

Fast and efficient direct conversion of 2-aminopyridine into 2,3-disubstituted imidazo[1,2-*a*]pyridines

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Abstract

A direct conversion of 2-aminopyridine into 2,3-disubstituted imidazo[1,2-*a*]pyridines was studied. A series of products was obtained in an efficient, simple and fast protocol. The scope and limitation of the transformation are also studied and was found that its effectiveness and the type of the substituent at 3-position, 3-(1-arylethane) and/or 3-(1-arylethene), is strongly dependent both on the catalyst and on the ketone aromatic substituent. The structures of the products were assigned by 1D and 2D NMR spectra and confirmed by X-ray analyses of selected samples.

Keywords: Imidazo[1,2-*a*]pyridines, 3-(1-arylethane) substituted, 3-(1-arylethene) substituted, NMR, X-ray

Introduction

Imidazo[1,2-*a*]pyridines are a class of *N*-bridged fused bicyclic compounds, which attracted significant attention in recent years due to the broad spectrum of pharmacological profiles displayed. For instance, such molecules have exhibited antiviral,¹ antimicrobial,² antitumor,³ anti-inflammatory,⁴ antiparasitic,⁵ hypnotic,⁶ and many other activities. In general, these profiles are shown to be strongly dependent on the nature of substituents at 2 and 3 positions.⁷

A number of methods have been developed for the synthesis of this important framework; the most exploiting 2-aminopyridine as starting material. The main part of the protocols involves initial coupling reactions between endocyclic nitrogen of 2-aminopyridine and various reagents, such as α -halocarbonyl compounds,⁸ diazoketones,⁹ oxothioamide,¹⁰ 1,2-diols,¹¹ 1-chloromethylbenzotriazole,¹² 1,2-bis(benzotriazolyl)-1,2-(dialkylamino)-ethanes,¹³ followed by

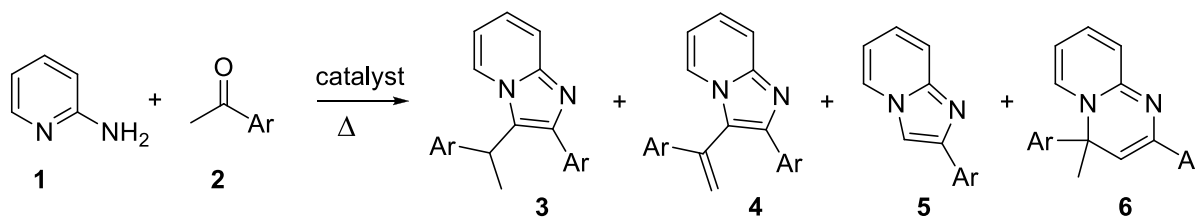
cyclization with the exocyclic amino group. However, these approaches generally suffer from such drawbacks as low yields and difficultly obtainable starting materials involving tedious workup procedures. More versatile procedures, allowing efficient preparation of compounds with variable substitution patterns, involve multi-component coupling transformations of 2-aminopyridine with aldehyde and unsaturated reagents, like isocyanides,¹⁴ nitrile,¹⁵ thiocyanates,¹⁶ alkynes,¹⁷ etc.

The reversed sequence, initial attack on the much less reactive exocyclic amino group and subsequent interaction with the endocyclic nitrogen, has also been applied. Whereas the reaction with aldehydes leading to 3-substituted products *via* aldimines is poorly studied,¹⁸ to the best of our knowledge, no records describe the preparation of 2,3-disubstituted compounds *via* ketimines.

Herein, we present a fast and simple efficient protocol for direct conversion of 2-aminopyridine into 2,3-disubstituted imidazo[1,2-*a*]pyridines. The scope and limitation of the transformation are also discussed.

Results and Discussion

A direct conversion of 2-aminopyridine into 2,3-disubstituted imidazo[1,2-*a*]pyridines was studied. A set of acetophenones was chosen in an attempt to examine the influence of different type of substituents on the transformation. Harsh conditions were applied in order to override the low reactivity of the exocyclic nitrogen. Numerous procedures for azomethine synthesis were tested with acetophenone, such as azeotropic distillation with Dean-Stark trap or in the presence of various watertrapping agents or catalysts. Insufficient results were obtained in all cases; up to 16% yields of imidazopyridine **3a**, in parallel with the corresponding azomethine and starting materials. Finally, effective conversion was achieved by using 5-fold excess of ketone in a solvent-free protocol at 200-220 °C in the presence of an acid catalyst. The efficiency of various acids was checked and was found that acetic and trifluoroacetic acid do not catalyze the transformation significantly, while *p*-toluenesulfonic and sulfuric acid lead to considerable conversion of 2-aminopyridine to **3a**. As shown on Scheme 1, three types of imidazopyridines differing at the substitution at 3-position were obtained depending both on the catalyst and on the ketone aromatic substituents.



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

As seen on Table 1, good conversions, 70-79%, were achieved in *p*-toluenesulfonic acid catalyzed reaction with acetophenone (entry 1), 4-methylacetophenone (entry 3) and 4-fluoroacetophenone (entry 4). The transformation proceeded very fast and clean, only single products and starting ketones were detected by TLC within 30-45 min. The compounds were easily purified by chromatography due to the substantial differences between their R_f -values and those of the ketones. The recovered acetophenones can be efficiently reused, which represent an additional advantage of the protocol. Contrary to *p*-toluenesulfonic acid catalyzed reaction, the sulfuric acid catalyzed transformation of acetophenone (entry 2) led to a mixture of imidazopyridines **3a** and **4a** in excellent total yield.

Table 1. Synthesis of imidazo[1,2-*a*]pyridines **3**, **4** and **5** and pyrido[1,2-*a*]pyrimidine **6**

Entry	Ar	Catalyst	Temperature, °C	Reaction time, min	Product, % isolated yield			
					3	4	5	6
1	Ph	<i>p</i> -TSA	210	45	76	-	-	-
2	Ph	H ₂ SO ₄	210	30	70	17	-	-
3	4-MeC ₆ H ₄	<i>p</i> -TSA	220	30	79	-	-	-
4	4-FC ₆ H ₄	<i>p</i> -TSA	200	45	70	-	-	-
5	1-naphthyl	<i>p</i> -TSA	220	45	39	-	-	-
6	1-naphthyl	<i>p</i> -TSA	300	30	48	-	-	-
7	4-OMeC ₆ H ₄	<i>p</i> -TSA	200	30	6	-	-	-
8	4-OMeC ₆ H ₄	<i>p</i> -TSA	220	30	23	14	28	-
9	4-OMeC ₆ H ₄	H ₂ SO ₄	200	30	13	10	13	-
10	4-NO ₂ C ₆ H ₄	<i>p</i> -TSA	150	50	-	-	-	4
11	4-NO ₂ C ₆ H ₄	H ₂ SO ₄	200	15	-	10	-	-

The reaction with sterically hindered aceto-1-naphthone led to **3d** formation as a sole product when *p*-toluenesulfonic acid was used, while complex mixture was obtained with sulfuric acid. The reaction conditions were varied and were found that higher temperature is required to override the steric factor; 39% yield of **3d** after 45 min heating at 220 °C vs 48% after 30 min heating at 300 °C (entry 5 vs entry 6).

In the case of 4-methoxyphenyl ketone, complex reaction mixtures were formed. The conditions were varied and were found that no conversion occurred at 150 °C even after 2-4 h. Methoxy derivative **3e** was obtained as a sole product, although in very poor yield (entry 7), after heating at 200 °C in the presence of *p*-toluenesulfonic acid in consecutive 15 min intervals in a pear-shaped flask. When increased the temperature to 220 °C (entry 8) or used round bottom flask, **3e** was obtained in better yield but together with two additional compounds, which structures were assigned by NMR spectra as 3-(1-arylethene) substituted imidazopyridine **4e** and monosubstituted product **5e** (Scheme 1). The same mixture was obtained by using sulfuric acid but in lower total yield (entry 9).

The experiments with nitroacetophenones showed that these ketones are not proper starting substrates for the transformation studied. No conversion was detected below 120 °C, while very complex reaction mixtures were obtained at higher temperatures in general, which separation was not reasonable. Successful transformation with 2-nitroacetophenone was not achieved in the presence of various catalysts, while pyridopyrimidine **6f** (entry 10) or 3-(1-arylethene) substituted imidazopyridine **4f** (entry 11) were formed as single products in very poor yields from 4-nitroacetophenone by using *p*-toluenesulfonic acid at 150 °C or sulfuric acid at 200 °C, respectively.

The structures of the products were assigned on the bases of the characteristic proton and carbon resonances in the NMR spectra and were confirmed by 2D experiments and crystallography analysis of selected samples.¹⁹ The NMR spectra of imidazo[1,2-*a*]pyridines **3** show a doublet for a methyl group, CH neighbour to CH₃, and a quaternary carbon at 123-125 ppm. The vinylated products **4** show characteristic signals for a terminal C=CH₂, while **5e** shows an additional singlet for aromatic CH, no CH-CH₃ and only one 4-methoxyphenyl group. The observed significant upfielding of CH-5 in the proton NMR spectra of compounds **3** and **4** in respect to monosubstituted product **5e** (Figure 1), can be explained by conformation with aromatic substituent at position 3 orientated towards the pyridinium ring, where CH-5 lies in the shielding zone of Ar-3. The spectra of pyrido[1,2-*a*]pyrimidine **6f** show a singlet for a methyl group, an additional singlet for aromatic CH and a quaternary carbon at 65 ppm.

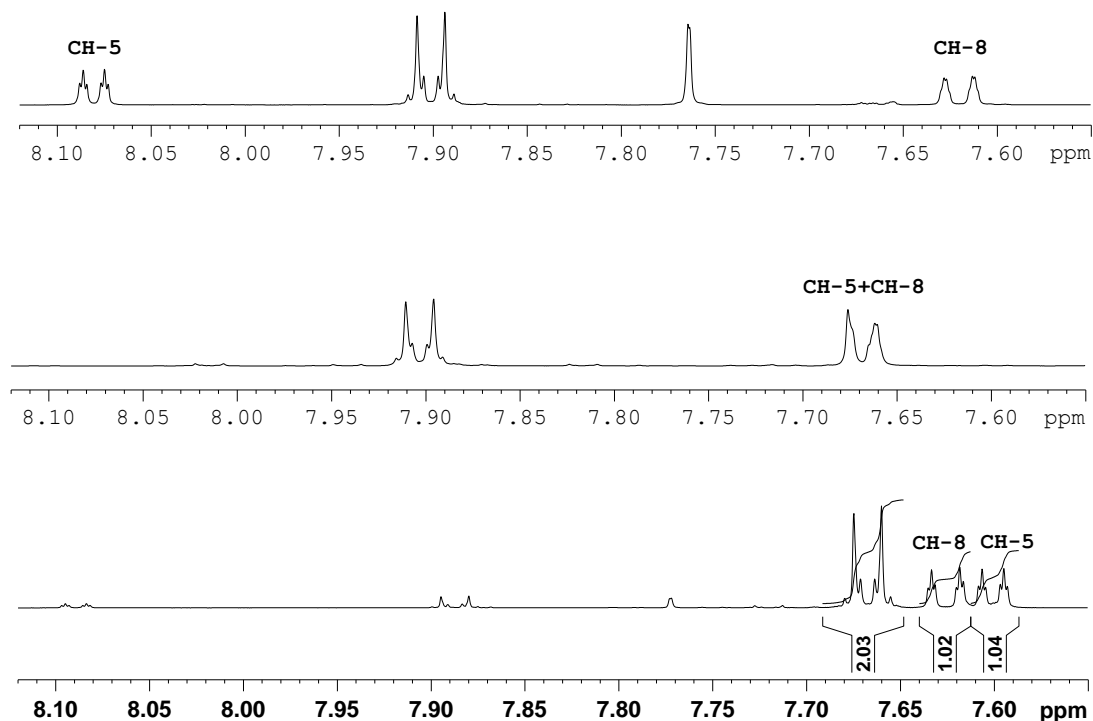


Figure 1. Partial proton spectra of **3e** (down), **4e** (middle), and **5e** (up).

The structures of the products **3a**, **4a** and **5e** were fully elucidated by X-ray diffraction methods (Table S1).¹⁹ An *ORTEP* view of **3a** is reported on Figure 2 together with the atomic labeling scheme. The crystals of compound contain two independent molecules in the asymmetric unit. The main structural dissimilarity between them relates to the positioning of the phenyl from the substituent at the 3 position, which is clearly demonstrated by the overlay of the two molecules shown on Figure 3a.

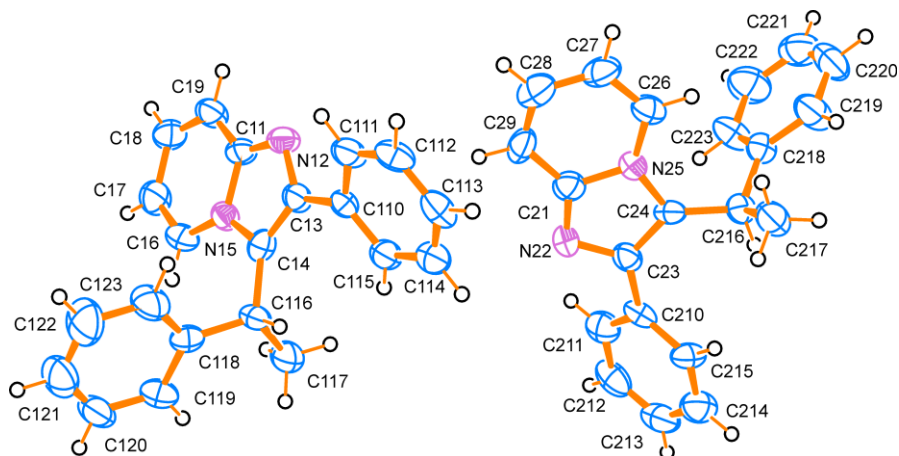


Figure 2. ORTEP view of **3a** with the atomic numbering scheme; ellipsoids are drawn at 50% probability, hydrogen atoms are shown as small spheres with arbitrary radii.

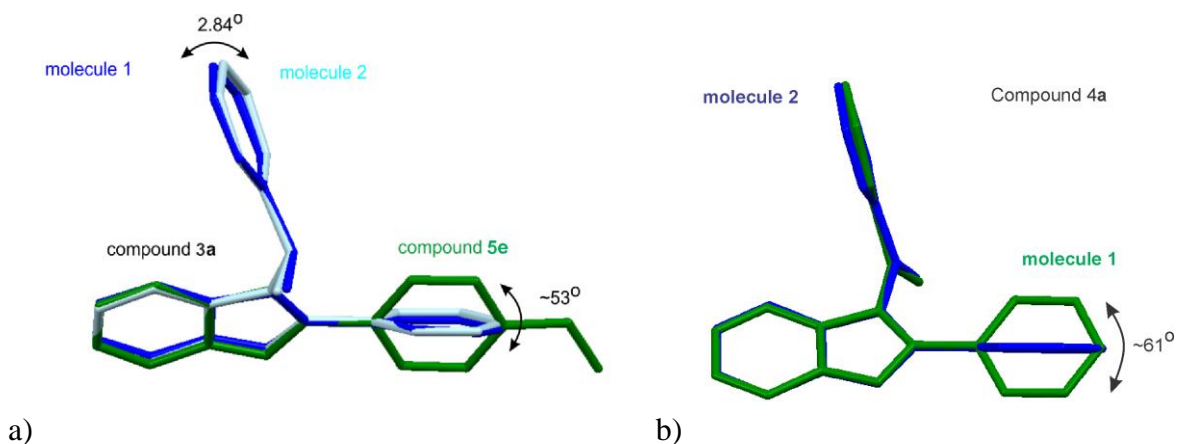


Figure 3. Overlay of the two independent molecules in the asymmetric unit of: a) **3a** and **5e**; a dark blue molecule 1 and a light blue molecule 2 of **3a** and a green molecule of **5e**; b) **4a**; a green molecule 1 and a blue molecule 2.

The structure of 3-(1-arylethene) substituted imidazo[1,2-*a*]pyridines **4** was confirmed by X-ray analysis of **4a**. An *ORTEP* view of the molecule is reported on Figure 4 together with the atomic labeling scheme. Compound **4a** crystallizes also with two independent molecules in the

asymmetric unit. As in **3a**, the dissimilarity between the two molecules of **4a** is associated to the rotation of the phenyl along C13-C110/C23-C210 (Figure 3b).

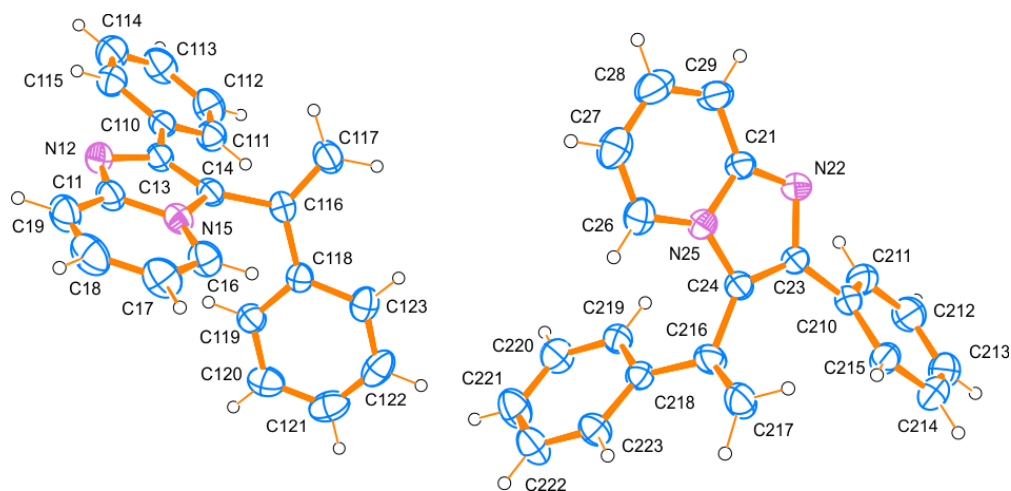


Figure 4. ORTEP view of **4a** with the atomic numbering scheme; ellipsoids are drawn at 50% probability, hydrogen atoms are shown as small spheres with arbitrary radii.

Compound **5e** crystallizes with one independent molecule in the asymmetric unit. An ORTEP view of the molecule is reported on Figure 5 together with the atomic labeling scheme. The main structural dissimilarity between compounds **3a** and **5e** relates to the positioning of the 2-phenyl with respect to the imidazo[1,2-*a*]pyridine one (Figure 3a).

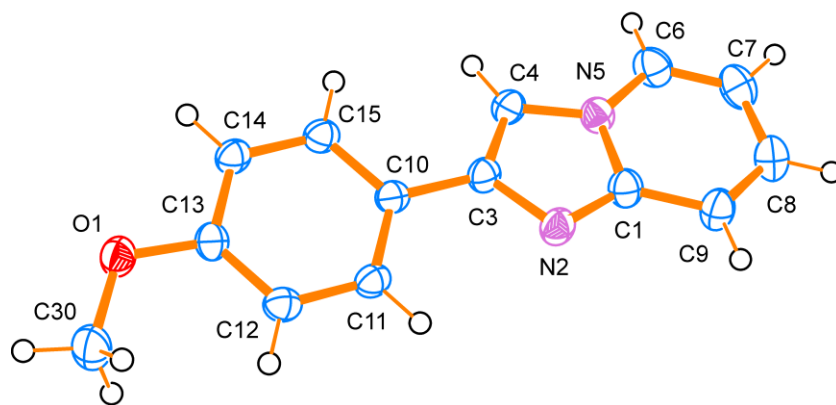


Figure 5. ORTEP view of **5e** with the atomic numbering scheme; ellipsoids are drawn at 50% probability, hydrogen atoms are shown as small spheres with arbitrary radii.

Conclusions

A direct conversion of 2-aminopyridine into 2,3-substituted imidazo[1,2-*a*]pyridines was studied. A series of products was obtained in an efficient, simple and fast protocol; 30-50 min heating in solventless conditions. The scope and limitation of the transformation are also studied and was found that its effectiveness and the type of the substituent at 3-position is strongly dependent both on the catalyst and on the ketone aromatic substituent. The *p*-toluenesulfonic acid catalyzed reaction of acetophenones without or with electrodonating substituents (acetophenone, 4-methylacetophenone, 4-fluoroacetophenone, and aceto-1-naphthone) resulted in 3-(1-arylethane) substituted imidazo pyridines as sole products in good yields. Contrary, the sulfuric acid catalyzed reaction led to excellent conversion but a mixture of 3-(1-arylethane) and 3-(1-arylethene) products were obtained. In the case of 4-methoxyacetophenone, both catalysts generated a mixture of products; 3-(1-arylethane) **3e**, 3-(1-arylethene) **4e** and unsubstituted at 3-position imidazopyridine **5e**; conversion being better with *p*-toluenesulfonic acid. With ketones possessing an electrowithdrawing substituent, 4-nitroacetophenone and 2-nitroacetophenone, successful conversion was achieved only in the first case. The 3-(1-arylethene) substituted imidazo[1,2-*a*]pyridine **4f** was obtained *via* sulfuric acid catalyzed reaction, while 2,4,4-trisubstituted pyrido[1,2-*a*]pyrimidine **6f** was isolated when *p*-toluenesulfonic acid was used; both as single products in poor yields.

Experimental Section

Synthesis

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography and R_f -values determination. Merck Silica gel 60 (0.040-0.063 mm) was used for flash chromatography purification of the products. The melting points were determined in capillary tubes on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system. The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) at 25 °C; the chemical shifts were quoted in ppm in δ -values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The assignment of the signals was confirmed by applying 2D techniques. The spectra were recorded as 10^{-1} M solutions in deuteriochloroform except NOESY experiments where 3×10^{-2} M solutions were used in order to avoid transmolecular interactions. The low resolution mass spectra were taken on a HP 5973 Mass Selective Detector, the high resolution mass spectra on a DFS High Resolution Magnetic Sector MS, Thermo Scientific.

Typical procedure

A mixture of 2-aminopyridine (1 mmol), acetophenone (5 mmol), and *p*-toluenesulphonic acid (10 mg) or sulfuric acid (0.1 ml) was heated at 150-300 °C for 30-50 min. The products were

purified by flash chromatography on silica gel by using mobile phase with a gradient of polarity from CH₂Cl₂ to acetone:CH₂Cl₂:hexane 2:10:10. The results are summarized on Table 1.

2-Phenyl-3-(1-phenylethyl)imidazo[1,2-*a*]pyridine (3a). R_f 0.27 (acetone:CH₂Cl₂ 5:95); mp 115.5-115.7 °C. ¹H NMR 1.841 (d, 3H, *J* 7.4, CH₃), 5.048 (q, 1H, *J* 7.4, CH-CH₃), 6.592 (td, 1H, *J* 1.2, 6.9, CH-6), 7.140 (ddd, 1H, *J* 1.1, 6.9, 9.0, CH-7), 7.269 (m, 3H, CH-2, CH-4 and CH-6 of Ph-3), 7.339 (tt, 2H, *J* 1.9, 7.2, CH-3 and CH-5 of Ph-3), 7.403 (tt, 1H, *J* 1.9, 7.4, CH-4 of Ph-2), 7.483 (tt, 2H, *J* 1.6, 7.0, CH-3 and CH-5 of Ph-2), 7.627 (dt, 1H, *J* 1.1, 6.9, CH-5), 7.679 (dt, 1H, *J* 1.2, 9.0, CH-8), 7.778 (dt, 2H, *J* 1.4, 6.9, CH-2 and CH-6 of Ph-2). ¹³C NMR 16.70 (CH₃), 33.78 (CH-CH₃), 111.56 (CH-6), 117.78 (CH-8), 122.96 (C_{quat}-3), 123.74 (CH-7), 124.53 (CH-5), 126.61 (CH-4 of Ph-3), 126.80 (CH-2 and CH-6 of Ph-3), 127.68 (CH-4 of Ph-2), 128.42 (CH-3 and CH-5 of Ph-2), 128.81 (CH-3 and CH-5 of Ph-3), 128.92 (CH-2 and CH-6 of Ph-2), 135.02 (C_{quat}-1 of Ph-2), 141.11 (C_{quat}-1 of Ph-3), 143.76 (C_{quat}-2), 144.86 (C_{quat}-9); HRMS (EI): calcd. for C₂₁H₁₈N₂ (M⁺) 298.1464, found 298.1466, 0.4 ppm error.

2-(4-Methylphenyl)-3-(1-(4-methylphenyl)ethyl)imidazo[1,2-*a*]pyridine (3b). R_f 0.27 (acetone:CH₂Cl₂ 5:95); mp 128.1-128.4 °C. ¹H NMR 1.691 (d, 3H, *J* 7.4, CH₃), 2.230 (s, 3H, CH₃ of 4-MePh-3), 2.315 (s, 3H, CH₃ of 4-MePh-2), 4.889 (q, 1H, *J* 7.4, CH-CH₃), 6.463 (td, 1H, *J* 1.1, 6.8, CH-6), 7.025 (m, 5H, CH-7 and CH of 4-MePh-3), 7.174 (d, 2H, *J* 7.9, CH-3 and CH-5 of 4-MePh-2), 7.515 (dt, 1H, *J* 1.1, 7.0, CH-5), 7.555 (m, 3H, CH-8 and CH-2 and CH-6 of 4-MePh-2). ¹³C NMR 16.75 (CH₃), 20.95 (CH₃ of 4-MePh-3), 21.29 (CH₃ of 4-MePh-2), 33.49 (CH-CH₃), 111.45 (CH-6), 117.71 (CH-8), 122.96 (C_{quat}-3), 123.61 (CH-7), 124.64 (CH-5), 126.74 (CH-2 and CH-6 of 4-MePh-3), 128.82 (CH-2 and CH-6 of 4-MePh-2), 129.18 (CH-3 and CH-5 of 4-MePh-2), 129.52 (CH-3 and CH-5 of 4-MePh-3), 132.18 (C_{quat}-1 of 4-MePh-2), 136.16 (C_{quat}-4 of 4-MePh-3), 137.43 (C_{quat}-4 of 4-MePh-2), 138.12 (C_{quat}-1 of 4-MePh-3), 143.74 (C_{quat}-2), 144.83 (C_{quat}-9); HRMS (EI): calcd. for C₂₃H₂₂N₂ (M⁺) 326.1783, found 326.1786, 0.9 ppm error.

2-(4-Fluorophenyl)-3-(1-(4-fluorophenyl)ethyl)imidazo[1,2-*a*]pyridine (3c). R_f 0.29 (acetone:CH₂Cl₂ 5:95); mp 164.2-164.6 °C. ¹H NMR 1.800 (d, 3H, *J* 7.4, CH₃), 4.900 (q, 1H, *J* 7.4, CH-CH₃), 6.611 (td, 1H, *J* 1.1, 6.8, CH-6), 6.998 (ddd, 2H, *J*₃₅ 2.1, *J*₂₃ 8.6, *J*_{3F} 8.8, CH-3 and CH-5 of 4-FPh-3), 7.145 (m, 3H, CH-7 and CH-3 and CH-5 of 4-FPh-2), 7.180 (ddd, 2H, *J*₂₆ 0.9, *J*_{2F} 5.2, *J*₂₃ 8.6, CH-2 and CH-6 of 4-FPh-3), 7.577 (dt, 1H, *J* 1.1, 7.0, CH-5), 7.642 (dt, 1H, *J* 1.1, 9.0, CH-8), 7.673 (ddd, 2H, *J*₂₆ 2.2, *J*_{2F} 5.4, *J*₂₃ 8.8, CH-2 and CH-6 of 4-FPh-2). ¹³C NMR 17.04 (CH₃), 33.27 (CH-CH₃), 111.92 (CH-6), 115.52 (d, *J*_{3F} 21.4, CH-3 and CH-5 of 4-FPh-2), 115.74 (d, *J*_{3F} 21.3, CH-3 and CH-5 of 4-FPh-3), 117.87 (CH-8), 122.62 (C_{quat}-3), 124.14 (CH-7), 124.39 (CH-5), 128.36 (d, *J*_{2F} 7.8, CH-2 and CH-6 of 4-FPh-3), 130.60 (d, *J*_{2F} 8.1, CH-2 and CH-6 of 4-FPh-2), 131.00 (d, *J*_{1F} 3.0, C_{quat}-1 of 4-FPh-2), 136.64 (d, *J*_{1F} 3.1, C_{quat}-1 of 4-FPh-3), 142.86 (C_{quat}-2), 144.90 (C_{quat}-9), 161.62 (d, *J*_{4F} 246.2, C_{quat}-4 of 4-FPh-3), 162.62 (d, *J*_{4F} 246.7, C_{quat}-4 of 4-FPh-2); HRMS (EI): calcd. for C₂₁H₁₆F₂N₂ (M⁺) 334.1276, found 334.1276, -0.2 ppm error.

2-(Naphthalen-1-yl)-3-(1-(naphthalen-1-yl)ethyl)imidazo[1,2-*a*]pyridine (3d). R_f 0.35 (acetone:CH₂Cl₂ 5:95); mp 162.4-162.7 °C; For simplicity, naphthyl group in NMR spectra is

assigned as Npt. Due to very closed or overlapped signals some interactions in 2D spectra are questionable; only the clear cross peaks are given. ¹H NMR 1.754 (d, 3H, *J* 7.4, CH₃), 4.751 (q, 1H, *J* 7.4, CH-CH₃), 6.578 (td, 1H, *J* 1.2, 6.9, CH-6), 7.145 (ddd, 1H, *J* 1.2, 6.8, 9.0, CH-7), 7.249 (dd, 1H, *J* 1.7, 8.5, CH of Npt), 7.441 (dt, 1H, *J* 1.6, 7.7, CH of Npt), 7.467 (dt, 1H, *J* 1.4, 6.8, CH of Npt), 7.494 (d, 1H, *J* 7.5, CH of Npt), 7.506 (d, 1H, *J* 7.0, CH of Npt), 7.520 (d, 1H, *J* 7.1, CH of Npt), 7.643 (dd, 1H, *J* 1.1, 7.0, CH-2 of Npt-2), 7.697 (m, 3H, CH-8 and 2 CH of Npt), 7.727 (dt, 1H, *J* 1.1, 7.0, CH-5), 7.753 (d, 1H, *J* 8.0, CH of Npt), 7.768 (d, 1H, *J* 8.3, CH of Npt), 7.902 (m, 2H, 2 CH of Npt), 8.028 (dd, 1H, *J* 1.0, 8.0, CH of Npt). ¹³C NMR 17.56 (CH₃), 34.70 (CH-CH₃), 111.91 (CH-6), 117.90 (CH-8), 123.97 (CH-7), 124.36 (CH-5), 124.57 (C_{quat-3}), 124.90 (CH of Npt), 125.02 (CH of Npt), 125.82 (CH of Npt), 125.85 (CH of Npt), 125.91 (CH of Npt), 126.27 (CH of Npt), 126.39 (CH of Npt), 126.55 (CH of Npt), 127.62 (CH of Npt), 127.82 (CH of Npt), 128.15 (CH of Npt), 128.32 (CH of Npt), 128.59 (CH of Npt), 128.69 (CH of Npt), 132.23 (C_{quat} of Npt), 132.66 (C_{quat} of Npt), 133.26 (C_{quat} of Npt), 133.45 (C_{quat} of Npt), 139.07 (C_{quat-1} of Npt-3), 143.07 (C_{quat-2}), 144.81 (C_{quat-9}); HRMS (EI): calcd. for C₂₉H₂₂N₂ (M⁺) 398.1778, found 398.1772, -1.4 ppm error.

2-(4-Methoxyphenyl)-3-(1-(4-methoxyphenyl)ethyl)imidazo[1,2-*a*]pyridine (3e). R_f 0.27 (acetone:CH₂Cl₂ 10:90); mp 109.1-109.3 °C. ¹H NMR 1.774 (d, 3H, *J* 7.4, CH₃), 3.776 (s, 3H, OCH₃ of 4-MeOPh-3), 3.848 (s, 3H, OCH₃ of 4-MeOPh-2), 4.928 (q, 1H, *J* 7.4, CH-CH₃), 6.559 (td, 1H, *J* 1.2, 6.8, CH-6), 6.838 (dt, 2H, *J* 2.1, 8.8, CH-3 and CH-5 of 4-MeOPh-3), 6.991 (dt, 2H, *J* 2.2, 8.8, CH-3 and CH-5 of 4-MeOPh-2), 7.099 (ddd, 1H, *J* 1.3, 6.7, 9.0, CH-7), 7.146 (dd, 2H, *J* 0.9, 8.9, CH-2 and CH-6 of 4-MeOPh-3), 7.601 (dt, 1H, *J* 1.1, 6.9, CH-5), 7.626 (dt, 1H, *J* 1.1, 9.0, CH-8), 7.668 (dd, 2H, *J* 2.2, 8.9, CH-2 and CH-6 of 4-MeOPh-2). ¹³C NMR 16.88 (CH₃), 33.08 (CH-CH₃), 55.27 (OCH₃ of 4-MeOPh-3), 55.33 (OCH₃ of 4-MeOPh-2), 111.50 (CH-6), 113.95 (CH-3 and CH-5 of 4-MeOPh-2), 114.17 (CH-3 and CH-5 of 4-MeOPh-3), 117.58 (CH-8), 122.73 (C_{quat-3}), 123.68 (CH-7), 124.60 (CH-5), 127.52 (C_{quat-1} of 4-MeOPh-2), 127.87 (CH-2 and CH-6 of 4-MeOPh-3), 130.10 (CH-2 and CH-6 of 4-MeOPh-2), 133.10 (C_{quat-1} of 4-MeOPh-3), 143.38 (C_{quat-2}), 144.77 (C_{quat-9}), 158.22 (C_{quat-4} of 4-MeOPh-3), 159.32 (C_{quat-4} of 4-MeOPh-2); HRMS (EI): calcd. for C₂₃H₂₂N₂O₂ (M⁺) 358.1676, found 358.1680, 1.0 ppm error.

2-(4-Phenyl)-3-(1-(4-phenyl)vinyl)imidazo[1,2-*a*]pyridine (4a). R_f 0.45 (acetone:CH₂Cl₂ 5:95), R_f 0.63 (acetone:CH₂Cl₂ 10:90); mp 123.6-123.9 °C. ¹H NMR 5.580 (d, 1H, *J* 0.9, ½ of CH₂=), 6.170 (d, 1H, *J* 0.9, ½ of CH₂=), 6.653 (dtd, 1H, *J* 1.1, 6.8, CH-6), 7.177 (ddd, 1H, *J* 1.1, 6.7, 9.0, CH-7), 7.264 (tt, 1H, *J* 1.3, 7.3, CH-4 of Ph-2), 7.333 (m, 5H, CH-3 and CH-5 of Ph-2 and CH-3, CH-4 and CH-5 of Ph-3), 7.387 (dt, 2H, *J* 1.3, 7.0, CH-2 and CH-6 of Ph-3), 7.634 (dt, 1H, *J* 1.1, 6.9, CH-5), 7.685 (dt, 1H, *J* 1.0, 9.0, CH-8), 7.934 (dt, 2H, *J* 1.9, 7.1, CH-2 and CH-6 of Ph-2). ¹³C NMR 112.24 (CH-6), 117.35 (CH-8), 120.12 (C_{quat-3}), 121.42 (CH₂=), 124.28 (CH-5), 124.71 (CH-7), 126.17 (CH-2 and CH-6 of Ph-3), 127.63 (CH-4 of Ph-2), 127.88 (CH-2 and CH-6 of Ph-2), 128.32 (CH-3 and CH-5 of Ph), 128.78 (CH-4 of Ph-3), 129.06 (CH-3 and CH-5 of Ph), 133.93 (C_{quat-1} of Ph-2), 137.58 (C_{quat}= and C_{quat-1} of Ph-3), 143.37 (C_{quat-2}),

144.81 ($C_{\text{quat-9}}$); HRMS (EI): calcd. for $C_{21}H_{16}N_2$ (M^+) 296.1308, found 296.1301, -2.5 ppm error.

2-(4-Methoxyphenyl)-3-(1-(4-methoxyphenyl)vinyl)imidazo[1,2-*a*]pyridine (4e). R_f 0.30 (acetone:CH₂Cl₂ 5:95), R_f 0.44 (acetone:CH₂Cl₂ 10:90); ¹H NMR 3.809 (s, 3H, OCH₃ of 4-MeOPh-3), 3.824 (s, 3H, OCH₃ of 4-MeOPh-2), 5.485 (d, 1H, J 0.8, ½ of CH₂=), 6.087 (d, 1H, J 0.8, ½ of CH₂=), 6.660 (td, 1H, J 1.2, 6.7, CH-6), 6.863 (dt, 2H, J 2.1, 8.9, CH-3 and CH-5 of 4-MeOPh-3), 6.898 (dt, 2H, J 2.1, 8.9, CH-3 and CH-5 of 4-MeOPh-2), 7.174 (ddd, 1H, J 0.9, 6.7, 9.2, CH-7), 7.330 (dt, 2H, J 2.1, 8.9, CH-2 and CH-6 of 4-MeOPh-3), 7.668 (m, 2H, CH-5 and CH-8), 7.903 (dt, 2H, J 2.1, 8.9, CH-2 and CH-6 of 4-MeOPh-2). ¹³C NMR 55.23 (OCH₃ of 4-MeOPh-3), 55.33 (OCH₃ of 4-MeOPh-2), 111.99 (CH-6), 113.76 (CH-3 and CH-5 of 4-MeOPh-2), 114.37 (CH-3 and CH-5 of 4-MeOPh-3), 117.12 (CH-8), 119.10 (CH₂=), 119.54 ($C_{\text{quat-3}}$), 124.23 (CH-5), 124.41 (CH-7), 126.75 ($C_{\text{quat-1}}$ of 4-MeOPh-2), 127.48 (CH-2 and CH-6 of 4-MeOPh-3), 129.06 (CH-2 and CH-6 of 4-MeOPh-2), 130.11 ($C_{\text{quat-1}}$ of 4-MeOPh-3), 137.17 ($C_{\text{quat=}}$), 143.12 ($C_{\text{quat-2}}$), 144.80 ($C_{\text{quat-9}}$), 159.20 ($C_{\text{quat-4}}$ of 4-MeOPh-2), 160.08 ($C_{\text{quat-4}}$ of 4-MeOPh-3); HRMS (EI): calcd. for $C_{23}H_{20}N_2O_2$ (M^+) 356.1519, found 356.1518, -0.4 ppm error.

2-(4-Nitrophenyl)-3-(1-(4-nitrophenyl)vinyl)imidazo[1,2-*a*]pyridine (4f). R_f 0.56 (acetone:CH₂Cl₂ 5:95), R_f 0.76 (acetone:CH₂Cl₂ 10:90); mp 178.7-178.9 °C (decomp.). ¹H NMR 5.889 (s, 1H, ½ of CH₂=), 6.473 (s, 1H, ½ of CH₂=), 6.821 (ddd, 1H, J 1.0, 6.7, 7.1, CH-6), 7.316 (ddd, 1H, J 1.1, 6.7, 9.1, CH-7), 7.528 (dt, 2H, J 2.0, 9.0, CH-2 and CH-6 of 4-NO₂Ph-3), 7.728 (dd, 1H, J 1.0, 9.1, CH-8), 7.738 (dd, 1H, J 1.1, 7.1, CH-5), 8.039 (dt, 2H, J 2.0, 9.0, CH-2 and CH-6 of 4-NO₂Ph-2), 8.176 (dt, 2H, J 2.0, 9.0, CH-3 and CH-5 of 4-NO₂Ph-2), 8.193 (dt, 2H, J 2.0, 9.0, CH-3 and CH-5 of 4-NO₂Ph-3). ¹³C NMR 113.56 (CH-6), 117.95 (CH-8), 120.34 ($C_{\text{quat-3}}$), 123.83 (CH-3 and CH-5 of 4-NO₂Ph-2), 123.90 (CH-5), 124.54 (CH-3 and CH-5 of 4-NO₂Ph-3), 125.69 (CH₂=), 126.23 (CH-7), 126.96 (CH-2 and CH-6 of 4-NO₂Ph-3), 128.22 (CH-2 and CH-6 of 4-NO₂Ph-2), 135.76 ($C_{\text{quat=}}$), 139.99 ($C_{\text{quat-1}}$ of 4-NO₂Ph-2), 141.17 ($C_{\text{quat-2}}$), 143.35 ($C_{\text{quat-1}}$ of 4-NO₂Ph-3), 145.45 ($C_{\text{quat-9}}$), 147.10 ($C_{\text{quat-4}}$ of 4-NO₂Ph-2), 148.08 ($C_{\text{quat-4}}$ of 4-NO₂Ph-3); HRMS (EI): calcd. for $C_{21}H_{14}N_4O_4$ (M^+) 386.1010, found 386.1017, 1.8 ppm error.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (5e). R_f 0.32 (acetone:CH₂Cl₂ 10:90); mp 129.4-129.6 °C. ¹H NMR 3.862 (s, 3H, OCH₃ of 4-MeOPh), 6.748 (td, 1H, J 1.1, 6.7, CH-6), 6.988 (dt, 2H, J 2.1, 8.9, CH-3 and CH-5 of 4-MeOPh), 7.152 (ddd, 1H, J 1.3, 6.7, 9.0, CH-7), 7.620 (dd, 1H, J 0.9, 9.0, CH-8), 7.764 (d, 1H, J 0.5, CH-3), 7.901 (dt, 2H, J 2.1, 8.9, CH-2 and CH-6 of 4-MeOPh), 8.081 (dt, 1H, J 1.1, 6.8, CH-5). ¹³C NMR 55.33 (OCH₃ of 4-MeOPh), 107.26 (CH-3), 112.25 (CH-6), 114.15 (CH-3 and CH-5 of 4-MeOPh), 117.28 (CH-8), 124.47 (CH-7), 125.49 (CH-5), 126.50 ($C_{\text{quat-1}}$ of 4-MeOPh), 127.30 (CH-2 and CH-6 of 4-MeOPh), 145.63 ($C_{\text{quat-9}}$), 145.72 ($C_{\text{quat-2}}$), 159.58 ($C_{\text{quat-4}}$ of 4-MeOPh); HRMS (EI): calcd. for $C_{14}H_{12}N_2O$ (M^+) 224.0944, found 224.0941, -1.4 ppm error.

4-Methyl-2,4-bis(4-nitrophenyl)-4H-pyrido[1,2-*a*]pyrimidine (6f). R_f 0.24 (acetone:CH₂Cl₂ 50:50); mp 148.6-148.8 °C (decomp.). ¹H NMR 2.111 (s, 3H, CH₃), 5.106 (s, 1H, CH-3), 6.039 (ddd, 1H, J 1.4, 6.4, 7.1, CH-7), 6.723 (dd, 1H, J 1.4, 9.1, CH-9), 6.743 (dd, 1H, J 1.5, 7.1, CH-

6), 6.962 (ddd, 1H, *J* 1.5, 6.4, 9.1, *CH*-8), 7.636 (tt, 2H, *J* 1.9, 8.9, *CH*-2 and *CH*-6 of 4-NO₂Ph-4), 7.834 (tt, 2H, *J* 1.9, 8.9, *CH*-2 and *CH*-6 of 4-NO₂Ph-2), 8.093 (tt, 2H, *J* 1.9, 8.9, *CH*-3 and *CH*-5 of 4-NO₂Ph-2), 8.173 (tt, 2H, *J* 1.9, 8.9, *CH*-3 and *CH*-5 of 4-NO₂Ph-4). ¹³C NMR 29.32 (*CH*₃), 64.90 (*C*_{quat}-4), 105.05 (*CH*-3), 110.05 (*CH*-7), 123.44 (*CH*-3 and *CH*-5 of 4-NO₂Ph-2), 124.16 (*CH*-3 and *CH*-5 of 4-NO₂Ph-4), 124.83 (*CH*-9), 126.39 (*CH*-2 and *CH*-6 of 4-NO₂Ph-2), 127.35 (*CH*-2 and *CH*-6 of 4-NO₂Ph-4), 133.47 (*CH*-6), 134.71 (*CH*-8), 140.11 (*C*_{quat}-4 of 4-NO₂Ph-2), 144.89 (*C*_{quat}-1 of 4-NO₂Ph-2), 147.33 (*C*_{quat}-4 of 4-NO₂Ph-4), 147.41 (*C*_{quat}-2), 151.48 (*C*_{quat}-10), 152.87 (*C*_{quat}-1 of 4-NO₂Ph-4); HRMS (EI): calcd. for C₂₁H₁₆N₄O₄ (M⁺) 388.1170, found 388.1166, 1.0 ppm error.

Crystallography

The crystals of **3a**, **4a** and **5e** were mounted on a glass capillary and all geometric and intensity data were taken from these crystals. Data collection using Mo-K_α radiation ($\lambda = 0.71073$ Å) was performed at room temperature on an Oxford diffraction Supernova diffractometer. The crystal data¹⁹ are collected on Table S1 (Supplementary Material). The structures were solved with SHELXS-97 and refined using full-matrix least-squares on *F*² with the SHELXL-97 package.²⁰

Supplementary Material

The description of 2D NMR spectra of the products and the crystallographic data are given in the Supplementary Material.

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19. The crystallographic data for the products of **3a**, **4a** and **5e** were deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 846146, CCDC 871761 and CCDC 847911, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; tel: +44 1223 762910; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk; <http://www.ccdc.cam.ac.uk/deposit>.
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