

PAPER

View Article Online
View Journal | View IssueCite this: *RSC Adv.*, 2019, 9, 6636Received 5th February 2019
Accepted 12th February 2019

DOI: 10.1039/c9ra00976k

rsc.li/rsc-advances

Electrophilic activation of nitroalkanes in efficient synthesis of 1,3,4-oxadiazoles†

Alexander V. Aksenov,^a Vladislav Khamraev,^a Nicolai A. Aksenov,^a
Nikita K. Kirilov,^a Dmitriy A. Domenyuk,^b Vladimir A. Zelensky^b
and Michael Rubin^{a,c}

A novel methodology for general and chemoselective preparation of non-symmetric 1,3,4-oxadiazoles is developed. This unusual reaction proceeds *via* polyphosphoric acid-assisted activation of nitroalkanes towards nucleophilic attack with acylhydrazides.

Introduction

Bioisosteric to carboxylate and carboxamide functionalities, 1,3,4-oxadiazoles are often considered among other privileged heterocyclic scaffolds for drug discovery.¹ Molecules possessing these key structural fragments have demonstrated a wide variety of important biological properties, including antibacterial, antimycobacterial, antifungal, insecticidal, herbicidal, anti-inflammatory, analgesic, anticonvulsant and anticancer activities.² Several medicinal agents featuring this heterocyclic ring have been marketed, including anti-HIV drug Raltegravir, antihypertensive Nesapidil, and anti-cancer agent Zibotentan (Fig. 1). This heterocyclic building block was also used for the construction of chiral catalysts³ and metal-selective chemosensors.⁴ A symmetrically substituted version of this system (5) can be easily obtained by cyclo-condensation of hydrazine hydrate with a variety of carbonyl compounds.⁵ Assembly of 1,3,4-oxadiazoles 4 with two different substituents is much more challenging, as it involves the selective reaction of hydrazine with two different carbonyl compounds, or their synthetic equivalents, to obtain non-symmetric *N,N'*-diacylhydrazide precursor 2 (Scheme 1). Such processes, especially when carried out in one-pot fashion, can be significantly complicated by side reactions involving *trans*-acylation of *N,N'*-diacylhydrazide intermediates with excess of the second carbonyl compound and leading to the formation of a mixture of non-symmetric (4) and symmetric (5) products. A variety of methods were suggested in an attempt to address this issue,

most of which are dealing with the moderation of the reactivity of the acylating reagent.⁶ In addition, different schemes involving cyclo-condensations of *N'*-alkylidene acylhydrazides,⁷ or re-cyclizations of tetrazoles,⁸ were also suggested. Herein we wish to report a new preparative method for selective assembly of non-symmetrically substituted 1,3,4-oxadiazoles employing nitroalkanes electrophilicity activated in the presence of polyphosphoric acid that serves as an acylating agent equivalent.

Results and discussion

For several years our group had a great interest in the development of novel acid-mediated cascade transformations of nitroalkenes and nitroalkanes targeting material science and medicinal chemistry applications. It was demonstrated that

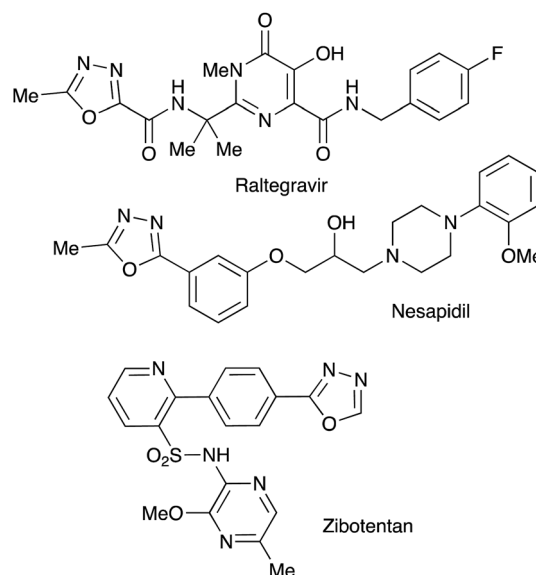


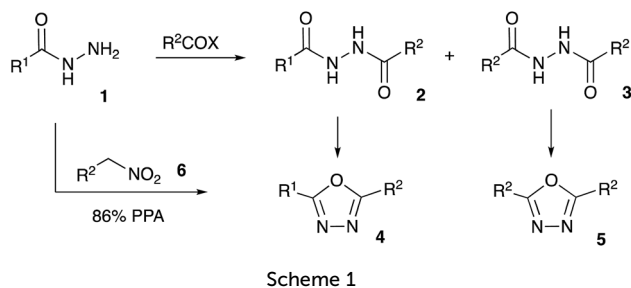
Fig. 1 1,3,4-Oxadiazoles in drug discovery and medicinal chemistry.

^aDepartment of Chemistry, North Caucasus Federal University, 1a Pushkin St., Stavropol 355009, Russian Federation. E-mail: alexaks05@rambler.ru

^bDepartment of General Practice Dentistry and Child Dentistry, Stavropol State Medical University, 310 Mira Street, Stavropol 355017, Russian Federation

^cDepartment of Chemistry, University of Kansas, 1567 Irving Hill Road, Lawrence, KS 66045-7582, USA. E-mail: mrubin@ku.edu; Tel: +1-785-864-5071

† Electronic supplementary information (ESI) available. CCDC 1875720, 1875721 and 1875723. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra00976k



nitroalkanes **6** dissolved in polyphosphoric acid (PPA) transform into phosphorylated nitronate **7** showing strong electrophilic properties. This unusual species can be used to design one-pot multi-step transformations involving various carbon-based nucleophiles.⁹ The utilization of nucleophilic amines was also demonstrated.¹⁰ Mechanistically, the latter process is related to the classical Nef reaction,¹¹ employing aniline species **8** instead of water. This reaction provides iminium ion **9**, that can be further employed as a convenient building block for the synthesis of heterocyclic compounds: oxazoles **10**, imidazoles **11**, and diazines **12–13** (Scheme 2).¹⁰ We wondered about the possibility of employing acylhydrazides **1** as nucleophilic components en route to the 1,3,4-oxazoles scaffolds. Indeed, such a nucleophilic attack to nitronate species **7** would afford (2-acylhydrazineyl)alkaniminium species **14**,¹² that should be well suited for an

intramolecular 5-*exo*-trig cyclization involving the carbonyl group of the hydrazide function and providing 4,5-dihydro-1,3,4-oxadiazol-3-ium ion **15**. The latter after deprotonation is expected to form 2,3-dihydro-1,3,4-oxadiazole **16**, which after the elimination of *O*-phosphorylated hydroxylamine would provide desired 1,3,4-oxadiazole **4** (Scheme 2).

To test this idea, a mixture benzohydrazide (**1a**, $R^1 = \text{Ph}$) and nitroethane (**6a**, $R^2 = \text{Me}$, 2.00 equiv.) was stirred in polyphosphoric acid (86% P_2O_5) at 70 °C (Table 1, entry 1). However, even after 90 min no reaction was observed. At 90 °C the reaction proceeded slowly and after 30 min the conversion reached 14%, however the main product of the reaction was 2,5-diphenyl-1,3,4-oxadiazole (**5a**, $R^2 = \text{Ph}$). At 110 °C (boiling point of nitroethane) the process proceeded to completion affording mixtures of 10% of non-symmetric product **4aa** and 55% symmetric oxadiazole **5a** (entry 3). The rest of the starting material polymerized forming highly polar resins. Employment of nitroethane (**6a**) in excess (3.00 equiv.) did not notably improve the reaction outcome (entries 4 and 5). Evidently, the symmetric product (**5a**) was formed *via* acid-mediated *trans*-acylation of **1a** to produce intermediate symmetric *N,N'*-diacylhydrazide **3a** ($R^2 = \text{Ph}$). In order to suppress this undesired process, we decided to add starting hydrazide **1a** in small portions over an extended period of time. This resulted in only marginal improvement, however, in the reactions carried out in the presence of stoichiometric amount of nitroethane (entry 6). Gradual increase of the concentration of nitroethane (entries 7–10) resulted in both the conversion and chemoselectivity of the process to achieve exclusive formation of product **5a** at 99% yield (entry 10). We also tested the possibility of employing Eaton's reagent (P_2O_5 in MeSO_3H) as a mixture that is often used as an alternative to PPA in synthesis, but in this medium hydrazide **6a** underwent complete hydrolysis to afford benzoic acid as the only detectable product of the reaction (entries 11 and 12).

With the optimized reaction conditions in hand we carried out the reaction between **1a** and **6a** in preparative

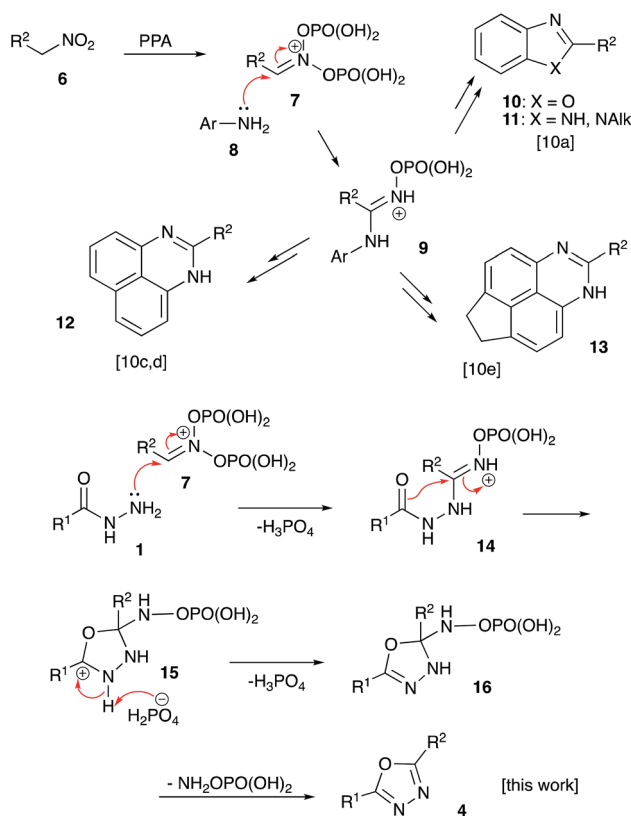
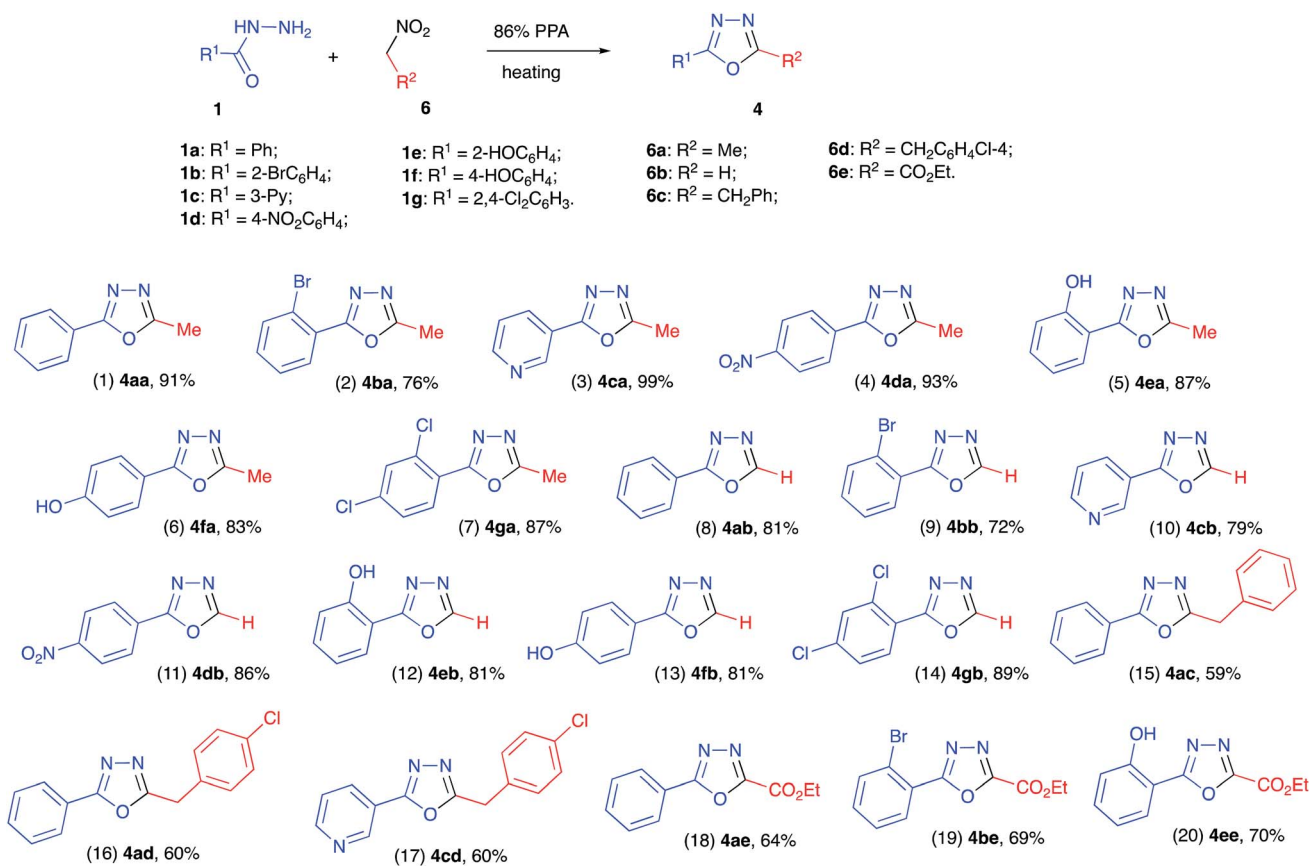


Table 1 Optimization of reaction conditions for cyclocondensation of **1a** and **6a** to produce oxadiazoles **4aa** and **5a**

	6a (equiv.)	Medium	T , °C (time)	4aa : 5a ^a
1	1.00	86% PPA	70 (1.5 h) ^b	0 : 0
2	1.00		90 (0.5 h) ^b	0 : 14
3	1.00		110 (0.5 h) ^b	10 : 55
4	3.00		90 (0.5 h) ^b	0 : 17
5	3.00		110 (1 h) ^b	31 : 61
6	1.00		110 (1 h) ^c	12 : 38
7	2.00		110 (1 h) ^c	63 : 25
8	3.00		110 (1 h) ^c	64 : 15
9	5.00		110 (1.5 h) ^c	94 : 6
10	7.00		110 (1.5 h) ^c	99 : 0
11	3.00	Eaton's reagent 1 : 7	110 (1 h)	0 : 0 ^d
12	3.00	Eaton's reagent 1 : 10	110 (1 h)	0 : 0 ^d

^a NMR yields of compounds **4a** and **5a** are shown. ^b Benzohydrazide was added in a single portion. ^c Benzohydrazide was slowly added by small portions. ^d Complete hydrolysis of benzohydrazide was observed, affording benzoic acid as sole product.





Scheme 3

scale (1.00 mmol). We were pleased to find, that oxadiazole **4aa** was obtained in this reaction as sole product and isolated in high yield (Scheme 3, entry 1). Hydrazides **1b–g**, derived from other aryl- and hetarylcarboxylic acids, also reacted with nitroethane (**6a**) smoothly, affording the corresponding heterocyclic products (entries 2–7). Remarkably, non-protected phenols **1e** and **1f** also reacted uneventfully, which showcases the dual role of polyphosphoric acid as a versatile reaction medium with acidic properties and as a reagent for the reversible installation of temporary protecting phosphatyl groups.

Thorough analysis of literature revealed that synthetic access to monosubstituted oxadiazoles is especially challenging, since preparation of non-symmetric bis-hydrazides **2** required for this cyclo-condensation is severely complicated by relatively high strength formic acid and elevated electrophilicity of formohydrazide derivatives.¹³ This problem can be typically circumvented by usage of orthoformates as acylating agents.¹⁴ We felt, however, that in our featured methodology, there should not be a dramatic difference between reactivity of nitroethane (**6a**) and nitromethane (**6b**). This would allow for the development of a very general synthetic protocol to access 1,3,4-oxadiazoles with different substitution patterns. To test this possibility, we carried out reactions with a series of benzohydrazides (**1a–g**) in the presence of excess nitromethane (**6b**) at

100 °C (boiling point of nitromethane). Gratifyingly, these reactions proceeded smoothly affording the corresponding 2-aryl-1,3,4-oxadiazoles **4ab–4gb** in high yields (Scheme 3, entries 8–14). Along the same lines, we tested the possibility of employing (2-nitroethyl)benzenes (**6c–d**) as electrophilic components in the featured transformation. These reactions were more sluggish, probably due to excessive steric hindrance in the phosphorylated nitronate intermediates **7**. It was found, however, that the cyclo-condensation could be pushed to complete conversion at 140 °C to afford the corresponding 5-benzylloxadiazoles **4ac**, **4ad**, and **4cd** albeit in somewhat lower yields (entries 15–17).

Another major challenge in chemistry of 1,3,4-oxadiazoles is associated with incorporation of ester substituents at C-2 of this heterocyclic scaffold.¹⁵ To address this issue we attempted the reaction of various benzohydrazides (**1a,b,e**) with ethyl 2-nitroacetate. We were pleased to discover that this reaction also proceeded smoothly under standard reaction conditions (temperature was raised to 130 °C to ensure complete conversion) affording the corresponding 1,3,4-oxadiazole-2-carboxylates as the sole isolable product (Scheme 3, entries 18–20).

The formation and structural identity of compounds **5a**, **4ga**, and **4ca** was unambiguously confirmed by a single crystal X-ray crystallography (Fig. 2).



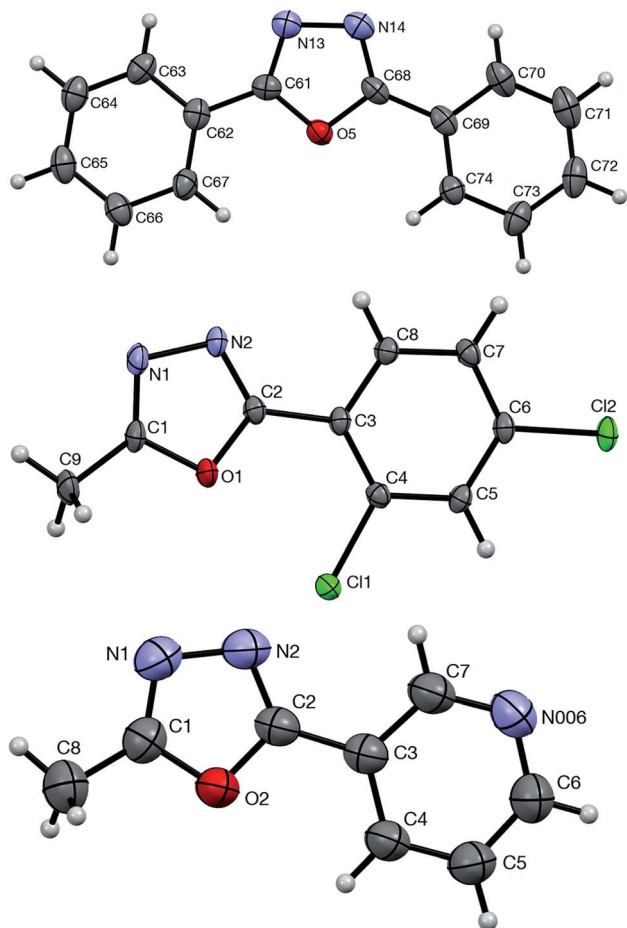


Fig. 2 ORTEP drawings of **5a** (top, CCDC #1875720), **4ga** (middle, CCDC #1875721), and **4ca** (bottom, CCDC #1875723) showing atom numbering schemes and 50% probability ellipsoids.

Conclusion

In conclusion, the novel one-pot multistep reaction sequence involving cyclo-condensation of acylhydrazides with electrophilicity-activated nitroalkanes was investigated. Careful optimization of the reaction conditions resulted in excellent chemo-selectivity of this newly developed synthetic protocol towards monosubstituted and non-symmetrically disubstituted 1,3,4-oxadiazoles. High yields of the resulting heterocyclic products and great functional group compatibility of this synthetic methodology was demonstrated.

Experimental part

General information

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with a BBO probe in CDCl_3 or $\text{DMSO}-d_6$, using TMS as an internal standard. High-resolution mass spectra were registered with a Bruker Maxis spectrometer (electrospray ionization, in MeCN solution, using $\text{HCO}_2\text{Na}-\text{HCO}_2\text{H}$ for calibration). Melting points were measured with a Stuart smp30 apparatus. All reactions were performed in oven-dried 5 mL round-bottomed

flasks open to the atmosphere, employing overhead stirring. The reaction progress and purity of isolated compounds were controlled by TLC on Silufol UV-254 plates, with EtOAc as eluent. PPA was obtained by dissolving of P_2O_5 in 85% ortho-phosphoric acid according to the published protocol.¹⁶ All reagents and solvents were purchased from commercial vendors and used as received. Physical and spectral properties of compound **5a** were identical to those reported in literature.¹⁷

2-Methyl-5-phenyl-1,3,4-oxadiazole (4aa V210). Typical procedure. A 10 mL Erlenmeyer flask equipped with magnetic bar and reflux condenser was charged with polyphosphoric acid (86% P_2O_5 , 1.5 g) and nitroethane (**6a**) (500 μL , 525 mg, 7.00 mmol) and heated while stirring at 105–115 $^\circ\text{C}$. Benzohydrazide (**1a**) (136 mg, 1.00 mmol) was added slowly in small portions over 1 h, and the mixture was heated for an additional 30 min, when TLC analysis showed the completion of the reaction. The mixture was diluted with water (5 mL), neutralized with 25% aqueous ammonia (4.5–5.0 mL is typically required), and extracted with EtOAc (4×5 mL). Combined organic phases were concentrated and the crude product was purified by preparative column chromatography eluting with EtOAc/petroleum ether mixture 1 : 1 to obtain the titled compound as a colorless solid, mp 63–65 $^\circ\text{C}$ (EtOAc), R_f 0.39 (EtOAc/petroleum ether, 1 : 1). Yield 146 mg (0.91 mmol, 91%). ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, J = 7.8 Hz, 2H), 7.55–7.46 (m, 3H), 2.61 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.0, 163.8, 131.7, 129.1, 126.8, 124.0, 11.3; IR (KBr, film, cm^{-1}): 3060, 2943, 1582, 1556, 1487, 1450, 1252, 1095, 1073, 1021, 959; HRMS (ESI TOF) calculated for $\text{C}_9\text{H}_8\text{N}_2\text{NaO}$ ($M + \text{Na}$)⁺ 183.0529, found 183.0531 (1.3 ppm).

2-(2-Bromophenyl)-5-methyl-1,3,4-oxadiazole (4ba V226). This material was obtained from 2-bromobenzohydrazide (**1b**) (215 mg, 1.00 mmol) and nitroethane (**6a**) (500 μL , 525 mg, 7.00 mmol). The reaction was carried at 105–115 $^\circ\text{C}$, and the titled compound was isolated as a yellowish oil, R_f 0.37 (EtOAc/petroleum ether, 1 : 3). Yield 199 mg (83%). ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.3, 164.0, 134.6, 132.5, 131.7, 127.7, 125.5, 121.7, 11.3; IR (KBr, film, cm^{-1}) 3071, 2932, 1586, 1435, 1347, 1241, 1098, 1021, 959; HRMS (ESI TOF) calculated for $\text{C}_9\text{H}_7\text{BrN}_2\text{NaO}$ ($M + \text{Na}$)⁺ 260.9634, found 260.9630 (1.7 ppm).

2-Methyl-5-(pyridin-3-yl)-1,3,4-oxadiazole (4ca V229). This material was obtained from nicotinohydrazide (**1c**) (137 mg, 1.00 mmol) and nitroethane (**6a**) (500 μL , 525 mg, 7.00 mmol). The reaction was carried out at 105–115 $^\circ\text{C}$, and the titled compound was isolated as a colorless solid, precipitated after aqueous work up and basification. No chromatographic purification was required. Mp 114–116 $^\circ\text{C}$ (EtOAc), R_f 0.43 (EtOAc/EtOH, 4 : 1). Yield 159 mg (0.99 mmol, 99%). ^1H NMR (400 MHz, CDCl_3) δ 9.25 (s, 1H), 8.77 (d, J = 4.7 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 7.9, 5.0 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.5, 162.7, 151.8, 147.2, 134.7, 124.2, 120.9, 11.9; IR (KBr, film, cm^{-1}) 3082, 3049, 2932, 1593, 1575, 1549, 1468, 1432, 1351, 1259, 1087, 1010, 988, 959; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_7\text{N}_3\text{NaO}$ ($M + \text{Na}$)⁺ 184.0481, found 183.0482 (0.2 ppm).



2-Methyl-5-(4-nitrophenyl)-1,3,4-oxadiazole (4da V233). This material was obtained from 4-nitrobenzohydrazide (**1d**) (181 mg, 1.00 mmol) and nitroethane (**6a**) (500 μ L, 525 mg, 7.00 mmol). The reaction was carried out at 105–115 °C, and the titled compound was isolated as a yellow solid, mp 168–170 °C (EtOAc), R_f 0.27 (EtOAc/petroleum ether, 1 : 1). Yield 191 mg (0.93 mmol, 93%). ^1H NMR (400 MHz, CDCl_3) δ 8.37 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 8.6 Hz, 2H), 2.67 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.9, 163.4, 149.6, 129.6, 127.8, 124.5, 11.3; IR (KBr, film, cm^{-1}) 3108, 3071, 3016, 2932, 1578, 1553, 1520, 1351, 1333, 1311, 1292, 1234, 1087, 1032, 867; HRMS (ESI TOF) calculated for $\text{C}_9\text{H}_7\text{N}_3\text{NaO}_3$ ($\text{M} + \text{Na}$) $^+$ 228.0380, found 228.0378 (0.8 ppm).

2-(5-Methyl-1,3,4-oxadiazol-2-yl)phenol (4ea V235). This material was obtained from 2-hydroxybenzohydrazide (**1e**) (152 mg, 1.00 mmol) and nitroethane (**6a**) (500 μ L, 525 mg, 7.00 mmol). The reaction was carried out at 105–115 °C, and the titled compound was isolated as a light-brown solid, mp 73–75 °C (acetone/EtOAc), R_f 0.38 (EtOAc/petroleum ether, 1 : 3). Yield 143 mg (0.87 mmol, 87%). ^1H NMR (400 MHz, CDCl_3) δ 10.12 (br, s, 1H), 7.73 (dd, J = 7.9, 1.5 Hz, 1H), 7.47–7.38 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.04–6.94 (m, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.7, 162.6, 157.6, 133.6, 126.5, 120.0, 117.7, 108.3, 11.2; IR (KBr, film, cm^{-1}) 3189, 3071, 2976, 2943, 1629, 1593, 1549, 1490, 1439, 1410, 1355, 1300, 1241, 1080, 1040, 963; HRMS (ESI TOF) calculated for $\text{C}_9\text{H}_8\text{N}_2\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$ 199.0478, found 199.0476, (1.0 ppm).

4-(5-Methyl-1,3,4-oxadiazol-2-yl)phenol (4fa V242). This material was obtained from 4-hydroxybenzohydrazide (**1f**) (152 mg, 1.00 mmol) and nitroethane (**6a**) (500 μ L, 525 mg, 7.00 mmol). The reaction was carried out at 105–115 °C, and the titled compound was isolated as a light-brown solid, mp 236–238 °C (acetone/EtOAc); R_f 0.30 (EtOAc/petroleum ether, 2 : 1). Yield 146 mg (0.83 mmol, 83%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.28 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 164.1, 163.1, 160.6, 128.3, 116.2, 114.4, 10.6. IR (KBr, film, cm^{-1}) 3156, 3020, 2947, 1611, 1589, 1494, 1377, 1289, 1234, 1164, 1120, 1073, 933, 853; HRMS (ESI TOF) calculated for $\text{C}_9\text{H}_8\text{N}_2\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$ 199.0478, found 199.0482 (1.9 ppm).

2-(2,4-Dichlorophenyl)-5-methyl-1,3,4-oxadiazole (4ga V240). This material was obtained from 2,4-dichlorobenzohydrazide (**1g**) (205 mg, 1.00 mmol) and nitroethane (**6a**) (500 μ L, 525 mg, 7.00 mmol). The reaction was carried out at 105–115 °C, and the titled compound was isolated as a colorless solid, mp 92–102 °C (EtOAc), R_f 0.50 (EtOAc/petroleum ether, 1 : 1). Yield 199 mg (0.87 mmol, 87%). ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.4, 162.7, 138.1, 133.9, 131.9, 131.3, 127.7, 121.9, 11.3; IR (KBr, film, cm^{-1}) 3104, 3086, 3009, 2936, 1589, 1564, 1454, 1417, 1270, 1241, 1106, 1018, 963, 879; HRMS (ESI TOF) calculated for $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 250.9749, found 250.9747 (0.8 ppm).

2-Phenyl-1,3,4-oxadiazole (4ab V216). This material was obtained from benzohydrazide (**1a**) (136 mg, 1.00 mmol) and nitromethane (**6b**) (581 μ L, 610 mg, 10.0 mmol). The reaction

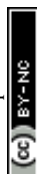
was carried out at 95–105 °C, and the titled compound was isolated as a colorless oil, R_f 0.24 (EtOAc/petroleum ether, 1 : 3). Yield 119 mg (0.81 mmol, 81%). ^1H NMR (400 MHz, CDCl_3) δ 8.48 (s, 1H), 8.11–8.05 (m, 2H), 7.57–7.49 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.9, 152.8, 132.2, 129.3, 127.2, 123.6; IR (KBr, film, cm^{-1}) 3064, 1578, 1556, 1487, 1450, 1355, 1248, 1091, 1076, 1025, 959, 930; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_6\text{N}_2\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 169.0372, found 169.0373 (0.3 ppm).

2-(2-Bromophenyl)-1,3,4-oxadiazole (4bb V232). This material was obtained from 2-bromobenzohydrazide (**1b**) (215 mg, 1.00 mmol) and nitromethane (**6b**) (581 μ L, 610 mg, 10.0 mmol). The reaction was carried out at 95–105 °C, and the titled compound was isolated as a yellow oil, R_f 0.28 (EtOAc/petroleum ether, 1 : 3). Yield 162 mg (0.72 mmol, 72%). ^1H NMR (400 MHz, CDCl_3) δ 8.57 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.9, 153.2, 134.7, 132.9, 131.9, 127.8, 125.1, 121.9; IR (KBr, film, cm^{-1}) 3119, 3002, 1597, 1575, 1516, 1457, 1432, 1234, 1109, 1084, 1025, 952; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_5\text{BrN}_2\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 246.9477, found 246.9479 (0.6 ppm).

2-(Pyridin-3-yl)-1,3,4-oxadiazole (4cb V230). This material was obtained from nicotinohydrazide (**1c**) (137 mg, 1.00 mmol) and nitromethane (**6b**) (581 μ L, 610 mg, 10.0 mmol). The reaction was carried out at 95–105 °C, and the titled compound was isolated after extraction with dichloromethane (4 \times 5 mL) as a colorless solid, mp 72–73 °C (EtOAc); R_f 0.51 (EtOAc/EtOH, 4 : 1). Yield 116 mg (0.79 mmol, 79%). ^1H NMR (400 MHz, CDCl_3) δ 9.31 (s, 1H), 8.84–8.76 (m, 1H), 8.55 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 8.0, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 162.9, 153.2, 152.9, 148.2, 134.6, 124.0, 120.2, 77.2; IR (KBr, film, cm^{-1}) 3332, 3071, 2998, 1608, 1586, 1556, 1512, 1468, 1432, 1267, 1131, 1102, 1073, 1021, 952, 897; HRMS (ESI TOF) calculated for $\text{C}_7\text{H}_5\text{N}_3\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 170.0325, found 170.0330 (3.1 ppm).

2-(4-Nitrophenyl)-1,3,4-oxadiazole (4db V245). This material was obtained from 4-nitrobenzohydrazide (**1d**) (181 mg, 1.00 mmol) and nitromethane (**6b**) (581 μ L, 610 mg, 10.0 mmol). The reaction was carried out at 95–105 °C, and the titled compound was isolated as a yellow solid, mp 152–153 °C (EtOAc), R_f 0.32 (EtOAc/petroleum ether, 1 : 2). Yield 165 mg (0.86 mmol, 86%). ^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 8.40 (d, J = 8.9 Hz, 2H), 8.30 (d, J = 8.9 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.3, 153.6, 149.9, 129.1, 128.3, 124.6; IR (KBr, film, cm^{-1}) 3163, 3108, 3075, 3009, 1611, 1560, 1520, 1333, 1311, 1296, 1113, 1065, 948, 853; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_5\text{N}_3\text{NaO}_3$ ($\text{M} + \text{Na}$) $^+$ 214.0223, found 214.0225 (1.1 ppm).

2-(1,3,4-Oxadiazol-2-yl)phenol (4eb V247). This material was obtained from 2-hydroxybenzohydrazide (**1e**) (152 mg, 1.00 mmol) and nitromethane (**6b**) (581 μ L, 610 mg, 10.0 mmol). The reaction was carried out at 95–105 °C, and the titled compound was isolated as a colorless solid, mp 84–86 °C (acetone), R_f 0.35 (EtOAc/petroleum ether, 1 : 3). Yield 131 mg (0.81 mmol, 81%); ^1H NMR (400 MHz, CDCl_3) δ 10.06 (s, 1H), 8.47 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.5, 157.8, 151.5, 134.2, 126.9, 120.2, 117.8, 107.9; IR (KBr,



film, cm^{-1}) 3222, 3148, 3068, 1769, 1728, 1626, 1586, 1549, 1490, 1406, 1303, 1256, 1157, 1095, 1058, 952; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_6\text{N}_2\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$ 185.0321, found 185.0320 (1.0 ppm).

4-(1,3,4-Oxadiazole-2-yl)phenol (4fb V260). This material was obtained from 4-hydroxybenzohydrazide (**1f**) (152 mg, 1.00 mmol) and nitromethane (**6b**) (581 μL , 610 mg, 10.0 mmol). The reaction was carried out at 95–105 $^\circ\text{C}$, and the titled compound was isolated as a colorless solid, mp 127–129 $^\circ\text{C}$ (acetone), R_f 0.34 (EtOAc/petroleum ether, 1 : 1). Yield 130 mg (0.81 mmol, 81%). ^1H NMR (400 MHz, CDCl_3) δ 10.33 (s, 1H), 9.23 (s, 1H), 7.85 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.8, 160.9, 153.8, 128.7, 116.2, 114.0; IR (KBr, film, cm^{-1}) 3147, 3027, 1615, 1597, 1498, 1384, 1285, 1245, 1179, 1128, 1065, 966, 941, 853; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_6\text{N}_2\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$: 185.0321, found 185.0326 (2.3 ppm).

2-(2,4-Dichlorophenyl)-1,3,4-oxadiazole (4gb V246). This material was obtained from 2,4-dichlorobenzohydrazide (**1g**) (205 mg, 1.00 mmol) and nitromethane (**6b**) (581 μL , 610 mg, 10.0 mmol). The reaction was carried out at 95–105 $^\circ\text{C}$, and the titled compound was isolated as a colorless solid, mp 141–151 $^\circ\text{C}$ (EtOAc), R_f 0.41 (EtOAc/petroleum ether, 1 : 2). Yield 192 mg (0.89 mmol, 89%). ^1H NMR (400 MHz, CDCl_3) δ 8.57 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.41 (dd, J = 8.5, 1.8 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 162.7, 153.2, 138.6, 134.2, 132.1, 131.4, 127.8, 121.4; IR (KBr, film, cm^{-1}) 3314, 3204, 3093, 3027, 1659, 1633, 1593, 1512, 1457, 1377, 1307, 1252, 1106, 1058, 959, 893, 864; HRMS (ESI TOF) calculated for $\text{C}_8\text{H}_4\text{Cl}_2\text{N}_2\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 236.9593, found 236.9588 (2.1 ppm).

2-Benzyl-5-phenyl-1,3,4-oxadiazole (4ac V251). This material was obtained from benzohydrazide (**1a**) (136 mg, 1.00 mmol) and (2-nitroethyl)benzene (**6c**) (202 μL , 226 mg, 1.50 mmol). The reaction was carried out at 130–135 $^\circ\text{C}$, and the titled compound was isolated as a colorless solid, mp 93–95 $^\circ\text{C}$ (EtOAc), R_f 0.35 (EtOAc/petroleum ether, 1 : 3). Yield 139 mg (0.59 mmol, 59%). ^1H NMR (400 MHz, CDCl_3) δ 8.04–7.97 (m, 2H), 7.52–7.45 (m, 3H), 7.36 (d, J = 4.3 Hz, 3H), 7.31 (dd, J = 8.6, 4.2 Hz, 1H), 4.29 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.4, 165.3, 134.0, 131.8, 129.12, 129.08, 129.0, 127.7, 127.0, 124.0, 32.1; IR (KBr, film, cm^{-1}) 3075, 2928, 2858, 1567, 1553, 1490, 1454, 1424, 1256, 1095, 1065, 1010, 959; HRMS (ESI TOF) calculated for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{NaO}$ ($\text{M} + \text{Na}$) $^+$: 259.0842, found 259.0842 (0.0 ppm).

2-(4-Chlorobenzyl)-5-phenyl-1,3,4-oxadiazole (4ad V253). This material was obtained from benzohydrazide (**1a**) (136 mg, 1.00 mmol) and 1-chloro-4-(2-nitroethyl)benzene (**6d**) (220 μL , 278 mg, 1.50 mmol). The reaction was carried out at 130–135 $^\circ\text{C}$, and the titled compound was isolated as a colorless solid, mp 107–109 $^\circ\text{C}$ (EtOAc); R_f 0.24 (EtOAc/petroleum ether, 1 : 3). Yield 162 mg (0.60 mmol, 60%). ^1H NMR (400 MHz, CDCl_3) δ 8.00 (dd, J = 8.0, 1.4 Hz, 2H), 7.53–7.45 (m, 3H), 7.32 (q, J = 8.6 Hz, 4H), 4.25 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.4, 164.9, 133.7, 132.4, 131.9, 130.3, 129.3, 129.2, 127.0, 123.8, 31.4; IR (KBr, film, cm^{-1}) 3068, 2928, 2855, 1553, 1490, 1450, 1380, 1194, 1087, 1010, 961; HRMS (ESI TOF) calculated for $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 293.0452, found 293.0460 (2.7 ppm).

2-(4-Chlorobenzyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (4cd V254). This material was obtained from nicotinohydrazide (**1c**) (137 mg, 1.00 mmol) and 1-chloro-4-(2-nitroethyl)benzene (**6c**) (220 μL , 278 mg, 1.50 mmol). The reaction was carried out at 130–135 $^\circ\text{C}$, and the titled compound was isolated as a colorless solid, mp 112–114 $^\circ\text{C}$ (EtOAc), R_f 0.34 (EtOAc/petroleum ether, 1 : 3). Yield 146 mg (0.54 mmol, 54%). ^1H NMR (400 MHz, CDCl_3) δ 9.22 (s, 1H), 8.77 (d, J = 4.3 Hz, 1H), 8.35 (d, J = 7.9 Hz, 1H), 7.49 (dd, J = 7.8, 4.9 Hz, 1H), 7.33 (q, J = 8.5 Hz, 4H), 4.28 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.7, 163.1, 151.8, 147.2, 134.9, 134.0, 132.0, 130.4, 129.4, 124.2, 120.7, 31.4; IR (KBr, film, cm^{-1}) 3090, 3064, 2958, 2925, 2855, 1567, 1490, 1413, 1256, 1186, 1084, 1007, 963, 853; HRMS calculated for $\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 294.0405, found 293.0395, (3.2 ppm).

Ethyl 5-phenyl-1,3,4-oxadiazole-2-carboxylate (4ae V269). This material was obtained from benzohydrazide (**1a**) (136 mg, 1.00 mmol) and ethyl 2-nitroacetate (**6e**) (165 μL , 200 mg, 1.50 mmol). The reaction was carried out at 120–130 $^\circ\text{C}$, and the titled compound was isolated as a colorless oil, R_f 0.47 (EtOAc/petroleum ether, 1 : 3). Yield 136 mg (0.64 mmol, 64%). ^1H NMR (400 MHz, CDCl_3) δ 8.20–8.14 (m, 2H), 7.63–7.58 (m, 1H), 7.57–7.52 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.6, 156.6, 154.6, 133.0, 129.4, 127.8, 122.9, 63.7, 14.3; IR (KBr, film, cm^{-1}) 3078, 2994, 2941, 1748, 1625, 1546, 1478, 1452, 1377, 1242, 1190, 1163, 1070, 1017, 841, 792, 713, 691; HRMS (ESI TOF) calculated for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}$) $^+$ 241.0584, found 241.0577 (2.8 ppm).

Ethyl 5-(2-bromophenyl)-1,3,4-oxadiazole-2-carboxylate (4be V273). This material was obtained from 2-bromobenzohydrazide (**1b**) (215 mg, 1.00 mmol) and ethyl 2-nitroacetate (**6e**) (165 μL , 200 mg, 1.50 mmol). The reaction was carried out at 120–130 $^\circ\text{C}$, and the titled compound was isolated as a colorless oil, R_f 0.30 (EtOAc/petroleum ether, 1 : 3). Yield 205 mg (0.69 mmol, 69%). ^1H NMR (400 MHz, CDCl_3) δ 8.00 (dd, J = 7.6, 1.8 Hz, 1H), 7.79 (dd, J = 7.8, 1.3 Hz, 1H), 7.49 (td, J = 7.5, 1.4 Hz, 1H), 7.44 (td, J = 7.7, 1.9 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.5, 157.0, 154.5, 134.9, 133.5, 132.2, 127.9, 124.4, 122.2, 63.8, 14.2; IR (KBr, film, cm^{-1}) 2985, 1748, 1598, 1535, 1441, 1377, 1298, 1253, 1186, 1167, 1100, 1028, 841, 770, 732; HRMS (ESI TOF) calculated for $\text{C}_{11}\text{H}_9\text{BrN}_2\text{NaO}_3$ ($\text{M} + \text{Na}$) $^+$ 318.9689, found 318.9692 (1.0 ppm).

Ethyl 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2-carboxylate (4ee V274). This material was obtained from 2-hydroxybenzohydrazide (**1e**) (152 mg, 1.00 mmol) and ethyl 2-nitroacetate (**6e**) (165 μL , 200 mg, 1.50 mmol). The reaction was carried out at 120–130 $^\circ\text{C}$, and the titled compound was isolated as a colorless oil, R_f 0.35 (EtOAc/petroleum ether, 1 : 3). Yield 164 mg (0.70 mmol, 70%). ^1H NMR (400 MHz, CDCl_3) δ 9.92 (s, 1H), 7.87 (dd, J = 7.9, 1.6 Hz, 1H), 7.53–7.46 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06–7.00 (m, 1H), 4.56 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.2, 158.4, 155.1, 154.2, 135.1, 127.4, 120.4, 118.0, 107.2, 63.9, 14.2; IR (KBr, film, cm^{-1}) 3245, 2986, 1748, 1625, 1542, 1493, 1377, 1313, 1242, 1186, 1163, 1058, 1021, 852, 751, 710, 676; HRMS (ESI TOF) calculated for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{NaO}_4$ ($\text{M} + \text{Na}$) $^+$ 257.0533, found 257.0532 (0.5 ppm).



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financed by the Russian Foundation for Basic Research (grant #18-33-20021 mol_a_ved) grants from the Ministry of Education and Science of the Russian Federation #4.1196.2017/4.6 and #4.4589.2017/6.7.

Notes and references

- 1 S. Sharma, P. K. Sharma, N. Kumar and R. Dudhe, *Pharma. Chemica.*, 2010, **2**, 253–263.
- 2 H. Khalilullah, M. J. Ahsan, M. Hedaitullah, S. Khan and B. Ahmed, *Mini-Rev. Med. Chem.*, 2012, **12**, 789.
- 3 Y. Zhou, W. H. Wang, W. Dou, X.-L. Tang and W.-S. Liu, *Chirality*, 2008, **20**, 110–114.
- 4 (a) X. L. Tang, X. H. Peng, W. Dou, J. Mao, J. R. Zheng, W. W. Qin, W.-S. Liu, J. Chang and X.-J. Yao, *Org. Lett.*, 2008, **10**, 3653–3656; (b) J. Zhang, L. Zhou, H. A. Al-Attar, K. Shao, L. Wang, D. Zhu, Z. Su, M. R. Bryce and A. P. Monkman, *Adv. Funct. Mater.*, 2013, **23**, 4667–4677.
- 5 See, for example: V. K. Tandon and R. B. Chhor, *Synth. Commun.*, 2001, **31**, 1727–1732.
- 6 See, for example: (a) B. J. Brown, I. R. Clemens and J. K. Neesom, *Synlett*, 2000, 131–133; (b) P. S. N. Reddy and P. P. Reddy, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1988, **27B**, 763–765.
- 7 (a) K. Du, X. Cao, P. Zhang and H. Zheng, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5318–5320; (b) C. Dobrota, C. C. Paraschivescu, I. Dumitru, M. Matache, I. Baci and L. L. Ruta, *Tetrahedron Lett.*, 2009, **50**, 1886–1888.
- 8 (a) C. Trecant, A. Dlubala, P. George, P. Pichat, I. Ripoche and Y. Troin, *Eur. J. Med. Chem.*, 2011, **46**, 4035–4041; (b) B. Verheyde and W. Dehaen, *J. Org. Chem.*, 2001, **66**, 4062–4064; (c) X. Jiang, R. A. Register, K. A. Killeen, M. E. Thompson, F. Pschenitzka and J. C. Sturm, *Chem. Mater.*, 2000, **12**, 2542–2549.
- 9 (a) N. A. Aksenov, A. V. Aksenov, O. N. Nadein, D. A. Aksenov, A. N. Smirnov and M. Rubin, *RSC Adv.*, 2015, **5**, 71620–71626; (b) A. V. Aksenov, N. A. Aksenov, O. N. Nadein and I. V. Aksenova, *Synlett*, 2010, 2628–2630.
- 10 (a) N. A. Aksenov, A. V. Aksenov, O. N. Nadein, D. A. Aksenov, A. N. Smirnov and M. Rubin, *RSC Adv.*, 2015, **5**, 71620–71626; (b) A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, A. S. Bijieva, I. V. Aksenova and M. Rubin, *Org. Biomol. Chem.*, 2015, **13**, 4289–4295; (c) A. V. Aksenov, N. A. Aksenov, D. S. Ovcharov, D. A. Aksenov, G. Griaznov, L. G. Voskressensky and M. Rubin, *RSC Adv.*, 2016, **6**, 82425–82431; (d) A. V. Aksenov, D. S. Ovcharov, N. A. Aksenov, D. A. Aksenov, O. N. Nadein and M. Rubin, *RSC Adv.*, 2017, **7**, 29927–29932; (e) A. V. Aksenov, N. A. Aksenov, S. V. Scherbakov, A. N. Smirnov, I. V. Aksenova, V. I. Goncharov and M. A. Rubin, *Russ. J. Org. Chem.*, 2017, **53**, 1081–1084; (f) A. I. Konovalov, *et al.*, *Russ. J. Org. Chem.*, 2018, **54**, 157–371.
- 11 For reviews, see: (a) R. Ballini and M. Petrini, *Adv. Synth. Catal.*, 2015, **357**, 2371–2402; (b) R. Ballini and M. Petrini, *Tetrahedron*, 2004, **60**, 1017–1047.
- 12 Formation of species **14** was unambiguously confirmed by high resolution ESI MS analysis of the reaction mixture. See ESI (page S55†) for details.
- 13 (a) M.-F. Pouliot, L. Angers, J.-D. Hamel and J.-F. Paquin, *Org. Biomol. Chem.*, 2012, **10**, 988–993; (b) Q. Gao, S. Liu, X. Wu, J. Zhang and A. Wu, *Org. Lett.*, 2015, **17**, 2960–2963.
- 14 (a) N. Salvanna, G. C. Reddy, B. R. Rao and B. Das, *RSC Adv.*, 2013, **3**, 20538–20544; (b) K. K. Gnanasekaran, B. Nammalwar, M. Murie and R. A. Bunce, *Tetrahedron Lett.*, 2014, **55**, 6776–6778; (c) T. Kawano, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2010, **132**, 6900–6901; (d) L.-H. Zou, J. Reball, J. Mottweiler and C. Bolm, *Chem. Commun.*, 2012, **48**, 11307–11309.
- 15 (a) J. Dost, M. Heschel and J. Stein, *J. Prakt. Chem.*, 1985, **327**, 109–116; (b) G. I. Elliott, J. R. Fuchs, B. S. J. Blagg, H. Ishikawa, H. Tao, Z.-Q. Yuan and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10589–10595; (c) J. Garfunkle, C. Ezzili, T. J. Rayl, D. G. Hochstatter, I. Hwang and D. L. Boger, *J. Med. Chem.*, 2008, **51**, 4392–4403.
- 16 (a) F. Uhlig, *Angew. Chem.*, 1954, **66**, 435–436; (b) A. L. Huhti and P. A. Gartaganis, *Can. J. Chem.*, 1956, **34**, 790–797.
- 17 Y.-D. Park, J.-J. Kim, H.-A. Chung, D.-H. Kweon, S.-D. Cho, S.-G. Lee and Y.-J. Yoon, *Synthesis*, 2003, 560–564.

