JOC The Journal of Organic Chemistry

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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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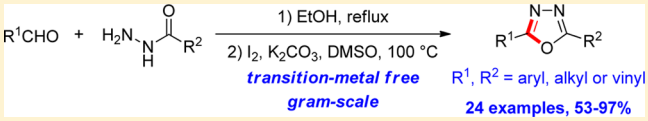
Supporting Information

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

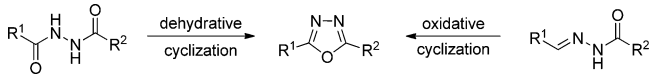
The intramolecular carbon−oxygen (C−O) bond formation via the oxidation of carbon−hydrogen (C−H) and oxygen−hydrogen (O−H) bonds has become a very useful tool for the construction of oxygen-containing heterocycles, which resulted in the discovery of numerous novel synthetic methods.[1−10] Compared with 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

X = I, Br, TsO, etc.

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, antidiabetic, 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

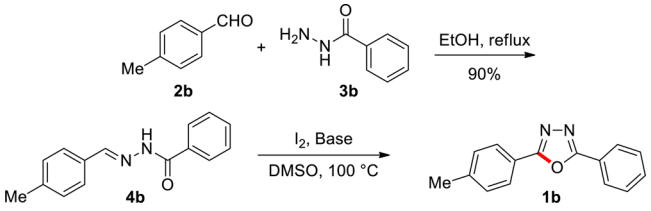


RESULTS AND DISCUSSION

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 achieved 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 °C being

Received: August 9, 2013
Published: September 23, 2013

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



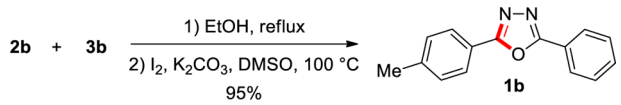
entry	base	time (h)	yield[b] (%)
1	Cs_2CO_3	0.5	84
2	K_2CO_3	1.0	96
3	NEt_3	6.0	trace
4	DBU	1.5	58

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

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.

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 redissolved 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 °C, 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 °C.

Then, a variety of aryl aldehydes (**2a**–**m**, 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**–**m**) oxadiazoles. As shown in Table 2, this methodology is compatible with a variety of electron-donating groups (EDGs, **2b**–**c**,**j**) and electron-withdrawing groups (EWGs, **2d**–**i**) on the arylaldehydes. Methyl- and nitro-substituting groups (**2b**,**g**,**h**) 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**,**j**) in as good yields as the monosubstituted ones did (entry 9 vs entries 5 and 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-Furyloxadiazole (**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).

In light of these encouraging results, we initiated further studies with aliphatic aldehydes (entries 14–17, Table 2). The desired oxadiazoles (**1n**–**q**) 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: 4° carbon (**2q**) > 3° carbon (**2p**) > 2° carbon (**2n**–**o**). 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**–**x**). Oxadiazoles **1v**–**w** 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**.

A plausible reaction mechanism for the formation of 1,3,4-oxadiazoles **1** is proposed (Scheme 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**.

CONCLUSIONS

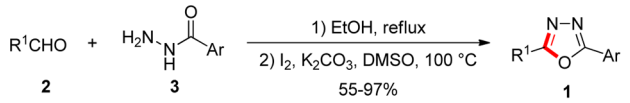
In summary, we have developed a simple and convenient oxidative C–O bond formation reaction for the synthesis of 1,3,4-oxadiazoles. This reaction can be applied to the crude acylhydrazones, obtained via the condensation of aldehydes and hydrazides, to give a series of symmetrical and asymmetrical 2,5-disubstituted 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.

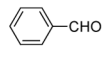
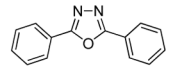
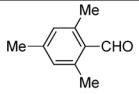
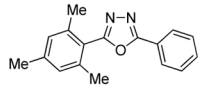
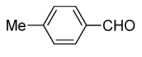
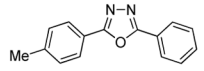
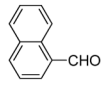
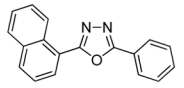
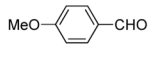
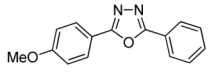
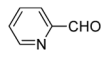
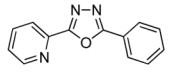
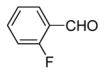
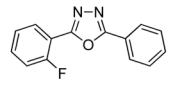
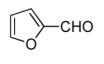
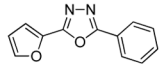
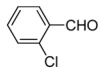
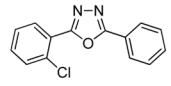
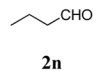
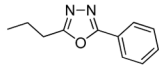
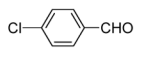
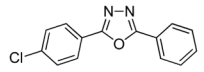
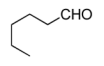
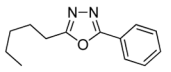
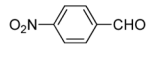
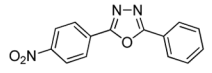
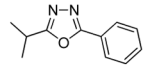
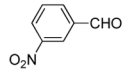
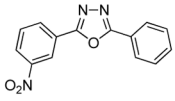
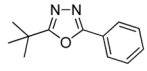
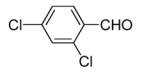
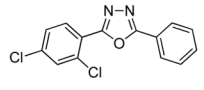
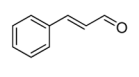
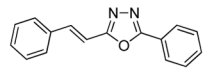
EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded on a 400 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

dx.doi.org/10.1021/jo401751h | J. Org. Chem. 2013, 78, 10337–10343

Table 2. Scope of Aldehydes 2[a]



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%

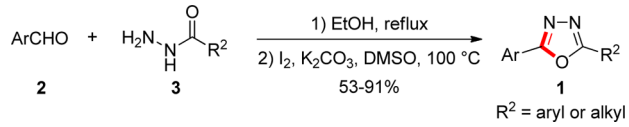
[a]Optimal reaction conditions: (1) condensation of **2** (1 mmol) and **3** (1 mmol) in EtOH at refluxing temperature; (2) I_2 (1.2 mmol), K_2CO_3 (3 mmol), DMSO, 100 °C. [b]Isolated yields after silica gel column chromatography. [c]The reaction was conducted on gram-scale. [d]This oxadiazole was obtained from the purified acyl hydrazone.

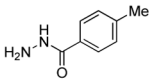
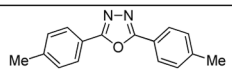
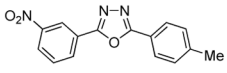
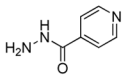
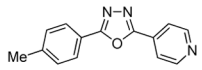
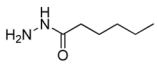
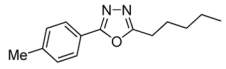
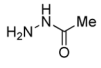
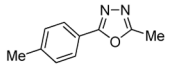
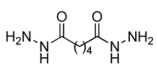
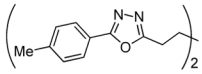
micromelting point apparatus without corrections. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE). High-resolution mass spectra (HRMS-ESI) were obtained on a Q-TOF mass spectrometer. Infrared (IR) spectra were obtained on an 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 redissolved 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 °C until the conversion was complete (monitored by TLC, 1−4 h). After being cooled to room temperature, it was treated with 5% $Na_2S_2O_3$ (20 mL), extracted with

dx.doi.org/10.1021/jo401751h | J. Org. Chem. 2013, 78, 10337−10343

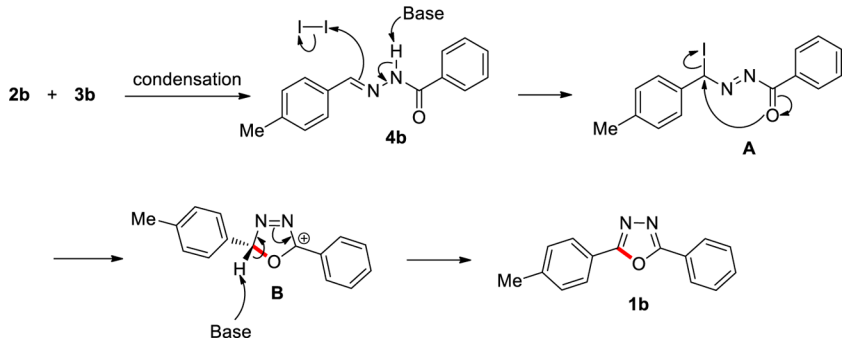
Table 3. Scope of Hydrazides 3[a]



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

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



EA (10 mL × 3). The combined organic layer was washed with brine (10 mL × 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 a white solid (168 mg, 0.76 mmol, 76%): mp 138−139 °C (lit.[32] mp 138−139 °C); 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 a white solid (225 mg, 0.95 mmol, 95%): mp 126−127 °C (lit.[33] mp 125 °C); 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.

dx.doi.org/10.1021/jo401751h | J. Org. Chem. 2013, 78, 10337−10343

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (1c). The product was obtained according to the general procedure, as a white solid (210 mg, 0.83 mmol, 83%): mp 150−151 °C (lit.[34] mp 150−151 °C); 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 a white solid (223 mg, 0.93 mmol, 93%): mp 120−122 °C; 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-F} = 1.4 Hz), 161.4 (d, J_{C-F} = 4.8 Hz), 160.0 (d, J_{C-F} = 257 Hz), 133.5 (d, J_{C-F} = 8.4 Hz), 131.8, 129.8 (d, J_{C-F} = 1.5 Hz), 129.1, 127.0, 124.6 (d, J_{C-F} = 3.7 Hz), 123.7, 117.0 (d, J_{C-F} = 20.8 Hz), 112.4 (d, J_{C-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 a white solid (227 mg, 0.88 mmol, 88%): mp 95−98 °C (lit.[35] mp 96−98 °C); 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 a white solid (204 mg, 0.80 mmol, 80%): mp 165−167 °C (lit.[36] mp 166 °C); 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 a light yellow solid (252 mg, 0.94 mmol, 94%): mp 222−223 °C; 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 a 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 °C (lit.[37] mp 150−151 °C); 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 °C; 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 a yellow solid (256 mg, 0.97 mmol, 97%): mp 92−94 °C (lit.[38] 91−92 °C); 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 a yellow solid (247 mg, 0.91 mmol, 91%): mp 120−122 °C (lit.[39] mp 120 °C); 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-(pyridin-2-yl)-1,3,4-oxadiazole (1l). The product was obtained according to the general procedure, as a yellow solid (184 mg, 0.83 mmol, 83%): mp 123−125 °C (lit.[40] mp 124−125 °C); 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 a white solid (117 mg, 0.55 mmol, 55%): mp 101−102 °C (lit.[41] mp 102−103 °C); 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 a 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 a 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 a 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,

dx.doi.org/10.1021/jo401751h | J. Org. Chem. 2013, 78, 10337−10343

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 a white solid (177 mg, 0.71 mmol, 71%): mp 123 °C; 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 a white solid (218 mg, 0.87 mmol, 87%): mp 175−177 °C; 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 °C; 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 a white solid (187 mg, 0.79 mmol, 79%): mp 143−144 °C; 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 a 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 a yellow solid (92 mg, 0.53 mmol, 53%): mp 99−101 °C; 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 a yellow solid (303 mg, 0.81 mmol, 81%): mp 150−154 °C; 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.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all of the oxadiazoles **1**. 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.

■ ACKNOWLEDGMENTS

We acknowledge the National Natural Science Foudation of China (No. 21172202) and the China Postdoctoral Science Foundation (No. 2013M530341) for financial support.

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