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Copper-catalyzed direct cross-coupling of 1,3,4-oxadiazoles with *N*-tosylhydrazones: efficient synthesis of benzylated 1,3,4-oxadiazoles†‡

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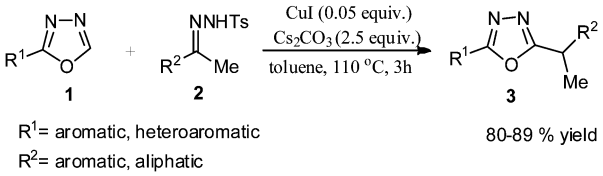
The first copper catalyzed direct C–H benzylation of 1,3,4-oxadiazoles using *N*-tosylhydrazones has efficiently been accomplished. Several substituted oxadiazoles have been prepared in high yields (80–89%) in 3 h.

Introduction

The oxadiazole system is an important structural motif for the development of various useful drugs. Compounds containing an oxadiazole moiety are known to possess a broad spectrum of biological activities including antimicrobial, anticancer, antiviral and antihypertensive properties.[1] They are also useful in medicinal chemistry as bioisosters for carbocyclic acids, esters and carboxyamides.[2] Some of the oxadiazole derivatives have been applied in the field of organic electronics[3] and multi-photon absorbing properties.[4] Because of such wide application of the substituted oxadiazoles in pharmacology and material science, the preparation of these compounds is an important task in organic synthesis. Here, we report an efficient copper catalyzed method for the synthesis of substituted 1,3,4-oxadiazole derivatives.

The metal mediated direct functionalization of C–H bonds of arenes and heteroarenes is highly useful for preparation of their derivatives.[5] Different metal catalysts such as palladium, rhodium and ruthenium have been applied for this transformation. In comparison to these catalysts copper catalysts have not yet been explored so much.[6] However, their activity is significant as well as they are easily available and less expensive. For all these reasons copper catalysts are of current interest for C–H activation of different arenes and heteroarenes.[6]

Recently, Daugulis and Do discovered the copper catalyzed alkenylation of polyfluoroarenes with alkenyl bromides.[6a] Copper catalyst has also been applied by Grierson *et al.* for alkenylation of oxazoles with vinyl bromides.[6b] Monguchi and his co-workers have utilized copper catalyst for arylation of 1,3-azoles.[6d]



Scheme 1 Copper-catalyzed C–C cross coupling.

In spite of all these efforts, the copper catalyzed cross-coupling reactions of heteroarene C–H bonds with sp^3 carbon are still limited. Recently, *N*-tosylhydrazones, prepared from carbonyl compounds have been found to be new type of coupling partner in transition metal catalyzed reactions.[7] In 2011 Wang *et al.* discovered the coupling reactions of *N*-tosylhydrazones with 1,3-azoles using copper as a catalyst.[7b] Similar reactions have been conducted by applying nickel and cobalt catalysts.[7e] However to our knowledge, the copper catalyzed C–H activation of 1,3,4-oxadiazoles by using *N*-tosylhydrazones has not yet been reported. Here, we disclose this reaction for direct benzylation of these heterocycles.

In continuation of our work[8] on the development of metal-mediated useful synthetic methodologies we observed that 1,3,4-oxadiazoles, when treated with *N*-tosylhydrazones in the presence of CuI and Cs_2CO_3 in toluene under reflux (110 °C), yielded the corresponding 2-benzylated derivatives in 3 h (Scheme 1).

Results and discussion

Initially, 2-phenyl 1,3,4-oxadiazole (**1a**) was treated with *N*-tosylhydrazone (**2a**) for optimization of the reaction conditions. The reaction was carried out with various metal compounds and different bases (Table 1).

The transformation was found to the most effective when CuI (0.05 equiv.) and Cs_2CO_3 (2.5 equiv.) were utilized in toluene at 110 °C (Table 1, entry 6). The reaction was completed in 3 h with a 82% yield. When the temperature was lowered the yield

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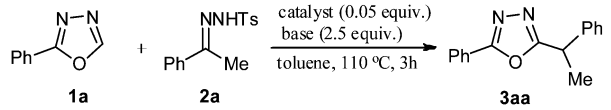
† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectrum of products. See DOI: 10.1039/c3ra42791a

‡ Part 235 in the series "studies on novel synthetic methodologies".

Table 1 Optimization for cross-coupling of 2-phenyl 1,3,4-oxadiazole (**1a**) with *N*-tosylhydrazone (**2a**) using different metal catalysts and various bases[a]

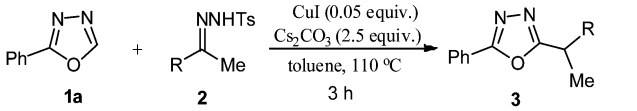


1a 2a 3aa

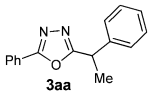
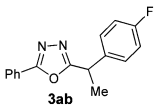
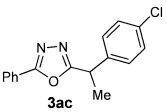
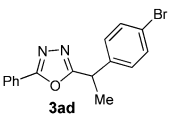
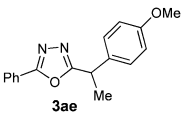
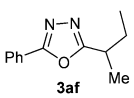
Entry	Catalyst (0.05 equiv.)	Base (2.5 equiv.)	Yield[b] [%]
1	CuO (nano)	LiO*t*Bu	28
2	Cu_2O	Cs_2CO_3	15
3	$CuFe_2O_4$ (nano)	LiO*t*Bu	32
4	CuI	K_3PO_4	48
5	CuI	LiO*t*Bu	68
6	CuI	Cs_2CO_3	82
7	CuI	Cs_2CO_3	45[c]
8	CuI	K_2CO_3	12
9	$Ni(OAc)_2$	Cs_2CO_3	NR[d]
10	$Ni(COD)_2$	LiO*t*Bu	NR[d]
11	$NiCl_2 \cdot H_2O$	Cs_2CO_3	NR[d]
12	CuBr	Cs_2CO_3	25
13	$Pd(PPh_3)_4$	LiO*t*Bu	NR[d]
14	$Pd(OAc)_2$	Cs_2CO_3	NR[d]
15	CuBr	Cs_2CO_3	25
16	$Cu(PPh_3)Br$	LiO*t*Bu	34
17	$Cu(PPh_3)Br$	Cs_2CO_3	42

[a] *Reaction conditions*: 2-phenyl 1,3,4-oxadiazole **1a** (1.0 mmol), *N*-tosylhydrazone **2a** (1.3 mmol), catalyst (0.05 equiv.), base (2.5 equiv.) at 110 °C over 3 h in toluene (3 mL). [b] Isolated yield of **3** after column chromatography. [c] Reaction was carried out at room temperature (27 °C). [d] No reaction.

Table 2 Copper-catalyzed direct cross coupling of 2-phenyl 1,3,4-oxadiazole (**1a**) with different *N*-tosylhydrazones (**2**)[a]



1a 2 3

Entry	2	R	Product 3	Yield[b] [%]
1	**2a**	Ph	 **3aa**	82
2	**2b**	4-FC_6H_4	 **3ab**	86
3	**2c**	4-ClC_6H_4	 **3ac**	83
4	**2d**	4-BrC_6H_4	 **3ad**	87
5	**2e**	4-$OMeC_6H_4$	 **3ae**	89
6	**2f**	C_2H_5	 **3af**	80

[a] *Reaction conditions*: 2-aryl 1,3,4-oxadiazole **1** (1.0 mmol), *N*-tosylhydrazone **2** (1.3 mmol), catalyst (0.05 equiv.), base (2.5 equiv.) at 110 °C over 3 h in toluene (3 mL). [b] Isolated yield of **3** after column chromatography.

was decreased and at the room temperature the yield was low (Table 1, entry 7). Instead of Cs_2CO_3, when the bases LiO*t*Bu and K_3PO_4 were used the conversion became less efficient (Table 1, entry 5 and 8). The catalytic activities of other copper catalysts such as CuO (nanoparticles), $CuFe_2O_4$ (nanoparticles), CuBr, Cu_2O and $Cu(PPh_3)Br$ were significantly weaker. Nickel and palladium based catalysts were completely inefficient to conduct the conversion. In absence of any catalyst the reaction did not proceed.

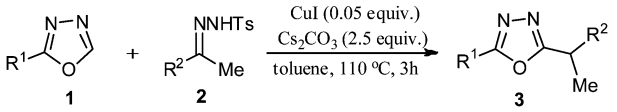
Following the standardization of the above reaction, direct benzylation and alkylation of 2-phenyl 1,3,4-oxadiazoles were carried out using various *N*-tosylhydrazones (Table 2). The *N*-tosylhydrazones used in the present conversion were derived from both aromatic as well as aliphatic ketones. 1,3,4-Oxadiazole having a non-aromatic substituent was also tested with aromatic *N*-tosylhadrazone. The reaction did not proceed and the starting material was recovered. Moreover, we tested the reaction of 1,3,4-oxadiazoles with *N*-tosylhydrazones derived from aldehydes but the conversion did not take place. The present reaction was completed in 3 h and the yields of the products were high (80–89%).

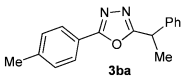
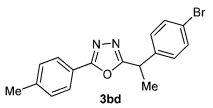
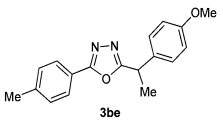
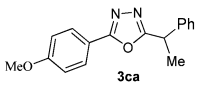
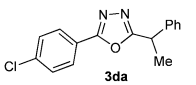
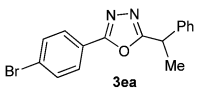
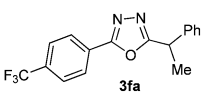
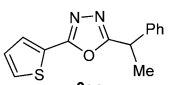
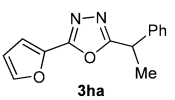
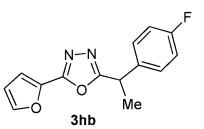
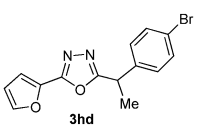
To further demonstrate, present copper-catalyzed direct cross-coupling reaction was carried out by using various 2-aryl-1,3,4-oxadiazoles and different *N*-tosylhydrazones (Table 3). The oxadiazoles contained both aromatic and heteroaromatic moieties at the C-2 position. We have observed the reaction conversion with different substituents (electronic withdrawing and electronic donating) on the 1,3,4-oxadiazoles as well as on *N*-tosylhydrazones. The yields of the products were not affected significantly with the electronic character of the substituent (Tables 2 and 3). However, the 1,3,4-oxadiazoles containing a non-aromatic substituent did not undergo the conversion under present reaction conditions, possibly due to the less reactivity of such oxadiazole compounds. The structures of the prepared oxadiazole derivatives were established from their spectral (IR, ^1H and ^{13}C NMR and ESIMS) and analytical data.

Further, *N*-tosylhydrazone prepared from benzophenone also reacted with 2-aryl-1,3,4-oxadiazoles and afforded the benzylated products in excellent yields (84–88%) (Scheme 2).

With an understanding of copper catalyzed cross-coupling reactions[7b,9] a plausible mechanism of the present transformation is shown in Scheme 3. Initially in the presence of base and the copper catalyst oxadiazole (**1**) form the heteroaryl copper species **A** (Scheme 3). This species reacted with the diazo

Table 3 Copper-catalyzed direct cross coupling of 2-aryl 1,3,4-oxadiazole (**1**) with different *N*-tosylhydrazones (**2**)[a]



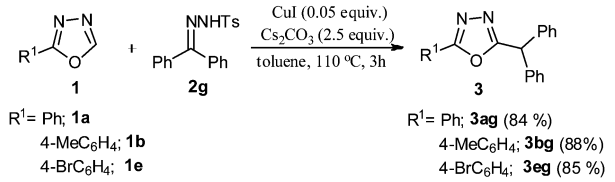
Entry	R^1(**1**)	R^2(**2**)	Product **3**	Yield[b] [%]
1	4-MeC_6H_4 (**1b**)	Ph (**2a**)	 **3ba**	83
2	4-MeC_6H_4 (**1b**)	4-BrC_6H_4 (**2d**)	 **3bd**	89
3	4-MeC_6H_4 (**1b**)	4-$OMeC_6H_4$ (**2e**)	 **3be**	85
4	4-$OMeC_6H_4$ (**1c**)	Ph (**2a**)	 **3ca**	86
5	4-ClC_6H_4 (**1d**)	Ph (**2a**)	 **3da**	82
6	4-BrC_6H_4 (**1e**)	Ph (**2a**)	 **3ea**	84
7	4-$CF_3C_6H_4$ (**1f**)	Ph (**2a**)	 **3fa**	87
8	2-Thienyl (**1g**)	Ph (**2a**)	 **3ga**	80
9	2-Furyl (**1h**)	Ph (**2a**)	 **3ha**	83
10	2-Furyl (**1h**)	4-FC_6H_4 (**2b**)	 **3hb**	85
11	2-Furyl (**1h**)	4-BrC_6H_4 (**2d**)	 **3hd**	88

[a] *Reaction conditions*: 2-aryl 1,3,4-oxadiazole **1** (1.0 mmol), *N*-tosylhydrazone **2** (1.3 mmol), catalyst (0.05 equiv.), base (2.5 equiv.) at 110 °C over 3 h in toluene (3 mL). [b] Isolated yield of **3** after column chromatography.

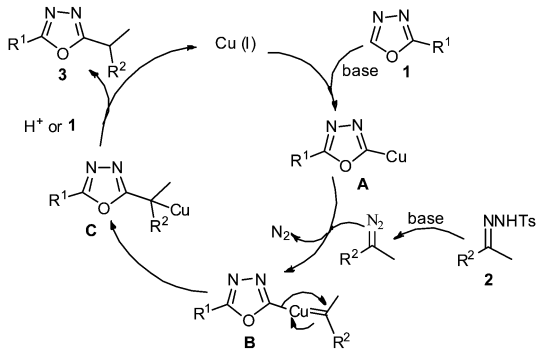
compound derived from the *N*-tosylhydrazone (**2**) by treatment with the base to produce the intermediate **B**. The latter was subsequently converted into **C** by 1,2-migration of the heteroaryl group from Cu to the α-carbon centre. Finally by interaction with proton or the starting oxadiazole (**1**) the intermediate **C** was converted into the product **3**.

Conclusions

In conclusion, we have developed for the first time an efficient copper catalyzed method for direct benzylation of aryl substituted 1,3,4-oxadiazoles using *N*-tosylhydrazones derived from ketones. The application of an easily available and less



Scheme 2 Copper-catalyzed direct cross-coupling of 2-aryl 1,3,4-oxadiazoles with *N*-tosylhydrazone derived from benzophenone.



Scheme 3 Plausible mechanism of copper-catalyzed benzylation of 2-aryl 1,3,4-oxadiazoles.

costly catalyst, high yields and rapid conversion are the advantages of the method. The method is a convenient access to various 1,3,4-oxadiazole derivatives.

Experimental section

General experimental procedure for benzylation of 1,3,4-oxadiazoles with *N*-tosylhydrazones

In a 10 mL round bottom flask CuI (9 mg, 0.05 equiv.), Cs_2CO_3 (812 mg, 2.5 equiv.), *N*-tosylhydrazone **2** (1.3 mmol) and 2-aryl 1,3,4-oxadiazole **1** (1.0 mmol) in toluene (3.0 mL) were taken. The reaction mixture was stirred at 110 °C for 3 h. The progress of the reaction was monitored by TLC. After the consumption of the starting materials, the reaction mixture was allowed to cool, and subsequently extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Concentration of the material *in vacuo* followed by flash chromatography on silica gel column afforded benzylated oxadiazole derivatives **3** in good yield.

2-Phenyl-5-(1-phenylethyl)-1,3,4-oxadiazole (3aa) (Table 2, entry 1)

Light yellow solid, mp: 71–74 °C, R_f 0.45 (20% EtOAc/hexane); IR (KBr): 1606, 1560, 1450, 1203 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 8.0 Hz), 7.51–7.42 (3H, m), 7.36–7.24 (5H, m), 4.42 (1H, q, J = 7.0 Hz), 1.82 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.8, 140.5, 131.8, 129.0, 127.8, 127.7, 127.3, 126.8, 124.0, 37.8, 19.7; ESIMS: m/z 251 $[M + H]^+$; anal. calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.81; H, 5.61; N, 11.23%.

2-(1-(4-Fluorophenyl)ethyl)-5-phenyl-1,3,4-oxadiazole (3ab) (Table 2, entry 2)

Yellow liquid, R_f 0.50 (20% EtOAc/hexane); IR (KBr): 1555, 1510, 1227, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.0 Hz), 7.51–7.42 (3H, m), 7.37–7.31 (2H, m), 7.08–7.01 (2H, m), 4.42 (1H, q, J = 7.0 Hz), 1.79 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.5, 164.9, 162.0 (d, J = 280.0 Hz), 136.0, 131.2, 128.9, 126.8, 123.8, 115.9 (d, J = 30.0 Hz), 36.6, 19.2; ESIMS: m/z 269 $[M + H]^+$; anal. calcd for $C_{16}H_{13}FN_2O$: C, 71.63; H, 4.88; N, 10.44. Found: C, 71.59; H, 4.85; N, 10.46%.

2-(1-(4-Chlorophenyl)ethyl)-5-phenyl-1,3,4-oxadiazole (3ac) (Table 2, entry 3)

Light yellow solid, mp: 70–73 °C, R_f 0.55 (20% EtOAc/hexane); IR (KBr): 1492, 1315, 1145, 1089 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 8.0 Hz), 7.52–7.43 (3H, m), 7.32–7.28 (4H, m), 4.40 (1H, q, J = 7.0 Hz), 1.82 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.8, 138.9, 132.0, 130.4, 129.2, 129.0, 128.8, 128.7, 126.9, 124.0, 36.9, 19.2; ESIMS: m/z 285, 287 $[M + H]^+$; anal. calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.52; H, 4.63; N, 9.78%.

2-(1-(4-Bromophenyl)ethyl)-5-phenyl-1,3,4-oxadiazole (3ad) (Table 2, entry 4)

White solid, mp: 150–152 °C, R_f 0.50 (20% EtOAc/hexane); IR (KBr): 1557, 1487, 1213, 1071 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.0 Hz), 7.54–7.43 (5H, m), 7.24 (2H, d, J = 8.0 Hz), 4.40 (1H, q, J = 7.0 Hz), 1.81 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.0, 139.3, 132.1, 132.0, 129.0, 128.9, 126.9, 126.8, 123.8, 121.5, 36.9, 19.2; ESIMS: m/z 329, 331 $[M + H]^+$; anal. calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.41; H, 4.01; N, 8.47%.

2-(1-(4-Methoxyphenyl)ethyl)-5-phenyl-1,3,4-oxadiazole (3ae) (Table 2, entry 5)

White solid, mp: 99–101 °C, R_f 0.35 (20% EtOAc/hexane); IR (KBr): 1553, 1458, 1080 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.0 Hz), 7.51–7.39 (3H, m), 7.29 (2H, d, J = 8.0 Hz), 6.90 (2H, d, J = 8.0 Hz), 4.39 (1H, q, J = 7.0 Hz), 3.79 (3H, s), 1.80 (3H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.5, 158.8, 145.1, 133.9, 132.0, 131.7, 128.9, 128.2, 126.2, 123.9, 114.0, 55.1, 36.5, 19.9; ESIMS: m/z 281 $[M + H]^+$; anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.87; H, 5.73; N, 9.98%.

2-(*sec*-Butyl)-5-phenyl-1,3,4-oxadiazole (3af) (Table 2, entry 6)

Light green liquid, R_f 0.30 (20% EtOAc/hexane); IR (KBr): 1553, 1458, 1080 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.08 (2H, d, J = 8.0 Hz), 7.60–7.47 (3H, m), 3.10 (1H, m), 1.99–1.70 (2H, m), 1.42 (3H, d, J = 7.0 Hz), 0.99 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.7, 148.4, 131.8, 129.0, 127.0, 124.1, 33.5, 27.9, 18.0, 11.6; ESIMS: m/z 203 $[M + H]^+$; anal. calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.23; H, 6.97; N, 13.89%.

2-(1-Phenylethyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (3ba) (Table 3, entry 1)

Colorless liquid, R_f 0.45 (20% EtOAc/hexane); IR (KBr): 1615, 1557, 1452, 1219 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.89 (2H, d, $J = 8.0$ Hz), 7.40–7.35 (3H, m), 7.31–7.22 (4H, m), 4.43 (1H, q, $J = 7.0$ Hz), 2.40 (3H, s), 1.82 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.0, 142.0, 138.3, 129.5, 128.8, 128.4, 127.2, 126.8, 120.9, 48.8, 21.1($2CH_3$); ESIMS: m/z 265 $[M + H]^+$; anal. calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.27; H, 6.08; N, 10.64%.

2-(1-(4-Bromophenyl)ethyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (3bd) (Table 3, entry 2)

Light yellow solid mp: 78–80 °C, R_f 0.50 (20% EtOAc/hexane); IR (KBr): 1497, 1420, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.88 (2H, d, $J = 8.0$ Hz), 7.45 (2H, d, $J = 8.0$ Hz), 7.25 (2H, d, $J = 8.0$ Hz), 7.22 (2H, d, $J = 8.0$ Hz), 4.39 (1H, q, $J = 7.0$ Hz), 2.40 (3H, s), 1.79 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.9, 142.0, 139.1, 132.0, 129.9, 129.7, 128.9, 127.6, 126.4, 121.2, 121.0, 36.9, 21.9, 19.4; ESIMS: m/z 345, 343 $[M + H]^+$; anal. calcd for $C_{17}H_{15}BrN_2O$: C, 59.49; H, 4.41; N, 8.16. Found: C, 59.52; H, 4.39; N, 8.19%.

2-(1-(4-Methoxyphenyl)ethyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (3be) (Table 3, entry 3)

White solid, mp: 86–88 °C, R_f 0.30 (20% EtOAc/hexane); IR (KBr): 1612, 1514, 1464, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.89 (2H, d, $J = 8.0$ Hz), 7.29 (2H, d, $J = 8.0$ Hz), 7.23 (2H, d, $J = 8.0$ Hz), 6.88 (2H, d, $J = 8.0$ Hz), 4.35 (1H, q, $J = 7.0$ Hz), 3.78 (3H, s), 2.37 (3H, s), 1.78 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8, 142.0, 132.1, 129.6, 129.5, 128.2, 127.0, 126.8, 121.2, 114.1, 55.2, 36.7, 21.5, 19.8; ESIMS: m/z 295 $[M + H]^+$; anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.17; N, 9.55%.

2-(4-Methoxyphenyl)-5-(1-phenylethyl)-1,3,4-oxadiazole (3ca) (Table 3, entry 4)

White solid, mp: 113–115 °C, R_f 0.28 (20% EtOAc/hexane); IR (KBr): 1609, 1562, 1511, 1446, 1243 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.91 (2H, d, $J = 8.0$ Hz), 7.40–7.21 (5H, m), 6.94 (2H, d, $J = 8.0$ Hz), 4.41 (1H, q, $J = 7.0$ Hz), 3.84 (3H, s), 1.80 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8, 145.1, 133.9, 132.0, 131.7, 128.9, 128.2, 126.2, 123.9, 114.0, 55.1, 36.5, 19.9; ESIMS: m/z 281 $[M + H]^+$; anal. calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.86; H, 5.74; N, 10.02%.

2-(4-Chlorophenyl)-5-(1-phenylethyl)-1,3,4-oxadiazole (3da) (Table 3, entry 5)

White solid, mp: 98–100 °C, R_f 0.50 (20% EtOAc/hexane); IR (KBr): 1606, 1582, 1483, 1254 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 (2H, d, $J = 8.0$ Hz), 7.45 (2H, d, $J = 8.0$ Hz), 7.39–7.27 (5H, m), 4.42 (1H, q, $J = 7.0$ Hz), 1.82 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.2, 140.4, 137.8, 129.2, 129.0, 128.1, 127.2, 127.0, 122.1, 38.6, 19.2; ESIMS: m/z 287, 285 $[M + H]^+$; anal. calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.51; H, 4.58; N, 9.81%.

2-(4-Bromophenyl)-5-(1-phenylethyl)-1,3,4-oxadiazole (3ea) (Table 3, entry 6)

Light yellow solid, mp: 88–90 °C, R_f 0.55 (20% EtOAc/hexane); IR (KBr): 1601, 1481, 1307, 1142 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (2H, d, $J = 8.0$ Hz), 7.59 (2H, d, $J = 8.0$ Hz), 7.35–7.13 (5H, m), 4.42 (1H, q, $J = 7.0$ Hz), 1.81 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.7, 144.3, 140.1, 132.2, 129.3, 129.1, 128.2, 127.2, 122.8, 37.5, 19.6; ESIMS: m/z 331, 329 $[M + H]^+$; anal. calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.41; H, 3.95; N, 8.49%.

2-(1-Phenylethyl)-5-(4-(trifluoromethyl) phenyl)-1,3,4-oxadiazole (3fa) (Table 3, entry 7)

White solid, mp: 108–110 °C, R_f 0.40 (20% EtOAc/hexane); IR (KBr): 1557, 1452, 1324, 1134 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (2H, d, $J = 8.0$ Hz), 7.31–7.12 (7H, m), 4.21 (1H, q, $J = 7.0$ Hz), 1.72 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.8, 144.4, 134.0, 129.2, 129.0, 128.9, 128.6, 127.2, 127.0, 126.9 (q, $J = 270.0$ Hz), 37.6, 21.5; ESIMS: m/z 319 $[M + H]^+$; anal. calcd for $C_{17}H_{13}F_3N_2O$: C, 64.15; H, 4.12; N, 8.80. Found: C, 64.12; H, 4.14; N, 8.78%.

2-(1-Phenylethyl)-5-(thiophene-2-yl)-1,3,4-oxadiazole (3ga) (Table 3, entry 8)

Light yellow solid, mp: 83–85 °C, R_f 0.45 (20% EtOAc/hexane); IR (KBr): 1599, 1558, 1427, 1238 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.69 (1H, m), 7.51 (1H, m), 7.39–7.27 (5H, m), 7.12 (1H, m), 4.41 (1H, q, $J = 7.0$ Hz), 1.82 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.6, 140.1, 130.0, 129.9, 129.1, 127.9, 127.6, 127.5, 37.7, 19.8; ESIMS: m/z 257 $[M + Na]^+$; anal. calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.58; H, 4.75; N, 10.89%.

2-(Furan-2-yl)-5-(1-phenylethyl)-1,3,4-Oxadiazole (3ha) (Table 3, entry 9)

Black solid, mp: 65–68 °C, R_f 0.42 (20% EtOAc/hexane); IR (KBr): 1636, 1520, 1452, 1168 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.60 (1H, m), 7.38–7.27 (5H, m), 7.09 (1H, m), 6.54 (1H, m), 4.40 (1H, q, $J = 7.0$ Hz), 1.81 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.0, 157.9, 145.6, 140.0, 139.0, 129.1, 127.2, 127.1, 113.9, 110.8, 37.2, 19.7; ESIMS: m/z 241$[M + H]^+$; anal. calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.01; H, 4.98; N, 11.68%.

2-(1-(4-Fluorophenyl)ethyl)-5-(furan-2-yl)-1,3,4-oxad-iazole (3hb) (Table 3, entry 10)

Black semi-solid, R_f 0.40 (20% EtOAc/hexane); IR (KBr): 1564, 1512, 1228, 1162 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (1H, m), 7.34–7.27 (2H, m), 7.11–7.00 (3H, m), 6.55 (1H, m), 4.41 (1H, q, $J = 7.0$ Hz), 1.79 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.9, 163.8, 160.4, 157.8, 145.9, 135.9, 129.0, 116.1, 116.0, 113.0, 112.2, 36.8, 19.9; ESIMS: m/z 259 $[M + H]^+$; anal. calcd for

$C_{14}H_{11}FN_2O_2$: C, 65.11; H, 4.29; N, 10.85. Found: C, 65.09; H, 4.27; N, 10.88%.

2-(1-(4-Bromophenyl)ethyl)-5-(furan-2-yl)-1,3,4-oxadi-azole (3hd) (Table 3, entry 11)

Black solid, mp: 118–120 °C, R_f 0.45 (20% EtOAc/hexane); IR (KBr): 1636, 1564, 1162, 1073 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (1H, m), 7.49 (2H, d, $J = 8.0$ Hz), 7.21 (2H, d, $J = 8.0$ Hz), 7.11 (1H, m), 6.57 (1H, m), 4.38 (1H, q, $J = 7.0$ Hz), 1.79 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.8, 157.9, 145.8, 139.1, 139.0, 132.0, 129.1, 121.5, 114.2, 112.0, 36.9, 19.2; ESIMS: m/z 321, 319 $[M + H]^+$; anal. calcd for $C_{14}H_{11}BrN_2O_2$: C, 52.69; H, 3.47; N, 8.78. Found: C, 52.71; H, 3.45; N, 8.76%.

2-Benzhydryl-5-phenyl-1,3,4-oxadiazole (3ag)

White solid, mp: 132–135 °C, R_f 0.45 (20% EtOAc/hexane); IR (KBr): 1562, 1491, 1455, 1290, 1179 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.02 (2H, d, $J = 8.0$ Hz), 7.58–7.48 (4H, m), 7.40–7.27 (9H, m), 5.82 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.2, 138.8, 132.0, 129.9, 128.8, 128.7, 128.3, 127.4, 127.0, 123.7, 48.5; ESIMS: m/z 313 $[M + H]^+$; anal. calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.71; H, 5.14; N, 8.99%.

2-Benzhydryl-5-(*p*-tolyl)-1,3,4-oxadiazole (3bg)

White solid, mp: 120–123 °C, R_f 0.40 (20% EtOAc/hexane); IR (KBr): 1555, 1497, 1453, 1179 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$): δ 7.91 (2H, d, $J = 8.0$ Hz), 7.43–7.27 (12H, m), 5.80 (1H, s), 2.40 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.3, 142.2, 138.5, 129.6, 128.8, 128.6, 127.5, 126.7, 121.0, 48.6, 21.7; ESIMS: m/z 327 $[M + H]^+$; anal. calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.94; H, 5.60; N, 8.53%.

2-Benzhydryl-5-(4-bromophenyl)-1,3,4-oxadiazole (3eg)

White solid, mp: 128–130 °C, R_f 0.40 (20% EtOAc/hexane); IR (KBr): 1602, 1554, 1483, 1275, 1082 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$): δ 7.89 (2H, d, $J = 8.0$ Hz), 7.62 (2H, d, $J = 8.0$ Hz), 7.41–7.28 (10H, m), 5.81 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.4, 138.2, 132.2, 128.8, 128.5, 128.2, 127.6, 122.6, 48.5; ESIMS: m/z 392, 390 $[M + H]^+$; anal. calcd for $C_{21}H_{15}BrN_2O$: C, 64.46; H, 3.86; N, 7.16. Found: C, 64.43; H, 3.87; N, 7.14%.

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References

1 (*a*) S. A. F. Rostom, M. A. Shalaby and M. A. El-Demellawy, *Eur. J. Med. Chem.*, 2003, **38**, 959; (*b*) K. K. Jha, A. Samad, Y. Kumar, M. Shaharyar, R. L. Khosa, J. Jain, V. Kumar and P. Sing, *Eur. J. Med. Chem.*, 2010, **45**, 4963; (*c*) P. Singh and P. K. Jangra, *Der Chemica Sinica*, 2010, **1**, 118; (*d*) C. S. de Oliveira, B. F. Lira, J. M. Barbosa-Filho, J. G. F. Lorenzo and P. F. de Athayde-Filho, *Molecules*, 2012, **17**, 10192.

2 (*a*) D. Leung, W. Du, C. Hardouin, H. Cheng, I. Hwang, B. F. Cravatt and D. L. Boger, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1423; (*b*) J. Bostrom, A. Hogner, A. Llinas, E. Wellner and A. T. Plowright, *J. Med. Chem.*, 2012, **55**, 1817.

3 (*a*) U. Mitschke and P. Bauerle, *J. Mater. Chem.*, 2000, **10**, 1471; (*b*) E. V. Zarudnitskii, I. I. Pervak, A. S. Merkulov, A. A. Yurcenko and A. A. Tolmachev, *Tetrahedron*, 2008, **64**, 10431.

4 G. S. He, L. S. Tan, Q. Zheng and P. N. Prasad, *Chem. Rev.*, 2008, **108**, 1245.

5 Some recent examples: (*a*) I. V. Seregin, V. Ryabova and V. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 7742; (*b*) J. Zhao, Y. Zhang and K. Cheng, *J. Org. Chem.*, 2008, **73**, 7428; (*c*) S. Yanagisawa, T. Sudo, R. Noyori and K. Itami, *Tetrahedron*, 2008, **64**, 6073; (*d*) G. Cusati and L. Djakovitch, *Tetrahedron Lett.*, 2008, **49**, 2499; (*e*) C. Verrier, C. Hoarau and F. Marsais, *Org. Biomol. Chem.*, 2009, **7**, 647; (*f*) J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem., Int. Ed.*, 2009, **48**, 9346; (*g*) T. Kawano, N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2010, **75**, 1764; (*h*) M. Miyasaka, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2010, **75**, 5421; (*i*) M. Kitahara, K. Hirano, H. Tsurugi, T. Satoh and M. Miura, *Chem.–Eur. J.*, 2010, **16**, 1772; (*j*) M. Yu, Y. Xie, C. Xie and Y. Zhang, *Org. Lett.*, 2012, **14**, 2164; (*k*) T. Shibata, S. Takasuya, S. Yuzava and T. Otani, *Org. Lett.*, 2012, **14**, 5106; (*l*) D. Yu, L. Lu and Q. Shen, *Org. Lett.*, 2013, **15**, 940.

6 (*a*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 1128; (*b*) F. Besselievre, S. Piguel, F. Mahuteau-Betzer and D. S. Grierson, *Org. Lett.*, 2008, **10**, 4029; (*c*) G. Brasche and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 1932; (*d*) D. Monguchi, A. Yamamura, T. Fujiwara, T. Somete and A. Mori, *Tetrahedron Lett.*, 2010, **51**, 850; (*e*) J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu and L. Liu, *Chem. Commun.*, 2011, **47**, 4300; (*f*) O. A. Tomashenko, E. C. Escudero-Adan, M. M. Belmonte and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2011, **50**, 3793.

7 (*a*) J. Barluenga, M. Tomas-Gamasa, F. Aznar and C. Valdes, *Nat. Chem.*, 2009, **1**, 494; (*b*) X. Zhao, G. Wu, Y. Zang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 3296; (*c*) J. Barluenga and C. Valdes, *Angew. Chem., Int. Ed.*, 2011, **50**, 7486; (*d*) A. Hamze, B. Treguier, J.-D. Brion and M. Alami, *Org. Biomol. Chem.*, 2011, **9**, 6200; (*e*) T. Yao, K. Hirano, T. Sato and M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 775; (*f*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560; (*g*) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236.

8 (*a*) B. Das, N. Salvanna, G. C. Reddy and P. Balasubramanyam, *Tetrahedron Lett.*, 2011, **52**, 6497; (*b*) B. Das, G. C. Reddy, P. Balasubramanyam and N. Salvanna, *Synthesis*, 2011, 816; (*c*) G. C. Reddy, P. Balasubramanyam, N. Salvanna and B. Das, *Eur. J. Org. Chem.*, 2012, 471; (*d*) B. Das, G. C. Reddy, P. Balasubramanyam and N. Salvanna, *Tetrahedron*, 2012, **68**, 300; (*e*) N. Salvanna, G. C. Reddy and B. Das, *Tetrahedron*, 2013, **69**, 2220.

9 For discussion of mechanism: (*a*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 12404; (*b*) L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196; (*c*) H.-Q. Do,

R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185; (*d*) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 3296; (*e*) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (*f*) F. Besselievre and S. Piguel, *Angew. Chem., Int. Ed.*, 2009, **48**, 9553; (*g*) E. R. Strieter, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 78; (*h*) T. Kawano, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2010, **132**, 6900.