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I_2-Triggered Reductive Generation of N-Centered Iminyl Radicals: An Isatin-to-Quinoline Strategy for the Introduction of Primary Amides

Qinghe Gao,[a,*] Zhaomin Liu,[a] Yakun Wang,[a] Xia Wu,[b] Jixia Zhang,[a] and Anxin Wu[b,*]

[a] School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan 453003, P. R. China.
Fax: (+86)-373-3831-652; phone: (+86)-373-3831-652; e-mail: gao_qinghe@xxmu.edu.cn

[b] Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. China.
Fax: (+86)-027-6786-7773; phone: (+ 86)-027-6786-7773; e-mail:chwuax@mail.ccnu.edu.cn

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Abstract. An efficient and alternative isatin-to-quinoline strategy illustrates the metal-like behavior of molecular iodine in the N-O reduction of ketoxime acetates. This process involves N-O/C-N bond cleavages and C-C/C-N bond formation to furnish pharmacologically significant quinoline-4-carboxamide derivatives. In this process, metal catalysts and extra oxidants are unnecessary. Mechanistic studies confirm the crucial role of molecular iodine in the iminyl radical generation process, in that molecular iodine can catalyze single-electron reduction coupling reactions in a manner similar to transition metals.

Keywords: Amidation; organocatalysis; iminyl radicals; drug design

Owing to the extraordinary properties of primary amides in chemistry as well as biology,[1] the introduction of primary amides into aryl and heterocyclic rings has been used as an efficient method in the design and fine tuning of the biological properties of the drug candidates.[2] As a consequence, there are many pharmaceuticals containing a primary-amide group,[3] including the analgesic and anti-inflammatory drug Ethenzamide, Frovatriptan for the treatment of migraine headaches, and the oral chemotherapy drug Temodar used in the treatment of certain brain cancers (Figure 1). As a result, a great deal of recent research in this field has focused on the development of more efficient and practical approaches to introduce this primary amide motif.[4] For example, ammonolysis of carboxylic acids species,[5] hydration of nitriles,[6] rearrangement of aldoximes,[7] aminocarbonylation of aryl halides or phenols,[8] Friedel–Crafts carboxamidation of arenes,[9] cleavage of C-C bonds,[10] oxidation of primary benzyl amines[11], and oxidative amidation of benzyl alcohols, aldehydes, or methylarenes.[12] Currently, the synthesis of primary amides relies heavily on transformations of specific functional groups. Undoubtedly, as an alternative, a conceptually novel approach, in which the new arenes are constructed during the amidation process, is highly attractive. Herein, we first demonstrate an efficient transamidation of isatins with ketoxime acetates allowing direct formation of quinolines and introduction of primary amides.

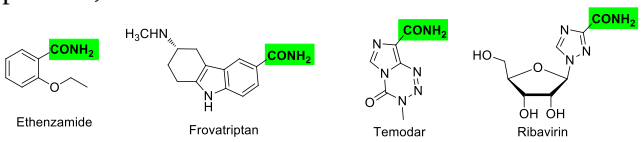

Figure 1. Selected examples of primary amide drugs.

Recently, ketoxime acetates as an internal oxidant have been widely used for the development of transition-metal-catalyzed α-C_{sp3}-H bond activation reactions.[13] In most cases, these oxime esters are known to undergo facile single-electron reduction to generate an iminyl radicals in the presence of low-valent Cu or Fe.[14] Because of its good capacity for electron transfer processes, molecular iodine has emerged as a promising replacement for these transition metals.[15] Among these transformations, molecular iodine in combination with peroxides (O-O) generates active hypervalent iodine species (I^+) in situ in a basic process. Thus, we speculate that

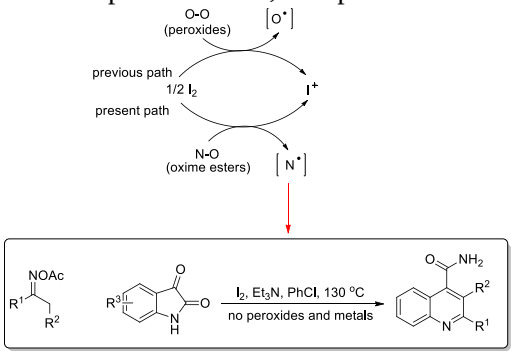

Figure 2. I_2-triggered reductive generation of N-Centered Radicals.

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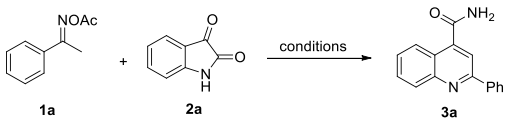
molecular iodine can take the place of these low-valent transition metals in the construction of *N*-containing heterocycles without peroxides, wherein oxime derivatives (N-O) serve as both internal oxidants and reactants. In this paper, we report our progress in the I_2-triggered redox-neutral reaction of ketoxime acetates with isatins for the synthesis of diverse quinoline-4-carboxamides (Figure 2), which are potential precursors of the privileged medicinal structures found use in a wide spectrum of medicinal targets: GPCRs, protein-protein interactions, ion channels and enzyme inhibitors.[16]

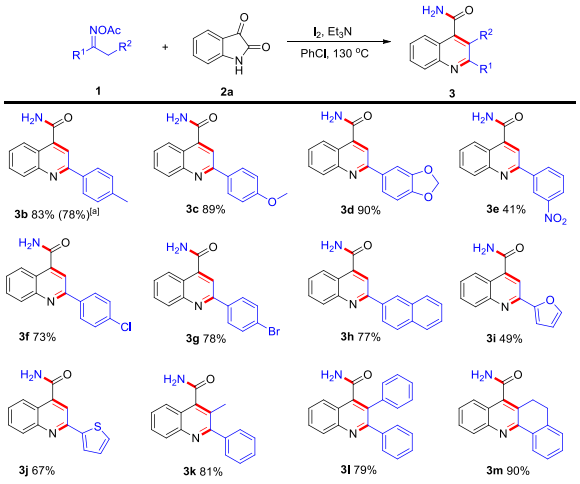
Table 1. Optimization of the reaction conditions.[a]



Entry	Base	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	Et_3N	L-proline	DMSO	120	n.d.
2	Et_3N	L-proline	DMF	120	n.d.
3	Et_3N	L-proline	anisole	120	54
4	Et_3N	L-proline	PhCl	120	80
5	Et_3N	L-proline	toluene	120	78
6	Et_3N	L-proline	dioxane	120	65
7	Et_3N	L-proline	H_2O	120	n.d.
8[c]	Et_3N	L-proline	PhCl	120	n.r.
9		L-proline	PhCl	120	trace
10	Et_3N		PhCl	120	84
11	Et_2NH		PhCl	120	67
12	DABCO		PhCl	120	trace
13	DBU		PhCl	120	trace
14	DMA		PhCl	120	19
15	quinoline		PhCl	120	48
16	Py		PhCl	120	57
17	Et_3N		PhCl	100	64
18	Et_3N		PhCl	110	79
19	**Et_3N**		**PhCl**	**130**	**86**
20	Et_3N		PhCl	140	86

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5mmol), I_2 (0.25 mmol), Et_3N (0.25 mmol), additive (0.05 mmol), solvent (2 mL). [b] Isolated yields; n.d. = no desired product; n.r. = no reaction. [c] In the absence of I_2.

Based on our previous works on oxidative cross-coupling in the I_2-DMSO system,[17] our initial efforts were focused on the model reaction of acetophenone oxime acetate **1a** with isatin **2a** in the presence of Et_3N and L-proline (Table 1). Disappointingly, no desired **3a** was observed when the reaction was carried out in DMSO (entry 1). We speculate that solvent might play an important role in this transformation. Therefore, different solvents such as DMF, anisole, chlorobenzene, toluene, 1,4-dioxane, and water were also investigated. Indeed, the quinoline-4-carboxamide product **3a** was obtained in the best yield when using chlorobenzene as a solvent (entries 2−7). It is noteworthy that both I_2 and Et_3N were essential to this reaction, based on the blank experiments (entries 8−9). Unexpectedly, this reaction could also work well in the absence of L-proline (entry 10), which was generally used to enhance electrophilic nature of **2a** C3 carbon.[18] When other bases such as Et_2NH, DABCO, DBU, *N*,*N*-dimethylaniline, quinolone, and pyridine, were applied instead of Et_3N, the yield of the desired product more or less decreased (entries 11−16). Further examination of the temperature showed that 130 °C proved to be the best, affording **3a** in 86% isolated yield (entries 17−20).



Scheme 1. Scope of ketoxime acetates. All yields are of isolated products. [a] Conducted on 10 mmol scale

With the optimized reaction conditions in hand, the generality and scope of this efficient and alternative isatin-to-quinoline strategy for the introduction of primary amides was explored. The reaction demonstrated a wide substrate scope of the ketoxime acetates (Scheme 1). Aryl ketone *O*-acetyloximes bearing electron-neutral (e.g., 4-Me), electron-rich (e.g., 4-OMe, 3,4-OCH_2O), and electron-deficient (e.g., 3-NO_2) on the phenyl ring were converted to the corresponding products in satisfactory yields (41−90%; **3b**−**3e**). In general, acetophenone oxime acetates with an electron-donating group showed higher reactivity than those with an electron-withdrawing group. Much to our satisfaction, the optimized conditions were mild enough to allow a broad range of halogenated (e.g., 4-Cl, 4-Br) substrates to be reacted (73−78%; **3f**−**3g**). Naphthalen-2-yl ethanone oxime acetate was also a suitable substrate for this reaction to provide the expected product (**3h**) in 77% yield. Meanwhile, the optimized conditions could be applied to heteroarene oxime acetates such as furanyl and thienyl, delivering

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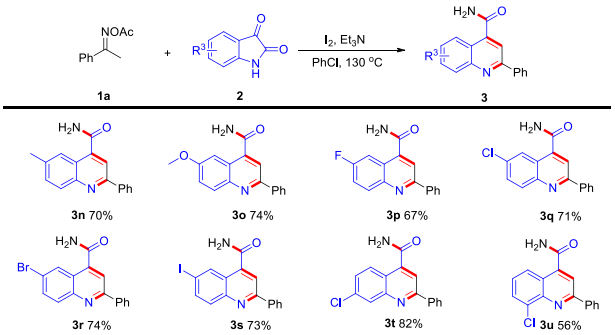
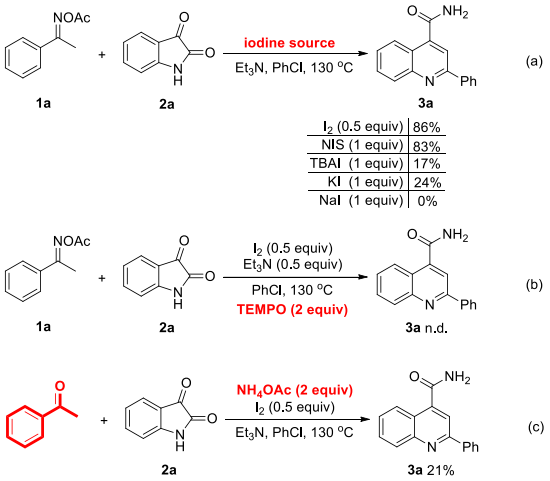
the corresponding products in 49% and 67% yields, respectively (**3i**–**3j**). Notably, oxime acetates derived from propiophenone, 1,2-diphenylethanone, and 3,4-dihydro-naphthalen-1(2*H*)-one could be accessed using this route to generate the ring-expansion product in good yields (79−90%; **3k**−**3m**). In addition, the structure of **3k** was unambiguously confirmed by X-ray crystallography.[19]



Scheme 2. Scope of isatins. All yields are of isolated products.

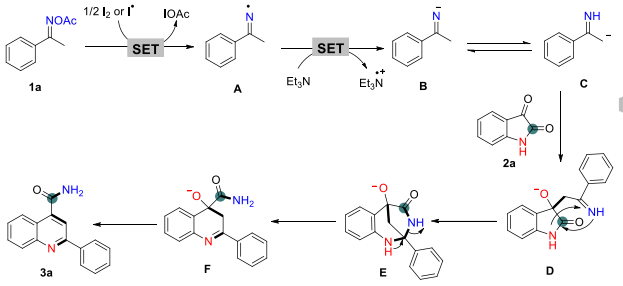
The scope of this reaction was subsequently extended to the representative isatins (Scheme 2). Isatins substituted with various useful substituents such as methyl, methoxy, and halogens (F, Cl, Br, and I) at the C-5 position showed good reactivity with acetophenone oxime acetate **1a**, leading to the corresponding primary amides **3n**–**3s** in 67−74% yields. However, a strong electron-withdrawing moiety (5-NO_2) prevented the reaction from proceeding under the standard conditions. Similarly, isatins substituted at the C6 and C7positions were also found to be effectual under the present reaction conditions, furnishing the chloro-substituted quinoline-4-carboxamides (55−92%; **3t**–**3u**). Notably, the quinoline scaffolds were formed with a diverse range of halogen atoms, providing enormous possibilities for further modification.

To understand the role of molecular iodine in this transamidation process, we applied different kinds of iodine source in the model reaction (Scheme 3a). As expected, an iodine radical source, NIS, showed a reactivity similar to that of molecular iodine. However, the commonly used iodide catalysts such as TBAI, KI, and NaI were less efficient for the formation of the desired product. Generally, the oxime could be converted to the corresponding iminyl radical in the presence of low-valent transition metal. Therefore, an inhibiton experiment for radical was carried out. When TEMPO was introduced into the reaction system, the formation of **3a** was completely suppressed (Scheme 3b). These results indicated that molecular iodine or iodine radical was capable of reducing the N-O bond of oxime via a single-electron transfer (SET) process. Finally, a Pfitzinger-type reaction of acetophenone with isatin and ammonium acetate gave the desired quinoline product in 21% yield (Scheme 3c). The direct condensation of amines and carboxylic acids from the Pfitzinger reaction requires very harsh conditions in order to circumvent the unreactive carboxylate-ammonium salt formation for the desired amide bond formation. We reasoned that this intrinsic difficulty might be mitigated by preinstalling a nitrogen atom as well as an internal oxidant in the reactant.



Scheme 3. Control experiments.

Although the exact reaction mechanism is unclear, one possible mechanism has been proposed using acetophenone oxime acetate **1a** and isatin **2a** as examples (Scheme 4). Initially, **1a** could be reduced by molecular iodine or iodine radical to generate the iminyl radical intermediate **A** and hypervalent iodine species (I^+). Subsequently, the highly active iminyl radical **A** was reductively quenched by Et_3N to produce the corresponding anion **B** which could isomerize to a strong nucleophile α-carbanion **C**.[20] This might explain why Et_3N was indispensable in this reaction system. Then, nucleophilic addition of **C** to carbonyl of **2a** formed intermediate **D**, followed by a ring-reconstruction to afford the bridged bicyclic intermediate **E**.[21] Finally, intermediate **E** underwent ring-opening and eliminated hydroxyl anion to access the desired product **3a**.



Scheme 4. A possible mechanism.

In conclusion, we have demonstrated that molecular iodine behave as a metal in the reductive

cleavage of the N-O bond of ketoxime acetates, generating of N-centered iminyl radicals. This strategy provides an efficient and alternative method for the synthesis of biologically useful quinoline-4-carboxamide derivatives from ketoxime acetates and isatins. The reaction was accomplished through N-O/C-N bond cleavages and new C-C/C-N bond formations, along with the activation of C_{sp3}-H bond. Importantly, this work provides an example for applying molecular iodine as a promising alternative to transition metal catalysts for single-electron reduction coupling reactions. Detailed mechanistic investigations and exploring new transformations of oxime acetates with molecular iodine are underway in our laboratory and will be reported in due course.

Experimental Section

General Procedure (**3a** as an example): A mixture of oxime acetates **1a** (0.5 mmol), indoline-2,3-dione **2a** (0.5 mmol), iodine (0.25 mmol), and Et_3N (0.25 mmol) in PhCl (2 mL) was stirred at 130 °C. After disappearance of the reactant (monitored by TLC), and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and evaporation. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the product **3a** as a yellow solid; yield: 86%.

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Qinghe Gao,* Zhaomin Liu, Yakun Wang, Xia Wu, Jixia Zhang, and Anxin Wu*