JOC The Journal of Organic Chemistry

Note

Metal-Free Synthesis of 2-N,N-Dialkylaminobenzoxazoles using Tertiary Amines as the Nitrogen Source

Mookda Pattarawarapan, Dolnapa Yamano, nittaya wiriya, and Wong Phakhodee

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00797 • Publication Date (Web): 24 Apr 2019

Just Accepted

ACS Publications

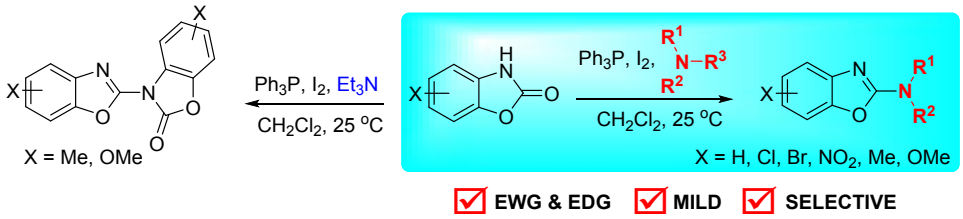
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Metal-Free Synthesis of 2-*N,N*-Dialkylaminobenzoxazoles using Tertiary Amines as the Nitrogen Source

Mookda Pattarawarapan[a,b], Dolnapa Yamano[a], Nitaya Wiriya[a], and Wong Phakhodee*[a,b]

[a]Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai 50200, Thailand

[b]Research Center on Chemistry for Development of Health Promoting Products from Northern Resources, Faculty of Science, Chiang Mai University, Chiang Mai, 50200, Thailand



Abstract

The unprecedented reaction of tertiary amines with 2(3*H*)-benzoxazolones has been investigated. In the presence of Ph_3P-I_2 reagent system, the reaction of both acyclic and cyclic aliphatic tertiary amines led to the formation of 2-*N,N*-dialkylaminobenzoxazoles with the selective cleavage of an alkyl group. Especially, *N*-(2-iodoethyl)piperazinyl derivatives were rapidly produced in good yields when using DABCO as the nitrogen source. Only in the cases when the nucleophilicity of the substrates exceeds that of the amine, competitive self-condensation of benzoxazolones then proceeds preferentially. $^{31}P\{1H\}$-NMR study suggested the involvement of an aryloxyphosphonium intermediate and/or possibly 2-iodobenzoxazole which activates the C-2 position of benzoxazolones toward nucleophilic aromatic substitution.

Keywords Tertiary amines; Benzoxazolones; Aminobenzoxazoles; Triphenylphosphine; Iodine

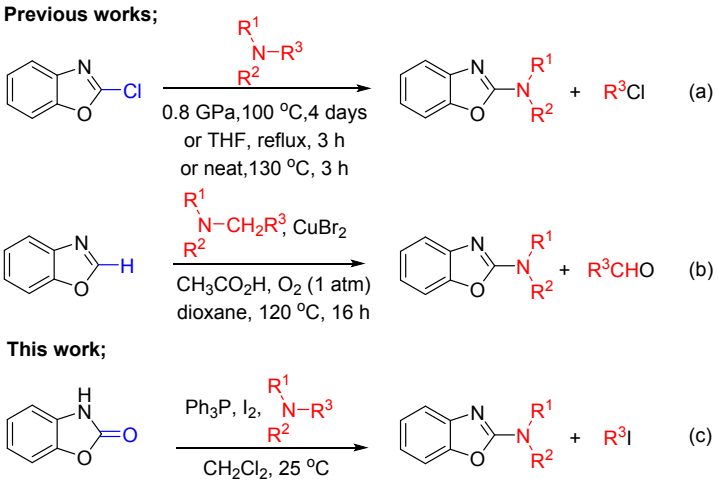
Tertiary amines are commonly used as base in organic reactions due to their solubility in several organic solvents, stability, and inertness. Nevertheless, the unusual role of tertiary amine as a secondary amine surrogate has already been observed under appropriate reaction conditions. While a number of metal-catalyzed aminations toward *N,N*-disubstituted products reported to date have been carried out with several substrates such as carboxylic acids, esters, sulfonyl chlorides, alkenes, alkynes, benzynes, and benzoxazoles,[1] the metal-free reaction of tertiary amines has rarely been explored. Most of which requires highly reactive substrates including anhydrides,[2] acyl chloride,[3] acyl iodide[4] and heteroaromatic halides (X = Cl),[5] otherwise harsh reaction conditions are strictly required.[6]

2-Aminobenzoxazoles are interesting structural motifs often found to be incorporated in a number of therapeutically important molecules.[7] A wide range of biological activities have already been observed. Particularly, 2-(*N*-alkylpiperazyl)benzoxazoles were described as potent 5-HT3-receptor agonists.[7h] Owing to their pharmaceutical importance, several approaches toward the synthesis of 2-aminobenzoxazoles have been introduced including S_NAr displacement of 2-substituted benzoxazoles (Cl[8]and CCl_3[9]), metal-catalyzed oxidative C–H bond amination of benzoxazoles[10] condensation of 2-aminophenol with iso(thio)cyanate,[11] isocyanide,[12] or dithiocarbamates,[13] as well as microwave-assisted direct amination of 2-mercaptobenzoxazoles.[14]

Despite numerous studies on the application of primary and secondary amines as the common nucleophile, there are only three reports on the synthesis of 2-aminobenzoxazoles using tertiary amines. Two of these studies involve S_NAr reaction of 2-chlorobenzoxazoles with *N*-alkyl tertiary amines (Scheme 1a).[5d,6b] Another study relies on Cu-catalyzed oxidative amination of benzoxazoles (Scheme 1b).[1h] Nevertheless, harsh conditions, long reaction times, and narrow substrate scope remain the major issues to be overcome. While the synthesis starting from 2-chlorobenzoxazoles requires extra preparation step toward the reactive

precursors using highly toxic $POCl_3$ or PCl_5,[15] the costs associated with residual catalyst removal in the metal–catalyzed reaction have prompted a great interest in developing metal-free reaction that enables the use of simple reagents as well as relatively low cost and highly abundant tertiary amines as the nitrogen source.

Scheme 1. Tertiary Amine as Nitrogen Source in the Synthesis of 2-Aminobenzoxazoles

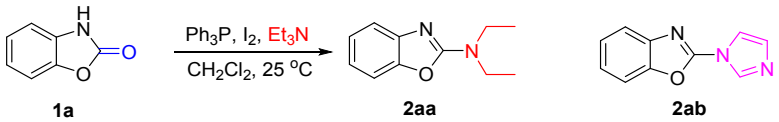


In our continuing work with Ph_3P-I_2-mediated synthesis,[16] we have unexpectedly isolated *N,N*-diethylsubstituted benzoxazole while performing amination reaction of 2(3*H*)-benzoxazolone using triethylamine as base. To the best of our knowledge, the direct amination of heterocyclic carbamate with tertiary amines has never been previously explored. This result thus encourages us to further investigate the scope and generality of the reaction of benzoxazolones with tertiary amines as shown in Scheme 1(c).

To establish the optimum conditions, amination of benzoxazolone **1a** with triethylamine (Et_3N) was chosen as a model reaction. Various set of reaction conditions were screened as summarized in Table 1. Using three equivalents of Et_3N in the presence of a 1:1

mixture of iodine and Ph_3P (1.5 equiv) in dichloromethane gave the corresponding diethyl substituted product **2aa** in 35% together with recovered starting material (entry 1). When the reaction was performed with 1.2 equivalents of Et_3N in the presence of other commonly used bases such as *N,N*-diisopropylethylamine (*i*-Pr_2NEt) and *N,N*-dimethylaminopyridine (DMAP), only low yield or trace amount of the desired product was obtained (entries 2-3). Interestingly, using imidazole led to a competitive formation of **2ab** in high yield indicating the greater nucleophilicity of this base relative to Et_3N (entry 4). To our delight, the yield of the respective product was improved when increasing the amount of Et_3N (entry 5). Unfortunately, longer reaction times, raising the temperature, or increasing the equivalents of the reagents did not further improve the product yield (entries 6-9).

Table 1. Optimization of the Reaction Conditions[a]



1a **2aa** **2ab**

entry	$Ph_3P:I_2$ (equiv)	Et_3N (equiv)	base (equiv)	conditions	%yield
1	1.5:1.5	3	-	CH_2Cl_2, 25 °C, 8 h	35
2	1.5:1.5	1.2	*i*-Pr_2NEt (3)	CH_2Cl_2, 25 °C, 8 h	19
3	1.5:1.5	1.2	DMAP (3)	CH_2Cl_2, 25 °C, 8 h	trace
4	1.5:1.5	1.2	imidazole (3)	CH_2Cl_2, 25 °C, 8 h	trace (72)[b]
5	**1.5:1.5**	**5**	**-**	**CH_2Cl_2, 25 °C, 8 h**	**52**
6	1.5:1.5	5	-	CH_2Cl_2, 25 °C, 16 h	48
7	1.5:1.5	5	-	toluene, 110 °C, 8 h	15
8	1.5:1.5	5	-	1,2-dichloroethane, 80 °C, 8 h	38
9	2.5:2.5	6	-	CH_2Cl_2, 25 °C, 8 h	44

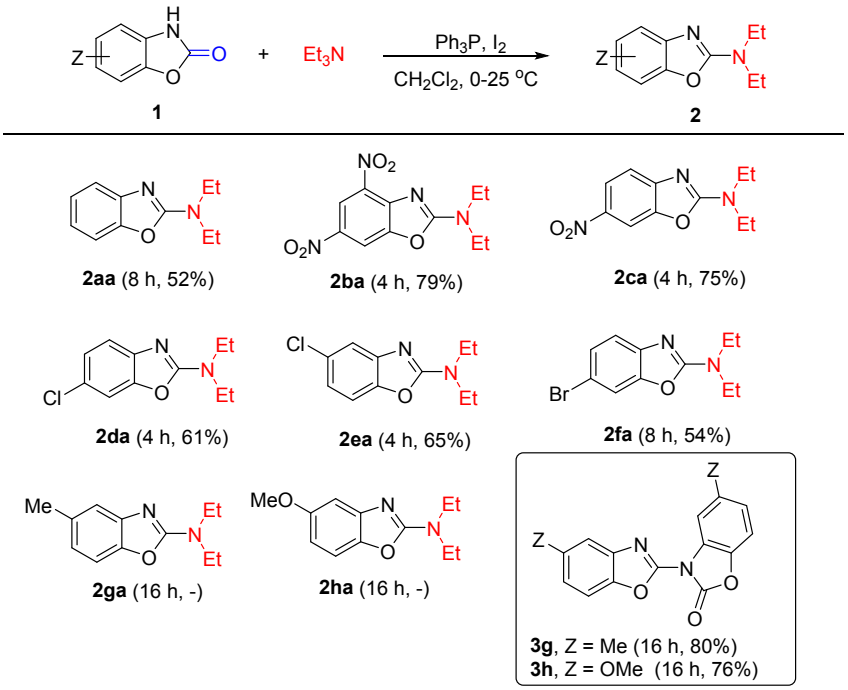
[a]Reaction conditions: **1a** (0.37 mmol) in 2 mL of solvent. [b]Yield of **2ab**.

Since both electronic nature of the substrate, basicity and nucleophilicity of tertiary amine are important factors determining the product yield and reaction rate, we next explored

the scope and limitations of the process with respect to substituted benzoxazolones and types of tertiary amines using the partially optimized reaction conditions (Table 1, entry 5). According to Scheme 2, benzoxazolones having different substituents, especially those bearing electron-withdrawing group, could be involved in the amination reaction. The reaction of triethylamine with electron-deficient substrates such as those containing chloro or nitro substituent proceeds in a faster rate and produces the corresponding diethylamino derivatives in higher yields when comparing with those without substituent or having bromo group. The ease of substitution could be attributed to the increase in electrophilicity of the benzoxazolone ring. Unfortunately, electron-rich substrates such as those having -Me or -OMe group failed to react with triethylamine under the applied reaction conditions. Instead, only self-condensed products **3g** and **3h** were isolated in high yields, respectively, indicating that these substrates once converted to the more reactive intermediates could undergo hydrolysis and coupling with each other. It should be noted that similar coupling product has been reported in the reaction involving 2-chlorobenzoxazole.[17]

The reaction of **1a** was further investigated with a variety of tertiary amines and the results were summarized in Table 2. Other aliphatic amines were found to behave similarly to triethylamine which provided the corresponding 2-dialkylaminobenzoxazoles in moderate to good yields. For symmetrical substituted amines, the deoxygenative amination was found to be dependent on the alkyl chain lengths as the reaction with trimethylamine proceeded more readily than that using tributylamine (entry 1 vs entry 2). Surprisingly, despite the ease of removal of the tentative benzyl iodide, tribenzylamine failed to react under the applied conditions (entry 3) or even upon prolong heating at 80 ^{o}C in 1,2-dichloroethane. These results suggested that either its weak basicity or the steric hindrance of the three benzyl groups may be responsible for the lack of reactivity of this amine.

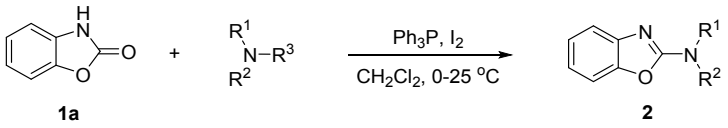
Scheme 2. Scope of Reaction of 2(3*H*)-Benzoxazolones with Triethylamine[a]



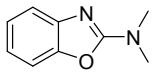
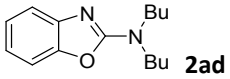
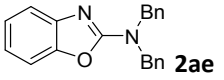
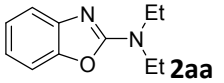
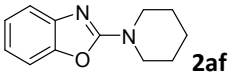
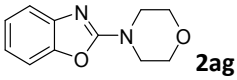
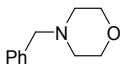
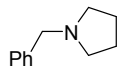
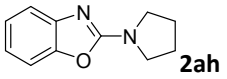
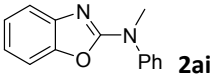
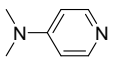
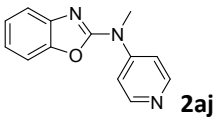
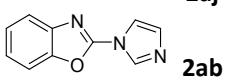
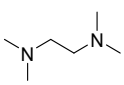
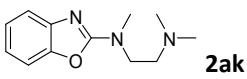
[a]Reaction conditions: **1** (0.74 mmol), Et_3N (3.70 mmol), Ph_3P (1.11 mmol), I_2 (1.11 mmol) in 5 mL CH_2Cl_2, 0-25 °C.

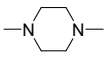
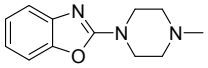
When using mixed tertiary acyclic amine such as *N,N*-diethylbenzylamine, debenzylation proceeded exclusively to give product **2aa** in moderate yield (entry 4). However, no reaction was observed with the more sterically hindered dibenzylethylamine (entry 5). The reaction with various *N*-substituted cyclic amines was also investigated and the expected products was obtained without detectable endocyclic C–N bond cleavage (see entries 6-10). Unfortunately, arylamines failed to undergo deoxygenative amination suggesting that the reaction is incompatible with amines having the C(sp^2)-N bond (entries 11-13).

Table 2. Amination of 1a with Various Tertiary Amines[a]



1a 2

entry	amine	product	time (h)	Yield (%)[b]
1	Me_3N	 **2ac**	4	70
2	Bu_3N	 **2ad**	16	45
3	Bn_3N	 **2ae**	16	NR
4	Et_2NBn	 **2aa**	16	41
5	$EtNBn_2$	**2ae**	16	NR
6		 **2af**	4	66
7		**2af**	8	59
8		 **2ag**	8	63
9		**2ag**	16	61
10		 **2ah**	16	57
11	Me_2NPh	 **2ai**	16	NR
12		 **2aj**	16	NR
13		 **2ab**	16	NR
14[b]		 **2ak** **2ac**	3	72 15

15[b]		 **2al**	3	67

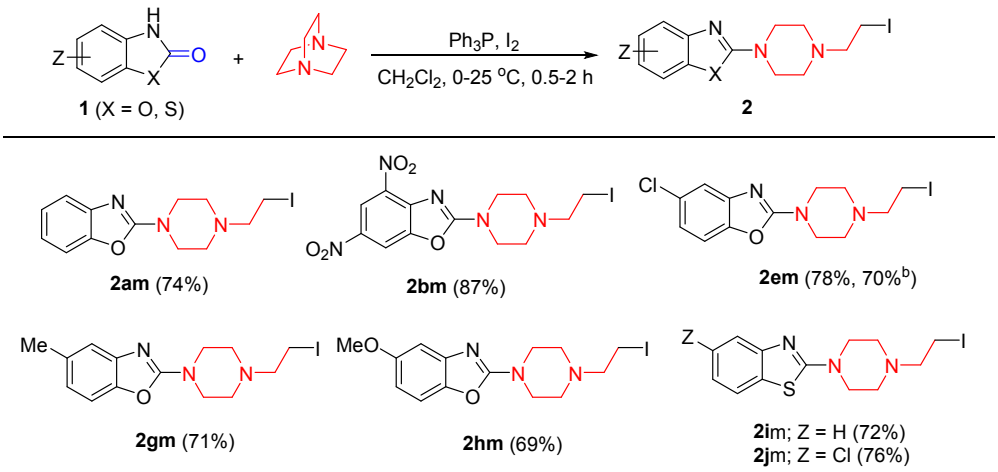
[a]Reaction conditions: **1** (0.74 mmol), amine (3.70 mmol), Ph_3P (1.11 mmol), I_2 (1.11 mmol) in 5 mL CH_2Cl_2, 0-25 °C. [b]amine (2.22 mmol).

Further studies with tertiary amines containing two nitrogen atoms such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and 1,4-dimethylpiperazine revealed another problem involving insoluble salt formation. Thus, to improve the product yields, it is necessary to decrease the amount of the amines used in the reaction. According to Table 2 (entries 14 and 15), an interesting selectivity was observed. Among the two possible *N*-dealkylation, the demethylated product **2ak** was isolated as a major product when **1a** was treated with TMEDA (entry 14). Monosubstituted product **2al** was also obtained exclusively when using 1,4-dimethylpiperazine as a nucleophile (entry 15).

With the success in the use of both acyclic and cyclic amines, we next explore the reaction with bicyclic amine using DABCO as the representative. Again, it was found that reducing the amount of DABCO leads to better yields as the formation of the tentative quaternary ammonium salts comprising substituted *N*-ethylpiperazinyl moiety[18] was minimized. According to Scheme 3, a range of benzoxazolones either those containing electron-withdrawing group or donating group underwent rapid amination with DABCO leading to the desired products **2am**-**2hm** in good yields under short reaction times. Notably, in the cases of using **1g** or **1h**, no trace of self-condensed product was detected indicating that DABCO is highly reactive as base and nucleophile. The scope of the reaction could also be extended to the synthesis of *N*-(2-iodoethyl)piperazinylbenzothiazoles using 2(3*H*)-benzothiazolones as the substrates (see compounds **2im** and **2jm**). The practical utility of the method was further demonstrated in a gram-scale synthesis of **2em**. In this case, no significant deteriorated effect on the product yield was observed when using only 1.2 equivalents of

DABCO with the addition of Et_3N as base. It is worth mentioning that this observation is highly useful since the monoarylated piperazines are promising candidates for the treatment of irritable bowel syndrome (IBS), dyspepsia, pain, anxiety, and psychosis.[7f,19] Additionally, the reported S_NAr-based approach using DABCO still suffers from very high temperature, long reaction times which is restricted to only electron-poor substrates.[5e,6c,18,20]

Scheme 3. **Reaction of 2(3*H*)-Benzoxazolones with DABCO**[a]

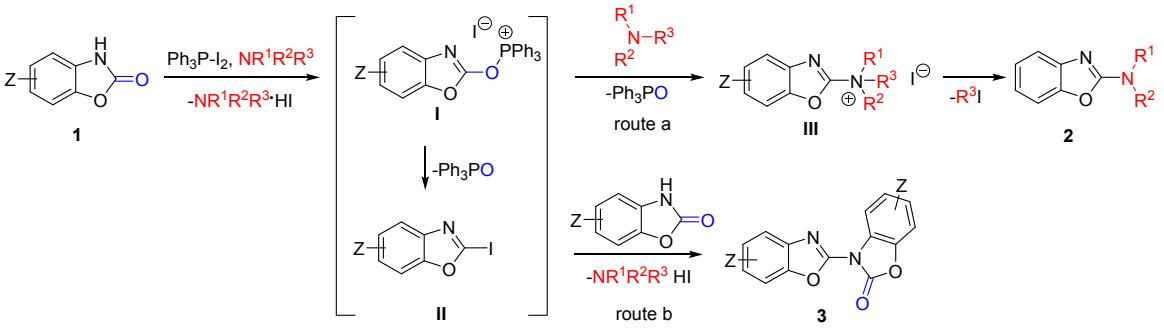


[a]Reaction conditions: **1** (0.74 mmol), DABCO (2.22 mmol), Ph_3P (1.11 mmol), I_2 (1.11 mmol) in 5 mL CH_2Cl_2, 0-25 °C. [b]Yield using 7.4 mmol of **1e**.

Based on the results obtained and previous reports by other related studies,[5d,6b,21] the reaction presumably proceeds via S_NAr process involving the initial formation of the activated aryloxyphosphonium intermediate **I** or possibly 2-iodobenzoxazole **II** generated in-situ (Scheme 4). Subsequent attacks by tertiary amine then gives rise to the formation of quaternary ammonium salts **III** (route a). Final, *N*-dealkylation by the action of iodide at the least steric C-N bond then provides the *N,N*-disubstituted products **2**. Provided that nucleophilicity of **1** is greater than that of the amine, competitive formation of **3** would be feasible (route b). To

gain insight into the role of phosphonium intermediates, ^{31}P-NMR study on the progress of the reaction between **1a** and Et_3N was carried out. According to Figure S1, addition of **1a** to the mixture of Ph_3P-I_2 containing Et_3N showed an appearance of a high intensity signal at δ_p 38.68 ppm suggesting the formation of **I**. An increase in the intensity of the triphenylphosphine oxide signal at δ_p -28.96 ppm with a simultaneous decrease of the phosphonium's signal upon prolonged reaction time indicated further reaction of **I** with nucleophiles which could be iodide or the remaining amine. It should be noted that no significant change in the phosphorous signals was observed when adding Et_3N to the Ph_3P/I_2 mixture suggesting that the possibility for the initial formation of diethylaminophosphonium iodide could be ruled out (see Figures S2 and S3 in ESI).

Scheme 4. Proposed Mechanism for the Reaction of Benzoxazolones with Tertiary Amine



In summary, we have disclosed for the first time an efficient metal-free procedure for the synthesis of 2-*N,N*-dialkylaminobenzoxazoles through the Ph_3P-I_2 activation of benzoxazolones toward S_NAr reaction with tertiary amines. The method is compatible with a broad range of substrates which enables rapid access to various 2-aminobenzoxazoles under mild conditions. Given the abundance, low cost, and relatively low toxicity of the tertiary

amines, the developed protocol is potentially useful as an alternative process toward interesti ng synthetic targets where other known amination methods are limited or ineffective. The ease of introducing of the *N*-(2-iodoethyl)piperazinyl group could also lead to further development toward more structural diversity and interesting bioactivity. Studies to expand the scope of reaction and to understand the mechanism underlying the Ph_3P-I_2 mediated reaction of heterocyclic amides, ureas, and other alicyclic carbamates are underway which will be reported in due course.

EXPERIMENTAL SECTION

Material and methods

All reagents including most of the 2(3*H*)-benzoxazolone precurors **1** (**1a**, **1c**-**1g**, **1i** and **1j**) were purchased from Sigma-Aldrich or TCI and used without further purification. Compound **1b**[22] and **1h**[23] were synthesized according to the reported procedures. The reaction was monitored by thin-layer chromatography carried out on silica gel plates ($60F_{254}$, MERCK, Germany) and visualized under UV light (254 nm). Column chromatography was performed over silica gel 60 (70–230 mesh, MERCK, Germany). Melting points were determined using Mettler Toledo DSC equipment at a heating rate of 6 ^{o}C/min and were uncorrected. NMR spectra were recorded using a Bruker AVANCE^{TM} (400 and 500 MHz for ^{1}H). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Splitting patterns are described as singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), quintet (qui), sextet (sex), multiplet (*m*), broad (*br*), doublet of doublets (*dd*), triplet of doublets (td) and doublet of doublet of doublets (ddd). High-resolution mass spectra (HRMS) were recorded using time-of-flight (TOF) via the atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI).

General procedure for the synthesis of 2-N,N-Dialkylaminobenzoxazoles 2

To a solution of iodine (280 mg, 1.11 mmol) in freshly distilled dichloromethane (5 mL) was added triphenylphosphine (288 mg, 1.11 mmol) at 0 °C under N_2. After that, amine (3.70 mmol) was added, followed by the addition of benzoxazolone **1** (0.74 mmol). The mixture was stirred at 0 °C for 5 min before warming up to room temperature. Upon completion of the reaction, the crude mixture was concentrated under reduced pressure then purified by column chromatography (CC) using ethyl acetate/hexanes as the eluent.

***N,N*-Diethylbenzo[*d*]oxazol-2-amine (2aa)**.[24] Colorless oil; (0.0734 g, 52% yield); R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.16 (td, J = 7.6, 1.2 Hz, 1H), 7.00 (td, J = 7.6, 1.2 Hz, 1H), 3.61 (q, J = 7.2 Hz, 4H), 1.30 (t, J = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.3, 148.9, 143.7, 123.8, 120.0, 115.8, 108.5, 43.0, 13.5.

2-(1*H*-Imidazol-1-yl)benzo[*d*]oxazole (2ab).[25] Yellow solid; (0.0992 g, 72% yield); mp 110-112 °C (lit.[25] mp 112 °C); R_f 0.26 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.73 (t, J = 1.5 Hz, 1H), 7.69 (dd, J = 7.5, 2.0 Hz, 1H), 7.55 (dd, J = 7.5, 2.0 Hz, 2H), 7.39 (td, J = 7.5, 2.0 Hz, 1H), 7.36 (td, J = 7.5, 2.0 Hz, 1H), 7.25 (d, J = 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.0, 149.0, 140.5, 135.9, 131.4, 125.5, 125.1, 119.7, 116.8, 110.5.

***N,N*-Diethyl-4,6-dinitrobenzo[*d*]oxazol-2-amine (2ba)**. Yellow oil; (0.1635 g, 79% yield); R_f 0.44 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (d, J = 2.0 Hz, 1H), 8.28 (d, J = 2.0 Hz, 1H), 3.84 (br s, 2H), 3.70 (br s, 2H), 1.38 (t, J = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.8, 150.7, 146.3, 138.9, 133.3, 117.7, 107.8, 44.6, 43.1, 13.6, 12.9; TOF-HRMS calcd for $C_{11}H_{12}N_4NaO_5$ $(M+Na)^+$ 303.0705, found 303.0709.

***N,N*-Diethyl-6-nitrobenzo[*d*]oxazol-2-amine (2ca)**.[26] Yellow solid; (0.1309 g, 75% yield); mp 110-112 °C (lit.[26] mp 112-114 °C); R_f 0.43 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 3.64 (q, *J* = 7.2 Hz, 4H), 1.33 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 150.6, 147.9, 140.9, 121.4, 114.4, 104.8, 43.4, 13.4.

6-Chloro-*N,N*-diethylbenzo[*d*]oxazol-2-amine (**2da**).[1h] Off-white solid; (0.1021 g, 61% yield); mp 60-62 °C; R_f 0.35 (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.55 (q, *J* = 7.2 Hz, 4H), 1.26 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 148.9, 142.5, 124.9, 124.0, 116.0, 109.3, 43.0, 13.4.

5-chloro-*N,N*-diethylbenzo[d]oxazol-2-amine (**2ea**).[1h] White solid; (0.1078 g, 65% yield); mp 60-62 °C; R_f 0.35 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.55 (q, *J* = 7.2 Hz, 4H), 1.26 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.5, 148.9, 142.5, 124.9, 124.0, 116.0, 109.3, 43.0, 13.4.

5-Bromo-*N,N*-diethylbenzo[*d*]isoxazol-3-amine (**2fa**). Colorless solid; (0.1073 g, 54% yield); mp 54-56 °C; R_f 0.27 (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 3.56 (q, *J* = 7.2 Hz, 4H), 1.27 (t, *J* = 7.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 149.3, 143.0, 126.8, 116.6, 112.0, 111.8 ,43.0, 13.4; TOF-HRMS calcd for $C_{11}H_{14}N_2O^{81}Br$ $(M+H)^+$, 271.0270, found 271.0286, for $C_{11}H_{14}N_2O^{79}Br$ $(M+H)^+$, 269.0290, found 269.0301.

5,5'-Dimethyl-2'*H*-[2,3'-bibenzo[*d*]oxazol]-2'-one (**3g**). White solid; (0.0832 g, 80% yield); mp 156-157 °C; R_f 0.35 (5% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.56 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 8.2, 1.0 Hz, 1H) 2.50 (s, 3H), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ

151.2, 149.5, 146.9, 140.4, 140.1, 135.2, 135.0, 127.2, 126.0, 125.5, 119.7, 114.2, 110.2, 109.9, 21.7, 21.6; TOF-HRMS calcd for $C_{16}H_{12}N_2NaO_3$ $(M+Na)^+$ 303.0746, found 303.0743.

5,5'-Dimethoxy-2'H-[2,3'-bibenzo[*d*]oxazol]-2'-one (**3h**). White solid; (0.1148 g, 76% yield); mp 160-162 °C; R_f 0.41 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.5 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 1H), 6.96 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.82 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.8, 157.2, 151.6, 149.6, 143.2, 140.8, 136.4, 127.9, 113.1, 111.0, 110.7, 110.3, 103.2, 100.6, 56.2 56.0; TOF-HRMS calcd for $C_{16}H_{12}N_2NaO_5$ $(M+Na)^+$ 335.0644, found 335.0647.

***N,N*-Dimethylbenzo[*d*]oxazol-2-amine** (**2ac**).[27] White solid; (0.0842 g, 70% yield); mp 89-90 °C (lit.[27] mp 90-91 °C); R_f 0.46 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.15 (td, *J* = 8.0, 1.0 Hz, 1H), 7.00 (td, *J* = 8.0, 1.0 Hz, 1H), 3.20 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.1, 149.1, 143.5, 123.9, 120.3, 116.0, 108.6, 37.7.

***N,N*-dibutylbenzo[*d*]oxazol-2-amine** (**2ad**).[10e] Yellow oil; (0.0540 g, 45% yield); R_f 0.36 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 3.53 (t, *J* = 7.6 Hz, 4H), 1.68 (quin, *J* = 7.6 Hz, 4H), 1.40 (sex, *J* = 7.6 Hz, 4H), 0.98 (t, *J* = 7.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6, 148.7, 143.7, 123.7, 119.8, 115.8, 108.4, 48.3, 30.1, 20.0, 13.9.

2-(Piperidin-1-yl)benzo[*d*]oxazole (**2af**).[24] Pale yellow solid; (0.0994 g, 66% yield); mp 70-73 °C (lit.[24] mp 72-75 °C); R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 7.5 Hz, 1H), 3.66 (s, 4H), 1.68 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) *δ* 162.5, 148.7, 143.4, 123.8, 120.3, 116.0, 108.6, 46.6, 25.3, 24.1.

2-Morpholinobenzo[*d*]oxazole (**2ag**).[24] White solid; (0.0951 g, 63% yield); mp 90-92 °C (lit.[24] mp 90-94 °C); R_f 0.20 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 3.82 (t, J = 4.5 Hz, 4H), 3.70 (t, J = 4.5 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.1, 148.8, 142.9, 124.1, 121.0, 116.5, 108.8, 66.2, 45.7.

2-(Pyrrolidin-1-yl)benzo[*d*]oxazole (2ah).[28] White solid; (0.0795 g, 57% yield); mp 135-137 °C (lit.[28] mp 136-137 °C); R_f 0.30 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 3.65 (s, 4H), 2.03 (s, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ) δ 161.0, 148.9, 143.4, 123.9, 120.2, 115.8, 108.7, 47.4, 25.6.

***N*^{1}-(Benzo[*d*]oxazol-2-yl)-*N*^{1},*N*^{2},*N*^{2}-trimethylethane-1,2-diamine** (**2ak**).[28] Yellow solid; (0.1167 g, 72% yield); mp 110-111 °C; R_f 0.28 (10% MeOH/EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.16 (td, J = 7.8, 1.2 Hz, 1H), 7.03 (td, J = 7.8, 1.2 Hz, 1H), 3.87 (t, J = 6.2 Hz, 2H), 3.33 (t, J = 6.2 Hz, 2H), 3.16 (s, 3H), 2.82 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 162.8, 149.0, 143.5, 124.5, 120.8, 116.2, 109.4, 54.5, 45.8, 43.5, 35.6.

2-(4-Methylpiperazin-1-yl)benzo[*d*]oxazole (**2al**).[24] White solid; (0.1085 g, 67% yield); mp 36-38 °C (lit.[24] mp 36-38 °C); R_f 0.26 (10% MeOH/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.0, 1.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.16 (td, J = 8.0, 1.0 Hz, 1H), 7.02 (td, J = 8.0, 1.5 Hz, 1H), 3.74 (t, J = 5.0 Hz, 4H), 2.54 (t, J = 5.0 Hz, 4H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, , $CDCl_3$) δ 162.2, 148.8, 143.1, 124.0, 120.7, 116.3, 108.7, 54.2, 46.2, 45.5.

2-(4-(2-Iodoethyl)piperazin-1-yl)benzo[*d*]oxazole (**2am**). Pale yellow oil; (0.1966 g, 74% yield); R_f 0.23 (20% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 3.70 (br s, 4H), 3.23

(t, J = 7.5 Hz, 2H), 2.80 (t, J = 7.5 Hz, 3H), 2.63 (br s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.9, 152.4, 146.3 , 128.1, 125.0 , 124.9, 119.9, 112.8, 64.4, 55.6, 49.2, 33.6; TOF-HRMS calcd for $C_{13}H_{17}IN_3O$ $(M+H)^+$ 358.0416, found 358.0419.

2-(4-(2-Iodoethyl)piperazin-1-yl)-5,7-dinitrobenzo[*d*]oxazole (**2bm**). Yellow oil; (0.2870 g, 87% yield); R_f 0.28 (30% EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 3.95 (br s, 4H), 3.25 (t, J = 7.5 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H), 2.70 (t, J = 5.0 Hz, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.8 , 149.1, 144.4, 138.1, 132.2, 116.4, 107.0, 58.7, 50.2, 29.5; TOF-HRMS calcd for $C_{13}H_{14}IN_5NaO_5$ $(M+Na)^+$ 469.9937, found 469.9935.

5-Chloro-2-(4-(2-iodoethyl)piperazin-1-yl)benzo[*d*]oxazole (**2em**). Pale yellow solid; (0.2253 g, 78% yield); mp 109-110 °C; R_f 0.31 (30% EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.98 (dd, J = 8.4, 2.0 Hz, 1H), 3.72 (t, J = 5.0 Hz, 4H), 3.23 (t, J = 8.0 Hz, 2H), 2.79 (t, J = 8.0 Hz, 2H), 2.62 (t, J = 5.0 Hz, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.0, 145.6, 142.7, 127.6, 118.7, 114.6, 107.5, 58.7, 49.9, 43.7; TOF-HRMS calcd for $C_{13}H_{16}{}^{37}ClIN_3O$ $(M+H)^+$ 393.9997, found 393.9993, for $C_{13}H_{16}{}^{35}ClIN_3O$ $(M+H)^+$ 392.0027, found 392.0024.

Gram-scale synthesis of 5-Chloro-2-(4-(2-iodoethyl)piperazin-1-yl)benzo[d]oxazole (2em)

To a solution of iodine (2.80 g, 11.1 mmol) in freshly distilled dichloromethane (25 mL) was added triphenylphosphine (2.88 g, 11.1 mmol) at 0 °C under N_2. After that, DABCO (0.9961 g, 8.8 mmol) and triethylamine (3.00 mL, 22.2 mmol) were sequentially added, followed by the addition of chlorzoxazone (**1e**, 1.2540 g, 7.4 mmol). The mixture was stirred at 0 °C for 5 min before warming up to room temperature. After completion of the reaction, the reaction was filtered and washed with ethyl acetate. The concentrated crude product was then purified

by CC on silica gel (0-30% ethyl acetate/hexane) to afford 5-chloro-2-(4-(2-iodoethyl)piperazin-1-yl)benzo[d]oxazole (**2em**, 2.0267 g, 70% yield) as a pale yellow solid.

2-(4-(2-Iodoethyl)piperazin-1-yl)-5-methylbenzo[*d*]oxazol (**2gm**). Pale yellow solid; (0.1957 g, 71% yield); mp 110-112 °C; R_f 0.33 (30% EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 1.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.5 Hz, 1H), 3.71 (t, *J* = 5.0 Hz, 4H), 3.24 (t, *J* = 8.0 Hz, 2H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.62 (t, *J* = 5.0 Hz, 4H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.5, 145.1, 141.3, 131.9, 119.6, 114.9, 106.3, 58.7, 50.0, 43.7, 19.7; TOF-HRMS calcd for $C_{14}H_{19}IN_3O$ $(M+H)^+$ 372.0573, found 372.0572.

2-(4-(2-iodoethyl)piperazin-1-yl)-5-methoxybenzo[*d*]oxazole (**2hm**). White solid; (0.1042 g, 69% yield); mp 105 -106 °C; R_f 0.38 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.59 (dd, *J* = 8.6, 2.4 Hz, 1H), 3.81 (s, 3H), 3.73 (t, *J* = 5.0 Hz, 4H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 5.0 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.8, 157.1, 144.0, 143.3, 108.6, 107.3, 101.4, 60.5, 55.9, 51.8, 45.4; TOF-HRMS calcd for $C_{14}H_{19}IN_3O_2$ $(M+H)^+$ 388.0522, found 388.0521.

2-(4-(2-Iodoethyl)piperazin-1-yl)benzo[*d*]thiazole (**2im**). Pale purple solid; (0.1993 g, 72% yield); mp 159-160 °C; R_f 0.32 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 5.5 Hz,, 4H), 3.22 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 5.5 Hz,, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.8, 150.8, 128.9, 124.2, 119.6, 118.9, 117.3, 58.6, 50.0, 46.4; TOF-HRMS calcd for $C_{13}H_{17}IN_3S$ $(M+H)^+$ 374.0188, found 374.0185.

5-Chloro-2-(4-(2-iodoethyl)piperazin-1-yl)benzo[*d*]thiazole (**2jm**). Pale yellow solid; (0.2294 g, 76% yield); mp 133-135 °C; R_f 0.35 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.0 Hz, 1H),

3.65 (t, J = 5.0 Hz, 4H), 3.23 (t, J = 7.5 Hz, 2H), 2.79 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 5.0 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 167.8, 152.0, 130.1, 127.2, 119.8, 119.5, 117.3, 58.6, 50.0, 46.5; TOF-HRMS calcd for $C_{13}H_{16}{}^{37}ClN_3S$ $(M+H)^+$ 409.9768, found 409.9763, for $C_{13}H_{16}{}^{35}Cl\ N_3S$ $(M+H)^+$ 407.9798, found 407.9796.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: Copies of ^{1}H NMR and ^{13}C NMR spectra for all products.

AUTHOR INFORMATION

Corresponding Author

*E-mail: wongp2577@gmail.com. Phone: +66 877286472. Fax: (+) 66-53-892277.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

Financial support from The Thailand Research Fund through the Royal Golden Jubilee Ph.D. Program to D.Y (Grant No. PHD/0023/2559) and N.W. (Grant No. PHD/0072/2559) is gratefully acknowledged. This work is also partially supported by Chiang Mai University, Thailand. Special appreciation to Chulabhorn Research Institute (CRI), Thailand for the HRMS analysis.

REFERENCES

(1) (a) Wang, Q.; Su, Y.; Li, L.; Huang, H. Transition-Metal Catalysed C-N Bond Activation. *Chem. Soc. Rev.* **2016**, *45*, 1257. (b) Xiong, B.; Zhu, L.; Feng, X.; Lei, J.; Chen, T.; Zhou, Y.; Han, L.-B.; Au, C.-T.; Yin, S.-F. Direct Amidation of Carboxylic Acids with Tertiary Amines. Amide Formation over Copper Catalysts through C-N Bond Cleavage. *Eur. J. Org. Chem.* **2014**, *2014*, 4244. (c) Bao, Y.-S.; Bao, Z.; Bao, A.; Baiyin, M.; Jia, M. Aminolysis of Aryl Ester Using Tertiary Amine as Amino Donor Via C-O and C-N Bond Activations. *J. Org. Chem.* **2014**, *79*, 803. (d) Bao, Y.-S.; Baiyin, M.; Bao, A.; Jia, M.; Bao, Z. Energy-Efficient Green Catalysis: Supported Gold Nanoparticle-Catalyzed Aminolysis of Esters with Inert Tertiary Amines by C-O and C-N Bond Activations. *J. Org. Chem.* **2014**, *79*, 6715. (e) Ji, J.; Liu, Z.; Liu, P.; Sun, P. Synthesis of Sulfonamides via Copper-Catalyzed Oxidative C-N Bond Cleavage of Tertiary Amines. *Org. Biomol. Chem.* **2016**, *14*, 7018. (f) Mane, R. S.; Bhanage, B. M. Palladium-Catalyzed Oxidative *N*-Dealkylation/Carbonylation of Tertiary Amines with Alkynes to α,β-Alkynylamides. *J. Org. Chem.* **2016**, *81*, 4974. (g) Ross, S. P.; Baire, B.; Hoye, T. R. Mechanistic Duality in Tertiary Amine Additions to Thermally Generated Hexadehydro-Diels-Alder Benzynes. *Org. Lett.* **2017**, *19*, 5705. (h) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. Copper-Catalyzed Oxidative Amination of Benzoxazoles via C-H and C-N Bond Activation: A New Strategy for Using Tertiary Amines as Nitrogen Group Sources. *Org. Lett.* **2011**, *13*, 522.

(2) Mariella, R. P.; Brown, K. H. Novel SNl Displacement. Reaction of Tertiary Amines with Acetic Anhydride. *Can. J. Chem.* **1971**, *49*, 3348.

(3) Cooley, J. H.; Evain, E. J. Amine Dealkylations with Acyl Chlorides. *Synthesis* **1989**, 1.

(4) (a) Voronkov, M. G.; Tsyrendorzhieva, I. P.; Rakhlin, V. I. Acyl Iodides in Organic Synthesis. Part XI. Unusual N-C Bond Cleavage in Tertiary Amines. *Russ. J. Org. Chem.* **2008**, *44*, 481. (b) Voronkov, M. G.; Tsyrendorzhieva, I. P.; Rakhlin, V. I. Acyl Iodides in Organic Synthesis. Reactions with Morpholine, Piperidine, and *N*-Hydrocarbylpiperidines. *Russ. J. Org. Chem.* **2010**, *46*, 794.

(5) (a) Reddy, N. D.; Elias, A. J.; Vij, A. *N*-Dealkylation of Aliphatic Tertiary Amines and Diamines with Cyanuric Chloride: Crystal Structure of 2,4-Dichloro-6-(*N*-Ethyl-*N*-isopropylamino)-*S*-triazine. *J. Chem. Res., Synop.* **1998**, 504. (b) Hamilton, G. L.; Backes, B. J. Dealkylative Functionalization of Tertiary Amines with Electron Deficient Heteroaryl Chlorides. *Tetrahedron Lett.* **2006**, *47*, 2229. (c) Lee, M.; Rucil, T.; Hesek, D.; Oliver, A. G.; Fisher, J. F.; Mobashery, S. Regioselective Control of the S_NAr Amination of 5-Substituted-2,4-Dichloropyrimidines Using Tertiary Amine Nucleophiles. *J. Org. Chem.* **2015**, *80*, 7757. (d) Matsumoto, K.; Hashimoto, S.; Otani, S. Acyclic Tertiary Amines as Nucleophiles in Substitution Reactions of Aromatic and Heteroaromatic Halides. *J. Chem. Soc., Chem. Commun.* **1991**, 306. (e) Koyioni, M.; Manoli, M.; Koutentis, P. A. The Reaction of DABCO with 4-Chloro-5*H*-1,2,3-dithiazoles: Synthesis and Chemistry of 4-[*N*-(2-Chloroethyl)piperazin-1-yl]-5*H*-1,2,3-dithiazoles. *J. Org. Chem.* **2016**, *81*, 615.

(6) (a) Lai, J.; Chang, L.; Yuan, G. I_2/TBHP Mediated C-N and C-H Bond Cleavage of Tertiary Amines toward Selective Synthesis of Sulfonamides and β-Arylsulfonyl Enamines: The Solvent Effect on Reaction. *Org. Lett.* **2016**, *18*, 3194. (b) Khalaf, A. I.; Alvarez, R. G.; Suckling, C. J.; Waigh, R. D. Unexpected Dealkylation During Nucleophilic Substitution: Synthesis of 2-*N,N*-Dialkylaminobenzoxazoles and Benzothiazoles. *Tetrahedron* **2000**, *56*, 8567. (c) Wang, H.-J.; Earley, W. G.; Lewis, R. M.; Srivastava, R. R.; Zych, A. J.; Jenkins, D. M.; Fairfax, D. J. An Efficient One-Pot,

Two-Step Synthesis of 4-Substituted 1-Heteroarylpiperazines under Microwave Irradiation Conditions. *Tetrahedron Lett.* **2007**, *48*, 3043.

(7) (a) Cox, C. D.; Breslin, M. J.; Whitman, D. B.; Schreier, J. D.; McGaughey, G. B.; Bogusky, M. J.; Roecker, A. J.; Mercer, S. P.; Bednar, R. A.; Lemaire, W.; Bruno, J. G.; Reiss, D. R.; Harrell, C. M.; Murphy, K. L.; Garson, S. L.; Doran, S. M.; Prueksaritanont, T.; Anderson, W. B.; Tang, C.; Roller, S.; Cabalu, T. D.; Cui, D.; Hartman, G. D.; Young, S. D.; Koblan, K. S.; Winrow, C. J.; Renger, J. J.; Coleman, P. J. Discovery of the Dual Orexin Receptor Antagonist [(7*R*)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the Treatment of Insomnia. *J. Med. Chem.* **2010**, *53*, 5320. (b) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile Derivatives: Inhibitors of Immune Complex Induced Inflammation. *J. Med. Chem.* **1988**, *31*, 1719. (c) Mizojiri, R.; Asano, M.; Tomita, D.; Banno, H.; Nii, N.; Sasaki, M.; Sumi, H.; Satoh, Y.; Yamamoto, Y.; Moriya, T.; Satomi, Y.; Maezaki, H. Discovery of Novel Selective Acetyl-CoA Carboxylase (ACC) 1 Inhibitors. *J. Med. Chem.* **2018**, *61*, 1098. (d) O'Donnell, C. J.; Rogers, B. N.; Bronk, B. S.; Bryce, D. K.; Coe, J. W.; Cook, K. K.; Duplantier, A. J.; Evrard, E.; Hajos, M.; Hoffmann, W. E.; Hurst, R. S.; Maklad, N.; Mather, R. J.; McLean, S.; Nedza, F. M.; O'Neill, B. T.; Peng, L.; Qian, W.; Rottas, M. M.; Sands, S. B.; Schmidt, A. W.; Shrikhande, A. V.; Spracklin, D. K.; Wong, D. F.; Zhang, A.; Zhang, L. Discovery of 4-(5-Methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (CP-810,123), a Novel α7 Nicotinic Acetylcholine Receptor Agonist for the Treatment of Cognitive Disorders in Schizophrenia: Synthesis, SAR Development, and in Vivo Efficacy in Cognition Models. *J. Med. Chem.* **2010**, *53*,

1222. (e) Pochetti, G.; Mitro, N.; Lavecchia, A.; Gilardi, F.; Besker, N.; Scotti, E.; Aschi, M.; Re, N.; Fracchiolla, G.; Laghezza, A.; Tortorella, P.; Montanari, R.; Novellino, E.; Mazza, F.; Crestani, M.; Loiodice, F. Structural Insight into Peroxisome Proliferator-activated Receptor γ Binding of Two Ureidofibrate-like Enantiomers by Molecular Dynamics, Cofactor Interaction Analysis, and Site-Directed Mutagenesis. *J. Med. Chem.* **2010**, *53*, 4354. (f) Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, K.; Konno, F. Benzoxazole Derivatives as Novel 5-HT3 Receptor Partial Agonists in the Gut. *J. Med. Chem.* **1998**, *41*, 3015. (g) Sleebs, B. E.; Kersten, W. J. A.; Kulasegaram, S.; Nikolakopoulos, G.; Hatzis, E.; Moss, R. M.; Parisot, J. P.; Yang, H.; Czabotar, P. E.; Fairlie, W. D.; Lee, E. F.; Adams, J. M.; Chen, L.; van Delft, M. F.; Lowes, K. N.; Wei, A.; Huang, D. C. S.; Colman, P. M.; Street, I. P.; Baell, J. B.; Watson, K.; Lessene, G. Discovery of Potent and Selective Benzothiazole Hydrazone Inhibitors of Bcl-Xl. *J. Med. Chem.* **2013**, *56*, 5514. (h) Yoshida, S.; Shiokawa, S.; Kawano, K.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. Orally Active Benzoxazole Derivative as 5-HT3 Receptor Partial Agonist for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome. *J. Med. Chem.* **2005**, *48*, 7075.

(8) (a) Uday Kumar, R.; Reddy, K. H. V.; Anil Kumar, B. S. P.; Satish, G.; Reddy, V. P.; Nageswar, Y. V. D. Metal Free Amination of 2-Chloroazoles in Aqueous Medium. *Tetrahedron Lett.* **2016**, *57*, 637. (b) Lahm, G.; Opatz, T. Unique Regioselectivity in the C(Sp^3)-H α-Alkylation of Amines: The Benzoxazole Moiety as a Removable Directing Group. *Org. Lett.* **2014**, *16*, 4201.

(9) Lester, R. P.; Bham, T.; Bousfield, T. W.; Lewis, W.; Camp, J. E. Exploring the Reactivity of 2-Trichloromethylbenzoxazoles for Access to Substituted Benzoxazoles. *J. Org. Chem.* **2016**, *81*, 12472.

(10) (a) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. Silver-Mediated Direct Amination of Benzoxazoles: Tuning the Amino Group Source from Formamides to Parent Amines. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (b) Chen, S.-C.; Li, N.; Tian, F.; Chai, N.-N.; He, M.-Y.; Chen, Q. Mild Direct Amination of Benzoxazoles Using Interpenetrating Cobalt(II)-Based Metal-Organic Framework as an Efficient Heterogeneous Catalyst. *Mol. Catal.* **2018**, *450*, 104. (c) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. Cobalt- and Manganese-Catalyzed Direct Amination of Azoles under Mild Reaction Conditions and the Mechanistic Details. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (d) Li, Y.; Liu, J.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. Nickel-Catalyzed C-H Direct Amination of Benzoxazoles with Secondary Amines. *Org. Biomol. Chem.* **2012**, *10*, 3715. (e) Li, Y.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. Copper-Catalyzed Direct Oxidative C-H Amination of Benzoxazoles with Formamides or Secondary Amines under Mild Conditions. *J. Org. Chem.* **2011**, *76*, 5444. (f) Singh, H.; Pal, P.; Sen, C.; Panda, A. B.; Ghosh, S. C. Heterogeneous Cu-MnO-Catalyzed Direct C-H Amination of Azoles Using O_2 as the Sole Oxidant. *Asian J. Org. Chem.* **2017**, *6*, 702.

(11) (a) Carpenter, R. D.; Kurth, M. J. A Rapid and Efficient Route to Benzazole Heterocycles. *Nat. Protoc.* **2010**, *5*, 1731. (b) Zhang, X.; Jia, X.; Wang, J.; Fan, X. An Economically and Environmentally Sustainable Synthesis of 2-Aminobenzothiazoles and 2-Aminobenzoxazoles Promoted by Water. *Green Chem.* **2011**, *13*, 413. (c) Murata, Y.; Matsumoto, N.; Miyata, M.; Kitamura, Y.; Kakusawa, N.; Matsumura, M.; Yasuike, S. One-Pot Reaction for the Synthesis of *N*-Substituted 2-Aminobenzoxazoles Using Triphenylbismuth Dichloride as Cyclodesulfurization Reagent. *J. Organomet. Chem.* **2018**, *859*, 18. (d) Yadav, V. K.; Srivastava, V. P.; Yadav, L. D. S. Iodide Catalyzed Synthesis of 2-Aminobenzoxazoles via Oxidative Cyclodesulfurization of Phenolic Thioureas with Hydrogen Peroxide. *Tetrahedron Lett.* **2018**, *59*, 252. (e)

Phakhodee, W.; Duangkamol, C.; Wiriya, N.; Pattarawarapan, M. Ultrasound-Assisted Synthesis of Substituted 2-Aminobenzimidazoles, 2-Aminobenzoxazoles, and Related Heterocycles. *Tetrahedron Lett.* **2016**, *57*, 5290. (f) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. Desulfurization Mediated by Hypervalent Iodine(III): A Novel Strategy for the Construction of Heterocycles. *Eur. J. Org. Chem.* **2008**, 6189.

(12) Liu, B.; Yin, M.; Gao, H.; Wu, W.; Jiang, H. Synthesis of 2-Aminobenzoxazoles and 3-Aminobenzoxazines via Palladium-Catalyzed Aerobic Oxidation of *O*-Aminophenols with Isocyanides. *J. Org. Chem.* **2013**, *78*, 3009.

(13) (a) Liu, M.; Zeng, M.-T.; Xu, W.; Wu, L.; Dong, Z.-B. Selective Synthesis of 2-Aminobenzoxazoles and 2-Mercaptobenzoxazoles by Using *O*-Aminophenols as Starting Material. *Tetrahedron Lett.* **2017**, *58*, 4352. (b) Guntreddi, T.; Allam, B. K.; Singh, K. N. Utilization of Carbon Disulfide as a Powerful Building Block for the Synthesis of 2-Aminobenzoxazoles. *RSC Adv.* **2013**, *3*, 9875.

(14) Tankam, T.; Srisa, J.; Sukwattanasinitt, M.; Wacharasindhu, S. Microwave-Enhanced on-Water Amination of 2-Mercaptobenzoxazoles to Prepare 2-Aminobenzoxazoles. *J. Org. Chem.* **2018**, *83*, 11936.

(15) (a) Singh, V.; Singh, A.; Singh, G.; Verma, R. K.; Mall, R. Novel Benzoxazole Derivatives Featuring Rhodanine and Analogs as Antihyperglycemic Agents: Synthesis, Molecular Docking, and Biological Studies. *Med. Chem. Res.* **2018**, *27*, 735. (b) Yan, S.; Zhang, C.; Wang, Y.-H.; Cao, Z.; Zheng, Z.; Hu, X.-P. Synthesis of New Chiral Ferrocenyl P,N-Ligands with a Benzoxazole Ring and Their Application in Ag-Catalyzed Asymmetric [3+2] Cycloaddition. *Tetrahedron Lett.* **2013**, *54*, 3669. (c) Ouyang, L.; Huang, Y.; Zhao, Y.; He, G.; Xie, Y.; Liu, J.; He, J.; Liu, B.; Wei, Y. Preparation, Antibacterial Evaluation and Preliminary Structure-Activity Relationship

(SAR) Study of Benzothiazol- and Benzoxazol-2-Amine Derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3044.

(16) Phakhodee, W.; Wangngae, S.; Pattarawarapan, M. Metal-Free Amidation of Carboxylic Acids with Tertiary Amines. *RSC Adv.* **2016**, *6*, 60287.

(17) Uchibori, Y.; Umeno, M.; Yoshioka, H. Nucleophilic Fluorination of Chlorinated *N*-Heterocycles with Tetrabutylphosphonium Hydrogen Difluoride and Dihydrogen Trifluoride. *Heterocycles* **1992**, *34*, 1507.

(18) Ross, S. D.; Finkelstein, M. Nucleophilic Displacement Reactions in Aromatic Systems. VII. The Ortho-Para Ratio in the Reactions of Nitrochlorobenzenes with Piperidine and with 1,4-Diazabicyclo[2.2.2]octane. *J. Am. Chem. Soc.* **1963**, *85*, 2603.

(19) Monge, A.; Pena, M. d. C.; Palop, J. A.; Caldero, J. M.; Roca, J.; Garcia, E.; Romero, G.; del Rio, J.; Lasheras, B. Synthesis of 2-Piperazinylbenzothiazole and 2-Piperazinylbenzoxazole Derivatives with 5-HT3 Antagonist and 5-HT4 Agonist Properties. *J. Med. Chem.* **1994**, *37*, 1320.

(20) (a) Wang, H.-J.; Wang, Y.; Csakai, A. J.; Earley, W. G.; Herr, R. J. Efficient *N*-Arylation/Dealkylation of Electron Deficient Heteroaryl Chlorides and Bicyclic Tertiary Amines under Microwave Irradiation. *J. Comb. Chem.* **2009**, *11*, 355. (b) Zhu, Q.; Yuan, Q.; Chen, M.; Guo, M.; Huang, H. Multicomponent Reactions with Cyclic Tertiary Amines Enabled by Facile C-N Bond Cleavage. *Angew. Chem., Int. Ed.* **2017**, *56*, 5101.

(21) (a) Liu, J.; Robins, M. J. S_NAr Displacements with 6-(Fluoro, Chloro, Bromo, Iodo, and Alkylsulfonyl)purine Nucleosides: Synthesis, Kinetics, and Mechanism. *J. Am. Chem. Soc.* **2007**, *129*, 5962. (b) Wan, Z.-K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. The Scope and Mechanism of Phosphonium-Mediated S_NAr Reactions in Heterocyclic Amides and Ureas. *J. Org. Chem.* **2007**, *72*, 10194.

(22) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Kida, H.; Sakamoto, T. The Optimization for Cyclization Reaction of 2-(2-Carbomethoxyethynyl)aniline Derivatives and Formal Synthesis of Pyrroloquinoline Quinone and Its Analogue Utilizing a Sequential Coupling-Cyclization Reaction. *Tetrahedron* **2005**, *61*, 12330.

(23) Hare, A. A.; Leng, L.; Gandavadi, S.; Du, X.; Cournia, Z.; Bucala, R.; Jorgensen, W. L. Optimization of *N*-Benzylbenzoxazol-2-ones as Receptor Antagonists of Macrophage Migration Inhibitory Factor (MIF). *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5811.

(24) Lamani, M.; Prabhu, K. R. Iodine-Catalyzed Amination of Benzoxazoles: A Metal-Free Route to 2-Aminobenzoxazoles under Mild Conditions. *J. Org. Chem.* **2011**, *76*, 7938.

(25) Hedidi, M.; Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Dorcet, V.; Chevallier, F.; Picot, L.; Thiery, V.; Mongin, F. Synthesis of C,N'-Linked Bis-Heterocycles Using a Deprotometalation-Iodination-*N*-Arylation Sequence and Evaluation of Their Antiproliferative Activity in Melanoma Cells. *Bioorg. Med. Chem.* **2014**, *22*, 3498.

(26) Simov, D.; Davidkov, K. Synthesis and IR Spectra of Some 2-Aminobenzoxazole Derivatives. *Khim. Geterotsikl. Soedin.* **1981**, 604.

(27) Ohno, K.; Ishida, W.; Kamata, K.; Oda, K.; Machida, M. Synthesis of 2-Dimethylaminobenzazoles via a Guanidine Intermediate. Reaction of 2-Substituted Aniline Derivatives with 2-Chloro-1,1,3,3-tetramethylformamidinium Chloride. *Heterocycles* **2003**, *59*, 317.

(28) Manolikakes, G.; Gavryushin, A.; Knochel, P. An Efficient Silane-Promoted Nickel-Catalyzed Amination of Aryl and Heteroaryl Chlorides. *J. Org. Chem.* **2008**, *73*, 1429.