Microwave-Assisted Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines using Manganese Dioxide

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Received 14 October 2005

Abstract: 4-Aryl- and 4-alkyl-1,4-dihydropyridines, prepared by microwave-assisted Hantzsch reaction, are readily and efficiently aromatized in only one minute using commercial manganese dioxide in the absence of an inorganic support at 100 °C under microwave irradiation. This rapid procedure is more efficient than microwave-assisted aromatization using Pd/C, iodine or *o*-iodoxybenzoic acid (IBX) and gives the dehydrogenated or 4-dealkylated product in 91–100% yield (13 examples).

Key words: aromatization, Hantzsch dihydropyridines, heterocycles, microwave synthesis, oxidation

Since its discovery by Hantzsch in 1881,[1] the preparation of 1,4-dihydropyridine-3,5-dicarboxylate (1,4-DHP) derivatives by condensation of an aldehyde, β-keto ester and ammonia has attracted substantial interest as a multicomponent condensation reaction that provides heterocycles of pharmacological importance.[2] The 1,4-DHP motif is found in a number of chemotherapeutic agents for the treatment of cardiovascular disease such as hypertension and angina pectoris,[3] including the 4-(2-chlorophenyl) derivatives amlodipine (**1**) and felodipine (**2**), 4-(2-nitrophenyl)DHP derivative nifedipine (**3**) and 4-(3-nitrophenyl) derivatives nicardipine (**4**), nimodipine (**5**) and nitrendipine (**6**), amongst others[2] (Figure 1). This important class of calcium channel antagonists relaxes the cardiac muscle by decreasing the transmembrane calcium current on binding[4] and so considerable effort has been devoted to establish efficient methods for their synthesis.

The metabolism of these drugs is catalyzed in the liver by cytochrome P-450[5] and commences by oxidative aromatization to give the corresponding 1,4-dehydro derivatives, which are largely devoid of pharmacological activity. Notably, the 1,4-DHP motif also features in hydride transfer biotransformations from the reduced nicotinamide adenine dinucleotide (NADH and NADPH) coenzymes, and analogues thereof, that mediate hydrogen transfer reactions in biological systems.[6] In order to understand and model these biological processes, and as a useful synthetic approach to polysubstituted pyridines, the oxidative aromatization of 1,4-DHP derivatives has received considerable attention from synthetic chemists. A wide variety of oxidants have been studied in the reaction, including urea nitrate,[7] peroxydisulfate-Co(II),[7] clay-supported ferric and cupric nitrate,[8] ceric ammonium nitrate,[9] pyridinium chlorochromate (PCC),[10] $BrCCl_3/h\nu$,[11] nitric acid,[12] nitric oxide,[13,14] *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[14] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[15] $Bi(NO_3)_3$,[16] $Zr(NO_3)_4$,[17] $Mn(OAc)_3$,[18] Pd/C,[19] I_2/MeOH,[20] $KMnO_4$,[19b,21] *tert*-butyl hydroperoxide,[22] Co(II)-catalyzed auto oxidation,[23] CrO_3,[24] and nitrous acid,[25] amongst others,[24,26] all with varying degrees of success.

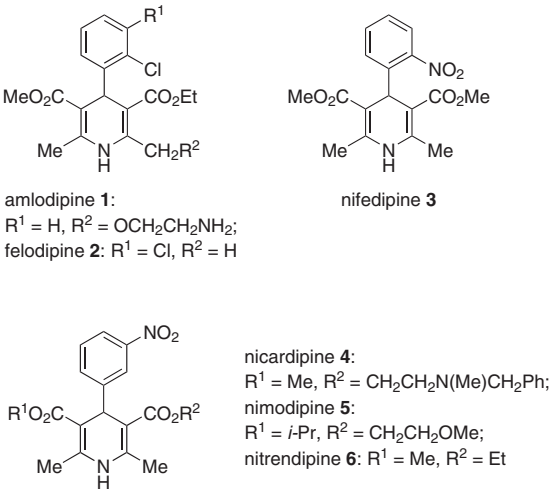


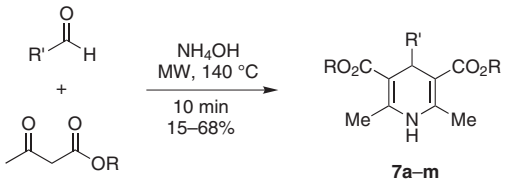
Figure 1 Some chemotherapeutic agents based upon 1,4-DHP derivatives for the treatment of cardiovascular disease.

Despite a plethora of methods for this transformation, prolonged reaction times, poor yields and the competing oxidative dealkylation of 4-benzyl- and *sec*-alkyl-substituted DHP substrates[25] has led to the investigation of many alternative procedures,[2,27] such as solvent free conditions,[12,16,26h] the use of sonication[8,15] and microwave (MW) heating,[2,7,12,15,16,26e,26h,28] in particular with MnO_2 as oxidant.[29,30] The first microwave-assisted method utilized MnO_2 supported on Mexican bentonite clay in a domestic oven, giving the corresponding pyridines in a very short time (10 min) and reasonable yield (47–100%).[29] A recent modification gave further improvements by immobilizing the MnO_2 on HZSM-5 zeolite,[30] but found that in the absence of an inorganic solid support incomplete reactions and alternative products were obtained. We now wish to report our own findings on new methods for the oxidative aromatization of 1,4-DHP derivatives that overcame these difficulties and prioritized the need for excellent yields using cheap, commercially available reagents coupled with

SYNTHESIS 2006, No. 8, pp 1283–1288
Advanced online publication: 27.03.2006
DOI: 10.1055/s-2006-926407; Art ID: P16805SS

microwave irradiation, to dramatically reduce reaction times.[31]

The 1,4-DHP derivatives required for this study were obtained by microwave-assisted Hantzsch synthesis,[2,32] in a single-mode microwave cavity synthesizer according to the conditions of Öhberg.[32d] A mixture of the aldehyde, β-keto ester and aqueous ammonia was irradiated at 140 °C to give the pure 1,4-DHP derivatives **7a–m** in poor to average yields following recrystallization (Scheme 1, Table 1). Although the yields for these transformations were disappointing (15–68%) next to Öhberg's report,[32d] they did compare reasonably with those obtained using equivalent conductive heating procedures and gave the product in high purity, on the basis of a comparison of physical and spectroscopic properties with literature data. Interestingly, the irradiation of ethyl acetoacetate, formaldehyde and aqueous ammonia (entry 9) gave a mixture of 1,4-DHP **7i** and the corresponding pyridine **8i**, in a ratio of 3.5:1, respectively, indicating that for this substrate spontaneous oxidative aromatization occurs at least in part under the reaction conditions.



Scheme 1 Microwave-assisted Hantzsch 1,4-DHP synthesis using a monomodal microwave synthesizer.

In the search for a rapid procedure for oxidative aromatization, 1,4-DHP **7a** was submitted to a range of conditions with a number of different oxidants, coupled with microwave irradiation (Table 2). Irradiating **7a** in a methanolic solution of iodine at 100 °C for 20 minutes failed to generate the product (entry 1), whereas the use of conductive heating at reflux for 24 hours gave pyridine **8a**.[20] Similarly irradiation over Pd/C in acetic acid at 120 °C for 10 minutes gave only a trace of product (entry 2), in contrast to conductive heating methods.[19] Conversion to the pyridine **8a** under microwave-assisted conditions was however facilitated using Pd/C by increasing the temperature to 180 °C (entry 3) but at these high temperatures a small amount of oxidative dealkylation also occurred, giving a mixture of products. The irradiation of a mixture of *o*-iodoxybenzoic acid (IBX) and **7a** in DMSO was also investigated, but at 180 °C a mixture of products was obtained (entry 4). Carrying out the reaction at a lower temperature in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) did overcome some of these difficulties (entry 5), but failed to effect complete conversion to pyridine **8a**. However, either heating a mixture of **7a** and manganese dioxide in dichloromethane at reflux overnight with conductive heating (entry 6) or at 100 °C for 1 minute in a monomodal microwave synthesizer (entry 7), gave pyridine **8a** in quantitative yield without the need for further purification. The facility and rapidity of the microwave-assisted procedure compares very favorably to traditional heating methods and demonstrates that no inorganic support is required for efficient conversion, despite previous reports.[29,30]

Table 1 Microwave-Assisted Synthesis of 1,4-DHP Derivatives **7a–m**

Entry	Product	R	R′	Yield (%)[a]
1	**7a**	Me	Ph	47
2	**7b**	Me	4-$NO_2C_6H_4$	15
3	**7c**	Me	4-ClC_6H_4	45
4	**7d**	Me	4-$MeOC_6H_4$	27
5	**7e**	Et	Ph	39
6	**7f**	Et	4-$NO_2C_6H_4$	36
7	**7g**	Et	4-ClC_6H_4	45
8	**7h**	Et	4-$MeOC_6H_4$	23
9	**7i**	Et	H	54[b]
10	**7j**	Et	Me	21
11	**7k**	Et	Et	68
12	**7l**	Et	*i*-Pr	21
13	**7m**	Et	$PhCH_2$	25

[a] Isolated yield of pure **7** after recrystallization.
[b] A 3.5:1 crude mixture of 1,4-DHP **7i** (42%) and pyridine **8i** (12%) was obtained by ^{1}H NMR spectroscopic analysis, which was used directly without purification.

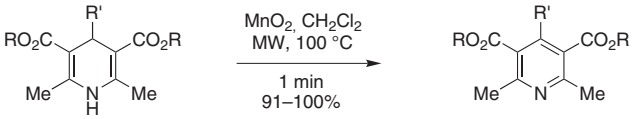
The scope of this rapid microwave-assisted oxidative aromatization was explored using 1,4-DHP derivatives **7a–m**

Table 2 Exploring Microwave-Assisted Methods for the Oxidative Aromatization of 1,4-DHP **7a**

Entry	Conditions[a]	Results
1	I_2, MeOH, MW, 100 °C, 20 min	**7a**, **8a** (trace)
2	Pd/C, AcOH, MW, 120 °C, 10 min	**7a**, **8a** (trace)
3	Pd/C, AcOH, MW, 180 °C, 10 min	**8a**[b]
4	IBX, DMSO, MW, 180 °C, 1 min	**8a**[c]
5	IBX, [Bmim]BF_4, MW, 120 °C, 1 min	**7a**:**8a** (1:17)
6	MnO_2, CH_2Cl_2, reflux, 18 h	**8a** (ca. 100%)
7	MnO_2, CH_2Cl_2, MW, 100 °C, 1 min	**8a** (ca. 100%)

[a] Initial MW irradiation power of 150 W was moderated throughout the course of the reaction in order to maintain the required temperature.
[b] Compound **8a** was contaminated with 4-dealkylated pyridine (R = Me, R′ = H), as shown by ^{1}H NMR spectroscopic analysis.
[c] Compound **8a** was contaminated with unidentified side products, as shown by ^{1}H NMR spectroscopic analysis.

(Scheme 2, Table 3) under the same reaction conditions. In all cases excellent yields of pyridines **8** were obtained. 4-Aryl substrates **7a–h** (entries 1–8) and 4-alkyl-1,4-DHP derivatives, where R′ = H, Me or Et, **7i–k** respectively (entries 9–11), gave the products of oxidative aromatization **8a–k**, whereas 4-*i*-Pr and 4-benzyl derivatives, **7l** and **7m** respectively, gave the product of oxidative dealkylation **8i** (entries 12 and 13). This observation is in accord with the reported behavior of these derivatives under oxidative conditions.[2] In the case of DHP derivative **7i**, which was generated in the Hantzsch reaction along with the corresponding pyridine **8i**, irradiating the crude mixture in the presence of MnO_2 completed conversion to tetrasubstituted pyridine **8i**, which was isolated in 51% overall yield over the two steps.



7a–m **8a–k**

Scheme 2 Oxidative aromatization of 1,4-DHP derivatives **7a–m** using MnO_2.

Table 3 Synthesis of Pyridines **8a–k** by Oxidative Aromatization or Oxidative Dealkylation of 1,4-DHP Derivatives **7a–m**

Entry	Substrate	Product	R	R′	Yield (%)[a]
1	**7a**	**8a**	Me	Ph	ca. 100
2	**7b**	**8b**	Me	4-$NO_2C_6H_4$	99
3	**7c**	**8c**	Me	4-ClC_6H_4	97
4	**7d**	**8d**	Me	4-$MeOC_6H_4$	96
5	**7e**	**8e**	Et	Ph	99
6	**7f**	**8f**	Et	4-$NO_2C_6H_4$	93
7	**7g**	**8g**	Et	4-ClC_6H_4	94
8	**7h**	**8h**	Et	4-$MeOC_6H_4$	99
9	**7i**[b]	**8i**	Et	H	94[b]
10	**7j**	**8j**	Et	Me	97
11	**7k**	**8k**	Et	Et	98
12	**7l**	**8i**	Et	H	91
13	**7m**	**8i**	Et	H	98

[a] Isolated yield of pure **8**.
[b] A mixture of **7i** and **8i** was used (51% overall yield over 2 steps).

In conclusion, microwave irradiation of 1,4-DHP derivatives at 100 °C in CH_2Cl_2 provides tetra- or pentasubstituted pyridines in only one minute without the use of an inorganic solid support. The reaction proceeds by either oxidative aromatization, for 4-aryl or linear primary 4-alkyl substrates, or oxidative dealkylation for 4-*sec*-alkyl or 4-benzyl substrates. This extremely facile and rapid process provides the target pyridines without the need for further purification and in excellent yield.

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical TLC was carried out using aluminum-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualized under UV light (at 254 and/or 360 nm). Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded, as a Nujol mull for solid samples or as a thin film between NaCl plates for liquid samples, in the range 4000–600 cm^{-1} on a Perkin-Elmer 1600 series FTIR spectrometer and peaks are reported in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz in $CDCl_3$ at 25 °C using a Bruker DPX 400 instrument and were reported in ppm. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

Microwave-Assisted Hantzsch 1,4-DHP Synthesis; Diethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (7e); Typical Procedure

According to the method of Öhberg,[32d] a mixture of benzaldehyde (0.27 g, 2.5 mmol), ethyl acetoacetate (1.63 g, 12.5 mmol), and 35% aq NH_4OH (0.17 g, 10.0 mmol) was irradiated for 10 min at 140 °C in a CEM Discover monomodal microwave synthesizer at an initial power of 150 W. The mixture was allowed to cool and concentrated in vacuo. Purification by column chromatography on silica, eluting with light petroleum–EtOAc (7:3), followed by recrystallization (aq EtOH) gave 1,4-DHP **7e** (0.294 g, 39%) as a pale-yellow solid; mp 158–160 °C (Lit.[33] mp 156–157 °C).

IR (Nujol): 3340, 1688, 1650, 1298, 1212, 1124, 1090, 1018, 827 cm^{-1}.

^1H NMR: δ = 7.20–7.02 (5 H), 5.74 (br s, 1 H), 4.92 (s, 1 H), 4.03 (m, 4 H), 2.25 (s, 6 H), 1.18 (t, 6 H, *J* = 7.1 Hz).

Dimethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (7a)

Pale-yellow solid; mp 199–200 °C (Lit.[34] mp 198–199 °C).

IR (Nujol): 3341, 1700, 1648, 1433, 1344, 1300, 1222, 1121, 1101, 1053, 1018, 764, 700 cm^{-1}.

^1H NMR: δ = 7.26 (m, 2 H), 7.22 (m, 2 H), 7.13 (m, 1 H), 5.74 (br s, 1 H), 5.04 (s, 1 H), 3.67 (s, 6 H), 2.35 (s, 6 H).

Dimethyl 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7b)

Yellow solid; mp 198–200 °C (Lit.[34] mp 198–199 °C).

IR (Nujol): 3341, 1704, 1650, 1519, 1345, 1216, 1123, 1097, 1016, 830 cm^{-1}.

^1H NMR: δ = 8.03 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 5.68 (br s, 1 H), 5.03 (s, 1 H), 3.58 (s, 6 H), 2.29 (s, 6 H).

Dimethyl 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7c)

Pale-yellow solid; mp 198 °C (Lit.[34] mp 194–196 °C).

IR (Nujol): 3333, 1697, 1650, 1345, 1306, 1210, 1121, 1020, 842 cm^{-1}.

^1H NMR: δ = 7.23 (m, 4 H), 5.70 (br s, 1 H), 5.00 (s, 1 H), 3.68 (s, 6 H), 2.37 (s, 6 H).

Dimethyl 4-(4-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7d)
Pale-yellow solid; mp 184–185 °C (Lit.[35] mp 181–183 °C).

IR (Nujol): 3345, 1694, 1650, 1303, 1271, 1212, 1174, 1121, 1094, 1049, 1026, 820 cm^{-1}.

^1H NMR: δ = 7.11 (d, *J* = 8.7 Hz, 2 H), 6.69 (d, *J* = 8.7 Hz, 2 H), 5.61 (br s, 1 H), 4.88 (s, 1 H), 3.69 (s, 3 H), 3.58 (s, 6 H), 2.27 (s, 6 H).

Diethyl 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7f)
Yellow solid; mp 131–132 °C (Lit.[36] mp 129–130 °C).

IR (Nujol): 3315, 1702, 1646, 1517, 1348, 1302, 1212, 1119, 1094, 1019, 824 cm^{-1}.

^1H NMR: δ = 8.01 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 5.65 (br s, 1 H), 5.04 (s, 1 H), 4.03 (m, 4 H), 2.30 (s, 6 H), 1.17 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7g)
Pale-yellow solid; mp 147–148 °C (Lit.[15] mp 144–146 °C).

IR (Nujol): 3354, 1695, 1650, 1334, 1298, 1213, 1169, 1086, 1015, 830 cm^{-1}.

^1H NMR: δ = 7.16 (d, *J* = 8.6 Hz, 2 H), 7.11 (d, *J* = 8.6 Hz, 2 H), 5.55 (br s, 1 H), 4.89 (s, 1 H), 4.03 (m, 4 H), 2.26 (s, 6 H), 1.15 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-(4-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7h)
Pale-yellow solid; mp 159–161 °C (Lit.[37] mp 159 °C).

IR (Nujol): 3339, 1690, 1649, 1301, 1253, 1213, 1121, 1088, 1030, 834 cm^{-1}.

^1H NMR: δ = 7.12 (d, *J* = 8.7 Hz, 2 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 5.48 (br s, 1 H), 4.87 (s, 1 H), 4.03 (m, 4 H), 3.69 (s, 3 H), 2.26 (s, 6 H), 1.15 (t, *J* = 7.1 Hz, 6 H).

Diethyl 2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7i)[38]
Pale-yellow solid, as a mixture of **7i** and **8i** (3.5:1), which was used without separation.

^1H NMR: δ= 5.18 (br s, 1 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 3.35 (s, 2 H), 2.27 (s, 6 H), 1.37 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-Methyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7j)
Colorless solid; mp 130–131 °C (Lit.[38] mp 131 °C).

IR (Nujol): 3343, 1697, 1641, 1493, 1299, 1224, 1099, 1061 cm^{-1}.

^1H NMR: δ = 5.41 (br s, 1 H), 4.13 (m, 4 H), 3.75 (q, *J* = 6.5 Hz, 1 H), 2.21 (s, 6 H), 1.24 (t, *J* = 6.9 Hz, 6 H), 0.90 (d, *J* = 6.5 Hz, 3 H).

Diethyl 4-Ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7k)
Pale-yellow solid; mp 111–112 °C (Lit.[39] mp 110 °C).

IR (Nujol): 3312, 1699, 1651, 1302, 1211, 1133, 1072, 999 cm^{-1}.

^1H NMR: δ = 5.48 (br s, 1 H), 4.11 (m, 4 H), 3.86 (t, *J* = 5.5 Hz, 1 H), 2.10 (s, 6 H), 1.29 (m, 2 H), 1.22 (t, *J* = 7.2 Hz, 6 H), 0.67 (d, *J* = 7.5 Hz, 3 H).

Diethyl 4-Isopropyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7l)
Yellow solid; mp 95–97 °C (Lit.[39] mp 97 °C).

IR (Nujol): 3342, 1694, 1650, 1298, 1216, 1089, 1049 cm^{-1}.

^1H NMR: δ = 5.42 (br s, 1 H), 4.12 (m, 4 H), 3.85 (d, *J* = 5.4 Hz, 1 H), 2.24 (s, 6 H), 1.53 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 6 H), 0.67 (d, *J* = 6.8 Hz, 6 H).

Diethyl 4-Benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7m)
Pale-yellow solid; mp 112–114 °C (Lit.[15] mp 114–116 °C).

IR (Nujol): 3330, 1694, 1656, 1299, 1241, 1214, 1099, 1054, 750, 699 cm^{-1}.

^1H NMR: δ = 7.07 (3 H), 6.93 (m, 2 H), 5.15 (br s, 1 H), 4.12 (d, *J* = 5.5 Hz, 1 H), 3.99 (m, 4 H), 2.51 (d, *J* = 5.5 Hz, 2 H), 2.11 (s, 6 H), 1.18 (t, *J* = 7.2 Hz, 6 H).

Microwave-Assisted Synthesis of Pyridines Using MnO_2; Diethyl 2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (8e); Typical Procedure
A mixture of **7e** (0.12 g, 0.36 mmol) and MnO_2 (0.32 g, 3.6 mmol) in CH_2Cl_2 (2 mL) was irradiated for 1 min at 100 °C in a CEM Discover monomodal microwave synthesizer at an initial power of 150 W. The mixture was allowed to cool, filtered though Celite and concentrated in vacuo to give pyridine **8e** (0.118 g, 99%) as a colorless solid; mp 63 °C (Lit.[25] mp 63–64 °C).

IR (Nujol): 1730, 1556, 1289, 1229, 1098, 1041, 754, 704 cm^{-1}.

^1H NMR: δ = 7.30–7.18 (m, 5 H), 3.94 (q, *J* = 7.1 Hz, 4 H), 2.53 (s, 6 H), 0.82 (t, *J* = 7.1 Hz, 6 H).

Dimethyl 2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (8a)
Colorless solid; mp 137 °C (Lit.[5] mp 135–136 °C).

IR (Nujol): 1732, 1556, 1288, 1113, 1036, 825 cm^{-1}.

^1H NMR: δ = 7.30 (3 H), 7.18 (m, 2 H), 3.46 (s, 6 H), 2.52 (s, 6 H).

Dimethyl 2,6-Dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (8b)
Pale-yellow solid; mp 150–152 °C (Lit.[23] mp 148 °C).

IR (Nujol): 1721, 1602, 1558, 1516, 1346, 1303, 1231, 1099, 1048, 834 cm^{-1}.

^1H NMR: δ = 8.19 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 3.50 (s, 6 H), 2.56 (s, 6 H).

Dimethyl 4-(4-Chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8c)
Colorless solid; mp 138–140 °C (Lit.[23] 137–139 °C).

IR (Nujol): 1731, 1556, 1241, 1211, 1098, 1039, 1019, 832 cm^{-1}.

^1H NMR: δ = 7.28 (d, *J* = 8.9 Hz, 2 H), 7.12 (d, *J* = 8.9 Hz, 2 H), 3.50 (s, 6 H), 2.53 (s, 6 H).

Dimethyl 4-(4-Methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8d)
Pale-yellow solid; mp 115–117 °C (Lit.[23] mp 115 °C).

IR (Nujol): 1731, 1609, 1562, 1513, 1292, 1245, 1180, 1111, 1030, 829 cm^{-1}.

^1H NMR: δ = 7.09 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 3.77 (s, 3 H), 3.51 (s, 6 H), 2.51 (s, 6 H).

Diethyl 2,6-Dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (8f)
Pale-yellow solid; mp 115–117 °C (Lit.[15] mp 114–116 °C).

IR (Nujol): 1723, 1601, 1556, 1518, 1349, 1295, 1230, 1105, 1045, 842 cm^{-1}.

^1H NMR: δ = 8.18 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 8.7 Hz, 2 H), 3.97 (q, *J* = 7.2 Hz, 4 H), 2.57 (s, 6 H), 0.92 (t, *J* = 7.2 Hz, 6 H).

Diethyl 4-(4-Chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8g)
Pale-yellow solid; mp 64–65 °C (Lit.[15] mp 65–67 °C).

IR (Nujol): 1731, 1556, 1231, 1103, 1044, 835 cm^{-1}.

^1H NMR: δ = 7.28 (d, *J* = 8.9 Hz, 2 H), 7.12 (d, *J* = 8.9 Hz, 2 H), 3.99 (q, *J* = 7.1 Hz, 4 H), 2.54 (s, 6 H), 0.91 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-(4-Methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8h)
Colorless solid; mp 49 °C (Lit.[37] mp 51–53 °C).

IR (Nujol): 1730, 1610, 1556, 1515, 1292, 1250, 1180, 1106, 1028, 832 cm^{-1}.

^1H NMR: δ = 7.13 (d, *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 3.97 (q, *J* = 7.1 Hz, 4 H), 3.75 (s, 3 H), 2.52 (s, 6 H), 0.93 (t, *J* = 7.1 Hz, 6 H).

Diethyl 2,6-Dimethylpyridine-3,5-dicarboxylate (8i)
Colorless solid; mp 72–73 °C (Lit.[18] mp 70–71 °C).

IR (Nujol): 1721, 1591, 1555, 1298, 1254, 1223, 1107, 1045, 772 cm^{-1}.

^1H NMR: δ = 8.60 (s, 1 H), 4.33 (q, *J* = 7.2 Hz, 4 H), 2.78 (s, 6 H), 1.34 (t, *J* = 7.2 Hz, 6 H).

Diethyl 2,6-Dimethyl-4-methylpyridine-3,5-dicarboxylate (8j)
Colorless oil.[25]

IR (film): 2981, 1727, 1567, 1446, 1285, 1220, 1106, 1042 cm^{-1}.

^1H NMR: δ = 4.34 (q, *J* = 7.1 Hz, 4 H), 2.46 (s, 6 H), 2.19 (s, 3 H), 1.32 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-Ethyl-2,6-dimethylpyridine-3,5-dicarboxylate (8k)
Colorless oil.[39]

IR (film): 2979, 1729, 1568, 1447, 1414, 1384, 1278, 1236, 1208, 1106, 1040, 860 cm^{-1}.

^1H NMR: δ = 4.34 (q, *J* = 7.1 Hz, 4 H), 2.52 (q, *J* = 7.6 Hz, 2 H), 2.45 (s, 6 H), 1.32 (t, *J* = 7.1 Hz, 6 H), 1.11 (t, *J* = 7.6 Hz, 3 H).

Acknowledgment

We thank the EPSRC for funding (GR/S41463 and GR/S25456) and Robert L. Jenkins for technical assistance.

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