Synthesis D. A. Chaplygin et al. Paper

Divergent Synthesis of Five-Membered Nitrogen Heterocycles via Cascade Reactions of 4-Arylfuroxans

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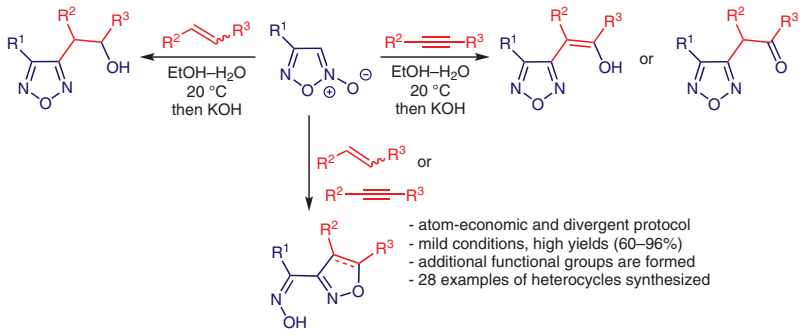

Received: 17.03.2020
Accepted after revision: 07.04.2020
Published online: 05.05.2020
DOI: 10.1055/s-0040-1707393; Art ID: ss-2020-t0146-op

Abstract A novel method for the synthesis of a diverse series of functionally substituted five-membered heterocyclic compounds via atom-economic, regio-, and diastereoselective one-pot reaction cascade was developed. This approach involves a ring opening in 4-arylfuroxans to α-oximinoarylacetonitrile oxides followed by [3+2] cycloaddition to various dipolarophiles to afford multisubstituted isoxazoles and isoxazolines. Subsequent azole–azole rearrangement of (oximino)isoxazolines/-isoxazoles, which can be conducted in a one-pot manner, results into functionally substituted furazans formation. The developed protocol is operationally simple, proceeds in mild conditions and with high yields of target heterocyclic systems. Overall, this study represents a new mode of isoxazole and 1,2,5-oxadiazole functionalization strategy, which is useful in medicinal and materials chemistry.

Key words nitrogen heterocycles, 1,2,5-oxadiazole, rearrangement, cascade reactions, [3+2] cycloaddition

Nitrogen heterocycles are the most frequently occurring structural motifs in various pharmaceuticals and promising drug candidates.[1] Recent analysis of a database of U.S. FDA approved drugs revealed that 59% of clinically used small-molecule medicines incorporate a nitrogen heterocycle subunit.[2] However, the construction of individual pharmaceutical scaffolds using known synthetic methodologies often involves multi-step and energy-consuming procedures or suffers from a lack of reproducibility and scalability. Therefore, a creation of novel step-economy protocols for the assembly of various nitrogen-containing heterocyclic scaffolds remains highly urgent.[3]

Among nitrogen heterocycles isoxazoles and their partially hydrogenated analogues isoxazolines are of special interest due to numerous pharmacological activities displayed by these heterocyclic systems.[4,5] In addition, isoxazole core is a common structural subunit in various pharmaceuticals, such as flucloxacillin, valdecoxib, and leflunomide. Another structural derivatives of isoxazole family – 1,2,5-oxadiazoles (furazans) – constitute an important class of heterocycles that have found a myriad of applications in organic chemistry.[6] Furazans possess a number of useful properties to be part of organic solar cells[7] and exhibit various pharmacological activities.[8] Recently, azofurazan derivative was recommended as a broad-spectrum antibiotic with a desired pharmacological profile.[9] On the other hand, furazan subunit is an essential structural motif in a number of modern energetic materials with excellent performance and a high level of environmental compatibility.[10]

Despite the structural similarity, synthetic routes to the isoxazole (isoxazoline) and furazan scaffolds are different. A construction of the isoxazole core is usually achieved through a [3+2] cycloaddition of various dipolarophiles to nitrile oxides, which are generated in situ from the corresponding chloroximes,[11] nitrolic acids,[12] or aliphatic nitro compounds[13] (Scheme 1a). However, these methods for nitrile oxides generation have some limitations on functional group tolerance and require an additional synthetic step for the preparation of the corresponding dipolar precursors.[13] An assembly of the 1,2,5-oxadiazole framework is usually accomplished via a dehydrative cyclization of tailor-made vicinal dioximes.[14] This process usually entails refluxing the precursor in a high-boiling solvent (100–150 °C) in the presence of a strong base, such as NaOH or KOH (Scheme 1b). However, such a method requires a multi-step preparation of dioxime precursors and usually suffers from harsh reaction conditions. These disadvantages preclude the presence of base-sensitive functional groups and stereocenters, elsewhere in the molecule.

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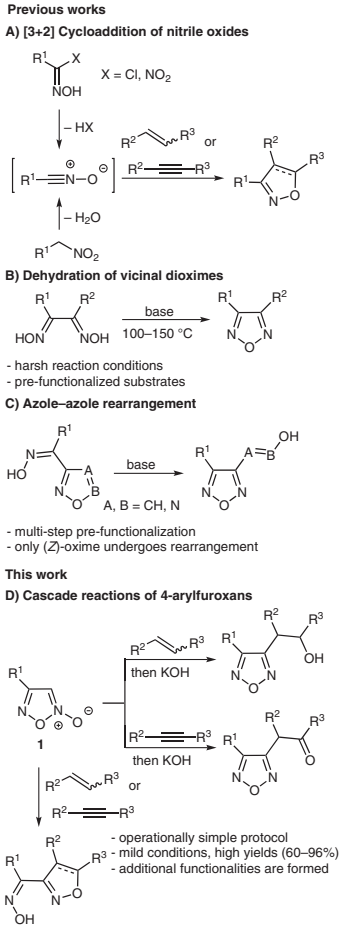
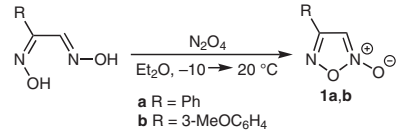


Scheme 1 Synthetic routes to isoxazoles and furazans

Another general approach for the synthesis of furazans is based on transformations of other more accessible heterocycles through the so-called azole-to-azole interconversion.[15,16] To accomplish this rearrangement the initial azole has to contain a ring-conjugated side chain reacting as a nucleophile (e.g., oxime group) toward the pivotal annular nitrogen atom in the S_Ni-type reaction followed by a cleavage of the adjacent bond to form a new azole.[17] However, main disadvantages of this method include a necessary step-by-step synthesis of oximes and their carbonyl precursors (Scheme 1c). In addition, this intramolecular process proceeds usually under considerably harsh conditions and, thus, preclude high levels of chemoselectivity and functional group tolerance in the synthesis of functionally substituted furazans. Therefore, new step-economy routes to the construction of both isoxazole and furazan derivatives from the same available starting materials are desirable. Herein, we describe a novel atom-economic and divergent approach to the assembly of isoxazole, isoxazoline, and furazan subunits via cascade reactions of 4-arylfuroxans (Scheme 1d).

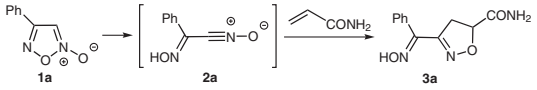
Initial 4-arylfuroxans **1a**,**b** were synthesized by an oxidation of the corresponding *amphi*-dioximes (Scheme 2).



Scheme 2 Synthesis of initial 4-arylfuroxans **1a**,**b**

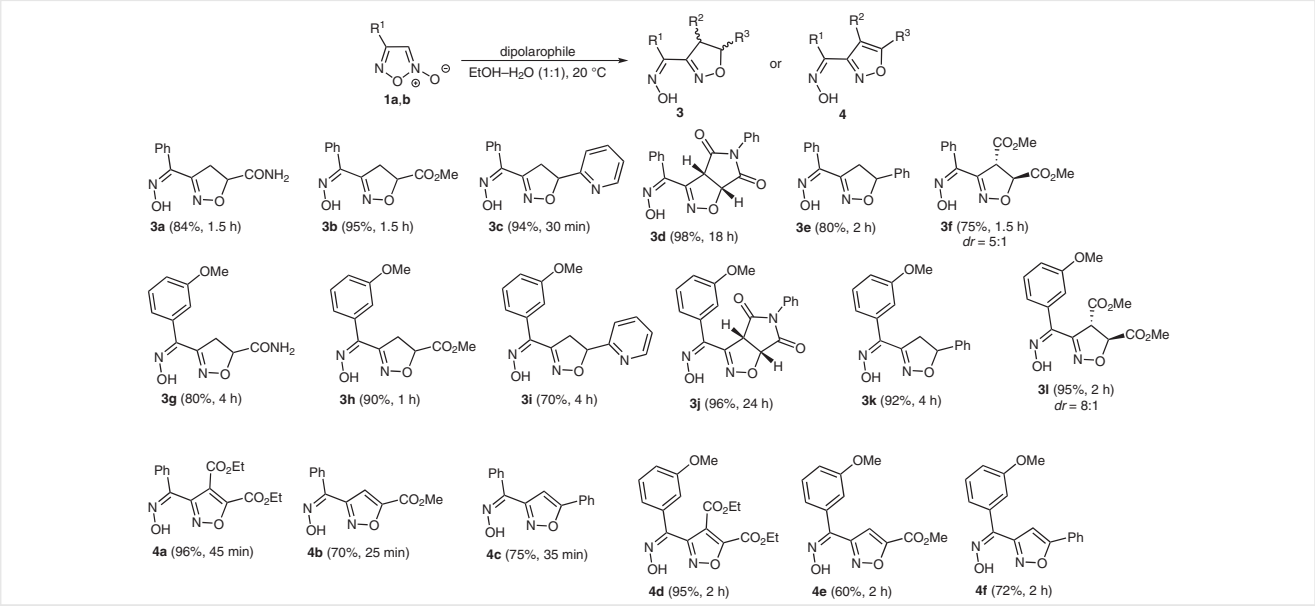
It is known, that 4-phenylfuroxan (**1a**) is capable to undergo the heterocyclic ring cleavage under mild conditions generating nitrile oxide **2a**.[18] We decided to use this furoxan reactivity mode to perform tandem ring opening/[3+2] cycloaddition sequence and to prepare a series of (oximino)isoxazoles and -isoxazolines. The accessible 4-phenylfuroxan (**1a**)[19] and acrylamide as dipolarophile were selected as model substrates. To optimize the conditions for the oxime **3a** synthesis, molar ratios of reagents, solvents, temperature, and reaction time were varied (Table 1). Reactions of furoxan **1a** and 2 equivalents of acrylamide in MeOH, EtOH, or H_2O either at 20 °C or under reflux were ineffective (entries 1–6).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Acrylamide (equiv)	Temp (°C)	Time (h)	Solvent	Yield (%)[b]
1	2	20	12	MeOH	–[c]
2	2	20	12	EtOH	–[c]
3	2	20	12	H_2O	–[c]
4	2	60	3	MeOH	–[d]
5	2	78	3	EtOH	–[d]
6	2	100	3	H_2O	–[d]
7	2	20	1.5	MeOH–H_2O (2:1)	77
8	2	20	4	MeOH–H_2O (5:1)	75
9	2	20	6.5	MeOH–H_2O (10:1)	73
10	1	20	3	EtOH–H_2O (1:1)	74
11	1.5	20	2	EtOH–H_2O (2:1)	78
12	2	20	1.5	EtOH–H_2O (1:1)	86
13	2.5	20	1.5	EtOH–H_2O (1:1)	83
14	3	20	1.5	EtOH–H_2O (1:1)	85
15	4	20	1.5	EtOH–H_2O (1:1)	83

[a] Reaction conditions: furoxan **1a** (0.6 mmol), acrylamide, solvent (4 mL), 20 °C.
[b] Isolated yields.
[c] No reaction.
[d] Decomposition of starting material was observed.



Scheme 3 Substrate scope for the synthesis of (oximino)isoxazolines **3** and (oximino)isoxazoles **4**. *Reagents and conditions*: furoxan **1a**,**b** (0.6 mmol), dipolarophile (1.2 mmol), EtOH–H_2O (1:1), 20 °C.

Target isoxazoline **3a** was obtained in a mixture of MeOH–H_2O. A decrease of H_2O amount did not affect the yields of the product **3a**, but reaction times increased (Table 1, entries 7–9). A replacement of MeOH with EtOH resulted generally in a yield increase (entries 11–15). Therefore, the optimal conditions were 2 equivalents of acrylamide in an EtOH–H_2O (1:1) mixture at 20 °C for 1.5 hours (entry 12).

The optimal conditions found were suitable for a representative range of C=C and C≡C dipolarophiles. Target benzoylisoxazoline oximes **3a–f** and benzoylisoxazole oximes **4a–c** were synthesized with complete regioselectivity and in high yields. Similar results were obtained in a reaction of 3-methoxyphenylfuroxan (**1b**) with same dipolarophiles (Scheme 3). The developed protocol tolerated well amide and ester functionalities in a dipolarophile structure. However, reaction times of furoxans **1a**,**b** with various dipolarophiles differed. In particular, reactions with acetylenes proceeded faster than with olefins and furoxan **1b** underwent tandem transformation slower than furoxan **1a**. The reactions with *N*-phenylmaleimide and dimethyl fumarate occurred diastereoselectively. Isoxazolines **3d** and **3j** were isolated as single diastereomers, while isoxazolines **3f** and **3l** were formed as a mixture of two diastereomers in a ratio of 5:1 for **3f** and 8:1 for **3l** according to ^{1}H NMR spectra. Although cycloaddition of internal olefins to nitrile oxides proceeds usually with complete diastereoselectivity, in the case of dimethyl fumarate a mixture of diastereoisomers may be observed due to epimerization.[13b–d] The synthesized compounds **3** and **4** were characterized by IR, ^{1}H, and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. In addition, structures of isoxazoline **3c** and isoxazole **4a** were unambiguously determined by single-crystal X-ray diffraction study (Figure 1). One signal of OH group in ^{1}H NMR spectra of compounds **3** and **4** along with the X-ray data unambiguously confirmed the *Z*-configuration of oxime groups.

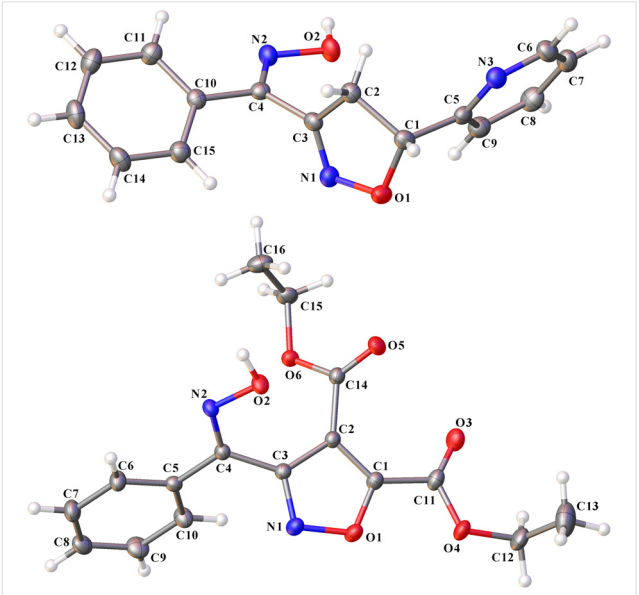


Figure 1 The general view of molecules of compounds **3c** (up) and **4a** (down). Atoms are represented by probability ellipsoids of atomic vibrations (p = 0.5%).

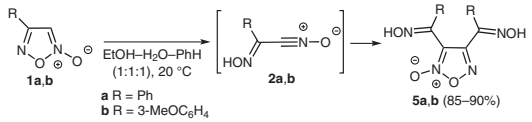
Indeed, the O2N2C4C3 torsion angles in crystals of both, **3c** and **4a**, are small [0.3(2)° and 3.0(2)°, respectively]. The oxime function is significantly rotated with respect to the

five-membered heterocycle: the N2C4C3N1 torsion angle equals to 94.1(2)° and 128.4(1)° in **3c** and **4a**, correspondingly. This, together with rather large C4–C3 bond lengths [1.490(2) and 1.481(2) Å, respectively for **3c** and **4a**], indicates the absence of meaningful π-conjugation between oxime and isoxazole (isoxazoline) fragments. By contrast, the oxime groups are more co-planar with the phenyl rings [the N2C4C10C11 and N2C4C5C6 torsion angles in **3c** and **4a**, respectively, equal to 24.4(3)° and 21.8(2)°]. The only meaningful difference between heterocycles in **3c** and **4a** is the expected non-planarity of isoxazoline fragment in **3c** resulting from the *envelope* conformation: the C1 atom outgoes from the O1N1C2C3 mean-squared plane on 0.290(2) Å.

According to the DFT calculations of isolated molecules of **3c** and **4a**, the influence of crystal packing effects on molecular structures is substantial in both compounds (Figure S1, see SI). The weighted root mean square deviations of the crystal and equilibrium isolated structures are 0.68 and 0.31 Å, for **3c** and **4a**, respectively. The difference in deviations can be rationalized not only by the presence of more flexible isoxazoline cycle in **3c** but also by effects of specific solvation in crystals, which were analyzed using geometric criteria (Figure 2). Particularly, there are strong intermolecular OH···N hydrogen bonds between oxime and pyridine moieties in **3c**, which bound molecules into chains [the O2···N3 distance is 2.701(2) Å, the O2–H2O···N3 angle is 172.5° with the O2–H2O distance being normalized on the idealized value of 0.993 Å]. By contrast, the **4a** molecules are aggregated into centrosymmetric dimers by weaker and less directional hydrogen bonds between oxime functions [O2···N2 2.784(2) Å, O2–H2···N2 157.0°]. These interactions clearly cannot cause significant changes of molecular conformation of **4a**.

Nonetheless, the *Z*-configuration of oxime groups persists in the isolated states: the O2N2C4C3 torsion angles are 4.3° and 1.5° in isolated molecules of **3c** and **4a**, respectively. Moreover, the rotation of the O2N2C4C3 torsion angle is substantially hindered according to the corresponding relaxed scans of potential energy surface for isolated species (35 steps by 10°). The energy barriers of rotation estimated at the least stable of available points for each compound (115.7° and 118.5° for **3c** and **4a**, respectively) are 82.3 and 78.8 kcal·mol^{-1}.

If a furoxan ring cleavage was performed in the absence of a dipolarophile, the formed nitrile oxides **2a**,**b** underwent dimerization to bis(oximino)furoxans **5a**,**b** in high yields (Scheme 4).



Scheme 4 Synthesis of bis(oximino)furoxans **5a**,**b**

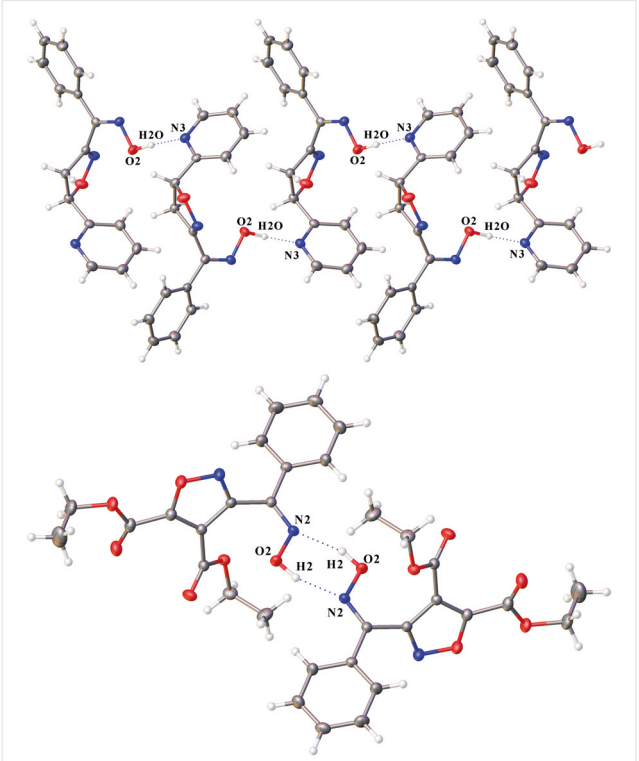
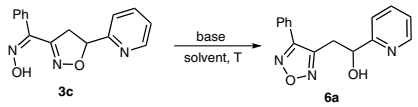


Figure 2 Fragments of crystal packing of **3c** (up) and **4a** (down) molecules

Next, a search of optimal conditions for a rearrangement of oximes **3** and **4** to the corresponding furazans was performed. Oxime **3c** was selected as a model substrate. Solvents, temperature, various bases, and reaction times were varied (Table 2). A thermal rearrangement of oxime **3c** by refluxing it in EtOH or $CHCl_3$ was unsuccessful (entries 1, 2). Stirring of oxime **3c** in a mixture of $CHCl_3$–H_2O in the presence of $NaHCO_3$ or K_2CO_3 in different molar ratios was also ineffective (entries 3–6). Target furazan **6a** was obtained under the action of KOH in alcoholic media. In all cases the reaction was accomplished within 30 minutes and furazan **6a** was formed almost quantitatively irrespective of the molar ratio **3c**:KOH (entries 7–10). To our delight, the rearrangement of oxime **3c** into furazan **6a** also efficiently occurred in EtOH–H_2O mixture (entry 11), which was used for the preparation of initial oxime **3c**. Therefore, this reaction medium could be suitable for the synthesis of furazans **6** via one-pot cascade transformation of 4-arylfuroxans.

Indeed, the found optimal reaction medium proved to be suitable to perform a one-pot cascade transformation of furoxans **1a**,**b** under the action of alkenes. Target furazans **6a–h** were prepared in high yields (Scheme 5). Reaction times for the isoxazolines **3** formation were the same as indicated on Scheme 3, while the rearrangement step was accomplished in 30 minutes after KOH addition in all cases. In

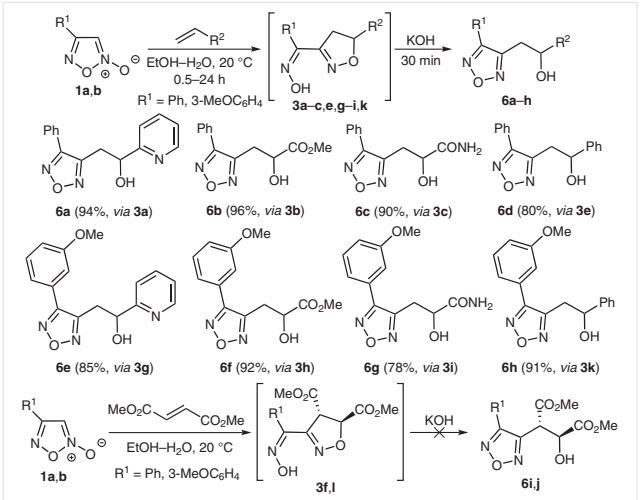
Table 2 Optimization of Rearrangement Conditions[a]



Entry	Solvent	Base (equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	EtOH	–	78	4	–[c]
2	$CHCl_3$	–	61	4	–[c]
3	$CHCl_3$/H_2O (1:1)	$NaHCO_3$ (1.5)	20	6	–[c]
4	$CHCl_3$/H_2O (1:1)	$NaHCO_3$ (3)	20	6	–[c]
5	$CHCl_3$/H_2O (1:1)	$NaHCO_3$ (4)	20	6	–[c]
6	$CHCl_3$/H_2O (1:1)	K_2CO_3 (4)	20	19	–[d]
7	EtOH	KOH (2)	20	0.5	94
8	EtOH	KOH (3)	20	0.5	96
9	EtOH	KOH (4)	20	0.5	95
10	MeOH	KOH (4)	20	0.5	93
11	EtOH–H_2O (1:1)	KOH (2)	20	0.5	92

[a] Reaction conditions: oxime **3c** (0.6 mmol), base, solvent (4 mL).
[b] Isolated yields.
[c] No reaction.
[d] Decomposition of starting material was observed.

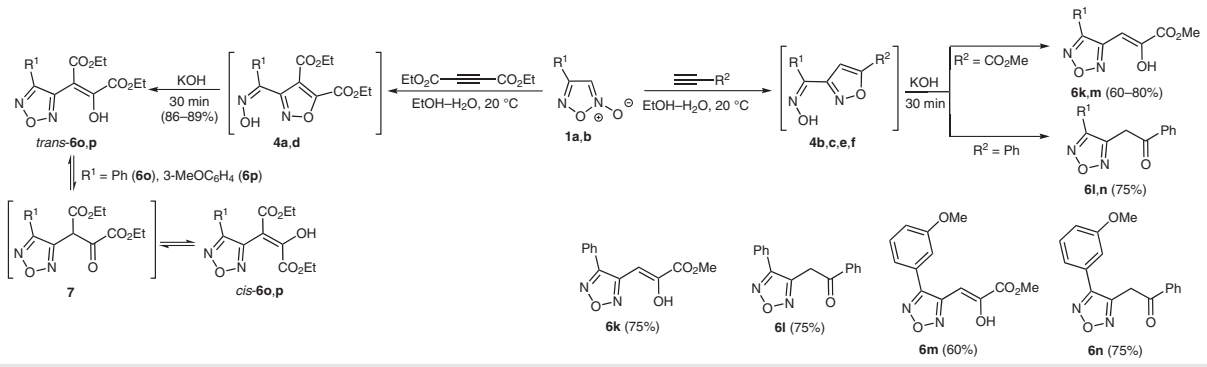
addition, we studied a scalability of the presented approach under the standard reaction conditions for the synthesis of isoxazoline **6d**. It was found that our protocol can be applied on a 0.5 g scale for the preparation of compound **6d** in the same yield. However, an introduction of dimethyl fumarate in the studied one-pot cascade process resulted in a complex mixture of products. Although ^{1}H NMR spectra of crude mixtures contained appropriate signals of furazans **6i**,**j**, attempts to isolate target products by column chromatography were unsuccessful. It seems that compounds **6i**,**j** underwent significant decomposition after their formation in basic medium. Presumably, such instability of diesters **6i**,**j** is caused by a high acidity of the proton of CH group linked to a strongly electron-withdrawing furazan ring, thus promoting anionic oligomerization.



Scheme 5 Scope of the one-pot cascade transformation of 4-arylfuroxans **1a**,**b** with alkenes. *Reagents and conditions*: **1a**,**b** (0.6 mmol), alkene (1.2 mmol), EtOH–H_2O (1:1, 4 mL), 20 °C, then a 25% solution of KOH (1.2 mmol) in EtOH.

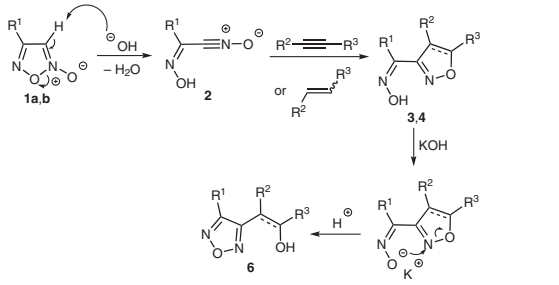
Cascade reactions of 4-arylfuroxans **1a**,**b** with acetylenes also afforded target furazans in good and high yields. It is interesting to note that the reaction of furoxans **1a**,**b** with methyl propiolate resulted in enols **6k**,**m**, while in the case of phenylacetylene ketones **6l**,**n** were formed. Analogous interaction of furoxans **1a**,**b** with diethyl acetylenedicarboxylate resulted in a mixture of *cis*- and *trans*-isomers **6o**,**p** in a ratio of 1:2. Isomerization of *trans*-**6o**,**p** into *cis*-forms is evidently proceeded via the keto form **7** (Scheme 6). The main advantage of the presented approach includes a direct installation of several functional groups to the furazan backbone.

A plausible mechanism for the developed one-pot cascade transformation of 4-arylfuroxans **1a**,**b** into furazans **6** is outlined in Scheme 7. Due to the strong electron-withdrawing effect of the furoxan ring, C–H bond in 4-arylfuroxans **1** is readily dissociated in EtOH–H_2O mixture followed by ring cleavage to α-oximinoarylacetonitrile oxide **2**.



Scheme 6 Scope of the one-pot cascade transformation of 4-arylfuroxans **1a**,**b** with alkynes. *Reagents and conditions*: **1a**,**b** (0.6 mmol), alkyne (1.2 mmol), EtOH–H_2O (1:1, 4 mL), 20 °C, then a 25% solution of KOH (1.2 mmol) in EtOH.

This reactivity pattern was previously shown to proceed in various reaction media, including EtOH–H_2O mixture.[18] Arguably, the presence of water as a highly polarizable solvent (ε = 78.4 at 298 K) promoted dissociation, which was not observed in less polar MeOH (ε = 32.7 at 298 K) or EtOH (ε = 24.3 at 298 K). At the same time, EtOH is required to dissolve the substrate. Subsequent [3+2] cycloaddition of intermediate **2** to a C=C or C≡C dipolarophile results in the formation of isoxazoline **3** (isoxazole **4**) incorporating *Z*-configuration of an oxime group. Upon addition of KOH, oxime group in compounds **3** and **4** is deprotonated promoting the azole–azole rearrangement to final functionally substituted furazans **6**.



Scheme 7 A plausible reaction mechanism for the formation of furazans **6**

In summary, we have developed an efficient divergent approach for the preparation of functionally substituted isoxazoles, isoxazolines, and furazans. This process is atom-economic, proceeds in mild conditions via generation of intermediate *Z*-oximes with high regio- and diastereoselectivity and in high yields of final heterocyclic systems. It is important to note that a wide range of (oximino)dihydroisoxazoles underwent azole–azole rearrangement for the first time. Thus, the developed functionalization protocol provides a direct access to a diverse series of 5-membered nitrogen heterocycles incorporating hydroxy, carbonyl, ester, and amide functionalities or their combination at the azole backbone, which enables the potential use of these molecular systems in medicinal and materials chemistry.

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) spectrometer and referenced to residual solvent peak. The chemical shifts are reported in ppm (δ); multiplicities are indicated by standard abbreviations. Coupling constants, *J*, are reported in hertz (Hz). The IR spectra were recorded on a Bruker 'Alpha' spectrometer in the range 400–4000 cm^{-1} (resolution 2 cm^{-1}). 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}). N_2 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. The melting points were determined on Stuart SMP20 apparatus and are uncorrected. Analytical 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. Column chromatography was performed on silica gel 60 Å (0.060–0.200 mm, Acros Organics). All solvents were purified and dried using standard methods prior to use. All standard reagents were purchased from Aldrich or Acros Organics and used without further purification. 4-Phenylfuroxan (**1a**)[19] was synthesized according to a published procedure.

X-ray diffraction studies of the **3c** crystal were performed using a Bruker APEX II Duo CCD diffractometer (MoKα-radiation, graphite monochromator, ω-scans), whereas the X-ray diffraction for **4a** was measured using a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (MoKα-radiation, graphite monochromator, shutterless ϕ- and ω-scan techniques). The intensity data were integrated by the SAINT program[20] and were corrected for absorption and decay using SADABS.[21] Both structures were solved by direct methods using SHELXS[22] and refined on F^2 using SHELXL-2018.[23] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The locations of H_2O and H_2 atoms in **3c** and **4a**, respectively, were found from the electron density-difference map; these atoms were refined with an individual isotropic displacement parameter. All other H_2 atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The main crystallographic data and refinement parameters are given in Table S1 of Supporting Information.[24]

The DFT calculations of isolated molecules of **3c** and **4a** were performed using the Gaussian 09 program[25] (rev. D01) at the PBE0[26,27]/6-311++G(d,p) level with the Grimme's D3 dispersion corrections and Becke–Jonson damping.[28] Standard convergence criteria were used for the optimization procedures and relaxed scans. Equilibrium structures of both compounds correspond to minimums on potential energy surface according to the calculations of Hessian of electronic energy (ultrafine grids, no imaginary modes were found).

4-(3-Methoxyphenyl)furoxan (1b)

A cooled solution of N_2O_4 (12.5 mmol, 0.8 mL) in anhyd Et_2O (4 mL) was added dropwise to a magnetically stirred solution of *amphi*-2-(hydroxyimino)-2-(3-methoxyphenyl)acetaldehyde oxime (1.94 g, 10 mmol) in Et_2O (20 mL) at –10 °C. The reaction mixture was allowed to stir and warm up to 20 °C for 1.5 h. Then the solvent was evaporated under reduced pressure, the crude product was crystallized from a mixture of MeOH and concd HCl (5:1) and washed with cold MeOH (4 mL) to afford **1b** as a white solid; yield: 1.50 g (78%); mp 85–86 °C; R_f = 0.67 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3127, 1608, 1586, 1481, 1440, 1392, 1287, 1271, 1214, 1188, 1040, 996, 943, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 7.09 (d, *J* = 8.5 Hz, 1 H, Ar), 7.25–7.31 (m, 3 H, Ar + Het), 7.43 (t, *J* = 7.9 Hz, 1 H, Ar).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.5, 102.4, 111.5, 117.5, 119.0, 127.2, 130.5, 156.3, 160.3.

Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.42; H, 4.29; N, 14.31.

4,5-Dihydroisoxazoles 3 and Isoxazoles 4; General Procedure

A solution of 4-arylfuroxan **1a**/**b** (0.6 mmol) in EtOH (2 mL) was added dropwise to a magnetically stirred mixture of the respective dipolarophile (1.2 mmol) in H_2O (2 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 0.5–24 h (TLC monitoring until consumption of initial furoxan **1**) and then extracted with $CHCl_3$ (5 × 2 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by gradient flash-column chromatography on SiO_2 using $CHCl_3$–EtOAc as eluent to afford the pure target product.

3-[(Hydroxyimino)(phenyl)methyl]-4,5-dihydroisoxazole-5-carboxamide (3a)

White solid; yield: 117 mg (84%); mp 127–128 °C; R_f = 0.34 (EtOAc).

IR (KBr): 3415, 3228, 3157, 2987, 1692, 1653, 1602, 1558, 1496, 1436, 1422, 1083, 905, 879 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.49–3.57 (m, 1 H), 3.64–3.74 (m, 1 H), 5.05–5.11 (m, 1 H), 7.42 (br s, 4 H), 7.57 (br s, 2 H), 7.68 (br s, 1 H), 12.19 (br s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 41.1, 78.9, 127.5, 128.9, 129.9, 134.6, 147.0, 153.1, 172.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}N_3O_3$: 234.0873; found: 234.0875.

Methyl 3-[(Hydroxyimino)(phenyl)methyl]-4,5-dihydroisoxazole-5-carboxylate (3b)

Yellow oil; yield: 141 mg (95%); R_f = 0.38 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3361, 2972, 2800, 1725, 1430, 1415, 1337, 1255, 1237, 1019, 1006, 839 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.51 (dd, *J* = 6.6, 6.7 Hz, 1 H), 3.62–3.68 (m, 1 H), 3.73 (s, 3 H), 5.25 (dd, *J* = 6.6, 6.7 Hz, 1 H), 7.34–7.43 (m, 5 H), 12.15 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 38.4, 52.9, 78.3, 128.2, 129.2, 129.4, 131.1, 149.3, 157.2, 170.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_4$: 249.0870; found: 249.0876.

Phenyl[5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl]methanone Oxime (3c)

Pale pink solid; yield: 151 mg (94%); mp 135–136 °C; R_f = 0.18 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3345, 2980, 2709, 1610, 1598, 1497, 1436, 1021, 1005, 938, 854, 769 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.73 (dd, *J* = 7.2, 11.0 Hz, 1 H), 3.89 (dd, *J* = 7.3, 11.0 Hz, 1 H), 5.83 (dd, *J* = 7.2, 11.0 Hz, 1 H), 7.39–7.43 (m, 4 H), 7.54 (d, *J* = 7.9 Hz, 1 H), 7.60–7.63 (m, 2 H), 7.88 (t, *J* = 7.6 Hz, 1 H), 8.63 (d, *J* = 4.9 Hz, 1 H), 12.16 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 42.8, 82.6, 122.0, 124.0, 127.6, 128.8, 129.8, 134.8, 137.7, 147.4, 149.9, 153.3, 159.1;

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_2$: 268.1081; found: 268.1088.

3-[(Hydroxyimino)(phenyl)methyl]-5-phenyl-3a*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (3d)

White solid; yield: 197 mg (98%); mp 129–130 °C; R_f = 0.28 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3421, 1710, 1597, 1502, 1449, 1393, 1204, 1104, 997 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 5.15 (d, *J* = 9.5 Hz, 1 H), 5.90 (d, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 7.5 Hz, 2 H), 7.46–7.61 (m, 8 H), 12.51 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 57.6, 80.9, 126.5, 127.2, 129.4, 129.6, 130.4, 132.0, 133.3, 135.1, 145.1, 149.7, 170.5, 172.8;

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}N_3O_4$: 336.0979; found: 336.0976.

Phenyl(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone Oxime (3e)

White solid; yield: 128 mg (80%); mp 103–104 °C; R_f = 0.64 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3239, 2963, 1727, 1566, 1494, 1427, 1413, 1260, 998, 771 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.43 (dd, *J* = 8.2, 11.0 Hz, 1 H), 3.90 (dd, *J* = 6.5, 11.0 Hz, 1 H), 5.77 (dd, *J* = 6.5, 8.2 Hz, 1 H), 7.34–7.44 (m, 8 H), 7.61 (br s, 2 H), 12.19 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 44.8, 82.4, 126.7, 127.6, 128.7, 128.9, 129.2, 129.8, 134.7, 141.1, 147.5, 153.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1128; found: 267.1129.

Dimethyl 3-[(Hydroxyimino)(phenyl)methyl]-4,5-dihydroisoxazole-4,5-dicarboxylate (3f)

A mixture of two diastereomers in 5:1 ratio; pale brown solid; yield: 138 mg (75%); mp 108–109 °C; R_f = 0.41 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3252, 2988, 1750, 1732, 1616, 1316, 1246, 1195, 1174, 1103, 1048, 981, 929, 775, 764 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ (major diastereoisomer) = 3.60 (s, 3 H), 3.77 (s, 3 H), 5.11 (d, *J* = 5.9 Hz, 1 H), 5.60 (d, *J* = 5.9 Hz, 1 H), 7.44 (br s, 3 H), 7.54 (br s, 2 H), 12.39 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ (major diastereoisomer) = 53.3, 58.2, 58.5, 81.0, 127.4, 128.9, 130.0, 134.4, 145.8, 150.0, 168.0, 169.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_6$: 307.0925; found: 307.0928.

3-[(Hydroxyimino)(3-methoxyphenyl)methyl]-4,5-dihydroisoxazole-5-carboxamide (3g)

White solid; yield: 126 mg (80%); mp 114–115 °C; R_f = 0.22 (EtOAc).

IR (KBr): 3405, 3188, 1661, 1599, 1585, 1470, 1291, 1253, 1217, 1096, 1032, 1013, 879, 786 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.48 (dd, *J* = 6.1, 6.2 Hz, 1 H), 3.62–3.83 (m, 4 H), 5.05–5.11 (m, 1 H), 6.98–7.00 (m, 1 H), 7.09–7.15 (m, 2 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.44 (br s, 1 H), 7.69 (br s, 1 H), 12.20 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 40.6, 55.1, 78.3, 112.1, 115.1, 119.3, 129.5, 135.3, 146.4, 152.5, 159.1, 171.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_3O_4$: 264.0978; found: 264.0987.

Methyl 3-[(Hydroxyimino)(3-methoxyphenyl)methyl]-4,5-dihydroisoxazole-5-carboxylate (3h)

Yellow oil; yield: 150 mg (90%); R_f = 0.58 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3356, 3007, 2957, 2840, 1744, 1601, 1579, 1490, 1435, 1289, 1230, 1185, 1162, 962, 880, 811, 790 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.55–3.61 (m, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 5.32 (dd, *J* = 5.6, 6.0 Hz, 1 H), 6.99–7.02 (m, 1 H), 7.10–7.14 (m, 2 H), 7.31–7.36 (m, 1 H), 12.25 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 40.5, 52.9, 55.6, 77.7, 112.8, 115.5, 119.9, 130.0, 130.9, 135.8, 146.6, 152.9, 170.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_5$: 279.0975; found: 279.0972.

(3-Methoxyphenyl)[5-(pyridin-2-yl)-4,5-dihydroisoxazol-3-yl]methanone Oxime (3i)

Pale pink solid; yield: 125 mg (70%); mp 117–118 °C; R_f = 0.14 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 2959, 2938, 2794, 1595, 1491, 1469, 1334, 1317, 1283, 1232, 1164, 1043, 1002, 969, 900, 853, 813, 787 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75–3.85 (m, 5 H), 5.82 (br s, 1 H), 6.99 (br s, 1 H), 7.14–7.19 (m, 2 H), 7.31–7.38 (m, 2 H), 7.51 (br s, 1 H), 7.85 (br s, 1 H), 8.60 (br s, 1 H), 12.15 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 42.3, 55.1, 81.9, 112.3, 115.0, 119.5, 121.5, 123.5, 129.5, 135.5, 137.2, 146.8, 149.4, 152.7, 158.6, 159.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3O_3$: 298.1186; found: 298.1180.

3-[(Hydroxyimino)(3-methoxyphenyl)methyl]-5-phenyl-3a*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (3j)

White solid; yield: 210 mg (96%); mp 185–186 °C; R_f = 0.36 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3329, 2997, 2970, 1709, 1600, 1582, 1492, 1468, 1431, 1395, 1332, 1255, 1205, 1155, 1044, 1025, 963, 869, 813, 700 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.79 (s, 3 H), 5.13 (d, *J* = 9.4 Hz, 1 H), 5.91 (d, *J* = 9.4 Hz, 1 H), 7.06 (d, *J* = 7.0 Hz, 1 H), 7.11–7.14 (m, 2 H), 7.26 (d, *J* = 7.5 Hz, 2 H), 7.39 (t, *J* = 8.1 Hz, 1 H), 7.46–7.55 (m, 3 H), 12.54 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.7, 57.6, 80.9, 111.4, 116.1, 119.1, 127.1, 129.4, 129.6, 130.6, 132.0, 134.6, 144.9, 149.6, 159.9, 170.5, 172.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}N_3O_5$: 366.1084; found: 366.1086.

(3-Methoxyphenyl)(5-phenyl-4,5-dihydroisoxazol-3-yl)methanone Oxime (3k)

White solid; yield: 163 mg (92%); mp 104–105 °C; R_f = 0.60 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3355, 2943, 2842, 1608, 1576, 1489, 1453, 1430, 1355, 1292, 1261, 1231, 1156, 1136, 1050, 1009, 960, 875, 809 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.38–3.43 (m, 1 H), 3.76 (s, 3 H), 3.82–3.92 (m, 1 H), 5.77 (dd, *J* = 2.9, 8.2 Hz, 1 H), 6.99–7.03 (m, 1 H), 7.11–7.17 (m, 2 H), 7.31–7.43 (m, 6 H), 12.19 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 44.8, 55.6, 82.3, 112.7, 115.5, 120.0, 126.7, 128.7, 129.1, 130.0, 136.0, 141.2, 147.3, 153.0, 159.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_3$: 297.1234; found: 297.1238.

Dimethyl 3-[(Hydroxyimino)(3-methoxyphenyl)methyl]-4,5-dihydroisoxazole-4,5-dicarboxylate (3l)

A mixture of two diastereomers in 8:1 ratio; pale brown oil; yield: 192 mg (95%); R_f = 0.37 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3376, 3008, 2958, 1744, 1601, 1580, 1491, 1438, 1290, 1257, 1212, 1017, 962, 889, 814, 789 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ (major diastereoisomer) = 3.59 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 5.59 (d, *J* = 6.0 Hz, 1 H), 6.99–7.03 (m, 1 H), 7.08–7.11 (m, 2 H), 7.34 (t, *J* = 9.0 Hz, 1 H), 12.40 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ (major diastereoisomer) = 52.9 (2 C), 55.1, 57.8, 80.6, 112.2, 115.2, 119.4, 129.6, 133.0, 145.2, 149.5, 159.2, 167.5, 168.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_7$: 337.1030; found: 337.1029.

Diethyl 3-[(Hydroxyimino)(phenyl)methyl]isoxazole-4,5-dicarboxylate (4a)

Yellow oil; yield: 191 mg (96%); R_f = 0.54 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3265, 2948, 2840, 1753, 1738, 1626, 1496, 1437, 1428, 1375, 1329, 1238, 1228, 1202, 1028, 890, 771, 752 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 7.42–7.45 (m, 3 H), 7.53–7.56 (m, 2 H), 12.34 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.5, 13.7, 61.6, 63.0, 116.1, 126.2, 128.7, 129.8, 133.4, 144.1, 155.5, 156.2, 159.0, 159.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_6$: 333.1079; found: 333.1081.

Methyl 3-[(Hydroxyimino)(phenyl)methyl]isoxazole-5-carboxylate (4b)

Pale yellow solid; yield: 103 mg (70%); mp 127–128 °C; R_f = 0.57 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3388, 3177, 3147, 1733, 1585, 1573, 1498, 1445, 1403, 1329, 1319, 1268, 1268, 1211, 1106, 1029, 1000, 968, 919, 771, 701 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.93 (s, 3 H), 7.43 (br s, 3 H), 7.53 (br s, 2 H), 7.60 (s, 1 H), 12.41 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 53.0, 111.7, 127.0, 128.5, 129.6, 133.9, 145.0, 156.5, 156.7, 159.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_4$: 247.0713; found: 247.0722.

Phenyl(5-phenylisoxazol-3-yl)methanone Oxime (4c)

White solid; yield: 119 mg (75%); mp 129–130 °C (Lit.[29] mp 129–130 °C); R_f = 0.67 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3027, 2876, 1570, 1442, 1429, 1270, 1057, 1044, 976, 957, 817, 764 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.39–7.44 (m, 4 H), 7.55–7.59 (m, 5 H), 7.95 (d, *J* = 6.9 Hz, 2 H), 12.25 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 102.7, 126.2, 127.1, 127.5, 129.0, 129.8, 129.9, 131.1, 134.9, 146.5, 157.2, 169.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2O_2$: 265.0972; found: 265.0962.

Diethyl 3-[(Hydroxyimino)(3-methoxyphenyl)methyl]isoxazole-4,5-dicarboxylate (4d)

Yellow oil; yield: 206 mg (95%); R_f = 0.45 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3390, 2985, 2940, 1747, 1604, 1579, 1468, 1391, 1370, 1319, 1217, 1192, 1106, 1055, 1013, 861, 822, 789 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.15 (t, J = 7.1 Hz, 3 H), 1.35 (t, J = 7.1 Hz, 3 H), 3.78 (s, 3 H), 4.20 (q, J = 7.1 Hz, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 7.02–7.08 (m, 2 H), 7.12–7.14 (m, 1 H), 7.35 (t, J = 8.0 Hz, 1 H), 12.36 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 14.0, 14.2, 55.6, 62.1, 63.5, 111.7, 115.9, 116.6, 119.4, 130.3, 135.2, 144.4, 156.0, 156.6, 159.5, 159.8, 160.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_7$: 363.1187; found: 363.1189.

Methyl 3-[(Hydroxyimino)(3-methoxyphenyl)methyl]isoxazole-5-carboxylate (4e)

White solid; yield: 99 mg (60%); mp 100–101 °C; R_f = 0.64 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3526, 3173, 3143, 1733, 1600, 1583, 1492, 1441, 1316, 1293, 1230, 1200, 1167, 1099, 1050, 1035, 978, 957, 893, 815, 799, 703 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H), 3.93 (s, 3 H), 7.01–7.10 (m, 3 H), 7.33 (t, J = 7.9 Hz, 1 H), 7.58 (s, 1 H), 12.43 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 53.5, 55.6, 112.1, 112.6, 115.7, 120.1, 130.1, 131.0, 135.7, 145.3, 157.0, 159.7, 159.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{13}N_2O_5$: 277.0740; found: 277.0738.

(3-Methoxyphenyl)(5-phenylisoxazol-3-yl)methanone Oxime (4f)

Yellow oil; yield: 127 mg (72%); R_f = 0.85 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3066, 2936, 2838, 1690, 1597, 1471, 1450, 1334, 1289, 1216, 1003, 843 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H), 7.02 (d, J = 8.1 Hz, 1 H), 7.09 (d, J = 7.7 Hz, 1 H), 7.15 (s, 1 H), 7.31–7.37 (m, 2 H), 7.54–7.56 (m, 3 H), 7.95 (d, J = 7.1 Hz, 2 H), 12.26 (s, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.1, 102.2, 112.0, 115.1, 119.6, 125.7, 126.6, 129.3, 129.6, 130.6, 135.7, 145.8, 156.6, 159.2, 168.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{15}N_2O_3$: 295.1077; found: 295.1074.

Bis(hydroxyimino)furoxans 5a,b; General Procedure

A solution of 4-arylfuroxan **1a**/**b** (0.6 mmol) in a mixture of EtOH–H_2O–benzene (1:1:1, total volume 6 mL) was stirred for 30 min at 20 °C. Then the product was extracted with $CHCl_3$ (5 × 2 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to afford crude products, which were additionally washed with *n*-pentane.

Synthesis and spectral characteristics of the furoxan **5a** were reported previously.[30]

[3,4-Bis(hydroxyimino)(3-methoxyphenyl)methyl]furoxan (5b)

White solid; yield: 98 mg (85%); mp 118–119 °C; R_f = 0.73 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3002, 1610, 1481, 1455, 1289, 1267, 1027, 978, 815, 774 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.79 (s, 6 H), 7.05 (d, J = 8.5 Hz, 2 H), 7.21–7.27 (m, 4 H), 7.36–7.41 (m, 2 H), 13.41 (br s, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.6, 55.7, 111.0, 111.7, 112.5, 116.8, 118.5, 118.7, 118.9, 120.3, 126.2, 129.8, 130.1, 130.7, 131.0, 132.7, 157.9, 160.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{17}N_4O_6$: 385.1064; found: 385.1060.

Furazans 6; General Procedure

A solution of 4-arylfuroxan **1a**/**b** (0.6 mmol) in EtOH (2 mL) was added dropwise to a magnetically stirred mixture of the respective dipolarophile (1.2 mmol) in H_2O (2 mL) at 20 °C. The resulting solution was stirred at 20 °C for 0.5–24 h (TLC monitoring until consumption of initial furoxan **1**) and then a solution of KOH (0.28 g, 1.2 mmol) in EtOH (190 μL) was added. The reaction mixture was stirred for 30 min at 20 °C, then concd HCl was added till pH 7. The resulting mixture was poured into H_2O (15 mL) and extracted with $CHCl_3$ (5 × 3 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 using $CHCl_3$–EtOAc as eluent to afford the target product.

2-(4-Phenyl-1,2,5-oxadiazol-3-yl)-1-(pyridin-2-yl)ethanol (6a)

Pale yellow solid; yield: 151 mg (94%); mp 83–84 °C; R_f = 0.22 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3065, 2940, 2847, 1593, 1573, 1451, 1438, 1385, 1072, 1002, 993, 896, 773, 753 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.21–3.28 (m, 1 H), 3.51–3.57 (m, 1 H), 4.94–4.99 (m, 1 H), 5.86 (br s, 1 H), 7.22–7.26 (m, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.58 (br s, 3 H), 7.77–7.81 (m, 3 H), 8.45 (d, J = 6.0 Hz, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.4, 71.7, 120.2, 122.4, 125.6, 128.4, 129.1, 130.4, 136.7, 148.4, 151.8, 154.5, 162.5.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_2$: 268.1081; found: 268.1088.

Methyl 2-Hydroxy-3-(4-phenyl-1,2,5-oxadiazol-3-yl)propanoate (6b)

Brown oil; yield: 143 mg (96%); R_f = 0.48 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3469, 2956, 1746, 1452, 1441, 1387, 1346, 1228, 1106, 1025, 1002, 993, 896, 773, 735 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.24 (dd, J = 5.3, 10.0 Hz, 1 H), 3.38 (dd, J = 5.3, 10.0 Hz, 1 H), 3.61 (s, 3 H), 4.45 (q, J = 6.0 Hz, 1 H), 5.96 (d, J = 6.0 Hz, 1 H), 7.58–7.60 (m, 3 H), 7.78–7.82 (m, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.2, 51.7, 68.4, 125.3, 128.4, 129.2, 130.6, 151.0, 154.4, 172.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_4$: 249.0870; found: 249.0876.

2-Hydroxy-3-(4-phenyl-1,2,5-oxadiazol-3-yl)propanamide (6c)

Yellow solid; yield: 126 mg (90%); mp 109–110 °C; R_f = 0.24 (EtOAc).

IR (KBr): 3415, 3228, 2987, 1692, 1653, 1602, 1572, 1558, 1450, 1422, 1312, 1270, 1252, 1008, 905, 766 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.03–3.11 (m, 1 H), 3.40–3.42 (m, 1 H), 4.18 (br s, 1 H), 5.89 (br s, 1 H), 7.28 (br s, 1 H), 7.35 (br s, 1 H), 7.59–7.62 (m, 3 H), 7.79–7.83 (m, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 29.2, 70.1, 126.0, 129.0, 129.6, 131.0, 152.2, 155.0, 175.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{12}N_3O_3$: 234.0873; found: 234.0875.

1-Phenyl-2-(4-phenyl-1,2,5-oxadiazol-3-yl)ethanol (6d)

White solid; yield: 128 mg (80%); mp 96–97 °C; R_f = 0.70 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3443, 3064, 1604, 1585, 1494, 1454, 1386, 1056, 1028, 896, 771 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.26–3.37 (m, 2 H), 4.88–4.92 (m, 1 H), 5.68 (br s, 1 H), 7.23–7.31 (m, 5 H), 7.59–7.61 (m, 3 H), 7.77–7.80 (m, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.8, 71.3, 126.0, 126.1, 127.8, 128.6, 128.9, 129.6, 131.0, 144.8, 152.3, 155.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1128; found: 267.1129.

2-[4-(3-Methoxyphenyl)-1,2,5-oxadiazol-3-yl]-1-(pyridin-2-yl)ethanol (6e)

Yellow solid; yield: 151 mg (85%); mp 96–97 °C; R_f = 0.19 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3189, 3008, 2934, 1593, 1572, 1474, 1437, 1339, 1323, 1246, 1213, 1175, 1107, 1077, 1031, 1003, 874, 794, 752 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.26 (dd, *J* = 6.2, 8.7 Hz, 1 H), 3.56 (dd, *J* = 4.6, 10.3 Hz, 1 H), 3.85 (s, 3 H), 4.96–5.02 (m, 1 H), 5.90 (d, *J* = 5.1 Hz, 1 H), 7.15 (dd, *J* = 2.6, 5.6 Hz, 1 H), 7.23–7.27 (m, 1 H), 7.35–7.40 (m, 2 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.78 (dt, *J* = 2.9, 7.7 Hz, 1 H), 8.45–8.48 (m, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.9, 55.8, 72.3, 114.2, 116.8, 120.7, 121.2, 122.9, 127.2, 130.8, 137.2, 148.9, 152.4, 154.9, 160.0, 163.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3O_3$: 298.1186; found: 298.1180.

Methyl 2-Hydroxy-3-[4-(3-methoxyphenyl)-1,2,5-oxadiazol-3-yl]propanoate (6f)

Red oil; yield: 163 mg (92%); R_f = 0.60 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3468, 2956, 1744, 1606, 1588, 1471, 1440, 1290, 1225, 1182, 1107, 1040, 1003, 843, 791 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.23 (dd, *J* = 7.9, 7.4 Hz, 1 H), 3.37–3.41 (m, 1 H), 3.62 (s, 3 H), 3.84 (s, 3 H), 4.40–4.46 (m, 1 H), 5.98 (d, *J* = 5.8 Hz, 1 H), 7.16–7.20 (m, 1 H), 7.33–7.36 (m, 2 H), 7.51 (t, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.7, 52.3, 55.8, 68.9, 114.3, 116.8, 121.1, 126.9, 130.9, 151.6, 154.8, 160.0, 173.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_5$: 279.0975; found: 279.0972.

2-Hydroxy-3-[4-(3-methoxyphenyl)-1,2,5-oxadiazol-3-yl]propanamide (6g)

White solid; yield: 123 mg (78%); mp 118–120 °C; R_f = 0.24 (EtOAc).

IR (KBr): 3394, 3180, 1660, 1636, 1585, 1559, 1469, 1291, 1255, 1217, 1175, 1096, 1050, 1000, 906, 839, 787, 714 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.07 (dd, *J* = 6.2, 8.9 Hz, 1 H), 3.35–3.43 (m, 1 H), 3.84 (s, 3 H), 4.19 (br s, 1 H), 5.94 (br s, 1 H), 7.14–7.18 (m, 1 H), 7.29 (br s, 1 H), 7.34–7.37 (m, 3 H), 7.50 (t, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 29.1, 55.8, 70.1, 114.2, 116.9, 121.2, 127.1, 130.9, 152.2, 154.8, 160.0, 175.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_3O_4$: 264.0978; found: 264.0987.

2-[4-(3-Methoxyphenyl)-1,2,5-oxadiazol-3-yl]-1-phenylethanol (6h)

Brown oil; yield: 162 mg (91%); R_f = 0.60 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3454, 3031, 1587, 1470, 1383, 1324, 1290, 1224, 1180, 1040, 847, 790, 716 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.17–3.33 (m, 2 H), 3.84 (s, 3 H), 4.85–4.89 (m, 1 H), 7.15–7.37 (m, 8 H), 7.50 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.7, 55.8, 71.4, 114.3, 116.7, 121.1, 126.1, 127.2, 127.8, 128.6, 130.9, 144.8, 152.3, 154.9, 160.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_3$: 297.1234; found: 297.1238.

Methyl 2-Hydroxy-3-(4-phenyl-1,2,5-oxadiazol-3-yl)acrylate (6k)

White solid; yield: 111 mg (75%); mp 239–240 °C; R_f = 0.57 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 2958, 1707, 1576, 1534, 1483, 1426, 1223, 1141, 988, 779 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.17 (s, 1 H), 3.58 (s, 3 H), 5.41 (br s, 1 H), 7.55–7.61 (m, 5 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 51.4, 77.4, 127.5, 128.7, 129.2, 130.0, 151.8, 153.2, 162.7, 168.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_4$: 247.0713; found: 247.0722.

1-Phenyl-2-(4-phenyl-1,2,5-oxadiazol-3-yl)ethanone (6l)

Pale yellow solid; yield: 119 mg (75%); mp 64–65 °C; R_f = 0.67 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3150, 3027, 2875, 1687, 1457, 1429, 1269, 1216, 1056, 976, 930, 817, 765, 671 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 5.11 (s, 2 H), 7.49–7.60 (m, 5 H), 7.68–7.74 (m, 3 H), 8.03 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.8, 125.4, 127.7, 128.3, 128.8, 129.1, 130.6, 134.0, 135.4, 149.6, 154.6, 194.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2O_2$: 265.0972; found: 265.0962.

Methyl 2-Hydroxy-3-[4-(3-methoxyphenyl)-1,2,5-oxadiazol-3-yl]acrylate (6m)

White solid; yield: 99 mg (60%); mp 236–237 °C; R_f = 0.65 ($CHCl_3$–EtOAc 3:1).

IR (KBr): 3424, 2979, 2961, 1698, 1591, 1547, 1492, 1434, 1364, 1323, 1240, 1214, 1188, 1144, 1034, 1001, 862, 789 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.62 (s, 3 H), 3.82 (s, 3 H), 5.50 (s, 1 H), 7.11–7.22 (m, 3 H), 7.49 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 51.3, 55.3, 77.2, 113.9, 115.5, 120.6, 128.5, 130.2, 151.5, 152.7, 159.4, 162.5, 168.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2O_5$: 277.0740; found: 277.0735.

2-[4-(3-Methoxyphenyl)-1,2,5-oxadiazol-3-yl]-1-phenylethanone (6n)

Brown oil; yield: 132 mg (75%); R_f = 0.60 ($CHCl_3$–EtOAc 3:1).

IR (neat): 3454, 3031, 1587, 1470, 1383, 1324, 1290, 1224, 1180, 1040, 847, 790, 716 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.68 (s, 3 H), 5.11 (s, 2 H), 7.05–7.09 (m, 1 H), 7.20 (br s, 1 H), 7.26 (d, *J* = 8.1 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 7.5 Hz, 2 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 8.02 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.8, 55.1, 112.9, 116.4, 120.0, 126.6, 128.3, 128.8, 130.4, 134.0, 135.4, 149.6, 154.5, 159.5, 194.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2O_3$: 295.0999; found: 295.1002.

Diethyl 2-Hydroxy-3-(4-phenyl-1,2,5-oxadiazol-3-yl)maleate (6o)

A mixture of *cis*- and *trans*-isomers; pale yellow solid; yield: 177 mg (89%); mp 138–139 °C; R_f = 0.78 (EtOAc–EtOH 3:1).

IR (KBr): 3434, 2986, 1734, 1670, 1450, 1372, 1267, 1105, 1031, 966, 862, 776 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.58 (t, *J* = 7.1 Hz, 3 H), 0.75 (t, *J* = 7.0 Hz, 1.5 H), 0.93 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 1.5 H), 3.64 (q, *J* = 7.1 Hz, 1 H), 3.73 (q, *J* = 7.0 Hz, 2 H), 3.94 (q, *J* = 7.0 Hz, 2 H), 4.08 (q, *J* = 7.1 Hz, 1 H), 7.45–7.51 (m, 4.5 H), 7.75 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.5 (2 C), 14.1, 14.4, 57.0, 59.2, 59.7, 60.6, 82.5, 126.9, 127.3, 127.4, 127.6, 128.0, 128.6, 129.0, 129.4, 129.9, 130.4, 151.6, 154.5, 165.8, 166.9, 169.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_6$: 333.1079; found: 333.1081.

Diethyl 2-Hydroxy-3-[4-(3-methoxyphenyl)-1,2,5-oxadiazol-3-yl]maleate (6p)

A mixture of *cis*- and *trans*-isomers; pale yellow solid; yield: 187 mg (86%); mp 101–102 °C; R_f = 0.74 (EtOAc–EtOH 3:1).

IR (KBr): 3434, 2986, 1726, 1660, 1535, 1468, 1368, 1257, 1002, 1035, 863, 781 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 7.1 Hz, 3 H), 1.00 (t, *J* = 7.1 Hz, 1.5 H), 1.23–1.29 (m, 4 H), 3.79 (s, 3 H), 3.82 (s, 1.5 H), 3.85 (q, *J* = 7.1 Hz, 2 H), 3.98 (q, *J* = 6.9 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 4.22 (q, *J* = 6.9 Hz, 1 H), 7.08–7.17 (m, 1.5 H), 7.26–7.33 (m, 2.5 H), 7.44 (t, *J* = 7.8 Hz, 1.5 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.5, 13.7, 13.8,,13.9, 55.2, 55.4, 59.4, 61.1, 111.9, 112.9, 113.2, 116.1, 116.6, 116.8, 119.6, 120.2, 127.3, 130.3, 130.5, 148.5, 148.9, 154.2, 159.5, 164.8, 165.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_7$: 363.1187; found: 363.1189.

Scale-Up Experiment for 1-Phenyl-2-(4-phenyl-1,2,5-oxadiazol-3-yl)ethanol (6d)

A solution of 4-phenylfuroxan (**1a**; 0.486 g, 3 mmol) in EtOH (10 mL) was added dropwise to a magnetically stirred solution of styrene (0.707 mL, 6 mmol) in H_2O (10 mL) at 20 °C. The resulting solution was stirred for 4 h at 20 °C and then a solution of KOH (0.34 g, 6 mmol) in EtOH (0.85 mL) was added. The reaction mixture was stirred for 40 min at 20 °C and concd HCl was added till pH 7. The resulting mixture was poured into H_2O (40 mL) and extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 to afford **6d**; yield: 638 mg (80%).

Funding Information

This work was supported by the Russian Foundation for Basic Research (grant 18-03-00332). The structure analysis and DFT calculations were supported by the Russian Science Foundation (project 18-73-10131).

Acknowledgment

Crystal structure determination of **3c** was performed with the financial support from Ministry of Science and Higher Education of the Russian Federation using the equipment of Center for molecular composition studies of INEOS RAS. Crystal structure determination of **4a** was performed in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707393.

References

(1) (a) Smith, J. M.; Dixon, J. A.; deGruyter, J. N.; Baran, P. S. *J. Med. Chem.* **2019**, *62*, 2256. (b) Krska, S. W.; DiRocco, D. A.; Dreher, S. D.; Shevlin, M. *Acc. Chem. Res.* **2017**, *50*, 2976. (c) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Nature* **2014**, *515*, 389. (d) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. *Nat. Chem.* **2016**, *8*, 1126. (e) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. *Science* **2018**, *362*, 6416, 799.

(2) (a) Das, P.; Delost, M. D.; Qureshi, M. H.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2019**, *62*, 4265. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(3) For recent examples, see: (a) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 6392. (b) Zhang, X.; McNally, A. *ACS Catal.* **2019**, *9*, 4862. (c) Boddy, A. J.; Affron, D. P.; Cordier, C. J.; Rivers, E. L.; Spivey, A. C.; Bull, J. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 1458. (d) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (e) Nicolaou, K. C.; Hale, C. R. H.; Nilewski, C.; Ioannidou, H. A. *Chem. Soc. Rev.* **2012**, *41*, 5185.

(4) (a) Naidu, K. M.; Suresh, A.; Subbalakshmi, J.; Sriram, D.; Yogeeswari, P.; Raghavaiah, P.; Sekhar, K. V. C. *Eur. J. Med. Chem.* **2014**, *87*, 71. (b) Sun, J.; Lin, C.; Qin, X.; Dong, X.; Tu, Z.; Tang, F.; Chen, C.; Zhang, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3129. (c) Perrone, M. G.; Vitale, P.; Panella, A.; Fortuna, C. G.; Scilimati, A. *Eur. J. Med. Chem.* **2015**, *94*, 252.

(5) (a) Dallanoce, C.; Magrone, P.; Matera, C.; Frigerio, F.; Grazioso, G.; DeAmici, M.; Fucile, S.; Piccari, V.; Frydenvang, K.; Pucci, L.; Gotti, C.; Clementi, F.; DeMicheli, C. *ChemMedChem* **2011**, *6*, 889. (b) Soni, A.; Rehman, A.; Naik, K.; Dastidar, S.; Alam, M. S.; Ray, A.; Chaira, T.; Shah, V.; Palle, V. P.; Cliffe, I. A.; Sattigeri, V. J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1482. (c) Kaur, K.; Kumar, V.; Sharma, A. K.; Gupta, G. K. *Eur. J. Med. Chem.* **2014**, *77*, 121.

(6) For reviews, see: (a) Paton, R. M. *1,2,5-Oxadiazoles*, In *Comprehensive Heterocyclic Chemistry II, Vol. 4*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Ed.; Pergamon: Oxford, **1996**, 229–266. (b) Nikonov, G. N.; Bobrov, S. *1,2,5-Oxadiazoles*, In *Comprehensive Heterocyclic Chemistry III, Vol. 5*; Katritzky, A. R.; Ramsden, C. A. V.; Scriven, E. F. V.; Taylor, R. J. K., Ed.; Elsevier: Amsterdam, **2008**, 316–393. (c) Fershtat, L. L.; Makhova, N. N. *Russ. Chem. Rev.* **2016**, *85*, 1097. (d) Zlotin, S. G.; Dalinger, I. L.; Makhova, N. N.; Tartakovsky, V. A. *Russ. Chem. Rev.* **2020**, *89*, 1. (e) Makhova, N. N.; Belen'kii, L. I.; Gazieva, G. A.; Dalinger, I. L.; Konstantinova,

L. S.; Kuznetsov, V. V.; Kravchenko, A. N.; Krayushkin, M. M.; Rakitin, O. A.; Starosotnikov, A. M.; Fershtat, L. L.; Shevelev, S. A.; Shirinian, V. Z.; Yarovenko, V. N. *Russ. Chem. Rev.* **2020**, *89*, 55.

(7) (a) Zhao, J.; Li, Y.; Hunt, A.; Zhang, J.; Yao, H.; Li, Z.; Zhang, J.; Huang, F.; Ade, H.; Yan, H. *Adv. Mater.* **2016**, *28*, 1868. (b) Cameron, J.; Abed, M. M.; Chapman, S. J.; Findlay, N. J.; Skabara, P. J.; Horton, P. N.; Coles, S. J. *J. Mater. Chem. C* **2018**, *6*, 3709.

(8) For selected examples, see: (a) Stepanov, A. I.; Astrat'ev, A. A.; Sheremetev, A. B.; Lagutina, N. K.; Palysaeva, N. V.; Tyurin, A. Y.; Aleksandrova, N. S.; Sadchikova, N. P.; Suponitsky, K. Yu.; Atamanenko, O. P.; Konyushkin, L. D.; Semenov, R. V.; Firgang, S. I.; Kiselyov, A. S.; Semenova, M. N.; Semenov, V. V. *Eur. J. Med. Chem.* **2015**, *94*, 237. (b) Pal, P.; Gandhi, H. P.; Kanhed, A. M.; Patel, N. R.; Mankadia, N. N.; Baldha, S. N.; Barmade, M. A.; Murumkar, P. R.; Yadav, M. R. *Eur. J. Med. Chem.* **2017**, *130*, 107. (c) Porta, F.; Gelain, A.; Barlocco, D.; Ferri, N.; Marchianò, S.; Cappello, V.; Basile, L.; Guccione, S.; Meneghetti, F.; Villa, S. *Chem. Biol. Drug Des.* **2017**, *90*, 820.

(9) Stokes, J. M.; Yang, K.; Swanson, K.; Jin, W.; Cubillos-Ruiz, A.; Donghia, N. M.; MacNair, C. R.; French, S.; Carfrae, L. A.; Bloom-Ackerman, Z.; Tran, V. M.; Chiappino-Pepe, A.; Badran, A. H.; Andrews, I. W.; Chory, E. J. Church G. M.; Brown, E. D.; Jaakkola, T. S.; Barzilay, R.; Collins, J. J. *Cell* **2020**, *180*, 688.

(10) For selected examples, see: (a) Zhang, Q.; Shreeve, J. M. *Chem. Rev*. **2014**, *114*, 10527. (b) Zhang, J.; Shreeve, J. M. *J. Am. Chem. Soc.* **2014**, *136*, 4437. (c) Palysaeva, N. V.; Gladyshkin, A. G.; Vatsadze, I. A.; Suponitsky, K. Yu.; Dmitriev, D. E.; Sheremetev, A. B. *Org. Chem. Front.* **2019**, *6*, 249. (d) Wei, H.; He, C.; Zhang, J.; Shreeve, J. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 9367. (e) Zhang, J.; Mitchell, L. A.; Parrish, D. A.; Shreeve, J. M. *J. Am. Chem. Soc.* **2015**, *137*, 10532. (f) Fershtat, L. L.; Makhova, N. N. *ChemPlusChem* **2020**, *85*, 13. (g) Sun, Q.; Shen, C.; Li, X.; Lin, Q.; Lu, M. *J. Mater. Chem. A* **2017**, *5*, 11063. (h) He, C.; Imler, G. H.; Parrish, D. A.; Shreeve, J. M. *J. Mater. Chem. A* **2018**, *6*, 16833.

(11) Kesornpun, C.; Aree, T.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 3997.

(12) Larin, A. A.; Fershtat, L. L.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron Lett.* **2017**, *58*, 3993.

(13) (a) Padwa, A.; Bur, S. *Adv. Heterocycl. Chem.* **2016**, *119*, 241. (b) Rosenau, T.; Adelwöhrer, C.; Hofinger, A.; Mereiter, K.; Kosma, P. *Eur. J. Org. Chem.* **2004**, 1323. (c) Trogu, E.; de Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2009**, *15*, 7940. (d) Maestri, G.; Caneque, T.; Della Ca', N.; Derat, E.; Catellani, M.; Chiusoli, G. P.; Malacria, M. *Org. Lett.* **2016**, *18*, 6108.

(14) For selected examples, see: (a) Nicolaides, D. N.; Gallos, J. K. *Synthesis* **1981**, 638. (b) Olofson, R. A.; Michelman, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1863. (c) Shaposhnikov, S. D.; Pirogov, S. V.; Mel'nikova, S. F.; Tselinsky, I. V.; Näther, C.; Graening, T.; Traulsen, T.; Friedrichsen, W. *Tetrahedron* **2003**, *59*, 1059.

(15) Boulton, A. J.; Katritzky, A. R.; Majid-Hamid, A. *J. Chem. Soc. C* **1967**, 2005.

(16) For reviews, see: (a) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141. (b) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49.

(17) For reviews, see: (a) Boulton, A. J.; Ghosh, P. B. *Adv. Heterocycl. Chem.* **1969**, *10*, 1. (b) Katritzky, A. R.; Gordeev, M. F. *Heterocycles* **1993**, *35*, 483.

(18) Burakevich, J. V.; Butler, R. S.; Volpp, G. P. *J. Org. Chem.* **1972**, *37*, 593.

(19) Wieland, H. *Justus Liebigs Ann. Chem.* **1921**, *424*, 107.

(20) *Bruker. APEX-III*; Bruker AXS Inc: Madison (WI, USA), **2018**.

(21) Krause, L.; Herbst-Irmer, R.; Sheldrick, G. M.; Stalke, D. *J. Appl. Crystallogr.* **2015**, *48*, 3.

(22) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2015**, *71*, 3.

(23) Sheldrick, G. M. *Acta Crystallogr., Sect. C* **2015**, *71*, 3.

(24) CCDC 1982203 (**3c**) and 1982204 (**4a**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 09, Revision D.01*; Gaussian, Inc: Wallingford, **2016**.

(26) Perdew, J.; Ernzerhof, M.; Burke, K. *J. Chem. Phys.* **1996**, *105*, 9982.

(27) Carlo, A.; Barone, V. *J. Chem. Phys.* **1999**, *110*, 6158.

(28) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, *32*, 1456.

(29) Vivona, N.; Macaluso, G.; Frenna, V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 483.

(30) Eaton, J. K.; Ruberto, R. A.; Kramm, A.; Viswanathan, V. S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2019**, *141*, 20407.