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Direct synthesis of 3,5-diaryl-1,2,4-oxadiazoles using 1-(2-oxo-2-arylethyl)pyridin-1-iums with benzamidines

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Abstract

An efficient domino protocol for the synthesis of 1,2,4-oxadiazole derivatives from readily available 1-(2-oxo-2-arylethyl)pyridin-1-iums and amidine hydrochlorides was developed. In this practical approach, *N*-acyl amidine precursors were formed firstly via a simple nucleophilic substitution, without the purification of *N*-acylamidine intermediates, and the following intramolecularly dehydrative cyclization gave 1,2,4-oxadiazole derivatives in the presence of I_2/K_2CO_3/DMSO, which exhibited excellent functional group tolerance and proceeded under simple experimental conditions.

KEYWORDS

1,2,4-oxadiazole, 1-(2-oxo-2-arylethyl)pyridin-1-ium, *N*-acyl amidine, intramolecularly dehydrative cyclization, benzamidine

1 | INTRODUCTION

1,2,4-Oxadiazole is an important motif of natural products such as potent antiproliferative marine phidianidines A and B (Figure 1) [1]. This motif is present in synthesized compounds with anti-prostate cancer agents [2], tumor-selective and apoptosis-inducing activity [3], anticonvulsant activity [4], antibiotics [5], antiviral activity [6], antiinflammatory activity [7], diuretic activity [8], GABA modulators [9], 5HT3 receptor antagonists [10], central nervous system depressant activity [11], and the potent sphingosine-1-phosphate receptor 1 (S1P1) agonist (Figure 1) [12]. Furthermore, many 3,5-disubstituted 1,2,4-oxadiazoles were investigated widely as potential drugs, for example, Ataluren, (3-(5-[2-fluorophenyl]1,2,4-oxadiazol-3-yl) benzoic acid, an oral investigational drug, used in the treatment of cystic fibrosis under phase-3 clinical trial (Figure 1) [13]. The mGlu5, (2-(3 [pyridin-2-yl]-1,2,4-oxadiazol-5-yl) benzonitrile, was used as a promising metabotropic glutamate subtype-5 receptor antagonist (Figure 1) [14]. And pleconaril also was used for the treatment of potentially life-threatening enterovirus infections [15].

In addition, 3,5-disubstituted 1,2,4-oxadiazoles exhibited exceptional applications in material sciences [16]. Owing to the inherent biological activity of these 1,2,4-oxadiazole derivatives, the construction of these motifs has drawn much attention throughout the years [17]. A number of methods for the synthesis of substituted 1,2,4-oxadiazoles have been explored, mainly including the cyclocondensation of amidoximes with acid chlorides/carboxylic acids and esters [18]. And yet, Zhou and Chen reported a tandem reaction for the synthesis of substituted 1,2,4-oxadiazoles via the palladium-catalyzed carbonylation of diaryliodonium salts with carbon monoxide and amidoximes, followed by the intramolecular dehydrative cyclization [19]. Recently, Vinaya and coworkers used *gem*-dibromomethylarenes as benzoic acid equivalents to afford the cyclocondensation with amidoximes for the synthesis of 1,2,4-oxadiazoles [20]. Another important method for the preparation of 1,2,4-oxadiazoles involved the 1,3-dipolar cycloaddition of nitrile oxides to nitriles or azetine derivatives [21]. For example, Hong and coworkers reported a Cu-catalyzed tandem method for the synthesis of 1,2,4-oxadiazoles from amides and nitriles by a rare oxidative N–O bond

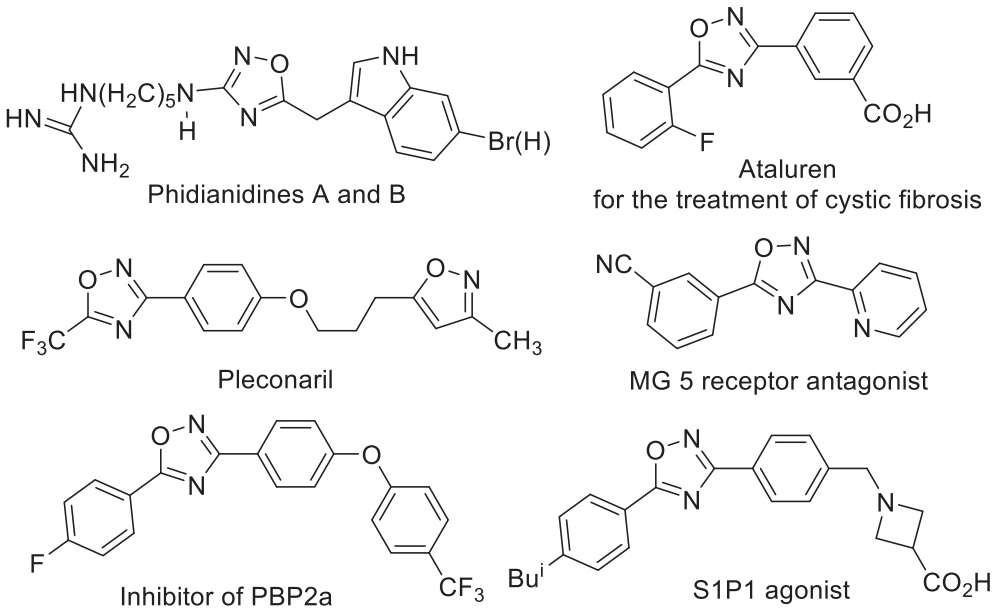
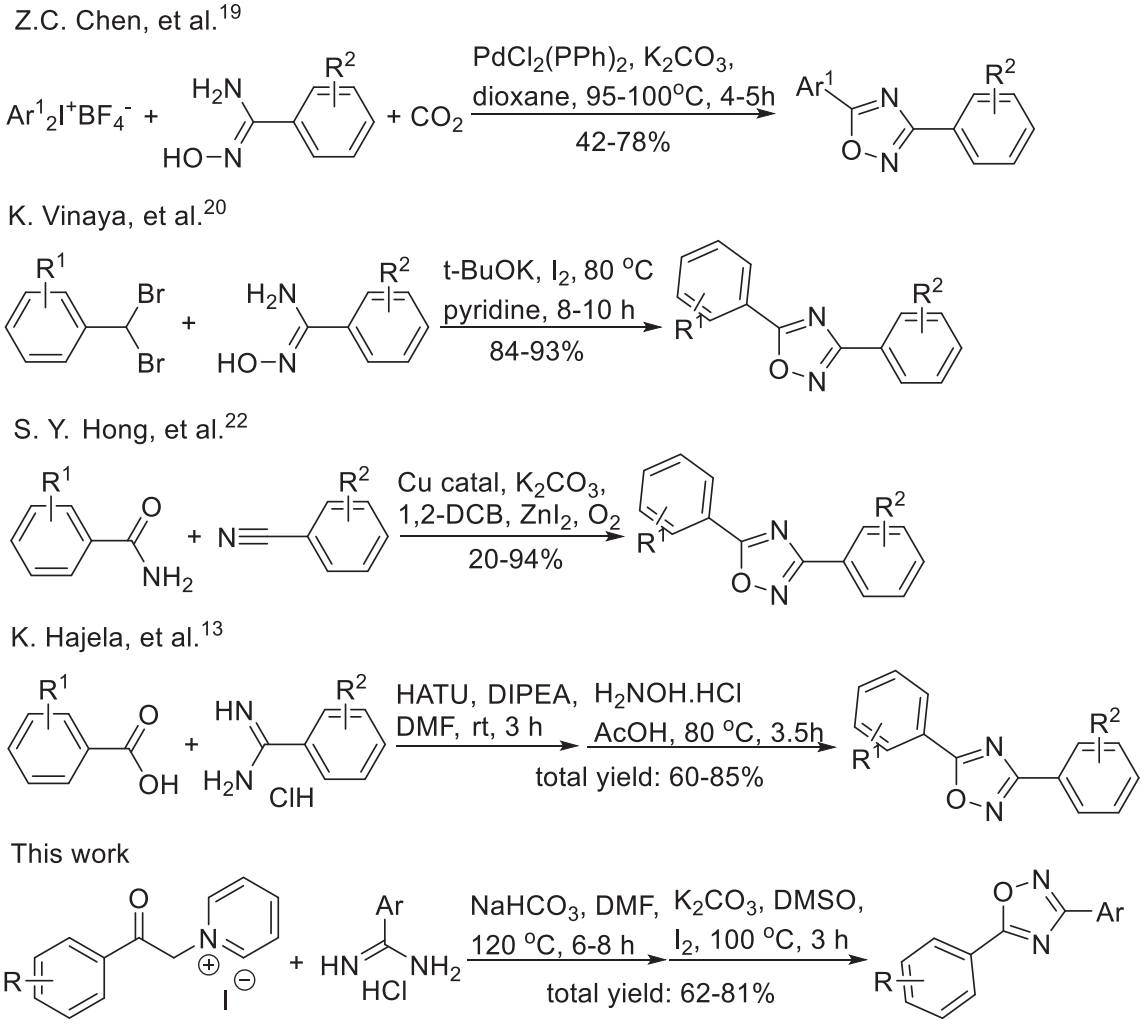


FIGURE 1 Selected natural products and bioactive compounds containing 1,2,4-oxadiazole moiety



SCHEME 1 Selected previous works and this work based on 1-(2-oxo-2-arylethyl)-pyridin-1-ium unit substrates

formation using O_2 as a sole oxidant (Scheme 1) [22]. In recent years, the metal-free direct condensation of amidines and carboxylic acids and intramolecular dehydrative cyclization drew a lot of attention. Hajela and coworkers used HATU (2-[7-azabenzotriazol-1-yl]-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) as a coupling reagent and *N*,*N*-diisopropylethylamine as base to promote direct condensation between benzoic acid and benzamidine hydrochloride; subsequently, the resultant *N*-acylamidine was reacted with hydroxylamine hydrochloride to give 1,2,4-oxadiazoles (Scheme 1) [13]. In addition, as an exceptional motif, 1,2,4-oxadiazole also was formed via rearrangements of other heterocycles [23].

1-(2-Oxo-2-arylethyl)pyridin-1-iums are very interesting and important starting materials in the field of synthetic organic chemistry. By using 1-(2-oxo-2-arylethyl) pyridin-1-iums as synthetic acyl methyl halide [24] or acyl halide equivalents [25], various applications have been explored in synthetic organic chemistry [26]. We also used 1-(2-oxo-2-arylethyl)pyridin-1-iums as building blocks and successfully applied the multicomponent reactions as a versatile and highly efficient synthetic strategy for the preparation of diversely cyclic compounds [27]. The nucleophilic substitution reaction of benzamidine hydrochloride as easily available substrates containing 1,3-dinitrogen with benzoic acid or acyl halide equivalents and the subsequent intramolecular dehydrative cyclization to synthesis efficiently 1,2,4-oxadiazoles are worth mentioning, and we attempted to use 1-(2-oxo-2-arylethyl)pyridin-1-iums as acyl halide equivalents to react with benzamidine hydrochloride in the presence of basic conditions for the construction of *N*-acylamidines. Soon afterwards, the *N*-acylamidines undergo intramolecular dehydrative cyclization to form a 1,2,4-oxadiazole scaffold using the I_2/K_2CO_3 [28] or *N*-bromosuccinimide/1,8-diazabicyclo [5.4.0]undec-7-ene (NBS/DBU) [29] oxidative system. To the best of our knowledge, there are no investigations available on the synthesis of 1,2,4-oxadiazoles starting from 1-(2-oxo-2-arylethyl)pyridin-1-iums. Although the synthesis of 1,2,4-oxadiazoles has been extensively researched, there were still many shortcomings such as harsh conditions, harmful substrate, excessive coupling reagents, and the difficult purification process. Therefore, the development of a simple and stable method for the synthesis of 1,2,4-oxadiazoles by using inexpensive and readily available reagents would be highly desirable. Herein, in continuation of our focus on the development of new methodologies for the synthesis of heterocycles using simple starting materials, detailed efforts to use the reaction of 1-(2-oxo-2-arylethyl)pyridin-1-iums with benzamidines for the synthesis of 1,2,4-oxadiazoles are described.

2 | RESULTS AND DISCUSSION

Firstly, our initial investigation commenced with the model reaction of 1-(2-oxo-2-arylethyl)pyridin-1-iums iodide **1a** with benzamidine hydrochloride (**2a**) in a basic medium. To our delight, the desired product *N*-(imino[*p*-tolyl]methyl)-4-methoxybenzamide (**3a**) was obtained in 70% isolated yield (Table 1, entry 1). To further improve the yield, various bases were evaluated (Table 1, entries 2–7). Substantially inorganic bases such as *t*-BuOK, K_2CO_3 as well as $NaHCO_3$ gave good yields of benzamide **3a**. Notably, the highest yield of 85% was produced in the presence of $NaHCO_3$ in *N*,*N*-dimethylformamide (DMF) (Table 1, entry 7). However, these common organic amines DBU, DABCO, and Et_3N were not beneficial to the reaction. Thus, screening of solvents was carried out (Table 1, entries 8–12); the reaction in DMSO, toluene, and CH_3CN offered benzamide **3a** in 66%, 62%, and 56% yield, respectively. However, the reaction did not take place in the presence of 1,4-dioxane and EtOH. Next, we studied the effect of temperature on this reaction and found that the reaction temperature (120°C) gave the best yield of the target product (Table 1, entry 13). Further decreasing the temperature to 110°C, a detrimentally lower yield of product **3a** was obtained (80%) (Table 1, entry 14).

Increasing the $NaHCO_3$ loading to 2.5 equiv. did not have a significant improvement under otherwise identical conditions (Table 1, entry 15). Lowering the $NaHCO_3$ loading to 1.0 equiv. still resulted in 64% yield, albeit requiring a reaction time of 10 h (Table 1, entry 16). Furthermore, we further attempted to change the ratio of pyridin-1-ium **1a** and benzamidine hydrochloride (**2a**); two relatively lower yields of the corresponding product **3a** were obtained (Table 1, entries 17–18). Finally, a series of experiments revealed that the optimal conditions were obtained as **1a** (1.0 mmol), 1.0 equiv. of **2a**, and 2.0 equiv. of $NaHCO_3$ in 6 ml of DMF at 120°C (Table 1, entry 13).

Recently, the efficiently oxidative cyclization of *N*-acylamidine was developed to synthesize diversely 3,5-disubstituted-1,2,4-oxadiazoles, mainly including the I_2/K_2CO_3 [28] and NBS/DBU [29] oxidative system. Reactions involving molecular iodine received enormous attention in past years because iodine is a nontoxic, commercially available, and inexpensive oxidant, which is extensively being employed in various annulation reactions [30]. Thus, the subsequent construction of oxadiazole scaffold through oxidative iodination and cyclization of *N*-(imino[aryl]methyl)benzamide **3a** was carried out in the presence of I_2/K_2CO_3/DMSO according to Hajela's method (Scheme 2) [28], which resulted in 87% yield of 1,2,4-oxadiazole **4a**.

Moreover, the I_2/K_2CO_3/DMSO oxidative cyclization proved to be the most appropriate (Scheme 2). Delighted

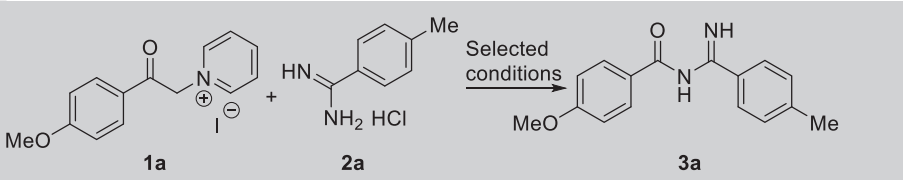
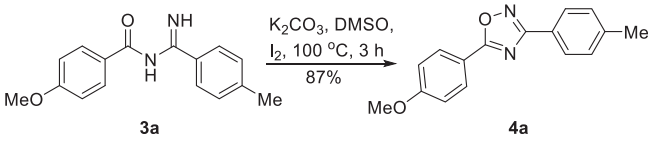


TABLE 1 Optimization of the reaction conditions for **3a**[a,b]

Entry	1a/2a (mmol)	Base (eq.)	Solvent	T (°C)	t (h)	Yield (%)
1	1:1	Cs_2CO_3(2.0)	DMF	130	6	70
2	1:1	t-BuOK(2.0)	DMF	130	6	64
3	1:1	K_2CO_3(2.0)	DMF	130	6	79
4	1:1	DBU(2.0)	DMF	130	24	0
5	1:1	DABCO(2.0)	DMF	130	24	0
6	1:1	Et_3N(2.0)	DMF	130	24	trace
7	1:1	$NaHCO_3$(2.0)	DMF	130	7	85
8	1:1	$NaHCO_3$(2.0)	toluene	Reflux	8	62
9	1:1	$NaHCO_3$(2.0)	1,4-Dioxane	Reflux	24	0
10	1:1	$NaHCO_3$(2.0)	CH_3CN	Reflux	8	56
11	1:1	$NaHCO_3$(2.0)	EtOH	Reflux	24	trace
12	1:1	$NaHCO_3$(2.0)	DMSO	130	8	66
13	1:1	$NaHCO_3$(2.0)	DMF	120	8	88
14	1:1	$NaHCO_3$(2.0)	DMF	110	8	80
15	1:1	$NaHCO_3$(2.5)	DMF	120	8	85
16	1:1	$NaHCO_3$(1.0)	DMF	120	10	64
17	1:2	$NaHCO_3$(2.0)	DMF	120	10	81
18	2:1	$NaHCO_3$(2.0)	DMF	120	10	88

[a]Unless otherwise noted, all reactions were carried out with 1-(2-oxo-2-arylethyl)pyridin-1-iums iodide **1a** (355.2 mg, 1.0 mmol), benzimidamide hydrochloride **2a** (170.6 mg, 1.0 mmol), and base in 6.0 mL of solvent.
[b]Isolated yield.



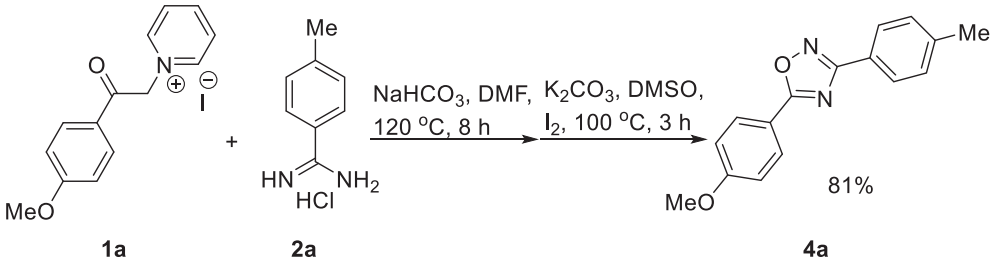
SCHEME 2 Synthesis of 1,2,4-oxadiazole **4a** from *N*-(imino[aryl]methyl)benzamide **3a** using I_2/K_2CO_3/DMSO

with the result, we further attempted to get rid of the purification of **3a** and directly used the unpurified **3a** for the next oxidative cyclization reaction. The result shown in Scheme 3 confirmed that the target product 1,2,4-oxadiazole **4a** was obtained efficiently in 81% yield via two steps without the purification of *N*-(imino[aryl]methyl)benzamide **3a** (Scheme 3).

The structure of 3,5-diaryl-1,2,4-oxadiazole **4a** was unambiguously solved by X-ray crystallography (Figure 2) [31]. X-Ray crystallographic analysis determined that product 3,5-diaryl-1,2,4-oxadiazole **4a** possess a 4-methylphenyl and a 4-methoxyphenyl substituent at C (3) and C (5) of 1,2,4-oxadiazole core.

The scope and limitations of this method were explored by performing the reaction of various pyridin-1-iums **1** and different benzamidines hydrochloride **2** under the optimized reaction conditions. 1-(2-Aryl-2-oxoethyl)pyridin-1-iums iodide **1** with electron-donating substituents (*p*-CH_3O, *p*-Me, *m*-Me, and *o*-Me) formed respective 3,5-diaryl-1,2,4-oxadiazoles **4a–4f** in good yields (67–81%), which also showed an apparent steric effect on the reaction. Similarly, 1-(2-aryl-2-oxoethyl) pyridin-1-iums iodide **1** bearing halogen substituents (*m*-Cl, *p*-Cl, 2,4-dichloro, *m*-Br and *p*-Br) gave corresponding products (Table 2, **4h-4k**, **4q**) in moderate yields (60%–76%), while 1-(2-aryl-2-oxoethyl)pyridin-1-ium iodide **1** bearing a strong electron-withdrawing substituent *p*-NO_2 furnished the 1,2,4-oxadiazoles **4a** in 62% yield. These results implied in the benzene ring of 1-(2-aryl-2-oxoethyl)pyridin-1-ium moiety that there was an

SCHEME 3 Synthesis of 1,2,4-oxadiazole **4a** from pyridin-1-ium **1a** and benzamidine hydrochloride **2a**



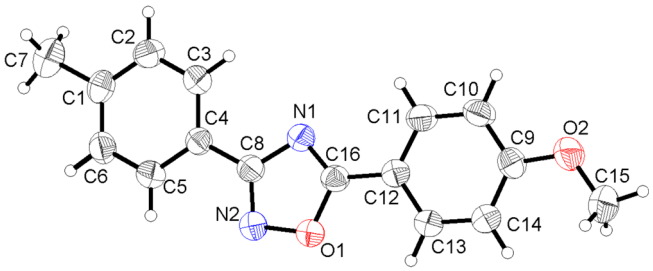


FIGURE 2 Molecular structure of 3,5-diaryl-1,2,4-oxadiazole **4a**, non-hydrogen atoms are shown at the 30% probability level

electronic effect. The substrates with electron-donating groups usually gave the corresponding 1,2,4-oxadiazoles with slightly higher yields compared to the electron-withdrawing groups on the 1-(2-aryl-2-oxoethyl)pyridin-1-iums **1** substrate.

Furthermore, a series of substituted benzamidines hydrochloride **2** were examined and the results are summarized in Table 2. Electron-donating (MeO, EtO, Me) groups attached to the aromatic ring of benzamidines were well tolerated, with the corresponding 1,2,4-oxadiazoles obtained in moderate to good yields (Table 2). Similarly, the benzamidines substituted by Cl and Br could be efficiently transformed into the corresponding products in moderate yields, which provided the possibility for further functionalization. These results demonstrated that substituted positions at the benzamidines have positive effects on the annulation. The scope of this reaction was extended by employing heteroaryl amidine hydrochloride with 1-(2-oxo-2-[*p*-methoxyphenyl]ethyl)pyridin-1-iums iodide or 1-(2-oxo-2-phenylethyl)pyridin-1-iums iodide, which afforded 1,2,4-oxadiazole **4l** and **4n** in 63% or 65%, respectively.

The structures of 3,5-diaryl-1,2,4-oxadiazoles **4b** and **4p** also were further confirmed by X-ray crystallography (Figure 3) [31].

On the basis of the above results and literature precedent, a plausible mechanism is depicted in Scheme 4. Firstly, in the presence of $NaHCO_3$, benzamidine hydrochloride (**2a-h**) was transferred to natural benzamidine, and the following nucleophilic addition to carbonyl of 1-(2-oxo-2-arylethyl)pyridin-1-iums iodide **1a-j** afforded the intermediate [**A**]. Intermediate [**A**] underwent a removal of pyridin-1-ium-1-ylmethanide to form *N*-(imino[aryl]methyl)benzamide [**B**]. Next, an oxidative iodination of the imino unit of intermediate [**B**] in the presence of K_2CO_3 gave a *N*-iodo intermediate [**C**], which then underwent the tautomerism to form easily the intermediate [**D**]. Finally, an intramolecular nucleophilic substitution occurred in the presence of K_2CO_3 to offer desired 3,5-diaryl-1,2,4-oxadiazoles **4a-s**.

3 | CONCLUSIONS

In summary, we have developed an efficient domino protocol for the synthesis of 1,2,4-oxadiazole derivatives from readily available 1-(2-oxo-2-arylethyl)-pyridin-1-iums and amidine hydrochlorides. In this practical approach, *N*-acyl amidine precursors were formed firstly via a simple nucleophilic substitution, without the purification of *N*-acylamidine intermediates; the following intramolecularly oxidative cyclization gave 1,2,4-oxadiazole derivatives in the presence of I_2/K_2CO_3/DMSO. Moreover, the sequential synthesis of 1,2,4-oxadiazole derivatives from 1-(2-oxo-2-arylethyl)pyridin-1-iums and amidine hydrochlorides exhibited excellent functional group tolerance and proceeded under simple experimental conditions, thus underscoring the unique reactivity of amidines and expanding the repertoire of the useful transformations of these reactive intermediates.

4 | EXPERIMENTAL SECTION

4.1 | General

All melting points were recorded using a Yanaco melting point apparatus and are uncorrected. The ^1H NMR (400 MHz) and ^{13}C NMR (150 MHz) spectra were recorded in a Bruker AV-400 and AV-600 spectrometer with TMS as internal reference in $CDCl_3$ solution. The *J* values are given in Hertz. IR spectra were recorded in a Nicolet FT-IR 5DX spectrometer, and samples were loaded neatly. High-resolution ESI mass spectra

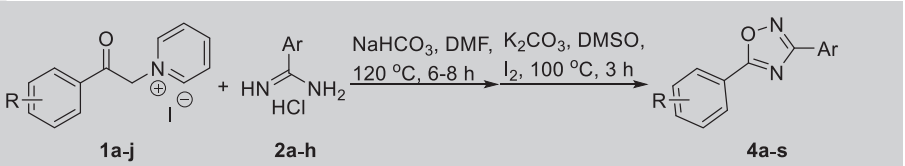


TABLE 2 Scopes of 1-(2-oxo-2-arylethyl)pyridin-1-iums iodide and benzimidamide hydrochloride[a,b]

Entry	R	Ar	t (h) 1st step	t (h) 2nd step	Product	Yield (%)[b]
1	*p*-MeO	*p*-MeC_6H_4	8	3	**4a**	81
2	*p*-MeO	*p*-BrC_6H_4	7	3	**4b**	75
3	*p*-MeO	*m*-BrC_6H_4	7	3	**4c**	67
4	*p*-Me	*p*-ClC_6H_4	7	3	**4d**	77
5	*m*-Me	*p*-ClC_6H_4	7	3	**4e**	74
6	*o*-Me	*p*-ClC_6H_4	8	3	**4f**	69
7	*p*-Br	*p*-ClC_6H_4	7	3	**4g**	74
8	*p*-Cl	*m*-BrC_6H_4	8	3	**4h**	64
9	*m*-Br	*p*-ClC_6H_4	7	3	**4i**	69
10	3,4-Cl	*m*-$MeOC_6H_4$	8	3	**4j**	68
11	3,4-Cl	C_6H_5	6	3	**4k**	76
12	*p*-MeO	Pyridin-3-yl	8	3	**4l**	63
13	*p*-MeO	*m*-$MeOC_6H_4$	7	3	**4m**	73
14	H	Pyridin-3-yl	6	3	**4n**	65
15	H	*m*-BrC_6H_4	6	3	**4o**	69
16	*m*-Me	*o*-$EtOC_6H_4$	8	3	**4p**	64
17	*m*-Cl	*o*-$EtOC_6H_4$	8	3	**4q**	60
18	*p*-MeO	*o*-$EtOC_6H_4$	8	3	**4r**	69
19	*p*-O_2N	*m*-BrC_6H_4	8	3	**4s**	62

[a]Reaction conditions: First step, substituted 1-(2-oxo-2-arylethyl)pyridin-1-iums iodide **1a-j** (1.0 mmol), substituted benzimidamide hydrochloride **2a-h** (1.0 mmol), sodium bicarbonate (168 mg, 2 mmol), *N,N*-Dimethylformamide (DMF) (6 ml), 120°C in oil bath, 6–8 h; second step, iodine (380.7 mg, 1.5 mmol), DMSO (6 ml), potassium carbonate (414.6 mg, 3.0 mmol), 100°C in oil bath, 3 h.
[b]Isolated yield.

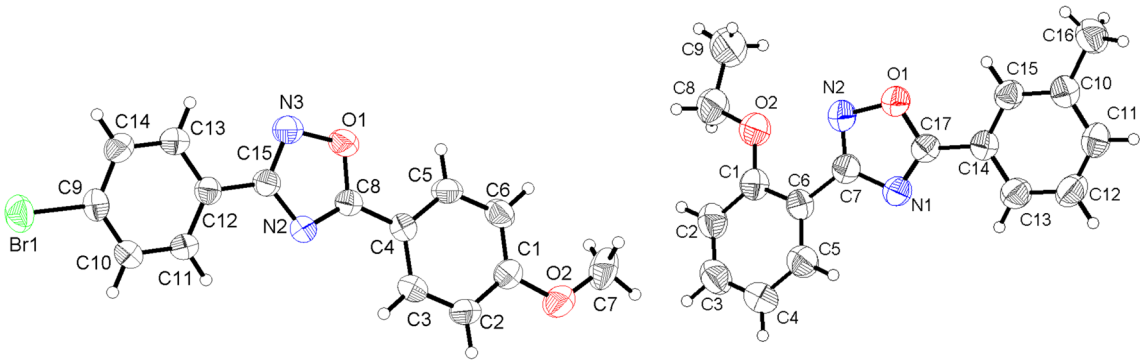
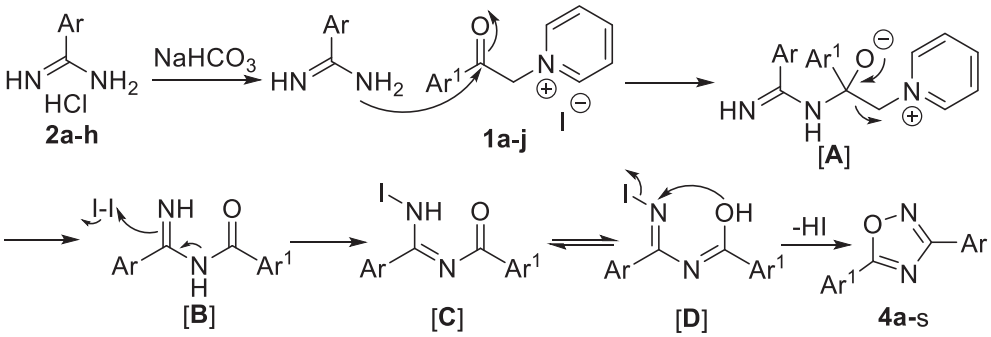


FIGURE 3 Molecular structure of 3,5-diaryl-1,2,4-oxadiazoles **4b** and **4p**, non-hydrogen atoms are shown at the 30% probability level

were obtained on a UHR-TOF maXis (ESI) mass spectrometer. X-Ray crystallographic analysis was performed with a SMART APEX-II diffractometer using monochromatic Mo KR radiation (λ) 0.71073 Å) and integrated with the SAINT-Plus program. All calculations were performed with programs from the SHELXTL

SCHEME 4 Mechanistic rationalization for the synthesis of 1,2,4-oxadiazole derivatives



crystallographic software package. Flash chromatography was performed on silica gel (230–400 mesh) eluting with an ethyl acetate–hexane mixture. All reactions were monitored by thin-layer chromatography (TLC).

4.1.1 | Preparation of *N*-(imino[*p*-tolyl] methyl)-4-methoxybenzamide (**3a**)

The mixture of 1-(2-oxo-2-[4-methoxyphenyl]ethyl) pyridin-1-iums iodide (**1a**, 355.2 mg, 1.0 mmol), 4-methylbenzimidamide hydrochloride (**2a**, 170.6 mg, 1.0 mmol) and sodium bicarbonate (168 mg, 2 mmol) in DMF (6 ml) was stirred at 120°C in oil bath for 8 h. After the completion of the reaction monitored by TLC (EtOAc/hexanes, 1/8, silica gel) and the removal of solvent via reduced pressure distillation, the cooled reaction mixture was added water (10 ml) and extracted with dichloromethane (10 ml × 2). The organic phase was washed with brine (15 ml) and dried over anhydrate sodium sulfate. After the removal of dichloromethane, the crude product was purified by flash chromatography (EtOAc/hexanes, 1/10, silica gel) to give a white solid product **3a** (236.1 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 10.71 (brs, 1H), 8.32 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 179.8, 166.2, 162.7, 142.8, 132.2, 131.6, 130.6, 129.4, 127.4, 113.2, 55.3, 21.5; HR-MS (ESI) calcd. For $C_{16}H_{17}N_2O_2$ $[(M + H)^+]$: 269.1290; found: 269.1281.

4.1.2 | General procedure for the synthesis of 3,5-diaryl-1,2,4-oxadiazoles **4a**-**s**

The mixture of substituted 1-(2-oxo-2-arylethyl)pyridin-1-iums iodide **1a**-**j** (1.0 mmol), substituted benzimidamide hydrochloride **2a**-**h** (1.0 mmol), and sodium bicarbonate (168 mg, 2 mmol) in DMF (6 ml) was stirred at 120°C in oil bath for 6–8 h. After the completion of the reaction monitored by TLC (EtOAc/hexanes, 1/2, silica gel) and then the removal of solvent via reduced pressure distillation, the cooled reaction mixture was added water (10 ml) and extracted with dichloromethane (10 ml × 2). The organic phase was washed with brine (15 ml) and dried over anhydrate sodium sulfate. After the removal of dichloromethane, the crude product was not further purified to use directly for the next step reaction. Subsequently, the crude product was dissolved in DMSO (6 ml), and iodine (380.7 mg, 1.5 mmol) and potassium carbonate (414.6 mg, 3.0 mmol) were added to the solution. The resultant mixture was stirred at 100°C in oil bath for 3 h. After the completion of the reaction monitored by TLC (EtOAc/hexanes, 1/10, silica gel) and the removal of solvent via reduced pressure distillation, water was added to the cooled reaction mixture (10 ml) and the mixture was extracted with dichloromethane (10 ml × 2). The organic phase was washed with brine (15 ml) and dried over anhydrate sodium sulfate. After the removal of dichloromethane, the yellowish crude product was purified by flash chromatography (EtOAc/hexanes, 1/20, silica gel) to give the desired products **4a**-**s**.

4.1.3 | 5-(4-methoxyphenyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (**4a**)

White solid, yield: 81%; m.p. 107.3–107.5°C (EA/PE); IR (KBr, cm^{-1}): ν 3450, 1619, 1502, 1361, 1256, 1180, 1027, 835, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.15 (dd, J_1 = 8.0, J_2 = 4.0 Hz, 2H), 8.05 (dd, J_1 = 8.0, J_2 = 4.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.3, 168.7, 163.0, 141.3, 130.0, 129.4, 127.3, 124.2, 116.9, 114.4, 55.4, 21.5; HR-MS (ESI) calcd. For $C_{16}H_{14}N_2NaO_2$ $[(M + Na)^+]$: 289.0953; found: 289.0948.

4.1.4 | 3-(4-Bromophenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (**4b**)

White solid, yield: 75%; m.p. 162.3–162.6°C (EA/PE); IR (KBr, cm^{-1}): ν 3450, 1623, 1500, 1358, 1257, 1177, 837, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.15 (dd, J_1 = 8.0, J_2 = 4.0 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.64

(dd, J_1 = 8.0, J_2 = 4.0 Hz, 2H), 7.04 (dd, J_1 = 8.0, J_2 = 4.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.7, 168.0, 163.2, 132.0, 130.0, 128.9, 126.0, 125.5, 116.6, 114.5, 55.5; HR-MS (ESI) calcd. For $C_{15}H_{11}BrN_2NaO_2$ [$(M + Na)^+$]: 352.9902; found: 352.9896.

4.1.5 | 3-(3-Bromophenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (**4c**)

White solid, yield: 67%; m.p.133.2–133.4°C (EA/PE); IR (KBr, cm^{-1}): ν 3452, 1612, 1498, 1427, 1346, 1258, 1174, 1020, 846, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.32 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.36 (dd, $J_1 = J_2$ = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.8, 167.6, 163.2, 133.9, 130.4, 130.3, 130.0, 129.0, 125.9, 122.8, 116.5, 114.5, 55.5; HR-MS (ESI) calcd. For $C_{15}H_{11}BrN_2NaO_2$ [$(M + Na)^+$]: 352.9902; found: 352.9895.

4.1.6 | 3-(4-Chlorophenyl)-5-(*p*-tolyl)-1,2,4-oxadiazole (**4d**)

White solid, yield: 77%; m.p. 93.6–93.8°C (EA/PE); IR (KBr, cm^{-1}): ν 3434, 2925, 1620, 1401, 1271, 1087, 836, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.13–8.07 (m, 4H), 7.48 (dd, J_1 = 8.0, J_2 = 4.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 176.0, 168.0, 143.6, 137.2, 129.8, 129.1, 128.7, 128.1, 125.5, 121.3, 21.7; HR-MS (ESI) calcd. For $C_{15}H_{11}ClN_2NaO$ [$(M + Na)^+$]: 293.0458; found: 293.0449.

4.1.7 | 3-(4-Chlorophenyl)-5-(*m*-tolyl)-1,2,4-oxadiazole (**4e**)

White solid, yield: 74%; m.p. 90.3–90.7°C (EA/PE); IR (KBr, cm^{-1}): ν 3446, 1636, 1356, 1102, 618; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.11 (d, J = 8.0 Hz, 2H), 8.02 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 4.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 176.0, 168.0, 139.0, 137.2, 133.6, 129.1, 129.0, 128.7, 128.6, 125.4, 125.2, 123.9, 21.3; HR-MS (ESI) calcd. For $C_{15}H_{11}ClN_2NaO$ [$(M + Na)^+$]: 293.0458; found: 293.0449.

4.1.8 | 3-(4-Chlorophenyl)-5-(*o*-tolyl)-1,2,4-oxadiazole (**4f**)

White solid, yield: 69%; m.p. 81.2–81.6°C (EA/PE); IR (KBr, cm^{-1}): ν 3448, 1637, 1411, 1359, 1093, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.15 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.51–7.46 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 2.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 176.5, 167.7, 139.1, 137.2, 132.3, 131.9, 130.1, 129.1, 128.8, 126.2, 125.5, 123.2, 21.9; HR-MS (ESI) calcd. For $C_{15}H_{11}ClN_2NaO$ [$(M + Na)^+$]: 293.0458; found: 293.0450.

4.1.9 | 5-(4-Bromophenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**4 g**)

White solid, yield: 74%; m.p.180.2–180.5°C (EA/PE); IR (KBr, cm^{-1}): ν 3448, 1639, 1407, 1355, 1091, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.09 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.0, 168.2, 137.4, 132.5, 129.5, 129.1, 128.8, 127.8, 125.2, 122.9; HR-MS (ESI) calcd. For $C_{14}H_8BrClN_2NaO$ [$(M + Na)^+$]: 356.9406; found: 356.9391.

4.1.10 | 3-(3-Bromophenyl)-5-(4-chlorophenyl)-1,2,4-oxadiazole (**4 h**)

White solid, yield: 64%; m.p. 159.4–159.7°C (EA/PE); IR (KBr, cm^{-1}): ν 3438, 1610, 1520, 1434, 1345, 1270, 1093, 928, 893, 796, 751, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.32 (s, 1H), 8.15 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.38 (dd, $J_1 = J_2$ = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.0, 167.9, 139.4, 134.2, 130.5, 130.4, 129.5, 129.4, 128.6, 125.9, 122.9, 122.5; HR-MS (ESI) calcd. For $C_{14}H_8BrClN_2NaO$ [$(M + Na)^+$]: 356.9406; found: 356.9375.

4.1.11 | 5-(3-Bromophenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**4i**)

White solid, yield: 69%; m.p. 157.5–157.7°C (EA/PE); IR (KBr, cm^{-1}): ν 3451, 1637, 1355, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.36 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.44 (dd, $J_1 = J_2$ = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 174.4, 168.2, 137.5, 135.7, 131.0, 130.6, 129.2, 128.8, 126.6, 125.9, 125.1, 123.1; HR-MS (ESI) calcd. For $C_{14}H_8BrClN_2NaO$ [$(M + Na)^+$]: 356.9406; Found: 356.9394.

4.1.12 | 5-(3,4-Dichlorophenyl)-3-(3-methoxyphenyl)-1,2,4-oxadiazole (**4j**)

White solid, yield: 68%; m.p.129.5–129.7°C (EA/PE); IR (KBr, cm^{-1}): ν 3449, 2965, 1614, 1550, 1464, 1384, 1345,

1241, 1121, 1043, 890, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.32 (s, 1H), 8.04 (d, J = 8.0.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.68–7.61 (m, 2H), 7.42 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.08 (dd, $J_1 = 8.0$, $J_2 = 4.0$ Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 173.6, 169.0, 159.9, 137.4, 133.7, 131.3, 130.0, 129.9, 127.6, 127.0, 123.9, 119.9, 117.9, 112.0, 55.4; HR-MS (ESI) calcd. For $C_{15}H_{10}Cl_2N_2NaO_2$ [$(M + Na)^+$]: 343.0017; found: 343.0009.

4.1.13 | 5-(3,4-Dichlorophenyl)-3-phenyl-1,2,4-oxadiazole (**4 k**)

White solid, yield: 76%; m.p.131.9–132.2°C (EA/PE); IR (KBr, cm^{-1}): ν 3423, 2977, 1526, 1453, 1402, 1362, 1248, 1049, 882, 741, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.32 (s, 1H), 8.15 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.55–7.50 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 173.7, 169.1, 137.3, 133.7, 131.4, 131.3, 129.9, 128.9, 127.5, 127.0, 126.4, 123.9; HR-MS (ESI) calcd. For $C_{14}H_8Cl_2N_2NaO$ [$(M + Na)^+$]: 312.9911; found: 312.9899.

4.1.14 | 5-(4-Methoxyphenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole (**4 l**)

White solid, yield: 63%; m.p. 148.6–148.9°C (EA/PE); IR (KBr, cm^{-1}): ν 3452, 1629, 1503, 1435, 1359, 1266, 1016, 758, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 9.39 (d, J = 4.0 Hz, 1H), 8.75 (d, J = 4.0 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 2H), 7.46 (dd, $J_1 = 8.0$, $J_2 = 4.0$ Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 176.0, 166.7, 163.3, 151.6, 148.4, 134.9, 130.1, 123.69, 123.55, 116.4, 114.5, 55.5; HR-MS (ESI) calcd. For $C_{14}H_{12}N_3O_2$ [$(M + H)^+$]: 254.0930; Found: 254.0925.

4.1.15 | 3-(3-Methoxyphenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (**4 m**)

White solid, yield: 73%; m.p. 91.3–91.6°C (EA/PE); IR (KBr, cm^{-1}): ν 3425, 2981, 1609, 1502, 1458, 1350, 1251, 1167, 1040, 896, 834, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.15 (d, J = 8.0 Hz, 2H), 7.76 (dd, J_1 = 8.0, $J_2 = 4.0$ Hz, 1H), 7.68 (s, 1H), 7.40 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.07–7.00 (m, 3H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.5, 168.7, 163.1, 159.8, 130.0, 129.8, 128.3, 119.9, 117.5, 116.8, 114.4, 112.0, 55.48, 55.42; HR-MS (ESI) calcd. For $C_{16}H_{14}N_2NaO_3$ [$(M + Na)^+$]: 305.0902; found: 305.0898.

4.1.16 | 5-Phenyl-3-(pyridin-3-yl)-1,2,4-oxadiazole (**4n**)

White solid, yield: 65%; m.p. 138.1–138.3°C (EA/PE); IR (KBr, cm^{-1}): ν 2980, 2314, 1768, 1554, 1451, 1406, 1364, 1066, 909, 828, 737, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 9.42 (s, 1H), 8.78 (d, J = 4.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 7.67–7.61 (m, 1H), 7.61–7.54 (m, 2H), 7.54–7.48 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 176.2, 166.8, 151.4, 148.2, 135.2, 133.0, 129.1, 128.2, 123.88, 123.84, 123.5; HR-MS (ESI) calcd. For $C_{13}H_{10}N_3O$ [$(M + H)^+$]: 224.0824; found: 224.0819.

4.1.17 | 3-(3-Bromophenyl)-5-phenyl-1,2,4-oxadiazole (**4o**)

White solid, yield: 69%; m.p. 91.1–91.3°C (EA/PE); IR (KBr, cm^{-1}): ν 2987, 2313, 1769, 1554, 1456, 1405, 1359, 1262, 1068, 893, 737, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.34 (s, 1H), 8.21 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 1H), 7.63 (dd, $J_1 = 8.0$, $J_2 = 4.0$ Hz, 2H), 7.56 (dd, $J_1 = 8.0$, $J_2 = 4.0$ Hz, 2H), 7.38 (dd, $J_1 = J_2 = 8.0$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 175.9, 167.8, 134.1, 132.9, 130.5, 130.3, 129.1, 128.8, 128.1, 125.9, 124.0, 122.9; HR-MS (ESI) calcd. For $C_{14}H_9BrN_2NaO$ [$(M + Na)^+$]: 322.9796; Found: 322.9797.

4.1.18 | 3-(2-Ethoxyphenyl)-5-(m-tolyl)-1,2,4-oxadiazole (**4p**)

White solid, yield: 64%; m.p.79.3–79.5°C (EA/PE); IR (KBr, cm^{-1}): ν 3427, 3060, 2974, 2312, 1562, 1473, 1390, 1274, 1160, 1041, 885, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.08–8.04 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.48–7.38 (m, 3H), 7.07 (dd, $J_1 = 8.0$, $J_2 = 4.0$ Hz, 2H), 4.22 (q, J = 8.0 Hz, 2H), 2.46 (s, 3H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 174.6, 167.4, 157.5, 138.9, 133.3, 132.1, 131.3, 128.9, 128.6, 125.2, 124.2, 120.5, 116.4, 112.9, 64.6, 21.3, 14.7; HR-MS (ESI) calcd. For $C_{17}H_{16}N_2NaO_2$ [$(M + Na)^+$]: 303.1109; found: 303.1110.

4.1.19 | 5-(3-Chlorophenyl)-3-(2-ethoxyphenyl)-1,2,4-oxadiazole (**4q**)

White solid, yield: 60%; m.p.124.2–124.4°C (EA/PE); IR (KBr, cm^{-1}): ν 2978, 2903, 1560, 1458, 1347, 1251, 1055, 887, 747, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.22 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.56 (dd, J_1 = 8.0, J_2 = 4.0 Hz, 1H), 7.52–7.44 (m, 2H),

7.11–7.03 (m, 2H), 4.22 (q, J = 8.0 Hz, 2H), 1.50 (t, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 173.2, 167.6, 157.5, 135.1, 132.5, 132.3, 131.3, 130.3, 128.1, 126.1, 126.0, 120.5, 116.1, 112.9, 64.6, 14.7; HR-MS (ESI) calcd. For $C_{16}H_{13}ClN_2NaO_2$ $[(M + Na)^+]$: 323.0563; found: 323.0562.

4.1.20 | 3-(2-Ethoxyphenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (**4r**)

White solid, yield: 69%; m.p. 69.8–70.2°C (EA/PE); IR (KBr, cm^{-1}): ν 2979, 1740, 1508, 1355, 1253, 1174, 1047, 755, 679; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.16 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.45 (dd, J_1 = J_2 = 8.0 Hz, 1H), 7.10–7.00 (m, 4H), 4.21 (q, J = 8.0 Hz, 2H), 3.89 (s, 3H), 1.50 (t, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 174.3, 167.3, 162.9, 157.5, 132.0, 131.3, 130.0, 120.5, 117.0, 116.5, 114.4, 112.9, 64.6, 55.4, 14.7; HR-MS (ESI) calcd. For $C_{17}H_{16}N_2NaO_3$ $[(M + Na)^+]$: 319.1059; Found: 319.1059.

4.1.21 | 3-(3-Bromophenyl)-5-(4-nitrophenyl)-1,2,4-oxadiazole (**4 s**)

White solid, yield: 62%; m.p. 170.6–170.8°C (EA/PE); IR (KBr, cm^{-1}): ν 3451, 1636, 1522, 1349, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.44–8.39 (m, 4H), 8.33 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.40 (dd, J_1 = J_2 = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 173.8, 168.2, 150.2, 134.5, 130.53, 130.51, 129.26, 129.22, 128.2, 126.0, 124.3, 123.0; HR-MS (ESI) calcd. For $C_{14}H_9BrN_3O_3$ $[(M + H)^+]$: 345.9827; found: 346.3308.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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[31] CCDC 2092755–2092757 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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