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Efficient Assembly of Mono- and Bis(1,2,4-oxadiazol-3-yl)furoxan Scaffolds via Tandem Reactions of Furoxanylamidoximes

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A general, facile, highly effective one-pot protocol for the synthesis of new types of heterocyclic systems incorporating mono- and bis(1,2,4-oxadiazol-3-yl)furoxan cores based on the tandem heterocyclization of furoxanylamidoximes with various aliphatic, aromatic, and heterocyclic carboxylic acid chlorides under very mild conditions (Cs_2CO_3,MeCN, 20 °C) h[illegible] been developed. In addition, a solvent-free approach for the (1,2,4-oxadiazol-3-yl)furoxan synthesis by the reaction of furoxanylamidoximes with trimethyl orthoformate catalyzed by $Sc(OTf)_3$ has been achieved. The advantages of step economy and scope make these reactions a powerful tool for assembling heterocyclic scaffolds of general chemistry and biomedical interest.

Introduction

A global trend in modern organic chemistry is the design of molecular systems with various degrees of complexity to maximize the incorporation of useful properties while optimizing cost and efficiency.[1] To solve this problem, it is necessary to create new, highly effective, room-temperature, regioselective one-pot methods for the synthesis of such structures. One-pot reactions involving two or more reactants lead to expedient assembly of molecules of high structural complexity in a convergent and synthetically efficient manner. These processes avoid the isolation and purification of intermediates, maximize the yield of the final product, minimize the waste of solvent and chromatographic stationary phases, and enhance the greenness of the transformations.[2] In particular, one-pot reactions have become an attractive tool in the design of new drug candidates with improved pharmacokinetic profiles by molecular hybridization of different compounds with known pharmacological activity.[3]

Recently,[4] we have developed general, facile, room-temperature method for the preparation of previously unknown heterocyclic systems incorporating 1,2,5-oxadiazole 2-oxide (furoxan) ring and various heterocyclic pharmacophores linked by S- and O-bridges. The furoxan moiety has in recent years been the subject of increased attention, pioneered by Gasco owing to a plethora of interesting biological activities related to the ability of furoxans to release NO.[5] In particular, a series of hybrid structures representing a combination of various pharmacologically active compounds with furoxan ring, potential NO donor, were synthesized.[6] Furthermore, furoxans are of interest as components of energetic formulations due to a positive formation enthalpy and the presence of two oxygen atoms in the ring.[7]

Among other five-membered heterocycles, 1,2,4-oxadiazole derivatives occupy a special place due to the growing importance of this heterocycle for the design of other heterocycles using their peculiar tendency to undergo molecular rearrangements[8] as well as for material construction (polymers, liquid crystals, luminescent materials).[9] However, most numerous applications of 1,2,4-oxadiazoles are in the design of biologically active compounds as bioisosters for amide or ester groups[10] (anti-diabetic,[11] antinflammatory,[12] anti-microbial,[13] anti-tumoral,[14] and neuroprotective[15] agents). These biologically active compounds are, as a rule, hybrid molecules containing, apart from the 1,2,4-oxadiazole ring, some aromatic or heterocyclic moieties linked by various aliphatic or heteroatomic spacers. Recently, 1,2,4-oxadiazoles have received attention as components of energetic structures.[16]

However, hybrid structures incorporating furoxan and 1,2,4-oxadiazole rings are virtually unknown. Only one work was published where 4-amino-3-(1,2,4-oxadiazol-3-yl)furoxan was obtained along with furoxanopyrimidine as a by-product upon treatment of 4-amino-3-(aminohydroxymoyl)furoxan with triethyl orthoformate catalyzed by $BF_3{\cdot}Et_2O$.[17]

There are two most common routes among the known synthetic strategies for the preparation of the 3,5-disubstituted 1,2,4-oxadiazoles **1** and **1'**: (1) [3+2]-cycloaddition of nitriles **2** to nitrile oxides **3** and (2) heterocyclization of *O*-acylamidoximes **4.** The latter

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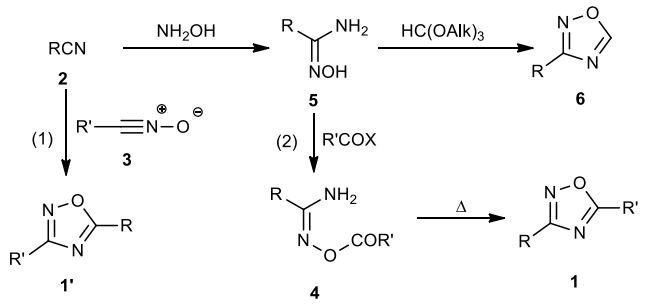
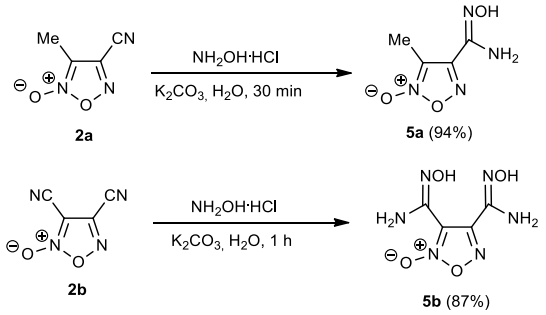
† Electronic Supplementary Information (ESI) available: All spectroscopic data of compounds. CCDC 1059467. For ESI and crystallographic data in CIF see DOI: 10.1039/x0xx00000x



Scheme 1 Various routes to 3-mono- and 3,5-disubstituted 1,2,4-oxadiazoles.



Scheme 2 Synthesis of furoxanylamidoximes **5a,b**.

compounds can be easily prepared by the reaction of nitriles **2** with hydroxylamine followed by reaction of the amidoxime **5** thus formed with activated derivatives of carboxylic acids (chlorides, esters, amides). 3-Monosubstituted 1,2,4-oxadiazoles **6** are prepared by the reaction of amidoximes **5** with trialkyl orthoformates (Scheme 1).

Pathway (1) is seldom applied as nitrile oxides are unstable and are usually prepared *in situ* in the presence of the corresponding nitriles. Recently,[18a] we used this approach for the synthesis of 3-nitro-1,2,4-oxadiazoles *via* [3+2]-cycloaddition of activated nitriles to nitroformonitrile oxide generated *in situ* by the cycloreversion of dinitrofuroxan catalyzed by ionic liquids. The second approach is much more attractive as the nitriles of aliphatic, aromatic, and heterocyclic carboxylic acids are readily accessible.

Here we present the results of our research on the development of general, effective, room-temperature one-pot methods for the preparation of wide series of new hybrid structures: mono- and bis(1,2,4-oxadiazol-3-yl)furoxans by the reaction of furoxanylamidoximes with various carboxylic acid chlorides in the presence of Cs_2CO_3 as well as with trimethyl orthoformate catalyzed by $Sc(OTf)_3$. Our research group has a great experience in the chemistry of furoxans including the synthesis of effective NO-donors.[18]

Results and discussion

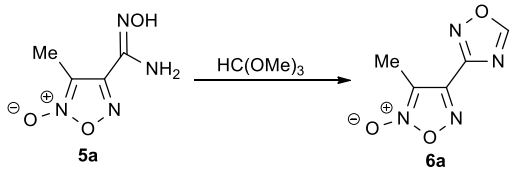
As the initial compounds, we selected two readily accessible cyanofuroxans: 3-methyl-4-cyanofuroxan **2a**[19] and 3,4-dicyanofuroxan **2b**.[20] The initial amidoximes **5a,b** were prepared in high yields by the reaction of nitriles **2a,b** with hydroxylamine hydrochloride in the presence of K_2CO_3. The reaction of hydroxylamine with dinitrile **2b** involved both nitrile groups (Scheme 2).

We began our investigations from the search for optimal conditions for the preparation of (1,2,4-oxadiazol-3-yl)furoxans **6a,b** by the reaction of amidoximes **5a,b** with trimethyl orthoformate. The formation of 1,2,4-oxadiazole ring by similar reactions is usually performed with Lewis acids as catalysts.[21] To optimize the reaction conditions, solvent-free reactions of amidoxime **5a** with trimethyl orthoformate were carried out in the presence of excess reagent (3.2 mol $HC(OMe)_3$ per mol of **5a**) using various Lewis acids catalysts and various temperatures (Table 1). The reaction of substrate **5a** with an excess of trimethyl orthoformate in the absence of any catalyst did not result in the formation of desired product **6a** (Table 1, entry 1). When 10 mol.% of $BF_3{\cdot}OEt_2$ was used as the catalyst at room temperature, no reaction occurred (Table 1, entry 2). The desired product **6a** was formed only at 80 °C in moderate yield (Table 1, entry 3). Compound **6a** was also obtained with the use of $Cu(OTf)_2$ or $PF_2(C_2F_5)_3$, but the yields were still quite low (38% and 19%, respectively, Table 1, entries 4,5). The best catalyst was found to be $Sc(OTf)_3$ (10 mol.%). The reaction was completed in 1 minute at 20 °C and resulted in 4-(1,2,4-oxadiazol-3-yl)-3-methylfuroxan **6a** formed in 86% yield (Table 1, entry 7).

The designed solvent-free protocol was found to be useful for the preparation of 3,4-bis(1,2,4-oxadiazol-3-yl)furoxan **6b**. The $Sc(OTf)_3$-catalyzed reaction of bisamidoxime **5b** with trimethyl orthoformate proceeded fast to give the target product in good yield (Scheme 3).

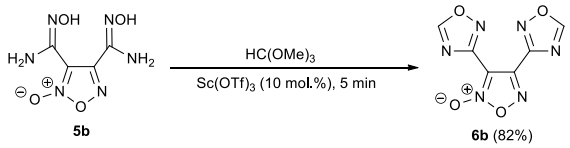
The main efforts of our research were focused on the development of one-pot method for the preparation of previously unknown hybrid molecules containing mono- and bis(1,2,4-oxadiazol-3-yl)furoxan scaffolds with various substituents at C(5) position of the 1,2,4-oxadiazole ring, namely, compounds **1** and **7**. For this aim, we investigated cyclocondensation of furoxanylamidoximes **5a,b** under the action of aliphatic, aromatic and heteroaromatic carboxylic

Table 1 Optimization of the reaction conditions for the formation of 3-methyl-4-(1,2,4-oxadiazol-3-yl)furoxan **6a**.



Entry	Lewis acid	T, °C	Time	Yield,
1	-	100	120 h	-[a]
2	$BF_3{\cdot}OEt_2$ (10 mol.%)	20	120 h	-[a]
3	$BF_3{\cdot}OEt_2$ (10 mol.%)	80	10 min	27
4	$Cu(OTf)_2$ (10 mol.%)	20	5 min	38
5	$PF_2(C_2F_5)_3$ (15 mol.%)	20	3 min	19
6	$Sc(OTf)_3$ (5 mol.%)	20	5 min	63
7	**$Sc(OTf)_3$ (10 mol.%)**	**20**	**1 min**	**86**

[a] No reaction.



Scheme 3 Synthesis of 3,4-bis(1,2,4-oxadiazol-3-yl)furoxan **6b**.

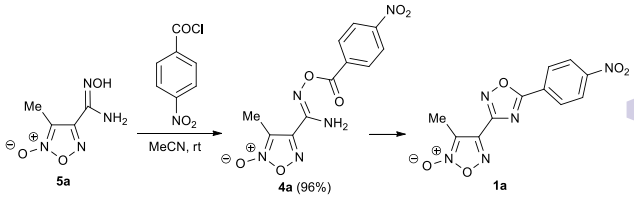
acid chlorides **8a-k** under Lewis acids catalysis or in the presence of bases. The acid chlorides **8** were selected as the most available activated derivatives of carboxylic acids. Two possibilities for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and carboxylic acid chlorides are usually applied. The first approach is regarded as a tandem reaction: a mixture of amidoxime **5** and carboxylic acid chloride is treated with a base followed by *in situ* heating of the formed *O*-acylamidoxime **4** to induce cyclization into 1,2,4-oxadiazole, e.g., by heating in a sealed tube at 175 °C in pyridine,[22] at 130 °C without a solvent,[13e] at 120 °C in DMF[23] or under Lewis acid catalysis.[24] For the cyclization of intermediate **4**, various bases are added, e.g., DBU,[25] TEA,[26] or Py.[27]

The second approach for the construction of 3,5-disubstituted 1,2,4-oxadiazole core involves preliminary isolation of the *O*-acylamidoximes **4** with the subsequent individual cyclization step proceeding in the presence of a condensation reagent. However, almost in all cases, long-term heating is required for the cyclization to proceed, e.g., refluxing in AcOH,[28] in acetone in the presence of K_2CO_3,[29] in dioxane in the presence of KF,[30] or in xylene.[31] Especially good results were obtained with TBAF as the condensation reagent. In this case, the cyclization is carried out without heating and the final products are formed in rather high yields.[32] One example of the 1,2,4-oxadiazole formation upon cyclization of *O*-acylamidoximes was accomplished at room temperature in the presence of aqueous NaOH.[8h] Unfortunately, the last-mentioned cyclization procedure is inapplicable in our case due to high sensitivity of furoxan ring to nucleophilic inorganic bases (e.g., alkali).[33]

To synthesize the desired (1,2,4-oxadiazol-3-yl)furoxans by the reaction of furoxanylamidoximes with carboxylic acid chlorides, we first chose the stepwise protocol. The furoxanylamidoxime **5a** and 4-nitrobenzoyl chloride **8a** were selected as model compounds. Their interaction in MeCN afforded *O*-(4-nitrobenzoyl)amidoxime **4a** in a nearly quantitative yield even in the absence of any base. Initially, several Lewis acids were investigated in the cyclization step (Table 2, entries 1-5), but the desired product **1a** was formed in low yield only with a stoichiometric amount of $PF_2(C_2F_5)_3$ and long-term heating (Table 2, entry 5). A good result was obtained under the action of TBAF, but the yield of the final product was only 54% (Table 2, entry 6). Relying on these results and in view of the known instability of furoxans to strong nucleophiles, we proposed that the use of relatively strong non-nucleophilic bases might be appropriate for the formation of 1,2,4-oxadiazole. Indeed, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) successfully promoted the reaction (Table 2, entry 7). Na_2CO_3 and K_2CO_3 in aprotic solvent (MeCN) were effective only at 50 °C (Table 2, entries 8-11), while the replacement of MeCN by DMF resulted in decomposition of initial compound **4a** (Table 2, entry 12) due to the increased basicity of the reaction medium. Stronger bases such as Rb_2CO_3 and Cs_2CO_3 were efficient at 20 °C (Table 2, entries 13,16); however, at higher temperature or with a lower amount of the base, the yields decreased (Table 2, entries 14,15,17). Hence, Cs_2CO_3 (1.0 equiv) in MeCN at 20 °C for 1 h was the best for the formation of (1,2,4-oxadiazol-3-yl)furoxan **1a** in an excellent yield within a short time and with cost efficiency (Table 2, entry 16).

This unanticipated and highly efficient approach to the (1,2,4-oxadiazol-3-yl)furoxan scaffold assembly encouraged us to examine the one-pot synthesis of compound **1a** from amidoxime **5a** and 4-nitrophenylbenzoyl chloride **8a** in the presence of bases that were sufficiently effective for the cyclization of *O*-acylamidoxime **4a**. The reaction was carried out at various molar ratios of the reactants and at various temperatures. The desired product **1a** was obtained almost in all cases (Table 3, entries 2-5,7-9). However, the best results were again obtained at the presence of Cs_2CO_3, but for one-pot synthesis of compound **1a**, two equivalents of Cs_2CO_3 were necessary, since one equivalent of Cs_2CO_3 was spent for neutralization of HCl formed and the second equivalent promoted the cyclization step, and the reaction was completed in 10 hours (TLC monitoring of the disappearance of intermediate **4a**) (Table 3, entry 7). An increase or decrease

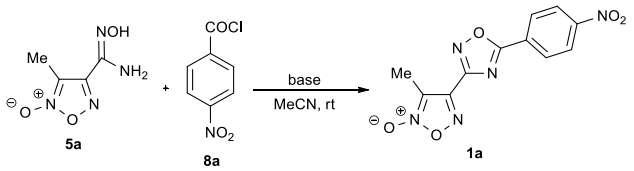
Table 2 Optimization of reaction conditions *via* stepwise protocol.



Entry	Reagent	Solvent	T, °C	Time, h	Yield[a] (%)
1	$Cu(OTf)_2$[b]	MeCN	20	72	-[c]
2	$Sc(OTf)_3$[b]	MeCN	20	72	-[c]
3	$PF_2(C_2F_5)_3$[d]	MeCN	80	96	-[c]
4	$PF_2(C_2F_5)_3$[d]	$[emim]PF_3(C_2F_5)_3$	100	72	Trace[e]
5	$PF_2(C_2F_5)_3$[f]	$[emim]PF_3(C_2F_5)_3$	100	72	15
6	TBAF·3H2O[f]	Dioxane	20	36	54
7	DBU[f]	MeCN	20	1	74
8	Na_2CO_3[f]	MeCN	20	120	-[c]
9	Na_2CO_3[f]	MeCN	50	2	69
10	K_2CO_3[f]	MeCN	20	120	Trace[e]
11	K_2CO_3[f]	MeCN	50	1	76
12	K_2CO_3[f]	DMF	20	72	-[g]
13	Rb_2CO_3[f]	MeCN	20	5	87
14	Rb_2CO_3[f]	MeCN	50	0.25	74
15	Cs_2CO_3[h]	MeCN	20	6	42
16	**Cs_2CO_3[f]**	**MeCN**	**20**	**1**	**96**
17	Cs_2CO_3[f]	MeCN	50	0.25	53

[a] Isolated yields. [b] 10 mol.%. [c] No reaction. [d] 20 mol. %. [e] Determined by ^1H NMR spectroscopy. [f] 100 mol.%. [g] Decomposition of compound **4a** was observed. [h] 50 mol.%.

Table 3 Optimization of reaction conditions *via* one-pot protocol.



Entry	Base (equiv)	T, °C	Time, h	Yield[a] (%)
1	DBU (2)	20	72	Trace
2	DBU (3)	20	24	41
3	K_2CO_3 (2)	50	30	75
4	K_2CO_3 (3)	50	5	69
5	Rb_2CO_3 (2)	50	2	64
6	Cs_2CO_3 (1)	20	48	-
7	**Cs_2CO_3 (2)**	**20**	**10**	**95**
8	Cs_2CO_3 (3)	20	10	91
9	Cs_2CO_3 (2)	50	1	73

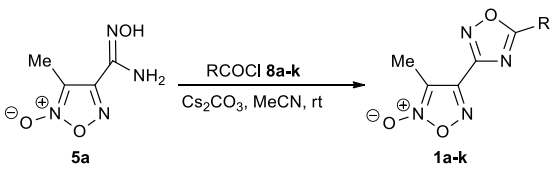
[a] Isolated yields.

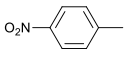
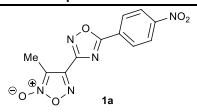
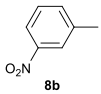
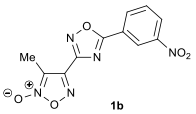
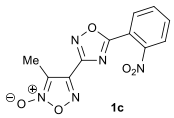
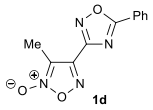
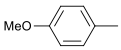
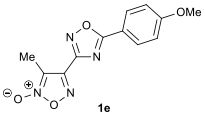
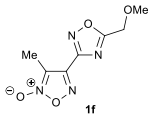
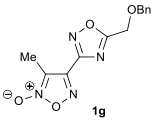
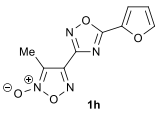
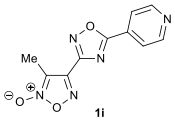
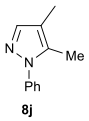
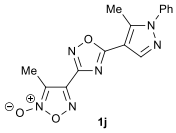
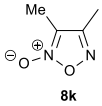
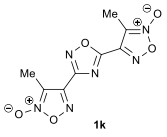
in the amount of Cs_2CO_3 or temperature rise resulted in a decrease in the yield (Table 3, entries 6,8,9). It is worth mentioning that the reaction times for the one-pot process were longer than the overall time of the two steps in the stepwise protocol. This may be due to the fact that under tandem one-pot reaction conditions, the Cs_2CO_3 solubility decreased because of the in situ formation of CsCl.

With the optimized conditions in hand, we estimated the range of substrates for the tandem process, and the results are summarized in Table 4. It was established that reaction times depend on the electronic effects of substituents in the initial carboxylic acid chloride. The reactions with aromatic carboxylic acid chlorides possessing electron-withdrawing groups **8a-c** and 3-methylfuroxan-4-carboxylic acid chloride **8k** (Table 4, entries 1-3, 11) were completed in 10 hours (TLC-monitoring of disappearance of the *O*-acylamidoxime intermediates, since the R_f values of *O*-acylamidoximes and 1,2,4-oxadiazoles differ significantly, see the Experimental section for details). Meanwhile, electron-donating groups in the aromatic ring and aliphatic substituents in acyl chlorides slowed down the reaction, but the yields of the final products were still good (Table 4, entries 5-7). To our delight, heterocyclic carboxylic acid chlorides containing furan, pyridine or pyrazole moieties reacted smoothly under the optimized conditions to give corresponding tandem products **1h-j** in high yields (Table 4, entries 8-10).

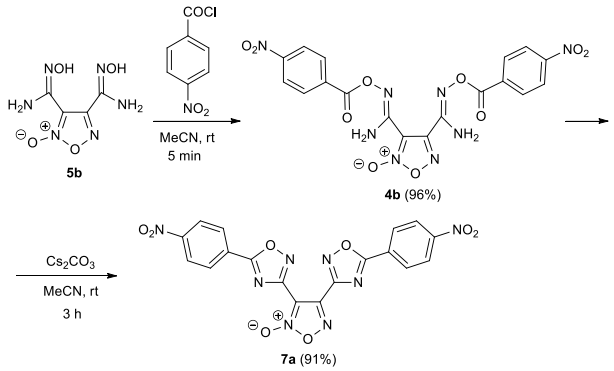
Next, we extended our approach to bis(amidoxime) **5b**. First, we have studied the stepwise protocol for the synthesis of 3,4-bis[5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl]furoxan **7a**. The acylation step proceeded fast with the formation of 3,4-bis(O-4-nitrobenzoyl)amidoxime **4b** in a nearly quantitative yield. The cyclization step was performed with two equivalents of Cs_2CO_3 and resulted in the formation of bis(oxadiazolyl)furoxan **7a** in excellent yield (Scheme 4).

Table 4 Substrate scope for one-pot synthesis of compounds **1a-k**.



Entry	R	Compounds **1a-k**	Time (h)	Yield[a] (%)
1	 8a	 1a	10	95
2	 8b	 1b	10	88
3	 8c	 1c	10	87
4	 8d	 1d	10	92
5	 8e	 1e	18	72
6	 8f	 1f	24	82
7	 8g	 1g	24	78
8	 8h	 1h	20	84
9	 8i	 1i	24	77
10	 8j	 1j	20	86
11	 8k	 1k	10	77

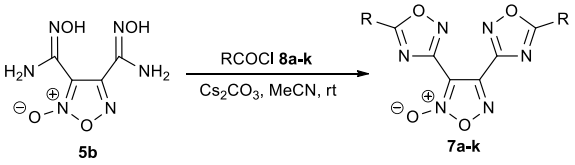
[a] Isolated yields.



Scheme 4 Cyclization of 3,4-bis(O-4-nitrobenzoyl)amidoxime **4b**.

Being encouraged by this result, we proceeded to one-pot synthesis of compounds **7a-k** from bis(amidoxime) **5b** and carboxylic acid chlorides **8a-k** (Table 5). It was found that duration of the reaction between amidoxime **5b** and carboxylic acid chloride **8a** was significantly greater (24 hours) than the duration of the similar reaction of amidoxime **5a** (10 hours, see Table 4) (TLC monitoring of disappearance of the *O*-acylamidoxime intermediates, since the R_f values of *O*-acylamidoximes and 1,2,4-oxadiazoles differ significantly, see Experimental section for details). Evidently, this difference is caused by a special feature of the furoxan ring structure. It is known that the C(3) carbon atom of the furoxan ring has a higher electron density than C(4) due to the resonance influence of the *N*-oxide oxygen atom.[34] An increase in the electron density on C(3) can result in higher electron density on the NH_2 group of intermediate **4b** and, hence, slow down the cyclization. Nevertheless, we succeeded in realization of the tandem one-pot protocol for the synthesis of 3,4-bis(1,2,4-oxadiazol-3-yl)furoxans **7a-k** containing aliphatic, aromatic, and heterocyclic substituents at the C(5) position of the 1,2,4-oxadiazole ring in good to excellent yields (70-89%, Table 5).

Table 5 Substrate scope for one-pot synthesis of compounds **7a-k.**



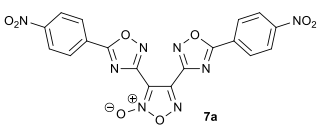
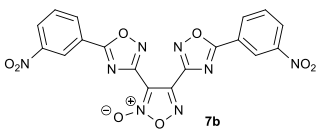
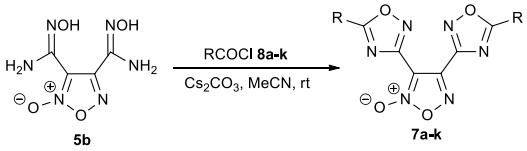
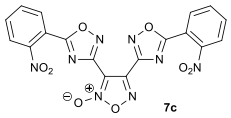
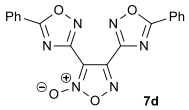
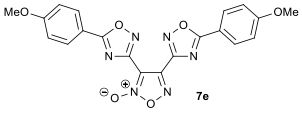
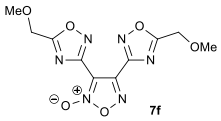
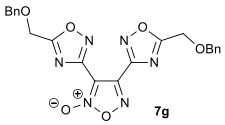
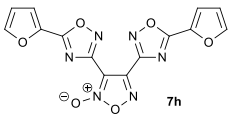
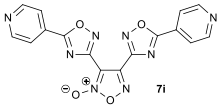
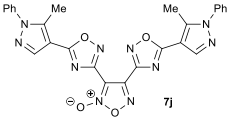
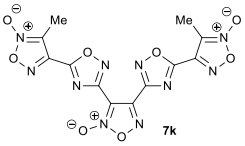
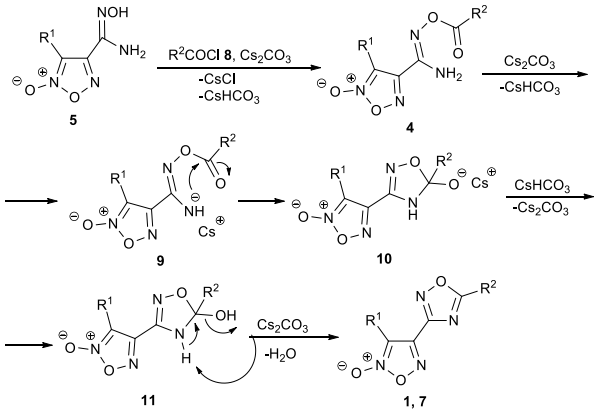
Entry	RCOCl	Compounds **7a-k**	Time (h)	Yield[a] (%)
1	**8a**		24	89
2	**8b**		24	86

Table 5 (*Contd.*)



Entry	RCOCl	Compounds **7a-k**	Time (h)	Yield[a] (%)
3	**8c**		24	75
4	**8d**		24	85
5	**8e**		48	70
6	**8f**		36	77
7	**8g**		36	73
8	**8h**		36	75
9	**8i**		36	74
10	**8j**		36	81
11	**8k**		24	70

[a] Isolated yields.



Scheme 5 Plausible mechanism for the formation of (1,2,4-oxadiazol-3-yl)furoxans.

A plausible mechanism for the Cs_2CO_3-mediated reaction of furoxanylamidoximes **5** with carboxylic acid chlorides **8** is outlined in Scheme 5. It seems that Cs_2CO_3 acts both as a base and a dehydrating reagent. Since Cs_2CO_3 is a strong base, one could expect the amino group deprotonation in *O*-acylamidoxime **4** with subsequent intramolecular nucleophilic cyclization in intermediate **9** to give the cesium salt of dihydro-1,2,4-oxadiazol-5-ol **10**. Cationic metathesis of salt **10** with $CsHCO_3$ results in "free" dihydro-1,2,4-oxadiazol-5-ol **11** and regeneration of Cs_2CO_3, which mediates the final dehydration step.

All of the synthesized (1,2,4-oxadiazol-3-yl)furoxans were characterized by spectral and analytical methods. Finally, we confirmed the structures of the 1,2,4-oxadiazole derivatives by a single-crystal X-ray diffraction study of the representative compound **1d** (Fig. 1).

The **1d** molecule are nearly flat in crystal with the only exceptions of hydrogen atoms of the methyl group: the C(10)C(5)C(4)O(3) and N(3)C(3)C(2)C(1) torsion angles are 5.1(3) and 2.5(3)° correspondingly, while the maximum deviation from the mean-square plane composed by all non-hydrogen atoms is 0.11(2) Å (for the C(9) atom). Being in line with rather short C(2)-C(3) and C(4)-C(5) bonds (1.465(3) and 1.461(3) Å, respectively) demonstrates a significant contribution of π-conjugation into the stabilization of molecule structure. The bond lengths distribution within heterocyclic fragments can be considered as expected for this class of

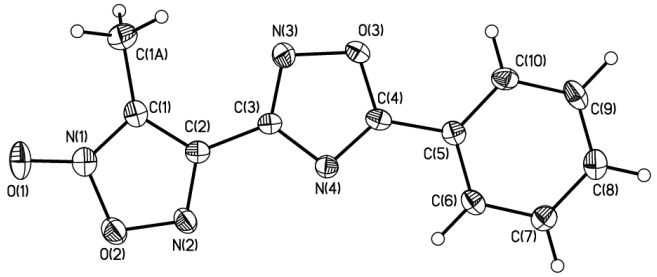


Fig. 1 The general view of the **1d** molecule. Atoms are represented by probability ellipsoids of atomic vibrations (ρ=50%).

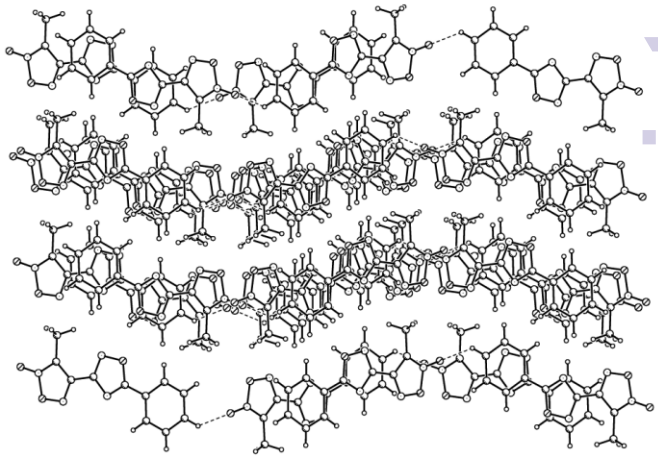


Fig. 2 A fragment of the crystal packing of **1d**, demonstrating layer-type structure. Non-covalent intermolecular O…π and C-H…π interactions are shown by dash lines.

compounds. In crystal molecules are stuck together by shortened O…π contacts between furoxan cycles (O(1)…C(1) 2.956(3) Å) and C-H…π contacts between the benzene ring and the furoxan fragment (C(8)…O(1) 3.310(3), with C-H bond length being normalized on 1.080 Å H(8)…O(1) 2.477 Å, angle C(8)-H(8)…O(1) – 133°) and form layers. The three-dimensional crystal structure is formed by weak H…H interactions between benzene rings (Fig. 2).

Conclusion

In summary, facile, effective, general, room-temperature one-pot methods for the construction of previously unknown heterocyclic systems containing 4-mono- and 3,4-bis(5-R-1,2,4-oxadiazol-3-yl)furoxans by tandem heterocyclization of the furoxanylamidoximes with aliphatic, aromatic, and heteroaromatic carboxylic acid chlorides under very mild conditions have been developed. The target compounds were prepared in good to excellent yields. To the best of our knowledge, our study is the first example of the application of Cs_2CO_3 in the synthesis of 1,2,4-oxadiazole derivatives. In addition, the possibility to obtain 4-mono- and 3,4-bis(1,2,4-oxadiazol-3-yl)furoxans in high yields has been exemplified by the solvent-free reaction of the furoxanylamidoximes with trimethyl orthoformate catalyzed by $Sc(OTf)_3$. The advantages of these new methods are operational simplicity, step economy, and the use of environmentally friendly Cs_2CO_3 and $Sc(OTf)_3$. The developed methods provide a powerful tool for the synthesis of an extensive series of new types of hybrid molecules – (1,2,4-oxadiazol-3-yl)furoxans, including heterocyclic sequences containing five heterocyclic fragments, e.g. a structure consisting of three furoxan rings linked by two 1,2,4-oxadiazole bridges. The study of cytotoxic activity of the synthesized compounds is now in progress.

Experimental Section

General remarks

All reactions were carried out in well-cleaned oven-dried glassware with magnetic stirring. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.13 and 75.47 MHz, respectively) and Bruker AC-200 (200.13 and 50.32 MHz, respectively) and referenced to residual solvent peak. The chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. The IR spectra were recorded on a Bruker "Alpha" spectrometer in the range 400-4000 cm^{-1} (resolution 2 cm^{-1}) as pellets with KBr or as a thin layer. Elemental analyses were performed by the CHN Analyzer Perkin-Elmer 2400. The melting points were determined on Kofler melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F_{254} aluminum sheets. The visualization of the TLC plates was accomplished with a UV light.

High resolution mass spectra were recorded on a Bruker microTOF spectrometer with electrospray ionization (ESI). All measurements were performed in a positive (+MS) ion mode (interface capillary voltage: 4500 V) with scan range *m/z*: 50-3000. External calibration of the mass spectrometer was performed with Electrospray Calibrant Solution (Fluka). A direct syringe injection was used for all analyzed solutions in MeCN (flow rate: 3 μL min^{-1}). Nitrogen was used as nebulizer gas (0.4 bar) and dry gas (4.0 L min^{-1}); interface temperature was set at 180 °C. All spectra were processed by using Bruker DataAnalysis 4.0 software package. MeCN (HPLC grade) for ESI-HRMS experiments was ordered from Merck and used as supplied. All samples for ESI-HRMS experiments were prepared in 1.5 mL Eppendorf tubes. All plastic disposables (Eppendorf tubes and tips) used in sample preparation were washed with MeCN before use.

3-Methyl-4-cyanofuroxan **2a** was prepared according to the method described in[19] and 3,4-dicyanofuroxan **2b** was prepared according to the method described in[20]. Carboxylic acid chlorides were prepared according to a known procedure.[36] MeCN and CH_2Cl_2 were distilled before use over the corresponding drying agents. All other reagents were purchased from Aldrich and used without further purification.

Crystallographic data.

Crystals of **1d** ($C_{11}H_8N_4O_3$, M = 244.21) are monoclinic, space group $P2_1/n$, at 120K: a = 6.5740(13), b = 22.414(5), c = 7.9769(16), β = 113.126(4), V = 1080.9(4) $Å^3$, Z = 4 (Z' = 1), d_{calc} = 1.501 $g \cdot cm^{-3}$, μ(MoKα) = 0.90 cm-1, F(000) = 2664. Intensities of 12165 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072Å, ω-scans, 2θ<56°] and 2625 independent reflections [Rint = 0.0924] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the isotropic-anisotropic approximation. The hydrogen atoms positions were calculated; hydrogen atoms were refined in the isotropic approximation within the riding model. For **1d**, the refinement converged to wR2 = 0.1429 and GOF = 1.032 for all independent reflections (R1 = 0.0625 was calculated against F for 1671 observed reflections with I>2σ(I)). All calculations were performed using SHELXTL PLUS 5.0.[35]

CCDC 1059467 contains the supplementary crystallographic data for 8a. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB21EZ, UK; or deposit@ccdc.cam.ac.uk).

Synthesis of amidoximes 5a,b.

A mixture of furoxancarbonitrile **2a,b** (6.48 mmol), hydroxylamine hydrochloride (0.68 g, 9.72 mmol for substrate **2a** and 1.35 g, 19.44 mmol for substrate **2b**) and K_2CO_3 (1.34 g, 9.72 mmol for substrate **2a** and 2.68 g, 19.44 mmol for substrate **2b**) in water (15 ml) was stirred for 30-60 min at room temperature. The solid formed was filtered off, washed with water and dried in air to afford amidoximes **5a,b**.

N'-Hydroxy-4-methyl-1,2,5-oxadiazole-3-carboximidamide oxide **5a**. White solid. Yield: 0.960 g (94%); mp. 123-125 °C; R_f = 0.35 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 2.26 (3H, s, Me), 5.47 (2H, br. s, NH_2), 10.50 (1H, br. s, NOH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 8.75 (Me), 109.20 (C-3 furoxan), 139.13 (C=NOH), 150.81 (C-4 furoxan). IR (KBr): 3479, 3376, 3000, 2891, 1687, 1660, 1610, 1537, 1462, 1361, 1281, 1176, 1124, 1048, 935, 870, 795, 639 cm^{-1}. Calcd for $C_4H_6N_4O_3$ (%): C, 30.38; H, 3.82; N, 35.43. Found (%): C, 30.31; H, 3.86; N, 35.36.

N^{3},N^{4}-dihydroxy-1,2,5-oxadiazole-3,4-dicarboximidamide 2-oxide **5b**. White solid. Yield: 1.14 g (87%); mp. 102-104 °C. R_f = 0.25 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 6.09 (4H, br. s, $2NH_2$), 10.09 (1H, br. s, NOH), 10.65 (1H, br. s, NOH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 109.25 (C-3 furoxan), 139.10 (C=NOH), 141.80 (C=NOH), 150.88 (C-4 furoxan). IR (KBr): 3464, 3373, 3314, 2872, 1650, 1583, 1539, 1503, 1419, 1363, 1313, 1230, 1100, 1022, 954, 750 cm^{-1}. Calcd for $C_4H_6N_6O_4$ (%): C, 23.77; H, 2.99; N, 41.58. Found (%): C, 23.72; H, 3.07; N, 41.64.

Synthesis of (1,2,4-oxadiazol-3-yl)furoxans 6a,b.

$Sc(OTf)_3$ (0.049 g, 0.1 mmol) was added at room temperature to the stirred suspension of amidoxime **5a,b** (1 mmol) in (0.3 mL for substrate **5a** and 0.6 mL for substrate **5b**). After 1-5 min the reaction mixture became homogenous and H_2O (6 mL) was added. The solid formed was filtered off, washed with water and dried in air to afford 1,2,4-oxadiazoles **6a,b**.

3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole **6a**. White solid. Yield: 144 mg (86%). mp. 103-105 °C. R_f = 0.6 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H: 2.49 (3H, s, Me), 9.04 (1H, s, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C: 8.66, 111.38, 146.50, 159.28, 165.92. IR (KBr): 2923, 1624, 1585, 1546, 1468, 1341, 1272, 1123, 856, 748, 716 cm^{-1}. Calcd for $C_5H_4N_4O_3$ (%): C, 35.72; H, 2.40; N, 33.33. Found (%): C, 35.63; H, 2.47; N, 33.39.

3-[4-(1,2,4-oxadiazol-3-yl)-2-oxido-1,2,5-oxadiazol-3-yl]-1,2,4-oxadiazole **6b**. White solid. Yield: 182 mg (82%). mp. 84-86 °C. R_f = 0.5 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 9.90 (1H, s, CH), 9.96 (1H, s, CH). ^{13}C NMR (50 MHz, DMSO-

d_6) δ_C: 106.14, 145.17, 155.44, 157.50, 168.19, 168.39. IR (KBr): 2931, 1628, 1581, 1542, 1433, 1352, 1276, 1116, 851, 741 cm^{-1}. Calcd for $C_6H_2N_6O_4$ (%): C, 32.44; H, 0.91; N, 37.84. Found (%): C, 32.37; H, 0.96; N, 37.91.

General procedure for the synthesis of *O*-(4-nitrobenzoyl)amidoximes 4a,b.

To the solution of amidoxime **5a,b** (1.0 mmol) in MeCN (3 mL) at stirring and room temperature 4-nitrobenzoyl chloride **8a** (1.0 mmol for substrate **5a** and 2.0 mmol for substrate **5b**) was added. The mixture was stirred for 3-5 min (TLC monitoring, eluent $CHCl_3$: EtOAc = 10 : 1 or 5 : 1), the solid formed was filtered off, washed with water, then with MeCN and dried in air.

4-Methyl-N'-[(4-nitrobenzoyl)oxy]-1,2,5-oxadiazole-3-carboximidamide 5-oxide **4a**. White solid. Yield: 295 mg (96%). mp. 210-212 °C. R_f = 0.1 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 2.36 (3H, s, Me), 7.61 (2H, s, NH_2), 8.32 (2H, d, ^3J = 8.6 Hz, H Ar), 8.48 (2H, d, ^3J = 8.6 Hz, H Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 8.65, 112.45, 124.57, 127.69, 129.72, 147.38, 150.27, 160.28, 174.64. Calcd for $C_{11}H_9N_5O_6$ (%): C, 43.00; H, 2.95; N, 22.80. Found (%): C, 42.92; H, 3.02; N, 22.86.

N'^{3},N'^{4}-Bis[(4-nitrobenzoyl)oxy]-1,2,5-oxadiazole-3,4-dicarboximidamide 2-oxide **4b**. White solid. Yield: 480 mg (96%). mp. 253-255 °C. R_f = 0.05 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 7.61 (4H, s, $2NH_2$), 8.25 (4H, d, ^3J = 6.4 Hz, H Ar), 8.40 (4H, d, ^3J = 6.4 Hz, H Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 108.23, 123.09, 130.93, 130.95, 131.00, 131.02, 133.90, 145.72, 147.43, 149.27, 150.06, 150.08, 161.23, 161.35. Calcd for $C_{18}H_{12}N_8O_{10}$ (%): C, 43.21; H, 2.42; N, 22.40. Found (%): C, 43.15; H, 2.49; N, 22.33.

General procedure for the synthesis of 1,2,4-oxadiazoles 1a-k.

The mixture of amidoxime **5a** (1.0 mmol), carboxylic acid chloride (1.0 mmol) and Cs_2CO_3 (2.0 mmol, 652 mg) in MeCN (3 mL) was stirred for 10-24 h at room temperature. Then H_2O (10 mL) was added. The solid formed was filtered off, washed with water and dried in air to afford 1,2,4-oxadiazoles **1a-e,h-k**. Compounds **1f,g** were extracted with CH_2Cl_2 (3x5 mL), the combined organic phase was washed with H_2O (15 mL) and dried over $MgSO_4$.

3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-5-(4-nitrophenyl)-1,2,4-oxadiazole **1a**. Light yellow solid. Yield: 274 mg (95%). mp. 186-188 °C. R_f = 0.6 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.44 (3H, s, Me), 8.46 (4H, s, H Ar). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.79, 112.59, 124.70, 127.78, 129.83, 147.50, 150.36, 160.40, 174.74. IR (KBr, cm^{-1}): 1619, 1564, 1530, 1472, 1345, 1279, 1129, 855, 747, 711, 639 cm^{-1}. Calcd for $C_{11}H_7N_5O_5$ (%): C, 45.68; H, 2.44; N, 24.22. Found (%): C, 45.61; H, 2.48; N, 24.27.

3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-5-(3-nitrophenyl)-1,2,4-oxadiazole **1b**. Light yellow solid. Yield: 254 mg (88%). mp. 173-175 °C. R_f = 0.6 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.46 (3H, s, Me), 7.98-8.03 (1H, m, H Ar), 8.59-8.64 (2H, m, H Ar), 8.86 (1H, s, H Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 8.76, 112.59, 122.73, 123.95, 128.16, 131.63, 134.19, 147.51, 148.29, 160.28, 174.66. IR (KBr): 1623, 1597, 1562, 1527, 1345, 1130, 1037, 929, 847, 747, 713, 635 cm^{-1}. HRMS (ESI) *m/z* for $C_{11}H_7N_5NaO_5$ $(M + Na)^+$: calcd 312.0339, found 312.0346. Calcd for $C_{11}H_7N_5O_5$ (%): C, 45.68; H, 2.44; N, 24.22. Found (%): C, 45.60; H, 2.51; N, 24.29.

3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-5-(2-nitrophenyl)-1,2,4-oxadiazole **1c**. Light yellow solid. Yield: 251 mg (87%). mp. 121-123 °C. R_f = 0.6 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.41 (3H, s, Me), 8.02-8.05 (2H, m, H Ar), 8.20-8.23 (1H, m, H Ar), 8.27-8.30 (1H, m, H Ar). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.69, 112.61, 116.47, 125.08, 131.85, 134.02, 134.81, 147.32, 148.06, 160.08, 173.54. IR (KBr): 1631, 1617, 1564, 1525, 1492, 1423, 1354, 1095, 1043, 925, 848, 787, 749, 720, 634 cm^{-1}. Calcd for $C_{11}H_7N_5O_5$ (%): C, 45.68; H, 2.44; N, 24.22. Found (%): C, 45.62; H, 2.37; N, 24.16.

3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-5-phenyl-1,2,4-oxadiazole **1d**. White solid. Yield: 224 mg (92%). mp. 162-164 °C. R_f = 0.65 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.43 (3H, s, Me), 7.69-7.76 (3H, m, H-3,4,5 Ph), 8.22 (2H, br. s, H-2,6 Ph). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.59, 112.39, 122.20, 127.93, 129.45, 133.78, 147.45, 159.87, 176.01. IR (KBr): 1624, 1607, 1557, 1494, 1426, 1350, 1124, 1037, 952, 923, 852, 750, 710, 686, 639 cm^{-1}. Calcd for $C_{11}H_8N_4O_3$ (%): C, 54.10; H, 3.30; N, 22.94. Found (%): C, 54.03; H, 3.36; N, 22.99.

5-(4-Methoxyphenyl)-3-(4-methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole **1e**. White solid. Yield 197 mg (72%). mp. 115-117 °C. R_f = 0.55 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.39 (3H, s, Me), 3.87 (3H, s, OMe), 7.18 (2H, d, ^3J = 8.1 Hz, H Ar), 8.11 (2H, d, ^3J = 8.1 Hz, H Ar). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 9.36, 56.24, 113.15, 115.24, 115.62, 130.86, 148.28, 160.54, 164.27, 176.67. IR (KBr): 1608, 1560, 1506, 1429, 1347, 1309, 1257, 1177, 1124, 1109, 1068, 1021, 951, 846, 765, 642 cm^{-1}. Calcd for $C_{12}H_{10}N_4O_4$ (%): C, 52.56; H, 3.68; N, 20.43. Found (%): C, 52.51; H, 3.74; N, 20.37.

5-(Methoxymethyl)-3-(4-methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole **1f**. Yellow oil. Yield 174 mg (82%). R_f = 0.65 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H: 2.47 (3H, s, Me), 3.55 (3H, s, OMe), 4.81 (2H, s, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C: 8.62, 59.64, 64.77, 111.31, 146.64, 159.74, 177.42. IR (thin layer with KBr): 2938, 2834, 1619, 1577, 1483, 1431, 1344, 1197, 1117, 1040, 950, 920, 848, 633 cm^{-1}. Calcd for $C_7H_8N_4O_4$ (%): C, 39.63; H, 3.80; N, 26.41. Found (%): C, 39.56; H, 3.85; N, 26.36.

5-[(Benzyloxy)methyl]-3-(4-methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole **1g**. Yellow oil. R_f = 0.55 ($CHCl_3$: EtOAc = 10 : 1). Yield 225 mg (78%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H: 2.49 (3H, s, Me), 4.75 (2H, s, CH_2OCH_2Ph), 4.88 (2H, s, CH_2OCH_2Ph), 7.39 (s, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C: 8.68, 62.04, 73.74, 111.32, 127.99, 128.30, 128.52, 135.97, 146.68, 159.80, 177.51. IR (thin layer with KBr): 3025, 2886, 2861, 1615, 1573, 1485, 1431, 1345, 1267, 1121, 1098, 1037, 950, 914, 851, 751, 699, 638 cm^{-1}. HRMS (ESI) *m/z* for $C_{13}H_{12}N_4NaO_4$ $(M + Na)^+$: calcd 311.0751, found 311.0745. Calcd for $C_{13}H_{12}N_4O_4$ (%): C, 54.17; H, 4.20; N, 19.44. Found (%): C, 54.11; H, 4.27; N, 19.45.

5-(2-Furyl)-3-(4-methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole **1h**. Yellow solid. Yield 196 mg (84%). mp. 82-84 °C. R_f = 0.45 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.41 (3H, s, Me), 6.92 (1H, br. s, H Het), 7.77 (1H, br. s, H

Het), 8.23 (1H, br. s, H Het). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.79, 112.64, 113.45, 119.16, 138.29, 147.56, 149.28, 159.90, 167.95. IR (KBr): 3149, 3130, 1615, 1543, 1468, 1428, 1344, 1287, 1238, 1164, 1126, 1038, 1025, 978, 899, 851, 778, 635 cm^{-1}. Calcd for $C_9H_6N_4O_4$ (%): C, 46.16; H, 2.58; N, 23.93. Found (%): C, 46.11; H, 2.64; N, 23.98.

4-[3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5-yl]pyridine **1i**. White solid. Yield 189 mg (77%). mp. 107-109 °C. R_f = 0.5 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 2.44 (3H, s, Me), 8.13 (2H, br. s, H Het), 8.93 (2H, br. s, H Het). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.80, 112.61, 121.42, 129.53, 147.55, 151.31, 160.39, 174.86. IR (KBr): 3048, 1625, 1573, 1544, 1493, 1417, 1349, 1282, 1125, 1080, 1036, 951, 930, 844, 760, 695, 637 cm^{-1}. Calcd for $C_{10}H_7N_5O_3$ (%): C, 48.98; H, 2.88; N, 28.56. Found (%): C, 49.04; H, 2.81; N, 28.64.

3-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-5-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-1,2,4-oxadiazole **1j**. Yellow solid. Yield 279 mg (86%). mp. 201-203 °C. R_f = 0.4 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 2.42 (3H, s, Me in furoxan), 2.69 (3H, s, Me in pyrazole), 7.60 (5H, s, Ph), 8.42 (1H, s, CH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 9.34, 12.47, 105.92, 113.21, 125.85, 129.59, 130.03, 138.68, 140.72, 143.27, 148.30, 160.21, 172.82. IR (KBr): 3110, 3080, 1617, 1576, 1499, 1455, 1403, 1379, 1342, 1233, 1119, 1034, 935, 845, 769, 699, 634 cm^{-1}. Calcd for $C_{15}H_{12}N_6O_3$ (%): C, 55.55; H, 3.73; N, 25.91. Found (%): C, 55.61; H, 3.64; N, 25.97.

3,5-Bis(4-methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole **1k**. Yellow solid. Yield 205 mg (77%). mp. 152-154 °C. R_f = 0.6 ($CHCl_3$: EtOAc = 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.43 (3H, s, Me), 2.47 (3H, s, Me). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.58, 8.78, 112.46, 112.67, 145.80, 147.14, 160.14, 166.64. IR (KBr): 1620, 1579, 1499, 1491, 1434, 1385, 1342, 1105, 1043, 995, 951, 926, 850, 766, 670, 632 cm^{-1}. HRMS (ESI) *m/z* for $C_8H_6N_6NaO_5$ (M + Na)$^+$: calcd 289.0292, found 289.0299. Calcd for $C_8H_6N_6O_5$ (%): C, 36.10; H, 2.27; N, 31.57. Found (%): C, 36.02; H, 2.35; N, 31.64.

General procedure for the synthesis of 1,2,4-oxadiazoles 7a-k.

The mixture of amidoxime **5b** (1.0 mmol), carboxylic acid chloride (2.0 mmol) and Cs_2CO_3 (4.0 mmol, 1.304 g) in MeCN (5 mL) was stirred for 24-48 h at room temperature. Then H_2O (10 mL) was added. The solid formed was filtered off, washed with water and dried in air to afford 1,2,4-oxadiazoles **7a-e,h-k**. Compounds **7f,g** were extracted with CH_2Cl_2 (3x5 mL), the combined organic phase was washed with H_2O (15 mL) and dried over $MgSO_4$.

5-(4-Nitrophenyl)-3-{4-[5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7a**. Yellow solid. Yield 413 mg (89%). mp. 211-213 °C. R_f = 0.65 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 8.36-8.47 (8H, m, H Ar). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 112.14, 124.66, 125.03, 127.52, 127.73, 129.79, 130.63, 148.16, 150.32, 150.86, 160.36, 160.68, 172.86, 174.69. IR (KBr): 3109, 3083, 1615, 1570, 1525, 1347, 1269, 869, 854, 734, 719 cm^{-1}. Calcd for $C_{18}H_8N_8O_8$ (%): C, 46.56; H, 1.74; N, 24.13. Found (%): C, 46.49; H, 1.67; N, 24.07.

5-(3-Nitrophenyl)-3-{4-[5-(3-nitrophenyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7b**. Yellow solid. Yield 399 mg (86%). mp. 193-195 °C. R_f = 0.65 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 7.88 (2H, br. s, H Ar), 8.49 (4H, br. s, H Ar), 8.78 (1H, br. s, H Ar), 8.88 (1H, br. s, H Ar). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 105.36, 122.70, 123.88, 123.96, 126.49, 127.84, 129.66, 131.18, 133.67, 133.75, 134.35, 144.90, 148.14, 148.21, 156.98, 159.09, 174.59, 174.79. IR (KBr): 3087, 1633, 1532, 1391, 1349, 1291, 1261, 1127, 1075, 1030, 947, 912, 872, 817, 740, 717, 667 cm^{-1}. HRMS (ESI) *m/z* for $C_{18}H_8N_8NaO_8$ (M + Na)$^+$: calcd 487.0357, found 487.0337. Calcd for $C_{18}H_8N_8O_8$ (%): C, 46.56; H, 1.74; N, 24.13. Found (%): C, 46.62; H, 1.66; N, 24.06.

5-(2-Nitrophenyl)-3-{4-[5-(2-nitrophenyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7c**. Yellow solid. Yield 348 mg (75%). mp. 146-148 °C. R_f = 0.65 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 7.61-7.87 (2H, m, H Ar), 8.02-8.29 (6H, m, H Ar). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 105.60, 115.81, 116.15, 124.59, 125.35, 131.47, 131.85, 132.04, 133.84, 134.02, 134.81, 135.64, 148.04, 149.06, 149.35, 156.78, 162.09, 173.35. IR (KBr): 2924, 1642, 1618, 1537, 1481, 1431, 1362, 1099, 1012, 913, 853, 793, 751, 636 cm^{-1}. Calcd for $C_{18}H_8N_8O_8$ (%): C, 46.56; H, 1.74; N, 24.13. Found (%): C, 46.51; H, 1.69; N, 24.17.

3-[2-Oxido-4-(5-phenyl-1,2,4-oxadiazol-3-yl)-1,2,5-oxadiazol-3-yl]-5-phenyl-1,2,4-oxadiazole **7d**. White solid. Yield 318 mg (85%). mp. 162-164 °C. R_f = 0.6 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 7.66-7.70 (6H, m, H-3,4,5 Ph), 8.11-8.16 (4H, m, H-2,6 Ph). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C: 106.17, 122.31, 122.42, 128.15, 128.32, 129.55, 129.81, 132.32, 134.05, 145.55, 156.92, 158.98, 176.53. IR (KBr): 3066, 1624, 1607, 1559, 1490, 1450, 1392, 1270, 1236, 1051, 1029, 976, 947, 811, 752, 714, 687 cm^{-1}. Calcd for $C_{18}H_{10}N_6O_4$ (%): C, 57.76; H, 2.69; N, 22.45. Found (%): C, 57.83; H, 2.74; N, 22.37.

5-(4-Methoxyphenyl)-3-{4-[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7e**. White solid. Yield 312 mg (72%). mp. 177-179 °C. R_f = 0.55 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 3.85 (6H, s, 2 OCH_3), 7.04 (4H, d, ^3J = 8.0 Hz, H Ar), 8.15 (4H, d, ^3J = 8.0 Hz, H Ar). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 55.50, 56.30, 113.89, 115.18, 115.73, 120.62, 130.21, 130.32, 131.86, 132.14, 133.39, 144.74, 146.84, 151.34, 162.49, 163.27. IR (KBr): 1612, 1572, 1513, 1444, 1331, 1282, 1221, 1184, 1101, 1068, 1024, 853, 772, 657 cm^{-1}. Calcd for $C_{20}H_{14}N_6O_6$ (%): C, 55.30; H, 3.25; N, 19.35. Found (%): C, 55.36; H, 3.34; N, 19.27.

5-(Methoxymethyl)-3-{4-[5-(methoxymethyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7f**. Yellow oil. Yield 239 mg (77%). R_f = 0.7 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.42 (3H, s, OMe), 3.45 (3H, s, OMe), 4.83 (2H, s, OCH_2), 4.88 (2H, s, OCH_2). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 58.85, 64.28, 64.33, 105.81, 145.27, 156.10, 158.18, 177.78, 178.04. IR (thin layer with KBr): 2939, 2830, 1632, 1578, 1451, 1366, 1274, 1197, 1121, 970, 919, 816 cm^{-1}. Calcd for $C_{10}H_{10}N_6O_6$ (%): C, 38.72; H, 3.25; N, 27.09. Found (%): C, 38.79; H, 3.32; N, 27.01.

5-([Benzyloxy]methyl)-3-{4-[5-([benzyloxy]methyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole

7g. White solid. Yield 337 mg (73%). mp. 62-64 °C. R_f = 0.65 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 4.67 (2H, s, CH_2OCH_2Ph), 4.70 (2H, s, CH_2OCH_2Ph), 4.79 (2H, s, CH_2OCH_2Ph), 4.82 (2H, s, CH_2OCH_2Ph), 7.35 (10H, s, 2 Ph). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 61.96, 73.57, 104.95, 128.03, 128.30, 128.52, 135.93, 144.75, 156.32, 158.51, 177.64. Calcd for $C_{22}H_{18}N_6O_6$ (%): C, 57.14; H, 3.92; N, 18.17. Found (%): C, 57.22; H, 3.85; N, 18.09.

5-(2-Furyl)-3-{4-[5-(2-furyl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7h**. Yellow solid. Yield 266 mg (75%). mp. 87-89 °C. R_f = 0.55 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 6.88-6.92 (2H, m, H Het), 7.67-7.79 (2H, m, H Het), 8.20-8.22 (2H, m, H Het). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 112.05, 112.26, 113.45, 119.21, 119.27, 138.07, 138.18, 148.19, 149.22, 149.34, 156.73, 158.71, 167.97, 168.19. IR (KBr): 3127, 1622, 1539, 1523, 1469, 1406, 1378, 1286, 1235, 1216, 1175, 1106, 1073, 1017, 945, 901, 761, 591 cm^{-1}. Calcd for $C_{14}H_6N_6O_6$ (%): C, 47.47; H, 1.71; N, 23.72. Found (%): C, 47.53; H, 1.62; N, 23.81.

4-{3-[2-Oxido-4-(5-pyridin-4-yl-1,2,4-oxadiazol-3-yl)-1,2,5-oxadiazol-3-yl]-1,2,4-oxadiazol-5-yl}pyridine **7i**. White solid. Yield 278 mg (74%). mp. 114-116 °C. R_f = 0.5 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 8.13 (4H, br. s, H Het), 8.95 (4H, br. s, H Het). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 111.13, 120.61, 121.38, 129.48, 130.19, 148.67, 151.27, 151.46, 159.84, 160.39, 172.13, 174.86. Calcd for $C_{16}H_8N_8O_4$ (%): C, 51.07; H, 2.14; N, 29.78. Found (%): C, 50.99; H, 2.22; N, 29.69.

5-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-3-{4-[5-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7j**. Yellow solid. Yield 433 mg (81%). mp. 235-237 °C. R_f = 0.5 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 2.70 (6H, s, CH_3), 7.59-7.67 (10H, m, Ph), 8.48 (2H, s, 2 CH). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 12.47, 12.72, 105.76, 105.92, 112.68, 113.21, 125.64, 125.85, 129.12, 129.59, 130.02, 130.64, 138.32, 138.68, 140.16, 140.72, 143.27, 143.75, 148.62, 160.01, 160.20, 172.81, 173.36. Calcd for $C_{26}H_{18}N_{10}O_4$ (%): C, 58.43; H, 3.39; N, 26.21. Found (%): C, 58.36; H, 3.47; N, 26.30.

5-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-3-{4-[5-(4-methyl-5-oxido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-3-yl]-2-oxido-1,2,5-oxadiazol-3-yl}-1,2,4-oxadiazole **7k.** Yellow solid. Yield 293 mg (70%). mp. 196-198 °C. R_f = 0.7 ($CHCl_3$: EtOAc = 5 : 1). ^{1}H NMR (200 MHz, DMSO-d_6) δ_H: 2.35 (3H, s, Me), 2.43 (3H, s, Me). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C: 8.32, 8.48, 109.25, 112.37, 112.40, 144.63, 145.61, 145.71, 157.12, 158.94, 166.43, 166.88. IR (KBr): 1624, 1586, 1493, 1481, 1431, 1389, 1321, 1115, 1040, 995, 854, 672, 634 cm^{-1}. Calcd for $C_{12}H_6N_{10}O_8$ (%): C, 34.46; H, 1.45; N, 33.49. Found (%): C, 34.39; H, 1.56; N, 33.43.

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