An efficient transition-metal-chloride/sodium-nitrite/TEMPO catalytic system for aerobic oxidative aromatisation of Hantzsch 1,4-dihydropyridines

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A facile and efficient transition-metal-chloride/sodium-nitrite/TEMPO catalytic system for aerobic oxidative aromatisation of Hantzsch 1,4-dihydropyridines in high yields under mild conditions is described.

Keywords: Hantzsch 1,4-dihydropyridines, aerobic oxidative aromatisation, transition metal chloride, sodium nitrite, TEMPO

Hantzsch ester 1,4-dihydropyridines (1,4-DHPs) as NADPH coenzyme analogues have been used for the study of the mechanism of the *in vivo* redox reaction.[1] The oxidation of 1,4-DHPs provided a facile access to their corresponding pyridine derivatives, some of which show anti-hyperlipidemic, anti-hyperglyacemic and anti-cancer activities.[2,3]

The methodology of oxidative aromatisation of 1,4-DHPs had been investigated using different oxidants. Recently, synthetic chemists have paid more attention to developing more environmentally friendly syntheses, such as using graphite oxide,[4] 9-phenyl-10-methylacridinium/O_2,[5] $Fe(ClO_4)_3/O_2$,[6] $Co(OAc)_2/O_2$,[7] and activated charcoal/O_2.[8] In spite of the potential utility of these reagents, most methods for the synthesis of 1,4-DHPs and their subsequent aromatisation suffer from drawbacks such as long reaction time,[5] use of toxic reagents[7] and high temperature.[4,8] Therefore, the development of more effective methods for aromatisation of DHPs is still required.

Reactions of DHPs with TEMPO or other N-oxides alone need long reaction times and afford low yields.[9–11] However, there have been reports that the combination of TEMPO and some metallic and non-metallic elements with variable valency,[12–14] such as Cu(I)/Cu(II), N(II)/N(V) and Cl(I)/Cl(VII), was a good catalytic system for many oxidations. A similar system has been reported using $FeCl_3/NaNO_2$/TEMPO as a catalyst for the aerobic oxidation of alcohols to aldehydes and ketones.[15] According to the facts mentioned above, we thought that the Cu(I or II)/N(III or VI)/TEMPO catalytic system might be effective in the oxidative aromatisation of 1,4-DHPs.

A preliminary experiment was carried out using diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1a**) as a model substrate with $Cu(NO_3)_2$/TEMPO as catalyst in CH_3CN/CH_3COOH under an oxygen atmosphere (balloon). A very low conversion rate was observed (Table 1, entry 1). Then the oxidative aromatisation of **1a** was carried out using $Cu(NO_3)_2/NaNO_2$/TEMPO and $CuCl_2/NaNO_2$/TEMPO instead of $Cu(NO_3)_2$/TEMPO as a catalytic system (Table 1, entries 2 and 3). We were pleased to find that the reaction took place smoothly. The success of this reaction prompted us to study the catalytic system of multivalent metallic salt/$NaNO_2$/TEMPO. So, various multivalent inorganic metallic salts and solvents were scanned in order to find a desired catalytic system. During the screening of a variety of reaction solvents, we found that CH_3CN/CH_3COOH or AcOEt/CH_3COOH were suitable for efficient conversion of 1,4-DHPs under an oxygen atmosphere at ambient pressure and temperature. The results are summarised in Table 1 and show that **1a** is readily converted into **2a** (Scheme 1) in the presence of $FeCl_3$, $MnCl_2$, $NiCl_2$, $CuCl_2$ and other copper salts (Table 1, entries 2–7, 9 and 15), and addition of CH_3COOH significantly accelerates the speed of the reaction (Table 1, entries 15,16, 23 and 24). Apart from copper salts, transition metal chlorides proved to be superior to the corresponding nitrates and sulfates (Table 1, entries 7–10 and 13–15). Interestingly, the catalytic oxidation system runs ineffectively in the absence of any one component of the catalytic system (Table 1, entries 1, 2 and 25–27).

$FeCl_3$ seems to be the superior metal salt as it is safe, cheap and environmentally friendly, and CH_3CN/CH_3COOH are preferred solvents because CH_3CN dissolves some 1,4-DHPs more easily than EtOAc. Therefore, a model aerobic oxidation of Hantzsch 1,4-DHPs with $FeCl_3/NaNO_2$/TEMPO as the catalytic system and CH_3CN/CH_3COOH as the solvent is established.

In order to evaluate the scope and limitations of this reaction system, different substrates were tested. The results are summarised in Table 2 (Scheme 2).

As shown in Table 2, in most cases, many 1,4-DHPs can be converted efficiently into the corresponding pyridine derivatives with high yields at room temperature using oxygen as the terminal oxidant. In some cases, replacement of $FeCl_3$ by $CuCl_2$ significantly enhances the oxidation reactions (Table 2, entries 2 and 7).

A possible mechanism for this catalytic system is presented in Scheme 3, which is a sequential cascade of double-cycle redox reactions.[13,15] In the presence of a weak acid (HOAc), TEMPO could convert 1,4-DHPs to its corresponding pyridines and itself be reduced to TEMPOH.[9] Then TEMPOH is oxidised to TEMPO by M[ox.] (high-valent metal)/NO_2^-, and M[ox.]/NO_2^- is reduced to M[red.] (low-valent metal)/NO, and M[red.]/NO is re-oxidised to M[ox.]/NO_2^- by O_2, wherein NO_2^- is formed via rapid oxidation of NO with O_2 in the presence of a weak acid.

In conclusion, the oxidative aromatisation of substituted Hantzsch 1,4-DHPs was achieved efficiently by using molecular oxygen as the terminal oxidant source with $FeCl_3/NaNO_2$/TEMPO (in some cases, with $CuCl_2/NaNO_2$/TEMPO) as the catalysts at room temperature. The addition of acetic acid can greatly accelerate the speed of the reaction. In short, it is a facile, convenient and high-yielding catalytic system.

Experimental

Commercially available reagents were used without further purification unless mentioned. All reactions were monitored by TLC. Visualisation of TLC plates was accomplished with an UV lamp. The column chromatography was performed using silica gel (200–300 mesh) with ethyl acetate/hexane as eluent. Melting points were recorded on a X-4 micro melting point apparatus. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker Spectrospin 500 MHz spectrometer using tetramethylsilane (TMS) as internal standard. All 1,4-dihydropyridines were synthesised according to literature methods.[5,16–18] All products were known and their physical and spectroscopic data were compared with the literature.

Synthesis of compounds **2a-t***; general procedure*

1,4-DHPs (1 mmol, dissolved in 10 mL acetonitrile), TEMPO (0.05 mmol), $FeCl_3 \cdot 6H_2O$ (0.05 mmol), $NaNO_2$ (0.05 mmol) and

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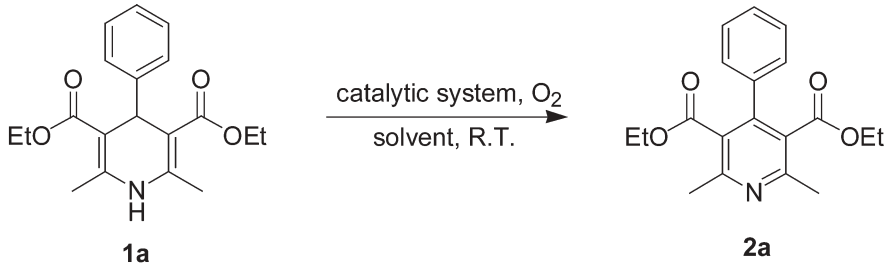
Table 1 Aromatisation of Hantzsch 1,4-dihydropyridines under different conditions[a]

Entry	Metal salt	TEMPO/mol%	$NaNO_2$/mol%	Solvent	Yield/%[b]
1	$Cu(NO_3)_2$	5	/	CH_3CN/CH_3COOH (5:1)	Trace
2	$Cu(NO_3)_2$	5	5	CH_3CN/CH_3COOH (5:1)	96
3	$CuCl_2$	5	5	CH_3CN/CH_3COOH (5:1)	96
4	$CuSO_4$	5	5	CH_3CN/CH_3COOH (5:1)	95
5	CuBr	5	5	CH_3CN/CH_3COOH (5:1)	95
6	CuCl	5	5	CH_3CN/CH_3COOH (5:1)	97
7	$MnCl_2$	5	5	CH_3CN/CH_3COOH (5:1)	97
8	$MnSO_4$	5	5	CH_3CN/CH_3COOH (5:1)	19
9	$NiCl_2$	5	5	CH_3CN/CH_3COOH (5:1)	95
10	$Ni(SO_4)_2$	5	5	CH_3CN/CH_3COOH (5:1)	15
11	$CoCl_2$	5	5	CH_3CN/CH_3COOH (5:1)	50
12	$CrCl_3$	5	5	CH_3CN/CH_3COOH (5:1)	20
13	$Fe_2(SO_4)_3$	5	5	CH_3CN/CH_3COOH (5:1)	26
14	$Fe(NO_3)_3$	5	5	CH_3CN/CH_3COOH (5:1)	40
15	$FeCl_3$	5	5	CH_3CN/CH_3COOH (5:1)	97
16[c]	$FeCl_3$	5	5	CH_3CN	92
17	$FeCl_3$	5	5	CH_2Cl_2/CH_3COOH (5:1)	30
18	$FeCl_3$	5	5	$EtOAc/CH_3COOH$ (5:1)	96
19	$FeCl_3$	5	5	CH_3COOH	19
20	$FeCl_3$	5	5	$EtOAc/H_2O/CH_3COOH$ (2.5:2.5:1)	15
21	$FeCl_3$	5	5	$AcOH/H_2O$ (1:1)	Trace
22	$FeCl_3$	5	5	$CH_3CN/H_2O/CH_3COOH$ (2.5:2.5:1)	20
23	$FeCl_3$	5	5	CH_3CN/conc. HCl (5:1)	36
24	$FeCl_3$	5	5	CH_3CN/HCOOH (5:1)	40
25	$FeCl_3$	/	5	CH_3CN/CH_3COOH (5:1)	Trace
26	$FeCl_3$	5	/	CH_3CN/CH_3COOH (5:1)	Trace
27	/	5	5	CH_3CN/CH_3COOH (5:1)	Trace
28[d]	$FeCl_3$	5	5	CH_3CN/CH_3COOH (5:1)	85
29[e]	$FeCl_3$	5	5	CH_3CN/CH_3COOH (10:1)	97

[a] General procedure: **1a** (0.5 mmol), metal salt (0.025 mmol), TEMPO (0.025 mmol), $NaNO_2$ (0.025 mmol), solvent (6 mL) at room temperature with an oxygen balloon for 1 h.
[b] Isolated yield.
[c] The reaction was completed in 10 h.
[d] 0.005 mmol $FeCl_3$ was used.
[e] CH_3CN (5ml) and CH_3COOH (0.5 mL) were used.



1a **2a**

Scheme 1 The oxidative aromatisation of **1a**.

CH_3COOH (1 mL) were added successively to a 25 mL three-necked round-bottom flask equipped with a magnetic stirrer and a thermometer. The resulting mixture was stirred at room temperature and ambient pressure with an oxygen balloon until the reaction was completed as monitored by TLC (5:1 ethyl acetate/petroleum ether as eluent). Saturated aqueous $NaHCO_3$ solution was added to make it neutral. The mixture was extracted with ethyl acetate three times. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (10:1 ethyl acetate/petroleum ether as eluent).

Diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (**2a**): Pale yellow solid, m.p. 60–61 °C (lit.[7] 61–62 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.36 (m, 3H), 7.27–7.25 (m, 2H), 4.01 (q, J = 7 Hz, 4H), 2.62 (s, 6H), 0.91 (t, J = 7 Hz, 6H).

Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (**2b**): Pale yellow solid, m.p. 69–70 °C (lit.[19] 69–70 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 4.41 (q, J = 7 Hz, 4H), 2.86 (s, 6H), 1.42 (t, J = 7 Hz, 6H).

Diethyl 4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2c**): Pale yellow oil (lit.[20] oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 2 Hz, 1H), 6.62 (d, J = 3 Hz, 1H), 6.48 (dd, J = 3 Hz, 2 Hz, 1H), 4.28 (q, J = 7 Hz, 4H), 2.58 (s, 6H), 1.23 (t, J = 7 Hz, 6H).

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2d**): Pale yellow solid, m.p. 64–65 °C (lit.[7] 65–66 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 4.04 (q, J = 7 Hz, 2H), 2.60 (s, 3H), 0.98 (t, J = 7 Hz, 3H).

Diethyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2e**): Pale yellow solid, m.p. 113–114 °C (lit.[20] 114–115 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, J = 9 Hz, 2H), 7.46 (d, J = 9 Hz, 2H), 4.04 (q, J = 7 Hz, 4H), 2.63 (s, 6H), 0.98 (t, J = 7 Hz, 6H).

Diethyl 4-(3-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2f**): Pale yellow oil (lit.[20] 62–63 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27–8.25 (m, 1H), 8.19–8.18 (m, 1H), 7.62–7.58 (m, 2H), 4.05 (q, J = 7 Hz, 4H), 2.63 (s, 6H), 1.00 (t, J = 7 Hz, 6H).

Dimethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (**2g**): Pale yellow solid, m.p. 99–100 °C (lit.[21] 99–100 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 3.94 (s, 6H), 2.86 (s, 6H).

Dimethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate (**2h**): Pale yellow solid, m.p. 76–77 °C (lit.[22] 78–80 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.94 (s, 6H), 2.52 (s, 6H), 2.26 (s, 3H).

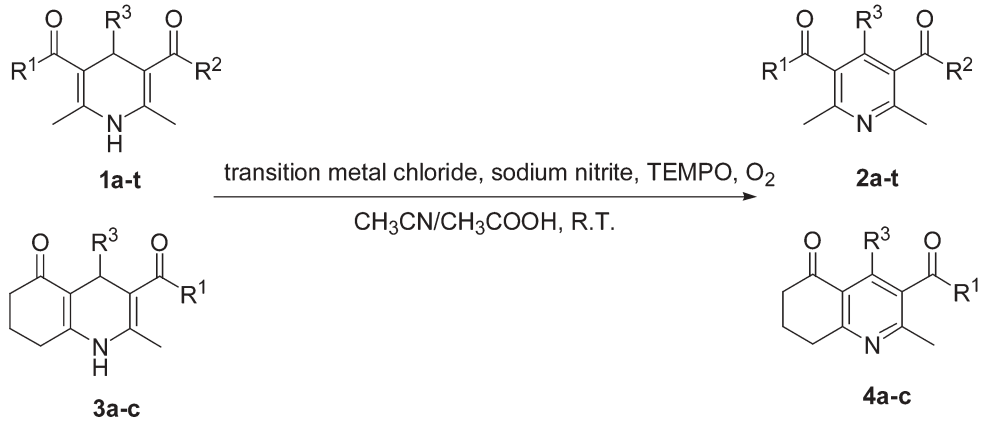
Dimethyl 4-propyl-2,6-dimethyl-3,5-pyridinedicarboxylate (**2i**): Pale yellow oil (lit.[23] oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 6H), 2.53–2.48 (m, 8H), 1.55–1.50 (m, 2H), 0.91 (t, J = 7 Hz, 3H).

Dimethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (**2j**): White solid, m.p. 133–134 °C (lit.[21] 134–136 °C). ^{1}H NMR (500 MHz,

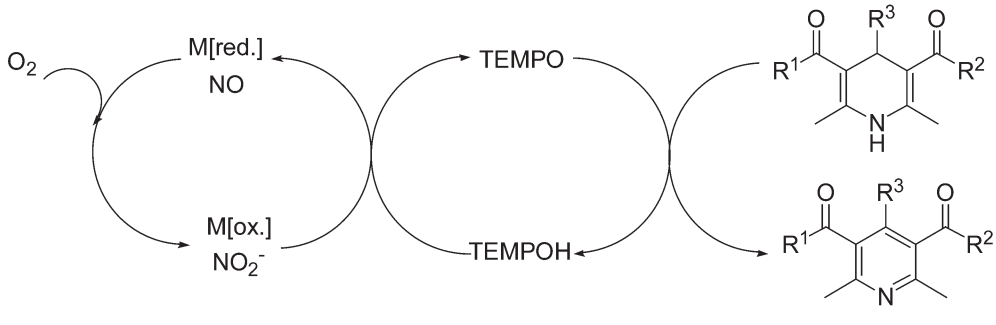
Table 2 Aromatisation of Hantzsch 1,4-dihydropyridines by transition metal chloride/sodium nitrite/TEMPO system[a]

Entry	Substrate	R^1	R^2	R^3	Time/min	Product	Yield/%[b]
1	**1a**	OEt	OEt	Ph	30	**2a**	97
2[c]	**1b**	OEt	OEt	H	30	**2b**	97(40)
3	**1c**	OEt	OEt	2-Furyl	30	**2c**	96
4	**1d**	OEt	OEt	*p*-ClC_6H_4	30	**2d**	98
5	**1e**	OEt	OEt	*p*-$NO_2C_6H_4$	50	**2e**	95
6	**1f**	OEt	OEt	*m*-$NO_2C_6H_4$	40	**2f**	98
7[c]	**1g**	OMe	OMe	H	30	**2g**	98(35)
8	**1h**	OMe	OMe	Me	30	**2h**	98
9	**1i**	OMe	OMe	*n*-Pr	40	**2i**	96
10	**1j**	OMe	OMe	Ph	30	**2j**	96
11	**1k**	OMe	OMe	2-Furyl	30	**2k**	94
12	**1l**	OMe	OMe	*p*-ClC_6H_4	30	**2l**	98
13	**1m**	OMe	OMe	*p*-$NO_2C_6H_4$	30	**2m**	98
14	**1n**	OMe	OMe	*m*-$NO_2C_6H_4$	50	**2n**	98
15	**1o**	OMe	OMe	*p*-PhC_4H_6	40	**2o**	97
16	**1p**	OMe	OMe	3,4-$(OCH_3)_2C_6H_4$	30	**2p**	97
17	**1q**	OMe	OMe	3,4-$(CH_2O_2)C_6H_3$	40	**2q**	93
18	**1r**	OMe	OEt	Ph	30	**2r**	98
19	**1s**	OMe	OEt	*p*-$NO_2C_6H_4$	50	**2s**	96
20	**1t**	OMe	OEt	*m*-$NO_2C_6H_4$	45	**2t**	97
21	**3a**	OEt		Ph	60	**4a**	92
22	**3b**	OEt		*p*-ClC_6H_4	60	**4b**	95
23	**3c**	OEt		*m*-$NO_2C_6H_4$	60	**4c**	90

[a]The reaction conditions were as follows: substrate (1 mmol), $FeCl_3$ (0.05 mmol), TEMPO (0.05mmol), $NaNO_2$ (0.05 mmol), CH_3CN (10 mL), CH_3COOH (1 mL) at Room temperature with an oxygen balloon for appropriate time.
[b]Isolated yield.
[c]The number on the outside of the parentheses is the isolated yield of the product with $CuCl_2$ as catalyst, and the one on the inside of the parentheses with $FeCl_3$ as catalyst.



Scheme 2 The oxidative aromatisation of many 1,4-DHPs.



Scheme 3 Proposed reaction mechanism.

$CDCl_3$): δ 7.39–7.37 (m, 3H), 7.25–7.23 (m, 2H), 3.54 (s, 6H), 2.61 (s, 6H).

Dimethyl 4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2k**): Pale yellow solid, m.p. 60–61 °C (lit.[21] 60–62 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 2 Hz, 1H), 6.61 (d, J = 3 Hz, 1H), 6.49 (dd, J = 3Hz, 2 Hz, 1H), 3.82 (s, 6H), 2.57 (s, 6H).

Dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2l**): Pale yellow solid, m.p. 138–140 °C (lit.[24] 137–139 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 3.58 (s, 3H), 2.60 (s, 3H).

Dimethyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2m**): Yellow solid, m.p. 147–148 °C (lit.[24] 148 °C). ^{1}H NMR

(500 MHz, $CDCl_3$): δ 8.27 (d, J = 9 Hz, 2H), 7.44 (d, J = 9 Hz, 2H), 3.57 (s, 6H), 2.64 (s, 6H).

Dimethyl 4-(3-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2n**): Pale yellow solid, m.p. 121–122 °C (lit.[25] 121 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28–8.26 (m, 1H), 8.17–8.16 (m, 1H), 7.60–7.59 (m, 2H), 3.60 (s, 6H), 2.63 (s, 6H).

Dimethyl 4-(4-biphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2o**): Yellow solid, m.p. 143–145 °C (lit.[26] 143–145 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65–7.63 (m, 4H), 7.49–7.32 (m, 5H), 3.58 (s, 6H), 2.62 (s, 6H).

Dimethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2p**): Pale yellow solid, m.p. 124–125 °C (lit.[27] 129–130 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, J = 8 Hz, 1H), 6.84–6.81 (m, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 3.61 (s, 6H), 2.59 (s, 6H).

Dimethyl 4-(3,4-methylenedioxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2q**): Pale yellow solid, m.p. 122–123 °C (lit.[27] 121–122 °C), ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (d, J = 8 Hz, 1H), 6.75 (d, J = 2 Hz, 1H), 6.71 (dd, J = 8 Hz, 2 Hz, 1H), 6.01 (s, 2H), 3.64 (s, 6H), 2.58 (s, 6H).

3-Ethyl 5-methyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (**2r**): Yellow solid, m.p. 64–65 °C. (lit.[28] 63.5–64.5 °C), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.37 (m, 3H), 7.26–7.24 (m, 2H), 4.01 (q, J = 7 Hz, 2H), 3.53 (s, 3H), 2.62 (s, 3H), 2.60 (s, 3H), 0.91 (t, J = 7 Hz, 3H).

3-Ethyl 5-methyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2s**):[29] Pale yellow solid, m.p. 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27–8.26 (m, 2H), 7.46–7.44 (m, 2H), 4.04 (q, J = 7 Hz, 2H), 3.57 (s, 3H), 2.64 (s, 3H), 2.63 (s, 3H), 0.99 (t, J = 7 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 167.66, 167.13, 156.32, 156.20, 147.86, 144.05, 143.27, 129.29, 126.22, 126.05, 123.28, 61.67, 52.40, 23.13, 13.70. HRMS *m/z* calcd for $C_{18}H_{18}N_2O_6$: 358.1165, found 358.1183.

3-Ethyl 5-methyl 4-(3-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2t**): Pale yellow oil (lit.[30] 59–61 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26–8.15 (m, 2H), 7.59–7.58 (m, 2H), 4.05 (q, J = 7 Hz, 2H), 3.58 (s, 3H), 2.62 (s, 3H), 2.61 (s, 3H), 0.99 (t, J = 7 Hz, 3H).

Synthesis of compounds **4a-c***; general procedure*

1,4-DHPs (1 mmol, dissolved in 10 mL acetonitrile), TEMPO (0.05 mmol), $FeCl_3{\cdot}6H_2O$ (0.05 mmol), $NaNO_2$ (0.05 mmol) and CH_3COOH (1 mL) were successively added to a 25 mL three-necked round-bottom flask equipped with a magnetic stirrer and a thermometer The resulting mixture was stirred at room temperature and ambient pressure with an oxygen balloon until the reaction was completed as monitored by TLC (3:1 ethyl acetate/petroleum ether as eluent). Saturated aqueous $NaHCO_3$ solution was added to make it neutral. The mixture was extracted with ethyl acetate three times. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, the crude product was recrystallised with alcohol.

Ethyl 4-phenyl-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**4a**): Pale yellow solid, m.p. 95–96 °C (lit.[5] 93–94 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.36 (m, 3H), 7.15–7.13 (m, 2H), 3.96 (q, J = 7 Hz, 2H), 3.21 (t, J = 6 Hz, 2H), 2.63–2.60 (m, 5H), 2.21–2.16 (m, 2H), 0.93 (t, J = 7 Hz, 3H).

Ethyl 4-(4-chlorophenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**4b**): Pale yellow solid, m.p. 149–150 °C (lit.[4] 151–152 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 4.01 (q, J = 7 Hz, 2H), 3.21 (t, J = 6 Hz, 2H), 2.63–2.60 (m, 5H), 2.21–2.16 (m, 2H), 0.99 (t, J = 7 Hz, 3H).

Ethyl 4-(3-nitrophenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**4c**): Pale yellow solid, m.p. 134–135 °C (lit.[5] 123–124 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26–8.24 (m,1H), 8.03 (t, J = 2 Hz, 1H), 7.58–7.47 (m, 2H), 4.00 (q, J = 7 Hz, 2H), 3.24 (m, 2H), 2.64–2.61 (m, 5H), 2.23–2.18 (m, 2H), 0.97 (t, J = 7 Hz, 3H).

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