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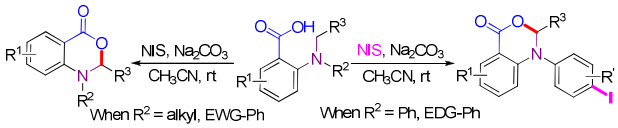
Graphical Abstract

NIS-Mediated Intramolecular Oxidative α-Functionalization of Tertiary Amines: Transition Metal-free Synthesis of 1,2-Dihydro-(4*H*)-3,1-benzoxazin-4-one Derivatives



Abstract: A novel method for direct α-functionalization of tertiary amines via NIS-mediated oxidative C–O bond formation, where NIS serves both as an oxidant and an iodination reagent, has been developed. The method provides an easy access to either iodinated or non-iodinated 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones, depending on the nature of the reactant, via a regioselective transition metal-free approach.

Cite this: DOI: 10.1039/c0xx00000x

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NIS-Mediated Intramolecular Oxidative α-Functionalization of Tertiary Amines: Transition Metal-free Synthesis of 1,2-Dihydro-(4*H*)-3,1-benzoxazin-4-one Derivatives

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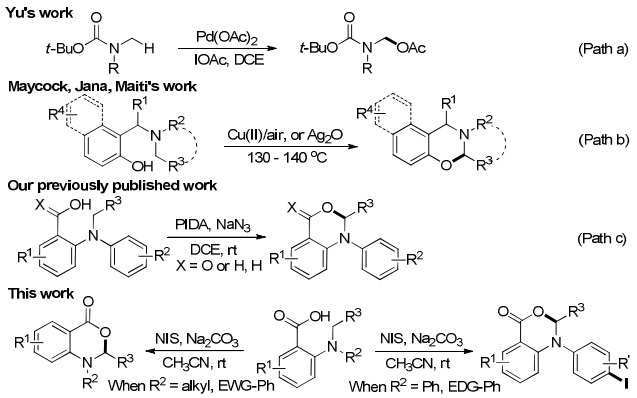
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A novel method for direct α-functionalization of tertiary amines via NIS-mediated oxidative C–O bond formation, where NIS serves both as an oxidant and an iodination reagent, has been developed. The method provides an easy access to either iodinated or non-iodinated 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-ones, depending on the nature of the reactant, via a regioselective transition metal-free approach.

Introduction

Cross-dehydrogenative coupling (CDC) reactions, which spares prefunctinalization of the substrates, boast high synthetic efficiency and atom economy; and have, hence, attracted much attention in recent decades.[1] Among the CDC reactions, selective functionalization of sp^3 C–H bonds adjacent to a nitrogen atom in simple amines is of fundamental significance in organic chemistry for the synthesis of nitrogen-containing compounds.[2] Classical strategies to realize such transformations have been achieved by utilizing transition-metals such as Ru,[3] Fe,[4] Cu,[5] V,[6] etc., with co-oxidant to afford an iminium cationic species, which subsequently reacts with various nucleophiles to form a C–C or C–heteroatom bond for the functionalization of the C–H bond adjacent to the nitrogen. As one of the most important branches of CDC reactions, direct C–O bond formation accomplished via selective sp^3 C–H bond functionalization of tertiary amines has been intensively studied for many years.[7] In 2006, a novel Pd-catalyzed highly selective acetoxylation of Boc-protected *N*-methylamines using IOAc as the oxidant and involving a Boc-directed C–H activation process, was developed by Yu and co-workers[8] (Scheme 1, path a). In 2013, Maycock[7a] group reported a copper-catalyzed regioselective intramolecular α-functionalization of tertiary amines to synthesize dihydro-1,3-oxazines via C–O bond formation. Similar works have also been achieved in 2014 by Jana[7b] and Maiti[5e] employing stoichiometric Ag_2O or catalytic amount of $CuCl_2{\cdot}H_2O$ under air, respectively (Scheme 1, path b). Lately, we reported a hypervalent iodine-mediated synthesis of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-one derivatives and 1,2-dihydro-(4*H*)-3,1-benzoxazine derivatives through intramolecular functionalization of sp^3 C–H bond of diaryl amines,[7c] an attractive metal-free protocol to functionalize sp^3 C–H bond adjacent to the nitrogen (Scheme 1, path c). Despite the significant progress made in this area in recent years,[9]

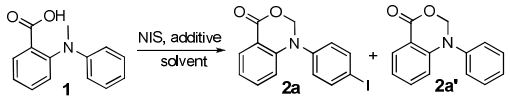


Scheme 1 Direct C–O bond formation via activation of the C–H bond adjacent to nitrogen in a tertiary amine

there is still much to be improved notably in the reaction selectivity, the expansion of substrate scope as well as the variety of the products.

Benzoxazin-4-one derivatives[10] are an important class of heterocyclic compounds, which exhibit a wide range of biological activities including anti-inflammatory effects,[11] inhibitor of human leukocyte elastase,[12] HSV-1 protase,[13] and have been used as potent inhibitors of chymotrypsin.[14] Iodinated 1H–benzoxazin–4–(H)–one derivatives can not only be readily functionalized by various coupling reactions for further application, but also be reported as inhibitors of MEK for the treatment of a variety of proliferative disease.[15] The importance of these benzoxazinones also resides in their occurrence in natural products and the application as precursors for the preparation of other heterocyclic compounds.[16] Traditionally, the general method for the synthesis of benzoxazin-4-one derivatives involves the condensation between an aromatic aldehyde and an anthranilic acid in the presence of an anhydride.[17] Kunai reported a straightforward access to benzoxazinones by CO_2 incorporation with a zwitterion arising from nucleophilic addition of imines to arynes.[18] However, efficient approaches to construct these molecules are still limited in number. On the other hand, *N*-halosuccinimides, aside from serving as halogenation reagents, have also been widely adopted as an oxidant to realize oxidative cyclization reactions in recent years.[19] We herein disclose a novel *N*-iodosuccinimide (NIS)-mediated protocol to access 1,2-

Table 1 Optimization of reaction conditions[a]



Entry	Oxidant (equiv)	Solvent	Additive (equiv)	Yield[b](%) of **2a′**	Yield[b](%) of **2a**
1[c]	NIS (2.0)	CH_3CN	--	15%	67
2	NIS (3.0)	CH_3CN	--	15%	73
3	NIS (3.0)	DCE	--	20%	68
4	NIS (3.0)	EA	--	17%	70
5	NIS (3.0)	THF	--	23%	65
6	NIS (3.0)	DMF	--	18%	45
7	NIS (3.0)	CH_3CN	$NaHCO_3$ (2.0)	<5	85
8	**NIS (3.0)**	**CH_3CN**	**Na_2CO_3** (2.0)	--	**93**
9	NIS (3.0)	CH_3CN	NaOAc (2.0)	<5	79
10	NIS (3.0)	CH_3CN	TEA (2.0)	trace	trace
11	I_2 (2.0)	CH_3CN	--	ND	ND
12	I_2 (2.0)	CH_3CN	Na_2CO_3 (2.0)	trace	10

[a] All reactions were carried out with **1a** (0.4 mmol) and oxidant in the specific solvent (c = 0.05 M). [b] Isolated yield. [c] 15% of the starting material was recovered. ND = No Desired product.

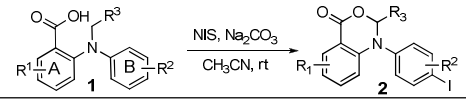
dihydro-(4*H*)-3,1-benzoxazin-4-one derivatives via α-functionalization of sp^3 C–H bond adjacent to the nitrogen of tertiary amines. To our knowledge, this is an unusual reported instance to form benzoxazinones or regioseletively iodinated benzoxazinones where NIS serves both as an oxidant and an iodination reagent (Scheme 1).

Results and Discussion

Initially, we postulated that treating *N*-methyl-*N*-phenylanthranilic acid **1a** with NIS would probably generate an iminum intermediate which could be attacked by the neighboring carboxylic acid group to afford the aminal **2a′**. However, only 15% yield of **2a′** was formed as the minor product, along with the major product of iodinated 1*H*-benzoxazin-4(*H*)-one **2a** formed in 65% yield. This result suggested a regioselective iodo-aromatic substitution occurred in addition to the expected oxidative annulation.

Following up with the initial result, we set out to explore the reaction conditions in hopes to enhance the chemoselectivity of the reaction, the main research interest of ours in identifying metal-free methods for the preparation of heterocycles.[20] The first study was on the effect of the oxidant amount. The results, with the amount of oxidant varying between 1.0 and 3.0 equiv, showed that compound **2a** was consistently the major product while **2a′**, the minor product (not shown). The solvent effect study showed that acetonitrile was the most effective in comparison to all the other solvents including DCE, ethyl acetate, TFE and DMF (Table 1, entries 1-6). None of the solvents, however, showed any significant influence on the chemoselectivity of the reaction. Further studies revealed that a basic additive could dramatically improve the selectivity as well as the yield (Table 1, entries 7 – 10), as we were able to isolate compound **2a** as the single product with a yield of 93% when Na_2CO_3 was applied as an additive (Table 1, entries 8). Additional bases such as K_2CO_3, Li_2CO_3 and pyridine were also examined, but no further enhancement of the yield was observed (not shown). Finally, molecular iodine was tested as a possible oxidant, yet only 10% yield of **2a** was isolated (Table 1, entries 11-12). Other *N*-halosuccinimides, NBS and NCS, were also investigated. When NBS was used as the oxidant, neither the corresponding annulated/brominated product nor **2a′** was observed. In contrast, when NCS was employed, the reaction proceeded smoothly to give the non-halogenated **2a′** in moderate 47% yield (not shown).

Table 2 Scope of the oxidative annulation and iodination reaction[a]



Entry	Substrate	Product	Yield[b](%)
1	**1a**	**2a**	93
2	**1b**	**2b**	75
3	**1c**	**2c**	90
4	**1d**	**2d**	77
5	**1e**	**2e**	81
6	**1f**	**2f**	76
7	**1g**	**2g**	95
8	**1h**	**2h**	88[c]
9	**1i**	**2i**	87[c]
10	**1j**	**2j**	63
11	**1k**	**2k**	68
12	**1l**	**2l**	41

[a] All reactions were carried out with **1** (0.4 mmol) in the presence of NIS (3.0 equiv) and Na_2CO_3 (2.0 equiv) in CH_3CN (c = 0.05 M). [b] Isolated yield. [c] NMR yield employing mesitylene as the internal standard.

To evaluate the efficiency and generality of the newly established method, various substituted diaryl tertiary amines were examined under the optimized conditions (Table 1, entry 8). As shown in Table 2, the corresponding 1,2-dihydro-(4*H*)-3,1-

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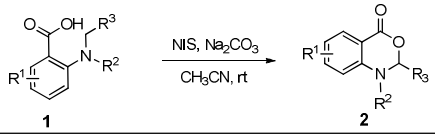
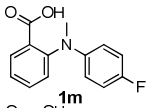
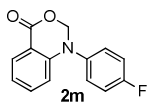
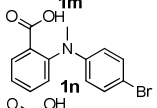
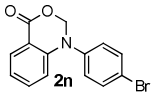
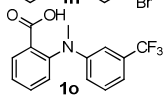
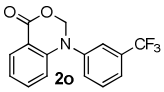
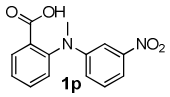
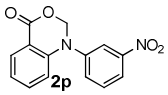
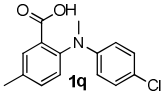
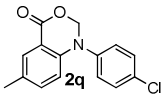
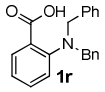
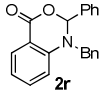
Table 3 Oxidative annulation of tertiary amines[a]



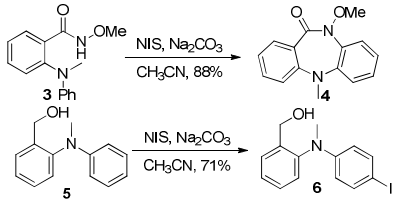
Entry	Substrate	Product	Yield[b](%)
1	 1m	 2m	91
2	 1n	 2n	85
3[c]	 1o	 2o	81
4[c]	 1p	 2p	73
5	 1q	 2q	75
6	 1r	 2r	43

[a] All reactions were carried out with **1** (0.4 mmol) in the presence of NIS (2.0 equiv) and Na_2CO_3 (2.0 equiv) in CH_3CN (c = 0.05 M). [b] Isolated yield. [c] The reaction mixture was heated to 60 °C.

benzoxazin-4-ones bearing a wide range of substitutions could be obtained in moderate to excellent yields. The substituent effect of R^1 proved to be minimal, with well tolerated both electron-withdrawing and -donating R^1 groups to give satisfactory yields (Table 2, entries 1-6). Larger alkyl groups of various sizes, such as benzyl, ethyl and hexyl were used to replace the methyl group as R^3. While the yields all remained unwaveringly high (Table 2, entries 7-9), the stability of the generated product decreased dramatically in those containing a long-chained alkyl group, as **2h** and **2i** were found to decompose readily during purification. Drastically different from the cases of R^1 and R^3, the substituent effect of R^2 was more pronounced. For substrates bearing one or more electron-donating groups on the B ring, diiodination occurred and diiodinated/annulated products were formed in moderate to good yields (Table 2, entries 10-12).

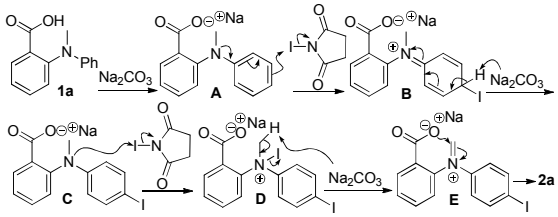
For substrates bearing an electron-withdrawing R^2 group, no iodination occurred but oxidative annulation proceeded smoothly (Table 3, entries 1-5). Electron-withdrawing R^2 groups such as halogens, NO_2 and CF_3 were all tolerated and the non-iodinated products were all obtained in great yields (Table 3, entries 1-4), including one case where there was an electron-donating $-CH_3$ group on the A ring (Table 3, entry 5). The dibenzylic substituted tertiary amine **1r** was also accessible and afforded the annulated product **2r** in a relatively low yield of 43%. To our disappointment, for *N*-methyl amines bearing protecting groups such as Ac or Ts, no desired reaction took place (not shown).

Attempts to expand the carboxylic acid functional group to a larger range of nucleophilic moieties for the same transformation turned out to be unsuccessful. As shown in Scheme 2, subjecting **3**, where the carboxylic acid in **1a** was replaced by an NH-OMe amide, to the same reaction under optimized conditions, a high yield of 1,4-benzodiazepine derivative **4**[20] was afforded instead. When the acid moiety was switched to an alcohol, no annulation took place but only para iodination which yielded amine **6** as the final product.



Scheme 2 Further investigation of scope of the reaction

To gain more insight into the reaction mechanism, some control experiments were carried out. Treatment of the cyclized compound **2a′** with NIS in the presence of Na_2CO_3 under the optimized conditions led to a completely recovery of the starting material, and this suggested that iodination occurs prior to cyclization. The hypothesis was supported by the successful conversion of substrates **1m** and **1n** to the corresponding annulated product in 91% and 85% yields, respectively. Another control experiment was to carry out the experiment in the presence of 2 equiv of a radical scavenger TEMPO. The unaffected high yield of the expected product excluded a radical process during the transformation.



Scheme 3 Proposed mechanism

On the basis of all the experiment results, we postulate a mechanistic pathway. Illustrated in Scheme 3, deprotonation of the acid resulted in the benzoate **A**, which underwent a typical electrophilic substitution reaction of aromatic ring to form C. Oxidation with the second equiv of NIS resulted in the formation ammonium **D** which was subsequently transformed into the corresponding iminum intermediate **E**. Finally, intramolecular annulation led to the ultimate formation of product **2a**. The regioselectivity of preferred para-substitution can be straightforwardly explained by the structure of the cationic **B**, which carries the electronic advantage over the meta-substituted counterparts and the stereo advantage over the ortho-substituted

one. Finally, the electrophilic substitution mechanism for the iodination effectively explains the negative effect of an electron-withdrawing R^2 group on the formation of the iodinated product, as well as the observation of multiple substitutions with an electron-donating R^2 group.

Conclusions

In conclusion, we have developed a novel NIS-mediated intramolecular α-functionalization reaction of tertiary amines via C–O bond formation to access synthetically and biologically interesting iodinated or non-iodinated 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-one derivatives. Besides its novelty as a CDC reaction, the one-pot procedure, mild reaction conditions, and transition metal-free feature render it a useful alternative to the existing methods for the preparation of benzoxazin-4-one derivatives.

Experimental Section

All reactions were carried out at room temperature under air unless otherwise noted. ^{1}H (600 MHz or 400 MHz) and ^{13}C (150 MHz or 100 MHz) NMR spectra were recorded at 25 ºC. The chemical shifts (δ) are reported in ppm with reference to TMS (0 ppm) and coupling constants (J) are given in Hz. High resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectroMeter. Melting points were determined with a MicroMelting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 40 °C in vacuum.

General procedure for the synthesis of substrate 1

To a solution of 2-iodobenzoic acid or 2-bromobenzoic acid derivative (10 mmol) in 1,4-dioxane (c = 0.3 M) was added Cu_2O (0.5 equiv), *N*-methylmorpholine (1.5 equiv), and aniline (1.5 equiv) or its derivative. The resulting mixture was refluxed under N_2 until the completion of the reaction. The mixture was filtered, and aqueous KOH solution (0.5 N, 2.5 equiv) was added to the residue and filtered. The filtrate was extracted with DCM to remove the impurities and the pH value of the water phase was adjusted to 4 using conc. HCl. The solid generated was filtered and dried. And the crude product was used directly without further purification.

To a solution of the crude product in DMF (c = 0.3 M) was slowly added NaH (2.5 equiv) at 0 ºC. And the mixture was stirred for 30 min, followed by the addition of methyl iodide (4.0 equiv) or the corresponding haloalkane. The reaction was allowed to stir at room temperature overnight. The mixture was poured into water and extracted with EA (3 × 80 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the corresponding esters.

To a solution of the ester in MeOH/H_2O (5:1, c = 0.6 M) was added KOH (2.0 equiv), and the resulting mixture was allowed to heat to reflux. Upon completion monitored by TLC, the mixture was concentrated and poured into water. The solution was acidified with conc. HCl, and the solid was filtered to give the desired product. If no precipitation, the reaction mixture was extracted with EA (3 × 60 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel to give the product.

Known substrates **1a**,[22] **1e**,[7c] **1f**,[7c] **1g**,[22] **1h**,[21] **1k**,[20] **1m-q**,[7c] **1r**,[7c] **3**[20] and **5**[7c] were prepared according to the literature procedures.

5-Methyl-2-(methyl(phenyl)amino)benzoic acid (1b). Yellowish solid (1.08 g), yield: 45% (over three steps), mp. 84 – 86 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.10 (s, 1H), 8.18 (s, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.10 – 7.04 (m, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 2H), 3.19 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 148.3, 148.2, 138.1, 135.8, 132.6, 129.3, 126.7, 125.6, 123.1, 118.6, 42.0, 21.0. HRMS (ESI) calcd for $C_{15}H_{16}NO_2^+$ [M + H^+] 242.1176, found 242.1171.

5-Methoxy-2-(methyl(phenyl)amino)benzoic acid (1c). Yellow solid (1.36 g), yield: 53% (over three steps), mp. 123 – 125 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.55 (brs, 1H), 7.84 (d, *J* = 2.9 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.11 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 2H), 3.88 (s, 3H), 3.20 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 158.6, 148.4, 143.4, 129.3, 128.0, 127.1, 123.1, 122.5, 118.5, 114.5, 55.9, 42.0. HRMS (ESI) calcd for $C_{15}H_{16}NO_3^+$ [M + H^+] 258.1125, found 258.1123.

3,4,5-Trimethoxy-2-(methyl(phenyl)amino)benzoic acid (1d). Brown solid (0.98 g), yield: 31% (over three steps), mp. 117 – 119 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.58 (brs, 1H), 7.67 (s, 1H), 7.32 – 7.26 (m, 2H), 7.03 (t, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.26 (s, 3H), 3.23 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 153.1, 150.9, 148.8, 147.7, 136.1, 129.1, 122.5, 121.8, 117.2, 108.7, 60.8, 60.1, 56.2, 39.5. HRMS (ESI) calcd for $C_{17}H_{20}NO_5^+$ [M + H^+] 318.1336, found 318.1335.

2-(Hexyl(phenyl)amino)benzoic acid (1i). Yellow oil (1.1 g), yield: 37% (over three steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.82 (s, 1H), 8.38 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 2H), 3.52 (s, 2H), 1.65 – 1.52 (m, 2H), 1.36 – 1.21 (m, 6H), 0.91 – 0.79 (d, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 149.2, 147.6, 134.7, 132.3, 129.4, 127.8, 127.5, 127.1, 123.7, 119.9, 54.6, 31.4, 26.9, 26.8, 22.5, 14.0. HRMS (ESI) calcd for $C_{19}H_{24}NO_2^+$ [M + H^+] 298.1802, found 298.1805.

2-(Methyl(*o*-tolyl)amino)benzoic acid (1j). Pale white solid (1.04 g), yield: 43% (over three steps), mp. 108 – 110 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.53 (brs, 1H), 8.30 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.45 (td, *J* = 7.9, 1.5 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.18 – 7.13 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.20 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 151.5, 146.4, 134.5, 132.7, 132.5, 132.0, 127.0, 126.4, 125.5, 124.7, 124.5, 120.4, 45.1, 19.0. HRMS (ESI) calcd for $C_{15}H_{16}NO_2^+$ [M + H^+] 242.1176, found 242.1172.

2-((3,5-Dimethoxyphenyl)(methyl)amino)benzoic acid (1l). Yellow solid (1.32 g), yield: 46% (over three steps), mp. 88 – 90 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.15 (brs, 1H), 8.35 (d, *J* = 6.8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.18 (s, 1H), 6.04 (s, 2H), 3.72 (s, 6H), 3.18 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 161.4, 150.4, 150.2, 135.0, 132.5, 128.0, 127.1, 126.0, 100.0, 97.8, 94.4, 55.4, 42.1. HRMS (ESI) calcd for $C_{16}H_{18}NO_4^+$ [M + H^+] 288.1230,

found 288.1231.

General procedure for the synthesis of compounds 2, 4 and 6

To a solution of *N*-alkyl-*N*-aryl anthranilic acids **1** (0.4 mmol) in CH_3CN (8 mL) was added NIS (1.2 mmol) followed by the addition of Na_2CO_3 (0.8 mmol) at ambient temperature. The reaction mixture was maintained at room temperature and monitored by TLC. Upon completion, the mixture was poured into sat. aqueous solution of $Na_2S_2O_3$ (30 mL) and extracted by ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine (1 × 80 mL). Dried over anhydrous Na_2SO_4, evaporation of the solvent under reduced pressure and purification of the crude residue by flash column chromatography on silica gel (EA/PE with 5‰TEA) afforded the desired products. For the synthesis of compounds **2m-r**, 2.0 equiv of NIS was used following the similar procedure mentioned above.

4-(4-Iodophenyl)isochroman-1-one (2a). White solid (131 mg), yield: 93%, mp. 129 – 131 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.50 – 7.44 (m, 1H), 7.17 – 7.11 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 146.0, 143.8, 138.8, 134.8, 131.1, 124.7, 123.1, 118.5, 117.3, 88.9, 80.5. HRMS (ESI) calcd for $C_{14}H_{11}{}^{127}INO_2^+$ [M + H^+] 351.9829, found 351.9823.

1-(4-Iodophenyl)-6-methyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2b). White solid (109.5 mg), yield: 75%, mp. 150 – 152 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.30 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.51 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.8, 144.4, 143.5, 138.7, 136.0, 133.4, 130.8, 124.2, 119.2, 117.7, 88.3, 80.7, 20.7. HRMS (ESI) calcd for $C_{15}H_{13}{}^{127}INO_2^+$ [M + H^+] 365.9985, found 365.9985.

1-(4-Iodophenyl)-6-methoxy-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2c). White solid (137.1 mg), yield: 90%, mp. 141 – 143 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 2.9 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.54 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 156.1, 145.0, 139.2, 138.6, 124.0, 123.8, 121.9, 119.3, 111.8, 87.9, 81.2, 55.9. HRMS (ESI) calcd for $C_{15}H_{13}{}^{127}INO_3^+$ [M + H^+] 381.9935, found 381.9937.

1-(4-Iodophenyl)-6,7,8-trimethoxy-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2d). Brown solid (135.8 mg), yield: 77%, mp. 57 – 59 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.7 Hz, 2H), 7.38 (s, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 151.5, 148.3, 145.8, 145.5, 138.2, 133.2, 123.5, 115.7, 107.0, 88.0, 82.9, 61.2, 60.5, 56.3. HRMS (ESI) calcd for $C_{17}H_{17}{}^{127}INO_5^+$ [M + H^+] 442.0146, found 442.0140.

7-Chloro-1-(4-iodophenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2e). White solid (124.7 mg), yield: 81%, mp. 152 – 154 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.96 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.50 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 147.1, 142.7, 141.5, 139.1, 132.5, 125.3, 123.3, 117.5, 114.8, 90.1, 80.3. HRMS (ESI) calcd for $C_{14}H_{10}{}^{35}Cl^{127}INO_2^+$ [M + H^+] 385.9439, found 385.9435.

6-Fluoro-1-(4-iodophenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2f). Pale solid (112.1 mg), yield: 76%, mp. 126 – 128 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.23 (td, *J* = 8.4, 3.0 Hz, 1H), 7.04 (dd, *J* = 9.0, 4.3 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.53 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 158.4 (d, $J_{C\text{-}F}$ = 243.7 Hz), 144.2, 142.2 (d, $J_{C\text{-}F}$ = 2.2 Hz) 138.9, 124.4, 122.8 (d, $J_{C\text{-}F}$ = 23.9 Hz), 121.3 (d, $J_{C\text{-}F}$ = 7.5 Hz), 119.0 (d, $J_{C\text{-}F}$ = 7.7 Hz), 116.5 (d, $J_{C\text{-}F}$ = 23.5 Hz), 88.9, 81.0. HRMS (ESI) calcd for $C_{14}H_{10}F^{127}INO_2^+$ [M +H+] 369.9735, found 369.9731.

1-(4-Iodophenyl)-2-phenyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2g). White solid (162.3 mg), yield: 95%, mp. 141 – 143 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.49 – 7.46 (m, 2H), 7.46 – 7.41 (m, 1H), 7.34 – 7.28 (m, 3H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.72 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 144.6, 144.4, 138.8, 137.1, 135.1, 130.7, 129.2, 128.8, 127.2, 124.9, 122.6, 119.2, 117.9, 90.9, 88.8. HRMS (ESI) calcd for $C_{20}H_{15}{}^{127}INO_2^+$ [M + H^+] 428.0142, found 428.0145.

1-(4-Iodophenyl)-2-methyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2h). 88% yield based on crude NMR within mesitylene as internal standard. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 1H), 5.69 (dd, *J* = 12.0, 6.0 Hz, 1H), 1.49 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 146.6, 142.4, 139.0, 135.1, 130.7, 128.5, 121.9, 118.4, 116.1, 91.2, 87.4, 19.9. HRMS (ESI) calcd for $C_{15}H_{13}{}^{127}INO_2^+$ [M + H^+] 365.9985, found 365.9981.

1-(4-Iodophenyl)-2-pentyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2i). 87% yield based on crude NMR within mesitylene as internal standard. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.60 (t, *J* = 6.7 Hz, 1H), 2.0 – 1.9 (m, 1H), 1.86 – 1.79 (m, 1H), 1.60 – 1.54 (m, 1H), 1.51 – 1.45 (m, 1H), 1.32 – 1.26 (m, 3H), 0.83 – 0.89 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 145.3, 144.3, 138.8, 135.0, 130.5, 126.7, 122.6, 119.8, 117.4, 91.7, 89.8, 33.3, 31.2, 24.6, 22.5, 13.9. HRMS (ESI) calcd for $C_{19}H_{21}{}^{127}INO_2^+$ [M + H^+] 422.0611, found 422.0610.

1-(2,4-Diiodo-6-methylphenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2j). White solid (123.7 mg), yield: 63%, mp. 147 – 149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 1.9 Hz, 1H), 7.71 (s, 1H), 7.63 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.25 (d, *J* = 8.6 Hz, 1H), 5.37 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.4, 147.1, 143.6, 140.8, 140.2, 139.6, 138.2, 136.9, 128.9, 117.8, 116.3, 93.3, 82.9, 79.8, 17.9. HRMS (ESI) calcd for $C_{15}H_{12}{}^{127}I_2NO_2^+$ [M + H^+] 491.8952, found 491.8956.

1-(2,4-Diiodo-5-methoxyphenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2k). White solid (137.9 mg), yield: 68%, mp. 166 – 168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.59 (s, 1H), 5.55 (s, 1H), 5.38 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 159.8, 148.5, 147.2, 146.8, 135.2, 131.1, 122.4, 117.7, 116.0, 111.2, 87.5, 86.2, 80.3, 56.8. HRMS (ESI) calcd for $C_{15}H_{12}{}^{127}I_2NO_3^+$ [M + H^+] 507.8901, found 507.8906.

1-(2,4-Diiodo-3,5-dimethoxyphenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2l). Brown oil (88 mg), yield: 41%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.3 Hz,

1H), 7.12 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.45 (s, 1H), 5.59 (s, 1H), 5.39 (d, J = 8.2 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 161.5, 160.7, 146.9, 135.2, 131.1, 122.4, 117.9, 116.0, 107.2, 85.2, 82.7, 80.5, 60.8, 57.1. HRMS (ESI) calcd for $C_{16}H_{14}{}^{127}I_2NO_4^+$ [M + H$^+$] 537.9007, found 537.9009.

1-(4-Fluorophenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2m).[7c] Yellow solid (88.5 mg), yield: 91%, mp. 76 – 78 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, J = 7.9 Hz, 1H), 7.46 (t, J = 7.1 Hz, 1H), 7.17 – 7.03 (m, 5H), 6.93 (d, J = 8.3 Hz, 1H), 5.51 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 160.3 (d, $J_{C\text{-}F}$ = 244.4 Hz), 147.0, 139.9, 135.0, 131.1, 125.5 (d, $J_{C\text{-}F}$ = 8.4 Hz), 122.5, 117.9, 116.7 (d, $J_{C\text{-}F}$ = 22.6 Hz), 116.5, 80.9.

1-(4-Bromophenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2n).[7c] Yellow solid (103 mg), yield: 85%, mp. 110 – 112 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, J = 7.7 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 3H), 5.54 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 146.1, 143.0, 135.0, 132.9, 131.1, 124.5, 123.1, 118.5, 118.3, 117.2, 80.6.

1-(3-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2o).[7c] Following the general procedure, the reaction mixture was heated to 60 °C. **2o** was obtained as pale solid (99.6 mg), yield: 85%, mp. 68 – 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.1 Hz, 1H), 7.53 (t, J = 8.4 Hz, 2H), 7.47 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 5.62 (s, 2H). 13C NMR (100 MHz, $CDCl_3$) δ 163.5, 145.7, 144.7, 135.0, 132.4 (q, $J_{C\text{-}F}$ = 32.4 Hz), 131.2, 130.4, 125.7, 123.6, 123.5 (q, $J_{C\text{-}F}$ = 270.9 Hz), 121.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 119.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 118.7, 117.7, 80.6.

1-(3-Nitrophenyl)-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2p).[7c] Following the general procedure, the reaction mixture was heated to 60 °C. **2p** was obtained as a yellow solid (79 mg), yield: 73%, mp. 131 – 133 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.57 (t, J = 8.0 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.66 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 149.2, 145.5, 144.9, 135.2, 131.4, 130.7, 127.6, 124.4, 119.4, 119.2, 118.2, 116.6, 80.5.

1-(4-Chlorophenyl)-6-methyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2q).[7c] White solid (82 mg), yield: 75%, mp. 109 – 111 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.35 – 7.29 (m, 3H), 7.04 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.3 Hz, 1H), 5.52 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 143.7, 143.2, 136.1, 133.3, 130.7, 130.2, 129.8, 123.8, 119.1, 117.5, 80.9, 20.8.

1-Benzyl-2-phenyl-1*H*-benzo[*d*][1,3]oxazin-4(2*H*)-one (2r).[7c] Yellow oil (54 mg), yield: 43%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.8, 1.3 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.34 – 7.29 (m, 5H), 7.28 – 7.24 (m, 3H), 6.95 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.33 (s, 1H), 4.63 (d, J = 16.1 Hz, 1H), 4.41 (d, J = 16.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 148.3, 136.9, 136.0, 135.4, 130.9, 129.4, 128.8, 128.9, 127.9, 127.5, 127.2, 120.8, 116.4, 116.0, 90.5, 53.3.

10-Methoxy-5-methyl-5*H*-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one (4).[21] White solid (89 mg), yield: 88%, mp. 125 – 127 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.6, 1.1 Hz, 1H), 7.49 (dd, J = 8.3, 1.4 Hz, 1H), 7.41 (td, J = 8.1, 1.6 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.15 – 7.03 (m, 4H), 3.87 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 153.0, 145.8, 133.9, 132.8, 132.1, 126.4, 125.6, 124.4, 123.1, 121.1, 118.5, 116.7, 62.3, 37.7.

(2-((4-Iodophenyl)(methyl)amino)phenyl)methanol (6). Yellow oil (96.3 mg), yield: 71%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.35 (td, J = 7.5, 1.7 Hz, 1H), 7.31 (td, J = 7.4, 1.3 Hz, 1H), 7.12 – 7.09 (m, 1H), 6.32 (t, J = 6.0 Hz, 2H), 4.54 (s, 2H), 3.18 (s, 3H), 2.03 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 145.6, 139.0, 137.7, 129.5, 129.1, 128.1, 127.3, 115.7, 79.0, 61.8, 39.9. HRMS (ESI) calcd for $C_{14}H_{15}{}^{127}INO^+$ [M + H$^+$] 340.0193, found 340.0195.

Acknowledgements

We acknowledge the National Science Foundation of China (#21472136) and the National Basic Research Project (2014CB932201) for financial support.

Notes and references

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† Electronic Supplementary Information (ESI) available: NMR spectra for all new compounds, See DOI:10.1039/b000000x/

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