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Copper-promoted direct amidation of isoindolinone scaffolds by sodium persulfate†

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Isoindolinones are ubiquitous structural motifs in natural products and pharmaceuticals. Establishing an efficient method for structural modification of isoindolinones could significantly facilitate new drug development. Herein, we describe copper-promoted direct amidation of isoindolinone scaffolds mediated by sodium persulfate. The method exhibits mild reaction conditions and high site-selectivity, and enables the structural modification of the drug indobufen ester with various amides with yields of 49 to 98%. It is also gram-scalable. Additionally, the reaction mechanism appears to involve a radical and a carbocationic pathway.

The amide is one of the most versatile functionalities in natural products and pharmaceutical chemistry.[1] According to the Comprehensive Medicinal Chemistry database, more than 25% of pharmaceuticals are amide-containing compounds.[2] Thus, chemists have developed many synthetic strategies to create amide bonds. Traditional strategies depend on coupling reagents,[3] such as 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDC), 1,1′-carbonyldiimidazole (CDI) and (benzotriazol-1-yloxy)tris(pyrrolidine)phosphonium hexafluorophosphate (PyBOP), to condense the carboxylic acids and amine groups. However, without relying on pre-installed functional groups, cross-dehydrogenative coupling (CDC) reaction is an alternative method to construct amides and is a promising method for late-stage modification of drug molecules.[4] Cross-dehydrogenative reaction for the construction of amides is showing significant advancement.[5] For example, Chang *et al.*[6] developed a CpRu(II) catalytic platform to achieve highly site-selective amidation at the benzylic position instead of at the tertiary C–H bonds at the same distance. Nozawa-Kumada and Kondo[7] *et al.* used *t*BuOO*t*Bu as an oxidant to accomplish Cu-catalyzed intramolecular oxidative C(sp3)–H amidation for the synthesis of β-lactams. Landais[8] *et al.* reported an efficient strategy to harness NFSI($(PhSO_2)_2NF$) or F-TEDA-PF_6 as oxidants to access benzylic carbamates. König[9] *et al.* reported a photoinduced copper(II)-di-*tert*-butyl peroxide catalytic system to realize the amidation of alkanes. Yet, despite these achievements, there is a great demand for methods that are more practical, convenient, sustainable, and environmentally compatible.[10]

Persulfates, such as $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$, are strong inorganic oxidants.[11] In addition, these agents are 'green' alternatives to other oxidants because they are low-cost, readily available, essentially nontoxic, and easy to handle.[12] Although persulfates have been used in many applications to transform C–H/C–C to C–X (X = N, O, S, P, B, Si, F, Br, I),[11] there have been relatively few studies on their use in mediating direct amidation. Yuan[13] *et al.* reported the use of $K_2S_2O_8$ as the oxidant in the direct oxidative amidation of quinoxalin-2(1*H*)-ones with a variety of aromatic and aliphatic amides. Truscello[14] *et al.* realized the α-amidoalkylation of N-heteroaromatic bases with amides in the presence of $Na_2S_2O_8$. Nevertheless, persulfates have great potential for broadening the number of direct amidation applications.

Isoindolinone skeletons are privileged structures in bioactive natural products and drug molecules (Fig. 1a).[15] For instance, lenalidomide is used to treat multiple myeloma.[16] Hericenone B and indobufen are antiplatelet aggregation drugs.[17] Many investigators have studied structural modifications at the *N*-benzylic (C3) position of isoindolinone skeletons because of the significant influence of the modifications on their biological activity.[18] However, to the best of our knowledge, direct amidation at the C3 position had not been realized. Hence, we report a direct benzylic amidation of isoindolinone scaffolds using $Na_2S_2O_8$ as an oxidant. The method features mild conditions, site-selectivity, good to excellent yields, and gram-scalability. In addition, we have determined the details of the reaction mechanism.

For structural simplification, we began this investigation with methylisoindolin-1-one as a model substrate. Commercially available pyrrolidin-2-one, which is widely used in drug discovery, was chosen as the amide source to optimize

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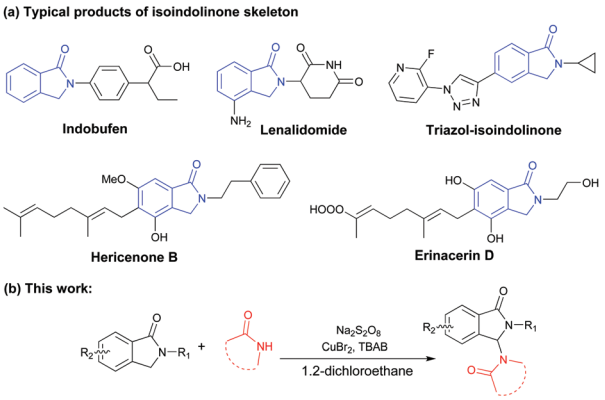


Fig. 1 (a) Typical products of the isoindolinone skeleton, (b) direct amidation of isoindolinone scaffolds mediated by $Na_2S_2O_8$.

the reaction conditions. We mixed 0.2 mmol methylisoindolin-1-one, 0.2 mmol pyrrolidin-2-one, and 0.4 mmol $Na_2S_2O_8$ in 2 mL 1,2-dichloroethane and reacted the mixture by refluxing at 80 °C. The desired product, 2-methyl-3-(2-oxopyrrolidin-1-yl) isoindolin-1-one (**2a**), was obtained in only 5% yield (entry 1, Table 1). Because transition metals can facilitate the formation of the $SO4^{\bullet-}$ radical and electron transfer,[19] we added catalytic amounts of transition metals, such as $CuBr_2$, $Pd(OAc)_2$, $AgNO_3$, and $FeCl_2$. Among them, $CuBr_2$ produced the best result, albeit still affording a relatively low yield of 59% (entries 2–5, Table 1).

Tetrabutylammonium bromide (TBAB) and tetrabutylammonium iodide (TBAI) are employed frequently as additives to promote persulfate-mediated oxidation.[20] Thus, we tested the effects of the addition of TBAB and TBAI (20% mmol). In the case of TBAB, the yield of **2a** increased to a nearly quantitative amount (97%), and TBAI afforded 91% yield (entries 6 and 7, Table 1). We also examined the effects of metal salts, such as Pd, Mn, Ag, and Fe, in the presence of TBAB. However, none of the yields were as high as that obtained with $CuBr_2$ (entries 8–11, Table 1; for more details, see ESI Table S1,† entries 10–16). We also evaluated other Cu(I)/Cu(II) species, such as CuBr, $CuCl_2$, CuI, and CuCl (entries 12–15, Table 1). Again, $CuBr_2$ was the most effective; other copper salts gave 56–86% yields (ESI Table S1,† entries 1–9). When the reaction was performed in the absence of $CuBr_2$, only a 15% yield of **2a** was obtained, indicating the significant role of the metal catalyst (entry 16, Table 1). The loadings of $Na_2S_2O_8$, TBAB, and $CuBr_2$ were also screened (ESI Table S2,† entries 15–20).

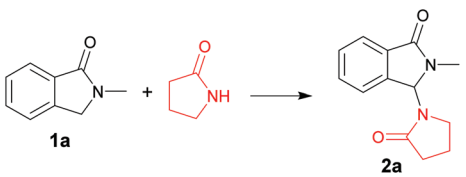
We also screened several common solvents. Highly polar solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) caused a considerable decrease in yields to 13% and 12%, respectively, whereas acetonitrile and tetrahydrofuran (THF) gave the products in 56% and 76% yields (ESI Table S2,† entries 4–10). $K_2S_2O_8$, even under microwave-assisted conditions,[13] and $(NH_4)_2S_2O_8$ produced lower yields compared with $Na_2S_2O_8$ (ESI Table S2,† entries 1–3), which might be ascribed to their different oxidation power and solubility in DCE.[11] Finally, we hypothesized that aerobic oxidation could inhibit the metal catalyst. Indeed, running the reaction in open air resulted in lower yield (entry 17, Table 1).

In summary, the foregoing experiments established the optimal reaction conditions for the transformation: 2 equiv. $Na_2S_2O_8$ as an oxidant, 10% mmol $CuBr_2$, 20% mmol TBAB, 1,2-dichloroethane as the solvent, and a reaction temperature of 80 °C (entry 6, Table 1).

With the optimized conditions in hand, we next assessed the versatility of the protocol with a variety of isoindolinone derivatives. *N*-Alkylisoindolinones (Scheme 1, **2a–2g**), which have different length or branched carbon chains in their *N*-termini, produced excellent yields (81–96%). Similarly, good to excellent yields (80–97%) were obtained with the *N*-phenylisoindolinone derivatives (Scheme 1, **2h–2s**). Notably, high site selectivity was achieved, and the amide was installed primarily at the C3 position, which was exemplified by products **2b**, **2c**, **2g**, **2j**, and **2k**. These results indicated that the C(sp3)–H at the C3 position of the isoindolinone skeleton was more prone to be activated than other secondary, tertiary, or benzylic centers. Furthermore, the reaction of 2-phenylisoindolin-1-one with *N*-pyrrolidone occurred successfully on a 5 mmol scale and produced 1.27 g of **2h** without apparent erosion (87% yield).

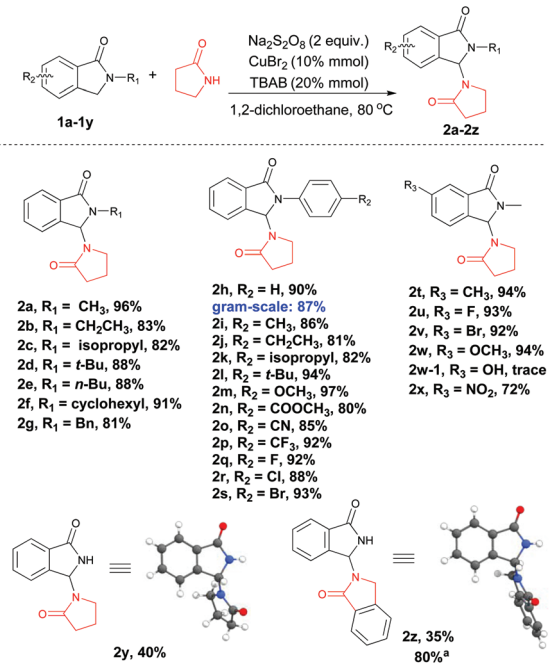
In addition, the substituents, either electron-donating or electron-withdrawing groups, located in the phenyl ring of the isoindolinone skeleton or *N*-terminus, affected the product

Table 1 Optimization of the reaction conditions[a]



Entry	Additive	PTC	Yield[b] (**2a**)
1	—	—	5
2	$CuBr_2$	—	59
3	$Pd(OAc)_2$	—	22
4	$AgNO_3$	—	37
5	$FeCl_2$	—	4
6	**$CuBr_2$**	**TBAB**	**97**
7	$CuBr_2$	TBAI	91
8	$Pd(OAc)_2$	TBAB	31
9	$AgNO_3$	TBAB	52
10	$FeCl_2$	TBAB	4
11	$Mn(OAc)_3$	TBAB	19
12	CuBr	TBAB	85
13	$CuCl_2$	TBAB	86
14	CuI	TBAB	64
15	CuCl	TBAB	56
16	—	TBAB	15
17[c]	$CuBr_2$	TBAB	54

[a] Reaction conditions: Methylisoindolin-1-one (0.2 mmol), pyrrolidin-2-one (0.2 mmol), $Na_2S_2O_8$ (0.4 mmol), additives (10% mmol), PTCs (20% mmol), and 1,2-dichloroethane (2 mL) at 80 °C for 24 h under a N_2 atmosphere. [b] Yield detected by HPLC based on three runs of each reaction. [c] Air conditions.



Scheme 1 Amidation of substituted isoindolinones with pyrrolidin-2-one. Reaction conditions: Isoindolinones (1 mmol), *N*-pyrrolidone (1 mmol), $Na_2S_2O_8$ (2 mmol), $CuBr_2$ (10% mmol), TBAB (20% mmol), and DCE (4 mL) at 80 °C for 24 h under a N_2 atmosphere, isolated yield. [a] Isoindolinone as the only substrate.

yields (**2h–2x**). By comparing the yields of **2m** and **2o**, **2t** and **2x**, we found that the electron-donating groups improved the yield, which could be attributed to the stabilization of the intermediates at the C3 position by electronic effects. Furthermore, the susceptible functionalities, such as $-OCH_3$, –CN and $-COOCH_3$, were well tolerated under the optimized reaction conditions (**2m–2o** and **2w**). Although the phenolic hydroxyl group was not tolerated (**2w–1**), the corresponding product could be obtained by the removal of the protective group, such as by demethylation with BBr_3, in a two-step procedure with 82% yield (ESI 3.2†). We obtained yields of 88–96% for halogen-substituted isoindolinone derivatives (**2q–2s**, **2u** and **2v**). The survival of a halogen substituent offered an opportunity for further functionalization. Interestingly, when the substituent was a hydrogen atom in the *N*-terminus, both cross-coupling and self-coupling reactions of isoindolinone occurred, and gave the corresponding products **2y** and **2z** in 40% and 35% yield, respectively. The dimer (**2z**) was obtained in 80% yield by using isoindolinone as the only substrate. Moreover, we confirmed the structures of **2y** and **2z** by X-ray crystallographic analysis (Scheme 2).

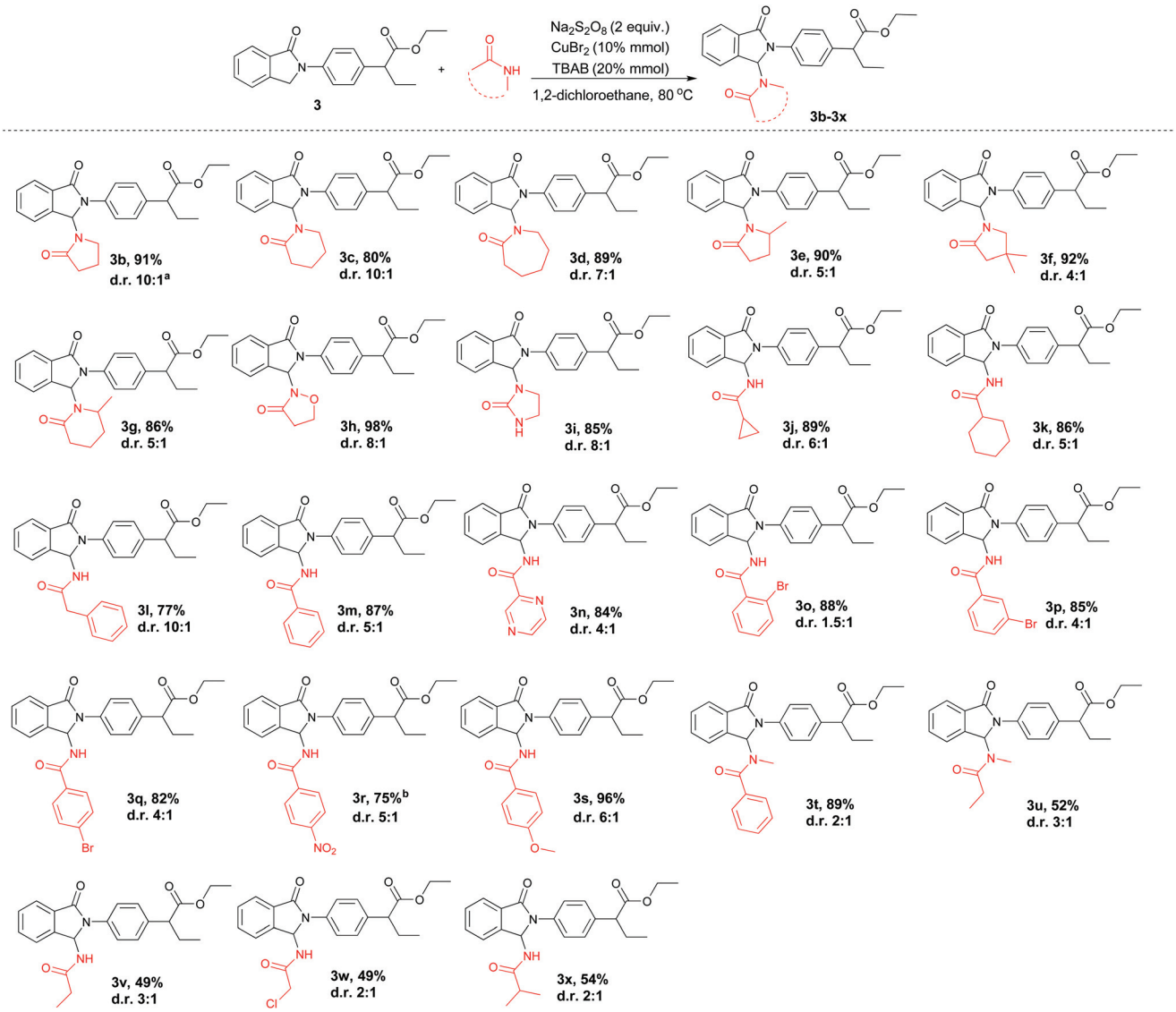
Having noticed the mildness, site selectivity, and satisfactory yields of the foregoing reactions, we applied the protocol to late-stage functionalization of indobufen. However, when we reacted indobufen with pyrrolidin-2-one under the standard conditions, we obtained only 45% yield of the title compound **3a**. After the carboxylic group was converted to the corresponding ethyl ester (**3**), the ester reacted well and gave 91% yield of the desired product (**3b**). We obtained similar results with 2-piperidone and caprolactam (**3c–3d**). However, with obvious steric hindrance, the substituted 2-pyrrolidone and 2-piperidone, which show important biological activities, were introduced successfully (**3e–3g**). Other coupling partners, such as 2-oxazolinone and 2-imidazolidone, resulted in 98% and 85% yields (**3h–3i**).

In addition to the lactam mentioned above, we employed primary amides as coupling partners (**3j–3s**) and obtained similar yields with the aliphatic ring-substituted amides. In addition, the cyclopropyl group-substituted amide was well tolerated (**3j**) without producing any by-product, which further indicated the mildness of our protocol. In the presence of another benzylic position, 2-phenylacetamide reacted well and afforded a 77% yield of **3l** with high site-selectivity. Good to excellent yields were also obtained when we replaced aliphatic amides with aryl amides, and even when the bromo moiety was substituted at the *ortho*, *meta*, and *para* positions (**3o–3q**). Notably, the electron-withdrawing nitro-group on aromatic amides (**3r**) led to a dramatic drop in their reactivity, and more reaction time was required for the completion of the reaction. Moreover, the yield was relatively lower than that with the electron-donating methoxyl-group (**3s**). Unlike lactam and cyclic amides, acyclic amides, even secondary acyclic amides, showed greatly reduced yields (49–54%), because their relatively higher reactivity led to the occurrence of side reactions (**3u–3x**).

After amide installation, diastereomers appeared because of the creation of new chiral centers. We used crude ^1H NMR to measure the diastereomeric ratio (dr) of chromatographically inseparable products (**3t** and **3u**), whereas the diastereomeric ratios of other molecules were determined after isolation. Notably, the diastereomeric ratios varied from 1.5 : 1 to 10 : 1, which implied that the reaction was not stereoselective.

We further tested the practicality of this protocol by increasing the scale of the reaction to 1.29 g ethyl ester indobufen (4 mmol) with 0.34 g pyrrolidin-2-one (4 mmol). The reaction proceeded successfully and produced the corresponding product in 90% yield without any loss of efficiency. Moreover, **3b** was readily hydrolyzed with 98% yield. Therefore, by a two-step process, we accomplished the benzylic structural modification of indobufen on a gram-scale (Fig. 2).

To obtain information about the reaction mechanism, we performed the reaction in the presence of the radical scavengers 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and butylated hydroxytoluene (BHT) (Fig. 3a and b). In these cases, the yield of **2a** was significantly reduced, and the TEMPO and BHT adducts were observed by high-resolution mass spectrometry (HRMS). When 5.0 equiv. of TEMPO were added to the reaction system, this conversion was completely inhibited. These results revealed that the reaction proceeded by a radical mechanism, and confirmed the generation of isoindolinone radicals. In addition, on omitting the copper salt, the yield of **2a** decreased from 97% to 15%, suggesting that $CuBr_2$ could greatly promote the transformation (Fig. 3c). Conversely, when we added 0.1 mmol H_2O under the standard conditions and replaced dichloroethane with acetonitrile, except for the separ-



Scheme 2 Amidation of indobufen ethyl ester. Reaction conditions: indobufen ethyl ester (1 mmol), amides (1 mmol), $Na_2S_2O_8$ (2 mmol), $CuBr_2$ (10% mmol), TBAB (20% mmol), and DCE (4 mL) at 80 °C for 24 h under a N_2 atmosphere, isolated yield. [a] The diastereomeric ratio of **3t** and **3u** was determined by crude ^{1}H NMR, whereas the diastereomeric ratios of other molecules were determined by isolated yields. [b] Standard conditions for 36 h.

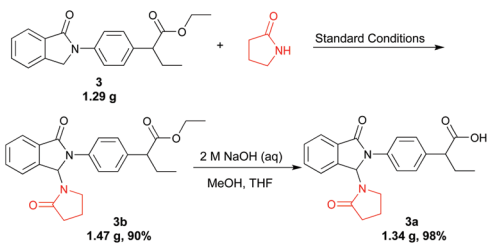


Fig. 2 Gram-scale preparation of the indobufen derivative.

ation of **2a** and **2a-1**, we observed the Ritter-type product **2a-2** by HRMS. This result pointed toward the formation of a carbocation in this reaction (Fig. 3d).

Considering the foregoing control experiments and earlier methodologies,[8,21] we propose a probable reaction mechanism in Fig. 4. Initially, sodium persulfate ($Na_2S_2O_8$) was reacted with TBAB to generate bis(tetrabutylammonium)peroxydisulfate, which is readily convertible to tetrabutylammonium sulfate radical-anions (I) by thermal decomposition.[11,15,22] The tetrabutylammonium sulfate radical (I) abstracts a hydrogen atom from isoindolinone to give the corresponding radical (**a**).[23] The planar resonance structure makes (**a**) more stable than other secondary, tertiary, or benzylic radicals. Then the isoindolinone radical (**a**) combines with $CuBr_2$ to afford Cu(III) adducts (**b**), which could lead to intermediate (**c**) after ligand exchange with pyrrolidin-2-one, providing the title product (**2a**) upon reductive elimination. However, we cannot exclude a carbocationic

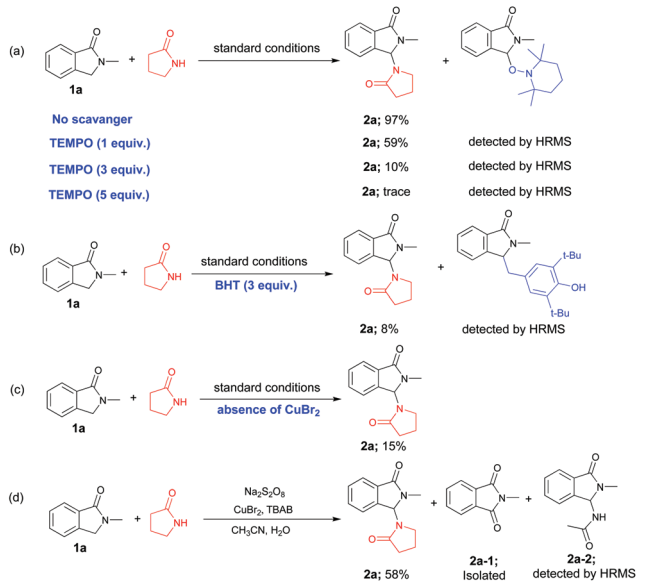


Fig. 3 Control experiments. Radical scavenging by TEMPO (a); Radical scavenging by BHT (b); The absence of copper salt (c); Carbocation verification experiment (d).

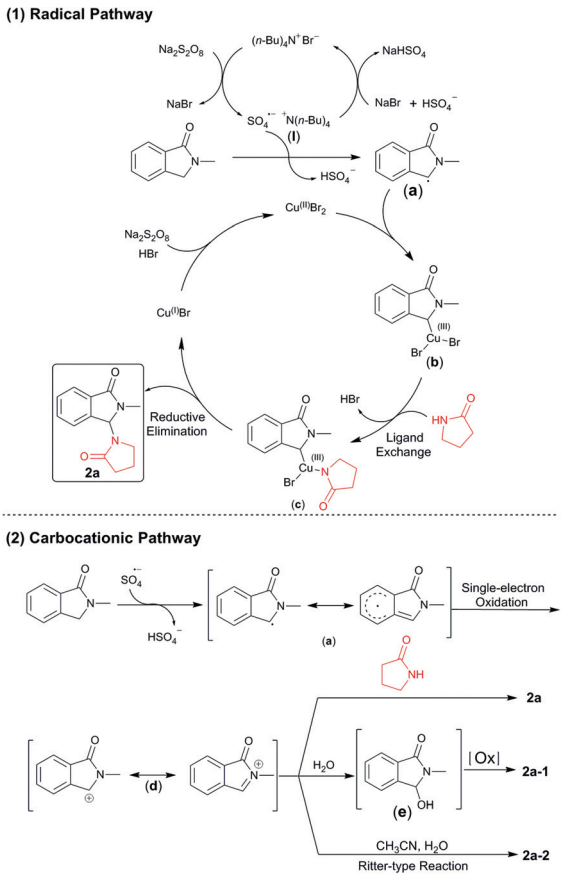


Fig. 4 Proposed mechanism.

process.[24] Benefitting from the stability, the isoindolinone radical (**a**) readily transforms into carbocation (**d**) by single-electron oxidation mediated by Cu or $SO_4^{\bullet-}$ species, and the carbocation reacts with nucleophiles, such as amides, to generate **2a**. The carbocation (**d**) also undergoes a nucleophilic addition with H_2O to produce (**e**), which is further oxidized to give **2a-1**. Under the same conditions, the carbocationic pathway can explain the generation of the Ritter-type product **2a-2**.

Conclusions

In conclusion, we have developed a copper-promoted method mediated by $Na_2S_2O_8$ to introduce amides into the benzylic position of isoindolinone scaffolds. Our protocol exhibits mildness, a broad substrate scope, and satisfactory yields to furnish a series of amide products, by a practical and convenient process. We also applied the method to the modification of indobufen with various amides, a process that will be useful in measuring structure–activity relationships and expanding practical applications of indobufen. We envision that this protocol will have broad applications in late-stage diversification of isoindolinone-containing natural products and drug molecules.

Author contributions

HFL and JXX performed the experiments. HFL and JL were responsible for data analysis. DJZ conceived and designed the experiments. HFL and DJZ co-wrote the manuscript. All authors read and approved the final version to be published.

Conflicts of interest

There are no conflicts to declare.

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