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Efficient synthesis of novel dipyridoimidazoles and pyrido[1′,2′;1,2]imidazo[4,5-*d*]pyridazine derivatives

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Abstract—Novel dipyrido[1,2-*a*;3′,4′-*d*]imidazoles **7a**–**d**, dipyrido[1,2-*a*;4′,3′-*d*]imidazoles **8a**,**c** and pyrido[1′,2′;1,2]imidazo[4,5-*d*]-pyridazine derivatives **9a**–**d** were synthesized by two pathways: thermal electrocyclic reaction of 3-alkenylimidazopyridine-2-oximes **10** and direct condensation of ethyl glycinate (or hydrazine) with 2,3-dicarbonylimidazo[1,2-*a*]pyridines **11**.

1. Introduction

The skeleton of carbolines or pyridazino[4,5-*b*]indole are of great interest owing to their varied and important biological properties. For example lavendamycin (**1**),[1] a potent antitumor antibiotic,[2] and ethyl 4-methyl-5-isopropyloxy-β-carboline-3-carboxylate (**2**), a synthetic compound, show significant memory enhancing effects in humans via interaction with the benzodiazepine receptor of the central nervous system.[3] Intoplicin (**3**) has been shown to display inhibitory activity against topoisomerase I and II enzymes.[4] The heterocyclic amines Trp-P-1 (**4a**) and Trp-P-2 (**4b**)[5] and 11-methylbenzo[*g*]pyridazin[4,5-*b*]indol-7(8*H*)-one (**5**) have interesting cytotoxic activities.[5,6] Recently, pyridopurine (**6a**), an analog of the genotoxic Glu-P-1 (**6b**) and Glu-P-2 (**6c**),[7] showed intercalant properties[8] (Fig. 1).

Pursuing our interest in the development of new nitrogen bridgehead azaindolizines[9] and in view of the pharmacological interest of these structures exemplified above, we focused on the synthesis of dipyrido[1,2-*a*;3′,4′-*d*], [1,2-*a*;4′,3′-*d*]imidazole **7**, **8** and pyrido[1′,2′;1,2]imidazo[4,5-*d*]-pyridazine derivatives **9**. To our knowledge, these fused conjugate ring systems have rarely been reported[10] and only with complicated synthetic approaches.

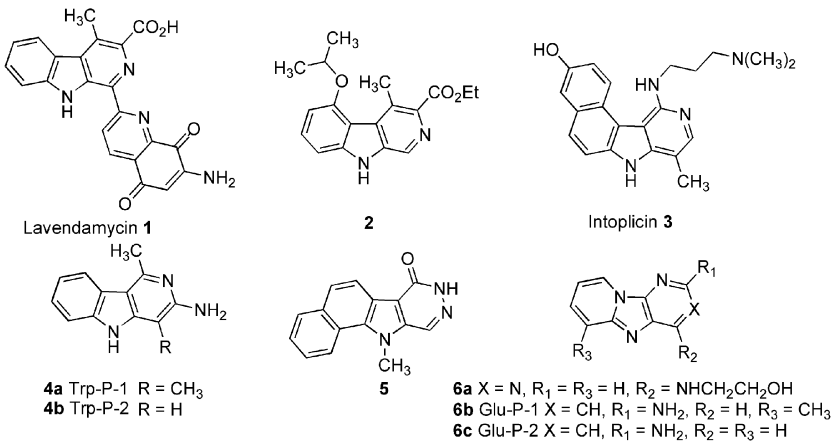

Figure 1.

Keywords: imidazo[1,2-*a*]pyridine; dipyridoimidazole; azacarboline; pyridoimidazopyridazine.
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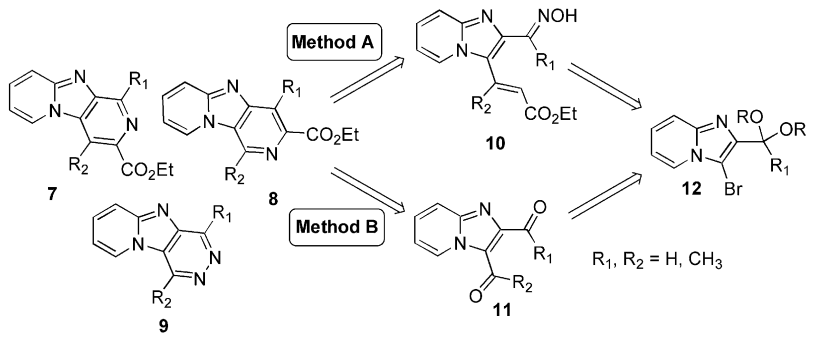


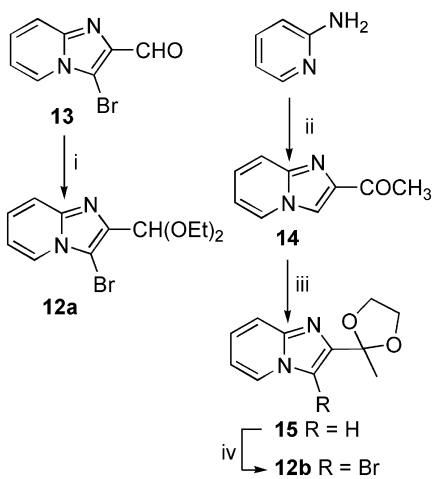
Scheme 1.

We report the heteroannulation via two pathways from the same bromoketal compounds **12**: thermal cyclization of vinyloxime **10** (method A)[11] and direct condensation of ethyl glycinate with dicarbonyl compounds **11** (method B)[12] as shown in Scheme 1.

2. Results and discussion

The first step in our synthesis required 2-ketal-3-bromoimidazo[1,2-*a*]pyridine compounds **12a**,**b**. Ketal protection of 3-bromo-2-formylimidazo[1,2-*a*]pyridine (**13**)[13] by ethanol in the presence of catalytic *p*-toluenesulfonic acid in benzene gave the desired acetal **12a**[9d] in 51% yield. Tchitchibabin cyclization[14] with 2-aminopyridine and bromobutanedione (prepared in situ from commercial butanedione) in ethanol gave 2-acetylimidazo[1,2-*a*]pyridine (**14**) in 24% yield (Scheme 2). Finally, compound **12b** was easily prepared by protection of the carbonyl group of **14** to yield **15** followed by bromination with NBS in acetonitrile.

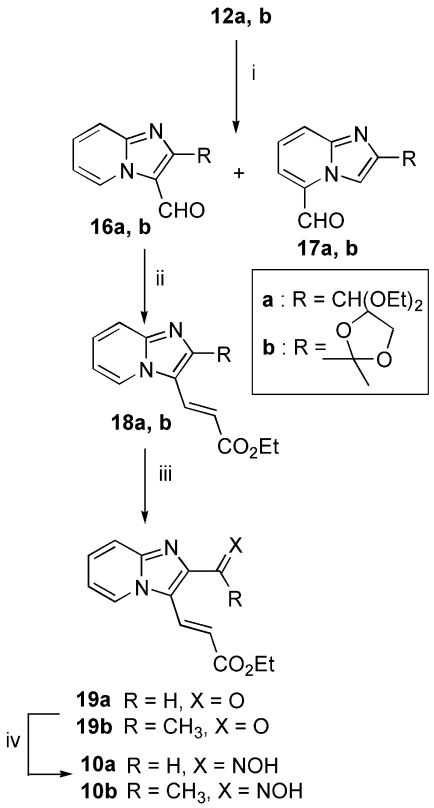
The synthetic route A involves preparation of vinyloximes **10** from **12a**,**b**. We investigated the formation of the 3-acrylate moiety by lithiation of **12**, electrophilic substitution with DMF or *N*-methyl-*N*-methoxyacetamide, followed by Wittig condensation.



Scheme 2. *Reagents and conditions*. (i) Ethanol, benzene, PTSA, Δ; (ii) EtOH, bromobutanedione, Δ; (iii) ethyleneglycol, benzene, PTSA, Δ; (iv) NBS, CH_3CN, Δ.

The halogen–metal exchange performed with **12a**,**b** using *n*-butyllithium at −60°C followed by quenching with DMF gave a mixture of aldehydes **16a**,**b** and **17a**,**b** (Scheme 3).

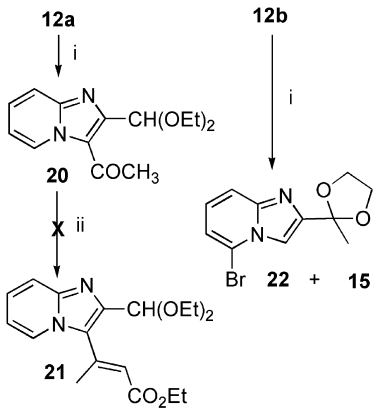
The main products were the expected 3-formyl derivatives **16a**,**b** (68–41%) while the minor isomers proved to be the 5-formyl compounds **17a**,**b** (18–14%). These unexpected compounds were probably obtained via lithiation at position 5 of **12a**,**b** followed by bromine–lithium isomerisation at positions 3, 5. This halogen-dance reaction has been observed in a pyridine series[15] and with some imidazo[1,2-*a*]pyrazine.[16] Wittig reactions using aldehydes **16a**,**b** and (carbethoxymethylene) triphenylphosphorane in THF under reflux gave the corresponding (*E*)-acrylates **18a**,**b**. Compounds **18a**,**b** were easily deprotected to provide the carbonyl group. The resulting **19a**,**b** treated with hydroxylamine hydrochloride and AcONa gave the desired



Scheme 3. *Reagents and conditions*. (i) 1/*n*-BuLi, THF, −60°C, 2/DMF, room temperature; (ii) Ph_3PCHCO_2Et, THF, reflux; (iii) CH_3CN/H_2O (3/1, v/v), HCl cat.; (iv) NH_2OH/HCl, AcONa, EtOH, 60°C.

oximes **10a**,**b**, which were fully characterized by NMR and mass spectra. The stereochemistry of the α,β-unsaturated esters **18a**,**b**, **19a**,**b** and **10a**,**b** were found by ^{1}H NMR data to possess the *E*-configuration ($J \approx 16$ Hz).

We sought to extend this method to 3-acetyl derivatives. Bromide **12a** was lithiated using *n*-butyllithium at −60°C, and the resulting solution was treated with an excess of *N*-methyl-*N*-methoxyacetamide according to Wai's procedure[17] to give the desired acetyl **20** (58%) and 2-diethoxymethylimidazo[1,2-*a*]pyridine[13] (30%). Attempts to extend the method to **12b** were unsuccessful and produced the 5-bromo derivative **22** (35%) and dehalogenated acetal **15** (24%) (Scheme 4).



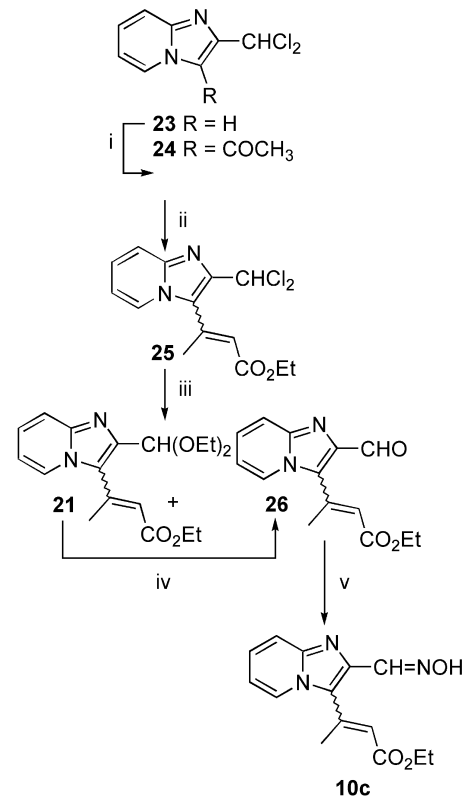
Scheme 4. *Reagents and conditions*. (i) 1/*n*-BuLi, THF, −60°C, 2/*N*-methyl-*N*-methoxyacetamide, room temperature; (ii) Ph_3PCHCO_2Et, THF, reflux.

Condensation of **20** with (carbethoxymethylene)triphenylphosphorane by a Wittig reaction in THF failed to give **21** and left only recovered starting material. Several solvents, temperature and reaction times were unsuccessful evaluated. We therefore, developed an alternative strategy, based on direct acylation[18] of dichloromethyl compound **23**.[13] Treatment of **23** with excess acetyl chloride in nitrobenzene at 210°C gave acetyl **24** in 33% yield (Scheme 5).

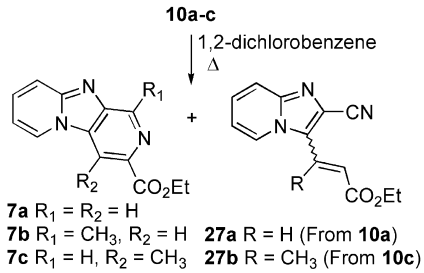
Condensation of **24** with (carbethoxymethylene)triphenylphosphorane gave the expected acrylate **25** in low yield (13%) and starting material (15%). Compound **25** was converted by Arbarca's method[19] (silver nitrate in ethanol) to give the minor acetal **21** (13%) and the major aldehyde **26** (50%). Compound **21** was easily transformed to **26** by acid hydrolysis in acetonitrile. Finally, treatment of **26** with hydroxylamine gave the desired oxime **10c**.

The electrocyclization reactions[11] of **10a**–**c** were carried out by heating in 1,2-dichlorobenzene. Conversion of **10a**–**c** to the cyclization products **7a**–**c** occurred in 16–54% yield. In the case of **10a**,**c**, nitrile derivatives **27a**,**b** were readily observed and easily separated by chromatography on alumina gel (Scheme 6).

The fact that thermolysis of oximes **10a**,**c** gave a mixture of expected dipyridoimidazoles **7a**,**c** and unexpected cyano derivatives **27a**,**b** prompted us to explore a new method of cyclization from dicarbonyl compounds **11a**–**d**. Hydrolysis



Scheme 5. *Reagents and conditions*. (i) Nitrobenzene, CH_3COCl (12 equiv.), 210°C; (ii) PH_3PCHCO_2Et, toluene, reflux; (iii) $AgNO_3$, EtOH, reflux; (iv) CH_3CN/H_2O (3/1, v/v), HCl cat.; (v) NH_2OH, HCl, AcONa, EtOH, 60°C.

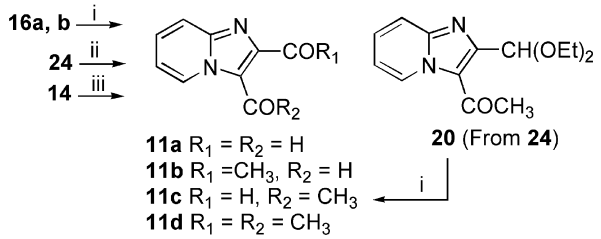


Scheme 6.

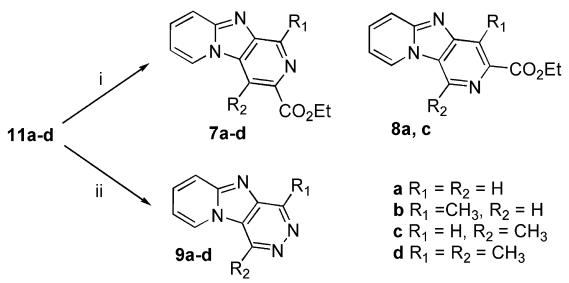
of acetals **16a**,**b** gave the corresponding carbonyls **11a**,**b** in good yields (73–97%) (Scheme 7).

Treatment of dichloromethyl **24** with silver nitrate, under the previous conditions, afforded the 2-formyl product **11c** as well as the acetal **20** in a ca. 2:1 ratio with a total yield of 76%. Deprotection of **20** yielded the required **11c** in high yield (90%). When acetyl compound **14** was treated under the same conditions used for **23**, it reacted to form the 2,3-diacetylimidazo[1,2-*a*]pyridine (**11d**).

Accordingly, we investigated the reactivity of 2,3-dicarbonyl compounds **11a**–**d** with ethyl glycinate using modified Meziane's method.[12d] A solution of dialdehyde **11a** (4.95 mmol) in ethanol was treated with excess ethyl glycinate (11.5 mmol) at room temperature for 20 h to give a mixture of isomeric dipyridoimidazoles **7a** and **8a** (Scheme 8). These compounds were readily separated by



Scheme 7. *Reagents and conditions*. (i) CH_3CN/H_2O (3/1, v/v), HCl cat.; (ii) $AgNO_3$, EtOH, Δ; (iii) CH_3COCl, nitrobenzene, 210°C.



Scheme 8. *Reagents and conditions*. (i) $NH_2CH_2CO_2Et$, EtOH, room temperature; (ii) NH_2NH_2, EtOH, room temperature.

column chromatography, and the isolated yields are shown in Table 1, entry 1.

Structural assignment of **8a** was secured by INEPT experiments. According to these results, we consider that compounds **7a** and **8a** initially resulted from condensation of the amino group of ethyl glycinate with the 2 or 3-formyl groups, respectively. The imino intermediates (not isolated) yielded the pyridine moiety after cyclization (Scheme 9).

Next, we examined the effects of the aldehyde and keto groups of 2-(or 3-)acetyls **11b** (or **11c**) in the presence of ethyl glycinate they gave essentially the annulated compounds **7b** and **8c**, respectively (Table 1, entries 3, 5). We thought that the initial reaction was done between the amine and the aldehydic function, more reactive than ketone group. Presumably, the intramolecular cyclization reaction of the imine formed on the second carbonyl group is, the determining stage of the reaction. This step preferably takes place on the aldehydic rather than on the ketonic function. In this way, by displacement of the equilibre aldehyde-imine, the initial ethyl glycinate condensation reaction preferably takes place on the acetyl group, leading to the corresponding dipyridoimidazoles **7b** and **8c**.

Table 1. Condensation of **11a–d** with ethyl glycinate and hydrazine

Entry	Dicarbonyl	Reagent	Product (yield (%))		
			7	**8**	**9**
1	**11a**	Ethyl glycinate	**7a** (12)	**8a** (39)	
2	**11a**	Hydrazine monohydrate			**9a** (89)
3	**11b**	Ethyl glycinate	**7b** (28)		
4	**11b**	Hydrazine monohydrate			**9b** (30)
5	**11c**	Ethyl glycinate		**8c** (61)	
6	**11c**	Hydrazine monohydrate			**9c** (63)
7	**11d**	Ethyl glycinate	**7d** (61)		
8	**11d**	Hydrazine monohydrate			**9d** (75)

In the same way, we studied the heterocyclization of the 2,3-diacetyl compound. Reaction of **11d** with ethyl glycinate over 8 days led to dimethyldipyridoimidazole **7d** as the only product in 61% yield (Table 1, entry 7). Structural determination of **7d** was achieved on the basis of NOESY experiments. The presence of strong NOESY effects between Me(C-4) and CH_2CH_3, and Me(C-4) and H-6, unequivocally pointed to the dipyrido[1,2-*a*;3′,4′-*d*]imidazolic structure.

In a similar way, we tested the reaction conditions of the above procedure with **11a–d** and hydrazine monohydrate. Substituted or unsubstituted pyridoimidazopyridazines **9a–d** were produced in 30–89% yields (Table 1, entries 2, 4, 6, 8).

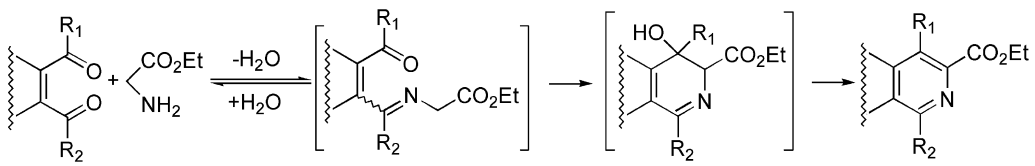
3. Conclusion

In summary, we describe two synthetic routes for the synthesis of new dipyridoimidazoles **7a–d**, **8a**,**c** and pyridoimidazopyridazines **9a–d**. These tricyclic systems were synthesized by electrocyclization of vinyloxime or by direct condensation of dicarbonyl compounds with ethyl glycinate or hydrazine monohydrate. In the case of ethyl glycinate, regioselectivity was observed. Work is now in progress to study the intercalating abilities and antitumor activities of all these chemical entities.

4. Experimental

4.1. General procedures

All column chromatography was performed with Merck neutral aluminium oxide 90 standardized (63–200 μm). All thin-layer chromatography was performed on Merck neutral aluminium oxide $60F_{254}$ plates. The plates were visualized with UV light (254 nm). Melting points were determined on an Electrothermal IA9300 (capillary) and are not corrected. NMR (400 MHz for ^1H or 100 MHz for ^{13}C) were recorded on a Bruker Avance 400 spectrophotometer using $CDCl_3$ as solvent unless otherwise specified. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane (TMS). Infrared spectra were recorded on a FTIR Nicolet Impact 410. Mass spectral analyses were



Scheme 9.

performed on a Hewlett–Packard 5985B or 5989A instrument. All air-sensitive reactions were run under argon atmosphere. All solvents were dried using common techniques.

4.1.1. 2-Acetylimidazo[1,2-*a*]pyridine (14). To a cooled solution (0°C) of butanedione (15.2 g, 177 mmol) was added dropwise bromine (6.1 mL, 119 mmol). The solution was stirred at room temperature for 4 h. A solution of 2-aminopyridine (6.90 g, 73.4 mmol) in EtOH (150 mL) was then added slowly. The mixture was refluxed for 6 h. After cooling, the solution was evaporated under vacuum. Water (100 mL) was poured into the crude product and the solution was basified with Na_2CO_3 (15.0 g, 142 mmol) and extracted with CH_2Cl_2 (3×40 mL). The organic layer was dried over Na_2SO_4 and the solvent of the filtrate was evaporated. The crude residue was purified by column chromatography on alumina gel with CH_2Cl_2 as eluent to give **14** (2.80 g, 24%); R_f=0.25 (CH_2Cl_2); mp 127–129°C; IR (KBr) 1670 cm^{-1}; MS *m/z* 160 (M^+, 79), 145 (100), 132 (14), 117 (41), 90 (21), 78 (17); ^1H NMR δ 2.65 (s, 3H), 6.82 (t, 1H, *J*=7 Hz), 7.20 (m, 1H), 7.60 (d, 1H, *J*=9 Hz), 8.09 (s, 1H), 8.12 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 27.1, 114.0, 114.8, 118.9, 126.1, 126.5, 144.1, 144.9, 195.7. Anal. calcd for $C_9H_8N_2O$: C: 67.49; H: 5.03; N: 17.49. Found: C: 67.55; H: 5.02; N: 17.52.

4.1.2. General procedure for the preparation of acetals 12 and 15. A solution of anhydrous ethanol or ethyleneglycol (466 mmol) in dry benzene (150 mL), the appropriate carbonyl (66.6 mmol) and a small quantity of *p*-toluenesulfonic acid (10%) was refluxed using a Dean–Stark separator. After cooling the solvent was removed to dryness and the residue was taken up with water (150 mL) and basified with Na_2CO_3 (7.50 g, 71 mmol). The resulting solution was extracted with CH_2Cl_2 (3×60 mL). After drying (Na_2SO_4) the organic solution was evaporated and the remaining viscous oil was chromatographed using CH_2Cl_2 as eluent.

From **13**: 3-bromo-2-diethoxymethylimidazo[1,2-*a*]pyridine (**12a**)[9b] reaction time 48 h, yield: 51% as an yellow oil; R_f=0.36 (CH_2Cl_2).

From **14**: 2-(2-methyl[1,3]dioxolan-2-yl)imidazo[1,2-*a*]pyridine (**15**) reaction time 40 h, yield: 87%; R_f=0.20 (CH_2Cl_2); mp 72–74°C; IR (KBr) 1189, 1041 cm^{-1}; MS *m/z* 204 (M^+, 10), 189 (44), 161 (100), 145 (89), 117 (23), 78 (48), 51 (31); ^1H NMR δ 1.82 (s, 3H), 4.01 (m, 4H), 6.73 (t, 1H, *J*=7 Hz), 7.12 (m, 1H), 7.56 (d, 1H, *J*=9 Hz), 7.57 (s, 1H), 8.07 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 25.4, 64.9, 106.2, 109.2, 112.3, 117.7, 124.6, 125.7, 145.1, 147.9. Anal. calcd for $C_{11}H_{12}N_2O_2$: C: 64.69; H: 5.92; N: 13.72. Found: C: 64.49; H: 5.93; N: 13.69.

4.1.3. 3-Bromo-2-(2-methyl[1,3]dioxolan-2-yl)imidazo[1,2-*a*]pyridine (12b). To a solution of **15** (5.0 g, 24.5 mmol) in acetonitrile (100 mL), was added *N*-bromosuccinimide (4.80 g, 26.95 mmol). The solution was stirred at reflux for 3 h. After cooling, the solution was concentrated in vacuo to dryness. Water (80 mL) was added and the aqueous solution was basified with Na_2CO_3 (4.00 g, 37.7 mmol) and extracted with CH_2Cl_2 (3×30 mL). The organic layers were dried (Na_2SO_4) and evaporated. Purification of the crude product by chromatography on alumina gel with CH_2Cl_2 as eluent afforded the desired product **12b** in 91% yield (6.29 g); R_f=0.51 (CH_2Cl_2); mp 58–60°C; IR (KBr) 1682, 1239, 1168 cm^{-1}; MS *m/z* 284 (M^++2, 31), 282 (M^+, 31), 269 (96), 267 (100), 241 (91), 239 (95), 225 (76), 223 (81), 197 (20), 87 (32), 78 (47), 51 (33); ^1H NMR δ 1.87 (s, 3H), 3.99 (t, 2H, *J*=5 Hz), 4.13 (t, 2H, *J*=5 Hz), 6.95 (t, 1H, *J*=7 Hz), 7.26 (m, 1H), 7.64 (d, 1H, *J*=9 Hz), 8.16 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 25.4, 64.9, 91.4, 106.3, 113.2, 117.9, 123.8, 125.1, 144.6, 144.7. Anal. calcd for $C_{11}H_{11}N_2O_2Br$: C: 46.66; H: 3.92; N: 9.89. Found: C: 46.54; H: 3.92; N: 9.92.

4.1.4. General procedure for metalation of 12a,b. To a cold solution (−60°C) of the appropriate bromo compound (25.9 mmol) in anhydrous THF (65 mL) was added dropwise *n*-BuLi (20 mL, 1.6 M in hexanes) when the mixture immediately became dark. To this solution was added dropwise the appropriate amides (34.1 mmol for DMF and 102.3 mmol for *N*-methyl-*N*-methoxyacetamide) in THF (15 mL). The mixture was returned back room temperature, stirred for 30 mn and poured into aqueous saturated ammonium chloride solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3×40 mL) dried (Na_2SO_4) and removed in vacuo. The crude product was chromatographed using CH_2Cl_2 as eluent.

From **12a** and DMF: to give in order of elution: 2-diethoxymethyl-3-formylimidazo[1,2-*a*]pyridine (**16a**) yield: 68% as an oil; R_f=0.57 (CH_2Cl_2); IR (CCl_4) 1650, 1497, 1327, 1259, 1139, 1067 cm^{-1}; MS *m/z* 248 (M^+, 2), 204 (24), 175 (73), 147 (23), 118 (24), 90 (10), 78 (100), 51 (20); ^1H NMR δ 1.19 (t, 6H, *J*=7 Hz), 3.62 (q, 2H, *J*=7 Hz), 3.70 (q, 2H, *J*=7 Hz), 5.81 (s, 1H), 7.02 (t, 1H, *J*=7 Hz), 7.50 (m, 1H), 7.73 (d, 1H, *J*=9 Hz), 9.58 (d, 1H, *J*=7 Hz), 10.38 (s, 1H); ^{13}C NMR δ 15.1, 62.4, 99, 115.5, 117.6, 121.4, 128.9, 130.4, 146.9, 155.5, 181.0. Anal. calcd for $C_{13}H_{16}N_2O_3$: C: 62.89; H: 6.50; N: 11.28. Found: C: 63.10; H: 6.48; N: 11.26. 2-Diethoxymethyl-5-formylimidazo[1,2-*a*]pyridine (**17a**) yield: 18%; R_f=0.30 (CH_2Cl_2); mp 81–83°C; IR (KBr) 1672, 1310, 1050 cm^{-1}; MS *m/z* 248 (M^+, 1), 204 (18), 175 (100), 147 (15), 90 (10), 78 (32); ^1H NMR δ 1.19 (t, 6H, *J*=7 Hz), 3.65 (m, 4H), 5.74 (s, 1H), 7.31 (m, 1H), 7.46 (d, 1H, *J*=7 Hz), 7.87 (d, 1H, *J*=9 Hz), 8.99 (s, 1H), 9.83 (s, 1H); ^{13}C NMR δ 15.2, 61.5, 98.4, 112.7, 122.5, 124.2, 125.9, 132.1, 145.1, 147.8, 184.4. Anal. calcd for $C_{13}H_{16}N_2O_3$: C: 62.89; H: 6.50; N: 11.28. Found: C: 62.75; H: 6.49; N: 11.31.

From **12a** and *N*-methyl-*N*-methoxyacetamide: to give in order of elution: 3-acetyl-2-diethoxymethylimidazo[1,2-*a*]pyridine (**20**) yield: 58% as an oil; R_f=0.56 (CH_2Cl_2); IR (CCl_4) 1641, 1499, 1332 cm^{-1}; MS *m/z* 262 (M^+, 1), 218 (20), 189 (100), 161 (15), 145 (18), 119 (18), 78 (51); ^1H NMR δ 1.26 (t, 6H, *J*=7 Hz), 2.83 (s, 3H), 3.71 (m, 4H), 5.96 (s, 1H), 7.06 (t, 1H, *J*=7 Hz), 7.47 (m, 1H), 7.76 (d, 1H, *J*=9 Hz), 9.78 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 15.2, 30.6, 62.8, 99.7, 115.3, 117.6, 120.9, 129.0, 129.2, 146.0, 151.7, 189.8. Anal. calcd for $C_{14}H_{18}N_2O_3$: C: 64.10; H: 6.92; N: 10.68. Found: C: 63.99; H: 6.90; N: 10.69. 2-Diethoxymethylimidazo[1,2-*a*]pyridine[13] yield: 30%; R_f=0.25 (CH_2Cl_2).

From **12b** and DMF: to give in order of elution (eluate with AcOEt/hexanes, 8/2, v/v): 3-formyl-2-(2-methyl[1,3]dioxolan-2-yl)imidazo[1,2-*a*]pyridine (**16b**) yield: 41%; R_f=0.64 (AcOEt/hexanes, 8:2); mp 123–125°C; IR (KBr) 1638, 1324, 1255, 1180 cm^{-1}; MS *m/z* 232 (M^+, 19), 217 (21), 189 (50), 187 (51), 173 (49), 161 (59), 145 (25), 87 (34), 78 (100), 51 (36); ^1H NMR δ 1.80, 4.04 (m, 4H), 7.02 (t, 1H, *J*=7 Hz), 7.45 (m, 1H), 7.69 (d, 1H, *J*=9 Hz), 9.54 (d, 1H, *J*=7 Hz), 10.30 (s, 1H); ^{13}C NMR δ 27.1, 65.0, 106.4, 115.4, 117.7, 120.6, 128.9, 129.9, 146.1, 158.9, 181.1. Anal. calcd for $C_{12}H_{12}N_2O_3$: C: 62.06; H: 5.21; N: 12.06. Found: C: 61.95; H: 5.22; N: 12.10. 5-Formyl-2-(2-methyl[1,3]-dioxolan-2-yl)imidazo[1,2-*a*]pyridine (**17b**) yield: 14%; R_f=0.46 (AcOEt/hexanes, 8:2); mp 114–116°C; IR (KBr) 1677, 1189, 1041 cm^{-1}; MS *m/z* 232 (M^+, 11), 217 (87), 189 (93), 173 (100), 90 (30); ^1H NMR δ 1.83 (s, 3H), 4.06 (m, 4H), 7.38 (m, 1H), 7.52 (d, 1H, *J*=7 Hz), 7.95 (d, 1H, *J*=9 Hz), 9.00 (s, 1H), 9.89 (s, 1H); ^{13}C NMR δ 25.6, 65.1, 106.4, 111.5, 122.6, 124.5, 125.9, 132.1, 145.5, 151.2, 184.5. Anal. calcd for $C_{12}H_{12}N_2O_3$: C: 62.06; H: 5.21; N: 12.06. Found: C: 62.04; H: 5.21; N: 12.05.

From **12b** and *N*-methyl-*N*-methoxyacetamide: to give in order of elution (eluate with AcOEt/hexanes, 6/4, v/v): 5-bromo-2-(2-methyl[1,3]dioxolan-2-yl)imidazo[1,2-*a*]-pyridine (**22**) yield: 35%; R_f=0.84 (AcOEt/hexanes, 6:4); mp 47–49°C; MS *m/z* 284 (M^++2, 10), 282 (M^+, 10), 269 (49), 267 (52), 241 (94), 239 (100), 225 (65), 223 65), 223 (74), 197 (22), 116 (52), 87 (52), 51 (32); ^1H NMR δ 1.73 (s, 3H), 3.98 (m, 4H), 6.95 (m, 2H), 7.54 (d, 1H, *J*=9 Hz), 7.68 (s, 1H); ^{13}C NMR δ 25.6, 65.2, 106.2, 110.5, 114.3, 116.4, 125.4, 145.6, 147.8. Anal. calcd for $C_{11}H_{11}N_2O_2Br$: C: 46.67; H: 3.92; N: 9.89. Found: C: 46.77; H: 3.93; N: 9.91. 2-(2-Methyl[1,3]dioxolan-2-yl)imidazo[1,2-*a*]pyridine (**15**) yield: 24%; R_f=0.43 (AcOEt/hexanes, 6:4).

4.1.5. General procedure for the preparation of vinyl compounds 18a,b and 25. A solution of the appropriate carbonyl (3.42 mmol) and (carbethoxymethylene)triphenylphosphorane (1.79 g, 5.14 mmol) in THF (40 mL) was heated under reflux for 72 h. After cooling, water was added (50 mL) and the solution was extracted with CH_2Cl_2 (3×20 mL). The extract was dried (Na_2SO_4) and the solvent was removed under vacuo. The residue was chromatographed using CH_2Cl_2 as eluent.

From **16a**: (*E*) ethyl 3-(2-diethoxymethylimidazo[1,2-*a*]pyridin-3-yl)propenoate (**18a**); yield: 85%; R_f=0.42 (CH_2Cl_2); mp 63–65°C; IR (KBr) 1701, 1623, 1519, 1497, 1342, 1273 cm^{-1}; MS *m/z* 318 (M^+, 10), 273 (16), 245 (100), 217 (10), 199 (52), 171 (61), 143 (32), 116 (14), 78 (73), 51 (17); ^1H NMR δ 1.29 (m, 6H, $3CH_3$), 1.37 (t, 3H, *J*=7 Hz), 3.31 (m, 4H), 4.25 (q, 2H, *J*=7 Hz), 5.86 (s, 1H), 6.55 (d, 1H, *J*=16 Hz), 7.00 (t, 1H, *J*=7 Hz), 7.33 (m, 1H), 7.73 (d, 1H, *J*=9 Hz), 8.18 (d, 1H, *J*=16 Hz), 8.38 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.4, 15.2, 60.5, 61.9, 98.5, 114.1, 116.1, 118.3, 118.6, 124.8, 126.3, 128.9, 146.1, 147.4, 167.4. Anal. calcd for $C_{17}H_{22}N_2O_4$: C: 64.13; H: 6.97; N: 8.80. Found: C: 64.09; H: 6.98; N: 8.79.

From **16b**: (*E*) ethyl 3-(2-methyl[1,3]dioxolan-2-yl)imidazo[1,2-*a*]pyridin-3-yl)propenoate (**18b**); (reaction time 9 h, using 3 equiv. of (carbethoxymethylene)triphenylphosphorane) yield: 52% as an oil; R_f=0.27 (CH_2Cl_2); IR (CCl_4) 1716, 1625, 1176 cm^{-1}; MS *m/z* 302 (M^+, 51), 287 (84), 259 (100), 213 (49), 171 (92), 143 (30), 87 (42), 78 (51); ^1H NMR δ 1.28 (t, 3H, *J*=7 Hz), 1.75 (s, 3H), 3.85 (t, 2H, *J*=6.5 Hz), 4.05 (t, 2H, *J*=6.5 Hz), 4.22 (q, 2H, *J*=7 Hz), 6.39 (d, 1H, *J*=16.5 Hz), 6.91 (t, 1H, *J*=7 Hz), 7.24 (m, 1H), 7.63 (d, 1H, *J*=9 Hz), 8.24 (d, 1H, *J*=16.5 Hz), 8.35 (d, 1H, *J*=6.5 Hz); ^{13}C NMR δ 14.4, 26.0, 60.6, 64.8, 107.1, 114.1, 114.5, 117.1, 118.6, 125.4, 126.3, 130.3, 146.4, 151.5, 167.5. Anal. calcd for $C_{16}H_{18}N_2O_4$: C: 63.56; H: 6.00; N: 9.27. Found: C: 63.55; H: 6.02; N: 9.29.

From **24**: ethyl 3-(2-dichloromethylimidazo[1,2-*a*]pyridin-3-yl)butenoate (**25**); (using toluene as solvent) to give in order of elution starting material yield: 15% and **25** yield: 13%; R_f=0.74 (CH_2Cl_2); mp 118–120°C; IR (KBr) 1709, 1634, 1223 cm^{-1}; MS *m/z* 316 (M^++4, 11), 314 (M^++2, 65), 312 (M^+, 94), 279 (31), 277 (94), 241 (64), 229 (51), 213 (23), 203 (32), 169 (100), 78 (50), 51 (36); ^1H NMR δ 1.34 (t, 3H, *J*=7 Hz), 2.55 (d, 3H, *J*=1.5 Hz), 4.25 (q, 2H, *J*=7 Hz), 6.10 (q, 1H, *J*=1.5 Hz), 6.89 (m, 2H), 7.29 (dd, 1H, *J*=7, 9 Hz), 7.68 (d, 1H, *J*=9 Hz), 7.95 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.2, 18.6, 60.5, 64.2, 113.9, 118.7, 122.2, 124.4, 124.5, 126.3, 141.1, 141.7, 145.2, 165.5. Anal. calcd for $C_{14}H_{14}N_2O_2Cl_2$: C: 53.69; H: 4.51; N: 8.94. Found: C: 53.58; H: 4.50; N: 8.92.

4.1.6. General procedure for hydrolysis of acetals. To a solution of the appropriate acetal (8.06 mmol) in 40 mL of CH_3CN/H_2O (3/1, v/v) was added a catalytic quantity of concentrated HCl (3 drops). The solution was heated. After cooling, the solution was basified with Na_2CO_3 (1.00 g, 9.43 mmol) and extracted with CH_2Cl_2 (3×20 mL). The extract was dried (Na_2SO_4) and evaporated to dryness to yield acetals.

From **16a**: 2,3-diformylimidazo[1,2-*a*]pyridine (**11a**); (reaction time 6 h at 70°C) yield: 97%; mp 179–181°C; IR (KBr) 1762, 1698, 1645, 1500, 1320, 1255 cm^{-1}; MS *m/z* 174 (M^+, 13), 146 (49), 118 (27), 90 (14), 78 (100), 63 (16), 51 (31); ^1H NMR δ 7.29 (t, 1H, *J*=7 Hz), 7.68 (m, 1H), 7.94 (d, 1H, *J*=9 Hz), 9.62 (d, 1H, *J*=7 Hz), 10.35 (s, 1H), 10.60 (s, 1H); ^{13}C NMR δ 117.6, 119.2, 123.4, 129.2, 130.8, 147.4, 148.5, 181.0, 189.2. Anal. calcd for $C_9H_6N_2O_2$: C: 62.07; H: 3.47; N: 16.09. Found: C: 61.92; H: 3.47; N: 16.12.

From **16b**: 3-acetyl-2-formylimidazo[1,2-*a*]pyridine (**11b**); (reaction time 3 h at 100°C) yield: 73%; mp 171–173°C; IR (KBr) cm^{-1}; MS *m/z* 188 (M^+, 25), 160 (53), 145 (40), 132 (57), 118 (57), 90 (34), 78 (100), 51 (36); ^1H NMR δ 2.80 (s, 3H), 7.19 (t, 1H, *J*=7 Hz), 7.59 (m, 1H), 7.83 (d, 1H, *J*=9 Hz), 9.59 (d, 1H, *J*=7 Hz), 10.57 (s, 1H); ^{13}C NMR δ 27.9, 117.0, 118.8, 123.2, 129.0, 130.4, 146.2, 149.2, 182.6, 197.0. Anal. calcd for $C_{10}H_8N_2O_2$: C: 63.83; H: 4.28; N: 14.89. Found: C: 63.78; H: 4.29; N: 14.88.

From **18a**: (*E*) ethyl 3-(2-formylimidazo[1,2-*a*]pyridin-3-yl)propenoate (**19a**); (reaction time 1 h at 100°C) yield: 94%; mp 130–132°C; IR (KBr) 1710, 1689, 1629, 1516, 1305, 1171 cm^{-1}; MS *m/z* 244 (M^+, 6), 171 (100), 143 (18),

116 (15), 89 (11), 78 (71), 64 (12), 51 (34); ^{1}H NMR δ 1.38 (t, 3H, J=7 Hz), 4.32 (q, 2H, J=7 Hz), 7.10 (t, 1H, J=7 Hz), 7.16 (d, 1H, J=16 Hz), 7.44 (dd, 1H, J=7, 9 Hz), 7.77 (d, 1H, J=9 Hz), 8.15 (d, 1H, J=16 Hz), 8.42 (d, 1H, J=7 Hz), 10.30 (s, 1H); ^{13}C NMR δ 14.3, 61.0, 115.7, 119.7, 121.3, 123.0, 125.1, 126.9, 127.8, 142.7, 146.4, 167.0, 188.6. Anal. calcd for $C_{13}H_{12}N_2O_3$: C: 63.93; H: 4.95; N: 11.47. Found: C: 63.98; H: 4.96; N: 11.48.

From **18b**: (*E*) ethyl 3-(2-acetylimidazo[1,2-*a*]pyridin-3-yl)propenoate (**19b**); (reaction time 3 h at 100°C) yield: 45%; mp 132–134°C; IR (KBr) 1710, 1677, 1506, 1308, 1177 cm^{-1}; MS *m*/*z* 258 (M$^+$, 9), 185 (100), 78 (40), 51 (12); ^{1}H NMR δ 1.35 (t, 3H, J=7 Hz), 2.77 (s, 3H), 4.29 (q, 2H, J=7 Hz), 6.86 (d, 1H, J=16.5 Hz), 7.04 (t, 1H, J=7 Hz), 7.39 (m, 1H), 7.73 (d, 1H, J=9 Hz), 8.33 (d, 1H, J=16.5 Hz), 8.43 (d, 1H, J=7 Hz); ^{13}C NMR δ 14.3, 28.4, 60.8, 115.2, 119.5, 119.9, 122.0, 125.3, 127.3, 129.2, 143.3, 145.6, 167.0, 197.1. Anal. calcd for $C_{14}H_{14}N_2O_3$: C: 65.11; H: 5.46; N: 10.85. Found: C: 64.89; H: 5.47; N: 10.81.

From **21**: ethyl 3-(2-formylimidazo[1,2-*a*]pyridin-3-yl)-butenoate (**26**); (reaction time 3 h at 70°C) yield: 90%; mp 152–154°C; IR (KBr) 1711, 1688, 1213, 1176 cm^{-1}; MS *m*/*z* 258 (M$^+$, 4), 185 (100), 78 (51), 51 (16); ^{1}H NMR δ 1.27 (t, 3H, J=7 Hz), 2.55 (s, 3H), 4.20 (q, 2H, J=7 Hz), 6.07 (s, 1H), 6.89 (t, 1H, J=7 Hz), 7.27 (m, 1H), 7.63 (d, 1H, J=9 Hz), 8.07 (d, 1H, J=7 Hz), 10.11 (s, 1H); ^{13}C NMR δ 14.1, 19.1, 60.5, 114.7, 119.4, 124.5, 124.6, 126.9, 130.3, 139.3, 142.2, 145.2, 165.3, 187.1. Anal. calcd for $C_{14}H_{14}N_2O_3$: C: 65.11; H: 5.46; N: 10.85. Found: C: 65.01; H: 5.48; N: 10.86.

From **20**: 3-acetyl-2-formylimidazo[1,2-*a*]pyridine (**11c**); (reaction time 3 h at 70°C) yield: 90%; mp 125–127°C; IR (KBr) 1711, 1640, 1495, 1203 cm^{-1}; MS *m*/*z* 188 (M$^+$, 6), 160 (60), 145 (81), 117 (18), 90 (28), 78 (100), 63 (20), 51 (50); ^{1}H NMR δ 2.87 (s, 3H), 7.17 (t, 1H, J=7 Hz), 7.56 (m, 1H), 7.84 (d, 1H, J=9 Hz), 9.68 (d, 1H, J=7 Hz), 10.40 (s, 1H); ^{13}C NMR δ 31.5, 117.0, 118.9, 122.5, 129.2, 129.8, 146.0, 146.6, 188.5, 190.3. Anal. calcd for $C_{10}H_8N_2O_2$: C: 63.83; H: 4.28; N: 14.89. Found: C: 63.97; H: 4.30; N: 14.92.

4.1.7. Standard procedure for acetylation of 14 and 23. To a solution of the appropriate compound (17.5 mmol) in nitrobenzene (150 mL) was added acetyl chloride (18.13 mL, 210 mmol). The mixture was heated at 130°C for 1 h and at 210°C (external temperature) for 6 h. After cooling, the solvent was removed to dryness and then water was added (200 mL). The aqueous layer was basified with Na_2CO_3 (20.0 g, 189 mmol), extracted with CH_2Cl_2 (3×80 mL) and dried (Na_2SO_4). The extract was concentrated under vacuo. The crude product was purified by chromatography on alumina gel using CH_2Cl_2 as eluent.

From **14**: 2,3-diacetylimidazo[1,2-*a*]pyridine (**11d**); yield: 48%; R_f=0.75 (CH_2Cl_2); mp 102–104°C; IR (KBr) 1700, 1640 cm^{-1}; MS *m*/*z* 202 (M$^+$, 85), 187 (100), 145 (57), 117 (19), 78 (33); ^{1}H NMR δ 2.67 (s, 3H), 2.79 (s, 3H), 7.07 (t, 1H, J=7 Hz), 7.48 (m, 1H), 7.73 (d, 1H, J=9 Hz), 9.53 (d, 1H, J=7 Hz). ^{13}C NMR δ 29.4, 30.8, 116.1, 118.3, 121.9, 128.9, 129.3, 145.6, 148.4, 191.0, 197.8. Anal. calcd for $C_{11}H_{10}N_2O_2$: C: 65.34; H: 4.98; N: 13.85. Found: C: 65.29; H: 4.99; N: 13.85.

From **23**[13]: 3-acetyl-2-dichloromethylimidazo[1,2-*a*]pyridine (**24**); (reaction time 9 h at 210°C) yield: 33%; R_f=0.88 (CH_2Cl_2); mp 140–142°C; IR (KBr) 1638, 1500, 1381, 1351 cm^{-1}; MS *m*/*z* 246 (M$^+$+4, 6), 244 (M$^+$+2, 34), 242 (M$^+$, 55), 231 (2), 229 (12), 227 (18), 207 (68), 209 (30), 201 (9), 199 (22), 197 (7), 193 (24), 172 (32), 165 (29), 129 (48), 78 (100), 51 (78); ^{1}H NMR δ 2.77 (s, 3H), 7.10 (t, 1H, J=7 Hz), 7.36 (s, 1H), 7.52 (m, 1H), 7.80 (d, 1H, J=9 Hz), 9.61 (d, 1H, J=7 Hz); ^{13}C NMR δ 30.4, 64.5, 116.1, 118.0, 119.0, 129.1, 130.0, 146.5, 149.7, 186.8. Anal. calcd for $C_{10}H_8N_2OCl_2$: C: 49.41; H: 3.32; N: 11.52. Found: C: 49.55; H: 3.33; N: 11.56.

4.1.8. General procedures for preparation of oximes 10a–c. To a stirred mixture of the appropriate carbonyl (0.94 mmol) in EtOH (10 mL) was added NH_2OH, HCl (70 mg, 0.98 mmol) in water (3 mL) and NaOAc (82 mg, 1 mmol) in water (3 mL). The solution was stirred at room temperature for 20 mn and at 60°C for 1 h. After cooling the solvent was removed under reduced pressure and water was added (5 mL). The mixture was cooled to 0°C. The resulting precipitate was filtered off, and washed with cold ethanol (2 mL) to give the title compounds.

From **19a**: (*E*) ethyl 3-(2-hydroxyiminomethylimidazo[1,2-*a*]pyridin-3-yl)propenoate (**10a**); yield: 62%; mp 227–229°C; IR (KBr) 2753, 1694, 1626, 1489, 1389, 1368, 1274 cm^{-1}; MS *m*/*z* 259 (M$^+$, 1), 241 (17), 196 (32), 186 (54), 170 (100), 141 (13), 78 (60), 51 (29); ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3H, J=7 Hz), 4.23 (q, 2H, J=7 Hz), 6.75 (d, 1H, J=16.5 Hz), 7.15 (t, 1H, J=7 Hz), 7.51 (m, 1H), 7.72 (d, 1H, J=9 Hz), 8.33 (d, 1H, J=16.5 Hz), 8.32 (s, 1H), 8.65 (d, 1H, J=7 Hz); ^{13}C NMR (DMSO-d_6) δ 14.3, 60.0, 114.3, 114.8, 117.4, 118.1, 127.2, 127.7, 129.6, 142.3, 144.5, 146.7, 166.9. Anal. calcd for $C_{13}H_{13}N_3O_3$: C: 60.23; H: 5.05; N: 16.21. Found: C: 60.37; H: 5.07; N: 16.18.

From **19b**: (*E*) ethyl 3-(2-(1-hydroxyiminoethyl)imidazo[1,2-*a*]pyridin-3-yl)propenoate (**10b**); (reaction time 18 h at 60°C) yield: 84%; mp 219–221°C; IR (KBr) 3150–2830, 1708, 1629, 1285, 1189 cm^{-1}; MS *m*/*z* 273 (M$^+$, 1), 200 (72), 184 (100), 183 (79), 78 (36); ^{1}H NMR (DMSO-d_6) δ 1.31 (t, 3H, J=7 Hz), 2.33 (s, 3H), 4.24 (q, 2H, J=7 Hz), 6.69 (d, 1H, J=16.5 Hz), 7.19 (t, 1H, J=7 Hz), 7.54 (m, 1H), 7.79 (d, 1H, J=9 Hz), 8.38 (d, 1H, J=16.5 Hz), 8.89 (d, 1H, J=7 Hz), 11.79 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 12.6, 14.3, 59.9, 113.1, 114.9, 117.1, 117.4, 127.3, 127.5, 131.3, 146.0, 146.1, 151.4, 167.1. Anal. calcd for $C_{14}H_{15}N_3O_3$: C: 61.53; H: 5.53; N: 15.38. Found: C: 61.49; H: 5.52; N: 15.41.

From **26**: ethyl 3-(2-hydroxyiminomethylimidazo[1,2-*a*]pyridin-3-yl)butenoate (**10c**); yield: 94%; mp 172–174°C; IR (KBr) 3200–2700, 1705, 1619, 1503, 1213, 1179 cm^{-1}; ^{1}H NMR δ 1.33 (t, 3H, J=7 Hz), 2.58 (s, 3H), 4.25 (q, 2H, J=7 Hz), 6.09 (s, 1H), 6.87 (t, 1H, J=7 Hz), 7.27 (m, 1H), 7.71 (d, 1H, J=9 Hz), 8.05 (d, 1H, J=7 Hz), 8.36 (s, 1H); ^{13}C NMR δ 14.3, 19.1, 60.5, 113.5, 118.4, 123.6, 124.3, 126.1, 126.4, 136.2, 142.8, 142.9, 145.7,

165.9. Anal. calcd for $C_{14}H_{15}N_3O_3$: C: 61.53; H: 5.53; N: 15.38. Found: C: 61.70; H: 5.53; N: 15.42.

4.1.9. General procedures for thermolysis of oximes 10a–c. A stirred mixture of the appropriate oxime (9.46 mmol) in 1,2-dichlorobenzene (80 mL) was refluxed for 21 h. After removal of solvent, the residue was purified by column chromatography on alumina gel with CH_2Cl_2/EtOH, (99/1, v/v) as eluent.

From **10a** to give in order of elution (*E*) ethyl 3-(2-cyanoimidazo[1,2-*a*]pyridin-3-yl)propenoate (**27a**); yield: 15%; R_f=0.77 (CH_2Cl_2/EtOH, 99:1); mp 141–143°C; IR (KBr) 2234, 1703, 1667, 1630, 1489, 1382, 1278, 1237 cm^{-1}; MS *m/z* 241 (M^+, 57), 213 (13), 196 (98), 169 (100), 141 (30), 78 (53), 51 (44); ^1H NMR δ 1.42 (t, 3H, *J*=7 Hz), 4.37 (q, 2H, *J*=7 Hz), 6.75 (d, 1H, *J*=16 Hz), 7.18 (t, 1H, *J*=7 Hz), 7.52 (m, 1H), 7.77 (d, 1H, *J*=9 Hz), 7.91 (d, 1H, *J*=16 Hz), 8.34 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.3, 61.3, 114.8, 115.7, 118.6, 119.3, 120.9, 124.0, 124.9, 126.8, 128.4, 146.6, 166.4. Anal. calcd for $C_{13}H_{11}N_3O_2$: C: 64.72; H: 4.60; N: 17.42. Found: C: 64.52; H: 4.59; N: 17.44. 3-Ethoxycarbonyldipyrido[1,2-*a*;3′,4′-*d*]imidazole (**7a**); yield: 50%; R_f=0.29 (CH_2Cl_2/EtOH, 99:1); mp 172–174°C; IR (KBr) 1703, 1282, 1243 cm^{-1}; MS *m/z* 241 (M^+, 13), 183 (15), 169 (100), 141 (8), 78 (35), 51 (16); ^1H NMR δ 1.50 (t, 3H, *J*=7 Hz), 4.55 (q, 2H, *J*=7 Hz), 7.04 (t, 1H, *J*=7 Hz), 7.64 (m, 1H), 7.81 (d, 1H, *J*=9 Hz), 8.58 (d, 1H, *J*=7 Hz), 8.79 (s, 1H), 9.40 (s, 1H); ^{13}C NMR δ 14.6, 62.1, 108.8, 112.6, 119.2, 126.1, 132.3, 133.4, 138.8, 143.1, 143.4, 151.0, 165.8. Anal. calcd for $C_{13}H_{11}N_3O_2$: C: 64.72; H: 4.60; N: 17.42. Found: C: 64.77; H: 4.60; N: 17.41.

From **10b**: 2-ethoxycarbonyl-2-methyldipyrido[1,2-*a*;3′,4′-*d*]imidazole (**7b**); yield: 54%; R_f=0.38 (CH_2Cl_2/EtOH, 99:1); mp 139–141°C; IR (KBr) 1697, 1246 cm^{-1}; MS *m/z* 255 (M^+, 12), 183 (100), 155 (12), 78 (42). ^1H NMR δ 1.42 (t, 3H, *J*=7 Hz), 3.02 (s, 3H), 4.47 (q, 2H, *J*=7 Hz), 6.96 (t, 1H, *J*=7 Hz), 7.53 (m, 1H), 7.76 (d, 1H, *J*=9 Hz), 8.47 (d, 1H, *J*=7 Hz), 8.57 (s, 1H); ^{13}C NMR δ 14.4, 20.8, 62.0, 107.1, 112.3, 119.1, 126.0, 131.7, 132.3, 138.1, 141.9, 150.0, 152.9, 165.9. Anal. calcd for $C_{14}H_{13}N_3O_2$: C: 65.87; H: 5.13; N: 16.46. Found: C: 66.02; H: 5.11; N: 16.44.

From **10c** to give in order of elution ethyl 3-(2-cyanoimidazo[1,2-*a*]pyridin-3-yl)butenoate (**27b**); yield: 2%; R_f=0.68 (CH_2Cl_2/EtOH, 99:1); mp 171–173°C; IR (KBr) 2238, 1712, 1219, 1181 cm^{-1}; MS *m/z* 255 (M^+, 71), 226 (15), 209 (87), 181 (100), 168 (24), 143 (36), 78 (92); ^1H NMR δ 1.28 (t, 3H, *J*=7 Hz), 2.62 (s, 3H), 4.20 (q, 2H, *J*=7 Hz), 6.19 (s, 1H), 6.94 (t, 1H, *J*=7 Hz), 7.31 (m, 1H), 7.61 (d, 1H, *J*=9 Hz), 8.11 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.2, 18.5, 60.7, 114.5, 115.0, 119.1, 123.2, 124.7, 127.5, 140.0, 145.2, 165.4, one carbon not observed. Anal. calcd for $C_{14}H_{13}N_3O_2$: C: 65.87; H: 5.13; N: 16.46. Found: C: 65.78; H: 5.15; N: 16.52. 3-Ethoxycarbonyl-4-methyldipyrido[1,2-*a*;3′,4′-*d*]imidazole (**7c**); yield: 16%; R_f=0.33 (CH_2Cl_2/EtOH, 99:1); mp 92–94°C; IR (KBr) 1704, 1254, 122, 1081 cm^{-1}; MS *m/z* 255 (M^+, 20), 183 (100), 155 (24), 78 (37); ^1H NMR δ 1.42 (t, 3H, *J*=7 Hz), 3.07 (s, 3H), 4.44 (q, 2H, *J*=7 Hz), 6.91 (t, 1H, *J*=7 Hz), 7.49 (m, 1H), 7.71 (d, 1H, *J*=9 Hz), 8.80 (d, 1H, *J*=7 Hz), 9.14 (s, 1H); ^{13}C NMR δ 14.4, 15.1, 61.8, 112.2, 119.2, 121.9, 128.1, 131.1, 132.9, 138.9, 140.8, 141.8, 150.6, 166.9. Anal. calcd for $C_{14}H_{13}N_3O_2$: C: 65.87; H: 5.13; N: 16.46. Found: C: 65.95; H: 5.13; N: 16.47.

4.1.10. Procedure for hydrolysis of compounds 24 and 25. A solution of the appropriate dichloride derivative (2.59 mmol) in EtOH (40 mL) was mixed with silver nitrate (2.64 g, 15.5 mmol) in hot water (5 mL). The mixture was refluxed for 3 h then cooled at room temperature. Concentrated hydrochloric acid was added until pH=1 (pH test paper). The silver salts were removed by filtration under reduced pressure, and the filtrate was basified with Na_2CO_3 (0.50 g, 4.72 mmol). The mixture was extracted with CH_2Cl_2 (3×20 mL) and the dried organic layers were evaporated to dryness. The product was purified by column chromatography on alumina gel using CH_2Cl_2/EtOH, (99/1, v/v) as eluent.

From **24**: to give in order of elution 3-acetyl-2-diethoxymethylimidazo[1,2-*a*]pyridine (**20**); yield: 23%; R_f=0.70 (CH_2Cl_2/EtOH, 99:1);. 3-Acetyl-2-formylimidazo[1,2-*a*]pyridine (**11c**); yield: 53%; R_f=0.26 (CH_2Cl_2/EtOH, 99:1).

From **25**: (reaction time 1 h, eluate with CH_2Cl_2 to give in order of elution ethyl 3-(2-diethoxymethylimidazo[1,2-*a*]pyridin-3-yl)butenoate (**21**); yield: 13% as an oil; R_f=0.48 (CH_2Cl_2); IR (CCl_4) 1717, 1172 cm^{-1}; MS *m/z* 332 (M^+, 5), 288 (15), 259 (100), 241 (17), 213 (31), 185 (35), 78 (28); ^1H NMR δ 1.23 (t, 6H, *J*=7 Hz), 1.32 (t, 3H, *J*=7 Hz), 2.57 (d, 3H, *J*=1.5 Hz), 3.69 (m, 4H), 4.23 (q, 2H, *J*=7 Hz), 5.72 (s, 1H), 6.08 (q, 1H, *J*=1.5 Hz), 6.82 (t, 1H, *J*=7 Hz), 7.20 (m, 1H), 7.65 (d, 1H, *J*=9 Hz), 8.04 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.3, 15.2, 19.5, 60.2, 61.8, 97.7, 113.0, 118.5, 122.6, 123.9, 124.3, 125.0, 141.8, 144.0, 144.8, 166.2. Anal. calcd for $C_{18}H_{24}N_2O_4$: C: 65.04; H: 7.28; N: 8.43. Found: C: 65.25; H: 7.31; N: 8.42. Ethyl 3-(2-formylimidazo[1,2-*a*]pyridin-3-yl)butenoate (**26**); yield: 50%; R_f=0.29 (CH_2Cl_2).

4.1.11. General procedure for the preparation of pyridazines 9a–d. To a solution of the appropriate carbonyl derivative (4.02 mmol) in EtOH (30 mL) was added hydrazine monohydrate (0.25 g, 5.00 mmol). The solution was stirred at room temperature for 2 h and concentrated under vacuo. The yellow precipated was filtered and washed with ether (5 mL).

From **11a**: pyrido[1′,2′;1,2]imidazo[4,5-*d*]pyridazine (**9a**); yield: 89%; mp 253–255°C; IR (KBr) 1641, 1583, 1564, 1481, 1355, 1259, 1149 cm^{-1}; MS *m/z* 170 (M^+, 100), 142 (12), 115 (20), 78 (97), 64 (31), 51 (51); ^1H NMR (DMSO-d_6) δ 7.34 (t, 1H, *J*=7 Hz), 7.88 (m, 1H), 7.95 (d, 1H, *J*=9 Hz), 9.34 (d, 1H, *J*=7 Hz), 9.81 (s, 1H), 10.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 113.2, 117.7, 126.9, 128.6, 133.9, 138.3, 140.4, 145.2, 149.8. Anal. calcd for $C_9H_6N_4$: C: 63.52; H: 3.55; N: 32.92. Found: C: 63.48; H: 3.54; N: 32.86.

From **11b**: 1-methylpyrido[1′,2′;1,2]imidazo[4,5-*d*]pyridazine (**9b**); yield: 30%; mp 186–188°C; IR (KBr) 1637, 1577, 1355, 1267 cm^{-1}; MS *m/z* 184 (M^+, 100), 155 (46), 78 (72), 63 (18), 51 (43); ^1H NMR δ 3.13 (s, 3H), 7.15 (t,

1H, *J*=7 Hz), 7.69 (m, 1H), 7.91 (d, 1H, *J*=9 Hz), 8.64 (d, 1H, *J*=7 Hz), 9.73 (s, 1H); ^{13}C NMR δ 18.4, 113.5, 119.1, 125.9, 126.3, 132.5, 135.6, 140.7, 149.7, 155.2. Anal. calcd for $C_{10}H_8N_4$: C: 65.21; H: 4.38; N: 30.42. Found: C: 65.12; H: 4.40; N: 30.31.

From **11c**: 4-methylpyrido[1′,2′;1,2]imidazo[4,5-*d*]pyridazine (**9c**); yield: 63%; mp 264–266°C; IR (KBr) 1635, 1475, 1309 cm^{-1}; MS *m*/*z* 184 (M^+,100), 155 (52), 78 (90), 51 (51); ^{1}H NMR δ 3.25 (s, 3H), 7.15 (t, 1H, *J*=7 Hz), 7.69 (m, 1H), 7.89 (d, 1H, *J*=9 Hz), 8.77 (d, 1H, *J*=7 Hz), 9.69 (s, 1H); ^{13}C NMR δ 20.7, 113.6, 119.0, 126.3, 127.8, 132.1, 140.9, 145.2, 146.6, 150.2. Anal. calcd for $C_{10}H_8N_4$: C: 65.21; H: 4.38; N: 30.42. Found: C: 65.19; H: 4.37; N: 30.51.

From **11d**: 1,4-dimethylpyrido[1′,2′;1,2]imidazo[4,5-*d*]pyridazine (**9d**); reaction time 1 h 30 min; yield: 75%; mp 211–213°C; IR (KBr) 1640, 770 cm^{-1}; MS *m*/*z* 198 (M^+, 100), 169 (45), 84 (22), 78 (27); ^{1}H NMR δ 3.06 (s, 3H), 3.19 (s, 3H), 7.14 (t, 1H, *J*=7 Hz), 7.67 (m, 1H), 7.91 (d, 1H, *J*=9 Hz), 8.76 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 18.1, 20.6, 113.6, 119.2, 125.5, 127.7, 131.7, 140.7, 145.3, 149.7, 153.9. Anal. calcd for $C_{11}H_{10}N_4$: C: 66.65; H: 5.08; N: 28.26. Found: C: 66.52; H: 5.10; N: 28.21.

4.1.12. General procedures for the preparation of dipyridoimidazoles. To a solution of the appropriate dicarbonyl compound (4.95 mmol) in anhydrous EtOH (55 mL) was added freshly prepared ethyl glycinate (1.18 g, 11.5 mmol) obtained by treatment of commercial ethyl glycinate hydrochloride with sodium hydroxyde according to the Hagenah's procedure.[20] The solution was stirred at room temperature until no more substrate was observed by TLC. The solvent was removed under vacuo and the residue was purified by column chromatography on alumina gel.

From **11a**: (reaction time 20 h (the solution became red after 20 mn), eluate with CH_2Cl_2/EtOH, (99/1, v/v)) to give in order of elution: 3-ethoxycarbonyldipyrido[1,2-*a*;4′,3′-*d*]imidazole (**8a**); yield: 39%; R_f=0.38 (CH_2Cl_2/EtOH, 99:1); mp 200–202°C; IR (KBr) 1721, 1298, 1231 cm^{-1}; MS *m*/*z* 241 (M^+, 9), 169 (100), 142 (10), 78 (21); ^{1}H NMR δ 1.55 (t, 3H, *J*=7 Hz), 4.61 (q, 2H, *J*=7 Hz), 7.17 (t, 1H, *J*=7 Hz), 7.75 (m, 1H), 7.92 (d, 1H, *J*=9 Hz), 8.76 (s, 1H), 8.82 (d, 1H, *J*=7 Hz), 9.56 (s, 1H); ^{13}C NMR δ 14.4, 61.9, 112.6, 117.1, 118.4, 126.2, 128.5, 132.5, 133.9, 143.5, 149.5, 151.2, 165.6. Anal. calcd for $C_{13}H_{11}N_3O_2$: C: 64.72; H: 4.60; N: 17.42. Found: C: 64.87; H: 4.58; N: 17.44. 3-Ethoxycarbonyldipyrido[1,2-*a*;3′,4′-*d*]imidazole (**7a**); yield: 12%.

From **11b**: (reaction time 40 h (the solution became red after 20 mn), eluate with CH_2Cl_2/EtOH, (99/1, v/v)) to give 2-ethoxycarbonyl-2-methyldipyrido[1,2-*a*;3′,4′-*d*]imidazole (**7b**); yield: 28%.

From **11c**: 3-ethoxycarbonyl-1-methyldipyrido[1,2-*a*;4′,3′-*d*]imidazole (**8c**); reaction time 1 h 30 min, eluate with CH_2Cl_2/EtOH, (99/1, v/v); yield: 61%; R_f=0.46 (CH_2Cl_2/EtOH, 99:1); mp 192–194°C; IR (KBr) 1703, 1248 cm^{-1}; MS *m*/*z* 255 (M^+, 12), 183 (100), 155 (14), 78 (12); ^{1}H NMR δ 1.48 (t, 3H, *J*=7 Hz), 3.22 (s, 3H), 4.53 (q, 2H, *J*=7 Hz), 7.09 (t, 1H, *J*=7 Hz), 7.65 (m, 1H), 7.86 (d, 1H, *J*=9 Hz), 8.57 (s, 1H), 8.83 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.5, 23.3, 62.0, 112.7, 115.7, 118.6, 127.6, 128.1, 131.6, 142.7, 144.9, 149.6, 151.2, 165.8. Anal. calcd for $C_{14}H_{13}N_3O_2$: C: 65.87; H: 5.13; N: 12.53. Found: C: 66.01; H: 5.14; N: 12.54.

From **11d**: 3-ethoxycarbonyl-1,4-dimethyldipyrido[1,2-*a*;3′,4′-*d*]imidazole (**7d**); reaction time 8 days, eluate with CH_2Cl_2; yield: 61%; R_f=0.19 (CH_2Cl_2); mp 143–145°C; IR (KBr) 1700, 1230 cm^{-1}; MS *m*/*z* 269 (M^+, 24), 197 (100), 169 (17), 78 (23), 51 (10); ^{1}H NMR δ 1.41 (t, 3H, *J*=7 Hz), 2.93 (s, 3H), 2.97 (s, 3H), 4.44 (q, 2H, *J*=7 Hz), 6.85 (t, 1H, *J*=7 Hz), 7.44 (m, 1H), 7.70 (d, 1H, *J*=9 Hz), 8.73 (d, 1H, *J*=7 Hz); ^{13}C NMR δ 14.3, 14.8, 20.2, 61.7, 112.0, 118.8, 119.0, 127.8, 130.5, 131.8, 138.8, 140.5, 149.5, 149.8, 167.2. Anal. calcd for $C_{15}H_{15}N_3O_2$: C: 66.90; H: 5.61; N: 15.60. Found: C: 66.83; H: 5.62; N: 15.59.

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