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Synthesis of 1,2,4-oxadiazoles utilizing ethyl 2-cyano-2-(2-nitrophenylsulfonyloxyimino) acetate (*ortho*-nosylOXY) as a catalyst and dehydrating reagent under microwave irradiation

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The present work describes the development of an optimized microwave-assisted synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes using ethyl 2-cyano-2-(2-nitrophenylsulfonyloxyimino) acetate (*ortho*-NosylOXY) as an activating agent of carboxylic acid for O-acylation step followed by cyclization step in one pot with significantly good yield. Interestingly, the same reagent, *ortho*-NosylOXY, acts as a catalyst for the first step and helps as a dehydrating agent for the second step. Moreover, by-products, Oxyma [ethyl 2-cyano-2-(hydroxyimino) acetate] and 2-nitrobenzenesulfonic acid can easily be recovered back and recycled further to prepare the reagent. This method is environment friendly and cost-effective.

Keywords: 1,2,4-Oxadiazoles, *ortho*-NosylOXY, O-Acylation, Cyclization, Environment friendly

1,2,4-Oxadiazoles are a class of heterocyclic compounds containing nitrogen and oxygen atoms. These are found: in many biologically active molecules, and possess various CNS (central nervous system) related activities[1]. Most of the nitrogen and oxygen-containing heterocyclic compounds are essentially used in medicines for the treatment of different types of fungal and bacterial infections along with the treatment of gastric ulcers, cancer, *etc.*[2] Five membered heterocyclic compounds show various types of biological activities including anti-bacterial[3], anti-malarial[4], anti-inflammatory[5], anti-fungal[6], and anti-convulsant[7]. 1,2,4-oxadiazoles have been described as good bioisosteres for ester or amide in a variety of biological models as a result of the increased hydrolytic and metabolic stability of the ring. The 1,2,4-oxadiazole ring system has also been used as a urea bioisostere in b3 adrenergic receptor agonists[8]. They have been incorporated into muscarinic agonists, benzodiazepine receptor agonists, serotoninergic (5-HT$_3$) antagonists, and antirhinovirals. In addition, they have also been used as dipeptide mimics[9]. These applications make this heterocycle a crucial structural motif in drug discovery.

In literature, many synthetic methods for the synthesis of 1,2,4-oxadiazoles are available[10]. Among those, the condensation of amidoximes with carboxylic acids with a coupling reagent was particularly attractive. Amidoximes are often either commercially available or easily accessible by reacting nitriles with hydroxylamines. Several coupling reagents have been used for this condensation such as CDI (*N, N*-carbonyldiimidazole)[11], EDC (1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide),[12] DCC (Dicyclohexylcarbidiimide)[12], HBTU [N-(benzotriazol-1-yl)-1,1,3,3-tetramethyl-uroniumhexafluoro phosphate][13], PS-PPh$_3$[14] and PS-BEMP (polymer-supported reagents)[15]. These coupling reagents have major drawbacks: (a) They generate much chemical waste. (b) Preparation protocols for these reagents involve harsh conditions and toxic reagents. For example, HBTU is synthesized using phosgene (inflammable, causes skin damage)[16]. (c) These reagents are difficult to recycle. (d) Furthermore, they generate undesired by-products, which are sometimes difficult to remove from the reaction mixture. Thus, they are neither environmentally friendly nor cost-effective. We describe herein a coupling reagent, ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino) acetate (*ortho*-NosylOXY, **I**, Fig. 1) that is devoid of the said drawbacks.

Results and Discussion

Ortho-NosylOXY has outstanding efficiency for coupling reactions and various organic transformations[17]. Herein, a simple approach for synthesizing 1,2,4-oxadiazole from a carboxylic acid using **I** is reported. Initially, we optimized the reaction conditions with 3,5-diphenyl-1,2,4-oxadiazole as a model substrate. Benzoic acid (1 equiv) was dissolved in acetonitrile. To this, **I** (1 equiv), and Hunig's base (iPr2NEt, DIPEA, 3 equiv) were added, and the reaction mixture was stirred for about 2-3 min. Then benzamidoxime (1 equiv) was added, and the reaction mixture was allowed to stir at RT for 2 h. We did not observe cyclized product (**4**); only intermediate **3** was formed exclusively with 90% yield. Further, this reaction mixture was refluxed for 10 h at 100°C, afforded the cyclized 1,2,4-oxadiazole (**4**) with 60% yield (Scheme 1). When we performed the reaction under microwave irradiation, surprisingly, the reaction worked within 5 min with excellent yield (98%). Thus, a higher conversion of 4 was obtained under microwave heating conditions in a much shorter reaction time.

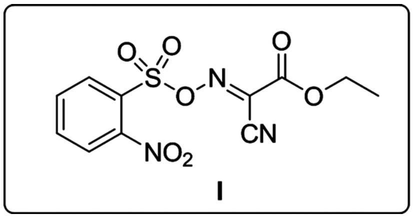
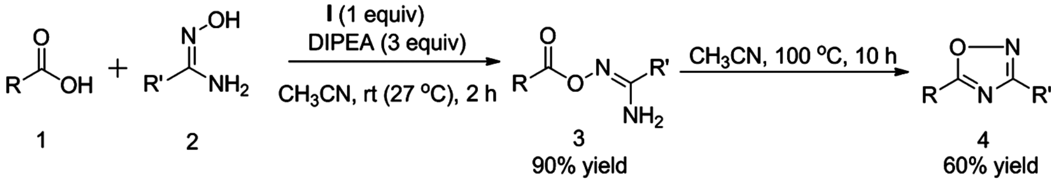


Fig. 1 — Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino) acetate (**I**, *ortho*-NosylOXY)

Next, we wanted to investigate whether the reaction works with a catalytic amount of **I**. We took the same model substrate with a varied amount of **I** and treated it under microwave irradiation. We observed that the reaction worked well with 0.1 equiv of **I**. However, in the absence of I, no coupling product was noted (Table 1, entry 6), and starting materials were recovered. We now wanted to discretely understand the effect of **I** in the first and second steps of the reaction.

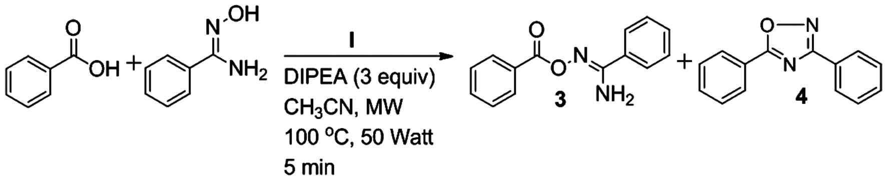
For the first step, we applied a milder MW condition and observed that with 1 equiv of **I** at 40°C and 20 W, the reaction gave the intermediate **3** in 5 min with good yield, exclusively.

Then we wanted to confirm that the first step in the mentioned condition also works with a catalytic amount of **I**. Thus, we took the varied amount of **I** and performed the first step of the reaction in mild conditions (40°C and 20 Watt). We observed that 0.1 equiv of **I** is sufficient for producing a high yield of **3**. However, the absence of **I** does not produce 3 at similar conditions



Scheme 1 — Synthesis of 1,2,4-oxadiazole under conventional heating conditions

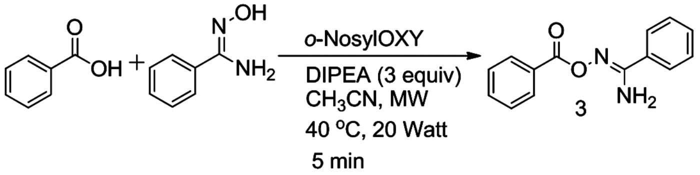
Table 1 — Optimization of amount of reagent I under microwave irradiation [a]



Entry	I	3 (Yield %) [b]	4 (Yield %) [b]
1	0.5 equiv	10	80
2	0.4 equiv	10	85
3	0.3 equiv	20	70
4	0.2 equiv	10	75
5	0.1 equiv	25	73
6	0.0 equiv	0	0

[a] Reaction conditions: substrate 1a (122 mg, 1 mmol), I (varied amount), DIPEA (387 mg, 3 mmol), benzamidoxime (136 mg, 1 mmol) and CH_3CN (2 mL), microwave irradiation (temperature was fixed at 100°C and upper limit of MW was fixed at 50 W), time of the reaction was fixed to 5 min. [b] Isolated yield

Table 2 — Optimization of amount of reagent I under microwave irradiation for the synthesis of O-acylamidoxime intermediate 3 [a]



Entry	I	3 (Yield %) [b]
1	0.5 equiv	90
2	0.4 equiv	91
3	0.3 equiv	90
4	0.2 equiv	91
5	0.1 equiv	91
6	0.0 equiv	0

[a] Reaction conditions: benzoic acid (122 mg, 1 mmol), *o*-NosylOXY (varied amount), DIPEA (387 mg, 3 mmol), benzamidoxime (136 mg, 1 mmol), and CH_3CN (2 mL), under microwave irradiation (upper limit of MW was fixed at 20 W, the temperature at 40°C, and reaction time at 5 min

[b] Isolated yield

(Table 2). We also performed HPLC; we observed only one peak corresponding to intermediate 3 with 0.1 equiv of **I** (Fig. 2a and Supporting information, Figure S54). However, in the absence of **I**, we did not observe the formation of **3**, only starting materials were noted (Fig. 2b and Supporting information, Figure S55).

Next, we wanted to investigate if there is any effect of **I** on the second step, *i.e.*, the dehydrative cyclization step, because we observed clear and consistent alteration of the yield and amount of the existing intermediate in the results summarized in Table 2. For that, we purified **3** and applied 120°C, under 50-Watt MW irradiation for 5 min, and observed the yield of 4 was only 12%, and 80% of 3 was unaltered (by HPLC) when **I** was absent (Fig. 2c and Supporting information, Figure S56). But when we used 0.1 equiv of **I**, the yield of **4** improved to be 85% (15% of 3 was left, temp 120°C) (Fig. 2d and Supporting information, Figure S57). Later, we applied 100°C under MW (the upper limit of the MW energy was fixed at 50 Watt) on purified 3; and observed no conversion to **4** in the absence of **I** (Fig. 3, black curve). However, when we used 0.1 equiv of **I**, the yield of **4** was only 55% in the same conditions (blue curve). After that, we increased the equivalence of **I** to improve the yield of **4**. For that, we used 0.5 equiv of reagent under the same conditions, and we observed the reaction yield increased to 81% (by HPLC, Fig. 3), and the starting material was 18% only. But when we used 1 equiv of **I**, 100% conversion of **3** to **4** was observed. No evidence of intermediate **3** was observed (Fig. 3).

The next question was how much time it takes to convert **3** to **4** with one equivalent of **I** under MW (100°C, 50 W). For that, we conducted a time-dependent HPLC analysis, and the result depicted in Fig. 4 confirmed that 5 min is necessary and sufficient for complete conversion in the said conditions.

As the same reagent is helpful for both steps, we wanted to adopt a single pot protocol. We have used 1 equiv of **I** for the final one-pot condensation/cyclization reaction to form 1,2,4-oxadiazole. The synthesis of 3,5-diphenyl-1,2,4-oxadiazole was used as a model reaction to optimize the conditions. We mixed benzoic acid (1 equiv), **I** (1 equiv), and Hunig's base (iPr_2NEt, DIPEA, 3 equiv) in acetonitrile, followed by the addition of benzamidoxime (1 equiv) and treated under microwave irradiation for 5 min. After completion of the reaction, the product was purified by column chromatography; an excellent yield (Table 3, entry 1) was obtained.

Next, we examined the effect of solvent variation. When low boiling solvents, such as EtOAc, THF, and $CHCl_3$were used, the yield of **4** was only 50%, 30%, and 10%, respectively (Table 3, entries 2, 3, and 4) with 90% *O*-acylamidoxime intermediate **3**. Further, there was no reaction in MeOH and DCM (Table 3, entries 5 and 6). However, with high boiling

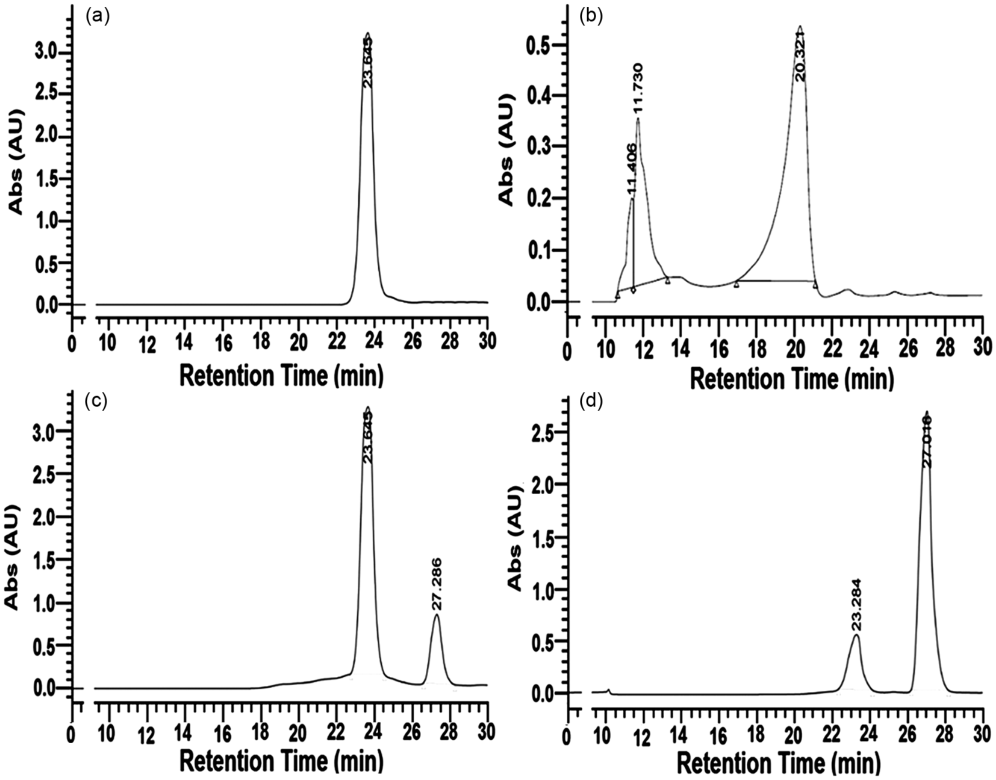


Fig. 2 — HPLC data: Benzoic acid (122 mg, 1 mmol), DIPEA (387 mg, 3 mmol), benzamidoxime (136 mg, 1 mmol) and CH_3CN (2 mL), in microwave irradiation, time of the reaction was fixed to 5 min (a) Formation of intermediate **3** (with 0.1 equiv of **I**, temp 40°C, 20 W) (b) Benzoic acid and benzamidoxime appeared (without reagent **I**, temp 40°C, 20 W). (c) Conversion of **3** to **4** without reagent **I** (temp 120°C, 50 W). (d) Conversion of **3** to **4** with 0.1 equiv of **I** (temp 120°C, 50 W)

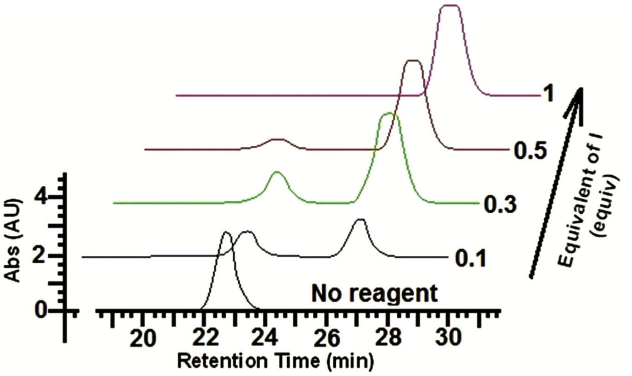


Fig. 3 — HPLC data: Conversion of **3** to **4** under microwave irradiation with varied amount of **I**, the reaction time was fixed to 5 min (temp 100°C, 50 W)

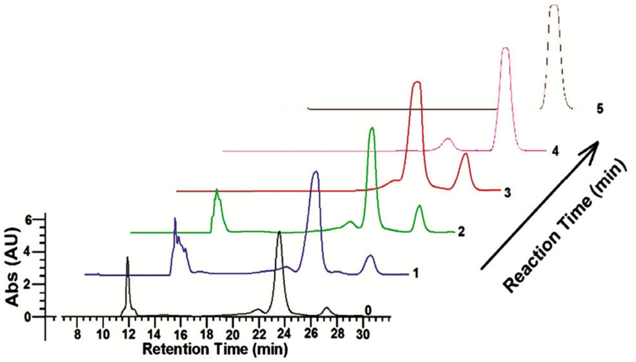
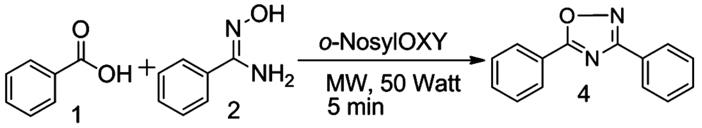


Fig. 4 — Time dependent HPLC data: Conversion of **3** to **4** under microwave irradiation (temp 100°C, 50 W) with 1 equiv of **I** and 3 equiv of DIPEA

solvents, *e.g.*, Toluene, DMF, Dioxane, and DMSO (entries 7, 8, 9, and 10), a higher yield of **4** was obtained, and 40% of *O*-acylamidoxime intermediate **3** was present along with that. However, in the case of CH_3CN, **3** disappeared completely and **4** was obtained in better yield (Table 3, entry 1). Thus, CH_3CN was found to be the best solvent.

Next, the effect of variation of bases on oxadiazole formation was investigated. The product formation was good in the presence of DBU, Et_3N, and K_2CO_3, (Table 3, entries 11, 12 and 13), but inadequate in the presence of DIPA, DABCO, and DMAP (entries 14, 15, and 16) despite prolonged heating in the microwave. We found DIPEA afforded excellent yield (entry 1). Therefore, DIPEA was accepted as a suitable base for the reaction. After that, the amount of DIPEA was optimized. The reaction did not proceed with

Table 3 — Optimization of the reaction conditions [a]



Entry	Solvent	Temp (°C)	Base	Yield (%) [b]
1	CH_3CN	100	DIPEA (3 equiv)	98
2	EtOAc	100	DIPEA (3 equiv)	50
3	THF	100	DIPEA (3 equiv)	30
4	$CHCl_3$	100	DIPEA (3 equiv)	10
5	MeOH	100	DIPEA (3 equiv)	0
6	DCM	100	DIPEA (3 equiv)	0
7	Toluene	100	DIPEA (3 equiv)	80
8	DMF	100	DIPEA (3 equiv)	82
9	Dioxane	100	DIPEA (3 equiv)	76
10	DMSO	100	DIPEA (3 equiv)	75
11	CH_3CN	100	DBU (3 equiv)	85
12	CH_3CN	100	Et_3N (3 equiv)	82
13	CH_3CN	100	K_2CO_3 (3 equiv)	80
14	CH_3CN	100	DIPA (3 equiv)	50
15	CH_3CN	100	DABCO (3equiv)	30
16	CH_3CN	100	DMAP (3 equiv)	10
17	CH_3CN	100	DIPEA (1 equiv)	0
18	CH_3CN	100	DIPEA (2 equiv)	60
19	CH_3CN	90	DIPEA (3 equiv)	30
20	CH_3CN	110	DIPEA (3 equiv)	90
21	CH_3CN	120	DIPEA (3 equiv)	85
22	CH_3CN	130	DIPEA (3 equiv)	70
23	CH_3CN	140	DIPEA (3 equiv)	0

[a] Reaction conditions: substrate **1a** (122 mg, 1 mmol), *ortho*-NosylOXY (327 mg, 1 mmol), DIPEA (387 mg, 3 mmol), benzamidoxime (136 mg, 1 mmol) and CH_3CN (2 mL), under microwave irradiation (upper limit of MW was fixed to 50 Watt), time of the reaction was fixed to 5 min, [b] Isolated yield

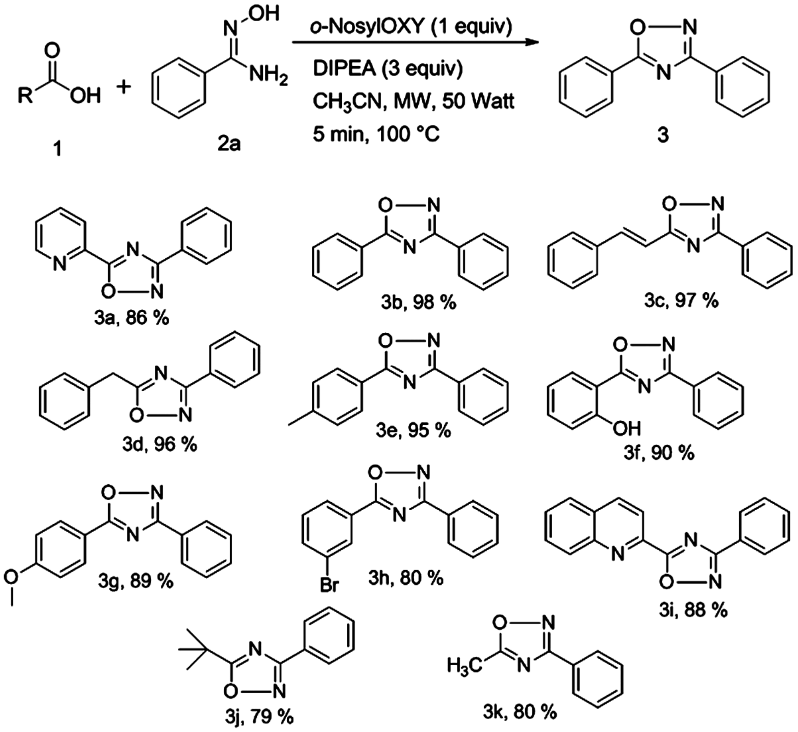
1 equiv of DIPEA (Table 3, entry 17), and product formation was moderate with 2 equiv (Table 3, entry 18), but worked much better with 3 equiv (entry 1). Thus 3 equiv of DIPEA was found to be necessary for the reaction.

After that effect of variation of temperature on the reaction was studied. We found that the presence of 3 equiv DIPEA in CH_3CN under microwave irradiation generated the best yield at 100°C. The yield of the product was lower in both below 100°C (entry 19) and above 100°C (entries 20-22); only intermediate **3** was observed, but the product was not observed at 140°C (entry 23).

With optimized reaction conditions in hand, we investigated the scope of reaction using a wide range of substituted carboxylic acid with benzamidoxime (Scheme 2). A broad range of carboxylic acids was tolerated under optimized conditions, including those bearing picolinic acid (3a), quinoline-2-carboxylic acid (3i), and halogen (3h) substituted at the *para*-position of the phenyl ring. Notably, pivalic acid reacted smoothly under optimized conditions to give the corresponding product (3j) in moderate yield.

The scope of the reaction was further expanded by reacting substituted carboxylic acids with different amidoximes. These substrates reacted smoothly under the optimized conditions to provide the desired products. All the products were characterized by NMR, IR, and ESI-MS. Out of all these, the product of entry **4c** was also confirmed with single crystal XRD (Fig. 5).

A plausible reaction mechanism for the formation of oxadiazole is explained through the formation of *O*-acylamidoxime intermediate (**3**) (Scheme 3). At first, activation of carboxylic acid (1) by **I** result in the formation of active Oxyma



Scheme 2 — Scope of carboxylic acid[a]

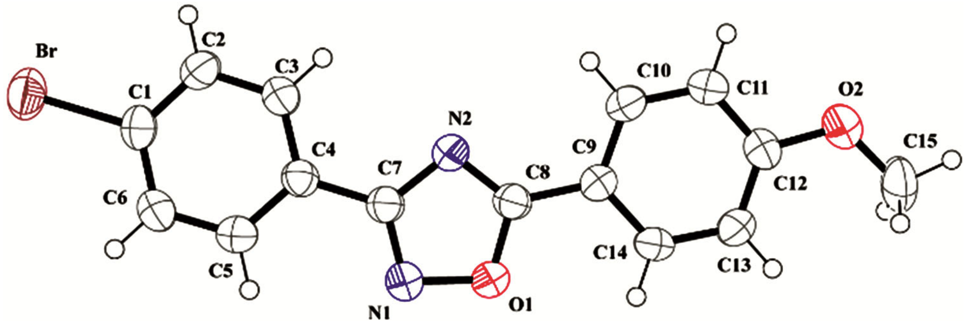


Fig. 5 — X-ray crystallographic structure of **4c** (ORTEP diagram with an ellipsoid of 50% probability, CCDC No. 1043141)

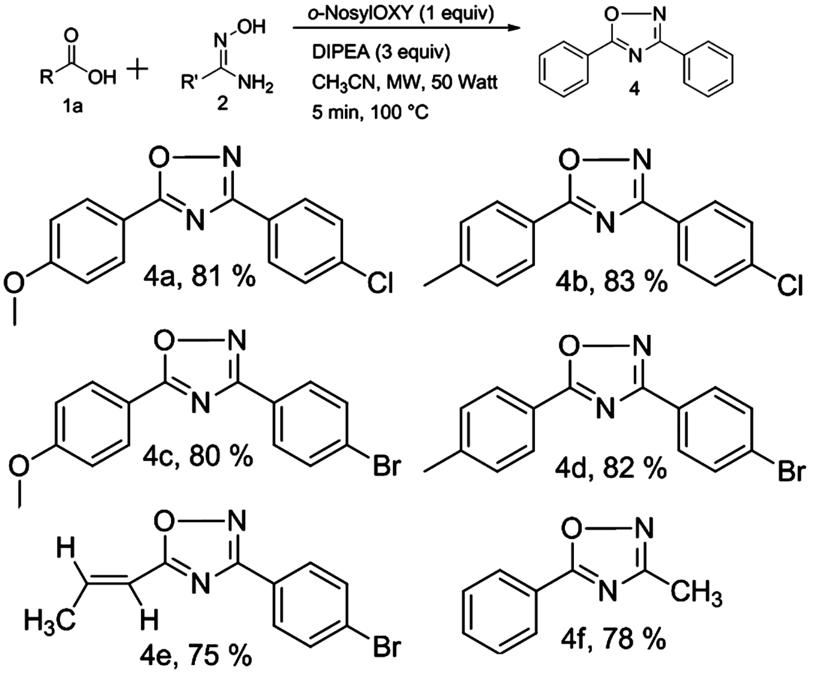
ester of carboxylic acid (**III**) form *via* transient intermediate (**II**). **III** could be isolated and characterized by ^{1}H, ^{13}C NMR, and HRMS. In a second step, amidoxime (**2**) may react with **II** and **III** to produce the *O*-acylamidoxime intermediate (**3**). **3** was isolated and characterized by ^{1}H, ^{13}C NMR, and HRMS (Supporting information, Figure S51-S53). According to the results in Table 2, the role of **I** for converting **1** to **3** is catalytic. Such catalytic conversion or regeneration of **I** can be explained as depicted in Scheme 4.

From the results demonstrated in Fig. 3, we do not see any linear correlation between the amount of **I** and the yield of 4. That indicates that the role of **I** for converting **3** to **4** may be dehydrative cyclization. A plausible mode of action of **I** for the conversion of **3** to **4** is depicted in Scheme 5.

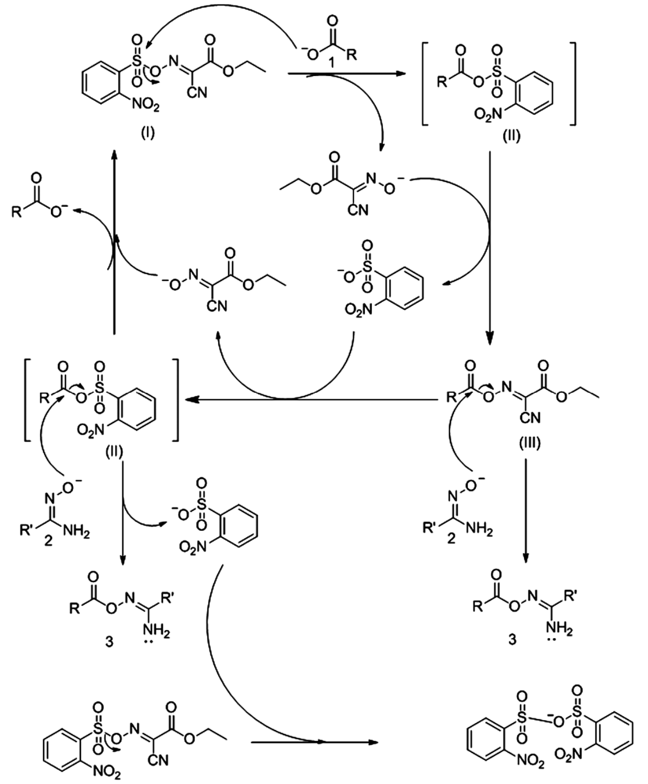
Experimental Section

General Information

All reagents were purchased from commercial sources. NMR spectra were recorded on 600 MHz and 400 MHz spectrometerusing $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) were reported in ppm, and spin-spin coupling constants (J) were given in Hz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass



Scheme 3 — Scope of amidoxime as substrates [a]

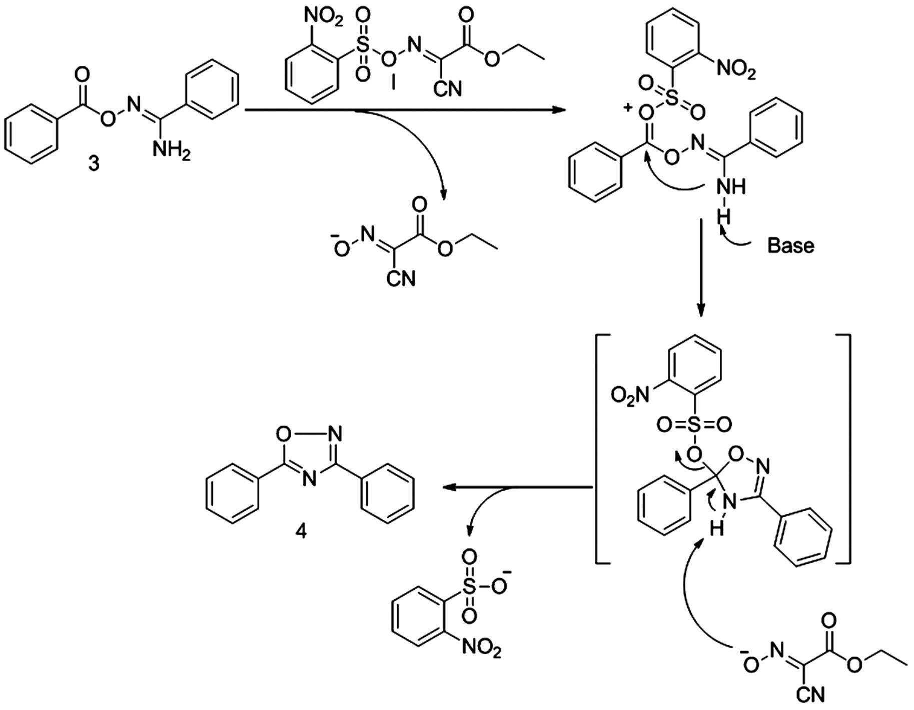


Scheme 4 — Catalytic formation of the *O*-acylamidoxime intermediate **3** using **I**

spectra were recorded on a Q-TOF ESI-MS instrument and Q-TOF LC/MS system. Reactions were monitored using thin-layer chromatography with silica gel GF254. The reaction products were purified by column chromatography using silica gel (60-120 mesh) using eluent EtOAc/Hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. Melting points were determined using a dedicated melting point measuring apparatus, and FT-IR spectra were recorded on an FT-IR spectrometer. X-Ray data were collected on a diffractometer equipped with a CCDc area detector using Mo/Kα radiation. The structures were solved by the direct method using *SHELLX-97* (Göttingen, Germany) software.

General procedure for the synthesis of 1,2,4-Oxadiazoles from carboxylic acids (one-pot protocol)

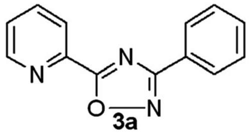
o-NosylOXY (1 mmol) was added to a stirred solution of carboxylic acid (1 mmol), and DIPEA (3 mmol) in Acetonitrile (2 mL) at RT. To above solutions, Amidoximes (1 mmol) was added. The reaction vessel was sealed and heated in the microwave at 100°C for 5 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with ethyl acetate, washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. The residue was purified on silica gel column chromatography using hexane and ethyl acetate.



Scheme 5 — A plausible mechanism for the synthesis of 1,2,4-oxadiazole **4** from **3** using **I**

Characterization Data

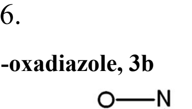
3-Phenyl-5-(pyridin-2-yl)-1,2,4-oxadiazole, 3a



3a

Solid (192 mg, 86%). m.p.113°C. R_f = 0.50 (EtOAc:Hexane), 2:8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86-8.85 (d, *J* = 4.0 Hz, 1H), 8.30-8.28 (d, *J* = 8.0 Hz, 1H), 8.22-8.20 (d, *J* = 7.6 Hz, 2H), 7.94-7.90 (t, *J* = 7.6 Hz, 1H), 7.53-7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 169.4, 150.8, 143.8, 137.5, 131.5, 129.0, 127.8, 126.8, 124.4; IR (KBr): 1647, 1569, 1446, 1364, 1175, 1072, 717, 693 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{13}H_{10}N_3O$: 224.0824. Found: 224.0836.

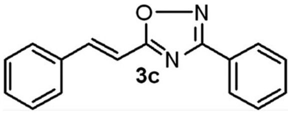
3,5-Diphenyl-1,2,4-oxadiazole, 3b



3b

Solid (435 mg, 98%). m.p.108-109°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.08 (d, *J* = 7.6 Hz, 2H), 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.61-7.58 (t, *J* = 7.2 Hz, 1H), 7.49-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 157.5, 133.2, 131.3, 129.7, 128.9, 128.7, 127.0; IR (KBr): 2985, 1636, 1542, 1353, 1243, 1130, 1032, 665 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}N_2O$: 223.0871. Found: 223.0880.

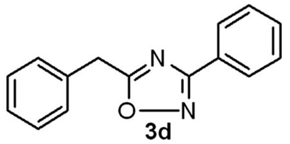
(E)-3-Phenyl-5-styryl-1,2,4-oxadiazole, 3c



3c

Solid (313 mg, 97%). m.p.95°C. R_f = 0.5 (EtOAc:Hexane, 2:8); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14-8.13 (m, 2H), 7.91- 7.88 (d, *J* = 16.2 Hz, 1H), 7.63-7.61 (d, *J* = 7.8 Hz, 2H), 7.51-7.50 (d, *J* = 7.2 Hz, 3H), 7.45-7.43 (d, *J* = 7.2 Hz, 3H), 7.09-7.07 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.5, 169.0, 142.9, 134.7, 131.4, 130.7, 129.3, 129.1, 128.1, 127.7, 127.2, 110.5; IR (KBr): 2923, 1644, 1578, 1540, 1444, 1361, 1294, 1118, 963, 761, 695 cm^{-1}; LRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{16}H_{13}N_2O$: 249.1028. Found: 249.1080.

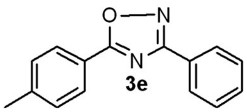
5-Benzyl-3-phenyl-1,2,4-oxadiazole, 3d



3d

Liquid (498 mg, 96%) R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.06 (d, J = 6.0 Hz, 2H), 7.47 (s, 3H), 7.37-7.25 (m, 5H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 163.5, 133.7, 131.3, 129.1, 129.0, 127.8, 127.6, 127.0, 33.2; IR (KBr): 2925, 1647, 1594, 1446, 1364, 1175, 1072, 717, 693 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{12}N_2O$: 237.1028. Found: 237.1029.

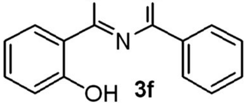
3-Phenyl-5-(*p*-tolyl)-1,2,4-oxadiazole, 3e



3e

Solid (403 mg, 95%). m.p.115-117°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 2H), 8.12-8.10 (d, J = 7.6 Hz, 2H), 7.52 (s, 3H), 7.36-7.34 (d, J = 7.6 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 169.1, 143.7, 131.3, 130.0, 129.0, 128.3, 127.7, 121.8, 22.0; IR (KBr): 1628, 1593, 1527, 1445, 1371, 1294, 1118, 968, 791, 698 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{13}N_2O$: 237.1028. Found: 237.1044.

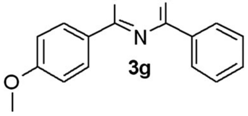
2-(3-Phenyl-1,2,4-oxadiazol-5-yl) phenol, 3f



3f

Solid (385 mg, 90%). m.p.155-156°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.11 (m, 2H), 8.01-7.98 (m, 1H), 7.56-7.50 (m, 4H), 7.16- 7.14 (d, J = 8.0 Hz, 1H), 7.06-7.02 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 167.2, 158.3, 135.4, 131.9, 129.2, 128.0, 127.7, 126.0, 120.3, 118.0, 108.3; IR (KBr): 1628, 1593, 1551, 1445, 1361, 1294, 1118, 963, 761, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}N_2O_2$: 239.0821. Found: 239.0830.

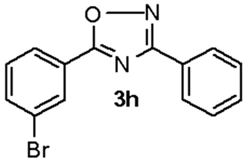
5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole, 3g



3g

Solid (359 mg, 89%). m.p.96°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.15 (d, J = 6.4 Hz, 4H), 7.51 (s, 3H), 7.04-7.02 (d, J =8.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 169.0, 163.4, 131.3, 130.3, 129.0, 127.7, 127.3, 117.1, 114.7, 55.7; IR (KBr): 2840, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 761, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{13}N_2O_2$: 253.0977. Found: 253.0963.

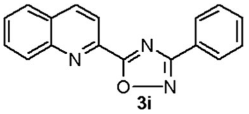
5-(3-Bromophenyl)-3-phenyl-1,2,4-oxadiazole, 3h



3h

Solid (288 mg, 80%). m.p.105-107°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39-8.38 (m, 1H), 8.18-8.15 (m, 3H), 7.75-7.73 (m, 1H), 7.54- 7.50 (m, 3H), 7.46- 7.43 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 169.3, 135.9, 131.6, 131.3, 130.9, 129.1, 127.8, 126.9, 126.3, 123.4; IR (KBr): 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 750, 695, 525 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{14}H_{10}BrN_2O$: 300.9977. Found: 300.9982.

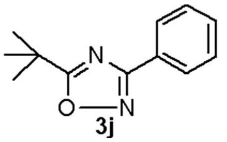
3-Phenyl-5-(quinolin-3-yl)-1,2,4-oxadiazole, 3i



3i

Liquid (408 mg, 88%). R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42- 8.35 (m, 3H), 8.26-8.24 (m, 2H), 7.93- 7.91 (d, J =8.0 Hz, 1H), 7.86-7.82 (t, J = 7.2 Hz, 1H), 7.70- 7.67 (t, J =8.0 Hz, 1H), 7.54- 7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 169.5, 148.3, 143.6, 137.9, 131.6, 131.0, 130.8, 129.3, 129.1, 129.0, 127.9, 126.8, 120.6; IR (KBr): 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 761, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{17}H_{12}N_3O$: 274.0980. Found: 274.0980.

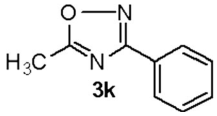
5-(tert-Butyl)-3-phenyl-1,2,4-oxadiazole, 3j



3j

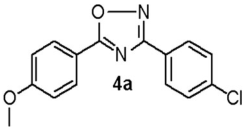
Liquid (239 mg, 79%). R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.38 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 168.3, 131.1, 128.9, 127.6, 127.4, 33.8, 28.6; IR (KBr): 2870, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 965, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O$: 203.1184. Found: 203.1184.

5-Methyl-3-phenyl-1,2,4-oxadiazole, 3k


3k

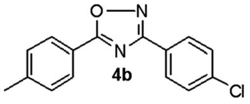
Solid (384 mg, 80%). R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 2H), 7.49 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 168.7, 131.3, 129.1, 127.6, 127.0, 12.6; IR (KBr): 2870, 1618, 1567, 1528, 1445, 1370, 1294, 1118, 1077, 965, 761, 690 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_9H_9N_2O$: 161.0715. Found: 161.0715.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole, 4a


4a

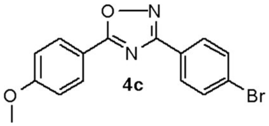
Solid (370 mg, 81%). m.p.142-150°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15- 8.08 (m, 4H), 7.48-7.46 (d, *J* =8.4 Hz, 2H), 7.04- 7.02 (d, *J* =8.4 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 168.2, 163.5, 137.4, 130.3, 129.3, 129.0, 125.9, 116.9, 114.7, 55.7; IR (KBr): 2840, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 756, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{12}ClN_2O_2$: 287.0587. Found: 287.0560.

3-(4-Chlorophenyl)-5-(p-tolyl)-1,2,4-oxadiazole, 4b


4b

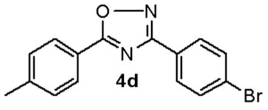
Solid (157 mg, 83%). m.p.126-131°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12- 8.08 (t, *J* = 8.0 Hz, 4H), 7.49-7.47 (d, *J* =8.4 Hz, 2H), 7.36- 7.34 (d, *J* =8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 168.3, 143.9, 137.5, 130.1, 129.4, 129.0, 128.4, 125.8, 121.6, 22.0; IR (KBr): 2870, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 756, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{12}ClN_2O$: 271.0638. Found: 271.0631.

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


4c

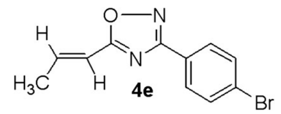
Liquid (264 mg, 80%). R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.13 (d, *J* =8.0 Hz, 2H), 8.04-8.02 (d, *J* =7.6 Hz, 2H), 7.64-7.62 (d, *J* =8.4 Hz, 2H), 7.05-7.03 (d, *J* =8.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 168.3, 163.5, 132.3, 130.3, 129.2, 126.3, 125.8, 116.9, 114.8, 55.7; IR (KBr): 2840, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 761, 695, 525 cm^{-1}.

3-(4-Bromophenyl)-5-(*p*-tolyl)-1,2,4-oxadiazole, 4d


4d

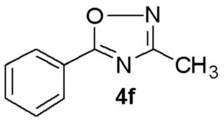
Solid (180 mg, 82%). m.p.146°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10- 8.03 (m, 4H), 7.65- 7.63 (d, *J* = 8.4 Hz, 2H), 7.36-7.34 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 168.4, 143.9, 132.3, 130.1, 129.2, 128.4, 126.3, 125.9, 121.6, 22.0; IR (KBr): 2870, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 963, 761, 695, 525 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{12}BrN_2O$: 315.0133. Found: 315.0124.

(E)-3-(4-Bromophenyl)-5-(prop-1-en-1-yl)-1,2,4-oxadiazole, 4e


4e

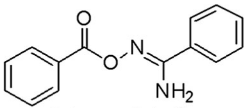
Solid (198 mg, 75%). m.p.143°C. R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.95 (d, *J* =5.6 Hz, 2H), 7.62-7.61 (d, *J* =5.6 Hz, 2H), 7.20-7.13 (m, 1H), 6.48-6.46 (m, 1H), 2.05-2.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 168.0, 143.4, 132.3, 129.1, 126.2, 125.8, 115.1, 19.1; IR (KBr): 2870, 1618, 1567, 1528, 1445, 1361, 1294, 1118, 965, 761, 695, 525 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{11}H_{10}BrN_2O$: 264.9977. Found: 264.9971.

3-Methyl-5-phenyl-1,2,4-oxadiazole, 4f


4f

Liquid (199 mg, 78%). R_f = 0.50 (EtOAc:Hexane, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-8.01 (d, *J* =8.0 Hz, 2H), 7.51-7.41 (m, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 167.9, 132.8, 129.2, 128.1, 124.3, 11.8; IR (KBr): 2870, 1618, 1567, 1528, 1445, 1370, 1294, 1118, 965, 761, 695 cm^{-1}; LRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_9H_8N_2NaO$: 183.0534. Found: 183.1127.

(Z)-*N′*-(Benzoyloxy)benzimidamide, Intermediate, 3



Intermediate **3**

Solid (216 mg, 90%). m.p.95-97°C. R_f = 0.50 (EtOAc:Hexane, 4:6); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.08 (d, *J* = 7.6 Hz, 2H), 7.77-7.75 (d, *J* = 7.6 Hz, 2H), 7.61-7.58 (t, *J* = 7.2 Hz, 1H), 7.49-7.41 (m, 5H), 7.26 (br, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.2, 157.5, 133.2, 131.3, 131.2, 131.1, 129.8, 129.7, 129.0, 128.9, 128.7, 127.0, 126.9; IR (KBr): 3380, 1729, 1613, 1583, 1268, 1092, 702 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{14}H_{13}N_2O_2$: 241.0977. Found: 241.0975.

Conclusions

In summary, we have studied the effect of microwave irradiation on the reaction of carboxylic acids with different amidoximes in the presence of a coupling reagent for the synthesis of 1,2,4-oxadiazoles. All reactions are completed within 5 min at 100°C. In this method, we found that *ortho*-NosylOXY reagents act as catalysts that result in higher yields. Additionally, we concluded that using microwave technology; it not only increased the yield but also reduced the reaction times from hours to minutes. Herein, we report the application of this approach in the development and synthesis of 1,2,4-oxadiazoles.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/ 58776.

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