Synthesis of Isoxazole-5-carboxylates by Cyclization of Oxime 1,4-Dianions with Diethyl Oxalate

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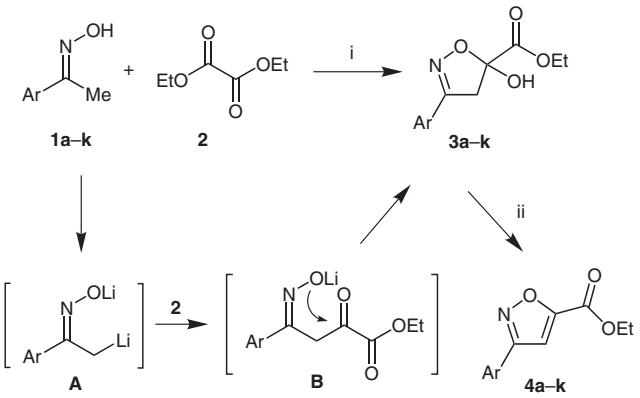
Abstract: The cyclization of oxime dianions with diethyl oxalate afforded 4,5-dihydro-5-hydroxyisoxazole-5-carboxylates, which were transformed into isoxazole-5-carboxylates by acid-mediated dehydration. The reaction of the dilithiated oximes of cycloheptanone and cyclooctanone resulted in the formation of 1,2-oxazin-6-ones rather than isoxazoles.

Keywords: cyclizations, dianions, oxalic acid derivatives, one-pot reactions, oximes

Functionalized isoxazoles are present in a variety of natural products and represent useful synthetic building blocks.[1a] They have shown considerable antimicrobial, antifungal, and herbicide activity.[1b] The isoxazole moiety is present in sulfonamide antibiotics (sulfisoxazoles, oxacillin, cloxacillin, and dicloxacillin),[2] antirheumatic and antiarthritic agents (leflunomide),[3] anti-inflammatory agents (isoxicam),[3] and antileprous agents and it is also present in a monoaminoxidase inhibitor used in psychotherapy.[2] The antipicornavirus and antimuscarinic activity of 5-alkyl-3-methylisoxazoles and 5-(aminomethyl)-3-phenylisoxazoles has been recognized.[4] A general approach to isoxazoles relies on 1,3-dipolar cycloaddition of nitrile oxides with alkynes or with alkenes containing a leaving group.[3,5] Isoxazoles have been prepared by cyclization reactions[6] of oxime dianions with esters,[7] *N*,*N*-dialkylbenzamides,[8] and Weinreb amides.[9] Recently, we have reported the synthesis of 1,2-oxazines by cyclization of oxime dianions with epibromohydrin.[10] Herein, we report a convenient synthesis of isoxazole-5-carboxylates by cyclization of oxime dianions with diethyl oxalate.

The reaction of the dianion of acetophenone oxime (**1a**), generated using *n*-butyllithium (2.5 equiv), with diethyl oxalate (**2**) afforded 4,5-dihydro-5-hydroxyisoxazole-5-carboxylate **3a** (Scheme 1, Table 1). During the optimization, the employment of diethyl oxalate proved to be important; the use of oxalyl chloride or ethyl 2-chloro-2-oxoacetate resulted in polymerization. In addition, the temperature, reaction time, and workup conditions proved to be important parameters. Best results were obtained when the dianion was stirred for 45 minutes at –78 °C and, subsequently, for 15 minutes at 20 °C. In fact, the conditions used for the generation of the dianion played a crucial role. Diethyl oxalate was added at –78 °C and the solution was warmed to ambient temperature over 16 hours. A saturated solution of ammonium chloride was used for the aqueous workup. The formation of **3a** can be explained by attack of the carbon atom of the dianion **A** onto **2** and subsequent regioselective attack of the oxygen atom onto the carbonyl rather than the ester group. Ketol **3a** was transformed into isoxazole **4a** by treatment with *p*-toluenesulfonic acid (toluene, reflux).[11]

The cyclization of diethyl oxalate with the dianions of methyl- and methoxy-substituted acetophenone oximes **1a–f** afforded the ketols **3a–f** which were transformed into isoxazoles **4a–f** (Scheme 1, Table 1). The naphthyl-substituted isoxazoles **4g**,**h** were prepared from acetonaphthone oximes **1g**,**h**. Starting with the chloro-, fluoro-, and trifluoromethyl-substituted acetophenone oximes **1i–k**, the ketols **3i–k** were prepared; the latter were transformed into the corresponding isoxazoles **4i–k**. The reactions of diethyl oxalate with the cyano- and nitro-substituted acetophenone oximes **1l** and **1m** were unsuccessful (formation of a complex mixture). This can be explained by the assumption that the generation of the required dianions failed, due to side-reactions of the cyano and the nitro group with *n*-butyllithium. The use of lithium diisopropylamide (rather than *n*-butyllithium) was equally unsuccessful.



Scheme 1 Synthesis of isoxazoles **4a–k**. *Reagents and conditions*: (i) 1. *n*-BuLi (2.5 equiv), –78 °C, 45 min; 2. r.t., 15 min; 3. **2**, –78 °C to r.t., 16 h; (ii) $TsOH \cdot H_2O$ (5.0 equiv), toluene, reflux, 6 h.

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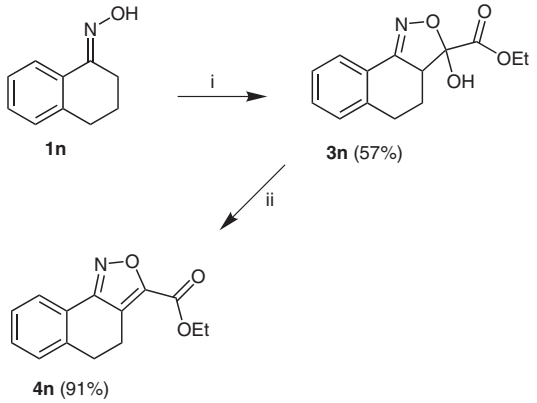
Table 1 Yields of **3a–k** and **4a–k**

3,4	Ar	Yield[a] (%)	
		3	**4**
a	Ph	40	94
b	4-MeC_6H_4	42	82
c	3-MeC_6H_4	37	79
d	2-MeC_6H_4	54	96
e	4-$(MeO)C_6H_4$	43	68
f	3-$(MeO)C_6H_4$	35	75
g	1-naphthyl	45	82
h	2-naphthyl	51	76
i	4-ClC_6H_4	39	74
j	4-FC_6H_4	52	79
k	4-$F_3CC_6H_4$	41	85
l	4-$O_2NC_6H_4$	0	–
m	4-$(NC)C_6H_4$	0	–

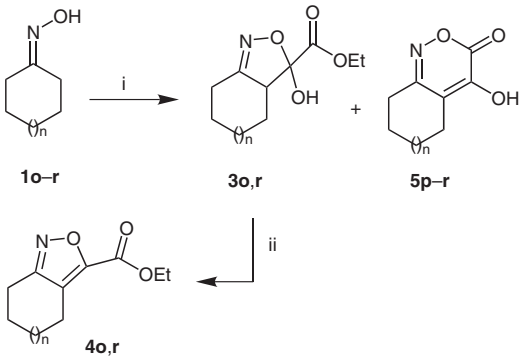
[a] Yield of isolated product.

The cyclization of tetralone oxime (**1n**) with diethyl oxalate afforded the ketol **3n** which was transformed into **4n** (Scheme 2).



Scheme 2 Synthesis of **3n** and **4n**. *Reagents and conditions*: (i) 1. *n*-BuLi (2.5 equiv), –78 °C, 1 h; 2. r.t., 10 min; (3) **2**, –78 °C to r.t., 16 h; (ii) $TsOH·H_2O$ (5.0 equiv), toluene, reflux, 6 h.

The cyclization of diethyl oxalate with the dianion of cyclohexanone oxime gave the ketol **3o** which was transformed into the isoxazole **4o** (Scheme 3, Table 2). Surprisingly, the cyclization of diethyl oxalate with cycloheptanone oxime afforded the 6,7-bicyclic 1,2-oxazin-6-one **5p** rather than the expected isoxazole. Likewise, the 6,8-bicyclic 1,2-oxazin-6-one **5q** was obtained in the cyclization of diethyl oxalate with cyclooctanone oxime. The cyclization of diethyl oxalate with cyclododecanone oxime resulted in the formation of a separable mixture of ketol **3r** and of 6,12-bicyclic 1,2-oxazin-6-one **5r**. Ketol **3r** was transformed into the 5,12-bicyclic isoxazole **4r**. The reaction of diethyl oxalate with the dianion of cyclopentanone oxime failed (formation of a complex mixture).



Scheme 3 Synthesis of **3o**,**r**, **4o**,**r**, and **5p**–**r**. *Reagents and conditions*: (i) 1. *n*-BuLi (2.5 equiv), –78 °C, 1 h; 2. r.t., 10 min; 3. **2**, –78 °C to r.t., 16 h; (ii) $TsOH·H_2O$ (5.0 equiv), toluene, reflux, 6 h.

Table 2 Products and Yields

3,4,5	n	Yield[a] (%)		
		3	**4**	**5**
o	1	55	78	0
p	2	0	–	47
q	3	0	–	39
r	7	53	62	21

[a] Yield of isolated product.

In conclusion, we have reported a convenient and regioselective synthesis of isoxazole-5-carboxylates by cyclization of oxime dianions with diethyl oxalate and subsequent dehydration. The reaction of the dilithiated oximes of cycloheptanone and cyclooctanone resulted in the formation of 1,2-oxazin-6-ones rather than isoxazoles.

All solvents were dried by standard methods and all reactions were performed under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. MS data was obtained by electron ionization (EI, 70 eV) or chemical ionization (CI, H_2O). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

Ethyl 4,5-Dihydro-5-hydroxyisoxazole-5-carboxylates 3; General Procedure

To a soln of oxime **1** in THF at –78 °C was added *n*-BuLi. The mixture was stirred at this temperature for 45 min and then at r.t. for 15 min. The mixture was cooled to –78 °C and diethyl oxalate was added. The mixture was warmed to r.t. over 16 h and sat. aq NH_4Cl (30 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the solvent was removed from the filtrate in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc, 10:1 to 3:1).

Ethyl 4,5-Dihydro-5-hydroxy-3-phenylisoxazole-5-carboxylate (3a)

Starting from oxime **1a** (0.270 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3a** as a slightly pink-colored solid; yield: 0.188 g (40%); mp 132 °C.

IR (KBr): 3229 (m), 2987 (w), 1743 (s), 1448 (m), 1363 (m), 1293 (m), 1215 (m) 1138 (m), 1077 (w), 912 (w), 760 (w), 690 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.45 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.95 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.60 (br s, OH), 7.45 (m, 3 H, Ar), 7.71 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 44.0 (CH_2), 63.5 (OCH_2CH_3), 103 (C), 126.9, 128.9, 130.7 (CH, Ar), 126.8 (C), 128.6 (C), 156.6 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 235 (M^+, 15), 117 (16).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.38; H, 5.67; N, 5.74.

Ethyl 4,5-Dihydro-5-hydroxy-3-(4-methylphenyl)isoxazole-5-carboxylate (3b)

Starting from oxime **1b** (0.298 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3b** as a yellow solid; yield: 0.209 g (42%); mp 135 °C.

IR (KBr): 3191 (m), 2986 (w), 1742 (s), 1361 (m), 1293 (m), 1209 (m), 1135 (m), 911 (m), 864 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 3.41 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.95 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.70 (br s, OH), 7.20 (d, ^3J = 8.4 Hz, 2 H, Ar), 7.60 (d, ^3J = 8.4 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.5 (CH_3), 44.4 (CH_2), 63.5 (OCH_2CH_3), 103.0 (C), 127.4, 129.9 (CH, Ar), 125.8, 141.0 (C, Ar), 156.5 (C, CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 249 (M^+, 17), 176 (100), 158 (8), 134 (45), 117 (15), 91 (72), 66 (30).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.33; H, 6.09; N, 5.32.

Ethyl 4,5-Dihydro-5-hydroxy-3-(3-methylphenyl)isoxazole-5-carboxylate (3c)

Starting from soln of oxime **1c** (0.298 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3c** as a colorless solid; yield: 0.184 g (37%); mp 91 °C.

IR (KBr): 3219 (m), 2983 (w), 1742 (s), 1368 (m), 1286 (m), 1210 (m), 1135 (m), 918 (m), 792 (m), 759 (m), 693 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 3.40 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.95 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.50 (br s, OH), 7.30–7.45 (m, 3 H, Ar), 7.5 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.3 (CH_3), 44.0 (CH_2), 63.9 (OCH_2CH_3), 103.1 (C), 124.4, 127.9, 129.1, 131.9 (CH, Ar), 128.5, 138.6 (C, Ar), 156.7 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 249 (M^+, 11), 176 (100), 134 (56), 117 (18), 108 (22), 91 (98).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.71; H, 6.14; N, 5.45.

Ethyl 4,5-Dihydro-5-hydroxy-3-(2-methylphenyl)isoxazole-5-carboxylate (3d)

Starting from oxime **1d** (0.298 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3d** as a yellow solid; yield: 0.269 g (54%); mp 53 °C.

IR (KBr): 3442 (m), 2985 (w), 1734 (s), 1372 (w), 1304 (w), 1214 (s), 1134 (m), 893 (w), 757 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 3.45 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.05 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.52 (br s, OH), 7.20–7.41 (m, 4 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 23.3 (CH_3), 46.2 (CH_2), 63.5 (OCH_2CH_3), 102.3 (C), 126.4, 129.1, 130.3, 132.1 (CH, Ar), 127.5, 138.3 (2C, Ar), 157.7 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 249 (M^+, 29), 176 (100), 130 (71), 117 (14), 91 (81), 66 (18).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.58; H, 6.08; N, 5.34.

Ethyl 4,5-Dihydro-5-hydroxy-3-(4-methoxyphenyl)isoxazole-5-carboxylate (3e)

Starting from oxime **1e** (0.332 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3e** as a colorless solid; yield: 0.228 g (43%); mp 122 °C.

IR (KBr): 3206 (m), 2981 (w), 1746 (s), 1607 (m), 1362 (m), 1297 (m), 1209 (m), 1134 (m), 1075 (w), 906 (w), 862 (m), 761 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.41 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.95 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.60 (br s, OH), 6.96 (d, ^3J = 9 Hz, 2 H, Ar), 7.60 (d, ^3J = 9 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 44.1 (CH_2), 55.4 (OCH_3), 63.5 (OCH_2CH_3), 103.1 (C), 114.4, 128.6 (CH, Ar), 121.2, 161.7 (C, Ar), 156.2 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 265 (M^+, 26), 192 (11), 149 (3).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.90; H, 5.75; N, 5.11.

Ethyl 4,5-Dihydro-5-hydroxy-3-(3-methoxyphenyl)isoxazole-5-carboxylate (3f)

Starting from oxime **1f** (0.332 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3f** as a colorless solid; yield: 0.186 g (35%); mp 110 °C.

IR (KBr): 3430 (m), 2977 (w), 1740 (s), 1609 (m), 1364 (m), 1296 (m), 1217 (m), 1135 (m), 1078 (w), 913 (w), 791 (w), 756 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.41 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.95 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.40 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.61 (br s, OH), 6.96 (dd, ^3J = 8.3 Hz, ^4J = 0.9 Hz, 1 H, Ar), 7.21–7.42 (m, 3 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 43.9 (CH_2), 55.4 (OCH_3), 63.5 (OCH_2CH_3), 103.2 (C), 111.4, 117.1, 119.6, 129.8 (CH, Ar), 129.8, 159.7 (C, Ar), 156.2 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 265 (M^+, 19), 192 (100), 149 (27), 106.5 (31), 92 (20), 77 (32).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.66; H, 5.80; N, 5.06.

Ethyl 4,5-Dihydro-5-hydroxy-3-(1-naphthyl)isoxazole-5-carboxylate (3g)

Starting from oxime **1g** (0.372 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3g** as a brownish oil; yield: 0.257 g (45%).

IR (KBr): 3452 (m), 2986 (w), 1739 (s), 1510 (m), 1370 (m), 1298 (m), 1215 (m), 1137 (m), 1076 (w), 898 (w), 865 (w), 778 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 3.60 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.23 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.41 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.70 (br s, OH), 7.52 (m, 4 H, Ar), 7.91 (m, 2 H, Ar), 8.90 (dd, ^3J = 8.5 Hz, ^4J = 0.8 Hz, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.05 (CH_2CH_3), 46.7 (CH_2), 63.6 (OCH_2CH_3), 103.2 (C), 124.8, 126.5, 126.9, 127.7, 128.1, 128.7, 131.4 (CH, Ar), 125.6, 130.6 (C, Ar), 133.9 (C, Ar), 157.3 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 285 (M^+, 37), 212 (25), 185 (42), 166 (100), 152 (37), 127 (78), 77 (11).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.84; H, 5.51; N, 4.75.

Ethyl 4,5-Dihydro-5-hydroxy-3-(2-naphthyl)isoxazole-5-carboxylate (3h)

Starting from oxime **1h** (0.372 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3h** as a colorless solid; yield: 0.291 g (51%); mp 121 °C.

IR (KBr): 3455 (m), 1726 (s), 1308 (m), 1225 (s), 1124 (m), 889 (w), 823 (w), 751 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.55 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.10 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.41 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.73 (br s, OH), 7.51 (m, 2 H, Ar), 7.85 (m, 3 H, Ar), 7.95 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 43.8 (CH_2), 63.6 (OCH_2CH_3), 103.3 (C), 123.5, 126.8, 127.4, 127.5, 127.9, 128.5, 128.7 (CH, Ar), 126.2, 132.9 (C, Ar), 134.2 (C, Ar), 156.7 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 285 (M^+, 1), 212 (34), 152 (148), 127 (44).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.06; H, 5.31; N, 4.75.

Ethyl 3-(4-Chlorophenyl)-4,5-dihydro-5-hydroxyisoxazole-5-carboxylate (3i)

Starting from oxime **1i** (0.340 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3i** as a slight brownish solid; yield: 0.212 g (39%); mp 132 °C.

IR (KBr): 3192 (m), 2985 (w), 1749 (s), 1366 (m), 1297 (m), 1203 (m), 1137 (m), 917 (m), 869 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.42 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.91 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.25 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.48 (d, 2 H, Ar), 7.71 (d, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 44.6 (CH_2), 62.0 (OCH_2CH_3), 104.6 (C), 128.6, 128.6, 128.9, 128.9 (CH, Ar), 127.8, 135.2 (C), 155.8 (CN), 167.9 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 270 (M^+, 1), 196 (100), 154 (70), 137 (39), 111 (45), 75 (23).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{12}H_{12}ClNO_4$: 269.0449; found: 269.0451.

Ethyl 3-(4-Fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (3j)

Starting with a soln of oxime **1j** (0.230 g, 1.5 mmol) in THF (20 mL) using 2.5 M *n*-BuLi in hexane (1.5 mL, 3.75 mmol) and diethyl oxalate (0.25 mL, 1.8 mmol) gave **3j** as a colorless solid; yield: 0.195 g (52%); mp 132 °C.

IR (KBr): 3193 (m), 2979 (w), 1747 (s), 1361 (m), 1292 (m), 1208 (m), 1135 (m), 913 (m), 867 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.42 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.95 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.82 (br s, OH), 7.14 (d, 2 H, Ar), 7.71 (d, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_2CH_3), 44.3 (CH_2), 63.9 (OCH_2CH_3), 103.7 (C), 116.3, 116.6 (^3J = 4.2 Hz, CH, Ar), 129.3, 129.3 (CH, Ar), 156.0 (C), 164.5 (d, ^1J = 250.8 Hz, CF), 166.1 (CN), 168.5 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 253 (M^+, 1), 180 (100), 138 (82), 121 (59), 109 (20), 75 (23).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{12}H_{12}FNO_4$: 253.0745; found: 253.0749.

Ethyl 5-Hydroxy-4,5-dihydro-3-[3-(trifluoromethyl)phenyl]isoxazole-5-carboxylate (3k)

Starting with a soln of oxime **1k** (0.406 g, 2.0 mmol) in THF (20 mL) using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3k** as a colorless solid; yield: 0.252 g (41%); mp 132 °C.

IR (KBr): 3198 (m), 2981 (w), 1749 (s), 1361 (m), 1290 (m), 1203 (m), 1131 (m), 923 (m), 861 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, CH_3), 3.42 (d, ^2J = 17.5 Hz, 1 H, CH_2), 3.93 (d, ^2J = 17.5 Hz, 1 H, CH_2), 4.25 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.82 (br s, OH), 7.52 (m, 1 H, Ar), 7.63 (d, 1 H, Ar), 7.93 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_2CH_3), 43.9 (CH_2), 64.1 (OCH_2CH_3), 104.1 (C), 123.6 (q, ^3J = 3.5 Hz, CH, Ar), 127.1 (q, ^3J = 3.5 Hz, CH, Ar), 129.4, 130.2 (CH, Ar), 124.3 (q, ^1J = 272.3 Hz, CF), 125.8 (C), 131.7 (q, ^2J = 32.8 Hz, C), 155.9 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 303 (M^+, 5), 230 (100), 171 (27), 145 (61), 121 (5), 75 (6).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{13}H_{12}F_3NO_4$: 303.0713; found: 303.0706.

Ethyl 3,3a,4,5-Tetrahydro-3-hydroxynaphtho[1,2-*c*]isoxazole-3-carboxylate (3n)

Starting with a soln of oxime **1n** (0.322 g, 2.0 mmol) in THF (20 mL) using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3n** as a slightly brown-colored solid; yield: 0.298 g (57%); mp 181 °C.

IR (KBr): 3405 (m), 2956 (w), 1740 (s), 1462 (w), 1366(w), 1295 (m), 1217 (m), 1173 (m), 1077 (w), 1051 (w), 846 (w), 769 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 2.05–2.15 (m, 2 H, CH_2), 2.92–3.13 (m, 2 H, CH_2), 3.91–4.04 (m, 1 H, CH), 4.41 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.55 (br s, OH), 7.10–7.42 (m, 3 H, Ar), 8.02 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.7, 29.9 (CH_2), 52.2 (CH), 63.9 (OCH_2CH_3), 102.5 (C), 126.1, 127.3, 129.3, 131.3 (CH, Ar), 124.8, 140.2 (2 C, Ar), 157.3 (CN), 168.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 261 (M^+, 24), 188 (62), 160 (61), 140 (4), 132 (34), 115 (36).

Ethyl 3,3a,4,5,6,7-Hexahydro-3-hydroxy-2,1-benzisoxazole-3-carboxylate (3o)

Starting with a soln of oxime **1o** (0.226 g, 2.0 mmol) in THF (20 mL) using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3o** as a colorless solid; yield: 0.234 g (55%); mp 61 °C.

IR (KBr): 3464 (m), 2942 (m), 1721 (s), 1452 (w), 1302 (m), 1236 (w), 1185 (s), 1098 (w), 1050 (w), 837 (m), 562 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.41–1.56 (m, 2 H, CH_2), 1.65–2.04 (m, 4 H, CH_2), 2.12–2.25 (m, 1 H, CH_2), 2.83–2.90 (m, 1 H, CH_2), 3.42–3.51 (dd, ^3J = 8.2 Hz, ^3J = 4.0 Hz, 1 H, CH), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.45 (br s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 23.3, 23.7, 24.3, 25.1 (CH_2), 52.2 (CH), 62.9 (OCH_2CH_3), 101.6 (C), 159.6 (CN), 168.8 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 213 (M^+, 3), 140 (65), 122 (57), 94 (68), 55 (100).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 55.86; H, 7.10; N, 6.26.

Ethyl 3,3a,4,5,6,7,8,9,10,11,12,13-Dodecahydro-3-hydroxycyclododec[*c*]isoxazole-3-carboxylate (3r) and 5,6,7,8,9,10,11,12,13,14-Decahydro-4-hydroxy-3*H*-cyclododec[*c*][1,2]oxazin-3-one (5r)

Starting with a soln of oxime **1r** (0.394 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **3r** as a colorless solid; yield: 0.315 g (53%); mp 79 °C; **5r** was also obtained as a yellow solid; yield: 0.105 g (21%); mp 174 °C.

3r:

IR (KBr): 3444 (s), 2932 (s), 1729 (s), 1250 (w), 1205 (m), 1023 (w), 849 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.42–1.91 (m, 18 H, CH_2), 2.18–2.29 (m, 1 H, CH_2), 2.51–2.62 (m, 1 H, CH_2), 3.67–3.7 (dd, ^3J = 8.3 Hz, ^3J = 4.0 Hz, 1 H, CH), 4.27–4.41 (m, 2 H, OCH_2CH_3), 4.48 (br s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 20.9, 23.1, 23.1, 23.6, 23.6, 24.0, 24.1, 24.4, 24.9, 25.9 (CH_2), 52.9 (CH), 63.3 (OCH_2CH_3), 102.5 (C), 162.9 (CN), 169.4 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 297 (M^+, 3), 224 (100), 178 (37), 140 (3), 136 (39), 122 (44), 86 (16).

Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.33; H, 9.22; N, 4.62.

5r:

IR (KBr): 3328 (m), 2932 (s) 1688 (s), 1647 (m), 1383 (s), 1197 (s), 687 (w), 526 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.81–1.02 (m, 1 H, CH_2), 1.25–1.63 (m, 12 H, CH_2), 1.63–1.94 (m, 3 H, CH_2), 2.46–2.58 (m, 2 H, CH_2), 2.58–2.70 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 23.5, 23.6, 25.6, 26.3, 26.8, 27.1, 27.2, 27.5, 29.3 (CH_2), 119.9, 144.6 (C), 160.6 (CN), 164.6 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 251 (M^+, 19), 206 (100), 178 (86), 154 (13), 141 (12), 136 (29), 122 (16), 95 (17).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{14}H_{21}NO_3$: 251.1516; found: 251.1512.

Ethyl 3-Phenylisoxazole-5-carboxylate (4a); Typical Procedure

To a soln of **3a** (0.100 g, 0.43 mmol) in toluene (20 mL) was added $TsOH·H_2O$ (0.405 g, 2.1 mmol) and the soln was refluxed for 6 h. The mixture was cooled to r.t. and sat. $NaHCO_3$ (20 mL) was added and the mixture was stirred for 15 min at r.t. The organic and aqueous layers were separated and the latter was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent removed from the filtrate in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc, 3:1) to give **4a** as a brownish oil; yield: 0.087 g (94%).

IR (KBr): 3428 (w), 2982 (w), 1723 (s), 1447 (s), 1292 (s), 1245 (s), 1024 (m), 768 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.42 (m, 3 H, Ar), 7.81 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_2CH_3), 62.7 (OCH_2CH_3), 107.7 (CH), 127.2, 129.5, 129.5, 130.9 (CH, Ar), 128.2 (C, Ar), 157.2 (C), 161.3 (CN), 163.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 217 (M^+, 92), 172 (21), 155 (10), 144 (100), 116 (63), 103 (13), 89 (14), 77 (68).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{12}H_{11}NO_3$: 217.0733; found: 217.0734.

Ethyl 3-(4-Methylphenyl)isoxazole-5-carboxylate (4b)

Starting from **3b** (0.103 g, 0.407 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.405 g, 2.1 mmol) gave **4b** as a slightly brown solid; yield: 0.077 g (82%).

IR (KBr): 3434 (w), 2985 (w), 1728 (s), 1447 (w), 1294 (s), 1248(s), 1016 (w), 922 (w), 820 (s), 766 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 2.41 (s, 3 H, CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.35 (d, 2 H, Ar), 7.71 (d, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_2CH_3), 21.5 (CH_3), 62.7 (OCH_2CH_3), 107.7 (CH), 127.4, 129.9 (CH, Ar), 12.8, 141.0 (C, Ar), 157.2 (C), 161.3 (CN), 163.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 231 (M^+, 65), 186 (5), 158 (100), 130 (63), 116 (6.6), 103 (8), 91 (35), 77 (9), 65 (21).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{13}H_{13}NO_3$: 231.0889; found: 231.0884.

Ethyl 3-(3-Methylphenyl)isoxazole-5-carboxylate (4c)

Starting with **3c** (0.102 g, 0.41 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.405 g, 2.1 mmol) gave **4c** as a brownish oil; yield: 0.074 g (79%).

IR (KBr): 3438 (w), 2988 (w), 1730 (s), 1441 (m), 1288 (s), 1258 (s), 1034 (m), 768 (m), 703 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 2.41 (s, 3 H, CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.42 (m, 2 H, Ar), 7.63 (d, 1 H, Ar), 7.68 (s, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (CH_2CH_3), 21.6 (CH_3), 62.9 (OCH_2CH_3), 107.7 (CH), 124.2, 127.7, 129.5, 132.1 (CH, Ar), 140.4 (C, Ar), 157.8 (C), 161.3 (CN), 163.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 231 (M^+, 92), 186 (19), 158 (100), 130 (75), 116 (16), 103 (19), 91 (91), 77 (23), 65 (67).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{13}H_{13}NO_3$: 231.0889; found: 231.0887.

Ethyl 3-(2-Methylphenyl)isoxazole-5-carboxylate (4d)

Starting from **3d** (0.105 g, 0.407 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.405 g, 2.1 mmol) gave **4d** as a brownish oil; yield: 0.091 g (96%).

IR (KBr): 3428 (w), 2988 (w), 1723 (s), 1447 (s), 1292 (s), 1278 (s), 1024 (m), 768 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 2.41 (s, 3 H, CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.32 (m, 3 H, Ar), 7.53 (d, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.1 (CH_3), 62.2 (OCH_2CH_3), 109.9 (CH), 126.1, 129.8, 130.4, 131.6 (CH, Ar), 127.6,136.9 (C, Ar), 156.8 (C), 161.3 (CN), 163.5 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 231 (M^+, 76), 186 (8), 158 (100), 130 (96), 116 (15), 103 (39), 91 (49.5), 77 (20), 65 (40).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{13}H_{13}NO_3$: 231.0889; found: 231.0883.

Ethyl 3-(4-Methoxyphenyl)isoxazole-5-carboxylate (4e)

Starting from **3e** (0.349 g, 1.31 mmol) in toluene (30 mL) and using $TsOH·H_2O$ (1.23 g, 6.47 mmol) gave **4e** as a brownish oil; yield: 0.219 g (68%).

IR (KBr): 3442 (w), 2979 (w), 1731 (s), 1454 (s), 1282 (s), 1252 (s), 1031 (m), 766 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.05 (d, 2 H, Ar*H*), 7.25 (s, 1 H, CH), 7.71 (d, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (CH_2CH_3), 54.3 (OCH_3), 62.6 (OCH_2CH_3), 107.5 (CH), 113.4, 127.2 (CH, Ar), 118.6, 154.7 (C, Ar), 158.5 (C), 159.3 (CN), 160.4 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 247 (M^+, 10), 202 (4), 174 (100), 146 (88.5), 131 (12), 103 (6), 91 (3), 77 (8), 69 (12).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{13}H_{13}NO_4$: 247.0839; found: 247.0833.

Ethyl 3-(3-Methoxyphenyl)isoxazole-5-carboxylate (4f)

Starting from **3f** (0.349 g, 1.31 mmol) in toluene (30 mL) and using $TsOH·H_2O$ (1.29 g, 6.79 mmol) gave **4f** as a brownish oil; yield: 0.243 g (75%).

IR (KBr): 3447 (w), 2977 (w), 1736 (s), 1452 (s), 1285 (s), 1252 (s), 1033 (m), 761 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.42 (m, 2 H, Ar), 7.05 (m, 1 H, Ar), 7.38 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 55.3 (OCH_3), 62.3 (OCH_2CH_3), 107.4 (CH), 111.7, 116.6, 119.3, 130.1 (CH, Ar), 127.5, 156.7 (C, Ar), 160.0 (C), 160.8 (CN), 162.8 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 247 (M^+, 32), 202 (10), 174 (100), 146 (38), 131 (8), 107 (75), 92 (56), 77 (68), 69 (18).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{13}H_{13}NO_4$: 247.0839; found: 247.0837.

Ethyl 3-(1-Naphthyl)isoxazole-5-carboxylate (4g)

Starting from **3g** (0.171 g, 0.60 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.574 g, 3.0 mmol) gave **4g** as a black oil; yield: 0.131 g (82%).

IR (KBr): 3436 (w), 2985 (w), 1734 (s), 1445 (w), 1285 (s), 1026 (w), 919 (w), 775 (m), 656 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 4.40 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.51 (m, 3 H, Ar), 7.70 (m, 1 H, Ar), 7.92 (m, 2 H, Ar), 8.34 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 62.6 (OCH_2CH_3), 110.6 (CH), 125.6, 125.6, 126.9, 127.8, 128.2, 128.5, 131.2 (CH, Ar), 125.1, 130.7, 133.8 (C, Ar), 156.9 (C), 160.3 (CN), 163.1 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 267 (M^+, 74), 194 (100), 174 (19), 166 (33), 127 (59), 109 (15), 81 (9), 77 (14), 69 (7).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{16}H_{13}NO_3$: 267.0890; found: 267.0895.

Ethyl 3-(2-Naphthyl)isoxazole-5-carboxylate (4h)

Starting from **3h** (0.173 g, 0.60 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.574 g, 3.0 mmol) gave **4h** as a black oil; yield: 0.122 g (76%).

IR (KBr): 3433 (w), 2978 (w), 1727 (s), 1431 (m), 1290 (s), 1253 (s), 1026 (m), 822 (m), 753 (m), 476 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 4.40 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.35 (s, 1 H, CH), 7.53 (m, 2 H, Ar), 7.97 (m, 4 H, Ar), 8.37 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (CH_2CH_3), 62.7 (OCH_2CH_3), 107.9 (CH), 123.9, 125.4, 127.3, 128.0, 128.2, 129.0, 129.7 (CH, Ar), 125.4, 133.3, 134.8 (C, Ar), 157.0 (C), 160.3 (CN), 163.1 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 267 (M^+, 94), 194 (100), 174 (14), 166 (56), 127 (79), 107 (5), 91 (5), 77 (14), 69 (13).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{16}H_{13}NO_3$: 267.0890; found: 267.0892.

Ethyl 3-(4-Chlorophenyl)isoxazole-5-carboxylate (4i)

Starting from **3i** (0.108 g, 0.40 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.405 g, 2.1 mmol) gave **4i** as a brownish solid; yield: 0.075 g (74%).

IR (KBr): 3443 (w), 3132 (w), 1728 (s), 1448 (w), 1284 (s), 1246(s), 1023 (w), 926 (w), 828 (s), 761 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.35 (d, 2 H, Ar), 7.71 (d, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 62.4 (OCH_2CH_3), 107.1 (CH), 128.1, 128.1, 129.4, 129.4 (CH, Ar), 126.3, 136.5 (C, Ar), 157.1 (CN), 161.3 (C), 163.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 251 (M^+, 33), 178 (100), 150 (33), 138 (5), 111 (10), 75 (15), 63 (2).

HRMS (CI): *m*/*z* (M^+) calcd for $C_{12}H_{10}ClNO_3$: 251.0339; found: 251.0339.

Ethyl 3-(4-Fluorophenyl)isoxazole-5-carboxylate (4j)

Starting from **3j** (0.126 g, 0.50 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.405 g, 2.1 mmol) gave **4j** as a brownish solid; yield: 0.093 g (79%).

IR (KBr): 3443 (w), 3132 (w), 1728 (s), 1448 (w), 1284 (s), 1246 (s), 1023 (w), 926 (w), 828 (s), 761 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.25 (m, 2 H, Ar), 7.84 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (CH_2CH_3), 62.4 (OCH_2CH_3), 107.2 (CH), 116.6, 116.8 (^3J = 4.2 Hz, CH, Ar), 129.4, 129.4 (CH, Ar), 124.3 (C, Ar), 163.9 (d, ^1J = 250.8 Hz, CF), 161.2 (C), 156.8.5 (CN), 162.2 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 235 (M^+, 71), 162 (100), 134 (77), 121 (10), 107 (18), 95 (19), 81 (3), 75 (11).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{12}H_{10}FNO_3$: 235.0639; found: 235.0638.

Ethyl 3-[3-(Trifluoromethyl)phenyl]isoxazole-5-carboxylate (4k)

Starting from **3k** (0.152 g, 0.50 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.405 g, 2.1 mmol) gave **4k** a brownish solid; yield: 0.121 g (85%).

IR (KBr): 3435 (w), 3126 (w), 1727 (s), 1423 (w), 1278 (s), 1246 (s), 1023 (w), 910 (w), 819 (s), 770 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.25 (s, 1 H, CH), 7.62 (m, 1 H, Ar), 7.83 (d, 1 H, Ar), 8.12 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_2CH_3), 62.9 (OCH_2CH_3), 106.6 (CH), 123.6 (q, ^3J = 3.5 Hz, CH, Ar), 127.1(q, ^3J = 3.5 Hz, CH, Ar), 129.4, 130.2 (CH, Ar), 124.3 (q, ^1J = 272.3 Hz, CF), 129.1 (C), 131.7 (q, ^2J = 32.8 Hz, C), 156.1 (CN), 161.3 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 285 (M^+, 24), 212 (100), 171 (2), 145 (13), 121 (1), 75 (6).

HRMS (CI): *m*/*z* (M^+) calcd for $C_{13}H_{10}F_3NO_3$: 285.0607; found: 285.0603.

Ethyl 4,5-Dihydronaphtho[1,2-*c*]isoxazole-3-carboxylate (4n)

Starting from **3n** (0.302 g, 1.15 mmol) in toluene (30 mL) and using $TsOH·H_2O$ (1.14 g, 6.0 mmol) gave **4n** as a black solid; yield: 0.254 g (91%); mp 181 °C.

IR (KBr): 3438 (w), 2928 (w), 1712 (s), 1641 (w), 1454 (s), 1369 (s), 1268 (s), 1174 (m), 783 (w), 716 (w), 687 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, ^3J = 7.1 Hz, 3 H, CH_3), 2.92–3.19 (m, 4 H, CH_2), 4.43 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 7.23–7.41 (m, 3 H, Ar), 8.02 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 18.9, 28.2 (CH_2), 61.9 (OCH_2CH_3), 121.4, 124.6 (C), 124.3, 127.2, 128.6, 130.4 (4 CH, Ar), 137.5, 154.2 (2 C, Ar), 157.4 (CN), 161.4 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 243 (M^+, 100), 198 (19), 170 (98), 143 (97), 127 (20), 115 (95), 89 (42), 77 (10), 69 (31).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{14}H_{13}NO_3$: 243.0890; found: 243.0881.

Ethyl 4,5,6,7-Tetrahydro-2,1-benzisoxazole-3-carboxylate (4o)

Starting from **3o** (0.358 g, 1.69 mmol) in toluene (30 mL) and using $TsOH·H_2O$ (1.596 g, 8.4 mmol) gave **4o** as a brownish oil; yield: 0.256 g (78%).

IR (KBr): 2947 (m), 1716 (s), 1363 (m), 1290 (s), 1176 (s), 1038 (m), 917 (w), 769 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.73–1.93 (m, 4 H, CH_2), 2.74–2.91 (m, 4 H, CH_2), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3, 21.4, 21.6, 21.7 (CH_2), 61.6 (OCH_2CH_3), 122.6, 154.5 (C), 157.6 (CN), 161.9 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 195 (M^+, 4), 166 (11), 150 (17), 138 (18), 122 (81), 95 (57), 80 (99), 67 (77).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{10}H_{13}NO_3$: 195.0890; found: 195.0893.

Ethyl 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododec[*c*]isoxazole-3-carboxylate (4r)

Starting from **3r** (0.282 g, 0.95 mmol) in toluene (20 mL) and using $TsOH·H_2O$ (0.905 g, 4.75 mmol) gave **4r** as a brownish oil; yield: 0.165 g (62%).

IR (KBr): 2933 (s), 2861 (m), 1725 (s), 1469 (m), 1299 (s), 1276 (s), 1176 (s), 1020 (m), 781 (m), 728 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.25–1.58 (m, 12 H, CH_2), 1.71–2.92 (m, 4 H, CH_2), 2.62–2.77 (m, 4 H, CH_2), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 20.0, 21.5, 22.4, 22.7, 24.1, 24.5, 25.5, 25.8, 26.9, 27.3 (CH_2), 61.8 (OCH_2CH_3), 125.5, 154.8 (C), 157.5 (CN), 165.0 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 279 (M^+, 11), 206 (100), 178 (11), 150 (4), 136 (6), 121 (2), 108 (4), 95 (6).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{16}H_{25}NO_3$: 279.1829; found: 279.1824.

6,7,8,9-Tetrahydro-4-hydroxycyclohept[*c*][1,2]oxazin-3(5*H*)-one (5p)

Starting from a soln of oxime **1p** (0.271 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 2.5 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **5p** as a pink solid; yield: 0.171 g (47%); mp 154 °C.

IR (KBr): 3188 (m), 2937 (m), 1718 (s), 1656 (m), 1385 (m), 1243 (w), 1177 (w), 1097 (w), 806 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.85 (m, 6 H, CH_2), 2.62–2.81 (m, 4 H, CH_2), 7.12 (br s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 27.2, 27.9, 31.3, 33.6 (CH_2), 120.5, 142.5 (C), 162.4 (CN), 164.4 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 181 (M^+, 19), 136 (100), 107 (29), 94 (9.9), 81 (76), 55 (46), 41 (52), 39 (29), 28 (37).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71; H, 6.22; N, 7.46.

5,6,7,8,9,10-Hexahydro-4-hydroxy-3*H*-cyclooct[*c*][1,2]oxazin-3-one (5q)

Starting from a soln of oxime **1q** (0.283 g, 2.0 mmol) in THF (20 mL) and using 2.5 M *n*-BuLi in hexane (2.0 mL, 5.0 mmol) and diethyl oxalate (0.3 mL, 2.2 mmol) gave **5q** as an orange solid; yield: 0.152 g (39%); mp 98 °C.

IR (KBr): 3398 (m), 3291 (m), 2927 (m), 1703 (s), 1653 (w), 1189 (w), 1125 (w), 865 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.63 (m, 4 H, CH_2), 1.74–1.91 (m, 4 H, CH_2), 2.60–2.73 (m, 2 H, CH_2), 2.73–2.82 (m, 2 H, CH_2), 7.56 (br s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 25.5, 25.9, 27.8, 29.9, 30.5 (CH_2), 119.9, 143.4 (C), 161.6 (CN), 164.6 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 195 (M^+, 4), 149 (35), 122 (16), 94 (32), 81 (16).

HRMS (EI, 70 eV): *m*/*z* (M^+) calcd for $C_{10}H_{13}NO_3$: 195.0895; found: 195.0892.

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