รายงานวิจัยฉบับสมบูรณ์

โครงการ

การสังเคราะห์ 1,3-Azoles และอนุพันธ์เฮทเทอโรไซเคิล โดยใช้เบสและไอโอดีนเป็นตัวกลางในการเปลี่ยนพันธะคาร์บอน-ไฮโดรเจนเป็นพันธะคาร์บอน-เฮทเทอโรอะตอม

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เดือน มิถุนายน ปี 2557

สัญญาเลขที่ MRG5580039

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ผู้วิจัย

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ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

สนับสนุนโดยสำนักงานคณะกรรมการการอุดมศึกษา
และสำนักงานกองทุนสนับสนุนการวิจัยและมหาวิทยาลัยมหิดล

กิตติกรรมประกาศ

ผู้วิจัย ดร.ศิริลตา ยศแผ่น ขอขอบคุณทุนพัฒนาศักยภาพในการทำวิจัยของอาจารย์รุ่นใหม่ ปี 2555 จากสำนักงานกองทุนสนับสนุนการวิจัย (สกว) ร่วมกับสำนักงานคณะกรรมการการอุดมศึกษา (สกอ) และมหาวิทยาลัยมหิดลสำหรับเงินทุนสนับสนุนการวิจัยในโครงการนี้

รหัสโครงการ: MRG5580039

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นักวิจัย: อ.ดร.ศิริลตา ยศแผ่น ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

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ระยะเวลาโครงการ: 2 กรกฎาคม 2555 – 1 กรกฎาคม 2557

Abstract

Many 2-Aminoazoles and their derivatives possess important biological and pharmaceutical properties. They are employed widely in medicinal chemistry, particularly in the treatment of brain diseases. In this research, two practical protocols for the synthesis of N-substituted 2-aminoazole derivatives are described. The first method is employing simple azole substrates, nitrogen nucleophiles, lithium *tert*-butoxide as the base, and iodine to mediate carbon–nitrogen bond formation. Another method is to employ CuCl catalyst, PPh_3 ligand, and Li*O*t*B*u base in the electrophilic amination reaction of benzoxazoles with O-benzoyl hydroxylamines. These two methods proceed at room temperature under an air atmosphere using a normal benchtop set-up, and enable the convenient preparation of various 2-aminobenzoxazole derivatives in good yields.

Keywords azole, 2-aminoazole, iodine, copper catalysis

บทคัดย่อ

สารอนุพันธ์ของ azole ที่มีหมู่ไนโตรเจนแทนที่ที่ตำแหน่งที่ C-2 (2-aminoazole) เป็นสารที่ออกฤทธิ์ทางชีวภาพ และมีการนำมาใช้ในการรักษาโรคเกี่ยวกับสมอง งานวิจัยนี้ได้ศึกษาและพัฒนาการสังเคราะห์สารในกลุ่มนี้โดยวิธีที่ง่ายๆ ทำได้สะดวกและมีประสิทธิภาพ 2 วิธีคือ วิธีที่ใช้ azole, เอมีน,เบส, ไอโอดีนที่อุณหภูมิและความดันปกติ และอีกวิธีคือการสังเคราะห์ด้วยปฏิกิริยาที่ใช้โลหะทองแดงเป็นตัวเร่งปฏิกิริยาอิเลกโทรฟิลิคแอมมิเนชั่นจากสารตั้งต้น benzoxazole และ *O*-benzoyl hydroxylamine โดยใช้ lithium *tert*-butoxide เบส วิธีการสังเคราะห์ทั้งสองวิธีนี้การสังเคราะห์นี้สามารถให้อนุพันธ์ของ benzoxazole หลายๆชนิดในปริมาณที่มากอย่างสะดวกและมีประสิทธิภาพ

คำหลัก:สาร azole, สาร 2-aminoazole, ไอโอดีน, การเร่งปฏิกิริยาโดยโลหะทองแดง

Executive Summary

รหัสโครงการ: MRG5580039
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นักวิจัย: อ.ดร.ศิริลตา ยศแผ่น ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล
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ระยะเวลาโครงการ: 2 กรกฎาคม 2555 – 1 กรกฎาคม 2557

บทนำ

Azole และสารอนุพันธ์ เป็นสารอินทรีย์ที่พบมากในสารสกัดจากธรรมชาติที่มีฤทธิ์ทางชีวภาพ และเป็นสารที่ใช้อย่างแพร่หลายในทางการแพทย์ ชีววิทยา เภสัชวิทยา (Figure 1)[1] โดยปกติแล้วการสังเคราะห์สารประเภทนี้สามารถทำได้จากปฏิกิริยา condensation ซึ่งต้องใช้อุณหภูมิที่ค่อนข้างสูง ใช้สารในปริมาณมาก มีกระบวนการการสังเคราะห์ที่ยุ่งยากหลายขั้นตอน มีข้อจำกัดมากมายทั้งกับหมู่ฟังก์ชั่นและโครงสร้างที่เฉพาะเจาะจงของสารตั้งต้น[2] นักวิจัยทางเคมีอินทรีย์จึงพยายามที่จะศึกษาค้นคว้าและพัฒนาวิธีต่างๆ สำหรับการสังเคราะห์สารอย่างมีประสิทธิภาพ โดยเฉพาะอย่างยิ่งกระบวนการสังเคราะห์ที่สามารถทำได้สะดวกที่อุณหภูมิและความดันปกติและไม่เป็นอันตรายต่อสิ่งแวดล้อม และการสังเคราะห์โดยใช้ตัวเร่งปฏิกิริยาจึงเริ่มเข้ามามีบทบาทมากขึ้นในระยะเวลาประมาณ 10 ปีที่ผ่านมานี้[3]

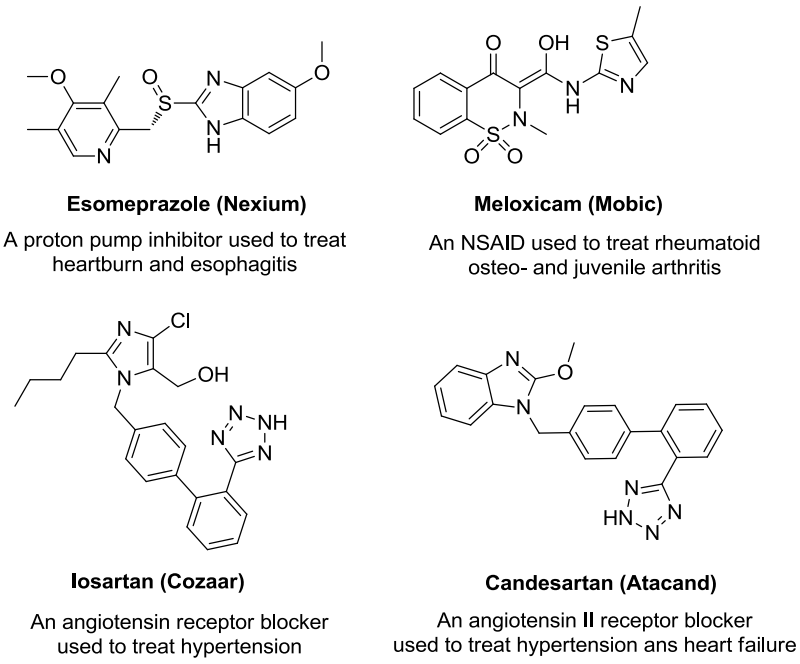
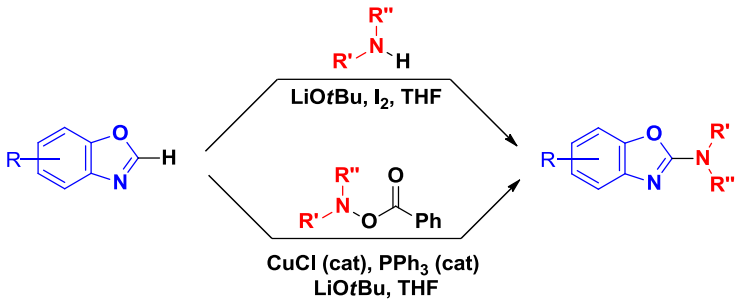


Figure 1: Examples of C-2 Substituted 1,3-Azole Compounds Used as Drugs.

งานวิจัยนี้ได้ศึกษาและพัฒนากระบวนการสังเคราะห์ azole โดยเฉพาะอย่างยิ่งสารในกลุ่ม 2-aminozole ซึ่งเป็นสารอนุพันธ์ของ azole ที่มีหมู่ไนโตรเจนแทนที่ที่ตำแหน่งที่ C-2 เนื่องจากสารพวกนี้เป็นสารที่ออกฤทธิ์ทางชีวภาพ และมีการนำมาใช้ในการรักษาโรคเกี่ยวกับสมอง[4]

ดังนั้นวัตถุประสงค์ของงานวิจัยนี้คือ

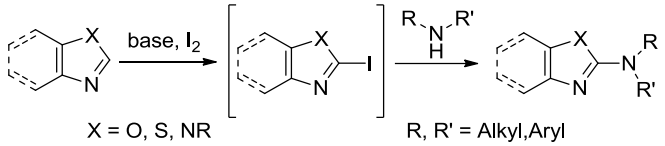
ศึกษาวิธีการสังเคราะห์ การสังเคราะห์ 1,3-Azoles และอนุพันธ์เฮทเทอโรไซเคิล ด้วยวิธี I_2-mediated Reaction และ วิธีการเร่งปฏิกิริยาโดยใช้โลหะตัวเร่ง



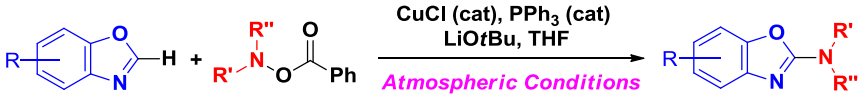
วิธีการทดลอง

งานวิจัยชิ้นนี้มีวัตถุประสงค์เพื่อศึกษาและพัฒนาการสังเคราะห์ N-substituted-2-amino-1,3-azoles ซึ่งเป็นสารที่ออกฤทธิ์ทางชีวภาพและใช้ในการศึกษาค้นคว้าเกี่ยวกับยารักษาโรคทางการแพทย์อย่างแพร่หลาย การดำเนินงานวิจัยแบ่งออกเป็น 2 ส่วนใหญ่ๆ คือ

(1) การสังเคราะห์ N-substituted-2-amino-1,3-azoles โดยใช้เบสและไอโอดีนเป็นตัวกลางในการเปลี่ยนพันธะในปฏิกิริยา



(2) การพัฒนาการสังเคราะห์ N-substituted-2-amino-1,3-azoles โดยใช้ตัวเร่งปฏิกิริยา



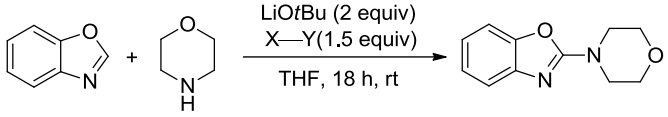
ซึ่งทั้งสองวิธีได้มีการศึกษาปฏิกิริยาและผลกระทบของตัวแปรต่างๆที่มีผลต่อปฏิกิริยา เช่น อุณหภูมิ ตัวทำละลาย เบส ตัวเร่ง และอื่นๆ ที่จำเป็นต่อปฏิกิริยา ว่าจะมีผลมากน้อยเพียงใด ซึ่งได้ใช้เทคนิคทาง GC, NMR analysis และนอกจากนั้นยังได้ประเมินขอบเขตและข้อจำกัดของปฏิกิริยา

โดยเฉพาะอย่างยิ่งการเปลี่ยนแปลงโครงสร้างของสารตั้งต้น โดยจะมีการพิสูจน์เอกลักษณ์ของสารด้วยเทคนิคทาง Nuclear Magnetic Resonance Spectroscopy (NMR), Infrared Spectroscopy (IR) และ Mass Spectroscopy (MS) สารที่สังเคราะห์ทุกตัวได้นำไปเปรียบเทียบกับข้อมูลรายงานทาง Literature ที่เกี่ยวข้อง

ผลการทดลอง

1. การสังเคราะห์ N-substituted-2-amino-1,3-azoles โดยใช้เบสและไอโอดีนเป็นตัวกลางในการเปลี่ยนพันธะในปฏิกิริยา

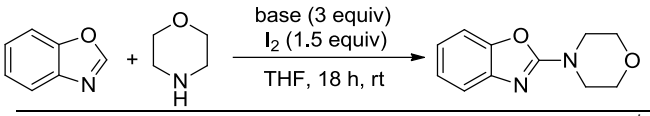
1.1 การศึกษาหาสภาวะที่เหมาะสมของปฏิกิริยา



Halogenating reagent (X—Y)	Isolated yield(%)
NCS	9
NBS	32
NIS	67
Br_2	60
I_2	89
None	0

Scheme 1. Effect of Halogenating Reagent.

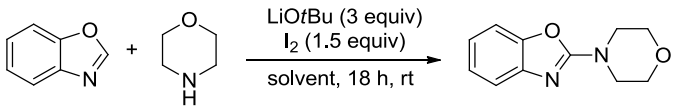
Table 1. Effect of inorganic bases.[a]



Entry	Base	Equiv	% Yield[b]
1	-	0	5
2	LiO*t*Bu	1	34
3	LiO*t*Bu	2	89
4	**LiO*t*Bu**	**3**	**100**
5	NaO*t*Bu	3	34
6	KO*t*Bu	3	19
7	KOMe	3	12
8	NaOH	3	15
9	Na_2CO_3	3	5
10	K_2CO_3	3	7
11	K_3PO_4	3	25
12	NaOAc	3	9

[a] Conditions: benzoxazole substrate (0.5 mmol; 1 equiv), base (0 —3 equiv), I_2 (1.5 equiv), THF (0.5 M. of benzoxazole substrate), morpholine (5 equiv, adding at t = 10 min), rt.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

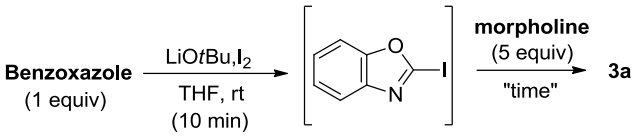
Table 2. Effect of solvents and concentrations.[a]



Entry	Solvent	Concentration (M)	% Yield[b]
1	**THF**	**0.5**	**100**
2	Dioxane	0.5	39
3	Et_2O	0.5	62
4	DMF	0.5	52
5	EtOAc	0.5	10
6	DCM	0.5	18
7	Toluene	0.5	13
8	Hexanes	0.5	9
9	THF	1	100
10	THF	0.2	100
11	THF	0.1	73

[a] Conditions: benzoxazole substrate (0.5 mmol; 1 equiv), LiO*t*Bu (3 equiv), I_2 (1.5 equiv), morpholine (5 equiv, adding at t = 10 min), rt.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

Table 3. Optimization studies: monitoring reaction time

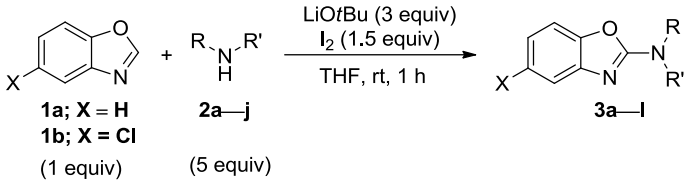


Entry	Reaction time after adding morphoine **2a**	% Yield[b]
1	1 min	55
2	5 min	90
3	10 min	95
4	30 min	98
5	1 h	100
6	1 h	31[c]
7	2 h	100
8	18 h	100

[a] Conditions: benzoxazole (0.5 mmol; 1 equiv), LiO*t*Bu (3 equiv), I_2 (1.5 equiv), THF (0.5 M. of benzoxazole substrate), morpholine (5 equiv, adding at t = 10 min), rt.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.
[c] Adding morpholine at t = 0 min.

1.2 การศึกษาหาขอบเขตและข้อจำกัดของปฏิกิริยา

Table 4. One-pot synthesis of 2-aminobenzoxazole derivatives.[a]

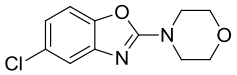
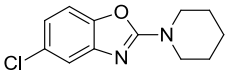


1a; X = H
1b; X = Cl
(1 equiv)

2a—j
(5 equiv)

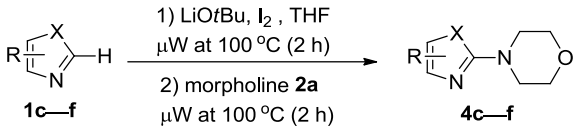
3a—l

Entry	Azole	Amine	Product	%Yield[b]
1		**2a**	**3a**	98
2		**2 b**	**3b**	87
3		**2c**	**3c**	80
4		**2d**	**3d**	92
5	**1a**	**2e**	**3e**	94
6		**2f**	**3f**	93
7		**2g**	**3g**	83
8		**2h**	**3h**	61
9		**2i**	**3i**	45
10		**2j**	**3j**	66

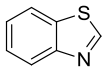
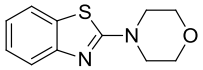
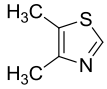
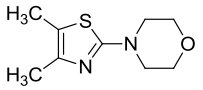
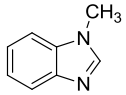
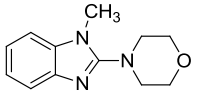
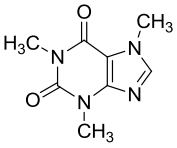
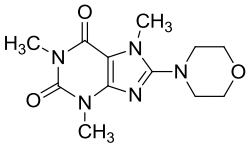
11	**1b**	 **2a**	 **3k**	64
12		 **2b**	 **3l**	65

[a] Benzozazole substrate (2 mmol), amines **2a—j** (5 equiv, adding t = 10 min), THF (0.5 M. of benzoxazole substrate). [b] Isolated yields are reported.

Table 5. Microwave synthesis of *N*-substituted 2-aminoazoles. [a]



1c—f (1 equiv) → **4c—f**

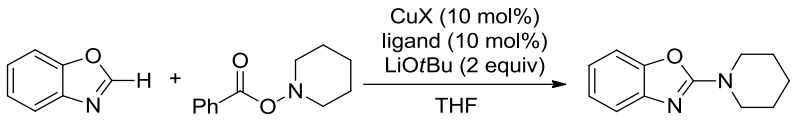
Entry	Azole	Product	% Yield[b]
1	 **1c**	 **4c**	54
2	 **1d**	 **4d**	10
3	 **1e**	 **4e**	33
4	 **1f**	 **4f**	19(31[c])

[a]Conditions: azole substrates **1c—f** (2 mmol; 1 equiv), LiO*t*Bu (3 equiv), I_2 (1.5 equiv), morpholine **2a** (5 equiv), THF (0.5 M of azole substrate). [b] Isolated yields are reported. [c] μW at 140 °C in DMF solvent

2. การพัฒนาการสังเคราะห์ N-substituted-2-amino-1,3-azoles โดยใช้ตัวเร่งปฏิกิริยา

2.1 การศึกษาหาสภาวะที่เหมาะสมของปฏิกิริยา

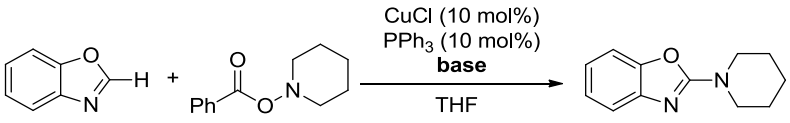
Table 6. Effect of Copper Source and Ligand.[a]



entry	copper salt	ligand	yield (%)[b]
1	CuI	PPh_3	55
2	CuBr	PPh_3	40
3	**CuCl**	**PPh_3**	**60**
4	$CuBr_2$	PPh_3	17
5	$CuCl_2$	PPh_3	58
6	$Cu(OAc)_2$	PPh_3	50
7	$Cu(OTf)_2$	PPh_3	50
8	-	-	0
9	-	PPh_3	0
10	CuCl	-	31
11	CuCl	phen	36
12	CuCl	bipy	21

[a]Conditions: benzoxazole (0.5 mmol, 1 equiv), *O*-benzoyl hydroxylamine (1.5 equiv), CuX (10 mol%), ligand (10 mol%), LiO*t*Bu (2 equiv), THF (2 mL), rt, 1 h. [b]Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

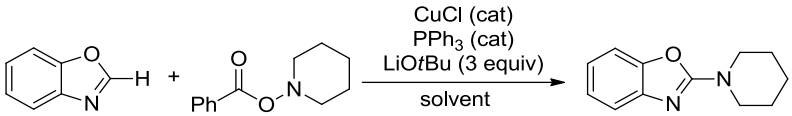
Table 7. Effect of Inorganic Base.[a]



entry	base	equiv	yield (%)[b]
1	-	-	0
2	LiO*t*Bu	2	60
3	NaO*t*Bu	2	19
4	KO*t*Bu	2	0
5	NaOH	2	0
6	K_3PO_4	2	< 2
7	Cs_2CO_3	2	< 2
8	NaOAc	2	0
9	LiO*t*Bu	1	49
10	**LiO*t*Bu**	**3**	**80**

[a]Conditions: benzoxazole (0.5 mmol, 1 equiv), *O*-Benzoyl hydroxylamine (1.5 equiv), CuCl (10 mol%), PPh_3 (10 mol%), base (1—3 equiv), THF (2 mL), rt, 1 h. [b]Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

Table 8. Optimization of Reaction Conditions.[a]

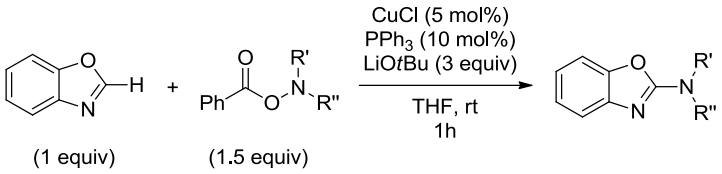


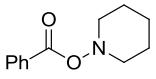
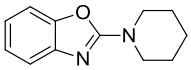
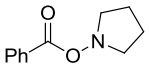
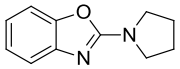
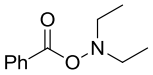
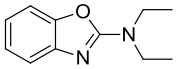
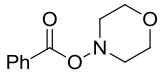
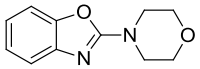
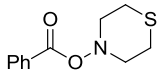
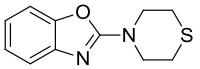
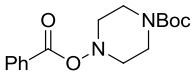
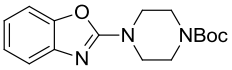
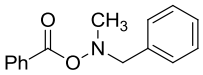
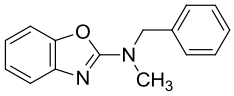
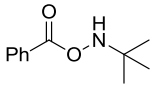
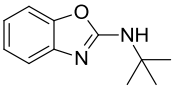
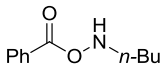
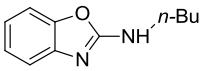
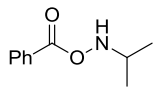
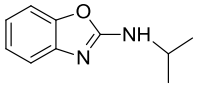
entry	CuCl (mol%)	PPh_3 (mol%)	solvent	yield (%)[b]
1	10	10	THF	80
2	20	20	THF	68
3	5	5	THF	88
4	2	2	THF	62
5	**5**	**10**	**THF**	**95**
6	5	10	toluene	83
7	5	10	dioxane	81
8	5	10	acetonitrile	72
9	5	10	DMF	21
10	5	10	DMSO	18

[a]Conditions: benzoxazole (0.5 mmol, 1 equiv), *O*-Benzoyl hydroxylamine (1.5 equiv), CuCl (cat), PPh_3 (cat), LiO*t*Bu (3 equiv), solvent (2 mL), rt, 1 h. [b]Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

2.2 การศึกษาหาขอบเขตและข้อจำกัดของปฏิกิริยา

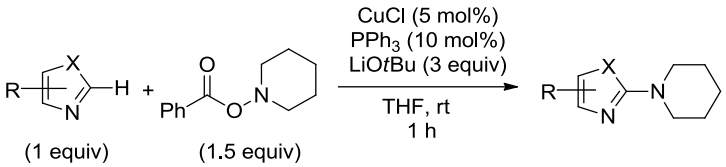
Table 9. Copper-Catalyzed Electrophilic Amination of Benzoxazole with Various *O*-Benzoyl Hydroxylamines.[a]

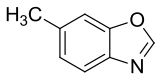
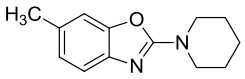
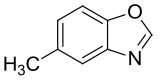
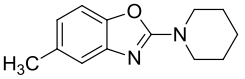
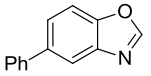
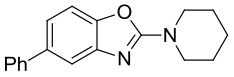
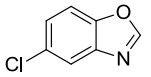
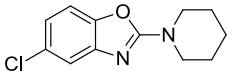
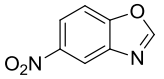
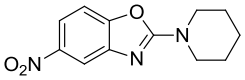
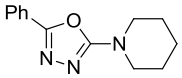
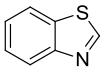
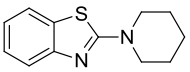
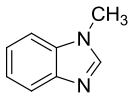
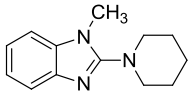


entry	*O*-benzoyl hydroxylamine	product	yield (%)[b]
1			91
2			40
3			74
4			54
5			45
6			50
7			75
8			16
9			<5[c]
10			0

[a]Conditions: benzoxazole (1 mmol, 1 equiv), *O*-benzoyl hydroxyamine (1.5 equiv), CuCl (5 mol%), PPh_3 (10 mol%), LiO*t*Bu (3 equiv), THF (4 mL), rt, 1 h. [b]Isolated yields after purification by chromatography. [c]detected by GCMS.

Table 10. Copper-Catalyzed Electrophilic Amination of Benzoxazole Derivatives with *O*-Benzoyl Hydroxylamine 2a.[a]

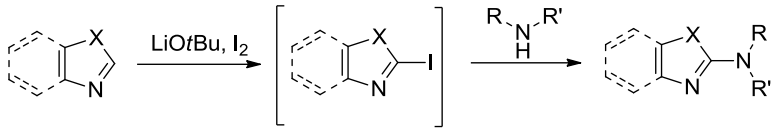


entry	azole	product	yield (%)[b]
1			86
2			73
3			90
4			66
5			61
6			72
7			0[c]
8			0[c]

[a]Conditions: benzoxazoles (1 mmol, 1 equiv), *O*-benzoyl hydroxyamine (1.5 equiv), CuCl (5 mol%), PPh_3 (10 mol%), LiO*t*Bu (3 equiv), THF (4 mL), rt, 1 h. [b]Isolated yields after purification by chromatography. [c]No reaction was detected by TLC/GCMS.

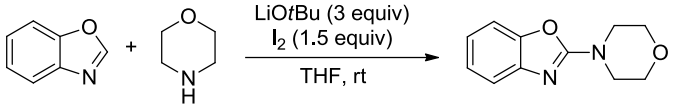
บทวิจารณ์

1. การสังเคราะห์ N-substituted-2-amino-1,3-azoles โดยใช้เบสและไอโอดีนเป็นตัวกลางในการเปลี่ยนพันธะในปฏิกิริยา

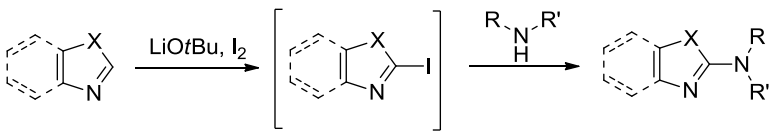


งานวิจัยในส่วนนี้ประกอบด้วยการศึกษาปัจจัยและตัวแปรต่างๆที่มีผลต่อปฏิกิริยาในการเปลี่ยนพันธะคาร์บอน-ไฮโดรเจน เป็นพันธะคาร์บอน-ไนโตรเจน (และอะตอมอื่นๆ) โดยใช้เบสและไอโอดีนเป็นตัวกลาง ซึ่งเราได้ค้นพบว่าปฏิกิริยาระหว่าง benzoxazole และเอมีน จะสามารถเกิดเป็น N-substituted-2-amino-1,3-azoles อย่างมีประสิทธิภาพ โดยใช้ ไอโอดีน และ LiO*t*Bu ซึ่งทำหน้าที่เป็นเบส ในตัวทำละลาย THF

จากผลการทดลองสภาวะที่ดีที่สุดในการสังเคราะห์ 2-N-substituted benzoxazole จาก benzoxazole และ เอมีน คือ ใช้ Benzoxazole (1 equiv), LiO*t*Bu (3 equiv), I_2 (1.5 equiv), THF (0.5 M of substrate), amine (5 equiv) กระบวนการนี้สามารถทำแบบ one-pot synthesis ภายใน 1 ชั่วโมง โดยที่ให้ใส่ amine ที่นาทีที่ 10



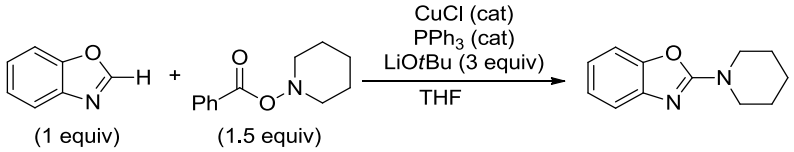
จากนั้นได้มีการทดสอบ scope ของปฏิกิริยานี้ โดยมีการทดสอบชนิดของ เอมีนทั้ง primary และ secondary พบว่าวิธีการนี้ใช้ได้กับเอมีนทั้งสองชนิด และให้ผลิตภัณฑ์ที่ต้องการในปริมาณมาก ในกรณีของ azole ตัวอื่นที่ไม่ใช่ benzoxazole พบว่าวิธีการสังเคราะห์นี้ไม่เกิดสารที่ต้องการที่อุณหภูมิปกติ มีการจึงใช้เทคโนโลยีการให้ความร้อนสารจากทาง microwave มาช่วย และพบว่า azole หลายๆชนิด สามารถเกิดปฏิกิริยานี้ได้ในปริมาณที่น่าพอใจ ซึ่งจากข้อมูลการทดลองต่างๆที่ได้รับสามารถสรุปเป็นกลไกการเกิดปฏิกิริยาได้ดังแสดง



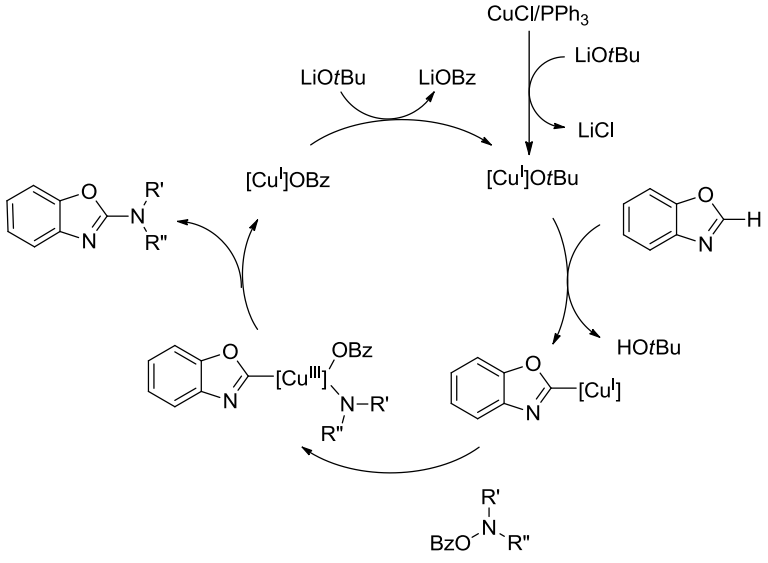
2. การพัฒนาการสังเคราะห์ N-substituted-2-amino-1,3-azoles โดยใช้ตัวเร่งปฏิกิริยา

เนื่องจากปัจจุบันนี้กระบวนการที่เกี่ยวข้องกับตัวเร่งปฏิกิริยากำลังได้รับความสนใจและนิยมอย่างมาก จึงได้นำเอาองค์ความรู้ต่างๆ ที่ได้รับจากงานในส่วนแรกมาใช้คิดค้นพัฒนาเป็นกระบวนการที่ใช้ตัวเร่งปฏิกิริยาในการสังเคราะห์อย่างมีประสิทธิภาพ โดยมีการศึกษาถึงตัวแปรและปัจจัยต่างๆที่เกี่ยวข้องกับการเร่งปฏิกิริยาและ scope รวมถึงความเป็นไปได้ในการประยุกต์ใช้ต่างๆ

โดยเริ่มจากการศึกษาปัจจัยและตัวแปรต่างๆที่มีผลต่อการสังเคราะห์ N-substituted-2-amino-1,3-azoles จาก benzoxazole และ eletrophilic nitrogen source ซึ่งสภาวะที่ดีที่สุดในการสังเคราะห์ 2-N-substituted benzoxazole จาก benzoxazole และ *O*-benzoyl hydroxylamine คือ ใช้ Benzoxazole (1 equiv), Li*O*t*B*u (3 equiv), *O*-Benzoyl hydroxylamine (1.5 equiv), THF (0.25 M of substrate), CuCl catalyst (5%), PPh_3 ligand (10%)



จากนั้นได้มีการทดสอบ scope ของปฏิกิริยานี้ โดยผลการทดลองพบว่าปฏิกิริยา Electrophilic Amination ของ benzoxazole กับ *O*-benzoyl hydroxylamine เกิดได้ดีกับ *O*-benzoyl hydroxylamine ที่มาจาก secondary amine สำหรับ primary amine จะมี yield ที่ต่ำหรือไม่เกิดปฏิกิริยา และสามารถสรุปเป็น catalytic cycle จากหลักฐานต่างๆ ทาง literature[5] ได้ดังนี้



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3. Selected references: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Ley, S. V.; Thomas, A.W. *Angew. Chem.* **2003**, *115*, 5558. (d) Ley, S. V.; Thomas, A.W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (e) Armstrong, A.; Collins, J. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 2282. (f) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (g) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (h) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178.
4. (a) Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2001**, 627. (b) Nogle, L. M.; Marquez, B. L.; Gerwick, W. H. *Org. Lett.* **2003**, *5*, 3. (c) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.
5. (a) Do, H.-Q.; Daugulis, O. *Org. Lett.* 2009, *11*, 421. (b) Popov, I.; Do, H.-Q.; Daugulis, O. *J. Org. Chem.* 2009, *74*, 8309. (c) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (e) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (f) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (g) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364. (h) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219.

Output จากโครงการวิจัยที่ได้รับทุน

1. Publications

(1.1) **Yotphan S***, Buekeaw D, Reutrakul V. A convenient one-pot synthesis of N-substituted 2-aminoazole derivatives. Synthesis. 2013;45(7):936-42.

(1.2) **Yotphan S***, Buekeaw D, Reutrakul V. Synthesis of 2-aminobenzoxazoles via copper-catalyzed electrophilic amination of benzoxazoles with *O*-benzoyl hydroxylamines. Tetrahedron. 2013;69(32):6627–33.

2. นักศึกษาที่จบการศึกษา

(2.1) นายดนุภัทร บัวแก้ว หลักสูตรวิทยาศาสตร์บัณฑิต มหาวิทยาลัยมหิดล จบการศึกษา 1 เมษายน พ.ศ. 2556

ภาคผนวก

A Convenient One-Pot Synthesis of N-Substituted 2-Aminoazole Derivatives

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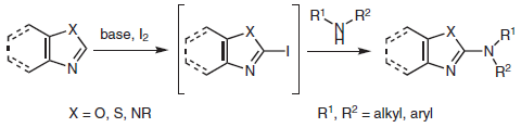
Abstract: A practical protocol for the one-pot synthesis of N-substituted 2-aminoazole derivatives is described, employing simple azole substrates, nitrogen nucleophiles, lithium *tert*-butoxide as the base, and iodine to mediate carbon–nitrogen bond formation. This method proceeds at room temperature under an air atmosphere using a normal benchtop set-up, or can be performed conveniently using microwave irradiation.

Key words: N-substituted 2-aminoazoles, iodine, one-pot synthesis, benzoxazole, carbon–nitrogen bond formation

There are a number of N-substituted 2-aminoazoles that possess biological and pharmaceutical activities, and many are employed in medicinal chemistry.[1,2] For example, 2-aminobenzoxazoles are very common scaffolds in a wide variety of therapeutic agents for the treatment of cancer,[2] central nervous system (CNS) disorders,[3] and insomnia.[4] Derivatives of 2-aminothiazoles are currently used as dopamine antagonists for early stage treatment of Parkinson's disease, and as anti-inflammatory and antibiotic agents.[5]

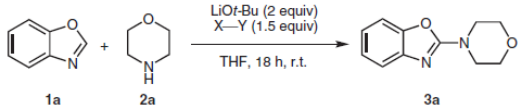
As a result of the various applications of N-substituted 2-aminoazoles in medicinal chemistry, the development of practical, convenient and efficient protocols for their preparation has been the subject of intense research effort. Classical methods for the synthesis of N-substituted 2-aminoazoles employ cyclocondensation reactions (e.g. the Hantzsch synthesis).[6] A more conventional and divergent method involves direct formation of a carbon–nitrogen (C–N) bond through a displacement reaction of 2-halo substituted azoles with amine nucleophiles.[7] However, metal-catalyzed carbon–nitrogen bond formation via cross-coupling, or carbon–hydrogen (C–H) bond functionalization methods are utilized increasingly in both industry and academia as potentially powerful and reliable approaches for the synthesis of these structural motifs.[5a,8,9] Oxidative coupling methods involving metal-free carbon–hydrogen bond functionalization and carbon–nitrogen bond formation have also been recognized as alternative and useful synthetic tools.[10]

Based on studies by Daugulis and co-workers, the in situ halogenation of acidic sp^2 C–H bonds in heterocycles and electron-deficient arenes can be achieved efficiently using an appropriate alkoxide or phosphate base, followed by halogenation of the intermediate anionic species with various halide electrophiles, for example, iodine (I_2), iodine monochloride (ICl), and carbon tetrachloride (CCl_4).[11] We have examined the synthesis of N-substituted 2-aminoazoles starting from simple azoles and nitrogen nucleophiles, by combining the in situ C-2 halogenation of azoles and subsequent nucleophilic attack of different amines on the halogenated azole intermediates into a one-pot protocol (Scheme 1).



Scheme 1 One-pot synthesis of N-substituted 2-aminoazoles

Benzoxazole (**1a**) and morpholine (**2a**) were chosen as model substrates for the optimization studies in the presence of various halogenating agents (NCS, NBS, NIS, Br_2 and I_2) (Scheme 2).[12] The reaction using iodine (1.5 equiv) as the halogenating agent in the presence of **1a** (1 mmol, 1 equiv), lithium *tert*-butoxide (2 equiv), and morpholine (**2a**) (5 equiv; added to the mixture after 10 min) in tetrahydrofuran, at room temperature under an air atmosphere, resulted in the highest isolated yield (89%) of the desired product **3a** (purified by column chromatography). Other halogenating agents (NCS, NBS, NIS and Br_2) gave lower yields under the same reaction conditions (9%, 32%, 67% and 60%, respectively). It is interesting to note that no product was obtained in the absence of the halogenating agent, which further suggested that iodine played an important role in this transformation.



Halogenating agent (X—Y)	Yield (%)
NCS	9
NBS	32
NIS	67
Br_2	60
I_2	89
none	0

Scheme 2 Effect of different halogenating agents (X–Y)

The strength of the base also proved to be important in this reaction. Upon examining the effects of various inorganic

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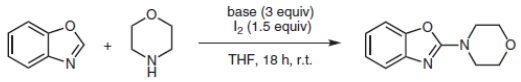
bases (Table 1), lithium *tert*-butoxide (3 equiv) was found to be the best (Table 1, entries 2–4). Other stronger bases (e.g. NaO*t*-Bu, KO*t*-Bu, KOMe and NaOH) gave significantly lower yields, probably due to decomposition of the starting benzoxazole (**1a**) (Table 1, entries 5–8). Low conversions were observed when weaker bases such as sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4) and sodium acetate (NaOAc) were employed (Table 1, entries 9–12).

Table 1 Effect of Inorganic Bases[a]



1a (1 equiv) 2a (5 equiv) 3a

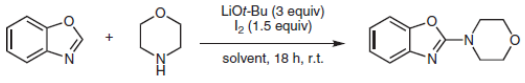
Entry	Base	Equiv	Yield (%)[b]
1	–	0	5
2	LiO*t*-Bu	1	34
3	LiO*t*-Bu	2	89
4	LiO*t*-Bu	3	100
5	NaO*t*-Bu	3	34
6	KO*t*-Bu	3	19
7	KOMe	3	12
8	NaOH	3	15
9	Na_2CO_3	3	5
10	K_2CO_3	3	7
11	K_3PO_4	3	25
12	NaOAc	3	9

[a] Reaction conditions: benzoxazole (**1a**) (0.5 mmol, 1 equiv), base (0–3 equiv), I_2 (1.5 equiv), THF (0.5 M soln of the benzoxazole substrate), morpholine (**2a**) (5 equiv; added to the mixture after 10 min), r.t.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

The effects of different solvents and concentrations were also evaluated (Table 2). Excellent conversions were obtained when tetrahydrofuran (0.2–1 M concentrations of the benzoxazole substrate) was used as the solvent (Table 2, entries 1, 9 and 10). Other polar aprotic solvents including 1,4-dioxane, diethyl ether, *N*,*N*-dimethylformamide, ethyl acetate and dichloromethane were less effective (Table 2, entries 2–6). Nonpolar solvents such as toluene and hexane gave poorer conversions compared to tetrahydrofuran (Table 2, entries 7 and 8). The addition of salts or other additives was not necessary for further optimization.

Using the optimized reaction conditions [**1a** (1 equiv), LiO*t*-Bu (3 equiv), I_2 (1.5 equiv) THF (0.5 M soln of the benzoxazole substrate), morpholine (**2a**) (5 equiv)], the progress of the reaction was monitored by GC analysis

Table 2 Effect of Solvents and Concentrations[a]



1a (1 equiv) 2a (5 equiv) 3a

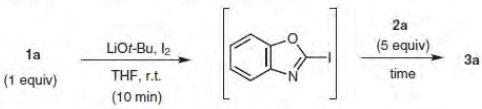
Entry	Solvent	Concn (M)	Yield (%)[b]
1	THF	0.5	100
2	1,4-dioxane	0.5	39
3	Et_2O	0.5	62
4	DMF	0.5	52
5	EtOAc	0.5	10
6	CH_2Cl_2	0.5	18
7	toluene	0.5	13
8	hexane	0.5	9
9	THF	1.0	100
10	THF	0.2	100
11	THF	0.1	73

[a] Reaction conditions: benzoxazole (**1a**) (0.5 mmol, 1 equiv), LiO*t*-Bu (3 equiv), I_2 (1.5 equiv), morpholine (**2a**) (5 equiv; added to the mixture after 10 min), r.t.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

(Table 3). This one-pot transformation was complete (≥99%) in one hour after adding morpholine (at $t = 10$ min) (Table 3, entry 5). Adding morpholine (**2a**) before ten minutes had elapsed resulted in incomplete conversion of the benzoxazole substrate into the iodide intermediate. When morpholine (**2a**) was added at the start of the reaction (t = 0 min), a much lower yield was obtained due to a competing reaction between **2a** and iodine (Table 3, entry 6). In addition, decomposition of the product was not observed under extended reaction times (Table 3, entries 7 and 8).

To test the scope of this protocol, the reactions of benzoxazoles **1a** and **1b** and different amine nucleophiles **2a–j** were examined (Table 4). The reaction proved to be general in nature, allowing the straightforward synthesis of a number of 2-aminobenzoxazole derivatives. The one-pot reactions of benzoxazole (**1a**) and secondary amines **2a–g** resulted in very high yields (80–98%) of the corresponding N-substituted 2-aminoazoles **3a–g**. Amines with sulfide (**2e**), *N*-methyl (**2f**), and *N*-*tert*-butoxycarbonyl (**2g**) groups tolerated the present synthetic conditions. The reactions of benzoxazole (**1a**) and primary amines such as cyclohexylamine (**2h**) and *N*-benzylamine (**2i**) afforded the corresponding products **3h** and **3i** in moderate yields (61% and 45% yields, respectively). Moreover, 8-aminoquinoline (**2j**), a less nucleophilic amine, is a viable substrate for this reaction, affording the desired product **3j** in

Table 3 Monitoring the Reaction Time[a]

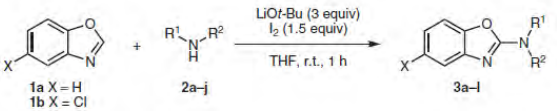


Entry	Time[b]	Yield (%)[c]
1	1 min	55
2	5 min	90
3	10 min	95
4	30 min	98
5	1 h	100
6	1 h	31[d]
7	2 h	100
8	18 h	100

[a] Reaction conditions: benzoxazole (**1a**) (0.5 mmol, 1 equiv), LiO*t*-Bu (3 equiv), I_2 (1.5 equiv), THF (0.5 M soln of the benzoxazole substrate), morpholine (**2a**) (5 equiv; added to the mixture after 10 min), r.t.
[b] Reaction time following the addition of morpholine (**2a**).
[c] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.
[d] Morpholine added at $t = 0$ min.

66% yield. Additionally, the reaction of 5-chlorobenzoxazole (**1b**) with morpholine (**2a**) and piperidine (**2b**) at room temperature afforded the expected products **3k** and **3l** in 64% and 65% yields, respectively, after one hour under the optimized reaction conditions. Hence, the presence of the chloro group at C-5 of the benzoxazole did not adversely affect the reaction.

Table 4 One-Pot Synthesis of 2-Aminobenzoxazole Derivatives[a]



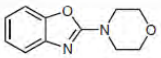
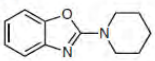
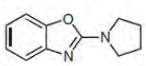
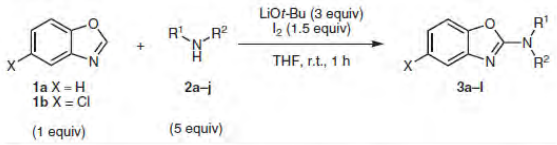
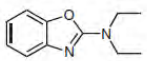
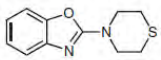
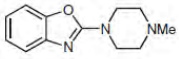
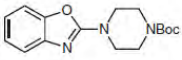
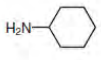
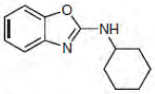
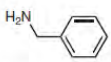
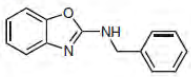
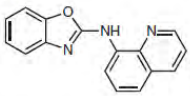
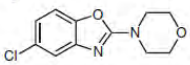
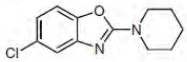
Entry	Benzoxazole	Amine	Product	Yield (%)[b]
1	**1a**	 **2a**	 **3a**	98
2	**1a**	 **2b**	 **3b**	87
3	**1a**	 **2c**	 **3c**	80

Table 4 One-Pot Synthesis of 2-Aminobenzoxazole Derivatives[a] (continued)



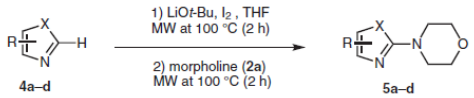
Entry	Benzoxazole	Amine	Product	Yield (%)[b]
4	**1a**	 **2d**	 **3d**	92
5	**1a**	 **2e**	 **3e**	94
6	**1a**	 **2f**	 **3f**	93
7	**1a**	 **2g**	 **3g**	83
8	**1a**	 **2h**	 **3h**	61
9	**1a**	 **2i**	 **3i**	45
10	**1a**	 **2j**	 **3j**	66
11	**1b**	 **2a**	 **3k**	64
12	**1b**	 **2b**	 **3l**	65

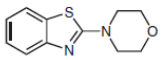
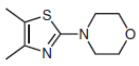
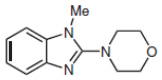
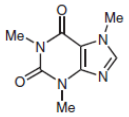
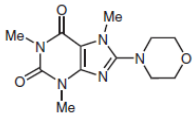
[a] Reaction conditions: benzoxazole **1** (2 mmol), LiO*t*-Bu (3 equiv), I_2 (1.5 equiv), amine **2a–j** (5 equiv; added to the mixture after 10 min), THF (0.5 M soln of the benzoxazole substrate), r.t., 1 h.
[b] Yield of isolated product.

With the less reactive thiazoles (**4a**,**b**) and imidazoles (**4c**,**d**), only a small amount of product or no reaction was observed at room temperature. This could be a result of the higher pK_a values of the C–H bonds at the C-2 positions of thiazoles and imidazoles.[13] A microwave irradiation method was therefore employed to facilitate

formation of the desired N-substituted 2-aminoazole derivatives. The corresponding products **5a–d** were obtained in moderate yields (Table 5, entries 1–4). The choice of solvent and temperature were investigated briefly; heating a mixture of benzothiazole (**4a**) and morpholine (**2a**) in tetrahydrofuran at 100 °C under microwave irradiation afforded a 54% yield of the corresponding N-substituted product **5a** (Table 5, entry 1). The N-substituted 2-aminoazole products **5b**,**c** were obtained in 10% and 33% isolated yields, respectively, via the above-mentioned approach (Table 5, entries 2 and 3). Additionally, the microwave-assisted reaction of caffeine (**4d**) and morpholine (**2a**) in *N*,*N*-dimethylformamide at 140 °C provided a 31% yield of the corresponding product **5d** (Table 5, entry 4).

Table 5 Microwave-Assisted Synthesis of N-Substituted 2-Aminoazoles[a]



Entry	Azole	Product	Yield (%)[b]
1	 **4a**	 **5a**	54
2	 **4b**	 **5b**	10
3	 **4c**	 **5c**	33
4	 **4d**	 **5d**	19 (31[c])

[a] Reaction conditions: azole **4** (2 mmol, 1 equiv), LiO*t*-Bu (3 equiv), I_2 (1.5 equiv), morpholine (**2a**) (5 equiv), THF (0.5 M soln of the azole substrate).
[b] Yield of isolated product.
[c] Yield obtained after MW irradiation at 140 °C in DMF.

In summary, we have reported an efficient protocol for the synthesis of azole derivatives bearing a nitrogen substituent at C-2, starting from simple azoles and nitrogen nucleophiles using iodine and lithium *tert*-butoxide to mediate carbon–nitrogen bond formation. This transformation can be carried out under an air atmosphere, or can be performed conveniently using microwave irradiation, demonstrating good scope and functional group tolerance. This procedure could be used as a convenient route to N-substituted 2-aminoazoles, which may show considerable potential in medicinal chemistry. Further development of an air-stable catalytic version of this reaction at ambient temperature is currently underway.

Unless otherwise specified, all reactions were carried out under an air atmosphere. All reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was dried over alumina under a nitrogen atmosphere. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2), (60 Å SiO_2, Merck Grade, 70–230 mesh). GC experiments were carried out with an Agilent 6890N GC-FID equipped with an Agilent column (HP-1, polysiloxane, 24.5 m × 0.32 mm ID × 0.17 μm). The microwave experiments were carried out using a single mode microwave reactor (CEM discover SP system). Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. IR spectra were recorded on an FT-IR Spectrum GX (Perkin Elmer), and only partial data are listed. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV-300 spectrometer in $CDCl_3$. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). High-resolution mass spectrometry was carried out at Mahidol University, Department of Chemistry Micro-Mass Facility.

Compounds 3a–l; General Procedure

To an oven-dried and N_2-flushed 20 mL scintillation vial, equipped with a magnetic stir bar, was added a mixture of benzoxazole **1** (2.00 mmol, 1.00 equiv), LiO*t*-Bu (0.48 g, 6.00 mmol, 3.00 equiv), and I_2 (0.76 g, 3.00 mmol, 1.50 equiv) in THF (4.00 mL, 0.50 M concentration of substrate). After stirring at r.t. for 10 min, amine **2** (10.0 mmol, 5.00 equiv) was added, and the mixture stirred at r.t. for an additional 1 h. Following completion of the reaction, deionized H_2O (10 mL) was added and the mixture was extracted with EtOAc (2 × 15 mL). The combined organic layer was concentrated in vacuo, and the crude residue was purified by SiO_2 column chromatography to afford the benzoxazole derivative.

2-(Morpholin-4-yl)benzoxazole (3a)[10a–e]

Compound **3a** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and morpholine (**2a**) (0.87 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3a** (0.40 g, 98%) as a yellow-orange solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 1 H), 7.30–7.28 (m, 1 H), 7.20 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.06 (dt, *J* = 7.8, 1.2 Hz, 1 H), 3.86–3.83 (m, 4 H), 3.73–3.70 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 148.7, 142.7, 124.1, 120.9, 116.4, 108.8, 66.2, 45.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.0977; found: 205.1001.

2-(Piperidin-1-yl)benzoxazole (3b)[10a–e]

Compound **3b** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and piperidine (**2b**) (0.85 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3b** (0.35 g, 87%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.35 (m, 1 H), 7.29–7.23 (m, 1 H), 7.16 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.00 (dt, *J* = 7.8, 1.2 Hz, 1 H), 3.67 (br s, 4 H), 1.69 (br s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4, 148.6, 143.3, 123.8, 120.2, 115.9, 108.5, 46.5, 25.2, 24.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O$: 203.1184; found: 203.1210.

2-(Pyrrolidin-1-yl)benzoxazole (3c)[10a,c,d]

Compound **3c** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and pyrrolidine (**2c**) (0.71 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3c** (0.30 g, 80%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 1 H), 7.29–7.25 (m, 1 H), 7.16 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.00 (dt, *J* = 7.8, 1.2 Hz, 1 H), 3.70–3.64 (m, 4 H), 2.07–2.03 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 149.0, 143.6, 123.8, 120.0, 115.9, 108.5, 47.4, 25.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1052.

***N*,*N*-Diethylbenzoxazole-2-amine (3d)**[10a–e]

Compound **3d** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and diethylamine (**2d**) (0.73 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3d** (0.35 g, 92%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 1 H), 7.28–7.24 (m, 1 H), 7.16 (dt, *J* = 7.8, 1.2 Hz, 1 H), 6.99 (dt, *J* = 7.8, 1.2 Hz, 1 H), 3.60 (q, *J* = 7.2 Hz, 4 H), 1.30 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 148.8, 143.6, 123.7, 119.9, 115.8, 108.4, 42.9, 13.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{15}N_2O$: 191.1184; found: 191.1213.

2-(Thiomorpholin-4-yl)benzoxazole (3e)

Compound **3e** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and thiomorpholine (**2e**) (1.03 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3e** (0.41 g, 94%) as a yellow solid; mp 90.2–92.0 °C.

IR (film): 3436, 2921, 1655, 1578, 1460, 1401, 1263, 1149, 969, 879, 796, 754, 741, 570, 425 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 1 H), 7.19–7.17 (m, 1 H), 7.10 (dt, *J* = 7.8, 1.2 Hz, 1 H), 6.95 (dt, *J* = 7.8, 1.2 Hz, 1 H), 3.94–3.89 (m, 4 H), 2.68–2.64 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 148.7, 142.9, 124.0, 120.7, 116.3, 108.7, 48.0, 26.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2OS$: 221.0749; found: 221.0745.

2-(4-Methylpiperazin-1-yl)benzoxazole (3f)[10a–c]

Compound **3f** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and 1-methylpiperazine (**2f**) (1.00 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, EtOAc–MeOH, 4:1) to afford pure compound **3f** (0.40 g, 93%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 7.09 (dt, *J* = 7.5, 0.9 Hz, 1 H), 6.95 (dt, *J* = 7.8, 0.9 Hz, 1 H), 3.65 (t, *J* = 5.1 Hz, 4 H), 2.44 (t, *J* = 5.1 Hz, 4 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 148.6, 142.9, 123.8, 120.5, 116.1, 108.6, 54.0, 46.1, 45.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}N_3O$: 218.1293; found: 218.1283.

***tert*-Butyl 4-(Benzoxazol-2-yl)piperazine-1-carboxylate (3g)**[10d]

Compound **3g** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and *tert*-butyl piperazine-1-carboxylate (**2g**) (1.86 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3g** (0.50 g, 83%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 1 H), 7.30–7.27 (m, 1 H), 7.22–7.17 (m, 1 H), 7.09–7.03 (m, 1 H), 3.71–3.68 (m, 4 H), 3.60–3.57 (m, 4 H), 1.51 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 154.6, 148.7, 142.8, 124.1, 120.9, 116.4, 108.8, 80.4, 45.4, 28.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_3$: 304.1661; found: 304.1655.

***N*-Cyclohexylbenzoxazole-2-amine (3h)**[14]

Compound **3h** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and cyclohexylamine (**2h**) (1.00 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3h** (0.26 g, 61%) as an orange-brown solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.16 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.03 (dt, *J* = 7.8, 1.2 Hz, 1 H), 5.36 (br s, 1 H), 3.76 (br s, 1 H), 2.17–2.13 (m, 2 H), 1.83–1.76 (m, 2 H), 1.70–1.64 (m, 1 H), 1.49–1.21 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 148.3, 143.0, 123.8, 120.5, 116.0, 108.6, 52.0, 33.4, 25.4, 24.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O$: 217.1341; found: 217.1337.

***N*-Benzylbenzoxazole-2-amine (3i)**[14]

Compound **3i** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and benzylamine (**2i**) (1.07 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3i** (0.20 g, 45%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 6 H), 7.19–7.15 (m, 1 H), 7.09 (dt, *J* = 7.8, 1.2 Hz, 1 H), 6.96 (dt, *J* = 7.8, 1.2 Hz, 1 H), 5.72 (br s, 1 H), 4.60 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 148.5, 142.8, 137.7, 128.8, 127.8, 127.6, 123.9, 120.9, 116.4, 108.8, 47.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}N_2O$: 225.1028; found: 225.1025.

***N*-(Quinolin-8-yl)benzoxazol-2-amine (3j)**

Compound **3j** was prepared from benzoxazole (**1a**) (0.24 g, 2.00 mmol) and 8-aminoquinoline (**2j**) (1.44 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3j** (0.35 g, 66%) as a pale yellow solid; mp 127.2–128.1 °C.

IR (film): 3446, 3358, 3061, 1642, 1577, 1531, 1456, 1334, 1240, 1165, 1003, 974, 822, 787, 737, 634, 587, 422 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 8.76–8.74 (m, 1 H), 8.65 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.56–7.48 (m, 2 H), 7.40–7.36 (m, 2 H), 7.31 (d, *J* = 7.8 Hz, 1 H), 7.17 (dt, *J* = 7.5, 1.2 Hz, 1 H), 7.07 (dt, *J* = 7.5, 1.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 148.2, 147.7, 142.8, 138.1, 136.3, 134.2, 128.1, 127.5, 124.1, 122.1, 121.8, 120.3, 117.6, 113.9, 109.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{12}N_3O$: 262.0980; found: 262.0976.

5-Chloro-2-(morpholin-4-yl)benzoxazole (3k)[10a]

Compound **3k** was prepared from 5-chlorobenzoxazole (**1b**) (0.31 g, 2.00 mmol) and morpholine (**2a**) (0.87 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3k** (0.30 g, 64%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 2.1 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 6.93 (dd, *J* = 8.4, 2.1 Hz, 1 H), 3.77–3.73 (m, 4 H), 3.63–3.60 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 147.3, 144.3, 129.4, 120.8, 116.6, 109.3, 66.1, 45.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{12}ClN_2O_2$: 239.0587; found: 239.0583.

5-Chloro-2-(piperidin-1-yl)benzoxazole (3l)[10d]
Compound **3l** was prepared from 5-chlorobenzoxazole (**1b**) (0.31 g, 2.00 mmol) and piperidine (**2b**) (0.85 g, 10.0 mmol). The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 4:1) to afford pure compound **3l** (0.31 g, 65%) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 2.1 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 6.92 (dd, *J* = 8.4, 2.1 Hz, 1 H), 3.62 (br s, 4 H), 1.67 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 147.2, 144.8, 129.0, 119.8, 115.9, 108.9, 46.2, 25.1, 23.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{12}ClN_2O$: 237.0795; found: 237.0793.

Compounds 5a–d; General Procedure
To an oven-dried and N_2-flushed 35 mL microwave vial equipped with a magnetic stir bar, was added a mixture of azole **4** (2.00 mmol, 1.00 equiv), Li*O*t-Bu (0.48 g, 6.00 mmol, 3.00 equiv), and I_2 (0.76 g, 3.00 mmol, 1.50 equiv) in THF or DMF (4.00 mL, 0.50 M concentration of substrate). After stirring at r.t. for 1 min, the vial was capped and the mixture was heated at 100 °C or 140 °C for 2 h in a single mode microwave reactor. Morpholine (**2a**) (0.87 g, 10.0 mmol, 5.00 equiv) was added and the mixture was then heated in the microwave reactor at 100 °C or 140 °C for an additional 2 h. After the reaction was complete, deionized H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2 × 15 mL). The combined organic layer was concentrated in vacuo, and the crude residue was purified by SiO_2 column chromatography to afford the desired product.

2-(Morpholin-4-yl)benzothiazole (5a)[15]
Compound **5a** was prepared from benzothiazole (**4a**) (0.27 g, 2.00 mmol) and morpholine (**2a**) (0.87 g, 10.0 mmol) via microwave irradiation in THF at 100 °C. The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 3:1) to afford pure compound **5a** (0.24 g, 54%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.48 (m, 2 H), 7.22 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.01 (dt, *J* = 7.8, 1.2 Hz, 1 H), 3.76–3.72 (m, 4 H), 3.54–3.41 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 152.4, 130.5, 126.0, 121.6, 120.7, 119.3, 66.2, 48.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2OS$: 221.0749; found: 221.0740.

4,5-Dimethyl-2-(morpholin-4-yl)thiazole (5b)
Compound **5b** was prepared from 4,5-dimethylthiazole (**4b**) (g, 2.00 mmol) and morpholine (**2a**) (0.87 g, 10.0 mmol) via microwave irradiation in THF at 100 °C. The crude residue was purified by flash column chromatography (SiO_2, hexane–EtOAc, 3:1) to afford pure compound **5b** (0.04 g, 10%) as a pale yellow solid; mp 115.4–116.1 °C.

IR (film): 3436, 2955, 2924, 2851, 1579, 1532, 1441, 1375, 1326, 1303, 1231, 1112, 1071, 1038, 911, 866, 644 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (t, *J* = 4.8 Hz, 4 H), 3.35 (t, *J* = 4.8 Hz, 4 H), 2.18 (s, 3 H), 2.12 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 143.8, 114.5, 66.2, 48.5, 14.7, 11.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{15}N_2OS$: 199.0905; found: 199.0901.

1-Methyl-2-(morpholin-4-yl)benzimidazole (5c)[16]
Compound **5c** was prepared from 1-methylbenzimidazole (**4c**) (g, 2.00 mmol) and morpholine (**2a**) (0.87 g, 10.0 mmol) via microwave irradiation in THF at 100 °C. The crude residue was purified by flash column chromatography (SiO_2, EtOAc–MeOH, 9:1) to afford pure compound **5c** (0.14 g, 33%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 1 H), 7.29–7.28 (m, 1 H), 7.24–7.22 (m, 2 H), 3.93 (t, *J* = 4.8 Hz, 4 H), 3.65 (s, 3 H), 3.35 (t, *J* = 4.8 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 141.3, 135.7, 121.8, 121.4, 118.2, 108.4, 66.6, 50.6, 30.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{1H}16N_3O$: 218.1293; found: 218.1286.

1,3,7-Trimethyl-8-(morpholin-4-yl)-3,7-dihydro-1*H*-purine-2,5-dione (5d)[17]
Compound **5d** was prepared from caffeine (**4d**) (0.39 g, 2.00 mmol) and morpholine (**2a**) (0.87 g, 10.0 mmol) via microwave irradiation in DMF at 140 °C. The crude residue was purified by flash column chromatography (SiO_2, EtOAc) to afford pure compound **5d** (0.18 g, 31%) as a white solid; mp 160.9–161.7 °C.

IR (film): 3447, 2964, 2865, 1702, 1660, 1513, 1444, 1284, 1215, 1119, 971, 912, 749, 519 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (t, *J* = 4.7 Hz, 4 H), 3.70 (s, 3 H), 3.46 (s, 3 H), 3.33 (s, 3 H), 3.20 (t, *J* = 4.8 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 155.0, 151.7, 147.3, 105.5, 66.3, 50.0, 32.4, 29.7, 27.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}N_5O_3$: 280.1410; found: 280.1405.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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Synthesis of 2-aminobenzoxazoles via copper-catalyzed electrophilic amination of benzoxazoles with *O*-benzoyl hydroxylamines

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ABSTRACT

An efficient copper-catalyzed electrophilic amination of benzoxazoles with *O*-benzoyl hydroxylamines is described, employing CuCl catalyst, PPh_3 ligand, and LiO^tBu base. This simple air-stable copper catalysis enables the preparation of various 2-aminobenzoxazole derivatives at room temperature in good yields.

1. Introduction

A number of 2-aminoazoles (2-*N*-substituted azoles) possess biological and pharmaceutical activities. They are employed widely as a building block for the development of promising drug candidates.[1,2] Particularly, 2-aminobenzoxazoles are ubiquitous scaffolds in a wide variety of therapeutic agents for a treatment of CNS disorders,[3] insomnia,[4] and Alzheimer's disease.[5]

Due to their significance, the development of versatile and practical protocols to achieve a variety of these 2-aminobenzoxazoles and other 2-aminoazole derivatives has been the subject of intense research effort. Over the past decade, the transition metal-catalyzed carbon–nitrogen (C–N) bond cross-coupling reactions, particularly Buchwald–Hartwig as well as Ullman couplings provide powerful, efficient, and reliable approaches for the synthesis of these structural motifs.[6] Recent methods involving the catalytic carbon–hydrogen (C–H) bond functionalization and C–N bond formation were also recognized as the potentially useful synthetic tools for these structural moieties.[7,8]

Additionally, an umpolung[9] electrophilic amination[10] using a reagent of type R_2N^+, such as halogenated amine, hydroxylamine, oxaziridine, and hydrazine, provides a practical tool to construct C–N bonds. This strategy allows the effective amination of both organometallic reagents[11] and heteroaromatic C–H bonds.[12]

Miura and co-workers recently reported the copper-catalyzed direct amination of electron-deficient heteroaryl substrates with chloroamines and hydroxylamines.[13] The use of these electrophilic amine reagents under copper catalysis enables the successful formation of heteroaryl–amino linkages at room temperature. Herein, we reported an alternative and straightforward synthetic approach to access 2-aminobenzoxazoles and their derivatives under atmospheric conditions by using the readily prepared *O*-benzoyl hydroxylamines as electrophilic amine reagents.[11d,14]

2. Results and discussion

We initiated the studies by choosing benzoxazole **1** and *O*-benzoyl hydroxylamine **2a** as substrates for the optimization under the atmospheric conditions (Table 1). To our delight, this reaction was complete within 1 h even at room temperature as monitored by GC analysis.[15] We screened various copper salts (Table 1, entries 1–7), and a combination of CuCl/PPh_3/LiO^tBu in THF showed higher catalytic activities (entry 3). No reaction was observed in the absence of copper and only 31% yield of product **3a** was obtained in the absence of PPh_3 ligand (entries 8–10). The use of phen (1,10-phenanthroline) and bipy (2,2′-bipyridine) ligands led to lower yields, 36 and 21%, respectively (entries 11 and 12).

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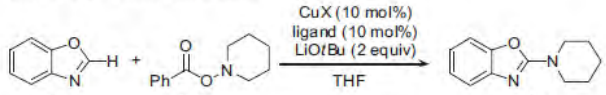
Table 1
Effect of copper source and ligand[a]



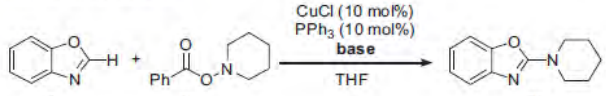
1 (1 equiv) 2a (1.5 equiv) 3a

Entry	Copper salt	Ligand	Yield[b] (%)
1	CuI	PPh_3	55
2	CuBr	PPh_3	40
3	*CuCl*	*PPh_3*	*60*
4	$CuBr_2$	PPh_3	17
5	$CuCl_2$	PPh_3	58
6	$Cu(OAc)_2$	PPh_3	50
7	$Cu(OTf)_2$	PPh_3	50
8	—	—	0
9	—	PPh_3	0
10	CuCl	—	31
11	CuCl	Phen	36
12	CuCl	Bipy	21

[a] Conditions: benzoxazole **1** (0.5 mmol, 1 equiv), **2a** (1.5 equiv), CuX (10 mol %), ligand (10 mol %), LiO^{t}Bu (2 equiv), THF (2 mL), rt, 1 h.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

We also studied the effect of inorganic base (Table 2, entries 1–8) and equivalency (entries 2, 9, and 10). The results in Table 2 showed that 3 equiv of LiO^{t}Bu can furnish product **3a** in very high yield (entry 10). On the other hand, other stronger bases such as NaO^{t}Bu, KO^{t}Bu, and NaOH, or weaker bases such as K_3PO_4, Cs_2CO_3, and NaOAc resulted in significantly lower yields or no reaction.

Table 2
Effect of inorganic base[a]



1 (1 equiv) 2a (1.5 equiv) 3a

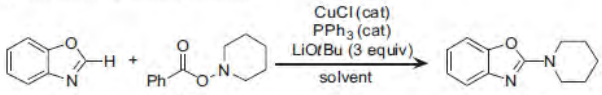
Entry	Base	Equiv	Yield[b] (%)
1	—	—	0
2	LiO^{t}Bu	2	60
3	NaO^{t}Bu	2	19
4	KO^{t}Bu	2	0
5	NaOH	2	0
6	K_3PO_4	2	<2
7	Cs_2CO_3	2	<2
8	NaOAc	2	0
9	LiO^{t}Bu	1	49
10	*LiO^{t}Bu*	*3*	*80*

[a] Conditions: benzoxazole **1** (0.5 mmol, 1 equiv), **2a** (1.5 equiv), CuCl (10 mol %), PPh_3 (10 mol %), base (1–3 equiv), THF (2 mL), rt, 1 h.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

Subsequent investigation of ratio of Cu to PPh_3 and solvent effect (Table 3, entries 1–10) established the combination of CuCl (5 mol %), PPh_3 (10 mol %), LiO^{t}Bu (3 equiv) in THF at rt for 1 h as the best catalytic conditions providing **3a** in 95% yield (Table 3, entry 5). Good yields of product **3a** can also be obtained when using 1,4-dioxane, toluene, and acetonitrile as solvent (Table 3; entries 6–8), whereas DMF and DMSO were much less effective (entries 9 and 10).

To test the generality of this protocol, reactions of benzoxazole **1** and a variety of *O*-benzoyl hydroxylamines (**2a–j**) were next examined for the C-2 amination under the optimized reaction

Table 3
Optimization of reaction conditions[a]



1 (1 equiv) 2a (1.5 equiv) 3a

Entry	CuCl (mol %)	PPh_3 (mol %)	Solvent	Yield[b] (%)
1	10	10	THF	80
2	20	20	THF	68
3	5	5	THF	88
4	2	2	THF	62
5	*5*	*10*	*THF*	*95*
6	5	10	Toluene	83
7	5	10	Dioxane	81
8	5	10	Acetonitrile	72
9	5	10	DMF	21
10	5	10	DMSO	18

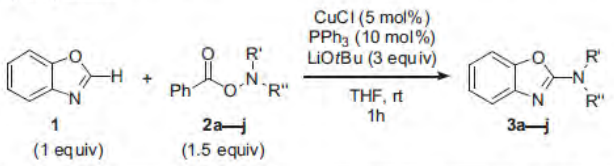
[a] Conditions: benzoxazole **1** (0.5 mmol, 1 equiv), **2a** (1.5 equiv), CuCl (cat), PPh_3 (cat), LiO^{t}Bu (3 equiv), solvent (2 mL), rt, 1 h.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

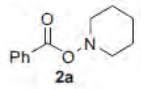
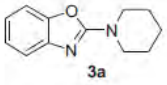
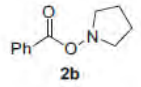
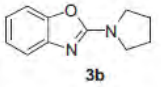
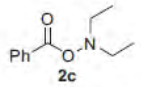
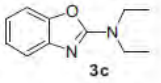
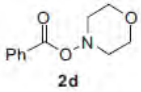
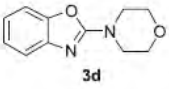
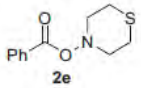
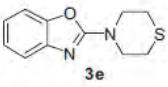
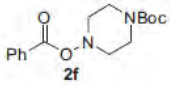
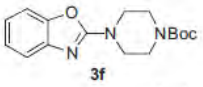
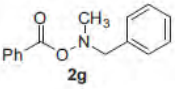
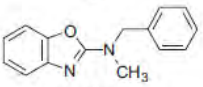
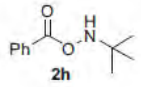
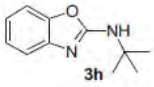
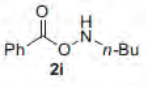
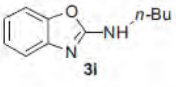
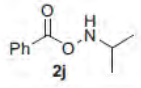
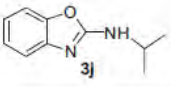
conditions (Table 4). The reactions of benzoxazole **1** with cyclic and acyclic *O*-benzoyl hydroxylamines (**2a–g**) derived from secondary alkylamines underwent smooth amination affording the corresponding 2-aminobenzoxazole derivatives **3a–g** in moderate to excellent isolated yields (entries 1–7). An additional oxygen or sulfur heteroatom in the *O*-benzoyl hydroxylamine structure is well tolerated, as shown by the successful reaction using morpholine **2d** or thiomorpholine **2e** derivatives (entries 4 and 5). The Boc **2f** and benzyl **2g** protecting groups on nitrogen are also compatible (entries 6 and 7). Therefore, further functionalization after the deprotection would be possible. On the other hand, copper-catalyzed electrophilic amination reaction of benzoxazole **1** and *O*-benzoyl hydroxylamine derived from primary amines showed somewhat lower efficiency. *O*-Benzoyl hydroxylamine **2h**, which was derived from *tert*-butylamine, provided 16% isolated yield of C-2 aminated benzoxazole product **3h** (entry 8). No reaction or only small amount of desired product was observed when using other primary amines derived *O*-benzoyl hydroxylamine reagents (e.g., entries 9 and 10).[15]

We also studied the substrate scope of benzoxazoles and other derivatives of azoles (Table 5). Under the optimized conditions, the copper-catalyzed reactions of methylbenzoxazoles (**4a** and **4b**) and *O*-benzoyl hydroxylamine **2a** afforded the corresponding C-2 aminated benzoxazole products **5a** and **5b** in high yields (86% and 73%, respectively; entries 1 and 2). In case of 5-phenylbenzoxazole substrate **4c**, excellent isolated yield of product **5c** was obtained (90%; entry 3). Moreover, the presence of chloro and nitro groups on the aromatic portion of benzoxazole substrates **4d** and **4e** did not have much significant effect in the reaction, therefore, amination reaction also proceeded without any difficulties furnishing products **5d** and **5e** in good yields (66% and 61%; entries 4 and 5). Interestingly, oxadiazole substrate **4f** can be converted to the corresponding C-2 aminated product **5f** with good efficiency (72% isolated yield; entry 6). Conversely, other azoles such as benzothiazole **4g** and *N*-methyl benzimidazole **4h** do not react under these conditions (entries 7 and 8). Only a small amount (less than 5%) of desired C-2 aminated azole was detected by GC–MS when LiO^{t}Bu was replaced by a stronger KO^{t}Bu base. This could be a result of the higher p*K*a values of the C–H bonds at C-2 position of thiazoles and imidazoles.[7a,16]

The plausible mechanism would involve (1) an initial complexation of copper salt with phosphine and *tert*-butoxide to

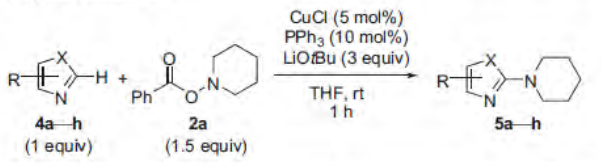
Table 4
Copper-catalyzed electrophilic amination of benzoxazole **1** with various *O*-benzoyl hydroxylamines[a]

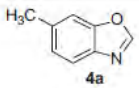
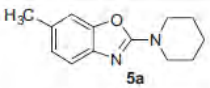
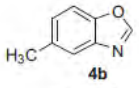
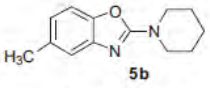
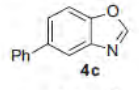
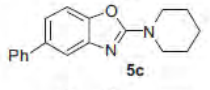
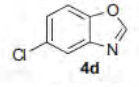
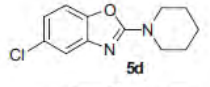
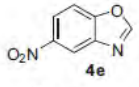
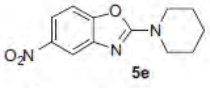
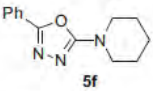
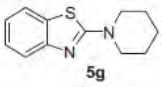
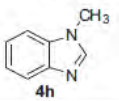
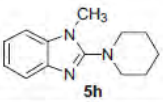


Entry	*O*-Benzoyl hydroxylamine	Product	Yield[b] (%)
1	 **2a**	 **3a**	91
2	 **2b**	 **3b**	40
3	 **2c**	 **3c**	74
4	 **2d**	 **3d**	54
5	 **2e**	 **3e**	45
6	 **2f**	 **3f**	50
7	 **2g**	 **3g**	75
8	 **2h**	 **3h**	16
9	 **2i**	 **3i**	<5[c]
10	 **2j**	 **3j**	0

[a] Conditions: benzoxazole **1** (1 mmol, 1 equiv), **2a–j** (1.5 equiv), CuCl (5 mol %), PPh_3 (10 mol %), LiO^tBu (3 equiv), THF (4 mL), rt, 1 h.
[b] Isolated yields after purification by chromatography.
[c] Detected by GC–MS.

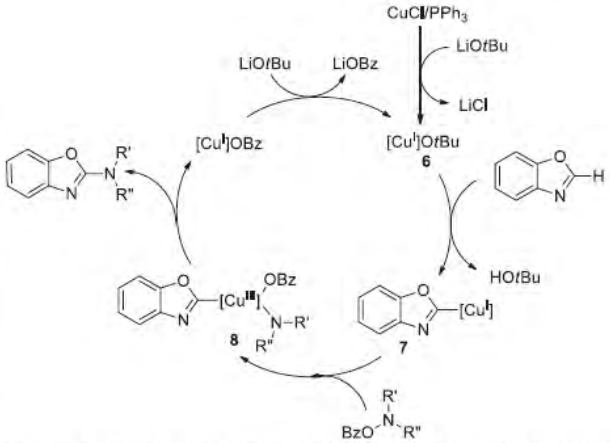
Table 5
Copper-catalyzed electrophilic amination of benzoxazole derivatives with *O*-benzoyl hydroxylamine **2a**[a]



Entry	Azole	Product	Yield[b] (%)
1	 **4a**	 **5a**	86
2	 **4b**	 **5b**	73
3	 **4c**	 **5c**	90
4	 **4d**	 **5d**	66
5	 **4e**	 **5e**	61
6	 **4f**	 **5f**	72
7	 **4g**	 **5g**	0[c]
8	 **4h**	 **5h**	0[c]

[a] Conditions: benzoxazoles **4a–h** (1 mmol, 1 equiv), **2a** (1.5 equiv), CuCl (5 mol %), PPh_3 (10 mol %), LiO^tBu (3 equiv), THF (4 mL), rt, 1 h.
[b] Isolated yields after purification by chromatography.
[c] No reaction was detected by TLC/GC–MS.

generate copper(I)-*tert*-butoxide complex **6**, (2) formation of the key intermediate azole-cuprate **7** assisted by anionic *tert*-butoxide (O^tBu) ligand,[17] (3) oxidative addition of complex **7** with *O*-benzoyl hydroxylamine by single electron transfer process to generate an intermediate **8** in higher oxidation state,[18] (4) reductive elimination of **8** to form new C–N bond of 2-aminobenzoxazole product and regenerate active copper species to resume the catalytic cycle (Scheme 1).[13b] Further efforts to study the detailed mechanism and expand the reaction scope of this chemistry are currently under investigation.



Scheme 1. Proposed plausible mechanism of the Cu-catalyzed electrophilic amination of benzoxazoles and *O*-benzoyl hydroxylamines.

3. Conclusion

In conclusion, we have disclosed an efficient synthetic protocol for the copper-catalyzed amination reaction of benzoxazoles and *O*-benzoyl hydroxylamines. This umpolung electrophilic amination strategy can be carried out under atmospheric conditions with good scope and functional group compatibility. This transformation allows the facile synthesis of a number of 2-aminobenzoxazole derivatives and serves as an alternative and convenient synthetic route to 2-aminobenzoxazoles, which are employed widely in medicinal chemistry.

4. Experimental section

4.1. General methods

Unless otherwise specified, all reactions were carried out under air atmosphere. All reagents were obtained from commercial suppliers and used without further purification. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). GC experiments were carried out with an Agilent 6890N GC-FID on chromatograph equipped with an Agilent column (HP-1, polysiloxane, 24.5 m×0.32 mm ID×0.17 μm). ^1H and ^{13}C NMR spectra were measured with Bruker AV-300 or AV-500 spectrometers in $CDCl_3$. NMR chemical shifts are reported in parts per million (ppm) relative to $CHCl_3$ (7.24 ppm for ^1H and 77.0 ppm for ^{13}C). IR spectra were recorded on an FTIR Spectrum GX (Perkin Elmer), and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are uncorrected. High-resolution mass spectroscopy analyses were carried out by Mahidol University, Department of Chemistry Micro-Mass Facility.

4.2. General procedure for the synthesis of compounds 2–5

4.2.1. General procedure for the preparation of O-benzoyl hydroxylamines ***2a–j***.[11d,14] A 100-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar was charged with benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv), dipotassium hydrogen phosphate (3.27 g, 18.8 mmol, 1.50 equiv), and *N,N*-dimethylformamide (30 mL). The suspension was stirred and amine (15.0 mmol, 1.20 equiv) was added via syringe in one portion. The flask was capped with a septum and the reaction mixture was stirred at room temperature for 1–24 h, during, which time a gradual change in coloration of the reaction mixture occurred. Deionized water (50 mL) was added and the contents were stirred vigorously for 30 min. The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (1×40 mL). The organic phase was collected and washed with saturated aqueous $NaHCO_3$ solution (2×25 mL). All of the aqueous fractions were combined and extracted with EtOAc (2×25 mL). All of the organic fractions were combined and washed with 30 mL of deionized water, 25 mL of brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The resulting crude product was purified by flash column chromatography to give the corresponding *O*-benzoyl hydroxylamine **2**. All physical data of the known compounds were in agreement with those reported in the literature.[11d,11l,14,19,20]

*4.2.2. General procedure for the preparation of 6-substituted benzoxazoles (**4c** and **4e**).*[8d,21] Most of benzoxazole substrates **4** used in this study are commercially available except **4c** and **4e**.

A 100-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar was charged with the corresponding 2-aminophenol derivative (5.00 mmol, 1.00 equiv) and triethyl orthoformate (8.50 mL, 60.0 mmol, 12.0 equiv). The reaction mixture was carefully heated to 150 °C for 6 h. Upon completion, the reaction mixture was cooled to room temperature and the excess orthoformate and ethanol byproduct were removed from the residue under reduced pressure. The crude product was further purified by silica gel (SiO_2) column chromatography to yield the desired substituted azole. All physical data of **4c** and **4e** were in agreement with those reported in the literature.[8d]

4.2.3. General procedure for the synthesis of compounds ***3a–h*** *and* ***5a–f***. A 20 mL oven-dried and N_2-flushed scintillation vial equipped with a magnetic stir bar was charged with benzoxazole or azole starting material (1.00 mmol, 1.00 equiv), *O*-benzoyl hydroxylamine (1.50 mmol, 1.50 equiv), CuCl (5.0 mg, 0.05 mmol, 0.05 equiv), PPh_3 (26.0 mg, 0.10 mmol, 0.10 equiv), LiO^tBu (0.24 g, 3.00 mmol, 3.00 equiv), and tetrahydrofuran (THF) (4.00 mL, 0.25 M concentration of substrate). The vial was capped, and the reaction mixture was stirred at room temperature for 1 h. Upon completion, distilled deionized H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2×15 mL). The solution was concentrated in vacuo, and the crude product was purified by SiO_2 column chromatography to afford a corresponding benzoxazole derivative. All physical data of the known compounds were in agreement with those reported in the literature.[8a,8d,13,14,22]

4.3. Analytical data for compounds 2a–j, 3a–h, 4c, 4e, 5a–f

*4.3.1. Piperidin-1-yl benzoate (**2a**).*[11d] Benzoyl hydroxylamine **2a** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and piperidine (1.28 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2a** (1.90 g, 75%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91–7.89 (m, 2H), 7.47–7.42 (m, 1H), 7.35–7.29 (m, 2H), 3.48–3.27 (m, 2H), 2.68–2.66 (m, 2H), 1.74–1.70 (m, 4H). 1.65–1.45 (m, 1H), 1.17–1.12 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 164.8, 132.9, 129.6, 129.4, 128.3, 57.5, 25.0, 23.3. HRMS (ESI+, *m/z*) Calcd for $C_{12}H_{15}NO_2Na$ $[M+Na]^+$ 228.1000. Found 228.1001.

*4.3.2. Pyrrolidin-1-yl benzoate (**2b**).* Benzoyl hydroxylamine **2b** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and pyrrolidine (1.07 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2b** (1.19 g, 50%) as an off-white solid. Mp=66.2–66.6 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.92 (m, 2H), 7.55–7.49 (m, 1H), 7.42–7.37 (m, 2H), 3.31–3.26 (m, 4H), 1.93 (s, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.2, 132.9, 129.5, 129.4, 128.3, 57.7, 22.2. IR (film): 3423, 2978, 1719, 1598, 1452, 1315, 1259, 1092, 1071, 1021, 948, 785, 719 cm^{-1}. HRMS (ESI+, *m/z*) Calcd for $C_{11}H_{13}NO_2Na$ $[M+Na]^+$ 214.0844. Found 214.0847.

*4.3.3. O-Benzoyl-N,N-diethyl hydroxylamine (**2c**).*[11d] Benzoyl hydroxylamine **2c** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and diethylamine (1.10 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2c** (1.42 g, 59%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99–7.96 (m, 2H), 7.48–7.45 (m, 1H), 7.38–7.33 (m, 2H), 2.98 (q, J=7.2 Hz, 4H), 1.11 (t, J=7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.6, 132.7, 129.4, 129.1, 128.1, 53.1, 11.5. HRMS (ESI+, *m/z*) Calcd for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 216.1000. Found 216.1019.

*4.3.4. Morpholino benzoate (**2d**).*[11d] Benzoyl hydroxylamine **2d** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and morpholine (1.31 g, 15.0 mmol, 1.20 equiv) following the general

procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2d** (1.97 g, 76%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J=7.5 Hz, 2H), 7.55–7.50 (m, 1H), 7.42–7.37 (m, 2H), 3.91–3.77 (m, 4H), 3.42–3.38 (m, 2H), 3.02–2.99 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.5, 133.1, 129.3, 129.0, 128.4, 65.7, 56.9. HRMS (ESI+, m/z) Calcd for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793. Found 230.0794.

*4.3.5. Thiomorpholino benzoate (**2e**).* Benzoyl hydroxylamine **2e** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and thiomorpholine (1.55 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2e** (1.77 g, 69%) as an off-white solid. Mp=80.9–81.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.97 (m, 2H), 7.58–7.53 (m, 1H), 7.45–7.40 (m, 2H), 3.65 (br s, 2H), 3.22 (br s, 2H), 2.86 (br s, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.4, 133.2, 129.4, 129.1, 128.4, 57.7, 26.6. IR (film): 3439, 2961, 2925, 1732, 1598, 1452, 1317, 1267, 1247, 1183, 1090, 1067, 979, 712 cm^{-1}. HRMS (ESI+, m/z) Calcd for $C_{11}H_{13}NO_2SNa$ $[M+Na]^+$ 246.0565. Found 246.0567.

*4.3.6. tert-Butyl 4-(benzoyloxy)piperazine-1-carboxylate (**2f**).*[11] Benzoyl hydroxylamine **2f** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (2.79 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2f** (2.74 g, 72%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.95 (m, 2H), 7.58–7.49 (m, 1H), 7.46–7.36 (m, 2H), 3.99 (br s, 1H), 3.40 (br s, 2H), 3.29 (br s, 2H), 2.89 (br s, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.5, 154.4, 133.2, 129.4, 129.0, 128.4, 80.2, 55.8, 42.0, 28.3. HRMS (ESI+, m/z) Calcd for $C_{16}H_{22}N_2O_4Na$ $[M+Na]^+$ 329.1477. Found 329.1469.

*4.3.7. O-Benzoyl-N-benzyl-N-methylhydroxylamine (**2g**).*[19] Benzoyl hydroxylamine **2g** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *N*-methyl-1-phenylmethanamine (1.93 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=9:1) to afford pure compound **2g** (1.96 g, 65%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09–8.05 (m, 2H), 7.64–7.55 (m, 1H), 7.52–7.25 (m, 7H), 4.16 (s, 2H), 2.92 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.9, 135.5, 132.8, 129.4, 129.3, 128.9, 128.4, 128.1, 127.7, 65.1, 46.1. HRMS (ESI+, m/z) Calcd for $C_{15}H_{15}NO_2Na$ $[M+Na]^+$ 264.1000. Found 264.0984.

*4.3.8. O-Benzoyl-N-(tert-butyl)hydroxylamine (**2h**).*[20] Benzoyl hydroxylamine **2h** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *tert*-butylamine (1.10 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2h** (1.95 g, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02–8.01 (m, 2H), 7.66 (br s, 1H), 7.56–7.54 (m, 1H), 7.46–7.43 (m, 2H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.8, 133.2, 129.3, 129.2, 128.5, 56.1, 26.6. IR (film): 3224, 2976, 1720, 1452, 1366, 1271, 1222, 1093, 1068, 1026, 996, 708 cm^{-1}. HRMS (ESI+, m/z) Calcd for $C_{11}H_{16}NO_2$ $[M+H]^+$ 194.1181. Found 194.1186.

*4.3.9. O-Benzoyl-N-butylhydroxylamine (**2i**).* Benzoyl hydroxylamine **2i** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *n*-butylamine (1.50 mL, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2i** (1.50 g, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01–7.99 (m, 2H), 7.86 (br s, 1H), 7.57–7.54 (m, 1H), 7.45–7.42 (m, 2H), 3.12 (t, J=7.5 Hz, 2H), 1.62–1.56 (m, 2H), 1.45–1.38 (m, 2H), 0.93 (t, J=7.5 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.9, 133.2, 129.4, 129.3, 128.5, 52.3, 29.2, 20.2, 13.9. IR (film): 3236, 2961, 2874, 1722, 1452, 1272, 1068, 1026, 710 cm^{-1}. HRMS (ESI+, m/z) Calcd for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 216.1000. Found 216.1002.

*4.3.10. O-Benzoyl-N-isopropylhydroxylamine (**2j**).* Benzoyl hydroxylamine **2j** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and isopropylamine (1.23 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2j** (1.71 g, 77%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.96 (m, 2H), 7.63 (br s, 1H), 7.50–7.48 (m, 1H), 7.41–7.35 (m, 2H), 3.31 (sep, J=6.3 Hz, 1H), 1.13 (d, J=6.3 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.6, 133.1, 129.1, 129.0, 128.4, 52.1, 19.7. IR (film): 3237, 2974, 1721, 1601, 1452, 1317, 1271, 1091, 1067, 1026, 708 cm^{-1}. HRMS (ESI+, m/z) Calcd for $C_{10}H_{13}NO_2Na$ $[M+Na]^+$ 202.0844. Found 202.0839.

*4.3.11. 2-(Piperidin-1-yl)benzoxazole (**3a**).*[8a] Compound **3a** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3a** (0.18 g, 91%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.35 (m, 1H), 7.29–7.23 (m, 1H), 7.16 (dt, J=7.8, 1.2 Hz, 1H), 7.00 (dt, J=7.8, 1.2 Hz, 1H), 3.67 (br s, 4H), 1.69 (br s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 162.4, 148.6, 143.3, 123.8, 120.2, 115.9, 108.5, 46.5, 25.2, 24.0. HRMS (ESI+, m/z) Calcd for $C_{12}H_{15}N_2O$ $[M+H]^+$ 203.1184. Found 203.1203.

*4.3.12. 2-(Pyrrolidin-1-yl)benzoxazole (**3b**).*[8a] Compound **3b** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and pyrrolidin-1-yl benzoate **2b** (0.29 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3b** (0.08 g, 40%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.36 (m, 1H), 7.29–7.25 (m, 1H), 7.16 (dt, J=7.8, 1.2 Hz, 1H), 7.00 (dt, J=7.8, 1.2 Hz, 1H), 3.70–3.64 (m, 4H), 2.07–2.03 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 161.0, 149.0, 143.6, 123.8, 120.0, 115.9, 108.5, 47.4, 25.6. HRMS (ESI+, m/z) Calcd for $C_{11}H_{13}N_2O$ $[M+H]^+$ 189.1028. Found 189.1055.

*4.3.13. N,N-Diethylbenzoxazole-2-amine (**3c**).*[8a] Compound **3c** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *O*-benzoyl-*N*,*N*-diethyl hydroxylamine **2c** (0.29 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3c** (0.14 g, 74%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.36 (m, 1H), 7.28–7.24 (m, 1H), 7.16 (dt, J=7.8, 1.2 Hz, 1H), 6.99 (dt, J=7.8, 1.2 Hz, 1H), 3.60 (q, J=7.2 Hz, 4H), 1.30 (t, J=7.2 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 162.2, 148.8, 143.6, 123.7, 119.9, 115.8, 108.4, 42.9, 13.4. HRMS (ESI+, m/z) Calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$ 191.1184. Found 191.1210.

*4.3.14. 2-Morpholinobenzoxazole (**3d**).*[8a] Compound **3d** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and morpholino benzoate **2d** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3d** (0.11 g, 54%) as a pale yellow solid. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.41–7.38 (m, 1H), 7.30–7.28 (m, 1H), 7.20 (dt, *J*=7.8, 1.2 Hz, 1H), 7.06 (dt, *J*=7.8, 1.2 Hz, 1H), 3.86–3.83 (m, 4H), 3.73–3.70 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.1, 148.7, 142.7, 124.1, 120.9, 116.4, 108.8, 66.2, 45.7. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}N_2O_2$ $[M+H]^+$ 205.0977. Found 205.0998.

*4.3.15. 2-Thiomorpholinobenzoxazole (**3e**).*[22] Compound **3e** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and thiomorpholino benzoate **2e** (0.33 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3e** (0.10 g, 45%) as a pale yellow solid. Mp=90.5–91.4 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.27 (m, 1H), 7.19–7.17 (m, 1H), 7.10 (dt, *J*=7.8, 1.2 Hz, 1H), 6.95 (dt, *J*=7.8, 1.2 Hz, 1H), 3.94–3.89 (m, 4H), 2.68–2.64 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 161.7, 148.7, 142.9, 124.0, 120.7, 116.3, 108.7, 48.0, 26.7. IR (film): 3436, 2921, 1655, 1578, 1460, 1401, 1263, 1149, 969, 879, 796, 754, 741, 570, 425 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}N_2OS$ $[M+H]^+$ 221.0749. Found 221.0741.

*4.3.16. tert-Butyl 4-(benzoxazol-2-yl)piperazine-1-carboxylate (**3f**).*[8d] Compound **3f** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate **2f** (0.46 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3f** (0.15 g, 50%) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.38 (m, 1H), 7.30–7.27 (m, 1H), 7.22–7.17 (m, 1H), 7.09–7.03 (m, 1H), 3.71–3.68 (m, 4H), 3.60–3.57 (m, 4H), 1.51 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.0, 154.6, 148.7, 142.8, 124.1, 120.9, 116.4, 108.8, 80.4, 45.4, 28.4. HRMS (ESI+, *m*/*z*) Calcd for $C_{16}H_{21}N_3O_3Na$ $[M+Na]^+$ 326.1481. Found 326.1478.

*4.3.17. N-Benzyl-N-methylbenzoxazol-2-amine (**3g**).*[8a] Compound **3g** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine **2g** (0.36 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=7:1) to afford pure compound **3g** (0.18 g, 75%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.25 (m, 7H), 7.18 (t, *J*=6.6 Hz, 1H), 7.01 (t, *J*=6.6 Hz, 1H), 4.75 (s, 2H), 3.12 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.9, 148.9, 143.5, 136.3, 128.6, 127.6, 127.5, 123.8, 120.3, 116.0, 108.6, 53.8, 35.0. HRMS (ESI+, *m*/*z*) Calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1184. Found 239.1195.

*4.3.18. N-(tert-Butyl)benzoxazol-2-amine (**3h**).*[23] Compound **3h** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *O*-benzoyl-*N*-(*tert*-butyl)hydroxylamine (**2h**) (0.29 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3h** (0.03 g, 16%) as an off-white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 1H), 7.09–7.06 (m, 1H), 6.96–6.94 (m, 1H), 5.20 (br s, 1H), 1.43 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.8, 148.1, 143.2, 123.7, 120.6, 116.4, 108.5, 52.0, 29.2. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{14}N_2ONa$ $[M+Na]^+$ 213.1004. Found 213.1015.

*4.3.19. 5-Phenylbenzoxazole (**4c**).*[8d] Compound **4c** was prepared from 2-amino-4-phenylphenol, 90% Aldrich technical grade (1.00 g, 5.00 mmol, 1.00 equiv) and triethyl orthoformate (8.50 mL, 60.0 mmol, 12.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=3:1) to afford pure compound **4c** (0.39 g, 79%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.99 (s, 1H), 7.66–7.57 (m, 4H), 7.50–7.31 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 152.9, 149.4, 140.7, 140.6, 138.6, 128.7, 127.5, 127.2, 125.1, 118.9, 110.8. HRMS (ESI+, *m*/*z*) Calcd for $C_{13}H_{10}NO$ $[M+H]^+$ 196.0762. Found 196.0760.

*4.3.20. 5-Nitrobenzoxazole (**4e**).*[8d] Compound **4e** was prepared from 2-amino-4-nitrophenol (0.77 g, 5.00 mmol, 1.00 equiv) and triethyl orthoformate (8.50 mL, 60.0 mmol, 12.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=3:1) to afford pure compound **4e** (0.42 g, 85%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, *J*=2.4 Hz, 1H), 8.36 (dd, *J*=9.0, 2.4 Hz, 1H), 8.25 (s, 1H), 7.70 (d, *J*=9.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 155.0, 153.4, 145.4, 140.5, 121.6, 117.1, 111.2. HRMS (ESI+, *m*/*z*) Calcd for $C_7H_4N_2O_3Na$ $[M+Na]^+$ 187.0120. Found 187.0128.

*4.3.21. 6-Methyl-2-(piperidin-1-yl)benzoxazole (**5a**).*[8d] Compound **5a** was prepared from 6-methylbenzoxazole **4a** (0.13 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5a** (0.19 g, 86%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J*=7.8 Hz, 1H), 7.00 (s, 1H), 6.90 (d, *J*=7.8 Hz, 1H), 3.59 (s, 4H), 2.35 (s, 3H), 1.63 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.1, 148.6, 140.7, 130.1, 124.3, 115.1, 108.8, 46.4, 25.1, 24.0, 21.2. HRMS (ESI+, *m*/*z*) Calcd for $C_{13}H_{16}N_2ONa$ $[M+Na]^+$ 239.1160. Found 239.1162.

*4.3.22. 5-Methyl-2-(piperidin-1-yl)benzoxazole (**5b**).*[8d] Compound **5b** was prepared from 5-methylbenzoxazole **4b** (0.13 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5b** (0.16 g, 73%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.02 (d, *J*=8.1 Hz, 1H), 6.72 (d, *J*=8.1 Hz, 1H), 3.57 (s, 4H), 2.31 (s, 3H), 1.60 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.6, 146.8, 143.5, 133.4, 120.9, 116.4, 107.9, 46.6, 25.2, 24.1, 21.5. HRMS (ESI+, *m*/*z*) Calcd for $C_{13}H_{17}N_2O$ $[M+H]^+$ 217.1341. Found 239.1346.

*4.3.23. 5-Phenyl-2-(piperidin-1-yl)benzoxazole (**5c**).*[8d] Compound **5c** was prepared from 5-phenylbenzoxazole **4c** (0.20 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5c** (0.25 g, 90%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.50 (m, 3H), 7.40 (t, *J*=7.8 Hz, 2H), 7.33–7.14 (m, 3H), 3.74–3.50 (m, 4H), 1.65 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.8, 148.3, 144.0, 141.7, 137.6, 128.5, 127.2, 126.8, 119.6, 114.7, 108.4, 46.6, 25.1, 24.0. HRMS (ESI+, *m*/*z*) Calcd for $C_{18}H_{18}N_2ONa$ $[M+Na]^+$ 301.1317. Found 301.1329.

*4.3.24. 5-Chloro-2-(piperidin-1-yl)benzoxazole (**5d**).*[8d] Compound **5d** was prepared from 5-chlorobenzoxazole **4d** (0.15 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5d** (0.16 g, 66%) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J*=2.1 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 6.94 (dd, *J*=8.4, 2.1 Hz, 1H), 3.63 (s, 4H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 163.0, 147.3, 144.8, 129.1, 119.8, 116.0, 109.0, 46.5, 25.2, 23.9. HRMS (ESI+, *m*/*z*) Calcd for $C_{12}H_{13}ClN_2ONa$ $[M+Na]^+$ 259.0614. Found 259.0607.

*4.3.25. 5-Nitro-2-(piperidin-1-yl)benzoxazole (**5e**).*[8d] Compound **5e** was prepared from 5-nitrobenzoxazole **4e** (0.16 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol,

1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5e** (0.15 g, 61%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J=2.1 Hz, 1H), 7.85 (dd, J=8.7, 2.1 Hz, 1H), 7.18 (d, J=8.7 Hz, 1H), 3.60 (br s, 4H), 1.63 (s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 163.7, 152.7, 145.0, 144.4, 116.6, 111.1, 107.9, 46.6, 25.2, 23.8. HRMS (ESI+, m/z) Calcd for $C_{12}H_{13}N_3O_3Na$ $[M+Na]^+$ 270.0855. Found 270.0868.

*4.3.26. 2-Phenyl-5-(piperidin-1-yl)-1,3,4-oxadiazole (**5f**).*[8d] Compound **5f** was prepared from 2-phenyl-1,3,4-oxadiazole **4f** (0.15 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5f** (0.16 g, 72%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95–7.83 (m, 2H), 7.49–7.38 (m, 3H), 3.61–3.52 (m, 4H), 1.69 (br s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.2, 158.9, 130.3, 128.7, 125.5, 124.7, 47.0, 24.8, 23.6. HRMS (ESI+, m/z) Calcd for $C_{13}H_{15}N_3ONa$ $[M+Na]^+$ 252.1113. Found 252.1102.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.127.

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