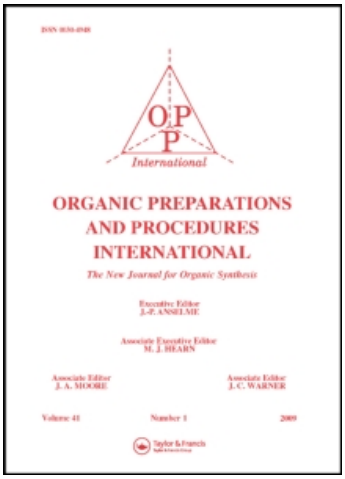

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FACILE SYNTHESIS OF ISOXAZOLE 4- AND 5-CARBALDEHYDES AND THEIR CONVERSION TO ISOXAZOLYL-1, 4-DIHYDROPYRIDINES

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FACILE SYNTHESIS OF ISOXAZOLE 4- AND 5-CARBALDEHYDES AND THEIR CONVERSION TO ISOXAZOLYL-1, 4-DIHYDROPYRIDINES

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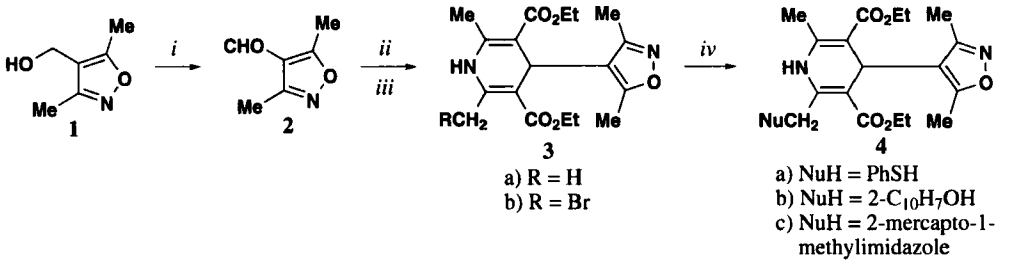
Isoxazoles[1] are important building blocks in the construction of more complex systems including a variety of natural products.[2] Isoxazole carbaldehydes are starting materials for isoxazole-1,4-dihydropyridines.[3] However, the instability of isoxazoles in the presence of oxidizing agents in acidic media (ring opening,[1d] and in some cases ring oxidation[1e]) narrows the choice of reagents for the oxidation of isoxazolyl carbinols to the corresponding isoxazole carbaldehydes in good yields; if the isoxazolyl carbinol is part of a complex molecule which is sensitive to acidic or basic reagents, then the choice of effective oxidants is narrower still. Our interest in the synthetic utility of isoxazoles,[4] coupled with the low yields achieved from the other oxidation methods,[5] led us to search for an efficient method of preparation of isoxazole carbaldehydes and corresponding 1,4-dihydropyridines.

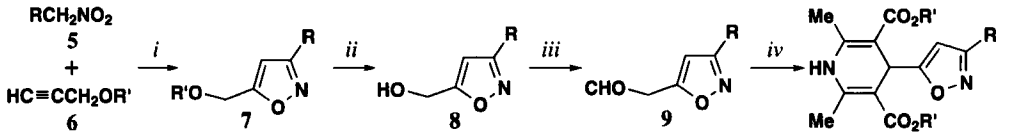
The examination of a variety of oxidizing agents led us to select $BaMnO_4$ as an efficient, mild, inexpensive, and hazard-free reagent for the selective oxidation of isoxazolyl carbinols to the corresponding carbaldehydes in improved yields compared to those obtained with neutral dichromate (65%),[5a] sodium dichromate in DMSO,[5b] PCC (78%),[5c,d] and MnO_2 (45%).[5e] Oxidation of isoxazolyl alcohol **1**[5a,6] with $BaMnO_4$,[7] gave excellent yields (90%) of the corresponding aldehyde (**2**), which was converted to 3,5-dicarbethoxy-4-(3,5-dimethyl-4-isoxazolyl)1,4-dihydropyridine (**3a**) (without aromatization to pyridines as is evident from ^1H NMR (NH, and CH chemical shifts of 1,4-dihydropyridine ring and lack of any pyridine CH), IR (NH stretch 3300-3500 cm^{-1}, and elemental analysis data). Compound **3a** was regioselectively monobrominated[8] at the C2-methyl of 1,4-dihydropyridine ring to give monobromo derivative (**3b**).[9] Addition of nucleophiles to the monobromide **3b** afforded isoxazolyl-1,4-dihydropyridines **4a-c** in 63-80% yields (*Scheme 1*).



i) $BaMnO_4$, C_6H_6, reflux, 3h; *ii*) 2 eq. ethyl acetoacetate, ammonia, EtOH, reflux, 20h; *iii*) Py, pyridiniumbromide perbromide, dichloromethane, -12°C, 1h; *iv*) NuH, NaH, THF, 0°C, 2h

Scheme 1

Cycloaddition of nitrile oxides generated *in situ*[10] from the nitro compounds (**5**),[11-12] to the tetrahydropyranyl or benzoyl derivatives of the propargyl alcohol (**6a,b**) produced isoxazoles **7a-h** in 48-52% yields. Removal of the protective group[13] led to the alcohols **8** which were oxidized by $BaMnO_4$ to the corresponding aldehydes **9**. Condensation of aldehydes **9** which gave 4-(5-isoxazolyl)1,4-dihydropyridines **10** without aromatization to pyridines (as is evident from ^{1}H NMR (NH, and CH chemical shifts of 1,4-dihydropyridine ring and lack of any pyridine CH), IR (NH stretch 3300-3500 cm^{-1}), and elemental analysis data (*Scheme2*).



a) R = *n*-C_3H_7, R' = THP
b) R = *n*-C_4H_9, R' = THP
c) R = *n*-C_5H_{11}, R' = THP
d) R = *n*-C_6H_{13}, R' = THP
e) R = *n*-C_8H_{17}, R' = THP
f) R = 3-Phenylpropyl, R' = THP

a) R = *n*-C_4H_9, R' = C_2H_5
b) R = *n*-C_6H_{13}, R' = C_2H_5
c) R = *n*-C_8H_{17}, R' = C_2H_5
d) R = *n*-C_4H_9, R' = CH_3

i) $POCl_3$, Et_3N, $CHCl_3$, 0°C, then r.t. overnight; *ii*) Amberlyst-15, MeOH, 45°C, 3-4 h, *iii*) $BaMnO_4$, C_6H_6; *iv*) 2 eq. ethyl or methyl acetoacetate, NH_3, EtOH, reflux, 48-96 h

Scheme 2

EXPERIMENTAL SECTION

Mps were determined using an Electrothermal 9100 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AC-80 FT-NMR using $CDCl_3$ as solvent unless otherwise specified. IR spectra were obtained on Shimadzu FT-IR 8101M and IR-408 spectrometers. Mass spectra were taken on Finnigan-Mat 8430 and Shimadzu QP1000 at70ev.

3,5-Dimethylisoxazolyl-4-carbinol (1).- colorless crystalline needles, 89% yield,[5a,6] mp. 66-67° (*lit.*[5a] 66°). ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.90 (s, 1H, O*H*), 4.40 (d, 2H, CH_2OH); IR (KBr): 3400-3200 (OH), 2950, 1620, 1420 cm^{-1}; MS: m/z (%), 128 (M^+, 35), 98 (20), 68 (22), 55 (25), 432 (100).

3,5-Dimethylisoxazole-4-carbaldehyde (2).- To a stirred solution of isoxazolyl alcohol **1** (1.95 g, 15.0 mmol) in dry benzene (75.0 mL), dry powder of $BaMnO_4$,[7] (34.59 g, 60.0 mmol) was added and was refluxed for 3 h and was cooled to room temperature. Filtration, rotary evaporation, and silica gel column chromatography (*n*-hexane:EtOAc, 5:1, R_f = 0.27) afforded aldehyde **2** (1.68 g, 90%) as pale yellow oil. IR (neat): 2995, 2855, 2850, 1690 (C=O), 1610 (C=C), 1420 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, C*H*$_3$), 2.70 (s, 3H, C*H*$_3$), 9.90 (s, 1H, C*H*O); MS: m/z (%), 125 (25), 110 (6).

Synthesis of 2,6-Dimethyl-3,5-dicarboethoxy-4-(3,5-dimethyl-4-isoxazolyl)-1,4-dihydropyridine (3a).- A solution of isoxazole aldehyde **2** (12.5 g, 117 mmol), ethyl acetoacetate (25.3 mL, 234 mmol), ammonium hydroxide (35.0 mL of 25% aqueous solution), and ethanol (120.0 mL) was refluxed for 20 hrs. The solution was concentrated and the semi solid yellow residue was purified by silica column chromatography (*n*-hexane:EtOAc, 3:2, R_f = 0.3) and recrystallized to give 1,4-dihydropyridine **3a** (23.45 g, 78%) as white crystalline needles, mp. 158°. IR (KBr): 3350-3240, 3050, 2980, 1707, 1650, 1500, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, 6H, *J* = 7.3, ester 2x CH_2CH_3), 2.40 (s, 3H, ISOX-C*H*$_3$), 2.60 (s, 6H, DHP-C*H*$_3$), 4.30 (q, 4H, *J* = 7.3 Hz, ester 2x CH_2CH_3), 4.98 (s, 1H, C*H*), 6.30 (br. s, 1H, N*H*); MS: m/z (%), 348 (35), 275 (50), 234 (100).

Synthesis of 2-Phenylthiomethyl-6-methyl-3,5-dicarboethoxy-4-(3,5-dimethyl-4-isoxazolyl)1,4-dihydropyridine (4a). Typical Procedure.- To a solution of **3a** (0.7 g, 2.0 mmol) in dichloromethane (20 mL) at -12° was added[9] pyridine (0.30 mL, 3.5 mmol) and pyridinum bromide perbromide (0.78 g, 2.2 mmol). The solution was stirred for 1 h (-12°) and after the completion of the reaction; it was diluted with cold CH_2Cl_2 (30.0 mL), washed with hydrochloric acid (2 x 25.0 mL of 2M), and ice-water (2 x 25.0 mL). The solution was then dried over $MgSO_4$ and the solvent was removed *in vacuo* without heating. The yellow residue was recrystallized from 10% ethyl acetate/n-hexane to give **3b**, as pale yellow solid, mp. 143° (0.86 g, 95%). IR (KBr): 3300-3240 (N-H), 3100, 3050, 2970, 2800, 1705 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.45 (t, 6H, *J* = 7.3, ester 2x CH_2CH_3), 2.40 (s, 3H, ISOX-C*H*$_3$), 2.60 (s, 3H, DHP-C*H*$_3$), 4.35 (q, 4H, *J* = 7.3 Hz, ester 2x CH_2CH_3), 4.75 (dd, 2H, *J* = 11 Hz, allylic C*H*$_2$Br), 5.03 (s, 1H, C*H*), 6.40 (br. s, 1H, N*H*). The crude bromide **3b** (0.427 g, 2 mmol) was diluted with cold anhydrous THF (5.0 mL) and poured over an ice-cooled solution of the thiophenolate ion [derived from thiophenol (0.20 mL, 2.0 mmol) and sodium hydride 60% (0.08 g, 2.2 mmol) in 15.0 mL of THF] and the mixture was stirred at 0° for 2 h and at room temperature for 3 h under N_2 atmosphere. After completion of the reaction, the solvent was removed *in vacuo* and was diluted with CH_2Cl_2 (25.0 mL), and washed with hydrochloric acid (20.0 mL of 2M) and brine (2 x 20.0 mL). The organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a yellow oil. Column chromatography over silica 60 (EtOAc:CH_2Cl_2, 1:9, R_f = 0.3) and recrystallization from EtOH-hexane gave the desired product **4a**, as a colorless solid, mp. 148° (0.684 g, 75%). IR (KBr): 3400-3000, 2990, 29885, 1680 (C=O), 1650 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.4 (t, 6H,

J = 7.3, ester 2x CH_2CH_3), 1.60 (s, 3H, CH_3), 2.20 (m, 3H, CH_3), 2.50 (s, 2H, CH_2-SPh), 4.00 (q, 4H, J = 7.3 Hz, ester 2x CH_2CH_3), 5.00 (s, 1H, C*H*), 6.80- 7.80 (m, 6H, NH and Ar-H).

Anal. Calcd for $C_{24}H_{28}N_2O_5S$: C, 63.10; H, 6.20; N, 6.10. Found: C, 63.22, H, 6.12; N, 6.11

Compound **4b** was synthesized in 80% yield as pale yellow oil in a similar manner by using the anion of 2-naphthol (EtO-Ac:CH_2Cl_2, 1:9, R_f = 0.33). IR (KBr) 3400-3150, 1690 (C=O), 1650 (C=N), 1630 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.05 (t, 6H, J = 7.3 Hz, ester 2x CH_2CH_3), 1.70-2.25 (m, 9H, CH_3), 2.25 (s, 2H), 3.75 (q, 4H, J = 7.3 Hz, ester 2x CH_2CH_3), 4.60 (s, 1H), 5.00 (s, 1H, C*H*), 6.70-7.40 (m, 7H, Ar*H*).

Anal. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.50; H, 6.20; N, 5.70. Found: C, 68.22; H, 6.21; N, 5.71

Compound **4c** was synthesized in 63% yield as pale yellow oil in a similar manner by using the anion of 2-mercapto-1-methylimidazole (EtOAc:CH_2Cl_2, 1:19, R_f = 0.17). IR (neat): 3300-3150, 3050, 2990, 2980, 780 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10 (t, 6H, J = 7.3 Hz, ester 2x CH_2CH_3), 2.00 (s, 3H), 2.10 (s, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.40 (s, 2H), 4.00 (q, 4H, J = 7.30 Hz, ester 2x CH_2CH_3), 7.30-7.80 (m, 2H), 9.70 (s, 1H).

Anal. Calcd for $C_{22}H_{28}N_4O_5S$: C, 57.30; H, 6.30; N, 12.19. Found: C, 57.20; H, 6.21; N, 12.10.

Synthesis of 3-*n*-Hexyl-5-isoxazolecarbinol (8d). Typical Procedure.- To an ice cooled solution of 1-nitroheptane **5d** (15.63 mL, 102 mmol)[12] and propargyl tetrahydropyranyl ether **6** (21.42 g, 153 mmol)[14] in dry $CHCl_3$ (114.0 mL) and triethylamine (39.9 mL, 288 mmmol) was added dropwise $POCl_3$ (10.0 mL, 108 mmol) in dry $CHCl_3$ (24.0 mL), and the mixture was poured in to water (300.0 mL), the organic layer was separated and dried over $CaCO_3$, and the solvent were removed *in vacuo*. The residue was purified by a rapid chromatography technique on silica gel (petroleum ether:EtOAc, 100:11, R_f = 0.3) to give **7d** as a pale yellow oil (14.16 g, 52%).[15] IR (neat) 3100, 1605 (C=C), 1450 cm^{-1}. A solution of **7d** (9.8 g, 36.7 mmol) in methanol (73.4 mL), Amberlyst H-15 (a macroreticular ion exchange resin containing strongly acidic SO_3H groups) (1.2 g, 1 meq) was stirred vigorously at 45° for 4 h.[12] Filtration and removal of solvent *in vacuo* gave a red residue, silica column chromatography (petroleum ether:EtOAc, 5:1, R_f = 0.25) left **8d** as pale yellow viscous oil (6 g, 90%). IR (KBr): 3400, 3100, 2900, 2850, 1600, 1450, 1370, 1270, 1190, 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, J = 7.0 Hz), 1.25 (m, 4H), 1.50 (m, 4H, J = 7.0 Hz), 2.60 (t, 2H, J = 7.0 Hz), 3.00 (br. s, O*H*). 4.75 (2H, CH_2OH), 6.20 (s, 1H, C*H*).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.63. Found: C, 65.46; H, 9.41; N, 7.56

The same operation was performed on **5a, 5b, 5c,5e**, and **5f** to obtain respectively compounds **8a, 8b, 8c, 8e**, and **8f.**

Synthesis of 3-*n*-Hexyl-5-isoxazolecarbinol (8a), pale yellow oil, 89%. IR (neat): 3400, 2950, 2850, 1600, 1450, 1270, 1060 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 7.0 Hz), 1.40 (m, 2H, J = 7.0 Hz), 2.55 (t, 2H, J = 7.0 Hz), 4.37 (br. s, O*H*). 4.66 (s, 2H, CH_2OH), 5.95 (s, 1H, C*H*).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.49; H, 7.90; N, 9.82

Synthesis of 3-*n*-Hexyl-5-isoxazolecarbinol (8b), pale yellow oil, 89%. IR (neat): 3400, 2950,

2850, 1600, 1450, 1420, 1370, 1270, 1130, 1060 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, *J* = 7.0 Hz), 1.40 (m, 4H, *J* = 7.0 Hz), 2.50 (t, 2H, *J* = 7.0 Hz), 4.30 (br. s, O*H*). 4.64 (s, 2H, CH_2OH), 6.00 (s, 1H, C*H*).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.98; H, 8.56; N, 8.99

Synthesis of 3-*n*-Hexyl-5-isoxazolecarbinol (8c), pale yellow oil, 90%. IR (neat): 3400, 2900, 2850, 1600, 1450, 1270, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.70 (t, 3H, *J* = 7.0 Hz), 1.25 (m, 6H), 2.40 (t, 2H, *J* = 7.0 Hz), 4.30 (s, 2H, CH_2OH), 4.80 (br. s, 1H, CH_2O*H*), 5.80 (s, 1H, C*H*).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.69; H, 8.97; N, 8.19

Synthesis of 3-n-Hexyl-5-isoxazolecarbinol (8e), white solid 94%, mp. 81°. Silica column chromatography (petroleum ether:EtOAc; 15:2, R_f = 0.22); IR (neat): 3500, 3150, 2900, 1616, 1466, 1304, 1140 cm^{-1}; ^1H NMR (DMSO): δ 0.80 (br. s, 3H), 1.20-1.60 (m, 12H), 2.60 (t, 2H, *J* = 7.3 Hz), 3.20 (br. s, 1H, CH_2O*H*). 6.20 (s, 2H), 6.30 (s, 1H, C*H*).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.32; H, 10.11; N, 6.68

Synthesis of 3-*n*-Hexyl-5-isoxazolecarbinol (8f), pale yellow oil, 89%. Silica column chromatography (petroleum ether: EtOAc:CH_2Cl_2, 3:1:1, R_f = 0.3); IR (neat): 3400, 3100, 2900, 1600, 1490, 1450, 1190 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.0 (m, 2H, *J* = 6.8 Hz), 2.70 (t, 4H, *J* = 6.8 Hz), 3.60 (br. s, 1H, CH_2O*H*). 4.70 (s, 2H, CH_2OH), 6.10 (s, 1H, ISOX-C*H*), 7.20 (s, 5H, Ar-*H*).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.69; H, 7.09; N, 6.31

Synthesis of 3-*n*-Pentyl-5-isoxazolecarbaldehyde (9c). Typical Procedure.- To a stirred solution of 3-n-pentyl-5-isoxazole carbinol **8c** (2.54 g, 15 mmol) in benzene (75.0 mL) dry powder of $BaMnO4$[7] (15.38 g, 60 mmol) was added and refluxed for 3 hrs. (TLC monitoring). Filtration, concentration, and silica column chromatography (petroleum ether:EtOAc, 5:1, R_f = 0.35) afforded isoxazole aldehyde **9c** (2.25 g, 90%) as a colorless oil; IR (neat): 3100, 2950, 2880, 1700 (C=O), 1580, 1455, 1280 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, *J* = 7.3 Hz), 1.45 (m, 6H, *J* = 7.3 Hz), 2.60 (t, 2H, *J* = 7.3 Hz), 6.80 (s, 1H, ISOX-C*H*), 9.80 (s, 1H, C*H*O).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.71; H, 7.90; N, 8.40

The same operation was performed on **8b, 8d, 8e**, and **8f** to obtain compounds **9b, 9d, 9e**, and **9f** respectively.

Synthesis of 3-*n*-Butyl-5-isoxazolecarbaldehyde (9b), pale yellow oil, 90% yield. Silica column chromatography (petroleum ether:EtOAc, 5:1, R_f = 0.32); IR (neat): 3100, 2950, 2850, 1700 (C=O), 1580 (C=C), 1455, 1375, 1280, 1120 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, CH_3), 1.50 (m, 4H, *J* = 7.3 Hz), 2.5 (t, 2H, *J* = 7.3 Hz), 6.80 (s, 1H, ISOX -C*H*), 9.80 (s, 1H, C*H*O).

Anal. Calcd for $C_8H_{11}NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 64.71; H, 5.89; N, 9.31

Synthesis of 3-*n*-Hexyl-5-isoxazolecarbaldehyde (9d), pale yellow oil, 92% yield. Silica column chromatography (petroleum ether: EtOAc, 7:1, R_f = 0.35); IR (neat): 3100, 2950, 2850, 1700 (C=O), 1580 (C=C), 1455, 1420, 1375, 1280, 1120 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H, CH_3), 1.25-1.65 (m, 8H, 4x CH_2), 2.70 (t, 2H, *J* = 7.3 Hz), 6.80 (s, 1H, ISOX-C*H*), 9.90 (s, 1H, C*H*O).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.42; H, 8.51; N, 7.68

Synthesis of 3-*n*-Octyl-5-isoxazolecarbaldehyde (9e), pale yellow oil, 92% yield. Silica column chromatography (petroleum ether:EtOAc, 10:1, R_f = 0.36); IR (neat): 3100, 2900, 2870, 1700 (C=O), 1590, 1450 (C=N), 1360, 1275, 1120 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, C*H*$_3$, *J* = 7.3 Hz), 1.15-1.70 (m, 12H, 6x C*H*$_2$), 2.76 (t, 2H, *J* = 7.3 Hz), 6.73 (s, 1H, ISOX -C*H*), 9.95 (s, 1H, C*H*O).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.90; H, 9.15; N, 6.69. Found: C, 69.00; H, 9.24; N, 6.80

Synthesis of 3-(3-Phenylpropyl)-5-isoxazolecarbaldehyde (9f), pale yellow oil, 65% yield. Silica column chromatography (petroleum ether:EtOAc, 5:1, R_f = 0.37); IR (neat): 3100, 2900, 2860, 1700 (C=O), 1590, 1450 (C=N), 1275 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.05 (m, 2H, C*H*$_2$), 2.55 (t, 4H), 6.65 (s, 1H, ISOX -C*H*), 7.22 (s, 5H, Ar-*H*), 9.80 (s, 1H, C*H*O).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.49; H, 6.07; N, 6.47.

Synthesis of 2,6-Dimethyl-3,5-dicarboethoxy-4-(3-*n*-butyl-5-isoxazolyl)-1,4-dihydropyridine (10a).- A solution of isoxazole aldehyde **9b** (1.2 g, 7.84 mmol), ethylacetoacetate (2.0 mL, 15.7 mmol), ammonium hydroxide (20.0 mL of 25%), and ethanol (20.0 mL) was refluxed for 72 h. The solution was concentrated and the viscous oil was purified by silica column chromatography (petroleum ether:EtOAc, 3:2, R_f = 0.43) to give **10a** as a colorless oil (4.5g, 76%). IR (film): 3300 (NH), 3240, 3100, 2950, 2850, 1700 (C=O), 1650 (C=N), 1620 (C=C), 1580, 1485 1420, 1360, 1320, 1270, 1200, 1150, 1110, 1090 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H, C*H*$_3$), 1.25 (t, 6H, *J* = 7.3 Hz, ester 2x CH_2CH_3), 1.45 (m, 4H), 2.20 (s, 6H), 2.60 (t, 2H, *J* = 7.3 Hz), 4.20 (q, 4H, *J* = 7.3 Hz, ester 2x CH_2CH_3), 5.30 (s, 1H, DHP-C*H*), 5.80 (s, 1H, ISOX -C*H*), 6.40 (br. s, 1H, N*H*). MS (70 ev, EI) m/z (%), M^+ (10), 42 (100).

Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.80; H, 7.41; N, 7.39. Found: C, 63.61; H, 7.18; N, 7.51

Synthesis of 2,6-Dimethyl-3,5-dicarboethoxy-4-(3-*n*-hexyl-5-isoxazolyl)-1,4-dihydropyridine (10b), white solid, mp. 73-74°, 81% yield. Silica column chromatography (petroleum ether:EtOAc; 3:2, R_f = 0.27); IR (KBr): 3300 (NH), 3100, 2950-2850, 1700 (C=O), 1650 (C=N), 1580 (C=C), 1490, 1420, 1370, 1260, 1200 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.64 (t, 3H, C*H*$_3$), 0.90-1.36 (m, 14H), 2.10 (s, 6H, 2x C*H*$_3$), 2.40 (t, 2H, C*H*$_2$), 3.90 (q, 4H, *J* = 7.3 Hz, ester 2x CH_2CH_3), 5.10 (s, 1H, DHP-C*H*), 5.60 (s, 1H, ISOX-C*H*), 6.70 (br.s, 1H, N*H*).

Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.31; H, 7.98; N, 6.93. Found: C, 65.50; H, 8.20; N, 7.10

Synthesis of 2,6-Dimethyl-3,5-dicarboethoxy-4-(3-*n*-octyl-5-isoxazolyl)-1,4-dihydropyridine (10c), white solid, mp. 69°, 72% yield. Silica column chromatography (petroleum ether:EtOAc, 4:1, R_f = 0.12); IR (KBr): 3300 (NH), 3100 (C=C-H), 2950-2850, 1700 (C=O), 1600 (C=C), 1590 (C=C), 1420, 1260, 1200 (C-C(=O)-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (t, 9H), 1.53 (m, 12H), 2.33 (s, 6H, 2x C*H*$_3$), 2.57 (t, 2H, *J* = 7.3 Hz, C*H*$_2$), 4.15 (q, 4H, *J* = 7.3 Hz, ester 2x CH_2CH_3), 5.32 (s, 1H, DHP-C*H*), 5.77 (s, 1H, ISOX-C*H*), 7.62 (br.s, 1H, N*H*); MS (70 ev, EI) m/z (%), 432.4, M^+ (18), 359.5 (M-CO_2Et, 80), 196.3 (100).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.61; H, 8.30; N, 6.47. Found: C, 66.30; H, 8.30; N, 6.70.

Synthesis of 2,6-Dimethyl-3,5-dicarbomethoxy-4-(3-*n*-butyl-5-isoxazolyl)-1,4-dihydropyridine (10d), white solid, mp. 149°, 85% yield, methyl acetoacetate was used instead of ethyl acetoacetate. Silica column chromatography (petroleum ether:EtOAc, 1:1, R_f = 0.42); IR (KBr): 3330 (NH), 3100 (C=C-H), 2950, 1700 (C=O), 1655 (C=N), 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.84 (t, 3H, CH_3, J = 7.3 Hz), 1.40 (m, 4H, J = 7.3 Hz), 2.20 (s, 6H, DHP-2x CH_3), 2.50 (t, 2H, J = 7.3 Hz, CH_2), 3.60 (s, 6H, ester 2x CH_3), 5.70 (s, 1H, ISOX-C*H*), 6.72 (br.s, 1H, N*H*); MS (70 ev, EI) m/z (%), M^+ (348.5), 289.4 (M-CO_2Et, 25), 224.3 (100), 41.2(63).
Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.90; H, 6.70; N, 7.80

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11. The required nitro compounds were prepared by a one-pot synthesis involving successive reactions of nitromethane respectively with aldehydes, acylating agents, and sodium borohydride.[11] 1-Nitroheptane (70%, bp. 80-83°, ~ 12-16 mmHg); IR 1550 (NO_2), 1380 cm^{-1}. 1-Nitrooctane (44%, bp. 90-94°, ~ 12-16 mmHg); IR 1550 (NO_2), 1380, 1130 cm^{-1}. 4-Phenyl-1-Nitroheptane (30%, eluent, petroleum ether: EtOAc; 10:1, $R_f = 0.28$); IR 3000, 1950, 1870, 1600,1550 (NO_2), 1375 cm^{-1}.

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13. a) Compound **6a** was prepared from propargyl alcohol[12] in 92% yield, (bp. 50-55°, ~ 12-16 mmHg); b) Compound **6b** was prepared from propargyl alcohol and benzoyl chloride in 94% yield (bp. 37-40°, ~ 12-16 mmHg).

14. a) The required 3-n-alkyl-5-[(tetrahydropyranyloxy)methyl]isoxazole was prepared accordingly, **7a**, (48%); IR (neat) 3100, 1605, 1480, 1200, 1120, 1070, 1130 cm^{-1}. **7b**, (48%); IR (neat) 3100, 1605, 1460-1420, 1200, 1120, 1070cm^{-1}. **7c**, (50%); IR (neat) 3100, 1605, 1460-1420, 1200, 1120, 1070cm^{-1}. **7e**, (56%); IR (neat) 3105, 1605, 1480-1420, 1200, 1120, 1070cm^{-1}. **7f**, yellow oil (40%, eluent, petroleum ether:EtOAc; 10:1, $R_f = 0.25$); IR (neat) 3105, 3050, 2900-2850, 1600, 1480, 1450, 1380, 1250, 1200, 1100, 1070cm^{-1}. b) The required 3-n-alkyl-5-[(phenyl carboxylate)methyl]isoxazole were prepared according to the procedure for **7d**. **7g**, (75%, petroleum ether: EtOAc; 9:1, $R_f = 0.45$); IR (neat) 3110, 3050, 1725, 1600, 1250, 1110cm^{-1}. **7h**, (75%, petroleum ether:EtOAc, 9:1, $R_f = 0.42$); IR (neat) 3150, 3050, 1730, 1600, 1260, 1100 cm^{-1}.

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