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Efficient Preparation of Imidazo[1,5-*a*]pyridine-1-carboxylic Acids

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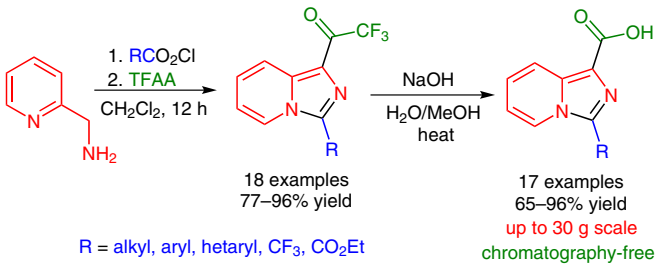

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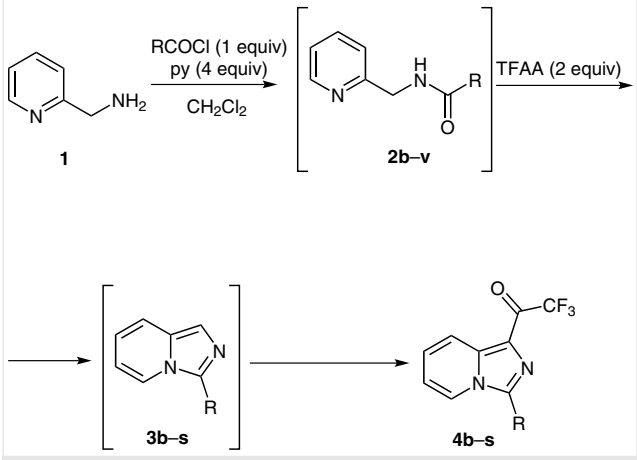
Abstract We report a novel and efficient approach to the synthesis of imidazo[1,5-*a*]pyridine-1-carboxylic acids. By using the reaction of 2-(aminomethyl)pyridine with acyl chlorides followed by one-pot treatment with trifluoroacetic anhydride, 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanones were obtained, which were then converted into imidazo[1,5-*a*]pyridine-1-carboxylic acids in high preparative yields through haloform cleavage.

Key words amides, cyclization, heterocycles, bicyclic compounds, acylation

Condensed heterocyclic compounds with annelated imidazole fragments possess a wide spectrum of biological activity. In particular, imidazo[1,2-*a*]pyridines display antiviral,[1] antiulcer,[2] and D_4-receptor antagonistic activities.[3] Imidazo[1,5-*a*]pyridine derivatives were tested for the treatment of inflammatory[4] and cardiovascular[5] diseases, cancer[6,7a–c] and cognitive impairment of Alzheimer's disease.[7d] Imidazo[1,5-*a*]pyridine-3-carboxylic acids derivatives[4,7b,7d] occupy an important place among these compounds. Despite their high biological potential, imidazo[1,5-*a*]pyridines belong to the least studied class of the imidazopyridines and their preparation is difficult.[4,7b,7d]

The most common and versatile approach to imidazo[1,5-*a*]pyridines is based on the cyclization of 2-(aminomethyl)pyridine amides **2** (Scheme 1) through the reaction with phosphorus oxychloride,[4,7,8] polyphosphoric acid,[9] and acetic anhydride in the presence of *p*-toluenesulfonic acid[10] or with acetoformic anhydride.[11] The relatively high temperatures required for these processes (80–100 °C) can cause side reactions that can reduce the yields to 14%,[12] especially for aliphatic acids amides. Alternatively, the use of propane phosphonic acid anhydride[13] gives good results in comparison with those obtained with the reagents mentioned above. However, prolonged heating is required for the reaction with free acid, which may cause destruction of sensitive groups such as carbamates. Trifluoromethanesulfonic anhydride[14] does not have this shortcoming because it acts at low temperature in the presence of base.



Scheme 1 One-pot synthesis of 2,2,2-trifluoro-1-(imidazo[1,5-*a*]pyridin-1-yl)ethanones **4** from 2-(aminomethyl)pyridine (**1**)

We have found that the reaction of trifluoroacetic anhydride (TFAA) with **2** in the presence of pyridine results in the formation of the imidazolium ring at low temperatures (–50 to –10 °C), while at the same time tryfluoroacetylation of the imidazolium ring takes place. This fact may be used for a one-pot production of trifluoro-1-(imidazo[1,5-*a*]pyridin-1-yl)ethanones, which are precursors of imidazo[1,5-*a*]pyridine-1-carboxylic acids.

We first optimized the reaction conditions for the cyclization of *N*-(pyridin-2-ylmethyl)acetamide (**2b**) to 3-methyl imidazo[1,5-*a*]pyridine (**3b**) (Scheme 1,R = Me). The

addition of equimolar amounts of TFAA in dichloromethane to a solution of **2b** in dichloromethane at room temperature gave a mixture of **3b** and its trifluoroacetic derivative **4b** together with starting compound (Table 1, entries 1 and 2).

A temperature decrease to –10 °C changed the ratio of the products only slightly (Table 1, entries 3 and 4). Addition of two equivalents of TFAA without a base increased the conversion of the starting compound, although the reaction was incomplete (entries 2 and 4). With the addition of triethylamine, almost pure 2,2,2-trifluoro-1-(3-methylimidazo[1,5-*a*]pyridin-1-yl)ethanone (**4b**) was obtained (entries 5–8). Thus, trifluoroacetic acid, which is produced in the reaction (Scheme 1), needs to be trapped by triethylamine to complete the acylation of the imidazopyridine ring. However, this is accompanied by the reaction between triethylamine and TFAA.[15] The replacement of triethylamine by pyridine increased the yields (entries 10 and 11), allowing the reaction to be carries out at –10 °C. These conditions were chosen to be standard for all further transformations.

Table 1 Yields of the Cyclodehydration–Acylation Reaction of **2b**

Entry	Base	Temp (°C)	TFAA (equiv)	Conv. (%)	Yield of **3b** (%)	Yield of **4b** (%)
1	–	20	1	42	24	18
2	–	20	2	50	–	50
3	–	–10	1	51	28	23
4	–	–10	2	59	–	59
5	Et_3N	20	1	56	31	25
6	Et_3N	20	2	68	8	60
7	Et_3N	–10	1	62	34	28
8	Et_3N	–10	2	80	10	70
9	pyridine	20	1	66	37	29
10	pyridine	20	2	100	–	80
11	pyridine	–10	2	100	–	90

We also found that TFAA can be added directly to the mixture of reactants without isolation of intermediates, which requires four equivalents of base to complete the reaction. This allows all three steps to be combined in a one-pot, three-step preparation of 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanones **4a**–**s** containing a range of functional groups (Table 2).

The above reaction conditions were applied to the preparation of **2b** and amides **2c**–**p** (Table 2). Linear aliphatic amides **2b**–**d**, **2g**, and **2l** formed 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanones **4b**–**d**, **4g**, and **4l** as pure products with high yields (86–95%; Table 2, entries 2–4, 7 and 12). Under the same conditions, other aliphatic (entries 5, 6, 8–11) and aromatic (entries 13–16) amides gave mixtures of the target compounds **4e**, **4f**, **4h**–**k**, and **4m**–**p** together with up to 30% of 2,2,2-trifluoro-1-[3-(trifluoromethyl)imidazo[1,5-*a*]pyridine-1-yl]-ethanone (**4q**), the formation of which can be explained by a reamidation reaction. The formation of byproducts was reduced to 7–15% by carrying out the reaction at –50 °C.

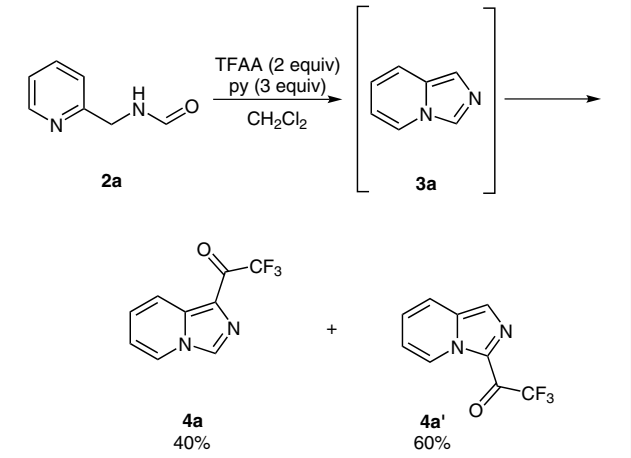
Table 2 Yields of 2,2,2-Trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanones **4a**–**s**[a]

Entry	R	Product	Temp. (°C)	Yield (%)
1	H	**4a**[b]	–10	36
2	Me	**4b**	–10	90
3	Et	**4c**	–10	92
4	*n*-Pr	**4d**	–10	95
5	*i*-Pr	**4e**	–50	83
6	*c*-Pr	**4f**	–50	81
7	*i*-Bu	**4g**	–10	89
8	*t*-Bu	**4h**	–50	77
9	*c*-Bu	**4i**	–50	79
10	*c*-Pent	**4j**	–50	81
11	*c*-Hex	**4k**	–50	83
12	$PhCH_2CH_2$	**4l**	–10	95
13	Ph	**4m**	–50	84
14	3-Py	**4n**	–50	83
15	4-Py	**4o**	–50	85
16	4-(2-Cl-Py)-	**4p**	–50	80
17	CF_3	**4q**	–10	96
18	EtO_2C	**4s**	–10	95

[a] Reaction time was 12 h for all entries.
[b] Formed together with 2,2,2-trifluoro-3-imidazo[1,5-*a*]pyridin-1-ylethanone (**4a′**).

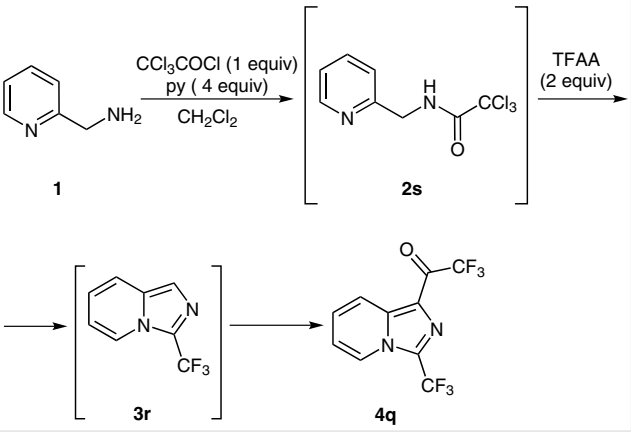
We then studied the reactivity of *N*-(pyridin-2-ylmethyl)formamide (**2a**; Scheme 2). The reaction with TFAA in the presence of pyridine resulted in a mixture of 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanone (**4a**) and 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-3-ylethanone (**4a′**) (Table 2 and Scheme 2) in 2:3 ratio according to the NMR spectroscopic analysis.

We applied the same reaction conditions to 2-(aminomethyl)pyridine amides with strong carboxylic acids such as trifluoroacetic, trichloroacetic, and ethyloxalic acids (**2q**–**s**; Scheme 1 and Table 2) that could potentially form an imidazo[1,5-*a*]pyridinium ring with electron-withdrawing groups in the 3-position. The reaction of **1** with three equivalents of TFAA and four equivalents of pyridine gave trifluoroacetamide **2q**, followed by cyclization to **3q** and acylation to 2,2,2-trifluoro-1-[3-(trifluoromethyl)imidazo[1,5-*a*]pyridin-1-yl]ethanone (**4q**; Scheme 1 and Table 2). The reaction of **2q** with one equivalent of TFAA at –15 to –10 °C provided a mixture of **2q**/**3q**/**4q** in a 1:2:1 ratio and



Scheme 2 Cyclization of the **2a** and acylation of the ring with TFAA

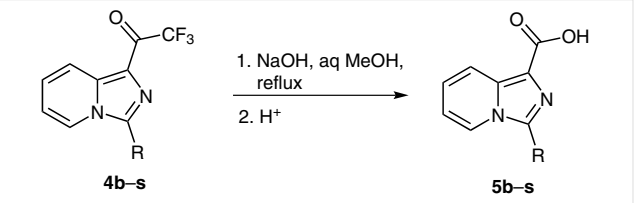
at –50 °C afforded 3-trifluoromethylimidazo[1,5-*a*]pyridine (**3q**) as a single product (Scheme 1). Trichloroacetamide **2r** with two equivalents of TFAA gave **4q** also as a sole product (Scheme 3). When ethyloxalic amide **2s** was treated with one equivalent of TFAA at –10 °C only non-acylated imidazo[1,5-*a*]pyridine **3s** was obtained (Scheme 1, R = CO_2Et). The acylation only took place with more than one equivalent of TFAA; with two equivalents of TFAA at room temperature the reaction was complete. Therefore, the rates of the acylation of the imidazo[1,5-*a*]pyridinium ring of ethyl imidazo[1,5-*a*]pyridine-3-carboxylate (**3s**) with TFAA is significantly lower than the cyclization rates of the starting amide in comparison with other aliphatic and aromatic amides. In the case of amides **2b**–**p**, the formation of a mixture of starting amide, non-acylated imidazo[1,5-*a*]pyridine **3b**–**p**, and product **4b**–**p** was observed with one equivalent of TFAA even at –50 °C.



Scheme 3 Reaction of the 2,2,2-trichloro-*N*-(pyridin-2-ylmethyl)acetamide (**2r**), obtained in situ from **1**, with TFAA

Methyl *N*-(pyridin-2-ylmethyl)carbamate (**2t**; R = MeO) was transformed into **4q** under standard cyclization conditions. *N*′,*N*′-Diethyl-*N*-(2-pyridylmethyl)urea (**2u**; R = Et_2N) was inert towards cyclization upon treatment with TFAA.

The 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanones **4b**–**s** were transformed into the corresponding carboxylic acids **5b**–**s** by haloform cleavage in high yields (Scheme 4 and Table 3). The reaction of **4s** was accompanied by hydrolysis of the ester group.



Scheme 4 Haloform cleavage of 2,2,2-trifluoro-1-(imidazo[1,5-*a*]pyridin-1-yl)ethanones **4b**–**s**

Table 3 Preparation of Imidazo[1,5-*a*]pyridine-1-carboxylic Acids through Haloform Cleavage[a]

Entry	R	Product	Yield (%)
1	Me	**5b**	65
2	Et	**5c**	72
3	*n*-Pr	**5d**	80
4	*i*-Pr	**5e**	77
5	*c*-Pr	**5f**	75
6	*i*-Bu	**5g**	85
7	*t*-Bu	**5h**	77
8	*c*-Bu	**5i**	79
9	*c*-Pent	**5j**	81
10	*c*-Hex	**5k**	83
11	$PhCH_2CH_2$	**5l**	95
12	Ph	**5m**	84
13	3-Py	**5n**	83
14	4-Py	**5o**	85
15	4-(2-Cl-Py)	**5p**	80
16	CF_3	**5q**	96
17	HO_2C	**5s**[b]	80

[a] Reaction time was 1 h for all entries.
[b] Ethyl (1-trifluoroacetyl)imidazo[1,5-*a*]pyridine-3-carboxylate **4s** (R = CO_2Et) was used as a starting compound.

In conclusion, a convenient, one-pot method for the synthesis of 2,2,2-trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanones and some imidazo[1,5-*a*]pyridines from 2-(aminomethyl)pyridine was developed. Trifluoroacetic anhydride was used for the cyclization of 2-(aminometh-

yl)pyridine amides followed by imidazolium ring acylation. The obtained trifluoroacetyl derivatives gave imidazo[1,5-*a*]pyridine-1-carboxylic acids by haloform cleavage in high preparative yields.

Starting materials and solvents were purchased from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded with a Varian VXR 400 instrument at 400 MHz. ^{13}C NMR spectra were recorded with a Varian VXR 400 instrument at 100 MHz. Chemical shifts are reported as parts per million (δ) downfield from an internal standard of tetramethylsilane, and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). HPLC-MS analysis was performed with an Agilent 1100 LC/MSD SL separations module and Mass Quad G1956B mass detector with electrospray ionization (+ve or –ve ion mode as indicated) and with HPLC performed using Zorbax SB-C18, Rapid Resolution HT Cartridge 4.6 × 30 mm 1.8-Micron (Agilent P/N:823975–902) i.d. column, at a temperature of 40 °C with gradient elution of 0–100% MeCN (with 1 mL/L HCO_2H): H_2O (with 1 mL/L HCO_2H) at a flow rate of 3 mL/min and a run time of 2.8 min. Compounds were detected at 215 nm with a Diode Array G1315B detector.

2,2,2-Trifluoro-1-imidazo[1,5-*a*]pyridin-1ylethanones 4b–d, 4g, 4l, with α-Unbranched Aliphatic Substituents, from 2-Aminomethylpyridine in One Pot; General Procedure

2-Aminomethylpyridine (1.5 g, 13.9 mmol) and pyridine (4.72 g, 59.6 mmol) were dissolved in CH_2Cl_2 (20 mL) and the solution was cooled by using an ice bath. A solution of acyl chloride (14.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 to –5 °C. After the addition, the mixture was stirred for 15 min, then a solution of TFAA (6.41 g, 30.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –15 to –10 °C (ice-salt bath). The reaction mixture was allowed to stand overnight in the bath, then it was washed with sat. aq $NaHCO_3$, dried (Na_2SO_4) and evaporated, or it was first evaporated and then washed with sat. $NaHCO_3$ and filtered.

2,2,2-Trifluoro-1-(3-methylimidazo[1,5-*a*]pyridin-1-yl)ethanone (4b)

Yield: 2.85 g (90%); beige solid; mp 177 °C.

^{1}H NMR (DMSO-d_6): δ = 2.7 (s, 3 H), 7.26 (t, *J* = 6.6 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 8.20 (d, *J* = 8.8 Hz, 1 H), 8.59 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 12.3, 116.1, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.2, 121.6, 125.4, 130.2, 138.3, 139.2, 171.4 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 230 (8) $[M + 2]^+$, 229 (100) $[M + 1]^+$, 159 (10) $[M – CF_3]^+$.

2,2,2-Trifluoro-1-(3-ethylimidazo[1,5-*a*]pyridin-1-yl)ethanone (4c)

Yield: 3.09 g (92%); yellow solid; mp 149–150 °C.

^{1}H NMR (DMSO-d_6): δ = 1.35 (t, *J* = 7.4 Hz, 3 H), 3.08 (q, *J* = 7.4 Hz, 2 H), 7.26 (t, *J* = 6.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 8.23 (d, *J* = 8.8 Hz, 1 H), 8.66 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 10.5, 19.1, 116.2, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.4, 121.7, 125.2, 130.3, 138.5, 143.5, 171.5 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 244 (12) $[M + 2]^+$, 243 (100) $[M + 1]^+$, 173 (7) $[M – CF_3]^+$.

2,2,2-Trifluoro-1-(3-propylimidazo[1,5-*a*]pyridin-1-yl)ethanone (4d)

Yield: 3.38 g (95%); beige solid; mp 98–100 °C.

^{1}H NMR (DMSO-d_6): δ = 1.00 (t, *J* = 6.7 Hz, 3 H), 1.77–1.82 (m, 2 H), 3.05 (t, *J* = 6.5 Hz, 2 H), 7.25 (t, *J* = 6.6 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 8.68 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 13.5, 19.5, 27.4, 116.2, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.4, 121.8, 125.3, 130.3, 138.4, 142.4, 171.5 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 258 (12) $[M + 2]^+$, 257 (100) $[M + 1]^+$, 187 (4) $[M – CF_3]^+$.

2,2,2-Trifluoro-1-[3-(2-methylpropyl)imidazo[1,5-*a*]pyridin-1-yl]ethanone (4g)

Yield: 3.34 g (89%); yellow solid; mp 118 °C.

^{1}H NMR (DMSO-d_6): δ = 0.96 (d, *J* = 6.3 Hz, 6 H), 2.12–2.23 (m, 1 H), 2.98 (d, *J* = 7.0 Hz, 2 H), 7.25 (t, *J* = 6.6 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 8.23 (d, *J* = 8.8 Hz, 1 H), 8.73 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 22.1, 26.7, 34.0, 116.3, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 121.9, 125.4, 130.2, 138.3, 141.8, 171.6 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 272 (18) $[M + 2]^+$, 271 (100) $[M + 1]^+$, 201 (2) $[M – CF_3]^+$.

2,2,2-Trifluoro-1-[3-(2-phenylethyl)imidazo[1,5-*a*]pyridin-1-yl]ethanone(4l)

Yield: 4.19 g (95%); off-white powder; mp 99–101 °C.

^{1}H NMR (DMSO-d_6): δ = 3.14 (t, *J* = 7.2 Hz, 2 H), 3.38 (t, *J* = 7.2 Hz, 2 H), 7.13–7.29 (m, 4 H), 7.29–7.35 (m, 2 H), 7.63 (t, *J* = 7.6 Hz, 1 H), 8.23 (d, *J* = 8.8 Hz, 1 H), 8.65 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 27.5, 31.9, 113.42, 116.2, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.3, 121.8, 125.27, 126.1, 128.2, 128.6, 130.3, 138.4, 140.6, 141.8, 171.6 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 320 (19) $[M + 2]^+$, 319 (100) $[M + 1]^+$.

Synthesis of 2,2,2-Trifluoro-1-(3-alkyl(aryl)imidazo[1,5-*a*]-pyridine-1-yl)ethanones 4e, 4f, 4h–k, 4m, with Aromatic and α-Branched Aliphatic Substituents, from 2-Aminomethylpyridine in One Pot; General Procedure

2-(Aminomethyl)pyridine (1.5 g, 13.9 mmol) and pyridine (4.72 g, 59.6 mmol) were dissolved in CH_2Cl_2 (20 mL), and the solution was cooled by using an ice bath. A solution of acyl chloride (14.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 to 5 °C. After the addition, the mixture was stirred for 15 min, then placed in an acetone-dry ice bath and a solution of TFAA (6.41 g, 30.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –50 to –40 °C. The mixture was stirred at this temperature for 2 h, then stirred overnight. The reaction solution was washed with sat. aq $NaHCO_3$, the CH_2Cl_2 layer was dried over Na_2SO_4 and evaporated. The product was purified by crystallization from methanol.

2,2,2-Trifluoro-1-[3-(1-methylethyl)imidazo[1,5-*a*]pyridin-1-yl]ethanone (4e)

Yield: 2.95 g (83%); beige solid; mp 113 °C.

^{1}H NMR (DMSO-d_6): δ = 1.36 (d, *J* = 6.2 Hz, 6 H), 3.54–3.63 (m, *J* = 6.2 Hz, 1 H), 7.26 (t, *J* = 6.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 8.25 (d, *J* = 8.8 Hz, 1 H), 8.74 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 6.2, 6.8, 115.8, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.6, 121.7, 125.3, 130.4, 138.6, 146.9, 171.5 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 258 (13) $[M + 2]^+$, 257 (100) $[M + 1]^+$, 187 (7) $[M – CF_3]^+$.

1-(3-Cyclopropylimidazo[1,5-*a*]pyridin-1-yl)-2,2,2-trifluoroethanone (4f)

Yield: 2.86 g (81%); orange solid; mp 132–133 °C.

^{1}H NMR (DMSO-d_6): δ = 0.97–1.03 (m, 2 H), 1.08–1.16 (m, 2 H), 2.42–2.52 (m, 1 H), 7.26 (t, *J* = 6.6 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 8.17 (d, *J* = 8.8 Hz, 1 H), 8.79 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 6.2, 6.8, 116.3, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.4, 121.3, 125.0, 130.4, 138.6, 143.5, 171.4 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 256 (17) $[M + 2]^+$, 255 (100) $[M + 1]^+$, 185 (7) $[M – CF_3]^+$.

1-(3-*tert*-Butylimidazo[1,5-*a*]pyridin-1-yl)-2,2,2-trifluoroethanone (4h)

Yield: 2.89 g (77%); yellow solid; mp 157–158 °C.

^{1}H NMR (DMSO-d_6): δ = 1.52 (s, 1 H), 7.21 (t, *J* = 6.6 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 8.29 (d, *J* = 8.8 Hz, 1 H), 8.94 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 18.1, 25.8, 30.4, 116.3, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.5, 121.7, 125.2, 130.4, 138.6, 144.9, 171.6 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 272 (14) $[M + 2]^+$, 271 (100) $[M + 1]^+$.

1-(3-Cyclobutylimidazo[1,5-*a*]pyridin-1-yl)-2,2,2-trifluoroethanone (4i)

Yield: 2.94 g (79%); pale yellow solid; mp 126–128 °C.

^{1}H NMR (DMSO-d_6): δ = 1.89–2.00 (m, 1 H), 2.05–2.17 (m, 1 H), 2.36–2.48 (m, 4 H), 4.00–4.12 (m, 1 H), 7.22 (t, *J* = 6.6 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 8.48 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 18.1, 25.8, 30.4, 116.3, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.5, 121.7, 125.2, 130.4, 138.6, 144.9, 171.6 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 270 (15) $[M + 2]^+$, 269 (100) $[M + 1]^+$, 242 (2) $[M + 2 – CO]^+$, 241 (15) $[M + 1 – CO]^+$, 171 (9) $[M + 2 – CO – CF_3]^+$.

1-(3-Cyclopentylimidazo[1,5-*a*]pyridin-1-yl)-2,2,2-trifluoroethanone (4j)

Yield: 3.17 g (81%); yellow solid; mp 101 °C.

^{1}H NMR (DMSO-d_6): δ = 1.60–1.72 (m, 2 H), 1.72–1.83 (m, 2 H), 1.83–1.98 (m, 2 H), 2.06–2.21 (m, 2 H), 3.60–3.71 (m, 1 H), 7.23 (t, *J* = 6.6 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 8.68 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 25.1, 30.2, 35.4, 116.2, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.4, 121.5, 125.2, 130.2, 138.7, 145.7, 171.5 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 284 (17) $[M + 2]^+$, 283 (100) $[M + 1]^+$, 213 (2) $[M – CF_3]^+$.

1-(3-Cyclohexylimidazo[1,5-*a*]pyridin-1-yl)-2,2,2-trifluoroethanone (4k)

Yield: 3.41 g (83%); yellow solid; mp 117 °C.

^{1}H NMR (DMSO-d_6): δ = 1.20–1.35 (m, 1 H), 1.37–1.51 (m, 2 H), 1.51–1.64 (m, 2 H), 1.64–1.74 (m, 1 H), 1.74–1.87 (m, 2 H), 1.87–2.02 (m, 2 H), 3.20–3.32 (m, 1 H), 7.23 (t, *J* = 6.6 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 8.24 (d, *J* = 8.8 Hz, 1 H), 8.75 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 25.2, 25.4, 30.1, 34.0, 116.2, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.5, 121.8, 125.3, 130.2, 138.4, 146.1, 171.6 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 298 (23) $[M + 2]^+$, 297 (100) $[M + 1]^+$.

2,2,2-Trifluoro-1-(3-phenylimidazo[1,5-*a*]pyridin-1-yl)ethanone (4m)

Yield: 3.38 g (84%); yellow solid; mp 143 °C.

^{1}H NMR (DMSO-d_6): δ = 7.27 (t, *J* = 6.6 Hz, 1 H), 7.57–7.67 (m, 3 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 4.8 Hz, 2 H), 8.34 (d, *J* = 8.8 Hz, 1 H), 8.76 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 117.2, 117.2 (q, $^1J_{C–F}$ = 291.4 Hz), 118.6, 123.0, 125.6, 128.0, 128.9, 129.2, 130.1, 131.0, 139.0, 140.5, 172.1 (q, $^2J_{C–F}$ = 33.3 Hz).

MS: *m*/*z* (%) = 292 (17) $[M + 2]^+$, 291 (100) $[M + 1]^+$, 121 (1) $[M – CF_3]^+$.

2,2,2-Trifluoro-1-(imidazo[1,5-*a*]pyridyl)ethanones 4a and 4a′

N-(2-Pyridylmethyl)formamide[16] (1.5 g, 11 mmol) and pyridine (2.88 g, 36.4 mmol) were dissolved in CH_2Cl_2 (20 mL), and the solution was cooled by using an ice-salt bath. A solution of TFAA (5.09 g, 24.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –15 to –10 °C. The reaction mixture was allowed to stand overnight in the bath, then the solvent was evaporated and the residue was treated with sat. aq $NaHCO_3$, filtered, and washed with water. After drying, the mixture of the isomers was separated by column chromatography (SiO_2, CH_2Cl_2).

The synthesis of compounds **4a** and **4a′** was reported by Khodakovskiy,[17] but compound **4a** was not isolated.

2,2,2-Trifluoro-1-(imidazo[1,5-*a*]pyridin-1-yl)ethanone (4a)

Yield: 2.85 g (90%); yellow solid; mp 219–220 °C.

^{1}H NMR (DMSO-d_6): δ = 7.14 (t, *J* = 6.6 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 8.26 (d, *J* = 8.8 Hz, 1 H), 8.59 (s, 1 H), 8.76 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 117.1 (q, $^1J_{C–F}$ = 291.4 Hz), 116.5, 118.2, 122.8, 126.6, 130.9, 131.9, 137.6, 172.0 (q, $^2J_{C–F}$ = 33.3 Hz).

^{19}F NMR (pyridine-d_5): δ = –72.21.

2,2,2-Trifluoro-1-(imidazo[1,5-*a*]pyridin-3-yl)ethanone (4a′)

Yield: 2.85 g (90%); yellow solid; mp 143–144 °C (Lit.[17] 142–143).

^{1}H NMR (DMSO-d_6): δ = 7.41 (t, *J* = 6.6 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.96 (s, 1 H), 8.09 (d, *J* = 8.8 Hz, 1 H), 9.59 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 116.6, 117.1 (q, $^1J_{C–F}$ = 292.4 Hz), 118.2, 118.6, 122.8, 126.6, 130.9, 131.9, 137.7, 172.0 (q, $^2J_{C–F}$ = 33.3 Hz).

2,2,2-Trifluoro-1-(3-pyridylimidazo[1,5-*a*]pyridin-1-yl)ethanones 4n–p; General Procedure

2-Aminomethylpyridine (1.5 g, 13.9 mmol) and pyridine (4.72 g, 59.6 mmol) were dissolved in CH_2Cl_2 (20 mL), and the solution was cooled by using an ice bath. The hydrochloride of pyridine-carboxylic acid chloride (14.3 mmol) was added portionwise at 0 to 5 °C to the reaction mixture (for **4p** a solution of acyl chloride in CH_2Cl_2 was added). After the addition, the mixture was stirred for 15 min, then a solution of trifluoroacetic anhydride (6.41 g, 30.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –15 to –10 °C (ice-salt bath). The mixture was allowed to stand overnight in the bath, then washed with sat. aq $NaHCO_3$, dried over Na_2SO_4, and evaporated, or it was first evaporated, then washed with sat. aq $NaHCO_3$ and filtered.

2,2,2-Trifluoro-1-(3-pyridin-3-ylimidazo[1,5-*a*]pyridin-1-yl)ethanone (4n)

Yield: 3.35 g (83%); pale beige solid; mp 185 °C.

^{1}H NMR (DMSO-d_6): δ = 7.28 (t, J = 6.6 Hz, 1 H), 7.65 (t, J = 5.6 Hz, 1 H), 7.72 (t, J = 7.6 Hz, 1 H), 8.32 (d, J = 7.4 Hz, 1 H), 8.36 (d, J = 8.8 Hz, 1 H), 8.79 (d, J = 3.7 Hz, 1 H), 8.83 (d, J = 6.6 Hz, 1 H), 9.05 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 117.1 (q, $^1J_{C-F}$ = 291.4 Hz), 117.3, 118.5, 123.2, 124, 124.4, 125.8, 136.5, 138.0, 139.0, 149.3, 150.6, 171.6 (q, $^2J_{C-F}$ = 33.3 Hz).

MS: m/z (%) = 293 (15) $[M + 2]^+$, 292 (100) $[M + 1]^+$.

2,2,2-Trifluoro-1-(3-pyridin-4-ylimidazo[1,5-*a*]pyridin-1-yl)ethanone (4o)

Yield: 3.43 g (85%); yellow solid; mp 183 °C.

^{1}H NMR (DMSO-d_6): δ = 7.33 (t, J = 6.6 Hz, 1 H), 7.76 (t, J = 7.6 Hz, 1 H), 7.90 (d, J = 2.8 Hz, 2 H), 8.35 (d, J = 8.8 Hz, 1 H), 8.81 (d, J = 2.8 Hz, 2 H), 8.93 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 117.0 (q, $^1J_{C-F}$ = 291.4 Hz), 117.5, 118.6, 122.4, 123.5, 125.8, 131.0, 135.3, 137.7, 139.1, 150.4, 172.3 (q, $^2J_{C-F}$ = 33.3 Hz).

MS: m/z (%) = 293 (15) $[M + 2]^+$, 292 (100) $[M + 1]^+$.

1-[3-(2-Chloropyridin-4-yl)imidazo[1,5-*a*]pyridin-1-yl]-2,2,2-trifluoroethanone (4p)

Yield: 3.62 g (80%); yellow solid; mp 257–258 °C.

^{1}H NMR (DMSO-d_6): δ = 7.34 (t, J = 6.6 Hz, 1 H), 7.76 (t, J = 7.6 Hz, 1 H), 7.91 (d, J = 3.1 Hz, 1 H), 7.96 (s, 1 H), 8.33 (d, J = 8.8 Hz, 1 H), 8.63 (d, J = 3.1 Hz, 1 H), 8.95 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 116.9 (q, $^1J_{C-F}$ = 291.4 Hz), 117.7, 118.4, 118.6, 122.0, 122.7, 123.5, 126.2, 131.5, 136.6, 138.8, 139.2, 150.8, 151.1, 172.0 (q, $^2J_{C-F}$ = 33.3 Hz).

MS: m/z (%) = 327 (5) $[M + 3]^+$, 326 (31) $[M + 2]^+$, 327 (16) $[M + 1]^+$, 326 (100) $[M]^+$.

3-(Trifluoromethyl)imidazo[1,5-*a*]pyridine (3q)

2-(Aminomethyl)pyridine (1.5 g, 13.9 mmol) and pyridine (4.72 g, 59.6 mmol) were dissolved in CH_2Cl_2 (35 mL), and the solution was cooled to –50 °C. A solution of TFAA (3.00 g, 14.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise at –10 to –5 °C, then a solution of trifluoroacetic anhydride (3.12 g, 14.9 mmol) in CH_2Cl_2 (15 mL) was added dropwise at –50 to –55 °C. The reaction mixture was allowed to stand at the same temperature for 1 h, then washed with sat. aq $NaHCO_3$, dried over Na_2SO_4, and evaporated.

Yield: 2.43 g (94%); pale yellow liquid.

^{1}H NMR (DMSO-d_6): δ = 7.00 (t, J = 6.6 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.63 (s, 1 H), 7.80 (d, J = 8.8 Hz, 1 H), 8.39 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 115.6, 118.5, 119.8 (q, $^1J_{C-F}$ = 267.6 Hz), 120.4, 121.8, 122.2 (q, $^3J_{C-F}$ = 2.1 Hz), 124.1 (q, $^2J_{C-F}$ = 40.1 Hz), 132.9.

^{19}F NMR (DMSO-d_6): δ = –62.07.

2,2,2-Trifluoro-1-[3-(trifluoromethyl)imidazo[1,5-*a*]pyridin-1-yl]ethanone (4q)

2-(Aminomethyl)pyridine (1.5 g, 13.9 mmol) and pyridine (4.72 g, 59.6 mmol) were dissolved in CH_2Cl_2 (20 mL), and the solution was cooled by using ice-salt bath. A solution of trifluoroacetic anhydride (9.32 g, 44.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –15 to –10 °C and the mixture was allowed to stand overnight in the bath. The solvent was evaporated and the residue was treated with sat. aq $NaHCO_3$, filtered, and washed with water.

Yield: 3.75 g (96%); white solid; mp 125 °C.

^{1}H NMR (DMSO-d_6): δ = 7.48 (t, J = 6.4 Hz, 1 H), 7.85 (t, J = 7.6 Hz, 1 H), 7.38 (d, J = 8.8 Hz, 1 H), 8.81 (d, J = 6.2 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 116.5 (q, $^1J_{C-F}$ = 290.9 Hz), 118.5 (q, $^1J_{C-F}$ = 269.5 Hz), 118.8, 118.9, 122.4, 125.4, 126.9 (q, $^2J_{C-F}$ = 40.1 Hz), 132.0, 139.0, 172.7 (q, $^2J_{C-F}$ = 34.0 Hz).

^{19}F NMR (DMSO-d_6): δ = –62.83, –72.25.

MS: m/z (%) = 284 (11) $[M + 2]^+$, 283 (100) $[M + 1]^+$.

Ethyl Imidazo[1,5-*a*]pyridine-3-carboxylate (3s)

2-(Aminomethyl)pyridine (1.5 g, 13.9 mmol) and pyridine (3.62 g, 45.8 mmol) were dissolved in CH_2Cl_2 (20 mL), and the solution was cooled by using an ice bath. A solution of ethyl oxalyl chloride (1.89 g, 13.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 to –5 °C. After addition, the mixture was stirred for 2 h and a solution of TFAA (3.06 g, 14.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –15 to –10 °C (ice-salt bath). The reaction mixture was allowed to stand overnight in the bath, then washed with sat. aq $NaHCO_3$, and the CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated.

Yield: 2.4 g (91%); white solid; mp 80 °C (Lit.[13] 80 °C).

The ^{1}H and ^{13}C NMR spectroscopic data were identical to those reported previously.[4,14,18]

Ethyl (1-Trifluoroacetyl)imidazo[1,5-*a*]pyridine-3-carboxylate (4s)

2-(Aminomethyl)pyridine (1.5 g, 13.9 mmol) and pyridine (5.55 g, 59.6 mmol) were dissolved in MeCN (30 mL), and the solution was cooled by using an ice bath. A solution of ethyl oxalyl chloride (1.89 g, 13.9 mmol) in MeCN (10 mL) was added dropwise at 0 to –5 °C. After the addition, the mixture was stirred for 2 h and a solution of TFAA (6.41 g, 30.5 mmol) in MeCN (15 mL) was added dropwise at –15 to –10 °C (ice-salt bath). The reaction mixture was allowed to stand overnight in the bath, then the mixture was poured in sat. aq sodium hydrocarbonate, filtered, and washed with water.

Yield: 3.77 g (95%); yellow solid; mp 225 °C.

^{1}H NMR (DMSO-d_6): δ = 1.40 (t, J = 6.6 Hz, 3 H), 4.48 (q, J = 6.6 Hz, 2 H), 7.51 (t, J = 6.6 Hz, 1 H), 7.86 (t, J = 7.6 Hz, 1 H), 8.40 (d, J = 8.8 Hz, 1 H), 9.45 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 14.2, 61.7, 116.6 (q, $^1J_{C-F}$ = 290.7 Hz), 118.5, 118.6, 123.1, 128.0, 129.1, 132.2, 139.0, 158.4, 172.9 (q, $^2J_{C-F}$ = 33.9 Hz).

MS: m/z (%) = 288 (14) $[M + 2]^+$, 287 (100) $[M + 1]^+$, 259 (3) $[M + 2 – CO]^+$, 242 (3) $[M + 2 – C_2H_5OH]^+$, 241 (23) $[M + 1 – C_2H_5OH]^+$.

3-Alkylimidazo[1,5-*a*]pyridine-1-carboxylic acids 5b–f; General Procedure

1-(3-Alkylimidazo[1,5-*a*]pyridine-1-yl)-2,2,2-trifluoroethanone **4b–f** (6 mmol) was dissolved in MeOH (20 mL), and a solution of NaOH (1.2 g, 30 mmol) in water (20 mL) was added. The mixture was heated at reflux for 1 h and, after cooling, MeOH was evaporated. HCl (3%) was added dropwise to the aqueous solution under cooling and stirring to obtain pH 5.3, then the solution was evaporated to dryness. The mixture was heated to reflux in 15% solution of CH_2Cl_2 in MeOH and filtered. The filter cake was washed with the hot solution mentioned above. The solvent was evaporated to give the desired product.

3-Methylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5b)

Yield: 0.69 g (65%); beige solid; mp 223–224 °C.

^{1}H NMR (DMSO-d_6): δ = 2.63 (s, 1 H), 6.92 (t, J = 6.6 Hz, 1 H), 7.19 (t, J = 7.6 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 8.29 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 12.2, 113.5, 118.6, 119.1, 123.5, 124.2, 133.9, 136.5, 164.0.

MS: m/z (%) = 178 (6) [M + 2]$^+$, 177 (70) [M + 1]$^+$, 160 (11) [M + 2 – H_2O]$^+$, 159 (100) [M + 1 – H_2O]$^+$, 131 (7) [M + 1 – H_2O – CO]$^+$, 105 (5) [M + 1 – H_2O – CO – C_2H_2]$^+$.

3-Ethylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5c)

Yield: 0.82 g (72%); light-brown solid; mp 167–169 °C.

^{1}H NMR (DMSO-d_6): δ = 1.33 (t, J = 7.4 Hz, 3 H), 2.99 (q, J = 7.4 Hz, 2 H), 6.9 (t, J = 6.6 Hz, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 8.32 (d, J = 6.6 Hz, 1 H), 12.06 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 10.9, 19.2, 113.44, 118.7, 119.4, 123.2, 124.1, 134.1, 140.9, 164.3.

MS: m/z (%) = 192 (11) [M + 2]$^+$, 191 (100) [M + 1]$^+$, 174 (12) [M + 2– H_2O]$^+$, 173 (96) [M + 1 – H_2O]$^+$, 145 (5) [M + 1 – H_2O – CO]$^+$, 105 (6) [M + 1 – H_2O – CO – C_3H_4]$^+$.

The synthesis of this substance was reported by Bermudez,[19] without any characterization.

3-Propylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5d)

Yield: 0.98 g (80%); light-brown solid; mp 145–146 °C.

^{1}H NMR (DMSO-d_6): δ = 0.94 (t, J = 6.8 Hz, 3 H), 1.71–1.83 (m, J = 7.2 Hz, 2 H), 2.96 (t, J = 7.1 Hz, 2 H), 6.87 (t, J = 6.6 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 8.35 (d, J = 6.6 Hz, 1 H), 12.18 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 13.7, 19.9, 27.5, 113.4, 118.7, 119.6, 123.3, 124.0, 134.8, 139.8, 164.3.

MS: m/z (%) = 206 (14) [M + 2]$^+$, 205 (100) [M + 1]$^+$, 188 (12) [M + 2 – H_2O]$^+$, 187 (96) [M + 1 – H_2O]$^+$, 159 (2) [M + 1 – H_2O – CO]$^+$.

3-(1-Methylethyl)imidazo[1,5-*a*]pyridine-1-carboxylic Acid (5e)

Yield: 0.94 g (77%); beige solid; mp 182–183 °C.

^{1}H NMR (DMSO-d_6): δ = 1.32 (d, J = 6.2 Hz, 6 H), 3.45–3.56 (m, J = 6.2 Hz, 1 H), 6.89 (t, J = 6.6 Hz, 1 H), 7.16 (t, J = 8.8 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 8.39 (d, J = 6.6 Hz, 1 H), 12.08 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 20.4, 25.0, 113.4, 118.8, 119.4, 123.1, 123.9, 134.0, 144.3, 164.2.

MS: m/z (%) = 206 (12) [M + 2]$^+$, 205 (100) [M + 1]$^+$, 188 (8) [M + 2 – H_2O]$^+$, 187 (70) [M + 1 – H_2O]$^+$, 159 (2) [M + 1 – H_2O – CO]$^+$.

3-Cyclopropylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5f)

Yield: 0.92 g (90%); brown solid; mp 175–176 °C.

^{1}H NMR (DMSO-d_6): δ = 0.88–0.99 (m, 2 H), 0.99–1.11 (m, 2 H), 2.29–2.42 (m, 1 H), 6.91 (t, J = 6.6 Hz, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 1 H), 8.52 (d, J = 6.6 Hz, 1 H), 12.16 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 6.3, 6.7, 113.6, 118.8, 119.1, 123.0, 124.2, 134.2, 141.0, 164.1.

MS: m/z (%) = 204 (13) [M + 2]$^+$, 203 (100) [M + 1]$^+$, 186 (10) [M + 2 – H_2O]$^+$, 185 (83) [M + 1 – H_2O]$^+$, 157 (6) [M + 1 – H_2O – CO]$^+$, 105 (3) [M + 1 – H_2O – CO – C_4H_4]$^+$.

The synthesis of this substance was reported by Trotter,[4] without any characterization.

3-Alkyl(aryl)imidazo[1,5-*a*]pyridine-1-carboxylic Acids 5g–q,s; General Procedure

2,2,2-Trifluoro-1-imidazo[1,5-*a*]pyridin-1-ylethanone (6 mmol) was dissolved in MeOH (20 mL) and a solution of NaOH (1.2 g, 30 mmol) in water (20 mL) was added. The mixture was heated at reflux for 1 h, then MeOH was evaporated, 10% aq citric acid was added dropwise to the aqueous residue under cooling and stirring until precipitate was obtained. The solid was filtered and washed with cold water three times. The product was dried on air at 50–60 °C.

3-(2-Methylpropyl)imidazo[1,5-*a*]pyridine-1-carboxylic Acid (5g)

Yield: 1.11 g (85%); brown solid; mp 141–143 °C.

^{1}H NMR (DMSO-d_6): δ = 0.93 (d, J = 6.3 Hz, 6 H), 2.08–2.20 (m, 1 H), 2.89 (d, J = 7.0 Hz, 2 H), 6.87 (t, J = 6.6 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 8.39 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 22.27, 26.97, 27.34, 113.4, 118.8, 119.9, 123.4, 123.9, 133.9, 139.3, 164.4.

MS: m/z (%) = 220 (13) [M + 2]$^+$, 219 (100) [M + 1]$^+$, 202 (6) [M + 2 – H_2O]$^+$, 201 (54) [M + 1 – H_2O]$^+$, 173 (2) [M + 1 – H_2O – CO]$^+$.

3-*tert*-Butylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5h)

Yield: 1.22 g (93%); beige solid; mp 298 °C (dec.).

^{1}H NMR (CF_3CO_2D): δ = 1.52 (s, 1 H), 7.16 (t, J = 6.6 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 1 H), 8.13 (d, J = 8.8 Hz, 1 H), 8.4 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (CF_3CO_2D): δ = 27.8, 36.4, 112.6, 121.5, 121.9, 126.3, 123.17, 132.5, 137.5, 149.6, 163.8.

MS: m/z (%) = 220 (12) [M + 2]$^+$, 219 (100) [M + 1]$^+$, 202 (5) [M + 2 – H_2O]$^+$, 201 (36) [M + 1 – H_2O]$^+$, 105 (3).

3-Cyclobutylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5i)

Yield: 1.08 g (83%); off-white solid; mp 177–179 °C.

^{1}H NMR (DMSO-d_6): δ = 1.87–1.98 (m, 1 H), 2.01–2.15 (m, 1 H), 2.37–2.49 (m, 4 H), 3.90–4.02 (m, 1 H), 6.86 (t, J = 6.6 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 1 H), 8.19 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 18.3, 26.2, 30.5, 113.5, 118.9, 119.8, 123.2, 124.1, 134.1, 142.4, 164.4.

MS: m/z (%) = 218 (12) [M + 2]$^+$, 217 (100) [M + 1]$^+$, 200 (12) [M + 2 – H_2O]$^+$, 199 (48) [M + 1 – H_2O]$^+$, 171 (10) [M + 1 – H_2O – CO]$^+$.

3-Cyclopentylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5j)

Yield: 1.2 g (87%); white solid; mp 180–183 °C.

^{1}H NMR (DMSO-d_6): δ = 1.60–1.74 (m, 2 H), 1.74–1.85 (m, 2 H), 1.85–1.99 (m, 2 H), 2.03–2.17 (m, 2 H), 3.48–3.60 (m, 1 H), 6.79 (t, J = 6.6 Hz, 1 H), 7.01 (t, J = 7.6 Hz, 1 H), 8.06 (d, J = 8.8 Hz, 1 H), 8.29 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 25.2, 30.4, 35.6, 113.1, 119.3, 122.9, 133.3, 142.5, 165.4.

MS: m/z (%) = 232 (14) [M + 2]$^+$, 231 (100) [M + 1]$^+$, 214 (5) [M + 2 – H_2O]$^+$, 213 (41) [M + 1 – H_2O]$^+$.

3-Cyclohexylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5k)

Yield: 1.3 g (89%); beige solid; mp 189–190 °C.

^{1}H NMR (DMSO-d_6): δ = 1.16–1.32 (m, 1 H), 1.32–1.48 (m, 2 H), 1.48–1.62 (m, 2 H), 1.62–1.71 (m, 1 H), 1.71–1.83 (m, 2 H), 1.83–2.00 (m, 2 H), 3.10–3.23 (m, 1 H), 6.79 (t, J = 6.6 Hz, 1 H), 7.01 (t, J = 7.6 Hz, 1 H), 8.06 (d, J = 8.8 Hz, 1 H), 8.29 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 25.6, 25.7, 30.5, 34.3, 113.4, 119.0, 120.0, 123.2, 123.9, 133.8, 143.7, 164.6.

MS: *m*/*z* (%) = 246 (17) [M + 2]$^+$, 245 (100) [M + 1]$^+$, 228 (6) [M + 2 – H_2O]$^+$, 227 (34) [M + 1 – H_2O]$^+$.

3-(2-Phenylethyl)imidazo[1,5-*a*]pyridine-1-carboxylic Acid (5l)

Yield: 1.47 g (92%); off-white powder; mp 175–177 °C.

^{1}H NMR (DMSO-d_6): δ = 3.11 (t, *J* = 7.2 Hz, 2 H), 3.29 (t, *J* = 7.2 Hz, 2 H), 6.85 (t, *J* = 6.6 Hz, 1 H), 7.11–7.21 (m, 2 H), 7.21–7.33 (m, 4 H), 7.99 (d, *J* = 8.8 Hz, 1 H), 8.33 (d, *J* = 6.6 Hz, 1 H), 12.23 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 27.6, 32.4, 113.4, 118.7, 119.6, 123.3, 124.1, 126.1, 128.3, 128.5, 134.1, 139.3, 141.0, 164.2.

MS: *m*/*z* (%) = 268 (12) [M + 2]$^+$, 267 (100) [M + 1]$^+$, 250 (5) [M + 2 – H_2O]$^+$, 249 (31) [M + 1 – H_2O]$^+$.

3-Phenylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5m)

Yield: 1.29 g (90%); off-white powder; mp 105–108 °C.

^{1}H NMR (DMSO-d_6): δ = 6.94 (t, *J* = 6.6 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.47–7.62 (m, 3 H), 7.76–7.83 (m, 2 H), 8.11 (d, *J* = 8.8 Hz, 1 H), 8.53 (d, *J* = 6.6 Hz, 1 H), 12.41 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 114.7, 119.1, 121.4, 123.5, 125.0, 128.4, 129.1, 129.1, 129.3, 134.9, 138.2, 164.2.

MS: *m*/*z* (%) = 240 (16) [M + 2]$^+$, 239 (100) [M + 1]$^+$, 222 (7) [M + 2 – H_2O]$^+$, 221 (44) [M + 1 – H_2O]$^+$, 193 (5) [M + 1 – H_2O – CO]$^+$.

The synthesis of this substance was reported by Kamal[7b] without any characterization.

3-Pyridin-3-ylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5n)

Yield: 1.26 g (88%); pale yellow solid; mp 251–253 °C.

^{1}H NMR (DMSO-d_6): δ = 6.98 (t, *J* = 6.6 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.61 (t, *J* = 5.6 Hz, 1 H), 8.14 (d, *J* = 8.8 Hz, 1 H), 8.28 (d, *J* = 7.4 Hz, 1 H), 8.61 (d, *J* = 6.6 Hz, 1 H), 8.71 (d, *J* = 3.7 Hz, 1 H), 9.04 (s, 1 H), 12.51 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 115.0, 119.0, 121.9, 123.7, 124.0, 125.3, 125.5, 135.2, 135.7, 135.8, 148.9, 149.9, 164.1.

MS: *m*/*z* (%) = 241 (15) [M + 2]$^+$, 240 (100) [M + 1]$^+$, 223 (4) [M + 2 – H_2O]$^+$, 222 (32) [M + 1 – H_2O]$^+$, 194 (2) [M + 1 – H_2O – CO]$^+$.

3-Pyridin-4-ylimidazo[1,5-*a*]pyridine-1-carboxylic Acid (5o)

Yield: 1.15 g (80%); yellow solid; mp 245–247 °C.

^{1}H NMR (DMSO-d_6): δ = 7.06 (t, *J* = 6.6 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.92 (d, *J* = 2.8 Hz, 2 H), 8.2 (d, *J* = 8.8 Hz, 1 H), 8.67–8.81 (m, 3 H), 12.65 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 115.4, 119.1, 122.0, 122.3, 124.0, 125.7, 135.3, 135.6, 136.4, 150.4, 164.0.

MS: *m*/*z* (%) = 241 (13) [M + 2]$^+$, 240 (100) [M + 1]$^+$, 222 (2) [M + 1 – H_2O]$^+$, 197 (1) [M + 2 – H_2O – C_2H_2]$^+$, 196 (7) [M + 1 – H_2O – C_2H_2]$^+$.

3-(2-Chloropyridin-4-yl)imidazo[1,5-*a*]pyridine-1-carboxylic Acid (5p)

Yield: 1.48 g (90%); pale yellow solid; mp 255–257 °C.

^{1}H NMR (DMSO-d_6): δ = 7.08 (t, *J* = 6.6 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 2.8 Hz, 1 H), 7.97 (s, 1 H), 8.17 (d, *J* = 8.8 Hz, 1 H), 8.57 (d, *J* = 2.8 Hz, 1 H), 8.80 (d, *J* = 6.6 Hz, 1 H), 12.67 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 114.7, 119.1, 121.4, 123.5, 125.0, 128.4, 129.1, 129.1, 129.3, 134.9, 138.2, 164.2.

MS: *m*/*z* (%) = 275 (17) [M + 2]$^+$, 274 (100) [M + 1]$^+$, 255 (6) [M + 2 – H_2O]$^+$, 256 (32) [M + 1 – H_2O]$^+$, 230 (2) [M + 1 – H_2O – CO]$^+$.

3-(Trifluoromethyl)imidazo[1,5-*a*]pyridine-1-carboxylic Acid (5q)

Yield: 1.3 g (94%); white solid; mp 277 °C.

^{1}H NMR (DMSO-d_6): δ = 7.21 (t, *J* = 6.3 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 8.57 (d, *J* = 6.3 Hz, 1 H), 12.93 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 116.8, 119.2, 119.2 (q, $^1J_{C–F}$ = 266.0 Hz), 121.7, 123.6, 125.0 (q, $^2J_{C–F}$ = 41.0 Hz), 126.8, 135.7, 163.3.

^{19}F NMR (DMSO-d_6): δ = –62.46.

MS: *m*/*z* (%) = 178 (6) [M + 2]$^+$, 177 (70) [M + 1]$^+$, 160 (11) [M + 2 – H_2O]$^+$, 159 (100) [M + 1 – H_2O]$^+$, 131 (7), 105 (5).

Imidazo[1,5-*a*]pyridine-1,3-dicarboxylic Acid (5s)

Yield: 1 g (81%); white solid; mp >300 °C.

^{1}H NMR (CF_3CO_2D): δ = 7.67 (t, *J* = 4.9 Hz, 1 H), 7.92 (t, *J* = 7.4 Hz, 1 H), 8.57 (d, *J* = 8.4 Hz, 1 H), 9.52 (d, *J* = 4.9 Hz, 1 H).

^{13}C NMR (CF_3CO_2D): δ = 117.0, 121.9, 124.4, 126.6, 128.5, 134.6, 137.6, 158.0, 163.1.

MS: *m*/*z* (%) = 208 (12) [M + 2]$^+$, 207 (100) [M + 1]$^+$, 189 (8) [M + 2 – H_2O]$^+$, 190 (54) [M + 1 – H_2O]$^+$, 146 (3) [M + 1 – H_2O – CO_2]$^+$, 145 (21) [M + 1 – H_2O – CO_2]$^+$, 117 (10) [M + 1 – H_2O – CO_2 – CO]$^+$.

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Supporting Information

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Primary Data

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