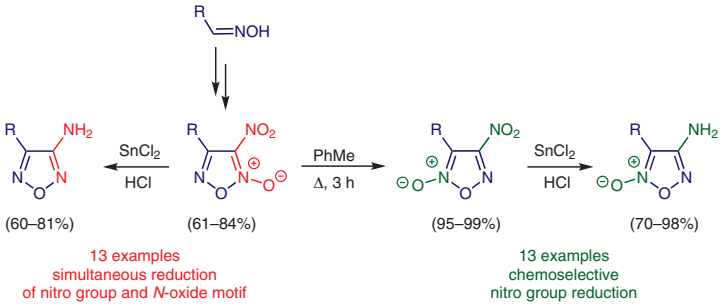
Synthesis L. L. Fershtat et al. Paper

N-Oxide-Controlled Chemoselective Reduction of Nitrofuroxans

Leonid L. Fershtat[*a]
Dmitry M. Bystrov[a,b]
Egor S. Zhilin[a,b]
Nina N. Makhova[a]

[a] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation
fershtat@bk.ru
[b] Department of Chemistry, Moscow State University, 119991 Moscow, Leninskie Gory 1-3, Russian Federation



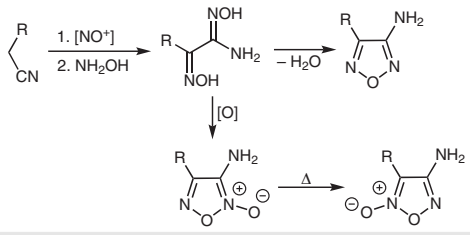
Received: 07.07.2018
Accepted after revision: 31.08.2018
Published online: 21.09.2018
DOI: 10.1055/s-0037-1611056; Art ID: ss-2018-t0462-op

Abstract A facile and chemoselective $SnCl_2$-mediated mild reduction of regioisomeric 3- and 4-nitrofuroxans for the synthesis of aminofurazans and aminofuroxans in good yields is developed. Reduction of 4-nitrofuroxans results in the selective formation of 4-aminofuroxans, while analogous reduction of 3-nitrofuroxans affords 3-aminofurazans as a result of simultaneous reduction of the nitro group and exocyclic N–O bond.

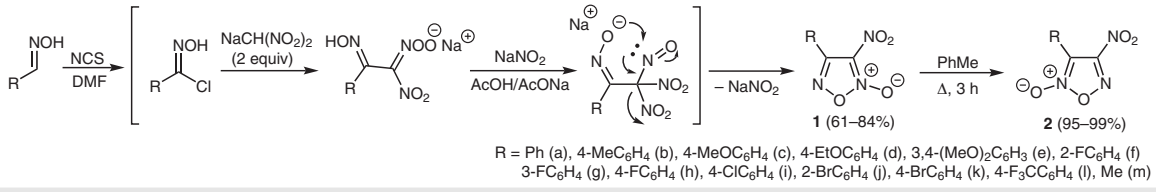
Key words furoxans, furazans, reduction, heterocycles, chemoselectivity

1,2,5-Oxadiazoles (furazans) and their *N*-oxides (furoxans) have found myriad applications in organic and medicinal chemistry, materials science, etc.[1] The 1,2,5-oxadiazole ring is a valuable scaffold in the design of promising drug candidates with antibacterial,[2] antiparasitic[3] and cytotoxic[4] activities. In addition, furoxan derivatives possess antiplatelet[5] and cardiovascular[6] properties due to their ability to facilitate exogenous NO release. The special interest in 1,2,5-oxadiazole chemistry is also attributed to the construction of high-energy systems incorporating additional nitrogen–oxygen explosophoric fragments.[7] This is connected with the aromaticity and planarity of the 1,2,5-oxadiazole subunit resulting in high density of furazan- and furoxan-containing derivatives. Moreover, in contrast to other nitrogen-containing heterocycles, furazans and furoxans possess 'active' oxygen atoms that are not bonded to hydrogen or carbon atoms and these atoms are therefore able to undergo oxidation in combustion or explosive degradation processes.

Aminofurazans and aminofuroxans are especially important precursors for the synthesis of various pharmacologically oriented or high-energy systems.[8] However, methods for the synthesis of amino-1,2,5-oxadiazoles usually involve exhaustive multistep procedures. The main route to aminofurazans is based on the cyclodehydration of vicinal dioximes (glyoximes), which in turn are prepared through a two-step sequence from the corresponding methylene-active nitriles (Scheme 1).[8a] Also, a one-pot procedure for the preparation of aminofurazans through the intermediate formation of aminoglyoximes by cascade reactions of 1,3-keto esters has been developed.[9] However, the cyclodehydration step is usually performed by refluxing the initial glyoxime in a high boiling solvent (100–150 °C) in the presence of a strong base. Various activating reagents including Ac_2O,[10] $SOCl_2$,[11] succinic anhydride[12] and urea[9] have been reported to facilitate this cyclization, but temperatures greater than 100 °C are typically required. Recently, 1,1′-carbonyldiimidazole was utilized for the preparation of aminofurazans from the corresponding pre-synthesized aminoglyoximes at ambient temperature.[13] Aminoglyoximes can also be used for the synthesis of aminofuroxans via oxidation reactions. Oxidation of aminoglyoximes with Br_2[14] or $K_3Fe(CN)_6$[14a] results in the regioselective formation of 3-amino-4-arylfuroxans, which can be thermally isomerized into the corresponding 4-amino isomers on heating in toluene.[14a] At the same time, the regioselective synthesis of 4-aminofuroxans can be achieved through the Schmidt rearrangement of acetylfuroxans[15] and the Curtius rearrangement of azidocarbonylfuroxans.[16] However, both



Scheme 1 Known methods for the synthesis of aminofurazans and aminofuroxans



Scheme 2 Synthesis of the initial nitrofuroxans

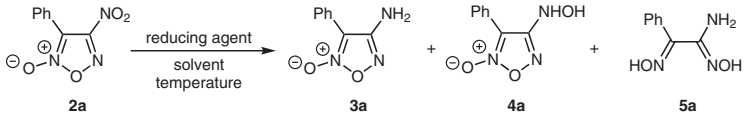
these approaches suffer from a narrow substrate scope and require preliminary multistep preparations of the corresponding functionally substituted furoxans.

Herein, we report a chemoselective *N*-oxide-controlled $SnCl_2$-mediated mild reduction of nitrofuroxans for the synthesis of aminofurazans and aminofuroxans. Reduction of 4-nitrofuroxans with $SnCl_2$/HCl results in the regio- and chemoselective formation of 4-aminofuroxans, while analogous reactions of 3-nitrofuroxans afford 3-aminofurazans.

Recent achievements in the chemistry of furoxans have enabled a direct access to 3- and 4-nitrofuroxans **1** and **2**.[17] For the synthesis of 3-nitrofuroxans, we used our recently developed approach based on the cascade one-pot reactions of aldoximes. This approach includes chlorination of the initial aldoximes, acylation of the intermediate chloroximes with dinitromethane sodium salt and subsequent nitrosation of the dinitromethyl derivatives and in situ intramolecular cyclization.[18] 3-Nitrofuroxans **1** are obtained in high yields in one synthetic step, do not require additional purification and can be quantitatively isomerized into the 4-nitrofuroxans **2**. Following this method, we prepared a series of 3- and 4-nitrofuroxans in good to high yields (Scheme 2).

4-Nitro-3-phenylfuroxan (**2a**) was chosen as a model substrate to optimize the reaction conditions. The reduction of the nitrofuroxan **2a** to the aminofuroxan **3a** by $SnCl_2$ has a single literature precedent described by Wieland in 1903.[19] Indeed, our attempt to reproduce this procedure resulted in target aminofuroxan **3a**, albeit in a low yield. In addition, furoxanylhydroxylamine **4a** as an intermediate

Table 1 Optimization of the Reaction Conditions[a]



Entry	Reducing agent (equiv)	Additive	Solvent	T (°C)	Time (h)	Yield (%)[b]		
						3a	**4a**	**5a**
1	$SnCl_2$ (5.0)	HCl	–	50 → 20	1	12	5	trace[c]
2	$SnCl_2$ (5.0)	HCl	–	5 → 20	2	26	20	–
3	$SnCl_2$ (5.0)	HCl	–	20	1	45	10	–
4	$SnCl_2$ (6.0)	HCl	–	20	1	62	17	–
5	$SnCl_2$ (8.0)	HCl	–	20	1	84	6	–
6	$SnCl_2$ (10.0)	HCl	–	20	1	98	–	–
7	$SnCl_2$ (13.0)	HCl	–	20	1	95	–	–
8	$SnCl_2$ (5.0)	–	EtOH	40	0.5	–	–	81
9	$SnCl_2$ (2.5)	HCl	EtOH	20	1	35	17	20
10	$SnCl_2$ (10.0)	50% H_2SO_4	–	20	3	–	67	–
11	$SnCl_2$ (10.0)	CF_3COOH	–	20	24	–[e]	–[e]	–[e]
12	Zn (5.0)	HCl	HFIP	20	2	7	–	39
13	$Na_2S_2O_4$ (3.0)[d]	–	EtOH/H_2O	20	4	trace[c]	–	–

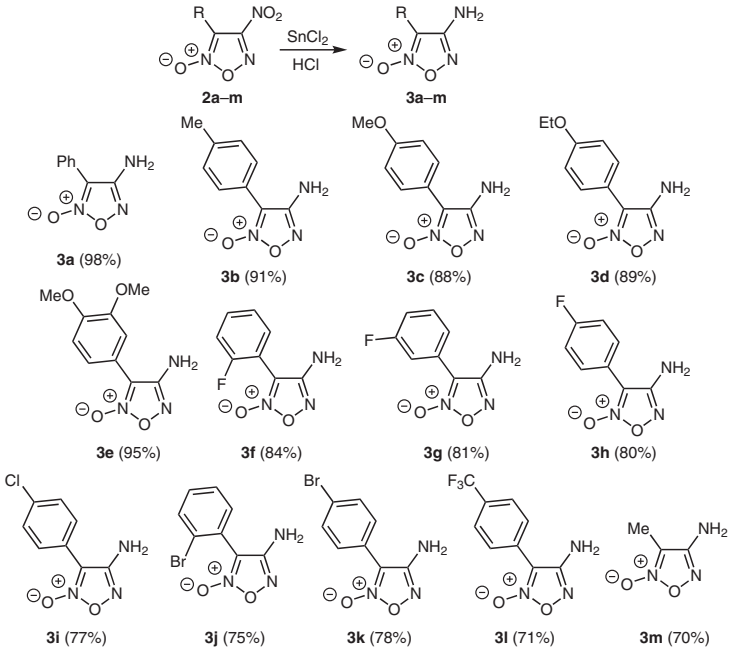
[a] Reaction conditions: 4-nitrofuroxan **2a** (1 mmol), reducing agent, concd HCl as an additive (7 mL), solvent (5 mL), stirring at the appropriate temperature.
[b] Yield of isolated products.
[c] According to ^{1}H NMR spectroscopy.
[d] Total decomposition of 4-nitrofuroxan **2a** was observed.
[e] No reaction.

product and aminoglyoxime **5a** as a result of furoxan ring reduction were also formed as side products (Table 1, entry 1). Performing an analogous reaction at lower temperature afforded a mixture of amine **3a** and hydroxylamine **4a** in nearly equimolar amount (Table 1, entry 2), while the reaction at room temperature increased the **3a**/**4a** ratio to 4.5:1 (Table 1, entry 3). A gradual increase of the amount of $SnCl_2$ provided higher yields of 4-aminofuroxan **3a** with 10 equivalents of $SnCl_2$ being the best (Table 1, entries 4–7). Interestingly, replacing HCl with EtOH resulted in the selective formation of aminoglyoxime **5a** in a good yield (Table 1, entry 8), while the HCl/EtOH combination afforded a mixture of all three products (Table 1, entry 9). Surprisingly, the utilization of 50% H_2SO_4 afforded hydroxylamine **4a** as the sole product (Table 1, entry 10), while CF_3COOH was ineffective (Table 1, entry 11). The use of either zinc[20a] or sodium dithionite[20b] to reduce the nitro group to an amine led to ring cleavage (Table 1, entries 12 and 13).

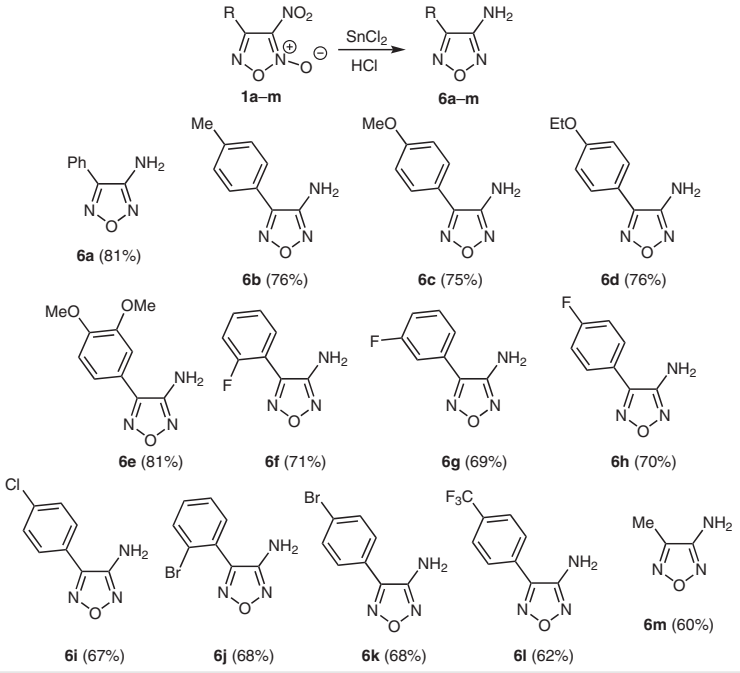
With optimized conditions in hand, we next investigated the substrate scope for the synthesis of 4-aminofuroxans. The target 4-aminofuroxans **3a–m** were all formed chemoselectively in good to high yields under very mild conditions at 20 °C using $SnCl_2$ (10 equiv) in concentrated HCl. In all cases, the endocyclic and exocyclic N–O bonds of the heterocyclic subunit were tolerated under these conditions and the furoxan ring remained unchanged. The yields of 4-aminofuroxans **3b–e** bearing electron-donating groups (alkyl, alkoxy) were higher (88–95%) than those of halogen-substituted 4-aminofuroxans **3f–k** (75–84%). Incorporation of a strong electron-withdrawing CF_3 group on the aromatic ring afforded target aminofuroxan **3l** in a good yield. To our delight, the reduction of 4-nitrofuroxan **2m** bearing an aliphatic substituent provided the corresponding aminofuroxan **3m** in 70% yield (Scheme 3).

Surprisingly, analogous reactions of the 3-nitrofuroxans **1a–m** did not provide the expected 3-aminofuroxans, but directly afforded aminofurazans **6a–m** in good yields as a result of the simultaneous reduction of the nitro group and the *N*-oxide motif. The yields of aminofurazans **6b–e** bearing electron-donating groups (alkyl, alkoxy) were slightly higher (75–81%) than those of halogen- and CF_3-substituted aminofurazans **6f–l** (62–71%). 3-Amino-4-methylfurazan (**6m**) was also formed in a good yield upon reduction of the corresponding 3-nitrofuroxan **1m** (Scheme 4). Arguably, the difference in the chemoselectivity of the reduction of regioisomeric 3- and 4-nitrofuroxans is attributed to the position of the *N*-oxide fragment in the furoxan ring. In 3-nitrofuroxans, the steric proximity of the nitro group and the exocyclic oxygen atom enables effective chelation of both oxygen motifs with $SnCl_2$. However, when the reduction of the 3-nitrofuroxan **1a** was stopped after 10 minutes, the corresponding 3-aminofuroxan was detected according to TLC and ^{1}H NMR data. This fact may serve as evidence that the reduction of the nitro group precedes the reduction of the *N*-oxide moiety in 3-nitrofuroxans.

In summary, we have developed a chemoselective *N*-oxide-controlled reduction of regioisomeric 3- and 4-nitrofuroxans under the action of $SnCl_2$/HCl. The reduction of 4-nitrofuroxans results in the regio- and chemoselective formation of 4-aminofuroxans, while the same reaction of 3-nitrofuroxans directly affords aminofurazans as a result of the simultaneous reduction of the nitro group and exocyclic



Scheme 3 Substrate scope for the reduction of 4-nitrofuroxans



Scheme 4 Substrate scope for the reduction of 3-nitrofuroxans

N–O bond. These conditions afford the target products in good yields and high purities without the need for column chromatography, thus providing a direct and general access to amino-1,2,5-oxadiazoles.

All reactions were carried out in well-cleaned, oven-dried glassware with magnetic stirring. The 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. Analytical thin-layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F_{254} aluminum sheets. The visualization of the TLC plates was accomplished with a UV light source. Melting points were determined on a Stuart SMP20 apparatus and are uncorrected. IR spectra were recorded on a Bruker 'Alpha' spectrophotometer in the range 400–4000 cm^{-1} (resolution: 2 cm^{-1}). ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AM-300 (300.13, 75.47 and 282.4 MHz, respectively) spectrometer and referenced to the residual solvent peak. ^{14}N NMR spectra were measured on a Bruker AM-300 (21.69 MHz) spectrometer using $MeNO_2$ (δ_{14N} = 0.0) as an external standard. ^{15}N NMR spectra were recorded on a Bruker DRX500 instrument (the frequency for ^{15}N was 50.7 MHz) at room temperature; experiment times were determined as recommended.[21] The chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. Elemental analysis was performed using a Perkin-Elmer 2400 CHN Analyzer. 3-Nitrofuroxans **1a**,**b**,**f**,**i**,**k**,**l** and 4-nitrofuroxans **2a**,**b**,**f**,**i**,**k**,**l** were prepared according to a described procedure.[18a]

Dinitromethane Sodium Salt[22]

Caution! Although we encountered no difficulties during the preparation and handling of dinitromethane sodium salt, it is a potentially explosive energetic material which is sensitive to impact and friction. Mechanical actions of this energetic material, involving scratching or scraping, must be avoided. Any manipulations must be carried out by using appropriate standard safety precautions.

Tetranitromethane (60 mL, 0.5 mol) was added to a solution of nitromethane (27 mL, 0.5 mol) in MeOH (150 mL) at room temperature and under mechanical stirring. The reaction mixture was cooled to –5 °C (dry ice bath) and a cold solution of NaOH (40 g, 1.0 mol) in MeOH (500 mL) was added dropwise. After the addition was complete, the mixture was stirred for 1 h at 0 °C. The solid was filtered off and washed with acetone (6 × 50 mL) and Et_2O (2 × 50 mL). The product was dried in air as a thin layer for 40 min and kept in a freezer. The obtained dinitromethane sodium salt can be stored at –20 °C for at least 4 months without decomposition.

Yield 49.3 g (77%).

3-Nitrofuroxans; General Procedure

NCS (0.29 g, 2.2 mmol) was added to a stirred solution of the corresponding carbaldehyde oxime (22 mmol) in anhydrous DMF (30 mL) at room temperature. The reaction mixture was heated to 35–40 °C (to initiate the chlorination), further NCS (2.65 g, 19.9 mmol) was added and the mixture was cooled to 30 °C. The resulting solution was stirred at room temperature for 1 h (TLC monitoring), then cooled to 0 °C and dinitromethane sodium salt (6.2 g, 48.4 mmol) was added. The mixture was stirred for an additional 30 min and left to stand in a refrigerator for 36 h. Next, anhydrous AcONa (5.7 g, 70 mmol) was added portionwise to the reaction mixture at 0–5 °C. The resulting mixture was stirred for 30 min and then AcOH (35 mL) was added dropwise at 0–5 °C. $NaNO_2$ (7.59 g, 110 mmol) was added portionwise, the reaction mixture was stirred for 30 min at 0–5 °C, then the

cooling bath was removed and stirring was continued at room temperature for 3 h. The reaction mixture was poured into H_2O (300 mL) and stirred for 30 min. The obtained solid was filtered off, washed with H_2O and dried in air.

4-(4-Methoxyphenyl)-3-nitrofuroxan (1c)

Yield: 4.02 g (77%); yellow solid; mp 82–83 °C; R_f = 0.53 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2972, 2943, 1648, 1584, 1543, 1518, 1469, 1438, 1401, 1346, 1291, 1253, 1051, 1009, 878, 848, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, CH_3), 7.07 (d, *J* = 8.9 Hz, 2 H, ArH), 7.67 (d, *J* = 8.9 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.6, 114.5, 115.8, 126.4, 130.6, 150.9, 162.7.

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –38.4 (s, NO_2).

Anal. Calcd for $C_9H_7N_3O_5$: C, 45.58; H, 2.97; N, 17.72. Found: C, 45.49; H, 3.09; N, 17.88.

4-(4-Ethoxyphenyl)-3-nitrofuroxan (1d)

Yield: 4.20 g (76%); yellow solid; mp 76–77 °C; R_f = 0.52 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2980, 2945, 1652, 1580, 1545, 1520, 1472, 1432, 1400, 1348, 1296, 1250, 1050, 1015, 850, 775 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.38 (t, *J* = 6.9 Hz, 3 H, CH_3), 4.14 (q, *J* = 6.9 Hz, 2 H, OCH_2), 7.13 (d, *J* = 8.6 Hz, 2 H, ArH), 7.71 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.0, 64.0, 115.0, 116.9, 128.4, 131.5, 152.8, 161.6.

^{14}N NMR (21.7 MHz, DMSO-d_6): δ = –36.2 (s, NO_2).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.61; N, 16.73. Found: C, 47.94; H, 3.48; N, 16.59.

4-(3,4-Dimethoxyphenyl)-3-nitrofuroxan (1e)

Yield: 4.41 g (75%); orange solid; mp 103–104 °C; R_f = 0.22 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2972, 2910, 2870, 1672, 1603, 1540, 1498, 1463, 1430, 1362, 1250, 1190, 1156, 1023, 882, 870, 856, 778 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 7.02 (d, *J* = 8.4 Hz, 1 H, ArH), 7.23 (s, 1 H, ArH), 7.31 (d, *J* = 8.4 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 56.1, 56.2, 111.2, 111.5, 115.9, 122.6, 126.7, 149.4, 150.9, 152.5.

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –38.4 (s, NO_2).

Anal. Calcd for $C_{10}H_9N_3O_6$: C, 44.95; H, 3.40; N, 15.73. Found: C, 45.09; H, 3.27; N, 15.62.

4-(3-Fluorophenyl)-3-nitrofuroxan (1g)

Yield: 4.06 g (82%); pale yellow solid; mp 76–77 °C; R_f = 0.63 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2873, 2798, 1644, 1627, 1542, 1519, 1462, 1402, 1352, 1242, 1153, 1004, 884, 868, 846, 793, 776 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 8.1 Hz, 1 H, ArH), 7.45–7.62 (m, 3 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 116.3 (d, *J* = 24.4 Hz), 119.4 (d, *J* = 21.0 Hz), 124.6, 124.9 (d, *J* = 3.2 Hz), 125.6 (d, *J* = 8.5 Hz), 130.9 (d, *J* = 8.3 Hz), 150.2, 162.6 (d, *J* = 248.9 Hz).

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –35.5 (s, NO_2).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –111.1 (s, F).

Anal. Calcd for $C_8H_4FN_3O_4$: C, 42.68; H, 1.79; N, 18.66. Found: C, 42.51; H, 1.93; N, 18.79.

4-(4-Fluorophenyl)-3-nitrofuroxan (1h)

Yield: 4.16 g (84%); pale yellow solid; mp 61–62 °C; R_f = 0.59 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2884, 2780, 1627, 1523, 1475, 1434, 1360, 1341, 1232, 1162, 1105, 1012, 984, 848, 782 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.31 (m, 2 H, ArH), 7.73–7.77 (m, 2 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 116.5 (d, *J* = 22.4 Hz), 120.0 (d, *J* = 3.4 Hz), 126.6, 131.4 (d, *J* = 9.0 Hz), 150.4, 165.0 (d, *J* = 254.4 Hz).

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –35.1 (s, NO_2).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –107.0 (s, F).

Anal. Calcd for $C_8H_4FN_3O_4$: C, 42.68; H, 1.79; N, 18.66. Found: C, 42.59; H, 1.63; N, 18.77.

4-(2-Bromophenyl)-3-nitrofuroxan (1j)

Yield: 5.22 g (83%); pale yellow solid; mp 74–76 °C; R_f = 0.61 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2895, 2835, 2797, 1645, 1592, 1540, 1513, 1445, 1413, 1346, 1268, 1202, 1058, 1027, 1004, 845, 790, 756 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.62 (m, 3 H, ArH), 7.75–7.81 (m, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 123.4 (2 C), 125.9, 128.0, 131.3, 133.3 (2 C), 151.1.

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –39.3 (s, NO_2).

Anal. Calcd for $C_8H_4BrN_3O_4$: C, 33.59; H, 1.41; N, 14.69. Found: C, 33.73; H, 1.29; N, 14.82.

4-Methyl-3-nitrofuroxan (1m)

Yield: 1.95 g (61%); white solid; mp 41–42 °C; R_f = 0.44 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2889, 1637, 1523, 1414, 1387, 1354, 1266, 1129, 988, 852, 807, 716 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.73 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.0, 126.9, 149.7.

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –37.3 (s, NO_2).

Anal. Calcd for $C_3H_3N_3O_4$: C, 24.84; H, 2.08; N, 28.96. Found: C, 24.71; H, 1.99; N, 29.09.

4-Nitrofuroxans 2; General Procedure

A mixture of a 3-nitrofuroxan **1** (10 mmol) in PhMe (25 mL) was heated at reflux temperature for 3 h. Evaporation of the solvent afforded the corresponding 4-nitrofuroxan **2** in nearly quantitative yield.

3-(4-Methoxyphenyl)-4-nitrofuroxan (2c)[18a]

Yield: 2.35 g (99%); yellow solid; mp 75–76 °C; R_f = 0.53 ($CHCl_3$/CCl_4, 1:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, OCH_3), 7.06 (d, ^3J = 8.7 Hz, 2 H, ArH), 7.57 (d, ^3J = 8.7 Hz, 2 H, ArH).

3-(4-Ethoxyphenyl)-4-nitrofuroxan (2d)[18a]

Yield: 2.48 g (99%); yellow solid; mp 87–88 °C; R_f = 0.50 ($CHCl_3$/CCl_4, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (t, ^3J = 6.8 Hz, 3 H, CH_3), 4.12 (q, ^3J = 6.8 Hz, 2 H, CH_2), 7.04 (d, ^3J = 8.2 Hz, 2 H, ArH), 7.55 (d, ^3J = 8.2 Hz, 2 H, ArH).

3-(3,4-Dimethoxyphenyl)-4-nitrofuroxan (2e)

Yield: 2.59 g (97%); orange solid; mp 92–93 °C; R_f = 0.24 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2965, 2941, 2840, 1614, 1574, 1529, 1494, 1457, 1435, 1368, 1262, 1234, 1180, 1142, 1118, 1016, 866, 811, 781 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 6.98 (d, J = 8.5 Hz, 1 H, ArH), 7.10 (s, 1 H, ArH), 7.16 (d, J = 8.5 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 56.0, 56.1, 109.2, 110.9, 111.0, 111.3, 122.5, 149.3, 151.9, 158.2.

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –33.9 (s, NO_2).

Anal. Calcd for $C_{10}H_9N_3O_6$: C, 44.95; H, 3.40; N, 15.73. Found: C, 44.79; H, 3.32; N, 15.92.

3-(3-Fluorophenyl)-4-nitrofuroxan (2g)

Yield: 2.23 g (99%); pale yellow solid; mp 58–59 °C; R_f = 0.58 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2910, 2726, 1612, 1572, 1509, 1484, 1459, 1367, 1294, 1218, 1110, 1072, 1007, 884, 841, 782 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.42 (m, 3 H, ArH), 7.54–7.62 (m, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 108.3, 116.1 (d, J = 24.8 Hz), 119.2 (d, J = 21.1 Hz), 121.2 (d, J = 8.7 Hz), 124.7 (d, J = 3.4 Hz), 131.0 (d, J = 8.3 Hz), 149.7, 162.6 (d, J = 249.3 Hz).

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –34.9 (s, NO_2).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –110.5 (s, F).

Anal. Calcd for $C_8H_4FN_3O_4$: C, 42.68; H, 1.79; N, 18.66. Found: C, 42.55; H, 1.63; N, 18.82.

3-(4-Fluorophenyl)-4-nitrofuroxan (2h)

Yield: 2.21 g (98%); pale yellow solid; mp 69–70 °C; R_f = 0.57 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2926, 2735, 1624, 1567, 1523, 1492, 1439, 1409, 1365, 1298, 1273, 1237, 1162, 1121, 1071, 987, 837, 784 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.32 (m, 2 H, ArH), 7.63–7.66 (m, 2 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 108.7, 115.4 (d, J = 3.5 Hz), 116.8 (d, J = 22.5 Hz), 131.3 (d, J = 8.1 Hz), 148.8, 164.4 (d, J = 255.0 Hz).

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –34.7 (s, NO_2).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.3 (s, F).

Anal. Calcd for $C_8H_4FN_3O_4$: C, 42.68; H, 1.79; N, 18.66. Found: C, 42.87; H, 1.96; N, 18.52.

3-(2-Bromophenyl)-4-nitrofuroxan (2j)

Yield: 2.72 g (95%); pale yellow solid; mp 70–71 °C; R_f = 0.60 ($CHCl_3$/CCl_4, 1:1).

IR (KBr): 2922, 2856, 1629, 1570, 1516, 1474, 1444, 1362, 1290, 1136, 1072, 1047, 985, 801, 770, 741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.59 (m, 3 H, ArH), 7.77–7.80 (m, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 109.3, 121.8, 124.3, 128.3, 131.7, 133.4, 133.5, 150.0.

^{14}N NMR (21.7 MHz, $CDCl_3$): δ = –35.3 (s, NO_2).

Anal. Calcd for $C_8H_4BrN_3O_4$: C, 33.59; H, 1.41; N, 14.69. Found: C, 33.46; H, 1.31; N, 14.92.

3-Methyl-4-nitrofuroxan (2m)[17b]

Yield: 1.39 g (96%); white solid; mp 68–69 °C; R_f = 0.48 ($CHCl_3$/CCl_4, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3).

Reduction of 3- and 4-Nitrofuroxans; General Procedure

$SnCl_2$ (1.90 g, 10 mmol) was added to a vigorously stirred mixture of the corresponding nitrofuroxan **1** or **2** (1 mmol) and concd HCl (7 mL) in one portion at room temperature. The reaction mixture was stirred for 1 h, then poured into H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The drying agent was removed by filtration, the solvent was evaporated in vacuo and the residue was triturated with H_2O. The solid product was filtered, washed with cold $CHCl_3$ (2 mL) and dried in air.

4-Amino-3-phenylfuroxan (3a)[14a]

Yield: 173 mg (98%); beige solid; mp 137–138 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.39 (br s, 2 H, NH_2), 7.52–7.59 (m, 3 H, ArH), 7.81 (d, J = 6.5 Hz, 2 H, ArH).

4-Amino-3-(4-tolyl)furoxan (3b)[14a]

Yield: 174 mg (91%); white solid; mp 176–177 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 6.35 (br s, 2 H, NH_2), 7.38 (d, J = 7.8 Hz, 2 H, ArH), 7.74 (d, J = 7.8 Hz, 2 H, ArH).

4-Amino-3-(4-methoxyphenyl)furoxan (3c)

Yield: 182 mg (88%); beige solid; mp 109–110 °C; R_f = 0.31 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3425, 3318, 3239, 2973, 2941, 2839, 1636, 1610, 1533, 1485, 1457, 1435, 1399, 1305, 1257, 1180, 1057, 1026, 979, 886, 830 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, CH_3), 6.14 (br s, 2 H, NH_2), 7.10 (d, J = 8.8 Hz, 2 H, ArH), 7.72 (d, J = 8.8 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.8, 115.0, 118.2, 129.7, 147.0, 155.7, 161.2.

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.04; H, 4.22; N, 20.45.

4-Amino-3-(4-ethoxyphenyl)furoxan (3d)

Yield: 197 mg (89%); beige solid; mp 118–119 °C; R_f = 0.24 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3398, 3326, 3238, 2978, 2930, 2884, 1638, 1592, 1512, 1464, 1411, 1255, 1186, 1162, 1117, 1046, 966, 840 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J = 7.0 Hz, 3 H, CH_3), 4.10 (q, J = 7.0 Hz, 2 H, OCH_2), 6.32 (br s, 2 H, NH_2), 7.10 (d, J = 8.8 Hz, 2 H, ArH), 7.75 (d, J = 8.8 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.0, 63.9, 109.6, 115.0, 115.3, 129.6, 157.4, 160.2.

Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.42; H, 4.90; N, 18.84.

4-Amino-3-(3,4-dimethoxyphenyl)furoxan (3e)

Yield: 225 mg (95%); beige solid; mp 178–179 °C; R_f = 0.16 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3393, 3323, 3232, 2981, 2948, 2846, 1619, 1596, 1521, 1487, 1442, 1415, 1357, 1258, 1226, 1196, 1180, 1156, 1093, 1015, 977 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, CH_3), 3.84 (s, 3 H, CH_3), 6.36 (br s, 2 H, NH_2), 7.15 (d, J = 8.4 Hz, 1 H, ArH), 7.36 (s, 1 H, ArH), 7.40 (d, J = 8.4 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 56.1, 109.6, 111.1, 112.3, 115.2, 121.3, 149.2, 150.7, 157.4.

Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.49; H, 4.83; N, 17.88.

4-Amino-3-(2-fluorophenyl)furoxan (3f)

Yield: 164 mg (84%); white solid; mp 133–134 °C; R_f = 0.40 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3336, 3241, 3206, 2879, 2814, 1648, 1638, 1578, 1533, 1474, 1457, 1408, 1316, 1208, 1112, 985, 880, 819, 764, 745 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.21 (br s, 2 H, NH_2), 7.36–7.46 (m, 2 H, ArH), 7.61–7.68 (m, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 113.8 (d, J = 14.6 Hz), 116.9 (d, J = 20.6 Hz), 125.5 (d, J = 3.3 Hz), 131.6 (d, J = 2.2 Hz), 133.2 (d, J = 8.3 Hz), 143.7, 156.3, 160.3 (d, J = 249.9 Hz).

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –113.5 (s, F).

Anal. Calcd for $C_8H_6FN_3O_2$: C, 49.24; H, 3.10; N, 21.53. Found: C, 49.40; H, 3.22; N, 21.29.

4-Amino-3-(3-fluorophenyl)furoxan (3g)

Yield: 158 mg (81%); white solid; mp 153–154 °C; R_f = 0.32 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3423, 3332, 3238, 2729, 1639, 1590, 1499, 1463, 1432, 1276, 1216, 1155, 1097, 987, 884, 784, 684 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.45 (br s, 2 H, NH_2), 7.40 (t, J = 7.8 Hz, 1 H, ArH), 7.59–7.69 (m, 3 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.1, 115.0 (d, J = 24.2 Hz), 117.6 (d, J = 20.9 Hz), 124.2 (d, J = 2.8 Hz), 125.3 (d, J = 9.2 Hz), 131.5 (d, J = 8.5 Hz), 157.2, 162.4 (d, J = 244.3 Hz).

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –112.4 (s, F).

Anal. Calcd for $C_8H_6FN_3O_2$: C, 49.24; H, 3.10; N, 21.53. Found: C, 49.11; H, 2.92; N, 21.74.

4-Amino-3-(4-fluorophenyl)furoxan (3h)

Yield: 156 mg (80%); white solid; mp 170–171 °C; R_f = 0.24 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3425, 3331, 3237, 2927, 2856, 2737, 1638, 1589, 1519, 1467, 1407, 1314, 1251, 1162, 1102, 964, 867, 835 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.40 (br s, 2 H, NH_2), 7.40–7.46 (m, 2 H, ArH), 7.85–7.90 (m, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.3, 116.6 (d, J = 22.2 Hz), 119.7 (d, J = 3.0 Hz), 130.7 (d, J = 8.8 Hz), 157.3, 163.2 (d, J = 248.9 Hz).

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –110.2 (s, F).

Anal. Calcd for $C_8H_6FN_3O_2$: C, 49.24; H, 3.10; N, 21.53. Found: C, 49.13; H, 3.24; N, 21.66.

4-Amino-3-(4-chlorophenyl)furoxan (3i)[14a]

Yield: 163 mg (77%); white solid; mp 165–166 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.41 (br s, 2 H, NH_2), 7.63 (d, J = 8.6 Hz, 2 H, ArH), 7.84 (d, J = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.2, 122.2, 129.5, 129.9, 135.3, 157.2.

^{15}N NMR (50.7 MHz, DMSO-d_6): δ = –329.1 (t, J = 84.9 Hz, NH_2), –52.0, –33.7.

4-Amino-3-(2-bromophenyl)furoxan (3j)

Yield: 192 mg (75%); white solid; mp 125–126 °C; R_f = 0.34 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3404, 3323, 3232, 2928, 2769, 1636, 1609, 1588, 1492, 1450, 1427, 1355, 1170, 957, 856 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.35 (br s, 2 H, NH_2), 7.51–7.59 (m, 3 H, ArH), 7.84 (d, J = 6.9 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 110.8, 124.3, 124.6, 128.8, 133.3, 133.4, 133.5, 157.4.

Anal. Calcd for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C, 37.39; H, 2.52; N, 16.58.

4-Amino-3-(4-bromophenyl)furoxan (3k)

Yield: 200 mg (78%); white solid; mp 174–175 °C; R_f = 0.31 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3384, 3320, 3232, 2873, 1638, 1586, 1491, 1460, 1392, 1305, 1158, 1114, 1072, 1010, 965, 874, 830 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.42 (br s, 2 H, NH_2), 7.74–7.81 (m, 4 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.3, 122.6, 124.0, 130.1, 132.4, 157.2.

Anal. Calcd for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C, 37.41; H, 2.23; N, 16.60.

4-Amino-3-[4-(trifluoromethyl)phenyl]furoxan (3l)

Yield: 174 mg (71%); white solid; mp 160–161 °C; R_f = 0.41 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3388, 3328, 3246, 2943, 2751, 1641, 1593, 1515, 1465, 1403, 1328, 1144, 1113, 1067, 967, 848 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.49 (br s, 2 H, NH_2), 7.93 (d, J = 8.3 Hz, 2 H, ArH), 8.04 (d, J = 8.3 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.1, 126.1 (q, J = 3.6 Hz), 127.9 (q, J = 274.5 Hz), 129.0, 129.9 (q, J = 32.1 Hz), 157.2, 160.2.

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –62.4 (s, CF_3).

Anal. Calcd for $C_9H_6F_3N_3O_2$: C, 44.09; H, 2.47; N, 17.14. Found: C, 43.95; H, 2.33; N, 17.38.

4-Amino-3-methylfuroxan (3m)[16]

Yield: 81 mg (70%); white solid; mp 132–133 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.01 (s, 3 H, CH_3), 6.26 (br s, 2 H, NH_2).

3-Amino-4-phenylfurazan (6a)[13]

Yield: 130 mg (81%); beige solid; mp 96–97 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.17 (br s, 2 H, NH_2), 7.56 (br s, 3 H, ArH), 7.77 (br s, 2 H, ArH).

3-Amino-4-(4-tolyl)furazan (6b)[9b]

Yield: 133 mg (76%); white solid; mp 142–143 °C; R_f = 0.51 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 6.16 (br s, 2 H, NH_2), 7.36 (d, J = 7.4 Hz, 2 H, ArH), 7.67 (d, J = 7.4 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 21.4, 123.1, 128.0, 130.1, 140.5, 147.3, 155.7.

3-Amino-4-(4-methoxyphenyl)furazan (6c)[9b]

Yield: 143 mg (75%); beige solid; mp 103–104 °C; R_f = 0.29 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, CH_3), 6.14 (br s, 2 H, NH_2), 7.10 (d, J = 8.9 Hz, 2 H, ArH), 7.72 (d, J = 8.9 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.8, 115.0, 118.2, 129.7, 147.0, 155.7, 161.2.

3-Amino-4-(4-ethoxyphenyl)furazan (6d)

Yield: 156 mg (76%); beige solid; mp 102–103 °C; R_f = 0.36 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3392, 3336, 3230, 2972, 2924, 2892, 1645, 1588, 1503, 1452, 1400, 1274, 1193, 1151, 1105, 1022, 977, 848 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J = 6.9 Hz, 3 H, CH_3), 4.10 (q, J = 6.9 Hz, 2 H, OCH_2), 6.13 (br s, 2 H, NH_2), 7.08 (d, J = 8.6 Hz, 2 H, ArH), 7.71 (d, J = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.0, 63.8, 115.5, 118.0, 129.7, 147.0, 155.7, 160.5.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.71; H, 5.28; N, 20.31.

3-Amino-4-(3,4-dimethoxyphenyl)furazan (6e)

Yield: 179 mg (81%); white solid; mp 146–147 °C; R_f = 0.23 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3419, 3340, 3083, 3002, 2980, 2944, 2841, 1624, 1596, 1537, 1495, 1462, 1433, 1407, 1303, 1252, 1224, 1175, 1144, 1026, 981, 850, 818 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 6.16 (br s, 2 H, NH_2), 7.11 (d, J = 8.4 Hz, 1 H, ArH), 7.28 (s, 1 H, ArH), 7.33 (d, J = 8.4 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.0, 56.1, 111.3, 112.4, 118.2, 121.1, 147.2, 149.4, 150.9, 155.7.

Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.43; H, 4.89; N, 18.83.

3-Amino-4-(2-fluorophenyl)furazan (6f)[9b]

Yield: 127 mg (71%); white solid; mp 115–116 °C; R_f = 0.47 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.21 (br s, 2 H, NH_2), 7.36–7.46 (m, 2 H, ArH), 7.61–7.68 (m, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 113.8 (d, J = 14.6 Hz), 116.9 (d, J = 20.6 Hz), 125.4 (d, J = 3.3 Hz), 131.6, 133.1 (d, J = 8.3 Hz), 143.7, 156.3, 160.3 (d, J = 249.9 Hz).

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –113.5 (s, F).

3-Amino-4-(3-fluorophenyl)furazan (6g)

Yield: 124 mg (69%); white solid; mp 110–111 °C; R_f = 0.38 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3450, 3328, 3241, 3071, 2874, 2757, 1637, 1588, 1524, 1475, 1450, 1405, 1307, 1198, 991, 887, 855, 798 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.28 (br s, 2 H, NH_2), 7.37–7.46 (m, 1 H, ArH), 7.57–7.65 (m, 3 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 115.1 (d, J = 23.4 Hz), 117.6 (d, J = 21.0 Hz), 124.5 (d, J = 2.9 Hz), 128.1 (d, J = 8.6 Hz), 131.7 (d, J = 8.4 Hz), 146.4 (d, J = 2.6 Hz), 155.7, 162.7 (d, J = 245.0 Hz).

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –112.5 (s, F).

Anal. Calcd for $C_8H_6FN_3O$: C, 53.63; H, 3.38; N, 23.46. Found: C, 53.79; H, 3.16; N, 23.29.

3-Amino-4-(4-fluorophenyl)furazan (6h)[9b]

Yield: 125 mg (70%); white solid; mp 133–134 °C; R_f = 0.42 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.22 (br s, 2 H, NH_2), 7.36–7.44 (m, 2 H, ArH), 7.80–7.86 (m, 2 H, ArH).

^{19}F NMR (282.4 MHz, DMSO-d_6): δ = –111.1 (s, F).

3-Amino-4-(4-chlorophenyl)furazan (6i)[9b]

Yield: 131 mg (67%); beige solid; mp 137–138 °C; R_f = 0.40 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.24 (br s, 2 H, NH_2), 7.61 (d, J = 7.4 Hz, 2 H, ArH), 7.79 (d, J = 7.4 Hz, 2 H, ArH).

3-Amino-4-(2-bromophenyl)furazan (6j)

Yield: 163 mg (68%); white solid; mp 102–103 °C; R_f = 0.32 ($CHCl_3$/EtOAc, 20:1).

IR (KBr): 3402, 3315, 3220, 2932, 2788, 1621, 1592, 1480, 1438, 1411, 1360, 1188, 942, 832 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.27 (br s, 2 H, NH_2), 7.45–7.54 (m, 3 H, ArH), 7.77 (d, J = 7.0 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 124.1, 124.5, 129.2, 133.1, 133.2, 133.3, 146.2, 155.9.

Anal. Calcd for $C_8H_6BrN_3O$: C, 40.03; H, 2.52; N, 17.50. Found: C, 39.89; H, 2.69; N, 17.36.

3-Amino-4-(4-bromophenyl)furazan (6k)[9b]

Yield: 163 mg (68%); white solid; mp 145–146 °C; R_f = 0.40 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.24 (br s, 2 H, NH_2), 7.71 (d, J = 8.6 Hz, 2 H, ArH), 7.76 (d, J = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 124.3, 125.2, 130.3, 132.6, 146.7, 155.7.

3-Amino-4-[4-(Trifluoromethyl)phenyl]furazan (6l)[13]

Yield: 143 mg (62%); pale yellow solid; mp 108–109 °C; R_f = 0.36 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.32 (br s, 2 H, NH_2), 7.91 (d, J = 8.3 Hz, 2 H, ArH), 8.00 (d, J = 8.3 Hz, 2 H, ArH).

3-Amino-4-methylfurazan (6m)[9a]

Yield: 59 mg (60%); white solid; mp 72–73 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.27 (s, 3 H, CH_3), 6.11 (br s, 2 H, NH_2).

1-Amino-2-phenylglyoxime (5a)[14a]

A suspension of the 4-nitrofuroxan **2a** (207 mg, 1 mmol) in 95% EtOH (5 mL) was heated to 40 °C and stirred until complete dissolution of the starting material had occurred. $SnCl_2$ (0.95 g, 5 mmol) was added and the mixture was stirred for 15 min, then poured into H_2O (100 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O and dried over $MgSO_4$.

Yield 145 mg (81%); white solid; mp 152–153 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.38 (br s, 2 H, NH_2), 7.22–7.29 (m, 2 H, Ph), 7.33–7.38 (m, 3 H, Ph), 10.06 (s, 1 H, OH), 11.42 (s, 1 H, OH).

4-(Hydroxyamino)-3-phenylfuroxan (4a)

$SnCl_2$ (1.90 g, 10 mmol) was added to a vigorously stirred mixture of 4-nitrofuroxan **2a** (207 mg, 1 mmol) and 50% H_2SO_4 (7 mL) in one portion at room temperature. The reaction mixture was stirred for 3 h then poured into H_2O (30 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The drying agent was removed by filtration, the solvent was evaporated in vacuo and the residue was triturated with H_2O. The solid product was filtered, washed with cold $CHCl_3$ (2 mL) and dried in air.

Yield: 129 mg (67%); white solid; mp 113–114 °C; R_f = 0.14 ($CHCl_3$/EtOAc, 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.55–7.62 (m, 3 H, ArH), 7.86 (d, J = 6.8 Hz, 2 H, ArH), 9.05 (br s, 1 H, OH), 9.50 (br s, 1 H, NH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.9, 123.0, 127.8, 128.1, 129.4, 130.7, 157.4.

Anal. Calcd for $C_8H_7N_3O_3$: C, 49.74; H, 3.65; N, 21.75. Found: C, 49.59; H, 3.78; N, 21.92.

Funding Information

This work was supported by the Russian Foundation for Basic Research (project 18-03-00332) and the Russian President's Council for Grants (project MK-1302.2017.3).

Acknowlegdment

NMR spectra were recorded 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-0037-1611056.

References

(1) (a) Paton, R. M. *1,2,5-Oxadiazoles*, In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 229–266. (b) Nikonov, G. N.; Bobrov, S. *1,2,5-Oxadiazoles*, In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A. V.; Scriven, E. F.; Taylor, R. J. K., Eds.; Elsevier: Amsterdam, **2008**, 316–393. (c) Fershtat, L. L.; Makhova, N. N. *Russ. Chem. Rev.* **2016**, *85*, 1097. (d) Fershtat, L. L.; Makhova, N. N. *ChemMedChem* **2017**, *12*, 622.

(2) Segretti, N. D.; Serafim, R. A. M.; Segretti, M. C. F.; Miyata, M.; Coelho, F. R.; Augusto, O.; Ferreira, E. I. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3988.

(3) Guglielmo, S.; Cortese, D.; Vottero, F.; Rolando, B.; Kommer, V. P.; Williams, D. L.; Fruttero, R.; Gasco, A. *Eur. J. Med. Chem.* **2014**, *84*, 135.

(4) (a) Kulikov, A. S.; Larin, A. A.; Fershtat, L. L.; Anikina, L. V.; Pukhov, S. A.; Klochkov, S. G.; Struchkova, M. I.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *ARKIVOC* **2017**, *(iii)*, 250. (b) Stepanov, A. I.; Astrat'ev, A. A.; Sheremetev, A. B.; Lagutina, N. K.; Palysaeva, N. V.; Tyurin, A. Yu.; 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.

(5) (a) Ustyuzhanina, N. E.; Fershtat, L. L.; Gening, M. L.; Nifantiev, N. E.; Makhova, N. N. *Mendeleev Commun.* **2016**, *26*, 513. (b) Ustyuzhanina, N. E.; Fershtat, L. L.; Gening, M. L.; Nifantiev, N. E.; Makhova, N. N. *Mendeleev Commun.* **2018**, *28*, 49.

(6) (a) Ferioli, R.; Folco, G. C.; Ferretti, C.; Gasco, A. M.; Medana, C.; Fruttero, R.; Civelli, M.; Gasco, A. *Br. J. Pharmacol.* **1995**, *114*, 816. (b) Bohn, H.; Brendel, J.; Martorana, P. A.; Schönafinger, K. *Br. J. Pharmacol.* **1995**, *114*, 1605.

(7) For selected examples, see: (a) Zhang, J.; Shreeve, J. M. *J. Am. Chem. Soc.* **2014**, *136*, 4437. (b) He, C.; Shreeve, J. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 772. (c) Zhang, J.; Mitchell, L. A.; Parrish, D. A.; Shreeve, J. M. *J. Am. Chem. Soc.* **2015**, *137*, 10532. (d) Lempert, D. B.; Sheremetev, A. B. *Chem. Heterocycl. Compd.* **2016**, *52*, 1070. (e) Pagoria, P. F.; Zhang, M.-X.; Zuckerman, N. B.; DeHope, A. J.; Parrish, D. A. *Chem. Heterocycl. Compd.* **2017**, *53*, 760. (f) Fershtat, L. L.; Ovchinnikov, I. V.; Epishina, M. A.; Romanova, A. A.; Lempert, D. B.; Muravyev, N. V.; Makhova, N. N. *ChemPlusChem* **2017**, *82*, 1315. (g) Fershtat, L. L.; Epishina, M. A.; Kulikov, A. S.; Ovchinnikov, I. V.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron* **2015**, *71*, 6764.

(8) (a) Makhova, N. N.; Kulikov, A. S. *Russ. Chem. Rev.* **2013**, *82*, 1007. (b) Fischer, D.; Klapoetke, T. M.; Stierstorfer, J. *Eur. J. Inorg. Chem.* **2014**, 5808. (c) Wei, H.; He, C.; Zhang, J.; Shreeve, J. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 9367. (d) He, C.; Gao, H.; Imler, G. H.; Parrish, D. A.; Shreeve, J. M. *J. Mater. Chem. A* **2018**, *6*, 9391. (e) Fershtat, L. L.; Radzhabov, M. R.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *ARKIVOC* **2017**, *(iii)*, 140. (f) Shin, D.-S.; Masciocchi, D.; Gelain, A.; Villa, S.; Barlocco, D.; Meneghetti, F.; Pedretti, A.; Han, Y.-M.; Han, D. C.; Kwon, B.-M.; Legnani, L.; Toma, L. *Med. Chem. Commun.* **2010**, *1*, 156. (g) Masciocchi, D.; Villa, S.; Meneghetti, F.; Pedretti, A.; Barlocco, D.; Legnani, L.; Toma, L.; Kwon, B.-M.; Nakano, S.; Asai, A.; Gelain, A. *Med. Chem. Commun.* **2012**, *3*, 592.

(9) (a) Sheremetev, A. B.; Shamshina, Yu. L.; Dmitriev, D. E. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 1032. (b) Sheremetev, A. B. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 1057.

(10) (a) 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. (b) Samsonov, V. A.; Sal'nikov, G. E.; Genayev, A. M. *Russ. Chem. Bull., Int. Ed.* **2009**, *58*, 2369.

(11) (a) Boulton, A. J.; Mathur, S. S. *J. Org. Chem.* **1973**, *38*, 1054. (b) Pollet, P.; Gelin, S. *Synthesis* **1979**, 977. (c) Zelenov, M. P.; Frolova, G. M.; Mel'nikova, S. F.; Tselinskii, I. V. *Chem. Heterocycl. Compd.* **1982**, *18*, 21. (d) Takahashi, T. T.; Satoh, J. Y.; Saitoh, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2277.
(12) (a) Olofson, R. A.; Michelman, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1863. (b) Britsun, V. N.; Borisevich, A. N.; Samoilenko, L. S.; Lozinskii, M. O. *Russ. J. Org. Chem.* **2005**, *41*, 745.
(13) Neel, A. J.; Zhao, R. *Org. Lett.* **2018**, *20*, 2024.
(14) (a) Gagneux, A. R.; Meier, R. *Helv. Chim. Acta* **1970**, *53*, 1883. (b) Bystrov, D. M.; Zhilin, E. S.; Fershtat, L. L.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *Adv. Synth. Catal.* **2018**, *360*, 3157.
(15) Makhova, N. N.; Blinnikov, A. N.; Khme'nitskii, L. I. *Mendeleev Commun.* **1995**, *5*, 56.
(16) Ovchinnikov, I. V.; Blinnikov, A. N.; Makhova, N. N. *Mendeleev Commun.* **1995**, *5*, 58.
(17) (a) Makhova, N. N.; Fershtat, L. L. *Tetrahedron Lett.* **2018**, *59*, 2317. (b) Fershtat, L. L.; Struchkova, M. I.; Goloveshkin, A. S.; Bushmarinov, I. S.; Makhova, N. N. *Heteroat. Chem.* **2014**, *25*, 226. (c) Matsubara, R.; Ando, A.; Saeki, Y.; Eda, K.; Asada, N.; Tsutsumi, T.; Shin, Y. S.; Hayashi, M. *J. Heterocycl. Chem.* **2016**, *53*, 1094. (d) Matsubara, R.; Eguchi, S.; Ando, A.; Hayashi, M. *Org. Biomol. Chem.* **2017**, *15*, 1965. (e) Ando, A.; Matsubara, R.; Takazawa, S.; Shimada, T.; Hayashi, M. *Asian J. Org. Chem.* **2016**, *5*, 886.
(18) (a) Fershtat, L. L.; Epishina, M. A.; Ovchinnikov, I. V.; Struchkova, M. I.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron Lett.* **2016**, *57*, 5685. (b) Fershtat, L. L.; Larin, A. A.; Epishina, M. A.; Kulikov, A. S.; Ovchinnikov, I. V.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron Lett.* **2016**, *57*, 4268.
(19) Wieland, H. *Liebigs Ann. Chem.* **1903**, *328*, 154.
(20) (a) Chen, X.-L.; Ai, B.-R.; Dong, Y.; Zhang, X.-M.; Wang, J.-Y. *Tetrahedron Lett.* **2017**, *58*, 3646. (b) Defilippi, A.; Sorba, G.; Calvino, R.; Garrone, A.; Gasco, A.; Orsetti, M. *Arch. Pharm.* **1988**, *321*, 77.
(21) Tsedilin, A. M.; Fakhrutdinov, A. N.; Eremin, D. B.; Zalesskiy, S. S.; Chizhov, A. O.; Kolotyrkina, N. G.; Ananikov, V. P. *Mendeleev Commun.* **2015**, *25*, 454.
(22) Zabka, J.; Simkova, L.; Jalovy, Z.; Polasek, M. *Eur. J. Mass Spectrom.* **2014**, *20*, 233.