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[4+1] Cycloaddition of *N*-acylimine derivatives with isocyanides: efficient synthesis of 5-aminooxazoles and 5-aminothiazoles

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ABSTRACT

[4+1] Cycloaddition reaction between isocyanides and *N*-acylimine derivatives generated from *N*-acyl *N*,*O*-acetals acting as isocyanophiles has been developed. These reactions proceeded smoothly and cleanly to afford the corresponding 5-aminooxazoles in high yields. This reaction was extended to the syntheses of 5-aminothiazoles by using *N*-thioacyl *N*,*O*-acetals. A wide range of *N*-acyl *N*,*O*-acetals, *N*-thioacyl *N*,*O*-acetals, and isocyanides were found to be applicable to this reaction.

1. Introduction

Oxazoles and thiazoles are both important classes of heterocyclic compounds and are frequently found in pharmaceuticals and natural products.[1,2] They also have applications in optical materials, serving as scintillant molecules or fluorescent dyes.[3] Owing to these unique properties, various methods of synthesizing oxazole derivatives have been investigated, and a number of techniques have recently been developed, including cyclodehydration reactions,[4] oxidations of oxazolinones,[5] direct derivations of the parent oxazole,[6] and metal-catalyzed cross coupling reactions.[7] These methods, however, are all highly limited in terms of the substrates with which they can be used. The use of isocyanides as reactive components during the synthesis of oxazoles is well established and the Passerini-type reaction of aldehydes with isocyanoacetamides in the presence of a chiral catalyst has been shown to afford enantioenriched oxazole derivatives.[8] Yu recently reported a variation of this reaction, which generates 5-aminooxazoles upon the addition of isocyanoacetamides to carbalkoxyketenes, which have been generated in situ.[9] The first example of the synthesis of 5-aminooxazoles was reported by Deyrup in 1972 and consisted of the nucleophilic addition of isocyanide to *N*-acylimine derivatives in the presence of $BF_3{\cdot}OEt_2$ to afford the products in moderate yields.[10] More recently, Ciufolini reported that the nucleophilic attack of isocyanides on *N*-acylimine precursors (the α-chloroglycinates) in the presence of an excess of a Lewis acid gives the corresponding 5-aminooxazoles in good yields.[11] These reactions show a great contribution for the synthesis of 5-aminooxazoles, although challenges still remain with regard to limitations in the range of applicable substrates or the reaction efficiency, especially an excess amount of Lewis acid was required. Over the past century, a large number of protocols have also been developed for the synthesis of 5-aminothiazoles, the *S*-analogues of the 5-aminooxazoles.[12,13] Nevertheless, many possible 5-aminothiazole derivatives are not readily accessed by employing the existing preparative methods. To address this deficiency, we herein report the [4+1] cycloaddition of isocyanides to *N*-acylimine derivatives, catalyzed by an organosilane compound, to afford various aminooxazoles. In addition, we expand the scope of this methodology to also synthesize 5-aminothiazoles.

The Passerini and Ugi reactions generally require a carboxylic acid, which activates an aldehyde or imine and traps a nitrilium cation to form an acyloxylated intermediate. Subsequent acyl transfer leads to the corresponding α-acyloxy or α-amino amides.[14] In our previous studies, either silanol or borinic acid played the role of the carboxylic acid in the Passerini-type reaction (Eq. 1).[15] Based on our success with these reactions, we reasoned that a compound composed of an electrophile (Z) and a nucleophile (X) (which we write in generic form as Z–X) could also perform essentially the same function as the carboxylic acid in a Passerini or Ugi-type reaction. In addition, we expanded this concept to the intramolecular trapping of the nitrilium intermediate in the Ugi-type reaction.

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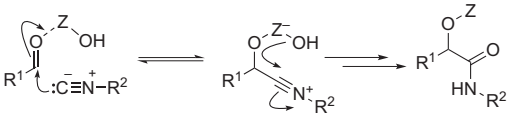
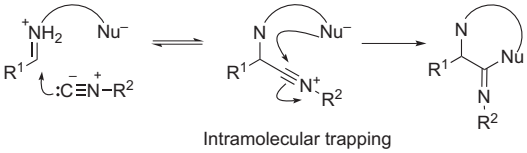
Thus, when a molecule contains both an electrophile (such as C=N) and a potential nucleophilic group (Nu^-), intramolecular trapping of the nitrilium intermediate should be readily achieved in a manner similar to the intermolecular version of the reaction (Eq. 2). Based on this concept, we have developed the catalyst-free [5+1] cycloaddition reaction of isocyanides, using *C,N*-cyclic *N*′-acyl azomethine imines as the 'isocyanophile'.[16] In the work reported herein, we demonstrate the use of *N*-acylimines as isocyanophiles capable of functioning as 1,4-dipoles to afford the desired heterocycles (Eq. 3).



(1)



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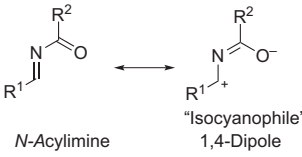


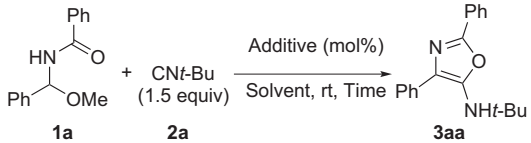
(3)

2. Results and discussions

We initially examined the ability of *N*-acylimines to act as 1,4-dipolar equivalents, capable of trapping an isocyanide as a C1 source during the synthesis of the corresponding 5-aminooxazole. Our early work employed the well-known compound *N*-acyl *N,O*-acetal **1a** as the *N*-acylimine precursor, as shown in Table 1, and we examined the reaction of **1a** and *tert*-butyl isocyanide (**2a**) in the presence of $Cu(OTf)_2$, $MgCl_2$, and $ZnCl_2$ in dichloromethane (entries 1–3). Unfortunately, these reactions were very sluggish or gave a complex mixture of products. In contrast, when the reaction was carried out in the presence of chlorotrimethylsilane (TMSCl) in dichloromethane at room temperature, 5-aminooxazole (**3aa**) was obtained in 82% yield after 10 min (entry 4).[17] When this same reaction was performed using 10 mol % TMSCl at room temperature, lower reactivity was observed (entry 5) while conditions in dichloroethane under reflux in the presence of 10 mol % TMSCl gave **3aa** in 88% yield after 10 min (entry 6). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was also found to be effective in this reaction, and it was gratifying to observe that 10 mol % of TMSOTf was sufficient to afford **3aa** in 96% yield at room temperature after 10 min (entry 7). This reaction proceeded smoothly in polar, ether, and cyclic ether solvents to generate **3aa** in high yields (entries 9–12). The reactivity was slightly less when toluene was used as a solvent, likely due to the reduced solubility of substrate **1a** (entry 13). In addition, we found that 1.1 equiv of isocyanide was sufficient to afford the product in high yield (entry 14). In contrast, the use of 10 mol % of triflic acid (TfOH) led to the decomposition of **1a** such that the desired product was obtained in only 78% yield (entry 15).

We next examined the range of isocyanides and *N*-acyl *N,O*-acetals (as the *N*-acylimine precursors), which were applicable to the present [4+1] cyclization reaction when using 10 mol % TMSOTf, with the results summarized in Table 2. From these results, we found that the optimized reaction conditions were applicable to a wide variety of isocyanides. The reactions of tertiary isocyanides (R^2=*t*-Bu, *t*-Oct) with **1a** gave the products in high yields after 20 min (entries 1 and 2) while, in the case of secondary and primary isocyanides **2c** and **2d**, low reactivities were observed to afford the corresponding products **3ac** and **3ad** in 69% and 48% yields,

Table 1
Reaction conditions and results for [4+1] cycloaddition reactions

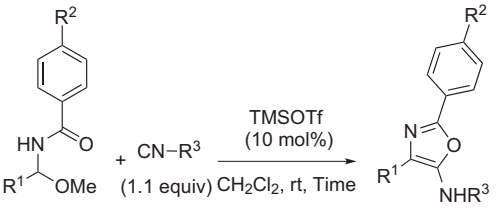


1a **2a** **3aa**

Entry	Additive/mol %	Solvent	Time	Yield/%
1	$Cu(OTf)_2$/120	CH_2Cl_2	10 min	Messy
2	$ZnCl_2$/120	CH_2Cl_2	18 h	48
3	$MgCl_2$/120	CH_2Cl_2	18 h	75
4	TMSCl/120	CH_2Cl_2	10 min	82
5	TMSCl/10	CH_2Cl_2	24 h	Trace
6[a]	TMSCl/10	$(CH_2Cl)_2$	10 min	88
7	TMSOTf/10	CH_2Cl_2	10 min	96
8	TMSOTf/120	CH_2Cl_2	10 min	99
9	TMSOTf/10	AcOEt	20 min	90
10	TMSOTf/10	MeCN	20 min	81
11	TMSOTf/10	THF	20 min	88
12	TMSOTf/10	Et_2O	20 min	80
13	TMSOTf/10	Toluene	10 min	72
14[b]	TMSOTf/10	CH_2Cl_2	20 min	99
15	TfOH/10	CH_2Cl_2	40 min	78

[a] The reaction was carried out under reflux.
[b] 1.1 equiv of **2a** was used.

Table 2
Summary of isocyanides and *N*-acyl *N,O*-acetals investigated



1 **2** **3**

Entry[a]	R^1	R^3	Time	Yield/%
1	Ph (**1a**)	*t*-Bu (**2a**)	20 min	99 (**3aa**)
2	Ph (**1a**)	*t*-Oct (**2b**)	20 min	81 (**3ab**)
3	Ph (**1a**)	*c*-Hex (**2c**)	2 h	69 (**3ac**)
4	Ph (**1a**)	Bn (**2d**)	2 h	48 (**3ad**)
5	Ph (**1a**)	Ph (**2e**)	3 h	79 (**3ae**)
6	Ph (**1a**)	4-$MeOC_6H_4$ (**2f**)	3 h	95 (**3af**)
7	Ph (**1a**)	4-BrC_6H_4 (**2g**)	24 h	98 (**3ag**)
8	Ph (**1a**)	4-$O_2NC_6H_4$ (**2h**)	24 h	Messy
9	1-Naphthyl (**1b**)	*t*-Bu (**2a**)	1 h	51 (**3ba**)
10	2-Naphthyl (**1c**)	*t*-Bu (**2a**)	1 h	97 (**3ca**)
11	4-$MeOC_6H_4$ (**1d**)	*t*-Bu (**2a**)	30 min	94 (**3da**)
12	4-BrC_6H_4 (**1e**)	*t*-Bu (**2a**)	1 h	73 (**3ea**)
13[b]	2-MeC_6H_4 (**1f**)	*t*-Bu (**2a**)	24 h	74 (**3fa**)
14[b]	3-MeC_6H_4 (**1g**)	*t*-Bu (**2a**)	24 h	83 (**3ga**)
15[b]	4-MeC_6H_4 (**1h**)	*t*-Bu (**2a**)	24 h	89 (**3ha**)
16[c]	Ph (**1i**)	*t*-Bu (**2a**)	1 h	92 (**3ia**)
17[d]	Ph (**1j**)	*t*-Bu (**2a**)	2 h	80 (**3ja**)

[a] R^2=H unless otherwise noted.
[b] Reaction was carried out in the presence of 1.0 equiv of TMSCl at room temperature.
[c] R^2=Me.
[d] R^2=Br.

respectively (entries 3 and 4). Phenyl isocyanide (**2e**) and aromatic isocyanides bearing electron donating or withdrawing groups at the *para* position also generated the corresponding heterocycles in high yields, although the reactivities of these compounds were lower than those exhibited by the aliphatic isocyanides (entries 5–7). Especially in the case of 4-nitrophenyl isocyanide (**2h**), a very complex mixture of products was produced (entry 8). The reactivity of various *N*-acyl *N*,*O*-acetals functioning as *N*-acylimine precursors with *tert*-butyl isocyanide (**2a**) was next examined by combining 1.0 equiv of the *N*-acyl *N*,*O*-acetals **1a**–**j** and 1.1 equiv of **2a**. In the case of the *N*-acylimine precursor **1b**, derived from 1-naphthaldehyde, the reaction was somewhat complex and the desired product **3ba** was obtained in only 51% yield. In contrast, **1c** (from 2-naphthaldehyde) was found to work well as a substrate and the respective product **3ca** was obtained in 97% yield (entries 9 and 10). We also examined substituted *N*-acyl *N*,*O*-acetals bearing electron-donating groups on the aromatic ring and similar levels of reactivity were observed with the 4-methoxyphenyl-substituted *N*-acyl *N*,*O*-acetal **1d** (entry 11). In the case of the substituted *N*-acyl *N*,*O*-acetal **1e** (with an electron-withdrawing group on the aromatic ring), the desired product **3ea** was obtained in 73% yield (entry 12).

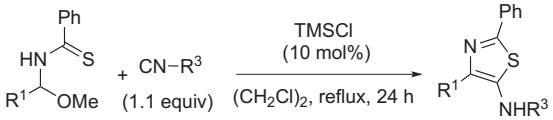
TMSOTf was found to be ineffective when reacting methylphenyl-substituted substrates and generated a complex mixture of products. We therefore performed subsequent reactions using 1.0 equiv of TMSCl as the promoter, which fortunately, allowed the reactions to proceed cleanly to afford the appropriate products. With regard to the substitution pattern of the *N*-acyl *N*,*O*-acetal, the 2-, 3-, and 4-methylphenyl substituents were all well tolerated, furnishing the corresponding 5-aminooxazoles in good yields (entries 13–15).

The effects of varying the substituent on the benzoyl group attached to the nitrogen were also examined and demonstrated that a methyl group on the aromatic moiety was more effective than a bromide, since these two groups resulted in 92% and 80% yields, respectively (entries 16 and 17). From these results, it was determined that the electron density of the *N*-acyl moiety plays an important role in trapping the nitrilium intermediate prior to the cyclization.

We have also attempted to use the reaction of *N*-thioacyl *N*,*O*-acetals with isocyanides in the presence of organosilane compounds as a means of preparing 5-aminothiazoles, with the results summarized in Table 3. The general reactivities of the *N*-thioacyl *N*,*O*-acetals were observed to be lower than those of the *N*-acyl *N*,*O*-acetals, such that the reaction of **4a** with 1.1 equiv of **2a** in the presence of 10 mol % of TMSOTf gave the desired 5-aminothiazole **5aa** in approximately 60% yield even when refluxing in CH_2Cl_2 (entries 1 and 2). The decomposition of **4a** was also observed under these conditions. Substituting TMSCl for TMSOTf allowed the intact recovery of the original **4a** although the reaction did not proceed at all (entry 3). We eventually determined that the reaction of **4a** with **2a** in the presence of 10 mol % of TMSCl in dichloroethane under reflux conditions gave the product **5aa** in 94% yield (entry 4).

We subsequently examined the ranges of isocyanides and *N*-thioacyl *N*,*O*-acetals applicable to the present [4+1] cyclization reaction, as shown in entries 5–14. The reactions of the aliphatic isocyanides (R^3=*t*-Bu, *t*-Oct or *c*-Hex) with **4a** gave the corresponding 5-aminothiazole derivatives in high yields (entries 4–6). In the cases of benzyl isocyanide (**2d**) and phenyl isocyanide (**2e**), however, the reactions were complicated and the desired 5-aminothiazoles were not obtained (entries 7 and 8). The reactivities of various *N*-thioacyl *N*,*O*-acetals with *tert*-butyl isocyanide (**2a**) were also examined by combining these compounds with 1.1 equiv of **2a** in the presence of TMSCl. Both the *N*-thioacylimine precursor **4b** derived from 1-naphthaldehyde and that **4c** obtained from 2-naphthaldehyde were found to work well as substrates by the use of 1.0 equiv of TMSCl and the respective products **5ba** and **5ca** were obtained in 90% and 93% yields, respectively (entries 9 and 10). Regarding the substitution pattern of the *N*-thioacyl *N*,*O*-acetal, the reaction proceeded despite the addition of 2-, 3-, and 4-methylphenyl substituents to the aromatic ring, furnishing the corresponding products (entries 11–13). In contrast, when an *N*-thioacyl *N*,*O*-acetal **4g** with an electron-withdrawing aromatic substituent was applied, the reaction did not proceed at all and only the starting material was recovered (entry 14).

Table 3
Summary of isocyanides and *N*-thioacyl *N*,*O*-acetals investigated



4 2 5

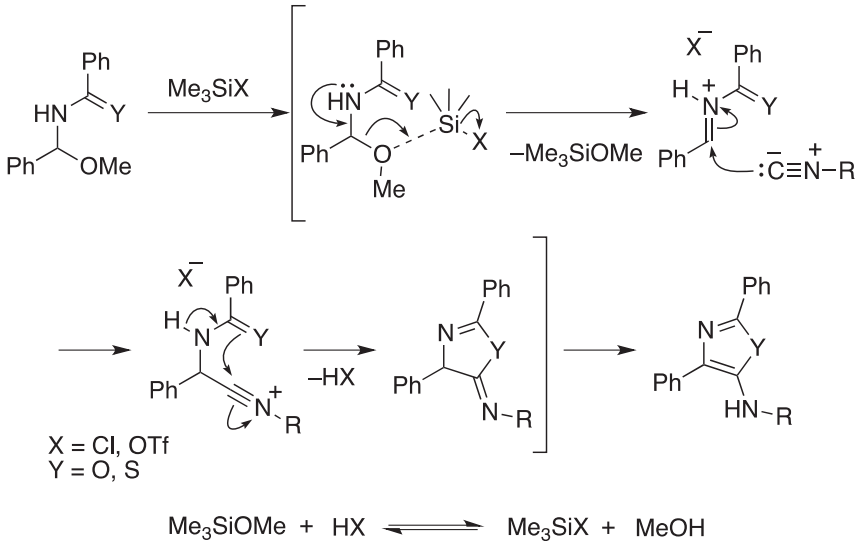
Entry	R^1	R^3	Yield/%
1[a]	Ph (**4a**)	*t*-Bu (**2a**)	60 (**5aa**)
2[b]	Ph (**4a**)	*t*-Bu (**2a**)	58 (**5aa**)
3[c]	Ph (**4a**)	*t*-Bu (**2a**)	No reaction
4	Ph (**4a**)	*t*-Bu (**2a**)	94 (**5aa**)
5	Ph (**4a**)	*t*-Oct (**2b**)	84 (**5ab**)
6	Ph (**4a**)	*c*-Hex (**2c**)	83 (**5ac**)
7	Ph (**4a**)	Bn (**2d**)	Messy
8	Ph (**4a**)	Ph (**2e**)	Messy
9[d]	1-Naphthyl (**4b**)	*t*-Bu (**2a**)	90 (**5ba**)
10[d]	2-Naphthyl (**4c**)	*t*-Bu (**2a**)	93 (**5ca**)
11	2-MeC_6H_4 (**4d**)	*t*-Bu (**2a**)	72 (**5da**)
12	3-MeC_6H_4 (**4e**)	*t*-Bu (**2a**)	63 (**5ea**)
13	4-MeC_6H_4 (**4f**)	*t*-Bu (**2a**)	78 (**5fa**)
14	4-BrC_6H_4 (**4g**)	*t*-Bu (**2a**)	No reaction

[a] Reaction was carried out in the presence of 10 mol % of TMSOTf at room temperature in CH_2Cl_2.
[b] Reaction was carried out in the presence of 10 mol % of TMSOTf in CH_2Cl_2 under reflux.
[c] Reaction was carried out at room temperature in CH_2Cl_2.
[d] Reactions were carried out in the presence of 1.0 equiv of TMSCl at room temperature.

In Scheme 1, we present our proposed mechanism for the [4+1] cycloaddition. In this mechanism, the methoxy group of the *N*-acyl *N*,*O*-acetal (Y=O) is activated by the organosilane compound and leaves, giving the *N*-acylimine derivative, which subsequently reacts with the isocyanide. The nitrilium intermediate thus generated is then trapped in an intramolecular fashion by the oxygen of the amide group to form the desired product. Based on the data presented in Table 1 (entry 15), triflic acid was not particularly effective, whereas TMSCl and TMSOTf may be able to regenerate during the reaction process and thus act as efficient catalysts.[18] The reaction mechanism associated with the syntheses of 5-aminothiazoles (Y=S) may well be the same as the above mechanism proposed for *N*-acyl *N*,*O*-acetals.

3. Conclusion

In conclusion, we have developed and demonstrated a [4+1] cycloaddition reaction between isocyanides and *N*-acylimine derivatives generated from *N*-acyl *N*,*O*-acetals acting as isocyanophiles. These reactions proceeded smoothly and cleanly to afford the corresponding 5-aminooxazoles in high yields. This reaction was extended to the syntheses of 5-aminothiazoles by using *N*-thioacyl *N*,*O*-acetals. A wide range of *N*-acyl *N*,*O*-acetals, *N*-thioacyl *N*,*O*-acetals, and isocyanides were found to be applicable to this reaction.



Scheme 1. Proposed reaction mechanism.

4. Experimental section

4.1. General

^{1}H NMR was recorded on a JEOL ECS 400 (400 MHz) NMR spectrometer. Chemical shifts δ are reported in parts per million using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (J), and integration. ^{13}C NMR spectra were recorded on JEOL ECS 400 (100 MHz) NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ=77.0 ppm). The IR spectra were measured on JASCO FT/IR-230 spectrometers. The MS spectra were recorded with JEOL SX-102A mass spectrometer and Bruker microtof II. All of the melting points were measured with YANAGIMOTO micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation. Flash column chromatography was performed by using Cica silica gel 60N, spherical neutral (37563-84).

N-Acyl *N*,*O*-acetals **1** and *N*-thioacyl *N*,*O*-acetals **4** were prepared following the literature.[19]

4.2. General procedure for the [4+1] cycloaddition reaction of *N*-acylimine precursor with isocyanide

To a solution of **1** (0.30 mmol) and **2** (0.33 mmol) in CH_2Cl_2 (2.7 mL), TMSOTf (0.03 mmol, 10 mol %) in CH_2Cl_2 (0.3 mL) was added and the whole was stirred at room temperature. The reaction mixture was diluted with satd $NaHCO_3$ aq (3 mL), then, organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 mL×3) and combined organic layers were washed with brine, dried over Na_2SO_4 then, concentrated. The residue was purified by silica gel column chromatography.

*4.2.1. N-(tert-Butyl)-2,4-diphenyloxazol-5-amine (**3aa**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3aa** (87 mg, 99% yield) as a white solid of mp=108.5–109.0 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.36 (s, 9H), 7.25 (m, 2H), 7.39–7.47 (m, 5H), 7.92 (d, J=8.7 Hz, 2H), 8.04 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): 30.3, 54.2, 125.1, 125.6, 125.8, 126.5, 127.9, 128.5, 128.6, 129.5, 132.6, 147.9, 155.0. IR (KBr): 3260, 2960, 1630, 1450, 1340, 1190, 1070, 970 cm^{-1}. HRMS-FAB (m/z): calcd for $C_{19}H_{21}N_2O$ [M^++H]: 293.1654. Found: 293.1652.

*4.2.2. 2,4-Diphenyl-N-(2,4,4-trimethylpentan-2-yl)oxazol-5-amine (**3ab**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ab** (85 mg, 81% yield) as a white solid of mp=135.2–136.0 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.07 (s, 9H), 1.38 (s, 6H), 1.72 (s, 2H), 7.25 (m, 2H), 7.37–7.45 (m, 5H), 7.83 (d, J=8.2 Hz, 2H), 8.00 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): 30.2, 31.7, 31.8, 55.0, 57.8, 125.5, 125.6, 127.8, 127.9, 128.6, 128.7, 128.9, 129.3, 132.9, 148.2, 154.4. IR (KBr): 3280, 2940, 1630, 1540, 1450, 1340, 1070, 970 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{23}H_{28}N_2ONa$ [M^++Na]: 371.2099. Found: 371.2101.

*4.2.3. N-Cyclohexyl-2,4-diphenyloxazol-5-amine (**3ac**).* Silica gel column chromatography (benzene/ethyl acetate=20/1) gave **3ac** (132 mg, 69% yield, 0.6 mmol scale) as a white amorphous. ^{1}H NMR (benzene-d_6): 0.74–1.37 (m, 8H), 1.55–1.66 (m, 2H), 3.02 (m, 1H), 6.87 (m, 1H), 7.02–7.10 (m, 6H), 7.26 (t, J=7.8 Hz, 2H), 8.10 (t, J=7.8 Hz, 2H). ^{13}C NMR (benzene-d_6): 24.9, 25.8, 34.0, 54.9, 125.8, 125.9, 126.4, 127.8, 128.5, 128.9, 129.3, 132.5, 133.9, 149.3, 154.0. IR (KBr): 3320, 2930, 2850, 1740, 1650, 1600, 1450, 1220 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{21}H_{22}N_2ONa$ [M^++Na]: 341.1630. Found: 341.1633.

*4.2.4. N-Benzyl-2,4-diphenyloxazol-5-amine (**3ad**).* Silica gel column chromatography (benzene/ethyl acetate=20/1) gave **3ad** (47 mg, 48% yield) as a white amorphous. ^{1}H NMR (benzene-d_6): 4.88 (s, 2H), 7.18–7.26 (m, 7H), 7.40–7.47 (m, 6H), 7.92 (m, 2H), 8.24 (s, 1H). ^{13}C NMR (benzene-d_6): 49.0, 126.0, 126.4, 126.8, 128.2, 128.6, 128.7, 128.8, 129.2, 129.5, 130.1, 133.5, 135.1, 140.4, 158.9, 162.4. IR (KBr): 3340, 2930, 1700, 1640, 1550, 1500, 1450, 1330 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{22}H_{18}N_2ONa$ [M^++Na]: 349.1317. Found: 349.1322.

*4.2.5. N,2,4-Triphenyloxazol-5-amine (**3ae**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ae** (74 mg, 79% yield) as a yellow solid of mp=130.1–131.0 °C (EtOH). ^{1}H NMR ($CDCl_3$): 5.66 (br s, 1H), 6.82 (d, J=7.8 Hz, 2H), 6.92 (t, J=7.8 Hz, 1H), 7.23–7.29 (m, 3H), 7.37 (t, J=7.8 Hz, 2H), 7.43–7.48 (m, 3H), 7.91 (d, J=8.7 Hz, 2H), 8.06 (m, 2H). ^{13}C NMR ($CDCl_3$): 114.5, 120.6, 126.1, 126.1, 127.5, 127.6, 128.5, 128.7, 129.5, 130.2, 130.8, 131.1, 141.4, 143.5,

157.4. IR (KBr): 3230, 3030, 1640, 1600, 1540, 1500, 1330, 1260, 1080, 990 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{16}N_2ONa$ [M^++Na]: 335.1160. Found: 335.1156.

*4.2.6. N-(4-Methoxyphenyl)-2,4-diphenyloxazol-5-amine (**3af**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3af** (97 mg, 95% yield) as a yellow solid of mp=110.5–111.3 °C (EtOH). ^1H NMR ($CDCl_3$): 3.70 (s, 3H), 5.47 (br s, 1H), 6.71–6.77 (m, 4H), 7.20 (m, 1H), 7.31 (t, *J*=8.2 Hz, 2H), 7.37–7.40 (m, 3H), 7.83 (d, *J*=8.2 Hz, 2H), 7.98 (m, 2H). ^{13}C NMR ($CDCl_3$): 55.5, 114.8, 116.0, 126.0, 127.3, 127.4, 128.4, 128.6, 128.7, 129.5, 130.0, 131.2, 137.0, 142.5, 154.0, 156.9. IR (KBr): 3340, 2830, 1640, 1510, 1290, 1230, 1080, 1040, 990 cm^{-1}. HRMS-FAB (*m*/*z*): calcd for $C_{22}H_{19}N_2O_2$ [M^++H]: 343.1447. Found: 343.1441.

*4.2.7. N-(4-Bromophenyl)-2,4-diphenyloxazol-5-amine (**3ag**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **3ag** (115 mg, 98% yield) as a yellow amorphous. ^1H NMR ($CDCl_3$): 5.67 (br s, 1H), 6.59 (d, *J*=8.7 Hz, 2H), 7.18–7.32 (m, 5H), 7.34–7.37 (m, 3H), 7.79 (d, *J*=6.8 Hz, 2H), 7.97 (m, 2H). ^{13}C NMR ($CDCl_3$): 112.7, 116.2, 126.1, 126.2, 127.2, 127.8, 128.6, 128.7, 130.4, 130.7, 131.1, 132.3, 141.7, 142.6, 157.7. IR (KBr): 3370, 3060, 1640, 1600, 1490, 1330, 1240, 1070 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{16}BrN_2O$ [M^++H]: 391.0446. Found: 391.0443.

*4.2.8. N-(tert-Butyl)-4-(naphthalen-1-yl)-2-phenyloxazol-5-amine (**3ba**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ba** (52 mg, 51% yield) as a white solid of mp=133.3–134.5 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 1.20 (s, 9H), 7.35–7.46 (m, 7H), 7.72 (d, *J*=6.7 Hz, 1H), 7.77 (d, *J*=7.8 Hz, 1H), 7.81 (m, 1H), 7.99 (d, *J*=6.7 Hz, 2H), 8.03 (m, 1H). ^{13}C NMR ($CDCl_3$): 30.2. 53.8, 120.8, 125.4, 125.5, 125.7, 126.0, 126.3, 127.4, 127.7, 128.3, 128.4, 128.7, 129.3, 129.4, 131.7, 134.0, 150.2, 154.3. IR (KBr): 3290, 1650, 1550, 1330, 1170, 1080 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{23}N_2O$ [M^++H]: 343.1810. Found: 343.1809.

*4.2.9. N-(tert-Butyl)-4-(naphthalen-2-yl)-2-phenyloxazol-5-amine (**3ca**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **3ca** (100 mg, 97% yield) as a yellow solid of mp=138.0–139.0 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 1.38 (s, 9H), 7.42–7.49 (m, 6H), 7.82 (d, *J*=7.7 Hz, 1H), 7.88 (m, 2H), 8.06 (d, *J*=7.7 Hz, 2H), 8.14 (d, *J*=8.7 Hz, 1H), 8.36 (s, 1H). ^{13}C NMR ($CDCl_3$): 30.4, 54.4, 124.3, 125.6, 125.7, 125.8, 126.1, 127.6, 127.9, 128.0, 128.1, 128.7, 128.9, 129.2, 130.2, 132.3, 133.6, 148.2, 155.3. IR (KBr): 3260, 2960, 1630, 1340, 1200, 1070 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{22}N_2ONa$ [M^++Na]: 365.1630. Found: 365.1633.

*4.2.10. N-(tert-Butyl)-4-(4-methoxyphenyl)-2-phenyloxazol-5-amine (**3da**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **3da** (90 mg, 94% yield) as a white solid of mp=78.4–79.1 °C (EtOH). ^1H NMR ($CDCl_3$): 1.25 (s, 9H), 3.77 (s, 3H), 6.88 (d, *J*=9.1 Hz, 2H), 7.19 (s, 1H), 7.32–7.38 (m, 3H), 7.83 (d, *J*=9.1 Hz, 2H), 7.96 (m, 2H). ^{13}C NMR ($CDCl_3$): 30.3, 54.2, 55.2, 113.4, 125.2, 125.6, 126.6, 127.3, 128.0, 128.6, 129.5, 146.7, 155.4, 158.4. IR (KBr): 3260, 2960, 1640, 1600, 1540, 1510, 1360, 1250, 1070 cm^{-1}. HRMS-DART (*m*/*z*): calcd for $C_{20}H_{23}N_2O_2$ [M^++H]: 323.1760. Found: 323.1759.

*4.2.11. 4-(4-Bromophenyl)-N-(tert-butyl)-2-phenyloxazol-5-amine (**3ea**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ea** (81 mg, 73% yield) as a white solid of mp=118.4–119.0 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 1.27 (s, 9H), 7.34–7.38 (m, 4H), 7.45 (d, *J*=8.2 Hz, 2H), 7.78 (d, *J*=8.2 Hz, 2H), 7.94 (m, 2H). ^{13}C NMR ($CDCl_3$): 30.3, 54.3, 120.2, 125.2, 125.7, 127.4, 127.6, 128.7, 129.7, 131.4, 147.7, 155.4. IR (KBr): 3260, 2970, 1640, 1540, 1490, 1360, 1200, 1070, 970 cm^{-1}. HRMS-FAB (*m*/*z*): calcd for $C_{19}H_{20}BrN_2O$ [M^++H]: 371.0759. Found: 371.0766.

*4.2.12. N-(tert-Butyl)-2-phenyl-4-(o-tolyl)oxazol-5-amine (**3fa**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **3fa** (67 mg, 73% yield) as a yellow amorphous. ^1H NMR ($CDCl_3$): 1.21 (s, 9H), 2.31 (s, 3H), 7.12–7.21 (m, 3H), 7.24–7.38 (m, 5H), 7.94 (d, *J*=7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): 20.5, 30.1, 53.8, 123.0, 125.4, 125.8, 127.9, 128.6, 129.3, 129.6, 130.6, 131.2, 133.6, 137.6, 149.1, 154.1. IR (KBr): 3230, 2970, 1720, 1680, 1600, 1510, 1230, 1030 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{22}N_2ONa$ [M^++Na]: 329.1630. Found: 329.1633.

*4.2.13. N-(tert-Butyl)-2-phenyl-4-(m-tolyl)oxazol-5-amine (**3ga**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ga** (76 mg, 83% yield) as a yellow oil. ^1H NMR ($CDCl_3$): 1.29 (s, 9H), 2.33 (s, 3H), 6.99 (d, *J*=7.3 Hz, 1H), 7.22 (t, *J*=7.8 Hz, 1H), 7.30–7.39 (m, 4H), 7.60 (d, *J*=7.8 Hz, 1H), 7.68 (br s, 1H), 7.95 (m, 2H). ^{13}C NMR ($CDCl_3$): 21.6, 30.3, 54.1, 122.6, 125.0, 125.6, 126.6, 127.3, 127.9, 128.4, 128.6, 129.4, 132.5, 138.1, 147.9, 154.9. IR (KBr): 3290, 2970, 1640, 1550, 1450, 1370, 1210, 1070 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{23}N_2O$ [M^++H]: 307.1810. Found: 307.1809.

*4.2.14. N-(tert-Butyl)-2-phenyl-4-(p-tolyl)oxazol-5-amine (**3ha**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **3ha** (81 mg, 89% yield) as a yellow amorphous. ^1H NMR ($CDCl_3$): 1.26 (s, 9H), 2.29 (s, 3H), 7.14 (d, *J*=8.3 Hz, 2H), 7.18 (s, 1H), 7.30–7.39 (m, 3H), 7.74 (d, *J*=7.8 Hz, 2H), 7.96 (d, *J*=7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 30.3, 54.2, 125.5, 125.6, 125.8, 127.8, 128.0, 129.2, 129.5, 133.0, 136.3, 147.5, 155.0. IR (KBr): 3260, 2970, 1640, 1550, 1480, 1360, 1230, 1070 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{22}N_2ONa$ [M^++Na]: 329.1630. Found: 329.1632.

*4.2.15. N-(tert-Butyl)-4-phenyl-2-(p-tolyl)oxazol-5-amine (**3ia**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ia** (84 mg, 92% yield) as a white solid of mp=110.0–110.6 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): 1.27 (s, 9H), 2.33 (s, 3H), 7.16–7.19 (m, 4H), 7.33 (t, *J*=7.8 Hz, 2H), 7.83–7.86 (m, 4H). ^{13}C NMR ($CDCl_3$): 21.4, 30.3, 54.2, 125.2, 125.6, 125.8, 126.5, 128.4, 128.8, 129.3, 132.7, 139.7, 147.5, 155.4. IR (KBr): 3260, 2970, 1640, 1500, 1360, 1200, 1070, 970 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{22}N_2O$ [M^++Na]: 329.1630. Found: 329.1629.

*4.2.16. 2-(4-Bromophenyl)-N-(tert-butyl)-4-phenyloxazol-5-amine (**3ja**).* Silica gel column chromatography (hexane/ethyl acetate=5/1) gave **3ja** (89 mg, 80% yield) as a white solid of mp=115.2–115.9 °C (EtOH). ^1H NMR ($CDCl_3$): 1.29 (s, 9H), 7.15–7.22 (m, 2H), 7.35 (t, *J*=7.8 Hz, 2H), 7.54 (d, *J*=8.2 Hz, 2H), 7.84 (d, *J*=8.2 Hz, 2H), 7.92 (d, *J*=7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 30.3, 54.2, 123.8, 124.9, 125.7, 126.7, 127.1, 128.5, 128.6, 131.9, 132.3, 148.2, 154.0. IR (KBr): 3260, 2960, 1630, 1540, 1500, 1440, 1360, 1190 cm^{-1}. HRMS-DART (*m*/*z*): calcd for $C_{19}H_{20}BrN_2O$ [M^++H]: 371.0759. Found: 371.0751.

*4.2.17. N-(tert-Butyl)-2,4-diphenylthiazol-5-amine (**5aa**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **5aa** (87 mg, 94% yield) as a yellow oil. ^1H NMR ($CDCl_3$): 1.25 (s, 9H), 7.24–7.39 (m, 7H), 7.72 (d, *J*=7.8 Hz, 2H), 7.83 (d, *J*=7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 29.5, 53.5, 125.6, 127.1, 127.1, 127.9, 128.7, 128.8, 128.9, 134.2, 135.2, 141.2, 155.2. IR (KBr): 3360, 3060, 2970, 1700, 1600, 1520, 1370, 1200 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{20}N_2SNa$ [M^++Na]: 331.1245. Found: 331.1247.

*4.2.18. 2,4-Diphenyl-N-(2,4,4-trimethylpentan-2-yl)thiazol-5-amine (**5ab**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **5ab** (92 mg, 84% yield) as a yellow oil. ^1H NMR

($CDCl_3$): 0.92 (s, 9H), 1.29 (s, 6H), 1.58 (s, 2H), 7.20–7.26 (m, 2H), 7.28–7.38 (m, 5H), 7.66 (d, J=7.3 Hz, 2H), 7.82 (d, J=7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): 29.5, 31.5, 31.6, 53.2, 57.0, 125.4, 127.0, 127.9, 128.6, 128.7, 128.7, 134.2, 135.2, 138.5, 141.9, 153.9. IR (KBr): 3390, 2960, 1660, 1600, 1580, 1490, 1370, 1220, 1070 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{23}H_{28}N_2SNa$ [M^++H]: 387.1871. Found: 387.1879.

*4.2.19. N-Cyclohexyl-2,4-diphenylthiazol-5-amine (**5ac**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **5ac** (83 mg, 83% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): 1.14–1.32 (m, 5H), 1.55 (m, 1H), 1.68 (m, 2H), 2.07 (m, 2H), 3.00 (m, 1H), 4.10 (d, J=7.3 Hz, 1H), 7.20–7.25 (m, 2H), 7.30 (t, J=7.8 Hz, 2H), 7.38 (t, J=7.8 Hz, 2H), 7.69 (d, J=8.2 Hz, 2H), 7.79 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): 24.7, 25.6, 33.4, 59.1, 125.2, 126.5, 127.1, 128.4, 128.6, 129.2, 133.9, 134.4, 135.4, 145.8, 151.6. IR (KBr): 3380, 2930, 2860, 1670, 1590, 1490, 1360, 1070 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{21}H_{22}N_2SNa$ [M^++Na]: 357.1401. Found: 357.1399.

*4.2.20. N-(tert-Butyl)-4-(naphthalen-1-yl)-2-phenylthiazol-5-amine (**5ba**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **5ba** (97 mg, 90% yield) as a yellow oil. ^{1}H NMR (benzene-d_6): 1.15 (s, 9H), 7.29–7.34 (m, 8H), 7.78 (d, J=7.8 Hz, 1H), 7.84 (d, J=7.3 Hz, 2H), 7.89 (d, J=7.3 Hz, 2H). ^{13}C NMR (benzene-d_6): 29.4, 53.7, 125.6, 125.8, 126.1, 126.5, 127.6, 128.3, 128.3, 128.4, 128.9, 129.2, 131.1, 132.1, 133.5, 134.1, 137.8, 142.7, 155.4. IR (KBr): 3380, 2970, 1600, 1520, 1500, 1470, 1400, 1220 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{23}H_{22}N_2SNa$ [M^++Na]: 381.1401. Found: 381.1400.

*4.2.21. N-(tert-Butyl)-4-(naphthalen-2-yl)-2-phenylthiazol-5-amine (**5ca**).* Silica gel column chromatography (hexane/ethyl acetate=10/1) gave **5ca** (100 mg, 93% yield) as a yellow oil. ^{1}H NMR (benzene-d_6): 1.24 (s, 9H), 7.26–7.41 (m, 6H), 7.75–7.96 (m, 6H), 8.18 (br s, 1H). ^{13}C NMR (benzene-d_6): 29.5, 53.7, 125.7, 125.9, 126.1, 126.4, 126.5, 127.6, 128.0, 128.3, 128.7, 129.9, 132.4, 132.5, 133.4, 134.0, 140.1, 142.0, 155.6. IR (KBr): 3380, 2970, 1600, 1520, 1500, 1470, 1400, 1220 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{23}H_{22}N_2SNa$ [M^++Na]: 381.1401. Found: 381.1405.

*4.2.22. N-(tert-Butyl)-2-phenyl-4-(o-tolyl)thiazol-5-amine (**5da**).* Silica gel column chromatography (benzene/ethyl acetate=10/1) gave **5da** (70 mg, 72% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): 1.19 (s, 9H), 2.23 (s, 3H), 7.18–7.34 (m, 8H), 7.83 (d, J=6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): 20.0, 29.4, 53.2, 125.4, 125.9, 128.2, 128.6, 129.9, 130.8, 133.5, 134.1, 138.1, 139.7, 142.1, 154.5. IR (KBr): 3350, 2970, 1690, 1600, 1540, 1360, 1220 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{20}H_{22}N_2SNa$ [M^++Na]: 345.1401. Found: 345.1400.

*4.2.23. N-(tert-Butyl)-2-phenyl-4-(m-tolyl)thiazol-5-amine (**5ea**).* Silica gel column chromatography (benzene/ethyl acetate=10/1) gave **5ea** (61 mg, 63% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): 1.19 (s, 9H), 2.23 (s, 3H), 7.18–7.34 (m, 8H), 7.84 (d, J=6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 29.4, 53.7, 124.8, 125.7, 128.1, 128.6, 128.7, 129.0, 129.1, 129.2, 133.8, 134.5, 138.5, 141.4, 155.3. IR (KBr): 3370, 2970, 1670, 1600, 1470, 1370, 1220 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{20}H_{22}N_2SNa$ [M^++Na]: 345.1401. Found: 345.1398.

*4.2.24. N-(tert-Butyl)-2-phenyl-4-(p-tolyl)thiazol-5-amine (**5fa**).* Silica gel column chromatography (benzene/ethyl acetate=10/1) gave **5fa** (75 mg, 78% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): 1.25 (s, 9H), 2.32 (s, 3H), 7.17–7.19 (m, 3H), 7.25–7.34 (m, 3H), 7.60 (d, J=8.2 Hz, 2H), 7.85 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.2, 29.4, 53.5, 125.2, 125.4, 127.8, 128.7, 129.3, 132.1, 134.1, 136.8, 140.3, 141.2, 155.2. IR (KBr): 3320, 2970, 1660, 1600, 1530, 1500, 1370, 1220 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{20}H_{22}N_2SNa$ [M^++Na]: 345.1401. Found: 345.1402.

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Supplementary data

A Supplementary data file (^{1}H and ^{13}C NMR) of newly synthesized is available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.016.

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