Methodology for Regioselective Synthesis of Substituted Pyridines via Intramolecular Oximino Malonate Hetero Diels-Alder Reactions

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Supporting Information

2-((*E*)-1-Oxo-hepta-4,6-dienyloxyimino)malononitrile (Entry 1, X = CN). To a stirred solution of 910 mg (7.22 mmol) of 4,6-heptadienoic acid in 25 mL of hexanes at rt was added 2.73 g (21.65 mmol) of oxalyl chloride and one drop of DMF. The solution was stirred at rt for 16 h, concentrated *in vacuo* and the residue was dissolved in 15 mL of dry benzene. To this solution was added 845 mg (7.22 mmol) of hydroxyimino malononitrile sodium salt. The resulting slurry was stirred for 18 h and then filtered. The filtrate was concentrated *in vacuo* to give 989 mg (67%) of the acyl oxime (**entry 1, X = CN**) as a light yellow oil: IR ($CDCl_3$) 2250, 1823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40-2.48 (m, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 4.96 (d, *J* = 10.1 Hz, 1H), 5.07 (d, *J* = 16.6 Hz, 1H), 5.60 (ddd, *J* = 14.3, 2.9, 2.9 Hz, 1H), 6.06 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.20 (ddd, *J* = 20.4, 10.2, 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (t), 31.9 (t), 105.3 (s), 108.5 (s), 114.7 (s), 117.3 (t), 130.8 (d), 133.6 (d), 136.8 (d), 166.3 (s); HRMS calcd for $C_{10}H_{10}N_3O_2$ (M^++H) 204.0774, found 204.0766.

2-Oxo-3,4,4a,7-tetrahydro-2*H*-pyridio[1,2-*b*][1,2]oxazine-8,8-dicarbonitrile (Entry 1, X = CN).

Procedure A: A solution of 205 mg (1.01 mmol) of the above acyl oxime (**entry 1, X = CN**) in 200 mL of dry toluene was stirred at reflux for 24 h. The solution was concentrated *in vacuo* to give a dark brown oil which was purified by flash column chromatography on silica gel eluting with hexanes-ethyl acetate (1:1) to give 139 mg (68%) of the cycloadduct (**entry 1, X = CN**) as a thick brown oil: IR ($CDCl_3$) 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.02 (dddd, *J* = 15.8, 7.9, 7.9, 1.6 Hz, 1H), 2.25 (dddd, *J* = 7.9, 4.5, 4.5, 4.5 Hz,

1H), 2.67 (ddd, *J* = 10.3, 7.9, 1.6 Hz, 1H), 2.90 (ddd, *J* = 15.9, 8.7, 7.1 Hz, 1H), 3.02 (dd, *J* = 15.9, 4.0 Hz, 1H), 3.18 (dd, *J* = 15.9, 4.0 Hz, 1H), 3.72-3.82 (m 1H), 5.65-5.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 24.7, 27.4, 36.7, 54.6, 58.7, 110.0, 112.7, 119.3, 127.0, 170.6; CIMS 204 (M^++H).

Procedure B: A solution of 83 mg (0.40 mmol) of acyl oxime (**entry 1, X = CN**) in 4 mL of dry dichloromethane was allowed to stand under 12 kbar of pressure at rt for 48 h. The solution was concentrated *in vacuo* to give a residual oil which was purified by flash column chromatography on silica gel eluting with hexanes-ether (1:3) to give 54 mg (65%) of cycloadduct (**entry 1, X = CN**) as a colorless oil which was identical to that obtained in procedure A.

6-(2-Carboxyethyl)pyridine-2-carbonitrile (Entry 1, X = CN). Procedure A: A solution of 140 mg (0.69 mmol) of cycloadduct (**entry 1, X = CN**) and 671 mg (2.06 mmol) of Cs_2CO_3 in 5 mL of dry DMF was stirred at rt for 18 h. The reaction mixture was diluted with 20 mL of ethyl acetate and acidified to pH 2 with 10% aqueous HCl. The aqueous layer was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 87 mg (72%) of the pyridine (**entry 1, X = CN**) as a light tan solid: mp 95-98.5 ˚C; IR ($CDCl_3$) 3550-2750, 2249, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82-2.90 (t, *J* = 8.2 Hz, 2H), 3.10-3.20 (t, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 6.6 Hz, 1H), 7.55 (d, *J* = 6.6 Hz, 1H), 7.75 (t, *J* = 8.8 Hz, 1H), 8.0-10.1 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.6 (t), 32.5 (t), 117.6 (s), 126.8 (d), 127.2 (d), 133.6 (s), 137.7 (d), 162.2 (s), 178.7 (s); CIMS 177 (M^++H).

2-Cyano-((*E*)-2-oxo-hepta-4,6-dienyloxyimino)acetic Acid Ethyl Ester (Entry 1, X = CO_2Et). To a stirred solution of 203 mg (1.61 mmol) of 4,6-heptadienoic acid and 229 mg (1.61 mmol) of ethyl cyanoglyoxylate-2-oxime in 5 mL of dry dichloromethane at rt was added 332 mg (1.61 mmol) of DCC in one portion. The mixture was stirred at rt for 1 h, filtered, and the filtrate was concentrated *in vacuo*. The residue was treated with 2 mL of ether and the slurry was filtered. The filtrate was concentrated *in vacuo* to give 361 mg (90%) of acyl oxime **(entry 1, X = CO_2Et**) as a thick pale yellow oil suitable for use in the next reaction: IR ($CDCl_3$) 2238, 1810, 1739 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.75 (t, *J* = 7.5 Hz, 3H), 0.88-0.95 (m, 2H), 2.0-2.1 (m, 2H), 3.77 (q, *J* = 7.5 Hz, 2H), 4.90 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 16.5 Hz, 1H),

5.30 (ddd, *J* = 16.5, 7.5, 7.5 Hz, 1H), 5.90 (dd, *J* = 15.0, 12.0 Hz, 1H), 6.20 (ddd, *J* = 16.6, 12.1, 12.1 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 13.9 (q), 27.5 (t), 31.8 (t), 64.2 (t), 107.7 (s), 116.7 (t), 131.2 (s), 131.6 (d), 133.5 (d), 137.7 (d), 157.4 (s), 167.1 (s); HRMS calcd for $C_{12}H_{15}N_2O_4$ (M^++H) 251.1032, found 251.1020.

8-Cyano-2-oxo-2,3,4,4a,7,8-hexahydro-pyrido[1,2-*b*][1,2]oxazine-8-carboxylic Acid Ethyl Ester (Entry 1, X = CO_2Et). Procedure A: A solution of 104 mg (0.44 mmol) of acyl oxime (**entry 1, X = CO_2Et**) in 88 mL of dry toluene was stirred at reflux for 24 h. The solution was concentrated *in vacuo* to give a thick brown oil. The residue was purified by flash column chromatography on silica gel eluting with hexanes-ether (1:3) to give 73 mg (70%) of the cycloadduct (**entry 1, X = CO_2Et**) as a thick colorless oil: IR ($CDCl_3$) 1756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, *J* = 7.3 Hz, 3H), 1.95 (dddd, *J* = 15.0, 7.5, 7.5, 1.5 Hz, 1H), 2.20 (dddd, *J* = 13.5, 7.5, 7.5, 7.5 Hz, 1H), 2.61 (ddd, *J* = 15.0, 9.0, 0.8 Hz, 1H), 2.77-2.91 (m, 2H), 3.10 (dd, *J* = 14.7, 1.8 Hz, 1H), 4.21-4.42 (m, 3H), 5.60-5.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3 (q), 25.7 (t), 27.4 (t), 34.8 (t), 56.2 (d), 62.2 (s), 63.6 (t), 116.9 (s), 119.3 (d), 127.0 (d), 164.5 (s), 172.3 (s); HRMS calcd for $C_{12}H_{15}N_2O_4$ (M^++H) 251.1032, found 251.1048.

Procedure B: A solution of 113 mg (0.55 mmol) of acyl oxime (**entry 1, X = CO_2Et**) in 8 mL of dry dichloromethane was allowed to stand under 12 kbar of pressure at rt for 48 h. The reaction was concentrated *in vacuo* to give a thick oil. The residue was purified by flash column chromatography on flash silica gel eluting with hexanes-ether (1:3) to give 86 mg (76%) of the cycloadduct (**entry 1, X = CO_2Et**) as a thick colorless oil which was identical to that obtained in procedure A.

6-(2-Carboxyethyl)pyridine-2-carboxylic Acid Ethyl Ester (Entry 1, X = CO_2Et). Procedure A: A solution of 175 mg (0.70 mmol) of cycloadduct (**entry 1, X = CO_2Et**) and 684 mg (2.10 mmol) of Cs_2CO_3 in 5.5 mL of dry DMF was stirred at rt for 18 h. The reaction mixture was diluted with 20 mL of ethyl acetate and acidified to pH 2 with 10% aqueous HCl. The aqueous layer was extracted with three 10-mL portions of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 107 mg (68%) of the pyridine (**entry 1, X = CO_2Et**) as a tan solid: mp 106.5-110 ˚C; IR ($CDCl_3$) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.40 (t, *J* = 5.0 Hz, 3H), 2.90 (t, *J* = 5.0 Hz, 2H), 3.30 (t, *J* = 5.0 Hz,

2H), 4.52 (q, *J* = 5.0 Hz, 2H), 7.48 (d, *J* = 6.3 Hz, 1H), 7.85 (dd, *J* = 12.6, 1.3 Hz, 1H), 8.10 (d, *J* = 6.3 Hz, 1H), 10.00-12.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.5 (q), 31.9 (t), 34.4 (t), 62.7 (t), 123.8 (d), 127.3 (d), 139.1 (d), 147.1 (s), 160.5 (s), 164.5 (s); HRMS calcd for $C_{11}H_{14}NO_4$ (M^++H) 224.0922, found 224.1884.

2-Oxo-7-phenyl-3,4,4a,7-tetrahydro-2*H*-pyrido[1,2-*b*][1,2]oxazine-8,8-dicarbonitrile (Entry 2, X = CN). To a solution of 200 mg (0.99 mmol) of 7-phenyl-4,6-heptadienoic acid in 5 mL of hexanes was added 374 mg (2.97 mmol) of oxalyl chloride in one portion via syringe. The solution was stirred at 70 ˚C for 2 h, and was concentrated *in vacuo*. The brown residue was dissolved in 30 mL of dry benzene and then 470 mg (2.33 mmol) of hydroxyimino malononitrile sodium salt was added in one portion. The solution was stirred for 16 h and filtered. The filtrate was concentrated *in vacuo* to give a brown oil which was dissolved in 200 mL of dry benzene and stirred at reflux for 20 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with hexanes-ethyl acetate (1:1) to give 143 mg (52%) of the cycloadduct (**entry 2, X = CN**) as a light tan solid: mp dec.>165˚C; IR ($CDCl_3$) 1779 cm^{-1}; ^{1}H NMR (acetone d_6, 400 MHz) δ 2.31 (dddd, *J* = 16.1, 10.9, 10.9, 3.2 Hz, 1H), 2.53 (dddd, *J* = 15.1, 7.9, 7.9, 7.9 Hz, 1H), 2.75 (ddd, *J* = 16.7, 8.5, 3.1 Hz, 1H), 3.05 (ddd, *J* = 18.4, 10.6, 7.8 Hz, 1H), 4.00 (ddd, *J* = 10.7, 1.8, 1.8 Hz, 1H), 4.68 (d, *J* = 4.7 Hz, 1H), 5.94 (dddd, *J* = 9.9, 2.3, 2.3, 2.3 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 7.42-7.46 (m, 3H), 7.55-7.76 (m, 2H); ^{13}C NMR (acetone d_6, 100 MHz), δ 25.5 (t), 28.0 (t), 52.6 (d), 60.2 (d), 61.5 (s), 112.8 (s), 124.1 (d), 127.3 (d), 127.5 (d), 129.8 (d), 130.4 (d), 131.8 (d), 136.1 (s), 171.3 (s); HRMS calcd for $C_{16}H_{14}N_3O_2$ (M^++H) 280.1086, found 280.1109.

3-(6-Cyano-5-phenylpyridin-2-yl)propionic Acid (Entry 2, X = CN). A solution of 244 mg (0.87 mmol) of cycloadduct (**entry 2, X = CN**) and 850 mg (2.61 mmol) of Cs_2CO_3 in 6.2 mL of dry DMF was stirred at rt for 18 h. The reaction was diluted with 30 mL of ethyl acetate and acidified to pH 2 with concentrated HCl. The aqueous layer was extracted with three 5-mL CH_2Cl_2 portions. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 174 mg (79%) of the pyridine (**entry 2, X = CN**) as a brown foam: IR ($CDCl_3$) 3660-2367, 2253, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80-3.00 (m, 2H), 3.15-3.46 (m, 2H), 7.24-7.61 (m, 7H), 7.74 (d, *J* = 8.0 Hz, 1H), 8.80-9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ 26.0, 30.7, 117.1, 126.8, 128.4, 128.9, 129.1, 129.4, 129.6, 129.7, 129.8, 138.4, 176.8; HRMS calcd for $C_{15}H_{13}N_2O_2$ (M^++H) 253.0977, found 253.0986.

Cyano-(2-oxo-7-phenyl-hepta-4*E*,6*E*-dienyloxyimino)acetic Acid Ethyl Ester (Entry 2, X = CO_2Et).[2] To a stirred solution of 105 mg (0.52 mmol) of 7-phenyl-4(*E*),6(*E*)-heptadienoic acid and 74 mg (0.52 mmol) of ethyl cyanoglyoxylate-2-oxime in 5 mL of dry dichloromethane at rt was added 107 mg (0.52 mmol) of DCC in one portion, and the reaction mixture was stirred for 3.5 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was treated with 3 mL of ether and filtered. The filtrate was concentrated *in vacuo* to give 160 mg (95%) of the acyl oxime (**entry 2, X = CN**) as a light yellow oil: IR ($CDCl_3$) 2117, 1809, 1788 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.39 (t , *J* = 7.2 Hz, 3H), 2.46-2.55 (m 2H), 2.65-2.70 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 5.70 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 6.21 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.40 (d, *J* = 17.1, 1H), 6.68 (dd, *J* = 14.4, 9.0 Hz, 1H), 7.15 (dd, *J* = 5.4, 5.4 Hz, 1H), 7.20 (dd, *J* = 5.4, 5.4 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.4 (q), 27.8 (t), 32.5 (t), 64.9 (t), 107.2 (s), 126.7 (d), 127.9 (d), 128.8 (d), 129.0 (d), 131.3 (d), 131.4 (s), 132.2 (d), 133.1 (d), 137.6 (s), 157.3 (s), 167.5 (s); HRMS calcd for $C_{18}H_{19}N_2O_4$ (M^++H) 327.1345, found 327.1369.

8-Cyano-7-phenyl-3,4,4a,7-tetrahydro-2*H*-pyrido[1,2*b*][1,2]oxazine-8-carboxylic Acid Ethyl Ester (Entry 2, X = CO_2Et). Procedure A. A solution of 124 mg (0.38mmol) of acyl oxime (**entry 2, X = CN**) in 76 mL of dry toluene was stirred at reflux for 38 h. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with hexanes-ethyl acetate, 1:1) to give 92 mg (74%) of cycloadduct (**entry 2, X = CN**) as a light yellow solid: mp 165-167 ˚C; IR ($CDCl_3$) 2255, 1756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, *J* = 7.2 Hz, 3H), 2.06-2.33 (m, 2H), 2.67 (ddd, *J* = 16.3, 7.8, 3.7 Hz, 1H), 2.94 (ddd, *J* = 16.3, 10.4, 8.2 Hz, 1H), 4.05 (d, *J* = 4.6 Hz, 1H), 4.29-4.43 (m, 2H), 4.53 (ddd, *J* = 9.3, 7.4, 2.0 Hz, 1H), 5.73 (dddd, *J* = 10.1, 2.3, 2.3, 2.3 Hz, 1H), 5.83 (d, *J* = 11.0 Hz, 1H), 7.34-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (q), 25.8 (t), 27.7 (t), 51.1 (d), 56.8 (d), 64.0 (t), 68.2 (s), 114.9 (s), 123.5 (d), 126.5 (d), 129.0 (d), 129.3 (d), 130.2 (d), 136.6 (s), 164. (s), 171.9 (s); HRMS calcd for $C_{18}H_{19}N_2O_4$ (M^++H) 327.1345, found 327.1376.

A small portion of the cycloadduct was dissolved in ethyl acetate and transferred to a 4 dram vial. The vial was sealed with aluminum foil, and the foil cover was pierced with a syringe needle. The solution was allowed to evaporate slowly over a 4 day period to afford X-ray quality crystals.

Procedure B. A solution of 81 mg (0.25 mmol) of acyl oxime (**entry 2, X = CN**) in 4 mL of dry dichloromethane was allowed to stand under 12 kbar of pressure at rt for 40 h. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with hexanes-ethyl acetate (1:1) to give 51 mg (63%) of the cycloadduct (**entry 2, X = CN**) as a light yellow solid which was identical to that obtained in procedure A.

6-(2-Carboethoxyethyl)-3-phenylpyridine-2-carboxylic Acid (Entry 2, X = CO_2Et). A solution of 110 mg (0.30 mmol) of cycloadduct (**entry 2, X = CN**) and 330 mg (1.01 mmol) of Cs_2CO_3 in 2.4 mL of dry DMF was stirred at rt for 17 h. The reaction mixture was diluted with 10 mL of ethyl acetate and acidified to pH 2 with 10% aqueous HCl. The aqueous layer was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concetrated *in vacuo* to give 72 mg (71%) of the pyridine (**entry 2, X = CN**) as a thick oil: IR ($CDCl_3$) 3671-2367, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, *J* = 7.3 Hz, 3H), 2.87-2.91 (m, 2H), 3.16-3.25 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 7.31 (d, *J* = 2.3 Hz, 2H) 7.39 (t, *J* = 2.3 Hz, 3H), 7.42-7.57 (m, 1H), 7.69 (d2, *J* = 7.8 Hz, 1H)m 9.80-10.2 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5 (q), 30.4 (t), 33.4 (t), 61.7 (t), 124.9 (d), 127.9 (d), 128.2 (d), 128.3 (d), 135.3 (s), 137.8 (d), 137.9 (d), 147.7 (s), 158.5 (s), 166.5 (s), 176.8 (s); HRMS calcd for $C_{17}H_{18}NO_4$ (M^++H) 300.1236, found 300.1218.

Cyano-(2-oxo-6-methyl-hepta-4,6-dienyloxyimino)acetic Acid Ethyl Ester (Entry 3). To a solution of 290 mg (2.07 mmol) of 6-methyl-4,6-heptadienoic acid and 294 mg (2.07 mmol) of ethyl cyanoglyoxylate-2-oxime in 5 mL of dry CH_2Cl_2 was added a solution of 427 mg (2.07 mmol) of DCC in 2 mL of CH_2Cl_2 in one portion. The reaction mixture was stirred for 2.5 h and then filtered. The filtrate was concentrated *in vacuo* to give a residue. The residue was diluted with 1 mL of ether, filtered and concentrated *in vacuo* to give 483 mg (88%) of acyl oxime (**entry 3**) as a thick yellow oil: IR (neat) 2932,

1810 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t *J* = 7.2 Hz, 3H), 1.81 (s, 3H), 2.54-2.59 (m, 2H), 2.73-2.77 (m, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 4.91 (d, *J* = 3.0 Hz, 2H), 5.65 (ddd, *J* = 15.7, 6.8, 6.8 Hz, 1H), 6.22 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 18.5 (q), 27.3 (t), 32.1 (t), 64.5 (t), 106.7 (s), 116.0 (t), 126.4 (d), 130.9 (s), 135.0 (d), 141.4 (s), 156.9 (s), 167.1 (s); HRMS calcd for $C_{13}H_{17}N_2O_4$ (M^++H) 265.1188, found 265.1177.

8-Cyano-6-methyl-3,4,4a,7-tetrahydro-2*H*-pyrido[1,2*b*][1,2]oxazine-8-carboxylic Acid Ethyl Ester (Entry 3). A solution of 453 mg (1.81 mmol) of the acyl oxime (**entry 3**) in 380 mL of toluene was stirred at reflux for 24 h. The reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography eluting with hexanes-ethyl acetate (1:1) to give 158 mg (35%) of the cycloadduct (**entry 3**) as a light yellow thick oil: IR (neat) 2982, 2252, 1756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.70 (s, 3H), 1.86 (dddd, *J* = 14.7, 10.4, 10.4, 4.3 Hz, 1H), 2.12 (dddd, *J* = 15.4, 7.6, 7.6, 7.6 Hz, 1H), 2.57 (ddd, *J* = 16.2, 8.1, 4.0 Hz, 1H), 2.76 (ddd, *J* = 17.4, 10.1, 7.3 Hz, 1H), 2.96 (d, *J* = 7.3 Hz, 1H), 4.18-4.24 (m, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.28 (d, *J* = 1.52 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.7, 25.6, 27.0, 38.0, 55.4, 62.3, 63.3, 116.4, 120.7, 127.3, 163.9, 171.8; HRMS calcd for $C_{13}H_{17}N_2O_4$ (M^++H) 265.1188, found 265.1177.

6-(2-Carboxyethyl)-4-methylpyridine-2-carboxylic Acid Ethyl Ester (Entry 3). A solution of 158 mg (0.60 mmol) of cycloadduct (**entry 3**) and 586 mg (1.80 mmol) of Cs_2CO_3 in 4.3 mL of dry DMF was stirred at rt for 18 h. The reaction was diluted with 15 mL of ethyl acetate and acidified to pH 2 with 10% aqueous HCl. The aqueous layer was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 115 mg (81%) of the pyridine (**entry 3**) as a light tan solid: mp 95-100 ˚C; IR ($CDCl_3$) 3671-2250, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, *J* = 7.1 Hz, 3H), 2.37 (s, 3H), 2.77 (t, *J* = 6.1 Hz, 2H), 3.11 (t, *J* = 6.1 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.20 (s, 1H), 7.78 (s, 1H), 10.64-10.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 21.0 (q), 31.2 (t), 33.8 (t), 61.9 (t), 124.2 (d), 127.1 (d), 146.3 (s), 150.3 (s), 159.8 (s), 164.3 (s), 175.4 (s); HRMS calcd for $C_{12}H_{15}NO_4$ (M^++H) 238.1079, found 238.1061.

2-(1-Oxo-hexa-3,5-dienyloxyimino)-malononitrile (Entry 4, X = CN). To a stirred solution of 500 mg (4.46 mmol) of 3,5-hexadienoic acid in 10 mL of benzene at 0 ˚C was added thionyl chloride (0.650 mL) dropwise via syringe. This solution was warmed to ambient temperature and stirred for 18 h. The mixture was partially concentrated *in vacuo* and then diluted with anhydrous benzene (5 mL). This process was repeated three times in order to remove excess thionyl chloride without fully concentrating the solution. The resulting solution was diluted with anhydrous benzene (5 mL) and then (hydroxyimino)-malononitrile sodium salt (678 mg, 5.80 mmol) was added, and the mixture was stirred at rt for 18 h. The solution was filtered and concentrated *in vacuo* to afford 642 mg (76%) of the dicyano acyl oxime **(entry 4, X = CN)** as a brown oil which was used directly in the next step: IR ($CDCl_3$) 2361, 2242, 1822 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.23 (m, 2 H), 5.65 (m, 1 H), 5.17 (d, *J* = 16.9 Hz, 1 H), 5.08 (d, *J* = 10.1 Hz, 1 H), 3.36 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 137.4, 135.9, 121.4, 119.5, 114.9, 108.3, 105.2, 35.8; APCIMS 190.1 (M^++H).

2-Oxo-2,3,3a,6-tetrahydro-isoxazolo[2,3a]pyridine-7,7-dicarbonitrile (Entry 4, X = CN). A solution of 1.00 g (5.29 mmol) of the above dinitrile acyl oxime **(entry 4, X = CN)** in 1.06 L of toluene was heated at reflux for 48 h. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography eluting with hexanes-ether (1:2 to 1:3) to give 669 mg (67%) of the dinitrile cycloadduct **(entry 4, X = CN)** as a tan solid: mp 130-132 ^oC; IR ($CDCl_3$) 2360, 2332, 1805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.02 (s, 2 H), 4.80 (m, 1 H), 3.05 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 125.8, 121.3, 113.4, 112.3, 59.0, 53.2, 33.4, 33.2; HRMS calcd for $C_9H_8N_3O_2$ (M^++H) 190.0617, found 190.0616.

(6-Cyano-pyridine-2-yl)-acetic Acid (Entry 4, X = CN, R = H). A solution of 100 mg (0.529 mmol) of dinitrile cycloadduct **(entry 4, X = CN)** and 362 mg (1.11 mmol) of Cs_2CO_3 in 4 mL of anhydrous DMF was stirred at ambient temperature for 18 h. The reaction mixture was diluted with EtOAc (3 mL), and acidified to pH 2 with 10% aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 1 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo.* The residual oil was triturated with chloroform, filtered, and the filtrate was concentrated *in vacuo*

to afford 58 mg (67%) of the pyridine **(entry 4, X = CN)** as a brown oil: IR ($CDCl_3$) 2923, 2239, 1722, 1588, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (t, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 4.0 Hz, 1 H), 7.10-7.25 (br s, 1H), 3.90 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 155.0, 137.0, 132.1, 126.8, 126.3, 115.8, 41.7; APCIMS 163.0 (M^++H, 100), 119.1 (M^++H -CO_2, 66); HRMS calcd for $C_8H_7N_2O_2$ (M^++H) 163.0508, found 163.0507.

Cyano-(1-oxo-hexa-3,5-dienyloxyimino)-acetic Acid Ethyl Ester (Entry 4, X = CO_2Et). A mixture of 3,5-hexadienoic acid (300 mg, 2.68 mmol) and ethyl cyanoglyoxylate-2-oxime (381 mg, 2.68 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at ambient temperature for 5 min. To this mixture was added DCC (552 mg, 2.68 mmol) in one portion and the resulting mixture was allowed to stir at rt for 2 h. The reaction was filtered and concentrated *in vacuo*. The residue was cooled to 0 ˚C, triturated with ether, filtered and concentrated *in vacuo* to afford 613 mg (97%) of the ester-nitrile acyl oxime **(entry 4, X = CO_2Et)** as a yellow oil which was used directly in the next step: IR ($CDCl_3$) 2238, 1808, 1738, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.30 (m, 2 H), 5.78 (m, 1 H), 5.24 (d, *J* = 14.6 Hz, 1 H), 5.16 (d, *J* = 10.5 Hz, 1 H), 4.46 (q, *J* = 7.3 Hz , 2 H), 3.44 (d, *J* = 7.3 Hz, 2 H), 1.42 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 165.65, 156.75, 136.28, 135.63, 131.15, 121.95, 118.40, 106.60, 63.37, 35.65, 13.91; CIMS 237.1 (M^++H), 209.1 (M^++H-CN).

7-Cyano-2-oxo-3,3a,6,7-tetahydro-2H-isoxazolo[2,3-a]pyridine-7-ethyl Ester (Entry 4, X = CO_2Et). A solution of 500 mg (2.12 mmol) of the above ester-nitrile acyl oxime **(entry 4, X = CO_2Et)** in 424 mL of anhydrous toluene was heated at reflux for 48 h. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography eluting with hexanes-ether (1:2 to 1:3) to give 112 mg (63%) of the ester-nitrile cycloadduct **(entry 4, X = CO_2Et)** as light yellow needles suitable for X-ray crystallography: mp 107-109 ^oC; IR ($CDCl_3$) 1803, 1746 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.98 (m, 2 H), 4.83 (m, 1 H), 4.39 (q, *J* = 7.3 Hz, 2 H), 3.25 (m, 1 H), 2.86 (m, 3 H), 1.38 (t, *J* = 6.8 Hz, 3 H,); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 174.1, 164.8, 125.3, 122.3, 117.1, 64.6, 63.9, 59.2, 33.5, 33.4, 14.3; HRMS calcd for $C_{11}H_{13}O_4N_2$ (M^++H) 237.0875, found 237.0885.

6-Ethoxycarbonylmethylpyridine-2-carboxylic Acid Ethyl Ester (Entry 4, X = CO_2Et, R = Et). A solution of 60 mg (0.254 mmol) of the ester-nitrile cycloadduct **(entry 4, X = CO_2Et)** and 248 mg (0.762 mmol) of Cs_2CO_3 in 2 mL of anhydrous DMF was stirred at ambient temperature for 9 h, diluted with EtOAc (3 mL) and acidified to pH 2 with 10% aqueous HCl solution. The organic layer was separated and the aqueous layer was then extracted with EtOAc (3 x 1 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in anhydrous EtOH (5 mL) and cooled to 0 °C. Thionyl chloride (0.111 mL) was added dropwise via syringe and the solution was heated at reflux for 18 h. The solution was concentrated *in vacuo,* the residue was cooled to 0 °C, basified with saturated K_2CO_3, and then diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). The organic layers were combined, washed with brine, dried (Mg_2SO_4), and concentrated *in vacuo* to afford 30 mg (53%) of the pyridine **(entry 4, X = CO_2Et, R = Et)** as a brownish-yellow oil: IR ($CDCl_3$) 1736, 1590, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (dd, *J* = 1.3, 7.8 Hz, 1 H), 7.81 (t, *J* = 7.8 Hz, 1 H), 7.52 (dd, *J* = 1.0, 7.8 Hz, 1 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.98 (s, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 165.1, 154.9, 148.0, 137.3, 127.3, 123.6, 61.9, 61.1, 43.7, 14.3, 14.1; HRMS calcd for $C_{12}H_{16}NO_4$ (M^++H) 238.1079, found 238.1074.

4-Methyl-2-(1-oxo-hexa-3,5-dienyloxyimino)-malononitrile (Entry 5, X = CN). To a stirred solution of 535 mg (4.24 mmol) of 4-methyl-3(*E*),5-hexadienoic acid in 25 mL of dry benzene at 0 ˚C was added thionyl chloride (0.62 mL) dropwise via syringe. This solution was warmed to ambient temperature and stirred for 18 h. The mixture was partially concentrated *in vacuo* and then diluted with anhydrous benzene (10 mL). This process was repeated three times in order to remove excess thionyl chloride without fully concentrating the solution. The resulting solution was diluted with benzene (10 mL) and then (hydroxyimino)-malononitrile sodium salt (595 mg, 5.09 mmol) was added, and the mixture was stirred at rt for 18 h. The solution was filtered and concentrated *in vacuo* to afford 692 mg (80%) of the dicyano acyl oxime **(entry 5, X = CN)** as a brown oil which was used directly in the next step: IR ($CDCl_3$) 2241, 1817 cm^-

[1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (dd, *J* = 11.3, 17.3 Hz, 1 H), 5.61 (t, *J* = 7.2 Hz, 1 H), 5.27 (d, *J* = 17.7 Hz, 1 H), 5.13 (d, *J* = 10.6 Hz, 1 H), 3.52 (d, *J* = 7.2 Hz, 2 H), 1.83 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.8, 140.2, 140.1, 119.0, 114.8, 114.6, 108.3, 105.3, 32.1, 12.7; APCIMS 204.1 (M^++H, 2).

4-Methyl-2-oxo-2,3,3a,6-tetrahydro-isoxazolo[2,3a]pyridine-7,7-dicarbonitrile (Entry 5, X = CN). A solution of 674 mg (3.32 mmol) of the above dinitrile acyl oxime **(entry 5, X = CN)** in 664 mL of anhydrous toluene was heated at reflux for 48 h. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography eluting with hexanes-ether (1:2 to 1:3) to give 416 mg (62%) of the dinitrile cycloadduct **(entry 5, X = CN)** as a tan solid: mp 113-114 ˚C; IR ($CDCl_3$) 2238, 2214, 1810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.65 (s, 1 H), 4.66 (t, *J* = 10.0 Hz, 1 H), 3.14 (dd, *J* = 11.4, 17.8 Hz, 1 H), 2.95 (m, 3 H), 1.83 (s, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 172.8, 133.7, 115.8, 113.9, 112.7, 62.5, 53.6, 34.0, 32.5, 20.3; HRMS calcd for $C_{10}H_{10}N_3O_2$ (M^++H) 204.0773, found 204.0769.

(5-Cyano-2-methylphenyl)acetic Acid (Entry 5, X = CN, R = H). A solution of 48 mg (0.236 mmol) of the dinitrile cycloadduct **(entry 5, X = CN)** and 192 mg (0.591 mmol) of Cs_2CO_3 in 2 mL of anhydrous DMF was stirred at ambient temperature for 18 h. The reaction mixture was diluted with EtOAc (3 mL), and acidified to pH 2 with 10% aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 1 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo.* The residual oil was triturated with chloroform, filtered, and the filtrate was concentrated *in vacuo* to afford 28 mg (67%) of the pyridine **(entry 5, X = CN)** as a brown oil: IR ($CDCl_3$) 2236, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 7.3 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 3.95 (s, 2 H), 2.43 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 151.2, 139.1, 137.5, 130.0, 127.4, 116.8, 40.2, 19.1; HRMS calcd $C_9H_9N_2O_2$ (M^++H) 177.0664, found 177.0670.

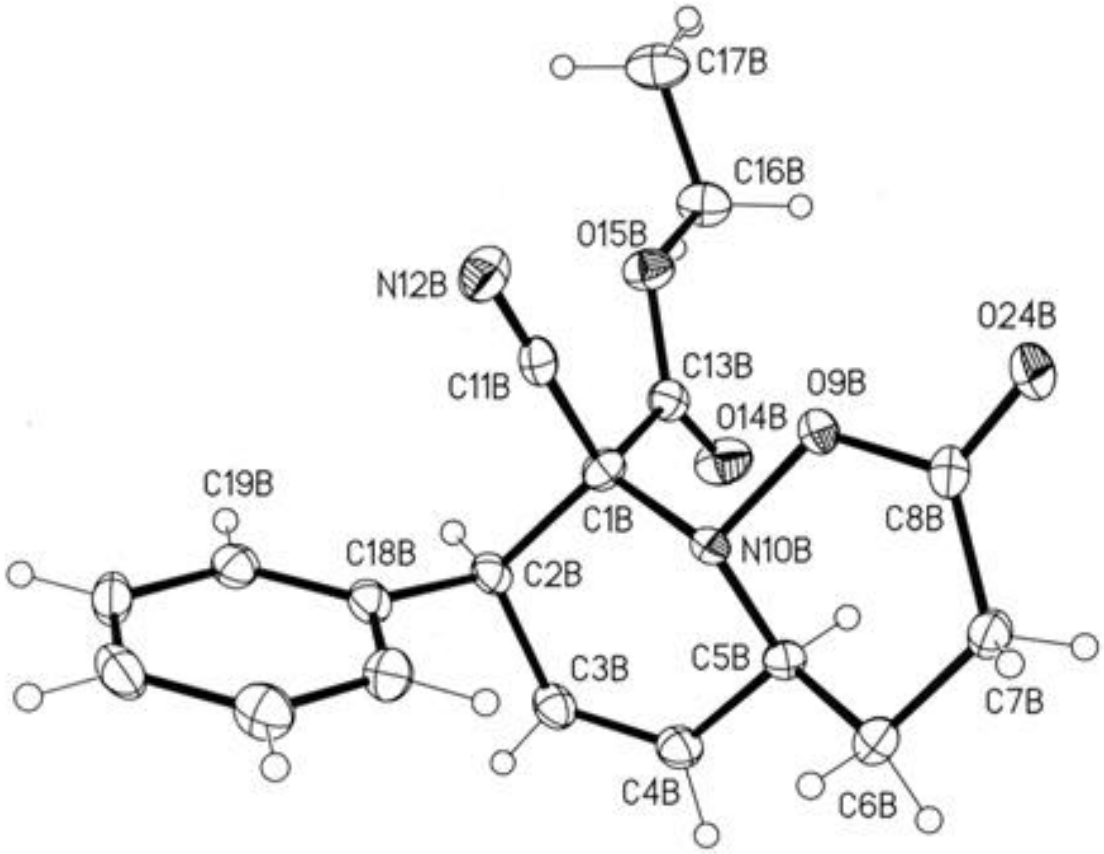
4-Methyl-cyano-(1-oxo-hexa-3,5-dienyloxyimino)acetic Acid Ethyl Ester (Entry 5, X = CO_2Et). A mixture of 4-methyl-3(*E*),5-hexadienoic acid (400 mg, 3.17 mmol) and ethyl cyanoglyoxylate-2-oxime (451 mg, 3.17 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at ambient temperature for 5 min. To this mixture was added DCC (654 mg, 3.17 mmol) in one portion. This mixture was stirred at rt for 2 h, filtered

and concentrated *in vacuo*. The residue was cooled to 0 ˚C, triturated with ether, filtered and concentrated *in vacuo* to afford 793 mg (100%) of the ester-nitrile acyl oxime **(entry 5, X = CO_2Et)** as a yellowish-orange oil which was used directly in the next step: IR ($CDCl_3$) 1809, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.42 (dd, *J* = 10.9, 17.3 Hz, 1 H), 5.65 (t, *J* = 7.3 Hz, 1 H), 5.25 (d, *J* = 17.8 Hz, 1 H), 5.10 (d, *J* = 10.9 Hz, 1 H), 4.48 (q, *J* = 6.8 Hz, 2 H), 3.50 (d, *J* = 7.3 Hz, 2 H), 1.83 (s, 3 H), 1.42 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 157.3, 140.3, 139.6, 131.5, 120.0, 114.1, 107.1, 64.9, 32.4, 14.4, 12.6; HRMS calcd for $C_{12}H_{15}N_2O_4$ (M^++H) 251.1032, found 251.1020.

7-Cyano-4-methyl-2-oxo-3,3a,6,7-tetrahydro-2H-isoxazolo[2,3-a]pyridine-7-carboxylic Acid Ethyl Ester (Entry 5, X = CO_2Et). A solution of 811 mg (3.24 mmol) of the above ester-nitrile acyl oxime **(entry 5, X = CO_2Et)** in 648 mL of toluene was heated at reflux for 48 h. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography eluting with hexanes-ether (1:2 to 1:3) to give 542 mg (67%) of the ester-nitrile cycloadduct **(entry 5, X = CO_2Et)** as light yellow solid: mp 97-99 ˚C; IR ($CDCl_3$) 1807, 1746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.64 (s, 1 H), 4.68 (t, *J* = 9.8 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.26 (m, 1 H), 2.82 (m, 3 H), 1.81 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 165.0, 133.0, 117.4, 116.8, 64.5, 64.3, 62.5, 33.7, 32.9, 20.3, 14.3; HRMS calcd for $C_{12}H_{15}N_2O_4$ (M^++H) 251.1032, found 251.1020.

3-Ethoxycarbonylmethyl-4-methylbenzoic Acid Ethyl Ester (Entry 5, X = CO_2Et, R = Et). A solution of 100 mg (0.400 mmol) of the ester-nitrile cycloadduct **(entry 5, X = CO_2Et)** and 274 mg (0.840 mmol) of Cs_2CO_3 in 3 mL of anhydrous EtOH was stirred at ambient temperature for 18 h. The mixture was then cooled to 0 ^oC, and thionyl chloride (0.24 mL) was added dropwise via syringe. This mixture was warmed to ambient temperature and stirred for 36 h. The resulting mixture was concentrated *in vacuo*, the residue cooled to 0 ^oC, basified with saturated K_2CO_3, and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to afford 38 mg (38%) of the diester pyridine **(entry 5, X = CO_2Et, R = Et)** as a light brown oil: IR ($CDCl_3$) 1735, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, *J* =

7.7 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2Hz, 2 H), 4.00 (s, 2 H), 2.36 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 165.6, 154.2, 146.0, 138.9, 137.1, 124.5, 62.1, 61.5, 42.6, 19.4, 14.7, 14.6; HRMS calcd for $C_{13}H_{18}NO_4$ (M^++H) 252.1236, found 252.1214.



ORTEP drawing of cycloadduct **15**