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A New Approach to the Synthesis of 2-Aminoimidazo[1,2-*a*]pyridine Derivatives Through Microwave-Assisted *N*-Alkylation of 2-Halopyridines

Juan A. Vega,[a] Juan J. Vaquero,[a] Julio Alvarez-Builla,[a]* Jesús Ezquerra[b] and Chafiq Hamdouchi[b]*

[a]Departamento de Química Orgánica, Universidad de Alcalá, 28871-Alcalá de Henares, Madrid. Spain.
[b]Centro de Investigación Lilly, S. A. Avda. de la Industria, 30, 28108-Alcobendas, Madrid, Spain.

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Abstract
A microwave (focused waves) assisted *N*-alkylation of 2-halopyridines provides a convenient entry to 2-amino-imidazo[1,2-*a*]pyridine derivatives after reaction of the alkylated substrates with cyanamide under basic conditions.

Keywords : Focused microwave ; Alkylation ; 2-Halopyridines ; Imidazo[1,2-a]pyridines

Enviroxime (**1**) is a potent antirhinoviral agent [1-3] though its poor oral bioavailability and undesirable side effects precludes its use as an effective drug for the treatment of the common cold. The analogous imidazo[1,2-*a*]pyridine derivatives **2** emerged as alternative candidates which may greatly improve the pharmacological profile.

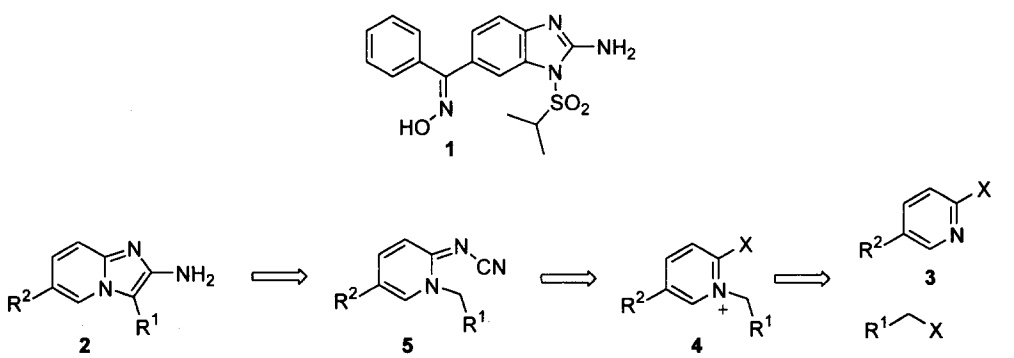

Figure 1

The most common approach for the synthesis of imidazo[1,2-*a*]pyridines is based on the condensation of 2-aminopyridines with carbonyl compounds [4,5]. Despite numerous

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applications, however, this method has a limited value in the construction of analogues such as **2**, with an amino moiety, and suffers from the lengthy sequences. Approaches based on the use of imidazoles as starting material to construct the imidazopyridine nucleus have also been described [6,7], but none of them allowed the introduction of an amino group at the 2-position. Hence a convenient approach to synthesis to these compounds is highly desirable because of the potential value in structure-activity studies.

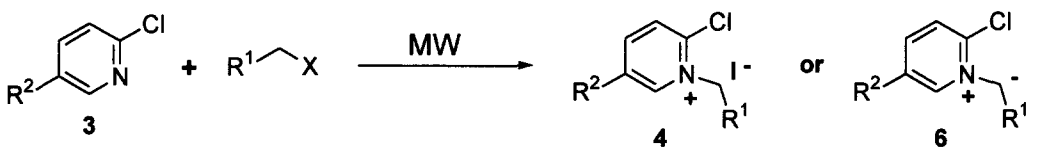
We designed and executed an expeditious approach to derivatives **2** (Figure 1) based on the alkylation of 2-halopyridines followed by nucleophilic halide displacement on pyridinium salts **4** with cyanamide and subsequent cyclization under basic conditions.

Although our initial studies demonstrated this approach to be successful, we faced the drawbacks associated with the alkylation of 2-chloropyridine **3**. The greatest concern we had was the poor nucleophilic character of the pyridine nitrogen atom. In all the cases that we have studied, a high temperature and reaction time ranging from hours to days were required, leading to low and erratic conversions. In order to allay this problem we decided to investigate the reaction under microwave (MW) irradiation [8-13]. Our effort to prove the viability of this new approach, that was applied successfully for accessing to 2-aminoimidazo[1,2-*a*]pyridine derivatives **2**, is the main subject of this report.

The reaction of 2-chloropyridine and 5-benzoyl-2-chloropyridine **3** (R^2=H, PhCO) with diverse chloromethyl alkylating reagents was investigated under conventional heating and microwave-assisted reactions conditions.

Our initial screening experiments revealed that the microwave *N*-alkylation reaction in the presence of sodium iodide using a domestic microwave oven [14-19] either in sealed or open vessels did not proceed satisfactorily [20-23]. However, when the reactions were conducted inside a monomode microwave reactor with focused waves [24-30], achieving a much more homogenous energy distribution, the reaction proceeded in good yields (Table).

Power of microwave, temperature, solvent and dilution were also variables included in the optimization. The best results of conversion were accomplished when the reaction was performed at 210 W. Regarding the solvent and dilution, we found that the yield increased considerably on increasing the concentration of 2-chloropyridine in acetonitrile.

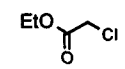
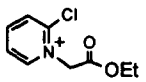
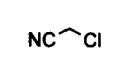
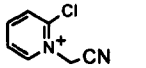
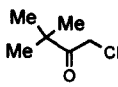
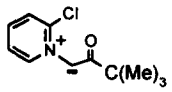
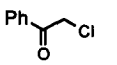
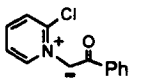
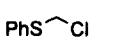
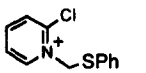
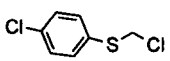
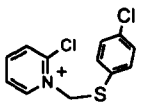
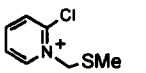
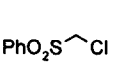
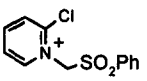
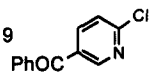
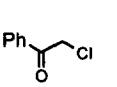
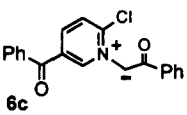
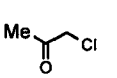
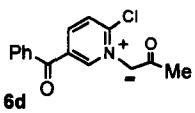


Scheme 1

The optimum yields were achieved when the mixture of 2-chloropyridine and the chloromethyl alkylating reagent were irradiated at 168-170 °C without solvent. Interestingly, in some cases (entries 3, 4, 9 and 10) the isolated product was not the expected pyridinium salt, instead the reaction progressed to the corresponding heterobetaines **6a-d** which were isolated in good to excellent yields. The scope and limitation of the procedure is shown in the Table. In all the reported cases, the use of microwave-assisted reactions conditions

resulted in a significant improvement of the yield of the alkylation and a reduction in the reaction time.

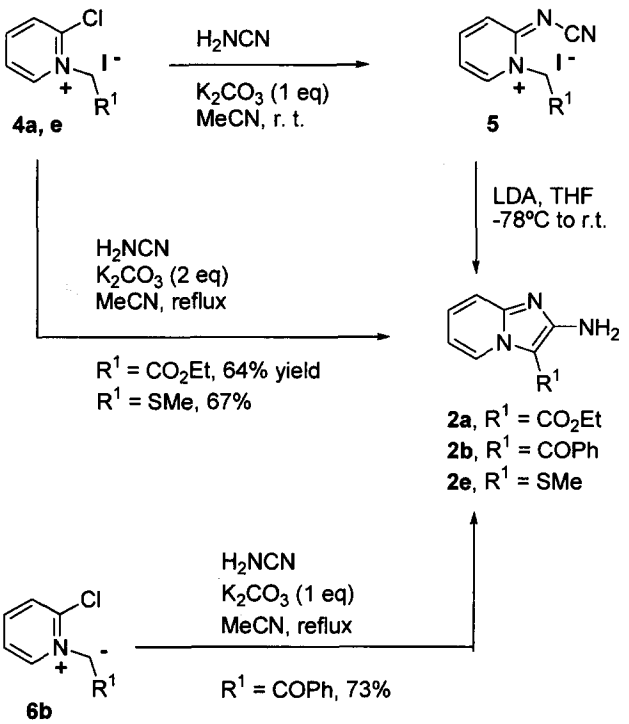
Table. Microwave-assisted alkylation of 2-chloropyridines

Entry	2-Halopyridine	Alkylating reagent	Product (4 or 6)	Yield (%) MW [time, min]	Thermal [time, h]
1			**4a** 	80 [40]	46[23]
2			**4b** 	56 [40]	10[50]
3			**6a** 	77 [35]	48[60]
4			**6b** 	91 [40]	35[20]
5			**4c** 	60 [35]	35[100]
6			**4d** 	48 [40]	37[58]
7			**4e** 	75 [40]	46[40]
8			**4f** 	0 [40]	0[70]
9			 **6c**	58 [40]	20[70]
10			 **6d**	55 [40]	17[70]

It should also be noted that the use of MW was especially crucial for the synthesis of compounds **4b**, **6c** and **6d** (entries 2, 9 and 10) which under conventional heating were formed with yields lower than 20%.

To prove that the reaction process is not limited to a small scale (see Experimental section) we performed the preparation of compounds **4a** and **6b** by varying the amount of reactants from 70 to 500 mg. The only significant change that was introduced in this process was the use of a larger reactor (33 cm^3). Neither the time of the process nor the yield of the reaction were affected under these conditions.

In the course of our investigations we have also noticed some limitations in the attempt to alkylate 2-chloropyridine with chloromethyl phenyl sulfone (Table, entry 8). The reaction failed under both conventional and microwave heating.



Scheme 2

In a preliminary examination, two representative examples of pyridinium derivatives (**4a** and **4e**) as well as **6b**, as representative of the heterobetainic compounds, were selected and treated with cyanamide in the presence of 1 equivalent of K_2CO_3 to give the cyano derivatives **5** in good yields. Subsequent treatment with LDA gave the desired 2-aminoimidazo[1,2-*a*]-pyridine derivatives **2**. We then found that compounds **4a**, **4c** and **6b** could also be converted in a one-pot procedure into their corresponding 2-aminoimidazo[1,2-*a*]pyridines **2a**, **2b** and **2e** by simply using 2 equivalents of K_2CO_3 and heating the reaction in refluxing acetonitrile. It should also be noted that the benzoyl at the 6-position was not tolerated in this process of conversion. Thus, attempts to convert the ylides **6c** or **6d** into their corresponding aminoimidazo[1,2-*a*]pyridines failed.

In summary, we have developed a new approach to the synthesis of substituted 2-aminoimidazo[1,2-*a*]pyridines. The key steps include the use of microwave focused

irradiation that allowed us to overcome the difficulties of the alkylation of 2-chloro-pyridines and the one-step procedure for the generation of 2-aminoimidazo moiety from the corresponding 2-chloropyridinium salts (or ylides).

Experimental

Melting points were determined on Buchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Unity 200 and Varian Unity 300 spectrometers and were referenced to TMS. IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Microanalyses were performed on a Heraeus CHN Rapid analyzer. MS were obtained on a Hewlett-Packard 5988 A spectrometer. All reagents were obtained from commercial sources and were used without purification. Flash chromatography was carried out on silica gel (400-630 mesh) and solvents were dried before using. The *N*-alkylation of 2-halopyridines was performed in a monomode microwave reactor (12 cm^3 capacity) fitted with a stirring system and an IR temperature detector (Synthewave 402 from Prolabo).

Synthesis of 1-Alkyl-2-chloropyridinium Salts **4**. *General Procedures*

Method A: A mixture of the 2-chloropyridine derivative **3** (3 mL, 32 mmol), the alkylating reagent (0.25 mmol) and NaI (0.042 g, 0.28 mmol) was irradiated in the focused microwave reactor at 210 W for 35-40 min. After irradiation for 4 min the reaction mixture was raised to 165-170 °C and this temperature was maintained throughout the irradiation time. The reaction mixture was treated with EtOH (3 mL), filtered and the filtrate evaporated under reduced pressure. The oily residue was washed with Et_2O (3 x 3 mL) and the solid obtained was subjected to a short pad of silica gel using EtOAc as eluent to eliminate the remaining 2-chloropyridine derivative and EtOH to isolate the corresponding salt, which was purified by recrystallization from the appropriate solvent.

To prove that the reaction process is not limited to a small scale, we performed the preparation of compounds **4a** and **6b** on a 500 mg scale. The only significant change that was introduced in this process was the use of a larger reactor. Neither the time of the process nor the yield of the reaction were affected under these conditions.

***Method B*:** The same amounts of reactants indicated in method A were heated at 165-170 °C for 20-100 h. The resulting pyridinium salts were isolated as indicated in the method described above.

2-Chloro-1-(ethoxycarbonylmethyl)pyridinium iodide (**4a**). Following the method A (40 min irradiation time) from the reaction of 2-chloropyridine (3 mL), ethyl bromoacetate (0.042 g,

0.25 mmol) and NaI (0.042 g, 0.28 mmol), 70 mg (80%) of **4a** were obtained. Method B afforded, after 23 h reaction time, 38 mg (46%). Mp 193-195 °C (brown powder, acetone). IR (KBr) 3416, 3001, 1739, 1605, 1432, 1217, 1190, 1018 cm^{-1} ;^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.20 (d, 1H, J=6.2 Hz); 8.66 (d, 1H, J=8.0 Hz); 8.29-8.21 (m, 1H); 8.18-8.14 (m, 1H); 5.74 (s, 2H); 4.27 (q, 2H, J=7.0 Hz); 1.24 (t, 3H, J=7.0 Hz) ppm. Calcd for $C_9H_{11}ClINO_2$: C, 33.00; H, 3.39; N, 4.28. Found : C, 33.35; H, 3.46; N, 4.06.

2-Chloro-1-(cyanomethyl)pyridinium Iodide **(4b)**. Using chloroacetonitrile (0.018 g, 0.25 mmol) as alkylating reagent, method A (40 min irradiation time) afforded 41 mg (56%) of **4b** and 7 mg (10%) were obtained following method B after heating for 50 h. Mp > 200 °C (dec.) (yellow powder, acetone). IR (KBr) 3807, 3417, 2219, 1657, 1619, 1425, 1151, 995 cm^{-1} ; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 7.74 (d, 1H, J=5.8 Hz); 7.52-7.47 (m, 1H); 6.46 (d, 1H, J=9.4 Hz); 6.29-6.26 (m, 1H); 4.97 (s, 2H) ppm. Calcd for $C_7H_6ClIN_2$: C, 29.97; H, 2.16; N, 9.99. Found C, 30.15; H, 2.36; N, 10.06.

2-Chloro-1-(3,3-dimethyl-2-oxobutyl)pyridinium Ylide **(6a)**. Using 2-chloropinacolone as alkylating reagent (0.034 g, 0.25 mmol) method A (35 min irradiation time) afforded 40 mg (77%) of the ylide **6a** and 25 mg (48%) were obtained following method B after heating for 60 h. Mp 88-89 °C (yellow powder, EtOAc). IR (KBr) 3417, 3115, 1640, 1497, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.04 (d, 1H, J=6.2 Hz); 9.40 (s, 1H); 8.45 (m, 1H); 8.10 (d, 1H, 8.8 Hz); 7.91-7.86 (m, 1H); 1.48 (s, 9H) ppm. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; N, 6.62. Found C, 62.35; H, 6.46; N, 6.54.

2-Chloro-1-(2-phenyl-2-oxoethyl)pyridinium Ylide **(6b)**. Using phenacyl bromide as alkylating reagent (0.05 g, 0.25 mmol), 51 mg (91%) of the ylide **6b** were obtained following method A (40 min irradiation time) and 19 mg (35%) following method B after heating for 20 h. Mp 98-100 °C (brown powder, acetone). IR (KBr) 3552, 3414, 1630, 1614, 1442, 1182, 932 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 9.40 (s, 1H); 9.25 (d, 1H, J=6.3 Hz); 8.50 (d, 2H, J=4 Hz); 8.07-7.90 (m, 3H); 7.70-7.61 (m, 3H) ppm. Calcd for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.05. Found C, 67.00; H, 4.21; N, 6.34.

2-Chloro-1-(phenylsulphanylmethyl)pyridinium Iodide **(4c)**. Using chloromethyl phenyl sulfide (0.037 g, 0.25 mmol) as alkylating reagent, method A (35 min irradiation time) afforded 52 mg (60%) of **4c** (brown oil) and 31 mg (35%) were obtained following method B after heating for 100 h. IR ($CHBr_3$) 3452, 1660, 1436, 1142 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 8.90 (d, 1H, J=5.7 Hz); 8.61-8.55 (m, 1H); 8.13-8.07 (m, 2H); 7.50-7.20 (m,

5H); 6.12 (s, 2H) ppm. Calcd for $C_{12}H_{11}ClINS$: C, 39.64; H, 3.05; N, 3.85. Found C, 40.00; H, 3.14; N, 3.96.

2-Chloro-1-(4-chlorophenylsulphanylmethyl)pyridinium Iodide **(4d)**. Using chloromethyl 4-chlorophenyl sulfide (0.045 g, 0.25 mmol) as alkylating reagent, method A (40 min irradiation time) afforded 79 mg (48%) of **4d** (brown oil) and 61 mg (37%) were obtained following method B after heating for 58 h. IR ($CHBr_3$) 3416, 1570, 1476, 1123 cm^{-1}; ^{1}H-NMR (200 MHz DMSO-d_6) δ 9.10 (d, 2H, J=6.7 Hz); 8.23 (d, 2H, J=6.8 Hz); 7.60-7.30 (m, 4H); 6.19 (s, 2H) ppm. Calcd for $C_{12}H_{10}Cl_2INS$: C, 36.21; H, 2.53; N, 3.52; Found C, 36.05; H, 2.24; N, 3.33.

2-Chloro-1-(methylsulphanylmethyl)pyridinium Iodide **(4e).** Using chloromethyl methyl sulfide (0.024 g, 0.25 mmol) as alkylating reagent, method A (40 min irradiation time) afforded 60 mg (75%) of **4e** and 35 mg (46%) were obtained following method B after heating for 40 h. Mp > 200 °C (dec.) (brown powder, EtOAc) IR (KBr) 3051, 2970, 1594, 1431, 1297, 1142, 1111 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.28 (d, 1H, J=6.6 Hz); 8.67 (d, 1H, J=8.0 Hz); 8.26-8.19 (m, 1H); 8.12-8.07 (m, 1H); 5.87 (s, 2H); 2.21 (s, 3H) ppm. Calcd for C_7H_9ClINS : C, 27.88; H, 3.01; N, 4.64. Found C, 27.92; H, 3.23; N, 4.78.

5-Benzoyl-2-chloro-1-(2-phenyl-2-oxoethyl)pyridinium Ylide **(6c)**. Using phenacyl bromide (0.034 g, 0.25 mmol), 5-benzoyl-2-chloropyridine (6.9 g, 31.8 mmol) and NaI (0,042 g, 0.28 mmol), method A (40 min irradiation time) afforded 48 mg (58%) of the ylide **6c** and 17 mg (20%) were obtained following method B after heating for 70 h. Mp 149-152 °C (brown powder, EtOAc). IR (KBr) 3440, 2344, 1680, 1721, 1630, 1446, 1036, 979 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 9.65 (s, 1H); 9.35 (s, 1H); 8.8 (d, 1H, J=8.5Hz); 8.65 (d, 1H, J=8.5Hz); 8.16-8.05 (m, 2H); 8.00-7.9 (m, 2H); 7.85-7.55 (m, 6H) ppm. Calcd for $C_{20}H_{14}ClNO_2$: C, 71.54; H, 4.20; N, 4.17. Found C, 71.92; H, 4.23; N, 4.38.

5-Benzoyl-2-chloro-1-(2-oxopropyl)pyridinium Ylide **(6d)**. Using chloroacetone (0.023 g, 0.25 mmol), 5-benzoyl-2-chloropyridine (6.9 g, 31.8 mmol) and NaI (0,042 g, 0.28 mmol) method A (40 min irradiation time) afforded 38 mg (55%) of the ylide **6d** and 12 mg (17%) were obtained following method B after heating for 70 h. Mp 63-65 °C (white powder, EtOAc). IR (KBr) 3449, 3117, 1727, 1669, 1317, 1027 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 9.54 (s, 1H); 8.7-8.6 (m, 1H); 8.6-8.5 (m, 1H); 7.89 (d, 2H, J=6.83 Hz); 7.8-7.7 (m, 1H); 7.66 (d, 2H, J=6.83); 7.6-7.5 (m, 1H); 2.70 (s, 3H) ppm. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.20. Found C, 65.93; H, 4.35; N, 5.16.

Synthesis of 2-Ylidencyanamidopyridine Derivatives **(5)**. *General Procedure.*

To a solution of the salt **4** or the ylide **6** (1 mmol) and cyanamide (0.046 g, 1.1 mmol) in dry MeCN (5 mL), K_2CO_3 (0.16 g, 1.15 mmol) was added and the mixture was stirred at room temperature for 4 h (**5d**) or 16 h (**5a, 5g**). The inorganic salts were separated by filtration and washed with MeCN (3 x 3mL). The filtrate and washes were evaporated under reduced pressure to give a residue which if solid was recrystallized from EtOAc or if oil purified by column chromatography (hexane/EtOAc 1:1).

1-(2-Ethoxy-2-oxoethyl)-1-H-pyridin-2-ylidencyanamide **(5a)**. Yield: 134 mg (64%). Mp 104-105 °C (white needles, acetone). IR (KBr) 3443, 2998, 2170, 1747, 1643, 1560, 1243, 1017 cm^{-1}; ^{1}H-NMR (300 MHz DMSO-d_6) δ 7.96 (d, 1H, J=6.6 Hz); 7.78 (ddd, 1H, J=1.4 Hz, J= 7.0, J=9.0 Hz); 7.13 (d, 1H, J=9.0 Hz); 6.73 (ddd, 1H, J=1.4 Hz, J=6.6 Hz, J=7.0); 4.9 (s, 2H); 4.16 (q, 2H, J=7.3 Hz); 1.19 (t, 3H, J=7.3 Hz) ppm. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found C, 58.43; H, 5.39; N, 20.59.

1-(2-Phenyl-2-oxoethyl)-1-H-pyridin-2-ylidencyanamide **(5d)**. Yield: 170 mg (73%). Mp.180 °C (dec) (white needles, EtOAc) IR (KBr) 3443, 3248, 2156, 1695, 1647, 1560, 1521, 1393, 1000 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.04 (d, 2H, J=7.0 Hz); 7.94 (dd, 1H, J=1.45 Hz, J=6.6 Hz); 7.84-7.78 (m, 1H); 7.76-7.70 (m, 1H); 7.59 (dd, 2H, J=7.0 Hz, J=8.0 Hz); 7.16 (d, 1H, J=8.8 Hz); 6.78 (ddd, 1H, J=1.45 Hz, J=6.6 Hz, J=7.0 Hz); 5.75 (s, 2H) ppm; Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found C, 70.77; H, 4.92; N, 17.46. MS (CI) *m/z* 238 (M+1).

1-(Methylsulphanylmethyl)-1-H-pyridin-2-ylidencyanamide **(5g)**. Yield: 75 mg (50%). Mp 115-116 °C. (white powder, EtOH). IR (KBr) 3082, 2160, 1637, 1514, 1450, 1384, 1151 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 1H, J=6.6 Hz); 7.49 (dd, 1H, J=6.6 Hz, J=9.15 Hz); 7.32 (d, 1H, J=9.15 Hz); 6.54 (dd, 1H, J=6.6 Hz, J=9.15 Hz); 5.16 (s, 2H); 2.23 (s, 3H). Calcd for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44. Found C, 53.75; H, 4.98; N, 23.33. MS (CI) *m/z* 179 (M+1).

Synthesis of 2-Aminoimidazo[1,2-a]pyridine Derivatives **(2)**

Method A: A mixture of **4** (1 mmol), cyanamide (1.1 mol) and K_2CO_3 (0.3 g, 2.2 mmol) in MeCN (14 mL) or **6** (1 mmol), cyanamide (1.1 mmol) and K_2CO_3 (0.15 g, 1.1 mmol) was refluxed for 13-20 h. The inorganic salts were separated by filtration, washed with MeCN (3 x 3mL) and the filtrate and washes evaporated under reduced pressure. The residue was subjected to column chromatography using acetone/EtOAc (1:1) as eluent to give **2**.

Method B: To a solution of **5** (1 mmol) in dry THF (20 mL at -78 °C), LDA (1.1 equiv.) was added. The mixture was allowed to warm to room temperature, stirred for 6-24 h and then quenched with NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (3 x 15mL), and the organic layers dried and evaporated. The residue was chromatographed as indicated in method A.

2-Amino-3-ethoxycarbonylimidazo[1,2-a]pyridine **(2a)**. Following method A, the reaction of **4a** (0.33 g, 1 mmol) was refluxed for 13 h to give 0,13 g (64%) of **2a**. Method B, afforded **2a** in a 70% yield (stirring was maintained at room temperature for 24 h). Mp 131-132 °C (EtOAc, yellow powder). IR (KBr) 3445, 3270, 3128, 2925, 1667, 1480, 1323, 1220, 1088, 845 cm^{-1}. ^{1}H-NMR (300 MHz $CDCl_3$) δ 9.20 (bs, 1H); 7.33-7.31 (m, 2H); 6.90-6.80 (m, 1H); 5.20 (s, 2H); 4.42 (q, 2H, J=6.9 Hz); 1.43 (t, 3H, J=6.9 Hz) ppm. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48; Found C, 58.23; H, 5.39; N, 20.56.

2-Amino-3-benzoylimidazo[1,2-a]pyridine **(2b)**. Following method A, the reactionn of **6b** (0.23 g ,1 mmol) was refluxed for 16 h to give 0.17 g (73%) of **2b**. Method B afforded **2b** in a 65% yield (the mixture was stirred at room temperature for 20 h). Mp 196-200 °C (yellow powder, EtOAc). IR (KBr) 3550, 3482, 3104, 1644, 1630, 1579, 1497, 1342, 1005, 759 cm^{-1}. ^{1}H-NMR (500 MHz DMSO-d_6) δ 9.12 (d, 1H, J=6.0 Hz); 7.60-7.53 (m, 5H); 7.52-7.49m, 1H); 7.37 (d, 1H, J=9.0 Hz); 6.98-6.96(m, 1H); 5.60 (s, 2H) ppm. ^{13}C-NMR (500 MHz DMSO-d_6) δ 183.11; 159.6; 148.54; 141.56; 131; 130.3; 129.3; 127.98; 115; 113.78; 108.24 ppm. Calcd for$C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; Found C, 70.55; H, 4.36; N, 17.58; MS, (CI) *m/z* 238 (M+1).

2-Amino-3-(methylsulphanyl)imidazo[1,2-a]pyridine **(2e)**. Following method A, the reaction of **4c** (0.3 g, 1 mmol) was refluxed for 20 h to give 0.12 g (67%) of **2e**. Method B afforded **2e** in a 55% yield (the reaction mixture was stirred for 6 h at room temperature) Mp 110-112 °C (dec) (yellow powder, EtOAc). IR (KBr) 3290, 2894, 1642, 1497, 1025, 754 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 1H, J=5.8 Hz); 7.35-7.25 (m, 1H); 7.17-7.14 (m, 1H); 6.84-6.79 (m, 1H); 4.4 (bs, 2H); 2.14 (s, 3H) ppm; MS (CI) *m/z* 178 (M+1).

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