



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

James M. Crawforth^{a,*}, Melissa Paoletti^b

^a Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

^b University of Camerino, Department of Chemical Sciences, Via S. Agostino, 162032 Camerino (MC), Italy

ARTICLE INFO

Article history:

Received 8 April 2009

Revised 1 June 2009

Accepted 12 June 2009

Available online 16 June 2009

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.

© 2009 Elsevier Ltd. All rights reserved.

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 A₂ 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 Fimier-type cyclisations⁵ 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.

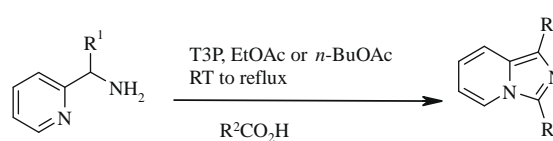
The general synthetic route is outlined in Scheme 1 and can be regarded as amide formation followed by dehydration. Propane phosphoric acid anhydride (T3P[®]) has been widely used in peptide and amide synthesis;⁹ however, it can also act as a water scavenger and has been used in the synthesis of nitriles 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 high-

er 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-ylmethylbenzamide **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.

* Corresponding author. Tel.: +44 1304649703.

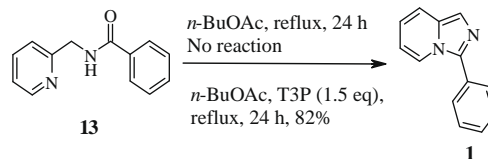
E-mail address: james.m.crawforth@pfizer.com (J.M. Crawforth).

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

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

Table 1 (continued)

Entry	R ¹	R ²	Product	Time/yield ^a (%)
12	H	2-Imid		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	<i>c</i> -Pent		3 h/73 ^b
2	Bn		3 h/66 ^b

^a Isolated yield.^b *n*-BuOAc was used as solvent.**Acknowledgements**

We thank Mr. Cris Laphorn for HR-MS analysis.

References and notes

- (a) Nakatsuka, M.; Shimamura, T. Jpn. Kokai Tokkyo JP 2001035664, 2001; *Chem Abstr.* **2001**, *134*, 170632; (b) Tominaga, T.; Kohama, T.; Takano, A. Jpn. Kokai Tokkyo JP 2001006877, 2001; *Chem Abstr.* **2001**, *134*, 93136; (c) Kitasawa, D.; Tominaga, T.; Takano, A. Jpn. Kokai Tokkyo JP 2001057292, 2001; *Chem Abstr.* **2001**, *134*, 200276.
- Nakamura, H.; Yamamoto, H.; PCT Int. Appl. WO 2005043630, 2005; *Chem Abstr.* **2005**, *142*, 440277.
- Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.
- Ford, F. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.

- Wasley, J. W. F. *J. Med. Chem.* **1985**, 28, 164.
- (a) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834; (b) Zimmer, H.; Glasgow, D. G.; McClanahan, M.; Novinson, T. *Tetrahedron Lett.* **1968**, 24, 2805.
 - Bourdais, J.; Omar, A. M. E. *J. Heterocycl. Chem* **1980**, 17, 555.
 - Moulin, A.; Garcia, S.; Martinez, J.; Fehrentz, J. *Synthesis* **2007**, 2667.
 - Shibahara, F.; Kiagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, 8, 5621.
 - Bernhagen, W. *Chim. Oggi* **1994**, 12, 9.
 - Meudt, A.; Scherer, S.; Nerdinger, S.; PCT Int. Appl. WO 2005070879, 2005; *Chem. Abstr.* **2005**, 143, 172649.
 - 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 (MgSO₄) 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%). ¹H NMR (400 MHz, CDCl₃) 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. ¹³C NMR (100 MHz, CDCl₃) 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 C₁₂H₁₀N₃ *m/z* 196.0873.