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One-Pot Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles Using Catalytic System NaOH–DMSO

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Abstract—One-pot convenient process was developed for the production of 3,5-disubstituted 1,2,4-oxadiazoles by reaction of amidoximes with anhydrides or acyl chlorides in a system NaOH–DMSO. The reaction proceeds at room temperature with high yields.

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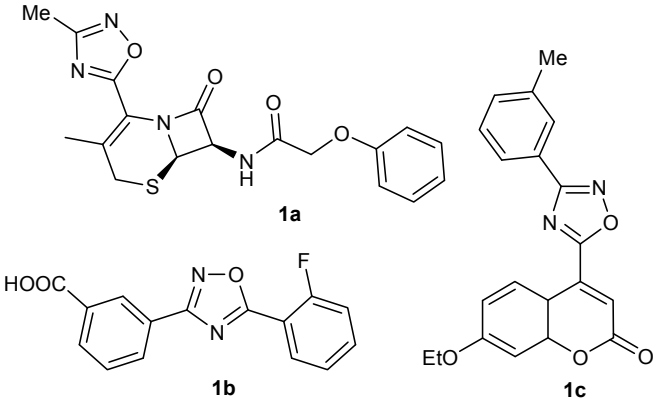
1,2,4-Oxadiazole derivatives exhibit versatile pharmaceutical properties [1–3]. Among them compounds were found with antibacterial activity [4, 5], in particular, tuberculocidal action (**1a**) [6], antitumor agents [7], neuroprotectors [8], agonists of sphingosine-1-phosphate receptors (S1P) [9], as well as inhibitors of glycogen phosphorylase [10] and of carbonic anhydrase isoform II (CAII) [11]. 1,2,4-Oxadiazole moiety is present in well-known drugs against coughing (libexine [12] and oxalomine [13]), and also in pharmaceutical ataluren (Translarna®) **1b** used in the treatment of Duchenne muscular dystrophy [14].

1,2,4-Oxadiazole derivatives are used in making new materials, in particular, of fluorescent dyes (**1c**) [15–17] (Scheme 1).

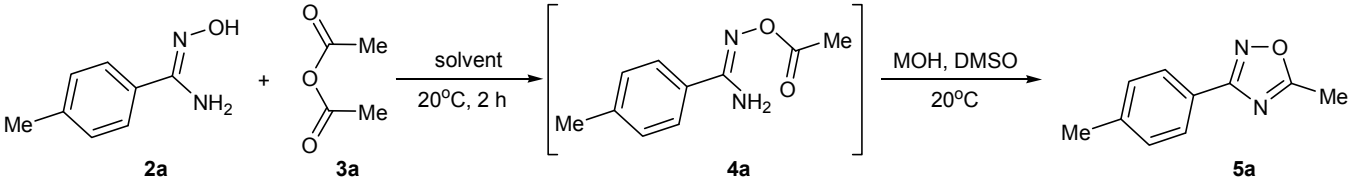
Scheme 1.



The majority of existing procedures of the synthesis of 1,2,4-oxadiazoles (amidoximes condensation with carbonic acids derivatives [18–21], 1,3-dipolar cycloaddition [22], oxidative addition of amides to nitriles [23], and oxidation of *N*-substituted amidoximes [24]) require reagents heating to elevated temperature that in some cases results in decomposition of target compounds and side products formation. One solution to this problem is performing the synthesis of 1,2,4-oxadiazole ring in a superbasic system MOH–DMSO [25]. This provides a possibility to prepare various 3,5-disubstituted-1,2,4-oxadiazoles in good yields at room temperature. Starting compounds for this reaction are *O*-acylamidoximes that usually are not isolated in the free state for the necessity of heir preparation and purification complicates the synthesis.

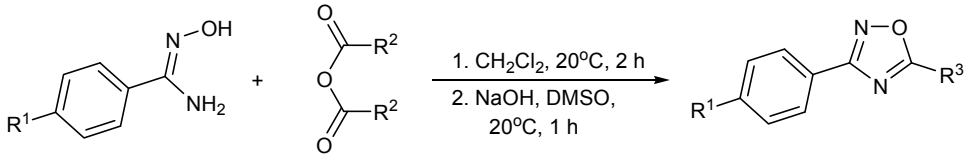
Lately we successfully used the system NaOH–DMSO in the reaction of amidoximes with esters, carboxylic acids, and cyclic anhydrides [26–28]. In this study we carried out the reaction of amidoximes with acylating agents, anhydrides and acyl chlorides, in a system MOH–DMSO. The procedure was optimized using a reaction of 4-methylbenzamidoxime **2a** with acetic anhydride **3a** in the system NaOH–DMSO (Table 1). The reaction of amidoximes with acylating agents according to published descriptions contains two successive stages: *O*-acylation of amidoxime **2** and cyclodehydration of intermediate

Scheme 2.



2a **3a** **4a** **5a**

Scheme 3.



2a–**2c** **3b**–**3e** **5b**–**5e**

2, R^1 = Me (**a**), Br (**b**), NO_2 (**c**); **3**, R^2 = Et (**b**), Ph (**c**), *i*-Pr (**d**), OBoc (**e**); **5**, R^1 = Br, R^3 = Et (**b**); R^1 = Me, R^3 = Ph (**c**); R^1 = NO_2, *i*-Pr (**d**); R^1 = Me, R^3 = OH (**e**).

compound **4** to 1,2,4-oxadiazole **5** (Scheme 2) [29]. Since NaOH accelerates the cyclodehydration stage [30], it was added 2 h after the beginning of the process.

Hence the experiment consisted of two operations: amidoxime **2a** was mixed with acetic anhydride **3a** in DMSO, then NaOH was added. To obtain a complete conversion of *O*-acylamidoxime in 1,2,4-oxadiazole 10 min [25] was insufficient, a mixture was isolated of the intermediate *O*-acylamidoxime **4a** and 1,2,4-oxadiazole **5a**, the latter prevailing (Table 1, run no. *1*). The increased time of the second stage made it possible to obtain compound **5a** in 62% yield without impurity of *O*-acylamidoxime **4a** (Table 1, run no. *2*). Further we explored the influence of the nature of the used hydroxide, reagents amount (of the base and the anhydride), and the reaction time on the yield of 1,2,4-oxadiazole **5a** (Table 1, runs nos. *3*–*9*). As alternative for DMSO in the first stage of *O*-acylamidoxime **4a** formation we tested three solvents: dichloromethane, acetone, and acetonitrile (Table 1, runs nos. *10*–*12*). The reason of this choice was firstly because of good solubility of the intermediate *O*-acylamidoxime, and secondly of the simplicity of solvent elimination. At the reaction in dichloromethane we succeeded to raise the yield of compound **5a** to 83%.

In keeping with this procedure we synthesized a series of 3,5-disubstituted-1,2,4-oxadiazoles using anhydrides and amidoximes as starting compounds (Scheme 3).

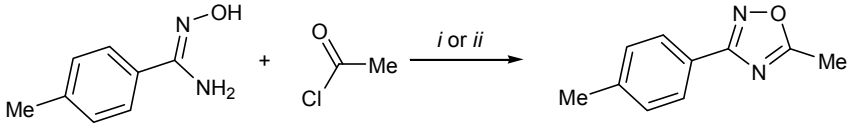
At the investigation of the reaction of amidoximes with acyl chlorides **6** we used as model the reaction of amidoxime **2a** with acetyl chloride **6a**. Unlike the reaction involving anhydrides it was necessary to use bases in the stage of acylation with acyl chlorides (to bind the forming HCl), $NaHCO_3$ was applied as a base. In the reaction of starting reagents **2a** and **6a** in DMSO 1,2,4-oxadiazole **5a** was obtained in a very low yield. Acylation in dichloromethane (similarly to the reaction with anhydrides) in the presence of $NaHCO_3$ followed by removal of the solvent and treatment of the residue with a mixture NaOH–DMSO at room temperature led

Table 1. Study of reaction between 4-methylbenzamidoxime **2a** with acetic anhydride **3a** (1 : 1)

Run no.	MOH, equiv	Solvent in the first stage[a]	Time of the second stage, h	Yield of **5a**, %
1	NaOH (2.0)	DMSO	0.2	34
2	NaOH (2.0)	DMSO	1	62
3	NaOH (2.5)	DMSO	1	62
4	NaOH (3.0)	DMSO	1	55
5	LiOH (2.0)	DMSO	1	63
6	KOH (2.0)	DMSO	1	60
7	NaOH (2.0)	DMSO	1	65[a]
8	NaOH (2.0)	DMSO	2	64
9	NaOH (2.0)	DMSO	24	65
10	**NaOH (1.0)**	**CH_2Cl_2**	**1**	**83**
11	NaOH (1.0)	Acetone	1	74
12	NaOH (1.0)	MeCN	1	69

[a] Time of the first stage 2 h.

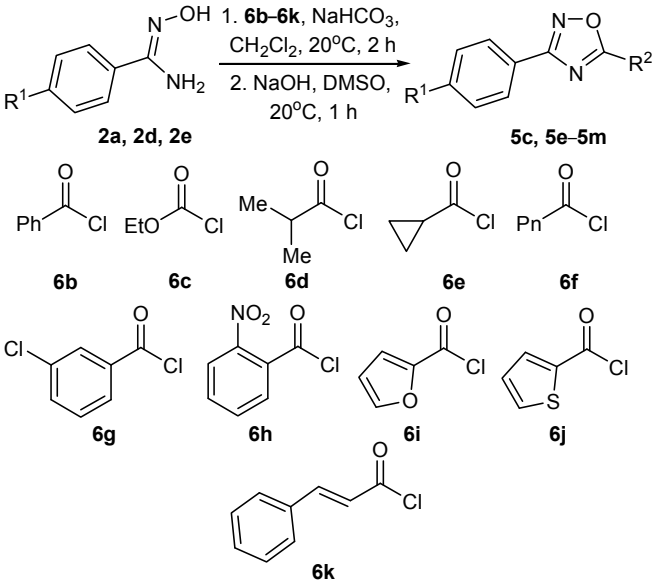
Scheme 4.

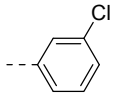
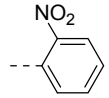
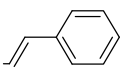


2a **6a** **5a**

i: 1. $NaHCO_3$, DMSO, 20°C, 2 h; 2. NaOH, DMSO, 20°C, 1 h, yield 31%;
ii: 1. $NaHCO_3$, CH_2Cl_2, 20°C, 2 h; 2. NaOH, DMSO, 20°C, 1 h, yield 77%.

Table 2. Synthesis of 1,2,4-oxadiazoles **5c** and **5e–5m**[a]



Acyl chloride	Reaction products	R^1	R^2	Yield, %
6b	**5c**	Me	Ph	75
6c	**5e**	Me	OH	74
6d	**5f**	H	*i*-Pr	61
6e	**5g**	Me		65
6f	**5h**	Me	Pentyl	72
6g	**5i**	Me		76
6h	**5j**	OMe		84
6i	**5k**	H		67
6j	**5l**	Me		78
6k	**5m**	H		79

[a] Reagents and solvents: 2 mmol of **2**, 2 mmol of **6**, 2.2 mmol of $NaHCO_3$, 2 mmol of NaOH, 10 mL of CH_2Cl_2, 1.5–2 mL of DMSO.

to the formation of compound **5a** in 77% yield (Scheme 4).

Finally we applied the developed procedure to the synthesis of a series of 3,5-disubstituted 1,2,4-oxadiazoles from various acyl chlorides **6b–6k** (Table 2). This procedure is applicable to the synthesis of 1,2,4-oxadiazoles both with aromatic (heteroaromatic) and aliphatic substituents.

The developed procedure makes it possible to prepare in a good yield and a satisfactory purity a wide set of potential biologically active 3,5-disubstituted 1,2,4-oxadiazoles from available starting compounds (amidoximes, acyl chlorides, and anhydrides) in a low toxic solvent DMSO at room temperature.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance DRX-400 (400 and 100 MHz respectively). As internal reference the signals served of residual protons and carbon atoms of the solvent: 2.50 (^1H) and 39.52 (^{13}C) ppm for solutions in DMSO-d_6; 7.26 (^1H) and 77.16 (^{13}C) ppm for solutions in $CDCl_3$. TLC was performed on Sulifol 201S plates, eluent petroleum ether–ethyl acetate, 2 : 1 v/v. Melting points were measured on an apparatus IA 9000 SERIES Digital Melting point. Mass spectra were taken on an instrument Shimadzu LCMS-2020 Single Quadru-pole Liquid (electrospray ionization, ESI). High resolution mass spectra were recorded on an instrument Bruker maXis HRMS-ESI-QTOF.

Reaction of 4-methylbenzamidoxime (2a) with acetic anhydride (3a) in DMSO. In 2 mL of DMSO was mixed 348 mg (2 mmol) of amidoxime **2a** and 0.19 mL (2 mmol) of acetic anhydride **3a**. The reaction mixture was stirred at room temperature for 2 h (Table 1), powdered MOH was added, and the obtained dispersion was stirred for desired time at room temperature. Then to the reaction mixture 20 mL of cold water was added and the formed precipitate was filtered off.

Reaction of 4-methylbenzamidoxime (2a) with acetyl chloride (6a) in DMSO. In 2 mL of DMSO was dissolved 348 mg (2 mmol) of amidoxime **2a**, the solution was cooled to 0°C and by portions maintaining the reaction mixture temperature below 5°C 0.15 mL (2 mmol) of acetyl chloride **6a** and 185 mg (2.2 mmol) of $NaHCO_3$ was added. The reaction mixture was warmed to room temperature, stirred for 2 h, and 80 mg (2 mmol) of powdered NaOH was added. The reaction mixture was stirred for 1 h at room temperature, then to the reaction mixture 20 mL of cold water was added and the formed precipitate was filtered off.

1,2,4-Oxadiazoles (5a–5m). General procedure. *a.* In 10 mL of dichloromethane 2 mmol of amidoxime **2** was dissolved and 2 mmol of anhydride **3** was added. The reaction mixture was stirred at room temperature for 2 h, then it was washed with 10 mL of $NaHCO_3$ solution and 10 mL of water, the organic layer was dried with Na_2SO_4 and evaporated at a reduced pressure. The residue was dissolved in 1.5–2 mL of DMSO and 80 mg (2 mmol) of preliminary ground NaOH was added. The reaction mixture was stirred at room temperature for 1 h and diluted with 20 mL of cold water. The formed precipitate was filtered off.

b. In 10 mL of dichloromethane was dissolved 2 mmol of amidoxime **2**, 185 mg (2.2 mmol) of $NaHCO_3$ was added. The reaction mixture was cooled to 0°C and by portions maintaining the reaction mixture temperature below 5°C 2 mmol of acyl chloride **3** was added. The reaction mixture was warmed to room temperature, stirred for 2 h, then it was washed with 10 mL of $NaHCO_3$ solution and 10 mL of water, the organic layer was dried with Na_2SO_4 and evaporated at a reduced pressure. The residue was dissolved in 1.5–2 mL of DMSO and 80 mg (2 mmol) of preliminary ground NaOH was added. The reaction mixture was stirred at room temperature for 1 h and diluted with 20 mL of cold water. The formed precipitate was filtered off.

5-Methyl-3-(4-methylphenyl)-1,2,4-oxadiazole (5a). Yield 285 mg (83%) (*a*), 268 mg (77%) (*b*); white powder, mp 77–79°C (mp 77–78°C [28]). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.37 s (3H, CH_3), 2.64 s (3H, CH_3), 7.36 d (2H$_{arom}$, *J* 7.9 Hz), 7.88 d (2H$_{arom}$, *J* 7.9 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 12.0 (CH_3), 21.1 (CH_3), 123.6 (C_{arom}), 126.9 (C_{arom}), 129.8 (C_{arom}), 141.4 (C_{arom}), 167.6 (C^3), 177.2 (C^5). Mass spectrum: *m/z* 175 $[M + H]^+$.

3-(4-Bromophenyl)-5-ethyl-1,2,4-oxadiazole (5b). Yield 319 mg (63%) (*a*), white powder, mp 39–40°C (mp 38–40°C [28]). ^{1}H NMR spectrum (DMSO), δ, ppm: 1.34 t (3H, CH_3, *J* 7.6 Hz), 2.98–3.05 m (2H), 7.77 d (2H$_{arom}$, *J* 8.6 Hz), 7.94 d (2H$_{arom}$, *J* 8.6 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 10.8 (CH_3), 20.1 (CH_2), 125.4 (C_{arom}), 126.0 (C_{arom}), 129.3 (C_{arom}), 131.8 (C_{arom}), 132.7 (C_{arom}), 167.1 (C^3), 181.6 (C^5). Mass spectrum: *m/z* 253 $[M + H]^+$.

3-(4-Methylphenyl)-5-phenyl-1,2,4-oxadiazole (5c). Yield 387 mg (82%) (*a*), 354 mg (75%) (*b*); white powder, mp 102–103°C (mp 102–103°C [28]). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.38 s (3H, CH_3), 7.38 d (2H$_{arom}$, *J* 8.0 Hz), 7.64 t (2H$_{arom}$, *J* 7.4 Hz), 7.72 t (1H$_{arom}$, *J* 7.4 Hz), 7.96 d (2H$_{arom}$, *J* 8.1 Hz), 8.15 d (2H$_{arom}$, *J* 7.1 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 21.2 (CH_3), 123.4 (C_{arom}), 123.5 (C_{arom}), 127.1 (C_{arom}), 127.9 (C_{arom}), 129.6 (C_{arom}), 127.9 (C_{arom}), 129.6 (C_{arom}), 129.8 (C_{arom}), 133.3 (C_{arom}), 141.6 (C_{arom}), 168.3 (C^3), 175.3 (C^5). Mass spectrum: *m/z* 237 $[M + H]^+$.

5-Isopropyl-3-(4-nitrophenyl)-1,2,4-oxadiazole (5d). Yield 382 mg (82%) (*a*), light yellow powder, mp 129–130°C (mp 128–130°C [25]). ^{1}H NMR spectrum (DMSO), δ, ppm: 1.40 d (6H, CH_3, *J* 6.9 Hz), 3.36–3.43 m (1H, CH), 8.26 d (2H$_{arom}$, *J* 9.0 Hz), 8.40 d (2H$_{arom}$, *J* 9.0 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 19.8 (CH_3), 26.9 (CH), 124.5 (C_{arom}), 128.5 (C_{arom}), 132.0 (C_{arom}), 149.2 (C_{arom}), 166.3 (C^3), 185.0 (C^5). Mass spectrum: *m/z* 234 $[M + H]^+$.

3-(4-Methylphenyl)-1,2,4-oxadiazol-5-ol (5e). Yield 303 mg (86%) (*a*), 261 mg (74%) (*b*); white powder, mp 206–208°C (mp 207–208°C [28]). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.37 s (3H, CH_3), 7.37 d (2H$_{arom}$, *J* 7.8 Hz), 7.69 d (2H$_{arom}$, *J* 8.1 Hz), 12.82 br.s (1H, NH). ^{13}C NMR spectrum (DMSO), δ, ppm: 12.1 (CH_3), 126.7 (C_{arom}), 127.6 (C_{arom}), 129.3 (C_{arom}), 146.5 (C_{arom}), 166.8 (C^3), 178.0 (C^5). Mass spectrum: *m/z* 177 $[M + H]^+$.

5-Isopropyl-3-phenyl-1,2,4-oxadiazole (5f). Yield 230 mg (61%) (*b*), colorless liquid [31]. ^{1}H NMR spectrum (DMSO), δ, ppm: 1.35 m (6H, CH_3), 3.25–3.30 br.m (1H, CH), 7.52 m (3H$_{arom}$), 7.97 m (2H$_{arom}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.2 (CH_3), 27.6 (CH), 127.1 (C_{arom}), 127.5 (C_{arom}), 128.8 (C_{arom}), 131.0 (C_{arom}), 168.2 (C^3), 183.9 (C^5). Mass spectrum: *m/z* 189 $[M + H]^+$.

3-(4-Methylphenyl)-5-cyclopropyl-1,2,4-oxadiazole (5g). Yield 192 mg (48%) (*b*), white powder, mp 54–55°C (mp 55–56°C [28]). ^{1}H NMR spectrum

(DMSO), δ, ppm: 1.13–1.19 m (2H, CH_2), 1.21–1.30 m (2H, CH_2), 2.33–2.40 m (4H, CH_3, CH), 7.33 d ($2H_{arom}$, *J* 7.9 Hz), 7.84 d ($2H_{arom}$, *J* 8.1 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 7.7 (CH_2), 10.4 (CH_2, CH_3), 21.5 (CH), 124.0 (C_{arom}), 127.3 (C_{arom}), 130.1 (C_{arom}), 141.5 (C_{arom}), 167.7 (C^3), 182.0 (C^5). Mass spectrum: *m/z* 201 $[M + H]^+$.

3-(4-Methylphenyl)-5-pentyl-1,2,4-oxadiazole (5h). Yield 332 mg (72%) (*b*), dark red liquid [32]. ^1H NMR spectrum (DMSO), δ, ppm: 0.90 t (3H, CH_3, *J* 6.3 Hz), 1.79 m (2H, CH_2), 1.85 m (4H, CH_2), 2.39 s (3H, CH_3), 2.93 t (2H, CH_2, *J* 7.5 Hz), 7.31 d ($2H_{arom}$, *J* 7.8 Hz), 7.88 d ($2H_{arom}$, *J* 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.8 (CH_3), 21.5 (CH_2), 22.2 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 31.2 (CH), 124.2 (C_{arom}), 127.3 (C_{arom}), 129.5 (C_{arom}), 141.3 (C_{arom}), 168.3 (C^3), 179.9 (C^5). Mass spectrum: *m/z* 231 $[M + H]^+$.

3-(4-Methylphenyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole (5i). Yield 411 mg (76%) (*b*), white powder, mp 85–87°C. ^1H NMR spectrum (DMSO), ppm: 2.41 s (3H, CH_3), 7.41 d ($2H_{arom}$, *J* 8.0 Hz), 7.70 t ($1H_{arom}$, *J* 7.9 Hz), 7.81 d ($1H_{arom}$, *J* 8.1 Hz), 7.99 d ($2H_{arom}$, *J* 8.1 Hz), 8.15 t ($2H_{arom}$, *J* 7.1 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 21.3 (CH_3), 123.6 (C_{arom}), 125.8 (C_{arom}), 127.0 (C_{arom}), 127.5 (C_{arom}), 127.8 (C_{arom}), 130.3 (C_{arom}), 132.0 (C_{arom}), 133.5 (C_{arom}), 134.6 (C_{arom}), 142.2 (C_{arom}), 168.8 (C^3), 174.5 (C^5). Found: *m/z* 271.0622 $[M + H]^+$. $C_{15}H_{12}ClN_2O$. M_{calc} 271.0633.

3-(4-Methoxyphenyl)-5-(2-nitrophenyl)-1,2,4-oxadiazole (5j). Yield 499 mg (84%) (*b*), light yellow powder, mp 133–134°C (mp 133–135°C [25]). ^1H NMR spectrum (DMSO), δ, ppm: 3.85 s (3H, OCH_3), 7.15 d ($2H_{arom}$, *J* 8.7 Hz), 7.99 m ($4H_{arom}$), 8.17 m ($1H_{arom}$), 8.25 m ($1H_{arom}$). ^{13}C NMR spectrum (DMSO), δ, ppm: 55.4 (OCH_3), 114.8 (C_{arom}), 117.7 (C_{arom}), 117.9 (C_{arom}), 124.9 (C_{arom}), 128.9 (C_{arom}), 131.5 (C_{arom}), 133.8 (C_{arom}), 134.1 (C_{arom}), 148.2 (C_{arom}), 162.0 (C_{arom}), 168.0 (C^3), 172.2 (C^5). Mass spectrum: *m/z* 298 $[M + H]^+$.

3-Phenyl-5-(furan-2-yl)-1,2,4-oxadiazole (5k). Yield 284 mg (67%) (*b*), white powder, mp 101–102°C (101–103°C [25]). ^1H NMR spectrum (DMSO), δ, ppm: 6.88 d.d ($1H_{arom}$, *J* 3.6, 1.7 Hz), 7.57–7.64 m ($3H_{arom}$), 7.65 d ($1H_{arom}$, *J* 3.6 Hz), 8.07 d.d ($2H_{arom}$, *J* 7.8, 1.6 Hz), 8.17–8.19 m ($1H_{arom}$). ^{13}C NMR spectrum (DMSO), δ, ppm: 113.5 (C_{arom}), 118.1 (C_{arom}), 126.3 (C_{arom}), 127.6 (C_{arom}), 129.7 (C_{arom}), 132.2 (C_{arom}), 139.5 (C_{arom}), 148.8 (C_{arom}), 167.8 (C^3), 168.4 (C^5). Mass spectrum: *m/z* 213 $[M + H]^+$.

3-(-Methylphenyl)-5-(thiophen-2-yl)-1,2,4-oxadiazole (5l). Yield 281 mg (58%) (*b*), white powder, mp 91–92°C (mp 90–92°C [25]). ^1H NMR spectrum (DMSO), δ, ppm: 2.40 s (3H, CH_3), 7.35–7.41 m ($3H_{arom}$), 7.95 d ($2H_{arom}$, *J* 8.0 Hz), 8.10 d.d ($2H_{arom}$, *J* 15.0, 6.8 Hz). ^{13}C NMR spectrum (DMSO), δ, ppm: 21.6 (CH_3), 123.6 (C_{arom}), 125.1 (C_{arom}), 127.5 (C_{arom}), 129.7 (C_{arom}), 130.3 (C_{arom}), 133.2 (C_{arom}), 134.5 (C_{arom}), 142.2 (C_{arom}), 168.6 (C^3), 171.4 (C^5). Mass spectrum: *m/z* 243 $[M + H]^+$.

(*E*)-3-Phenyl-5-(2-phenylethenyl)-1,2,4-oxadiazole (5m). Yield 392 mg (79%) (*b*), white powder, mp 95–97°C (mp 92–93°C [33]). ^1H NMR spectrum (DMSO), δ, ppm: 7.31 d (1H, =CH, *J* 16.4 Hz), 7.48–7.51 m ($3H_{arom}$), 7.57–7.59 m ($3H_{arom}$), 7.83–7.84 m ($2H_{arom}$), 7.97 d (1H, =CH, *J* 16.4 Hz), 8.12–8.14 m ($2H_{arom}$). ^{13}C NMR spectrum (DMSO), δ, ppm: 110.9 (HtCH=), 127.8 (C_{arom}), 128.8 (C_{arom}), 129.4 (C_{arom}), 129.6 (C_{arom}), 129.7 (C_{arom}), 131.2 (C_{arom}), 131.9 (C_{arom}), 135.3 (C_{arom}), 143.4 (PhCH=), 167.9 (C^3), 174.1 (C^5). Found: *m/z* 249.1022 $[M + H]^+$. $C_{16}H_{13}N_2O$. M_{calc} 249.1029.

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