A NOVEL METHOD OF PREPARATION OF 3-ACYLIMIDAZO[1,2-*a*]PYRIDINES

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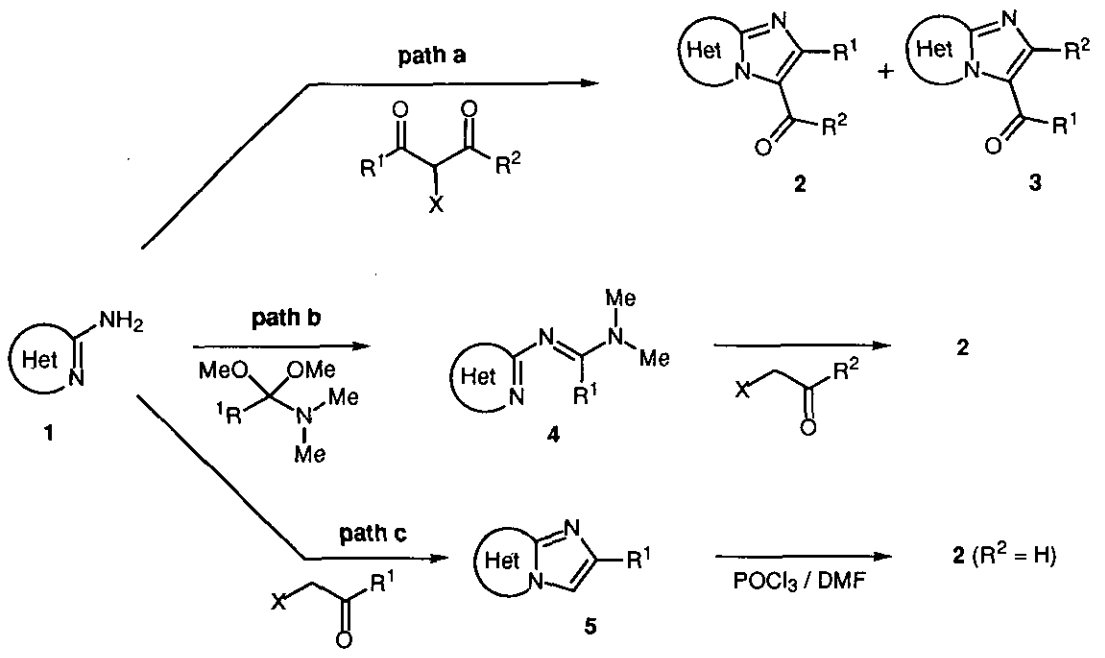
Abstract - A series of 2-substituted 3-acylimidazo[1,2-*a*]pyridines were synthesized in good to moderate yields from secondary amidino ketones and bromine in acetic acid. Cyclocondensation of the α-bromo-β-amidino ketones (**6**) led to the corresponding *trans*-dihydroimidazoles (**13**), which may yield spontaneously the stable 3-acylimidazo[1,2-*a*]pyridines (**2**) after dehydrogenation.

In recent years, the synthesis of 3-acylimidazo[1,2-*x*]azines has attracted much attention. These compounds were reported as potent ligands of the mitochondrial benzodiazepine receptors.[1] Other works mentioned for these agents potential anti-inflammatory activities[2] and uterine-relaxing, antibronchospastic and cardio-stimulating properties.[3]

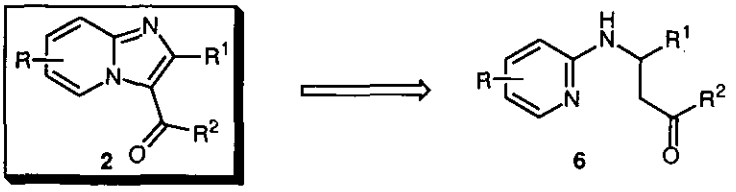
In the literature, few methods depicted the preparation of 3-acylimidazo[1,2-*x*]azines (Scheme 1). These methods encompass the Chichibabin reaction (path a) which involves the condensation of primary heterocyclic amidines (**1**) with α-halo β-diketones.[4] However, this procedure is not regioselective since both the 3-acylheterocyclic compounds (**2**) and (**3**) can be obtained depending on the nature of substituents R^1 and R^2. Another method involves endocyclic alkylation with α-halo ketone of the compound (**4**), an aza vinylogue of the corresponding *N,N*-dimethylamidine (path b).[5] However, this method cannot be extended to 2-acylimidazolic compounds (**2**) (R^1 = COR). It is noteworthy that the Vilsmeier-Haack reaction (path c) onto 2-substituted imidazoheterocycles (**5**) affords the corresponding 3-formyl derivatives (**2**) (R^2 = H).[6,7]

During our investigations on 3-acylimidazo[1,2-*a*]pyridines, we were particularly interested in compounds bearing an ester group in position 2.



Scheme 1

However, none of the methods cited above allowed a satisfactory route to such compounds. Retrosynthetically, compounds (**2**) (with $R^1 = CO_2Et$) could be prepared from the β–amidino ketones (**6**) (Scheme 2) by a three steps procedure including successive halogenation, cyclization and dehydrogenation as illustrated in Scheme 5. In a preliminary communication,[8] we reported that the adducts (**6**) were easily prepared from enols and heteroaromatic imines (**7**) or hydroxyaminal intermediates (**8**). We now provide full experimental details including the following steps leading to 3-acylimidazo[1,2-*a*]pyridines.

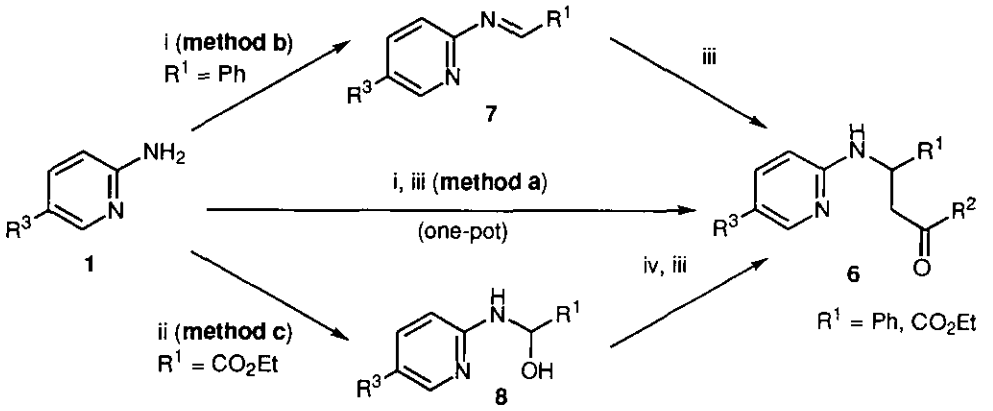


Scheme 2

RESULTS AND DISCUSSION

The Schiff bases (**7**)[9] or its corresponding hydroxyaminals (**8**)[8] were selected by us as valuable intermediates for the preparation of differently substituted amidino ketones (**6**) following different

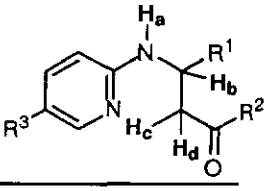
pathways (methods a-c, Scheme 3). The starting amidines (1) were reacted with various enolizable ketones or their corresponding silyl enol ethers, in the presence of trimethylsilyl triflate (TMSOTf).[8]



i: PhCHO ; ii: EtO_2CCHO ; iii: TMSOTf, $MeCOR^2$ or $CH_2=C(OTMS)R^2$, MeCN ; iv: TMSCl, Et_3N, CH_2Cl_2

Scheme 3

Table 1 : Preparation of Compounds (**6a-f**) and Their Typical ^1H NMR Data.

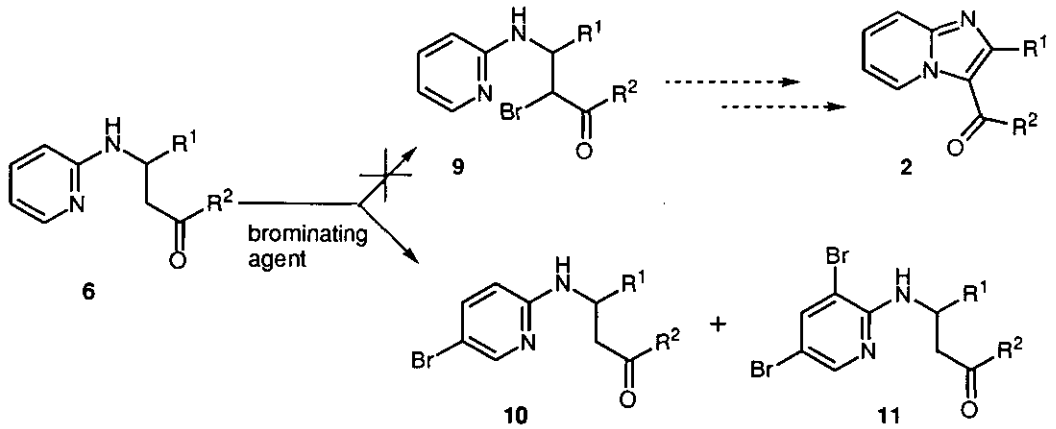


No.	R^1	R^2	R^3	Method	Yield (%)	mp (°C)	^1H NMR($CDCl_3$) H_a (d)	H_b (m)	H_c, H_d
6a	Ph	Ph	H	a	53	125	5.75 J=7.1	5.4-5.5	3.48, 3.67[b] J=16.5, 6.7, 5.8
6b	Ph	*p*-MeO-Ph	H	b	75(49)[a]	111	5.94 J=7.1	5.4-5.5	3.37, 3.58[b] J=16.2, 7.0, 5.7
6c	Ph	*t*-Bu	H	b	34(22)[a]	107	5.94 J=7.5	5.2-5.3	2.94, 3.13[b] J=16.8, 6.4, 6.0
6d	CO_2Et	Ph	H	c	31	oil	5.49 J=7.9	5.1-5.2	3.72[c]
6e	Ph	Ph	Me	a	50	112	5.62 J=7.2	5.4-5.5	3.45, 3.65[b] J=16.5, 6.8, 5.8
6f	CO_2Et	Ph	Me	c	32	oil	5.51 J=8.0	5.1-5.2	3.61[c]

[a]overall yield in parentheses starting from the amidine (**1**).[b]ABX pattern. [c]multiplet.

Typical ^1H NMR signals of the amidino ketones (**6a-f**) highlighted a doublet signal at 5.72 ± 0.23 ppm, exchangeable with D_2O, corresponding to the NH proton H_a, and an ABX system for the two methylene protons H_c, H_d and the methine proton H_b (see Table 1).

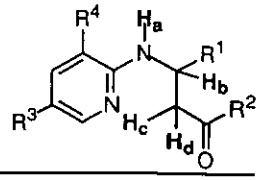
Bromination of the secondary amidino ketones (**6**) with bromine was investigated. The formation of the expected α-bromo ketone (**9**) or its cyclic counterpart (**2**) was not detected (Scheme 4). However, a mixture of 5-bromo and 3,5-dibromo adducts (**10**) and (**11**) was isolated in various ratios depending on the bromination reaction conditions used.



Scheme 4

When 1 equivalent of bromine was added to **6a** in basic or in acidic conditions, the monobromo derivative (**10a**) was the major compound in the mixture (80% and 70% respectively). With *N*-bromosuccinimide (1 equivalent), the 5-bromo derivative (**10a**) was obtained quantitatively. The use of 2 equivalents of NBS led to the 3,5-dibromo adduct (**11a**) in 93 % yield (Table 2). For compounds (**6**) deriving from 2-aminopyridine, we observed a preferential bromination of the pyridine nucleus at the 5 and 3 positions rather than a halogenation of the α-position of the ketone in the side chain. The successive bromination process was confirmed by ^{13}C NMR using the Attach Proton Test technique (APT) . The APT spectrum of compound (**6a**) exibits two typical tertiary carbon signals for carbons C_5 and C_3 of the pyridine ring at 113.2 ppm and 107.4 ppm respectively, whereas a quaternary carbon signal at 107.5 ppm assigned to the carbon C_5 of the monobromo derivative (**10a**), and two characteristic quaternary carbon signals for C_5 and C_3 (106.1 and 105.7 ppm) of the dibromo derivative (**11a**) were recorded. These observations were consistent with the results reported in the literature.[10-12] The pyridine adducts (**6b-f**) were then submitted to quantitative bromination by means of one or two equivalents of NBS to afford 3,5-dibromo (compounds **11b-d**) or 3-bromo (compounds **11e-f**) pyridine derivatives (Table 2).

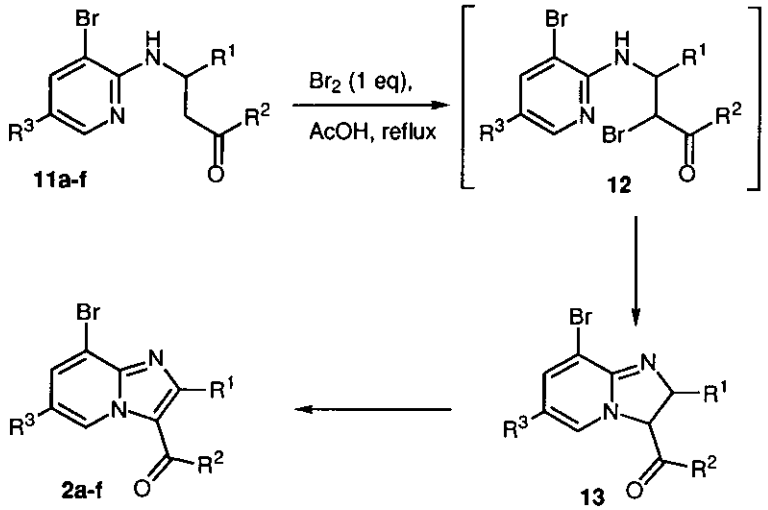
Table 2:Preparation of Compounds (**10a**, **11a-f**) and Their Typical ^{1}H NMR Data.



No.	R^1	R^2	R^3	R^4	Reaction Time (h)	Yield (%)	mp (°C)	^{1}H NMR ($CDCl_3$) H_a (d)	H_b (m)	H_c, H_d
10a	Ph	Ph	Br	H	2 min[a]	99[c]	149-150	5.52	5.3-5.4	3.47, 3.66
								J=7.1		J=16.6, 6.6, 5.5
11a	Ph	Ph	Br	Br	1[b]	93[c]	123-124	6.15	5.7-5.8	3.51, 3.81
								J=7.4		J=16.5, 6.0, 5.8
11b	Ph	*p*-MeO-Ph	Br	Br	3[b]	97[d]	126	6.26	5.6-5.8	3.43, 3.72
								J=7.6		J=16.3, 5.9, 5.8
11c	Ph	*t*-Bu	Br	Br	24[b]	99[d]	79-80	6.42	5.6-5.8	2.97, 3.31
								J=7.5		J=16.7, 5.8, 5.4
11d	CO_2Et	Ph	Br	Br	2[b]	83[d]	oil	6.16	5.1-5.2	3.65, 3.80
								J=7.7		J=17.8, 4.5, 4.4
11e	Ph	Ph	Me	Br	2.5[a]	80[d]	oil	5.96	5.8-5.9	3.53, 3.84
								J=7.7		J=16.5, 6.1, 5.6
11f	CO_2Et	Ph	Me	Br	0.5[a]	86[c]	oil	5.96	5.1-5.2	3.67, 3.81
								J=7.8		J=16.4, 4.6, 4.6

[a]NBS (1 equivalent). [b]NBS (2 equivalents). [c]isolated yield after flash chromatography (EtOAc-Hexane 1:3). [d]isolated yield after flash chromatography (EtOAc-Hexane 1:2).

Introduction of a bromine atom in the α-position of the ketone in compounds (**11a-f**) was then investigated. Thus the compound (**11a**) was refluxed with bromine (1 equivalent) in acetic acid for 6 h and unexpectedly the corresponding 3-benzoylimidazo[1,2-*a*]pyridine (**2a**) was obtained in 86% yield (Table 3, Entry 1). When the reaction was stopped after 1.5 h, the dihydroimidazo[1,2-*a*]pyridine (**13a**) and compound (**2a**) were isolated in 34% and 29% yield respectively along with unreacted (9%) **11a** (Entry 2). In a mechanistic point of view, a probable preliminary α-bromination of the ketone (**11a**) allows cyclocondensation of the resulting intermediate (**12a**) into the corresponding dihydroimidazole (**13a**), which yielded quantitatively its stable imidazolic derivative (**2a**), [13] after facile oxidation (Scheme 5). The easy loss of hydrogen leads to energy stabilization of the fused bicyclic aromatic system in **2**. The total conversion of **13a** into **2a**, when refluxing it overnight in dioxane, supported our hypothesis.

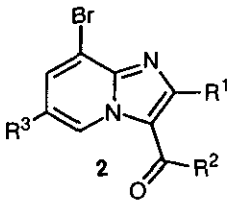


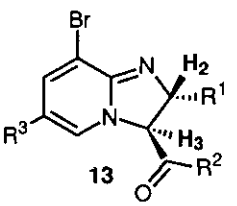
Scheme 5

In the same experimental conditions, the *p*-methoxybenzoyl derivative (**11b**) was found less reactive and led to a mixture of dihydroimidazole (**13b**) and imidazole (**2b**) derivatives in equimolecular amounts (compare Entries 3 and 2). Less reactivity and increasing relative amounts of dihydroimidazole (**13**) were observed with the *t*-butyl ketone (**11c**) (compare Entries 4 and 2). Thus, electron-donating mesomeric (*p*-methoxy-phenyl in **11b**), or more pronounced inductive effects (*t*-butyl in **11c**) decrease the acidity of the proton H_3, and probably dramatically influence the bromination step before cyclocondensation. Moreover, the facile dehydrogenation reaction may be correlated with the electron deficiency of the carbon C_3 bearing H_3 in the dihydroimidazolic intermediate (**13**), as illustrated by progressive deshielding of H_3, when comparing ^{1}H NMR of **13c** (5.29 ppm), **13b** (5.64 ppm) and **13a** (5.76 ppm). Thus the dehydrogenation step is strongly affected by the presence of an electrodonating group in position 3, and modulated by both the nature of the R^2 substituent, and the reaction time.

Theoretically, compounds (**13**) should be obtained as mixtures of *cis*- and *trans*-diastereoisomers. However, only one pair of diastereoisomers was detected by ^{1}H and ^{13}C NMR. ^{1}H NMR spectrum exibits a typical AB pattern for protons H_2 and H_3 with a vicinal coupling constant $J_{2\text{-}3}$ of 6.4 ±0.2 ppm, which is consistent with the *trans* configuration according to results previously reported in the literature for structurally-related compounds.[14] Predominant formation of the more stable *trans*-diastereoisomers may be explained by the conversion of the more hindred *cis*- into the *trans*-form *via* an inversion of configuration at the C_3 carbon bearing the acyl group, and involving keto enol equilibrium in acidic medium.

Table 3 : Preparation of Imidazo[1,2-*a*]pyridines (**2**) and Dihydroimidazo[1,2-*a*]pyridines (**13**).





Entry	Starting Material	R^1	R^2	R^3	Reaction Time (h)	Yield of **2** %	Yield of **13** %	^{1}H NMR ($CDCl_3$) of **13**		
								H_2	H_3	J_{2-3}
1	**11a**	Ph	Ph	Br	6	86	0	-	-	-
2	**11a**	Ph	Ph	Br	1.5	29	34	5.01	5.76	6.5
3	**11b**	Ph	*p*-MeO-Ph	Br	24	50	50	5.04	5.64	6.6
4	**11c**	Ph	*t*-Bu	Br	48	9	59	5.02	5.29	6.4
5	**11d**	CO_2Et	Ph	Br	16	58	trace[a]	4.73	6.44	6.2
6	**11e**	Ph	Ph	Me	6	78	trace[a]	5.02	5.66	6.5
7	**11f**	CO_2Et	Ph	Me	16	53	trace[a]	4.75	6.42	6.2

[a]based on ^{1}H NMR.

In summary we reported herein the reaction of secondary amidino ketones with bromine in acetic acid leading to 2-substituted 3-acylimidazo[1,2-*a*]pyridines. The method is versatile, as various substituents have been introduced in position 2 and 3 of the imidazole ring. Moreover the procedure allowed an easy access to 2,3-diacylimidazo[1,2-*a*]pyridines.

EXPERIMENTAL SECTION

Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz on a Brucker 200 AC spectrometer with Me_4Si as the internal standard (δ (ppm). ^{13}C NMR spectra were recorded at 50 MHz on the same instrument using the $CDCl_3$ solvent peak at δ 77.0 ppm as the reference. Elemental analyses (CHN) were performed by the analytical group (Department of Chemistry, University Louis Pasteur-Strasbourg I). Flash chromatography was run on Gerdura SI 60 ((0.040-0.063 mm) Merck). Acetonitrile was distilled from phosphorus pentoxide. Dichloromethane was distilled from calcium hydride. Ethyl glyoxylate was a generous gift from Hoechst -

Roussel Pharmaceuticals, Stains - France, and was distilled from phosphoric acid (1%) and phosphorus pentoxide (1%) before use.

Typical procedure for the synthesis of amidino ketones (6) (method a).

1,3-Diphenyl-3-(5-methylpyridin-2-yl)aminopropan-1-one (6e).

Benzaldehyde (1.1 g, 10 mmol) was added to a solution of 2-amino-5-methylpyridine (1.08 g, 10 mmol) in dry MeCN (30 mL), under argon. The mixture was stirred at 20 °C for 2 h, and acetophenone (1.2 g, 10 mmol) and TMSOTf (4.26 mL, 21 mmol) were added successively. The mixture was stirred at 20 °C for 1.5 h. Then, saturated aqueous solution of potassium fluoride (30 mL) was added and the heterogeneous solution was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed under reduce pressure. The residue was purified by flash chromatography on silica gel (EtOAc-hexane, 1:3) to afford **6e** (1.58 g, 50%) as a white solid: mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.45, 3.65 (ABX system, 2H, J=16.5, 6.8 and 5.8), 5.4-5.5 (m, 1H), 5.62 (d, 1H, J=7.2), 6.31 (d, 1H, J=8.4), 7.1-7.5 (m, 9H), 7.8-7.9 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 17.1, 45.7, 52.8, 107.1, 121.8, 126.4, 127.0, 128.0, 128.4, 128.5, 132.9, 137.0, 138.1, 142.8, 147.6, 156.1, 197.8; Anal. Calcd for $C_{21}H_{20}N_2O$, H_2O: C,75.42; H,6.03; N,8.37. Found: C,75.14; H,6.01; N,8.12.

1,3-Diphenyl-3-(pyridin-2-yl)aminopropan-1-one (6a).

Yellow solid: mp 125°C; ^{1}H NMR ($CDCl_3$) δ 3.48, 3.67 (ABX system, 2H, J=16.5, 6.7 and 5.8), 5.4-5.5 (m, 1H), 5.75 (d, 1H, J=7.1), 6.37 (d, 1H, J=8.4), 6.54 (dd, 1H, J=6.9 and 5.0), 7.2-7.6 (m, 9H), 7.9-8.0 (m, 2H), 8.08 (dd, 1H, J=5.0 and 1.6); ^{13}C NMR ($CDCl_3$) δ 45.5, 52.4, 107.4, 113.2, 126.4, 127.2, 128.1, 128.5, 128.6, 133.2, 136.7, 137.3, 142.4, 148.0, 157.7, 197.9; Anal. Calcd for $C_{20}H_{18}N_2O$, 0.5 H_2O: C, 77.15; H, 5.82; N, 8.99 Found: C, 77.63; H, 6.04; N, 8.58.

Typical procedure for the synthesis of amidino ketones (6) (method b).

1-(4-Methoxyphenyl)-3-phenyl-3-(pyridin-2-yl)aminopropan-1-one (6b).

p-Methoxyacetophenone (1.5 g, 10 mmol) and TMSOTf (4.6 mL, 21 mmol) were succesively added to a solution of 2-benzylideneaminopyridine[9] (1.82 g, 10 mmol) in dry MeCN (30 mL), under argon. The mixture was stirred at 20 °C for 2.5 h and after standard work-up (similar to method a) **6b** (2.49 g, 75%) was afforded: mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 3.37, 3.58 (ABX system, 2H, J=16.2, 7.0 and 5.7), 3.77 (s, 3H), 5.4-5.5 (m, 1H), 5.94 (d, 1H, J=7.1), 6.35 (d, 1H, J=8.4), 6.50 (ddd, 1H, J=7.1, 5.1 and 0.6),

6.85 (d, 2H, J=8.9), 7.1-7.3 (m, 4H), 7.4-7.5 (m, 2H), 7.87 (d, 2H, J=8.9), 8.06 (dd, 1H, J=5.1 and 1.2) ; ^{13}C NMR ($CDCl_3$) δ 45.1, 52.4, 55.1, 107.2, 112.8, 113.5, 126.2, 126.9, 128.4, 129.6, 130.2, 137.0, 142.6, 147.8, 152.8, 163.3, 196.1; Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.92; H, 6.30; N, 8.50.

4,4-Dimethyl-1-phenyl-1-(pyridin-2-yl)aminopentan-3-one (6c).

White solid: mp 106-107°C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9H), 2.94, 3.13 (ABX system, 2H, J=16.8, 6.4 and 6.0), 5.2-5.3 (m, 1H), 5.94 (d, 1H, J=7.5), 6.33 (d, 1H, J=8.4), 6.49 (ddd, 1H, J=7.2, 5.1 and 0.9), 7.1-7.4 (m, 6H), 8.04 (ddd, 1H, J=5.1, 1.7 and 0.6); ^{13}C NMR ($CDCl_3$) δ 25.6, 43.8, 44.0, 52.1, 107.0, 112.9, 126.3, 126.9, 128.3, 137.2, 142.6, 147.8, 157.9, 213.1; Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.50; H, 8.12; N, 9.94.

Typical procedure for the synthesis of amidino ketones (6) (method c).

Preparation of the hydroxyaminal (8f).

Compound (**8f**) was synthesized from 2-amino-5-methylpyridine and freshly distilled ethyl glyoxylate following the procedure previously reported for the preparation of **8d**,[8] (89%); oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J=7.1), 2.18 (s, 3H), 4.27 (q, 2H, J=7.1), 5.78 (br, 2H), 6.50 (d, 1H, J=8.4), 7.31 (d, 1H, J=8.4), 7.89 (s, 1H).

2-(5-Methylpyridin-2-yl)amino-4-oxo-4-phenylbutanoic acid ethyl ester (6f).

Trimethylsilyl chloride (0.45 mL, 3.6 mmol) and triethylamine (0.5 mL, 3.6 mmol) were successively added at -78 °C to a solution of hydroxyaminal (**8f**) (0.65 g, 3.1 mmol) in dry CH_2Cl_2 (30 mL). The cooling bath was removed, and after 20 min, TMSOTf (0.69 mL, 3.6 mmol) was added. Further 10 min later 1-phenyl-1-trimethylsilyloxyethylene (0.73 mL, 3.6 mmol) was added. The mixture was stirred at room temperature for 4 h. After standard work-up (similar to method a), **6f** (0.31 g, 32%) was afforded as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, J=7.1), 2.00 (s, 3H), 3.5-3.7 (m, 2H), 4.09 (q, 2H, J=7.1), 5.0-5.1 (m, 1H), 5.51 (d, 1H, J=8.0), 6.34 (d, 1H, J=8.4), 7.06 (d, 1H, J=8.4), 7.2-7.4 (m, 3H), 7.7-7.9 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.6, 16.8, 40.5, 50.1, 60.7, 108.5, 121.6, 127.7, 128.1, 132.9, 136.1, 137.8, 146.6, 155.2, 172.5, 197.5; Anal. Calcd for $C_{18}H_{20}N_2O_3.H_2O$: C, 65.44; H, 6.10; N, 8.47. Found: C, 65.58; H, 5.75; N, 8.24.

4-Oxo-4-phenyl-2-(pyridin-2-yl)aminobutanoic acid ethyl ester (6d).

Oil; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J=7.1), 3.6-3.8 (m, 2H), 4.19 (q, 2H, J=7.1), 5.1-5.2 (m, 1H), 5.49 (d, 1H, J=7.9), 6.47 (d, 1H, J=8.4), 6.56 (ddd, 1H, J=6.9, 5.1 and 0.7), 7.3-7.6 (m, 4H), 7.9-8.0 (m, 2H), 8.06 (dd, 1H, J=4.9 and 0.9); ^{13}C NMR ($CDCl_3$) δ 14.0, 40.8, 50.0, 61.3, 109.3, 113.3, 128.0, 128.5, 133.3, 136.2, 137.1, 147.4, 156.9, 172.6, 197.6; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.33; H, 5.82; N, 9.12.

Bromination of compounds (6a-f) with NBS: Typical procedure.

3-(5-Bromopyridin-2-yl)amino-1,3-diphenylpropan-1-one (10a).

N-Bromosuccinimide (0.18 g, 1 mmol) was added to a solution of **6a** (0.3 g, 1 mmol) in dry CH_2Cl_2. The mixture was stirred at 20°C for 2 min and the solvent was removed under reduce pressure. The crude residue (0,50 g) was purified by flash chromatography on silica gel (EtOAc-hexane, 1:3) to afford **10a** (0.38 g, 100%): mp 149-150 °C; ^{1}H NMR ($CDCl_3$) δ 3.47, 3.66 (ABX system, 2H, J=16.6, 6.6 and 5.5), 5.3-5.4 (m, 1H), 5.52 (d, 1H, J=7.0),6.28 (d, 1H, J=8.7), 7.2-7.6 (m, 9H), 7.9-8.0 (m, 2H), 8.08 (d, 1H, J=2.5); ^{13}C NMR ($CDCl_3$) δ 45.3, 52.6, 107.5, 109.0, 126.3, 126.4, 127.4, 128.1, 128.6, 128.7, 133.4, 138.6, 139.6, 142.0, 156.3, 197.9; Anal. Calcd for $C_{20}H_{17}N_2OBr$: C, 63.00; H, 4.49; N, 7.35. Found: C, 62.94; H, 4.59; N, 7.39.

Compounds (**11a-f**) were synthesized from compounds (**6a-f**) and NBS (for **11a-d**, 2 equivalents and for **11e-f**, 1 equivalent) following the same procedure.

3-(3,5-Dibromopyridin-2-yl)amino-1,3-diphenylpropan-1-one (11a).

Yellow solid: mp 123-124°C; ^{1}H NMR ($CDCl_3$) δ 3.51, 3.81 (ABX system, 2H, J=16.5, 6.0 and 5.8), 5.7-5.8 (m, 1H), 6.15 (d, 1H, J=7.4), 7.2-7.6 (m, 8H), 7.73 (d, 1H, J=2.0), 7.9-8.0 (m, 2H), 8.04 (d, 1H, J=2.0); ^{13}C NMR ($CDCl_3$) δ 44.2, 52.1, 105.7, 106.1, 126.3, 126.4, 127.3, 128.1, 128.6, 128.7, 133.3, 136.8, 141.6, 141.8, 152.5, 198.4; Anal. Calcd for $C_{20}H_{16}N_2OBr_2$: C, 52.20; H, 3.50; N, 6.09. Found: C, 52.02; H, 3.50; N, 6.11.

3-(3,5-Dibromopyridin-2-yl)amino-1-(4-methoxyphenyl)-3-phenylpropan-1-one (11b).

Yellow solid: mp 126°C; ^{1}H NMR ($CDCl_3$) δ 3.43, 3.72 (ABX system, 2H, J=16.3, 5.9 and 5.8), 3.85 (s, 3H), 5.6-5.8 (m, 1H), 6.26 (d, 1H, J=7.6), 6.90 (d, 2H, J=8.9), 7.2-7.4 (m, 5H), 7.71 (d, 1H, J=2.1), 7.89 (d, 2H, J=8.8), 8.02 (d, 1H, J=2.1); ^{13}C NMR ($CDCl_3$) δ 44.6, 53.2, 56.3, 106.6, 106.9,

114.7, 127.4, 128.1, 129.5, 130.8, 131.4, 142.0, 143.0, 153.5, 164.5, 197.8; Anal. Calcd for $C_{21}H_{18}N_2O_2Br_2$: C, 51.46; H, 3.70; N, 5.71. Found: C, 51.81; H, 3.82; N, 5.56.

1-(3,5-Dibromopyridin-2-yl)amino-4,4-dimethyl-1-phenylpentan-3-one (11c).

Solid : mp 79-80°C; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9H), 2.97, 3.31 (ABX system, 2H, J=16.7, 5.8 and 5.4), 5.6-5.8 (m, 1H), 6.42 (d, 1H, J=7.5), 7.2-7.4 (m, 5H), 7.71 (d, 1H, J=2.1), 8.03 (d, 1H, J=2.1); ^{13}C NMR ($CDCl_3$) δ 25.5, 42.0, 44.3, 51.8, 105.5, 105.7, 126.2, 127.0, 128.3, 138.7, 140.9, 141.9, 152.4, 214.3; Anal. Calcd for $C_{18}H_{20}N_2OBr_2$: C, 49.12; H, 4.58; N, 6.36. Found: C, 49.37; H, 4.47; N, 6.26.

2-(3,5-Dibromopyridin-2-yl)amino-4-oxo-4-phenylbutanoic acid ethyl ester (11d).

Oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, J=7.1), 3.65, 3.80 (ABX system, 2H, J=17.8, 4.5 and 4.4), 4.21 (q, 2H, J=7.1), 5.1-5.2 (m, 1H), 6.16 (d, 1H, J=7.7), 7.4-7.6 (m, 3H), 7.73 (d, 1H, J=2.1), 7.9-8.0 (m, 2H), 8.06 (d, 1H, J=2.1); ^{13}C NMR ($CDCl_3$) δ 13.9, 40.3, 50.7, 61.4, 105.8, 106.5, 128.0, 128.5, 133.3, 136.4, 141.3, 146.7, 152.5, 171.6, 197.5; Anal. Calcd for $C_{17}H_{16}N_2O_3Br_2$: C, 44.76; H, 3.54; N, 6.14. Found: C, 44.73; H, 3.39; N, 6.15.

3-(3-Bromo-5-methylpyridin-2-yl)amino-1,3-diphenylpropan-1-one (11e).

Oil: ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 3.53, 3.84 (ABX system, 2H, J=16.5, 6.1and 5.6), 5.8-5.9 (m, 1H), 5.96 (d, 1H, J=7.7), 7.2-7.6 (m, 9H), 7.86 (s, 1H), 7.9-8.0 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.7, 44.6, 52.1, 105.3, 122.8, 126.5, 127.0, 128.0, 128.3, 128.8, 132.9, 137.1, 140.2, 142.5, 146.2, 151.9, 198.3; Anal. Calcd for $C_{21}H_{19}N_2OBr$: C, 63.81; H, 4.84; N, 7.09. Found: C, 64.01; H, 5.01; N, 6.82.

2-(3-Bromo-5-methylpyridin-2-yl)amino-4-oxo-4-phenylbutanoic acid ethyl ester (11f).

Oil: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, J=7.2), 2.15 (s, 3H), 3.67, 3.81 (ABX system, 2H, J=16.4, 4.6 and 4.6), 4.22 (q, 2H, J=7.2), 5.1-5.2 (m, 1H), 5.96 (d, 1H, J=7.8), 7.4-7.6 (m, 4H), 7.85 (d, 1H, J=0.8), 7.9-8.0 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.8, 40.7, 50.8, 61.2, 105.6, 123.4, 128.0, 128.4, 133.2, 136.6, 140.6, 145.8, 151.9, 172.1, 197.7; Anal. Calcd for $C_{18}H_{19}N_2O_3Br$: C, 55.26; H, 4.89; N, 7.16. Found: C, 55.48; H, 4.94; N, 7.02.

Preparation of 3-acylimidazo[1,2-*a*]pyridines (2a-f).

Typical procedure: 3-benzoyl-6,8-dibromo-2-phenylimidazo[1,2-*a*]pyridine (2a).

A solution 1N of bromine in acetic acid (3.3 mL, 0.33 mmol) was added to a solution of **11a** (0.15 g, 0.33 mmol) in acetic acid (5 mL). The mixture was refluxed for 6 h, and the solvent was removed under reduce pressure. The residue was dissolved in CH_2Cl_2 (30 mL). The organic layer was washed with 10% aqueous NaOH (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue was crystallized from CH_2Cl_2/EtOH to give **2a** (0.13 g, 86%): mp 255 °C; ^{1}H NMR ($CDCl_3$) δ 7.1-7.2 (m, 5H), 7.3-7.4 (m, 3H), 7.5-7.6 (m, 2H), 7.88 (d, 1H, J=1.9), 9.65 (d, 1H, J=1.9); ^{13}C NMR ($CDCl_3$) δ 108.4, 112.0, 121.4, 126.0, 127.5, 128.0, 128.1, 128.8, 129.7, 130.5, 132.5, 133.2, 134.2, 137.9, 154.9, 187.7; Anal. Calcd for $C_{20}H_{12}N_2OBr_2$: C, 52.66; H, 2.65; N, 6.14. Found: C, 52.64; H, 2.60; N, 6.03.

When the reaction was stopped after 1.5 h, compounds (**2a**) and (**13a**) were isolated in 29 and 34% yield respectively along with unreacted **11a** (9%), after flash chromatography on silica gel (EtOAc-hexane 1:4).

Compounds (**2b-f**) and (**13b-c**) were prepared following the same procedure (see Table 3).

3-Benzoyl-6,8-dibromo-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine (13a).

Yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.01 (d, 1H, J=6.5), 5.76 (d, 1H, J=6.5), 7.07 (d, 1H, J=1.8), 7.1-7.2 (m, 2H), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 72.6, 75.7, 93.7, 108.5, 127.0, 127.7, 128.4, 128.9, 129.0, 129.1, 132.6, 134.5, 141.5, 141.9, 154.4, 193.5.

6,8-Dibromo-3-(4-methoxybenzoyl)-2-phenylimidazo[1,2-*a*]pyridine (2b).

White powder: mp 236 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 6.60 (d, 2H, J=8.9), 7.0-7.2 (m, 3H), 7.3-7.4 (m, 2H), 7.53 (d, 2H, J=8.9), 7.81 (d, 1H, J=1.7), 9.45 (d, 1H, J=1.7); ^{13}C NMR ($CDCl_3$) δ 55.3, 107.8, 111.7, 113.2, 121.2, 127.9, 128.5, 130.1, 130.2, 132.0, 132.7, 133.0, 133.8, 143.5, 153.3, 163.2, 185.9; Anal. Calcd for $C_{21}H_{14}N_2O_2Br_2$: C, 51.88; H, 2.90; N,5.76. Found: C, 52.15; H, 2.83; N, 5.78.

6,8-Dibromo-3-(4-methoxybenzoyl)-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine (13b).

Yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3H), 5.04 (d, 1H, J =6.6), 5.64 (d, 1H, J=6.6), 6.87 (d, 2H, J=7.6), 6.98 (d, 1H, J=1.6), 7.2-7.4 (m, 6H), 7.67 (d, 2H, J=7.6); ^{13}C NMR ($CDCl_3$) δ 55.6, 73.0, 75.4, 93.5, 108.4, 114.1, 125.4, 127.1, 128.3, 128.9, 131.5, 134.8, 141.1, 141.9, 154.3, 164.6, 191.9.

6,8-Dibromo-2-phenyl-3-pivaloylimidazo[1,2-*a*]pyridine (2c).

Light yellow powder: mp 168-169 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 7.4-7.5 (m, 3H), 7.6-7.7 (m, 2H), 7.68 (d, 1H, J=1.9), 8.29 (d, 1H, J=1.9); ^{13}C NMR ($CDCl_3$) δ 27.4, 46.6, 107.2, 112.2, 121.8,

124.8, 126.1, 128.9, 129.5, 131.8, 134.6, 142.5, 147.9, 206.5; Anal. Calcd for $C_{18}H_{16}N_2OBr_2$: C, 49.57; H, 3.90; N, 6.42. Found: C, 49.43; H, 3;80; N, 6.17.

6,8-Dibromo-2-phenyl-3-pivaloyl-2,3-dihydroimidazo[1,2-*a*]pyridine (13c).

Yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9H), 5.02 (d, 1H, J=6.4), 5.29 (d, 1H, J=6.4), 6.72 (d, 1H, J=1.8), 7.2-7.4 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.3, 43.7, 73.0, 73.8, 93.6, 108.8, 127.0, 128.2, 128.8, 132.3, 141.4, 141.5, 154.2, 208.8.

3-Benzoyl-6,8-dibromo-2-ethoxycarbonylimidazo[1,2-*a*]pyridine (2d).

Yellow powder: mp 215 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=7.1), 3.89 (q, 2H, J=7.1), 7.4-7.6 (m, 3H), 7.7-7.8 (m, 2H), 7.87 (d, 1H, J=1.5), 9.25 (d, 1H, J=1.5); ^{13}C NMR ($CDCl_3$) δ 13.7, 62.2, 109.9, 113.2, 124.1, 126.9, 128.8, 129.1, 133.6, 134.6, 139.2, 143.0, 143.4, 162.4, 186.5; Anal. Calcd for $C_{17}H_{12}N_2O_3Br_2$: C, 45.16; H, 2.68; N, 6.20. Found: C, 45.56; H, 2.98; N, 5.84.

3-Benzoyl-8-bromo-6-methyl-2-phenylimidazo[1,2-*a*]pyridine (2e).

Yellow powder: mp 173-174 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 7.0-7.2 (m, 5H), 7.2-7.4 (m, 3H), 7.4-7.5 (m, 2H), 7.58 (d, 1H, J=1.3), 9.23 (d, 1H, J=1.3); ^{13}C NMR ($CDCl_3$) δ 18.0, 110.7, 121.0, 124.5, 125.1, 127.5, 127.6, 128.1, 129.4, 130.2, 131.7, 133.7, 133.8, 138.3, 144.1, 154.4, 187.3; Anal. Calcd for $C_{21}H_{15}N_2OBr$: C, 64.47; H, 3.86; N, 7.16. Found: C, 64.53; H, 3.68; N, 6.97.

3-Benzoyl-8-bromo-2-ethoxycarbonyl-6-methylimidazo[1,2-*a*]pyridine (2f).

Light yellow powder: mp 176-177 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7.1), 2.35 (s, 3H), 3.82 (q, 2H, J=7.1), 7.4-7.6 (m, 4H), 7.7-7.8 (m, 2H), 8.85 (d, 1H, J=1.2); ^{13}C NMR ($CDCl_3$) δ 13.4, 18.1, 61.6, 111.6, 123.5, 125.9, 128.4, 128.7, 132.6, 134.2, 134.3, 139.3, 142.5, 143.3, 162.6, 186.4; Anal. Calcd for $C_{18}H_{15}N_2O_3Br$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.98; H, 3.67; N, 7.09.

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