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Amination of 3-Substituted Benzofuran-2(3*H*)-ones Triggered by Single-Electron Transfer

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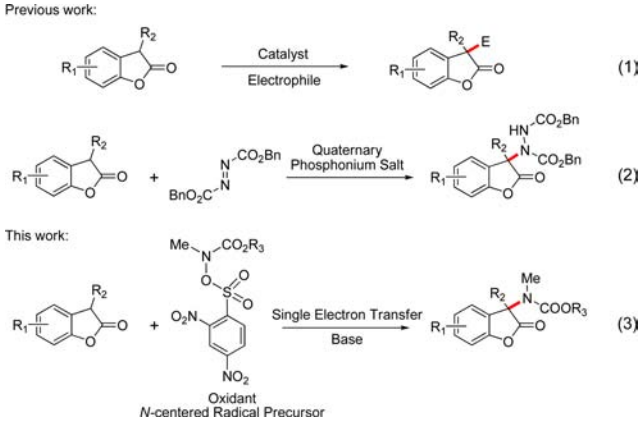
Supporting Information

ABSTRACT: An efficient amination reaction of 3-substituted benzofuran-2(3*H*)-ones promoted by cesium carbonate was developed. A putative mechanism involving a single-electron-transfer event was proposed, which represents a new reactivity for benzofuran-2(3*H*)-ones.

Benzofuran-2(3*H*)-ones with a quaternary carbon center at the C3 position are found in many natural products and medicinal molecules that exhibit biological and pharmaceutical properties.[1] Consequently, research for efficient methods for the construction of 3,3′-disubstituted benzofuran-2(3*H*)-ones is attractive in organic synthesis. Among the various synthetic approaches, 3-substituted benzofuran-2(3*H*)-ones have been frequently used as nucleophiles to react with a number of electrophiles to construct 3,3-disubstituted benzofuran-2(3*H*)-one architectures (Scheme 1, eq 1).[2] These achievements mainly focused on the construction of the C−C bond at the C3 position of benzofuran-2(3*H*)-ones;[3] however, methodologies for C−heteroatom bond formation,[4−6] especially for C−N bond formation of 3-substituted benzofuran-2(3*H*)-ones, have been scarcely studied. To date, electrophilic amination of 3-aryl benzofuran-2(3*H*)-ones reported by Ma et al. is the only example (Scheme 1, eq 2).[5,7] While HP-136 (5,7-di-*tert*-butyl-3-(3,4-dimethylphenyl)benzofuran-2(3*H*)-one) and its analogues are well-known as important carbon-centered radical antioxidants,[8,9] the development of methodologies using 3-arylbenzofuran-2(3*H*)-ones as radical substrates remains unexplored. On the other hand, mechanistic studies have shown that a deprotonation-initiated electron transfer may be the main pathway for the hydrogen transfer of 3-arylbenzofuran-2(3*H*)-ones.[10] Meanwhile, MacMillan and co-workers have proven that the dinitrobenzenesulfonic carbamates can generate an electrophilic *N*-centered radical in the presence of the electron-rich enamine under a photoinduced SET event.[11] Chi and co-workers found that these compounds can oxidize Breslow intermediates.[12] Furthermore, Rovis and co-workers proved electron-deficient nitrobenzenes can be utilized as single-electron-oxidation reagents in *N*-heterocyclic carbene catalysis.[13]

Scheme 1. Strategy for the Amination of 3-Substituted Benzofuran-2(3*H*)-ones



Based on the aforementioned results, we envisioned that dinitrobenzenesulfonic carbamate (E^{red} ~ −1.0 V vs ferrocenium/ferrocene, see the Supporting Information) can be used as a single-electron oxidant and *N*-centered radical source for the amination of 3-substituted benzofuran-2(3*H*)-ones (anion oxidative potential E^{ox} −0.54 V vs ferrocenium/ferrocene) under basic conditions (Scheme 1, eq 3) toward the construction of a core structure of bacterial peptide deformylase inhibitor fumimycin.[1f] Continuing our recent research program

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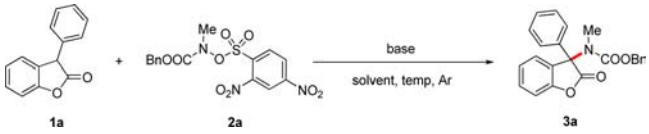
on the synthesis of 3,3′-disubstituted benzofuran-2(3*H*)-ones,[14] herein we report a radical amination reaction. This methodology may open an avenue to new chemistry for benzofuran-2(3*H*)-ones.

We initially evaluated the hypothesis with the model reaction between 3-phenylbenzofuran-2(3*H*)-one **1a** and dinitrobenzenesulfonic carbamate **2a** in acetonitrile under Ar protection (Table 1, entry 1). To our delight, the desired amination

Table 1. Optimization of the Reaction Conditions[a]



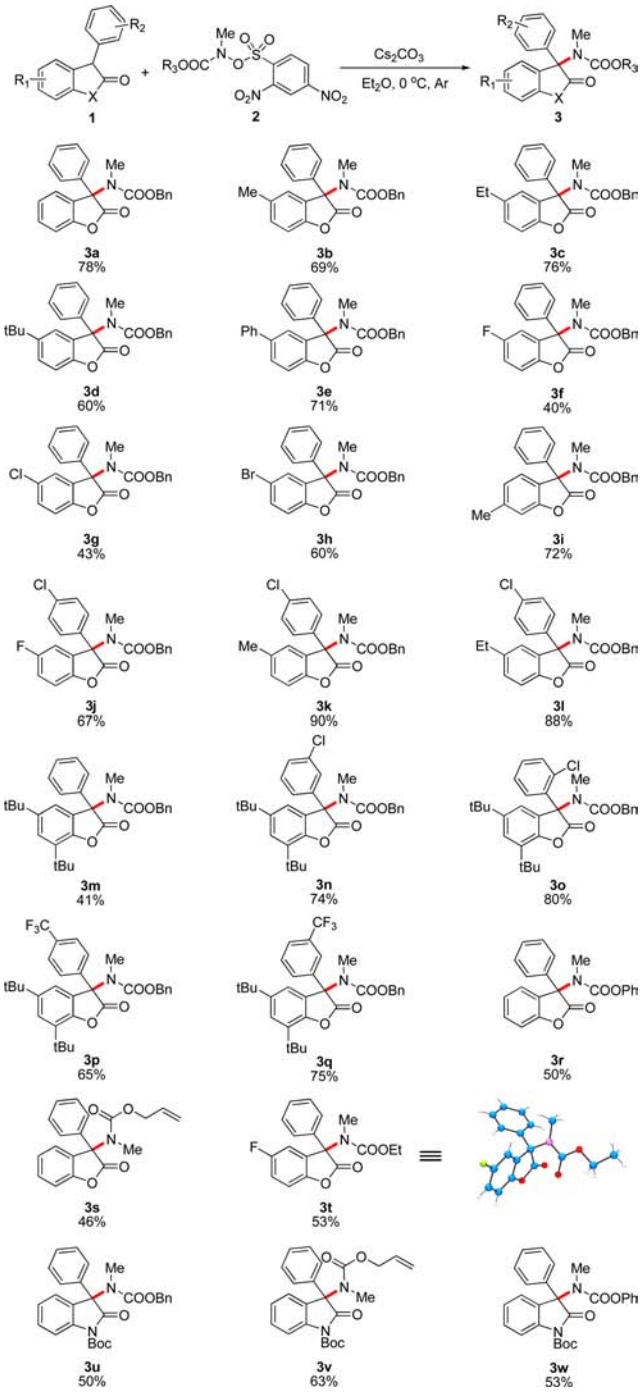
entry	base	solvent	time (h)	temp (°C)	yield[b] (%)
1	TMG	AN	18	25	47
2	DBU	AN	18	25	34
3	Et_3N	AN	18	25	28
4	DABCO	AN	18	25	35
5	Cs_2CO_3	AN	18	25	50
6	NaOH	AN	18	25	16
7	Cs_2CO_3	DMF	14	25	8
8	Cs_2CO_3	MeOH	14	25	18
9	Cs_2CO_3	DMSO	14	25	43
10	Cs_2CO_3	EA	22	25	37
11	Cs_2CO_3	THF	22	25	35
12	Cs_2CO_3	DCM	14	25	50
13	Cs_2CO_3	toluene	22	25	36
14	Cs_2CO_3	Et_2O	22	25	59
15	Cs_2CO_3	anisole	75	25	57
16	Cs_2CO_3	MTBE	52	25	51
17	Cs_2CO_3	Et_2O	65	0	65
18[c]	Cs_2CO_3	Et_2O	65	0	78

[a]Unless noted, the reaction was carried out with **1a** (0.2 mmol), **2a** (0.1 mmol), and 0.3 mmol of base in 0.4 mL of solvent under argon atmosphere. [b]Isolated yield. [c]20 mg of 4 Å molecular sieves was added.

product **3a** was obtained in the presence of tetramethylguanidine (TMG). Encouraged by this result, several bases were then screened (Table 1, entries 1−6). Among the examined bases, cesium carbonate is more effective than others, in which **3a** was isolated in 50% yield. The next solvent examination with cesium carbonate as the base showed that diethyl ether was the optimal one, which gave the amination product **3a** in 59% yield (Table 1, entries 5 and 7−16). Gratifyingly, lowering the reaction temperature and adding 4 Å molecular sieves to the reaction system can both lead to a further increase of the yield of **3a** (Table 1, entries 17−18). Finally, the optimal conditions were found by performing the reaction with 0.2 mmol of **1**, 0.1 mmol of **2**, 0.3 mmol of cesium carbonate, and 20 mg of 4 Å molecular sieves in 0.4 mL of diethyl ether at 0 °C. Under these conditions, the reaction provided the amination product **3a** with 78% yield.

With the optimal reaction conditions in hand, we subsequently evaluated the substrate scope of 3-substituted benzofuran-2(3*H*)-ones by the reaction with dinitrobenzenesulfonic carbamate **2a**. As exhibited in Scheme 2, the scope is quite broad. Whether electron-donating or electron-withdrawing R_1 groups at the 5- or 6-position of the benzofuran-2(3*H*)-ones **1** were employed, the amination reactions proceeded smoothly to give the corresponding products **3b−i**

Scheme 2. Substrate Scope of the Amination Reaction[a−c]



[a]The reaction was carried out with **1** (0.2 mmol), **2** (0.1 mmol), 0.3 mmol of Cs_2CO_3, and 20 mg of 4 Å molecular sieves in 0.4 mL of Et_2O at 0 °C under argon atmosphere for 3 days. Isolated yield. [b]TMG was used to obtain **3f−i,s,t**. [c]The structure of **3t** was determined by X-ray analysis.[15]

in moderate to good yields (40−76%). When 3-*p*-chlorine phenyl benzofuran-2(3*H*)-one-type substrates were used, corresponding amination products **3j−l** can also be obtained with good to very good yields (67−90%). Further exploration of the reaction scope was focused on the steric hindrance of the substrates, 5,7-di-*tert*-butyl-substituted benzofuran-2(3*H*)-ones, which had been widely studied as radical antioxidants. To our delight, the reactions with the five examined 5,7-di-*tert*-butyl-

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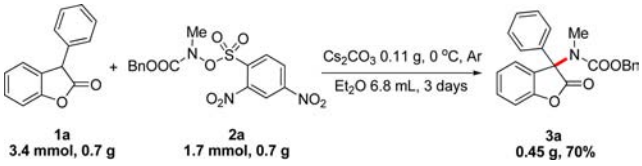
substituted benzofuran-2(3*H*)-ones showed good activities, which afforded the desired products **3m−q** in 41−80% yields.

In order to further extend the substrate scope, three dinitrobenzenesulfonic carbamates were investigated under the optimal conditions. As expected, the amination products **3r−t** were obtained with moderate yields (46−53%). Furthermore, 3-phenyloxindole was also compatible in this strategy, providing **3u−w** in 50−63% yields.

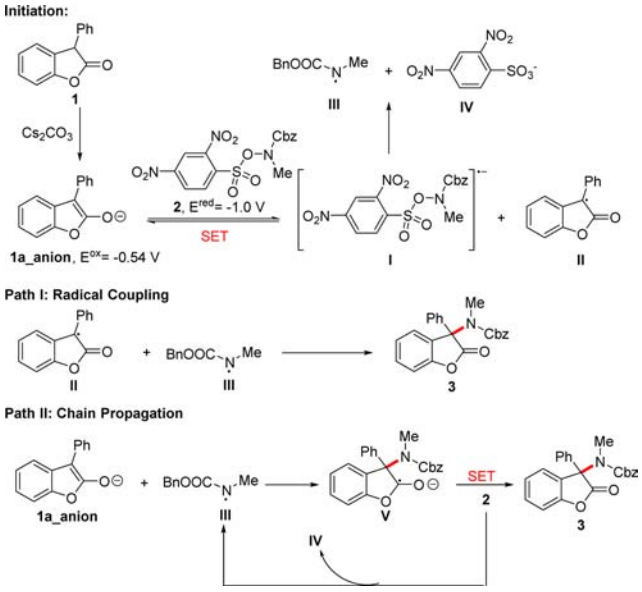
Additionally, we performed a large-scale reaction with substrate **1a** and **2a** to demonstrate the synthetic value of this new methodology (Scheme 3). As a result, the desired product **3a** was obtained in 70% yield.

Scheme 3. Large-Scale Synthesis of 3a



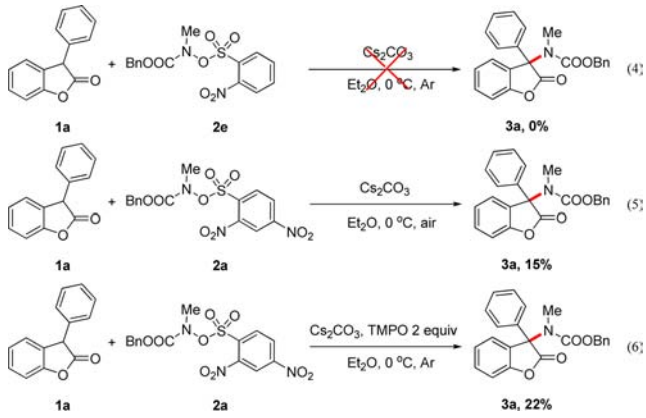
Based on the measured potentials and previous study,[11−13] we believe that an electron-transfer process is necessary to initiate the reaction (Scheme 4). According to the extensive

Scheme 4. Putative Mechanism



studies in the literature, the electron transfer may occur between the donor and acceptor within an 1.0 V (i.e., 23.1 kcal/mol) energy gap.[16] In our case, the energy gap evaluated from their respective redox potentials (**1a_anion** −0.54 V and **2a** −1.0 V) is 0.46 V, which is a value well below the 1.0 criterion. The failed employment of more weaker oxidants ($E^{red} \sim -1.2$ V),[12] such as mononitrobenzenesulfonic carbamate **2e**, supported the hypothesis (Scheme 5, eq 4). The unfavorable electron-transfer step should be the rate-determining step, which is consistent with the observed long reaction time (Table 1). Through exothermic N−O bond cleavage,[17] the generated radical-anion intermediate **I** is prone to collapse to release **III** and 2,4-dinitrobenzenesulfonate **IV**, which would compensate for the endothermic electron transfer. Actually, such types of *N*-centered radicals **III** and 2,4-dinitrobenzenesulfonate **IV** have

Scheme 5. Control Experiments



been observed by Chi and co-workers in their previous study.[12] There are two competitive pathways that can deliver product **3**. One is the direct radical coupling between **II** and **III**. The other is a chain-propagation procedure. The electrophilic radical **III** is trapped by another enolate **1a_anion**, leading to the formation of intermediate **V**. Next, the oxidation of unstable adduct **V** by **2** will release the product **3** and regenerate radical **III**. The observation of low yields of product when the reaction was conducted in the presence of TMPO or exposed to air provided further evidence for the above-mentioned radical mechanisms (Scheme 5, eqs 5 and 6).[18]

In conclusion, we have discovered a novel oxidative amination of 3-substituted benzofuran-2(3*H*)-ones triggered by a single-electron-transfer event. The reaction scope is quite substantial, and a range of 3-arylbenzofuran-2(3*H*)-ones and oxindoles as well as dinitrobenzenesulfonic carbamates were tolerated under the reaction conditions, giving the corresponding amination products in moderate to high yields (up to 90%). Two radical mechanisms were proposed to describe the reaction. The development of an asymmetric version of this amination strategy is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00163.

Experimental procedures, cyclic voltammogram, and ^{1}H and ^{13}C NMR spectral data for compounds **3a−w** (PDF)
X-ray data for **3t** (CIF)

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Author Contributions

§C.Y. and Y. L. contributed equally.

Notes

The authors declare no competing financial interest.

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(18) TMPO can react with benzofuranyl radical **II** and suppress the "radical coupling" pathway. However, it may not trap N-radical **III** because of its weaker N−O bond. Meanwhile, the bulky volume of TMPO makes it difficult to trap the crowded intermediate **V**. Thus, product **3** can be obtained through the chain-propagation pathway.

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