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One-Pot Synthesis of 2,5-Diaryl 1,3,4-Oxadiazoles via Di-*tert*-butyl Peroxide Promoted *N*-Acylation of Aryl Tetrazoles with Aldehydes

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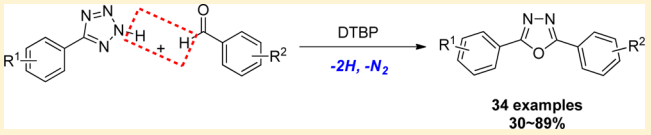
Supporting Information

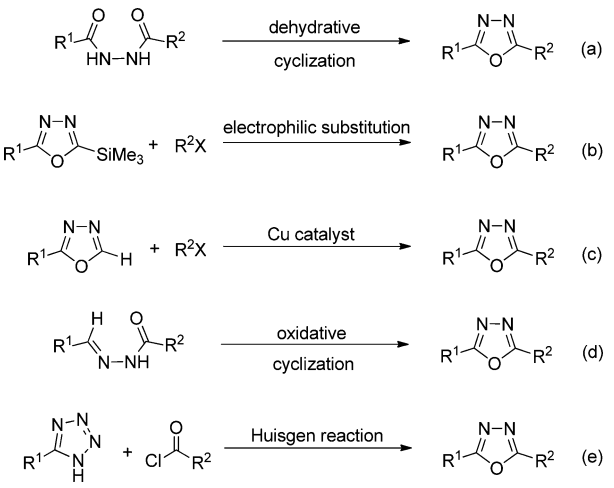
ABSTRACT: A metal- and base-free protocol for one-pot synthesis of 2,5-diaryl 1,3,4-oxadiazoles via a radical-promoted cross-dehydrogenative coupling strategy was developed. This reaction involved the *N*-acylation of aryl tetrazoles with aryl aldehydes, followed by thermal rearrangement. A wide range of aryl tetrazoles and aryl aldehydes survived the reaction conditions to deliver the corresponding products in moderate to good yields.



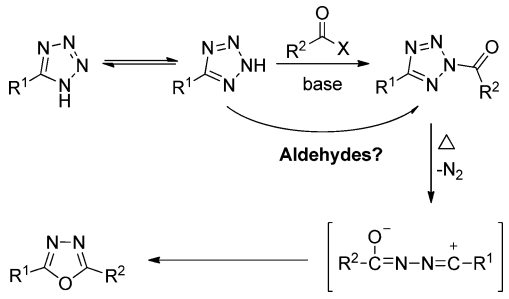
2,5-Diaryl 1,3,4-oxadiazoles are of great importance due to their wide applications in pharmaceutical chemistry and material science. They have shown a wide range of biological properties, including antimicrobial, anti-inflammatory, anticonvulsant, and antiviral properties.[1] They are also useful surrogates of acids, esters, and carboxamides.[2] Moreover, their unique optoelectronic properties make them particularly attractive in material science.[3]

Traditionally, 2,5-diaryl 1,3,4-oxadiazoles were prepared via the following methods (Scheme 1): (a) dehydrative cyclization of 1,2-diacylhydrazines;[4] (b) electrophilic substitution of 2-substituted-5-trimethylsilyl-1,3,4-oxadiazole with electrophiles;[5] (c) copper-mediated coupling reaction of aryl halides with preformed 2-substituted 1,3,4-oxadiazole;[6] (d) oxidative cyclization of *N*-acylhydrazones in the presence of various oxidizing agents or catalysts;[7] and (e) the Huisgen 1,3,4-oxadiazole synthesis.[8] However, there are still some limitations associated with these procedures. For example, a large excess amount of corrosive reagents such as $SOCl_2$, PPA, $POCl_3$, and H_2SO_4 were used in the dehydrative cyclization process (route a). For routes b and c, substituted 1,3,4-oxadiazoles should be preformed as the starting materials. Although oxidative cyclization of *N*-acylhydrazones attracted much attention due to its high atom-economy, a metal catalyst as well as hazardous oxidants were employed (route d). Compared with other methods, the Huisgen reaction is a facile approach to afford the corresponding 2,5-disubstituted 1,3,4-oxadiazoles (route e). Initially, acylated tetrazole is formed via *N*-acylation of tetrazole with a carboxylic acid anhydride or acid chloride. A 1,5-dipole (nitrileimine) is subsequently generated by elimination of nitrogen, followed by cyclization, to provide the final product (Scheme 2).[8b] While acknowledging the pioneering work in this field, some drawbacks such as the use of relatively corrosive acylation reagents and base additives are still the issues to be addressed.

Scheme 1. Different Pathways for Preparation of 2,5-Disubstituted 1,3,4-Oxadiazoles



Scheme 2. Mechanism of Huisgen Reaction



Recently, the cross-dehydrogenative coupling (CDC) reactions have attracted considerable attention.[9] This strategy provides a powerful tool to construct more complex compounds with simple starting materials. In this context, we envisioned that,

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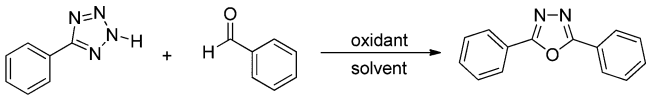
if the acylated tetrazoles could be synthesized via direct coupling reaction between 5-aryl-2*H*-tetrazoles and aldehydes, the 2,5-disubstituted 1,3,4-oxadiazoles could then be generated via thermal rearrangement. Meanwhile, high atom efficiency and reduced waste could be achieved. Just recently, we realized the alkylation of tetrazoles with methylarenes or alkyl ethers via CDC reaction.[10] Inspired by the results, herein, we report a metal- and base-free, radical-promoted one-pot synthesis of 2,5-diaryl 1,3,4-oxadiazoles.

Initially, 5-phenyl-2*H*-tetrazole **1a** and benzaldehyde **2a** were selected as the model substrates to optimize the reaction conditions (Table 1). Pleasingly, a 45% yield of product **3a** was

Table 1. Screening the Optimized Reaction Conditions[a]



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

entry	oxidant	temp (°C)	*t* (h)	solvent	yield (%)[b]
1	DTBP	110	12	CH_3CN	45
2	TBPB	110	12	CH_3CN	20
3	BPO	110	12	CH_3CN	43
4	DCP	110	12	CH_3CN	25
5	TBHP	110	12	CH_3CN	trace
6	H_2O_2	110	12	CH_3CN	trace
7	DTBP	110	12		27
8	DTBP	110	12	EtOAc	20
9	DTBP	110	12	DMF	trace
10	DTBP	110	12	toluene	trace
11	DTBP	110	12	dioxane	trace
12	DTBP	110	12	THF	NR[c]
13	DTBP	110	12	DMSO	NR[c]
14	DTBP	110	12	$ClCH_2CH_2Cl$	70
15	DTBP	110	24	$ClCH_2CH_2Cl$	87
16	DTBP	110	24	$ClCH_2CH_2Cl$	78[d]
17	DTBP	110	24	$ClCH_2CH_2Cl$	41[e]
18	DTBP	120	12	$ClCH_2CH_2Cl$	68
19	DTBP	120	24	$ClCH_2CH_2Cl$	71
20	DTBP	110	24	$ClCH_2CH_2Cl$	84[f]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), oxidant (2.0 equiv) (DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide, TBPB = *tert*-butyl peroxybenzoate, BPO = benzoyl peroxide, DCP = dicumyl peroxide), solvent (3.0 mL), under air, sealed tube. [b]Isolated yield. [c]No reaction. [d]DTBP (3.0 equiv). [e]DTBP (1.0 equiv). [f]Under nitrogen.

obtained using di-*tert*-butyl peroxide (DTBP, 2 equiv) as oxidant in acetonitrile (Table 1, entry 1). Replacing DTBP by other peroxides such as *tert*-butyl peroxybenzoate (TBPB), benzoyl peroxide (BPO), and dicumyl peroxide (DCP) afforded the corresponding product in poor yields (Table 1, entries 2−4). Trace amounts of **3a** were observed in the presence of *tert*-butyl hydroperoxide (TBHP) and H_2O_2 (Table 1, entries 5 and 6). The effect of solvent on the model reaction was also surveyed (Table 1, entries 7−14). Relatively lower yields were obtained when the reaction took place in ethyl acetate or under solvent-free conditions (20% and 27%, respectively). Reaction in other solvents including DMF, toluene, and dioxane gave trace amounts of products, whereas no reaction was observed in THF and DMSO. Encouragingly, a 70% yield of **3a** was obtained when the reaction was conducted in 1,2-dichloroethane. Further prolonging the reaction time to 24 h afforded the desired product in 87% yield (Table 1, entry 15). Moreover, increasing the amount of DTBP to 3 equiv slightly decreased the yield, while only 41% yield was obtained when 1 equiv of DTBP was employed (Table 1, entries 16 and 17). Finally, the survey on the reaction temperature and reaction atmosphere showed that 110 °C and air were the optimum (Table 1, entries 18−20).

With these results in hand, we began to examine the scope and generality of the present method (Table 2). Generally, most of the aryl tetrazoles reacted with benzaldehyde smoothly to give the desired products in moderate to good yields (**3a**−**3g**). For the *para*-substituted tetrazoles, a series of functional groups such as methyl, chloro, fluoro, trifluoromethyl, and methoxyl survived well under the reaction conditions. Among them, tetrazole bearing electron-withdrawing group such as −F gave relatively lower yield (**3f**, 43%). For *para*-hydroxyl substituted tetrazole, only a trace amount of the desired product was detected (**3n**). The steric hindrance showed negligible influence on the reaction, affording the products **3c** and **3d** in good yields (81% and 74%, respectively). Finally, a series of symmetrical and unsymmetrical 2,5-aryl 1,3,4-oxadiazoles were also obtained in good yields via reactions between aryl tetrazoles and substituted aldehydes (**3i**−**3m**).

To further explore the scope of this protocol, a series of aldehydes were then investigated. The results are summarized in Table 3. To our delight, aryl aldehydes with various substituents coupled with 5-phenyl-2*H*-tetrazole smoothly to afford the desired products in moderate to good yields. Various functional groups including methyl, methoxyl, chloro, fluoro, trifluoromethyl, nitro, cyano, and methylthio groups survived the reaction conditions. Aldehydes bearing strong electron-withdrawing groups such as $-CF_3$ and $-NO_2$ gave relatively lower yields (**3g′**, 50%; **3o**, 30%), while 4-formylbenzonitrile showed good reactivity to afford product **3q** in 89% yield. Obvious steric hindrance influence was observed for *ortho*-substituted aldehydes, and moderate yields were obtained (**3s**, 48%; **3t**, 51%; **3u**, 46%, respectively). 1-Naphthaldehyde also showed good reactivity to deliver **3v** in 81% yield. Moreover, 4-hydroxybenzaldehyde and furfural were inert, and only trace amounts of products were observed. Some aliphatic aldehydes were also checked (although they are not shown in Table 3); however, they still gave poor results. This may be attributed to the fact that these intermediates or starting materials are not stable under such reaction conditions (see the mechanism).

To gain insight into the mechanism, some control experiments were conducted (Scheme 3). The reaction did not occur in the absence of DTBP (Scheme 3, eq 1). When 2 equiv of radical scavenger, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), was added to the reaction mixture under standard conditions, no desired product was obtained. Instead, the acylated TEMPO was detected by HPLC-MS. This result indicated that an acyl radical may be involved in this reaction (Scheme, eq 2). To rule out the possibility that the reaction proceeded through direct coupling of an acyl radical and nitrogen radical, we ran the reaction in the absence of aldehyde. Expectedly, no coupling product from tetrazole and TEMPO was observed (Scheme, eq 3). When benzoic acid or *tert*-butyl benzoperoxoate was used instead of benzaldehyde, no product was detected, indicating that these compounds were not intermediates (Scheme 3, eq 4). To verify whether an acyl cation was formed in this reaction, a control experiment was conducted by addition of methanol under standard conditions. It was found that methyl esters could be formed in 17% yield (Scheme 3, eq 5).

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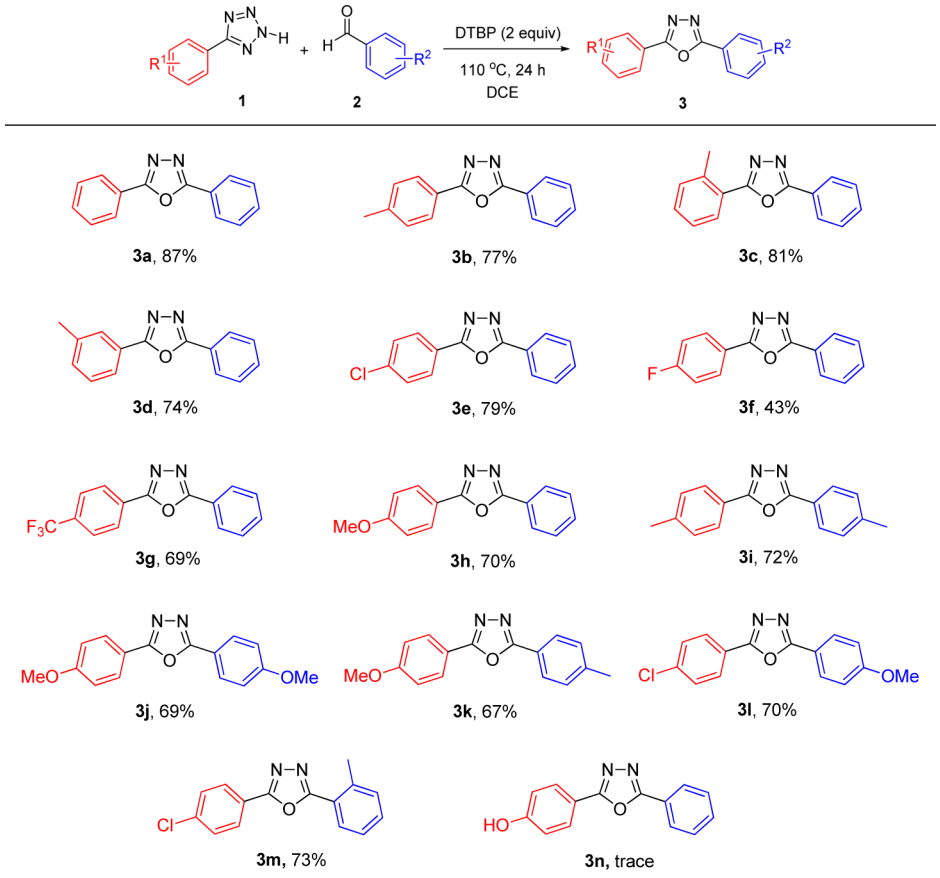
Table 2. Reaction Scope for Aryl Tetrazoles[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), DTBP (1 mmol, 2 equiv), 1,2-dichloroethane (3 mL), 110 °C, 24 h. Isolated yields.

On the basis of these experimental results and literature,[11] a possible mechanism is proposed in Scheme 4. Initially, homolytic cleavage of DTBP produces *tert*-butoxy radical. This radical abstracts one H atom of aldehyde to form **A**, which is further oxidized by another *tert*-butoxy radical to form acyl cation **B**. Then, a nucleophilic reaction of tetrazole to **B** under the assistance of *tert*-butoxy anion provides the acylated tetrazole **C**. Finally, thermal decomposition of **C** affords the desired product **3**.

In conclusion, a radical-promoted direct coupling of aryl tetrazoles with aldehydes, followed by thermal rearrangement to generate 2,5-diaryl 1,3,4-oxadiazoles, has been developed. This protocol provides a simple approach for the preparation of 1,3,4-oxadiazole derivatives. A series of functional groups survived the reaction conditions to give the corresponding products in moderate to good yields.

EXPERIMENTAL SECTION

General Information. Chemicals were used as received without special purification unless stated otherwise. ^{1}H and ^{13}C NMR were recorded at ambient temperature on a 400 MHz NMR spectrometer. NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) as the internal standard. The coupling constants J are given in Hz. Melting points (mp) are determined with an MPA 100 apparatus and are not corrected. High-resolution mass spectrometry (HRMS) was performed on a TOF MS instrument with an ESI source.

General Procedure for the Synthesis of 2,5-Diaryl 1,3,4-oxadiazoles. A sealed tube equipped with a magnetic stir bar was charged with aryl tetrazole (0.50 mmol), aryl aldehyde (1.0 mmol), di-*tert*-butyl-peroxide (1.0 mmol, 146 mg), and 1,2-dichloroethane (3.0 mL). The reaction mixture was stirred at 110 °C for 24 h. After reaction, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under vacuum, and the residue was purified by silica gel chromatography using a mixture of PE/EA to afford the desired product **3**.

*2,5-Diphenyl-1,3,4-oxadiazole (**3a** and **3a′**).*[7g] White solid (**3a** and **3a′**: 97 mg, 87%), mp: 138−139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.12 (m, 4H), 7.56−7.50 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.5, 131.7, 129.0, 126.9, 123.9 ppm; HRMS (ESI): Calcd for $C_{14}H_{10}N_2NaO$ $(M + Na)^+$ 245.0685, found 245.0690.

*2-Phenyl-5-(p-tolyl)-1,3,4-oxadiazole (**3b** and **3b′**).*[7g] White solid (**3b**, 91 mg, 77%; **3b′**, 86 mg, 73%), mp: 122−124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.12 (m, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.54−7.48 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.7, 164.3, 142.2, 131.6, 129.7, 129.6, 129.0, 126.8, 124.0, 121.1, 21.6 ppm; HRMS (ESI): Calcd for $C_{15}H_{12}N_2NaO$ $(M + Na)^+$ 259.0842, found 259.0847.

*2-Phenyl-5-(o-tolyl)-1,3,4-oxadiazole (**3c** and **3c′**).*[12] White solid (**3c**, 96 mg, 81%; **3c′**, 83 mg, 70%), mp: 110−111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (dd, J = 7.4, 2.2 Hz, 2H), 7.95−7.91 (m, 2H), 7.53 (m, 3H), 7.51−7.33 (m, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.7, 164.5, 138.9, 132.5, 131.6, 129.0, 128.9, 127.4, 126.8, 124.0, 123.9, 123.7, 21.3 ppm; HRMS (ESI): Calcd for $C_{15}H_{12}N_2NaO$ $(M + Na)^+$ 259.0842, found 259.0851.

*2-Phenyl-5-(m-tolyl)-1,3,4-oxadiazole (**3d** and **3d′**).* White solid (**3d**, 87 mg, 74%; **3d′**, 80 mg, 68%), mp: 112−113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.12 (m, 2H), 7.95−7.91 (m, 2H), 7.53−7.48 (m, 3H), 7.42−7.34 (m, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.7, 164.4, 138.9, 132.5, 131.6, 129.0, 128.9, 127.4, 126.9, 124.0, 123.9, 123.7, 21.3 ppm; HRMS (ESI): Calcd for $C_{15}H_{12}N_2NaO$ $(M + Na)^+$ 259.0842, found 259.0848.

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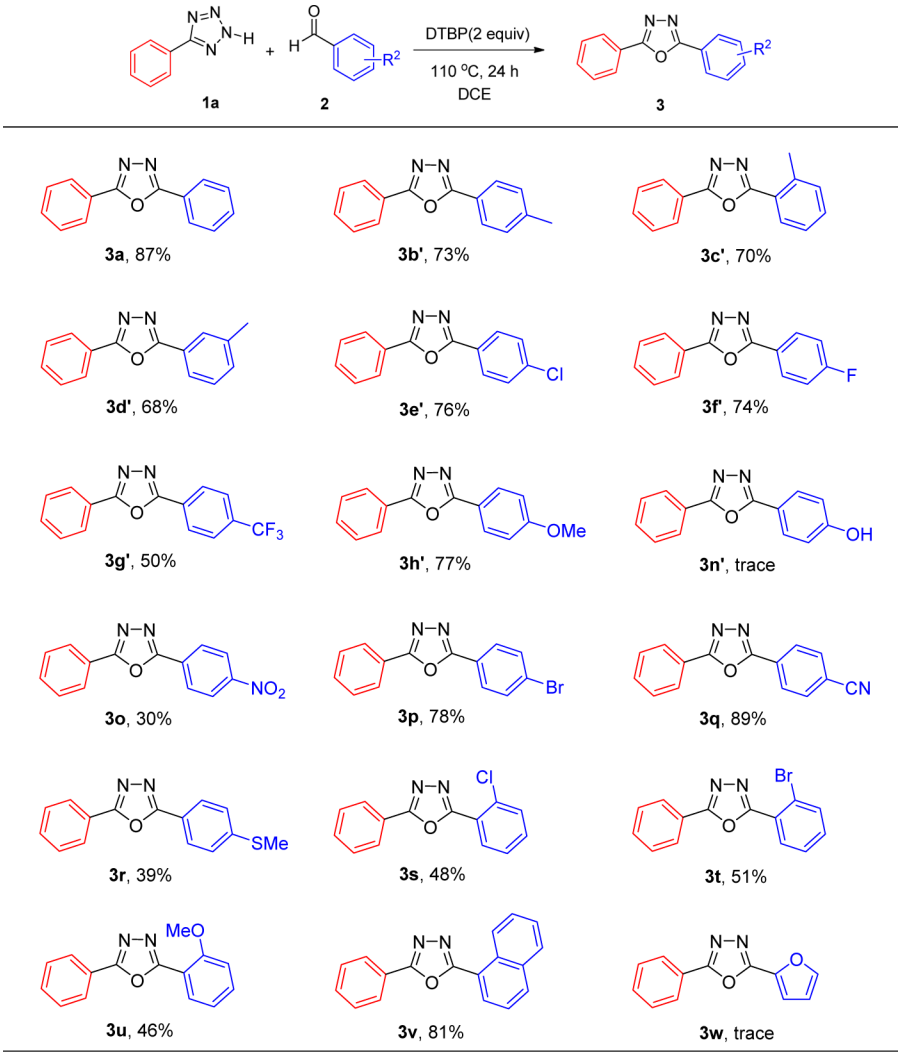
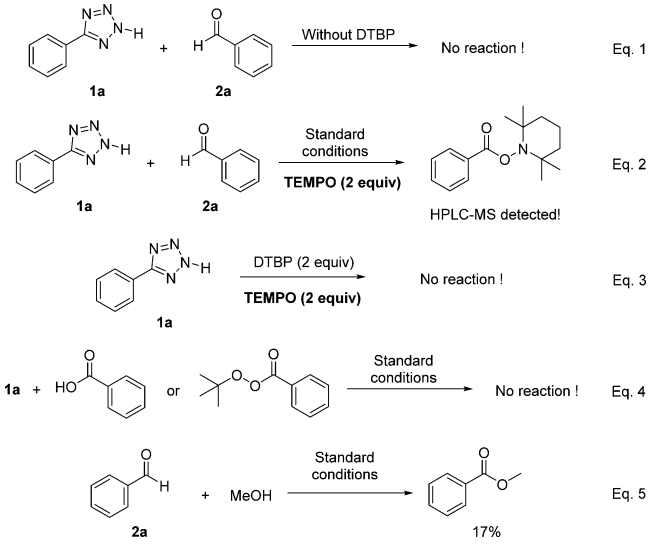
Table 3. Reaction Scope for Aldehydes[a]

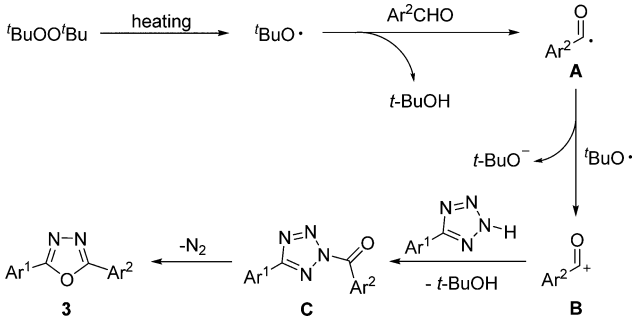


[a]Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), DTBP (1 mmol, 2 equiv), 1,2-dichloroethane (3 mL), 110 °C, 24 h. Isolated yields.

Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



*2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**3e** and **3e′**).*[7g] White solid (**3e**, 101 mg, 79%; **3e′**, 97 mg, 76%), mp: 161−162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J = 6.6 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.55−7.49 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.7, 163.7, 137.9, 131.8, 129.4, 129.1, 128.1, 126.9, 123.7, 122.3 ppm; HRMS (ESI): Calcd for $C_{14}H_9ClN_2NaO$ $(M + Na)^+$ 279.0296, found 279.0291.

*2-(4-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (**3f** and **3f′**).*[7g] White solid (**3f**, 52 mg, 43%; **3f′**, 89 mg, 74%), mp: 148−149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16−8.10 (m, 4H), 7.57−7.50 (m, 3H), 7.23 (dd, J = 16.4, 7.8 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.9 (d, J_{C-F} = 227.9 Hz), 164.6, 163.5, 131.7, 129.2 (d, J_{C-F} = 8.8 Hz), 129.1, 126.9, 123.8, 120.2 (d, J_{C-F} = 3.3 Hz), 116.4 (d, J_{C-F} = 22.3 Hz)

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ppm; HRMS (ESI): Calcd for $C_{14}H_9FN_2NaO$ $(M + Na)^+$ 263.0591, found 263.0595.

*2-Phenyl-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (**3g** and **3g′**).*[7g] White solid (**3g**, 100 mg, 69%; **3g′**, 72 mg, 50%), mp: 153−155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, J = 8.2 Hz, 2H), 8.14−8.12 (m, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.59−7.51 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.1, 163.3, 133.2 (d, J_{C-F} = 32.8 Hz), 132.0, 129.1, 127.2, 127.1, 127.0, 126.1 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 273.2 Hz), 123.5 ppm; HRMS (ESI): Calcd for $C_{15}H_9F_3N_2NaO$ $(M + Na)^+$ 313.0559, found 313.0563.

*2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3h** and **3h′**).*[7g] White solid (**3h**, 88 mg, 70%; **3h′**, 97 mg, 77%), mp: 147−149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11−8.10 (m, 2H), 8.05 (d, J = 8.4 Hz, 2H) 7.51−7.50 (m, 3H), 7.01 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.4, 164.0, 162.3, 131.4, 128.9, 128.6, 126.7, 124.0, 116.3, 114.4, 55.4 ppm; HRMS (ESI): Calcd for $C_{15}H_{12}N_2NaO_2$ $(M + Na)^+$ 275.0791, found 275.0786.

*2,5-Di-p-tolyl-1,3,4-oxadiazole (**3i**).*[13] White solid (90 mg, 72%), mp: 170−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, J = 7.5 Hz, 4H), 7.31 (d, J = 7.4 Hz, 4H), 2.42 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.4, 142.1, 129.7, 126.7, 121.1, 21.6 ppm; HRMS (ESI): Calcd for $C_{16}H_{14}N_2NaO$ $(M + Na)^+$ 273.0998, found 273.0992.

*2,5-Bis(4-methoxyphenyl)-1,3,4-oxadiazole (**3j**).*[7g] White solid (97 mg, 69%), mp: 157−159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, J = 8.1 Hz, 4H), 7.01 (d, J = 8.2 Hz, 4H), 3.87 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.0, 162.1, 128.5, 116.5, 114.4, 55.4 ppm; HRMS (ESI): Calcd for $C_{16}H_{14}N_2NaO_3$ $(M + Na)^+$ 305.0897, found 305.0894.

*2-(4-Methoxyphenyl)-5-(p-tolyl)-1,3,4-oxadiazole (**3k**).*[7g] Yellow solid (89 mg, 67%), mp: 137−138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 8.3 Hz, 2H), 7.99 (d, J = 7.7 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 3.87 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.2, 162.2, 142.0, 129.7, 128.6, 126.7, 121.2, 116.5, 114.4, 55.4, 21.6 ppm; HRMS (ESI): Calcd for $C_{16}H_{14}N_2NaO_2$ $(M + Na)^+$ 289.0947, found 289.0952.

*2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**3l**).*[7g] White solid (100 mg, 70%), mp: 164−166 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, J = 8.1 Hz, 4H), 7.49 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 3.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.6, 162.4, 137.7, 129.4, 128.7, 128.0, 122.5, 116.1, 114.5, 55.4 ppm; HRMS (ESI): Calcd for $C_{15}H_{11}ClN_2NaO_2$ $(M + Na)^+$ 309.0401, found 309.0407.

*2-(4-Chlorophenyl)-5-(o-tolyl)-1,3,4-oxadiazole (**3m**).* Light yellow solid (99 mg, 73%), mp: 134−136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (dd, J = 19.0, 8.0 Hz, 3H), 7.51 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.39−7.30 (m, 2H), 2.76 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.9, 163.3, 138.5, 137.9, 131.8, 131.3, 129.4, 128.9, 128.1, 126.2, 122.7, 122.4, 22.1 ppm; HRMS (ESI): Calcd for $C_{15}H_{11}ClN_2NaO$ $(M + Na)^+$ 293.0452, found 293.0454.

*2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (**3o**).*[13] Yellow solid (40 mg, 30%), mp: 222−224 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 8.4 Hz, 2H), 8.16−8.14 (m, 2H), 7.58−7.51 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.4, 162.8, 149.7, 132.3, 129.2, 129.1, 127.8, 127.1, 124.4, 123.3 ppm; HRMS (ESI): Calcd for $C_{14}H_9N_3NaO_3$ $(M + Na)^+$ 290.0536, found 290.0531.

*2-(4-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (**3p**).*[7g] White solid (117 mg, 78%), mp: 169−171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (dd, J = 7.8, 1.6 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.57−7.49 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.7, 163.8, 132.4, 131.9, 129.1, 128.2, 126.9, 126.4, 123.6, 122.8 ppm; HRMS (ESI): Calcd for $C_{14}H_9BrN_2NaO$ $(M + Na)^+$ 322.9790, found 322.9793.

*4-(5-Phenyl-1,3,4-oxadiazol-2-yl)benzonitrile (**3q**).* White solid (110 mg, 89%), mp: 178−180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 8.2 Hz, 2H), 8.14 (d, J = 6.9 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.60−7.53 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.3, 163.0, 132.8, 132.2, 130.5, 129.2, 127.3, 127.0, 123.3, 117.9, 115.1 ppm; HRMS (ESI): Calcd for $C_{15}H_9N_3NaO$ $(M + Na)^+$ 270.0638, found 270.0646.

*2-(4-(Methylthio)phenyl)-5-phenyl-1,3,4-oxadiazole (**3r**).* White solid (52 mg, 39%), mp: 113−115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 4.1 Hz, 2H), 8.02 (d, J = 7.8 Hz, 2H), 7.53 (brs, 3H), 7.34 (d, J = 7.8 Hz, 2H), 2.53 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.3, 164.2, 143.9, 131.6, 129.0, 127.1, 126.8, 125.7, 123.9, 120.0, 14.9 ppm; HRMS (ESI): Calcd for $C_{15}H_{12}N_2NaOS$ $(M + Na)^+$ 291.0563, found 291.0570.

*2-(2-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**3s**).*[13] Light yellow solid (61.4 mg, 48%), mp: 96−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dd, J = 17.2, 7.0 Hz, 3H), 7.61−7.39 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.0, 163.0, 133.0, 132.4, 131.9, 131.2, 131.1, 129.1, 127.1, 127.0, 123.7, 123.1 ppm; HRMS (ESI): Calcd for $C_{14}H_9ClN_2NaO$ $(M + Na)^+$ 279.0296, found 279.0293.

*2-(2-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (**3t**).* Light yellow solid (76 mg, 51%), mp: 155−156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (dd, J = 7.7, 1.6 Hz, 2H), 8.05 (dd, J = 7.7, 1.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.58−7.50 (m, 4H), 7.42−7.37 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.3, 163.6, 134.6, 132.5, 131.9, 131.7, 129.2, 127.7, 127.1, 125.3, 123.8, 121.5 ppm; HRMS (ESI): Calcd for $C_{14}H_9BrN_2NaO$ $(M + Na)^+$ 322.9790, found 322.9785.

*2-(2-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3u**).* White solid (58 mg, 46%), mp: 120−121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.12 (m, 2H), 8.01 (d, J = 7.5 Hz, 1H), 7.53−7.47 (m, 4H), 7.11−7.06 (m, 2H), 3.99 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.3, 163.3, 157.9, 133.0, 131.5, 130.4, 129.0, 126.9, 124.1, 120.7, 111.9, 56.0 ppm; HRMS (ESI): Calcd for $C_{15}H_{12}N_2NaO_2$ $(M + Na)^+$ 275.0791, found 275.0794.

*2-(Naphthalen-1-yl)-5-phenyl-1,3,4-oxadiazole (**3v**).*[14] Yellow solid (110 mg, 81%), mp: 120−122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.30 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 7.3 Hz, 1H), 8.20−8.17 (m, 2H), 8.04 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.73−7.69 (m, 1H), 7.62−7.52 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 164.5, 164.1, 133.8, 132.6, 131.7, 130.1, 129.1, 128.7, 128.3, 128.1, 127.0, 126.7, 126.2, 124.8, 123.9, 120.5 ppm; HRMS (ESI): Calcd for $C_{18}H_{12}N_2NaO$ $(M + Na)^+$ 295.0842, found 295.0844.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all the compounds are available in the Supporting Information. 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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