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# $Pd(OAc)_2$ catalyzed C–H activation of 1,3,4-oxadiazoles and their direct oxidative coupling with benzothiazoles and aryl boronic acids using $Cu(OAc)_2$ as an oxidant☆

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ABSTRACT

The first direct oxidative coupling of 1,3,4-oxadiazoles with benzothiazoles has been accomplished using $Pd(OAc)_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant. The similar combination of the catalyst and the oxidant has also been applied for direct arylation of 1,3,4-oxadiazoles with aryl boronic acids. Several novel oxadiazole derivatives have been prepared in high yields following both the methods.



## 1. Introduction

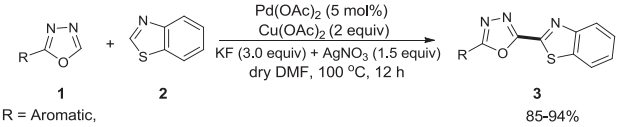
Substituted oxadiazoles possess different important biological activities. They work as ester and amide bioisosters.[1] They also act as anticonvulsants and microbial agents.[2] In addition, oxadiazole derivatives have multiphoton absorbing properties.[3] Some of these compounds are utilized in development of organic electronics.[4] Due to such valuable applications[1–4] in pharmaceutical and material sciences the synthesis of oxadiazole derivatives is highly desirable.

The transformation of C–H bond of heteroarenes to C–C bond in the presence of a metal catalyst is an important method to generate their derivatives.[5] The process is atom economic. The two-fold C–H bond activation has been utilized for cross-coupling of heteroarenes with carbocyclic arenes or other heteroarenes.[6] Transition metal catalyzed direct oxidative C–H activation of two very similar partners to form unsymmetrical biheteroaryl molecules is of great interest[7] but is quite rare because of their tendency to undergo homocoupling.[8] Recently Fagnou et al. developed Pd(II) catalyzed oxidative coupling of unpreactivated heteroaryls with unactivated arenes by two-fold C–H activation.[6a,b] Xi et al. made oxidative cross-coupling of xanthines with furans and thiophenes.[7h] Miura et al. developed Cu(II) mediated oxidative cross-coupling of 1,3,4-oxadiazoles with terminal alkynes.[7i] Ofial et al. reported palladium mediated dehydrogenative cross-coupling of azoles with imidazoles.[7j]

However to our knowledge, metal mediated cross-coupling of 1,3,4-oxadiazoles with benzothiazoles has not yet been reported. Here we disclose the Pd-catalyzed first direct oxidative coupling of these two heteroarenes. The direct arylation of 1,3,4-oxadiazoles with aryl boronic acids using the similar catalyst has also been reported here.

## 2. Results and discussion

In continuation of our work[9] on the C–H activation of heteroarenes we observed that 1,3,4-oxadiazoles when treated with benzothiazole using $Pd(OAc)_2$ (as a catalyst) and $Cu(OAc)_2$ (as an oxidant) in the presence of KF and $AgNO_3$ (as an additive) in dry DMF at 100 °C, afforded the cross-coupling compounds in 12 h (Scheme 1). The products were formed in high yields (85–94%).




**Scheme 1.** $Pd(OAc)_2$ catalyzed oxidative coupling of 1,3,4-oxadiazoles with benzothiazole.

☆ Part 233 in the series, 'Studies on novel synthetic methodologies'.

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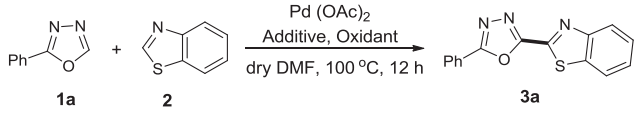
Initially, 2-phenyl 1,3,4-oxadiazole (**1a**) was treated with benzothiazole (**2**) for optimization of the reaction conditions. The reaction was conducted with variable amounts of $Pd(OAc)_2$ and different oxidants. As an additive only KF or a combination of KF and $AgNO_3$ was used (Table 1).

**Table 1**
Optimization studies of $Pd(OAc)_2$ catalyzed C–H activation of 2-phenyl 1,3,4-oxadiazole **1**(**a**) with benzothiazole **2**[a]




| Entry | $Pd(OAc)_2$ (mol %) | Oxidant (equiv) | Additive (equiv) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 5 | $Cu(OAc)_2$ (1.0) | — | Trace |
| 2 | 5 | — | KF (3.0)+$AgNO_3$ (1.5) | — |
| 3 | 5 | $Cu(OAc)_2$ (1.0) | KF (1.0) | <10 |
| 4 | 10 | $Cu(OAc)_2$ (1.0) | KF (3.0)+$AgNO_3$ (1.5) | 46 |
| 5 | 10 | TEMPO (1.0) | KF (3.0)+$AgNO_3$ (1.5) | 20 |
| 6 | 10 | TBHP (1.0) | KF (3.0)+$AgNO_3$ (1.5) | 21 |
| 7 | 10 | Benzoquinone | KF (3.0)+$AgNO_3$ (1.5) | 20 |
| 8 | 10 | $Cu(OAc)_2$ (2.0) | KF (3.0)+$AgNO_3$ (1.5) | 92 |
| **9** | **5** | **$Cu(OAc)_2$ (2.0)** | **KF (3.0)+$AgNO_3$ (1.5)** | **92** |
| 10 | 5 | $Cu(OAc)_2$ (2.0) | KF (3.0)+$AgNO_3$ (1.5) | 92[c,d] |
| 11 | 5 | $Cu(OAc)_2$ (10) | KF (3.0)+$AgNO_3$ (1.5) | 42 |
| 12 | — | $Cu(OAc)_2$ (2.0) | KF (3.0)+$AgNO_3$ (1.5) | —[e] |

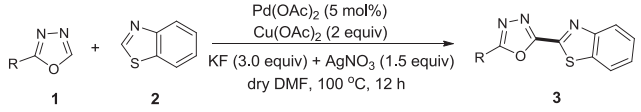
Bold entry signifies optimized reaction condition.
[a] Reaction conditions: 2-phenyl 1,3,4-oxadiazole **1a** (1.0 mmol), benzothiazole **2** (1.3 mmol), $Pd(OAc)_2$ (mol %), oxidant (equiv), additive (equiv), at 100 °C, over 12 h in dry DMF.
[b] Isolated yield of **3a** after column chromatography.
[c] Reaction was carried out at 160 °C.
[d] At room temperature no product could be formed.
[e] Almost quantitative recovery of starting materials.

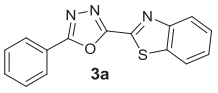
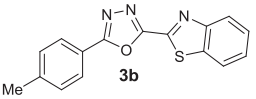
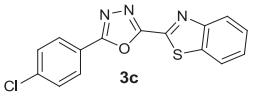
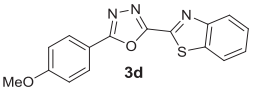
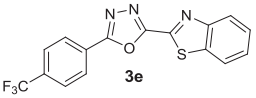
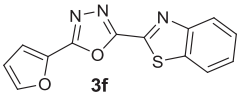
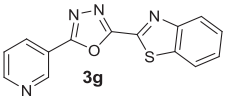
The present conversion was found to be most effective when $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ (2.0 equiv) along with the additive, KF (3.0 equiv) and $AgNO_3$ (1.5 equiv) were used in dry DMF at 100 °C (Table 1, entry 9). The yield was 92% after 12 h. When the reaction was conducted at higher temperature (160 °C) the yield was not increased (Table 1, entry 10). But at room temperature no product could be detected within 12 h. The yield was not affected if the amount of $Pd(OAc)_2$ was increased to 10 mol % (Table 1, entry 8). However, in the absence of $Cu(OAc)_2$ the present conversion did not proceed and in the absence of the additive only a trace amount of the product was formed (Table 1, entry 1 and 2). Even with only KF the yield was poor (>10%) (Table 1, entry 3). Instead of $Cu(OAc)_2$ some other oxidizing agents, such as TBHP, TEMPO, and benzoquinone were also used but the yields were low (~20%) (Table 1, entry 5–7). However, only with $Cu(OAc)_2$ [without using $Pd(OAc)_2$] the conversion did not take place at all (Table 1, entry 12). The reaction was also attempted in toluene as solvent but yield was low.

The above standardization method was followed for cross-coupling of various 1,3,4-oxadiazoles with benzothiazole to prepare a series of oxadiazole derivatives (Table 2). Both the arene and heteroarene moieties were attached with the starting oxadiazoles. The products were formed in high yields (85–94%) in 12 h. No any side product could be isolated. Structures of the prepared oxadiazoles were settled from their spectral (IR, $^1H$ and $^{13}C$ NMR, and ESIMS) and analytical data.

On the basis of understanding of metal catalyzed cross-coupling reactions,[5–10] a plausible mechanism of present conversion is shown in Scheme 2. The reaction possibly proceeds through double C–H bond cleavage of two heteroarenes followed by the C–C bond coupling strategy. The mixed hetero aryl–Pd complex **A** is the key intermediate, which underwent reductive elimination to form the product **3**. $Pd^0$ species generated by this sequence was possibly

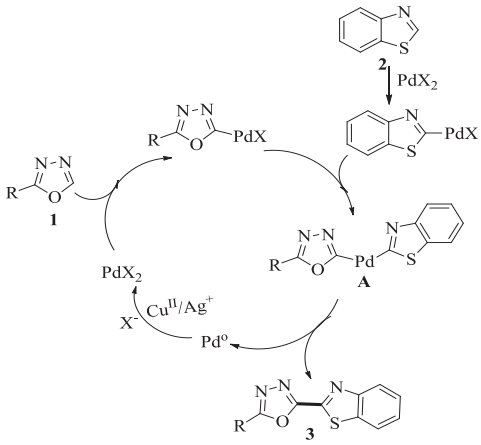
**Table 2**
$Pd(OAc)_2$ catalyzed C–H activation of 1,3,4-oxadiazoles with benzothiazole[a]




| Entry | **1** | R | Product **3** | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **1a** | $C_6H_5$ |  **3a** | 92 |
| 2 | **1b** | 4-$MeC_6H_4$ |  **3b** | 91 |
| 3 | **1c** | 4-$ClC_6H_4$ |  **3c** | 85 |
| 4 | **1d** | 4-$OMeC_6H_4$ |  **3d** | 94 |
| 5 | **1e** | 4-$CF_3C_6H_4$ |  **3e** | 88 |
| 6 | **1f** | 2-Furyl |  **3f** | 91 |
| 7 | **1g** | 3-Nicotinyl |  **3g** | 89 |

[a] Reaction conditions: 2-aryl 1,3,4-oxadiazole **1** (1.0 mmol), benzothiazole **2** (1.3 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2 equiv), KF (3.0 equiv), $AgNO_3$ (1.5 equiv) at 100 °C, over 12 h in dry DMF.
[b] Isolated yield of **3** after column chromatography.

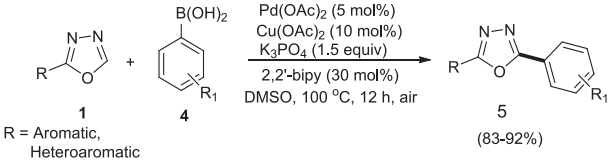
oxidized by Cu(II)/Ag(I) to regenerate Pd(II) to complete the catalytic cycle. The presence of Ag(I) may also be facilitate the cleavage of C–H bond of the heteroarenes to form complex **A**.[7j]




**Scheme 2.** Plausible mechanism of C–H activation of 1,3,4-oxadiazoles with benzothiazoles.

We have not got any homocoupling product. The reaction was spectroscopically ($^1H$ NMR) monitored during an interval of 3 h. Only the cross-coupling product was detected. The yield was increased with time and the highest yield was observed in 12 h.

The combination of $Pd(OAc)_2$ and $Cu(OAc)_2$ has also been employed for direct arylation of 1,3,4-oxadiazole by treatment with aryl boronic acid (Scheme 3). 2,2′-Bipyridine was used as a ligand and $K_3PO_4$ as a base. The reaction was conducted in DMSO at 100 °C under aerobic conditions. The products were formed in high yields (83–92%) in 12 h.

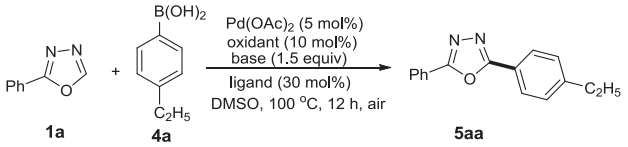



**Scheme 3.**

The direct arylation of heteroarenes through metal catalyzed C–H bond functionalization is an important method for the preparation of aryl substituted heteroarenes.[11] Miura et al. developed Ni-catalyzed C–H activation of azoles with aryl boronic acids.[11c] You et al. reported the same reaction using Pd–Cu bimetallic system as a catalyst.[11i] Here we have utilized our developed system (catalyst, oxidant, ligand, and base) used above for the coupling of oxadiazoles with benzothiazoles.

Initially for standardization of the conversion 2-phenyl 1,3,4-oxadiazole (**1a**) was treated with 4-ethyl phenyl boronic acid (**4a**) under different conditions. The amount of $Pd(OAc)_2$ was variable and different oxidants, bases, and ligands were used (Table 3). The present conversion was observed to undergo most efficiently when $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ (10 mol %) were employed using $K_3PO_4$ (base) and 2,2′-bipyridine (ligand) in DMSO at 100 °C under air. The yield was maximum (89%) in 12 h. At room temperature the reaction did not proceed. In absence of $Pd(OAc)_2$ and $Cu(OAc)_2$ or either of them the reaction was also not successful, $K_3PO_4$ and $Cs_2CO_3$ decreased the yields of the products and under the ligand-free conditions the yield were very low. In an inert atmosphere ($N_2$) only a trace amount of product was formed.

**Table 3**
Optimization studies of $Pd(OAc)_2$ catalyzed C–H activation of 2-phenyl 1,3,4-oxadiazoles with 4-ethyl phenyl boronic acid[a]

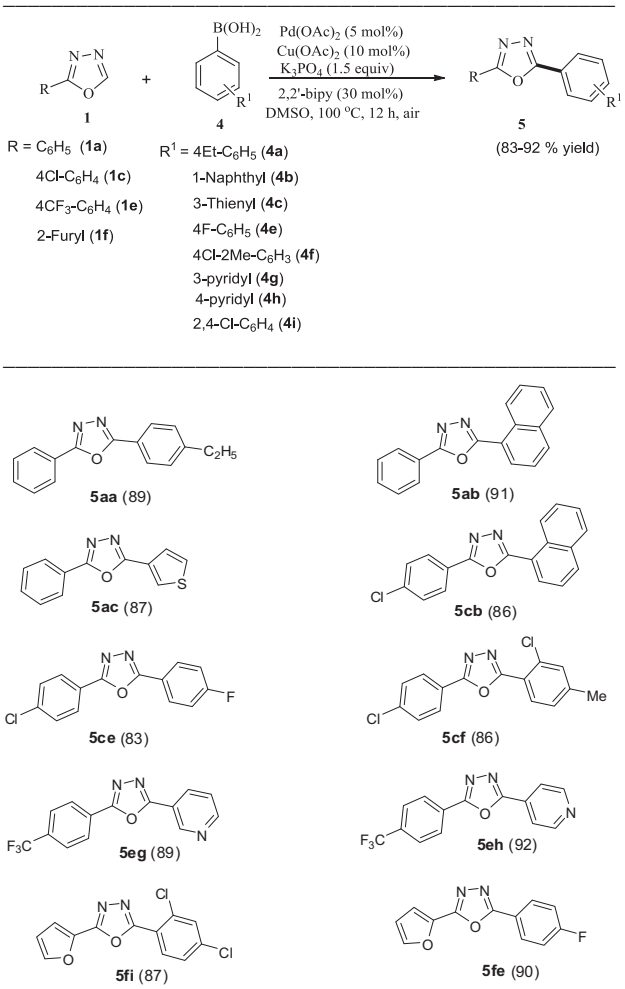



| Entry | Oxidant (10 mol %) | Base (1.5 equiv) | Ligand (30 mol %) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | — | $K_3PO_4$ | — | <5 |
| 2 | $Cu(OAc)_2$ | $K_3PO_4$ | — | 10 |
| 3 | TEMPO | $K_3PO_4$ | DMEDA | 40 |
| 4 | TBHP | $K_3PO_4$ | Phen | 68 |
| 5 | $Cu(OAc)_2$ | $Cs_2CO_3$ | Bipy | 78 |
| 6 | $Cu(OAc)_2$ | $K_3PO_4$ | DMEDA | 72 |
| 7 | TEMPO | $Cs_2CO_3$ | Bipy | 35 |
| **8** | **$Cu(OAc)_2$** | **$K_3PO_4$** | **Bipy** | **89** |
| 9 | TBHP | $Cs_2CO_3$ | Bipy | 42 |
| 10 | $Cu(OAc)_2$ | $K_3PO_4$ | Phen | 84 |
| 11 | $Cu(OAc)_2$ | $Na_2CO_3$ | Bipy | 49 |
| 12 | $Cu(OAc)_2$ | $K_3PO_4$ | Bipy | N.R[c] |

Bold entry signifies optimized reaction condition.
[a] Reaction conditions: 2-phenyl 1,3,4-oxadiazole **1a** (1.0 mmol), 4-ethyl phenyl boronic acid **4a** (1.3 mmol), $Pd(OAc)_2$ (5 mol %), oxidant (10 mol %), base (1.5 equiv), ligand (30 mol %) over 12 h in DMSO under air.
[b] Isolated yield of **5aa** after column chromatography.
[c] Absence of $Pd(OAc)_2$, no reaction took place.

Following the standardization of the above reaction, direct arylation of different 1,3,4-oxadiazoles was carried out using various boronic acids (Table 4). The oxadiazoles as well as boronic acids contained both aryl and heteroaryl moieties. Boronic acids having halogen (X=Cl, F) underwent the conversion smoothly, but the reaction did not proceed with the boronic acids containing –CN or –COOR group. In absence of $Pd(OAc)_2$ no reaction took place (Table 3, entry 12). Following the present method several known and unknown oxadiazole derivatives were prepared. The structures of the compounds were established from the spectral (IR, $^1H$ and $^{13}C$ NMR, and ESIMS) and analytical data.

**Table 4**
$Pd(OAc)_2$ catalyzed oxidative coupling of 1,3,4-oxadiazoles with aryl boronic acid[a,b]

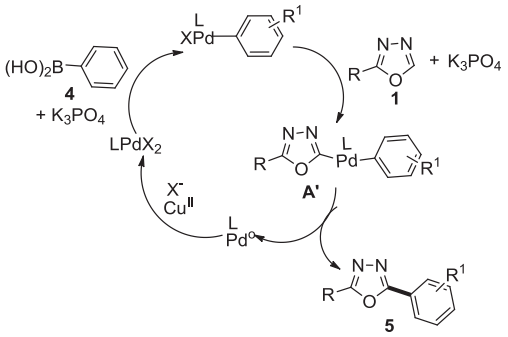



[a]Reaction conditions: 2-aryl 1, 3, 4-oxadiazole **1** (1.0 mmol), aryl boronic acid **4** (1.3 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), $K_3PO_4$ (1.5 equiv), 2, 2'-bipy (30 mol%) over 12 h in DMSO under air. [b]In parenthesis, isolated yield of **5** after column chromatography.

With an understanding of the metal-catalyzed direct arylation of heteroarenes[11] a plausible mechanism of the above conversion is presented in Scheme 4. The initial interaction of divalent palladium (in assistance with the ligand) with boronic in the presence of the base produced the aryl palladium complex, which reacted with the oxadiazole to afford the key intermediate **A′**. The reductive elimination of **A′** yielded the arylated product **5**. The resulting $Pd^0$ was oxidized to $Pd^{II}$ in the presence of $Cu^{II}$ for complete the catalytic cycle.

## 3. Conclusions

In conclusion, we have developed an efficient method for C–H activation of 1,3,4-oxadiazoles using $Pd(OAc)_2$ as a catalyst and




**Scheme 4.**

$Cu(OAc)_2$ as an oxidant. The method has been applied for direct coupling of these heteroarenes with benzothiazole and aryl boronic acids to prepare their derivatives. The $Pd(OAc)_2$ catalyzed cross-coupling of oxadiazoles and benzothiazole has been reported here for the first time.

## 4. Experimental section

### 4.1. General

Melting points were measured on a Buchi 510 apparatus and are uncorrected. The spectra were recorded with the following instruments; IR: Perkin–Elmer RX FT-IR spectrophotometer; ESIMS: VG-Autospec micromass spectrometer. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a 200 MHz and 50 MHz spectrometers using the solvent peak as internal reference ($CDCl_3$, $\delta$ H: 7.26; $\delta$ C: 77.0). Data are reported in the following order: chemical shift ($\delta$) in parts per million; multiplicities are indicated s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; coupling constants ($J$) are in hertz. All reactions were monitored by thin-layer chromatography (TLC) using silica gel $F_{254}$ pre-coated plates. Visualization was accomplished with UV-light or $I_2$ stain. Organic reactions were dried over anhydrous $Na_2SO_4$. Solvents for the catalytic reactions were technical grade. Solvents for chromatography (EtOAc, hexane) were technical grade and distilled prior to use.

### 4.2. General procedure for oxidative cross-coupling of 2-aryl 1,3,4-oxadiazole with benzothiazole

In a 10 mL round bottom flask $Pd(OAc)_2$ (5 mol %, 11.3 mg), $Cu(OAc)_2$ (2 equiv, 404 mg), KF (3.0 equiv, 174 mg), $AgNO_3$ (1.5 equiv, 255 mg), 2-aryl 1,3,4-oxadiazole (1 mmol), and benzothiazole (1.3 mmol) were taken in dry DMF (2.5 mL). The reaction mixture was stirred for 10 min at room temperature then heated at 100 °C for 12 h. The progress of the reaction was monitored by TLC. After consumption of starting material the reaction mixture was allowed to cool and subsequently extracted with EtOAc. The combined organic extracts were dried over anhydrous $Na_2SO_4$. Concentration in vacuo followed by column chromatography (EtOAc/hexane: 5:95 to 10:90) gave pure compound **3** in 85–94% yield.

### 4.3. General procedure for oxidative coupling of 1,3,4-oxadiazoles with aryl boronic acid

In a 10 mL round bottom flask $Pd(OAc)_2$ (5 mol %, 11 mg), $Cu(OAc)_2$ (10 mol %, 20 mg), 2,2′-bipyridine (30 mol %, 44 mg) and $K_3PO_4$ (1.5 mmol, 318.3 mg), aryl boronic acid (1.3 mmol), and 2-aryl 1,3,4-oxadiazole (1.0 mmol)were added to a solution of DMSO (2.5 mL) under air. The reaction mixture was stirred for 10 min at room temperature then heated at 100 °C for 12 h. The progress of the reaction was monitored by TLC. After consumption of starting material the reaction mixture was allowed to cool and subsequently extracted with EtOAc. The combined organic extracts were dried over anhydrous $Na_2SO_4$. Concentration in vacuo followed by column chromatography (EtOAc/hexane: 5:95 to 10:90) gave pure compound **5** in 83–92% yield.

### 4.4. Spectral data of all compounds are given below

*4.4.1. 2-(Benzo[d]thiazol-2-yl)-5-phenyl-1,3,4-oxadiazole (**3a**) (Table 2, entry 1).* Light yellow solid, mp: 159–161 °C, $R_f$ 0.37 (20% EtOAc/hexane); IR (KBr): 2272, 1626, 1540, 1464, 1309 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.32–8.24 (2H, m, Ar–H), 8.12 (1H, m, Ar–H), 7.99 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 7.66–7.49 (5H, m, Ar–H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 165.9, 160.2, 153.6, 151.0, 135.4, 132.2, 129.1, 127.9, 127.8, 127.7, 124.3, 123.2, 122.0; ESIMS: $m/z$ 280 $[M+H]^+$; Anal. Calcd for $C_{15}H_9N_3OS$: C, 64.50; H, 3.25; N, 15.04. Found: C, 64.52; H, 3.22; N, 15.07.

*4.4.2. 2-(Benzo[d]thiazol-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (**3b**) (Table 2, entry 2).* Light yellow solid, mp: 148–150 °C, $R_f$ 0.35 (20% EtOAc/hexane); IR (KBr): 2380, 1618, 1539, 1491, 1316 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.27 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 8.12 (2H d, $J$ 8.0 Hz, Ar–H), 8.02 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 7.63–7.52 (2H, m, Ar–H), 7.38 (2H, d, $J$ 8.0 Hz, Ar–H), 2.42 (3H, s, $-CH_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 166.1, 160.0, 153.3, 150.9, 143.2, 135.2, 130.0, 127.2, 127.0, 126.8, 124.5, 122.0, 21.9; ESIMS: $m/z$ 294 $[M+H]^+$; Anal. Calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32. Found: C, 65.48; H, 3.82; N, 14.36.

*4.4.3. 2-(Benzo[d]thiazol-2-yl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (**3c**) (Table 2, entry 3).* White viscous liquid, $R_f$ 0.35 (20% EtOAc/hexane); IR (KBr): 2382, 1693, 1537, 1309 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.22–8.11 (2H, m, Ar–H), 7.94 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 7.61–7.42 (5H, m, Ar–H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 165.1, 160.2, 153.5, 150.8, 139.2, 135.8, 129.9, 129.0, 127.5, 127.4, 125.0, 122.1; ESIMS: $m/z$ 314, 316 $[M+H]^+$; Anal. Calcd for $C_{15}H_8ClN_3OS$: C, 57.42; H, 2.57; N, 13.39. Found: C, 57.46; H, 2.54; N, 13.41.

*4.4.4. 2-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**3d**) (Table 2, entry 4).* White solid, mp: 144–146 °C, $R_f$ 0.41 (30% EtOAc/hexane); IR (KBr): 2385, 1609, 1492, 1428, 1257 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.25 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 8.20 (2H, d, $J$ 8.0 Hz, Ar–H), 8.02 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 7.68–7.52 (2H, m, Ar–H), 7.04 (2H, d, $J$ 8.0 Hz, Ar–H), 3.92 (3H, s, $-OCH_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 166.1, 163.0, 159.9, 153.8, 151.2, 135.5, 129.6, 127.1, 127.0, 124.9, 122.1, 114.6, 55.8; ESIMS: $m/z$ 310 $[M+H]^+$; Anal. Calcd for $C_{16}H_{11}N_3O_2S$: C, 62.12; H, 3.58; N, 13.58. Found: C, 62.09; H, 3.61; N, 13.55.

*4.4.5. 2-(Benzo[d]thiazol-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (**3e**) (Table 2, entry 5).* Pink solid, mp: 147–149 °C, $R_f$ 0.51 (30% EtOAc/hexane); IR (KBr): 2417, 1553, 1462, 1627, 1126 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.39 (2H, d, $J$ 8.0 Hz, Ar–H), 8.22 (1H, d, $J$ 8.0 Hz, Ar–H), 8.00 (1H, d. $J$ 8.0 Hz, Ar–H), 7.82 (2H, d, $J$ 8.0 Hz, Ar–H), 7.63–7.50 (2H, m, Ar–H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 165.0, 160.9, 153.4, 150.5, 136.0, 133.8, 127.9, 127.5, 127.4, 126.7 (q, $J$ 30.0 Hz), 126.4, 125.1, 122.0; ESIMS: $m/z$ 348 $[M+H]^+$; Anal. Calcd for $C_{16}H_8F_3N_3OS$: C, 55.33; H, 2.32; N, 12.10. Found: C, 55.35; H, 2.34; N, 12.07.

*4.4.6. 2-(Benzo[d]thiazol-2-yl)-5-(furan-2-yl)-1,3,4-oxadiazole (**3f**) (Table 2, entry 6).* Dark solid, mp: 153–155 °C, $R_f$ 0.35 (20% EtOAc/hexane); IR (KBr): 2414, 1623, 1518, 1451, 1312 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.20 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 7.99 (1H, dd, $J$ 8.0, 2.0 Hz, Ar–H), 7.72 (1H, m, Ar–H), 7.60–7.48 (2H, m, Ar–H), 7.37

(1H, m, Ar–H), 6.68 (1H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 159.5, 158.7, 153.2, 150.1, 146.7, 145.8, 135.2, 127.9, 127.8, 124.5, 122.0, 115.9, 112.2; ESIMS: *m/z* 270 $[M+H]^+$; Anal. Calcd for $C_{13}H_7N_3O_2S$: C, 57.98; H, 2.62; N, 15.60. Found: C, 58.01; H, 2.59; N, 15.62.

*4.4.7. 2-(Benzo[d]thiazol-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (**3g**) (Table 2, entry 7).* Light yellow solid, mp: 157–159 °C, $R_f$ 0.51 (40% EtOAc/hexane); IR (KBr): 2407, 1596, 1536, 1458, 1314 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 9.45 (1H, d, *J* 2.0 Hz, Ar–H), 8.82 (1H, m, Ar–H), 8.54 (1H, dd, *J* 8.0, 2.0 Hz, Ar–H), 8.28 (1H, dd, *J* 8.0, 2.0 Hz, Ar–H), 8.02 (1H, dd, *J* 8.0, 2.0 Hz, Ar–H), 7.66–7.50 (3H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 163.8, 160.6, 153.3, 153.1, 152.2, 148.2, 135.5, 134.9, 127.9, 127.8, 125.0, 124.0, 121.8, 119.8; ESIMS: *m/z* 303 $[M+Na]^+$; Anal. Calcd for $C_{14}H_8N_4OS$: C, 59.99; H, 2.88; N, 19.99. Found: C, 60.01; H, 2.86; N, 20.02.

*4.4.8. 2-(4-Ethylphenyl)-5-phenyl-1,3,4-oxadiazole (**5aa**) (Table 4).* White solid, mp: 114–116 °C, $R_f$ 0.42 (20% EtOAc/hexane); IR (KBr): 2397, 1612, 1548, 1488, 1269 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.17–8.10 (2H, m, Ar–H), 8.02 (2H, d, *J* 8.0 Hz, Ar–H), 7.58–7.50 (3H, m, Ar–H), 7.32 (2H, d, *J* 8.0 Hz, Ar–H), 2.72 (2H, q, *J* 7.0 Hz, $-CH_2-$), 1.28 (3H, t, *J* 7.0 Hz, $-CH_3$); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 164.8, 164.5, 148.8, 131.8, 129.1, 128.8, 127.2, 127.1, 124.1, 121.2, 29.0, 15.2; 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, 76.76; H, 5.68; N, 11.16.

*4.4.9. 2-(Naphthalen-1-yl)-5-phenyl-1,3,4-oxadiazole (**5ab**) (Table 4).* Brown solid, mp: 113–115 °C, $R_f$ 0.40 (20% EtOAc/hexane); IR (KBr): 2395, 1605, 1547, 1449, 1267 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.49 (1H, m, Ar–H), 8.22–8.16 (3H m, Ar–H), 7.93 (2H, d, *J* 8.0 Hz, Ar–H), 7.84 (1H, m, Ar–H), 7.59–7.50 (5H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 165.0, 134.9, 133.1, 131.8, 129.1, 129.0, 128.0, 127.9, 127.3, 127.2, 127.1, 124.2, 123.4, 121.1; ESIMS: *m/z* 273 $[M+H]^+$; Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.42; H, 4.41; N, 10.32.

*4.4.10. 2-Phenyl-5-(thiophen-3-yl)-1,3,4-oxadiazole (**5ac**) (Table 4).* Light yellow solid, mp: 117–119 °C, $R_f$ 0.45 (20% EtOAc/hexane); IR (KBr): 2402, 1590, 1481, 1448, 1261 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.13–8.07 (3H, m, Ar–H), 7.72 (1H, m, Ar–H), 7.55–7.42 (4H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 163.9, 161.3, 131.8, 129.1, 127.5, 126.9, 126.1, 125.3, 123.9; ESIMS: *m/z* 229 $[M+H]^+$; Anal. Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.12; H, 3.57; N, 12.24.

*4.4.11. 2-(4-Chlorophenyl)-5-(naphthalen-1-yl)-1,3,4-oxadiazole (**5cb**) (Table 4).* White solid, mp: 163–165 °C, $R_f$ 0.38 (20% EtOAc/hexane); IR (KBr): 2412, 1603, 1474, 1270 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.58 (1H, m, Ar–H), 8.19 (1H, d, *J* 8.0 Hz, Ar–H), 8.11 (2H, d, *J* 8.0 Hz, Ar–H), 7.94 (2H, d, *J* 8.0 Hz, Ar–H), 7.85 (1H, d, *J* 8.0 Hz, Ar–H), 7.59–7.50 (4H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 165.0, 163.9, 138.1, 134.5, 132.7, 129.4, 128.9, 128.7, 128.1, 127.9, 127.8, 127.3, 127.1, 123.0, 122.5, 120.8; ESIMS: *m/z* 307, 309 $[M+H]^+$; Anal. Calcd for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.43; H, 3.64; N, 9.17.

*4.4.12. 2-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (**5ce**) (Table 4).* White solid, mp: 207–209 °C, $R_f$ 0.37 (20% EtOAc/hexane); IR (KBr): 2408, 1606, 1489, 1229 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.18–8.10 (2H, m, Ar–H), 8.04 (2H, d, *J* 8.0 Hz, Ar–H), 7.51 (2H, d, *J* 8.0 Hz, Ar–H), 7.21 (2H, t, *J* 8.0 Hz, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 166.4 (d, *J* 280.0 Hz), 164.0, 137.2, 129.6, 129.2 (d, *J* 100 Hz), 128.4, 122.8, 120.2, 116.9 (d, *J* 25.0 Hz); ESIMS: *m/z* 275, 277 $[M+H]^+$; Anal. Calcd for $C_{14}H_8ClFN_2O$: C, 61.22; H, 2.94; N, 10.20. Found: C, 61.24; H, 2.93; N, 10.18.

*4.4.13. 2-(2-Chloro-4-methylphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (**5cf**) (Table 4).* Yellow solid, mp: 160–162 °C, $R_f$ 0.39 (20% EtOAc/hexane); IR (KBr): 2384, 1604, 1465, 1253 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.11–8.00 (3H, m, Ar–H), 7.50 (2H, d, *J* 8.0 Hz, Ar–H), 7.12–7.03 (2H, m, Ar–H), 2.43 (3H, s, $-CH_3$); $^{13}$C NMR (50 MHz $CDCl_3$): δ 164.0, 145.2, 145.1, 144.0, 138.1, 129.5, 128.4, 125.8, 122.3, 118.2, 118.1, 21.2; ESIMS: *m/z* 305, 307, 309 $[M+H]^+$; Anal. Calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.06; H, 3.27; N, 9.21.

*4.4.14. 2-(Pyridin-3-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (**5eg**) (Table 4).* Brown solid, mp: 165–167 °C, $R_f$ 0.45 (50% EtOAc/hexane); IR (KBr): 2405, 1605, 1547, 1492, 1323 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 9.41 (1H, d, *J* 2.0 Hz, Ar–H), 8.84 (1H, dd, *J* 7.0, 2.0 Hz, Ar–H), 8.45 (1H, dt, *J* 8.0, 2.0 Hz, Ar–H), 8.31 (2H, d, *J* 8.0 Hz, Ar–H), 7.84 (2H, d, *J* 8.0 Hz, Ar–H), 7.52 (1H, dd, *J* 8.0, 7.0 Hz, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 164.2, 163.5, 152.9, 148.2, 134.9, 133.5, 128.0, 127.3, 126.9, 124.0, 122.1 (q, *J* 227 Hz), 120.2; ESIMS: *m/z* 292 $[M+H]^+$; Anal. Calcd for $C_{14}H_8F_3N_3O$: C, 57.74; H, 2.77; N, 14.43. Found: C, 57.71; H, 2.75; N, 14.47.

*4.4.15. 2-(Pyridin-4-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (**5eh**) (Table 4).* Brown solid, mp: 168–170 °C, $R_f$ 0.45 (50% EtOAc/hexane); IR (KBr): 2394, 1614, 1498, 1242 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.88 (2H, d, *J* 7.0 Hz, Ar–H), 8.30 (2H, d, *J* 8.0 Hz, Ar–H), 7.99 (2H, d, *J* 7.0 Hz, Ar–H), 7.82 (2H, d, *J* 8.0 Hz, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 164.2, 163.5, 151.1, 144.3, 131.0, 127.9, 126.3, 126.1, 124.0 (q, *J* 227 Hz), 120.6; ESIMS: *m/z* 292 $[M+H]^+$; Anal. Calcd for $C_{14}H_8F_3N_3O$: C, 57.74; H, 2.77; N, 14.43. Found: C, 57.76; H, 2.73; N, 14.41.

*4.4.16. 2-(2,4-Dichlorophenyl)-5-(furan-2-yl)-1,3,4-oxadiazole (**5fi**) (Table 4).* Brown solid, mp: 183–185 °C, $R_f$ 0.40 (20% EtOAc/hexane); IR (KBr): 2408, 1631, 1453, 1279 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.21 (1H, m, Ar–H), 7.99 (1H, dd, *J* 8.0 Hz, 2.0 Hz, Ar–H), 7.69 (1H, d, *J* 2.0 Hz, Ar–H), 7.62 (1H, d, *J* 8.0 Hz, Ar–H), 7.28 (1H, m, Ar–H), 6.64 (1H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 162.3, 158.1, 146.5, 139.5, 136.4, 133.9, 131.5, 128.8, 126.2, 123.3, 115.0, 112.8; ESIMS: *m/z* 281$[M+H]^+$; Anal. Calcd for $C_{12}H_6Cl_2N_2O_2$: C, 51.27; H, 2.15; N, 9.97. Found: C, 51.24; H, 2.17; N, 9.94.

*4.4.17. 2-(4-Fluorophenyl)-5-(furan-2-yl)-1,3,4-oxadiazole (**5fe**) (Table 4).* Brown solid, mp: 130–132 °C, $R_f$ 0.40 (20% EtOAc/hexane); IR (KBr): 2412, 1632, 1605, 1497, 1233 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 8.20–8.08 (2H, m, Ar–H), 7.62 (1H, m, Ar–H), 7.28–7.15 (3H, m, Ar–H), 6.61 (1H, m, Ar–H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 165.0 (d, *J*=280 Hz), 157.7, 145.9, 129.4 (d, *J* 5.0 Hz), 126.8, 120.1, 116 (d, *J* 30.0 Hz), 115.2, 112.3; ESIMS: *m/z* 231 $[M+H]^+$; Anal. Calcd for $C_{12}H_7FN_2O_2$: C, 62.61; H, 3.07; N, 12.17. Found: C, 62.63; H, 3.04; N, 12.14.

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.12.080.

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