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EFFICIENT SYNTHESIS OF NEW POLYFUNCTIONALIZED THIA-DIAZAACENAPHTHYLENES FROM IMIDAZO[1,2-*a*]PYRIDINES

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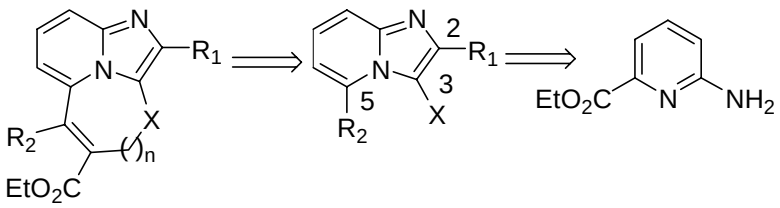
Abstract-New heterocycles containing sulfur and nitrogen with an azaindolizine moiety were synthesized. The imidazo[1,2-*a*]pyridine-2,5-dicarboxylates (**9a**, **b**, **10a**, **b**) and 5-formylimidazo[1,2-*a*]pyridine-2-carboxylates (**17a**, **b**) treated with ethyl thioglycolate and lithium hydroxide underwent ring closure yielding the multifunctional[2,3,3]cyclazines (**13**) and (**18**). Under similar conditions, the imidazo[1,2-*a*]pyridinecarbaldehydes (**22a**, **b**) and (**29a**, **b**) were converted into the linearly cyclized compounds thieno[3,2-*b*]imidazo[1,2-*a*]pyridines (**23**, **31**) and a *peri* annulated product thiadiazaacenaphthylene (**30)**.

INTRODUCTION

The skeleton of imidazo[1,2-*a*]pyridine (IP), an aza-analog of indolizine, is an important pharmacophore for therapeutic drugs. IP compounds have been used to reduce neurotoxin injury associated with anoxia or ischemia,[1] and employed as antiviral agents,[2] ligands for benzodiazepine receptors.[3] More recently, the development of methods for the regiocontrolled synthesis of multifunctional heterocycles has given access to new compounds: in particular, works on IP fused at C(5)-C(3) have been extended to include cyclazines,[4] a tricyclic ring system.[5] These triazaacenaphthylene compounds were shown to display platelet-derived growth factor (PDGF) inhibitory activity.[6] Thiadiazaacenaphthylenes have also been successfully prepared.[7] Our interest in annulation in IPs[8] prompted us to study a synthetic approach to obtain novel multifunctional cyclazines. In the course of our work using nitro-IP as a synthetic auxiliary,[9] we previously described the nucleophilic aromatic substitution reaction by displacement of the nitro

group of some 3-nitro-IP with thioglycolate anion. We failed to complete the construction of the cyclazine skeleton *via* a Dieckmann reaction (Scheme 1).[10]

Scheme 1



R_1 = H, CHO, CO_2Et
R_2 = H, OH
X = O, S
n = 0, 1

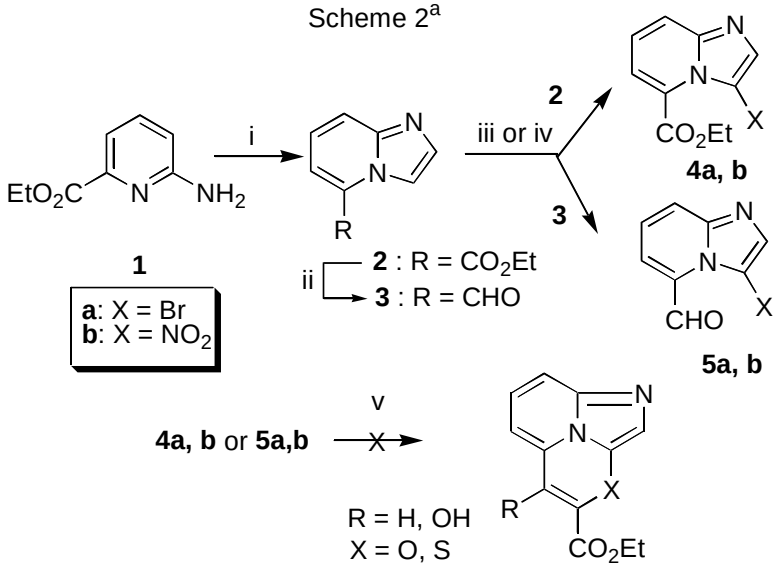
R_1 = H, CHO, CO_2Et
R_2 = CHO, CO_2Et
X = Br, NO_2

In continuation of our work on novel cyclazine synthesis, we focused on 2-, 3- and 5-functionalized IPs. In addition, when the introduction of functional groups (ester, formyl) into the 5-position of IP was tried, a *peri* annulation took place under mild conditions. We detail here a new synthetic approach to the construction of imidazopyridothiazines for screening as potential immunostimulants.

RESULTS AND DISCUSSION

Starting material ethyl 2-aminopyridine-6-carboxylate (**1**) was readily prepared from commercially available 2-amino-6-methylpyridine *via N*-acetylation, oxidation, deacetylation, and esterification by reported procedures[11] (Scheme 2).

Scheme 2[a]



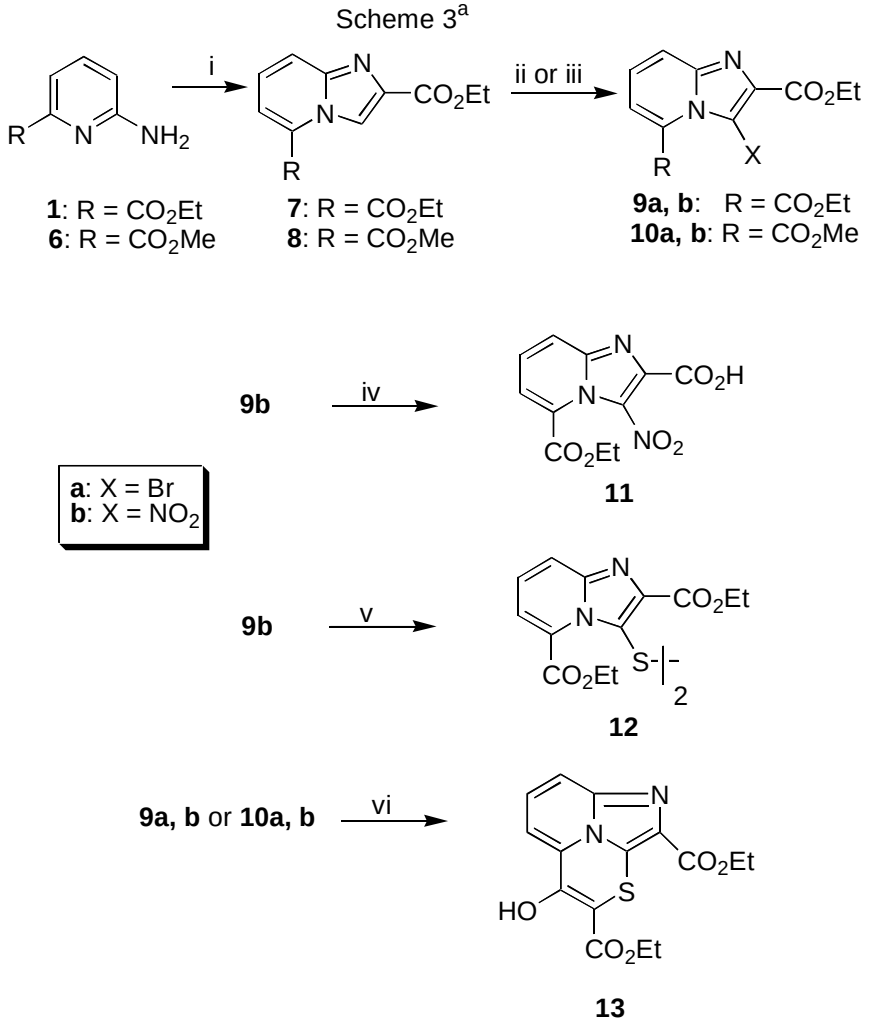
[a]Reagents and conditions: (i) $ClCH_2CHO$, EtOH, reflux; (ii) DIBALH, -70 °C, THF; (iii) Br_2, AcOH, rt; (iv) H_2SO_4, HNO_3, rt; (v) $HOCH_2CO_2Et$, $HSCH_2CH_2CO_2Et$ or $HSCH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C.

The compound (**1**)[11] reacted with chloroacetaldehyde in refluxing ethanol to afford the imidazopyridine (**2**), which was converted to the corresponding aldehyde (**3**) under Yamanaka's conditions.[12] The bromination of **2** and **3** (bromine in AcOH) or the nitration (H_2SO_4/HNO_3) at room temperature gave 3-bromo- and 3-nitro-IP (**4a**, **5a**) and (**4b**, **5b**) respectively[13] (see general details in EXPERIMENTAL).

Compounds (**4a**, **b**) were treated in dry DMF with an equivalent of ethyl glycolate (or ethyl 3-mercaptopropionate or ethyl thioglycolate) and an excess of lithium hydroxide[9, 14, 15] but the expected tricyclic ester was not obtained and the starting material was recovered. Similarly, **5a**, **b** were also recovered unchanged even after two days at low and room temperature.

However, the presence of an electon-withdrawing group in position 2 promotes the substitution of iodo- or nitro groups at position 3 of IP.[9, 16] Accordingly, we investigated the reactivity of the diesters (**9a**, **b** and **10a**, **b**), readily obtained in two steps from the esters (**1**)[11] and (**6**),[11] respectively (Scheme 3).

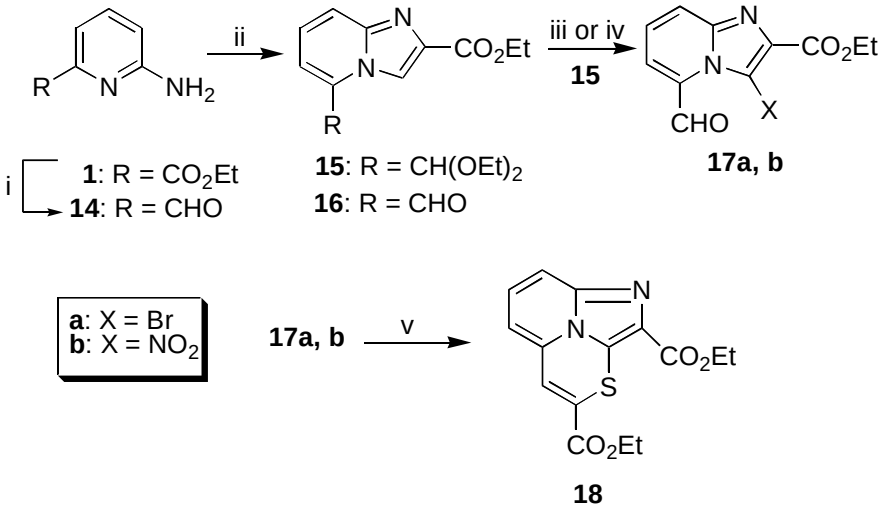
Scheme 3[a]



[a]Reagents and conditions: (i) $BrCH_2COCO_2Et$, EtOH, reflux; (ii) Br_2, AcOH, rt; (iii) H_2SO_4, HNO_3, rt; (iv) $HOCH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C; (v) $HSCH_2CH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C; (vi) $HSCH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C.

After treatment of **9b** with ethyl glycolate anion in DMF, the product was not the annulated tricyclic compound but the acid (**11**). When **9b** was allowed to react with ethyl 3-mercaptopropionate in DMF containing lithium hydroxide under cooling in ice-bath, we isolated the corresponding disulfide (**12**). A reasonable explanation for the formation of compound (**12**) would be a β-elimination in the basic medium, giving the arylthiol anion which attacks another compound (**9b**).[15] Also, when **9a**, **b** were allowed to react with an equivalent ethyl thioglycolate and excess lithium hydroxide in DMF, the product was the expected diethyl 5-hydroxy-3-thio[1,8-*b*]diazaacenaphthylene-2,4-dicarboxylate (**13**). The structure of the cyclazine (**13**) was supported by ^{1}H and ^{13}C NMR spectra. The analysis of INEPT data between H-6 (δ 7.00) and C-5 (δ 163.1), methylene proton signals at δ 4.12 and 4.26 and the carbonyl carbons of esters (δ 162.5 and 166.0) showed that the cyclization took place on the 5-ester group of compounds (**9**, **10**) by *peri* annulation. This structure was further confirmed by the same reaction of **10a**, **b** in LiOH/DMF. Disappearance of the 5-COOMe and 3-Br (or 3-NO_2) groups in compounds (**10a**, **b**) supported that the cyclization was a *peri* annulation. A similar reaction was performed between the 3- and 5-positions of the aldehydes (**17a**, **b**) (Scheme 4).

Scheme 4[a]

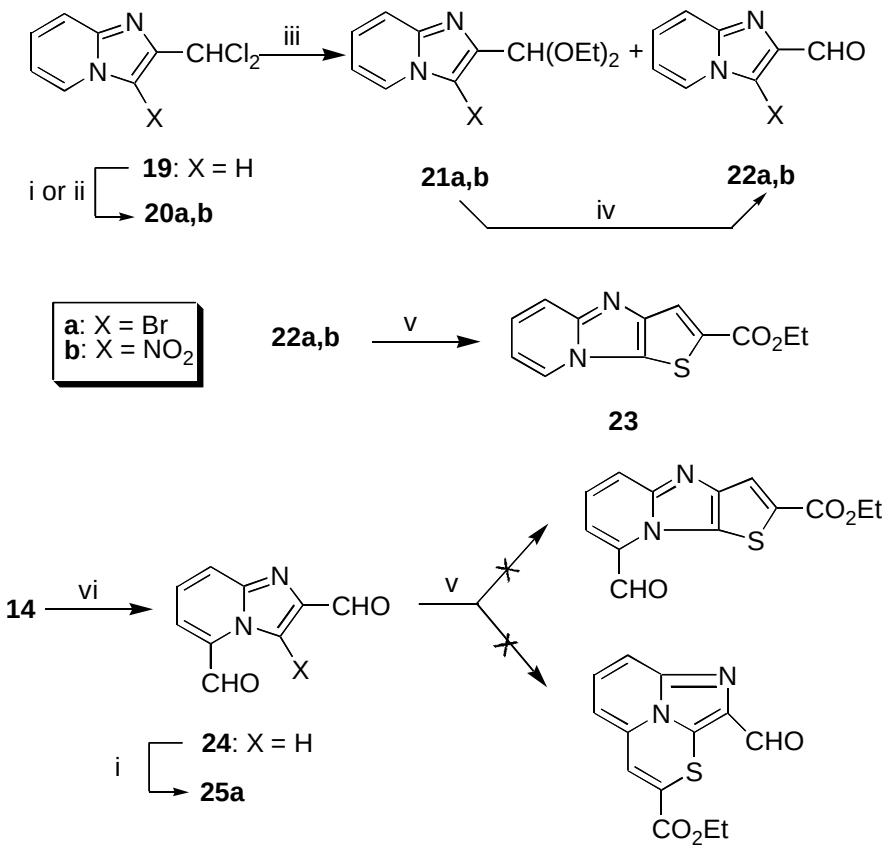


[a]Reagents and conditions: (i) (a) tritylmethyl chloride, NEt_3, $CHCl_3$, rt; (b) DIBALH, toluene, -70 °C; (c) AcOH/water (5/5, v/v), reflux; (ii) $BrCH_2COCO_2Et$, EtOH, reflux; (iii) Br_2, AcOH, rt; (iv) H_2SO_4, HNO_3, rt; (v) $HSCH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C.

N-Tritylation, reduction with DIBAL-H and final removal of the trityl group for compound (**1**) according to the literature[17] provided the amino aldehyde (**14**), whose condensation with ethyl bromopyruvate gave **15** and **16** in 18 and 1% yields, respectively. Subsequent bromination and nitration of compound (**15**) afforded compounds (**17a**, **b**). Treatment of compounds (**17a**, **b**) with ethyl thioglycolate and excess lithium hydroxide in DMF yielded **18** in 23 and 24% yields, respectively. The structure was confirmed by

the presence of a singlet H-7 signal at δ 7.53 and the disappearance of an aldehyde proton signal. To study further the nucleophilic displacement at the 3-position, we investigated the effect of an electron-withdrawing group such as formyl group in the 2-position (Scheme 5).

Scheme 5[a]



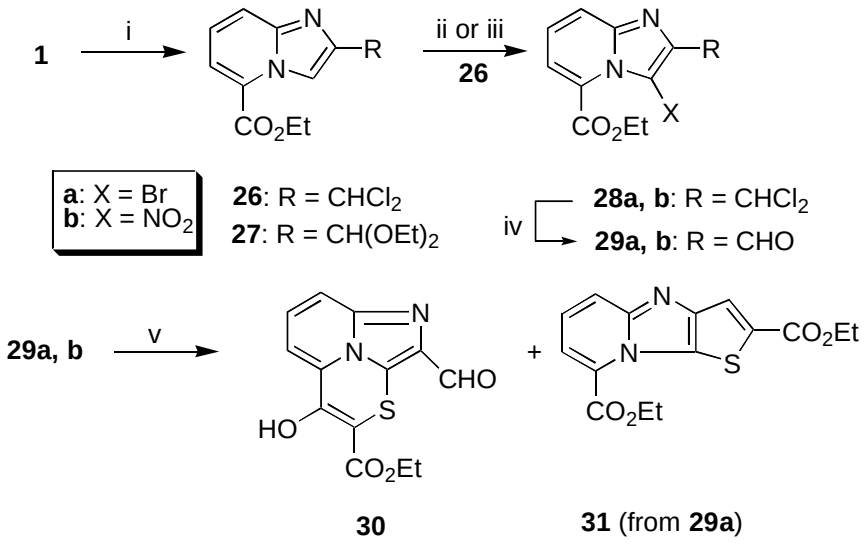
[a]Reagents and conditions: (i) Br_2, AcOH, rt; (ii) H_2SO_4,HNO_3, rt; (iii) $AgNO_3$, EtOH/water (8/1,v/v), reflux; (iv) MeCN/water (3/1,v/v), HCl, reflux; (v) $HSCH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C; (vi) (a) $ClCH_2COCHCl_2$, DME, rt; (b) EtOH, reflux.

Compounds (**20a**, **b**) were obtained by nitration and bromination of **19**.[19] This route could be used to prepare substituted 2-carbaldehyde of IP. Compound (**20a**)[18] was further converted under Arbaca's conditions[19] (silver nitrate in ethanol/water) to give **21a** and **22a** in 11 and 54% yields, respectively. Hydrolysis of **21a** in MeCN gave **22a** in 97%. Aldehyde (**22b**) was obtained from **20b** under similar conditions. Under the conditions of the substitution reaction, the nitro and bromo compounds (**22a**, **b**), activated by the adjacent carbaldehyde function, were readily displaced and a base-catalyzed cyclization gave **23** in a very low yield of 1%. This new structure is of obvious pharmacological interest as a potential immunostimulant by analogy with Levamisol®.[20]

To develop these annulations on the 2- or 5-positions, we synthesized the dialdehydes (**24**) and (**25a**) from **14** while no nitration of **24** was observed.

However, attempt to extend this method failed, recovering only starting material (**25a**). We therefore decided to continue our study as shown in Scheme 6.

Scheme 6[a]



[a]Reagents and conditions: (i) (a) $ClCH_2COCHCl_2$, DME, rt; (b) EtOH, reflux; (ii) Br_2, AcOH, rt; (iii) H_2SO_4, HNO_3, rt; (iv) $AgNO_3$, EtOH/water (8/1, v/v), reflux; (v) $HSCH_2CO_2Et$ (1 equiv.), LiOH (2 equiv.), DMF, -10 °C.

Condensation of **1** with 1,1,3-trichloroacetone in refluxing ethanol gave **26** and **27**. The nitration or bromination of **26**, following treatment with silver nitrate, yielded (**29a**, **b**) in 39 and 49%, respectively. The reaction of **29a** with ethyl thioglycolate provided **31** as a linear annulation product in 8% yield and compound (**30**) in 23% yield, while the reaction of **29b** with ethyl thioglycolate afforded only compound (**30**) in 24% yield.

In summary, we report new tricyclic systems, fused imidazo[1,2-*a*]pyridines (**13**, **18**, **23**, **30** and **31**), containing sulfur and nitrogen atoms. These tricyclic systems were synthesized by displacement of a bromo (or nitro) group by ethyl thioglycolate anion and subsequent base-catalyzed ring closure. We have found that the presence of an electron-withdrawing group in the 2-position is necessary to achieve the substitution in the 3-position.

EXPERIMENTAL

Instrumentation. Melting points were determined on a capillary apparatus and are not corrected. NMR (400 MHz for ^1H or 100 MHz for ^{13}C) were recorded on a Bruker AC 400 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. IR spectra were recorded on a Nicolet Impact 410 spectrophotometer. MS spectral

analyses were performed on a Hewlett-Packard 5985B or 5989A instrument. Toluene was dried over Na. Other dry solvents were stored over molecular sieves.

2-Aminopyridine-6-carbaldehyde (14): A mixture of 2-tritylaminopyridine-6-carbaldehyde[17] (400 mg, 1.10 mmol) and aqueous 50% acetic acid (6.5 mL) was refluxed for 1 h to give precipitates which were removed by filtration. The filtrate was poured onto ice-water and was made basic with aqueous 20% NH_4OH solution. The mixture was extracted with methylene chloride, the combined organic layer was dried over Na_2SO_4 and evaporated to dryness to give red solid **14**, which were used in the next reaction without further purification. Yield: 82 mg (61%); mp 121-123 °C (decomp); IR (KBr) ν: 3374, 2924, 1701, 1600, 1573, 1457, 1270, 1156, 798 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 6.39 (s, 2H), 6.74 (d, 1H, *J* = 8 Hz), 7.10 (d, 1H, *J* = 7 Hz), 7.60 (m, 1H), 9.75 (s, 1H). *Anal*. Calcd for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.24; H, 4.93; N, 23.03.

Ethyl imidazo[1,2-*a*]pyridine-5-carboxylate (**2**)**:** To a solution of ester (**1**)[11] (5.81 g, 35 mmol) and 5.00 g of $NaHCO_3$ in 250 mL of ethanol were added (12.4 g, 158 mmol) of a solution of chloroacetaldehyde (~ 50 wt.% in water). The mixture was refluxed for 9 h and the solvent was removed. Water (200 mL) were added and the residue was basified with Na_2CO_3 and extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Chromatography on alumina eluting with CH_2Cl_2 afforded the imidazopyridine (**2**). Yield: 5.31 g (80%); mp 79-81 °C, recrystallization solvent: H_2O/Ethanol (1/5); IR (KBr) ν: 1720, 1280, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.44 (t, 3 H, *J* = 7 Hz), 4.45 (q, 2 H, *J* = 7 Hz), 7.21 (dd, 1 H, *J* = 7, 9.5 Hz), 7.80 (s, 1 H), 7.82 (d, 1 H, *J* = 7 Hz), 7.87 (d, 1 H, *J* = 8.5 Hz), 8.82 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 62.0, 114.8, 118.8, 122.2, 122.8, 126.1, 134.8, 146.1, 161.9; MS m/z 190 (M^+, 100), 162 (82), 145 (68), 117 (38), 63 (23). *Anal*. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.32; H, 5.27; N, 14.80.

Imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3**)**:** To a solution of ester (**2**) (0.3 g, 1.58 mmol) in 50 mL of methylene chloride at –70 °C was added 24 mL (24 mmol) of 1 M DIBAL-H solution in methylene chloride. After stirring at this temperature for 2 h, 24 mL (24 mmol) of the same DIBAL-H solution was added. After 1 h, 10 mL of methanol and 2 mL of water were added. The reaction mixture was warmed to rt, poured into 50 mL of water and extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4 and removed under reduced pressure. Chromatography on neutral alumina eluting with methylene chloride afforded **3**: yield (0.18 g, 79%); mp 115-117 °C, recrystallization solvent: H_2O/Ethanol (1/5); IR (KBr) ν: 1670, 1295, 1135, 780, 750 cm^{-1}; ^1H NMR ($CDC1_3$) δ: 7.35 (dd, 1 H, *J* = 8.5, 7 Hz), 7.50 (d, 1 H, *J* = 7 Hz), 7.82 (s, 1 H), 7.95 (d, 1 H, *J* = 8.5 Hz), 8.99 (s, 1 H), 9.88 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ: 114.5, 122.3, 124.4, 126.0, 132.1, 136.2, 145.5, 184.6. *Anal*. Calcd for $C_8H_6N_2O_2$: C,

65.75; H, 4.11; N, 19.18. Found C, 65.49; H, 4.13; N, 19.10.

General Procedure for the Preparation of Esters (7, 8 and 16). To a solution of the appropriate 2-aminopyridine derivatives (8.55 mmol) in 70 mL of ethanol was added ethyl bromopyruvate (3.85 g, 19.74 mmol). The mixture was refluxed for 5 h and the solvent was removed. The residue was diluted in water (60 mL) and basified with Na_2CO_3. The solution was extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure and gave the required products.

Diethyl imidazo[1,2-*a*]pyridine-2,5-dicarboxylate (7): (from **1**[11]). The residue was chromatographed on neutral alumina eluting with methylene chloride-ethanol (97/3, v/v) to afford **7** as a white solid: yield 65%; mp 115-117 °C, recrystallization solvent: H_2O/Ethanol (1/4); IR (KBr) ν: 1727, 1628, 1518, 1255, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.48 (m, 6H), 4.51 (m, 4H), 7.34 (m, 1H), 7.87 (d, 1H, *J* = 7 Hz), 7.96 (d, 1H, *J* = 9 Hz), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 14.5, 61.2, 62.4, 119.3, 120.0, 124.1, 124.2, 126.7, 137.7, 145.8, 161.4, 163.2; MS m/z 262 (M^+, 20), 190 (100), 161 (20), 118 (22). *Anal*. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.77; H, 5.35; N, 10.72.

Imidazo[1,2-*a*]pyridine-2,5-carboxylic acid 2-ethyl-5-methyl diester (8): (from **6**[11]). The residue was chromatographed on neutral alumina eluting with methylene chloride-ethanol (97/3, v/v) to give a white solid **8**: yield: 93%; mp 111-113 °C, recrystallization solvent: H_2O/Ethanol (1/4); IR (KBr) ν: 1724, 1628, 1440, 1257, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.43 (t, 3H, *J* = 7 Hz), 4.02 (s, 3H), 4.46 (q, 2H, *J* = 7 Hz), 7.30 (dd, 1H, *J* = 9, 7 Hz), 7.83 (d, 1H, *J* = 7 Hz), 7.93 (d, 1H, *J* = 9 Hz), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.5, 53.1, 61.2, 119.2, 120.2, 124.2, 124.2, 126.4, 137.7, 145.8, 161.8, 163.1; MS m/z 248 (M^+, 20), 176 (100), 116 (22), 104 (22), 90 (22). *Anal*. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.29; H, 4.85; N, 11.33.

Ethyl 5-diethoxymethylimidazo[1,2-*a*]pyridine-2-carboxylate (15): (from **14**). According to the general procedure for **7**, the obtained residue was chromatographed on neutral alumina eluting with methylene chloride. The first fraction gave **15** as a yellow oil. Yield: 18 %; IR (KBr) ν: 2980, 1742, 1717, 1546, 1266, 1221, 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.19 (t, 6H, *J* = 7 Hz), 1.38 (t, 3H, *J* = 7 Hz), 3.57 (q, 4H, *J* = 7 Hz), 4.41 (q, 2H, *J* = 7 Hz), 5.58 (s, 1H), 7.05 (d, 1H, *J* = 7 Hz), 7.21 (dd, 1H, *J* = 9, 7 Hz), 7.62 (d, 1H, *J* = 9 Hz), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.4, 15.0, 61.0, 61.8, 97.8, 112.4, 116.3, 118.9, 125.3, 134.8, 136.8, 145.8, 163.5; MS m/z 292 (M^+, 10), 248 (40), 219 (64), 173 (100), 147 (30), 90 (27), 78 (29). *Anal*. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.87; H, 6.87; N, 9.61. The second fraction gave **ethyl 5-formylimidazo[1,2-*a*]pyridine-2-carboxylate (16):** yield: 1%; mp 121-123 °C, recrystallization solvent: H_2O/Ethanol (1/4); ^1H NMR ($CDCl_3$) δ: 1.51 (t, 3H, *J* = 7 Hz), 4.55 (q, 2H,

J = 7 Hz), 7.56 (dd, 1H, *J* = 9, 7 Hz), 7.68 (d, 1H, *J* = 7 Hz), 8,16 (d, 1H, *J* = 9 Hz), 9.62 (s, 1H), 10.01 (s, 1H). *Anal*. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.79; H, 4.60; N, 12.89.

General Procedure for the Synthesis of 19, 24 and 26 by Condensation of 2-Aminopyridine Derivatives with 1,1,3-Trichloroacetone. To a stirred solution of the appropriate 2-aminopyridine derivatives (18.07 mmol) in 1,2-dimethoxyethane (DME) (20 mL) was added dropwise a solution of 1,1,3-trichloroacetone (2.88 g, 20.92 mmol) in 5 mL of DME. The mixture was stirred at rt for 4 h. After filtration, the solid obtained was poured into ethanol solution (70 mL) and heated under reflux for 12 h. The cooled solution was evaporated and water (100 mL) was added, the suspension made alkaline with Na_2CO_3 and extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure. The residue was chromatographed on alumina eluting with methylene chloride to give the required products.

2-Dichloromethylimidazo[1,2-*a*]pyridine (19): (from **2-aminopyridine**). Yield: 71%; mp 123-125 °C (lit.,[18] 127-129 °C).

Imidazo[1,2-*a*]pyridine-2,5-dicarbaldehyde (24): (from **6**[11]). Yield: 5%; mp 169-171 °C, recrystallization solvent: H_2O/Ethanol (1/4); IR (KBr); ν: 1700, 1673, 1326, 1048, 788, 592 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.58 (dd, 1H, *J* = 7, 9 Hz), 7,70 (d, 1H, *J* = 7 Hz), 8.11 (d, 1H, *J* = 9 Hz), 9.61 (s, 1H), 9.99 (s, 1H), 10.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 118.1, 124.9, 126.0, 127.4, 133.0, 145.5, 145.9, 184.3, 187.4; MS m/z 174 (M^+, 100), 146 (45), 118 (51), 106 (41), 78 (65). *Anal*. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.31; H, 3.45; N, 16.15.

Ethyl 2-dichloromethylimidazo[1,2-*a*]pyridine-5-carboxylate (26): (from **1**[11]). The first fraction gave **26**. Yield: 41%; mp 98-100 °C, (recrystallization solvent: H_2O/Ethanol (1/4); IR (KBr) ν: 2976, 1722, 1276, 1258, 1144, 769, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.48 (t, 3H, *J* = 7 Hz), 4.51 (q, 2H, *J* = 7 Hz), 7.00 (s, 1H), 7.33 (dd, 1H, *J* = 9, 7 Hz), 7.84 (d, 1H, *J* = 7 Hz), 7.89 (d, 1H, *J* = 9 Hz), 9.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.2, 62.4, 65.7, 112.9, 119.4, 123.1, 124.0, 126.5, 145.8, 146.1, 161.4; MS m/z 276 (M^++ 4, 2), 274 (M^++ 2, 14), 272 (M^+, 22), 237 (100), 209 (77), 73 (49). *Anal*. Calcd for $C_{11}H_{10}N_2O_2Cl_2$: C, 48.37; H, 3.69; N, 10.26. Found: C, 48.56; H, 3.67; N, 10.30. Further fraction gave a yellow oil **ethyl 2-diethoxymethylimidazo[1,2-*a*]pyridine-5-carboxylate (27)**: yellow oil; Yield: 19%; IR (KBr) ν: 2976, 2930, 2889, 1726, 1698, 1272, 1148, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.30 (t, 6H, *J* = 7 Hz), 1.47 (t, 3H, *J* = 7 Hz), 3.73 (q, 4H, *J* = 7 Hz), 4.49 (q, 2H, *J* = 7 Hz), 5.82 (s, 1H), 7.24 (dd, 1H, *J* = 9, 7 Hz), 7.79 (d, 1H, *J* = 7 Hz), 7.88 (d, 1H, *J* = 9 Hz), 8.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 15.3, 61.6, 62.1, 98.6, 118.8, 120.5, 122.5, 122.9, 126.2, 145.8, 146.3, 161.8; MS m/z 292 (M^+, 1), 248 (22), 219 (100), 191 (56), 78 (16). *Anal*. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.84; N, 9.58. Found: C, 61.87; H, 6.87; N, 9.64.

General Procedure for the Bromination of Compounds (2, 3, 7, 8, 15, 19, 24 and 26). To a solution of the appropriate carbonyl derivatives (2.63 mmol) in 8 mL of acetic acid was added dropwise a solution of bromine (0.53 g, 3.31 mmol) in 2 mL of acetic acid. The solution was stirred at rt for 24 h. The precipitate was filtered and washed with ether. The filtrate was diluted in 5 mL of water, basified with Na_2CO_3 and extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure to give the required bromo products.

Ethyl 3-bromoimidazo[1,2-*a*]pyridine-5-carboxylate (4a): (from **2**). Yield: 82%; mp 129-131 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 2622, 1726, 1637, 1280, 1193, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.39 (t, 3H, *J* = 7 Hz), 4.46 (q, 2H, *J* = 7 Hz), 7.19 (m, 2H), 7.66 (s, 1H), 7.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.9, 62.3, 95.7, 116.47, 120.8, 122.9, 128.9, 136.6, 146.7, 161.6; MS m/z 270 (M^++ 2, 51), 268 (M^+,48), 189 (30), 161 (75), 145 (83), 86 (66), 84 (100). *Anal*. Calcd for $C_{10}H_9N_2O_2Br$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.80; H, 3.35; N, 10.45.

Diethyl 3-bromoimidazo[1,2-*a*]pyridine-5-carbaldehyde (5a): (from **3**). Yield: 65%; mp 99-101 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 2919, 1675, 1140, 845, 799 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.35 (m, 1H), 7.65 (d, 1H, *J* = 7 Hz), 7.75 (s, 1H), 7.90 (d, 1H, *J* = 9 Hz), 11.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 94.7, 118.9, 123.3, 123.9, 134.6, 137.6, 147.4, 182.5; MS m/z 226 (M^++ 2, 21), 224 (M^+, 20), 145 (100). *Anal*. Calcd for $C_8H_5N_2OBr$: C, 42.85; H, 2.24; N, 12.49. Found: C, 42.87; H, 2.23; N, 12.49.

Diethyl 3-bromoimidazo[1,2-*a*]pyridine-2,5-dicarboxylate (9a): (from **7**). Yield: 37%; mp 106-108 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 2979, 1724, 1185, 798, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.46 (m, 6H), 4.52 (m, 4H), 7.27 (m, 1H), 7.34 (m, 1H), 7.84 (d, 1H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ: 13.8, 14.2, 61.4, 62.6, 100.7, 117.6, 121.8, 125.0, 130.2, 135.3, 145.6, 161.3, 161.7; MS m/z 342 (M^++ 2, 72), 340 (M^+, 70), 270 (100), 233 (23), 217 (63), 196 (39), 150 (24). *Anal*. Calcd for $C_{13}H_{13}N_2O_4Br$: C, 45.77; H, 3.84; N, 8.21. Found: C, 45.95; H, 3.82; N, 8.24.

3-Bromoimidazo[1,2-*a*]pyridine-2,5-dicarboxylic acid 2-ethyl-5-methyl diester (10a): (from **8**). Yield: 66%; mp 87-89 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 1712, 1511, 1182, 796, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.42 (t, 3H, *J* = 7 Hz), 3.99 (s, 3H), 4.45 (q, 2H, *J* = 7 Hz), 7.22 (dd, 1H, *J* = 7, 1 Hz), 7.29 (dd, 1H, *J* = 9, 7 Hz), 7.78 (dd, 1H, *J* = 9, 1 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.2, 52.9, 61.4, 100.6, 117.7, 122.0, 125.0, 129.9, 135.4, 145.6, 161.8, 161.9; MS m/z 328 (M^++ 2, 35), 326 (M^+, 33), 254 (79), 196 (72), 136 (100), 115 (100), 103 (70), 92 (43), 76 (61), 64 (100). *Anal*. Calcd for $C_{12}H_{11}N_2O_4Br$: C, 44.06; H, 3.39; N, 8.56. Found: C, 44.23; H, 3.37; N, 8.59.

Ethyl 3-bromo-5-formylimidazo[1,2-*a*]pyridine-2-carboxylate (17a): (from **15**). Yield: 75%; mp 146-148 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 2924, 2852, 1718, 1685, 1618, 1525, 1252, 1054, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.53 (t, 3H, *J* = 7 Hz), 4.56 (q, 2H, *J* = 7 Hz), 7.47 (m, 1H), 7.69 (d, 1H, *J* = 7 Hz), 8.01 (d, 1H, *J* = 9 Hz), 11.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.4, 61.9, 99.7, 120.2, 125.0, 125.4, 128.0, 135.7, 146.2, 161.9, 182.3; MS m/z 298 (M^++ 2, 19), 296 (M^+, 17), 226 (33), 217 (100), 145 (56), 90 (32), 78 (47). *Anal*. Calcd for $C_{11}H_9N_2O_3Br$: C, 44.47; H, 3.05; N, 9.46. Found: C, 44.64; H, 3.03; N, 9.46.

3-Bromo-2-dichloromethylimidazo[1,2-*a*]pyridine (20a)[18]: (from **20**[18]). Yield: 67%; mp 98-100 °C (lit.,[18] 100-102 °C).

3-Bromoimidazo[1,2-*a*]pyridine-2,5-dicarbaldehyde (25a): (from **24**). Yield: 77%; mp 171-173 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 2838, 1700, 1673, 1048, 788 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.51 (dd, 1H, *J* = 9, 7 Hz), 7.73 (dd, 1H, *J* = 7, 1 Hz), 8.00 (dd, 1H, *J* = 9, 1 Hz), 10.27 (s, 1H), 11.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 99.7, 121.0, 125.3, 125.8, 135.9, 140.7, 147.1, 181.9, 185.8; MS m/z 254 (M^++ 2, 13), 252 (M^+, 14), 173 (100), 145 (33), 90 (39), 78 (29). *Anal*. Calcd for $C_9H_5N_2O_2Br$: C, 42.72; H, 1.99; N, 11.07. Found: C, 42.89; H, 1.98; N, 11.11.

Ethyl 3-bromo-2-dichloromethylimidazo[1,2-*a*]pyridine-5-carboxylate (28a): (from **26**). Yield: 39%; mp: 97-99 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 1738, 1281, 1061, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.37 (t, 3H, *J* = 7 Hz), 4.44 (q, 2H, *J* = 7 Hz), 6.95 (s, 1H), 7.25 (m, 1H), 7,29 (d, 1H, *J* = 7 Hz), 7.76 (d, 1H, *J* =9 Hz); ^{13}C NMR ($CDCl_3$) δ: 13.9, 62.6, 63.5, 93.1, 117.5, 121.0, 124.9, 129.6, 143.4, 146.0, 160.8; MS m/z 354 (M^++ 4, 16),352 (M^++ 2, 36), 350 (M^+, 19), 317 (84), 179 (46), 151 (72), 124 (36), 112 (53), 100 (40). *Anal*. Calcd for $C_{11}H_9N_2O_2BrCl_2$: C, 37.53; H, 2.58; N, 7.96. Found: C, 37.68; H, 2.56; N, 7.99.

General Procedure for the Nitration of Compounds (2, 3, 7, 8, 15, 19 and 26). To a solution of the appropriate compounds (10.52 mmol) in 11.2 mL of sulfuric acid was added dropwise 1.8 mL of 65% nitric acid at –10 °C. The solution was left to stand at rt for 4 h and then poured onto ice. The mixture was basified with Na_2CO_3 and extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure to give the required nitro products.

Ethyl 3-nitroimidazo[1,2-*a*]pyridine-5-carboxylate (4b): (from **2**). Yield: 74%; mp 74-76 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 2989, 1727, 1291, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, *J* = 7 Hz), 4.51 (q, 2H, *J* = 7 Hz), 7,71 (m, 2H), 8.01 (m, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 63.0, 119.3, 121.7, 129.2, 131.1, 134.9, 138.6, 147.0, 161.3; MS m/z 235 (M^+, 56), 189 (70), 161

(100), 150 (35), 117 (69), 106 (35), 90 (37), 78 (41). *Anal*. Calcd for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 51.27; H, 3.84; N, 17.94.

3-Nitroimidazo[1,2-*a*]pyridine-5-carbaldehyde (5b): (from **3**). Yield: 75%; mp 114-116 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 1689, 1625, 1521, 1459, 1250, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.82 (m, 2H), 8.10 (m, 1H), 8.61 (s, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 122.6, 123.7, 129.2, 134.5, 135.2, 139.3, 146.5, 180.6; MS m/z 191 (M^+, 17), 117 (74), 106 (43), 90 (100), 78 (72). *Anal*. Calcd for $C_8H_5N_3O_3$: C, 50.27; H, 2.61; N, 21.98. Found: C, 50.47; H, 2.63; N, 22.06.

Diethyl 3-nitroimidazo[1,2-*a*]pyridine-2,5-dicarboxylate (9b): (from **7**). Yield: 70%; mp 65-67 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 1732, 1630, 1265, 1025, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.46 (m, 6H), 4.52 (m, 4H), 7.68 (m, 1H), 7.77 (d, 1H, *J* = 7 Hz), 8.01 (d, 1H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.0, 14.1, 62.8, 63.2, 120.5, 122.5, 128.9, 130.0, 132.8, 135.4, 143.5, 160.6, 160.7; MS m/z 307 (M^+, 55), 261 (66), 233 (100), 217 (50), 187 (53), 151 (31), 131 (37), 119 (25), 103 (42), 78 (35). *Anal*. Calcd for $C_{13}H_{13}N_3O_6$: C, 50.82; H, 4.26; N, 13 .68. Found: C, 50.47; H, 4.24; N, 13.73.

3-Nitroimidazo[1,2-*a*]pyridine-2,5-dicarboxylic acid 2-ethyl 5-methyl diester (10b): (from **8**). Yield: 85%; mp 87-89 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 2975, 1736, 1239, 833, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.46 (t, 3H, *J* = 7 Hz), 4.01 (s, 3H), 4.54 (q, 2H, *J* = 7 Hz), 7.69 (m, 1H), 7.77 (d, 1H, *J* = 7 Hz), 8.02 (d, 1H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.0, 53.3, 62.8, 120.6, 122.6, 128.9, 129.7, 132.8, 135.5, 143.5, 160.7, 161.0; MS m/z 293 (M^+, 31), 247 (64), 203 (33), 137 (97), 131 (59), 119 (41), 103 (100), 92 (41), 76 (67). *Anal*. Calcd for $C_{12}H_{11}N_3O_6$: C, 49.15; H, 3.78; N, 14.33. Found: C, 49.34; H, 3.76; N, 14.38.

Ethyl 5-Formyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (17b): (from **15**). Yield: 22%; mp 118-119 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 2926, 1726, 1696, 1267, 812 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.46 (t, 3H, *J* = 7 Hz), 4.52 (q, 2H, *J* = 7 Hz), 7.82 (dd, 1H, *J* = 9, 7 Hz), 7.92 (d, 1H, *J* = 7 Hz), 8.15 (d, 1H, *J* = 9 Hz), 9.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.1, 62.9, 125.0, 126.3, 128.3, 133.7, 134.2, 134.9, 142.6, 160.4, 181.0; MS m/z 263 (M^+, 10), 146 (32), 123 (45), 105 (67), 78 (100), 51 (100). *Anal*. Calcd for $C_{11}H_9N_3O_5$: C, 50.20; H, 3.41; N, 15.96. Found: C, 50.40; H, 3.43; N, 16.02.

2-Dichloromethyl-3-nitroimidazo[1,2-*a*]pyridine (20b): (from **19**[18]). Yield: 86%; mp 134-136 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 1486, 1369, 1255, 824, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.42 (t, 1H, *J* = 7 Hz), 7.66 (s, 1H), 7.78 (m, 1H), 7.97 (d, 1H, *J* = 9 Hz), 9.43 (d, 1H, *J* = 7 Hz); ^{13}C

NMR ($CDCl_3$) δ: 63.0, 117.9, 119.1, 126.0, 127.6, 131.8, 144.7, 147.1; MS m/z 249 (M^++ 4, 1), 247 (M^++ 2, 8), 245 (M^+, 13), 175 (20), 130 (21), 78 (100), 51 (52). *Anal*. Calcd for $C_8H_5N_3O_2Cl_2$: C, 39.05; H, 2.05; N, 17.08. Found: C, 39.20; H, 2.04; N, 17.14.

Ethyl 2-dichloromethyl-3-nitroimidazo[1,2-*a*]pyridine-5-carboxylate (28b): (from **26**). Yield: 85%; mp 109-111 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 1740, 1186, 812, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.43 (t, 3H, *J* = 7 Hz), 4.48 (q, 2H, *J* = 7 Hz), 7.50 (s, 1H), 7.77 (m, 2H), 8.05 (d, 1H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.2, 63.2, 63.3, 120.2, 121.9, 128.3, 130.3, 131.0, 145.2, 146.0, 161.7; MS m/z 321 (M^++ 4, 2), 319 (M^++ 2, 15), 317 (M^+, 24), 271 (51), 243 (100), 227 (31), 179 (28), 150 (55), 119 (38), 103 (42), 91(28), 78 (77). *Anal*. Calcd for $C_{11}H_9N_3O_4Cl_2$: C, 41.53; H, 2.83; N, 13 .21. Found: C, 41.69; H, 2.81; N, 13.26.

General Procedure for Hydrolysis of Compounds (20a, 20b, 28a and 28b). A solution of the appropriate 2-dichloromethyl derivative (1.78 mmol) in 10 mL of ethanol was mixed with silver nitrate (1.91 g, 11.21 mmol) in hot water (4 mL). The mixture was boiled (3 h), then cooled at rt, and concentrated hydrochloric acid was added until pH = 1. The silver salts were removed by filtration under reduced pressure, and the filtrate was basified with Na_2CO_3. The mixture was extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure.

3-bromo-2-diethoxymethylimidazo[1,2-*a*]pyridine (21a): (from **20a**). The residue was chromatographed on alumina eluting with methylene chloride. The first fraction gave **21a** as a yellow oil Yield: 11%; IR (KBr) ν: 2975, 2927, 1718, 1294, 1120, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.31 (m, 6H), 3.77 (m, 4H), 5.83 (s, 1H), 6.97 (t, 1H, *J* = 7 Hz), 7.29 (m, 1H), 7.67 (d, 1H, *J* = 9 Hz), 8.17 (d, 1H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.4, 62.0, 93.4, 97.6, 113.5, 118.5, 124.0, 125.3, 141.8, 145.3; MS m/z 225 (M^+- 74, 57), 197 (21), 90 (30), 78 (100), 63 (24), 51 (41). *Anal*. Calcd for $C_{12}H_{15}N_2O_2Br$: C, 48.16; H, 5.01; N, 9.36. Found: C, 48.35; H, 4.98; N, 9.39. The second fraction gave **3-bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (22a)**: Yield: 54%; mp 121-123 °C (lit.,[18] 123-125 °C).

2-Diethoxymethyl-3-nitroimidazo[1,2-*a*]pyridine (21b): (from **20b**). Yield: 21%; mp 69-71 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 2874, 1465, 1369, 1324, 1214, 1054, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.29 (m, 6H), 3.85 (m, 4H), 6.39 (s, 1H), 7.31 (t, 1H, *J* = 7 Hz), 7.66 (m, 1H), 7.91 (d, 1H, *J* = 9 Hz), 8.45 (d, 1H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.2, 63.3, 96.1, 117.0, 119.0, 127.6, 129.2, 130.8, 145.2, 149.1; MS m/z 220 (M^+- 45, 20), 192 (57), 118 (40), 78 (100), 51 (28). *Anal*. Calcd for $C_{12}H_{15}N_3O_4$ C, 54.33; H, 5.70; N, 15.84. Found: C, 54.54; H, 5.67; N, 15.90.

Ethyl 3-Bromo-2-formylimidazo[1,2-*a*]pyridine-5-carboxylate (29a): (from **28a**). Yield: 39%; mp 69-71 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 2985, 1726, 1702, 1277, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, *J* = 7 Hz), 4.53 (q, 2H, *J* = 7 Hz), 7.33 (d, 1H, *J* = 7 Hz), 7.39 (m, 1H), 8.83 (d, 1H, *J* = 9 Hz), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 62.9, 101.4, 118.4, 122.4, 125.8, 130.4, 140.4, 146.7, 185.8; MS m/z 298 (M^++ 2, 64), 296 (M^+, 62), 217 (30), 173 (98), 167 (100), 161 (20). *Anal*. Calcd for $C_{11}H_9N_2O_3Br$: C, 44.47; H, 3.05; N, 9.43. Found: C, 44.64; H, 3.03; N, 9.46.

Ethyl 2-Formyl-3-nitroimidazo[1,2-*a*]pyridine-5-carboxylate (29b): (from **28b**). Yield: 49%; mp 79-81 °C, recrystallization solvent: Ethanol; IR (KBr) ν: 2812, 1721, 1684, 1259, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, *J* = 7 Hz), 4.53 (q, 2H, *J* = 7 Hz), 7.77 (m, 1H), 7.81 (dd, 1H, *J* = 7, 1 Hz), 8.08 (dd, 1H, *J* = 8, 1 Hz), 10.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.2, 62.2, 119.9, 121.8, 130.6, 131.5, 131.6, 140.7, 146.9, 161.3, 184.3; MS m/z 263 (M^+, 71), 189 (100), 173 (52), 122 (38), 83 (21). *Anal*. Calcd for $C_{11}H_9N_3O_5$: C, 50,20; H, 3,45; N, 15,96. Found: C, 50.40; H, 3.43; N, 16.02.

General Procedure for Hydrolysis of Compounds (21a and 21b). To a well stirred solution containing the appropriate bromo or nitro compound (4.03 mmol) in 40 mL of MeCN/H_2O (3/1, v/v), 0.5 mL of concentrated hydrochloric acid were added. The mixture was stirred at reflux during 1 h and left to stand at rt. The mixture was extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure to give the required products.

3-Bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (22a): (from **21a**). Yield: 93%; mp 121-123 °C (lit.,[18] 123-125 °C).

3-Nitroimidazo[1,2-*a*]pyridine-2-carbaldehyde (22b): (from **21b**). Yield: 65%; mp 113-115 °C, recrystallization solvent: H_2O/Ethanol (3/5); IR (KBr) ν: 1707, 1518, 1214, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.48 (t, 1H, *J* = 7 Hz), 7.79 (m, 1H), 8.03 (d, 1H, *J* = 9 Hz), 9.49 (d, 1H, *J* = 7 Hz), 10.84 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 118.8, 120.4, 127.5, 131.8, 141.7, 136.2, 144.5, 184.9; MS m/z 192 (M^++ 1, 57), 118 (40), 78 (100), 51 (28). *Anal*. Calcd for $C_8H_5N_3O_3$: C, 50.27; H, 2.64; N, 21.98. Found: C, 50.47; H, 2.62; N, 22.06.

General Procedure for Compounds (13, 18, 23, 30 and 31). To a well stirred, cold solution (-10 °C) containing the appropriate bromo (or nitro) compound (1.32 mmol) and ethyl thioglycolate (327 mg, 0.3 mL) in 3.6 mL of dried DMF was added portionwise lithium hydroxyde (135 mg, 5.62 mmol). The mixture was left to stand at rt for 3 h, and the solution was poured onto ice-water. The precipitated was collected to give the required cyclazines compounds.

Diethyl 5-hydroxy-3-thia-1,8b-diazaacenaphthylene-2,4-dicarboxylate (13): Yields: 55% (from **9a**); 87% (from **9b**); 24% (from **10a**); 76% (from **10b**); mp 171-173 °C, recrystallization solvent: H_2O/Ethanol (1/2); IR (KBr) ν: 3549, 2987, 1701, 1655, 1282, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.24 (t, 3H, *J* = 7 Hz), 1.31 (t, 3H, *J* = 7 Hz), 3.99 (br s, 1H), 4.12 (q, 2H, *J* = 7 Hz), 4.26 (q, 2H, *J* = 7 Hz), 7.00 (m, 2H), 7.14 (d, 1H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.3, 14.5, 59.4, 59.9, 79.6, 109.0, 119.5, 123.3, 127.0, 127.5, 136.2, 144.5, 162.5, 163.0, 165.9; MS m/z 334 (M^+, 4), 122 (23), 105 (100), 77 (63), 75 (25), 51 (38). *Anal*. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.19; N, 8.38. Found: C, 54.09; H, 4.20; N, 8.41.

Diethyl 3-thia-1,8b-diazaacenaphthylene-2,4-dicarboxylate (18): Yields: 38% (from **17a**); 61% (from **17b**); mp > 400 °C, recrystallization solvent: H_2O/Ethanol (1/2); IR (KBr) ν: 1735, 1686, 1269, 1048, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.88 (t, 6H, *J* = 7 Hz), 4.76 (q, 2H, *J* = 7 Hz), 4.89 (q, 2H, *J* = 7 Hz), 6.89 (d, 1H, *J* = 7 Hz), 7.36 (dd, 1H, *J* = 9, 7 Hz), 7.46 (d, 1H, *J* = 9 Hz), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.9, 14.0, 60.5, 61.1, 79.0, 113.9, 120.9, 121.2, 125.7, 127.5, 129.4, 134.6, 146.5, 161.2, 161.9; MS m/z 318 (M^+, 100), 290 (32), 246 (47), 218 (100), 172 (39), 146 (18), 129 (30), 69 (53), 55 (32). *Anal*. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.81; H, 4.41; N, 8.83.

Ethyl thieno[3,2-*b*]imidazo[1,2-*a*]pyridine-2-carboxylate (23): yellow oil, yields: 1% (from **22a**); 1% (from **22b**); ^1H NMR ($CDCl_3$) δ: 1.36 (t, 3H, *J* = 7 Hz), 4.32 (q, 2H, *J* = 7 Hz), 6.96 (m, 1H), 6.99 (s, 1H), 7.32 (m, 1H), 7.59 (d, 1H, *J* = 9 Hz), 8.12 (d, 1H, *J* = 7 Hz). *Anal*. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.75; H, 4.07; N, 11.41.

Ethyl 2-formyl-5-hydroxy-3-thia-1,8b-diazaacenaphthylene-4-carboxylate (30): Yields: 23% (from **29a**); 24% (from **30b**); mp 181-183 °C, recrystallization solvent: H_2O/Ethanol (1/2); IR (KBr) ν: 1682, 1665, 1523, 1292, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.42 (t, 3H, *J* = 7 Hz), 3.99 (br s, 1H), 4.39 (q, 2H, *J* = 7 Hz), 6.69 (d, 1H, *J* = 7 Hz), 6.84 (dd, 1H, *J* = 9, 7 Hz), 7.08 (d, 1H, *J* = 9 Hz), 9.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.1, 63.4, 93.8, 110.2, 121.0, 122.1, 128.2, 131.4, 135.9, 145.9, 154.1, 167.8, 186.7; MS m/z 290 (M^+, 100), 244 (93), 217 (53), 188 (36), 84 (20), 49 (21). *Anal*. Calcd for $C_{13}H_{10}N_2O_4S$: C, 53.79; H, 3.47; N, 9.65. Found: C, 54.00; H, 3.45; N, 9.68. The aqueous layer, after extraction with methylene chloride, was acidified by using acetic acid solution to precipitate **diethyl thieno[3,2-*b*]imidazo[1,2-*a*]pyridine-2,8-dicarboxylate (31):** Yield: 8% (from **29a**); mp 261-263 °C, recrystallization solvent: H_2O/Ethanol (1/2); IR (KBr) ν: 1712, 1501, 1388, 1277, 1236, 1195, 1089, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.47 (t, 3H, *J* = 7 Hz), 1.52 (t, 3H, *J* = 7 Hz), 4.47 (t, 2H, *J* = 7 Hz), 4.61 (q, 2H, *J* = 7 Hz), 7.40 (dd, 1H, *J* = 9, 7 Hz), 7.87 (dd, 1H, *J* = 7, 1 Hz), 8.01 (dd, 1H, *J* = 9, 1 Hz), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 14.5, 61.5, 62.9, 117.7, 121.8, 123.7, 124.4, 126.0, 130.5, 134.3, 150.1, 151.5, 162.2, 163.3; MS m/z

318 (M^+, 38), 85 (69), 84 (100), 49 (86). *Anal*. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.81; H, 4.41; N, 8.83.

5-Ethoxycarbonyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylic acid (11). To a well stirred, cold solution (ice bath) containing (**9b**) (498 mg, 1.62 mmol) and ethyl glycolate (0.3 mL, 3.17 mmol) in 3.50 mL of DMF was added portionwise lithium hydroxyde (135 mg, 5.62 mmol). The mixture was left to stand at rt for 3 h and the solution was poured into ice-water, and acidified with acetic acid to give a solid which was collected and dried under reduced pressure to give **11**. Yield: 171 mg (38%); mp 149-151 °C, recrystallization solvent: H_2O/Ethanol (1/2); IR (KBr) ν: 3554, 1716, 1628, 1383, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.32 (t, 3H, *J* = 7 Hz), 4.39 (q, 2H, *J* = 7 Hz), 7.92 (m, 2H), 8.21 (dd, 1H, *J* = 8, 2 Hz,), 12.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 62.8, 121.1, 122.4, 129.2, 130.8, 130.9, 139.3, 144.2, 160.8, 162.7; MS m/z 279 (M^+, 8), 235 (40), 189 (63), 161 (95), 145 (30), 120 (100), 106 (37), 91 (60), 78 (68). *Anal*. Calcd for $C_{11}H_9N_3O_6$: C, 47.31; H, 3.22; N, 15.05. Found: C, 47.50; H, 3.21; N, 15.11.

Tetraethyl 3,3'-Dithiodiimidazo[1,2-*a*]pyridine-2,2',4,4'-tetracarboxylate (12). To a well stirred, cold solution (ice bath) containing (**9b**) (498 mg, 1.62 mmol) and ethyl 3-mercaptopropionate (0.28 mL, 2.15 mmol) in 3.21 mL of DMF was added portionwise lithium hydroxyde (135 mg, 5.62 mmol). The mixture was left to stand at rt for 3 h and the solution was poured onto ice-water, and acidified with acetic acid to give a solid which was collected and dried under reduced pressure to give **12**. Yield: 450 mg (95%); mp 146-148 °C, recrystallization solvent: H_2O/Ethanol (1/2); IR (KBr) ν: 1735, 1712, 1303, 1194, 1204, 803, 788 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.36 (t, 12H, *J* = 7 Hz), 4.30 (q, 8H, *J* = 7 Hz), 7.06 (d, 2H, *J* = 6 Hz), 7.40 (m, 2H), 7.86 (d, 2H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ: 13.8, 14.3, 61.6, 62.5, 116.6, 120.4, 121.5, 126.9, 131.1, 142.2, 147.0, 161.6, 162.5; MS m/z 586 (M^+, 1), 293 (31), 248 (39), 203 (70), 176 (100), 70 (26). *Anal*. Calcd for $C_{26}H_{26}N_4O_8S_2$: C, 53.24; H, 4.43; N, 9.55. Found: C, 53.45; H, 4.41; N, 9.58.

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