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Efficient oxidative cyclization of *N*-acylhydrazones for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles using *t*-BuOI under neutral conditions

Abstract: An efficient procedure for the oxidative cyclization of *N*-acylhydrazones was developed utilizing *tert*-butyl hypoiodite (*t*-BuOI), which is generated *in situ* from *t*-BuOCl and NaI. A variety of 2,5-disubstituted 1,3,4-oxadiazoles were synthesized in high yields within short reaction time. The method is also suitable for cyclization of *N*-acylhydrazones derived from heterocyclic aldehydes and aliphatic aldehydes. Mild reaction conditions and simple workup operations make the procedure a good alternative for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.

Keywords: metal-free reaction; *N*-acylhydrazones; oxadiazoles; oxidative cyclization.

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Introduction

2,5-Disubstituted 1,3,4-oxadiazoles represent an important heterocyclic scaffold that can be found in many natural products and synthetic compounds. Some of them show significant bioactivities, such as anti-inflammatory [1], anticonvulsant [2], antioxidant [3], and anthelmintic activities [4]. Certain oxadiazoles are known for their unique optoelectronic properties and they are utilized in energy-efficient, full-color, flat-panel displays and organic molecular devices [5–7]. As a consequence, extensive efforts have been directed towards the development of methods for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.

To date, several synthetic methods have been reported for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles. One of the common methods involves cyclization of diacylhydrazines in dehydrating media or in the presence of an acidic catalyst, such as $SOCl_2$ [8, 9], TsCl [10], $POCl_3$ [11, 12], silica-supported dichlorophosphate [13], or silica sulfuric acid [14]. Direct reaction of carboxylic acids, acid chlorides, or aldehydes with acid hydrazides for the synthesis of 1,3,4-oxadiazoles have also been reported. Ceric ammonium nitrate (CAN) [15], 2-chloro-1,3-dimethylimidazolinium chloride (CMC) [16], trichloroisocyanuric acid (TCCA) [17], P_2O_5 [18], and I_2 under solvent-free conditions using a grinding technique [19] were employed to promote transformation. The most popular approaches are oxidative cyclization of *N*-acylhydrazones with various oxidants, such as $Cu(OTf)_2/O_2$ [20], I_2/HgO [21], tetravalent lead reagent [22], chloramine T [23], N-chlorosuccinimide [24], or hypervalent iodine [25].

However, some problems associated with the oxidative cyclization procedures of *N*-acylhydrazones include the use of toxic, expensive reagents and complicated workup procedures. *N*-Acylhydrazones derived from heterocyclic aldehydes or aliphatic aldehydes usually show low reactivity [20, 23–25], which was a big challenge.

Recently, Minakata and coworkers have found that *t*-BuOI, which is a powerful iodinating reagent, can be utilized for the synthesis of heterocyclic compounds and formation of N–N bonds [26–32]. With *t*-BuOI, oximes can be oxidized to corresponding aldehydes or ketones in high yields and some alkanes can be iodinated followed a radical pathway [33, 34]. High reactivity and wide substrate tolerance make *t*-BuOI a very useful reagent in organic synthesis. The byproduct, *t*-BuOH, has low toxicity [35] and can be easily removed from the reaction mixture by washing with water or rotary evaporation, which makes the workup processes simple.

Inspired by these developments and in continuation of our efforts on the metal-free oxidative reactions [36–38], herein, we report a metal-free method for the synthesis of 2,5-disubstitued 1,3,4-oxadiazoles from *N*-acylhydrazones using *t*-BuOI as an oxidant.

Table 1 Optimization of the reaction conditions for compound **2a** (Equation 1)[a].

Entry	Solvent	NaI (equiv.)	*t*-BuOCl (equiv.)	Isolated yield (%)
1	H_2O	1.2	1.2	Trace
2	EtOH	1.2	1.2	48
3	EtOAc	1.2	1.2	87
4	DMC[b]	1.2	1.2	94
5	DMC	0	1.1	Trace
6	DMC	1.2	0	0
7	DMC	1.0	1.0	85
8	DMC	1.1	1.1	90

[a]**1a** (0.3 mmol), NaI, *t*-BuOCl, solvent 3 ml, rt, 15 min.
[b]DMC, dimethyl carbonate.

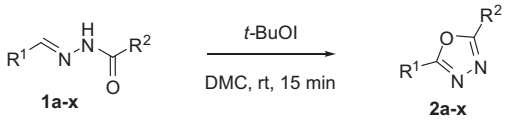
Results and discussion

N-Benzylidenebenzohydrazide (**1a**) was chosen as the model substrate for optimization studies (Table 1 and Equation 1). Initially, various solvents, including water, ethanol, ethyl acetate, and dimethyl carbonate (DMC), were screened for the reaction. It was found that among the solvents tested, DMC gave the highest yield of the product, 2,5-diphenyl-1,3,4 oxadiazole **2a** (Table 1, entries 1–4). As control experiment, the reaction was carried out in the presence of *t*-BuOCl without NaI, and only a trace amount of **2a** was detected (Table 1, entry 5). In the absence of *t*-BuOCl, no product was formed (Table 1, entry 6). These results demonstrate that both *t*-BuOCl and NaI are necessary for the reaction to proceed, which suggests that *t*-BuOI is generated *in situ* during the reaction. Finally, the optimized procedure was developed as follows: the reaction in DMC is carried out at room temperature for 15 min in the presence of 1.2 equivalents of *t*-BuOCl and 1.2 equivalents of NaI.

With the optimized reaction conditions in hand, the substrate scope was then investigated. To our satisfaction, the reaction shows a wide scope for the structure of *N*-acylhydrazones. *N*-Benzoylhydrazones derived from aromatic aldehydes bearing electron-donating groups, such as Me, OMe, PhO, on the benzene ring were all smoothly converted to the corresponding 1,3,4-oxadiazoles in excellent yields (Equation 1, **2b–d**). Substrates possessing electron-withdrawing groups, such as Cl, Br, NO_2, on the aromatic ring also exhibit good reactivity and gave 2,5-disubstituted 1,3,4-oxadiazoles in good yields (Equation 1, **2e–h**). *N*-(1-Naphthalenylmethylidene)benzohydrazide also reacted well to give the corresponding product **2i** in a high yield. It should be pointed out that the reactions of substrates derived from heterocyclic or aliphatic aldehydes gave the corresponding products **2j–n** in moderate yields.

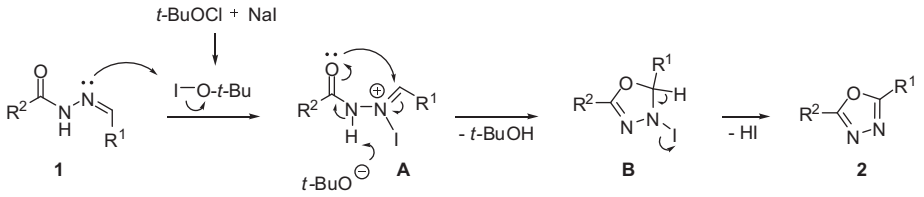
To further establish the general utility of this transformation, substrates originating from different acid hydrazides were tested under optimized conditions. Substrates derived from various aromatic acid hydrazides bearing electron-donating or electron-withdrawing groups on the aromatic ring, such as Me, OMe, Cl, all gave the substituted oxadiazoles in excellent yields (Equation 1, **2o–v**). When *N′*-propylidene-4-chlorobenzohydrazide derived from 4-chlorobenzohydrazide and an aliphatic aldehyde was used in the reaction, the corresponding product **2w** was isolated in 77% yield (Equation 1). The heterocyclic acid hydrazide **1x** also showed high reactivity to give product **2x** in the yield of 83%.

To gain insights into the reaction pathway, several control experiments were designed. When the reaction was carried out in dark or in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, a radical-trapping reagent), no decrease of the yields of the products was observed. This suggests that a radical pathway presumably does not occur in the reaction. It can be suggested that



(1)

a: R^1 = Ph, R^2 = Ph
b: R^1 = 4-MeC_6H_4, R^2 = Ph
c: R^1 = 4-$MeOC_6H_4$, R^2 =Ph
d: R^1 = 3-$PhOC_6H_4$, R^2 = Ph
e: R^1 = 4-ClC_6H_4, R^2 = Ph
f: R^1 = 4-BrC_6H_4, R^2 = Ph
g: R^1 = 2-BrC_6H_4, R^2 = Ph
h: R^1 = 4-$NO_2C_6H_4$, R^2 = Ph
i: R^1 = 1-naphthyl, R^2 = Ph
j: R^1 = 2-furyl, R^2 = Ph
k: R^1 = 2-thienyl, R^2 = Ph
l: R^1 = Bn, R^2 = Ph
m: R^1 = *s*-Bu, R^2 = Ph
n: R^1 = heptyl, R^2 = Ph
o: R^1 = Ph, R^2 = 2-MeC_6H_4
p: R^1= R^2 = 4-ClC_6H_4
q: R^1 = R^2 = 4-MeC_6H_4
r: R^1 = R^2 = 4-$MeOC_6H_4$
s: R^1 = 4-MeC_6H_4, R^2 = 4-ClC_6H_4
t: R^1 = 4-BrC_6H_4, R^2 = 4-MeC_6H_4
u: R^1 = 2-BrC_6H_4, R^2 = 4-$MeOC_6H_4$
v: R^1= 4-BrC_6H_4, R^2 = 4-MeC_6H_4
w: R^1= Et, R^2 = 4-ClC_6H_4
x: R^1 = Bn, R^2 = 2-furyl



Scheme 1 Plausible mechanism of the reaction.

the polar activation of C-N double bonds using *t*-BuOI as an electrophile may be the key step in this transformation. According to the above observations and the unique properties of *t*-BuOI [39–41], a plausible mechanism is proposed in Scheme 1. Initially, *t*-BuOI is formed *in situ* from *t*-BuOCl and NaI. Nucleophilic attack of *N*-acylhydrazones on *t*-BuOI generates the intermediate **A**. Intramolecular cyclization of **A** leads to the formation of **B.** Elimination of HI from **B** yields the final product **2**.

Conclusion

An efficient method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles using *t*-BuOI as an oxidant was developed. The reaction is carried out in DMC at room temperature under metal-free conditions. Wide substrate scope and high yields make this method a promising alternative for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.

Experimental

All solvents and reagents were obtained from commercial sources and used without further purification. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Advance 500 spectrometer at ambient temperature in $CDCl_3$ or DMSO-d_6. ESI-MS were recorded on a Thermal Finnigan TSQ Quantum ultra AM spectrometer using a TRB-5MS (30 m×0.25 mm×0.25 mm) column. Melting points were determined on a Yamato melting point apparatus Model MP-21. Silica gel (200–300 mesh) was used for column chromatographic separations and purifications. Petroleum ether (PE) refers to the fraction boiling at 60–90°C. Most of the 2,5-disubstituted 1,3,4-oxadiazoles obtained are known compounds with physical and spectral properties in agreement with those reported in the literature.

N-Acylhydrazones were prepared by condensation of one equivalent of a hydrazide and an aldehyde in ethanolic medium under reflux condition for 10 h [20]. The precipitate formed was filtered and washed with diethyl ether affording the corresponding *N*-acylhydrazone.

***N*-Benzylidenebenzohydrazide (1a)** Yield 98%; this compound was obtained as white solid, mp 207–208°C ([18], mp 208°C).

***N*-(4-Methylbenzylidene)benzohydrazide (1b)** Yield 95%; this compound was obtained as white solid, mp 219–220°C ([18], mp 218°C).

***N*-(4-Methoxybenzylidene)benzohydrazide (1c)** Yield 91%; this compound was obtained as white solid, mp 147°C ([18], mp 146°C).

***N*-(3-Phenoxybenzylidene)benzohydrazide (1d)** Yield 93%; this compound was obtained as white solid, mp 157–159°C ([42], mp 158–160°C).

***N*-(4-Chlorobenzylidene)benzohydrazide (1e)** Yield 96%; this compound was obtained as white solid, mp 223–224°C ([18], mp 225°C).

***N*-(4-Bromobenzylidene)benzohydrazide (1f)** Yield 94%; this compound was obtained as white solid, mp 226–228°C ([18], mp 225°C).

***N*-(2-Bromobenzylidene)benzohydrazide (1g)** Yield 86%; this compound was obtained as white solid, mp 201–203°C [43].

***N*-(4-Nitrobenzylidene)benzohydrazide (1h)** Yield 99%; this compound was obtained as yellow solid, mp 242°C ([18], mp 245°C).

***N*-(Naphthalen-1-ylmethylene)benzohydrazide (1i)** Yield 88%; this compound was obtained as white solid, mp 170–172°C [43].

***N*-(2-Furylmethylene)benzohydrazide (1j)** Yield 74%; this compound was obtained as light yellow solid, mp 181–183°C [43].

***N*-(2-Thienylmethylene)benzohydrazide (1k)** Yield 80%; this compound was obtained as brown solid, mp 213–214°C [43].

***N*-Phenethylidenebenzohydrazide (1l)** Yield 82%; this compound was obtained as white solid, mp 149–151°C [44].

***N*-(2-Methylbutylidene)benzohydrazide (1m)** Yield 71%; this compound was obtained as white solid, mp 88–90°C; ^{1}H NMR ($CDCl_3$): δ 10.01 (br, NH), 7.82 (d, 2H, CH, *J* = 7 Hz), 7.50 (d, 1H, CH, *J* = 7 Hz), 7.43–7.46 (m, 1H, CH), 7.35 (t, 2H, CH, *J* = 7 Hz), 2.35–2.40 (m, 1H, CH), 1.34–1.48 (m, 2H, CH_2), 1.04 (d, 3H, CH_3, *J* = 7 Hz), 0.85 (t, 3H, CH_3, *J* = 7 Hz). ^{13}C NMR ($CDCl_3$): δ 164.4, 157.4, 133.3, 131.8, 128.5, 127.5, 38.4, 27.5, 17.4, 11.6. HR-MS. Calcd for $C_{12}H_{15}ClN_2O$ (M+1): m/z 239.0879, found m/z 239.0878.

***N*-Octylidenebenzohydrazide (1n)** Yield 79%; this compound was obtained as white solid, mp 70–73°C [44].

***N*-Benzylidene-2-methylbenzohydrazide (1o)** Yield 85%; this compound was obtained as white solid, mp 173–174°C [45].

***N*-(4-Chlorobenzylidene)-4-chlorobenzohydrazide (1p)** Yield 90%; this compound was obtained as white solid, mp 220–221°C ([46], mp 219–222°C).

***N*-(4-Methyl-benzylidene)-4-methyl-benzohydrazide (1q)** Yield 86%; this compound was obtained as white solid, mp 213–215°C [47].

***N*-(4-Methoxy-benzylidene)-4-methoxy-benzohydrazide (1r)** Yield 85%; this compound was obtained as white solid, mp 182°C ([48], mp 180°C).

***N*-(4-Methyl-benzylidene)-4-chloro-benzohydrazide (1s)** Yield 91%; this compound was obtained as white solid, mp 210°C ([46], mp 212–213°C).

***N*-(4-Bromobenzylidene)-4-chlorobenzohydrazide (1t)** Yield 88%; this compound was obtained as white solid, mp 248–250°C [49].

***N*-(2-Bromobenzylidene)-4-methoxybenzohydrazide (1u)** Yield 89%; this compound was obtained as white solid, mp 164–165°C; ^{1}H NMR (DMSO-d_6): δ 11.99 (br, NH), 8.80 (s, 1H, CH), 7.92–8.00 (m, 3H, CH), 7.67–7.68 (m, 1H, CH), 7.35–7.45 (m, 2H, CH), 7.04–7.06 (m, 2H, CH), 3.83 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 163.1, 162.6, 145.8, 133.7, 133.6, 132.1, 130.1, 128.6, 127.7, 125.6, 124.0, 114.2, 55.9. HR-MS. Calcd for $C_{15}H_{13}BrN_2O_2$ (M+1): m/z 333.0168, found 333.0171.

***N*-(3-Phenoxy-benzylidene)-2-methyl-benzohydrazide (1v)** Yield 87%; this compound was obtained as light yellow solid, mp 156–158°C. ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 11.74 (br, NH), 8.26 (s, CH), 7.35–7.48 (m, 6H, CH), 7.25–7.32 (m, 2H, CH), 7.15–7.19 (m, 2H, CH), 7.05–7.10 (m, 2H, CH), 6.96–6.97 (m, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 165.7, 157.8, 147.1, 136.8, 136.4, 135.7, 130.7, 130.4, 127.9, 126.1, 124.4, 123.3, 120.8, 119.7, 119.5, 116.0. HR-MS. Calcd for $C_{13}H_{12}N_2O_2$ (M+1): 331.1371, found 331.1372.

***N*-Propylidene-4-chlorobenzohydrazide (1w)** Yield 68%; this compound was obtained as white solid, mp 170–171°C ([50], mp 170–173°C).

***N*-Phenethylidene-2-furancarbohydrazide (1x)** Yield 77%; this compound was obtained as white solid, mp 147–149°C; ^{1}H NMR ($CDCl_3$): δ 9.65 (br, NH), 7.62 (s, 1H, CH), 7.40 (s, 1H, CH), 7.19–7.28 (m, 6H, CH), 6.45–6.47 (m, 1H, CH), 3.66 (m, 2H, CH); ^{13}C NMR ($CDCl_3$): δ 154.8, 150.6, 146.5, 144.5, 136.0, 129.0, 128.8, 127.0, 116.1, 112.4, 39.0. HR-MS. Calcd for $C_{13}H_{12}N_2O_2$ (M+1): m/z 229.0901, found m/z 229.0895.

General cyclization procedure

t-BuOCl (0.36 mmol) was added to the mixture of hydrazide **1a–x** (0.3 mmol) and NaI (0.36 mmol) in DMC (3 ml). The mixture was stirred at room temperature for 15 min, treated with ethyl acetate (5 ml), and successfully washed with saturated $Na_2S_2O_3$ solution (5 ml) and water (2×5 ml). The organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. In most cases the desired solid was formed with high purity. If necessary, the crude product was purified on silica gel column using petroleum ether/ethyl acetate (10:1) as eluent.

2,5-Diphenyl-[1,3,4]oxadiazole (2a) Yield 94%; this compound was obtained as white solid, mp 138–139°C ([20], yield 85%; mp 136–138°C); ^{1}H NMR ($CDCl_3$): δ 7.53–7.58 (m, 6H, CH), 8.17 (m, 4H, CH).

2-*p*-Tolyl-5-phenyl-[1,3,4]oxadiazole (2b) Yield 95%; this compound was obtained as white solid, mp 124–125°C ([20], yield 85%; mp 121–122°C); ^{1}H NMR ($CDCl_3$): δ 8.14–8.16 (m, 2H, CH), 8.03–8.05 (m, 2H, CH), 7.54–7.56 (m, 3H, CH), 7.33–7.35 (m, 2H, CH), 2.46 (s, 3H).

2-(4-Methoxyphenyl)-5-phenyl-[1,3,4]oxadiazole (2c) Yield 87%; this compound was obtained as white solid, mp 148–149°C ([20], yield 80%; mp 149–150°C); ^{1}H NMR ($CDCl_3$): δ 8.13–8.15 (m, 2H, CH), 8.08–8.10 (m, 2H, CH), 7.53–7.55 (m, 3H, CH), 7.04–7.05 (m, 2H, CH), 3.90 (s, 3H, CH_3).

2-(3-Phenoxyphenyl)-5-phenyl-[1,3,4]oxadiazole (2d) Yield 91%; this compound was obtained as white solid; mp 129–130°C; ^{1}H NMR ($CDCl_3$): δ 8.13 (m, 2H, CH), 7.89 (m, 1H, CH), 7.79 (s, 1H, CH), 7.49–7.57 (m, 4H, CH), 7.39 (m, 2H, CH), 7.15 (m, 2H, CH), 7.08 (m, 2H, CH); ^{13}C NMR ($CDCl_3$): δ 164.7, 164.1, 158.0, 156.5, 131.9, 130.6, 130.1, 129.1, 127.0, 125.5, 124.0, 123.8, 121.9, 121.7, 119.3, 117.0. HR-MS. Calcd for $C_{20}H_{14}N_2O_2$ (M+1): m/z 315.1061, found m/z 315.1058.

2-(4-Chlorophenyl)-5-phenyl-[1,3,4]oxadiazole (2e) Yield 91%; this compound was obtained as white solid, mp 161–162°C ([20], yield 93%; mp 161–162°C); ^{1}H NMR ($CDCl_3$): δ 8.15 (m, 2H, CH), 8.10 (m, 2H, CH), 7.54 (m, 5H, CH).

2-(4-Bromophenyl)-5-phenyl-[1,3,4]oxadiazole (2f) Yield 89%; this compound was obtained as white solid, mp 169–170°C ([20], yield 93%; mp 169–170°C); ^{1}H NMR ($CDCl_3$): δ 8.14 (m, 2H, CH), 8.02 (m, 2H, CH), 7.69 (m, 2H, CH), 7.56 (m, 3H, CH).

2-(2-Bromophenyl)-5-phenyl-[1,3,4]oxadiazole (2g) Yield 94%; this compound was obtained as white solid, mp 152–153°C ([9], yield 82%; mp 152–154°C); ^{1}H NMR ($CDCl_3$): δ 8.16 (m, 2H, CH), 8.07 (m, 1H, CH), 7.79 (m, 1H, CH), 7.56 (m, 3H, CH), 7.49 (m, 1H, CH), 7.42 (m, 1H, CH).

2-(4-Nitrophenyl)-5-phenyl-[1,3,4]oxadiazole (2h) Yield 76%; this compound was obtained as yellow solid, mp 208–210°C ([18], yield 88%; mp 207°C); ^{1}H NMR ($CDCl_3$): δ 8.42 (m, 2H, CH), 8.34 (m, 2H, CH), 8.16 (m, 2H, CH), 7.59 (m, 3H, CH).

2-Naphthalen-1-yl-5-phenyl-[1,3,4]oxadiazole (2i) Yield 94%; this compound was obtained as white solid, mp 119–120°C ([51], yield 24.3%; mp 120°C); ^{1}H NMR ($CDCl_3$): δ 9.30–9.31 (m, 1H, CH), 8.29 (m, 1H, CH), 8.21–8.22 (m, 2H, CH), 8.06 (m, 1H, CH), 7.95 (m, 1H, CH), 7.73 (m, 1H, CH), 7.60 (m, 5H, CH).

2-(2-Furyl)-5-phenyl-[1,3,4]oxadiazole (2j) Yield 77%; this compound was obtained as white solid, mp 100–102°C ([20], yield 54%; mp 98–100°C); ^{1}H NMR ($CDCl_3$): δ 8.14 (m, 2H, CH), 7.68 (m, 1H, CH), 7.54 (m, 3H, CH), 7.25 (m, 1H, CH), 6.64 (m, 1H, CH).

2-(2-Thienyl)-5-phenyl-[1,3,4]oxadiazole (2k) Yield 85%; this compound was obtained as white solid, mp 112–113°C ([20], yield 58%, mp 114–115°C); ^{1}H NMR ($CDCl_3$): δ 8.13 (m, 2H, CH), 7.85 (m, 1H, CH), 7.56 (m, 4H, CH), 7.21 (m, 1H, CH).

2-Benzyl-5-phenyl-[1,3,4]oxadiazole (2l) Yield 87%; this compound was obtained as white solid, mp 100–102°C ([52], yield 66%; 102.3–102.8°C); ^{1}H NMR ($CDCl_3$): δ 8.01 (m, 2H, CH), 7.49 (m, 3H, CH), 7.36 (m, 4H, CH), 7.30 (m, 1H, CH).

2-*sec*-Butyl-5-phenyl-[1,3,4]oxadiazole (2m) Yield 81%, this compound was obtained as oil. ^{1}H NMR ($CDCl_3$): δ 8.02 (m, 2H, CH), 7.47 (m, 3H, CH), 3.07 (m, 1H, CH), 1.88 (m, 1H, CH_2), 1.73 (m, 1H, CH_2), 1.40 (d, 3H, CH_3, *J* = 7.0Hz), 0.96 (t, 3H, CH_3, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 170.2, 164.6, 131.5, 129.0, 125.8, 124.8, 33.2, 27.8, 17.7, 11.5. HR-MS. Calcd for $C_{12}H_{15}ClN_2O$ (M+1): m/z 237.0722, found m/z 237.0719.

2-Heptyl-5-phenyl-[1,3,4]oxadiazole (2n) Yield 75%; this compound was obtained as oil ([13], yield 95%; oil); ^{1}H NMR ($CDCl_3$): δ 8.04 (m, 2H, CH), 7.51 (m, 3H, CH), 2.92 (t, 2H, CH_2, *J* = 7.5Hz), 1.85 (m, 2H, CH_2), 1.30–1.45 (m, 8H, CH_2), 0.89 (t, 3H, CH_3, *J* = 6.8 Hz).

2-*o*-Tolyl-5-phenyl-[1,3,4]oxadiazole (2o) Yield 94%; this compound was obtained as white solid, mp 96–98°C ([10], yield 63%; mp 96°C); ^{1}H NMR ($CDCl_3$): δ 8.15 (m, 2H, CH), 8.06 (m, 1H, CH), 7.55 (m, 3H, CH), 7.45 (m, 1H, CH), 7.37 (m, 2H, CH), 2.79 (s, 3H, CH_3).

2,5-Bis-(4-chlorophenyl)-[1,3,4]oxadiazole (2p) Yield 89%; this compound was obtained as white solid, mp 248–250°C ([20], yield 78%; mp 250–251°C); ^{1}H NMR ($CDCl_3$): δ 8.08 (d, 4H, CH, *J* = 8.5 Hz), 7.53 (d, 4H, CH, *J* = 8.5 Hz).

2,5-Di-*p*-tolyl-[1,3,4]oxadiazole (2q) Yield 92%; this compound was obtained as white solid, mp 172–174°C ([24], yield 72%; mp 178°C); ^{1}H NMR ($CDCl_3$): δ 8.03 (d, 4H, CH, *J* = 8.0 Hz), 7.33 (d, 4H, CH, *J* = 8.0 Hz), 2.44 (s, 6H, CH_3).

2,5-Bis-(4-methoxyphenyl)-[1,3,4]oxadiazole (2r) Yield 90%; this compound was obtained as white solid, mp 158–160°C ([20], yield 83%; mp 158–160°C); ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 4H, CH, *J* = 8.8 Hz), 7.03 (d, 4H, CH, *J* = 8.8 Hz), 3.90 (s, 6H, CH_3).

2-(4-Chlorophenyl)-5-*p*-tolyl-[1,3,4]oxadiazole (2s) Yield 88%; this compound was obtained as white solid, mp 204–206°C ([24], yield 65%; mp 204°C); ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 2H, CH, *J* = 8.5 Hz), 8.03 (d, 2H, CH, *J* = 8.5 Hz), 7.52 (d, 2H, CH, *J* = 8.5 Hz), 7.35 (d, 2H, CH, *J* = 8.5 Hz), 2.45 (s, 3H, CH_3).

2-(4-Bromophenyl)-5-*p*-tolyl-[1,3,4]oxadiazole (2t) Yield 91%; this compound was obtained as white solid, mp 204–206°C ([53], yield 82%; mp 208°C); ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 4H, CH), 7.69 (m, 2H, CH), 7.34 (m, 2H, CH), 2.45 (s, 3H, CH_3).

2-(2-Bromophenyl)-5-(4-methoxyphenyl)-[1,3,4]oxadiazole (2u) Yield 87%; this compound was obtained as white solid, mp 139–141°C; ^{1}H NMR ($CDCl_3$): δ 8.09 (m, 2H, CH), 8.04 (m, 2H, CH), 7.47 (m, 1H, CH), 7.40 (m, 1H, CH), 7.04 (m, 2H, CH), 3.90 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 165.1, 163.1, 162.6, 134.6, 132.4, 131.7, 128.9, 127.7, 125.4, 121.5, 116.2, 114.6, 55.5. HR-MS. Calcd for $C_{15}H_{11}N_2O_2$ (M+1): m/z 331.0009, found m/z 331.0011.

2-(3-Phenoxyphenyl)-5-*o*-tolyl-[1,3,4]oxadiazole (2v) Yield 89%; this compound was obtained as white solid, mp 98–100°C; ^{1}H NMR ($CDCl_3$): δ 8.02 (m, 1H, CH), 7.87 (m, 1H, CH), 7.77 (m, 1H, CH), 7.49 (t, 1H, CH, *J* = 8.0 Hz), 7.33–7.45 (m, 5H, CH), 7.17 (m, 2H, CH), 7.08 (m, 2H, CH); ^{13}C NMR ($CDCl_3$): δ 165.0, 163.7, 158.1, 156.4, 138.5, 131.9, 130.6, 130.1, 129.0, 126.2, 125.5, 124.1, 122.9, 121.8, 121.6, 119.4, 116.8, 22.2. HR-MS. Calcd for $C_{21}H_{16}N_2O_2$ (M+1): m/z 329.1215, found m/z 329.1214.

2-(4-Chlorophenyl)-5-ethyl-[1,3,4]oxadiazole (2w) Yield 77%; this compound was obtained as white solid, mp 90–92°C ([14], yield 90%; mp 93–94°C); ^{1}H NMR ($CDCl_3$): δ 7.98 (d, 2H, CH, *J* = 8.5 Hz), 7.48 (d, 2H, CH, *J* = 8.5 Hz), 2.96 (q, 2H, CH_2, *J* = 8.0 Hz), 1.45 (t, 3H, CH_3, *J* = 8.0 Hz).

2-Benzyl-5-(2-furyl)-[1,3,4]oxadiazole (2x) Yield 83%; this compound was obtained as white solid, mp 149–150°C ([12], yield 62%; mp 151°C); ^{1}H NMR ($CDCl_3$): δ 7.59 (m, 1H, CH), 7.34 (m, 4H, CH), 7.30 (m, 1H, CH), 7.10 (m, 1H, CH), 6.55 (m, 1H, CH), 4.25 (s, 2H, CH2).

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