The shift of the methyl group of **1a** to the terminal position of the olefin (R^2 = H, R^3 = Me) dramatically decreased the reaction efficiency (**4f** in Scheme 3), while substrates with cycloalkenyl groups worked well and gave a series of therapeutically valuable tricyclic structures in moderate to high yields (**4g**–**4j**, 42–84% yields). Substrates with a cyclohexenyl group are more reactive in this process, leading to higher reaction efficiencies.

Having established the scope of the method, we sought to elucidate the reaction mechanism. The formation of product **2a** was inhibited by the presence of TEMPO (Scheme S2B), again suggesting a radical mechanism. Considering the fact that HIR-mediated radical decarboxylations start from the homolysis of the iodine–oxygen bond,[6b,7e] as well as the observation that the nitrogen of phenyl oxamic acid plays an essential role in its decarboxylative functionalization probably via the direct

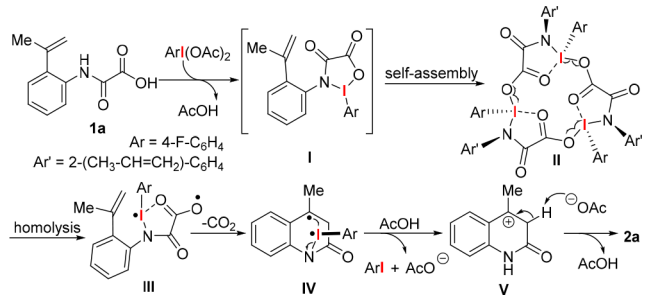
Scheme 3. Scope of the Hypervalent Iodine(III)-Mediated Intramolecular Decarboxylative Heck-Type Reaction[a]



[a]See general procedure F for the experimental details. Isolated yields are reported unless otherwise noted.

interaction with HIR (Schemes S2C, S3–S5) and the established self-assembly theory of amino acid derived benziodazole,[11] it is reasonable to conclude that a macrocyclic iodine(III) trimer **II** with three directive secondary I···O bonds might be generated *in situ* in this process via the self-assembly of the highly distorted cyclic iodine(III) monomer **I** (Scheme 4).[12]

Scheme 4. Proposed Mechanism



The relatively higher ring strain of this macrocyclic structure, including the angle strain and transannular strain, might enable the homolysis of the iodine–oxygen bond at room temperature (Scheme S6). It should be noted that this process usually proceeds at high temperature, under UV light, or using visible light in the presence of a photocatalyst.[7e,13] However, the homolysis of the iodine–oxygen bond enabled by the ring strain of the highly distorted five-membered cyclic iodine(III) intermediate **I** cannot be completely excluded. Based on these studies, a plausible mechanism was proposed (Scheme 4). The reaction is initiated through the formation of the cyclic iodine(III) monomer **I**, enabling the subsequent self-assembly to form a macrocyclic trimer **II**. The ring-strain-induced homolysis of the newly formed iodine–oxygen bond leads to the generation of diradical intermediate **III**. The decarboxylation and radical addition to the olefin followed by the intramolecular aryliodine radical mediated oxidation result in the formation of a benzylic cation intermediate **V** with

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concomitant release of 4-FC_6H_4I. The formation of this cation intermediate was further supported by the fact that the replacement of the Me in **1a** with CF_3 completely suppressed the reaction (Scheme S2D). Finally, under the assistance of a suitable base, the E1 elimination from this intermediate gives thermodynamically stable product **2a**. Further validation of this proposed mechanism is still ongoing in our laboratory.

In conclusion, we describe here the first hypervalent iodine(III)-mediated intramolecular decarboxylative Heck-type reaction of 2-vinyl-phenyl oxamic acids. Various 2-quinolinones were synthesized in moderate to excellent yields at room temperature using this method. This protocol is metal-free and operationally simple, displays excellent chemoselectivity and functional group compatibility, and features a distinct ring-strain-enabled radical decarboxylation mechanism. These advantages will likely render this reaction a useful tool for the synthesis of medicinally valuable 2-quinolinone structures and the design of new decarboxylative coupling reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03503.

Experimental details and characterization data (PDF)
^{1}H NMR spectra (ZIP)

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Notes

The authors declare no competing financial interest.

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