Three-component solvent-free synthesis of highly substituted bicyclic pyridines containing a ring-junction nitrogen†

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An efficient one-pot, three-component synthesis of highly substituted bicyclic pyridines containing a ring-junction nitrogen, starting from simple and readily available materials, is described. Cyclocondensation of heterocyclic ketene aminals (HKAs), triethoxymethane, and active methylene compounds by refluxing under solvent-free and catalyst-free conditions, provided bicyclic pyridines in excellent yields.

Introduction

Nowadays, one of the pivotal areas in green chemistry is searching for environmentally benign reaction media to replace the commonly used organic solvents in chemical processes.[1] In this context, solvent-free processes for organic transformations would be promising from the viewpoint of green chemistry and sustainable development.[2]

Conventional step-by-step synthetic methods cannot meet the demands of high-throughput screening,[3] which constrains the synthesis of potential therapeutic agents and drug research and development. To meet these demands, combinatorial methods of synthesis have been developed among which the parallel synthesis of single compounds now plays a prominent role. Multicomponent reactions (MCRs)[4] are particularly attractive for parallel synthesis because large arrays of compounds with diverse substitution patterns can be prepared in one step from relatively simple starting materials.[5] MCRs have significant advantages over classical step-by-step approaches not only from an atom economy and environmentally friendly viewpoint, but also because they have straightforward experimental procedures.

Bicyclic pyridines containing a ring-junction nitrogen are a common structural motif in a wide range of natural products and pharmacologically active molecules, such as antiviral,[6] antibacterial,[7] herbicidal,[8] antifungal,[9] antitumor (NSC649900 and NSC682011, Fig. 1)[10] and antiulcer agents (zolimidine, Fig. 1),[11] β-amyloid formation inhibitors (zolpidem, Fig. 1),[12] ACE inhibitors (A58365A and A58365B, Fig. 1),[13] human rhinovirus 3C protease inhibitors,[14] α,β-peptide aggregation inhibitors,[15] agonists of benzodiazepine receptor,[16] calcium channel blockers,[17] cyclin-dependent kinases inhibitors,[18] GABAA receptor modulators,[19] and so on.[20] Therefore, considerable attention has been paid to developing efficient methods for the synthesis of these kinds of bicyclic pyridines. The synthetic routes to these compounds have been revised in detailed by Hamama[21] and others.[22] Although various approaches for the preparation of the bicyclic pyridines containing a ring-junction nitrogen framework have been developed by a number of organic or pharmaceutical chemists,[23–25] the environmentally friendly and highly selective one-pot solvent-free preparation for these highly substituted bicyclic pyridines has rarely been studied.

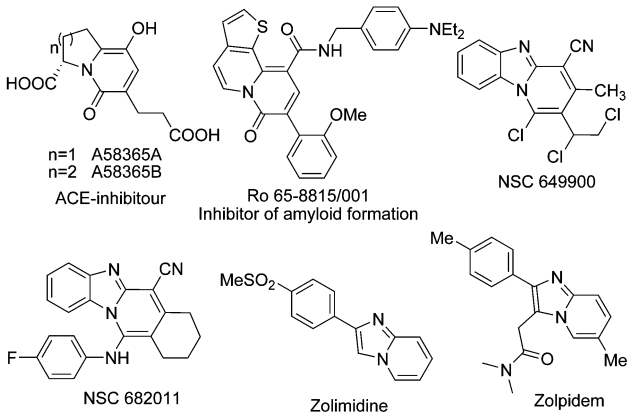

Fig. 1 The natural products and synthetic compounds of medicinal interest that possess a bicyclic pyridine framework.

Heterocyclic ketene aminals (HKAs) have been frequently found as pharmacophores and could play important roles in drug discovery. As a type of versatile synthetic intermediate, HKAs have been used for the synthesis of a wide variety of heterocyclic and fused heterocyclic compounds,[23,24] including herbicides, pesticides,[26] anticancer agents,[23] anti-anxious agents,[27] antileishmanial agents[28] and antibacterial and antitherapeutic drugs.[29]

Results and discussion

MCRs can be used to synthesize a number of drug-like scaffold compounds in a single step, simply by varying the reaction substrates. HKAs are rarely used in MCRs. In this paper, we wish to report a novel method to synthesize bicyclic pyridine derivatives **4** by refluxing HKAs **1**, triethoxymethane

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† Electronic supplementary information (ESI) available: General procedures and spectroscopic data, including copies of ^{1}H and ^{13}C NMR spectra. CCDC reference number 784140. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0gc00373e

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2 and active methylene compounds **3** under solvent-free and conditions with no catalyst, forming the target compounds with excellent yields (Table 1).

In the initial stage, an easily available starting material, 2-(nitromethylene)imidazolidine **1a** was reacted with triethoxymethane **2** and ethyl 4,4,4-trifluoro-3-oxobutanoate **3** in one-pot, under solvent-free and catalyst-free conditions. After refluxing for only 30 min, the reaction successfully produced the bicyclic pyridines **4a** with an excellent yield (94%) (Table 1, entry 1). The product was carefully identified by spectroscopic data and high-resolution mass spectroscopy.

To explore the scope and limitations of this method, HKAs **1a–o**, *N*,*O*-acetals **1p–r** and *N*,*S*-acetals **1s–v** were used as substrates to react with triethoxymethane **2** and ethyl 4,4,4-trifluoro-3-oxobutanoate **3** (Table 1, entries 1–15, 16–18 and 19–22, respectively). The results demonstrated that HKAs, with various substituents and different ring sizes, were all good substrates for the one-pot cyclocondensation reaction (Table 1, entries 1–15). The reactions usually took 30–60 min at reflux until completion and gave the products with excellent yields.

To verify the structure of the product bicyclic pyridines, **4m** was selected as a representative compound and characterized by X-ray crystallography as shown in Fig. 2 (CCDC 784140).[30]

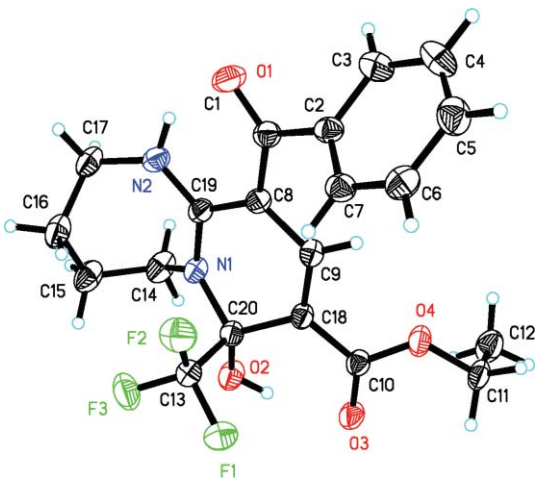
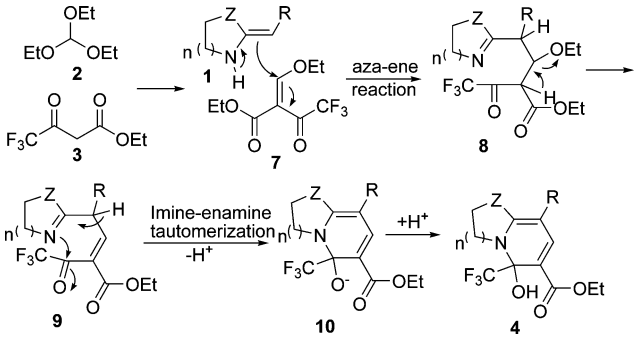


Fig. 2 ORTEP diagram of ethyl 7-hydroxy-10-(4-methyl-benzoyl)-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*]-[1,3]diazepine-8-carboxylate (**4m**); ellipsoids are drawn at 30% probability level.

A proposed mechanism for the three-component reaction is depicted in Scheme 1. Triethoxymethane **2** reacted with ethyl 4,4,4-trifluoro-3-oxobutanoate **3** to form ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate **7**. Then, **7** reacted with an HKA **1** possibly *via* an aza–ene[31] mechanism to obtain **8**. Then, intermediate **8** removed the ethanol to give **9**. Compound **9** underwent a process of imine–enamine tautomerization and cyclization to form **10**. Finally, **10** formed the final product **4**.

The scope of this synthetic method was extended to other active methylene compounds such as diethyl malonate **5a** and ethyl 2-cyanoacetate **5b**. The results are summarized in Table 2. This demonstrated that diethyl malonate **5a** and ethyl 2-cyanoacetate **5b** were also good substitutes in this synthetic procedure (Table 2, entries 1–3 *vs.* 4–6).



Scheme 1 Proposed mechanism for the three-component reaction.

The *E* factors are about 0.57–0.88 for the synthesis of compounds **4** and **6**.

Preliminary results for biological activity against human tumor cell lines[32] according to the literature[33] showed the target compounds **4** possess good anticancer activities against the K562, HL60 (see supplementary information†). It demonstrated that this concise and environmentally friendly process has great potential to be applied to parallel synthesis in drug discovery.

Conclusions

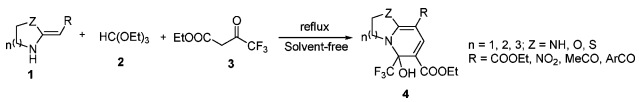
To summarize, we have achieved the one-pot, three-component synthesis of highly functional bicyclic pyridines containing a ring-junction nitrogen under solvent-free and catalyst-free conditions. Using different types of HKAs or *N*,*O*-acetals or *N*,*S*-acetals and different kinds of active methylene compounds, such as 4,4,4-trifluoro-3-oxobutanoate, diethyl malonate and ethyl 2-cyanoacetate with triethoxymethane, as building blocks, we could construct novel libraries of highly substituted bicyclic pyridines that make this method suitable for combinatorial and parallel synthesis in drug discovery. Consequently, a library of bicyclic pyridine derivatives was rapidly constructed using this protocol. On the other hand, the generality with respect to the substrate scope, facile accessibility to the starting materials is also highly appealing.

Experimental

General information

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, $CDCl_3$ and DMSO-d_6 were used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMS were performed on an Agilent LC/MSD TOF instrument. All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh). The raw materials **1a**–**1w** were synthesized according to the literature.[34–37]

Table 1 One-pot synthesis of bicyclic pyridine derivatives **4** under solvent-free conditions



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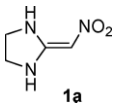
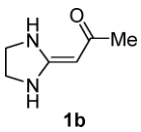
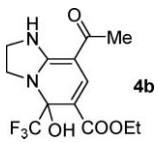
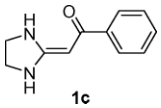
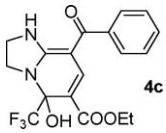
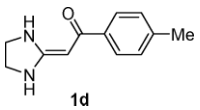
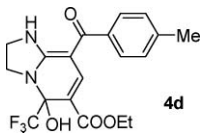
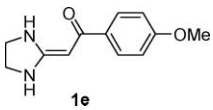
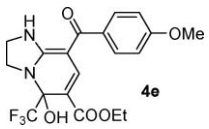
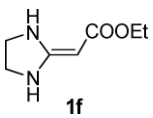
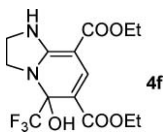
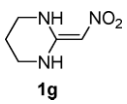
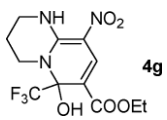
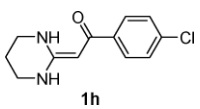
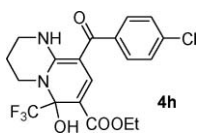
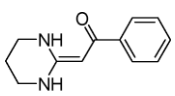
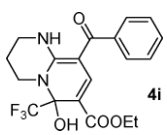
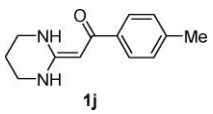
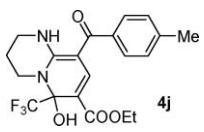
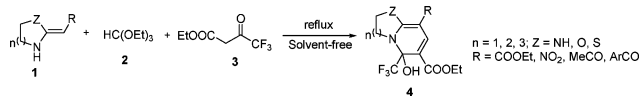
1	 **1a**	 **4a**	30	94
2	 **1b**	 **4b**	41	87
3	 **1c**	 **4c**	35	90
4	 **1d**	 **4d**	36	90
5	 **1e**	 **4e**	33	93
6	 **1f**	 **4f**	32	92
7	 **1g**	 **4g**	34	92
8	 **1h**	 **4h**	50	82
9	 **1i**	 **4i**	44	89
10	 **1j**	 **4j**	45	89

Table 1 *(Contd.)*



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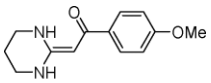
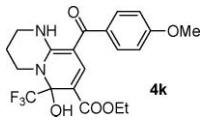
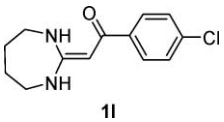
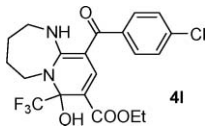
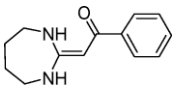
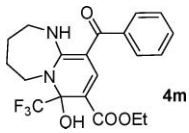
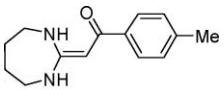
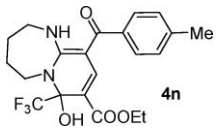
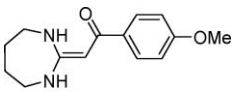
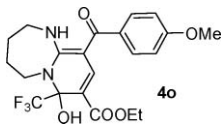
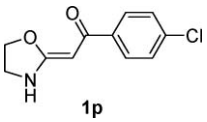
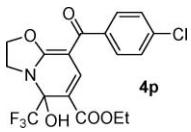
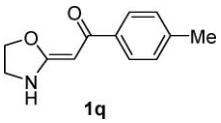
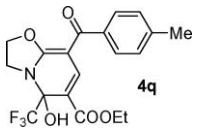
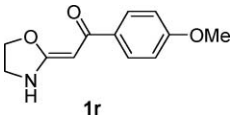
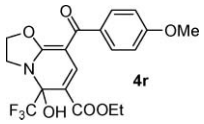
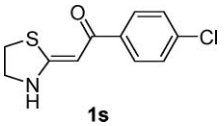
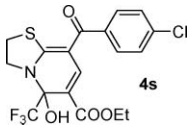
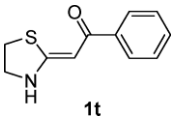
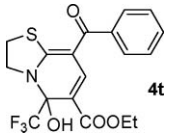
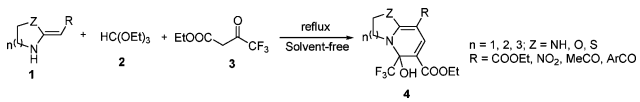
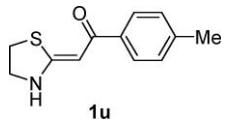
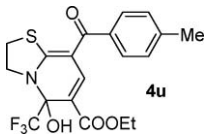
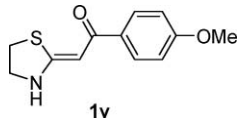
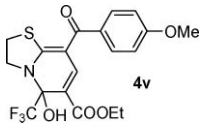
11	 1k	 4k	40	91
12	 1l	 4l	59	78
13	 1m	 4m	46	81
14	 1n	 4n	45	86
15	 1o	 4o	40	88
16	 1p	 4p	55	83
17	 1q	 4q	50	84
18	 1r	 4r	48	86
19	 1s	 4s	39	89
20	 1t	 4t	34	93

Table 1 *(Contd.)*



1 2 3 4

Entry	1	4	Time/min	Yield (%)[a,b]
21	 1u	 4u	33	91
22	 1v	 4v	30	94

[a] Isolated yields after silica gel chromatography. [b] Yield of isolated product from reaction on a 2.5 mmol scale.

General procedure

HKAs derivatives **1** (2.5 mmol), triethoxymethane **2** (3 mmol) and active methylene compounds (ethyl 4,4,4-trifluoro-3-oxobutanoate **3** or diethyl malonate **5a** or ethyl 2-cyanoacetate **5b**) (3 mmol) were placed into a 25 mL round-bottom flask and the mixture was refluxed. The resulting solution was stirred for 1–3 h until the HKAs derivatives **1** were completely consumed. The mixture was diluted with EtOAc (50 mL × 2) and quenched with water (50 mL). The organic layer was dried by Na_2SO_4, concentrated, and purified by flash column chromatography (petroleum ether/EtOAc = 6/1) to afford product **4** or **6** with 78-94% yield. The products were further identified by FTIR, NMR and HRMS, being in good agreement with the assigned structures.

Ethyl 5-hydroxy-8-nitro-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate (4a). Yellow solid; Mp 187–192 °C; IR (KBr): 3358, 3086, 1675, 1597, 1460, 1385, 1207, 1078, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3H, CH_3), 3.92–4.16 (m, 4H, NCH_2CH_2N), 4.28–4.30 (m, 2H, OCH_2), 7.74 (s, 1H, CH), 8.32 (br, 1H, OH), 8.36 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 43.9, 44.8, 62.2, 84.5 (d, J = 35.0 Hz), 101.5, 108.9, 124.4 (d, J = 292.5 Hz), 135.6, 155.2, 168.2; HRMS (TOF ES$^+$): m/z calcd for $C_{11}H_{13}F_3N_3O_5$ [(M+H)$^+$], 324.0802; found, 324.0804.

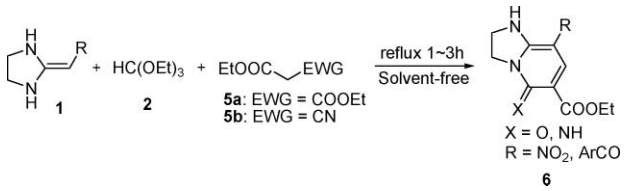
Ethyl 8-acetyl-5-hydroxy-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate (4b). White solid; Mp 107–108 °C; IR (KBr): 3347, 2990, 1664, 1586, 1497, 1388, 1210, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 3.81–4.00 (m, 4H, NCH_2CH_2N), 4.25–4.29 (m, 2H, OCH_2), 7.81 (s, 1H, CH), 7.95 (br, 1H, OH), 9.05 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.7, 25.4, 43.6, 43.6, 61.2, 84.3 (d, J = 32.5 Hz), 92.4, 96.9, 125.0 (d, J = 293.8 Hz), 141.9, 159.3, 168.8, 192.6; HRMS (TOF ES$^+$): m/z $C_{13}H_{16}F_3N_2O_4$ [(M+H)$^+$], 321.1057; found, 321.1058.

Ethyl 8-benzoyl-5-hydroxy-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate (4c). White solid; Mp 163–166 °C; IR (KBr): 3294, 2987, 1662, 1591, 1499, 1089, 1025, 752, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H, CH_3), 3.80–4.10 (m, 4H, NCH_2CH_2N), 4.11–4.18 (m, 2H, OCH_2), 7.42–7.54 (m, 5H, PhH), 7.84 (s, 1H, CH), 7.92 (br, 1H, OH), 9.33 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 43.8, 44.2, 61.2, 84.2 (d, J = 33.8 Hz), 91.7, 97.3, 125.1 (d, J = 295.0 Hz), 128.6, 128.7, 131.0, 139.7, 143.6, 160.4, 168.8, 191.0; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{18}F_3N_2O_4$ [(M+H)$^+$], 383.1213; found, 383.1216.

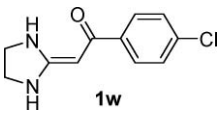
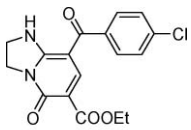
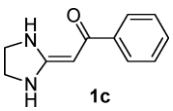
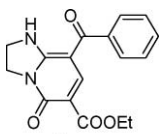
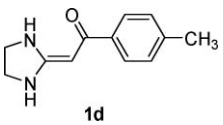
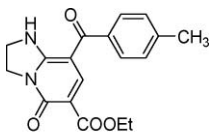
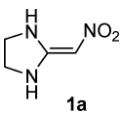
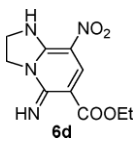
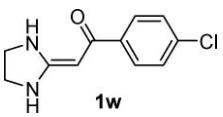
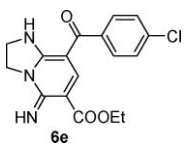
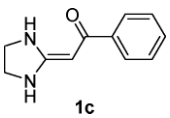
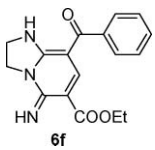
Ethyl 5-hydroxy-8-(4-methylbenzoyl)-5-(trifluoromethyl)-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxylate (4d). White solid; Mp 168–171 °C; IR (KBr): 3322, 2977, 1656, 1582, 1498, 1401, 1309, 1083, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 2.44 (s, 3H, $ArCH_3$), 3.85–4.19 (m, 4H, NCH_2CH_2N), 4.08–4.22 (m, 2H, OCH_2), 7.27 (t, J = 7.6 Hz, 2H, ArH), 7.47 (d, J = 7.6 Hz, 2H, ArH), 7.90 (s, 1H, CH), 7.97 (br, 1H, OH), 9.34 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 21.9, 43.8, 43.8, 61.2, 84.2 (d, J = 33.8 Hz), 91.7, 97.1, 125.6 (d, J = 295.0 Hz), 128.9, 129.3, 136.9, 141.4, 143.7, 160.5, 168.9, 191.0; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{20}F_3N_2O_4$ [(M+H)$^+$], 397.1370; found, 397.1372.

Ethyl 5-hydroxy-8-(4-methoxybenzoyl)-5-(trifluoromethyl)-1,2,3,5-tetrahydro- imidazo[1,2-*a*]pyridine-6-carboxylate (4e). White solid; Mp 1801–185 °C; IR (KBr): 3288, 2987, 1654, 1594, 1400, 1253, 1170, 1088, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3H, CH_3), 3.89 (s, 3H, OCH_3), 3.88–4.07 (m, 4H, NCH_2CH_2N), 4.19 (q, J = 7.1 Hz, 2H, OCH_2), 6.95 (d, J = 8.5 Hz, 2H, ArH), 7.54 (d, J = 8.5 Hz, 2H, ArH), 7.88 (s, 1H, CH), 7.97 (br, 1H, OH), 9.28 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 43.5, 43.8, 55.8, 61.1, 84.2 (d, J = 33.8 Hz), 91.6, 96.8, 113.9, 125.7 (d, J = 293.8 Hz), 130.8, 132.2, 143.8, 160.5, 162.1, 168.9, 190.3; HRMS (TOF

Table 2 One-pot synthesis of bicyclic pyridine derivatives **6** under solvent-free conditions



1 2 6

Entry	HKAs **1**	**5**	**6**	Time/min	Yield (%)[a,b]
1	 **1w**	**5a**	 **6a**	80	89
2	 **1c**	**5a**	 **6b**	80	90
3	 **1d**	**5a**	 **6c**	60	94
4	 **1a**	**5b**	 **6d**	120	94
5	 **1w**	**5b**	 **6e**	180	95
6	 **1c**	**5b**	 **6f**	180	89

[a] Isolated yields after silica gel chromatography. [b] Yield of isolated product from reaction on a 2.5 mmol scale.

ES$^+$): *m*/*z* calcd for $C_{19}H_{20}F_3N_2O_5$ [(M+H)$^+$], 413.1319; found, 413.1322.

Diethyl 5-hydroxy-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarboxylate (4f). White solid; Mp 146–149 °C; IR (KBr): 3398, 3308, 2988, 1638, 1575, 1411, 1332, 1216, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18–1.47 (m, 6H, CH_3), 3.74–4.05 (m, 4H, NCH_2CH_2N), 4.19–4.29 (m, 4H, OCH_2), 7.83 (s, 1H, CH), 7.91 (br, 1H, OH), 8.02 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 14.7, 43.5, 44.1, 60.0, 61.0, 80.5, 84.7 (q, *J* = 33.8 Hz), 96.2, 125.7 (q, *J* = 295.0 Hz), 141.5, 159.4, 166.8, 169.0; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{14}H_{18}F_3N_2O_5$ [(M+H)$^+$], 351.1162; found, 351.1164.

Ethyl 6-hydroxy-9-nitro-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4g). Yellow solid; Mp 147–151 °C; IR (KBr): 3182, 2982, 1668, 1607, 1539, 1474, 1370, 1018, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3H, CH_3), 1.94–1.98 (m, 1H, CH_2), 2.08–2.13 (m, 1H, CH_2), 3.46–3.54 (m, 2H, CH_2), 3.61–3.65 (m, 1H, CH_2), 3.64–3.97 (m, 1H, CH_2), 4.22–4.27 (m, 2H, OCH_2), 8.40 (s, 1H, CH), 8.42 (br, 1H, OH), 10.70 (br, 1H, NH); ^{13}C

HMR (125 MHz, $CDCl_3$): δ = 14.5, 19.7, 39.7, 40.5, 62.2, 84.4 (q, J = 33.8 Hz), 100.2, 111.3, 124.5 (q, J = 293.8 Hz), 135.9, 151.8, 168.5; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{15}F_3N_3O_5$ [(M+H)$^+$], 338.0958; found, 338.0959.

Ethyl 9-(4-chlorobenzoyl)-6-hydroxy-6-(trifluoromethyl)-2,3,4,6-tetrahydro- 1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4h). Yellow solid; Mp 168–173 °C; IR (KBr): 3429, 2979, 1657, 1595, 1508, 1239, 1174, 1099, 816 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 6.9 Hz, 3H, CH_3), 1.99–2.08 (m, 2H, CH_2), 3.40–3.43 (m, 1H, NCH_2), 3.54–3.58 (d, m, 2H, NCH_2), 3.94–3.98 (m, 1H, NCH_2), 4.17 (q, J = 6.9 Hz, 2H, OCH_2), 7.4 (d, J = 8.1 Hz, 2H, ArH), 7.43 (d, J = 8.1 Hz, 2H, ArH), 7.70 (s, 1H, CH), 8.63 (br, 1H, OH), 11.79 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 20.1, 39.2, 39.9, 61.2, 84.0 (d, J = 32.5 Hz), 94.1, 95.5, 125.3 (d, J = 295.0 Hz), 128.7, 130.5, 136.7, 139.0, 143.7, 156.5, 169.0, 190.2; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{19}ClF_3N_2O_4$ [(M+H)$^+$], 431.0980; found, 431.0984.

Ethyl 9-benzoyl-6-hydroxy-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4i). Yellow solid; Mp 149–151 °C; IR (KBr): 3427, 2983, 1645, 1598, 1509, 1395, 1241, 1181, 751, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.0 Hz, 3H, CH_3), 1.99–2.08 (m, 2H, CH_2), 3.41–3.45 (m, 1H, NCH_2), 3.55–3.59 (m, 2H, NCH_2), 3.96–3.99 (m, 1H, NCH_2), 4.16 (q, J = 7.0 Hz, 2H, OCH_2), 7.42–7.51 (m, 5H, PhH), 7.78 (s, 1H, CH), 8.66 (br, 1H, OH), 11.88 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 20.2, 39.2, 39.9, 61.1, 84.1 (d, J = 33.8 Hz), 94.2, 95.0, 125.4 (d, J = 295.0 Hz), 128.4, 129.0, 130.6, 140.7, 144.3, 156.6, 169.1, 191.8; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{20}F_3N_2O_4$ [(M+H)$^+$], 397.1370; found, 397.1369.

Ethyl 6-hydroxy-9-(4-methylbenzoyl)-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4j). Yellow solid; Mp 165–170 °C; IR (KBr): 3374, 2984, 1651, 1601, 1503, 1373, 1236, 1176, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.1 Hz, 3H, CH_3), 1.78–2.08 (m, 2H, CH_2), 2.42 (s, 3H, $ArCH_3$), 3.40–3.98 (m, 3H, NCH_2CH_2N), 4.16 (q, J = 7.1 Hz, 2H, OCH_2), 7.23 (d, J = 7.8 Hz, 2H, ArH), 7.40 (d, J = 7.8 Hz, 2H, ArH), 7.81 (s, 1H, CH), 8.68 (br, 1H, OH), 11.91 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 20.2, 21.9, 39.2, 39.9, 61.1, 84.1 (q, J = 32.5 Hz), 94.2, 94.7, 125.4 (q, J = 293.8 Hz), 129.1, 129.2, 137.9, 141.0, 144.5, 156.6, 169.1, 191.7; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{22}F_3N_2O_4$ [(M+H)$^+$], 411.1526; found, 411.1525.

Ethyl 6-hydroxy-9-(4-methoxybenzoyl)-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4k). Yellow solid; Mp: 148–150 °C; IR (KBr): 3428, 2980, 1645, 1597, 1506, 1372, 1249, 1173, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20–1.23 (m, 3H, CH_3), 1.98–2.08 (m, 2H, CH_2), 3.40–3.56 (m, 3H, NCH_2CH_2N), 3.87 (s, 3H, OCH_3), 3.89–3.96 (m, 1H, NCH_2), 4.15–4.19 (m, 2H, OCH_2), 6.95 (d, J = 6.4 Hz, 2H, ArH), 7.49 (d, J = 6.4 Hz, 2H, ArH), 7.83 (s, 1H, CH), 8.71 (br, 1H, OH), 11.88 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 20.2, 39.2, 39.9, 55.8, 61.0, 84.1 (d, J = 32.5 Hz), 94.1, 94.4, 113.7, 125.5 (d, J = 295.0 Hz), 131.1, 133.2, 144.5., 156.5, 161.9, 169.1, 191.1; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{22}F_3N_2O_5$ [(M+H)$^+$], 427.1475; found, 427.1473.

Ethyl 10-(4-chlorobenzoyl)-7-hydroxy-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4l). White solid; Mp 145–146 °C; IR (KBr): 3421, 2946, 1654, 1589, 1367, 1236, 1167, 1097, 807 cm^{-1}: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H, CH_3), 1.81–1.90 (m, 2H, CH_2), 2.02–2.05 (m, 2H, CH_2), 3.49–3.55 (m, 2H, NCH_2), 3.68–3.73 (m, 1H, NCH_2), 4.15–4.20 (m, 2H, OCH_2), 4.47–4.51 (m, 1H, NCH_2), 7.38–7.67 (m, 4H, ArH), 7.66 (s, 1H, CH), 9.05 (br, 1H, OH), 11.59 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 25.4, 25.5, 43.5, 45.2, 61.4, 84.3 (d, J = 32.5 Hz), 96.4, 96.7, 125.1 (d, J = 292.5 Hz), 128.7, 130.7, 137.0, 139.1, 144.0, 163.1, 169.1, 190.6; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{21}ClF_3N_2O_4$ [(M+H)$^+$], 445.1136; found, 445.1145.

Ethyl 10-benzoyl-7-hydroxy-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4m). White solid; Mp 119–121 °C; IR (KBr): 3433, 2969, 1647, 1578, 1496, 1364, 1096, 759, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3H, CH_3), 1.79–1.95 (m, 2H, CH_2), 2.01–2.07 (m, 2H, CH_2), 3.48–3.54 (m, 2H, NCH_2), 3.67–3.72 (m, 1H, CH_2), 4.10–4.16 (m, 2H, OCH_2), 4.47–4.51 (m, 1H, NCH_2), 7.40–7.50 (m, 5H, PhH), 7.73 (s, 1H, CH), 9.06 (br, 1H, OH), 11.66 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 25.4, 25.5, 43.4, 45.2, 61.2,84.3 (d, J = 32.5 Hz), 96.2, 96.6, 125.1 (d, J = 292.5 Hz), 128.4, 129.2, 130.9, 140.6, 144.6, 163.2, 169.3, 192.2; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{22}F_3N_2O_4$ [(M+H)$^+$], 411.1526; found, 411.1533.

Ethyl 7-hydroxy-10-(4-methylbenzoyl)-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4n). White solid; Mp 138–139 °C; IR (KBr): 3427, 2933, 1650, 1589, 1369, 1236, 1169, 1098, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 6.9 Hz, 3H, CH_3), 1.80–1.88 (m, 2H, CH_2), 2.00–2.03 (m, 2H, CH_2), 2.41 (s, 3H, $ArCH_3$), 3.46–3.52 (m, 2H, NCH_2), 3.67–3.70 (m, 1H, NCH_2), 4.16 (t, J = 6.9 Hz, 2H, OCH_2), 4.48–4.51 (m, 1H, NCH_2), 7.22 (d, J = 7.5 Hz, 2H, ArH), 7.40 (d, J = 7.5 Hz, 2H, ArH), 7.76 (s, 1H, CH), 9.09 (br, 1H, OH), 11.65 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 21.9, 25.4, 25.6, 43.5, 45.3, 61.2, 84.4 (q, J = 33.8 Hz), 96.0, 96.6, 125.0 (q, J = 292.5 Hz), 129.1, 129.4, 137.9, 141.3, 144.7, 163.3, 169.3, 192.2; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{24}F_3N_2O_4$ [(M+H)$^+$], 425.1683; found, 425.1691.

Ethyl 7-hydroxy-10-(4-methoxybenzoyl)-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4o). White solid; Mp 138–140 °C; IR (KBr): 3176, 2945, 1652, 1595, 1494, 1366, 1164, 1031, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H, CH_3), 1.78–1.87 (m, 2H, CH_2), 1.99–2.04 (m, 2H, CH_2), 3.45–3.48 (m, 2H, NCH_2), 3.67–3.70 (m, 1H, NCH_2), 3.86 (s, 3H, OCH_3), 4.17 (q, J = 7.0 Hz, 2H, OCH_2), 4.48– 4.52 (m, 1H, NCH_2), 6.93 (d, J = 8.3 Hz, 2H, ArH), 7.49 (d, J = 8.3 Hz, 2H, ArH), 7.77 (s, 1H, CH), 9.11 (br, 1H, OH), 11.59 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 25.4, 25.6, 43.4, 45.3, 55.8, 61.2, 84.4 (d, J = 32.5 Hz), 95.7, 96.6, 113.7, 125.2 (d, J = 293.8 Hz), 131.4, 133.2, 144.8, 162.1, 163.2, 169.3, 191.5; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{24}F_3N_2O_5$ [(M+H)$^+$], 441.1632; found, 441.1644.

Ethyl 8-(4-chlorobenzoyl)-5-hydroxy-5-(trifluoromethyl)-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (4p). White solid; Mp: 156–158 °C; IR (KBr): 3178, 2980, 1663, 1600, 1529, 1345, 1262, 1179, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3H, CH_3), 4.03–4.08 (m, 2H, NCH_2), 4.25–4.29 (m, 2H, OCH_2), 4.63–4.72 (m, 2H, OCH_2), 7.37 (d, J = 8.3 Hz, 2H, ArH), 7.49 (d, J = 8.3 Hz, 2H, ArH), 7.94 (s, 1H, CH), 8.13 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 43.5, 61.9, 70.3, 85.8 (q, J = 33.8 Hz), 91.2, 99.9, 124.7 (q, J = 292.5 Hz), 128.6, 130.2, 137.6, 139.0, 142.7, 163.9, 168.7, 188.0; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{16}ClF_3NO_5$ [(M+H)$^+$], 418.0664; found, 418.0665.

Ethyl 5-hydroxy-8-(4-methylbenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (4q). White solid; Mp 164–168 °C; IR (KBr): 3200, 2982, 1662, 1601, 1524, 1345, 1177, 1012, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3H, CH_3), 2.39 (s, 3H, $ArCH_3$), 3.98–4.03 (m, 2H, NCH_2), 4.24 (d, J = 6.5 Hz, 2H, OCH_2), 4.62–4.68 (m, 2H, OCH_2), 7.19 (d, J = 7.5 Hz, 2H, ArH), 7.46 (d, J = 7.5 Hz, 2H, ArH), 7.94 (s, 1H, CH), 8.14 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 22.0, 43.5, 61.7, 70.3, 85.9 (q, J = 32.5, Hz), 91.4, 99.2, 124.8 (q, J = 293.8 Hz), 129.0, 129.1, 137.7, 142.1, 143.4, 163.8, 168.9, 189.2; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{19}F_3NO_5$ [(M+H)$^+$], 398.1210; found, 398.1213.

Ethyl 5-hydroxy-8-(4-methoxybenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (4r). White solid; Mp 169–171 °C; IR (KBr): 3184, 3000, 1677, 1596, 1512, 1263, 1167, 1019, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.2 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.01–4.06 (m, 2H, NCH_2), 4.23–4.28 (m, 2H, OCH_2), 4.63–4.70 (m, 2H, OCH_2), 6.90 (d, J = 8.6 Hz, 2H, ArH), 7.57 (d, J = 8.6 Hz, 2H, ArH), 7.95 (s, 1H, CH), 8.14 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 43.5, 55.7, 61.7, 70.2, 85.9 (q, J = 33.8 Hz), 91.3, 99.0, 113.6, 124.8 (q, J = 292.5 Hz), 131.1, 132.9, 143.5, 162.6, 163.6, 168.8, 188.3; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{19}F_3NO_6$ [(M+H)$^+$], 414.1159; found, 414.1157.

Ethyl 8-(4-chlorobenzoyl)-5-hydroxy-5-(trifluoromethiyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4s). Yellow solid; Mp 145–148 °C; IR (KBr): 3262, 2983, 1664, 1590, 1453, 1245, 1175, 1099, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3H, CH_3), 3.19–3.24 (m, 1H, NCH_2), 3.32–3.39 (m, 1H, SCH_2), 4.00–4.06 (m, 1H, SCH_2), 4.24 (q, J = 7.0 Hz, 2H, OCH_2), 4.35–4.39 (m, 1H, NCH_2), 7.44 (d, J = 8.1 Hz, 2H, ArH), 7.54 (d, J = 8.1 Hz, 2H, ArH), 7.73 (s, 1H, CH), 8.20 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 29.4, 50.1, 62.0, 86.2 (q, J = 33.8 Hz), 100.2, 103.8, 124.8 (q, J = 293.8 Hz), 129.0, 130.6, 137.0, 137.9, 140.3, 168.0, 168.7, 188.7; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{16}ClF_3NO_4S$ [(M+H)$^+$], 434.0435; found, 434.0434.

Ethyl 8-benzoyl-5-hydroxy-5-(trifluoromethyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4t). Yellow solid; Mp 129–132 °C; IR (KBr): 3441, 2987, 1658, 1583, 1498, 1397, 1252, 1182, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.0 Hz, 3H, CH_3), 3.19–3.23 (m, 1H, NCH_2), 3.31–3.37 (m, 1H, SCH_2), 3.99–4.06 (m, 1H, SCH_2), 4.22 (q, J = 7.0 Hz, 2H, OCH_2), 4.33–4.37 (m, 1H, NCH_2), 7.44–7.60 (m, 5H, PhH), 7.79 (s, 1H, CH), 8.19 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 29.3, 50.1, 61.8, 86.2 (d, J = 33.8 Hz), 99.9, 104.1, 124.7 (d, J = 292.5 Hz), 128.7, 129.1, 131.7, 138.6, 140.8, 167.7, 168.8, 190.1; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{17}F_3NO_4S$ [(M+H)$^+$], 400.0825; found, 400.0828.

Ethyl 5-hydroxy-8-(4-methylbenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4u). Yellow solid; Mp 122–123 °C; IR (KBr): 3273, 2986, 1664, 1581, 1453, 1248, 1176, 1102, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, J = 6.7 Hz, 3H, CH_3), 2.42 (s, 3H, $ArCH_3$), 3.18–3.20 (m, 1H, NCH_2), 3.30–3.33 (m, 1H, SCH_2), 3.99–4.04 (m, 1H, SCH_2), 4.22 (q, J = 6.7 Hz, 2H, OCH_2), 4.32–4.36 (m, 1H, NCH_2), 7.26 (d, J = 7.5 Hz, 2H, ArH), 7.51 (d, J = 7.4 Hz, 2H, ArH), 7.82 (s, 1H, CH), 8.21 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 21.9, 29.3, 50.0, 61.8, 86.2 (q, J = 33.8 Hz), 99.7, 104.2, 124.9 (q, J = 293.8 Hz), 129.3, 129.4, 135.8, 140.9, 142.3, 167.6, 168.9, 189.9; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{19}F_3NO_4S$ [(M+H)$^+$], 414.0981; found, 414.0983.

Ethyl 5-hydroxy-8-(4-methoxybenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4v). Yellow solid; Mp 135–137 °C; IR (KBr): 3214, 2993, 1657, 1593, 1452, 1388, 1260, 1020, 847 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3H, CH_3), 3.17–3.21 (m, 1H, NCH_2), 3.30–3.34 (m, 1H, SCH_2), 3.87 (s, 3H, OCH_3), 3.97–4.01 (m, 1H, SCH_2), 4.23 (q, J = 7.0 Hz, 2H, OCH_2), 4.34–4.38 (m, 1H, NCH_2), 6.97 (d, J = 8.6 Hz, 2H, ArH), 7.60 (d, J = 8.6 Hz, 2H, ArH), 7.83 (s, 1H, CH), 8.23 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 29.4, 50.0, 55.8, 61.8, 86.2 (q, J = 33.8 Hz), 99.5, 104.1, 114.0, 124.9 (q, J = 293.8 Hz), 131.0, 131.4, 141.0, 162.7, 167.3, 168.9, 189.1; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{19}F_3NO_5S$ [(M+H)$^+$], 430.0931; found, 430.0930.

Ethyl 1,2,3,5-tetrahydro-8-(4-chlorobenzoyl)-5-oxoimidazo-[1,2-*a*]pyridine-6-carboxylate (6a). Yellow solid; Mp 280–281 °C; IR (KBr): 3494, 2981, 1727, 1568, 1224, 1171 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, J = 6.6 Hz, 3H, CH_3), 4.01–4.06 (m, 2H, NCH_2), 4.25–4.28 (m, 4H, NCH_2 and OCH_2), 7.45 (d, J = 7.2 Hz, 2H, ArH), 7.63 (d, J = 7.2 Hz, 2H, ArH), 8.41 (s, 1H, CH), 8.80 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8, 43.6, 44.0, 61.2, 97.8, 107.4, 129.3, 130.1, 137.0, 138.1, 149.5, 158.3, 158.6, 165.2, 191.7; HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{15}ClN_2NaO_4$ [(M+Na)$^+$], 369.0613; found, 369.0618.

Ethyl 1,2,3,5-tetrahydro-8-benzoyl-5-oxoimidazo[1,2-*a*]-pyridine-6-carboxylate (6b). Yellow solid; Mp 234–236 °C; IR (KBr): 3302, 2981, 1727, 1568, 1224, 1171, 1105 cm^{-1}; ^1H NMR (500 MHz, CH_3OD+DMSO-d_6): δ = 0.74 (t, J = 6.7 Hz, 3H, CH_3), 3.68–3.72 (m, 2H, NCH_2), 3.77 (q, J = 6.7 Hz, 2H, OCH_2), 4.02–4.10 (m, 2H, NCH_2), 5.39 (s, 1H, CH), 7.18–7.30 (m, 5H, ArH and CH); ^{13}C NMR (125 MHz, CH_3OD+DMSO-d_6): δ = 12.3, 41.4, 43.7, 59.2, 85.1, 105.8, 126.2, 127.5, 127.5, 139.7, 153.6, 156.2, 158.2, 166.5, 194.0; HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{16}N_2NaO_4$ [(M+Na)$^+$], 335.1002; found, 335.1008.

Ethyl 1,2,3,5-tetrahydro-8-(4-methylbenzoyl)-5-oxoimid-azo-[1,2-*a*]pyridine-6-carboxylate (6c). Yellow solid; Mp 203–205 °C; IR (KBr): 3266, 2978, 1694, 1632, 1571, 1275, 1120 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 0.86 (t, J = 6.9 Hz, 3H, CH_3), 2.32 (s, 3H, $ArCH_3$), 3.64–3.71 (m, 2H, NCH_2), 3.83 (q,

J = 6.9 Hz, 2H, OCH_2), 4.02–4.07 (m, 2H, NCH_2), 5.29 (s, 1H, CH), 7.15 (d, J = 7.3 Hz, 2H, ArH), 7.20 (d, J = 7.3 Hz, 2H, ArH), 7.88 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.0, 21.1, 42.3, 44.5, 59.9, 84.3, 107.4, 127.1, 129.2, 137.4, 138.1, 154.3, 155.2, 158.1, 167.2; HRMS (TOF ES$^-$): m/z calcd for $C_{18}H_{17}N_2O_4$ [(M-H)$^+$], 325.1194; found, 325.1204.

Ethyl 1,2,3,5-tetrahydro-5-imino-8-nitroimidazo[1,2-*a*]-pyridine-6-carboxylate (6d). Yellow solid; Mp 213–216 °C; IR (KBr): 3493, 2984, 1688, 1535, 1376, 600 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.27–1.31 (m, 3H, CH_3), 3.70–4.00 (m, 4H, NCH_2CH_2N), 4.18–4.24 (m, 2H, OCH_2), 8.41 (s, 1H, CH), 8.81 (br, 1H, NH), 11.40 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 45.2, 47.1, 60.7, 98.9, 114.2, 137.7, 150.8, 153,4, 165.1; HRMS (TOF ES$^+$): m/z calcd for $C_{10}H_{13}N_4O_4$ [(M+H)$^+$], 253.0931; found, 253.0915.

Ethyl 1,2,3,5-tetrahydro-5-imino-8-(4-chlorobenzoyl)-imidazo[1,2-*a*]pyridine-6-carboxylate (6e). Yellow solid; Mp 219–226 °C; IR (KBr): 3494, 2982, 1669, 1569, 1374, 1224, 717 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.22–1.25 (m, 3H, CH_3), 3.96–4.00 (m, 2H, NCH_2), 4.10-4.17 (m, 4H, NCH_2 and OCH_2), 7.61–7.66 (m, 4H, ArH), 7.96 (s, 1H, CH), 8.08 (br, 1H, NH), 9.69 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9, 43.7, 43.8, 59.5, 98.6, 117.3, 118.4, 129.0, 130.4, 136.4, 137.2, 150.5, 157.2, 167.0, 189.6; HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{17}ClN_3O_3$ [(M+H)$^+$], 346.0953; found, 346.0974.

Ethyl 1,2,3,5-tetrahydro-5-imino-8-benzoylimidazo[1,2-*a*]-pyridine-6-carboxylate (6f). Yellow solid; Mp: 195–197 °C; IR (KBr): 3494, 2985, 1652, 1536, 1374, 1231, 759 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.24–1.27 (m, 3H, CH_3), 3.99–4.01 (m, 2H, NCH_2), 4.12-4.21 (m, 4H, NCH_2 and OCH_2), 7.59–7.65 (m, 5H, PhH), 7.89 (s, 1H, CH), 9.12 (br, 1H, NH), 9.60 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9, 43.7, 43.8, 59.5, 98.7, 117.3, 118.4, 128.4, 128.9, 131.5, 138.6, 150.4, 157.3, 167.0, 190.8; HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{18}N_3O_3$ [(M+H)$^+$], 312.1343; found, 312.1348.

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