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REGULAR ARTICLE

Convenient two-step one-pot synthesis of 3-substituted imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]pyridazines

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Abstract. A convenient and novel two-step one-pot method for the synthesis of 3-substituted imidazo[1,2-*a*]pyridines and 3-substituted imidazo[1,2-*b*]pyridazines was developed through the reaction of heterocyclic amines and *N*, *N*-dimethylformamide dimethyl acetate with active electrophiles RCH_2Br (R = CO_2Et, CN, COPh, 4'-MeO-PhCO and 4'-F-PhCO). This protocol provides a simple and practical approach to 3-substituted fused imidazo-heterocyclic compounds in moderate to high yields.

Keywords. Imidazo[1, 2-*a*]pyridine; imidazo[1, 2-*b*]pyridazine; heterocyclic amine; active electrophiles.

1. Introduction

Imidazo[1,2-*a*]pyridines exhibit diverse biological properties such as anticonvulsant,[1] antimicrobial,[2] antiviral,[3] antiparasitic,[4] anti-inflammatory,[5] antituberculosis[6] and inhibitory effects on DNA oxidation and quenching radicals.[7] They are also ligands for major inhibitory neurotransmitter receptors.[8] Consequently, many useful synthetic methods have been reported in the literature. Generally, such nitro-containing fused heterocycles are prepared through the condensation of heterocyclic amines with α-haloketones in the presence of an inorganic base at high temperatures.[9] This method also produces 2-substituted products. Recently, some novel synthetic approaches have been developed to construct 3-substituted imidazo[1,2-*a*]pyridines.[10] Although a number of investigations have been carried out, developing a convenient and library-friendly method is still desirable in hit-to-lead drug discovery, which requires quick follow-up to construct 3-substituted imidazo[1,2-*a*]pyridines from readily accessible starting materials in a single operation under mild conditions. Herein, we report a two-step one-pot approach to the synthesis of 3-substituted imidazo[1,2-*a*]pyridines. Commercially available 2-aminopyridine and its derivatives were reacted with DMF-DMA (*N*, *N*-dimethylformamide dimethyl acetate) to produce the corresponding intermediates in near quantitative yields, which were subsequently condensed with active electrophiles, such as ethyl bromoacetate, bromoacetonitrile, 2-bromoacetophenone, 2-bromo-4'-methoxyacetophenone or 2-bromo-4'-fluoroacetophenone in the same flask without isolation to afford the desired 3-substituted imidazo[1,2-*a*]pyridines.

2. Experimental

2.1 *Materials and physical measurements*

All 2-aminopyridines **1a**–**1f**, 6-chloropyridazin-3-amine **6** and active electrophiles **3a**–**3e** were purchased from Nanjing Chemical Reagent Co., Ltd., (Nanjing, China, Purity more than 97%), all reagents and solvents were used as received. Column chromatography was performed using silica gel (200–300 mesh). Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz) at 25 °C, using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts (δ ppm) are reported with respect to tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded using the Electrospray

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Ionization Method (ESI) on Agilent mass spectrometers (G1969A LC/MSD TOF and 6545 Q-TOF LC/MS). Melting points were measured on a WRS-1 apparatus and are uncorrected.

2.2 *Synthesis of 3-substituted imidazo[1,2-a]pyridines **4a-4n** and **5a-5f***

2.2a *Typical procedure for preparation of **4a–4h** (**4a** as an example):*: A solution of 0.094 g 2-aminopyridine (**1a**, 1 mmol) and 0.24 g DMF-DMA (2 mmol) in 2 mL DMF was stirred at 65 °C for 2 h. Then, 0.126 g $NaHCO_3$ (1.5 mmol) and 0.217 g ethyl bromoacetate (**3a**, 1.3 mmol) were added sequentially. The mixture was stirred at 85 °C. After the reaction was completed as monitored by thin layer chromatography (TLC), it was diluted with 20 mL water and extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:6) to afford pure product **4a**.

2.2.1a *Ethyl imidazo[1,2-a]pyridine-3-carboxylate **4a***:[11] White solid; M.p.: 50–51 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400MHz): 1.43 (t, J = 7.2 Hz, 3H, CH_3); 4.42 (q, J = 7.2Hz, 2H, CH_2); 7.05 (t, J = 6.8 Hz, 1H, ArH); 7.42 (t, J = 8.4 Hz, 1H, ArH); 7.74 (d, J = 8.8 Hz, 1H, ArH); 8.31 (s, 1H, ArH); 9.31 (d, J = 6.8Hz, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 180.58, 148.35, 141.42, 127.59, 127.39, 117.79, 115.77, 114.14, 60.38, 14.41. HRMS-ESI: Calcd. for $C_{10}H_{11}N_2O_2(M+H)^+$: 191.0815, Found: 191.0811.

2.2.1b *Ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate **4b***:[10b] Light brown solid; M.p.: 109–110 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 1.42 (t, J = 7.2 Hz, 3H, CH_3); 4.42 (q, J = 7.2 Hz, 2H, CH_2); 7.50 (dd, J_1 = 9.2 Hz, J_2 = 1.8 Hz, 1H, ArH); 7.64 (d, J = 9.6 Hz, 1H, ArH); 8.29 (s, 1H, ArH); 9.51 (d, J = 2.0 Hz, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 160.34, 146.73, 141.49, 130.92, 127.83, 118.35, 116.12, 109.22, 60.74, 14.39. HRMS-ESI: Calcd. for $C_{10}H_{10}BrN_2O_2(M+H)^+$: 268.9920, Found: 268.9915.

2.2.1c *Ethyl 6-chloroimidazo[1,2-a]pyridine-3-carboxylate **4c***:[12] White solid; M.p.: 92 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 1.44 (t, J = 7.2 Hz, 3H, CH_3); 4.44 (q, J = 7.2 Hz, 2H, CH_2); 7.41 (dd, J_1 = 9.6 Hz, J_2 = 2.0 Hz, 1H, ArH); 7.70 (d, J = 9.6 Hz, 1H, ArH); 8.30 (s, 1H, ArH); 9.41 (d, J = 2.4 Hz, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 160.33, 146.62, 141.69, 128.76, 125.67, 122.64, 118.05, 116.25, 60.72, 14.39. HRMS-ESI: Calcd. for $C_{10}H_{10}ClN_2O_2(M+H)^+$: 225.0425, Found: 225.0417.

2.2.1d *Ethyl 6-fluoroimidazo[1,2-a]pyridine-3-carboxylate **4d***:[13] White solid; M.p.: 52–53 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 1.42 (t, J = 7.2 Hz, 3H, CH_3); 4.42 (q, J = 7.2 Hz, 2H, CH_2); 7.34 (td, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, ArH); 7.71 (dd, J_1 = 9.6 Hz, J_2 = 4.8Hz, 1H, ArH); 8.30 (s, 1H, ArH); 9.28 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 160.42, 154.06 (d, J_{C-F} = 237.3 Hz), 145.85, 141.95 (d, J_{C-F} = 2.5 Hz), 119.18 (d, J_{C-F} = 25.1 Hz), 118.11 (d, J_{C-F} = 8.9 Hz), 114.96 (d, J_{C-F} = 42.6 Hz), 109.99, 60.67, 14.39. HRMS-ESI: Calcd. for $C_{10}H_{10}FN_2O_2(M+H)^+$: 209.0721, Found: 209.0713.

2.2.1e *Iimidazo[1,2-a]pyridine-3-carbonitrile **4e***:[14] White solid; M.p.: 160 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.15 (t, J = 7.2 Hz, 1H); 7.50 (t, J = 7.2 Hz, 1H); 7.81 (d, J = 9.2 Hz, 1H); 8.20 (s, 1H); 8.40 (d J = 9.2 Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 147.20, 142.47, 128.32, 125.66, 118.69, 115.09, 111.13, 98.20. HRMS-ESI: Calcd. for $C_8H_6N_3(M+H)^+$: 144.0556, Found: 144.0550.

2.2.1f *(Imidazo[1,2-a]pyridin-3-yl)phenylmethanone **4f***:[10b] White solid; M.p.: 110–111 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 7.33 (t, J = 7.4 Hz, 1H); 7.57 (t, J = 7.6 Hz, 2H); 7.68 (m, 2H); 7.87 (t, J = 7.4 Hz, 3H); 8.24 (s, 1H); 9.63 (d, J = 7.2Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 184.82, 149.05, 145.63, 139.24, 132.04, 129.45, 128.88, 128.83, 128.59, 123.52, 117.73, 115.15. HRMS-ESI: Calcd. for $C_{14}H_{11}N_2O$ $(M+H)^+$: 223.0866, Found: 223.0856.

2.2.1g *(Imidazo[1,2-a]pyridin-3-yl)(4'-methoxyphenyl) methanone **4g***:[10b] White solid; M.p.: 113–114 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 3.91 (s, 3H, CH_3); 7.03 (d, J = 8.8 Hz, 2H, ArH); 7.26 (t, J = 7.2 Hz, 1H, ArH); 7.67 (t, J = 8.4 Hz, 1H, ArH); 7.89 (d J = 8.8 Hz, 2H, ArH); 7.99 (d, J = 9.2 Hz, 1H, ArH); 8.25 (s, 1H, ArH); 9.71 (d, J = 6.8 Hz, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 183.40, 163.45, 146.53, 140.41, 131.20, 131.01, 130.94, 129.04, 123.21, 116.63, 116.15, 114.14, 55.61. HRMS-ESI: Calcd. for $C_{15}H_{13}N_2O_2(M+H)^+$: 253.0972, Found: 253.0947.

2.2.1h *(4'-Fluorophenyl)(imidazo[1,2-a]pyridin-3-yl)methanone **4h***:[10b] White solid; M.p.: 132–133 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.16–7.26 (m, 3H); 7.60 (t, J = 7.8 Hz, 1H); 7.83(d J = 8.8 Hz, 1H); 7.90–7.95 (m, 2H); 8.21 (s, 1H); 9.73 (d, J = 6.8 Hz, 1H). ^{13}C NMR (δ, ppm in DMSO-d_6, 100 MHz): 182.32; 164.37 (d, J_{C-F} = 198.6 Hz); 148.54; 145.36; 135.31; 131.56 (d, J_{C-F} = 7.2 Hz); 130.17; 128.45; 122.81; 117.52; 115.76 (d, J_{C-F} = 17.4Hz); 115.74. HRMS-ESI: Calcd. for $C_{14}H_{10}FN_2O$ $(M+H)^+$: 241.0772, Found: 241.0757.

2.2b *Typical procedure for preparation of **4i–4n** (**4i** as an example)*: A solution of 0.173 g 2-amino-5-bromopyridine (**1b**, 1 mmol) and 0.24 g DMF-DMA (2 mmol) in 2 mL DMF was stirred at 65 °C for 3 h. Then, 0.126 g $NaHCO_3$ (1.5 mmol), 0.033 g KI (0.2 mmol) and 0.156 g bromoacetonitrile (**3b**, 1.3 mmol) were added sequentially. The mixture was stirred at 85 °C. After the reaction was completed as monitored by TLC, it was diluted with 20 mL water and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform/hexane, 3:1) to afford pure product **4i**.

2.2.2a *6-Bromoimidazo[1,2-a]pyridine-3-carbonitrile **4i***:[10d] White solid; M.p.: 194–196 °C. ^{1}H NMR (δ, ppm in

$CDCl_3$, 400 MHz): 7.47 (dd, $J_1 = 9.8$ Hz, $J_2 = 2.0$ Hz, 1H); 7.74 (d, $J = 9.6$ Hz, 1H); 8.17 (s, 1H); 8.42 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 145.85, 142.66, 132.00, 125.81, 119.20, 110.52, 110.08, 98.54. HRMS-ESI: Calcd. for $C_8H_5BrN_3(M+H)^+$: 221.9661, Found: 221.9652.

2.2.2b *6-Chloroimidazo[1,2-a]pyridine-3-carbonitrile* ***4j***: [15] Light yellow solid; M.p.: 195–198 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.53 (dd, $J_1 = 9.6$ Hz, $J_2 = 1.8$ Hz, 1H); 7.68 (d, $J = 9.6$Hz, 1H); 8.15 (s, 1H); 8.52 (d, $J = 1.6$ Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 145.66, 142.77, 132.00, 129.90, 123.64, 119.20, 118.96, 110.45, 109.99. HRMS-ESI: Calcd. for $C_8H_5ClN_3(M+H)^+$: 178.0167, Found: 178.0158.

2.2.2c *6-fluoroimidazo[1,2-a]pyridine-3-carbonitrile* ***4k***: [16] White solid; M.p.: 173–176 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 7.70 (td, $J_1 = 10.0$ Hz, $J_2 = 2.0$ Hz, 1H); 7.92 (dd, $J_1 = 9.8$ Hz, $J_2 = 5.2$ Hz, 1H); 8.48 (s, 1H); 8.98 (t, $J = 3.0$ Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 154.50 (d, $J_{C-F} = 241.6$ Hz), 144.79, 143.02 (d, $J_{C-F} = 2.4$ Hz), 120.43 (d, $J_{C-F} = 25.1$ Hz), 119.23 (d, $J_{C-F} = 8.9$ Hz), 112.99 (d, $J_{C-F} = 41.2$ Hz), 110.53, 99.61. HRMS-ESI: Calcd. for $C_8H_5FN_3(M+H)^+$: 162.0462, Found: 162.0459.

2.2.2d *(6-Bromoimidazo[1,2-a]pyridin-3-yl)phenylmethanone* ***4l***: [10b] White solid; M.p.: 143–145 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.57 (t, $J = 7.6$ Hz, 2H); 7.67 (t, $J = 7.2$ Hz, 1H); 7.79–7.86 (m, 4H); 8.25 (s, 1H); 9.70 (s, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 184.70, 147.34, 145.40, 138.78, 132.70, 132.29, 128.96, 128.80, 128.65, 123.53, 118.20, 110.05. HRMS-ESI: Calcd. for $C_{14}H_{10}BrN_2O$ $(M + H)^+$: 300.9971, Found: 300.9955.

2.2.2e *(6-Chloroimidazo[1,2-a]pyridin-3-yl)phenylmethanone* ***4m***: [10c] White solid; M.p.: 138 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 7.59 (t, $J = 7.4$ Hz, 2H); 7.69 (t, $J = 7.4$ Hz, 1H); 7.78 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.0$ Hz, 1H); 7.88 (d, $J = 7.2$ Hz, 2H); 7.94 (d, $J = 9.6$ Hz, 1H); 8.31 (s, 1H); 9.68 (d, $J = 1.6$ Hz, 1H). ^{13}C NMR (δ, ppm in DMSO-d_6, 100 MHz): 183.78, 146.75, 145.38, 138.26, 132.36, 130.49, 128.78, 128.72, 126.01, 123.16, 122.32, 118.26. HRMS-ESI: Calcd. for $C_{14}H_{10}ClN_2O$ $(M + H)^+$: 257.0476, Found: 257.0454.

2.2.2f *(6-Fluoroimidazo[1,2-a]pyridin-3-yl)phenylmethanone* ***4n***: [10c] Light yellow solid; M.p.: 131–132 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 7.58 (t, $J = 7.6$ Hz, 2H); 7.68 (t, $J = 7.4$ Hz, 1H); 7.80 (td, $J_1 = 8.6$ Hz, $J_2 = 2.4$ Hz, 1H); 7.87 (d, $J = 8.4$ Hz, 2H); 7.97 (dd, $J_1 = 9.6$ Hz, $J_2 = 5.2$ Hz, 1H); 8.30 (s, 1H); 9.62 (dd, $J_1 = 5.0$ Hz, $J_2 = 2.6$ Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 184.72; 154.80 (d, $J_{C-F} = 239.7$ Hz); 145.14; 143.56 (d, $J_{C-F} = 1.7$ Hz); 138.38; 132.62; 128.80 (d, $J_{C-F} = 2.9$ Hz); 121.94 (d, $J_{C-F} = 24.9$ Hz); 117.48 (d, $J_{C-F} = 9.7$ Hz); 116.601; 116.172. HRMS-ESI: Calcd. for $C_{14}H_{10}FN_2O$ $(M + H)^+$: 241.0772, Found: 241.0767.

2.2c *Typical procedure for preparation of* ***5a–5f*** *(****5a*** *as an example)*: A solution of 0.11 g 2-amino-3-hydroxypyridine (**1e**, 1 mmol) and 0.24 g DMF-DMA (2 mmol) in 2 mL DMF was stirred at 65 °C for 2 h. Then, 0.252 g $NaHCO_3$ (3 mmol) and 0.417 g ethyl bromoacetate (**3a**, 2.5 mmol) were added sequentially. The mixture was stirred at 85 °C. After the reaction was completed as monitored by thin layer chromatography (TLC), it was diluted with 20 mL water and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform/hexane, 1:1) to afford pure product **5a**.

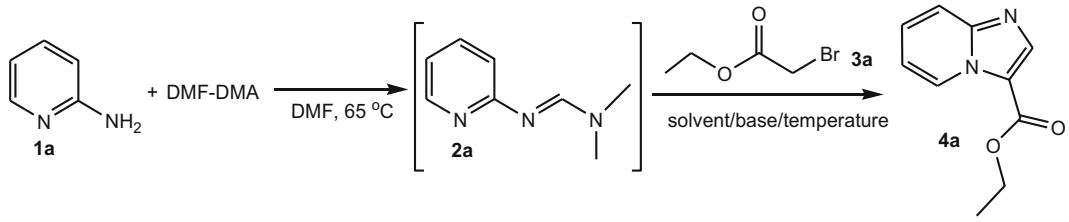
2.2.3a *Ethyl 8-(2-ethoxy-2-oxoethoxy)H-imidazo[1,2-a]pyridine-3-carboxylate* ***5a***: White solid, M.p.: 93–95 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 1.29 (t, $J = 7.2$ Hz, 3H, CH_3), 1.43 (t, $J = 7.2$ Hz, 3H, CH_3), 4.28 (q, $J = 7.2$ Hz, 2H, CH_2), 4.42 (q, $J = 7.2$ Hz, 2H, CH_2), 4.98 (s, 2H, CH_2), 6.72 (d, $J = 7.6$ Hz, 1H, ArH), 6.93 (t, $J = 7.4$ Hz, 1H, ArH), 8.26 (s, 1H, ArH), 9.00 (d, $J = 6.8$ Hz, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 168.11, 160.57, 147.02, 142.34, 140.37, 121.44, 116.87, 113.88, 107.16, 66.28, 61.51, 60.51, 14.40, 14.11. HRMS-ESI: Calcd. for $C_{14}H_{17}N_2O_5$ $(M+H)^+$: 293.1132, Found: 293.1123.

2.2.3b *8-(Cyanomethoxy)H-imidazo[1,2-a]pyridine-3-carbonitrile* ***5b***: Light brown solid; M.p.: 229–230 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 5.47 (s, 2H, CH_2), 7.23 (m, 2H, ArH), 8.39 (d, $J = 5.2$ Hz, 1H, ArH), 8.43 (s, 1H, ArH). ^{13}C NMR (δ, ppm in DMSO-d_6, 100 MHz): 145.96, 142.68, 140.85, 121.56, 116.40, 115.42, 111.67, 109.08, 99.22, 54.99. HRMS-ESI: Calcd.. for $C_{10}H_7N_4O$ $(M + H)^+$: 199.0614, Found: 199.0608.

2.2.3c *2-(3-BenzoylH-imidazo[1,2-a]pyridin-8-yloxy)-1-phenylethanone* ***5c***: White solid, M.p.: 209–211 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 5.97 (s, 2H, CH_2), 7.20 (m, 2H, ArH), 7.60 (t, $J = 7.6$ Hz, 4H, ArH), 7.71 (m, 2H, ArH), 7.90 (d, $J = 7.2$ Hz, 2H, ArH), 8.06 (d, $J = 7.6$ Hz, 2H, ArH), 8.19 (s, 1H, ArH), 9.28 (d, $J = 6.8$ Hz, 1H, ArH). ^{13}C NMR (δ, ppm in DMSO-d_6, 100 MHz): 194.19, 184.39, 147.38, 144.49, 142.71, 139.16, 134.54, 134.44, 132.64, 129.35, 129.16, 128.36, 124.11, 121.53, 116.12, 109.65, 71.45. HRMS-ESI: Calcd. for $C_{22}H_{17}N_2O_3(M + H)^+$: 357.1234, Found: 357.1225.

2.2.3d *Ethyl6-bromo-8-(2-ethoxy-2-oxoethoxy)H-imidazo[1,2-a]pyridine-3-carboxylate* ***5d***: White solid, M.p.: 92–94 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 1.31 (t, $J = 7.0$ Hz, 3H, CH_3), 1.43 (t, $J = 7.0$ Hz, 3H, CH_3), 4.30 (q, $J = 7.2$ Hz, 2H, CH_2), 4.43 (q, $J = 7.2$ Hz, 2H, CH_2), 4.97 (s, 2H, CH_2), 6.81 (s, 1H, ArH), 8.21 (s, 1H, ArH), 9.17 (s, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 400 MHz): 167.60, 160.29, 146.66, 140.95, 140.27, 121.59, 117.03, 111.40, 108.55, 66.42, 61.80, 60.80, 14.36, 14.11. HRMS-ESI: Calcd. for $C_{14}H_{16}BrN_2O_5(M+H)^+$: 371.0237, Found: 371.0231.

2.2.3e *6-Bromo-8-(cyanomethoxy)H-imidazo[1,2-a]pyridine-3-carbonitrile* ***5e***: Light brown solid, M.p.: 207–208 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 5.50 (s, 2H, CH_2), 7.46 (s, 1H, ArH), 8.43 (s, 1H, ArH), 8.66 (s, 1H, ArH). ^{13}C NMR (δ, ppm in DMSO-d_6, 100 MHz): 145.70, 142.83,



Scheme 1. Synthesis of ethyl imidazo[1,2-*a*]pyridine-3-carboxylate **4a**.

139.63, 121.70, 116.11, 112.31, 111.16, 108.89, 99.79, 55.29. HRMS-ESI: Calcd. for $C_{10}H_6BrN_4O$ $(M + H)^+$: 276.9719, Found: 276.9715.

2.2.3f *2-(3-Benzoyl-6-bromoH-imidazo[1,2-a]pyridin-8-yloxy)-1-phenylethanone* ***5f***: Light yellow solid, M.p.: 212–215 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 6.01 (s, 2H, CH_2), 7.51 (s, 1H, ArH), 7.61 (t, J = 7.6 Hz, 4H, ArH), 7.71 (m, 2H, ArH), 7.90 (d, J = 7.2 Hz, 2H, ArH), 8.06 (d, J = 7.2 Hz, 2H, ArH), 8.21 (s, 1H, ArH), 9.42(s, 1H, ArH). ^{13}C NMR (δ, ppm in DMSO-d_6, 100 MHz): 193.50, 184.50, 147.52, 144.25, 141.47, 138.81, 134.55, 134.40, 132.86, 129.26, 129.19, 128.43, 124.25, 121.17, 112.64, 109.83, 71.84. HRMS-ESI: Calcd. for $C_{22}H_{16}BrN_2O_3$ $(M + H)^+$: 435.0339, Found: 435.0332.

2.2d *Typical procedure for preparation of 3-substituted imidazo[1,2-b]pyridazines* ***8a–8c****(****8a*** *as an example)*: A solution of 0.130 g 6-chloropyridazin-3-amine (**6**, 1 mmol) and 0.24 g DMF-DMA (2 mmol) in 2 mL DMF was stirred at 65 °C for 3 h. Then, 0.126 g $NaHCO_3$(1.5 mmol), 0.033 g KI (0.2 mmol) and 0.217 g ethyl bromoacetate (**3a**, 1.3 mmol) were added sequentially. The mixture was stirred at 85 °C. After the reaction was completed as monitored by TLC, it was diluted with 20 mL water and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform/hexane, 3:1) to afford pure product **8a**.

2.2.4a *Ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate* ***8a***: Light brown solid; M.p: 92–93 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 1.45 (t, J = 7.2 Hz, 3H, CH_3); 4.48 (q, J = 7.0 Hz, 2H, CH_2); 7.28 (d, J = 9.2 Hz, 1H, ArH); 8.03 (d, J = 9.6 Hz, 1H, ArH); 8.39 (s, 1H, ArH). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 158.20, 148.38, 140.93, 140.67, 127.40, 121.51, 120.48, 61.08, 14.33. HRMS-ESI: Calcd. for $C_9H_9ClN_3O_2$ $(M + H)^+$: 226.0378, Found: 226.0377.

2.2.4b *6-Chloroimidazo[1,2-b]pyridazine-3-carbonitrile* ***8b***:[11] Light yellow solid; M.p.: 143–144 °C. ^{1}H NMR (δ, ppm in $CDCl_3$, 400 MHz): 7.34 (d, J = 9.6 Hz, 1H); 8.07 (d, J = 9.6 Hz, 1H); 8.26 (s, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 159.83, 149.39, 141.72, 139.61, 127.74, 123.00, 109.12. HRMS-ESI: Calcd. for $C_7H_4ClN_4$ $(M+H)^+$: 179.0119, Found: 179.0113.

2.2.4c *(6-Chloroimidazo[1,2-b]pyridazin-3-yl)(phenyl)methanone* ***8c***:[10a] Light yellow solid; M.p.: 257–258 °C. ^{1}H NMR (δ, ppm in DMSO-d_6, 400 MHz): 7.59 (t, J = 7.4 Hz, 2H); 7.69 (t, J = 9.6 Hz, 2H); 7.99 (d, J = 7.2 Hz, 2H); 8.28 (s, 1H); 8.44 (d, J = 9.6 Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$, 100 MHz): 182.53, 149.32, 140.31, 140.19, 137.69, 133.36, 129.43, 128.79, 126.95, 126.85, 123.59. HRMS-ESI: Calcd. for $C_{13}H_9ClN_3O$ $(M + H)^+$: 258.0429, Found: 258.0420.

3. Results and Discussion

3.1 *Optimization of the reaction conditions of* ***4a***

Initially, we found that treatment of 2-aminopyridine **1a** with DMF-DMA in DMF at 65 °C resulted in the formation of (*E*)-*N*, *N*-dimethy-*N*′-(pyridin-2-yl)-formamidine **2a** clearly by TLC in consistence with literature report.[17]

Then, we turned our attention to the optimization of reaction conditions of the second step, namely the cyclization process between the intermediate **2a** and ethyl bromoacetate **3a**, to establish an efficient two-step one-pot procedure for the synthesis of ethyl imidazo[1,2-*a*]pyridine-3-carboxylate **4a** (Scheme 1). As shown in Table 1, different bases and solvents were investigated at varied temperatures. The reaction was found to proceed smoothly in the presence of 1.5 equivalent of $NaHCO_3$ in DMF at 85 °C, delivering the product **4a** in 83% yield (Table 1, entry 1). Decrease or increase in temperature had no positive effect on the reaction efficiency (Table 1, entry 2–3). Switching to other solvents such as EtOH and dioxane, led to inferior results (Table 1, entries 4–5). Other inorganic and organic bases were also found to promote this transformation albeit in relatively low yields (Table 1, entry 6–12). Taken together, we found that the optimal protocol for the second step of preparing **4a** was to conduct the reaction in DMF at 85 °C with 1.5 equivalent of $NaHCO_3$ as a base. The complete synthesis of **4a** was adopted as a two-step one-pot procedure.

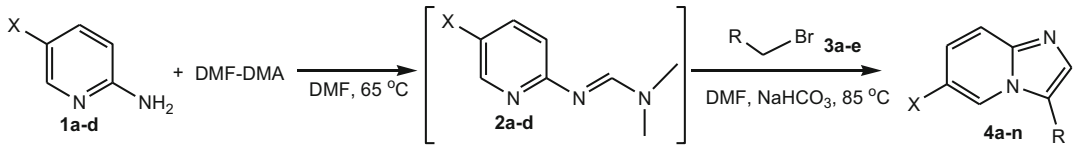
3.2 *Synthesis of 3-substituted imidazo[1,2-a]pyridines* ***4a–4n***

With the above optimized two-step one-pot procedure, the reactions of 2-aminopyridine **1a** and DMF-DMA with several active electrophiles RCH_2Br

Table 1. Optimization of the reaction conditions for the second-step condensation of **4a**[a].

Entry	Base	Solvent	Time (h)[b]	Temperature (°C)[c]	Yield (%)[d]
1	$NaHCO_3$	DMF	1	85	83
2	$NaHCO_3$	DMF	1.5	75	81
3	$NaHCO_3$	DMF	1	95	79
4	$NaHCO_3$	EtOH	3	reflux	63
5	$NaHCO_3$	Dioxane	1.5	85	65
6	Na_2CO_3	DMF	2	85	70
7	Na_2CO_3	EtOH	3	reflux	51
8	Na_2CO_3	Dioxane	2	85	56
9	K_2CO_3	DMF	1	85	65
10	NaOH	DMF	1	85	47
11	C_5H_5N	DMF	7	85	39
12	Et_3N	DMF	5	85	46

[a]Reaction conditions: 2-Aminopyridine **1a** (1.0 mmol) and DMF-DMA (2.0 equiv) were mixed and stirred in DMF (2 mL) at 65 °C for 2 h. Then, ethyl bromoacetate **3a** (1.3 equiv) and base (1.5 equiv) were added and the stirring continued for additional 1–7 h. [b]Reaction time for the second step. [c]Reaction temperature for the second step. [d]Isolated yield based on **1a**.



Scheme 2. Synthesis of 3-substituted imidazo[1,2-*a*]pyridines **4a**–**4n**.

(R = CN, CO_2Et, COPh, 4'-MeO-PhCO and 4'-F-PhCO) **3a**–**3e** were carried out successfully to give corresponding 3-substituted imidazo[1,2-*a*]pyridines **4a**, **4e**–**4h** in good yields (Scheme 2, Table 2, entry 1, 5–8). 2-Amino-5-halopyridines **1b**–**1d** and DMF-DMA with ethyl bromoacetate **3a** also participated well in this conversion (Scheme 2, Table 2, entry 2–4). However, further expansion of the two-step one-pot process to the reaction of 2-amino-5-halopyridines **1b**–**1d** and DMF-DMA with bromoacetonitrile **3b** or 2-bromoacetophenone **3c** under the same reaction conditions gave the desired bicyclic products in very low yields (< 20%), along with some unknown by-products. Fortunately, the addition of 20 mol% KI into the second-step reaction mixture significantly improved the yields because bromide group in **3b**–**3c** could be substituted with iodide to generate more reactive iodoacetonitrile and 2-iodoacetophenone. With KI as an additive in the second step, we successfully conducted the reactions of **1b**–**1d** and DMF-DMA with bromoacetonitrile **3b** or 2-bromoacetophenone **3c** to afford the corresponding 3-substituted imidazo[1,2-*a*]pyridines **4i**–**4n** in moderate to good yields (Scheme 2, Table 2, entries 9–14).

The results presented in Table 2 demonstrated that electron-withdrawing groups in the pyridine ring reduced the reactivity to form the products. 2-Aminopyridine **1a** afforded the desired products in high yields ranging from 74% to 89% (Tables 2, entry 1 and 5–8). On the other hand, the reactions of **1b**–**1d** (containing Br, Cl and F, respectively) and DMF-DMA with **3a** required longer reaction time and the yields were slightly lower compared with **1a** (Tables 2, entry 1–4). As for the reactions of **1b**–**1d** and DMF-DMA with less reactive electrophiles **3b** and **3c**, 20 mol% KI was necessary for better yields (Tables 2, entry 9–14), most likely through more reactive iodide species.

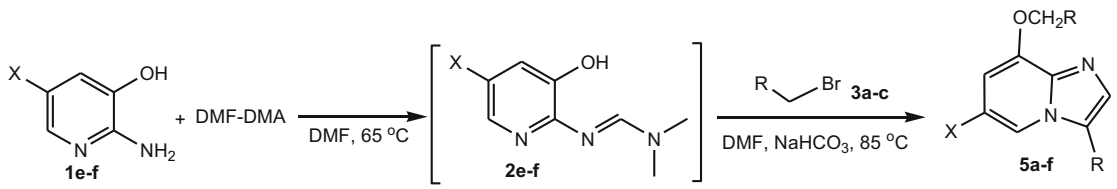
3.3 *Synthesis of 3-substituted imidazo[1,2-a]pyridines **5a–5f***

During the course of expanding the substrate scope of the two-step one-pot reaction, we found that the reaction of 2-amino-3-hydroxypyridine **1e** and DMF-DMA with ethyl bromoacetate **3a** under the optimal reaction conditions (without KI) gave rise to the formation of an unexpected product **5a** in which the hydroxyl group underwent a substitution reaction with the active electrophile along with the imidazole ring formation. However, intermediate **2e** was detected as the major product by TLC analysis. Notably, the substitution reaction still occurred inevitably without $NaHCO_3$ or adding the solution of 0.8 equivalent of **3a**–**3c** in DMF dropwise in the second step of the reaction. Finally, when 2.5 equivalent of **3a**–**3c** and 2.5 equivalent of

Table 2. Substitution of compounds **1-4** according to Scheme 2[a].

Entry	1	X	3	Time(h)[b]	Product	Yield (%)[c]
1	**1a**	H	**3a** (R = CO_2Et)	1	**4a**	83
2	**1b**	Br	**3a** (R = CO_2Et)	3	**4b**	80
3	**1c**	Cl	**3a** (R = CO_2Et)	3	**4c**	76
4	**1d**	F	**3a** (R = CO_2Et)	4	**4d**	73
5	**1a**	H	**3b** (R = CN)	1	**4e**	78
6	**1a**	H	**3c** (R = COPh)	1	**4f**	89
7	**1a**	H	**3d** (R = 4′-MeO-PhCO)	1	**4g**	74
8	**1a**	H	**3e** (R = 4′-F-PhCO)	1	**4h**	87
9[d]	**1b**	Br	**3b** (R = CN)	3	**4i**	75
1[d]	**1c**	Cl	**3b** (R = CN)	3	**4j**	71
11[d]	**1d**	F	**3b** (R = CN)	4	**4k**	59
12[d]	**1b**	Br	**3c** (R = COPh)	1.5	**4l**	87
13[d]	**1c**	Cl	**3c** (R = COPh)	1.5	**4m**	78
14[d]	**1d**	F	**3c** (R = COPh)	2	**4n**	68

[a]Reaction conditions: 2-Aminopyridine or its derivatives **1a**–**1f** (1.0 mmol) and DMF-DMA (2.0 equiv) were mixed and stirred in DMF (2 mL) at 65 °C for 2–3 h. Then, active electrophiles **3a**–**3e** (1.3 equiv) and $NaHCO_3$ (1.5 equiv) were added and the stirring continued at 85 °C for additional 1–4 h. [b]Reaction time for the second step. [c]Isolated yield based on **1a**–**1f**. [d]The second step of the reaction was run with 0.2 equivalent of KI.



Scheme 3. Synthesis of 3-substituted imidazo[1,2-*a*]pyridines **5a**–**5f**.

Table 3. Substitution of compounds **1**, **2** and **5** according to Scheme 3[a].

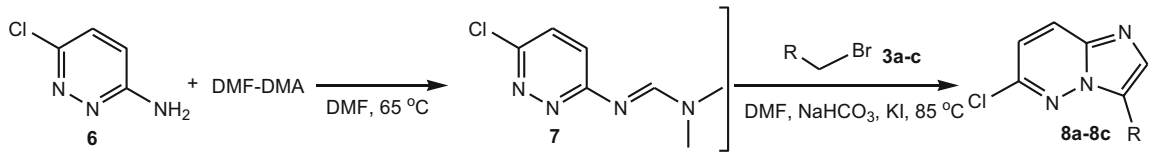
Entry	1	X	3	Time (h)[b]	Product	Yield (%)[c]
1	**1e**	H	**3a** (R = CO_2Et)	1	**5a**	84
2	**1e**	H	**3b** (R = CN)	1	**5b**	74
3	**1e**	H	**3c** (R = COPh)	1	**5c**	75
4	**1f**	Br	**3a** (R = CO_2Et)	1	**5d**	72
5	**1f**	Br	**3b** (R = CN)	3	**5e**	64
6	**1f**	Br	**3c** (R = COPh)	3	**5f**	67

[a]Reaction conditions: 2-Amino-3-hydroxypyridine **1e**–**1f** (1.0 mmol) and DMF-DMA (2.0 equiv) were mixed and stirred in DMF (2 mL) at 65 °C for 1 h. Then, active electrophiles **3b**–**3c** (2.5 equiv), $NaHCO_3$ (3 equiv) were added and the stirring continued at 85 °C for additional 1–3 h. [b]Reaction time for the second step. [c]Isolated yield based on **1e**–**1f**.

$NaHCO_3$ were used in the second step of the reaction, various 3-substituted imidazo[1,2-*a*]pyridines **5a**–**5f** were obtained in good yields (Scheme 3, Table 3).

3.4 *Synthesis of 3-substituted imidazo[1,2-b]pyridazines **8a**–**8c***

For further investigation, 6-chloropyridazin-3-amine **6** was also tested to synthesize the corresponding 3-substituted fused imidazo-heterocyclic compounds. Intermediate (*E*)-*N*′-(6-chloropyridazin-3-yl)-*N*, *N*-dimethyformamidine **7** that formed in near quantitative yield, as detected by TLC,[17] subsequently reacted with **3a**–**3c** in situ and afforded the desired 3-substituted imidazo[1,2-*b*]pyridazines **8a**–**8c** in moderate yields with $NaHCO_3$ as a base and KI (20 mol%) as an additive at 85 °C (Scheme 4, Table 4). This reaction represents a novel approach for the synthesis of 3-substituted imidazo[1,2-*b*]pyridazines.



Scheme 4. Synthesis of 3-substituted imidazo[1,2-*b*]pyridazines **8a**–**8c**.

Table 4. Synthesis of 3-substituted imidazo[1,2-*b*]pyridazines **8a**–**8c**[a].

Entry	**3**	Time (h)[b]	Product	Yield (%)[c]
1	**3a** (R = CO_2Et)	3	**8a**	73
2	**3b** (R = CN)	4	**8b**	60
3	**3c** (R = COPh)	3	**8c**	57

[a]Reaction conditions: 6-Chloropyridazin-3-amine **6** (1.0 mmol) and DMF-DMA (2.0 equiv) were mixed and stirred in DMF (2 mL) at 65 °C for 3 h. Then, active electrophiles **3a**–**3c** (1.3 equiv), $NaHCO_3$ (1.5 equiv) and KI (0.2 equiv) were added and the stirring continued at 85 °C for additional 3–4 h. [b]Reaction time for the second step. [c]Isolated yield based on **6**.

4. Conclusions

In summary, we have developed a convenient and straight-forward two-step one-pot method for the preparation of a wide variety of 3-substituted imidazo [1,2-*a*]pyridines and 3-substituted imidazo[1,2-*b*]pyrid azines from readily available starting materials. The second step of the reaction is based on the condensation of intermediate (*E*)-*N*,*N*-dimethy-*N*′-(pyridin-2 -yl)-formamidine and its derivatives or (*E*)-*N*′-(6-chloro pyridazin-3-yl)-*N*, *N*-dimethyformamidine with active electrophiles RCH_2Br (R = CN, CO_2Et, COPh, 4'-MeO-PhCO and 4'-F-PhCO) in the presence of $NaHCO_3$.

Supplementary Information (SI)

Copies of the original spectra (^1H NMR, ^{13}C NMR, mass, etc.) of all the molecules reported in the experimental section are included in Supplementary Information. Supplementary Information is available at www.ias.ac.in/chemsci.

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References

1. Fradley R L, Guscott M R, Bull S, Hallett D J, Goodacre S C, Wafford K A, Garrett E M, Newman R J, O'Meara G F, Whiting P J, Rosahl T W, Dawson G R, Reynolds D S and Atack J R 2007 Differential contribution of $GABA_A$ receptor subtypes to the anticonvulsant efficacy of benzodiazepine site ligands *J. Psychopharmacol.* **21** 384; (b) Ulloora S, Shabaraya R, Aamir S and Adhikari A V 2013 New imidazo[1,2-*a*]pyridines carrying active pharmacophores: Synthesis and anticonvulsant studies *Bioorg. Med. Chem. Lett.* **23** 1502
2. (a) Ramachandran S, Panda M, Mukherjee K, Choudhury N R, Tantry S J, Kedari C K, Ramachandran V, Sharma S, Ramya V K, Guptha S and Sambandamurthy V K 2013 Synthesis and structure activity relationship of imidazo[1,2-*a*]pyridine-8-carboxamides as a novel antimycobacterial lead series *Bioorg. Med. Chem. Lett.* **23** 4996; (b) Shukla N M, Salunke D B, Yoo E, Mutz C A, Balakrishna R and David S A 2012 Antibacterial activities of Groebke-Blackburn-Bienaymé-derived imidazo[1,2-*a*]pyridin-3-amines *Bioorg. Med. Chem. Lett.* **20** 5850
3. (a) Elkakmaoui A, Gueiffier A, Miiavet J C, Blache Y and Chapat J P 1994 Synthesis and antiviral activity of 3-substituted imidazo[1,2-*a*]pyridine *Bioorg. Med. Chem. Lett.* **4** 1937; (b) Lhassani M, Chavignon O, Chezal J M, Teuladeb J C, Chapat J P, Snoeckc R, Andrei G, Balzarini J, De Clercq E and Gueiffier A 1999 Synthesis and antiviral activity of imidazo[1,2-a]pyridines *Eur. J. Med. Chem.* **34** 271; (c) Enguehard-Gueiffier C, Musiu S, Henry N, Véron J-B, Mavel S, Neyts J, Leyssen P, Paeshuyse J and Gueiffier A 2013 3-Biphenylimidazo[1,2-*a*]pyridines or [1,2-*b*]pyridazines and analogues, novel Flaviviridae inhibitors *Eur. J. Med. Chem.* **64** 448; (d) Manvar P, Shaikh F, Kakadiya R, Mehariya K, Khunt R, Pandey B and Shah A 2016 Synthesis of novel imidazo[1,2-*a*]pyridine-4-hydroxy-2H-coumarins by Groebke–Blackburn–Bienaymé multicomponent reaction as potential NS5B inhibitors *Tetrahedron* **72** 1293
4. Marchand P, Bazin M-A, Pagniez F, Riviere G, Bodero L, Marhadour S, Nourrisson M-R, Picot C, Ruchaud S, Bach S, Baratte B, Sauvain M, Pareja D C, Vaisberg A J and Le Pape P 2015 Synthesis, antileishmanial activity and cytotoxicity of 2,3-diaryl- and 2,3,8-trisubstituted imidazo[1,2-*a*]pyrazines *Eur. J. Med. Chem.* **103** 381

5. (a) Zhou J P, Ding Y W, Zhang H B, Xu L and Dai Y 2008 Synthesis and anti-inflammatory activity of imidazo[1,2-*a*]pyridine derivatives *Chin. Chem. Lett.* **19** 669; (b) Lacerda R B, De Lima C K F, Da Silva L, Romeiro N C, Miranda A L P, Barreiro E J and Fraga C A M 2009 Discovery of novel analgesic and anti-inflammatory 3-arylamine-imidazo[1,2-*a*]pyridine symbiotic prototypes *Bioorg. Med. Chem.* **17** 74
6. Moraski G C, Oliver A G, Markley L D, Cho S, Franzblau S G and Miller M J 2014 Scaffold-switching: An exploration of 5,6-fused bicyclic heteroaromatics systems to afford antituberculosis activity akin to the imidazo[1,2-*a*]pyridine-3-carboxylate *Bioorg. Med. Chem. Lett.* **24** 3493
7. Xi G L and Liu Z Q 2015 Introducing ferrocene into imidazo[1,2-*a*]pyridine by Groebke three-component-reaction for scavenging radicals and inhibiting DNA oxidation *Tetrahedron* **71** 9602
8. (a) Goodacre S C, James H D, Charles H A, Philip J, Margaret K S, John M K, William M K and Michael R 2005 *Imidazo-pyridine derivatives as ligands for GABA receptors* U. S. Patent 0165048 A1; (b) Blackaby W P, Atack J R, Bromidge F, Castro J L, Goodacre S C, Hallett D J, Lewis R T, Marshall G R, Pike A, Smith A J, Street L J, Tattersall D F D and Waord K A 2006 Imidazo[1,2-*a*]pyrimidines as functionally selective GABAA ligands *Bioorg. Med. Chem. Lett.* **16** 1175; (c) Goodacre S C, Street L J, Hallett D J, Crawforth J M, Kelly S, Owens A P, Blackaby W P, Lewis R T, Stanley J, Smith A J, Ferris P, Sohal B, Cook S M, Pike A, Brown N, Wafford K A, Marshall G, Castro J L and Atack J R 2006 Imidazo[1,2-*a*]pyrimidines as functionally selective and orally bioavailable GABA$\alpha 2/\alpha 3$ binding site agonists for the treatment of anxiety disorders *J. Med. Chem.* **49** 35
9. (a) Paudler W W and Blewitt H L 1965 Ten π-electron nitrogen heterocyclic compounds.II. Bromination of imidazo[l,2-*a*]pyridines *J. Org. Chem.* **30** 4081; (b) Sablayrolles C, Cros G H, Milhavet J C, Rechenq E, Chapat J P, Boucard M, Serrano J J and McNeill J H 1984 Synthesis of imidazo[1,2-*a*]pyrazine derivatives with uterine-relaxing, antibronchospastic, and cardiac-stimulating properties *J. Med. Chem.* **27** 206; (c) Sharma S, Saha B, Sawant D and Kundu B 2007 Synthesis of novel N-Rich polycyclic skeletons based on azoles and pyridines *J. Comb. Chem.* **9** 783; (d) Harris A R, Nason D M, Collantes E M, Xu W J, Chi Y S, Wang Z H, Zhang B Z, Zhang Q J, Gray D L and Davoren J E 2011 Synthesis of 5-bromo-6-methyl imidazopyrazine, 5-bromo and 5-chloro-6-methyl imidazopyridine using electron density surface maps to guide synthetic strategy *Tetrahedron* **67** 9063
10. (a) Podergajs S, Stanovnik B and Tisler M 1984 A new approach for the synthesis of fused imidazoles: the synthesis of 3-acyl-substituted imidazo(1,2-x)azines *Synthesis* 263; (b) Gome O, Salgado-Zamora H, Reyes A and Campos M E 2010 A revised approach to the synthesis of 3-acyl imidazo[1,2-*a*]pyridines *Heterocycl. Commun.* **16** 99; (c) Cao H, Liu X H, Liao J Q, Huang J P, Qiu H F, Chen Q L and Chen Y Y 2014 Copper(I)- and palladium(II)-catalyzed cyclizations enable a convenient synthesis of functionalized imidazo[1,2-*a*]pyridine aldehydes/ketones and 3-vinyl imidazo[1,2-a]pyridines *J. Org. Chem.* **79** 11209; (d) Kim O, Jeong Y, Lee H, Hong S-S and Hong S 2011 Design and synthesis of imidazopyridine analogues as inhibitors of phosphoinositide 3-kinase signaling and angiogenesis *J. Med. Chem.* **54** 2455; (e) Bangade V M, Reddy B C, Thakur P B, Babu B M and Meshram H M 2013 DABCO catalyzed highly regioselective synthesis of fused imidazo-heterocycles in aqueous medium *Tetrahedron Lett.* **54** 4767
11. Kosary J, Kasztreiner E, Rabloczky G and Kurthy M 1989 Synthesis and cardiotonic activity of 2,4-diamino-1.3,5-triazines *Eur. J. Med. Chem.* **24** 97
12. Fan H L, Li X, Lai X and Cao J T 2016 *Method for synthesis of 6-bromoimidazo [1,2-a]pyridine-3-carboxylic acid* C. N. Patent 103965190 B
13. Fan H L, Li X, Lai X S and Cao J T 2014 *Process for synthesis 6-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid* C. N. Patent Appl. 103864786 A
14. Sucunza D, Samadi A, Chioua M, Silva D B, Yunta C, Infantes L, Carreiras M C, Soriano E and Marco-Contelles J 2011 A practical two-step synthesis of imidazo[1,2-***a***]pyridines from *N*-(prop-2-yn-1-yl)pyridin-2-amines *Chem. Commun.* **47** 5043
15. Xi N 2014 *Preparation of heteroaromatic compounds as protein kinase modulators for treatment of hyperproliferative disorders* U. S. Patent Appl. 0134133
16. Eastwood P R, Gonzalez R J, Gomez C E and Bach T J 2011 *Fused heteroaryl imidazolone derivatives as JAK inhibitors and their preparation and use for the treatment of diseases* E. P. Patent Appl. 2397482
17. (a) Cunningham I D, Blanden J S, Llor J, Muñoz L and Sharratt A P 1991 Chemistry of amidines. Part 1. Determination of the site of initial protonation in *N′*-Pyridylformamidines *J. Chem. Soc. Perkin Trans.* **2** 1747; (b) Huntsman E and Balsells J 2005 New Method for the General Synthesis of [1,2,4]Triazolo[1,5-*a*]pyridines *Eur. J. Org. Chem.* 3761; (c) Omar G G, Héctor S Z and Elena C A 2014 Tertiary formylated amines by microwave irradiation of *N,N*-dimethyl-*N′*-(2-pyridyl)formamidines with methyl vinyl ketone *Heterocycl. Commun.* **20** 21