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Palladium(II)-catalyzed cyclization of heterocyclic ketene aminals with (*E*)-ethyl 2,3-diiodoacrylates: selective synthesis of bicyclic pyrroles and bicyclic pyridones

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ABSTRACT

A concise and efficient synthesis of novel bicyclic pyrroles has been achieved by $PdCl_2$-catalyzed cyclic condensation of six-membered heterocyclic ketene aminals (HKAs) or seven-membered HKAs with ethyl 2,3-diiodoacrylate and diethyl 2,3-diiodofumarate in the presence of Cs_2CO_3, respectively. A series of novel bicyclic pyridones have also been obtained via five-membered HKAs with diethyl 2,3-diiodofumarate under the optimized conditions in moderate yields. These reactions are the first application of a transition metal to catalyze the building blocks HKAs to form the bicyclic pyrrole library via condensation reaction.

1. Introduction

Pyrrole derivatives are a class of important organic compounds and serve as key structural building blocks in numerous natural products, synthetic biological medicinal agents, and functional materials.[1–5] As a result, more and more pyrroles have been synthesized by various methods including Knorr,[6] Paal–Knorr,[1e,7] and multicomponent reactions.[8] Bicyclic pyrroles, one class of pyrrole derivatives, are particularly important due to their broad spectrum of excellent biological activities.[9] Some characteristic examples of these compounds are shown in Fig. 1, i.e., (−)-longmide B methyl ester (with cytotoxic activity)[9a] and axinohydantion (which inhibits protein kinase C).[9b,10]

Similarly, bicyclic pyridones represent a class of important organic molecules, which have attracted the interest of both medicinal and synthetic chemists. Bicyclic pyridones are core structures in many drugs, including anti-cancer compounds[11] and acetylcholinesterase inhibitors[12,13] (Fig. 1, A58365A). Therefore, various synthetic methods have been developed to prepare bicyclic pyridones[14] including [2+2+2] cycloaddition of alkynes and isocyanates,[14a–d] acyl-ketene imine cyclocondensation,[14e] 6π-electrocyclic ring closure,[14f] Diels–Alder cyclization,[14g] rhodium-catalyzed tandem reaction of cyclization–cycloaddition-ring opening,[14h] and so on.[14i,j] Among them, the heterocyclic ketene aminals (HKAs) based methods developed by the Huang[15] group have been received wide attention. However, these methods usually suffer from the use of expensive metal reagents, tedious workup procedures, or the products lack of diversity. Hence, it is still important to explore efficient and novel synthetic methods in order to meet present drug discovery and high-throughput screening needs.

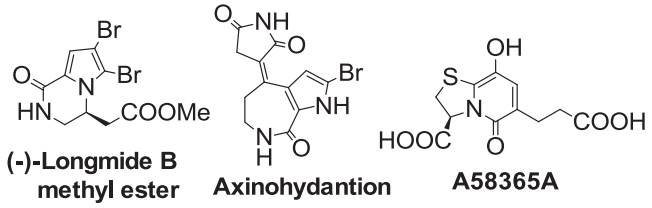

Fig. 1. Biologically active bicyclic pyrroles and a bicyclic pyridone.

HKAs are fascinating and versatile intermediates of a variety of fused heterocyclic compounds,[16] which are frequently found in pharmacophores.[17–23] However, palladium(II) catalyzed bicyclic pyrroles formation from HKAs has not been reported. Moreover, in

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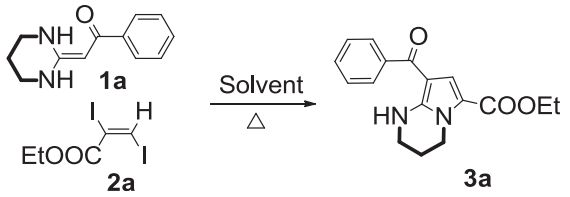
continuation of our research interests regarding the development of the synthesis and applications of HKAs for new drug discovery,[24] herein we report a $PdCl_2$ catalyzed synthesis of bicyclic pyrroles from HKAs.

2. Result and discussion

$PdCl_2$-catalyzed cyclic condensation of HKAs with **2a** and **2b** was investigated, respectively. The method is efficient and operationally simple. New pyrroles **3a**–**t** were synthesized in 71–93% yields and five new bicyclic pyridones **4a**–**e** were also constructed in 60–67% yields.

In the initial experiment, HKAs **1a** and ethyl 2,3-diiodofumarate **2a** were chosen as the model substrates to optimize the reaction conditions (catalyst, base, solvent, and temperature). The results were listed in Table 1. The reaction was not able to proceed in the absence of catalyst (Table 1, entries 1–12, respectively). When the catalyst $PdCl_2$ and the base Cs_2CO_3 were added with EtOH as the solvent, we obtained product **3a** in 43% yield. DMSO was found to be the best solvent, and the yield was improved to 73% (Table 1, entry 15). Next, the reaction was performed without base and gave lower yield (Table 1, entry 17), indicating base could efficiently promote this reaction. However, the reaction did not give satisfactory yield when using Et_3N as the base, so Cs_2CO_3 was the best base (Table 1, entry 18). Then, the amount of Cs_2CO_3 was tested (Table 1, entries 19, 20) and it was found that the amount of base could affect the yield of **3a**. After that, the stoichiometry of substrates **1a** and **2a** was also tested (Table 1, entries 21, 22). It was clear that use of a 1.1:1 molar ratio of **1a**/**2a** gave better results (Table 1, entries 21). Finally, the model reaction was performed at different temperatures, such as: 130 °C, 70 °C; or rt, and the results suggest that the yields of **3a** decreased at all of these temperatures (Table 1, entries 23–25). Thus, the reaction conditions were optimized with the presence of $PdCl_2$ (0.1 equiv) and Cs_2CO_3 (1.0 equiv) in DMSO as the solvent at 100 °C.

Table 1
Optimization of the reaction conditions



Entry	Solvent	Catalyst	Base	T (°C)	Time (h)	Yield[h] (%)
1[a]	EtOH	—	—	100	20	n.r.
2[a]	Toluene	—	—	100	18	n.r.
3[a]	DMSO	—	—	100	21	n.r.
4[a]	Dioxane	—	—	100	20	n.r.
5[a]	EtOH	—	Et_3N[e]	100	16	n.r.
6[a]	Toluene	—	Et_3N[e]	100	21	n.r.
7[a]	DMSO	—	Et_3N[e]	100	18	n.r.
8[a]	Dioxane	—	Et_3N[e]	100	15	n.r.
9[a]	EtOH	—	Cs_2CO_3[e]	100	17	n.r.
10[a]	Toluene	—	Cs_2CO_3[e]	100	22	n.r.
11[a]	DMSO	—	Cs_2CO_3[e]	100	20	n.r.
12[a]	Dioxane	—	Cs_2CO_3[e]	100	20	n.r.
13[a]	EtOH	$PdCl_2$[d]	Cs_2CO_3[e]	100	8	43
14[a]	Toluene	$PdCl_2$[d]	Cs_2CO_3[e]	100	6	60
15[a]	DMSO	$PdCl_2$[d]	Cs_2CO_3[e]	100	5	73
16[a]	Dioxane	$PdCl_2$[d]	Cs_2CO_3[e]	100	6	52
17[a]	DMSO	$PdCl_2$[d]	—	100	8	38
18[a]	DMSO	$PdCl_2$[d]	Et_3N[e]	100	8	41
19[a]	DMSO	$PdCl_2$[d]	Cs_2CO_3[f]	100	5	71
20[a]	DMSO	$PdCl_2$[d]	Cs_2CO_3[g]	100	5	58
21[b]	DMSO	$PdCl_2$[d]	Cs_2CO_3[e]	100	5	82
22[c]	DMSO	$PdCl_2$[d]	Cs_2CO_3[e]	100	5	70
23[b]	DMSO	$PdCl_2$[d]	Cs_2CO_3[e]	130	5	61
24[b]	DMSO	$PdCl_2$[d]	Cs_2CO_3[e]	rt	24	n.r.
25[b]	DMSO	$PdCl_2$[d]	Cs_2CO_3[e]	70	8	43

n.r.=no reaction.
[a] The reaction was performed with **1a** (1.0 mmol), **2a** (1.0 mmol).
[b] Compounds **1a** (1.1 mmol), **2a** (1.0 mmol).
[c] Compounds **1a** (1.0 mmol), **2a** (1.1 mmol).
[d] $PdCl_2$ (10 mol %).
[e] Base (1.0 mmol).
[f] Base (2.0 mmol).
[g] Base (0.1 mmol).
[h] Isolated yield based on **2a**.

With the optimal reaction conditions, we explored the scope and limitations of the condensation reactions using different HKAs and ethyl 2,3-diiodoacrylate **2a** or diethyl 2,3-diiodofumarate **2b** (Table 2). First, we tested the scope of substrates **1** (Table 2, entries 1–15). Various six-membered HKAs were used to react with **2a**, and similar reactivities were observed (Table 2, entries 2–5). It is shown that the substituents on the aromatic ring of HKAs had some influence on the yield. The substituted aromatic ring of HKAs with electron-withdrawing groups, such as fluoro and chloro groups (Table 2, entries 4, 5) reacted faster and gave higher yields than those with electron-donating groups, such as methyl and methoxyl groups (Table 2, entries 2, 3). Next, the seven-membered HKAs (Table 2, entries 6–10) were also employed in this process, and all reactions proceeded well, giving the corresponding bicyclic pyrroles **3f**–**j**. The seven-membered HKAs gave higher yields in shorter time than six-membered HKAs, however, five-membered HKAs **1k**–**o** didn't afford any product (Table 2, entries 11–15).

In an endeavor to expand the scope of substrates **2** (Table 2, entries 16–30), diethyl 2,3-diiodofumarate **2b** was reacted with six-membered HKAs (**1a**–**e**) with both electron-withdrawing and electron-donating groups to give bicyclic pyrroles **3k**–**o** (Table 2, entries 16–20). Compared to ethyl 2,3-diiodoacrylate **2a**, the yields of the diethyl 2,3-diiodofumarate **2b** were lower. The following seven-membered HKAs **1f**–**j** were also employed under the optimum reaction conditions with **2b** to obtain similar bicyclic pyrroles **3p**–**t** in higher yields (84–90%) (Table 2, entries 21–25). Both electron-donating and electron-withdrawing groups on aromatic rings of HKAs were also tolerated, although the former gave slightly reduced yields.

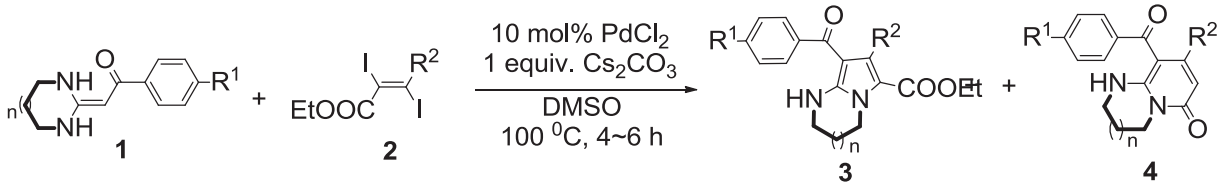
In order to further investigate the scope of HKAs, five-membered HKAs **1k**–**o** were also employed to react with diethyl 2,3-diiodofunarate **2b**. Surprisingly, the desired bicyclic pyrroles **3** were not obtained, instead we isolated the bicyclic pyridones **4** in moderate yields (Table 2, entries 26–30). It is shown, the substituent on the aromatic HKAs **1k**–**o** had little influence on the yield. However, the ring sizes are crucial to the reactions. It is easy to fuse a six-membered ring to a five-membered ring, while the five-membered ring of HKAs **1k**–**o** could not fuse another five-membered ring owing to the tension of the ring, which was too high to form bicyclic fused products.

To further investigate the reaction, we shortened the reaction time (Table 2, entry 29 vs Scheme 1) and obtained a small amount of product **4d** and a large amount of the bicyclic pyridone **5a**, which contains iodine (Scheme 1). This indicated that **5a** may be a precursor of **4d** (Scheme 2).

Products **3**, **4**, and **5a** were characterized by their ^1H HMR, ^{13}C NMR, IR, and HRMS spectra, which were in agreement with the proposed structures. We obtained a single crystal of product **3g** and the X-ray diffraction structure was shown in Fig. 2.[25]

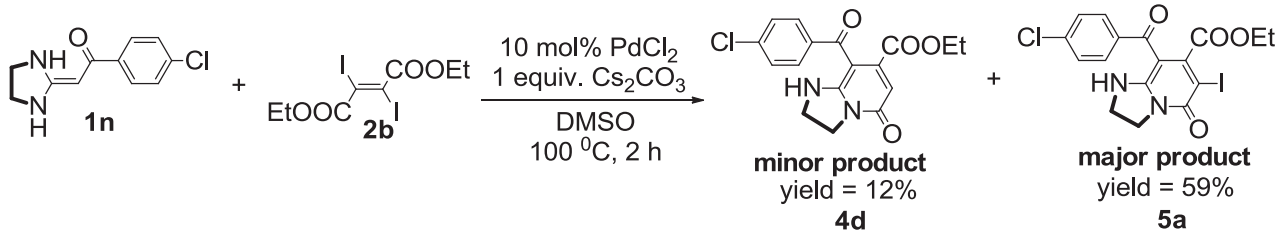
Based on the above experimental results, a possible mechanism for the formation of bicyclic pyrroles **3** is proposed and depicted in Scheme 2. First, a small part of the HKA acts as a ligand to react with the $PdCl_2$ catalyst and forms a complex **6**. This complex is an effective catalyst for the formation of the oxidative addition products

Table 2
Preparation of the bicyclic pyrrole **3** or bicyclic pyridine **4**[a]



Entry	**1**/*n*, R^1	**2**/R^2	Time (h)	**3**/Yield[b] (%)	**4**/Yield[b] (%)
1	**1a**/*n*=1, R^1=H	**2a**/R^2=H	5	**3a**/82	—
2	**1b**/*n*=1, R^1=CH_3	**2a**/R^2=H	6	**3b**/81	—
3	**1c**/*n*=1, R^1=OCH_3	**2a**/R^2=H	6	**3c**/78	—
4	**1d**/*n*=1, R^1=Cl	**2a**/R^2=H	5	**3d**/82	—
5	**1e**/*n*=1, R^1=F	**2a**/R^2=H	4.5	**3e**/84	—
6	**1f**/*n*=2, R^1=H	**2a**/R^2=H	5	**3f**/89	—
7	**1g**/*n*=2, R^1=CH_3	**2a**/R^2=H	5.5	**3g**/87	—
8	**1h**/*n*=2, R^1=OCH_3	**2a**/R^2=H	6	**3h**/86	—
9	**1i**/*n*=2, R^1=Cl	**2a**/R^2=H	4	**3i**/92	—
10	**1j**/*n*=2, R^1=F	**2a**/R^2=H	4	**3j**/93	—
11	**1k**/*n*=0, R^1=H	**2a**/R^2=H	8	—	—
12	**1l**/*n*=0, R^1=CH_3	**2a**/R^2=H	8	—	—
13	**1m**/*n*=0, R^1=OCH_3	**2a**/R^2=H	9	—	—
14	**1n**/*n*=0, R^1=Cl	**2a**/R^2=H	8	—	—
15	**1o**/*n*=0, R^1=F	**2a**/R^2=H	11	—	—
16	**1a**/*n*=1, R^1=H	**2b**/R^2=COOEt	5	**3k**/74	—
17	**1b**/*n*=1, R^1=CH_3	**2b**/R^2=COOEt	6	**3l**/73	—
18	**1c**/*n*=1, R^1=OCH_3	**2b**/R^2=COOEt	6	**3m**/71	—
19	**1d**/*n*=1, R^1=Cl	**2b**/R^2=COOEt	5	**3n**/76	—
20	**1e**/*n*=1, R^1=F	**2b**/R^2=COOEt	5	**3o**/77	—
21	**1f**/*n*=2, R^1=H	**2b**/R^2=COOEt	5	**3p**/85	—
22	**1g**/*n*=2, R^1=CH_3	**2b**/R^2=COOEt	6	**3q**/85	—
23	**1h**/*n*=2, R^1=OCH_3	**2b**/R^2=COOEt	6	**3r**/84	—
24	**1i**/*n*=2, R^1=Cl	**2b**/R^2=COOEt	4.5	**3s**/90	—
25	**1j**/*n*=2, R^1=F	**2b**/R^2=COOEt	4	**3t**/90	—
26	**1k**/*n*=0, R^1=H	**2b**/R^2=COOEt	6	—	**4a**/63
27	**1l**/*n*=0, R^1=CH_3	**2b**/R^2=COOEt	6	—	**4b**/67
28	**1m**/*n*=0, R^1=OCH_3	**2b**/R^2=COOEt	6	—	**4c**/60
29	**1n**/*n*=0, R^1=Cl	**2b**/R^2=COOEt	6	—	**4d**/64
30	**1o**/*n*=0, R^1=F	**2b**/R^2=COOEt	5	—	**4e**/65

[a] The reaction was performed with **1** (1.1 mmol), **2** (1.0 mmol), $PdCl_2$ (10 mol %), Cs_2CO_3 (1.0 mmol), and the solvent DMSO (10 ml) at 100 °C.
[b] Isolated yields based on **2**.



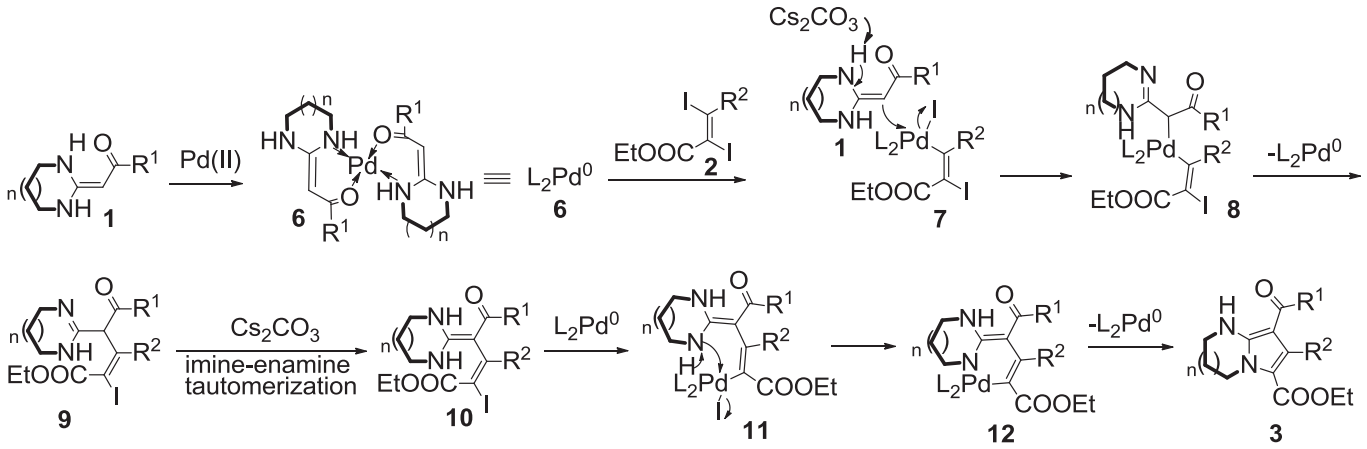
Scheme 1. Preparation of the bicyclic pyridines.

7. Next, the HKAs **1**, as aza-ene reaction components, react with intermediates **7** to afford **8**, which undergoes reductive elimination to give intermediates **9**. Then, rapid imine–enamine tautomerization leads to the formation of **10**, which again undergoes oxidative addition with the catalyst **6** (L_2Pd^0) to give **11**. The key intermediates **12** are formed by the intramolecular reaction of **11**. Finally, **12** undergoes reductive elimination to give the final products **3**, and the complexes **6** re-enter the catalytic cycle.

A proposed mechanism of the synthesis of bicyclic pyridones **4d** is also depicted in Scheme 3. First, the five-membered HKAs **1** react with **2b** in the presence of $PdCl_2$ and Cs_2CO_3 to form the intermediates **10**, which is similar to the mechanism of bicyclic pyrroles **3** synthesis in Scheme 2. Then, the NH group of intermediates **10** attacks the ester intramolecularly to give the product **5a**, which is reduced to the final product **4d**.

3. Conclusion

In summary, we have successfully developed a concise and efficient synthesis of novel bicyclic pyrroles and bicyclic pyridones by cyclic condensation of HKAs with ethyl 2,3-diiodoacrylate or diethyl 2,3-diiodofumarate in the presence of $PdCl_2$, excess HKAs and Cs_2CO_3. The ring sizes of the HKA have a significant influence on the products. For five-membered HKAs, they can exclusively react with diethyl 2,3-diiodofumarate to provide bicyclic pyridones, and the yields of these reactions are not related to the substituents of the HKAs. For the six- or seven-membered HKAs, they can react with not only ethyl 2,3-diiodoacrylate but also diethyl 2,3-diiodofumarate to give the corresponding bicyclic pyrroles. In addition, seven-membered HKAs and HKAs bearing electron-withdrawing groups could provide higher yields. For the first



Scheme 2. The possible reaction mechanism for the formation of **3**.

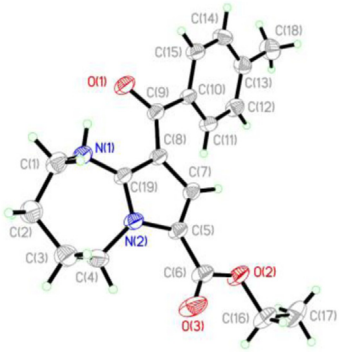
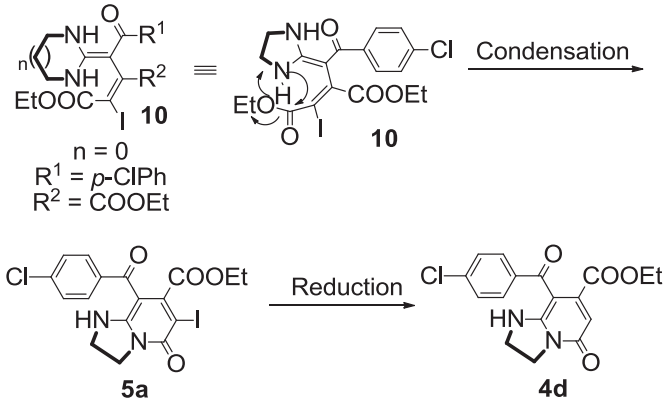


Fig. 2. X-ray crystal structure of **3g**; ellipsoids are drawn at 30% probability level.



Scheme 3. Plausible mechanism for the formation of **4d**.

time, we have developed transition metal catalyzed bicyclic pyrroles and bicyclic pyridones synthesis and these structures are playing unique roles in medicinal chemistry.

4. Experimental

4.1. 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 parts per million, J values are given in hertz, and deuterated $CDCl_3$ andDMSO-d_6 were used as the solvent. IR spectra were recorded on an FT-IR Thermo Nicolet Avatar 360 using KBr pellets. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on an 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 using silica gel (200–300 mesh). Compounds **1** were prepared according to the literature.[26] Compounds **2a** were prepared according to the literature.[27] The materials were purchased from Aldrich Corporation Limited.

4.2. Preparation of compound 2b

Compound **2b** was synthesized by the following method:[28] To a 100 ml round-bottom flask, diethyl acetylene dicarboxylate (10.0 mmol, 1.70 g) and iodine (12.0 mmol, 3.04 g) in $CHCl_3$ were added. The resulting mixture was heated to reflux and stirred until all starting acetylene was consumed, as indicated by TLC. After cooled to rt, the reaction mixture was washed with 20% aq sodium thiosulfate solution (40 ml) and concentrated under reduced pressure. The residue was dissolved in ethanol (15 ml) and the product was precipitated by the addition of water (15 ml). Recrystallization from methanol/water furnished a white solid **2b** (9.3 mmol, 3.95 g) in 93% yield.

*4.2.1. Diethyl 2,3-diiodofunarate **2b**.* White solid; mp 107–109 °C; IR (KBr): 2976, 1715, 1473, 1368, 1257, 1023 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.39 (t, J=7.0 Hz, 6H, CH_3), 4.36 (q, J=7.0 Hz, 4H, OCH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.8, 63.1, 87.9, 164.7; HRMS (TOF ES$^+$): m/z calcd for $C_8H_{10}I_2O_4$ [M$^+$], 423.8668; found, 423.8658.

4.3. Typical procedure for the preparation of bicyclic pyrroles 3 and pyridones 4

To a 25 ml round-bottom flask, HKAs **1** (1.1 mmol) and substrate **2** (1.0 mmol) were added to a solution of DMSO (10 ml). $PdCl_2$ (0.1 mmol) and Cs_2CO_3 (1.0 mmol) were then added to the above mixture. The resulting solution was stirred at 100 °C for about 4–6 h until the substrates **2** were completely consumed. The mixture was cooled to rt, then quenched with a saturated solution of $Na_2S_2O_3$ (20 ml) and extracted with EtOAc (50 ml×3). The organic layers were combined, dried over brine and over anhydrous

Na_2SO_4, concentrated, and purified by flash column chromatography to give the products **3** or **4**.

4.3.1. Ethyl 8-benzoyl-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrimidine-6-carboxylate ***3a***. Yellow solid; mp 120–123 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.21 (t, J=7.1 Hz, 3H, CH_3), 1.98–2.00 (m, 2H, CH_2), 3.30–3.48 (m, 2H, NCH_2), 4.15 (q, J=7.2 Hz, 2H, OCH_2), 4.19–4.21 (m, 2H, CH_2N), 6.87 (s, 1H, CH=), 7.49–7.53 (m, 3H, ArH), 7.62–7.63 (m, 2H, ArH), 7.94 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.7, 20.8, 37.9, 42.7, 102.8, 115.7, 118.6, 128.0, 128.7, 130.9, 140.7, 149.3, 160.5, 188.1; IR (KBr): 3352, 2973, 1695, 1618, 1534, 1348, 1165, 739 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{19}N_2O_3$ [(M+H)$^+$], 299.1390; found, 299.1398.

4.3.2. Ethyl 8-(4-methylbenzoyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrimidine-6-carboxylate ***3b***. Yellow solid; mp 108–110 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.21 (t, J=7.2 Hz, 3H, CH_3), 1.98–2.00 (m, 2H, CH_2), 2.36 (s, 3H, $ArCH_3$), 3.36–3.38 (m, 2H, NCH_2), 4.14 (q, J=7.1 Hz, 2H, OCH_2), 4.18–4.20 (m, 2H, CH_2N), 6.88 (s, 1H, CH=), 7.29 (d, J=7.8 Hz, 2H, ArH), 7.53 (d, J=7.9 Hz, 2H, ArH), 7.89 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.7, 20.8, 21.3, 37.9, 42.7, 59.6, 102.8, 115.6, 118.7, 128.1, 129.2, 137.9, 140.9, 149.3, 160.5, 188.0; IR (KBr): 3348, 2975, 1690, 1612, 1539, 1219, 1168, 756 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{21}N_2O_3$ [(M+H)$^+$], 313.1547; found, 313.1556.

4.3.3. Ethyl 8-(4-methoxybenzoyl)-1,2,3,4-tetrahydropyrrolo-[1,2-a] pyrimidine-6-carboxylate ***3c***. Yellow solid; mp 128–130 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.22 (t, J=7.0 Hz, 3H, CH_3), 1.98–2.00 (m, 2H, CH_2), 3.36–3.38 (m, 2H, NCH_2), 3.82 (s, 3H, OCH_3), 4.13–4.16 (m, J=7.1 Hz, 2H, OCH_2), 4.17–4.20 (m, 2H, CH_2N), 6.93 (s, 1H, CH=), 7.03 (d, J=8.6 Hz, 2H, ArH), 7.64 (d, J=8.6 Hz, 2H, ArH), 7.88 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.7, 20.8, 37.9, 42.7, 55.7, 59.7, 102.7, 114.0, 115.5, 118.7, 149.3, 160.6, 161.6, 187.1; IR (KBr): 3352, 2978, 1732, 1687, 1523, 1214, 1101, 1024, 774 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}N_2NaO_4$ [(M+Na)$^+$], 351.1315; found, 351.1322.

4.3.4. Ethyl 8-(4-chlorobenzoyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrimidine-6-carboxylate ***3d***. Yellow solid; mp 169–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.22 (t, J=7.0 Hz, 3H, CH_3), 1.98–2.00 (m, 2H, CH_2), 4.15 (q, J=6.9 Hz, 2H, OCH_2), 4.19–4.20 (m, 2H, CH_2N), 6.86 (s, 1H, CH=), 7.57 (d, J=8.1 Hz, 2H, ArH), 7.65 (d, J=8.1 Hz, 2H, ArH), 7.95 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.7, 20.7, 37.9, 42.7, 59.7, 102.6, 116.0, 118.3, 128.9, 129.9, 135.7, 139.2, 149.1, 160.5, 186.5; IR (KBr): 3341, 2970, 1682, 1616, 1537, 1219, 1172, 1090, 760 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}ClN_2NaO_3$ [(M+Na)$^+$], 355.0820; found, 355.0826.

4.3.5. Ethyl 8-(4-fluorobenzoyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrimidine-6-carboxylate ***3e***. Yellow solid; mp 142–146 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.19 (t, J=7.1 Hz, 3H, CH_3), 1.96–1.98 (m, 2H), 4.13 (q, J=7.2 Hz, 2H, OCH_2), 4.15–4.18 (m, 2H, CH_2N), 6.85 (s, 1H, CH_2=), 7.28–7.31 (m, 2H, ArH), 7.67–7.70 (m, 2H, ArH), 7.91 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.7, 20.8, 37.9, 42.7, 59.6, 102.6, 115.7, 118.4, 130.5, 137.1, 149.4, 160.5, 162.8, 164.8, 186.6; IR (KBr): 3354, 2966, 1693, 1614, 1537, 1220, 1167, 1090, 841, 764 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}FN_2NaO_3$ [(M+Na)$^+$], 339.1115; found, 339.1113.

4.3.6. Ethyl 9-benzoyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]-diazepine-7-carboxylate ***3f***. Yellow solid; mp 88–89 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.19 (t, J=6.9 Hz, 3H, CH_3), 1.79–1.82 (m, 4H, CH_2CH_2), 3.28–3.30 (m, 2H, NCH_2), 4.12 (q, J=7.0 Hz, 2H, OCH_3), 4.28–4.30 (m, 2H, CH_2N), 6.86 (s, 1H, CH=), 7.46–7.53 (m, 2H, ArH), 7.58–7.62 (m, 2H, ArH), 7.93 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.5, 26.6, 28.9, 45.3, 46.9, 60.0, 105.1, 117.2, 120.2, 128.1, 128.7, 131.3, 140.1, 157.1, 160.7, 189.8; IR (KBr): 3352, 2978, 1732, 1687, 1523, 1214, 1174, 1101, 774 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}N_2NaO_3$ [(M+Na)$^+$], 335.1366; found, 335.1373.

4.3.7. Ethyl 9-(4-methylbenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo-[1,2-a][1,3]-diazepine-7-carboxylate ***3g***. Yellow solid; mp 94–97 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.19 (t, J=7.1 Hz, 3H, CH_3), 1.80–1.82 (m, 4H, CH_2CH_2), 2.35 (s, 3H, $ArCH_3$), 3.27–3.29 (m, 2H, NCH_2), 4.13 (q, J=7.0 Hz, 2H, OCH_2), 4.29–4.30 (m, 2H, CH_2N), 6.94 (s, 1H, CH=), 7.28 (d, J=7.8 Hz, 2H, ArH), 7.53 (d, J=7.8 Hz, 2H, ArH), 7.91 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.6, 21.3, 26.6, 28.9, 45.4, 46.9, 59.9, 105.2, 117.0, 120.2, 128.3, 129.3, 137.4, 141.4, 157.1, 160.7, 189.6; IR (KBr): 3300, 2922, 1689, 1601, 1208, 1091, 1174, 762 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{23}N_2O_3$ [(M+H)$^+$], 327.1703; found, 327.1710.

4.3.8. Ethyl 9-(4-methoxybenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo-[1,2-a][1,3]-diazepine-7-carboxylate ***3h***. Yellow solid; mp 87–91 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.23 (t, J=7.1 Hz, 3H, CH_3), 1.81–1.84 (m, 4H, CH_2CH_2), 3.29–3.31 (m, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.32–4.33 (m, 2H, CH_2N), 7.00 (s, 1H, CH=), 7.05 (d, J=8.5 Hz, 2H, ArH), 7.67 (d, J=8.5 Hz, 2H, ArH), 7.91 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.7, 26.7, 29.1, 45.5, 47.0, 55.7, 59.9, 105.2, 114.1, 116.9, 120.1, 130.4, 132.6, 157.1, 160.7, 162.0, 188.7; IR (KBr): 3300, 2921, 1688, 1600, 1431, 1228, 1169, 1090, 764 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{22}N_2NaO_4$ [(M+Na)$^+$], 365.1472; found, 365.1479.

4.3.9. Ethyl 9-(4-chlorobenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]-diazepine-7-carboxylate ***3i***. Yellow solid; mp 103–108 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.22 (t, J=7.1 Hz, 3H, CH_3), 1.81–1.85 (m, 4H, CH_2CH_2), 3.33–3.38 (m, 2H, NCH_2), 4.16 (q, J=7.0 Hz, 2H, OCH_2), 4.32–4.33 (m, 2H, CH_2N), 6.93 (s, 1H, CH=), 7.58 (d, J=8.0 Hz, 2H, ArH), 7.67 (d, J=8.0 Hz, 2H, ArH), 7.96 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.6, 26.6, 28.8, 45.3, 47.0, 60.0, 104.9, 117.4, 119.9, 128.9, 130.1, 136.1, 138.8, 157.2, 160.6, 188.2; IR (KBr): 3309, 2938, 1692, 1435, 1167, 1089, 845, 772 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}ClN_2O_3$ [(M+Na)$^+$], 369.0976; found, 369.0985.

4.3.10. Ethyl 9-(4-fluorobenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo-[1,2-a][1,3]-diazepine-7-carboxylate ***3j***. Yellow solid; mp 201–204 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.99 (t, J=7.0 Hz, 3H, CH_3), 1.57–1.61 (m, 4H, CH_2CH_2), 3.09–3.12 (m, 2H, NCH_2), 3.93 (q, J=6.9 Hz, 2H, OCH_2), 4.09–4.10 (m, 2H, CH_2N), 6.70 (s, 1H, CH=), 7.08–7.12 (m, 2H, ArH), 7.48–7.51 (m, 2H, ArH), 7.70 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=14.6, 26.6, 28.9, 45.3, 47.0, 59.9, 105.0, 115.8, 117.3, 120.0, 130.9, 136.6, 157.2, 160.6, 165.0, 188.2; IR (KBr): 3282, 2917, 1692, 1605, 1436, 1218, 1164, 1095, 841 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}FN_2NaO_3$ [(M+Na)$^+$], 353.1272; found, 353.1278.

4.3.11. Diethyl 8-benzoyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidine-6,7-dicarboxylate ***3k***. Yellow solid; mp 167–169 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.96 (t, J=6.9 Hz, 3H, CH_3), 1.16 (t, J=6.9 Hz, 2H, CH_3), 1.99–2.02 (m, 2H), 3.36–3.39 (m, 2H, NCH_2), 3.47–3.49 (m, 2H, CH_2N), 4.11–4.17 (m, 4H, OCH_2, OCH_2), 7.38–7.45 (m, 5H, ArH), 7.83 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.2, 20.8, 37.9, 43.0, 60.3, 60.8, 101.5, 114.2, 123.9, 127.3, 128.1, 130.5, 141.2, 148.1, 159.9, 165.0, 189.8; IR (KBr): 3352, 2978, 1730, 1621, 1526, 1271, 1174, 775 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{22}N_2NaO_5$ [(M+Na)$^+$], 393.1421; found, 393.1425.

4.3.12. Diethyl 8-(4-methylbenzoyl)-1,2,3,4-tetrahydropyrrolo[1,2-a] pyrimidine-6,7-dicarboxylate ***3l***. Yellow solid; mp 184–186 °C; ^{1}H

NMR (500 MHz, DMSO-d_6): δ=0.98 (t, 3H, CH_3), 1.18 (t, 3H, CH_3), 1.99–2.01 (m, 2H, CH_2), 2.34 (s, 3H, $ArCH_3$), 3.36–3.38 (m, 2H, NCH_2), 3.53–3.54 (m, 2H, CH_2N), 4.13–4.17 (m, 4H, OCH_2, OCH_2), 7.18–7.20 (d, J=6.2 Hz, 2H, ArH), 7.28–7.30 (d, J=6.6 Hz, 2H, ArH), 7.77 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.3, 20.8, 21.3, 37.9, 43.4, 60.2, 60.8, 101.6, 114.1, 123.9, 127.5, 128.6, 138.5, 140.5, 148.0, 159.9, 165.0, 189.7; IR (KBr): 3352, 2978, 1732, 1687, 1621, 1214, 1174, 1015, 774 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{24}N_2NaO_5$ [(M+Na)$^+$], 407.1577; found, 407.1585.

4.3.13. Diethyl 8-(4-methoxybenzoyl)-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrimidine-6,7-dicarboxylate ***3m***. Yellow solid; mp 164–168 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.01 (t, J=7.0 Hz, 3H, CH_3), 1.16–1.19 (t, J=7.2 Hz, 3H, CH_3), 1.99–2.01 (m, 2H, CH_2), 3.34–3.37 (m, 2H, NCH_2), 3.61–3.64 (m, 2H, CH_2N), 3.81 (s, 3H, OCH_3), 4.12–4.17 (m, 4H, OCH_2, OCH_2), 6.93 (d, J=8.1 Hz, 2H, ArH), 7.40 (d, J=8.1 Hz, 2H, ArH), 7.67 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.3, 20.9, 37.8, 43.1, 55.7, 60.2, 60.9, 101.6, 113.4, 114.0, 123.9, 129.5, 133.7, 147.8, 159.9, 161.5, 189.0; IR (KBr): 3349, 2979, 1729, 1690, 1102, 1028, 785 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{24}N_2NaO_6$ [(M+Na)$^+$], 423.1527; found, 423.1537.

4.3.14. Diethyl 8-(4-chlorobenzoyl)-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrimidine-6,7-dicarboxylate ***3n***. Yellow solid; mp 167–172 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.00 (m, J=7.0 Hz, 3H, CH_3), 1.16 (t, J=7.0 Hz, 3H, CH_3), 1.99–2.01 (m, 2H, CH_2), 3.50–3.57 (m, 2H, CH_2N), 4.10–4.16 (m, 4H, OCH_2, OCH_2), 7.38 (d, J=7.9 Hz, 2H, ArH), 7.47 (d, J=7.9 Hz, 2H, ArH), 7.88 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.3, 20.7, 37.8, 43.0, 60.3, 61.0, 101.3, 114.5, 123.6, 128.2, 129.2, 135.3, 139.8, 148.2, 159.8, 165.0, 188.3; IR (KBr): 3348, 2977, 1731, 1689, 1524, 1214, 1174, 1100, 772 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{21}ClN_2NaO_5$ [(M+Na)$^+$], 427.1031; found, 427.1036.

4.3.15. Diethyl 8-(4-fluorobenzoyl)-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrimidine-6,7-dicarboxylate ***3o***. Yellow solid; mp 169–171 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.99 (t, 3H, CH_3), 1.15 (t, 3H, CH_3), 1.98–2.02 (m, 2H, CH_2), 3.32–3.35 (m, 2H, NCH_2), 3.54–3.56 (m, 2H, CH_2N), 4.10–4.15 (m, 4H, OCH_2, OCH_2), 7.21–7.23 (m, 2H, ArH), 7.42–7.44 (m, 2H, ArH), 7.83 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.3, 20.8, 37.9, 43.1, 60.3, 61.0, 101.4, 114.3, 115.0, 123.7, 130.0, 137.7, 148.1, 159.9, 162.6, 165.0, 188.3; IR (KBr): 3327, 2979, 1617, 1524, 1409, 1173, 1102, 1075, 777 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{21}FN_2NaO_5$ [(M+Na)$^+$], 411.1327; found, 411.1328.

4.3.16. Diethyl 9-benzoyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]diazepine-7,8-dicarboxylate ***3p***. Yellow solid; mp 91–93 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.93 (t, 3H, CH_3), 1.16 (t, 3H, CH_3), 1.78–1.82 (m, 4H, CH_2CH_2), 3.20–3.24 (m, 2H, NCH_2), 3.46–3.47 (m, 2H, CH_2N), 4.13–4.15 (m, 4H, OCH_2, OCH_2), 7.41–7.50 (m, 5H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.6, 14.0, 26.4, 28.7, 45.8, 47.5, 60.9, 104.9, 117.2, 123.4, 127.8, 128.3, 131.4, 140.4, 154.6, 160.2, 164.6, 191.1; IR (KBr): 3309, 1696, 1612, 1519, 1212, 1162, 698 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{24}N_2NaO_5$ [(M+Na)$^+$], 407.1577; found, 407.1585.

4.3.17. Diethyl 9-(4-methylbenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]-diazepine-7,8-dicarboxylate ***3q***. Yellow solid; mp 103–107 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.93 (t, J=7.2 Hz, 3H, CH_3), 1.17 (t, J=6.9 Hz, 3H, CH_3), 1.77–1.81 (m, 4H, CH_2CH_2), 2.33 (s, 3H, $ArCH_3$), 3.17–3.19 (m, 2H, NCH_2), 3.48–3.53 (m, 2H, CH_2N), 4.11–4.17 (m, 4H, OCH_2, OCH_2), 7.20 (d, J=7.8 Hz, 2H, ArH), 7.37 (d, J=8.0 Hz, 2H, ArH), 7.40 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.6, 14.0, 21.3, 26.4, 28.9, 45.9, 47.5, 60.9, 105.2, 117.1, 123.3, 128.1, 128.8, 137.7, 141.6, 154.4, 160.3, 164.6, 190.9; IR (KBr): 3326, 2940, 1733, 1701, 1544, 1404, 1100, 781 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{26}N_2NaO_5$ [(M+Na)$^+$], 421.1734; found, 421.1740.

4.3.18. Diethyl 9-(4-methoxybenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]diazepine-7,8-dicarboxylate ***3r***. Yellow solid; mp 121–123 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.97 (t, J=7.0 Hz, 3H, CH_3), 1.19 (t, J=7.1 Hz, 3H, CH_3), 1.78–1.82 (m, 4H, CH_2CH_2), 3.17–3.19 (m, 2H, NCH_2), 3.60–3.64 (m, 2H, CH_2N), 3.81 (s, 3H, OCH_3), 4.15–4.19 (m, 4H, OCH_2, OCH_2), 6.96 (d, J=8.4 Hz, 2H, ArH), 7.25 (br, 1H), 7.49 (d, J=8.3 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.1, 26.5, 29.1, 46.0, 47.5, 55.8, 60.8, 60.9, 105.5, 113.6, 117.1, 123.2, 130.2, 133.0, 154.0, 160.3, 162.2, 164.7, 190.0; IR (KBr): 3327, 2945, 1701, 1605, 1429, 1163, 1025, 791 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{26}N_2NaO_6$ [(M+Na)$^+$], 437.1683; found, 437.1690.

4.3.19. Diethyl 9-(4-chlorobenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]-diazepine-7,8-dicarboxylate ***3s***. Yellow solid; mp 130–133 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.98 (t, J=7.1 Hz, 3H, CH_3), 1.18 (t, J=7.0 Hz, 3H, CH_3), 1.79–1.84 (m, 4H, CH_2CH_2), 3.24–3.26 (m, 2H, NCH_2), 3.55–3.57 (m, 2H, CH_2N), 4.13–4.17 (m, 4H, OCH_2, OCH_2), 7.46–7.50 (m, 5H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.1, 26.3, 28.7, 45.8, 47.6, 60.9, 61.0, 104.7, 117.4, 123.0, 128.4, 129.8, 136.1, 139.2, 154.6, 160.1, 164.5, 189.6; IR (KBr): 3331, 2944, 1729, 1606, 1404, 1159, 782 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{23}ClN_2NaO_5$ [(M+Na)$^+$], 441.1188; found, 441.1196.

4.3.20. Diethyl 9-(4-fluorobenzoyl)-2,3,4,5-tetrahydro-1H-pyrrolo-[1,2-a][1,3]-diazepine-7,8-dicarboxylate ***3t***. Yellow solid; mp 126–127 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.74 (t, 3H, CH_3), 0.95 (t, 3H, CH_3), 1.54–1.60 (m, 4H, CH_2CH_2), 2.98–3.10 (m, 2H, NCH_2), 3.33–3.36 (m, 2H, CH_2N), 3.90–3.93 (m, 4H, OCH_2, OCH_2), 7.00–7.02 (m, 2H, ArH), 7.21 (br, 1H, NH), 7.28–7.31 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.7, 14.1, 26.4, 28.8, 45.8, 47.6, 60.9, 61.0, 104.9, 115.2, 117.3, 123.1, 130.6, 137.1, 154.5, 160.2, 163.1, 164.6, 189.6; IR (KBr): 3328, 2940, 1707, 1604, 1237, 1098, 843, 789 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{23}FN_2NaO_5$ [(M+Na)$^+$], 425.1483; found, 425.1476.

4.3.21. Ethyl 8-benzoyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]-pyridine-7-carboxylate ***4a***. Yellow solid; mp 168–172 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.88 (m, J=6.8 Hz, 3H, CH_3), 3.38–3.40 (m, 2H, CH_2N), 3.78–3.81 (m, 2H, NCH_2), 4.08 (q, J=6.8 Hz, 2H, OCH_2), 5.77 (s, H, CH=), 7.41–7.49 (m, 5H, ArH), 8.63 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.6, 43.1, 43.7, 61.6, 93.8, 106.7, 128.0, 128.6, 131.6, 140.8, 146.1, 156.5, 160.1, 166.7, 191.5; IR (KBr): 3350, 2974, 1736, 1667, 1605, 1556, 1242, 1042, 755 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}N_2NaO_4$ [(M+Na)$^+$], 335.1002; found, 335.1002.

4.3.22. Ethyl 8-(4-methylbenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-7-carboxylate ***4b***. Yellow solid; mp 156–159 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.88 (t, J=7.0 Hz, 3H, CH_3), 2.32 (s, 3H, $ArCH_3$), 3.41–3.45 (m, 2H, NCH_2), 3.77–3.80 (m, 2H, CH_2N), 4.07 (q, J=7.0 Hz, 2H, OCH_2), 5.76 (s, 1H, CH=), 7.21 (d, J=7.8 Hz, 2H, ArH), 7.35 (d, J=7.9 Hz, 2H, ArH), 8.53 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.5, 21.3, 43.1, 43.7, 61.6, 94.0, 106.5, 128.1, 129.1, 138.1, 141.9, 146.1, 156.4, 160.1, 166.8, 191.3; IR (KBr): 3356, 2978, 1660, 1599, 1564, 1331, 1245, 1047, 772 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}N_2NaO_4$ [(M+Na)$^+$], 349.1159; found, 349.1168.

4.3.23. Ethyl 8-(4-methoxybenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]-pyridine-7-carboxylate ***4c***. Yellow solid; mp 163–164 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.92 (t, J=6.3 Hz, 3H, CH_3), 3.32–3.35 (m, 2H, CH_2N), 3.53–3.56 (m, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 4.09 (q, J=6.3 Hz, 2H, OCH_2), 5.76 (s, 1H, CH=), 6.97 (d, J=7.3 Hz, 2H, ArH), 7.47 (d, J=7.3 Hz, 2H, ArH), 8.44 (br, 1H, NH); ^{13}C NMR (125 MHz,

DMSO-d_6): δ=13.7, 43.1, 43.8, 55.8, 61.5, 93.8, 106.4, 113.9, 130.2, 133.5, 146.0, 156.2, 159.8, 162.2, 166.8, 190.4; IR (KBr): 3350, 2978, 1742, 1659, 1596, 1248, 1173, 829, 780 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}N_2NaO_5$ [$(M+Na)^+$], 365.1108; found, 365.1112.

4.3.24. Ethyl 8-(4-chlorobenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo [1,2-a]pyridine-7-carboxylate ***4d***. Yellow solid; mp 183–185 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.91 (t, J=7.3 Hz, 3H, CH_3), 3.46–3.50 (m, 2H, NCH_2), 3.76–3.80 (m, 2H, CH_2N), 4.08 (q, J=7.3 Hz, 2H, OCH_2), 5.78 (s, 1H, CH=), 7.45–7.49 (m, 4H, ArH), 8.65 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.6, 43.2, 43.7, 61.8, 93.7, 107.0, 128.7, 130.0, 136.4, 139.6, 145.8, 156.5, 160.1, 166.7, 190.2; IR (KBr): 3348, 2991, 1728, 1671, 1604, 1559, 1249, 1046, 772 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{15}ClN_2NaO_4$ [$(M+Na)^+$], 369.0613; found, 369.0621.

4.3.25. Ethyl 8-(4-fluorobenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo [1,2-a]pyridine-7-carboxylate ***4e***. Yellow solid; mp 165–166 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=0.70 (t, J=7.2 Hz, 3H, CH_3), 3.26–3.30 (m, 2H, NCH_2), 3.55–3.58 (m, 2H, CH_2N), 3.85 (q, J=7.2 Hz, 2H, OCH_2), 5.55 (s, 1H, CH=), 7.01–7.04 (m, 2H, ArH), 7.29–7.32 (m, 2H, ArH), 8.40 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.6, 43.2, 43.7, 61.6, 93.6, 107.0, 111.5, 130.7, 137.6, 145.8, 156.5, 159.9, 163.1, 165.1, 166.7, 190.0; IR (KBr): 3352, 2988, 1667, 1601, 1240, 1182, 791 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{15}FN_2NaO_4$ [$(M+Na)^+$], 353.0908; found, 353.0913.

4.3.26. Ethyl 8-(4-chlorobenzoyl)-6-iodo-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-7-carboxylate ***5a***. Yellow solid; mp 194–196 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.08 (t, J=7.1 Hz, 3H), 3.70–3.77 (m, 2H, NCH_2), 4.12 (q, J=7.1 Hz, 2H, OCH_2), 7.47–7.52 (m, 4H, ArH), 8.41 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ=13.6, 43.3, 45.0, 61.9, 74.4, 96.9, 128.4, 130.8, 136.7, 137.9, 150.8, 156.1, 157.9, 166.6, 189.9; IR (KBr): 3352, 3444, 1729, 1657, 1604, 1360, 1218, 1046, 686 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{14}ClIN_2NaO_4$ [$(M+Na)^+$], 494.9579; found, 494.9582.

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