

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

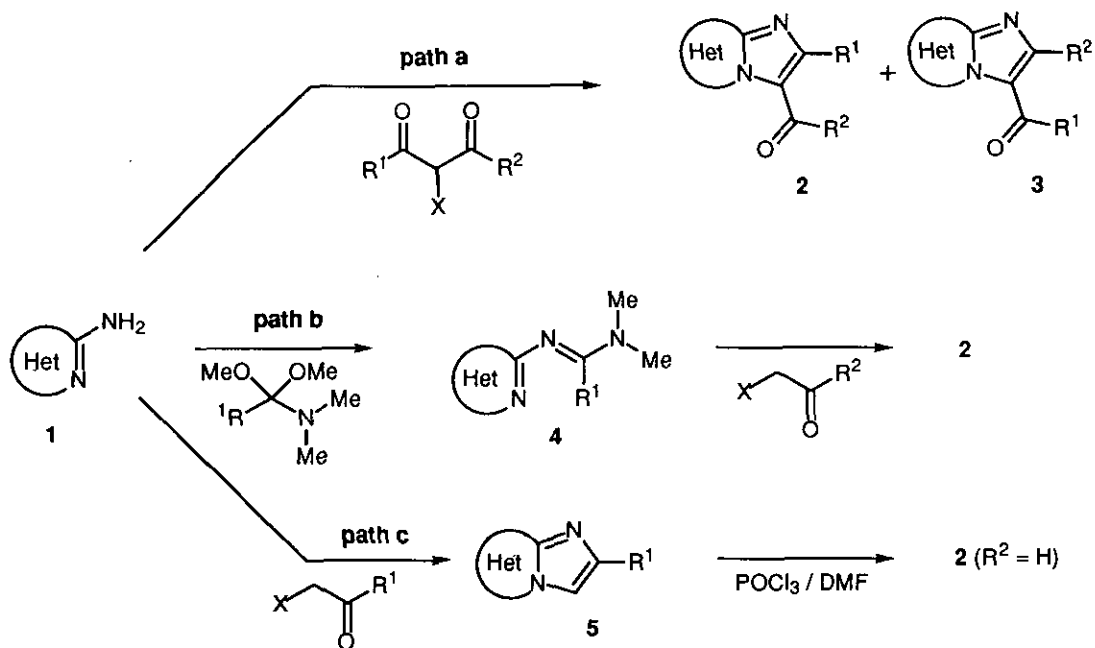
Jean-Luc Moutou, Martine Schmitt, Valérie Collot, and Jean-Jacques Bourguignon*

Laboratoire de Pharmacochimie Moléculaire, UPR 421 du CNRS,
Faculté de Pharmacie, 74, route du Rhin
67400 ILLKIRCH-GRAFFENSTADEN France

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.

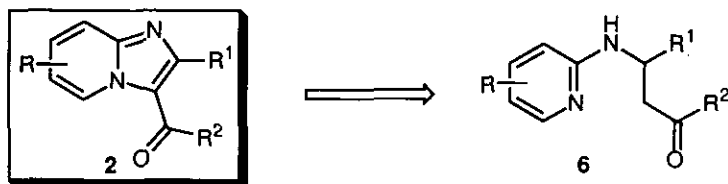
In recent years, the synthesis of 3-acylimidazo[1,2-*x*]azines has attracted much attention. These compounds were reported as potent ligands of the mitochondrial benzodiazepine receptors.¹ Other works mentioned for these agents potential anti-inflammatory activities² and uterine-relaxing, antibronchospastic 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 R¹ and R². 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**) (R¹ = COR). It is noteworthy that the Vilsmeier-Haack reaction (path c) onto 2-substituted imidazoheterocycles (**5**) affords the corresponding 3-formyl derivatives (**2**) (R² = 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 R¹ = CO₂Et) 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.

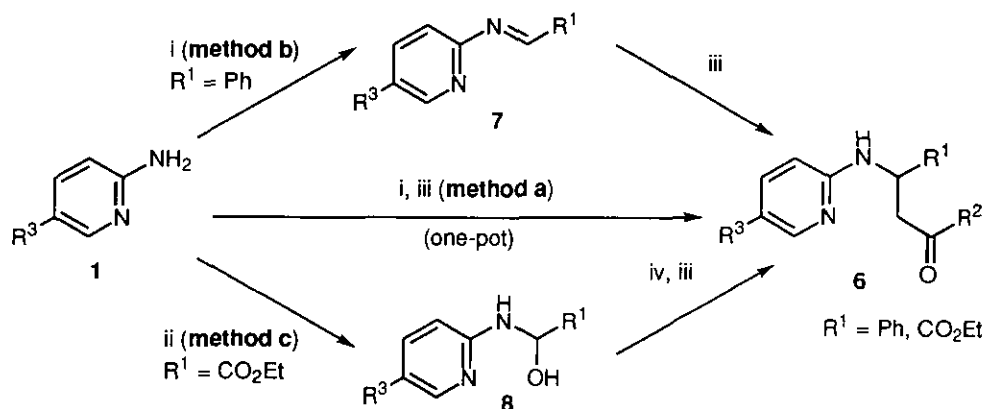


Scheme 2

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

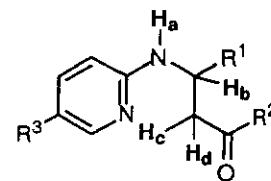
pathways (methods a-c, Scheme 3). The starting amidines (**1**) were reacted with various enolizable ketones or their corresponding silyl enol ethers, in the presence of trimethylsilyl triflate (TMSOTf).⁸



i: PhCHO ; ii: EtO₂CCHO ; iii: TMSOTf, MeCOR² or CH₂=C(OTMS)R², MeCN ; iv: TMSCl, Et₃N, CH₂Cl₂

Scheme 3

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

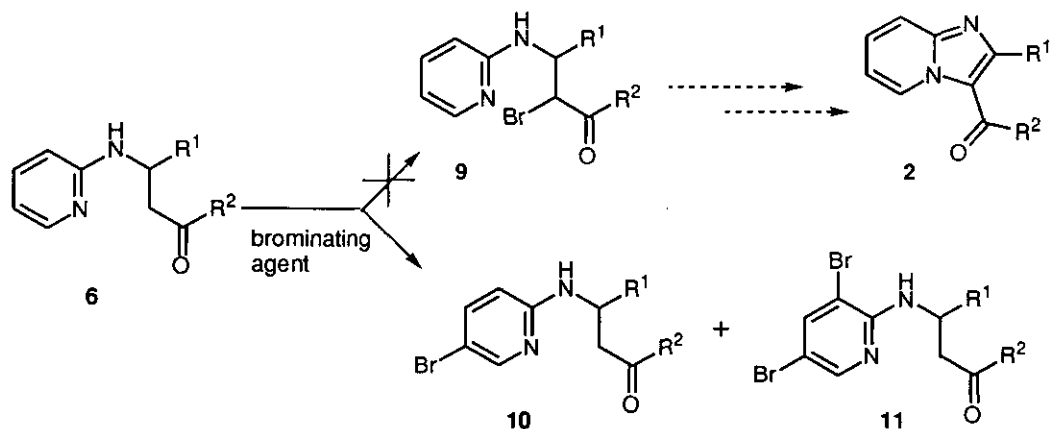


No.	R ¹	R ²	R ³	Method	Yield (%)	mp (°C)	¹ H NMR(CDCl ₃)		
							H _a (d)	H _b (m)	H _c , H _d
6a	Ph	Ph	H	a	53	125	5.75	5.4-5.5	3.48, 3.67 ^b
6b	Ph	<i>p</i> -MeO-Ph	H	b	75(49) ^a	111	5.94	5.4-5.5	3.37, 3.58 ^b
							J=7.1	J=16.5, 6.7, 5.8	
6c	Ph	<i>t</i> -Bu	H	b	34(22) ^a	107	5.94	5.2-5.3	2.94, 3.13 ^b
							J=7.5	J=16.8, 6.4, 6.0	
6d	CO ₂ Et	Ph	H	c	31	oil	5.49	5.1-5.2	3.72 ^c
6e	Ph	Ph	Me	a	50	112	5.62	5.4-5.5	3.45, 3.65 ^b
							J=7.2	J=16.5, 6.8, 5.8	
6f	CO ₂ Et	Ph	Me	c	32	oil	5.51	5.1-5.2	3.61 ^c
							J=8.0		

^aoverall yield in parentheses starting from the amidine (**1**).^bABX pattern. ^cmultiplet.

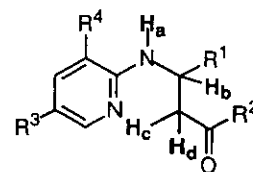
Typical ¹H NMR signals of the amidino ketones (**6a-f**) highlighted a doublet signal at 5.72 ± 0.23 ppm, exchangeable with D₂O, corresponding to the NH proton H_a, and an ABX system for the two methylene protons H_c, H_d and the methine proton H_b (see Table 1).

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

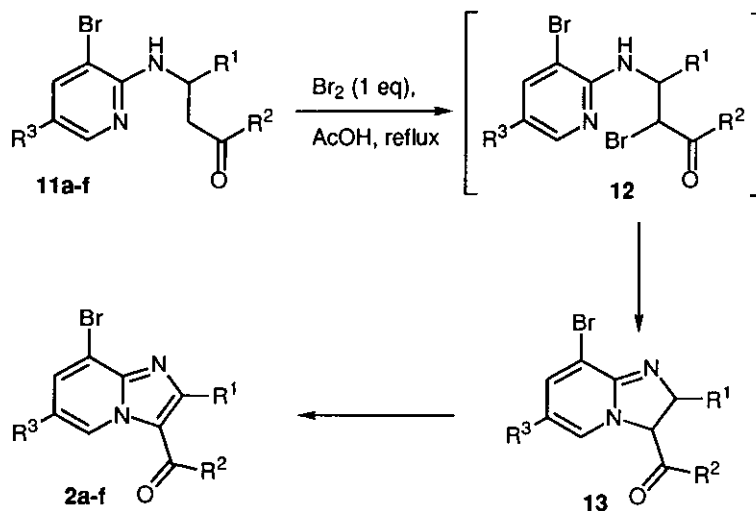
When 1 equivalent of bromine was added to **6a** in basic or in acidic conditions, the monobromo derivative (**10a**) was the major compound in the mixture (80% and 70% respectively). With *N*-bromosuccinimide (1 equivalent), the 5-bromo derivative (**10a**) was obtained quantitatively. The use of 2 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**) exhibits 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 ¹H 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
11a	Ph	Ph	Br	Br	1 ^b	93 ^c	123-124	6.15	5.7-5.8	3.51, 3.81
										J=7.4
11b	Ph	<i>p</i> -MeO-Ph	Br	Br	3 ^b	97 ^d	126	6.26	5.6-5.8	3.43, 3.72
										J=7.6
11c	Ph	<i>t</i> -Bu	Br	Br	24 ^b	99 ^d	79-80	6.42	5.6-5.8	2.97, 3.31
										J=7.5
11d	CO ₂ Et	Ph	Br	Br	2 ^b	83 ^d	oil	6.16	5.1-5.2	3.65, 3.80
										J=7.7
11e	Ph	Ph	Me	Br	2.5 ^a	80 ^d	oil	5.96	5.8-5.9	3.53, 3.84
										J=7.7
11f	CO ₂ Et	Ph	Me	Br	0.5 ^a	86 ^c	oil	5.96	5.1-5.2	3.67, 3.81
										J=7.8

^aNBS (1 equivalent). ^bNBS (2 equivalents). ^cisolated yield after flash chromatography (EtOAc-Hexane 1:3). ^disolated yield after flash chromatography (EtOAc-Hexane 1:2).

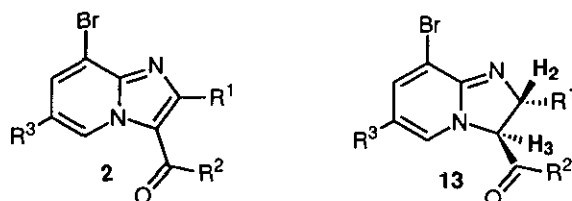
Introduction of a bromine atom in the α -position of the ketone in compounds (11a-f) was then investigated. Thus the compound (11a) was refluxed with bromine (1 equivalent) in acetic acid for 6 h and unexpectedly the corresponding 3-benzoylimidazo[1,2-*a*]pyridine (2a) was obtained in 86% yield (Table 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 H₃, and probably dramatically influence the bromination step before cyclocondensation. Moreover, the facile dehydrogenation reaction may be correlated with the electron deficiency of the carbon C₃ bearing H₃ in the dihydroimidazolic intermediate (**13**), as illustrated by progressive deshielding of H₃, when comparing ¹H 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 R² 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 ¹H and ¹³C NMR. ¹H NMR spectrum exhibits a typical AB pattern for protons H₂ and H₃ with a vicinal coupling constant J_{2,3} 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 hindered *cis*- into the *trans*-form via an inversion of configuration at the C₃ 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	<i>p</i> -MeO-Ph	Br	24	50	50	5.04	5.64	6.6
4	11c	Ph	<i>t</i> -Bu	Br	48	9	59	5.02	5.29	6.4
5	11d	CO ₂ Et	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 ₂ Et	Ph	Me	16	53	trace ^a	4.75	6.42	6.2

^abased on ¹H 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. ¹H NMR spectra were recorded at 200 MHz on a Bruker 200 AC spectrometer with Me₄Si as the internal standard (δ (ppm)). ¹³C NMR spectra were recorded at 50 MHz on the same instrument using the CDCl₃ 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 CH₂Cl₂. The organic layer was dried (Na₂SO₄), 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₁H₂₀N₂O, H₂O: 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₀H₁₈N₂O, 0.5 H₂O: 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 successively added to a solution of 2-benzylideneaminopyridine⁹ (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; ¹H NMR (CDCl₃) 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 $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_2$: 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; ^1H 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 $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$: 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: ^1H 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: ^1H 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 $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O}$: 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; ^1H 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 $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3$: 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 $149\text{-}150^\circ\text{C}$; ^1H 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 $\text{C}_{20}\text{H}_{17}\text{N}_2\text{OBr}$: 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 $123\text{-}124^\circ\text{C}$; ^1H 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 $\text{C}_{20}\text{H}_{16}\text{N}_2\text{OBr}_2$: 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 ; ^1H 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; 1H 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: 1H 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: 1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 3.53, 3.84 (ABX system, 2H, $J=16.5$, 6.1 and 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: 1H 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 CH₂Cl₂ (30 mL). The organic layer was washed with 10% aqueous NaOH (30 mL), dried (Na₂SO₄), filtered and evaporated. The residue was crystallized from CH₂Cl₂/EtOH to give **2a** (0.13 g, 86%): mp 255 °C; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₀H₁₂N₂OBr₂: 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: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₁H₁₄N₂O₂Br₂: 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: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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: 1H 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; 1H 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; 1H 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; 1H 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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