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Synthesis of 2-Aryl/Heteroaryloxazolines from Nitriles under Metal- and Catalyst-Free Conditions and Evaluation of Their Antioxidant Activities

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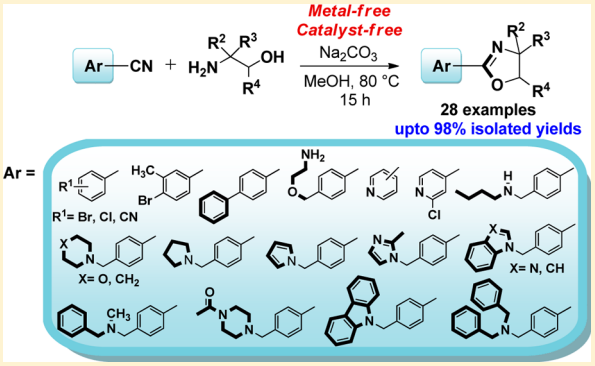
Supporting Information

ABSTRACT: The synthesis of structurally diverse 2-aryl/heteroaryloxazolines from nitriles and aminoalcohols has been achieved under metal- and catalyst-free conditions in good to excellent yields. An array of functional groups are well-tolerated, thus, allowing the introduction of many important biologically active motifs such as azoles, ring-fused azoles, saturated heterocyclics, and amines in 2-aryloxazoline scaffolds. An evaluation of the antioxidant properties using the DPPH (diphenyl picryl hydrazyl) assay method shows the pyrrole-functionalized 2-aryloxazoline to be the best antioxidant among all the synthesized 2-aryl/heteroaryloxazolines.



INTRODUCTION

2-Aryloxazoline scaffolds have been the core structures of many biologically active molecules that exhibit cytotoxic,[1a] antibacterial,[1b] antitumor,[1c,d] antidepressant,[1e,f] anti-Alzheimer's,[1g] or deferrating[1h] activities (Figure 1). Also, these moieties are used as synthetic intermediates,[2] protecting groups,[3] ligands,[4] or chiral auxiliaries[5] in many organic transformations. Furthermore, many polyoxazolines are useful biomaterials for drug and gene delivery, and stimuli-responsive systems.[6] In addition, oxazolines can also be dehydrogenated to produce oxazoles, another important class of bioactive molecules.[7] Recently, the antioxidant properties of aryl-substituted 2-oxazolines have also been explored.[8]

A number of chemical methods have been developed for the synthesis of 2-aryl/heteroaryloxazoline scaffolds using β-hydroxyl amides, olefins, carboxylic acids, esters, nitriles, aldehydes, or other carbonyl-containing compounds.[9−12] The transition-metal-catalyzed methods such as carbonylative cyclization of aryl bromides with 2-chloroethanamine[10] or direct arylation of C−H bond of nonaromatic oxazolines[11] often require long reaction hours at high reaction temperatures (>100 °C) and have limited substrate scope. Several catalysts such as $ZnCl_2$, Bi (III) salts, $ZrOCl_2{\cdot}8H_2O$, clay, cellulose sulfuric acid, silica sulfuric acid, $H_3PW_{12}O_{40}$, Cu complexes, and S−Co (II) salts have been used for the activation of nitriles toward nucleophilic addition by aminoalcohols.[12] Although the aforementioned methods are promising synthetic strategies for 2-aryl/heteroaryloxazolines, however, lack of general applicability, use of less abundant and expensive reagents or catalysts, harsh reaction conditions, high reaction temperatures, or long reaction hours limit their application. Moreover, contamination of drug-related precursors with even traces of transition metals can cause severe problems. As a result, there is a need to develop a general, cost-effective, and metal-free procedure for the synthesis of 2-aryl/heteroaryloxazolines for pharmaceutical purposes.

Herein, we describe metal- and catalyst-free condensation of nitriles with aminoalcohols for the synthesis of 2-aryl/heteroaryloxazolines and an evaluation of their antioxidant properties. Recently, we reported sodium carbonate-promoted coupling of esters with aminoalcohols for the synthesis of *N*-(hydroxyalkyl)cinnamamides,[13] whereby reaction of ester (*E*)-methyl *p*-cyanocinnamate (**7**) with 2-aminoethanol (**8a**) in the presence of Na_2CO_3 as base in methanol afforded major amounts of (*E*)-*N*-(2-hydroxyethyl)-4-cyanocinnamamide (**9**) along with a minor amount of oxazoline (*E*)-*N*-(2-hydroxyethyl)-4-(4,5-dihydrooxazol-2-yl)cinnamamide (**10**) under aerial conditions (Scheme 1). Intrigued by direct oxazoline formation from nitrile and aminoalcohol without the use of any metal catalyst or high temperature, we decided to further optimize the reaction conditions to obtain better yields of oxazolines.

RESULTS AND DISCUSSION

From our previous work (Scheme 1),[13] we inferred that the yield of oxazoline **10** increased upon increase in reaction time. Therefore, we began our work with the reaction of commercially available 4-bromobenzonitrile (**11a**) with 2-aminoethanol (**8a**) for the synthesis of 2-(4-bromophenyl)-

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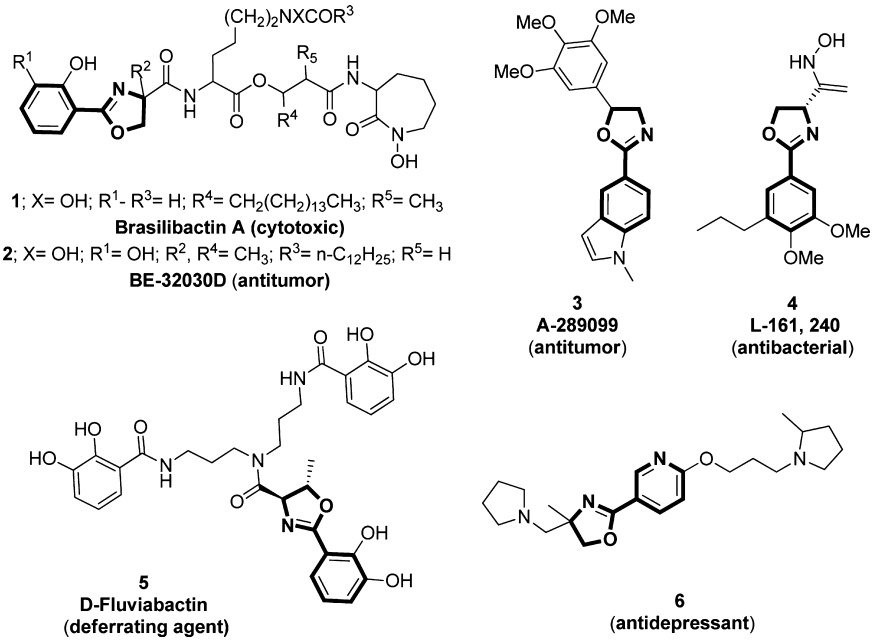
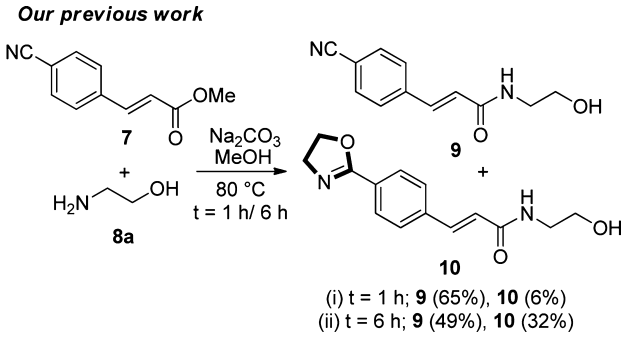


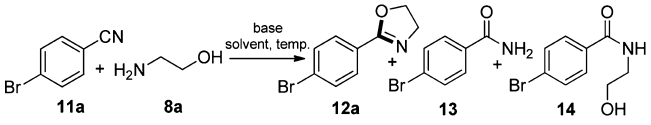
Figure 1. Examples of 2-aryl/heteroaryloxazoline-scaffold-based bioactive molecules.

Scheme 1. Formation of Oxazoline Ring[13]



4,5-dihydrooxazole (**12a**) by employing Na_2CO_3 as the base at 80 °C in MeOH under aerial conditions. The TLC monitoring of the reaction mixture at different time intervals showed the complete consumption of nitrile **11a** in 15 h affording 47% yield of the desired product **12a** together with the formation of 9% of 4-bromobenzamide (**13**) and 44% of 4-bromo-*N*-(2-hydroxyethyl)benzamide (**14**) (Table 1, entry 1). However, performing the same reaction under nitrogen atmosphere in dry MeOH significantly improved the yield of desired oxazoline **12a** to 89% with much reduced yields of byproducts **13** and **14** (Table 1, entry 2).[15c] Among different types of bases screened for this reaction, DBU gave 83% yield of **12a** (Table 1, entry 3) whereas other bases like NaOH, NaOMe, Et_3N, K_2CO_3, and NaOAc furnished much lower yields (11−77%) of the desired product (Table 1, entries 4−8). Interestingly, base-free conditions afforded 80% yield of **12a** along with traces of byproducts (Table 1, entry 9). Although **12a** could be isolated as the almost exclusive product under base-free conditions with good yield, the presence of Na_2CO_3 furnished better yield of the desired product. So, we decided to use Na_2CO_3 as the base in this transformation. Next, when we tried to reduce the reaction time from 15 to 10 h, the yield of **12a** dropped to 64% (Table 1, entry 10). The use of other solvents, such as EtOH, THF, and toluene resulted in unsatisfactory yields of **12a**

Table 1. Optimization of Reaction Conditions for the Synthesis of 12a[a]



				yield (%)[b]		
entry	base	temp (°C)	solvent	**12a**	**13**	**14**
1[c]	Na_2CO_3	80	MeOH	47	9	44
2	Na_2CO_3	80	MeOH	89	9	<5
3	DBU	80	MeOH	83	13	<5
4	NaOH	80	MeOH	11	30	45
5	NaOMe	80	MeOH	50	41	<5
6	Et_3N	80	MeOH	58	13	11
7	K_2CO_3	80	MeOH	75	24	traces
8	NaOAc	80	MeOH	77	14	<10
9		80	MeOH	80	traces	traces
10[d]	Na_2CO_3	80	MeOH	64	10	<5
11	Na_2CO_3	80	EtOH	55	12	14
12	Na_2CO_3	110	toluene	58	19	traces
13[e]	Na_2CO_3	60	THF	15		
14[f]	Na_2CO_3	80	MeOH	32	5	62
15[g]	Na_2CO_3	r.t.	MeOH	71	traces	traces
16	Na_2CO_3	60	MeOH	66	10	19

[a]**11a** (1.0 mmol), **8a** (5.0 mmol), base (1.0 mmol), dry solvent (1.0 mL), 80 °C, 15 h, under nitrogen atmosphere unless otherwise noted. [b]Isolated yields. [c]Under aerial conditions in undried MeOH. [d]Reaction run for 10 h. [e]Recovery yield of **11a** was 85%. [f]Using 3.0 mmol of **8a**. [g]Reaction carried out for 62 h.

(Table 1, entries 11−13). Furthermore, the amount of **8a** was also found to be crucial to obtain high conversions, thus, a decrease in the amount of **8a** from 5.0 to 3.0 mmol reduced the desired product yield to 32% (Table 1, entry 14). The reaction could also be performed at room temperature, affording **12a** in 71% yield although with traces of byproducts; however, 62 h of reaction time was required (Table 1, entry 15). Lowering the

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reaction temperature to 60 °C reduced the yield of **12a** to 66% (Table 1, entry 16). After a series of attempts, we concluded that the best conversion could be carried out using nitrile (1.0 mmol) and aminoalcohol (5.0 mmol) together with anhydrous Na_2CO_3 (1.0 mmol) as base for 15 h in dry MeOH (1.0 mL) as solvent under nitrogen atmosphere at 80 °C.

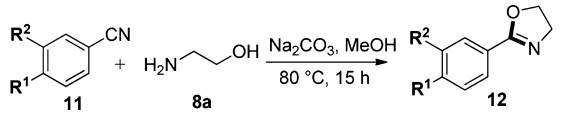
The formation of **14** during the reaction of nitrile **11a** with **8a** led us to speculate **14** as the probable intermediate in the transformation of nitrile **11a** to oxazoline **12a**. However, reaction with **14** as the starting precursor in place of nitrile **11a** did not show any traces of oxazoline formation. This ruled out the participation of **14** as an intermediate in this transformation.

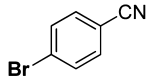
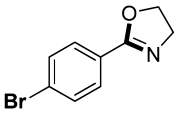
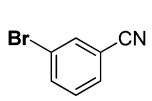
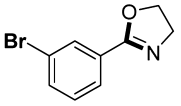
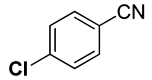
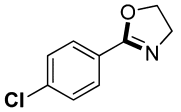
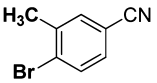
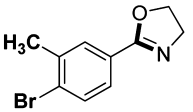
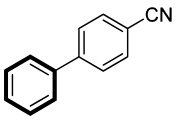
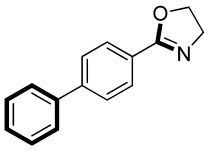
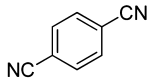
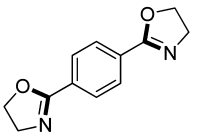
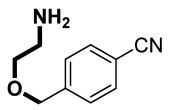
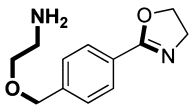
With the optimized reaction conditions, a variety of aryl nitriles produced the desired oxazolines in good to excellent yields (Table 2). Both electron-donating as well as electron-withdrawing groups were well-tolerated. The halide substituted nitriles **11a−d** condensed well with **8a**, thus, expanding the scope for further derivatization of 2-aryloxazolines. The presence of an electron-donating group such as methyl reduced the reactivity of aryl nitriles in the reaction, affording 74% of **12d** as compared to 89% of **12a** (Table 2, entries 1 and 4). The reaction with dinitrile, 1,4-dicyanobenzene (**11f**), produced 71% yield of the corresponding bisoxazoline product **12f** selectively with no monooxazoline formation (Table 2, entry 6). Also, the unprotected amino group in nitrile **11g** was unaffected under the basic reaction conditions employed in this protocol, thus, producing the corresponding oxazoline **12g** in 88% yield (Table 2, entry 7).

The heteroaryl nitriles with a pyridine ring were also found to be compatible substrates under the optimized reaction conditions (Table 3). The 2-heteroaryloxazolines **16a−c** were successfully synthesized with nicotinonitrile- and isonicotinonitrile-based substrates in 83−97% yields. Furthermore, the effect of an electron-withdrawing group was noticeable when condensation of 2-chloroisonicotinonitrile (**15c**) with **8a** produced 97% of the desired oxazoline **16c**, as compared to isonicotinonitrile (**15b**) which produced **16b** in 85% yield (Table 3, entries 2 and 3).

Furthermore, 2-aryloxazoline derivatives bearing nitrogen heterocycles are also important structural scaffolds in natural product chemistry and pharmaceutical agents that exhibit antidiabetic, anti-Alzheimer's, antibiotic, antihypertensive, and deferrating activities.[1g,h,14] This turned our attention toward the preparation of structurally diverse 2-aryloxazoline derivatives functionalized with synthetically and biologically important *N*-substituted cyclic and acyclic groups such as azoles, ring-fused azoles, saturated heterocycles, and amines (Table 4). As summarized in Table 4, both aliphatic and aromatic heterocycles gave the corresponding 2-aryloxazolines in moderate to good yields (44−71%). The saturated heterocycles such as morpholine, *N*-acetylated piperazine, piperidine, and pyrrollidine in nitrile precursors **17a−d** were well-tolerated in this transformation, affording the corresponding oxazolines **18a−d** in moderate to good yields (44−64%, Table 4, entries 1−4). The acetyl group in substrate **17b**, which is a reactive site for nucleophilic addition, remained unaffected under the employed reaction conditions. It is worth noting that mGluR5 modulators such as **19** and **20**, useful in the treatment of psychiatric and mood disorders, have been partially incorporated in the oxazolines **18c** and **18d**.[14c] Similarly, the indole- and benzimidazole-functionalized oxazoline scaffolds **18g** and **18h**, which were isolated in 48% and 71% yields respectively (Table 4, entries 7 and 8), constitute a part of the skeleton of compounds **21** and **22**, which are used in the treatment of central nervous system disorders related to or affected by the histamine-3-receptors.[1g] Structures of **18g** and **18h** were confirmed by X-ray diffraction (Figures S1,S2, Supporting Information). Also, the nitriles substituted with *N*-alkylated or *N*-benzylated amines **17i−k** performed well as precursors in reaction with **8a**, affording the desired products **18i−k** in 47−69% yields (Table 4, entries 9−11). The NH group that is sensitive to basic conditions was not affected during the reaction of nitrile **17i**, thus, providing scope for further derivatization (Table 4, entry 9). However, carbazole bearing nitrile **17l** could not be activated toward oxazoline ring formation, which could be due to its poor solubility in methanol.

Table 2. Scope of Aryl Nitriles in Oxazoline Formation[a]



Entry	11	12	Yield (%)[b]
1	 **11a**	 **12a**	89
2	 **11b**	 **12b**	83
3	 **11c**	 **12c**	75
4	 **11d**	 **12d**	74
5	 **11e**	 **12e**	52
6	 **11f**	 **12f**	71
7	 **11g**	 **12g**	88

[a]Reaction conditions: **11** (1.0 mmol), **8a** (5.0 mmol), anhydrous Na_2CO_3 (1.0 mmol), dry MeOH (1.0 mL), 80 °C, 15 h, under nitrogen atmosphere. [b]Isolated yields.

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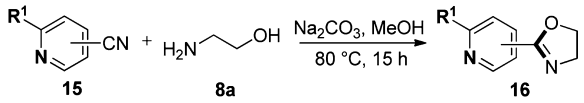
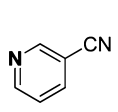
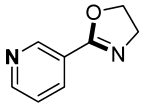
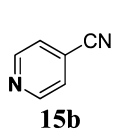
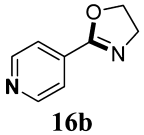
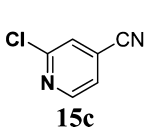
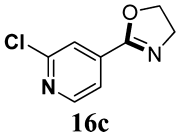
Table 3. Scope of Heteroaryl Nitriles in Oxazoline Formation[a]



15 8a 16

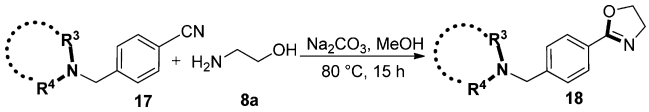
Entry	15	16	Yield (%)[b]
1	 **15a**	 **16a**	83
2	 **15b**	 **16b**	85
3	 **15c**	 **16c**	97

[a]Reaction conditions: **15** (1.0 mmol), **8a** (5.0 mmol), anhydrous Na_2CO_3 (1.0 mmol), dry MeOH (1.0 mL), 80 °C, 15 h, under nitrogen atmosphere. [b]Isolated yields.

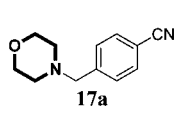
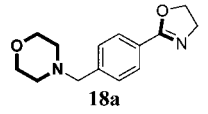
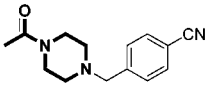
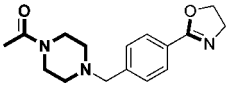
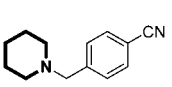
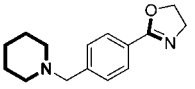
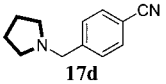
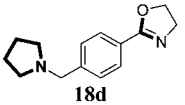
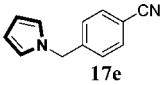
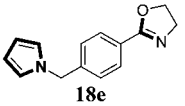
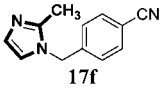
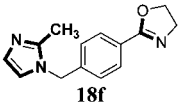
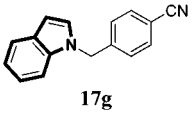
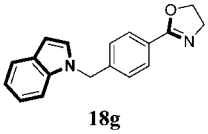
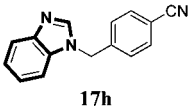
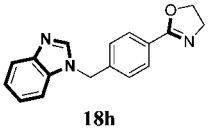
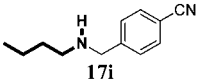
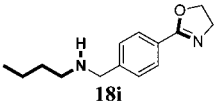
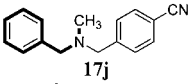
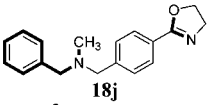
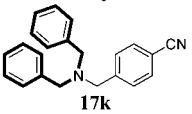
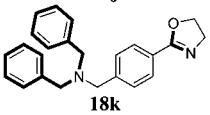
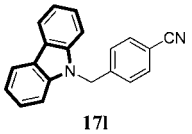
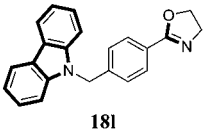
After the successful screening of nitriles, a variety of aminoalcohols were screened as the condensation partners in the oxazoline formation reaction. As shown in Table 5, the selected aminoalcohols afforded moderate to excellent yields (28−98%) of the desired products **23a−e** under the optimized reaction conditions (Table 5, entries 1−5). Use of 2.0 equiv of Na_2CO_3 with aminoalcohols **8b** and **8c** improved the yields of corresponding oxazolines **23a** and **23b** from 57% to 98% and 55% to 71% respectively (Table 5, entries 1 and 2). However, no significant improvements in the isolated yields of products could be observed with other aminoalcohols **8e** and **8f** on using 2.0 equiv of Na_2CO_3. Moreover, the heteroaryl nitrile **15c** proved to be more effective substrate for sterically hindered aminoalcohol **8e**, giving oxazoline **23e** in 98% yield in contrast to the aryl nitrile **11a** which afforded only 28% of compound **23d** with **8e** (Table 5, entries 4 and 5). The reaction conditions were also suitable for the formation of six-membered oxazine ring in **23f**, albeit in moderate (58%) yield (Table 5, entry 6). Additionally, the same conditions could also be applied to the synthesis of 2-arylimidazolines. The use of ethane-1,2-diamine (**8g**) in place of aminoalcohols **8a−f**, produced 2-arylimidazoline **23g** in moderate (54%) yield (Table 5, entry 7).

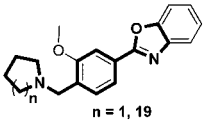
On the basis of above results, a plausible mechanism for the synthesis of oxazolines from nitriles and aminoalcohols is depicted in Scheme 2. The initial step is the in situ formation of imidate **I** via nucleophilic addition of methanol to nitrile group under basic conditions.[15b,c] Then, **I** is further attacked by the aminoalcohol nitrogen affording *β*-hydroxyamidine **II** which undergoes in situ intramolecular cyclization with subsequent loss of ammonia, to form oxazoline ring (Scheme 2).[15a] With reduced amount of aminoalcohol, alcoholysis of the intermediate imidate ester occurs leading to the formation of normal esters via decomposition of ortho esters.[15d] Furthermore, the subsequent reaction of normal esters with aminoalcohols produces the transamidation products.[15e] Therefore, use of 5.0 mmol of aminoalcohol produced oxazoline **12a** as the major

Table 4. Synthesis of Substituted 2-Aryloxazolines[a,b]



17 8a 18

Entry	17	18	Yield (%)[c]
1	 **17a**	 **18a**	51
2	 **17b**	 **18b**	44
3	 **17c**	 **18c**	64
4	 **17d**	 **18d**	57
5[d]	 **17e**	 **18e**	46
6	 **17f**	 **18f**	60
7	 **17g**	 **18g**	48
8	 **17h**	 **18h**	71
9	 **17i**	 **18i**	59
10	 **17j**	 **18j**	69
11	 **17k**	 **18k**	47
12	 **17l**	 **18l**	n.r.



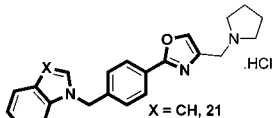


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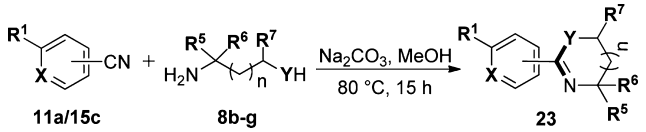
Table 4. continued

[a]Reaction conditions: **17** (1.0 mmol), **8a** (5.0 mmol), anhydrous Na_2CO_3 (1.0 mmol), dry MeOH (1.0 mL), 80 °C, 15 h, under nitrogen atmosphere. [b]Unreacted nitriles and minor amounts of amides were also isolated along with the desired oxazolines during column purification. [c]Isolated yields. [d]Structure of amide **18ea** was confirmed by X-ray diffraction (Figure S3, Supporting Information).

Table 5. Screening of Aminoalcohols[a,b]



11a/15c 8b-g 23

Entry	Nitrile	8b-g	23	Yield (%)[c]
1	**11a**	**8b**	**23a**	57 (98)[d]
2	**11a**	**8c**	**23b**	55 (71)[d]
3	**11a**	**8d**	**23c**	92
4	**11a**	**8e**	**23d**	28
5	**15c**	**8e**	**23e**	98
6	**11a**	**8f**	**23f**	58
7	**11a**	**8g**	**23g**	54

[a]Reaction conditions: **11a**/**15c** (1.0 mmol), **8b**−**g** (5.0 mmol), anhydrous Na_2CO_3 (1.0 mmol), dry MeOH (1.0 mL), 80 °C, 15 h, under nitrogen atmosphere. [b]Unreacted nitriles and minor amounts of amides were also isolated along with the desired oxazolines during column purification in all the cases excluding entry 5. [c]Isolated yields. [d]Using 2.0 mmol of Na_2CO_3.

product, whereas, use of 3.0 mmol of aminoalcohol produced major amount of transamidation product **14** with reduced yield of the oxazoline **12a**.

Antioxidant Activity of Synthesized 2-Aryl/Heteroaryloxazolines. The antioxidant activity of the synthesized 2-aryl/heteroaryloxazolines was measured with a simple and rapid DPPH radical scavenging method using ascorbic acid as the standard.[16] The sample solutions (1 mg mL^{-1}) of all the compounds were prepared in methanol. The freshly prepared DPPH (1.0 mL, 3×10^{-4} M) solution was added to 2.5 mL of the sample solution and allowed to react at room temperature for 30 min. After 30 min, the absorbance was measured at 517 nm. The experiment was repeated three times. The percentage of antioxidant activity are summarized in Table 6. Among all the synthesized 2-aryl/heteroaryloxazolines, 2-(4-((1*H*-pyrrol-1-yl)methyl)phenyl)-4,5-dihydrooxazole (**18e**) exhibited maximum antioxidant activity (81%) at the concentration of 1 mg mL^{-1} with an IC_{50} value of 320 μg mL^{-1} (1.42 mM), whereas compounds **23a**, **18b**, and **18g** showed moderate antioxidant activity (51−57%). Notably, the antioxidant potential of compound **18e** could be seen even at lower concentrations (750, 500, 250, and 125 μg mL^{-1}) (Figure 2). The DPPH scavenging potential of **18e** was found to decrease with decrease in concentration. The effectiveness of **18e** over other compounds in scavenging DPPH activity shows the significance of pyrrole nucleus in enhancing the antioxidant capability of 2-aryloxazolines.[8c,17]

Scheme 2. Proposed Mechanism for the Synthesis of Oxazolines from Nitriles

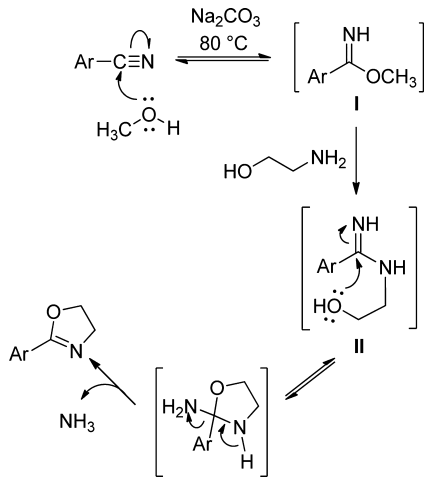


Table 6. Antioxidant Activity Data for 2-Aryl/Heteroaryloxazolines

compd	DPPH scavenging (%)[a]	compd	DPPH scavenging (%)[a]
12a	28	**18f**	22
12b	25	**18g**	52
12c	3	**18h**	32
12d	32	**18i**	23
12e	17	**18j**	40
12f	19	**18k**	25
12g	35	**23a**	57
16a	31	**23b**	22
16b	36	**23c**	3
16c	49	**23d**	21
18a	36	**23e**	16
18b	51	**23f**	22
18c	25	**23g**	29
18d	44	ascorbic acid[b]	97
18e	**81**		

[a]Results are mean of three different experiments. [b]Standard.

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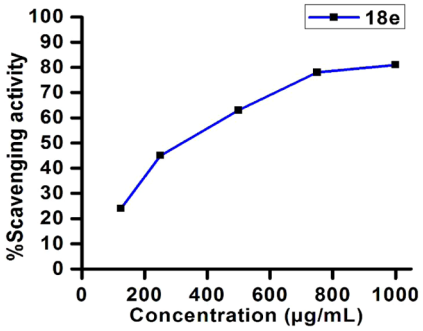

Figure 2. % Scavenging activity vs concentration of compound **18e**.

CONCLUSIONS

In conclusion, a variety of aryl and heteroaryl nitriles were successfully activated under metal- and catalyst-free conditions delivering 2-aryl/heteroaryloxazoline scaffolds with wide skeletal diversity. A small library of 2-aryloxazolines functionalized with biologically active motifs such as azoles, ring-fused azoles, saturated heterocyclics, and amines could be successfully synthesized in moderate to good yields. The pyrrole-functionalized 2-aryloxazoline displayed maximum antioxidant activity among all the 2-aryl/heteroaryloxazolines tested. The general applicability of the experimental procedure, operational simplicity, ready availability of the starting materials, and presence of functional group handle in many of the synthesized 2-aryl/heteroaryloxazolines will promote their synthesis for pharmaceutical applications.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere using standard Schlenk techniques. All solvents were dried according to standard procedures. Column chromatography was carried out with silica gel 60−120 mesh. The ^{1}H (400 MHz) and ^{13}C{^{1}H} (100 MHz) NMR spectra were recorded in $CDCl_3$ at 25 °C. The chemical shifts are expressed in parts per million (δ) relative to residual solvent protons of $CDCl_3$: δ 7.24 for ^{1}H NMR and δ 77.0 for ^{13}C{^{1}H} NMR. The following abbreviations are used for multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High-resolution mass spectra were measured on a high-resolution TOF instrument with electrospray ionization (ESI). Melting points are uncorrected. The nitrile substrates **17a**,[18] **17c**,[19] and **17d−l**[20−27] were prepared according to the literature.

*Synthesis of 4-(2-Aminoethoxy)methyl)benzonitrile (**11g**).* A mixture of 4-(bromomethyl)benzonitrile (0.981g, 5.0 mmol), 2-aminoethanol (1.53 g, 25.0 mmol), and anhydrous Na_2CO_3 (0.53 g, 5.0 mmol) in dry MeOH (5.0 mL) was stirred under nitrogen atmosphere at 80 °C for 4 h. On completion of reaction, the reaction mixture was concentrated to give a viscous residue. Purification of the crude reaction mixture by column chromatography on silica gel ($CHCl_3$/MeOH = 32:1 afforded compound **11g** (0.705 g, 80%) as a yellow solid. mp = 71−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 3.85 (s, 2H), 3.66 (t, J = 5.0 Hz, 2H), 2.77 (t, J = 5.1 Hz, 2H), 1.93 (br s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.3, 132.1, 128.6, 118.8, 110.6, 60.7, 52.9, 50.5; IR (KBr, υ cm^{-1}): 3422, 3246, 3089, 2920, 2861, 2228, 1625, 1492, 1347, 1295, 1235, 1204, 1179, 1143, 1106, 1053, 990, 961, 923, 856; HRMS (ESI-TOF) m/z: [M + H]$^{+}$ calcd for $C_{10}H_{13}N_2O$, 177.1022; found, 177.1026.

*Synthesis of 4-((4-Acetylpiperazin-1-yl)methyl)benzonitrile (**17b**).* A mixture of 4-(bromomethyl)benzonitrile (0.981 g, 5.0 mmol), *N*-acetylpiperazine (0.641 g, 5.0 mmol), and potassium hydroxide (1.12 g, 20.0 mmol) in dry THF (10.0 mL) was stirred under nitrogen atmosphere at room temperature for 2 days. On completion of reaction, the reaction mixture was concentrated to give a viscous residue. Purification of the crude reaction mixture by column chromatography on silica gel ($CHCl_3$/MeOH = 32:1 afforded compound **17b** (1.075 g, 88%) as a white solid. mp = 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 3.60 (t, J = 5.1 Hz, 2H), 3.54 (s, 2H), 3.44 (t, J = 5.1 Hz, 2H), 2.42−2.38 (m, 4H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.9, 143.4, 132.2, 129.4, 118.8, 111.1, 62.2, 53.1, 52.7, 46.2, 41.3, 21.3; IR (KBr, υ cm^{-1}): 3462, 3068, 2997, 2919, 2867, 2810, 2225, 1638, 1438, 1421, 1368, 1350, 1306, 1250, 1138, 995; HRMS (ESI-TOF) m/z: [M + H]$^{+}$ calcd for $C_{14}H_{18}N_3O$, 244.1444; found, 244.1451.

General Experimental Procedure for the Synthesis of 2-Aryl/Heteroaryloxazolines. To a solution of nitrile (1.0 mmol) and anhydrous Na_2CO_3 (106 mg, 1.0 mmol) in dry methanol (1.0 mL) under nitrogen atmosphere, aminoalcohol (5.0 mmol) was added, and the reaction mixture was stirred at 80 °C for 15 h. After 15 h, the reaction mixture was cooled to room temperature and concentrated. Purification of the crude reaction mixture by column chromatography on silica gel (PE/EtOAc or $CHCl_3$/MeOH) afforded the desired 2-aryl/heteroaryloxazoline products.

*2-(4-Bromophenyl)-4,5-dihydrooxazole (**12a**).*[12j] Column chromatography purification (PE/EtOAc = 9:1) afforded compound **12a** (198.2 mg, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 4.38 (t, J = 9.6 Hz, 2H), 4.00 (t, J = 9.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.8, 131.5, 129.6, 126.7, 125.9, 67.7, 54.9.

*2-(3-Bromophenyl)-4,5-dihydrooxazole (**12b**).*[9i] Column chromatography purification (PE/EtOAc = 9:1) afforded compound **12b** (187.8 mg, 83%) as a colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 4.36 (t, J = 9.8 Hz, 2H), 3.99 (t, J = 9.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.2, 134.1, 131.0, 129.8, 129.5, 126.6, 122.2, 67.7, 54.8.

*2-(4-Chlorophenyl)-4,5-dihydrooxazole (**12c**).*[12j] Column chromatography purification (PE/EtOAc = 9:1) afforded compound **12c** (135.6 mg, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 4.42 (t, J = 9.8 Hz, 2H), 4.04 (t, J = 9.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.7, 137.3, 129.4, 128.5, 126.2, 67.7, 54.9.

*2-(4-Bromo-3-methylphenyl)-4,5-dihydrooxazole (**12d**).*[28] Column chromatography purification (PE/EtOAc = 19:1) afforded compound **12d** (178.3 mg, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.56−7.50 (m, 2H), 4.37 (t, J = 9.6 Hz, 2H), 3.99 (t, J = 9.6 Hz, 2H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.9, 138.0, 132.3, 130.2, 128.3, 126.8, 126.7, 67.6, 54.8, 22.7.

*2-((1,1′-Biphenyl)-4-yl)-4,5-dihydrooxazole (**12e**).*[10] Column chromatography purification (PE/EtOAc = 9:1) afforded compound **12e** (115.8 mg, 52%) as a white solid. ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.5 Hz, 2H), 7.65−7.60 (m, 4H), 7.46−7.42 (m, 2H), 7.38−7.34 (m, 1H), 4.48 (t, J = 9.8 Hz, 2H), 4.09 (t, J = 9.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 143.9, 140.2, 128.8, 128.6,127.9, 127.1, 127.0, 126.5, 67.6, 54.9.

*1,4-Bis(4,5-dihydrooxazol-2-yl)benzene (**12f**).*[12j] Column chromatography purification (PE/EtOAc = 1:1) afforded compound **12f** (152.5 mg, 71%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 4H), 4.42 (t, J = 9.8 Hz, 4H), 4.05 (t, J = 9.8 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.0, 130.2, 128.1, 67.7, 55.0.

*2-((4-(4,5-Dihydrooxazol-2-yl)benzyl)oxy)ethanamine (**12g**).* Column chromatography purification ($CHCl_3$/MeOH = 13:1) afforded compound **12g** (194.3 mg, 88%) as a white solid. mp = 49−51 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.41 (t, J = 9.6 Hz, 2H), 4.03 (t, J = 9.6 Hz, 2H), 3.87 (s, 2H), 3.67 (t, J = 5.1 Hz, 2H), 2.81 (t, J = 5.0 Hz, 2H), 2.66 (br s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 143.1, 128.3, 128.1, 126.6, 67.6, 60.8, 54.9, 53.1, 50.5; IR (KBr, υ cm^{-1}): 3312, 2934, 2850, 1647, 1572, 1513, 1458, 1417, 1364, 1262, 1217, 1076, 1020, 978, 945, 838, 769, 682, 667; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{17}N_2O_2$, 221.1285; found, 221.1295.

*2-(Pyridin-3-yl)-4,5-dihydrooxazole (**16a**).*[12j] Column chromatography purification ($CHCl_3$/MeOH = 49:1) afforded compound **16a** (123.1 mg, 83%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, J = 1.8 Hz, 1H), 8.66 (dd, J = 5.0, 1.8 Hz, 1H), 8.17 (dt, J = 7.8, 1.8 Hz, 1H), 7.31 (ddd, J = 7.8, 5.0, 0.9 Hz, 1H), 4.42 (t, J = 9.6 Hz, 2H), 4.04 (t, J = 9.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.6, 151.9, 149.4, 135.4, 123.8, 123.1, 67.7, 54.9.

*2-(Pyridin-4-yl)-4,5-dihydrooxazole (**16b**).*[12j] Column chromatography purification ($CHCl_3$/MeOH = 49:1) afforded compound **16b** (126 mg, 85%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 5.5 Hz, 2H), 7.77 (d, J = 6.1 Hz, 2H), 4.45 (t, J = 9.8 Hz, 2H), 4.08 (t, J = 9.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.0, 150.2, 135.1, 121.9, 67.9, 55.1.

*2-(2-Chloropyridin-4-yl)-4,5-dihydrooxazole (**16c**).* Column chromatography purification (PE/EtOAc = 4:1) afforded compound **16c** (177.5 mg, 97%) as a white solid. mp = 102−103 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, J = 4.9 Hz, 1H), 7.80 (s, 1H), 7.70−7.69 (m, 1H), 4.46 (t, J = 9.8 Hz, 2H), 4.09 (t, J = 9.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.9, 152.1, 150.1, 138.0, 122.8, 120.6, 68.1, 55.1; IR (KBr, υ cm^{-1}): 3313, 2925, 1653, 1595, 1545, 1473, 1388, 1259, 1137, 1077, 976, 942, 775, 728, 696, 476; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_8ClN_2O$, 183.0320; found, 183.0350.

*2-(4-(Morpholin-4-ylmethyl)phenyl)-4,5-dihydrooxazole (**18a**).* Column chromatography purification ($CHCl_3$/MeOH = 49:1) afforded compound **18a** (125 mg, 51%) as a light yellow solid. mp = 67−69 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 4.38 (t, J = 9.6 Hz, 2H), 4.01 (t, J = 9.6 Hz, 2H), 3.68−3.66 (m, 4H), 3.49 (s, 2H), 2.42−2.39 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 141.2, 129.0, 128.1, 126.6, 67.5, 66.8, 63.0, 54.8, 53.5; IR (KBr, υ cm^{-1}): 2957, 2855, 2810, 1718, 1651, 1573, 1513, 1480, 1455, 1417, 1351, 1333, 1286, 1261, 1116, 1071, 1035, 1008, 976, 944, 915, 867, 799, 756, 680; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2$, 247.1441; found, 247.1443.

*1-(4-(4-(4,5-Dihydrooxazol-2-yl)benzyl)piperazin-1-yl)-ethanone (**18b**).* Column chromatography purification ($CHCl_3$/MeOH = 49:1) afforded compound **18b** (127.3 mg, 44%) as a white solid. mp = 144.145 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.40 (t, J = 9.6 Hz, 2H), 4.03 (t, J = 9.6 Hz, 2H), 3.59 (t, J = 5.0 Hz, 2H), 3.53 (s, 2H), 3.43 (t, J = 5.0 Hz, 2H), 2.41−2.38 (m, 4H), 2.04 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.9, 164.4, 141.1, 128.9, 128.1, 126.7, 67.5, 62.4, 54.8, 53.0, 52.7, 46.2, 41.3, 21.3; IR (KBr, υ cm^{-1}): 2943, 2908, 2804, 2771, 1629, 1434, 1349, 1309, 1268, 1256, 1235, 1145, 1104, 1068, 1017, 1002, 988, 940, 898, 850, 732, 676, 622, 582; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_2$, 288.1707; found, 288.1715.

*2-(4-(Piperidin-1-ylmethyl)phenyl)-4,5-dihydrooxazole (**18c**).* Column chromatography purification ($CHCl_3$/MeOH = 49:1) afforded compound **18c** (155.6 mg, 64%) as a light yellow solid. mp = 70−72 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 4.39 (t, J = 9.5 Hz, 2H), 4.02 (t, J = 9.5 Hz, 2H), 3.52 (s, 2H), 2.39 (br s, 4H), 1.61−1.55 (m, 4H), 1.43−1.40 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 129.3, 128.1, 126.6, 67.5, 63.2, 54.9, 54.3, 25.6, 24.0; IR (KBr, υ cm^{-1}): 3281, 2930, 2854, 2795, 1718, 1652, 1458, 1417, 1362, 1261, 1101, 1069, 1039, 1020, 945, 865, 801, 679; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$, 245.1648; found, 245.1657.

*2-(4-(Pyrrolidin-1-ylmethyl)phenyl)-4,5-dihydrooxazole (**18d**).* Column chromatography purification ($CHCl_3$/MeOH = 9:1) afforded compound **18d** (130.3 mg, 57%) as a yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$ δ 7.83 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 4.36 (t, J = 9.6 Hz, 2H), 3.99 (t, J = 9.6 Hz, 2H), 3.59 (s, 2H), 2.46−2.45 (m, 4H), 1.74−1.72 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 142.7, 128.7, 128.0, 126.2, 67.5, 60.3, 54.8, 54.1, 23.3; IR (KBr, υ cm^{-1}): 2966, 2877, 2797, 1648, 1416, 1363, 1330, 1261, 1196, 1125, 1070, 1020, 976, 944, 881, 849, 730, 681; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O$, 231.1492; found, 231.1505.

*2-(4-((1H-Pyrrol-1-yl)methyl)phenyl)-4,5-dihydrooxazole (**18e**).* Column chromatography purification ($CHCl_3$/MeOH = 99:1) afforded compound **18e** (103.7 mg, 46%) as a white solid. mp = 75−76 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 6.68−6.67 (m, 2H), 6.19−6.18 (m, 2H), 5.10 (s, 2H), 4.42 (t, J = 9.6 Hz, 2H), 4.04 (t, J = 9.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 141.4, 128.5, 127.0, 126.7, 121.1, 108.7, 67.5, 54.8, 52.9; IR (KBr, υ cm^{-1}): 2928, 1641, 1390, 1261, 1182, 1068, 940, 862, 732, 696; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$, 227.1179; found, 227.1172.

*2-(4-(2-Methylimidazol-1-ylmethyl)-phenyl)-4,5-dihydrooxazole (**18f**).* Purification by preparative TLC on silica gel G ($CHCl_3$/MeOH = 19:1) afforded compound **18f** (144.2 mg, 60%) as a dark yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.85 (s, 1H), 6.75 (s, 1H), 4.97 (s, 2H), 4.31 (t, J = 9.6 Hz, 2H), 3.93 (t, J = 9.6 Hz, 2H), 2.19 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7, 144.6, 139.3, 128.4, 127.1, 127.0, 126.2, 119.7, 67.4, 54.5, 49.1, 12.6; IR (KBr, υ cm^{-1}): 2923, 1648, 1420, 1364, 1263, 1078, 1020, 987, 943, 832, 724, 688; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}N_3O$, 242.1288; found, 242.1292.

*1-(4-(4,5-Dihydrooxazol-2-yl)-benzyl)-1H-indole (**18g**).* Column chromatography purification (PE/EtOAc = 9:1) afforded compound **18g** (133.3 mg, 48%) as a yellow solid. mp = 122−123 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.26−7.22 (m, 1H),

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7.18−7.10 (m, 5H), 6.58−6.57 (m, 1H), 5.36 (s, 2H), 4.41 (t, J = 9.6 Hz, 2H), 4.04 (t, J = 9.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 140.8, 136.1, 128.7, 128.6, 128.2, 127.0, 126.6, 121.8, 121.0, 119.6, 109.6, 101.9, 67.6, 54.8, 49.8; IR (KBr, υ cm^{-1}): 3046, 2929, 2874, 1648, 1459, 1418, 1356, 1333, 1316, 1260, 1193, 1179, 1068, 1016, 976, 943, 824, 748, 722, 671; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}N_2O$, 277.1335; found, 277.1343.

2-(4-((1H-Benzo[d]imidazol-1-yl)methyl)phenyl)-4,5-dihydrooxazole (**18h**). Column chromatography purification (PE/EtOAc = 9:1) afforded compound **18h** (196.9 mg, 71%) as a white solid. mp = 154−155 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.90−7.87 (m, 2H), 7.82−7.80 (m, 1H), 7.28−7.17 (m, 5H), 5.37 (s, 2H), 4.39 (t, J = 9.6 Hz, 2H), 4.02 (t, J = 9.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.0, 143.9, 143.1, 138.6, 133.7, 128.8, 127.8, 126.9, 123.2, 122.4, 120.4, 109.9, 67.6, 54.9, 48.5; IR (KBr, υ cm^{-1}): 2927, 2903, 2874, 1648, 1611, 1497, 1460, 1434, 1415, 1359, 1286, 1261, 1200, 1188, 1066, 1014, 972, 942, 826, 752, 721, 670; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}N_3O$, 278.1288; found, 278.1294.

N-(4-(4,5-Dihydrooxazol-2-yl)benzyl)butan-1-amine (**18i**). Column chromatography purification ($CHCl_3$/MeOH = 13:1) afforded compound **18i** (135.9 mg, 59%) as a yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 4.34 (t, J = 9.8 Hz, 2H), 3.96 (t, J = 9.8 Hz, 2H), 3.74 (s, 2H), 2.54 (t, J = 7.3 Hz, 2H), 2.27 (br s, 1H), 1.46−1.38 (m, 2H), 1.31−1.22 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 143.7, 128.1, 127.8, 126.1, 67.4, 54.6, 53.4, 48.9, 31.9, 20.3, 13.8; IR (KBr, υ cm^{-1}): 3292, 2960, 2875, 2485, 1925, 1648, 1613, 1573, 1513, 1458, 1416, 1362, 1262, 1216, 1074, 1106, 1074, 1020, 977, 945, 850, 753, 680, 665; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O$, 233.1648; found, 233.1655.

N-Benzyl-(4-(4,5-dihydrooxazol-2-yl)benzyl)methylamine (**18j**). Column chromatography purification (PE/EtOAc = 19:1) afforded compound **18j** (192 mg, 69%) as a white solid. mp = 54−56 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.31−7.24 (m, 4H), 7.21−7.17 (m, 1H), 4.36 (t, J = 9.6 Hz, 2H), 3.99 (t, J = 9.4 Hz, 2H), 3.51−3.49 (m, 4H), 2.13 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 142.8, 138.9, 128.9, 128.8, 128.2, 128.0, 127.0, 126.3, 67.5, 61.8, 61.4, 54.8, 42.2; IR (KBr, υ cm^{-1}): 3029, 2934, 2840, 2788, 1649, 1452, 1413, 1361, 1260, 1070, 1019, 975, 944, 871, 846, 736, 699, 679; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{21}N_2O$, 281.1648; found, 281.1643.

N,N-Dibenzyl-1-(4-(4,5-dihydrooxazol-2-yl)phenyl)-methanamine (**18k**). Column chromatography purification (PE/EtOAc = 2:1) afforded compound **18k** (137.6 mg, 47%) as a colorless viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 7.3 Hz, 4H), 7.24 (t, J = 7.3 Hz, 4H), 7.17−7.13 (m, 2H), 4.33 (t, J = 9.8 Hz, 2H), 3.96 (t, J = 9.8 Hz, 2H), 3.50 (s, 2H), 3.47 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 143.3, 139.3, 128.7, 128.6(8), 128.2, 128.1, 127.0, 126.3, 67.5, 57.9, 57.6, 54.8; IR (KBr, υ cm^{-1}): 3061, 3028, 2929, 2878, 2799, 1649, 1494, 1453, 1416, 1362, 1329, 1260, 1122, 1070, 1020, 975, 944, 746, 699, 680; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{25}N_2O$, 357.1961; found, 357.1977.

4-((1H-Pyrrol-1-yl)methyl)benzamide (**18ea**). Column chromatography purification ($CHCl_3$/MeOH = 49:1) afforded compound **18ea** (30 mg, 15%) as a white solid. mp = 105−106 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.68 (t, J = 2.0 Hz, 2H), 6.20 (t, J = 2.0 Hz, 2H), 6.11 (br, 1H), 5.95 (br, 1H), 5.11 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.0, 142.5, 127.8, 127.4, 127.0, 121.2, 108.9, 52.9; IR (film, υ cm^{-1}): 3386, 3185, 2923, 2853, 1648, 1396, 1282, 1087, 723; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{12}N_2ONa$, 223.0842; found, 223.0846.

2-(4-Bromophenyl)-4,5-dihydro-4-methyloxazole (**23a**). Column chromatography purification (PE/EtOAc = 9:1) afforded compound **23a** (135.9 mg, 57%) as a colorless liquid. With 2.0 mmol of Na_2CO_3, 98% (234.6 mg) of **23a** was isolated. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 4.53−4.49 (m, 1H), 4.40−4.31 (m, 1H), 3.94 (t, J = 7.9 Hz, 1H), 1.34 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.7, 131.6, 129.7, 126.7, 125.9, 74.2, 62.0, 21.3; IR (KBr, υ cm^{-1}): 3284, 2973, 2930, 2871, 1718, 1648, 1593, 1488, 1452, 1399, 1366, 1333, 1260, 1174, 1077, 1012, 1174, 1077, 1012, 990, 887, 837, 727, 670; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}BrNO$, 240.0019; found, 240.0025; $[\alpha]_D^{28}$ +57.4 (c 1.0 in $CHCl_3$).

2-(4-Bromophenyl)-4,5-dihydro-5-methyloxazole (**23b**). Column chromatography purification (PE/EtOAc = 9:1) afforded compound **23b** (131.8 mg, 55%) as a colorless liquid. With 2.0 mmol of Na_2CO_3, 71% (170.7 mg) of **23b** was isolated. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 4.86−4.77 (m, 1H), 4.10 (dd, J = 14.7, 9.8 Hz, 1H), 3.56 (dd, J = 14.7, 7.9 Hz, 1H), 1.39 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.0, 131.5, 129.6, 126.9, 125.8, 76.5, 61.6, 21.0; IR (KBr, υ cm^{-1}): 3284, 2973, 2930, 2871, 1718, 1648, 1593, 1488, 1452, 1399, 1366, 1333, 1260, 1174, 1077, 1012, 990, 887, 837, 727, 670; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}BrNO$, 240.0019; found, 240.0021; $[\alpha]_D^{28}$ −18.0 (c 1.0 in $CHCl_3$).

2-(4-Bromophenyl)-4,5-dihydro-4-hydroxymethyl-4-methyloxazole (**23c**).[29] Column chromatography purification ($CHCl_3$/MeOH = 99:1) afforded compound **23c** (247.1 mg, 92%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 8.2 Hz, 1H), 4.07 (d, J = 8.2 Hz, 1H), 3.77 (d, J = 11.9 Hz, 1H), 3.45 (d, J = 11.9 Hz, 1H), 3.06 (br, 1H), 1.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6, 131.5, 129.9, 126.4, 125.9, 75.0, 72.0, 67.8, 23.6.

2-(4-Bromophenyl)-4,5-dihydro-4,4-dimethyloxazole (**23d**).[9c] Column chromatography purification (PE/EtOAc = 19:1) afforded compound 23**d** (70.4 mg, 28%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 4.08 (s, 2H), 1.35 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.3, 131.5, 129.7, 126.9, 125.8, 79.2, 67.7, 28.3.

2-(2-Chloropyridin-4-yl)-4,5-dihydro-4,4-dimethyloxazole (**23e**).[30] Column chromatography purification (PE/EtOAc = 19:1) afforded compound **23e** (205.8 mg, 98%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40−8.38 (m, 1H), 7.76 (s, 1H), 7.64−7.62 (m, 1H), 4.09 (s, 2H), 1.32 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.1, 151.9, 149.9, 138.3, 122.8, 120.6, 79.4, 68.1, 28.1.

2-(4-Bromophenyl)-5,6-dihydro-4H-1,3-oxazine (**23f**).[12j] Column chromatography purification (PE/EtOAc = 9:1) afforded compound **23f** (138.2 mg, 58%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 4.29 (t, J = 5.5 Hz, 2H), 3.53 (t, J = 5.8 Hz,

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2H), 1.95−1.89 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.7, 132.9, 131.0, 128.4, 124.7, 65.1, 42.5, 21.7.

*2-(4-Bromophenyl)-4,5-dihydro-1H-imidazole (**23g**).*[31] Column chromatography purification ($CHCl_3$/MeOH = 16:1) afforded compound **23g** (120.8 mg, 54%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 3.77 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.8, 131.6, 129.3, 128.5, 125.0, 50.4.

*4-Bromobenzamide (**13**).*[32] Column chromatography purification (PE/EtOAc = 4:1) afforded compound **13** (18 mg, 9%) as a white solid (Table 1, entry 1). ^1H NMR (400 MHz, DMSO-d_6): δ 8.03 (br s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.45 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 166.9, 133.4, 131.2, 129.6, 125.0.

*4-Bromo-N-(2-hydroxyethyl)benzamide (**14**).*[33] Column chromatography purification (EtOAc) afforded compound **14** (107.4 mg, 44%) as a white solid (Table 1, entry 1). ^1H NMR (400 MHz, DMSO-d_6): δ 8.52 (t, J = 5.9 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 4.72 (t, J = 5.5 Hz, 1H), 3.49 (q, J = 5.9 Hz, 2H), 3.31−3.28 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 165.4, 133.5, 131.2, 129.3, 124.6, 59.5, 42.2.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra of compounds **11g**, **17b**, **12a−g**, **16a−c**, **18a−k**, **18ea**, **23a−g**, **13**, and **14**, HRMS spectra for **11g**, **17b**, **12g**, **16c**, **18a−k**, **18ea**, **23a** and **23b** along with CIF of **18g**, **18h** and **18ea** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Dr. Anita Tandon.

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