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A one-pot synthesis of imidazo[1,5-*a*]pyridines

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ABSTRACT

A one-pot synthesis of imidazo[1,5-*a*]pyridines starting from a carboxylic acid and 2-methylaminopyridines allowing introduction of various substituents at the 1- and 3-positions is achieved using propane phosphoric acid anhydride in ethyl or *n*-butyl acetate at reflux.

The imidazo[1,5-*a*]pyridines are an important class of heterocyclic compounds owing to their photophysical and biological properties. They have found utility in a number of areas of research including potential applications in organic light-emitting diodes (OLED)[1] and thin-layer field effect transistors (FET).[2] In addition they have been investigated in a wide range of potential pharmaceutical applications, including HIV-protease inhibitors,[3] and Thromboxane A_2 synthesis inhibitors.[4] Therefore, a widely applicable and convenient method for the synthesis of this ring system would be of interest. Existing synthetic routes target the imidazo[1,5-*a*]pyridines from the corresponding *N*-2-pyridylmethylamides with Filmier-type cyclisations[5] and strong acid condensations.[3] Alternative methods include the cyclisation of *N*-2-pyridylmethyl thioamides with DCC,[6] mercury(II) acetate,[7] or more recently, iodine.[8]

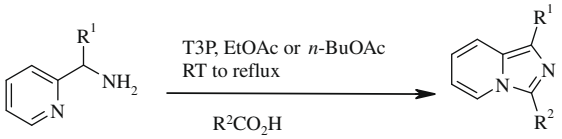
Herein we report a new and simple one-pot procedure to access imidazo[1,5-*a*]pyridines starting from carboxylic acids and 2-methylaminopyridines using propane phosphoric acid anhydride (T3P®) in ethyl or *n*-butyl acetate.

The general synthetic route is outlined in Scheme 1 and can be regarded as amide formation followed by dehydration. Propane phosphoric acid anhydride (T3P®) has been widely used in peptide and amide synthesis;[9] however, it can also act as a water scavenger and has been used in the synthesis of nitriles from either a primary amide, or a carboxylic acid and ammonium chloride directly.[10] We envisaged that these two properties could be combined to provide a concise one-pot route to imidazo[1,5-*a*]pyridines and our initial experiments demonstrated that a one-pot approach to this ring system was feasible.

Reaction of 2-methylaminopyridine and benzoic acid in ethyl acetate at reflux furnished 3-phenyl-imidazo[1,5-*a*]pyridine **1** in 76% isolated yield, albeit requiring an extended reaction time, (Table 1). To address this the reaction was repeated running at a higher temperature using *n*-butyl acetate as solvent. This gave 3-phenyl-imidazo[1,5-*a*]pyridine **1** in an improved 85% isolated yield, but more importantly, a greatly reduced reaction time of 18 h. In order to confirm that the final ring closing dehydration was mediated by T3P® and not just a thermal process, a control experiment was undertaken (Scheme 2). *N*-Pyridin-2-ylmethyl-benzamide **13** was prepared via a standard amide coupling reaction. Subsequent heating at reflux in *n*-butyl acetate for 24 h and monitoring by LC–MS showed no reaction. Addition of 1.5 equiv of T3P® to the reaction and heating for a further 24 h, gave 3-phenyl-imidazo[1,5-*a*]pyridine **1** in 82% isolated yield. Turning our attention to the scope of the reaction, a number of experiments with different substrates were carried out (Table 1).[11] The reaction appears very general, with not only alkyl groups, compounds **1–5**, but also heterocyclic groups being well tolerated, products **9–12**.

It is interesting to note that an imidazole moiety required no protection and gave a reasonable yield of 3-(1*H*-imidazol-2-yl)-imidazo[1,5-*a*]pyridine **12**. The methyl ester **6** also gave a good yield with no sign of hydrolysis, indicating the mild nature of the conditions. The reaction could also be performed using quinolin-2-yl-methylamines to furnish the imidazo[1,5-*a*]quinoline ring system in products **14** and **15** in good yield (Table 2).

In conclusion, we have presented a new and efficient one-pot synthesis of the imidazo[1,5-*a*]pyridine and imidazo[1,5-*a*]quinoline ring systems in good yields which allows the introduction of various substituents at the 1 and 3 positions. We are presently expanding the scope of the reaction to other ring systems.



Scheme 1.

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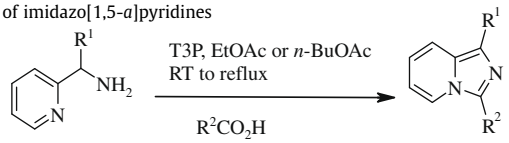
Table 1
Synthesis of imidazo[1,5-*a*]pyridines



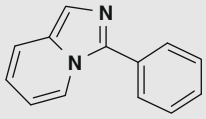
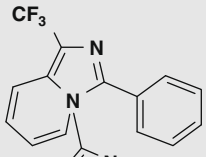
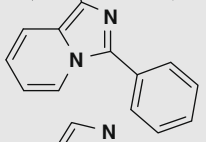
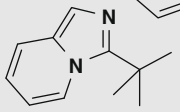
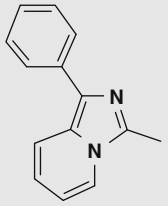
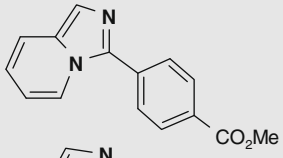
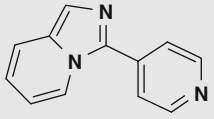
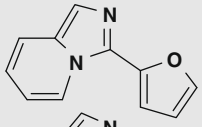
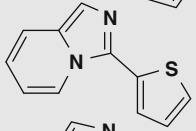
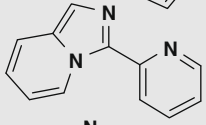
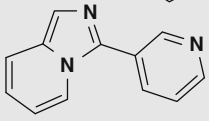
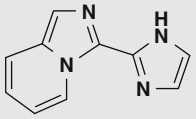
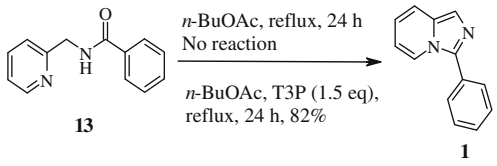
Entry	R^1	R^2	Product	Time/yield[a] (%)
1	H	Ph	**1** 	96 h/76[b] 18
2	CF_3	Ph	**2** 	h/85[c] 24 h/33[c]
3	Me	Ph	**3** 	3 h/88[c]
4	H	*t*-Bu	**4** 	18 h/88[c]
5	Ph	Me	**5** 	3 h/82[c]
6	H	*p*-$MeCO_2Ph$	**6** 	48 h/60[b]
7	H	4-py	**7** 	18 h/72[c]
8	H	2-Furan	**8** 	24 h/75[c]
9	H	2-Thienyl	**9** 	5 h/78[c]
10	H	2-py	**10** 	18 h/72[c]
11	H	3-py	**11** 	18 h/67[c]

Table 1 (*continued*)

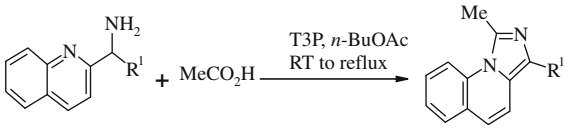
Entry	R^1	R^2	Product	Time/yield[a] (%)
12	H	2-Imid	**12** 	17 h/52[c]

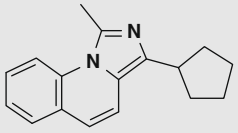
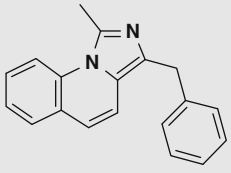
[a] Isolated yield.
[b] T3P® was added to a suspension of the 2-methylaminopyridine and acid in EtOAc at rt and then the mixture was heated at reflux.
[c] *n*-BuOAc was used as solvent.



Scheme 2. Control experiment.

Table 2
Synthesis of imidazo[1,5-*a*]quinolines



Entry	R^1	Product	Time/yield[a] (%)
1	*c*-Pent	**14** 	3 h/73[b]
2	Bn	**15** 	3 h/66[b]

[a] Isolated yield.
[b] *n*-BuOAc was used as solvent.

Acknowledgements

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References and notes

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11. *General procedure for the synthesis of imidazo[1,5-a]pyridines*. To a solution of 2-methylaminopyridine (500 mg, 4.6 mmol) in *n*-butyl acetate (25 ml) at rt was added 3-pyridinecarboxylic acid (588 mg, 5.3 mmol). To the resulting slurry was added T3P® (Aldrich 50% solution in EtOAc, 7.5 ml), and after complete addition, the solution was stirred at rt for 1 h, before being heated at reflux for 17 h. The cooled reaction mixture was washed with saturated sodium bicarbonate solution (2×30 ml), the organic phase dried ($MgSO_4$) and concentrated in vacuo to a colourless oil. The residue was purified by flash chromatography over silica gel to yield 3-pyridin-3-yl-imidazo[1,5-*a*]pyridine **11** (600 mg, 67%).^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, t, J = 6.8 Hz) 6.79 (1H, dd, J = 9.2, 6.4 Hz) 7.47 (1H, dd, J = 8.0, 4.9 Hz) 7.54 (1H, d, J = 9.0 Hz) 7.62 (1H, s) 8.12–8.16 (1H, m) 8.26 (1H, d, J = 7.0 Hz) 8.68 (1H, dd, J = 4.7, 1.6 Hz) 9.10 (1H, d, J = 2.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.7, 119.1, 119.6, 121.0, 121.8, 124.1, 127.0, 132.3, 135.4, 148.7, 149.8 ppm. HR-MS (ESI) *m/z* 196.0875 $[M+H]^+$. Calcd for $C_{12}H_{10}N_3$ *m/z* 196.0873.