Cu(I)-catalysed oxidative coupling of 2-aminopyridines with β-keto esters: synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates

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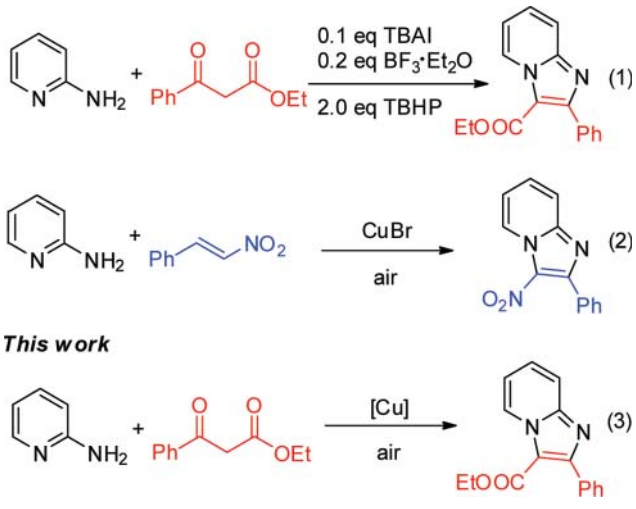
A simple, economical, and environmentally friendly copper-catalysed direct oxidative C–N coupling of 2-aminopyridines with β-keto esters using air as oxidation agent for the creation of imidazo[1,2-*a*]pyridine-3-carboxylates is demonstrated. Imidazo[1,2-*a*]pyridine is the basic skeleton for a wide range of biological and pharmacological compounds.

Keywords: imidazo[1,2-*a*]pyridine-3- carboxylates, 2-aminopyridines, β-keto esters, copper, oxidative coupling, green synthesis

The imidazo[1,2-*a*]pyridine moieties appear as basic skeletons in a wide range of biologically interesting and pharmacologically important compounds.[1–4] In addition, imidazo[1,2-*a*]pyridine derivatives have been widely used as fluorescent dyes.[5–8] Thus, considerable effort had been devoted towards the development of an efficient and green methodology for the synthesis of imidazo[1,2-*a*]pyridines.[9–18] Recently, it was reported that TBAI could catalyse the direct oxidative C–N coupling of 2-aminopyridines with β-keto esters and 1,3-diones to afford imidazo[1,2-*a*]pyridines using tert-butyl hydroperoxide (TBHP) as the oxidant [Scheme 1, Eqn (1)].[19] Although the TBAI/TBHP oxidising system was used instead of stoichiometric amounts of hypervalent iodine reagent,[18] the process still suffers from the use of moisture sensitive $BF_3{\cdot}Et_2O$ as the co-catalyst and TBHP as the oxidant, which could result in *t*-BuOH as a byproduct. On the other hand, Yan and co-workers[20] have developed an efficient method for the direct synthesis of 3-nitro-imidazo[1,2-*a*]pyridines from aminopyridines and nitro-olefins based on copper-catalysed single electron transfer (SET) processes using air as the oxidant [Scheme 1, Eqn (2)]. This method is excellent because air is the ideal oxidant due to its abundance, low cost, and lack of toxic byproducts and the copper-catalysts are inexpensive, readily available and easily handled. However, imidazo[1,2-*a*]pyridine-3-carboxylates, which are useful intermediates for the synthesis of pharmaceutically important compounds[21] were not synthesised using this appealing method. Here we report a green and facile synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates via copper-catalysed SET processes using air as the oxidant [Scheme 1, Eqn (3)].



Scheme 1

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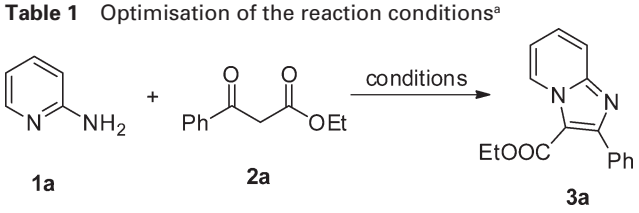
Initially, the oxidative coupling of 2-aminopyridine (**1a**) with ethyl 2-benzoylacetate (**2a**) was chosen as a model reaction and several copper (I) salts, such as CuCl, CuBr and CuI, (Table 1, entries 1–3) and copper (II) salts, such as $Cu(OAc)_2$, $Cu(OTf)_2$ and $CuCl_2$(Table 1, entries 4 and 5) were tested using DMF as solvent at 70 °C. CuI showed the highest activity for this reaction and resulted in 49% yield (Table 1, entries 3). Although the reaction time could be significantly shortened to 30 h when O_2 was employed as oxidant, the yield was not increased. Thus, air was chosen as the oxidant for its abundance, low cost, and convenience. Other solvents, such as CH_3CN, $MeNO_2$, dioxane and DMA proved to be less effective for the reaction (Table 1, entries 9–12). Furthermore, the yield decreased when the temperature was changed to 80 or 60 °C (Table 1, entries 13 and 14).

Various substituted 2-aminopyridines and β-keto esters were investigated using CuI as a catalyst in DMF. The results are listed in Table 2. 2-Phenyl-imidazo[1,2-*a*]pyridine-3-carboxylates were prepared in moderate yield when 3-, 4- and 5-methyl substituted 2-aminopyridines were used as substrates. In contrast, when 4-chloro-2-aminopyridine was used as substrate, only 10% of the desired product was obtained (Table 2, entry 5). On the other hand, methyl, chloro and methoxyl groups in the *para* position of β-keto esters have no significant influence on the reaction.

On the basis of Yan's study[20] and the above experimental results, a mechanism for the reaction is proposed (Scheme 2). Enamination of β-keto esters **2** with 2-aminopyridines **1** affords

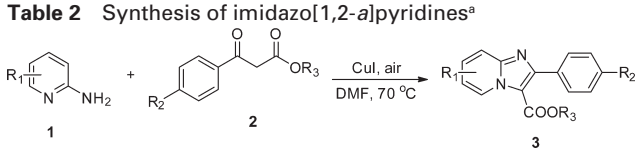
Table 1 Optimisation of the reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Temp./°C	Time/h	Yield/%[b]
1	CuCl	Air	DMF	70	60	11
2	CuBr	Air	DMF	70	60	18
3	CuI	Air	DMF	70	60	49
4	$Cu(OTf)_2$	Air	DMF	70	60	6
5	$Cu(OAc)_2$	Air	DMF	70	60	13
6	$CuCl_2$	Air	DMF	70	60	15
7	CuI	O_2	DMF	70	30	48
9	CuI	Air	MeCN	70	60	27
10	CuI	Air	$MeNO_2$	70	60	Trace
11	CuI	Air	dioxane	70	60	22
12	CuI	Air	DMA	70	60	Trace
13	CuI	Air	DMF	80	60	40
14	CuI	Air	DMF	60	60	30

[a] Reaction conditions: **1a** (0.60 mmol), **2a** (0.50 mmol), catalysts (0.05 mmol), 2 mL of solvent, in an open tube. [b] Isolated yield based on **2a**.

Table 2 Synthesis of imidazo[1,2-*a*]pyridines[a]



Entry	R_1	R_2	R_3	Product	Yield/%[b]
1	**1a**, H	**2a**, H	Et	**3a**	49
2	**1b**, 3-Me	**2a**, H	Et	**3b**	32
3	**1c**, 4-Me	**2a**, H	Et	**3c**	28
4	**1d**, 5-Me	**2a**, H	Et	**3d**	38
5	**1e**, 4-Cl	**2a**, H	Et	**3e**	10
6	**1a**, H	**2b**, MeO	Et	**3f**	41
7	**1b**, 3-Me	**2b**, MeO	Et	**3g**	34
8	**1d**, 5-Me	**2b**, MeO	Et	**3h**	34
9	**1a**, H	**2c**, Me	Et	**3i**	53
10	**1d**, 5-Me	**2c**, Me	Et	**3j**	42
11	**1a**, H	**2d**, Cl	Me	**3k**	45

[a] Reaction conditions: **1** (0.60 mmol), **2** (0.50 mmol), CuI (0.05 mmol), 2 mL of DMF, in an open tube at 70 °C for 60 h. [b] Isolated yield based on **2**.

β-enamino esters **I**, which undergo one-electron oxidation with a copper catalyst to form intermediate **II**. Then hydride abstraction with oxidation forms intermediate **III**. Finally, intramolecular nucleophilic addition of intermediate **III** to intermediate **IV** and the subsequent proton elimination gives product **3**.

In conclusion, we have developed a direct Cu(I)-catalysed one-pot method for the synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates with aminopyridines and β-keto esters under air. The procedure, using air as the oxidative agent, is a simple, economical and environmentally friendly protocol for the synthesis of imidazo-[1,2-*a*]pyridines-carboxylates.

Experimental

Melting points were measured on a Büchi B-545. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AVANCE III 500 (500 MHz) instrument in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) were reported in ppm and coupling constants *J* are given in Hz. ESI–MS spectra were determined on a LCQ Deca XP Plus ion-trap mass spectrometer, Commercially obtained reagents were used without further purification.

Synthesis of imidazo[1,2-a]pyridines (**3**)*; typical procedure*

A mixture of **1** (0.60 mmol), **2** (0.50 mmol), and CuI (9.5 mg, 0.05 mmol) in DMF (2 mL) was stirred at 70 °C under air for 60 h. After the mixture was cooled to room temperature, the resulting mixture was diluted with ethyl acetate (15 mL) and filtered through celite. The filtrate was washed with brine (10mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the residues were purified by column chromatography, eluting with petroleum ether/EtOAc to give pure **3**.

*Ethyl 2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate* (**3a**): White solid, m.p. 65–66 °C (lit.[19] 66–67 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (d, *J* = 7.0 Hz, 1H), 7.87–7.65 (m, 3H), 7.54–7.34 (m, 4H), 7.04 (td, *J* = 6.9, 1.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 153.6, 147.1, 134.5, 130.2, 128.7, 128.4, 127.9, 127.5, 117.5, 114.1, 112.0, 60.4, 14.0.

*Ethyl 8-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate* (**3b**): White solid, m.p. 110–111 °C (lit.[19] 113–114 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, *J* = 6.9 Hz, 1H), 8.11–7.70 (m, 2H), 7.57–7.34 (m, 3H), 7.29–7.16 (m, 1H), 6.93 (t, *J* = 7.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.68 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 153.1, 147.3, 134.9, 130.2, 128.5, 127.5, 126.7, 126.0, 114.0, 112.4, 60.3, 17.1, 13.9.

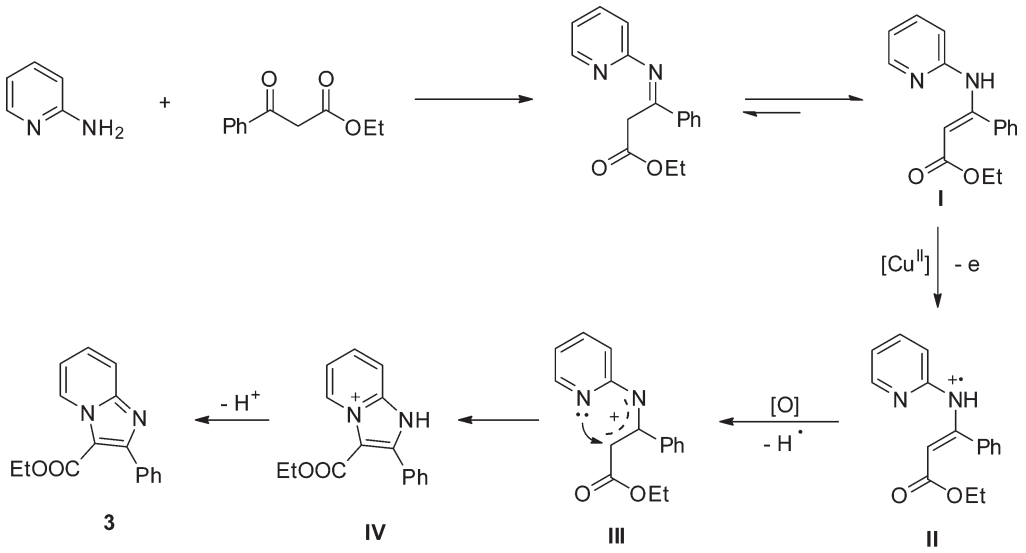
*Ethyl 7-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate* (**3c**): White solid, m.p. 89–90 °C (lit.[19] 90–91 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 7.1 Hz, 1H), 7.76 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.50 (s, 1H), 7.42 (d, *J* = 6.6 Hz, 3H), 7.26 (s, 1H), 6.87 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 153.6, 147.5, 139.4, 134.6, 130.2, 128.6, 127.5, 116.6, 116.1, 111.5, 60.3, 21.4, 14.0.

*Ethyl 6-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate* (**3d**): White solid, m.p. 71–72 °C (lit.[19] 72–74 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.75 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.46–7.38 (m, 3H), 7.29 (dd, *J* = 9.1, 1.5 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 153.3, 146.1, 134.6, 130.9, 130.2, 128.6, 127.5, 126.2, 124.0, 116.7, 111.7, 60.4, 18.5, 14.0.

*Ethyl 6-chloro-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate* (**3e**): White solid, m.p. 116–117 °C (lit.[19] 117–119 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, 1H, *J* = 1.1 Hz), 7.75–7.73 (m, 2H), 7.67 (d, 1H, *J* = 9.3 Hz), 7.45–7.39 (m, 4H), 4.31 (q, 2H, *J* = 7.1 Hz), 1.22 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 154.1, 145.4, 134.1, 130.2, 129.3, 129.0, 127.7, 126.4, 122.5, 117.8, 112.4, 60.8, 14.0.

*Ethyl 2-(4-methoxyl-phenyl)imidazo[1,2-*a*]pyridine-3-carboxylate* (**3f**): White solid, m.p. 78–79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (d, *J* = 7.0 Hz, 1H), 7.76 (dd, *J* = 12.1, 5.4 Hz, 3H), 7.47–7.41 (m, 1H), 7.03 (td, *J* = 6.9, 1.0 Hz, 1H), 7.00–6.94 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 160.1, 153.4, 147, 1, 131.6, 128.4, 127.8, 126.8, 117.3, 113.8, 113.0, 111.6, 60.4, 55.3, 14.1. HRMS Calcd for $C_{17}H_{16}N_2O_3$ $[M+H]^+$: 297.1239. Found: 297.1232.

*Ethyl 8-methyl-2-(4-methoxyl-phenyl)imidazo[1,2-*a*]pyridine-3-carboxylate* (**3g**): White solid, m.p. 88–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 6.9 Hz, 1H), 7.76–7.71 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.00–6.94 (m, 2H), 6.91 (t, *J* = 7.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.67 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C



Scheme 2 Plausible reaction mechanism.

NMR (125 MHz, $CDCl_3$) δ 161.3, 160.0, 152.9, 147.3, 131.6, 127.2, 126.7, 126.1, 113.8, 113.0, 112.0, 60.3, 55.3, 17.0, 14.1. HRMS Calcd for $C_{18}H_{18}N_2O_3$ $[M+H]^+$: 311.1396. Found: 311.1387.

*Ethyl 6-methyl-2-(4-methoxyl-phenyl)imidazo[1,2-*a*]pyridine-3-carboxylate* (**3h**): White solid, m.p. 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.29 (d, *J* = 0.9 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 2.42 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 160.1, 153.1, 146.1, 131.6, 130.8, 127.0, 126.3, 123.8, 116.5, 113.0, 111.3, 60.3, 55.3, 18.5, 14.1. HRMS Calcd for $C_{18}H_{18}N_2O_3$ $[M+H]^+$: 311.1396. Found: 311.1386.

*Ethyl 2-(4-methyl-phenyl)imidazo[1,2-*a*]pyridine-3-carboxylate* (**3i**): White solid, m.p. 86–88 °C (lit.[21] 90–93 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, *J* = 7.0 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.44 – 7.39 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.01 (td, *J* = 6.9, 1.0 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 153.8, 147.1, 138.6, 131.5, 130.1, 128.3, 128.2, 127.8, 60.4, 21.4, 14.1. HRMS Calcd for $C_{17}H_{16}N_2O_2$ $[M+H]^+$: 281.1290. Found: 281.1286.

*Ethyl 6-methyl-2-(4-methyl-phenyl)imidazo[1,2-*a*]pyridine-3-carboxylate* (**3j**): Lxq110: White solid, m.p. 84–86 °C (lit.[21] 73–75 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (d, *J* = 0.6 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.27 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 153.5, 146.1, 138.4, 131.7, 130.8, 130.1, 128.2, 126.2, 123.8, 116.6, 111.5, 60.3, 21.4, 18.5, 14.1. HRMS Calcd for $C_{18}H_{18}N_2O_2$ $[M+H]^+$: 295.1447. Found: 295.1434.

*Methyl 2-(4-chloro-phenyl)imidazo[1,2-*a*]pyridine-3-carboxylate* (**3k**): White solid, m.p. 129–130 °C (lit.[19] 130–132 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (dd, 1H, *J* = 6.7 Hz, *J* = 1.1 Hz), 7.70 (d, 3H, *J* = 8.3 Hz), 7.39–7.44 (m, 3H), 7.02 (dt, 1H, *J* = 6.7 Hz, *J* = 1.1 Hz), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 152.4, 147.2, 134.8, 132.9, 131.4, 128.4, 128.2, 127.9, 117.5, 114.3, 111.7, 51.3.

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