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Article

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I_2-Mediated Oxidative C−O Bond Formation for the Synthesis of 1,3,4-Oxadiazoles from Aldehydes and Hydrazides

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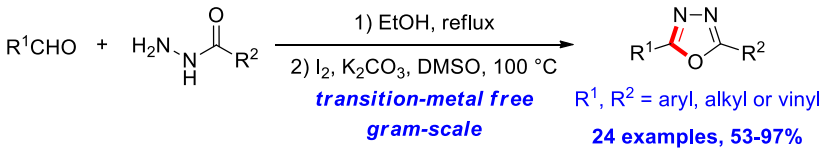


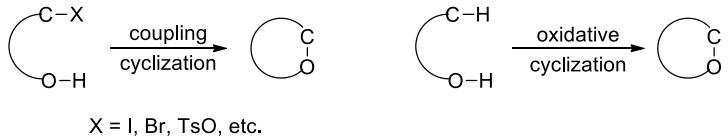
Abstract: A practical and transition metal-free oxidative cyclization of acylhydrazones into 1,3,4-oxadiazoles has been developed by employing stoichiometric molecular iodine in the presence of potassium carbonate. The conditions of this cyclization reaction also work well with crude acylhydrazone substrates obtained from the condensation of aldehydes and hydrazides. A series of symmetrical and asymmetrical 2,5-disubstituted (aryl, alkyl and/or vinyl) 1,3,4-oxadiazoles can be conveniently generated in an efficient and scalable fashion.

Introduction

The intramolecular carbon−oxygen (C−O) bond formation via the oxidation of carbon−hydrogen (C−H) and oxygen−hydrogen (O−H) bonds has become a very useful tool for the construction of oxygen-containing heterocycles, which resulted in the discovery of numerous novel synthetic methods.[1-10] Compared with the coupling cyclization (Scheme 1), this oxidative cyclization strategy does not require prefunctionalization of the reaction center, which makes the substrates

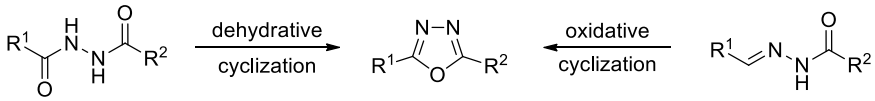
more accessible and allows more efficient synthesis of structurally diverse products. Many recent developments published in literature, however, require the use of hypervalent iodine,[1,2] transition metal-catalyzed aerobic oxidative cyclization,[3] $FeCl_3$,[4] etc. In this work, we report a simple, molecular iodine-mediated and transition metal-free approach that oxidatively forms the C−O bond in an intramolecular setting.

Scheme 1. Coupling and Oxidative Cyclization for the Construction of Oxygen-containing Heterocycles



1,3,4-Oxadiazoles are important five-membered aromatic heterocycles that have been widely used in many compounds with broad pharmaceutical and biological activities,[11-17] including antibacterial, anti-inflammatory, anticonvulsant, anticancer, anti-diabetic, analgesic, antiviral and antifungal properties. A number of methods have been developed for the synthesis of 1,3,4-oxadiazoles.[3,18-22] Generally, these methodologies can be divided into two classes (Scheme 2): a) dehydrative cyclization of 1,2-diacylhydrazines using reagents such as $SOCl_2$, PPA, $POCl_3$, H_2SO_4; b) oxidative cyclization of acylhydrazones utilizing oxidants (e.g. hypervalent iodines, chloramine T, CAN, $FeCl_3$, PbO_2, Br_2, $KMnO_4$, HgO/I_2) or via Cu(II) catalyzed aerobic oxidation. Yet, there are still limitations associated with these methods, such as, harsh reaction conditions, hazardous materials, limited substrate scope and/or scalability. Therefore, more general and eco-friendly procedures for the synthesis of 1,3,4-oxadiazoles from easily available starting materials are still highly desirable. This promoted us to explore for a simpler and more efficient methodology.

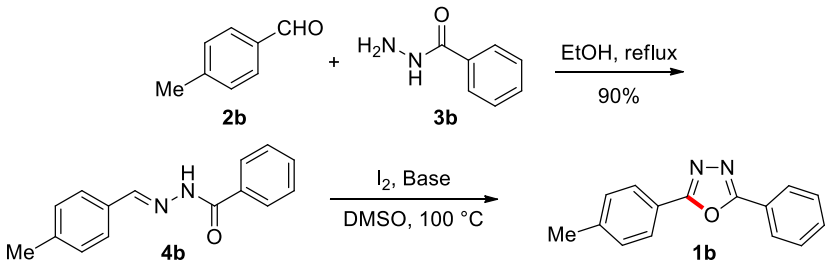
Scheme 2. Two Classical Strategies for the Construction of 1,3,4-Oxadiazole Framework



Results and Discussion

Molecular iodine plays an important role in organic synthesis, owing to its commercial availability, low cost, and low toxicity.[23-24] Recently, it has been successfully employed to synthesize indole derivatives[25-27] and oxazoles.[28-30] Inspired by these advances, we sought to investigate the application of this reagent in oxadiazole synthesis.[31] Our investigation started with the cyclization of benzoyl hydrazone **4b** to the corresponding 1,3,4-oxadiazole **1b** (Table 1). The substrate **4b** was readily prepared via the condensation of 4-methylbenzaldehyde (**2b**, 1 equiv) and benzohydrazide (**3b**, 1 equiv) in ethanol at refluxing temperature in 90% yield. The oxidative cyclization of **4b** was acheived by ultilizing molecualr iodine in the presence of cesium carbonate. Our initial screening of reaction conditions indicated that DMSO was the most effective media for this conversion, with 100 ºC being the optimal temperature. It needs at least 1.2 equiv of iodine, 3.0 equiv of the base to complete the transformation with the yield of 84% (entry 1). Further optimization demonstrated that the usage of potassium carbonate as base gave the best result (96% yield, entry 2). With organic base, like triethylamine (entry 3) or DBU (entry 4), the yields of product **1b** were significantly lower.

Table 1. Screening of Reaction Conditions for the Synthesis of 1,3,4-Oxadiazole **1b** from Benzoyl Hydrazone **4b**[a]



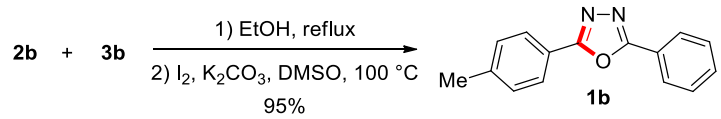
entry	base	time	yield[b]
1	Cs_2CO_3	0.5 h	84%
2	K_2CO_3	1.0 h	96%
3	NEt_3	6.0 h	trace
4	DBU	1.5 h	58%

[a] Optimal reaction conditions: I_2 (1.2 mmol), K_2CO_3 (3.0 mmol), DMSO, 100 ºC. [b] Isolated yields after silica gel column

chromatography.

With these results in hand, we sought to probe the feasibility of using crude benzoyl hydrazone **4b** for this transformation. After the first-step condensation was complete (monitored by TLC), the solvent was evaporated under reduced pressure to give the crude intermediate **4b**, which was then re-dissolved in DMSO, followed by the treatment of molecular iodine and potassium carbonate. To our delight, the desired oxadiazole **1b** was generated in equally good yield (95%) at 100 ºC, when 1.2 equiv of iodine and 3 equiv of potassium carbonate were used (Scheme 3).

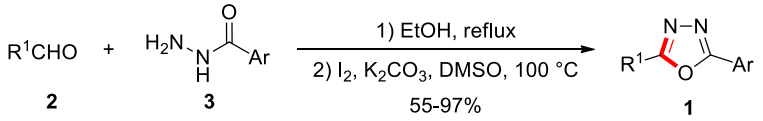
Scheme 3. Direct Synthesis of 1,3,4-Oxadiazole **1b** from benzaldehyde **2b** and hydrazide **3b**[a]



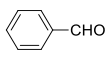
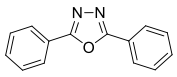
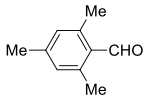
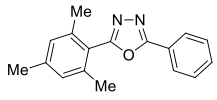
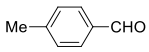
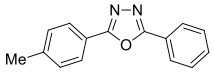
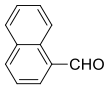
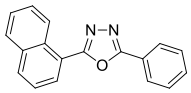
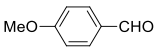
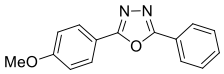
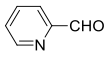
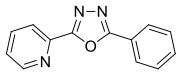
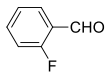
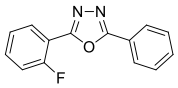
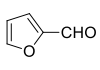
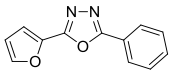
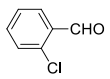
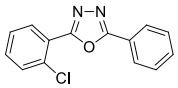
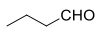
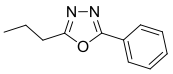
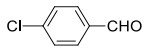
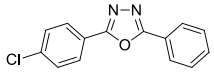
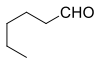
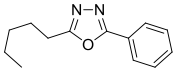
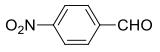
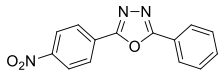
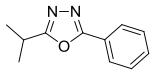
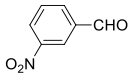
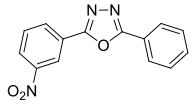
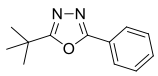
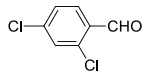
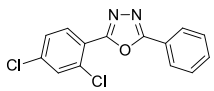
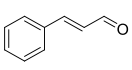
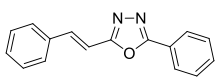
[a] Optimal reaction conditions: 1) condensation of **2** (1 mmol) and **3** (1 mmol) in EtOH at refluxing temperature; 2) I_2 (1.2 mmol), K_2CO_3 (3 mmol), DMSO, 100 ºC.

Then, a variety of aryl aldehydes (**2a**−**2m**, entries 1-13, Table 2) were subjected to these optimal reaction conditions to examine the scope and generality of this method. These aldehydes were first condensed with benzohydrazide, followed by the iodine-mediated oxidative cyclization to afford a series of symmetric (**1a**) and asymmetric (**1b**−**1m**) oxadiazoles. As shown in Table 2, this methodology is compatible with a variety of electron-donating groups (EDGs, **2b**−**2c**, **2j**) and electron-withdrawing groups (EWGs, **2d**−**2i**) on the arylaldehydes. Methyl- and nitro- substituting groups (**2b**, **2g**−**2h**) are among the best, giving excellent yields of products. Taking 3-nitrobenzaldehyde (**2h**) as an example, the reaction was successfully carried out in gram scale. Multiple substituted arylaldehydes produced the oxadiazole products (**1i**−**1j**) in as good yields as the mono-substituted ones did (entry 9 *vs* entries 5-6; entry 10 *vs* entry 2). α-Naphthylaldehyde (**2k**, entry 11) and pyridine-2-aldehyde (**2l**, entry 12) were also converted to the desired oxadiazoles in good yield. 2-Furyl oxadiazole (**1m**) was obtained from 2-furaldehyde (**2m**) in moderate yield with some unidentified byproducts during both the first-step condensation and the following cyclization (entry 13).

Table 2. Scope of Aldehydes **2**[a]



R^1 = aryl, alkyl or vinyl

entry	aldehyde (**2**)	product (**1**)	Yield[b]	entry	aldehyde (**2**)	product (**1**)	Yield[b]
1	 **2a**	 **1a**	76%	10	 **2j**	 **1j**	97%
2	 **2b**	 **1b**	95%	11	 **2k**	 **1k**	91%
3	 **2c**	 **1c**	83%	12	 **2l**	 **1l**	83%
4	 **2d**	 **1d**	93%	13	 **2m**	 **1m**	55%
5	 **2e**	 **1e**	88%	14	 **2n**	 **1n**	72%
6	 **2f**	 **1f**	80%	15	 **2o**	 **1o**	75%
7	 **2g**	 **1g**	94%	16	 **2p**	 **1p**	91%
8	 **2h**	 **1h**	98% (91%[c])	17	 **2q**	 **1q**	97%
9	 **2i**	 **1i**	89%	18[d]	 **2r**	 **1r**	71%

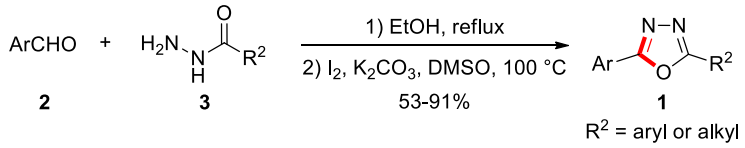
[a] Optimal reaction conditions: 1) condensation of **2** (1 mmol) and **3** (1 mmol) in EtOH at refluxing temperature; 2) I_2 (1.2 mmol),

K_2CO_3 (3 mmol), DMSO, 100 ºC. [b] Isolated yields after silica gel column chromatography. [c] The reaction was conducted on gram-scale. [d] This oxadiazole was obtained from the purified acyl hydrazone.

In light of these encouraging results, we initiated further studies with aliphatic aldehydes (entries 14-17, Table 2). The desired oxadiazoles (**1n−1q**) were successfully obtained under the optimal reaction conditions. Interestingly, we noticed that the yields of products were somehow related to the degree of the α-carbons of aldehydes in this order: 4º carbon (**2q**) > 3º carbon (**2p**) > 2º carbon (**2n−2o**). In addition, reaction of cinnamaldehyde (**2r**) with benzohydrazide formed 5-vinyl substituted oxadiazole **1r** in 71% yield.

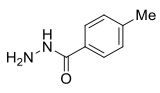
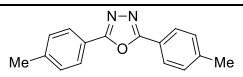
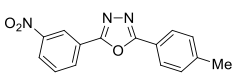
To further explore the reaction scope, we replaced benzohydrazide with other hydrazides (Table 3). 4-Methyl benzohydrazide (**3s**) reacted with 4-methylbenzaldehyde and 3-nitrobenzaldehyde under the optimal reaction conditions to give symmetric (**1s**) and asymmetric (**1t**) oxadiazoles, respectively. Isonicotinohydrazide (**3u**) was converted to the desired product **1u** in good yield with the corresponding aldehyde. Aliphatic hydrazides (R^2 group in hydrazides **3** is alkyl) also work well (**3v-3x**). Oxadiazoles **1v−1w** were successfully achieved in moderate to good yields. The relatively low yield of **1w** might be due to the side reaction of the acetyl group in acyl hydrazone **4w** (e.g. haloform reaction). Reaction of dihydrazide **3x** and 4-methylbenzaldehyde afforded the symmetric dioxadiazole **1x**.

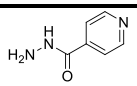
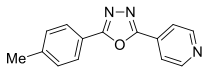
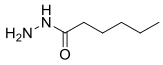
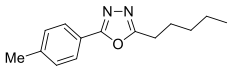
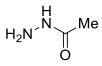
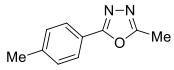
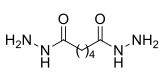
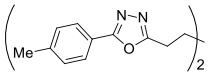
Table 3. Scope of Hydrazides **3**[a]



2 **3** **1**

R^2 = aryl or alkyl

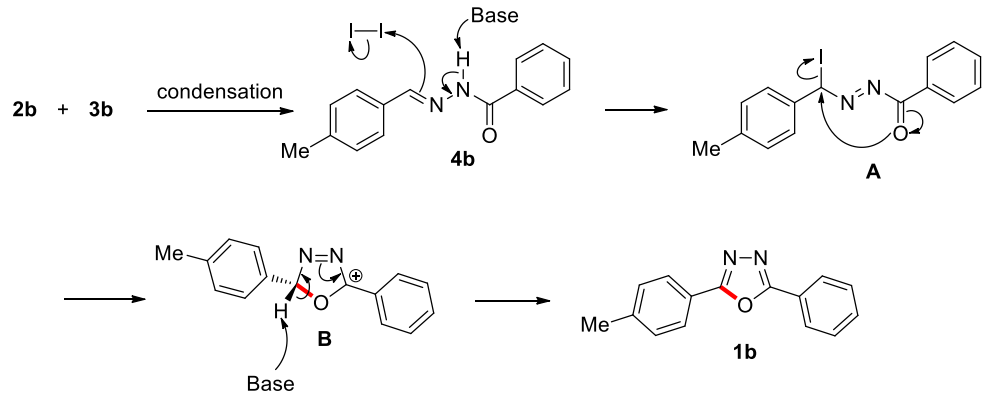
entry	Hydrazide (**3**)	product (**1**)	yield[b]
1	 **3s**	 **1s**	87%
2		 **1t**	91%

3	 **3u**	 **1u**	79%
4[c]	 **3v**	 **1v**	80%
5[c,d]	 **3w**	 **1w**	53%
6	 **3x**	 **1x**	81%

[a] Optimal reaction conditions: 1) condensation of **2** (1 mmol) and **3** (1 mmol) in EtOH at refluxing temperature; 2) I_2 (1.2 mmol), K_2CO_3 (3 mmol), DMSO, 100 ºC. [b] Isolated yields after silica gel column chromatography. [c] Oxadiazoles were obtained from purified acyl hydrazones. [d] 2 mmol of I_2 was used in this reaction.

A plausible reaction mechanism for the formation of 1,3,4-oxadiazoles **1** is proposed (Schems 4).[25] Taking the formation of **1b** as an example, the base-promoted oxidative iodination of benzoyl hydrazone **4b** generates an iodide intermediate **A**. Consequently, the intemediate **B** is formed via a S_N2'-type cyclization of **A**, with a new C−O bond formed. Finally, the subsequent deprotonation by base affords the oxadiazole structure **1b**.

Scheme 4. Proposed Mechanism for the Formation of 1,3,4-Oxadiazole **1b**



Conclusions

In summary, we have developed a simple and convenient oxidative C−O bond formation reaction

for the synthesis of 1,3,4-oxadiazoles. This reaction can be applied to the crude acylhydrazones, obtained via the condensation of aldehydes and hydrazides, to give a series of symmetrical and asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles. It works with a range of aldehydes (aryl, alkyl and vinyl substituted) and hydrazides (both aryl and alkyl substituted), showing good functional-group tolerance. This versatility allows the efficient synthesis of structurally diverse 1,3,4-oxadiazoles under mild reaction conditions. In this transition metal-free methodology, the oxidative cyclization was accomplished by employing stoichiometric molecular iodine in the presence of potassium carbonate, which makes it friendlier to the environment. In addition, the reaction can be safely conducted on gram scale.

Experimental Section

General Information. ^{1}H NMR spectra were recorded on a 400 MHz or 300 MHz (^{13}C NMR spectra were recorded on a 100 MHz) spectrometer. Chemical shift values are given in ppm and referred as the internal standard to TMS (tetramethylsilane). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet and dd, doublet of doublets. The coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined on a micromelting point apparatus without corrections. Flash column chromatography was performed over silica gel 200-300 mesh, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE). High-resolution mass spectra (HRMS-ESI) were obtained on a Q-TOF Mass Spectrometer. Infrared (IR) spectra were obtained on a FTIR spectrometer.

General Procedure for the Synthesis of 2,5-Disubstituted-1,3,4-oxadiazoles 1. A solution of aldehydes **2** (1.0 mmol) and acyl hydrazine **3** (1.0 mmol) in EtOH (10 mL) was refluxed until the condensation was complete (monitored by TLC, 3-11 h), and then the solvent was evaporated under reduced pressure, and the resulting residue was re-dissolved in DMSO (5 mL), followed by addition of potassium carbonate (3 mmol), iodine (1.2 mmol) in sequence. The reaction mixture was stirred at 100 ^{o}C until the conversion was complete (monitored by TLC, 1−4 h). After cooled to room temperature, it was treated with 5% $Na_2S_2O_3$ (20 mL), extracted with EA (10 mL x 3). The combined organic layer was washed with brine (10 mL x 1), dried over anhydrous sodium sulfate and concentrated. The given residue was purified through silica gel column

chromatography using a mixture of ethyl acetate (EA) and petroleum ether (PE) as eluent to afford the desired oxadiazoles **1**.

2,5-Diphenyl-1,3,4-oxadiazole (1a). The product was obtained according to the general procedure, as white solid (168 mg, 0.76mmol, 76%). mp 138-139 ºC (ref. 138-139 ºC);[32] R_F = 0.35 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.13 (m, 4H), 7.54-7.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 131.7, 129.0, 126.9, 123.9; IR (KBr): 3057, 3007, 2992, 1604, 1546, 1484, 1445, 1267, 1069, 784, 711, 686; HRMS (m/z) (M+Na) calcd for $C_{14}H_{10}N_2ONa$: 245.0685, found 245.0677.

2-phenyl-5-(p-tolyl)-1,3,4-oxadiazole (1b). The product was obtained according to the general procedure, as white solid (225 mg, 0.95 mmol, 95%). mp 126-127 ºC (ref. 125 ºC);[33] R_F = 0.25 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.13 (m, 2H), 8.04 (d, J = 8.0 Hz, 2H), 7.55-7.53 (m, 3H), 7.34 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 164.3, 142.2, 131.6, 129.7, 129.0, 126.8, 124.0, 121.1, 21.6; IR (KBr): 3058, 3025, 2915, 1782, 1550, 1496, 1445, 1174, 1076, 822, 782, 687; HRMS (m/z) (M+Na) calcd for $C_{15}H_{12}N_2ONa$: 259.0842, found 259.0831.

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (1c). The product was obtained according to the general procedure, as white solid (210mg, 0.83 mmol, 83%). mp 150-151 ºC (ref. 150-151 ºC);[34] R_F = 0.30 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.11 (m, 2H), 8.09-8.06 (m, 2H), 7.55-7.51 (m, 3H), 7.04-7.02 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 164.1, 162.3, 131.5, 129.0, 128.6, 126.8, 124.0, 116.4, 114.5, 55.4; IR (KBr): 3011, 2955, 2843, 1616, 1503, 1313, 1263, 1179, 1078, 831, 738, 684; HRMS (m/z) (M+Na) calcd for $C_{15}H_{12}N_2O_2Na$: 275.0791, found 275.0791.

2-(2-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (1d). The product was obtained according to the general procedure, as white solid (223 mg, 0.93 mmol, 93%). mp 120-122 ºC; R_F = 0.30 (EA/PE 20:80); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19-8.14 (m, 3H), 7.59-7.53 (m, 4H), 7.37-7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (d, $J_{C\text{-}F}$ = 1.4 Hz), 161.4 (d, $J_{C\text{-}F}$ = 4.8 Hz), 160.0 (d, $J_{C\text{-}F}$ = 257 Hz), 133.5 (d, $J_{C\text{-}F}$ = 8.4 Hz), 131.8, 129.8 (d, $J_{C\text{-}F}$ = 1.5 Hz), 129.1, 127.0, 124.6 (d, $J_{C\text{-}F}$ = 3.7 Hz), 123.7, 117.0 (d, $J_{C\text{-}F}$ = 20.8 Hz), 112.4 (d, $J_{C\text{-}F}$ = 11.7 Hz); HRMS (m/z) (M+Na) calcd for $C_{14}H_9FN_2ONa$: 263.0591, found 263.0591.

2-(2-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (1e). The product was obtained according to the general procedure, as white solid (227mg, 0.88 mmol, 88%). mp 95-98 ºC (ref. 96-98 ºC);[35] R_F = 0.30 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.15 (m, 2H), 8.12 (dd, J = 7.6, 1.6 Hz, 1H), 7.59-7.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.0, 133.0, 132.4, 131.9, 131.3, 131.2, 129.1, 127.1, 127.0, 123.7, 123.2; IR (KBr): 3067, 2922, 1594, 1550, 1489, 1454, 1433, 1087, 779, 729, 687; HRMS (m/z) (M+Na) calcd for $C_{14}H_9ClN_2ONa$: 279.0296, found 279.0290.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (1f). The product was obtained according to the general procedure, as white solid (204 mg, 0.80 mmol, 80%). mp 165-167 ºC (ref. 166 ºC);[36] R_F = 0.35 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.12 (m, 2H), 8.10-8.07 (m, 2H), 7.58-7.51 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.7, 138.0, 131.8, 129.4, 129.1, 128.1, 126.9, 123.7, 122.4; IR (KBr): 3086, 3061, 2918, 1605, 1550, 1478, 1406, 1089, 1011, 839, 730, 688; HRMS (m/z) (M+Na) calcd for $C_{14}H_9ClN_2ONa$: 279.0296, found 279.0283.

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (1g). The product was obtained according to the general procedure, as light yellow solid (252 mg, 0.94 mmol, 94%). mp 222-223 ºC; R_F = 0.25 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, J = 8.8 Hz, 2H), 8.35 (d, J = 8.8 Hz, 2H), 8.18-8.16 (m, 2H), 7.61-7.55 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.3, 163.2, 149.6, 132.8, 129.9, 129.4, 128.5, 127.4, 125.0, 123.5; IR (KBr): 3220, 3074, 2844, 1607, 1553, 1515, 1339, 1078, 859, 718, 690; HRMS (m/z) (M+Na) calcd for $C_{14}H_9N_3O_3Na$: 290.0536, found 290.0533.

2-(3-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (1h). The product was obtained according to the general procedure, as light yellow solid (1 mmol scale: 261 mg, 0.98 mmol, 98%; 7 mmol scale: 1.71 g, 6.40 mmol, 91%). mp 150-151 ºC (ref. 150-151 ºC);[37] R_F = 0.25 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (t, J = 2.0 Hz, 1H), 8.52-8.50 (m, 1H), 8.43-8.41 (m, 1H), 8.18-8.16 (m, 2H), 7.77 (t, J = 8.0 Hz, 1H), 7.61-7.54 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 162.6, 148.6, 132.4, 132.2, 130.4, 129.2, 127.1, 126.1, 125.5, 123.3, 121.7; IR (KBr): 3083, 2924, 2862, 1608, 1526, 1443, 1349, 1269, 1091, 779, 713, 690; HRMS (m/z) (M+Na) calcd for $C_{14}H_9N_3O_3Na$: 290.0536, found 290.0522.

2-(2,4-Dichlorophenyl)-5-phenyl-1,3,4-oxadiazole (1i). The product was obtained according to the general procedure, as white solid (259 mg, 0.89 mmol, 89%). mp 121-122 ºC; R_F = 0.25

(EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.13 (m, 2H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.58-7.53 (m, 3H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 162.3, 138.1, 133.8, 132.0, 131.8, 131.2, 129.1, 127.6, 127.0, 123.5, 121.7; IR (KBr): 3085, 2924, 2849, 1593, 1551, 1457, 1400, 1107, 839, 734, 690; HRMS (m/z) (M+H) calcd for $C_{14}H_9Cl_2N_2O$: 291.0086, found 291.0086.

2-Mesityl-5-phenyl-1,3,4-oxadiazole (1j). The product was obtained according to the general procedure, as yellow solid (256 mg, 0.97 mmol, 97%). mp 92-94 ºC (ref. 91-92 ºC);[38] R_F = 0.35 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.10 (m, 2H), 7.55-7.51 (m, 3H), 7.00 (s, 2H), 2.35 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 163.9, 141.0, 138.7, 131.6, 129.1, 128.9, 126.8, 124.0, 121.1, 21.3, 20.5; IR (KBr): 3072, 2956, 2918, 2857, 1894, 1609, 1551, 1480, 1448, 1048, 866, 704, 689; HRMS (m/z) (M+Na) calcd for $C_{17}H_{16}N_2ONa$: 287.1155, found 287.1155.

2-(Naphthalen-2-yl)-5-phenyl-1,3,4-oxadiazole (1k). The product was obtained according to the general procedure, as yellow solid (247 mg, 0.91 mmol, 91%). mp 120-122 ºC (ref. 120 ºC);[39] R_F = 0.35 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (d, *J* = 8.8 Hz, 1H), 8.28 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.22-8.18 (m, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.62- 7.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 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; IR (KBr): 3089, 3053, 1549, 1527, 1443, 1249, 1070, 805, 772, 690; HRMS (m/z) (M+Na) calcd for $C_{18}H_{12}N_2ONa$: 295.0842, found 295.0842.

2-Phenyl-5-(pyridine-2-yl)-1,3,4-oxadiazole (1l). The product was obtained according to the general procedure, as yellow solid (184 mg, 0.83 mmol, 83%). mp 123-125 ºC (ref. 124-125 ºC);[40] R_F = 0.25 (EA/PE 50:50); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 4.8 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.23-8.21 (m, 2H), 7.91 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.59-7.51 (m, 3H), 7.48 (dd, *J* = 7.6, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 163.8, 150.3, 143.6, 137.2, 132.0, 129.0, 127.2, 125.7, 123.6, 123.2; IR (KBr): 3090, 3051, 1586, 1548, 1486, 1457, 1276, 1069, 970, 794, 714, 688; HRMS (m/z) (M+Na) calcd for $C_{13}H_9N_3ONa$: 246.0638, found 246.0638.

2-(Furan-2-yl)-5-phenyl-1,3,4-oxadiazole (1m). The product was obtained according to the general procedure, as white solid (117 mg, 0.55 mmol, 55%). mp 101-102 ºC (ref. 102-103 ºC);[41]

R_F = 0.30 (EA/PE 30:70); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.10 (m, 2H), 7.67 (m, 1H), 7.55-7.50 (m, 3H), 7.23 (d, *J* = 3.2 Hz, 1H), 6.62 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 157.4, 145.7, 139.4, 131.8, 129.0, 127.0, 123.5, 114.1, 112.2; IR (KBr): 3141, 3109, 2923, 1633, 1519, 1490, 1450, 1173, 1082, 898, 776, 688; HRMS (m/z) (M+Na) calcd for $C_{12}H_8N_2O_2Na$: 235.0478, found 235.0475.

2-Phenyl-5-propyl-1,3,4-oxadiazole (1n). The product was obtained according to the general procedure, as pale yellow oil (136 mg, 0.72 mmol, 72%). R_F = 0.20 (EA/PE 25:75); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.02 (m, 2H), 7.52-7.47 (m, 3H), 2.91 (t, *J* = 7.2 Hz, 2H), 1.93-1.84 (m, 2H), 1.06 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 164.6, 131.4, 128.9, 126.7, 124.0, 27.2, 20.1, 13.6; IR (KBr): 3063, 2967, 2875, 1964, 1898, 1609, 1571, 1450, 1252, 1068, 1005, 776, 691; HRMS (m/z) (M+Na) calcd for $C_{11}H_{12}N_2ONa$: 211.0842, found 211.0849.

2-Pentyl-5-phenyl-1,3,4-oxadiazole (1o). The product was obtained according to the general procedure, as pale yellow oil (163 mg, 0.75 mmol, 75%). R_F = 0.25 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.02 (m, 2H), 7.54-7.46 (m, 3H), 2.92 (t, *J* = 7.6 Hz, 2H), 1.89-1.81 (m, 2H), 1.44-1.35 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 164.6, 131.4, 128.9, 126.6, 124.0, 31.1, 26.2, 25.3, 22.1, 13.8; IR (KBr): 3063, 2931, 2871, 1728, 1609, 1572, 1450, 1245, 1087, 960, 776, 691; HRMS (m/z) (M+Na) calcd for $C_{13}H_{16}N_2ONa$: 239.1155, found 239.1153.

2-Isopropyl-5-phenyl-1,3,4-oxadiazole (1p). The product was obtained according to the general procedure, as yellow oil (172 mg, 0.91 mmol, 91%). R_F = 0.25 (EA/PE 15:85); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.03 (m, 2H), 7.53-7.47 (m, 3H), 3.33-3.23 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 164.5, 131.4, 128.9, 126.6, 124.0, 26.4, 20.0; IR (KBr): 3063, 2976, 2877, 1610, 1568, 1483, 1450, 1366, 1154, 1068, 961, 778, 691; HRMS (m/z) (M+Na) calcd for $C_{11}H_{12}N_2ONa$: 211.0842, found 211.0833.

2-(Tert-butyl)-5-phenyl-1,3,4-oxadiazole (1q). The product was obtained according to the general procedure, as colorless oil (195 mg, 0.97 mmol, 97%). R_F = 0.25 (EA/PE 20:80); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.03 (m, 2H), 7.52-7.48 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 164.5, 131.4, 128.9, 126.7, 124.1, 32.4, 28.2; IR (KBr): 3062, 2974, 2873, 1609, 1561, 1449, 1355, 1158, 1084, 779, 705, 692; HRMS (m/z) (M+Na) calcd for $C_{12}H_{14}N_2ONa$:

225.0998, found 225.0998.

(*E*)-2-Phenyl-5-styryl-1,3,4-oxadiazole (1r). The product was obtained according to the general procedure using purified acyl hydrazone **4r**, as white solid (177 mg, 0.71 mmol, 71%). mp 123 ºC; R_F = 0.29 (EA/PE 10:90); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.11 (m, 2H), 7.64 (d, *J* = 16.4 Hz, 1H), 7.60-7.57 (m, 2H), 7.56-7.50 (m, 3H), 7.45-7.39 (m, 3H), 7.10 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 164.0, 138.9, 134.7, 131.7, 130.0, 129.05, 129.00, 127.5, 126.9, 123.8, 110.0; IR (KBr): 3062, 2621, 2850, 1644, 1547, 1523, 1446, 1014, 971, 760, 694; HRMS (m/z) (M+H) calcd for $C_{16}H_{13}N_2O$: 249.1022, found 249.1027.

2,5-Di-p-tolyl-1,3,4-oxadiazole (1s). The product was obtained according to the general procedure, as white solid (218 mg, 0.87 mmol, 87%). mp 175-177 ºC; R_F = 0.30 (EA/PE 15:85); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-8.00 (m, 4H), 7.33-7.30 (m, 4H); 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 142.1, 129.7, 126.8, 121.2, 21.6; IR (KBr): 3064, 1616, 1589, 1546, 1492, 1468, 1063, 780, 738, 689; HRMS (m/z) (M+Na) calcd for $C_{16}H_{14}N_2ONa$: 273.0998, found 273.0998.

2-(3-Nitrophenyl)-5-(p-tolyl)-1,3,4-oxadiazole (1t). The product was obtained according to the general procedure, as white solid (256 mg, 0.91 mmol, 91%). mp 177-178 ºC; R_F = 0.25 (EA/PE 25:75); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94-8.93 (m, 1H), 8.52-8.49 (m, 1H), 8.43-8.39 (m, 1H), 8.06-8.04 (m, 2H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.38-7.35 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.4, 162.4, 148.6, 142.9, 132.4, 130.3, 129.9, 127.0, 125.9, 125.6, 121.6, 120.5, 21.7; IR (KBr): 3094, 2922, 2860, 1612, 1528, 1495, 1347, 1087, 823, 729, 705; HRMS (m/z) (M+Na) calcd for $C_{15}H_{11}N_3O_3Na$: 304.0693, found 304.0685.

2-(Pyridin-4-yl)-5-(p-tolyl)-1,3,4-oxadiazole (1u). The product was obtained according to the general procedure, as white solid (187 mg, 0.79 mmol, 79%). mp 143-144 ºC; R_F = 0.25 (EA/PE 50:50); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 5.6 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.99-7.98 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 162.4, 150.8, 142.9, 131.0, 129.9, 127.0, 120.5, 120.2, 21.6; IR (KBr): 3043, 2919, 1610, 1538, 1495, 1481, 1412, 1059, 828, 728, 700; HRMS (m/z) (M+Na) calcd for $C_{14}H_{11}N_3ONa$: 260.0794, found 260.0794.

2-pentyl-5-(p-tolyl)-1,3,4-oxadiazole (1v). The product was obtained according to the general

procedure using purified acyl hydrazone **4v**, as pale yellow oil (184 mg, 0.80 mmol, 80%). R_F = 0.20 (EA/PE 20:80); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H), 2.42 (s, 3H), 1.88-1.81 (m, 2H), 1.44-1.35 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 164.7, 141.9, 129.6, 126.6, 121.3, 31.1, 26.3, 25.4, 22.2, 21.5, 13.8; IR (KBr): 3030, 2969, 2870, 1915, 1618, 1571, 1500, 1458, 1181, 1083, 1009, 824, 792; HRMS (m/z) (M+Na) calcd for $C_{14}H_{18}N_2ONa$: 253.1311, found 253.1311.

2-Methyl-5-(p-tolyl)-1,3,4-oxadiazole (1w). The product was obtained according to the general procedure using purified acyl hydrazone **4w**, as yellow solid (92 mg, 0.53 mmol, 53%). mp 99-101 ºC; R_F = 0.30 (EA/PE 30:70); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.60 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.3, 142.0, 129.7, 126.6, 121.2, 21.6, 11.0; IR (KBr): 3046, 2919, 2849, 1593, 1498, 1248, 1089, 829, 734, 700; HRMS (m/z) (M+Na) calcd for $C_{10}H_{10}N_2ONa$: 197.0685, found 197.0685.

1,4-Bis(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)butane (1x). The product was obtained according to the general procedure, as yellow solid (303 mg, 0.81 mmol, 81%). mp 150-154 ºC; R_F = 0.20 (EA/PE 20:80); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.4 Hz, 4H), 7.28 (d, J = 8.1 Hz, 4H), 3.03-2.98 (m, 4H), 2.42 (s, 6H), 2.05-2.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.9, 164.9, 142.0, 129.6, 126.7, 121.1, 25.7. 25.0. 21.5; IR (KBr): 3031, 2921, 2850, 1613, 1571, 1499, 1177, 1085, 823, 724; HRMS (m/z) (M+Na) calcd for $C_{22}H_{22}N_4O_2Na$: 397.1635, found 397.1623.

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Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of all the oxadiazoles **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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