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A Metal-Free Route to 2-Aminooxazoles by Taking Advantage of the Unique Ring Opening of Benzoxazoles and Oxadiazoles with Secondary Amines

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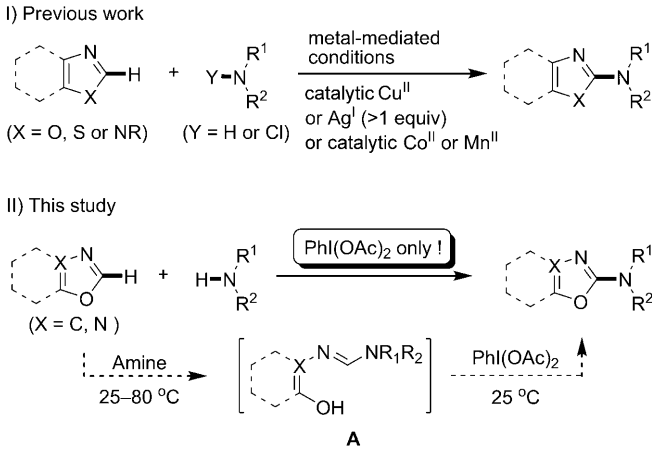
Recognizing the value of (hetero)arylamine motifs in biological and pharmaceutical sciences, chemists continue to devise novel and more practical methods for their synthesis.[1] Buchwald–Hartwig-type amination reactions and those mediated by copper are the most powerful and reliable methods available for N arylation.[2] However, since these procedures employ aryl halides as the starting material, the direct amination of a C–H bond in heteroaromatics would be beneficial, thus avoiding additional halogenation steps to obtain halogenated derivatives. In this context, recent examples of metal-mediated C–N bond formation in azoles represent important contributions to this area (Scheme 1).



Scheme 1. Amination of the C–H bond in oxazoles.

In 2009, Mori et al.[3] and Schreiber et al.[4] reported the copper-catalyzed amination and amidation of heteroaromatics, respectively. Although C–N bond formation takes place regioselectively at the 2-position of azoles, the reaction conditions employed were rather harsh (120–140 °C). More recently, Miura developed a milder catalytic protocol for the amination of azoles.[5] Despite the fact that the reaction proceeds at ambient temperature, it requires chloroamine precursors as the amine source.

We have previously revealed an oxidative dehydrogenative approach for the amination of azoles by using stoichiometric amounts of silver.[6a] More recently, we also developed a catalytic version of this approach by using Co or Mn catalysts in the presence of peroxide as the oxidant and a carboxylic acid additive.[6b] In the latter procedure, we found that a ring-opened adduct, *o*-hydroxyamidine (**A**, Scheme 1), was also generated as a minor product along with the desired amination product when the reaction was carried out in the absence of the acid additive.[6b] Subsequent studies revealed that secondary amines are capable of opening benzoxazoles to afford amidine adducts, especially under neat conditions. At first glance, this result was surprizing as the ring opening of benzoxazoles under neutral conditions had not been reported previously, although some carbanions were known to open azole rings under harsher conditions. For example, allyl magnesium halides are capable of performing ring-opening reactions on benzoxazoles and benzothiazoles at low temperatures.[7a,b] Nitrobenzoxazoles also provide ring-opened products through addition of base or carbanions.[7c] In addition, the generation of an unstable ring-opened intermediate of isocyanophenolate was proposed in the Pd-catalyzed direct arylation of benzoxazoles.[8]

Although amidines are a prevalent structural motif in medicinal chemistry, displaying high bioactivities,[9] their use as a synthon for the formation of various amine-containing compounds has been less widespread. This is especially noteable upon considering that although imines exhibit a variety of reactivity through addition, reduction, or cycloaddition reactions, the structurally analogous amidines have not been frequently utilized except in limited cyclization sequences.[10] As we were particularly interested in the synthesis of 2-aminooxazoles, the easily obtainable *ortho*-hydroxyamidine adducts triggered our curiosity about the posibility for a subsequent cyclization reaction leading to the desired products. As the ring-closing reaction of *ortho*-hydroxyimines is already known,[11,15] we were curious whether the same oxidation conditions could be employed for the ring closure of *ortho*-hydroxyamidines. Presented herein is a new route, based on our hypothesis, for the highly efficient amination of oxazoles by using iodobenzene diacetate as the oxidant.[12] Our findings are highly significant as they provide

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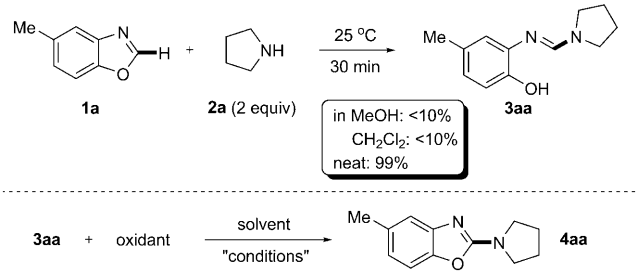
the first example of a metal-free route to 2-aminooxazoles[13] under very mild conditions.

5-Methylbenzoxazole (**1a**) was chosen as a model substrate to react with pyrrolidine (**2a**) for the optimization of the ring-opening and subsequent ring-closing reaction (Table 1). Although poor conversion was observed in solution, such as in methanol or dichloromethane, a quantitative yield of *o*-hydroxybenzamidine (**3aa**) was obtained with the use of pyrrolidine (2 equiv) in 30 min at room temperature. Equipped with a simple but highly efficient route to amidines, we next scrutinized the ring-closing reaction under various conditions. Although cyclization was sluggish with oxone, persulfate, or peroxide oxidants (Table 1, entries 1–3), hypervalent iodine species cyclize **3aa** to form 2-aminobenzoxazole **4aa**, the efficiency of which varied depending on the iodinate employed. For instance, the use of iodobenzene diacetate (1.1 equiv) in dichloromethane resulted in complete conversion within 5 min at room temperature to give **4aa** in 94% yield as shown by NMR spectroscopy (Table 1, entry 4). On the other hand, other iodine(III) sources, such as $PhI(OPiv)_2$ (Piv = *tert*-butylcarbonyl), $PhI(OCOCF_3)$, or PhI(OH)OTs (Ts = tosyl, the Koser reagent), offered lower yields under otherwise identical conditions.

Table 1. Optimization of the reaction conditions.[a,b]

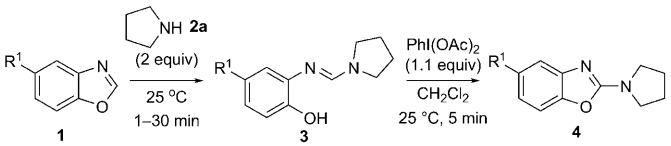


Entry	Oxidant	Solvent	*t* [min]	*T* [°C]	Yield [%][c]
1	oxone	$(CH_2)_2Cl_2$	120	80	<5[d]
2	$K_2S_2O_8$	$(CH_2)_2Cl_2$	120	80	<5[d]
3	T-HYDRO[e]	$(CH_2)_2Cl_2$	120	80	<5[d]
4	$PhI(OAc)_2$	CH_2Cl_2	5	25	94
5	$PhI(OPiv)_2$	CH_2Cl_2	5	25	73
6	$PhI(OCOCF_3)_2$	CH_2Cl_2	5	25	56
7	PhI(OH)OTs	CH_2Cl_2	5	25	30
8	$PhI(OAc)_2$	dioxane	15	25	40
9	$PhI(OAc)_2$	toluene	15	25	28
10	$PhI(OAc)_2$	CH_3CN	15	25	55

[a] Conditions for amidine formation: **1a** (0.5 mmol) and **2a** (1 mmol) for 30 min at 25 °C. [b] Conditions for the cyclization reaction: amidine **3aa** (0.5 mmol) and oxidant (0.55 mmol) in the indicated solvent (3 mL). [c] NMR spectroscopic yield. [d] 5-Methylbenzoxazole was recovered in about 30% yield. [e] T-HYDRO is the trademark name for 70 wt% *tert*-butyl hydroperoxide in water.

Benzoxazoles substituted with various functional groups also underwent the two step amination reaction in high overall yields (Table 2). Interestingly, little electronic effect of the substituents was observed in both the ring-opening and closing steps. In fact, amidine adducts were obtained in high yields irrespective of the substituents' electronic properties. Oxidative cyclization of amidines readily proceeded by using iodobenzene diacetate (1.1 equiv) within 5 min at 25 °C to afford 2-pyrrolidinylbenzoxazole derivatives in good yields. The relatively moderate yield obtained from 5-nitrobenzoxazole (Table 2, entry 6) is due to the instability of the amidine adduct (**3fa**) and the 2-aminobenzoxazole product (**4fa**).

Table 2. Substrate scope with regard to benzoxazoles.[a,b]



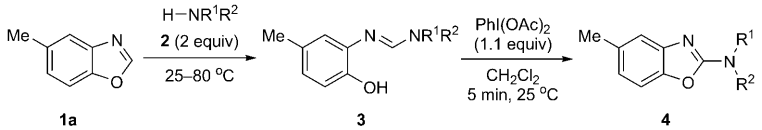
Entry	R^1		*t* [min]	Yield of **3** [%][c]		Yield of **4** [%][c]	
1	OMe	**1b**	25	98	**3ba**	73	**4ba**
2	Me	**1a**	30	99	**3aa**	91	**4aa**
3	H	**1c**	15	96	**3ca**	75	**4ca**
4	Ph	**1d**	5	98	**3da**	73	**4da**
5	Cl	**1e**	5	99	**3ea**	93	**4ea**
6	NO_2	**1f**	1	60	**3fa**	53	**4fa**

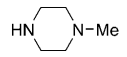
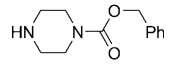
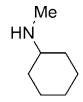
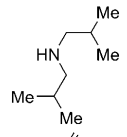
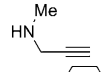
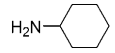
[a] Amidine formation: **1** (0.5 mmol) and **2a** (1 mmol), neat. [b] Ring-closing step: **3** (0.5 mmol) and $PhI(OAc)_2$ (1.1 equiv) in CH_2Cl_2 (3 mL) at 25 °C for 5 min under an air atmosphere. [c] Isolated yields.

We next investigated the tolerance for the amine counterpart in the ring-opening reaction of 5-methylbenzoxazole and the subsequent ring closing of the corresponding *ortho*-hydroxyarylamidines (Table 3). Cyclic amines, such as piperidine (**2b**), 2-methylpyrrolidine (**2c**), morpholine (**2d**), and *N*-methylpiperazine (**2e**), all smoothly underwent the ring-opening reaction with **1a** to provide amidine adducts in excellent yields (Table 3, entries 1–4). In addition, the subsequent cyclization of the amidines was easy under the mild conditions (5 min at 25 °C), leading to the corresponding 2-amino-5-methylbenzoxazoles in good yields. The reaction of cyclic amines bearing functional groups such as *N*-bezyloxycarbonylpiperazine (**2f**) was also smooth, providing the desired product **4af** in an acceptable yield (Table 3, entry 5).

Acyclic amines also turned out to be facile reactants although some substrates needed higher reaction temperatures to obtain full conversion in the ring-opening step. For instance, the reaction of dibenzylamine (**2g**) with **1a** proceeded efficiently at 80 °C to give adduct **3ag**, which was subsequently cyclized to form **4ag** in good yield (Table 3, entry 6). In addition, the two-step procedure with both *N*-methylcyclohexylamine (**2h**) and diisobutylamine (**2i**) took place readily (Table 3, entries 7 and 8, respectively). It is noteable that most functional groups examined were compatible with the conditions, as demonstrated by the reaction of both diallylamine (**2j**, Table 3, entry 9) and *N*-methyl-*N*-propargylamine (**2k**, Table 3, entry 10). The amination reaction could be scaled up without difficulty (Table 3, entry 9). However, when primary amines were subjected to the standard conditions, poor yields of the corresponding amidines

Table 3. Scope of amines to react with 5-methylbenzoxazole.[a,b]



Entry	Amine **2**		T [°C]	t [h]	Yield of **3** [%][c]		Yield of **4** [%][c]	
1		**2b**	25	1	99	**3ab**	74	**4ab**
2		**2c**	25	5	96	**3ac**	69	**4ac**
3		**2d**	80	12	96	**3ad**[d]	70	**4ad**
4		**2e**	25	10	98	**3ae**	78	**4ae**
5		**2f**	25	10	96	**3af**	61	**4af**
6		**2g**	80	12	79	**3ag**	79	**4ag**
7		**2h**	80	12	98	**3ah**	61	**4ah**
8		**2i**	80	12	89	**3ai**	90	**4ai**
9[e]		**2j**	80	12	96	**3aj**	78	**4aj**
10		**2k**	25	12	89	**3ak**	62	**4ak**
11			80	12	< 5		–	–

[a] Conditions for amidine formation: **1a** (0.5 mmol) and **2** (1 mmol), neat. [b] Conditions for ring-closing step: **3** (0.5 mmol) and $PhI(OAc)_2$ (1.1 equiv) in CH_2Cl_2 (3 mL) at 25 °C for 5 min under an air atmosphere. [c] Isolated yields. [d] NMR yield of **3ad** due to its instability. [e] This reaction was carried out on a gram scale.

were obtained (Table 3, entry 11). Aniline derivatives were also unreactive under these conditions.

After successful exploration of the scope of the reaction towards reactants, benzoxazoles and amines, we turned our attention to other types of azole. Accordingly, we selected 1,3,4-oxadiazoles to search for a similar ring-opening and -closing reaction to afford 2-aminated oxadiazoles. This consideration was for two reasons: 2-aminooxadiazoles are one of the highly interesting pharmaceutical motifs that show a broad spectrum of biological activities.[13] In addition, it was intriguing to see whether the same ring-opening process takes place with this type of non-fused heterocycle. We were delighted to observe that oxadiazoles do indeed undergo the two-step procedure, although an elevated temperature (80 °C) was required for the ring-opening step (Table 4). It should be mentioned that the isolated amidine adducts (**6**) are present in the form of acylhydrazino amidines rather than the tautomeric enol form, as shown by the NMR and IR spectral data.[14] Pleasingly, the subsequent oxidative ring-closing step of the obtained amidine adducts takes place smoothly under the aforementioned optimized mild conditions.

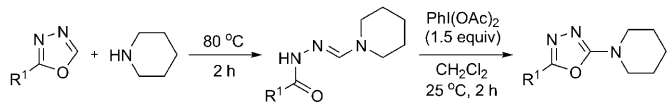
When the reaction of 2-substituted oxadiazoles with piperidine (3 equiv, **2b**) was carried out neat, the ring-opened adducts were obtained in excellent yields. In addition, the reaction efficiency was hardly influenced by electronic variations in the substituents on the non-fused heterocycle.

Indeed, oxadiazoles bearing phenyl (**5a**), 1-naphthyl (**5b**), 4-trifluoromethyl- (**5c**), 4-chloro- (**5d**), and 4-methoxyphenyl (**5e**) groups all underwent the ring-opening reaction with piperidine to give the corresponding acylhydrazino amidines **6ab–eb** in excellent yields. Oxidative cyclization of acyclic intermediates **6** also proceeded efficiently to give the 2-aminooxadiazoles **7ab–eb** under mild conditions.

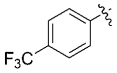
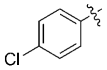
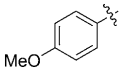
Under the aforementioned standard reaction conditions, a range of secondary amines readily participated in the ring-opening and -closing transformation of 2-phenyloxadiazole (**5a**) to afford 2-amino-1,3,4-oxadiazoles in good yields (Table 5). For instance, pyrrolidine (**2a**), a substituted piperidine **2l**, morpholine (**2d**), and *N*-methylpiperazine (**2e**) were all readily aminated at the 2-position of oxadiazole (Table 5, entries 1, 2, 3, and 4, respectively). Functional groups such as benzyloxycarbonyl (**2f**) or a bisallyl moiety (**2j**) were compatible with the employed conditions (Table 5, entries 5–6).

As the outcome of this process is identical to the oxidative nucleophilic substitution of hydrogen (ONSH)[15] with amine nucleophiles, an equilibrium might be operating between the ring-opened *o*-hydroxyarylamidine species and the ring-closed benzoxazoline adduct.[6b] As a result, it was envisioned that a one-pot procedure could be performed by mixing the benzoxazole, amine, and iodobenzene diacetate together. However, the desired product was not obtained under the new reaction conditions and it was observed that iodobenzene diacetate completely decomposed. Further studies revealed that secondary amines quickly reacted with iodobenzene diacetate at room temperature, leading to the decomposition of the oxidant. To overcome this limitation, a sequential one-pot procedure was considered, in which the reagents were added step by step in one pot. After confirming complete conversion of benzoxazole to the amidine adduct by TLC, dichoromethane was added to the reaction mixture as the solvent, followed by the addition of iodobenzene diacetate (2.2 equiv). A complete cyclization reaction was observed within a few minutes at room temperature for a range of amine substrates, as shown in Scheme 2, demonstrating that the one-pot procedure is simple and convenient to carry out for the preparation of 2-aminoazoles starting from azoles and amines.

Table 4. Preparation of 2-aminooxadiazoles.[a,b]

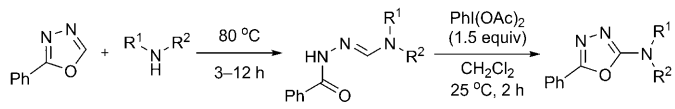


5 2b (3 equiv) 6 7

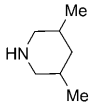
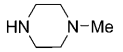
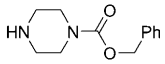
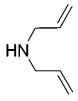
Entry	R^1		Yield of 6 [%][c]		Yield of 7 [%][c]	
1		5a	98	6ab	73	7ab
2		5b	99	6bb	80	7bb
3		5c	96	6cb	78	7cb
4		5d	93	6db	65	7db
5		5e	91	6eb	72	7eb

[a] Amidine formation: **5** (0.5 mmol) and **2b** (1.5 mmol), neat. [b] Conditions for ring-closing step: **6** (0.5 mmol) and $PhI(OAc)_2$ (1.5 equiv) in CH_2Cl_2 (3 mL) at 25 °C for 2 h under an air atmosphere. [c] Isolated yields.

Table 5. Substrate scope with regard to amines in the reaction with oxadiazole **5a**.[a,b]

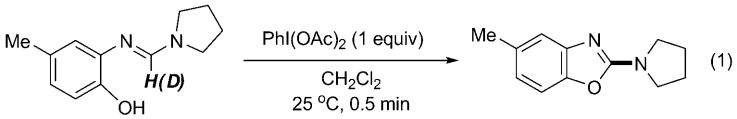


5a 2 (3 equiv) 6 7

Entry	Amine 2		t [h]	Yield of 6 [%][c]		Yield of 7 [%][c]	
1		2a	3	81	6aa	61	7aa
2		2l	5.5	97	6al	73	7al
3		2d	9	98	6ad	72	7ad
4		2e	10	94	6ae	76	7ae
5		2f	12	97	6af	69	7af
6		2j	12	60	6aj	65	7aj

[a] Amidine formation: **5a** (0.5 mmol) and **2** (1.5 mmol), neat. [b] Conditions for ring-closing step: **6** (0.5 mmol) and $PhI(OAc)_2$ (1.5 equiv) in CH_2Cl_2 (3 mL) at 25 °C for 2 h under an air atmosphere. [c] Isolated yields.

A competition experiment between an *ortho*-hydroxyamidine (**3aa**) and its deuterated derivative (**3aa-*d***), which was easily prepared according to the procedure presented herein upon the reaction of pyrrolidine with 2-deuterated 5-methylbenzoxazole,[14] was subsequently performed to determine any kinetic isotope effects [Eq. (1)]. It was observed that the oxidative cyclization reaction does not exhibit kinetic isotope effects ($k_H/k_D = 1.0$), which implies that the cleavage of the C–H bond alpha to the nitrogen of the amidine adduct is not involved in the rate-determining step.



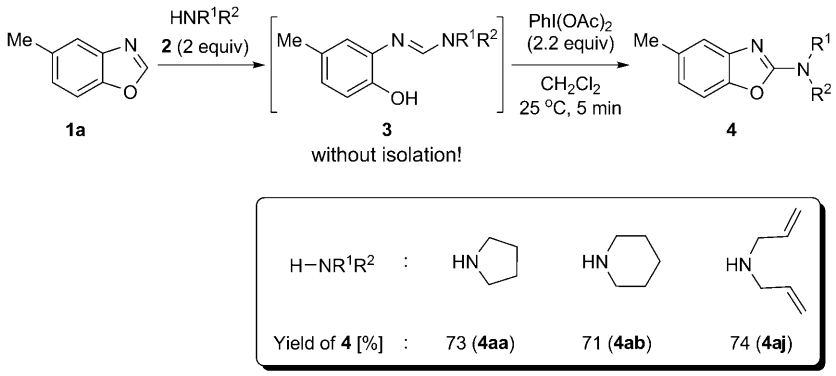
3aa (3aa-*d*) k_H/k_D = 1.0 (1)

Although the exact mechanistic details are not clear at this stage, it is assumed that the I^{III} species initially coordinates to the amidino nitrogen rather than the phenolic oxygen. This is followed by a ring closure to form the desired product through a benzoxazoline adduct, which may be the key species sensitive to oxidation, with concurrent elimination of iodobenzene and acetic acid (Scheme 3).[16] On the other hand, if an alternative pathway operates, in which the I^{III} [17] species reacts first with the phenolic oxygen, a quinone-type intermediate might be produced[18] that could inhibit the desired oxidative ring-closing step.

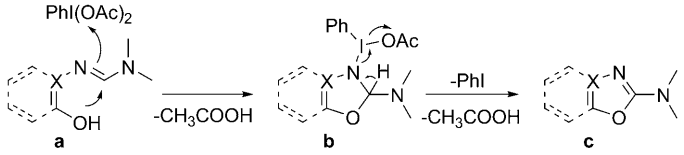
In summary, we have developed a new metal-free system for the amination of azoles with amines through a unique ring-opening and subsequent ring-closing strategy. The addition of amines to azoles is highly efficient under neat and mild conditions to give the amidine adducts. Oxidative cyclization of the amidine adducts was readily achieved within a short time at room temperature by using iodobenzene diacetate as the oxidant. The two-step procedure can also be performed in a one-pot process without isolation of the amidine intermediate. The overall reaction is highly attractive from a synthetic point of view in that the reaction is free from the use of acid, base, or metallic catalysts and the optimal reaction conditions are mild. This procedure, therefore, is anticipated to be a powerful tool for the synthesis of 2-aminobenzoxazoles and oxadiazoles, which are important pharmacophores of high biological activity.

Experimental Section

Representative procedure: Pyrrolidine (**2a**, 1 mmol) was added to a round-bottomed flask charged with neat 5-methylbenzoxazole (**1a**, 0.5 mmol) and the solution was stirred for 30 min at 25 °C under an air atmosphere. The crude product mixture was diluted with CH_2Cl_2 (15 mL), washed with a saturated solution of NaCl (3×10 mL) and the aqueous layer was again extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain analytically pure 4-methyl-2-(pyrrolidin-1-ylmethyleneamino)phenol (**3aa**) in 99% yield. After dissolving this amidine adduct in dichloromethane (3 mL), $PhI(OAc)_2$ (1.1 equiv) was added, and the reaction mixture was stirred for 5 min at 25 °C under an air atmosphere. The mixture was then diluted with CH_2Cl_2 (15 mL), washed with a saturated solution of $NaHCO_3$ (3×15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers



Scheme 2. The one-pot procedure for the preparation of 2-aminobenzoxazoles.[14]



Scheme 3. A proposed pathway for the $PhI(OAc)_2$-mediated ring-closing reaction of *o*-hydroxy-*N*-aryl-*N*,*N*-dialkylformamidine.

were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford 5-methyl-2-(pyrrolidin-1-yl)benzoxazole (**4aa**, 91%).

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Keywords: amination · azoles · C–N bond formation · iodine · ring-opening processes · ring-closing processes

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