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One-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles containing an alkenyl moiety

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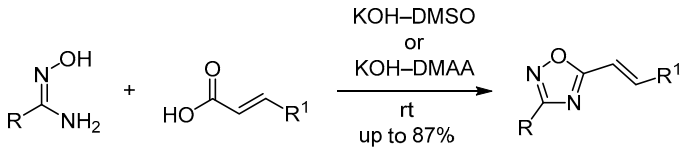


R = Ph, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-Py, 4-Py
R^1 = Ph, 3-$O_2NC_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, Th

A one-pot method was developed for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles containing an alkenyl fragment, which entails the preparation of *O*-acylamidoximes and their subsequent cyclization using *N*,*N*'-dimethylacetamide as a solvent. The proposed method allows to significantly reduce the overall synthesis time by carrying out all steps sequentially in a single reactor, avoiding the step of isolation of the intermediate *O*-acylamidoxime, leading to the production of 5-alkenyl-1,2,4-oxadiazoles in high yields.

Keywords: alkenyl aromatic carboxylic acids, 5-alkenyl-1,2,4-oxadiazoles, amidoximes, 3,5-disubstituted 1,2,4-oxadiazoles, *O*-acylation, cyclodehydration, one-pot synthesis.

1,2,4-Oxadiazoles are widely used in pharmaceutical chemistry.[1] They are used in antitussive drugs such as Perebron[2] and Libexin,[2] and the antiviral agent pleconaril.[3] Being serotonin agonists, 1,2,4-oxadiazoles are used to treat migraine.[4] A number of 1,2,4-oxadiazoles have been shown to exhibit antitumor activity.[5,6] 3,5-Disubstituted 1,2,4-oxadiazoles also exhibit anti-inflammatory,[5a,6] antimicrobial,[1] analgesic,[6] hypotensive[7] activity; they may be used in the treatment of Parkinson's disease,[4,5d,8] cystic fibrosis,[1,9] Duchenne muscular dystrophy,[1] Alzheimer's disease.[1,5d] 5-Alkenyl- and 5-styryl-1,2,4-oxadiazoles have inhibitory activity against phosphodiesterase 4, a therapeutic target in asthma therapy, and are included in the composition of many drugs for the treatment of lung diseases.[1] In addition, 5-alkenyl-1,2,4-oxadiazoles are promising non-nucleoside agents for the treatment of dengue fever[10] and also possess antiproliferative activity.[11]

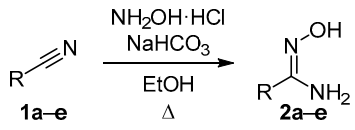
There are two classical methods for the preparation of 1,2,4 oxadiazoles: 1,3-dipolar cycloaddition of nitriles to nitrile oxides and acylation of amidoximes with carboxylic acids or their derivatives.[1] A common method for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles is the reaction of a nitrile with nitrile oxide.[12] However, nitrile oxides actively enter into addition reactions with compounds containing multiple bonds. Due to the fact that the aim of our work was to obtain 1,2,4-oxadiazoles containing a carbon–carbon double bond in the side chain, this method for the preparation of oxadiazoles is not suitable due to the possibility of the formation of byproducts.

The aim of this work is the one-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles containing an alkenyl moiety. The method proposed by us makes it possible to significantly reduce the overall synthesis time and can be used to obtain 5-alkenyl-1,2,4-oxadiazoles in high yields. In the present work, the synthesis of 5-alkenyl-1,2,4-oxadiazoles was carried out by the reaction of amidoximes[13] and activated carboxylic acids, followed by intramolecular cyclodehydration of the obtained *O*-acylamidoximes by the action of alkali.

The corresponding aromatic amidoximes were used as starting compounds in the preparation of 5-alkenyl-1,2,4-oxadiazoles. Amidoximes **2a**–**e** were synthesized by the Tiemann method[14] from nitriles **1a**–**e** (Scheme 1).

The most widely used method for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles is the cyclization of *O*-acylamidoximes preceded by the acylation of amidoximes with carboxylic acids or their derivatives such as esters, anhydrides, or acid halides.[1] Cyclization of

Scheme 1



O-acylamidoximes can be carried out in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), and *N*,*N*'-carbonyldiimidazole (CDI). This requires a long reaction time at high temperature.[4] It is also possible to carry out cyclization by microwave irradiation using water or a mixture of water with acetone as a solvent.[15] This reaction can be carried out in the presence of tetrabutylammonium fluoride. Although this method allows the cyclization to be carried out at room temperature, it also has a number of disadvantages associated with the corrosiveness of fluorine ions and the need for a microwave source.

It is known that the strength of many bases in aqueous DMSO is higher than in other solvents. This makes it possible to obtain 3,5-disubstituted 1,2,4-oxadiazoles by cyclization of *O*-acylamidoximes in a strongly alkaline medium at room temperature. It was found that alkali metal hydroxides (KOH, NaOH, LiOH) are the best reagents for the cyclodehydration of *O*-acylamidoximes.[16] A series of 1,2,4-oxadiazoles containing an alkenyl moiety was obtained by carrying out the reaction in a strongly alkaline KOH–DMSO medium. Notably, it was found that the presence of electron-donating or electron-withdrawing substituents did not affect the reaction rate.[17]

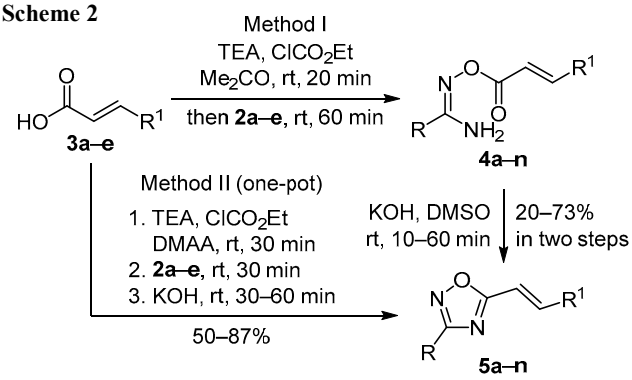
In the course of this work, 1,2,4-oxadiazoles were synthesized by two methods (Scheme 2). According to method I, *O*-acylation of amidoximes **2a**–**e** with carboxylic acids **3a**–**e** in Me_2CO solution in the presence of activators triethylamine (TEA) and ethyl chloroformate was carried out in the first step to form *O*-acylamidoximes **4a**–**n**. The second step involved intramolecular cyclodehydration of *O*-acylamidoximes **4a**–**n** in the KOH–DMSO system at 20–25°C.[17] The disadvantage of this method is the long synthesis time and relatively low yields of target products **5a**–**n** (Table 1).

According to method II, the preparation of 5-alkenyl-1,2,4-oxadiazoles **5a**–**n** from amidoximes **2a**–**e** and carboxylic acids **3a**–**e** proceeded without isolating the intermediate *O*-acylamidoximes **4a**–**n**. Both steps of the preparation of oxadiazoles **5a**–**n** were carried out sequentially in one reactor; *N*,*N*'-dimethylacetamide (DMA) was used as a solvent. The reaction time was 90–120 min; cyclization was effected in the presence of KOH at 20–25°C.

Performing the reaction in DMA solution leads to an insignificant increase in the duration of the cyclization step, as well as the need to use a twofold excess of KOH. The use of DMA as a solvent makes it possible to increase the yields of the reaction products (Table 1), as well as to reduce the total synthesis time due to elimination of the step of isolation of intermediate *O*-acylamidoximes **4a**–**n**.

The structure of the obtained 5-alkenyl-1,2,4-oxadiazoles **5a**–**n** was determined on the basis of IR and ^{1}H and ^{13}C NMR spectroscopy data. In the IR spectra of the obtained compounds **5a**–**n**, the characteristic absorption

Scheme 2



5 a R = R^1 = Ph; **b** R = Ph, R^1 = 3-$O_2NC_6H_4$;
c R = Ph, R^1 = 4-ClC_6H_4; **d** R = Ph, R^1 = Th;
e R = 3-$O_2NC_6H_4$, R^1 = Ph; **f** R = 3-$O_2NC_6H_4$, R^1 = Th;
g R = 3-$O_2NC_6H_4$, R^1 = 3-ClC_6H_4; **h** R = 4-$O_2NC_6H_4$, R^1 = Th;
i R = 4-$O_2NC_6H_4$, R^1 = 4-ClC_6H_4; **j** R = 3-Py, R^1 = Ph;
k R = 3-Py, R^1 = 2-ClC_6H_4; **l** R = 3-Py, R^1 = 4-ClC_6H_4;
m R = 3-Py, R^1 = Th; **n** R = 4-Py, R^1 = Th

bands are observed at 1625–1664 cm^{-1} (C=C), corresponding to the signals of the carbon–carbon double bond, and at 1535–1573 cm^{-1} (C=N) and 1168–1222 cm^{-1} (C–O), corresponding to the signals of the oxadiazole ring. The presence of a characteristic band at 955–980 cm^{-1} indicates the *trans* configuration of the substituents at the double bond.

In the ^{1}H NMR spectra of oxadiazoles **5a**–**n**, signals of double bond protons characteristic of these compounds are observed at 6.85–7.21 and 7.84–8.04 ppm with SSCC of 16.4 Hz (this SSCC value indicates the *trans* configuration of the compounds), as well as signals of the aromatic protons. The spectra do not show the signal of the amino group (at ~6 ppm), which is characteristic of the corresponding *O*-acylamidoximes **4a**–**n**. Therefore, it can be concluded that the intramolecular cyclodehydration reaction is completed and the resulting compounds correspond to the proposed structure.

To conclude, a one-pot method for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles containing an alkenyl fragment has been developed, which entails the use of DMA as a solvent and carrying out all steps of the synthesis sequentially in one reactor. The proposed method allows to significantly reduce the overall synthesis time, as

Table 1. Reaction conditions and yields of 5-alkenyl-1,2,4-oxadiazoles **5a**–**n**

Compound	Yield, %		Compound	Yield, %	
	Method I*	Method II**		Method I*	Method II**
5a	45	67	**5h**	–	80
5b	49	50	**5i**	–	67
5c	73	75	**5j**	51	80
5d	66	72	**5k**	–	86
5e	43	74	**5l**	20	86
5f	56	87	**5m**	65	73
5g	–	75	**5n**	60	59

* Method I: acylation (TEA, ethyl chloroformate, Me_2CO, 20–25°C, 20 + 60 min); cyclization (KOH–DMSO, 1:1, 20–25°C, 10–60 min).[17]
** Method II: acylation (TEA, ethyl chloroformate, DMA, 20–25°C, 30 + 30 min); cyclization (KOH–DMA, 1:2, 20–25°C, 30–60 min).[18]

well as to obtain 5-alkenyl-1,2,4-oxadiazoles in high yields. The compounds described in the article, 10 of which are novel, are of practical interest, as they may exhibit biological activity.

Experimental

IR spectra were registered on a Spectrum RX Fourier transform spectrometer with samples as a suspension in petroleum jelly. Mathematical processing of the spectra was carried out using the Spectrum 5.0.1 software. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were acquired on a Bruker 400 Avance spectrometer in $CDCl_3$ with the residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei) serving as the standard. Mathematical processing of the spectra was carried out using the MestReNova software. High-resolution mass spectra were recorded on a Bruker Maxis HRMS-ESI-qTOF mass spectrometer, electrospray ionization in positive ion detection mode. Mathematical processing of the spectra was carried out using the Bruker Compass DataAnalysis 4.0 software. Melting points were determined on an Electrothermal IA 9300 Series apparatus by the capillary method. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates, eluent heptane–EtOAc, 1:1, visualization under UV light.

Amidoximes **2a**–**e** were synthesized by a known method.[14]

Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles 5a–**e** (General method). Method I. Synthesis of *O*-acylamidoximes **4a**–**n**. Acid **3a**–**e** (2.5 mmol) was dissolved in Me_2CO (10 ml), TEA (0.30 g, 3.0 mmol) was added, followed by dropwise addition of ethyl chloroformate (0.33 g, 3.0 mmol). The resulting mixture was stirred at 20–25°C for 20 min. Amidoxime **2a**–**e** (2.5 mmol) was added, and stirring was continued at 20–25°C for 60 min. The mixture was poured into H_2O (100 ml), the formed precipitate was filtered off and dried. Cyclization of *O*-acylamidoximes **4a**–**n**. KOH (2.0 mmol) was added to a solution of *O*-acylamidoxime **4a**–**n** (2.0 mmol) in DMSO (2 ml), and the resulting mixture was stirred at 20–25°C for 10–60 min. The mixture was poured into H_2O (20 ml), the formed precipitate was filtered off and dried. The compounds were purified by recrystallization from EtOH.

Method II. Acid **3a**–**e** (2.0–2.5 mmol) was dissolved in DMA (2 ml), TEA (2.4–3.0 mmol) and ethyl chloroformate (2.4–3.0 mmol) were added, and the resulting mixture was stirred at 20–25°C for 30 min. Amidoxime **2a**–**e** (2.0–2.5 mmol) was added, and stirring was continued at 20–25°C for 30 min. Finely ground KOH (4.0–5.0 mmol) was added, and the mixture was stirred at 20–25°C for 30–60 min. Isolation and purification of products was carried out similarly to method I.

3-Phenyl-5-(2-phenylethenyl)-1,2,4-oxadiazole (5a). Yield 324 mg (45%, method I), 440 mg (67%, method II), colorless powder, mp 93–94°C (mp 95–97°C[17]). IR spectrum, ν, cm^{-1}: 1664 (CH=CH), 1577 (Ar), 1538 (C=N), 1168 (C–O), 971 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.43–7.45 (3H, m, H Ar); 7.50–7.52 (3H, m, H Ar); 7.61–7.63 (2H, m, H Ar); 7.90 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.12–8.15 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 110.4 (HC=C<u>H</u>–Het); 127.1 (C Ar); 127.6 (2C Ar); 128.1 (2C Ar); 129.0 (C Ar); 129.2 (2C Ar); 130.7 (2C Ar); 131.2 (C Ar); 134.6 (C Ar); 142.8 (HC=C<u>H</u>–Ar); 168.9 (C-3); 175.4 (C-5). Found, *m*/*z*: 249.1029 $[M+H]^+$. $C_{16}H_{13}N_2O$. Calculated, *m*/*z*: 249.1022.

5-[2-(3-Nitrophenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (5b). Yield 340 mg (49%, method I), 460 mg (50%, method II), yellow powder, mp 155–159°C.[18] IR spectrum, ν, cm^{-1}: 1652 (CH=CH), 1617, 1591, 1575 (Ar), 1558, 1547, 1533 (NO_2), 973 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.21 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.44–7.53 (3H, m, H Ar); 7.65 (1H, t, *J* = 8.0, H Ar); 7.92–7.96 (2H, dd, *J* = 16.8, *J* = 6.5, HC=C<u>H</u>–Ar, H Ar); 8.13 (2H, d, *J* = 7.6, H Ar); 8.28 (1H, d, *J* = 8.1, H Ar); 8.48 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 113.4 (HC=C<u>H</u>–Het); 122.5 (C Ar); 124.8 (C Ar); 126.8 (C Ar); 127.6 (2C Ar); 129.0 (2C Ar); 130.3 (C Ar); 131.5 (C Ar); 133.5 (C Ar); 136.2 (C Ar); 139.8 (HC=C<u>H</u>–Ar); 169.0 (C-3); 174.4 (C-5). Found, *m*/*z*: 294.0877 $[M+H]^+$. $C_{16}H_{12}N_3O_3$. Calculated, *m*/*z*: 294.0873.

5-[2-(4-Chlorophenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (5c). Yield 373 mg (73%, method I), 500 mg (75%, method II), colorless powder, mp 154–156°C.[18] IR spectrum, ν, cm^{-1}: 1648 (CH=CH), 1573 (C=N), 1174 (C–O), 975 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.04 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.42 (2H, d, *J* = 8.5, H Ar); 7.49–7.56 (5H, m, H Ar); 7.84 (2H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.11–8.14 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 110.9 (HC=C<u>H</u>–Het); 127.0 (C Ar); 129.2 (2C Ar); 129.5 (2C Ar); 127.0 (C Ar); 131.3 (2C Ar); 133.0 (C Ar); 136.6 (C Ar); 141.3 (HC=C<u>H</u>–Ar); 168.9 (C-3); 175.1 (C-5). Found, *m*/*z*: 283.0638 $[M+H]^+$. $C_{16}H_{12}ClN_2O$. Calculated, *m*/*z*: 283.0633.

3-Phenyl-5-[(2-thiophen-2-yl)ethenyl]-1,2,4-oxadiazole (5d). Yield 419 mg (66%, method I), 457 mg (72%, method II), colorless powder, mp 101–102°C.[18] IR spectrum, ν, cm^{-1}: 1638 (CH=CH), 1554 (C=N), 1526, 1503 (Ar), 1222 (C–O), 956 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.86 (1H, d, *J* = 16.1, HC=C<u>H</u>–Het); 7.09–7.12 (1H, dd, *J* = 5.0, *J* = 3.7, H Ar); 7.35 (1H, d, *J* = 3.6, H Ar); 7.44 (1H, d, *J* = 5.0, H Ar); 7.49–7.52 (3H, m, H Ar); 7.99 (1H, d, *J* = 16.1, HC=C<u>H</u>–Ar); 8.11–8.13 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 109.1 (HC=C<u>H</u>–Het); 127.1 (C Ar); 127.6 (2C Ar); 128.4 (C Ar); 129.0 (3C Ar); 131.1 (C Ar); 131.3 (C Ar); 135.2 (HC=C<u>H</u>–Ar); 139.8 (C Ar); 168.8 (C-3); 175.1 (C-5). Found, *m*/*z*: 255.0594 $[M+H]^+$. $C_{14}H_{11}N_2OS$. Calculated, *m*/*z*: 255.0587.

3-(3-Nitrophenyl)-5-(2-phenylethenyl)-1,2,4-oxadiazole (5e). Yield 315 mg (43%, method I), 542 mg (74%, method II), light-yellow powder, mp 155–156°C (mp 160–162°C[19]). IR spectrum, ν, cm^{-1}: 1646 (CH=CH), 1623 (Ar), 1579 (C=N), 1536, 1348 (NO_2), 1214 (C–O), 980 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.45–7.48 (3H, m, H Ar); 7.63–7.65 (2H, m, H Ar); 7.70 (1H, t, *J* = 8.0, H Ar); 7.95 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.36–8.39 (1H, m, H Ar); 8.47 (1H, d, *J* = 7.8, H Ar); 9.00–9.01 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 109.8 (HC=C<u>H</u>–Het); 122.7 (C Ar); 125.8 (C Ar); 128.2 (2C Ar); 129.0 (C Ar); 129.3 (C Ar); 130.1 (C Ar); 130.9 (2C Ar); 133.1 (C Ar); 134.3 (HC=C<u>H</u>–Ar);

143.7 (C Ar); 148.7 (C Ar); 167.2 (C-3); 176.1 (C-5). Found, *m*/*z*: 294.0876 $[M+H]^+$. $C_{16}H_{12}N_3O_3$. Calculated, *m*/*z*: 294.0873.

3-(3-Nitrophenyl)-5-[2-(thiophen-2-yl)ethenyl]-1,2,4-oxadiazole (5f). Yield 419 mg (56%, method I), 651 mg (87%, method II), colorless powder, mp 151–152°C.[18] IR spectrum, ν, cm^{-1}: 1640 (CH=CH), 1610 (Ar), 1560, 1513 (C=N), 1537, 1340 (NO_2), 1206 (C–O), 959 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.86 (1H, d, *J* = 16.0, HC=C<u>H</u>–Het); 7.12–7.13 (1H, dd, *J* = 5.0, *J* = 3.7, H Ar); 7.38 (1H, d, *J* = 3.6, H Ar); 7.47 (1H, d, *J* = 5.1, H Ar); 7.70 (1H, d, *J* = 8.0, H Ar); 8.04 (1H, d, *J* = 16.0, HC=C<u>H</u>–Ar); 8.36–8.39 (1H, m, HAr); 8.44–8.46 (1H, m, H Ar); 8.98–8.99 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 108.5 (HC=C<u>H</u>–Het); 122.7 (C Ar); 125.8 (C Ar); 128.6 (C Ar); 129.4 (C Ar); 130.1 (C Ar); 131.6 (C Ar); 133.1 (C Ar); 136.1 (HC=C<u>H</u>–Ar); 139.6 (C Ar); 148.8 (C Ar); 167.2 (C-3); 175.9 (C-5). Found, *m*/*z*: 300.0438 $[M+H]^+$. $C_{14}H_{10}N_3O_3S$. Calculated, *m*/*z*: 300.0437.

5-[2-(3-Chlorophenyl)ethenyl]-3-(3-nitrophenyl)-1,2,4-oxadiazole (5g). Yield 614 mg (75%, method II), light-yellow powder, mp 154–159°C.[18] IR spectrum, ν, cm^{-1}: 1642 (CH=CH), 1623 (Ar), 1556 (C=N), 1541, 1351 (NO_2), 1202, 1188 (C–O), 974 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.38–7.41 (2H, m, H Ar); 7.50–7.52 (1H, m, H Ar); 7.62 (1H, s, H Ar); 7.71 (1H, t, *J* = 8.0, H Ar); 8.04 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.37–8.39 (1H, dd, *J* = 8.2, *J* = 1.3, H Ar); 8.46 (1H, t, *J* = 7.7, H Ar); 8.99–9.00 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 111.3 (HC=C<u>H</u>–Het); 122.8 (C Ar); 125.9 (C Ar); 126.3 (C Ar); 127.9 (C Ar); 128.8 (C Ar); 130.2 (C Ar); 130.5 (C Ar); 130.8 (C Ar); 133.1 (C Ar); 135.4 (C Ar); 136.1 (C Ar); 142.0 (HC=C<u>H</u>–Ar); 148.8 (C Ar); 167.3 (C-3); 175.7 (C-5). Found, *m*/*z*: 328.0486 $[M+H]^+$. $C_{16}H_{11}ClN_3O_3$. Calculated, *m*/*z*: 328.0483.

3-(4-Nitrophenyl)-5-[2-(thiophen-2-yl)ethenyl]-1,2,4-oxadiazole (5h). Yield 598 mg (80%, method II), light-yellow powder, mp 189–190°C.[18] IR spectrum, ν, cm^{-1}: 1633 (CH=CH), 1609 (Ar), 1553 (C=N), 1533, 1526, 1339 (NO_2), 1196 (C–O), 967 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.86 (1H, d, *J* = 16.0, HC=C<u>H</u>–Het); 7.11–7.13 (1H, dd, *J* = 5.0, *J* = 3.7, H Ar); 7.37 (1H, d, *J* = 3.6, H Ar); 7.47 (1H, d, *J* = 5.0, H Ar); 8.02 (1H, d, *J* = 16.0, HC=C<u>H</u>–Ar); 8.30–8.32 (2H, m, H Ar); 8.35–8.37 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 108.5 (HC=C<u>H</u>–Het); 124.2 (2C Ar); 128.5 (2C Ar); 128.6 (C Ar); 129.5 (C Ar); 131.6 (C Ar); 133.1 (C Ar); 136.1 (HC=C<u>H</u>–Ar); 139.6 (C Ar); 149.6 (C Ar); 167.3 (C-3); 176.0 (C-5). Found, *m*/*z*: 300.0442 $[M+H]^+$. $C_{14}H_{10}N_3O_3S$. Calculated, *m*/*z*: 300.0437.

5-[2-(4-Chlorophenyl)ethenyl]-3-(4-nitrophenyl)-1,2,4-oxadiazole (5i). Yield 548 mg (67%, method II), light-yellow powder, mp 194–195°C (mp 195–197°C[19]). IR spectrum, ν, cm^{-1}: 1647 (CH=CH), 1610, 1590 (Ar), 1547 (C=N), 1518, 1347 (NO_2), 1182, 1203 (C–O), 967 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.05 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.43 (2H, d, *J* = 8.5, H Ar); 7.56 (2H, d, *J* = 8.5, H Ar); 7.88 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.32–8.37 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 110.4 (HC=C<u>H</u>–Het); 124.3 (2C Ar); 128.6 (2C Ar); 129.3 (2C Ar); 129.6 (2C Ar); 132.8 (C Ar); 133.0 (C Ar); 137.0 (C Ar); 136.1 (HC=C<u>H</u>–Ar); 149.7 (C Ar); 167.4 (C-3); 175.9 (C-5). Found, *m*/*z*: 328.0490 $[M+H]^+$. $C_{16}H_{11}ClN_3O_3$. Calculated, *m*/*z*: 328.0483.

3-[5-(2-Phenylethenyl)-1,2,4-oxadiazol-3-yl]pyridine (5j). Yield 323 mg (51%, method I), 506 mg (80%, method II), colorless powder, mp 129–130°C.[18] IR spectrum, ν, cm^{-1}: 1645 (CH=CH), 1597, 1578 (Ar), 1535 (C=N), 1186 (C–O), 977 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.45–7.46 (3H, m, H Ar); 7.62–7.65 (3H, m, H Ar); 7.94 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.61 (1H, d, *J* = 8.0, H Ar); 8.81 (1H, d, *J* = 4.0, H Ar); 9.41 (1H, d, *J* = 1.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 109.9 (HC=C<u>H</u>–Het); 124.1 (2C Ar); 124.3 (C Ar); 128.2 (2C Ar); 129.3 (C Ar); 130.9 (2C Ar); 134.4 (HC=C<u>H</u>–Ar); 136.0 (C Ar); 143.7 (C Ar); 147.6 (C Ar); 150.7 (C Ar); 166.5 (C-3); 176.1 (C-5). Found, *m*/*z*: 250.0974 $[M+H]^+$. $C_{15}H_{12}N_3O$. Calculated, *m*/*z*: 250.0975.

3-{5-[2-(2-Chlorophenyl)ethenyl]-1,2,4-oxadiazol-3-yl}-pyridine (5k). Yield 607 mg (86%, method II), colorless powder, mp 194–195°C.[18] IR spectrum, ν, cm^{-1}: 1645 (CH=CH), 1601, 1580 (Ar), 1538 (C=N), 1189 (C–O), 968 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.10 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.33–7.39 (2H, m, H Ar); 7.43–7.49 (2H, m, H Ar); 7.73–7.75 (1H, m, H Ar); 8.33 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.40–8.42 (1H, dt, *J* = 7.9, *J* = 1.8, H Ar); 8.77 (1H, d, *J* = 3.6, H Ar); 9.37 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 112.5 (HC=C<u>H</u>–Het); 123.3 (C Ar); 123.8 (C Ar); 127.4 (C Ar); 127.6 (C Ar); 130.5 (C Ar); 131.6 (C Ar); 132.7 (C Ar); 134.9 (C Ar); 136.2 (C Ar); 139.2 (HC=C<u>H</u>–Ar); 148.9 (C Ar); 152.2 (C Ar); 167.1 (C-3); 175.4 (C-5). Found, *m*/*z*: 284.0588 $[M+H]^+$. $C_{15}H_{11}ClN_3O$. Calculated, *m*/*z*: 284.0585.

3-{5-[2-(4-Chlorophenyl)ethenyl]-1,2,4-oxadiazol-3-yl}-pyridine (5l). Yield 141 mg (20%, method I), 607 mg (86%, method II), colorless powder, mp 184–185°C.[18] IR spectrum, ν, cm^{-1}: 1648 (CH=CH), 1599, 1579 (Ar), 1537 (C=N), 1189 (C–O), 966 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.05 (1H, d, *J* = 16.4, HC=C<u>H</u>–Het); 7.43 (2H, d, *J* = 8.5, H Ar); 7.56 (2H, d, *J* = 8.5, H Ar); 7.63–7.66 (1H, dd, *J* = 7.3, *J* = 4.6, H Ar); 7.88 (1H, d, *J* = 16.4, HC=C<u>H</u>–Ar); 8.60 (1H, d, *J* = 7.6, H Ar); 8.81 (1H, d, *J* = 3.2, H Ar); 9.41 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 110.5 (HC=C<u>H</u>–Het); 123.8 (C Ar); 124.1 (C Ar); 129.3 (2C Ar); 129.6 (2C Ar); 132.8 (C Ar); 135.6 (C Ar); 136.9 (C Ar); 142.1 (HC=C<u>H</u>–Ar); 148.0 (C Ar); 151.3 (C Ar); 166.7 (C-3); 175.7 (C-5). Found, *m*/*z*: 284.0590 $[M+H]^+$. $C_{15}H_{11}ClN_3O$. Calculated, *m*/*z*: 284.0585.

3-{5-[2-(Thiophen-2-yl)ethenyl]-1,2,4-oxadiazol-3-yl}-pyridine (5m). Yield 415 mg (65%, method I), 466 mg (73%, method II), colorless powder, mp 155–157°C.[18] IR spectrum, ν, cm^{-1}: 1633 (CH=CH), 1600, 1580 (Ar), 1554 (C=N), 1201 (C–O), 955 (*trans* CH=CH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.85 (1H, d, *J* = 16.0, HC=C<u>H</u>–Het); 7.12–7.13 (1H, dd, *J* = 4.9, *J* = 3.8, H Ar); 7.38 (1H, d, *J* = 3.5, H Ar); 7.48 (1H, d, *J* = 5.0, H Ar); 7.66–7.67 (1H, dd, *J* = 7.7, *J* = 5.0, H Ar); 8.03 (1H, d, *J* = 16.0, HC=C<u>H</u>–Ar); 8.63 (1H, d, *J* = 7.8, H Ar); 8.81 (1H, d, *J* = 4.2, H Ar); 9.40 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 108.4 (HC=C<u>H</u>–Het); 123.9 (C Ar); 124.2 (C Ar); 128.5 (C Ar);

129.4 (C Ar); 131.5 (C Ar); 135.7 (C Ar); 136.0 (HC=C<u>H</u>–Ar); 139.6 (2C Ar); 147.9 (C Ar); 151.1 (C Ar); 166.5 (C-3); 175.8 (C-5). Found, *m*/*z*: 256.0538 $[M+H]^+$. $C_{13}H_{10}N_3OS$. Calculated, *m*/*z*: 256.0539.

4-{5-[2-(Thiophen-2-yl)ethenyl]-1,2,4-oxadiazol-3-yl}-pyridine (5n). Yield 383 mg (60%, method I), 376 mg (59%, method II), colorless powder, mp 127–128°C.[18] IR spectrum, ν, cm^{-1}: 1625 (CH=CH), 1607, 1581 (Ar), 1554 (C=N), 1210, 1171 (C–O), 961 (*trans* CH=CH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.85 (1H, d, *J* = 16.0, HC=C<u>H</u>–Het); 7.12–7.13 (1H, dd, *J* = 4.9, *J* = 3.8, H Ar); 7.38 (1H, d, *J* = 3.5, H Ar); 7.49 (1H, d, *J* = 5.0, H Ar); 8.04 (1H, d, *J* = 16.0, HC=C<u>H</u>–Ar); 8.21 (2H, d, *J* = 5.5, H Ar); 8.84 (2H, d, *J* = 5.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 108.4 (HC=C<u>H</u>–Het); 121.8 (2C Ar); 128.6 (C Ar); 129.5 (C Ar); 131.7 (C Ar); 135.6 (C Ar); 136.2 (HC=C<u>H</u>–Ar); 139.6 (C Ar); 149.8 (C Ar); 167.0 (C-3); 176.1 (C-5). Found, *m*/*z*: 256.0543 $[M+H]^+$. $C_{13}H_{10}N_3OS$. Calculated, *m*/*z*: 256.0539.

Supplementary information file containing ^1H and ^{13}C NMR and mass spectra of compounds **5a**–**n** is available at the journal website http://link.springer.com/journal/10593

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