

Study on DDQ-promoted synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from acid hydrazides and aldehydes

Karolina Jasiak,^a Agnieszka Kudelko,*^a Wojciech Zieliński,^a and Nikodem Kuźnik^b

^aDepartment of Chemical Organic Technology and Petrochemistry, The Silesian University of Technology, Krzywoustego 4, PL-44100 Gliwice, Poland

^bDepartment of Organic Chemistry, Bioorganic Chemistry and Biotechnology, The Silesian University of Technology, Krzywoustego 4, PL-44100 Gliwice, Poland

Email: Agnieszka.Kudelko@polsl.pl

Dedicated to Prof. Jacek Mlochowski on the occasion of his 80th anniversary

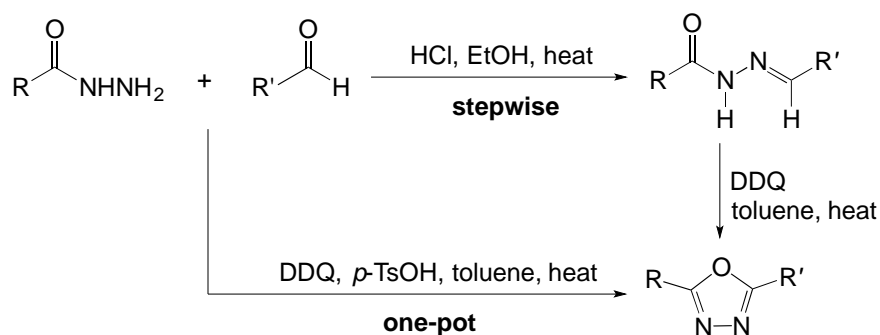
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Abstract

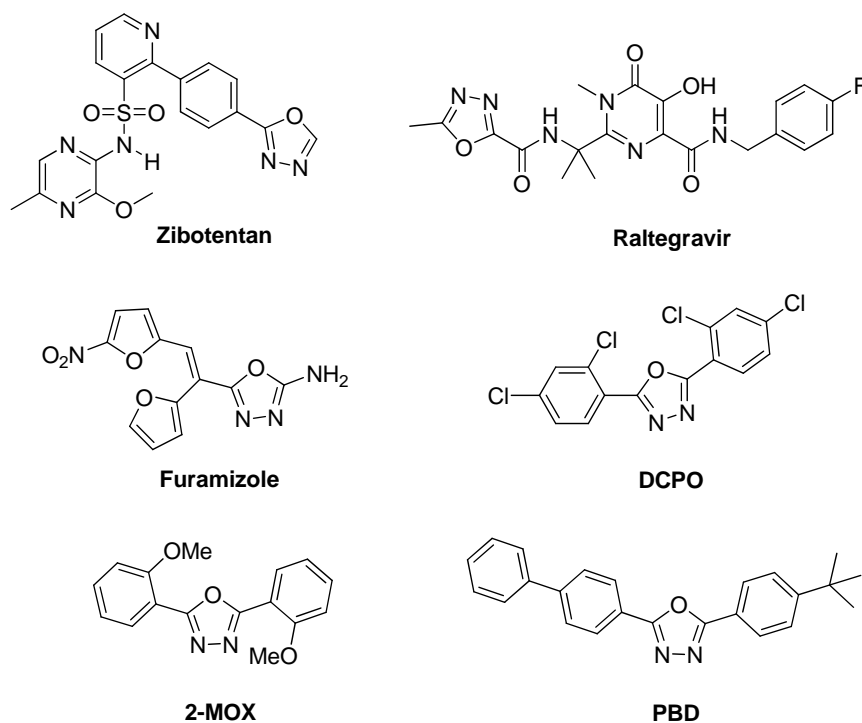
A facile stepwise synthesis of 2,5-disubstituted 1,3,4-oxadiazoles proceeding via oxidative cyclization of *N*-acylhydrazones is reported. The reaction is efficiently promoted by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the desired products mostly in high yields and in relatively short times. The final 1,3,4-oxadiazole derivatives are also synthesized directly from acid hydrazides and aldehydes in a one-pot procedure. The substrate scope and limitations of the reported transformation are discussed in detail.



Keywords: 1,3,4-Oxadiazoles, heterocycles, *N*-acylhydrazones, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), oxidative cyclization, one-pot synthesis

Introduction

1,3,4-Oxadiazoles constitute an important group of five-membered aromatic heterocycles that have attracted significant attention due to their wide range of pharmaceutical and agricultural applications.¹ These heterocyclic compounds have been reported to exhibit various biological activities, including antimicrobial,²⁻³ antiviral,⁴ anticonvulsant,⁵ analgesic,⁶ anti-inflammatory,⁷⁻⁹ antitubercular,¹⁰ antihypertensive¹¹ and antidiabetic properties.¹² They have also been known to act as bioisosteres for carboxylic acids,¹³ esters¹⁴ and amides.¹⁵ These bioisosteric replacements have been utilized in medicinal chemistry to design new drugs. Some compounds possessing the 1,3,4-oxadiazole ring are currently being evaluated in late phase of clinical trials, including Zibotentan as an anticancer agent,¹⁶ Raltegravir as a HIV integrase inhibitor for antiretroviral therapy¹⁷ and Furamizole as an antibiotic drug¹⁸⁻¹⁹ (Scheme 1). Therefore, 1,3,4-oxadiazole derivatives have been successfully applied to numerous drug discovery programs across a broad spectrum of disease areas. Additionally, these heterocyclic molecules have found agricultural application as potential crop protection agents²⁰⁻²² and plant growth regulators.²³ Symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole (DCPO) and its analogues are known insecticides against houseflies, faceflies and hornflies.²⁴ They have been utilized also in the production of heat-resistant polymers, optical brighteners and blowing agents.²⁵⁻²⁸ 2,5-Bis(2-methoxyphenyl)-1,3,4-oxadiazole (2-MOX) has been reported to display strong inhibition for mild steel corrosion in acid media.²⁹ In addition, π -conjugated arrangements containing the electron-deficient 1,3,4-oxadiazole scaffold, such as 2-(4-biphenyl)-5-(4-*tert*-butylphenyl)-1,3,4-oxadiazole (PBD), have attracted considerable interest in the field of material science due to their high photoluminescence quantum efficiency, durability and thermal stability. Therefore, they have been used as electron conducting and hole blocking (ECHB) materials in organic light-emitting diodes, photovoltaic cells and photosensitive materials.³⁰⁻³³



Scheme 1. Structures of some 1,3,4-oxadiazoles used in medicine, agriculture and material science.

The first synthesis of 1,3,4-oxadiazoles was reported by Ainsworth in 1954.³⁴ The most popular method for preparation of these heterocyclic compounds involves oxidative cyclization of *N*-acylhydrazones with various oxidizing agents such as ceric ammonium nitrate,³⁵ potassium permanganate,³⁶ ferric chloride,³⁷ tetravalent lead reagents,³⁸ mercuric oxide/iodine,³⁹ bromine/sodium acetate,⁴⁰ chloramine T⁴¹, hypervalent iodine reagents,⁴²⁻⁴⁷ iodine/hydrogen peroxide⁴⁸ or cross-linked poly[styrene(iodoso diacetate)].⁴⁹ Electrooxidative cyclization of *N*-acylhydrazones have also been reported.⁵⁰ Another common synthetic route comprises dehydrative cyclization of *N,N'*-diacylhydrazines utilizing reagents such as polyphosphoric acid,⁵¹ sulfuric acid,⁵² thionyl chloride,⁵³⁻⁵⁴ phosphorus oxychloride,⁵⁵⁻⁵⁶ phosphorus pentoxide,⁵⁷ triflic anhydride,⁵⁸ boron trifluoride diethyl etherate⁵⁹ and the Burgess reagent.⁶⁰ Besides these methods, 2,5-disubstituted 1,3,4-oxadiazoles have also been synthesized by photoisomerization of 1,2,4-oxadiazoles,⁶¹ heterocyclization of semicarbazide, thiosemicarbazide and selenosemicarbazide derivatives,⁶²⁻⁶⁴ as well as *N*-acylation and subsequent ring opening/closing of starting tetrazoles.⁶⁵⁻⁶⁶ In recent years, one-pot syntheses of these compounds from acid hydrazides with carboxylic acids,⁶⁷ aromatic aldehydes³⁵ or orthoesters⁶⁸⁻⁷⁰ have also been described in the literature.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has attracted significant attention since it was first synthesized by Thiele and Günther in 1906.⁷¹ DDQ is a highly effective oxidizing agent and has been successfully utilized for various organic transformations, including aromatization, deprotection of functional groups, dehydrogenation and potential applications for the formation of carbon-carbon bonds.⁷²⁻⁷⁹

Our previous studies on oxidative cyclization of a narrow group of *N*-aroylhydrazones demonstrated the effectiveness and selectivity of DDQ for the synthesis of 1,3,4-oxadiazoles conjugated via an ethenyl linker to benzene, thiophene and furan rings.⁸⁰ We reported that the formation of such heterocycles could proceed via intermediate *N'*-(arylmethylidene)-3-arylacrylohydrazides or directly from α,β -unsaturated acid hydrazides and aromatic aldehydes in a one-pot procedure. The examined compounds possessed an unsaturated C=C double bond, that was prone to oxidation. The obtained results encouraged us to investigate further the general utility and application of DDQ for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles. The present work was undertaken to explore the possibility of oxidative cyclization of a wide variety of saturated both aromatic and aliphatic *N*-acylhydrazones without an ethenyl linker. This approach seemed to be quite promising due to high reactivity, commercial availability and recyclability of DDQ.

Results and Discussion

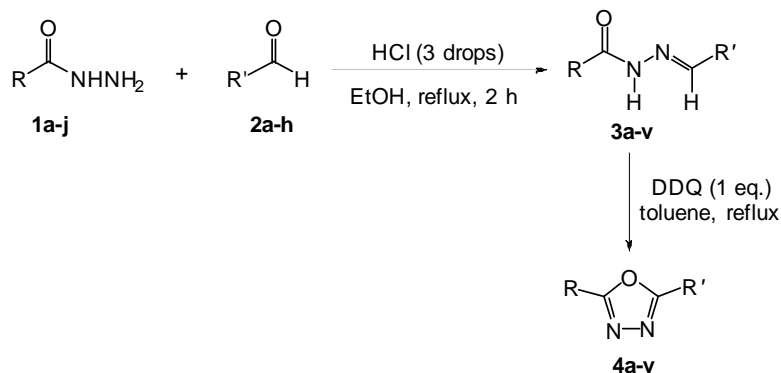
Hydrazides of aromatic and aliphatic carboxylic acids **1a-j** served as precursors for the synthesis of 1,3,4-oxadiazole derivatives. These compounds were obtained from their respective carboxylic acids according to a two-step synthetic procedure described in literature.⁸¹ The starting acids were esterified with methanol in the presence of catalytic H₂SO₄ to form the appropriate methyl esters, which were treated with excess hydrazine hydrate, yielding the desired hydrazides in satisfactory yields (73-89%).

Our studies on the synthesis of the title 1,3,4-oxadiazoles began with a stepwise pathway proceeding via *N*-acylhydrazones. These acyclic intermediates **3a-v** were easily prepared by HCl-catalyzed condensation of acid hydrazides **1a-j** with the selected aromatic and aliphatic aldehydes **2a-h** in ethanol. The obtained *N*-acylhydrazones **3a-s** precipitated immediately after mixing the reagents and were recrystallized from ethanol according to a well-known literature protocol.⁸² The structure of the synthesized compounds **3a-s** were identified by elemental analysis and spectroscopic methods (¹H and ¹³C NMR, MS, UV, IR). However, *N*-acylhydrazones **3t-v** containing aliphatic chains were not isolated from the post-reaction mixture due to the

presence of numerous by-products and problematic separation. Their presence and yields were confirmed by NMR studies.

The resulting series of *N*-acylhydrazones **3a-v** was subjected to heating at reflux with equimolar amounts of DDQ in toluene in order to determine the scope of their oxidative cyclization. To our satisfaction, the reaction exhibited a broad substrate scope, high functional group tolerance and proceeded smoothly to give a wide range of 2,5-disubstituted 1,3,4-oxadiazoles **4a-v**, mostly in good yields (Table 1).

Table 1. Synthesis of *N*-acylhydrazones **3a-v** and 2,5-disubstituted 1,3,4-oxadiazoles **4a-v**



Entry	R	R'	<i>N</i> -Acylhydrazone 3		1,3,4-Oxadiazole 4		
			Yield (%) ^a	Mp (°C)	Yield (%) ^a	Time (h)	Mp (°C)
a	Ph	Ph	85	209-211	77	3	138-139
b	Ph	4-MeO-C ₆ H ₄	94	158-160	92	2	145-146
c	Ph	4-O ₂ N-C ₆ H ₄	79	246-248	70	5	205-206
d	Ph	2-furyl	88	182-183	80	3	101-102
d'	2-furyl	Ph	90	225-226	86	2	101-102
e	Ph	2-thienyl	92	205-206	90	3	117-118
f	Ph	9-anthryl	81	260-262	72	7	145-147
g	Ph	PhCH(CH ₃)	83	188-190	75	5	71-73
h	3-MeO-C ₆ H ₄	2-furyl	90	183-185	85	3	94-96
i	3-MeO-C ₆ H ₄	2-thienyl	93	170-171	91	3	92-94
j	3-MeO-C ₆ H ₄	9-anthryl	84	244-245	76	6	204-206
k	4-MeO-C ₆ H ₄	9-anthryl	86	251-253	79	6	133-135
l	3-Cl-C ₆ H ₄	2-furyl	83	187-189	74	5	120-122
m	3-Cl-C ₆ H ₄	9-anthryl	78	254-256	68	7	152-154
n	4-Cl-C ₆ H ₄	9-anthryl	76	289-290	65	7	233-235
o	4-O ₂ N-C ₆ H ₄	9-anthryl	73	297-300	61	7	238-240
p	2-furyl	2-thienyl	96	211-213	94	2	110-111
q	PhCH ₂	Ph	80	149-151	52	10	108-110
r	PhCH ₂	Et	69	85-86	27	10	-
s	C ₁₅ H ₃₁	Ph	65	93-95	18	10	108-109
t	C ₁₅ H ₃₁	Et	12 ^b	-	traces	20	-
u	C ₆ H ₁₃	Ph	25 ^b	-	traces	20	-
v	C ₆ H ₁₃	Et	10 ^b	-	traces	20	-

^a Isolated yields. ^b Based on NMR study.

It should be mentioned that the great advantage of the methodology using DDQ is the fact that the reduced by-product (DDQ-H₂) could be readily removed by filtration and oxidized with MnO₂ in order to recycle back into DDQ. Our initial investigations of the substrate scope were conducted with *N*-acylhydrazones **3a-c** originating from benzhydrazide (**1a**) and various benzaldehydes. The results shown in Table 1, demonstrated that this methodology displayed excellent compatibility with a variety of functional groups on the benzene ring of the precursor aldehyde. However, *N*-benzoylhydrazones derived from benzaldehydes bearing an electron-donating group, such as the methoxy-containing example **3b**, gave a higher yield of the desired product in comparison to the substrate with an electron-withdrawing group, such as the nitro-containing species **3c**, due to the resonance stabilization involving the methoxy group. These promising results encouraged us to further studies with polycyclic aromatic and heterocyclic aldehydes. 5-Phenyl-1,3,4-oxadiazoles containing furan and thiophene rings **4d-e**, were successfully obtained in high yields (80-90%, Table 1). *N'*-(9-Anthrylmethylene)benzhydrazide (**3f**) also reacted smoothly under the typical reaction conditions to afford the desired product **4f** in 72% yield.

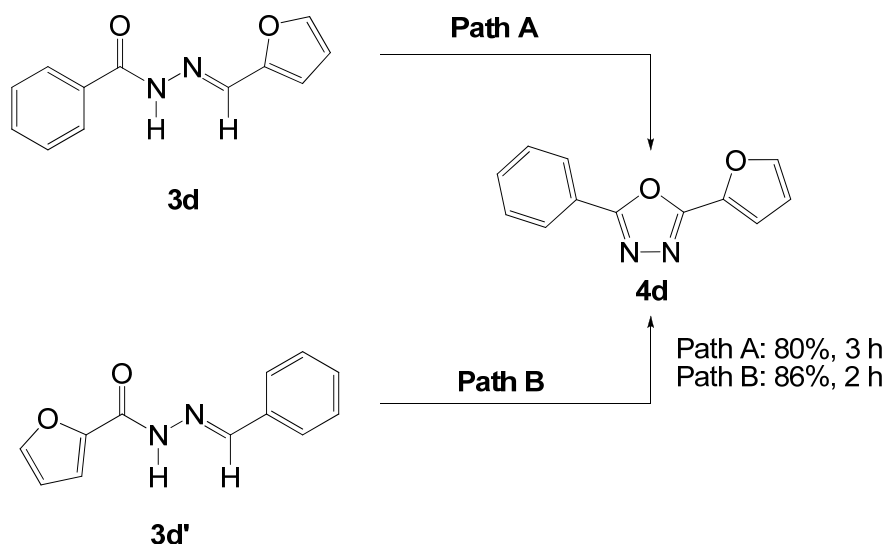
To explore the generality and scope of this reaction further, we tested various *N*-benzoylhydrazones **3h-o** derived from *meta*- and *para*-substituted benzhydrazides possessing different groups such as OMe, NO₂, Cl. All these substrates **3h-o** underwent oxidative cyclization to give the corresponding 1,3,4-oxadiazoles **4h-o** in yields ranging from 61 to 91%. We noticed that this synthetic method was also compatible with various substituents on the aromatic ring of the benzhydrazide. However, *N*-benzoylhydrazones substituted with an electron-donating group **3h-k** reacted faster giving higher yields of the final products compared to those bearing an electron-withdrawing group **3l-o**. This observation in the trend of yields is due to the fact that an electron-donating substituent stabilizes the oxygen-centred radical formed in the reaction of an *N*-acylhydrazone with DDQ.

This methodology was also successful for *N*-furoylhydrazones **3d',p** derived from 2-furancarbohydrazide (**1f**). These substrates **3d',p** were smoothly converted into the corresponding products **4d',p** in high yields (86-94%, Table 1). The best result was obtained in the reaction conducted with *N'*-(2-thienylmethylene)-2-furancarbohydrazide (**3p**, 94%) due to the fact that heterocyclic rings such as furan and thiophene are found to be stable under the reaction conditions. As shown in Table 1, higher yields were observed in the final 1,3,4-oxadiazoles containing heterocycles. A similar trend of yields was also noticed for the formation of the acyclic *N*-acylhydrazones **3a-s**.

Additionally, aliphatic hydrazides and aliphatic aldehydes were also subjected to the protocol in order to investigate the scope of the protocol further. Among the tested compounds were *N*-acylhydrazones **3q-v** derived from hydrazides such as phenylacetic acid hydrazide, heptanoic acid hydrazide or palmitic acid hydrazide and aldehydes such as benzaldehyde or propionaldehyde. Initially, *N'*-benzylidene-2-phenylacetohydrazide (**3q**) was heated with DDQ and afforded the final product **4q** in satisfactory yield (52%, Table 1). However, when the benzene ring of the precursor aldehyde was replaced with an aliphatic chain (*e.g.* R' = Et), the reactivity of the substrate greatly decreased and 2-ethyl-5-(phenylmethyl)-1,3,4-oxadiazole (**4r**) was produced only in low yield (27%). Further, aliphatic hydrazides were also investigated in this reaction. *N*-Acyldhydrazone **3s** originating from palmitic acid hydrazide and benzaldehyde underwent oxidative cyclization to form the corresponding product **4s** in only 18% yield. The results shown in Table 1 demonstrate that this methodology works well when both of the counterparts are aromatic (R = R' = Ar). When both of the counterparts were aliphatic (R = C₁₅H₃₁, C₆H₁₃; R' = Et), the studied DDQ-promoted oxidative cyclization was not successful. The transformations with *N*-acylhydrazones **3t-v** containing aliphatic chains required long reaction times and gave trace amounts of the desired 1,3,4-oxadiazoles **4t-v**. This observation in the trend of

yields is due to the decomposition of these acyclic substrates during the reaction and the formation of numerous unidentified by-products.

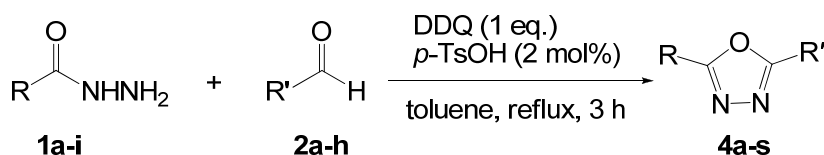
It should be noted that the final products can be synthesized via two alternative pathways, that utilize different substrates. As shown in Scheme 2, 2-(2-furyl)-5-phenyl-1,3,4-oxadiazole (**4d**) was obtained from *N'*-(2-furylmethylene)benzhydrazide (**3d**, Path A) or *N'*-benzylidene-2-furancarbohydrazide (**3d'**, Path B). While Path B gave a slightly better result in terms of both yield and time in comparison to Path A, based on the above observations, we concluded that there is no significant correlation between the type of starting substrate and the reaction yield.



Scheme 2. Two distinct pathways for the formation of 2-(2-furyl)-5-phenyl-1,3,4-oxadiazole (**4d**).

In addition, the synthesis of the final 1,3,4-oxadiazoles **4a-s** could be performed as a one-pot procedure without isolation and purification of the intermediate *N*-acylhydrazones **3a-s**. For this purpose, the starting acid hydrazides **1a-i** were heated at reflux with the appropriate aldehydes **2a-h** in dry toluene, in the presence of catalytic *p*-TsOH and DDQ. To our delight, all substrates underwent smooth oxidative cyclization to form 2,5-disubstituted 1,3,4-oxadiazoles **4a-s**, mostly in good yields (22-95%, Table 2). The one-pot procedure proved to be useful and effective, giving the desired products in yields comparable to results obtained using a two-step reaction sequence. It is also worth noting that the one-pot synthetic methodology saves time, energy and the excessive usage of solvents by eliminating the isolation of the intermediates.

The structures of all the synthesized 1,3,4-oxadiazoles **4a-v** were confirmed by elemental analyses and spectroscopic methods. The ^1H NMR spectroscopic studies proved the successful DDQ-promoted oxidative cyclization of *N*-acylhydrazones **3a-v** by the disappearance of peaks corresponding to CH=N and NH protons. Additionally, we observed the disappearance of signals belonging to CH=N and C=O carbon atoms in the ^{13}C NMR spectra. The diagnostic signals corresponding to two ring carbon atoms C2 and C5 were seen in the range of 157-169 ppm. The chemical shifts of these carbon atoms were dependent on the substituents at the 2- and 5-positions of the 1,3,4-oxadiazole ring.

Table 2. Formation of the title 1,3,4-oxadiazole derivatives **4a-s** directly from acid hydrazides **1a-i** and aldehydes **2a-h**

Product	R	R'	Yield (%) ^a
4a	Ph	Ph	79
4b	Ph	4-MeO-C ₆ H ₄	92
4c	Ph	4-O ₂ N-C ₆ H ₄	71
4d	Ph	2-furyl	80
4d'	2-furyl	Ph	85
4e	Ph	2-thienyl	92
4f	Ph	9-anthryl	74
4g	Ph	PhCH(CH ₃)	76
4h	3-MeO-C ₆ H ₄	2-furyl	87
4i	3-MeO-C ₆ H ₄	2-thienyl	94
4j	3-MeO-C ₆ H ₄	9-anthryl	76
4k	4-MeO-C ₆ H ₄	9-anthryl	80
4l	3-Cl-C ₆ H ₄	2-furyl	76
4m	3-Cl-C ₆ H ₄	9-anthryl	68
4n	4-Cl-C ₆ H ₄	9-anthryl	64
4o	4-O ₂ N-C ₆ H ₄	9-anthryl	61
4p	2-furyl	2-thienyl	95
4q	PhCH ₂	Ph	50
4r	PhCH ₂	Et	28
4s	C ₁₅ H ₃₁	Ph	22

^a Isolated yields.

To confirm the structures of the final products **4**, an X-ray analysis was also performed on a typical example. The molecular structure of 2-(3-chlorophenyl)-5-(2-furyl)-1,3,4-oxadiazole (**4l**), with the atomic numbering scheme, is depicted in Figure 1. There are very few structures of unsymmetrically substituted 1,3,4-oxadiazoles with 2-furyl and phenyl substituents in The Cambridge Crystallographic Database 2015 (Figure 2, JUGZIU,⁸³ LODZUZ,⁸⁴ PODZIR⁸⁵ and for comparison a symmetrical structure NAXDOF⁸⁶). However, all of them have the same opposite, trans conformation of the C-O bonds in the oxadiazole and furan rings. Although, the molecules express a high degree of planarity, not exceeding 13 ° (there is a perpendicular benzene ring in PODZIR due to another azole fragment in the R group), **4l** belongs to the most planar structures within this small family (the plane of the furyl ring forms a 5.20 ° (0.23) angle with the oxadiazole ring, while the latter is twisted out 4.57 ° (0.20) from the plane of the phenyl ring). A weak C-H...N intermolecular interaction (2.748 Å) is found between a furan fragment and another oxadiazole moiety.

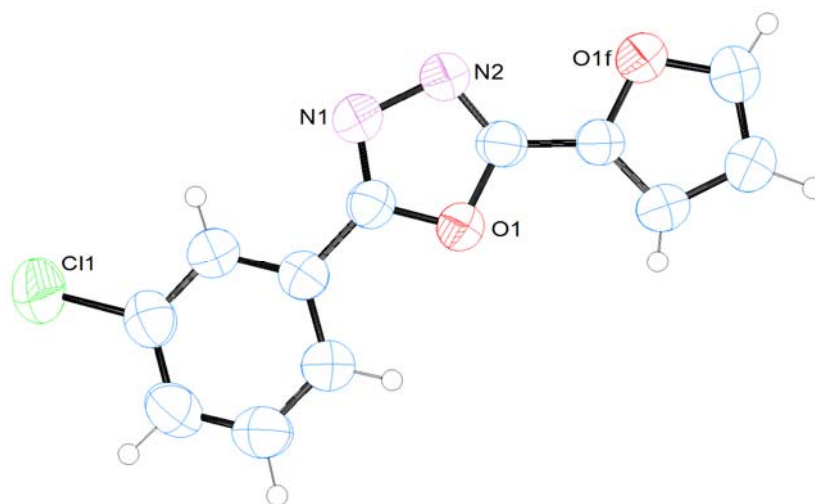


Figure 1. X-Ray structure of 2-(3-chlorophenyl)-5-(2-furyl)-1,3,4-oxadiazole (**41**) with 50% probability ellipsoids.

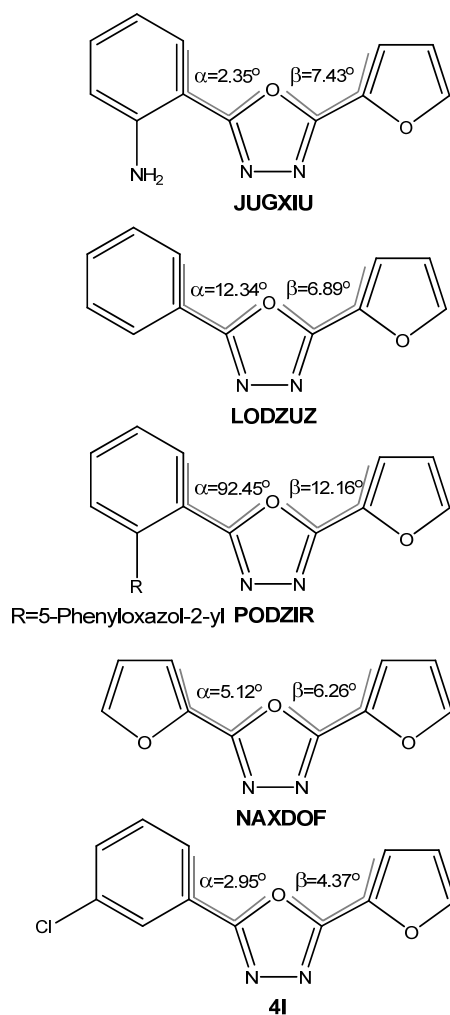


Figure 2. The X-ray structures and the torsion angles for the structurally related 1,3,4-oxadiazoles to **41**.

Conclusion

We have demonstrated the general utility and application of DDQ for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. We have reported that the formation of such heterocycles proceeded smoothly via intermediate *N*-acylhydrazones or directly from acid hydrazides and aldehydes in a one-pot procedure. The studied DDQ-promoted oxidative cyclization was successful especially for the conjugated arrangements. This methodology is a promising alternative for the preparation of a variety of 1,3,4-oxadiazole derivatives due to compatibility with a wide range of substrates, good functional group tolerance, short reaction times, high yields, the use of easy accessible, non-toxic reagents and the possibility of regeneration of the oxidizing agent.

Experimental Section

General. All solvents and reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Stuart SMP3 melting point apparatus without corrections. ^1H and ^{13}C NMR spectra were recorded on an Agilent 400-MR spectrometer using DMSO- d_6 or CDCl_3 as the solvent and TMS as the internal standard. Elemental analyses were performed with a VarioEL analyser. FT-IR spectra were recorded between 4000 and 650 cm^{-1} on an FT-IR Nicolet 6700 apparatus with a Smart iTR accessory. UV-Vis spectra were recorded on a Jasco V-650 spectrophotometer. High-resolution mass spectra were obtained on a Waters ACQUITY UPLC/Xevo G2QTof instrument. Thin-layer chromatography was performed on silica gel 60 F₂₅₄ (Merck) TLC plates using benzene/EtOAc (3:1 v/v) as the mobile phase. Column chromatography was carried out using Merck silica gel (200-300 mesh) and benzene/EtOAc (3:1 v/v) as the eluent.

General procedure for the synthesis of *N*-acylhydrazones 3a-s. *N*-acylhydrazones **3a-s** were prepared by HCl-catalyzed condensation of acid hydrazides **1a-i** with the selected aromatic and aliphatic aldehydes **2a-h** in ethanol according to the procedure described in the literature.⁸² The resulting precipitate was isolated by filtration, washed with EtOH and then recrystallized from EtOH to afford the pure *N*-acylhydrazone **3a-s**.

***N'*-(4-Benzylidenebenzhydrazone) (3a).** White solid, yield 85%, 0.95 g, mp 209-211 °C (lit.:⁸⁷ mp 209-210 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.29.

***N'*-(4-Methoxybenzylidene)benzhydrazone (3b).** Beige solid, yield 94%, 1.20 g, mp 158-160 °C (lit.:⁸⁸ mp 159-160 °C). R_f (benzene/EtOAc, 3:1 v/v) 0.18.

***N'*-(4-Nitrobenzylidene)benzhydrazone (3c).** Yellow solid, yield 79%, 1.06 g, mp 246-248 °C (lit.:⁸⁹ mp 247-248 °C). R_f (benzene/EtOAc, 3:1 v/v) 0.24.

***N'*-(2-Furylmethylene)benzhydrazone (3d).** Beige solid, yield 88%, 0.94 g, mp 182-183 °C (lit.:⁹⁰ mp 183 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.13.

***N'*-(2-Benzylidene-2-furancarbohydrazone) (3d').** White solid, yield 90%, 0.96 g, mp 225-226 °C (lit.:⁹¹ mp 225.8-226.4 °C). R_f (benzene/EtOAc, 3:1 v/v) 0.22.

***N'*-(2-Thienylmethylene)benzhydrazone (3e).** Beige solid, yield 92%, 1.06 g, mp 205-206 °C (lit.:⁹² mp 205-207 °C). R_f (benzene/EtOAc, 3:1 v/v) 0.29.

***N'*-(2-Anthrylmethylene)benzhydrazone (3f).** Yellow solid, yield 81%, 1.31 g, mp 260-262 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.36. IR (ATR, ν_{max} , cm^{-1}): 3203, 3047, 1942, 1603, 1580, 1544, 1519, 1490, 1446, 1409, 1371, 1288, 1186, 1163, 1149, 1018, 1001, 976, 923, 906, 879, 841, 785, 688. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 7.58-7.69 (7H, m, Anth: C2-H, C3-H, C6-H, C7-H, Ph: C3-H, C4-H, C5-H), 8.06 (2H, d, J 8.0 Hz, Ph: C2-H,

C6-H), 8.17 (2H, d, J 8.8 Hz, Anth: C4-H, C5-H), 8.74 (1H, s, Anth: C10-H), 8.79 (2H, d, J 8.8 Hz, Anth: C1-H, C8-H), 9.71 (1H, s, CH=N), 12.13 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ_{C} 124.9, 125.1, 125.5, 125.7, 127.2, 127.6, 128.6, 129.0, 129.6, 130.9, 131.9, 133.4, 147.0, 163.1. UV-Vis (MeOH, λ_{max} , nm): 254.5 ($\epsilon \cdot 10^{-3}$ 32.07 $\text{cm}^{-1} \text{M}^{-1}$). Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}$ (324.38): C, 81.46; H, 4.97; N, 8.64%. Found: C, 81.40; H, 4.99; N, 8.68%. HRMS calcd for $(\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}+\text{H})^+$: 325.1335; found 325.1337.

***N'*-(2-Phenylpropylidene)benzhydrazide (3g)**. White solid, yield 83%, 1.05 g, mp 188-190 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.26. IR (ATR, ν_{max} , cm^{-1}): 3212, 3053, 2967, 2934, 1970, 1602, 1556, 1492, 1453, 1379, 1351, 1288, 1185, 1161, 1136, 1096, 1076, 1043, 1019, 999, 938, 880, 783, 761, 679. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.43 (3H, d, J 6.8 Hz, CH_3), 3.76 (1H, q, J 6.8 Hz, CH), 7.24-7.38 (5H, m, PhCH), 7.47-7.56 (3H, m, Ph: C3-H, C4-H, C5-H), 7.84-7.89 (3H, m, CH=N, Ph: C2-H, C6-H), 11.47 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ_{C} 18.7, 42.1, 126.7, 127.3, 127.4, 128.3, 128.7, 131.5, 133.5, 142.6, 154.4, 162.9. UV-Vis (MeOH, λ_{max} , nm): 201.5 ($\epsilon \cdot 10^{-3}$ 26.93 $\text{cm}^{-1} \text{M}^{-1}$), 252.5 (16.41). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$ (252.31): C, 76.16; H, 6.39; N, 11.10%. Found: C, 76.21; H, 6.42; N, 11.09%. HRMS calcd for $(\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}+\text{H})^+$: 253.1335; found 253.1332.

***N'*-(2-Furylmethylene)-3-methoxybenzhydrazide (3h)**. Beige solid, yield 90%, 1.10 g, mp 183-185 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.15. IR (ATR, ν_{max} , cm^{-1}): 3151, 3053, 2841, 2158, 1600, 1570, 1545, 1475, 1429, 1394, 1346, 1239, 1220, 1195, 1135, 1076, 1062, 1021, 994, 960, 927, 889, 862, 687. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 3.84 (3H, s, OCH_3), 6.65 (1H, dd, J 3.6, 1.6 Hz, Fu: C4-H), 6.94 (1H, d, J 3.6 Hz, Fu: C5-H), 7.15-7.18 (1H, m, PhOCH_3 : C4-H), 7.43-7.50 (3H, m, PhOCH_3 : C2-H, C5-H, C6-H), 7.86 (1H, d, J 1.6 Hz, Fu: C3-H), 8.37 (1H, s, CH=N), 11.76 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ_{C} 55.3, 112.2, 112.8, 113.5, 117.4, 119.7, 129.6, 134.7, 137.6, 145.2, 149.4, 159.2, 162.8. UV-Vis (MeOH, λ_{max} , nm): 202.0 ($\epsilon \cdot 10^{-3}$ 20.81 $\text{cm}^{-1} \text{M}^{-1}$), 210.5 (20.45), 313.0 (29.22). Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$ (244.25): C, 63.93; H, 4.95; N, 11.47%. Found: C, 63.94; H, 4.99; N, 11.50%. HRMS calcd for $(\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3+\text{H})^+$: 245.0921; found 245.0920.

***N'*-(2-Thienylmethylene)-3-methoxybenzhydrazide (3i)**. Beige solid, yield 93%, 1.21 g, mp 170-171 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.26. IR (ATR, ν_{max} , cm^{-1}): 3185, 3040, 2836, 1644, 1584, 1517, 1483, 1466, 1427, 1368, 1329, 1234, 1218, 1190, 1163, 1137, 1082, 1037, 993, 944, 904, 853, 753, 669. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 3.84 (3H, s, OCH_3), 7.14-7.18 (2H, m, PhOCH_3 : C4-H, Th: C4-H), 7.42-7.50 (4H, m, PhOCH_3 : C2-H, C5-H, C6-H, Th: C3-H), 7.68 (1H, d, J 4.0 Hz, Th: C5-H), 8.69 (1H, s, CH=N), 11.77 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ_{C} 55.3, 112.8, 117.4, 119.7, 127.8, 128.9, 129.6, 130.9, 134.8, 139.1, 143.0, 159.2, 162.7. UV-Vis (MeOH, λ_{max} , nm): 201.5 ($\epsilon \cdot 10^{-3}$ 21.78 $\text{cm}^{-1} \text{M}^{-1}$), 212.5 (20.79), 266.5 (8.23), 319.5 (23.45). Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ (260.31): C, 59.98; H, 4.65; N, 10.76%. Found: C, 59.92; H, 4.68; N, 10.80%. HRMS calcd for $(\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}+\text{H})^+$: 261.0692; found 261.0690.

***N'*-(2-Anthrylmethylene)-3-methoxybenzhydrazide (3j)**. Yellow solid, yield 84%, 1.49 g, mp 244-245 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.43. IR (ATR, ν_{max} , cm^{-1}): 3190, 3053, 2961, 2932, 2832, 1932, 16001, 1587, 1467, 1426, 1411, 1367, 1329, 1241, 1184, 1160, 1137, 1076, 1033, 951, 924, 896, 874, 852, 788, 670. ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 3.89 (3H, s, OCH_3), 7.21-7.24 (1H, m, PhOCH_3 : C4-H), 7.53 (1H, t, J 8.0 Hz, PhOCH_3 : C5-H), 7.58-7.69 (6H, m, Anth: C2-H, C3-H, C6-H, C7-H, PhOCH_3 : C2-H, C6-H), 8.17 (2H, d, J 8.8 Hz, Anth: C4-H, C5-H), 8.73 (1H, s, Anth: C10-H), 8.79 (2H, d, J 8.8 Hz, Anth: C1-H, C8-H), 9.70 (1H, s, CH=N), 12.09 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ_{C} 55.4, 113.0, 117.5, 119.8, 124.9, 125.1, 125.4, 125.5, 127.1, 129.0, 129.6, 129.7, 130.9, 134.8, 147.1, 159.3, 162.8. UV-Vis (MeOH, λ_{max} , nm): 212.0 ($\epsilon \cdot 10^{-3}$ 10.31 $\text{cm}^{-1} \text{M}^{-1}$), 255.0 (32.69). Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_2$ (354.40): C, 77.95; H, 5.12; N, 7.90%. Found: C, 77.97; H, 5.08; N, 7.96%. HRMS calcd for $(\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_2+\text{H})^+$: 355.1441; found 355.1442.

***N'*-(2-Anthrylmethylene)-4-methoxybenzhydrazide (3k)**. Yellow solid, yield 86%, 1.52 g, mp 251-253 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.33. IR (ATR, ν_{max} , cm^{-1}): 3171, 3034, 2920, 2850, 1941, 1605, 1560, 1541, 1508, 1458, 1410, 1366, 1308, 1290, 1161, 1151, 1115, 1065, 1027, 1013, 973, 906, 880, 788, 762, 694. ^1H NMR (400

MHz, DMSO-*d*₆): δ_{H} 3.87 (3H, s, OCH₃), 7.14 (2H, d, *J* 8.0 Hz, PhOCH₃: C3-H, C5-H), 7.57-7.68 (4H, m, Anth: C2-H, C3-H, C6-H, C7-H), 8.05 (2H, d, *J* 8.0 Hz, PhOCH₃: C2-H, C6-H), 8.16 (2H, d, *J* 8.8 Hz, Anth: C4-H, C5-H), 8.72 (1H, s, Anth: C10-H), 8.79 (2H, d, *J* 8.8 Hz, Anth: C1-H, C8-H), 9.68 (1H, s, CH=N), 12.01 (1H, s, NH). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ_{C} 55.4, 113.8, 124.9, 125.2, 125.4, 125.5, 127.1, 129.0, 129.5, 129.6, 130.9, 135.9, 146.3, 160.7, 162.1. UV-Vis (MeOH, λ_{max} , nm): 213.0 ($\epsilon \cdot 10^{-3}$ 14.22 cm⁻¹ M⁻¹), 255.0 (61.76). Anal. Calcd for C₂₃H₁₈N₂O₂ (354.40): C, 77.95; H, 5.12; N, 7.90%. Found: C, 77.92; H, 5.15; N, 7.89%. HRMS calcd for (C₂₃H₁₈N₂O₂+H)⁺: 355.1441; found 355.1445.

N'-(2-Furylmethylene)-3-chlorobenzhydrazide (3l). Beige solid, yield 83%, 1.03 g, mp 187-189 °C. *R*_f (benzene/EtOAc, 3:1 v/v) 0.22. IR (ATR, ν_{max} , cm⁻¹): 3149, 3131, 3003, 1623, 1566, 1548, 1477, 1464, 1420, 1395, 1345, 1269, 1223, 1162, 1076, 1024, 999, 974, 891, 818, 803, 787, 657. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 6.66 (1H, dd, *J* 3.6, 1.6 Hz, Fu: C4-H), 6.97 (1H, d, *J* 3.6 Hz, Fu: C5-H), 7.58 (1H, t, *J* 8.0 Hz, PhOCl: C5-H), 7.67 (1H, d, *J* 8.0, PhOCl: C6-H), 7.87-7.90 (2H, m, Fu: C3-H, PhOCl: C4-H), 7.95 (1H, s, PhOCl: C2-H), 8.35 (1H, s, CH=N), 11.88 (1H, s, NH). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ_{C} 112.2, 113.8, 126.4, 127.2, 130.5, 131.5, 133.3, 135.3, 138.0, 145.3, 149.3, 161.6. UV-Vis (MeOH, λ_{max} , nm): 203.5 ($\epsilon \cdot 10^{-3}$ 28.16 cm⁻¹ M⁻¹), 232.5 (8.51), 313.5 (29.76). Anal. Calcd for C₁₂H₉ClN₂O₂ (248.67): C, 57.96; H, 3.65; N, 11.27%. Found: C, 57.99; H, 3.66; N, 11.22%. HRMS calcd for (C₁₂H₉ClN₂O₂+H)⁺: 249.0425; found 249.0428.

N'-(2-Anthrylmethylene)-3-chlorobenzhydrazide (3m). Yellow solid, yield 78%, 1.40 g, mp 254-256 °C; *R*_f (benzene/EtOAc, 3:1 v/v) 0.46. IR (ATR, ν_{max} , cm⁻¹): 3187, 3055, 1644, 1545, 1474, 1442, 1410, 1367, 1341, 1288, 1269, 1162, 1077, 1017, 972, 953, 926, 896, 879, 840, 788, 663, 655. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.58-7.72 (7H, m, Anth: C2-H, C3-H, C6-H, C7-H, PhOCl: C5-H, C6-H), 8.02 (1H, d, *J* 8.0, PhOCl: C4-H), 8.11 (1H, s, PhOCl: C2-H), 8.17 (2H, d, *J* 8.8 Hz, Anth: C4-H, C5-H), 8.74 (1H, s, Anth: C10-H), 8.78 (2H, d, *J* 8.8 Hz, Anth: C1-H, C8-H), 9.70 (1H, s, CH=N), 12.21 (1H, s, NH). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ_{C} 124.8, 124.9, 125.5, 126.5, 127.2, 127.3, 129.0, 129.6, 129.8, 130.6, 130.9, 131.7, 133.4, 135.4, 147.6, 161.6. UV-Vis (MeOH, λ_{max} , nm): 255.0 ($\epsilon \cdot 10^{-3}$ 37.46 cm⁻¹ M⁻¹). Anal. Calcd for C₂₂H₁₅ClN₂O (358.82): C, 73.64; H, 4.21; N, 7.81%. Found: C, 73.65; H, 4.17; N, 7.88%. HRMS calcd for (C₂₂H₁₅ClN₂O+H)⁺: 359.0946; found 359.0949.

N'-(2-Anthrylmethylene)-4-chlorobenzhydrazide (3n). Yellow solid, yield 76%, 1.36 g, mp 289-290 °C. *R*_f (benzene/EtOAc, 3:1 v/v) 0.46. IR (ATR, ν_{max} , cm⁻¹): 3190, 3054, 1913, 1623, 1593, 1544, 1489, 1443, 1397, 1366, 1341, 1273, 1179, 1162, 1147, 1075, 1061, 972, 953, 922, 887, 788, 695. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.58-7.70 (6H, m, Anth: C2-H, C3-H, C6-H, C7-H, PhOCl: C3-H, C5-H), 8.08 (2H, d, *J* 8.0, PhOCl: C2-H, C6-H), 8.17 (2H, d, *J* 8.8 Hz, Anth: C4-H, C5-H), 8.74 (1H, s, Anth: C10-H), 8.77 (2H, d, *J* 8.8 Hz, Anth: C1-H, C8-H), 9.68 (1H, s, CH=N), 12.17 (1H, s, NH). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ_{C} 124.8, 124.9, 125.5, 125.7, 127.1, 128.6, 128.9, 129.5, 129.6, 130.8, 132.0, 136.6, 147.3, 161.9. UV-Vis (MeOH, λ_{max} , nm): 255.0 ($\epsilon \cdot 10^{-3}$ 50.98 cm⁻¹ M⁻¹). Anal. Calcd for C₂₂H₁₅ClN₂O (358.82): C, 73.64; H, 4.21; N, 7.81%. Found: C, 73.61; H, 4.22; N, 7.83%. HRMS calcd for (C₂₂H₁₅ClN₂O+H)⁺: 359.0946; found 359.0944.

N'-(2-Anthrylmethylene)-4-nitrobenzhydrazide (3o). Yellow solid, yield 73%, 1.35 g, mp 297-300 °C. *R*_f (benzene/EtOAc, 3:1 v/v) 0.43. IR (ATR, ν_{max} , cm⁻¹): 3179, 3049, 2159, 1980, 1625, 1602, 1521, 1489, 1446, 1413, 1371, 1339, 1320, 1271, 1190, 1163, 1106, 1077, 1015, 960, 922, 896, 837, 790, 679. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.59-7.70 (4H, m, Anth: C2-H, C3-H, C6-H, C7-H), 8.19 (2H, d, *J* 8.8 Hz, Anth: C4-H, C5-H), 8.28 (2H, d, *J* 8.8, PhNO₂: C2-H, C6-H), 8.45 (2H, d, *J* 8.8, PhNO₂: C3-H, C5-H), 8.74 (1H, s, Anth: C10-H), 8.77 (2H, d, *J* 8.8 Hz, Anth: C1-H, C8-H), 9.70 (1H, s, CH=N), 12.37 (1H, s, NH). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ_{C} 123.7, 124.8, 125.6, 125.8, 127.3, 129.0, 129.2, 129.7, 129.9, 130.9, 139.0, 148.2, 157.7, 161.4. UV-Vis (MeOH, λ_{max} , nm): 254.0 ($\epsilon \cdot 10^{-3}$ 33.44 cm⁻¹ M⁻¹). Anal. Calcd for C₂₂H₁₅N₃O₃ (369.37): C, 71.54; H, 4.09; N, 11.38%. Found: C, 71.50; H, 4.02; N, 11.37%. HRMS calcd for (C₂₂H₁₅N₃O₃+H)⁺: 370.1186; found 370.1184.

***N'*-(2-Thienylmethylene)-2-furancarbohydrazide (3p)**. White solid, yield 96%, 1.06 g, mp 211-213 °C (lit.:⁹³ mp 210-212 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.16.

***N'*-Benzylidene-2-phenylacetohydrazide (3q)**. White solid, yield 80%, 0.95 g, mp 149-151 °C (lit.:⁹⁴ mp 149-150 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.29.

***N'*-Propylidene-2-phenylacetohydrazide (3r)**. White solid, yield 69%, 0.66 g, mp 85-86 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.12.⁹⁵

***N'*-Benzylidenepalmitohydrazide (3s)**. White solid, yield 65%, 1.17 g, mp 93-95 °C (lit.:⁹⁶ mp 93-97 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.35.

General procedure for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles 4a-s. DDQ (0.57 g, 2.50 mmol) was added to a stirred solution of *N*-acylhydrazone **3a-s** (2.50 mmol) in dry toluene (30 mL). The reaction mixture was refluxed until TLC analysis indicated complete consumption of the starting material (3-10 h). After cooling to room temperature, the formed precipitate was filtered off and the filtrate was concentrated on a rotary evaporator. The crude residue was subjected to silica gel column chromatography using benzene/EtOAc (3:1 v/v) as the eluent to yield the pure 2,5-disubstituted 1,3,4-oxadiazole **4a-s**.

General procedure for the one-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles 4a-s. To a stirred solution of acid hydrazide **1a-i** (2.50 mmol) and aldehyde **2a-h** (2.50 mmol) in dry toluene (30 mL) were added *p*-TsOH (0.01 g, 0.05 mmol) and DDQ (0.57 g, 2.50 mmol). The mixture was stirred at reflux until the starting material was completely consumed (monitored by TLC, 3 h) and then cooled down to room temperature. After filtration and evaporation of solvent from the filtrate, the resulting residue was purified by silica gel column chromatography (benzene/EtOAc, 3:1 v/v), affording the pure 1,3,4-oxadiazole derivative **4a-s**.

2,5-Diphenyl-1,3,4-oxadiazole (4a). White solid, yield 79%, 0.44 g, mp 138-139 °C (lit.:⁹⁷ mp 139 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.53.

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (4b). White solid, yield 92%, 0.58 g, mp 145-146 °C (lit.:⁹⁸ mp 146 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.43.

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (4c). Beige solid, yield 71%, 0.42 g, mp 205-206 °C (lit.:⁹⁹ mp 205-207 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.50.

2-(2-Furyl)-5-phenyl-1,3,4-oxadiazole (4d). White solid, yield 80%, 0.45 g, mp 101-102 °C (lit.:³⁸ mp 101 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.45.

2-(2-Furyl)-5-phenyl-1,3,4-oxadiazole (4d'). White solid, yield 85%, 0.41 g, mp 101-102 °C (lit.:³⁸ mp 101 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.45.

2-Phenyl-5-(2-thienyl)-1,3,4-oxadiazole (4e). White solid, yield 92%, 0.53 g, mp 117-118 °C (lit.:³⁸ mp 117.5 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.51.

2-(9-Anthryl)-5-phenyl-1,3,4-oxadiazole (4f). Yellow solid, yield 74%, 0.60 g, mp 145-147 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.64. IR (ATR, ν_{\max} , cm^{-1}): 3050, 3005, 2156, 1940, 1646, 1565, 1549, 1448, 1411, 1370, 1300, 1267, 1222, 1172, 1149, 1071, 1035, 947, 922, 861, 824, 755, 682. ¹H NMR (400 MHz, CDCl₃): δ_{H} 7.50-7.58 (7H, m, Anth: C2-H, C3-H, C6-H, C7-H, Ph: C3-H, C4-H, C5-H), 8.03-8.08 (4H, m, Anth: C1-H, C4-H, C5-H, C8-H), 8.20 (2H, dd, *J* 8.0, 2.0 Hz, Ph: C2-H, C6-H), 8.66 (1H, s, Anth: C10-H). ¹³C NMR (100.6 MHz, CDCl₃): δ_{C} 117.2, 123.5, 123.9, 125.0, 125.7, 127.1, 127.7, 128.7, 129.1, 131.0, 131.4, 131.9, 163.1, 165.8. UV-Vis (MeOH, λ_{\max} , nm): 203.0 ($\epsilon \cdot 10^{-3}$ 23.97 $\text{cm}^{-1} \text{M}^{-1}$), 252.5 (56.23). Anal. Calcd for C₂₂H₁₄N₂O (322.36): C, 81.97; H, 4.38; N, 8.69%. Found: C, 81.99; H, 4.34; N, 8.71%. HRMS calcd for (C₂₂H₁₄N₂O+H)⁺: 323.1179; found 323.1181.

2-Phenyl-5-(1-phenylethyl)-1,3,4-oxadiazole (4g). Beige solid, yield 76%, 0.48 g, mp 71-73 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.46. IR (ATR, ν_{\max} , cm^{-1}): 3029, 2981, 1958, 1610, 1561, 1549, 1491, 1449, 1383, 1269, 1250, 1204, 1190, 1098, 1029, 1015, 960, 921, 796, 773, 714, 684. ¹H NMR (400 MHz, CDCl₃): δ_{H} 1.82 (3H, d, *J* 7.2 Hz, CH₃), 4.43 (1H, q, *J* 7.2 Hz, CH), 7.25-7.30 (1H, m, PhCH), 7.35 (4H, d, *J* 4.4 Hz, PhCH), 7.43-7.49

(3H, m, Ph: C3-H, C4-H, C5-H), 7.99 (2H, dd, *J* 8.0, 2.0 Hz, Ph: C2-H, C6-H). ¹³C NMR (100.6 MHz, CDCl₃): δ_C 19.6, 37.5, 124.0 (two signals merged), 126.8, 127.3, 127.5, 128.9, 131.5, 140.3, 164.9, 168.7. UV-Vis (MeOH, λ_{max}, nm): 203.0 (ε·10⁻³ 31.80 cm⁻¹ M⁻¹), 251.5 (23.32). Anal. Calcd for C₁₆H₁₄N₂O (250.30): C, 76.78; H, 5.64; N, 11.19%. Found: C, 76.83; H, 5.60; N, 11.21%. HRMS calcd for (C₁₆H₁₄N₂O+H)⁺: 251.1179; found 251.1177.

2-(2-Furyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (4h). Beige solid, yield 87%, 0.53 g, mp 94-96 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.37. IR (ATR, ν_{max}, cm⁻¹): 3124, 3105, 3005, 2965, 2833, 2159, 1617, 1602, 1549, 1533, 1451, 1430, 1380, 1326, 1279, 1168, 1159, 1118, 1078, 1066, 972, 964, 903, 844, 791, 681. ¹H NMR (400 MHz, CDCl₃): δ_H 3.90 (3H, s, OCH₃), 6.63 (1H, dd, *J* 3.6, 1.6 Hz, Fu: C4-H), 7.07-7.10 (1H, m, PhOCH₃: C4-H), 7.23 (1H, dd, *J* 3.6, 0.8 Hz, Fu: C5-H), 7.42 (1H, t, *J* 8.0 Hz, PhOCH₃: C5-H), 7.65 (1H, t, *J* 2.0 Hz, PhOCH₃: C2-H), 7.66-7.68 (1H, m, PhOCH₃: C6-H), 7.70 (1H, dd, *J* 1.6, 0.8 Hz, Fu: C3-H). ¹³C NMR (100.6 MHz, CDCl₃): δ_C 55.5, 111.5, 112.2, 114.1, 118.3, 119.3, 124.6, 130.2, 139.4, 145.7, 157.4, 159.9, 163.9. UV-Vis (MeOH, λ_{max}, nm): 202.0 (ε·10⁻³ 31.59 cm⁻¹ M⁻¹), 293.5 (30.68). Anal. Calcd for C₁₃H₁₀N₂O₃ (242.23): C, 64.46; H, 4.16; N, 11.56%. Found: C, 64.50; H, 4.13; N, 11.58%. HRMS calcd for (C₁₃H₁₀N₂O₃+H)⁺: 243.0764; found 243.0769.

2-(3-Methoxyphenyl)-5-(2-thienyl)-1,3,4-oxadiazole (4i). Beige solid, yield 94%, 0.61 g, mp 92-94 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.51. IR (ATR, ν_{max}, cm⁻¹): 3104, 3077, 2941, 2839, 2159, 1615, 1585, 1550, 1462, 1423, 1367, 1343, 1321, 1283, 1219, 1193, 1089, 1031, 965, 937, 887, 867, 837, 779, 653. ¹H NMR (400 MHz, CDCl₃): δ_H 3.90 (3H, s, OCH₃), 7.07-7.10 (1H, m, PhOCH₃: C4-H), 7.19 (1H, dd, *J* 5.2, 4.0 Hz, Th: C4-H), 7.42 (1H, t, *J* 8.0 Hz, PhOCH₃: C5-H), 7.57 (1H, dd, *J* 5.2, 1.2 Hz, Th: C3-H), 7.64 (1H, t, *J* 2.0 Hz, PhOCH₃: C2-H), 7.66-7.69 (1H, m, PhOCH₃: C6-H), 7.83 (1H, dd, *J* 4.0, 1.2 Hz, Th: C5-H). ¹³C NMR (100.6 MHz, CDCl₃): δ_C 55.5, 111.6, 118.1, 119.3, 124.7, 125.2, 128.1, 129.7, 130.1, 130.2, 159.9, 160.8, 163.9. UV-Vis (MeOH, λ_{max}, nm): 201.5 (ε·10⁻³ 33.02 cm⁻¹ M⁻¹), 300.0 (25.63). Anal. Calcd for C₁₃H₁₀N₂O₂S (258.30): C, 60.45; H, 3.90; N, 10.85%. Found: C, 60.51; H, 3.88; N, 10.89%. HRMS calcd for (C₁₃H₁₀N₂O₂S+H)⁺: 259.0536; found 259.0530.

2-(9-Anthryl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (4j). Yellow solid, yield 76%, 0.67 g, mp 204-206 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.58. IR (ATR, ν_{max}, cm⁻¹): 3053, 2955, 2834, 2159, 1959, 1600, 1568, 1541, 1481, 1431, 1359, 1327, 1285, 1267, 1198, 1184, 1162, 1099, 1077, 1018, 951, 924, 844, 785, 683. ¹H NMR (400 MHz, CDCl₃): δ_H 3.89 (3H, s, OCH₃), 7.10-7.13 (1H, m, PhOCH₃: C4-H), 7.44 (1H, t, *J* 8.0 Hz, PhOCH₃: C5-H), 7.50-7.57 (4H, m, Anth: C2-H, C3-H, C6-H, C7-H), 7.74 (1H, t, *J* 2.0 Hz, PhOCH₃: C2-H), 7.75-7.78 (1H, m, PhOCH₃: C6-H), 8.02-8.08 (4H, m, Anth: C1-H, C4-H, C5-H, C8-H), 8.67 (1H, s, Anth: C10-H). ¹³C NMR (100.6 MHz, CDCl₃): δ_C 55.5, 111.6, 117.2, 118.5, 119.5, 125.0, 125.7, 127.7, 128.3, 128.7, 130.3, 131.0, 131.4, 131.5, 160.1, 163.1, 165.7. UV-Vis (MeOH, λ_{max}, nm): 220.5 (ε·10⁻³ 25.87 cm⁻¹ M⁻¹), 253.0 (45.02). Anal. Calcd for C₂₃H₁₆N₂O₂ (352.39): C, 78.39; H, 4.58; N, 7.95%. Found: C, 78.35; H, 4.52; N, 7.98%. HRMS calcd for (C₂₃H₁₆N₂O₂+H)⁺: 353.1285; found 353.1283.

2-(9-Anthryl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (4k). Yellow solid, yield 80%, 0.71 g, mp 133-135 °C. R_f (benzene/EtOAc, 3:1 v/v) 0.45. IR (ATR, ν_{max}, cm⁻¹): 3053, 2935, 2843, 2568, 2158, 2041, 1958, 1612, 1588, 1564, 1542, 1445, 1428, 1409, 1330, 1307, 1201, 1117, 1086, 1004, 961, 923, 886, 784, 700, 676. ¹H NMR (400 MHz, CDCl₃): δ_H 3.88 (3H, s, OCH₃), 7.04 (2H, dd, *J* 8.0, 2.0 Hz, PhOCH₃: C3-H, C5-H), 7.49-7.56 (4H, m, Anth: C2-H, C3-H, C6-H, C7-H), 8.04-8.08 (4H, m, Anth: C1-H, C4-H, C5-H, C8-H), 8.12 (2H, dd, *J* 8.0, 2.0 Hz, PhOCH₃: C2-H, C6-H), 8.65 (1H, s, Anth: C10-H). ¹³C NMR (100.6 MHz, CDCl₃): δ_C 55.5, 114.6, 116.4, 117.5, 125.1, 125.6, 127.6, 128.7, 128.9, 130.1, 131.0, 131.3, 131.4, 162.5, 165.7. UV-Vis (MeOH, λ_{max}, nm): 202.0 (ε·10⁻³ 72.75 cm⁻¹ M⁻¹), 253.0 (56.63). Anal. Calcd for C₂₃H₁₆N₂O₂ (352.39): C, 78.39; H, 4.58; N, 7.95%. Found: C, 78.42; H, 4.59; N, 7.91%. HRMS calcd for (C₂₃H₁₆N₂O₂+H)⁺: 353.1285; found 353.1284.

2-(3-Chlorophenyl)-5-(2-furyl)-1,3,4-oxadiazole (4l). Beige solid, yield 76%, 0.47 g, mp 120-122 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.51. IR (ATR, ν_{max}, cm⁻¹): 3126, 3070, 2177, 1629, 1580, 1548, 1449, 1439, 1351, 1282, 1268, 1225, 1176, 1117, 1099, 1078, 1067, 998, 963, 903, 885, 843, 706, 662. ¹H NMR (400 MHz, CDCl₃):

δ_{H} 6.64 (1H, dd, J 3.6, 1.6 Hz, Fu: C4-H), 7.26 (1H, dd, J 3.6, 0.8 Hz, Fu: C5-H), 7.45-7.54 (2H, m, PhOCl: C5-H, C6-H), 7.64 (1H, dd, J 1.6, 0.8 Hz, Fu: C3-H), 8.02 (1H, dd, J 8.0, 2.0 Hz, PhOCl: C4-H), 8.11 (1H, s, PhOCl: C2-H). ^{13}C NMR (100.6 MHz, CDCl_3): δ_{C} 112.3, 114.4, 125.0, 125.1, 126.9, 130.4, 131.8, 135.2, 139.2, 145.9, 157.7, 162.8. UV-Vis (MeOH, λ_{max} , nm): 201.0 ($\epsilon \cdot 10^{-3}$ 29.53 $\text{cm}^{-1} \text{M}^{-1}$), 235.5 (9.05), 293.5 (29.14). Anal. Calcd for $\text{C}_{12}\text{H}_7\text{ClN}_2\text{O}_2$ (246.65): C, 58.43; H, 2.86; N, 11.36%. Found: C, 58.37; H, 2.90; N, 11.33%. HRMS calcd for $(\text{C}_{12}\text{H}_7\text{ClN}_2\text{O}_2+\text{H})^+$: 247.0269; found 247.0261.

2-(9-Anthryl)-5-(3-chlorophenyl)-1,3,4-oxadiazole (4m). Brown solid, yield 68%, 0.61 g, mp 152-154 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.60. IR (ATR, ν_{max} , cm^{-1}): 3055, 2158, 1958, 1671, 1626, 1538, 1478, 1445, 1364, 1324, 1287, 1263, 1230, 1169, 1144, 1089, 1022, 999, 950, 923, 854, 803, 773. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.46-7.58 (6H, m, Anth: C2-H, C3-H, C6-H, C7-H, PhOCl: C5-H, C6-H), 8.00-8.03 (1H, m, PhOCl: C4-H), 8.07-8.10 (4H, m, Anth: C1-H, C4-H, C5-H, C8-H), 8.18 (1H, t, J 2.0 Hz, PhOCl: C2-H), 8.68 (1H, s, Anth: C10-H). ^{13}C NMR (100.6 MHz, CDCl_3): δ_{C} 116.9, 123.5, 124.9, 125.2, 125.7, 127.1, 127.8, 128.8, 130.5, 131.0, 131.4, 131.6, 131.9, 135.3, 163.4, 164.7. UV-Vis (MeOH, λ_{max} , nm): 202.0 ($\epsilon \cdot 10^{-3}$ 81.36 $\text{cm}^{-1} \text{M}^{-1}$), 253.0 (54.40). Anal. Calcd for $\text{C}_{22}\text{H}_{13}\text{ClN}_2\text{O}$ (356.80): C, 74.06; H, 3.67; N, 7.85%. Found: C, 74.05; H, 3.72; N, 7.87%. HRMS calcd for $(\text{C}_{22}\text{H}_{13}\text{ClN}_2\text{O}+\text{H})^+$: 357.0789; found 357.0791.

2-(9-Anthryl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (4n). Brown solid, yield 64%, 0.57 g, mp 233-235 °C R_f (benzene/EtOAc, 3:1 v/v) 0.63. IR (ATR, ν_{max} , cm^{-1}): 3058, 2924, 2852, 2147, 1958, 1651, 1602, 1583, 1569, 1544, 1483, 1444, 1410, 1363, 1264, 1199, 1180, 1143, 1090, 1007, 967, 923, 888, 785, 693. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.52-7.58 (6H, m, Anth: C2-H, C3-H, C6-H, C7-H, PhOCl: C3-H, C5-H), 8.02 (2H, dd, J 8.0, 2.0 Hz, PhOCl: C2-H, C6-H), 8.08-8.14 (4H, m, Anth: C1-H, C4-H, C5-H, C8-H), 8.69 (1H, s, Anth: C10-H). ^{13}C NMR (100.6 MHz, CDCl_3): δ_{C} 116.9, 122.4, 124.9, 125.7, 127.8, 128.4, 128.8, 129.6, 131.0, 131.4, 131.6, 138.3, 163.3, 165.0. UV-Vis (MeOH, λ_{max} , nm): 202.0 ($\epsilon \cdot 10^{-3}$ 74.67 $\text{cm}^{-1} \text{M}^{-1}$), 253.5 (21.42). Anal. Calcd for $\text{C}_{22}\text{H}_{13}\text{ClN}_2\text{O}$ (356.80): C, 74.06; H, 3.67; N, 7.85%. Found: C, 74.02; H, 3.69; N, 7.80%. HRMS calcd for $(\text{C}_{22}\text{H}_{13}\text{ClN}_2\text{O}+\text{H})^+$: 357.0789; found 357.0786.

2-(9-Anthryl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (4o). Brown solid, yield 61%, 0.56 g, mp 238-240 °C; R_f (benzene/EtOAc, 3:1 v/v) 0.70. IR (ATR, ν_{max} , cm^{-1}): 3049, 2158, 1970, 1716, 1660, 1626, 1610, 1558, 1486, 1442, 1415, 1294, 1265, 1229, 1199, 1175, 1089, 1009, 969, 923, 884, 776, 681. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.47-7.56 (4H, m, Anth: C2-H, C3-H, C6-H, C7-H), 8.00-8.11 (4H, m, Anth: C1-H, C4-H, C5-H, C8-H), 8.32 (2H, d, J 8.8 Hz, PhNO_2 : C2-H, C6-H), 8.41 (2H, d, J 8.8 Hz, PhNO_2 : C3-H, C5-H), 8.71 (1H, s, Anth: C10-H). ^{13}C NMR (100.6 MHz, CDCl_3): δ_{C} 116.3, 124.5, 124.7, 125.8, 128.0, 128.9, 129.1, 129.4, 131.0, 131.4, 132.0, 149.7, 164.1, 165.2. UV-Vis (MeOH, λ_{max} , nm): 202.0 ($\epsilon \cdot 10^{-3}$ 71.08 $\text{cm}^{-1} \text{M}^{-1}$), 253.0 (18.92). Anal. Calcd for $\text{C}_{22}\text{H}_{13}\text{N}_3\text{O}_3$ (367.36): C, 71.93; H, 3.57; N, 11.44%. Found: C, 71.89; H, 3.55; N, 11.49%. HRMS calcd for $(\text{C}_{22}\text{H}_{13}\text{N}_3\text{O}_3+\text{H})^+$: 368.1030; found 368.1029.

2-(2-Furyl)-5-(2-thienyl)-1,3,4-oxadiazole (4p). Beige solid, yield 95%, 0.52 g, mp 110-111 °C (lit.:¹⁰⁰ mp 110 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.47. IR (ATR, ν_{max} , cm^{-1}): 3124, 3104, 3073, 1974, 1633, 1520, 1432, 1424, 1407, 1355, 1237, 1170, 1075, 1065, 1027, 992, 965, 898, 859, 843, 766, 656. ^1H NMR (400 MHz, CDCl_3): δ_{H} 6.62 (1H, dd, J 3.6, 2.0 Hz, Fu: C4-H), 7.19 (1H, dd, J 4.8, 3.6 Hz, Th: C4-H), 7.22 (1H, dd, J 3.6, 0.8 Hz, Fu: C5-H), 7.58 (1H, dd, J 4.8, 1.2 Hz, Th: C3-H), 7.67 (1H, dd, J 2.0, 0.8 Hz, Fu: C3-H), 7.83 (1H, dd, J 3.6, 1.2 Hz, Th: C5-H). ^{13}C NMR (100.6 MHz, CDCl_3): δ_{C} 112.2, 114.2, 124.7, 128.2, 130.0, 130.3, 139.2, 145.7, 156.8, 160.2. UV-Vis (MeOH, λ_{max} , nm): 201.0 ($\epsilon \cdot 10^{-3}$ 5.52 $\text{cm}^{-1} \text{M}^{-1}$), 252.5 (6.73), 307.0 (16.86). Anal. Calcd for $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_2\text{S}$ (218.23): C, 55.04; H, 2.77; N, 12.84%. Found: C, 55.10; H, 2.81; N, 12.82%. HRMS calcd for $(\text{C}_{10}\text{H}_6\text{N}_2\text{O}_2\text{S}+\text{H})^+$: 219.0223; found 219.0222.

2-Phenyl-5-(phenylmethyl)-1,3,4-oxadiazole (4q). Colourless solid, yield 50%, 0.30 g, mp 108-110 °C (lit.:¹⁰¹ mp 109-110 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.41.

2-Ethyl-5-(phenylmethyl)-1,3,4-oxadiazole (4r). Colourless liquid, yield 28%, 0.13 g, R_f (benzene/EtOAc, 3:1 v/v) 0.44. IR (ATR, ν_{\max} , cm^{-1}): 3012, 2990, 2937, 1587, 1560, 1499, 1454, 1422, 1379, 1193, 1169, 1081, 1033, 975, 961, 800, 725, 696. ^1H NMR (400 MHz, CDCl_3): δ_{H} 1.21 (3H, t, J 7.6 Hz, CH_3), 2.80 (2H, q, J 7.6 Hz, CH_2), 4.25 (2H, s, CH_2), 7.22-7.36 (5H, m, Ph). ^{13}C NMR (100.6 MHz, CDCl_3): δ_{C} 11.0, 19.1, 31.3, 127.7, 129.3, 129.5, 135.4, 165.7, 168.4. UV-Vis (MeOH, λ_{\max} , nm): 207.0 ($\epsilon \cdot 10^{-3}$ 12.69 $\text{cm}^{-1} \text{M}^{-1}$). Anal. calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ (188.23): C, 70.19; H, 6.43; N, 14.88; Found: C, 70.23; H, 6.41; N, 14.82. HRMS calcd for $(\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}+\text{H})^+$: 189.1022; found 189.1026.

2-Pentadecyl-5-phenyl-1,3,4-oxadiazole (4s). White solid, yield 22%, 0.20 g, mp 108-109 °C (lit.¹⁰² mp 107-109 °C); R_f (benzene/EtOAc, 3:1 v/v) 0.56.

X-ray single crystal measurement. Measurements of the diffraction intensities were performed on a KUMA KM4 four-circle diffractometer, $\text{MoK}\alpha$ radiation, $\omega/2\theta$ scan mode, θ range 2.77-20.00°. Crystallographic data for **4l** were deposited with the Cambridge Crystallographic Data Centre as supplementary publications number: CCDC 1470234. A complete listing of the atomic coordinates of x, y, and z can be obtained free of charge, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+int) 44-1223 336 033; e-mail: deposit@ccdc.cam.ac.uk], upon quoting the depository numbers, names of the authors and the journal citation.

Crystal data for compound 4l. The crystal chosen for X-ray analysis, obtained from recrystallization from chloroform, was a clear yellow block with the approximate dimensions of 0.8×0.6×0.3 mm. $\text{C}_{12}\text{H}_7\text{ClN}_2\text{O}_2$ (246.65 g mol^{-1}) crystallizes in the monoclinic system, space group $\text{P}2_1/\text{n}$, with $a=9.0212(18)$, $b=7.6689(15)$, $c=16.124(3)$ Å, $\beta=101.95(3)^\circ$, $V=1091.3(4)$ Å³, $Z=4$, $\mu(\text{MoK}\alpha)=0.339$ mm^{-1} , and $D_{\text{calcd}}=1.501$ cm^{-3} . A total of 2163 reflections were collected to $2\theta_{\max}=40.00^\circ$ ($h: -8 \rightarrow 8$; $k: 0 \rightarrow 7$; $l: 0 \rightarrow 15$), of which 1015 were unique. In refinements, weights were used according to the scheme $w=1/[\sigma^2(F_o^2)+(0.1451P)^2+0.10P]$, where $P=(F_o^2+2F_c^2)/3$. The refinement of 183 parameters converged to the final agreement factors $R=0.0577$ for 912 reflections with $F_o > 4\sigma(F_o)$ and $R_w=0.1670$, and $S=1.082$ for all observed reflections. The electron density of the largest difference peak was found to be 0.33 $\text{e}\text{\AA}^{-3}$, while that of the largest difference hole was 0.24 $\text{e}\text{\AA}^{-3}$.

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