Chemoselective Reduction of Functionalized 5-Nitroisoxazoles: Synthesis of 5-Amino- and 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles

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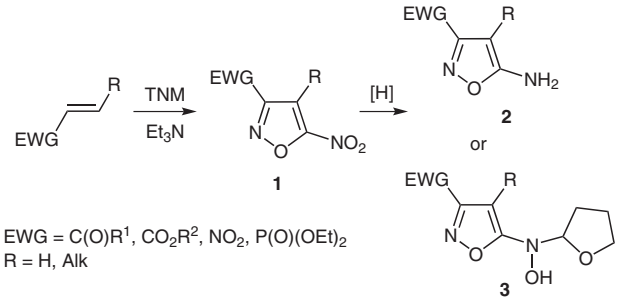
Abstract: Reduction by using $SnCl_2$ of easily accessible 5-nitroisoxazoles substituted with an electron-withdrawing group (EWG) has been studied. Whereas the reaction in ethanol yielded 5-aminoisoxazoles, performing the reaction in tetrahydrofuran gave previously unknown 5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles. Both reduction procedures were optimized to afford the corresponding products in good to excellent yields. Some mechanistic details concerning the inclusion of the tetrahydrofuranyl moiety into the reaction product are discussed

Key words: reduction, chemoselectivity, isoxazoles, radical reaction, tetrahydrofuran



Scheme 1 Synthesis of functionalized 5-nitroisoxazoles and reduction of the nitro group

The significant interest in isoxazole derivatives stems from their versatility as synthetic building blocks and their application in various fields such as agriculture, industry, and medicine.[1] In particular, aminoisoxazoles are known to possess a wide range of physiological activities, for example, cytotoxic (anticancer),[2] biocidal,[3] anti-inflammatory and immune-suppressive[4] activities. Amino-substituted isoxazoles are also employed in the preparation of fused heterocyclic systems, such as isoxazolopyridines, isoxazolopyrimidines, and isoxazolodiazepines, which represent valuable scaffolds in pharmacological agents.[5] The majority of existing approaches to 3- and 5-aminoisoxazoles include ring-closure reactions of organic nitriles with hydroxylamine[5,6] or halogenooximes.[5,7] However, in a number of cases these methods are of low regioselectivity and produce mixtures of 3- and 5-aminoisoxazoles. Moreover, the substituents that can be present in such molecules are generally limited to alkyl and aryl groups. Thus the development of new, effective regioselective approaches to functionalized 5-aminoisoxazoles remains a challenge.

We have recently elaborated a novel preparative method for the synthesis of a large variety of functionalized 5-nitroisoxazoles **1** by the reaction of tetranitromethane (TNM) with electrophilic alkenes in the presence of triethylamine (Scheme 1).[8]

Clearly, nitro-substituted heterocycles of type **1** are highly reactive compounds that may be used as precursors for a range of functionalized aminoisoxazoles and other valuable isoxazole derivatives. Continuing our research, we have studied in detail functionalized 5-nitroisoxazoles in reduction reactions and found that, depending on the conditions applied, 5-aminoisoxazoles **2** or previously unknown 5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles **3** were formed (Scheme 1).

Herein we propose a simple method for the synthesis of functionalized 5-aminoisoxazoles and 5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles from the reduction of corresponding 5-nitroisoxazoles, which are easily available by heterocyclization of commercial electrophilic alkenes.

A brief study of known mild reducing agents, such as Zn/NH_4Cl, Zn/AcOH, $Fe/CaCl_2$, $SnCl_2/HCl$, $SnCl_2/EtOH$, N_2H_4-H_2O/Ni_{Raney}, HCO_2NH_4-Pd/C, and Al/Hg by using 5-nitroisoxazole **1a** as a model compound revealed that 5-aminoisoxazole **2a** was generated as the sole product when zinc and acetic acid or tin(II) chloride and ethanol were used. In the case of zinc and acetic acid, the best yield of aminoisoxazole was achieved when the reaction was carried out at 0 to –10°C for three hours. When using the tin(II) chloride and ethanol system, complete conversion of the starting nitro-compound into amine could be achieved by the use of a five-fold excess of the reducing agent, and keeping the reaction mixture at room temperature for one hour. Under these conditions we obtained a series of 5-aminoisoxazoles with an additional functional group in the 3-position (Table 1).

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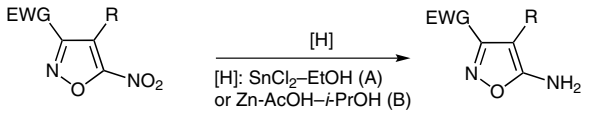
Table 1 Synthesis of 5-Aminoisoxazoles[a]



1a–k **2a–k**

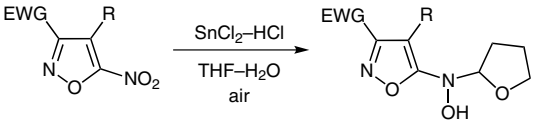
Entry	Amine **2**	R	EWG	Yield of **2** (%)[b]
1	**2a**	H	C(O)Me	75 (A) 50 (B)
2	**2b**	H	C(O)Et	79 (A) 49 (B)
3	**2c**	-C(O)(CH$_2$)$_3$-		58 (A)
4	**2d**	H	CO_2Me	60 (A) 73 (B)
5	**2e**	H	CO_2t-Bu	25 (A) 87 (B)
6	**2f**	H	CO_2CH_2Ad[c]	75 (A)
7	**2g**	H	CO_2CH_2Ph	72 (A)
8	**2h**	Et	CO_2Et	75 (A)
9	**2i**	$(CH_2)_3Cl$	CO_2Et	65 (A)
10	**2j**	H	$P(O)(OEt)_2$	90 (A)
11	**2k**	H	$C(O)NH_2$	50 (A)

[a] Reaction conditions: Method A: 5-nitroisoxazole (0.6 mmol), $SnCl_2$ (3.0 mmol for **1a–g**, **k** and 6 mmol for **1h–j**), 96% EtOH (2 mL), r.t., 2 h (or 3 h for **1h–j**); Method B: 5-nitroisoxazole (0.6 mmol), Zn (2.2 mmol), AcOH (4.2 mmol), *i*PrOH (6 mL), –10 to 0 °C, 3 h.
[b] Isolated yield. Reducing systems are given in parentheses.
[c] Ad = 1-adamantyl.

Reduction with the tin(II) chloride and ethanol system was employed for the majority of compounds which were obtained in high yields. In the case of the reduction of nitroisoxazoles **1h–j** (Table 1, entries 8–10) larger excesses of $SnCl_2$ (7–10 equiv) and longer reaction time (3 h) were needed for the reaction to reach completion. The structure of 5-aminoisoxazoles was confirmed by X-ray crystal structure analysis of a typical compound **2b**.[9]

By studying the influence of the reaction conditions, we found that reduction of the model 5-nitroisoxazole **1a** by tin(II) chloride and hydrochloric acid in tetrahydrofuran resulted in the formation of unexpected product **3a**, which was shown to be hydroxylaminoisoxazole containing a tetrahydrofuran moiety covalently attached to the molecule (Table 2, entry 1). Tetrahydrofuran radical addition to different classes of organic compounds in the presence of radical initiators is well-documented. The addition of the tetrahydrofuran-2-yl radical to double C=C[10] and triple C≡C[11] bonds, and to C=O and C=N[12] groups is known. There are a few reports that describe the addition of tetrahydrofuran to activated C–X bonds in alkenes,[13] alkynes,[14] aryl compounds,[15] fullerene,[16] oxime ethers,[17] and also the addition to S–S (in disulfides),[18] activated O–H (alcohols),[19] and N–H (amines) bonds.[20] To the best of our knowledge, the radical addition of tetrahydrofuran to N=O bonds with the formation of tetrahydrofuranyl substituted hydroxylamine has not been described. However, compounds including such a fragment could be of interest due to their reactivity[21] and potential pharmaceutical applications.[22]

Table 2 Synthesis of 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles[a]



1a–j,l,m **3a–j,l,m**

Entry	Hydroxylamine **3**	R	EWG	Yield of **3** (%)[b]
1	**3a**	H	C(O)Me	80
2	**3b**	H	C(O)Et	77
3	**3c**	-C(O)(CH$_2$)$_3$-		68
4	**3d**	H	CO_2Me	78
5	**3e**	H	CO_2t-Bu	80
6	**3f**	H	CO_2CH_2Ad[c]	65
7	**3g**	H	CO_2CH_2Ph	68
8	**3h**	Et	CO_2Et	70
9	**3i**	$(CH_2)_3Cl$	CO_2Et	81
10	**3j**	H	$P(O)(OEt)_2$	82
11	**3l**	H	C(O)Ph	54
12	**3m**	H	NO_2	46

[a] Reaction conditions: 5-nitroisoxazole (0.3 mmol), $SnCl_2$ (0.9 mmol for **1a–g**, **l**, **m**, and 1.5 mmol for **1h–j**), H_2O (5.5 mL), THF (5.5 mL), concd. HCl (0.5 mL), 0 °C, 2 h (or 3 h for **1h–j**).
[b] Isolated yield.
[c] Ad = 1-adamantyl.

The novel reaction of the radical addition of tetrahydrofuran to the N=O bond prompted us to examine the reaction with other 5-nitroisoxazoles. By optimizing the reaction conditions for model compound **1a** we found that highly purified tetrahydrofuran did not react with nitroisoxazoles. When AIBN or benzoyl peroxide were used as radical initiators in catalytic amounts, the desired product **3a** was obtained in approximately 50% yields (on the basis of ^{1}H NMR spectra). In the course of our investigation we found that the present reaction could be successfully carried out when air was bubbled for several hours into tetrahydrofuran that had been previously distilled over sodium hydroxide. This simple method of initiation of tetrahydrofuranyl radicals was used for the synthesis of target isoxazoles. In all cases, 5-[hydroxy(tetrahydrofuran-2-

yl)amino]isoxazoles were obtained in good yields. The results of the reduction of a number of 5-nitroisoxazoles by $SnCl_2$–HCl in tetrahydrofuran are presented in Table 2. To avoid partial decomposition of the isoxazole fragment, the reduction was carried out at 0 °C for two hours. For 5-nitroisoxazoles **1h–j** (entries 8–10) the reaction time was increased to three hours and greater amounts of $SnCl_2$ were used (see the Experimental Section). The reaction conditions detailed above were applied to a variety of 5-nitroisoxazoles to provide 5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles in good isolated yields (Table 2).

It should be noted that 3,5-dinitroisoxazole **1m** (Table 2, entry 12) afforded only 5-hydroxylamine **3m**, with the retention of the nitro group in the 3-position both under standard conditions and by using a large excess of $SnCl_2$ (mol ratio $SnCl_2$/**1m**, 10:1). The structure of **3m** was unambiguously confirmed on the basis of X-ray crystal structure analysis (Figure 1).

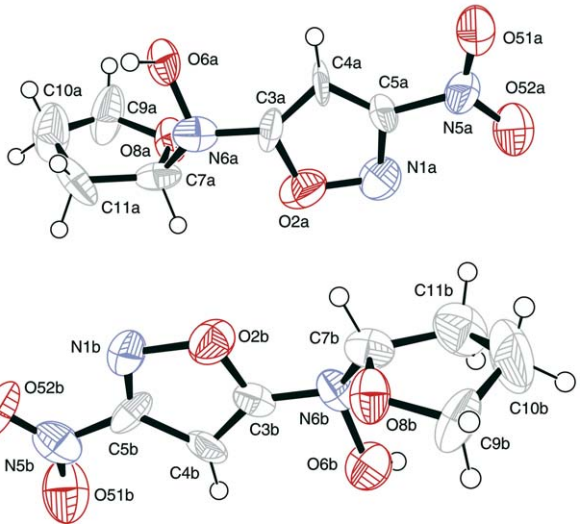
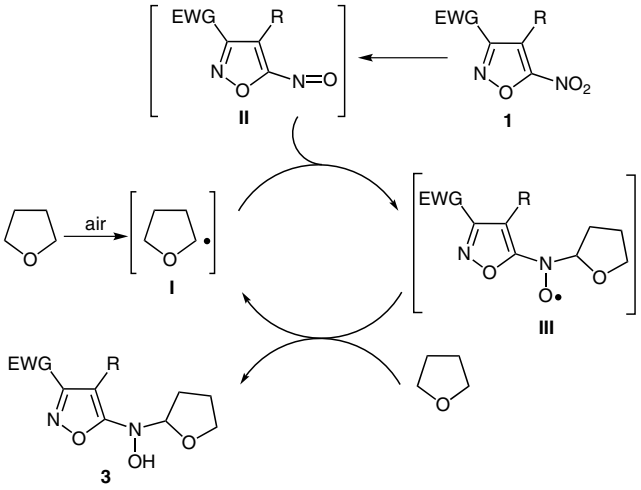


Figure 1 X-ray crystal structure of 5-[hydroxy(tetrahydrofuran-2-yl)amino]-3-nitroisoxazole (**3m**) (thermal ellipsoids are shown with 50% probability level)[23]

Taking into account the experimental conditions and literature data[10–20] we assumed that the reaction proceeds through a radical mechanism (Scheme 2).

It is likely that radical species, formed as a result of involving atmospheric oxygen in the reaction with tetrahydrofuran under daylight, participate in the abstraction of a labile α-hydrogen atom from tetrahydrofuran, giving tetrahydrofuran-2-yl radical **I**. 5-Nitrosoisoxazole **II** is generated in the reduction of 5-nitroisoxazole **1** by $SnCl_2$. This intermediate adds the radical **I** to produce intermediate **III**. Subsequent reaction of tetrahydrofuran with **III** leads to product **3** and generates radical **I**. In this way, the radical cycle mechanism may be completed.

In conclusion, we have developed a simple regioselective method for the synthesis of functionalized 5-aminoisoxazoles and the previously unknown 5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles. Our strategy is based on



Scheme 2 Proposed mechanism for the formation of 5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles

chemoselective reduction of 5-nitroisoxazoles by tin(II) chloride, which affords either the adducts with tetrahydrofuran or aminoisoxazoles, depending crucially on which solvent was used.

^1H (400.0 MHz), ^{13}C (100.6 MHz) and ^{31}P (161.9 MHz) NMR spectra were recorded with an Agilent 400-MR NMR spectrometer at r.t.; chemical shifts (δ) were measured with reference to the solvent $CDCl_3$ for ^1H (δ = 7.24 ppm) and ^{13}C (δ = 77.13 ppm), and 85% H_3PO_4 for ^{31}P as external standard. Accurate mass measurements (HRMS) were measured with a Bruker microOTOF II mass spectrometer using electrospray ionization (ESI) and a time-of-flight (TOF) detector. X-ray diffraction analysis was carried out with equipment diffractometer STADI VARI Pilatus-100K. Analytical thin-layer chromatography was carried out with silica gel plates (supported on aluminum); detection was achieved by irradiation under a UV lamp (254 and 365 nm) and chemical staining (5% aqueous solution of $KMnO_4$). Column chromatography was performed on silica gel (230–400 mesh). Starting 5-nitroisoxazoles **1a–m** were synthesized by our original procedures.[8] Other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use.

1-Adamantylmethyl 5-nitroisoxazole-3-carboxylate (1f)

Synthesized by our original procedure[8] from 1-adamantylmethyl acrylate (1.01 g, 4.59 mmol), TNM (2.25 g, 11.48 mmol), Et_3N (0.927 g, 9.18 mmol) in 1,4-dioxane (15 mL).

Yield: 0.96 g (68%); pale-yellow crystals; mp 95–96 °C; R_f 0.59 ($CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (br s, 3 H, $3CH_2$), 1.60 (br s, 3 H, $3CH_2$), 1.63–1.68 (m, 3 H, $3CH_2$), 1.71–1.77 (m, 3 H, $3CH_2$), 1.98–2.04 (m, 3 H, 3CH), 4.02 (s, 2 H, CH_2O), 7.37 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (3CH), 33.5 (C), 36.7 ($3CH_2$), 39.1 ($3CH_2$), 76.4 (CH_2O), 102.3 (CH), 157.8 (C), 158.3 (C), 165.6 (CNO_2).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{18}N_2O_5Na^+$: 329.1108; found: 329.1099.

Synthesis of 5-Aminoisoxazoles; General Procedure

Method A: To a stirred solution of 5-nitroisoxazole (0.6 mmol) in 96% EtOH (2 mL), $SnCl_2$ (580 mg, 3.0 mmol for **1a–g**, **k**; and 1140 mg, 6 mmol for **1h–j**) was added in one portion at r.t. The resulting

mixture was stirred for 2 h (or 3 h for **1h**–**j**), then the solvent was evaporated in vacuo and the residue was dissolved in $CHCl_3$ (20 mL) and washed with sat. aq $NaHCO_3$ (resulting in a solution at pH 8). The aqueous phase was extracted with $CHCl_3$ (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by preparative column chromatography on silica gel [petroleum ether–EtOAc, 4:1 (for **2d**–**i**), or $CHCl_3$–MeOH, 20:1 (for **2a**–**c**, **j**, **k**].

Method B: To a stirred solution of 5-nitroisoxazole (0.6 mmol) and glacial AcOH (260 mg, 4.2 mmol) in *i*-PrOH (6 mL), Zn powder (140 mg, 2.2 mmol) was added in one portion at –10 to 0 °C. The resulting mixture was stirred at this temperature for 3 h, then filtered and the solvent was evaporated in vacuo. The residue was dissolved in chloroform (10 mL) and washed with sat. aq $NaHCO_3$ (resulting in a solution at pH 8). The aqueous phase was extracted with $CHCl_3$ (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified according to method A.

1-(5-Aminoisoxazol-3-yl)ethanone (2a)
Yield: 57 mg (75%, A); 38 mg (50%, B); colorless crystals; mp 133–135 °C; R_f 0.37 ($CHCl_3$).

IR (Nujol): 3350, 3030, 1700, 1660, 1612 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 4.58 (br s, 2 H, NH_2), 5.50 (s, 1 H CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9 (CH_3), 78.3 (CH), 163.4 (C), 169.6 (C), 192.8 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_5H_7N_2O_2^+$: 127.0508; found: 127.0494.

1-(5-Aminoisoxazol-3-yl)propan-1-one (2b)
IR (Nujol): 3360, 3030, 1710, 1646, 1605 cm^{-1}.

Yield: 66 mg (79%, A); 40 mg (49%, B); colorless crystals; mp 127–129 °C; R_f 0.24 ($CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.3 Hz, 3 H, CH_3), 3.00 (q, ^3J = 7.3 Hz, 2 H, CH_2), 4.59 (br s, 2 H, NH_2), 5.50 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.5 (CH_3), 32.8 (CH_2), 78.5 (CH), 163.0 (C), 169.4 (C), 195.8 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_6H_9N_2O_2^+$: 141.0664; found: 141.0655.

3-Amino-5,6-dihydro-2,1-benzisoxazol-7(4*H*)-one (2c)
Yield: 53 mg (58%, A); colorless crystals; mp 95–97 °C; R_f 0.06 (petroleum ether–EtOAc, 5:1).

IR (Nujol): 3320, 3050, 1715, 1660, 1650, 1610 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.10–2.16 (m, 2 H, CH_2), 2.50–2.55 (m, 2 H, CH_2), 2.62–2.66 (m, 2 H, CH_2), 4.62 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (CH_2), 23.7 (CH_2), 40.3 (CH_2), 95.2 (C), 157.8 (C), 165.6 (C), 192.8 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_7H_9N_2O_2^+$: 153.0664; found: 153.0659.

Methyl 5-Aminoisoxazole-3-carboxylate (2d)
Yield: 51 mg (60%, A); 62 mg (73%, B); colorless crystals; mp 137–139 °C; R_f 0.29 (petroleum ether–EtOAc, 5:1).

IR (Nujol): 3330, 3060, 1710, 1655, 1610, 1380, 1240, 1020 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, CH_3), 4.63 (br s, 2 H, NH_2), 5.55 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ = 52.4 (OCH_3), 79.4 (CH), 156.8 (C), 161.1 (C), 171.1 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_5H_7N_2O_3^+$: 143.0457; found: 143.0452.

***tert*-Butyl 5-Aminoisoxazole-3-carboxylate (2e)**
Yield: 28 mg (25%, A); 96 mg (87%, B); colorless crystals; mp 125–127 °C; R_f 0.29 ($CHCl_3$–MeOH, 20:1).

IR (Nujol): 3440, 3050, 3010, 1720, 1650, 1605, 1380, 1245 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 9 H, 3 CH_3), 4.62 (br s, 2 H, NH_2), 5.51 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (3 CH_3), 80.7 (CH), 83.2 (C), 158.8 (C), 159.5 (C), 169.4 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{13}N_2O_3^+$: 185.0926; found: 185.0921.

1-Adamantylmethyl 5-aminoisoxazole-3-carboxylate (2f)
Yield: 124 mg (75%, A); colorless crystals; mp 174–176 °C; R_f 0.41 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3440, 3300, 3010, 1715, 1645, 1610, 1375, 1240, 1025 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.58 (br s, 3 H, 3 CH_2), 1.59 (br s, 3 H, 3 CH_2), 1.61–1.67 (m, 3 H, 3 CH_2), 1.68–1.75 (m, 3 H, 3 CH_2), 1.95–2.01 (m, 3 H, 3 CH), 3.92 (s, 2 H, CH_2O), 4.62 (br s, 2 H, NH_2), 5.52 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (3 CH), 33.4 (C), 36.8 (3 CH_2), 39.2 (3 CH_2), 75.0 (CH_2O), 80.7 (CH), 157.5 (C), 160.6 (C), 169.5 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{20}N_2O_3Na^+$: 299.1366; found: 299.1355.

Benzyl 5-Aminoisoxazole-3-carboxylate (2g)
Yield: 94 mg (72%, A); pale-pink crystals; mp 112 °C; R_f 0.19 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3440, 3320, 3012, 1725, 1640, 1600, 1470, 1385, 1210, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.68 (br s, 2 H, NH_2), 5.34 (s, 2 H, CH_2O), 5.51 (s, 1 H, CH), 7.31–7.37 (m, 3 H, Ph), 7.40–7.42 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.4 (CH_2O), 80.6 (CH), 128.52 (2 CH, Ph), 128.55 (CH, Ph), 128.61 (2 CH, Ph), 134.9 (C, Ph), 157.2 (C), 160.3 (C), 169.8 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_3Na^+$: 241.0584; found: 241.0590.

Ethyl 5-Amino-4-ethylisoxazole-3-carboxylate (2h)
Yield: 83 mg (75%, A); colorless crystal; mp 72–74 °C; R_f 0.28 ($CHCl_3$).

IR (Nujol): 3440, 3320, 3010, 1725, 1645, 1605, 1475, 1380, 1225 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, ^3J = 7.5 Hz, 3 H, CH_3), 1.41 (t, ^3J = 7.2 Hz, 3 H, CH_3), 2.49 (q, ^3J = 7.5 Hz, 2 H, CH_2), 4.41 (q, ^3J = 7.2 Hz, 2 H, CH_2O), 4.51 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 ($J_{C–H}$ = 127 Hz, CH_3), 14.1 ($J_{C–H}$ = 127 Hz, CH_3), 14.9 ($J_{C–H}$ = 129 Hz, CH_2), 61.6 ($J_{C–H}$ = 148 Hz, CH_2O), 96.4 (C), 155.1 (C), 161.0 (C), 166.7 (C).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.20; H, 6.71; N, 15.28.

Ethyl 5-Amino-4-(3-chloropropyl)isoxazole-3-carboxylate (2i)
Yield: 91 mg (65%, A); colorless crystals; mp 101–103 °C; R_f 0.33 ($CHCl_3$).

IR (Nujol): 3460, 3410, 3330, 3010, 1705, 1655, 1610, 1480, 1375, 1240 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.1 Hz, 3 H, CH_3), 2.01–2.08 (m, 2 H, CH_2), 2.68 (t, ^3J = 6.7 Hz, 2 H, CH_2), 3.58 (t, ^3J = 6.0 Hz, 2 H, CH_2), 4.41 (q, ^3J = 7.1 Hz, 2 H, CH_2), 4.69 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 18.2 (CH_2), 31.8 (CH_2), 44.6 (CH_2Cl), 61.7 (CH_2O), 92.4 (C), 155.1 (C), 160.9 (C), 168.0 (C).

Anal. Calcd for $C_9H_{13}ClN_2O_3$: C, 46.46; H, 5.63; N, 12.04. Found: C, 46.30; H, 5.69; N, 11.89.

Diethyl (5-Aminoisoxazol-3-yl)phosphonate (2j)
Yield: 120 mg (90%, A); colorless crystals; mp 90–92 °C; R_f 0.20 ($CHCl_3$–MeOH, 20:1).

IR (Nujol): 3350, 3000, 1650, 1590, 1252, 1045–1010 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, ^3J = 7.1 Hz, 6 H, $2CH_3$), 4.17–4.27 (m, 4 H, $2CH_2$), 5.19 (br s, 2 H, NH_2), 5.39 (d, $^3J_{P–H}$ = 1.3 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 ($J_{C–P}$ = 6 Hz, $2CH_3$), 63.5 ($J_{C–P}$ = 6 Hz, $2CH_2$), 82.1 ($J_{C–P}$ = 22 Hz, CH), 156.6 ($J_{C–P}$ = 210 Hz, C), 169.9 ($J_{C–P}$ = 13 Hz, C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.46.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_7H_{14}N_2O_4P^+$: 221.0691; found: 221.0694.

Anal. Calcd for $C_7H_{13}N_2O_4P$: C, 38.19; H, 5.95; N, 12.72. Found: C, 38.48; H, 5.75; N, 12.53.

5-Aminoisoxazole-3-carboxamide (2k)
Yield: 38 mg (50%, A); colorless crystals; mp 180 °C (dec.).

IR (Nujol): 3350, 3200, 3060, 1650, 1612 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.37 (s, 1 H, CH). The signals of 2 NH_2-groups are aligned with the signals of solvent.

^{13}C NMR (100 MHz, CD_3OD): δ = 76.6 (CH), 159.3 (C), 163.1 (C), 172.1 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_4H_6N_3O_2^+$: 128.0460; found: 128.0455.

Synthesis of 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazoles; General Procedure
THF was distilled over NaOH, then air was bubbled through the distillate for 10 h prior its use in the reaction. To a stirred solution of 5-nitroisoxazole (0.3 mmol) in a mixture of H_2O–THF (1:1, 11 mL), $SnCl_2$ (170 mg, 0.9 mmol for **1a**–**g**, **l**, **m**; and 285 mg, 1.5 mmol for **1h**–**j**) was added in one portion, then concd. HCl (0.5 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 2 h (or 3 h for compounds **1h**–**j**), then THF was evaporated in vacuo and sat. aq $NaHCO_3$ was added to the residue until pH 8 was reached. The aqueous phase was extracted with $CHCl_3$ (3 × 7 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by preparative column chromatography on silica gel [petroleum ether–EtOAc, 2:1, or $CHCl_3$–MeOH, 20:1 for **3j**].

1-{5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazol-3-yl}ethanone (3a)
Yield: 51 mg (80%); yellow oil; R_f 0.37 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3300, 3170, 3010, 1710, 1640, 1600, 1470, 1380, 1060 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87–1.97 (m, 1 H, CH_2), 2.05–2.28 (m, 3 H, $2CH_2$), 2.55 (s, 3 H, CH_3), 3.83–3.88 (m, 1 H, CH_2O), 4.03–4.09 (m, 1 H, CH_2O), 5.58 (dd, ^3J = 4.1, ^3J = 6.9 Hz, 1 H, CHO), 5.93 (s, 1 H, CH), 6.78 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (CH_2), 27.0 (CH_3), 27.9 (CH_2), 69.9 (CH_2O), 84.5 (CH), 92.2 (CHO), 162.6 (C), 172.9 (C), 192.5 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{13}N_2O_4$: 213.0870; found: 213.0864.

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.62; N, 12.96.

1-{5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazol-3-yl}propan-1-one (3b)
Yield: 52 mg (77%); yellow oil; R_f 0.43 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3300, 3170, 3012, 1710, 1640, 1600, 1470, 1380, 1070 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.92–2.00 (m, 1 H, CH_2), 2.11–2.32 (m, 3 H, $2CH_2$), 3.01 (q, ^3J = 7.3 Hz, 2 H, CH_2), 3.87–3.92 (m, 1 H, CH_2O), 4.08–4.13 (m, 1 H, CH_2O), 5.62 (dd, ^3J = 4.0, ^3J = 6.9 Hz, 1 H, CHO), 5.97 (s, 1 H, CH), 6.92 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.5 (CH_3), 25.3 (CH_2), 27.9 (CH_2), 32.9 (CH_2), 70.0 (CH_2O), 84.7 (CH), 92.3 (CHO), 162.2 (C), 172.6 (C), 195.6 (C=O).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.24; H, 6.18; N, 12.15.

3-[Hydroxy(tetrahydrofuran-2-yl)amino]-5,6-dihydro-2,1-benzisoxazol-7(4*H*)-one (3c)
Yield: 49 mg (68%); yellow crystals; mp 94–96 °C; R_f 0.13 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3298, 3005, 1714, 1622, 1590, 1470, 1382, 1035 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–2.00 (m, 1 H, CH_2), 2.05–2.22 (m, 4 H, $2CH_2$), 2.25–2.33 (m, 1 H, CH_2), 2.61–2.64 (m, 2 H, CH_2), 2.75–2.90 (m, 2 H, CH_2), 3.88–3.94 (m, 1 H, CH_2O), 4.09–4.14 (m, 1 H, CH_2O), 5.59 (dd, ^3J = 4.1, ^3J = 7.0 Hz, 1 H, CHO), 7.06 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (CH_2), 23.5 (CH_2), 25.4 (CH_2), 28.0 (CH_2), 40.3 (CH_2), 69.9 (CH_2O), 92.3 (CHO), 102.7 (C), 157.9 (C), 167.3 (C), 192.8 (C=O).

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.48; H, 6.02; N, 11.63.

Methyl 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate (3d)
Yield: 53 mg (78%); yellow oil; R_f 0.21 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3280, 3010, 1728, 1610, 1475, 1382, 1115, 1060 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–2.01 (m, 1 H, CH_2), 2.11–2.32 (m, 3 H, $2CH_2$), 3.88–3.93 (m, 1 H, CH_2O), 3.96 (s, 3 H, CH_3), 4.08–4.13 (m, 1 H, CH_2O), 5.63 (dd, ^3J = 4.0, ^3J = 7.0 Hz, 1 H, CHO), 6.04 (s, 1 H, CH), 6.74 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 ($J_{C–H}$ = 132 Hz, CH_2), 27.9 ($J_{C–H}$ = 132 Hz, CH_2), 52.8 ($J_{C–H}$ = 148 Hz, CH_3), 70.0 ($J_{C–H}$ = 148 Hz, CH_2O), 86.9 ($J_{C–H}$ = 191 Hz, CH), 92.2 ($J_{C–H}$ = 163 Hz, CHN), 156.7 (C), 160.5 (C), 172.8 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{13}N_2O_4$: 213.0870; found: 213.0864.

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.11; H, 5.22; N, 12.38.

***tert*-Butyl 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate (3e)**
Yield: 65 mg (80%); yellow oil; R_f 0.40 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3300, 3010, 1732, 1640, 1600, 1475, 1380, 1040 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 9 H, $3CH_3$), 1.90–1.97 (m, 1 H, CH_2), 2.09–2.30 (m, 3 H, $2CH_2$), 3.86–3.91 (m, 1 H, CH_2O), 4.06–4.11 (m, 1 H, CH_2O), 5.59 (dd, ^3J = 4.0, ^3J = 7.0 Hz, 1 H, CHO), 5.96 (s, 1 H, CH), 6.72 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (CH_2), 27.9 (CH_2), 28.0 ($3CH_3$), 69.9 (CH_2O), 83.5 (C), 87.0 (CH), 92.4 (CHO), 158.1 (C), 159.1 (C), 172.6 (C).

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.39; H, 6.64; N, 9.98.

1-Adamantylmethyl 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate (3f)
Yield: 70 mg (65%); colorless crystals; mp 144–145 °C; R_f 0.25 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3300, 3010, 1725, 1645, 1610, 1475, 1370, 1060 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (br s, 3 H, $3CH_2$), 1.55 (br s, 3 H, $3CH_2$), 1.58–1.65 (m, 3 H, $3CH_2$), 1.66–1.74 (m, 3 H, $3CH_2$), 1.82–1.92 (m, 1 H, CH_2), 1.93–1.98 (m, 3 H, 3CH), 2.05–2.27 (m, 3 H, $2CH_2$), 3.80–3.86 (m, 1 H, CH_2O), 3.92 (s, 2 H, CH_2O), 4.02–4.07 (m, 1 H, CH_2O), 5.57 (dd, ^3J = 4.0, ^3J = 7.0 Hz, 1 H, CHO), 5.95 (s, 1 H, CH), 7.35 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (CH_2), 27.85 (CH_2), 27.9 (3CH), 33.4 (C), 36.8 ($3CH_2$), 39.1 ($3CH_2$), 69.9 (CH_2O), 75.2 (CH_2O), 86.6 (CH), 92.2 (CHO), 156.8 (C), 160.2 (C), 173.0 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{26}N_2O_5Na^+$: 385.1734; found: 385.1728.

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.75; H, 7.36; N, 7.56.

Benzyl 5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate (3g)
Yield: 62 mg (68%); pale-brown oil; R_f 0.15 (petroleum ether–EtOAc, 3:1).

IR (Nujol): 3300, 3280, 3070, 3020, 1715, 1645, 1612, 1585, 1470, 1180, 1070 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88–1.99 (m, 1 H, CH_2), 2.00–2.29 (m, 3 H, $2CH_2$), 3.82–3.91 (m, 1 H, CH_2O), 4.03–4.10 (m, 1 H, CH_2O), 5.38 (s, 2 H, CH_2O), 5.57–5.61 (m, 1 H, CHO), 6.02 (s, 1 H, CH), 6.71 (br s, 1 H, OH), 7.31–7.49 (m, 5 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (CH_2), 27.9 (CH_2), 67.5 (CH_2O), 69.9 (CH_2O), 86.9 (CH), 92.2 (CHO), 128.50 (2CH, Ph), 128.56 (CH, Ph), 128.61 (2CH, Ph), 134.9 (C, Ph), 156.7 (C), 159.8 (C), 172.9 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_5^+$: 305.1132; found: 305.1138.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{16}N_2O_5Na^+$: 327.0951; found: 327.0955.

Ethyl 4-Ethyl-5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate (3h)
Yield: 57 mg (70%); colorless crystals; mp 74–76 °C; R_f 0.40 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3280, 3008, 1720, 1610, 1480, 1382, 1110, 1070 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, ^3J = 7.5 Hz, 3 H, CH_3), 1.42 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.88–1.98 (m, 1 H, CH_2), 1.99–2.07 (m, 1 H, CH_2), 2.09–2.16 (m, 2 H, CH_2), 2.69 (q, ^3J = 7.5 Hz, 2 H, CH_2), 3.89–3.95 (m, 1 H, CH_2O), 4.06–4.11 (m, 1 H, CH_2O), 4.44 (q, ^3J = 7.1 Hz, 2 H, CH_2), 5.40–5.43 (m, 1 H, CHO), 6.38 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 15.0 (CH_3), 15.4 (CH_2), 25.2 (CH_2), 28.4 (CH_2), 61.8 (CH_2O), 69.4 (CH_2O), 93.7 (CHO), 110.3 (C), 155.6 (C), 160.4 (C), 167.5 (C).

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.34; H, 6.91; N, 10.28.

Ethyl 4-(3-Chloropropyl)-5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate (3i)
Yield: 77 mg (81%); yellow oil; R_f 0.40 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3310, 3015, 1735, 1612, 1565, 1480, 1370, 1200, 1075 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.87–1.97 (m, 2 H, CH_2), 2.00–2.17 (m, 4 H, $2CH_2$), 2.82–2.86 (m, 2 H, CH_2), 3.57 (t, ^3J = 6.5 Hz, 2 H, CH_2), 3.87–3.92 (m, 1 H, CH_2O), 4.05–4.10 (m, 1 H, CH_2O), 4.42 (q, ^3J = 7.1 Hz, 2 H, CH_2O), 5.46–5.49 (m, 1 H, CHO), 6.91 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 19.4 (CH_2), 25.2 (CH_2), 28.4 (CH_2), 33.0 (CH_2), 44.7 (CH_2Cl), 62.0 (CH_2O), 69.5 (CH_2O), 93.3 (CHO), 105.8 (C), 155.6 (C), 160.4 (C), 168.4 (C).

Anal. Calcd for $C_{13}H_{19}ClN_2O_5$: C, 48.98; H, 6.01; N, 8.79. Found: C, 48.89; H, 6.12; N, 8.78.

Diethyl {5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazol-3-yl}phosphonate (3j)
Yield: 75 mg (82%); yellow oil; R_f 0.36 ($CHCl_3$–MeOH, 20:1).

IR (Nujol): 3290, 3010, 1640, 1610, 1470, 1380, 1250, 1020 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (dt, ^3J = 7.1 Hz, $^4J_{P–H}$ = 0.5 Hz, 3 H, CH_3), 1.37 (dt, ^3J = 7.1 Hz, $^4J_{P–H}$ = 0.5 Hz, 3 H, CH_3), 1.86–1.96 (m, 1 H, CH_2), 2.12–2.19 (m, 2 H, CH_2), 2.29–2.36 (m, 1 H, CH_2), 3.84–3.89 (m, 1 H, CH_2O), 4.07–4.12 (m, 1 H, CH_2O), 4.16–4.27 (m, 4 H, $2CH_2$), 5.65 (dd, ^3J = 4.0, ^3J = 7.1 Hz, 1 H, CHO), 5.76 (d, $^3J_{H–P}$ = 1.2 Hz, 1 H, CH), 8.80 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 ($J_{C–P}$ = 6 Hz, $2CH_3$), 25.4 (CH_2), 28.1 (CH_2), 63.9 (d, $J_{C–P}$ = 6 Hz, CH_2), 64.1 (d, $J_{C–P}$ = 6 Hz, CH_2), 69.9 (CH_2O), 87.7 ($J_{C–P}$ = 22 Hz, CH), 91.8 (CHO), 155.7 ($J_{C–P}$ = 211 Hz, C), 173.2 ($J_{C–P}$ = 13 Hz, C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.55.

Anal. Calcd for $C_{11}H_{19}N_2O_6P$: C, 43.14; H, 6.25; N, 9.15. Found: C, 43.28; H, 6.29; N, 9.21.

{5-[Hydroxy(tetrahydrofuran-2-yl)amino]isoxazol-3-yl}(phenyl)methanone (3l)
Yield: 45 mg (54%); yellow oil; R_f 0.38 (petroleum ether–EtOAc, 3:1).

IR (Nujol): 3350, 3010, 2990, 1695, 1645, 1600, 1580, 1528, 1350, 1045 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90–2.00 (m, 1 H, CH_2), 2.08–2.33 (m, 3 H, $2CH_2$), 3.87–3.92 (m, 1 H, CH_2O), 4.08–4.13 (m, 1 H, CH_2O), 5.64 (dd, ^3J = 4.1, ^3J = 7.0 Hz, 1 H, CHO), 5.95 (s, 1 H, CH), 6.12 (br s, 1 H, OH), 7.47–7.50 (m, 2 H, Ph), 7.59–7.63 (m, 1 H, Ph), 8.23–8.25 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (CH_2), 27.9 (CH_3), 27.9 (CH_2), 70.0 (CH_2O), 87.0 (CH), 92.3 (CHO), 128.5 (2CH, Ph), 130.6 (2CH, Ph), 134.0 (CH, Ph), 135.6 (C, Ph), 162.4 (C), 172.1 (C), 186.1 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_4$: 275.1026; found: 275.1024.

5-[Hydroxy(tetrahydrofuran-2-yl)amino]-3-nitroisoxazole (3m)
Yield: 30 mg (46%); yellow crystals; mp 108–110 °C; R_f 0.31 (petroleum ether–EtOAc, 2:1).

IR (Nujol): 3280, 3005, 1645, 1610, 1510, 1340, 1045 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.06 (m, 1 H, CH_2), 2.12–2.33 (m, 3 H, $2CH_2$), 3.91–3.96 (m, 1 H, CH_2O), 4.10–4.15 (m, 1 H, CH_2O), 5.67 (dd, J = 4.1, 6.9 Hz, 1 H, CHO), 6.18 (s, 1 H, CH), 6.49 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (CH_2), 28.0 (CH_2), 70.2 (CH_2O), 81.5 (CH), 91.8 (CHO), 167.5 (br s, CNO_2), 174.0 (C).

Anal. Calcd for $C_7H_9N_3O_5$: C, 39.07; H, 4.22; N, 19.53. Found: C, 39.33; H, 4.33; N, 19.54.

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(23) Crystallographic data for compound **3m** (CCDC-865299) can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.