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One-pot two-step tandem reactions for selective synthesis of pyrrolo[2,1-*a*]-isoquinolines and dihydro-, tetrahydro-derivatives

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ABSTRACT

A sequential one-pot two-step tandem reaction for selective and efficient synthesis of pyrrolo[2,1-*a*]-isoquinoline and its dihydro- and tetrahydro-derivatives has been developed. The tandem reactions of isoquinoline, α-halogenated methylene compounds, aromatic aldehydes, and cyanoacetamide firstly give tetrahydropyrrolo[2,1-*a*]isoquinolines as main products. The corresponding pyrrolo[2,1-*a*]isoquinolines and dihydropyrrolo[2,1-*a*]isoquinolines can be obtained directly by controlling oxidation with DDQ. The mechanism of this tandem reaction involved the 1,3-dipolar cycloaddition of isoquinolinium ylide as the key step. A unique elimination of the amido group preferring to the cyano group has been observed.

1. Introduction

As one kind of reactive azomethine ylides, heteroaromatic *N*-ylide has been used extensively in cycloadditions for the synthesis of the fused heterocycles with a nitrogen at the point of fusion.[1–4] Heteroaromatic *N*-ylides, such as pyridinium, thiazolium, quinolinium, isoquinolinium methylides are readily available from the alkylation of azaaromatic heterocycles and sequential deprotonation reaction.[5–7] The 1,3-dipolar cycloaddition of heteroaromatic *N*-methylides with electron-deficient alkynes and alkenes provided a convenient route to novel nitrogen bridged heterocycles, such as indolizines and benzo-fused derivatives.[8–11] Recently we realized that the versatile reactivity and easy in situ formation of azaaromatic *N*-ylide can be used to design new multicomponent reactions and found some interesting results. Previous work showed that polysubstituted pyridines,[11] cyclopropanes,[12] dihydrofuranes,[13] zwitterionic salts,[14] and pyrido[1,2-*a*]benzimidazole derivatives[15] could be produced efficiently from multicomponent cyclization reactions involving heteroaromatic *N*-ylide with electron-deficient alkenes bearing versatile functional groups. In continuation of our efforts to develop new multicomponent reactions we investigate the reactivity of different kinds of active methylene compounds in the reactions. Here we wish to report the efficient synthesis of pyrrolo[2,1-*a*]isoquinoline and its dihydro- and tetrahydro-derivatives via new four-component reactions of isoquinoline, active α-halogenomethylene compounds, aromatic aldehydes, and cyanoacetamide.

2. Results and discussions

In an exploratory study the ethanol solution of *p*-methoxybenzaldehyde, cyanoacetamide, and *N*-ethoxycarbonylmethylisoquinolinium bromide, which was prepared in situ from the reaction of isoquinoline with ethyl α-bromoacetate, was stirred at room temperature for about 24 h in the presence of triethylamine as base catalyst. After workup it was interesting to find that pyrrolo[2,1-*a*]isoquinoline (**1a**), dihydropyrrolo[2,1-*a*]isoquinoline (**2a**), and tetrahydropyrrolo[2,1-*a*]isoquinoline (**3a**) were separated in about 10%, 25%, and 42% yields, respectively (Scheme 1). This result clearly showed that an 1,3-dipolar addition of isoquinolinium ylide to in situ formed active arylidene cyanoacetamide took place and compounds **1a** and **2a** came from the dehydrogenation and elimination process of initially formed 1,3-dipolar cycloadduct **3a** in air. Pyrrolo[2,1-*a*]isoquinoline and its dihydro-, tetrahydro-analogs are one important kinds of heterocycles and perform very interesting biological activities.[16,17] In principle there are two most general methods for their synthesis. One is 1,3-cycloaddition of isoquinolinium ylide with active alkynes and alkenes.[6b,18,19] Another is the Huisgen 1,4-dipolar addition, in which the intermediate formed in situ by the addition of isoquinoline to electron-deficient alkynes and then reacted with dipolarophilic reagents.[20,21] Here the preliminary result of one-pot tandem reaction gave a new strategy to develop efficient synthetic

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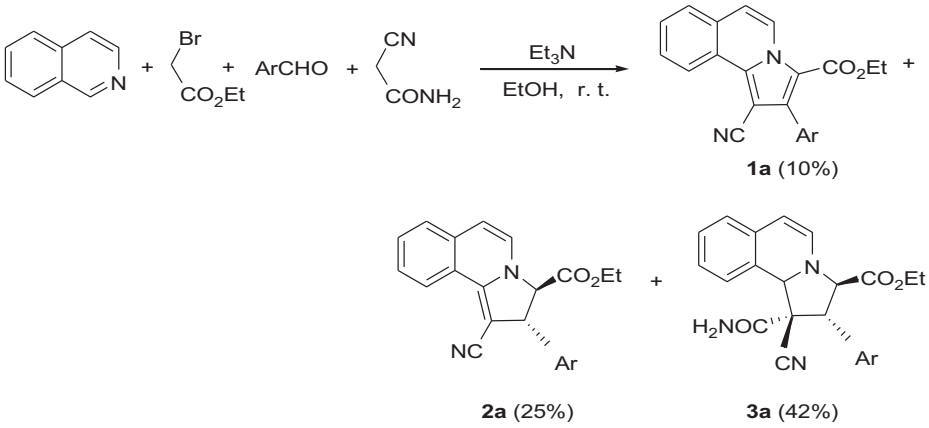


Scheme 1. 1,3-dipolar cycloaddition via the four-component reaction.

procedure for the selective preparation of pyrrolo[2,1-*a*]isoquinoline and its tetrahydro- and dihydro-derivatives.

It has long been known that the 1,3-dipolar cycloadduct of heteroaromatic *N*-ylide with electron-deficient olefins is not always thermally stable, which is mainly due to the loss of aromaticity of the heteroaromatic ring.[22,23] One effective method to solve this problem is the dehydrogenation of cycloadducts with sequential oxidation to recover aromatic system. For this purpose versatile procedures and oxidizing reagents were employed.[24,25] Here we used one of the most common reagents DDQ as the dehydrogenating reagent. Thus after accomplishing the 1,3-dipolar cycloaddition, 2 M ratios of DDQ was added to the resulting mixture and the whole system was stirred at room temperature for additional 8 h. We were delighted to find that the dehydrogenated pyrrolo[2,1-*a*]isoquinoline (**1a**) was successfully obtained in 85% yield (Table 1, entry 1). Then various aromatic aldehydes were employed in the reactions and the each reaction proceeded smoothly to give the corresponding pyrrolo[2,1-*a*]isoquinolines **1b**–**g** in 72–82% yields (Table 1, entries 2–7). Benzaldehydes bearing with both stronger electron-donating and electron-withdrawing substituents afforded the desired products in very satisfactory yields. This result clearly showed that a one-pot tow-step tandem reaction for the efficient synthesis of pyrrolo[2,1-*a*]isoquinolines has been successfully established. The pyrrolo[2,1-*a*]isoquinolines **1a**–**g** were fully characterized by ^{1}H and ^{13}C NMR, MS, IR spectra, and elemental analysis. Their structures were further confirmed by determination of the single crystal of compound **1b** (Fig. 1). It should be pointed out that in the formation process of pyrrolo[2,1-*a*]isoquinolines the amido group was eliminated out, while the cyano group was maintained in the target molecule.

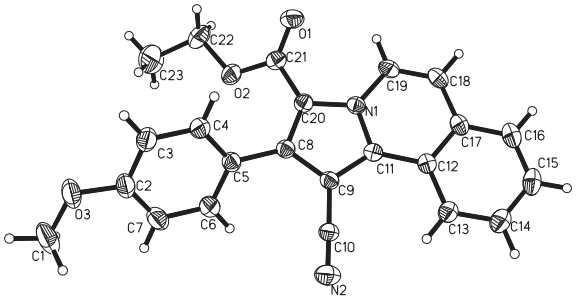
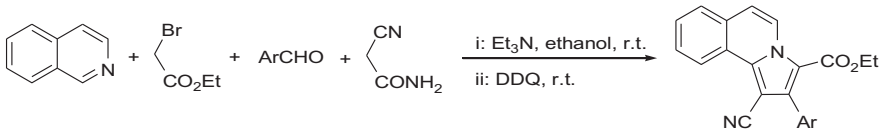


Fig. 1. Molecular structure of pyrrolo[2,1-*a*]isoquinoline **1b**.

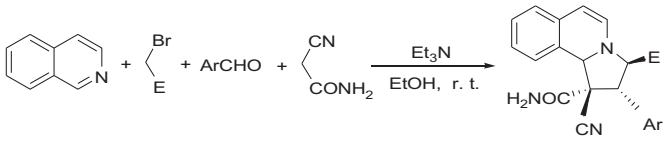
To further extend the utility of this domino reaction, the reactivity of other active α-halogenated methylene compounds was also explored. A mixture of previously formed *N*-*p*-nitrobenzylisoquinolinium bromide, aromatic aldehydes, and cyanoacetoamide in the presence of triethylamine as base catalyst was heated at about 50 °C for several hours. Then 2 M ratios of DDQ were added and the oxidation reaction was finished at room temperature in 8 h. By using this one-pot two-step reaction procedure the expected pyrrolo[2,1-*a*]isoquinolines **4a**–**f** were prepared in 77–94% yields (Table 2, entries 1–6). Under similar reaction conditions, the reactions of α-phenacyl bromide and *N*,*N*-diethyl chloroacetamide also gave pyrrolo[2,1-*a*]isoquinolines **4g**–**r** in 60–80% (Table 2, entries 7–18). Totally 18 functionalized pyrrolo[2,1-*a*]isoquinolines were successfully prepared and their structures were fully characterized with spectroscopic methods. Two representative single crystal structures of **4d** (Fig. 2) and **4i** were also determined.

Table 1
Synthesis of pyrrolo[2,1-*a*]isoquinolines **1a**–**g** from reactions of ethyl α-bromoacetate



Entry	Compd	Ar	Yield (%)
1	**1a**	*p*-$CH_3OC_6H_4$	85
2	**1b**	*p*-$CH_3C_6H_4$	75
3	**1c**	C_6H_4	72
4	**1d**	*p*-FC_6H_4	82
5	**1e**	*m*-ClC_6H_4	82
6	**1f**	*p*-BrC_6H_4	78
7	**1g**	*m*-$NO_2C_6H_4$	78

Table 2
Synthesis of pyrrolo[2,1-*a*]isoquinolines **4a**–**r** from tandem reactions



Entry	Compd	E	Ar	Yield (%)
1	**4a**	*p*-$NO_2C_6H_4$	C_6H_4	80
2	**4b**	*p*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	87
3	**4c**	*p*-$NO_2C_6H_4$	*p*-$CH_3OC_6H_4$	94
4	**4d**	*p*-$NO_2C_6H_4$	*p*-BrC_6H_4	92
5	**4e**	*p*-$NO_2C_6H_4$	*m*-ClC_6H_4	91
6	**4f**	*p*-$NO_2C_6H_4$	*p*-FC_6H_4	77
7	**4g**	COC_6H_5	C_6H_4	62
8	**4h**	COC_6H_5	*p*-$CH_3C_6H_4$	71
9	**4i**	COC_6H_5	*p*-$CH_3OC_6H_4$	68
10	**4j**	COC_6H_5	*p*-BrC_6H_4	62
11	**4k**	COC_6H_5	*m*-ClC_6H_4	78
12	**4l**	COC_6H_5	*p*-FC_6H_4	63
13	**4m**	$CONEt_2$	C_6H_4	67
14	**4n**	$CONEt_2$	*p*-$CH_3C_6H_4$	73
15	**4o**	$CONEt_2$	*p*-$CH_3OC_6H_4$	80
16	**4p**	$CONEt_2$	*p*-BrC_6H_4	75
17	**4q**	$CONEt_2$	*m*-ClC_6H_4	60
18	**4r**	$CONEt_2$	*m*-$NO_2C_6H_4$	63

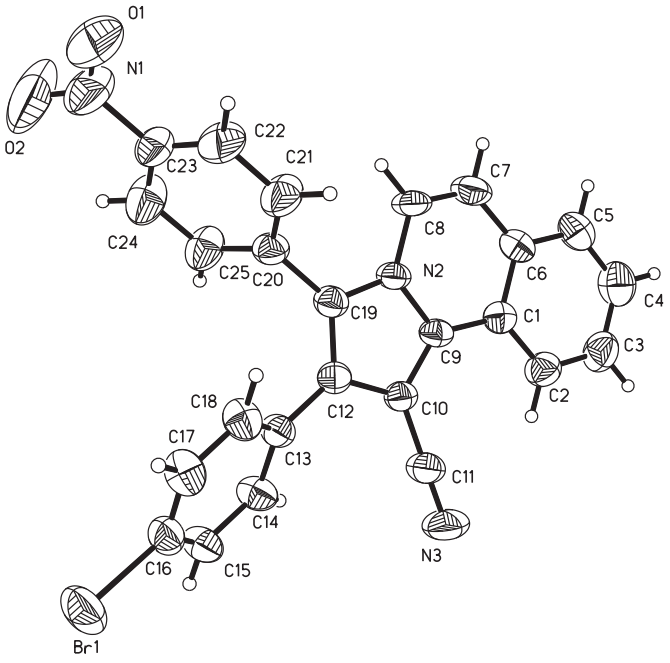
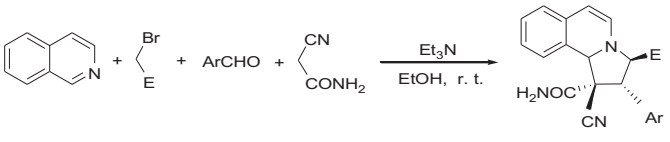


Fig. 2. Molecular structure of pyrrolo[2,1-*a*]isoquinoline **4d**.

These results indicated that this one-pot two-step tandem reaction is quite general and has very broad substrate scopes.

Encouraged by these results, we turned our attention to attempt to isolate directly the 1,3-dipolar cycloadducts of isoquinolinium ylide. In order to block dehydrogenation and elimination process we carried out the triethylamine catalyzed tandem reaction of *N*-ethoxycarbonylmethylisoquinolinium bromide, aromatic aldehydes, and cyanoamide in a nitrogen atmosphere at room temperature for 6 h. To our delight tetrahydropyrrolo[2,1-*a*]isoquinolines existed as main products in the reaction mixture and nearly no dehydrogenated products were detected by TLC analysis. After workup the desired tetrahydropyrrolo[2,1-*a*]isoquinolines **3a**–**d** were obtained in 62–80% yields (Table 3, entries 1–4). Under similar

Table 3
Synthesis of tetrahydropyrrolo[2,1-*a*]isoquinolines **3a**–**g** from tandem reactions



Entry	Compd	E	Ar	Yield (%)
1	**3a**	CO_2Et	*p*-$CH_3OC_6H_4$	82
2	**3b**	CO_2Et	Ph	76
3	**3c**	CO_2Et	*m*-ClC_6H_4	68
4	**3d**	CO_2Et	*m*-$NO_2C_6H_4$	80
5	**3e**	*p*-$NO_2C_6H_4$	*p*-$(CH_3)_3CC_6H_4$	63
6	**3f**	*p*-$NO_2C_6H_4$	*p*-BrC_6H_4	73
7	**3g**	*p*-$NO_2C_6H_4$	*m*-ClC_6H_4	82

conditions the tandem reactions of *p*-nitrobenzyl bromide gave the tetrahydropyrrolo[2,1-*a*]isoquinolines **3e**–**g** in 63–82% yields (Table 3, entries 1–4). The structures of the prepared tetrahydropyrrolo[2,1-*a*]isoquinolines **3a**–**g** were also fully characterized by ^1H and ^{13}C NMR, MS, IR spectra, and elemental analysis. For examples in the ^1H NMR spectrum of **3b**, the two protons of amido group are anisotropic and showed two broadly singlet at 6.07, 6.02 ppm. The ethoxyl group showed one quartet at 4.17 ppm and one triplet at 1.20 ppm. The three protons at tetrahydropyrrole ring display one singlet at 5.66 ppm and two doublets at 4.54, 4.37 ppm with the vicinal coupling constant J=8.5 Hz. In the ^1H NMR spectrum of **3f** the three protons at tetrahydropyrrole ring display one singlet at 5.86 ppm and two doublets at 5.16, 3.93 ppm with the vicinal coupling constant J=9.7 Hz. The similar peak pattern and coupling constant were also observed in other ^1H NMR spectra of the prepared tetrahydropyrrolo[2,1-*a*]isoquinolines **3a**–**g**. According to the careful analysis of ^1H NMR data and comparison with the earlier reported results[5,6] we could tentatively conclude that only one diastereoisomer of tetrahydropyrrolo[2,1-*a*]isoquinolines **3a**–**g** was produced in this tandem 1,3-dipolar addition. The X-ray diffraction determination of single crystal **3g** (Fig. 3) clearly showed that 2-*p*-nitrophenyl group and 3-*m*-chlorophenyl group existed in trans-configuration. These results also revealed that the isoquinolinium ylide assisted tandem 1,3-dipolar addition is a highly diastereoselective reaction.

We noticed that the pyrrolo[2,1-*a*]isoquinolines were efficiently prepared by oxidation of the initially formed tetrahydropyrrolo[2,1-*a*]isoquinolines with 2 M ratios of DDQ as oxidizing reagent. If less

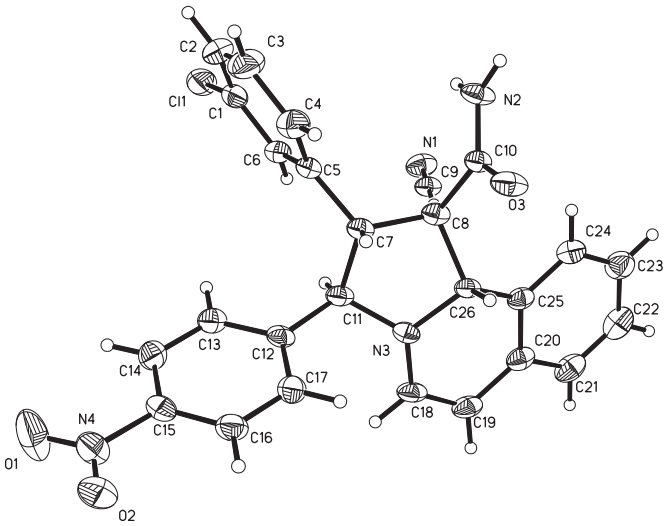
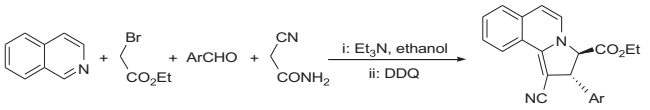


Fig. 3. Molecular structure of tetrahydropyrrolo[2,1-*a*]isoquinoline **3g**.

amount of DDQ was used the oxidation might be stopped at the formation of dihydropyrrolo[2,1-*a*]isoquinoline stage. Thus we carried out the oxidation reaction by addition of 1 M ratio of DDQ to the system of the 1,3-dipolar cycloaddition of *N*-ethoxycarbonylmethylisoquinolinium bromide, aromatic aldehydes, and cyanoacetamide. The expected dihydropyrrolo[2,1-*a*]isoquinolines **2a**–**f** are successfully prepared in 54–68% yields (Table 4). It should be pointed that the very pure dihydropyrrolo[2,1-*a*]isoquinolines **2a**–**f** were obtained by merely filtration and recrystallization steps. By using 1 equiv of DDQ the amido group was eliminated and cyano group was remained in the molecule of dihydropyrrolo[2,1-*a*]isoquinolines **2a**–**f**. The stereochemistry of **2a**–**f** should be the same with that of the initial formed 1,3-dipolar cycloadducts **3a**–**g**. Thus the aryl group and the esteric group are in trans-configuration, which was confirmed by the ^{1}H NMR spectra and the single crystal structure of **2b** (Fig. 4). As an example in ^{1}H NMR spectrum of **2d** the two protons of dihydropyrrole ring display two doublets at 4.59, 4.50 ppm with vicinal coupling constant J=5.3 Hz.

Table 4
Synthesis of dihydropyrrolo[2,1-*a*]isoquinolines **2a**–**f** from tandem reactions



Entry	Compd	Ar	Yield (%)
1	**2a**	*p*-$CH_3OC_6H_4$	65
2	**2b**	*p*-$CH_3C_6H_4$	68
3	**2c**	Ph	60
4	**2d**	*p*-BrC_6H_4	60
5	**2e**	*m*-ClC_6H_4	54
6	**2f**	*m*-$NO_2C_6H_4$	65

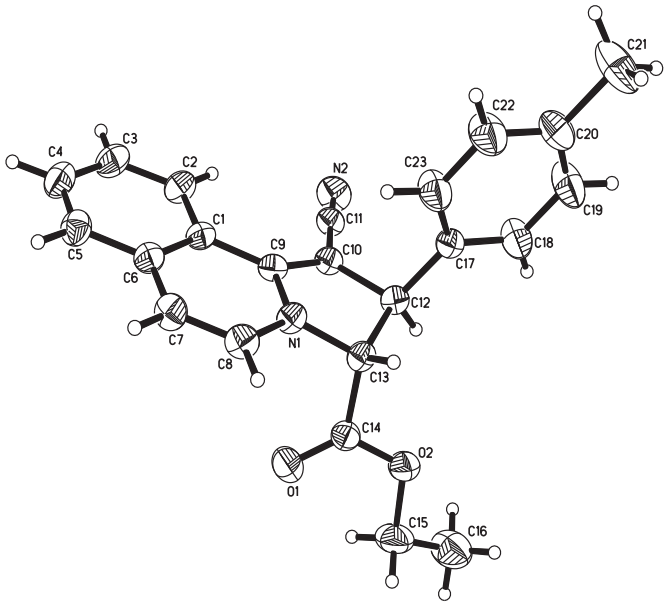


Fig. 4. Molecular structure of dihydropyrrolo[2,1-*a*]isoquinoline **2b**.

To explain the mechanism of this one-pot multicomponent reaction, we propose a plausible reaction course with the reaction of ethyl α-bromoacetate, which is illustrated in Scheme 2. The first step is the addition of ethyl α-bromoacetate to isoquinoline to yield *N*-ethoxycarbonylmethylisoquinolinium bromide (**A**), which in turn converts to isoquinolinium ylide (**B**) by deprotonation of triethylamine. It is needed to state that 2 equiv amounts of triethylamine were employed in the reaction. One equivalent was for the generation of ylide (**B**) and the rest for catalyzing the following reaction. The second step is triethylamine catalyzed Knoevenagel condensation of aromatic aldehyde with cyanoacetamide to give arylidene cyanoacetamide (**C**). The third step is 1,3-dipolar cycloaddition of isoquinolinium ylide (**B**) to arylidene cyanoacetamide (**C**) to afford the tetrahydropyrrolo[2,1-*a*]isoquinolin (**3**). By addition of DDQ as oxidizing reagent, an amido group was eliminated from tetrahydropyrrolo[2,1-*a*]isoquinoline (**3**) to yield dihydropyrrolo[2,1-*a*]isoquinoline (**2**). At last further oxidation with DDQ gave the pyrrolo[2,1-*a*]isoquinoline (**1**) as the final product. In this proposed reaction mechanism the key step is the 1,3-dipolar cycloaddition of isoquinolinium ylide (**B**) to electron-deficient olefin (**C**). These two reactants were both formed in situ from the starting material precursors in reaction system.

In the converting process of tetrahydropyrrolo[2,1-*a*]isoquinoline (**3**) to dihydropyrrolo[2,1-*a*]isoquinoline (**2**) one unique feature of this tandem reaction is that the amido group was eliminated out and the cyano group was maintained in the molecule. The cyano group is a good leaving group in many organic reactions. In order to probe the credibility of our proposed mechanistic scheme and shed more light on the formation of pyrrolo[2,1-*a*]isoquinoline, we employed ethyl cyanoacetate to replace cyanoacetamide in the tandem reaction. The tandem reactions of *N*-ethoxycarbonylmethylisoquinolinium bromide, ethyl cyanoacetate with *p*-methoxy and *m*-chlorobenzaldehyde (Scheme 3) gave pyrrolo[2,1-*a*]isoquinolines **1a** and **1e** in moderate yields. The formation of pyrrolo[2,1-*a*]isoquinolines **1a** and **1e** clearly indicated that the ethyl ester group was eliminated and the cyano group still remained in the molecule. This result strongly suggested that the amido and esteric group could be eliminated more quickly than that of cyano group in this reaction condition.

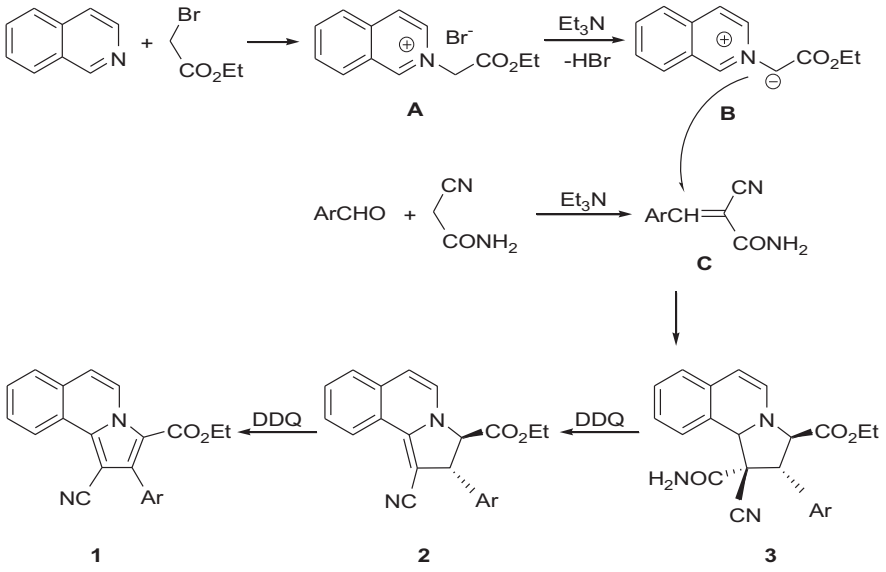
In summary, we have developed a new one-pot two-step reaction involving isoquinoline, aromatic aldehyde, cyanoacetamide, and reactive α-halomethylene compounds for the synthesis of pyrrolo[2,1-*a*]isoquinoline and its dihydro- and tetrahydro-derivatives. This protocol not only provides an effective methodology for the preparation of the functionalized pyrrolo[2,1-*a*]isoquinolines, but also opens a brand way for employing heteroaromatic *N*-ylide intermediate to design new multicomponent reaction. The mechanism of this tandem reaction believed involving 1,3-dipolar cycloaddition of heteroaromatic *N*-ylide. A unique elimination of the amido group preferring to the cyano group is also observed. We are currently investigating the expansion of the scope of the reaction to other α-halogen substituted carbonyl compounds and its application to the synthesis of other heterocyclic systems.

3. Experimental section

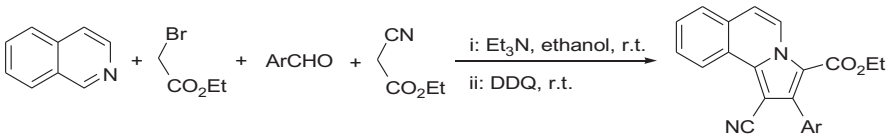
3.1. General procedure for the synthesis of pyrrolo[2,1-*a*] isoquinolines 1a–g

A mixture of ethyl α-bromoacetate (2.2 mmol, 0.367 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was stirred at room temperature for about 1.5 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.168 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred at room temperature for additional 6–8 h . Then the DDQ (4.0 mmol, 0.908 g) was added. The resulting mixture was stirred at room temperature for 8 h. The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product for analysis.

Compound **1a**: White solid, yield: 85%, mp 180–182 °C, IR (KBr): 3136 (w), 2979 (w), 2209 (m), 1697 (vs), 1612 (m), 1517 (m), 1428 (m), 1402 (m), 1370 (m), 1298 (s), 1246 (s), 1187 (s), 1088 (s), 1033 (w), 801 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.32 (d, J=7.2 Hz, 1H, CH), 8.97 (d, J=6.4 Hz, 1H, CH), 7.74 (s, 1H, ArH), 7.64 (d, J=3.4 Hz, 2H,



Scheme 2. The reaction mechanism of the tandem four-component reactions.



1a: Ar = *p*-$CH_3OC_6H_4$, 51%; **1e**: Ar = *m*-ClC_6H_4, 59%

Scheme 3. The synthesis of pyrrolo[2,1-*a*]isoquinolines from the reactions of ethyl cyanoacetate.

ArH), 7.44 (d, *J*=7.4 Hz, 2H, ArH), 7.18 (d, *J*=7.2 Hz, 1H, ArH), 7.01 (d, *J*=7.4 Hz, 2H, ArH), 4.21 (d, *J*=6.5 Hz, 2H, CH_2), 3.88 (s, 3H, CH_3O), 1.09 (t, *J*=6.6 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 159.8, 139.5, 136.1, 131.6, 131.4, 131.2, 129.4, 129.1, 128.5, 127.1, 124.6, 123.8, 123.5, 117.4, 114.8, 114.3, 113.3, 87.7, 77.3, 77.1, 76.9, 60.6, 55.3, 13.8. MS (*m*/*z*): 371.60 ($[M+1]^+$, 100%). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C 74.58, H 4.90, N 7.56. Found: C 74.64, H 5.23, N 7.29.

Compound **1b**: White solid, yield: 75%, mp 166–168 °C, IR (KBr): 3138 (w), 2983 (w), 2903 (w), 2208 (m), 1697 (vs), 1517 (m), 1406 (m), 1370 (m), 1346 (m), 1248 (m), 1189 (s), 1118 (w), 1088 (s), 1021 (w), 798 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.35 (d, *J*=7.2 Hz, 1H, CH), 9.01 (d, *J*=6.0 Hz, 1H, CH), 7.77 (d, *J*=5.7 Hz, 1H, ArH), 7.66 (d, *J*=3.5 Hz, 2H, ArH), 7.39 (d, *J*=7.1 Hz, 2H, ArH), 7.27 (d, *J*=7.8 Hz, 2H, ArH), 7.21 (d, *J*=7.2 Hz, 1H, ArH), 4.10 (q, *J*=6.4 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.06 (t, *J*=6.4 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.1, 139.9, 138.2, 136.2, 129.9, 129.5, 129.2, 128.6, 128.5, 127.1, 126.9, 124.7, 124.0, 123.9, 123.6, 117.3, 114.9, 114.4, 87.8, 60.9, 60.6, 21.4, 13.7. MS (*m*/*z*): 355.63 ($[M+1]^+$, 100%). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C 77.95, H 5.12, N 7.90. Found: C 77.68, H 5.40, N 7.75.

Compound **1c**: White solid, yield: 72%, mp 172–174 °C, IR (KBr): 3146 (w), 2978 (w), 2210 (m), 1688 (vs), 1515 (m), 1403 (s), 1371 (s), 1342 (m), 1249 (m), 1187 (s), 1122 (w), 1087 (m), 1016 (w), 806 (w), 743 (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.36 (d, *J*=7.2 Hz, 1H, CH), 9.00 (d, *J*=6.1 Hz, 1H, CH), 7.77 (d, *J*=5.5 Hz, 1H, ArH), 7.66 (d, *J*=3.6 Hz, 2H, ArH), 7.48–7.45 (m, 5H, ArH), 7.22 (d, *J*=7.2 Hz, 1H, ArH), 4.17 (q, *J*=6.4 Hz, 2H, CH_2), 1.01 (t, *J*=6.4 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 139.7, 136.2, 132.6, 129.9, 129.5, 129.2, 128.6, 128.4, 127.8, 127.1, 124.6, 123.8, 123.7, 123.6, 117.1, 115.0, 114.5, 87.7, 60.0, 13.6. MS (*m*/*z*): 341.34 ($[M+1]^+$, 100%). Anal. Calcd for $C_{22}H_{16}N_2O_2$: C 77.63, H 4.74, N 8.23. Found: C 77.85, H 5.17, N 7.76.

Compound **1d**: White solid, yield: 82%, mp 174 °C, IR (KBr): 3078 (w), 2976 (w), 2216 (m), 1693 (s), 1602 (w), 1519 (m), 1402 (m), 1292 (m), 1222 (m), 1184 (m), 1081 (m), 1012 (m), 810 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.35 (d, *J*=7.4 Hz, 1H, ArH), 8.98 (d, *J*=5.4 Hz, 1H, CH), 7.77 (s, 1H, CH), 7.67 (d, *J*=4.0 Hz, 2H, ArH), 7.47 (t, *J*=5.2 Hz, 2H, ArH), 7.22 (d, *J*=7.3 Hz, 1H, ArH), 7.17 (t, *J*=8.0 Hz, 2H, ArH), 4.19 (q, *J*=7.0 Hz, 2H, CH_2), 1.06 (t, *J*=6.9 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 162.1, 160.8, 138.6, 136.2, 131.9, 131.8, 129.6, 129.2, 128.7, 128.5, 127.2, 124.6, 123.8, 123.5, 117.0, 115.2, 115.0, 114.9, 114.5, 87.7, 60.7, 13.7. MS (*m*/*z*): 359.30 ($[M+1]^+$, 100%). Anal. Calcd for $C_{22}H_{15}FN_2O_2$: C 73.73, H 4.22, N 7.82. Found: C 73.40, H 4.61, N 7.63.

Compound **1e**: White solid, yield: 82%, mp 176–178 °C, IR (KBr): 3147 (w), 2986 (w), 2214 (m), 1694 (s), 1595 (w), 1518 (w), 1433 (w), 1371 (m), 1342 (w), 1248 (m), 1187 (m), 1097 (m), 1077 (m), 802 (m), 747 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.40 (d, *J*=7.4 Hz, 1H, ArH), 9.02 (d, *J*=6.7 Hz, 1H, CH), 7.80 (d, *J*=6.5 Hz, 1H, CH), 7.17–7.69 (m, 2H, ArH), 7.48 (s, 1H, ArH), 7.43–7.40 (m, 3H, ArH), 7.27 (s, 1H, ArH), 4.20 (q, *J*=7.0 Hz, 2H, CH_2), 1.06 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 137.8, 136.2, 134.3, 133.6, 130.4, 129.7, 129.2, 129.1, 128.7, 128.1, 127.2, 124.5, 123.7, 123.4, 116.8, 115.3, 114.5, 87.5, 60.8, 13.6. MS (*m*/*z*): 374.75 ($[M+1]^+$, 100%), 378.02 ($[M+3]^+$, 27%). Anal. Calcd for $C_{22}H_{15}ClN_2O_2$: C 70.50, H 4.03, N 7.47. Found: C 70.29, H 4.45, N 7.22.

Compound **1f**: White solid, yield: 78%, mp 168–170 °C, IR (KBr): 3140 (w), 2982 (w), 2211 (m), 1098 (s), 1517 (m), 1408 (m), 1370 (m), 1345 (m), 1250 (m), 1209 (w), 1187 (s), 1119 (w), 1089 (m), 1013 (w), 800 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.35 (d, *J*=7.4 Hz, 1H, ArH), 8.97 (d, *J*=5.0 Hz, 1H, CH), 7.77 (d, *J*=2.8 Hz, 1H, CH), 7.67 (d, *J*=4.8 Hz, 2H, ArH), 7.61 (d, *J*=7.5 Hz, 2H, ArH), 7.37 (d, *J*=7.5 Hz, 2H, ArH), 7.23 (d, *J*=7.4 Hz, 1H, ArH), 4.20 (q, *J*=6.9 Hz, 2H, CH_2), 1.10 (t, *J*=6.9 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 138.3, 136.3, 131.7, 131.6, 131.5, 131.1, 129.7, 129.2, 128.7, 127.2, 124.6, 123.8, 123.5, 122.8, 116.9, 115.2, 114.4, 87.5, 60.8, 13.7. MS (*m*/*z*): 419.51 ($[M+1]^+$,

100%), 421 ([M+3]$^+$, 47%). Anal. Calcd for $C_{22}H_{15}BrN_2O_2$: C 63.02, H 3.61, N 6.68. Found: C 62.76, H 3.83, N 6.40.

Compound **1g**: White solid, yield: 78%, mp 196 °C, IR (KBr): 3145 (w), 3081 (w), 2215 (m), 1695 (s), 1523 (s), 1403 (m), 1348 (s), 1252 (m), 1195 (s), 1095 (m), 805 (m), 747 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.43 (d, J=7.4 Hz, 1H, CH), 9.00 (d, J=4.6 Hz, 1H, ArH), 8.41 (s, 1H, ArH), 8.43 (d, J=8.2 Hz, 1H, CH), 7.87 (d, J=7.3 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.72–7.67 (m, 3H, ArH), 7.30 (d, J=7.3 Hz, 1H, ArH), 4.20 (q, J=7.0 Hz, 2H, CH_2), 1.01 (t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 147.7, 136.6, 136.5, 136.0, 134.4, 130.0, 129.3, 129.0, 128.9, 127.3, 125.7, 124.6, 123.8, 123.5, 123.3, 116.5, 115.7, 114.6, 87.5, 61.0, 13.6. MS (m/z): 385.35 ([M−1]$^+$, 100%). Anal. Calcd for $C_{22}H_{15}N_3O_4$: C 68.57, H 3.92, N 10.90. Found: C 68.58, H 4.26, N 10.65.

3.2. General procedure for the synthesis of pyrrolo[2,1-*a*] isoquinolines 4a–r

A mixture of *p*-nitrobenzyl bromide (2.2 mmol, 0.475 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was heated at 50 °C for about 4 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.168 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred for additional 10–12 h . Then the DDQ (4.0 mmol, 0.908 g) was added. The resulting mixture was stirred at room temperature for 8 h. The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product.

Compound **4a**: Yellow solid, yield: 80%, mp 184–186 °C, IR (KBr): 3079 (w), 2857 (w), 2210 (s), 1599 (m), 1518 (vs), 1454 (m), 1376 (m), 1349 (vs), 1285 (m), 1106 (m), 738 (m), 705 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.99 (d, J=6.6 Hz, 1H, CH), 8.29 (d, J=6.2 Hz, 2H, ArH), 7.86 (d, J=7.2 Hz, 1H, CH), 7.71 (d, J=5.3 Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.54 (d, J=5.9 Hz, 2H, ArH), 7.34 (s, 5H, ArH), 7.05 (s, 1H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 136.2, 134.8, 131.7, 131.3, 130.7, 129.8, 128.9, 128.8, 128.7, 128.4, 128.2, 127.4, 124.6, 124.4, 123.5, 122.9, 121.0, 117.9, 114.6, 100.0, 85.7. MS (m/z): 390.37 ([M+1]$^+$, 100%). Anal. Calcd for $C_{25}H_{15}N_3O_2$: C 77.11, H 3.88, N 10.79. Found: C 76.75, H 4.34, N 10.50.

Compound **4b**: Yellow solid, yield: 87%, mp 202–204 °C, IR (KBr): 3131 (w), 2919 (w), 2210 (m), 1595 (m), 1518 (s), 1374 (w), 1343 (vs), 1288 (w), 1110 (w), 859 (w), 795 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.96 (d, J=8.1 Hz, 1H, CH), 8.28 (d, J=8.3 Hz, 2H, ArH), 7.85 (d, J=7.4 Hz, 1H, CH), 7.69 (d, J=7.7 Hz, 1H, ArH), 7.65 (t, J=7.7 Hz, 1H, ArH), 7.58 (t, J=7.3 Hz, 1H, ArH), 7.52 (d, J=8.3 Hz, 2H, ArH), 7.20 (d, J=7.6 Hz, 2H, ArH), 7.15 (d, J=7.6 Hz, 2H, ArH), 7.02 (d, J=7.4 Hz, 1H, ArH), 2.35 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.1, 136.3, 134.7, 131.7, 130.8, 129.6, 129.5, 128.8, 128.7, 128.4, 128.3, 127.3, 124.5, 124.4, 123.4, 122.8, 120.0, 118.0, 114.5, 85.7, 21.3. MS (m/z): 403.54 ([M+1]$^+$, 100%). Anal. Calcd for $C_{26}H_{17}N_3O_2$: C 77.41, H 4.25, N 10.42. Found: C 77.28, H 4.57, N 9.84.

Compound **4c**: Yellow solid, yield: 94%, mp 174–176 °C, IR (KBr): 3128 (w), 2935 (w), 2210 (m), 1597 (m), 1518 (s), 1342 (vs), 1246 (s), 1176 (m), 1108 (m), 1025 (m), 859 (m), 799 (m), 748 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.96 (d, J=7.7 Hz, 1H, CH), 8.29 (d, J=7.2 Hz, 2H, ArH), 7.85 (d, J=6.2 Hz, 1H, CH), 7.69 (d, J=7.3 Hz, 1H, ArH), 7.65 (t, J=6.3 Hz, 1H, ArH), 7.59 (d, J=6.6 Hz, 1H, ArH), 7.53 (d, J=7.3 Hz, 2H, ArH), 7.24 (d, J=7.1 Hz, 2H, ArH), 7.02 (d, J=6.5 Hz, 1H, ArH), 6.88 (d, J=7.2 Hz, 2H, ArH), 3.81 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 147.4, 136.4, 134.7, 131.7, 131.0, 130.5, 128.8, 128.7, 128.4, 127.3, 124.5, 124.4, 123.5, 123.4, 122.7, 121.0, 118.0, 114.5, 114.3, 85.6, 55.3. MS (m/z): 419.12 ([M+1]$^+$, 100%). Anal. Calcd for $C_{26}H_{17}N_3O_3$: C 74.45, H 4.09, N 10.02. Found: C 74.20, H 4.47, N 9.66.

Compound **4d**: Yellow solid, yield: 92%, mp 192–194 °C, IR (KBr): 3082 (w), 2210 (m), 1594 (m), 1519 (s), 1372 (w), 1343 (vs), 1288 (m), 1109 (m), 1074 (w), 1008 (m), 859 (m), 792 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.95 (d, J=8.0 Hz, 1H, CH), 8.32 (d, J=8.2 Hz, 2H, ArH), 7.84 (d, J=7.2 Hz, 1H, CH), 7,71 (d, J=7.6 Hz, 1H, ArH), 7.68 (t, J=7.6 Hz, 1H, ArH), 7.61 (d, J=7.2 Hz, 1H, ArH), 7.53 (d, J=8.2 Hz, 1H, ArH), 7.48 (d, J=8.0 Hz, 2H, ArH), 7.19 (d, J=8.0 Hz, 2H, ArH), 7.05 (d, J=7.2 Hz, 1H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 135.8, 135.0, 132.1, 131.7, 131.3, 130.3, 129.3, 129.0, 128.9, 128.4, 127.4, 124.6, 124.5, 123.5, 123.0, 122.6, 120.9, 117.7, 114.9, 85.4. MS (m/z): 468.23 ([M+1]$^+$, 100%), 450.50 ([M+3]$^+$, 58%). Anal. Calcd for $C_{25}H_{14}BrN_3O_2$: C 64.12, H 3.01, N 8.97. Found: C 63.71, H 3.56, N 8.62.

Compound **4e**: Yellow solid, yield: 91%, mp 206–208 °C, IR (KBr): 3068 (w), 2930 (w), 2208 (m), 1597 (m), 1522 (s), 1378 (m), 1349 (vs), 1289 (w), 860 (w), 793 (m), 743 (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.98 (d, J=7.9 Hz, 1H, CH), 8.32 (d, J=7.8 Hz, 2H, ArH), 7.84 (d, J=7.0 Hz, 1H, CH), 7.73 (d, J=7.5 Hz, 1H, ArH), 7.96 (t, J=7.3 Hz, 1H, ArH), 7.62 (t, J=7.3 Hz, 1H, ArH), 7.54 (d, J=7.9 Hz, 2H, ArH), 7.31 (s, 3H, ArH), 7.21 (d, J=7.0 Hz, 1H, ArH), 7.06 (d, J=7.1 Hz, 1H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 135.7, 134.9, 134.6, 133.2, 131.7, 130.1, 129.7, 129.0, 128.9, 128.5, 128.4, 128.1, 127.4, 124.8, 124.6, 124.5, 123.5, 123.3, 120.9, 117.5, 114.9, 85.6. MS (m/z): 424.39 ([M+1]$^+$, 100%), 426.8 ([M+3]$^+$, 38%). Anal. Calcd for $C_{25}H_{14}ClN_3O_2$: C 70.84, H 3.33, N 9.91. Found: C 70.63, H 3.78, N 9.70.

Compound **4f**: Yellow solid, yield: 77%, mp 178–180 °C, IR (KBr): 3080 (w), 2211 (m), 1597 (m), 1519 (s), 1344 (s), 1224 (m), 1157 (m), 1105 (m), 1045 (w), 855 (m), 769 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.98 (d, J=8.0 Hz, 1H, CH), 8.32 (d, J=8.4 Hz, 2H, ArH), 7.85 (d, J=7.4 Hz, 1H, CH), 7.73 (d, J=7.6 Hz, 1H, ArH), 7.69 (t, J=7.4 Hz, 1H, ArH), 7.62 (t, J=7.3 Hz, 1H, ArH), 7.54 (d, J=7.0 Hz, 2H, ArH), 7.30 (t, J=5.7 Hz, 2H, ArH), 7.06 (t, J=7.0 Hz, 3H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.4, 161.8, 147.6, 135.9, 134.8, 131.7, 131.6, 131.5, 129.6, 128.9, 128.8, 128.5, 127.4, 127.3, 124.5, 124.4, 123.4, 123.0, 120.9, 117.8, 116.0, 115.9, 114.7, 85.6. MS (m/z): 407.55 ([M−1]$^+$, 100%). Anal. Calcd for $C_{25}H_{14}BrN_3O_2$: C 73.70, H 3.46, N 10.31. Found: C 73.55, H 3.81, N 9.78.

3.3. General procedure for the synthesis of pyrrolo[2,1-*a*] isoquinolines 4g–l

In a 50 mL round bottom flask a mixture of phenacyl bromide (2.2 mmol, 0.438 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was stirred at 50 °C for 4 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.168 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred at 50 °C for additional 18–30 h. Then the DDQ (4.0 mmol, 0.908 g) was added. The resulting mixture was stirred at room temperature for 8 h. The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product for analysis.

Compound **4g**: White solid, yield: 62%, mp 190 °C, IR (KBr): 3058 (w), 2217 (m), 1623 (vs), 1518 (m), 1450 (m), 1398 (s), 1372 (m), 1348 (s), 1292 (w), 804 (w), 780 (w), 749 (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.12 (d, J=6.0 Hz, 1H, CH), 9.08 (d, J=6.4 Hz, 1H, CH), 7.80 (d, J=5.4 Hz, 1H, ArH), 7.71 (s, 2H, ArH), 7.51 (d, J=6.9 Hz, 2H, ArH), 7.24 (s, 4H, ArH), 7.13 (s, 3H, ArH), 7.08 (t, J=6.5 Hz, 2H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.7, 139.6, 138.2, 136.7, 132.2, 131.5, 130.4, 129.8, 129.7, 128.7, 128.2, 128.1, 127.8, 127.3, 124.4, 124.1, 123.7, 122.4, 117.4, 115.3, 86.8. MS (m/z): 373.95 ([M+1]$^+$, 100%). Anal. Calcd for $C_{26}H_{16}N_2O$: C 83.85, H 4.33, N 7.52. Found: C 83.57, H 4.51, N 7.29.

Compound **4h**: White solid, yield: 71%, mp 144 °C, IR (KBr): 3138 (w), 2983 (w), 2903 (w), 2208 (m), 1697 (vs), 1517 (m), 1406 (m), 1370 (m), 1346 (m), 1248 (m), 1189 (s), 1118 (w), 1088 (s), 798 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.07 (d, J=7.5 Hz, 1H, ArH), 9.03 (d, J=7.9 Hz, 1H, CH), 7.76 (d, J=7.2 Hz, 1H, CH), 7.66 (d, J=3.8 Hz, 2H, ArH), 7.50 (d, J=7.6 Hz, 2H, ArH), 7.24 (d, J=7.2 Hz, 1H, ArH), 7.19 (d, J=7.5 Hz, 1H, ArH), 7.12 (d, J=7.7 Hz, 1H, ArH), 7.19 (d, J=7.5 Hz, 2H, ArH), 7.08 (t, J=7.5 Hz, 2H, ArH), 6.92 (d, J=7.6 Hz, 1H, ArH), 2.21 (s,

3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.7, 139.7, 138.2, 138.1, 136.6, 132.0, 130.3, 129.7, 129.6, 128.8, 128.6, 128.5, 127.7, 127.2, 124.4, 124.0, 123.6, 122.3, 117.5, 115.1, 86.8, 21.2. MS (*m*/*z*): 387.04 ($[M+1]^+$, 100%). Anal. Calcd for $C_{27}H_{18}N_2O$: C 83.92, H 4.69, N 7.25. Found: C 83.57, H 4.90, N 6.88.

Compound **4i**: White solid, yield: 68%, mp 206 °C, IR (KBr): 2963 (w), 2219 (m), 1629 (s), 1521 (s), 1454 (m), 1429 (m), 1394 (s), 1349 (s), 1250 (vs), 1176 (m), 967 (m), 896 (m), 800 (s). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.12 (d, *J*=7.3 Hz, 1H, CH), 9.06 (d, *J*=6.8 Hz, 1H, CH), 7.79 (d, *J*=6.3 Hz, 1H, ArH), 7.69 (d, *J*=3.6 Hz, 2H, ArH), 7.51 (d, *J*=7.4 Hz, 2H, ArH), 7.27 (t, *J*=7.5 Hz, 1H, ArH), 7.23 (d, *J*=7.3 Hz, 1H, ArH), 7.17 (d, *J*=7.4 Hz, 2H, ArH), 7.10 (t, *J*=7.2 Hz, 2H, ArH), 6.66 (d, *J*=7.4 Hz, 2H, ArH), 3.72 (s, 3H, CH_3O). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.7, 159.5, 139.5, 138.2, 136.7, 132.2, 131.7, 129.7, 128.6, 127.8, 127.2, 124.4, 124.0, 123.8, 123.6, 122.3, 117.6, 115.1, 113.7, 86.7, 55.2. MS (*m*/*z*): 403.80 ($[M+1]^+$, 100%). Anal. Calcd for $C_{27}H_{18}N_2O_2$: C 80.58, H 4.51, N 6.96. Found: C 80.70, H 4.83, N 6.75.

Compound **4j**: White solid, yield: 62%, mp 162 °C, IR (KBr): 3055 (w), 2218 (m), 1627 (s), 1516 (m), 1450 (w), 1404 (m), 1378 (m), 1348 (vs), 1252 (w), 1172 (w), 895 (m), 798 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.12 (d, *J*=7.5 Hz, 1H, ArH), 9.06–9.04 (m, 1H, CH), 7.82–7.80 (m, 1H, CH), 7.71 (t, *J*=3.7 Hz, 2H, ArH), 7.49 (d, *J*=7.7 Hz, 2H, ArH), 7.33 (t, *J*=7.4 Hz, 1H, ArH), 7.26–7.25 (m, 3H, ArH), 7.14–7.11 (m, 3H, ArH), 7.10 (s, 1H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.4, 138.2, 138.0, 136.8, 132.4, 131.8, 131.3, 130.6, 130.0, 129.7, 129.6, 128.8, 127.9, 127.3, 124.4, 124.1, 123.6, 122.7, 122.4, 117.1, 115.1, 86.6. MS (*m*/*z*): 451.63 ($[M+1]^+$, 100%), 453.49 ($[M+1]^+$, 97%). Anal. Calcd for $C_{26}H_{15}BrN_2O$: C 69.19, H 3.35, N 6.21. Found: C 68.84, H 3.78, N 5.96.

Compound **4k**: White solid, yield: 78%, mp 140 °C, IR (KBr): 3137 (w), 3088 (w), 2220 (m), 1626 (s), 1521 (m), 1456 (m), 1398 (s), 1350 (vs), 969 (m), 903 (m), 805 (m), 755 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.15 (d, *J*=6.2 Hz, 1H, CH), 9.06 (d, *J*=6.1 Hz, 1H, CH), 7.81 (s, 1H, ArH), 7.72 (d, *J*=4.0 Hz, 2H, ArH), 7.50 (d, *J*=7.0 Hz, 2H, ArH), 7.28–7.27 (m, 2H, ArH), 7.21 (s, 1H, ArH), 7.15–7.10 (m, 5H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.5, 138.2, 137.9, 136.8, 133.9, 133.3, 132.4, 130.7, 129.9, 129.8, 129.5, 129.4, 128.9, 128.3, 127.9, 127.3, 124.4, 124.1, 123.6, 122.6, 116.9, 115.6, 87.7. MS (*m*/*z*): 407.73 ($[M+1]^+$, 100%), 409.26 ($[M+1]^+$, 55%). Anal. Calcd for $C_{26}H_{15}ClN_2O$: C 76.75, H 3.72, N 6.89. Found: C 76.45, H 4.17, N 6.50.

Compound **4l**: White solid, yield: 63%, mp 136–138 °C, IR (KBr): 3026 (w), 2217 (w), 1620 (m), 1524 (m), 1445 (w), 1395 (w), 1349 (vs), 970 (w), 913 (w), 868 (w). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 9.21 (d, *J*=7.5 Hz, 1H, ArH), 9.07–9.05 (m, 1H, CH), 7.99 (d, *J*=8.2 Hz, 1H, CH), 7.96 (t, *J*=1.7 Hz, 1H, ArH), 7.86–7.84 (m, 1H, ArH), 7.76–7.74 (m, 2H, ArH), 7.70 (d, *J*=7.7 Hz, 1H, ArH), 7.48 (d, *J*=7.3 Hz, 2H, ArH), 7.40 (t, *J*=7.9 Hz, 1H, ArH), 7.33 (d, *J*=7.5 Hz, 1H, ArH), 7.23 (t, *J*=7.5 Hz, 1H, ArH), 7.08 (t, *J*=7.7 Hz, 2H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.1, 147.5, 138.1, 136.9, 136.8, 135.7, 133.4, 132.5, 130.2, 129.8, 129.5, 129.3, 129.0, 128.0, 127.4, 125.8, 124.4, 124.0, 123.5, 122.9, 122.8, 116.6, 116.0, 86.8. MS (*m*/*z*): 418.56 ($[M+1]^+$, 100%). Anal. Calcd for $C_{26}H_{15}N_3O_3$: C 74.81, H 3.62, N 10.07. Found: C 74.67, H 3.99, N 9.64.

3.4. General procedure for the synthesis of pyrrolo[2,1-*a*]-isoquinolines 4m–r

In a 50 mL round bottom flask a mixture of *N*,*N*-diethyl chloroacetamide (2.2 mmol, 0.329 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was heated at 50 °C for about 5 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.168 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred at 50 °C for additional 6–8 h . Then the DDQ (4.0 mmol, 0.908 g) was added. The resulting mixture was stirred at room temperature for 8 h. The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product for analysis.

Compound **4m**: White solid, yield: 67%, mp 210 °C, IR (KBr): 3079 (w), 2970 (w), 2934 (w), 2208 (s), 1614 (vs), 1550 (m), 1521 (s), 1486 (m), 1458 (s), 1376 (s), 1275 (m), 1152 (w), 1082 (w), 798 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.95 (s, 1H, CH), 8.02 (d, *J*=6.8 Hz, 1H, CH), 7.70 (d, *J*=6.4 Hz, 1H, ArH), 7.64 (d, *J*=7.6 Hz, 3H, ArH), 7.59 (d, *J*=6.0 Hz, 1H, ArH), 7.47 (t, *J*=7.5 Hz, 2H, ArH), 7.43–7.40 (m, 1H, ArH), 7.07 (d, *J*=7.1 Hz, 1H, ArH), 3.82 (q, *J*=6.3 Hz, 1H, CH_2), 3.28 (q, *J*=6.3 Hz, 1H, CH_2), 3.13 (q, *J*=6.5 Hz, 1H, CH_2), 2.75 (q, *J*=6.8 Hz, 1H, CH_2), 1.17 (t, *J*=6.9 Hz, 3H, CH_3), 0.62 (t, *J*=6.8 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.9, 134.9, 131.4, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 127.3, 124.3, 123.3, 122.7, 119.2, 118.0, 114.5, 83.5, 43.0, 39.3, 13.8, 12.3. MS (*m*/*z*): 368.75 ($[M+1]^+$, 100%). Anal. Calcd for $C_{24}H_{21}N_3O$: C 78.45, H 5.76, N 11.44. Found: C 78.41, H 6.22, N 11.27.

Compound **4n**: White solid, yield: 73%, mp 270 °C, IR (KBr): 2972 (w), 2210 (m), 1617 (vs), 1554 (w), 1521 (m), 1456 (m), 1375 (m), 1273 (m), 1150 (m), 1084 (w), 797 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.94 (d, *J*=8.1 Hz, 1H, CH), 8.02 (d, *J*=7.4 Hz, 1H, CH), 7.70 (t, *J*=7.8 Hz, 1H, ArH), 7.64 (t, *J*=7.6 Hz, 1H, ArH), 7.58 (t, *J*=7.4 Hz, 1H, ArH), 7.52 (d, *J*=7.8 Hz, 2H, ArH), 7.28 (d, *J*=8.3 Hz, 2H, ArH), 7.06 (d, *J*=7.4 Hz, 1H, ArH), 3.82 (q, *J*=6.7 Hz, 1H, CH_2), 3.30 (q, *J*=6.7 Hz, 1H, CH_2), 3.14 (q, *J*=7.0 Hz, 1H, CH_2), 2.76 (q, *J*=7.0 Hz, 1H, CH_2), 2.40 (s, 3H, CH_3), 1.19 (t, *J*=7.1 Hz, 3H, CH_3), 0.64 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 138.5, 134.9, 129.7, 129.4, 128.9, 128.7, 128.5, 128.4, 127.3, 124.3, 123.4, 122.7, 118.9, 118.1, 114.4, 83.5, 43.0, 39.3, 21.3, 13.9, 12.3. MS (*m*/*z*): 382.72 ($[M+1]^+$, 100%). Anal. Calcd for $C_{25}H_{23}N_3O$: C 78.71, H 6.08, N 11.02. Found: C 78.65, H 6.50, N 10.76.

Compound **4o**: White solid, yield: 80%, mp 226 °C, IR (KBr): 2971 (w), 2209 (m), 1619 (vs), 1550 (m), 1520 (m), 1455 (m), 1375 (m), 1247 (m), 1175 (w), 872 (w), 795 (w). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.92 (d, *J*=8.1 Hz, 1H, CH), 8.01 (d, *J*=7.4 Hz, 1H, CH), 7.68 (d, *J*=7.8 Hz, 1H, ArH), 7.62 (t, *J*=7.6 Hz, 1H, ArH), 7.57 (d, *J*=7.9 Hz, 3H, ArH), 7.05 (d, *J*=7.4 Hz, 1H, ArH), 7.01 (d, *J*=8.4 Hz, 2H, ArH), 3.85 (s, 3H, CH_3O), 3.82 (q, *J*=6.7 Hz, 1H, CH_2), 3.29 (q, *J*=6.7 Hz, 1H, CH_2), 3.15 (q, *J*=7.0 Hz, 1H, CH_2), 2.77 (q, *J*=7.0 Hz, 1H, CH_2), 1.19 (t, *J*=7.0 Hz, 3H, CH_3), 0.66 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 159.9, 134.8, 130.2, 129.1, 128.6, 128.5, 128.4, 127.3, 124.2, 123.7, 123.3, 122.7, 118.8, 118.1, 114.4, 83.4, 55.4, 43.0, 39.4, 13.9, 12.4. MS (*m*/*z*): 398.72 ($[M+1]^+$, 100%). Anal. Calcd for $C_{25}H_{23}N_3O_2$: C 75.54, H 5.83, N 10.57. Found: C 75.21, H 6.17, N 10.40.

Compound **4p**: White solid, yield: 75%, mp 247 °C, IR (KBr): 2973 (w), 2207 (m), 1616 (vs), 1524 (s), 1435 (m), 1377 (m), 1345 (s), 1270 (m), 1212 (w), 1151 (w), 1077 (w), 861 (w), 794 (w), 698 (w). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.91 (d, *J*=8.1 Hz, 1H, CH), 7.97 (d, *J*=7.4 Hz, 1H, CH), 7.70 (d, *J*=7.8 Hz, 1H, ArH), 7.64 (t, *J*=7.5 Hz, 1H, ArH), 7.62–7.57 (m, 3H, ArH), 7.52 (d, *J*=8.1 Hz, 2H, ArH), 7.08 (d, *J*=7.4 Hz, 1H, ArH), 3.81 (q, *J*=6.7 Hz, 1H, CH_2), 3.33 (q, *J*=6.7 Hz, 1H, CH_2), 3.13 (q, *J*=7.0 Hz, 1H, CH_2), 2.79 (q, *J*=6.9 Hz, 1H, CH_2), 1.21 (t, *J*=6.9 Hz, 3H, CH_3), 0.69 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 134.9, 132.2, 130.5, 128.9, 128.7, 128.4, 127.7, 127.4, 124.1, 123.3, 122.9, 122.5, 119.2, 117.7, 114.8, 83.3, 43.1, 39.4, 14.0, 12.4. MS (*m*/*z*): 448.64 ($[M+1]^+$, 100%), 446.55 ($[M+3]^+$, 80%). Anal. Calcd for $C_{24}H_{20}BrN_3O$: C 64.58, H 4.52, N 9.41. Found: C 64.25, H 4.79, N 9.11.

Compound **4q**: White solid, yield: 60%, mp 196 °C, IR (KBr): 2960 (w), 2224 (w), 1621 (w), 1523 (m), 1480 (w), 1459 (m), 1347 (m), 1380 (m), 1312 (w), 1278 (w), 1212 (w), 788 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.92 (d, *J*=7.7 Hz, 1H, CH), 8.00 (d, *J*=7.3 Hz, 1H, ArH), 7.71 (d, *J*=7.7 Hz, 1H, CH), 7.66–7.63 (m, 1H, ArH), 7.61–7.57 (m, 3H, ArH), 7.45–7.39 (m, 2H, ArH), 7.09 (d, *J*=7.3 Hz, 1H, ArH), 3.93 (q, *J*=6.7 Hz, 1H, CH_2), 3.22 (q, *J*=6.7 Hz, 1H, CH_2), 3.14 (q, *J*=7.0 Hz, 1H, CH_2), 2.77 (q, *J*=7.0 Hz, 1H, CH_2), 1.20 (t, *J*=7.0 Hz, 3H,

CH_3), 0.69 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 135.0, 134.8, 133.1, 130.3, 128.9, 128.7, 128.6, 128.5, 127.5, 127.4, 127.1, 124.2, 123.4, 122.6, 119.5, 117.6, 114.8, 83.4, 43.1, 39.4, 13.9, 12.3. MS (m/z): 402.65 ($[M+1]^+$, 100%). Anal. Calcd for $C_{24}H_{20}ClN_3O$: C 71.73, H 5.02, N 10.46. Found: C 71.40, H 5.38, N 10.15.

Compound **4r**: White solid, yield: 63%, mp 184–186 °C, IR (KBr): 2976 (w), 2207 (m), 1616 (vs), 1524 (s), 1435 (m), 1377 (m), 1345 (s), 1270 (m), 1212 (w), 1151 (w), 861 (w), 794 (w). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.93 (d, J=8.1 Hz, 1H, CH), 8.48 (s, 1H, ArH), 8.29 (d, J=8.1 Hz, 1H, CH), 8.04 (d, J=7.6 Hz, 1H, ArH), 7.98 (d, J=7.3 Hz, 1H, ArH), 7.74 (d, J=7.7 Hz, 1H, ArH), 7.69 (q, J=7.8 Hz, 2H, ArH), 7.63 (t, J=7.0 Hz, 1H, ArH), 7.14 (d, J=7.3 Hz, 1H, ArH), 3.87 (q, J=5.7 Hz, 1H, CH_2), 3.30 (q, J=5.8 Hz, 1H, CH_2), 3.17 (q, J=6.3 Hz, 1H, CH_2), 2.83 (q, J=6.4 Hz, 1H, CH_2), 1.18 (t, J=6.3 Hz, 3H, CH_3), 0.73 (t, J=6.3 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3, 148.6, 135.2, 134.9, 133.2, 130.1, 129.2, 128.9, 128.5, 127.5, 126.2, 124.1, 123.7, 123.4, 123.3, 119.9, 117.3, 115.2, 83.4, 43.2, 39.5, 14.1, 12.4. MS (m/z): 413.77 ($[M+1]^+$, 100%). Anal. Calcd for $C_{24}H_{20}N_4O_3$: C 69.89, H 4.89, N 13.58. Found: C 69.50, H 5.13, N 13.26.

3.5. General procedure for the preparation of tetrahydropyrrolo[2,1-*a*]isoquinolines 3a–g

In an atmosphere of nitrogen a mixture of ethyl α-bromoacetate (2.2 mmol, 0.367 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was stirred at room temperature for about 1.5 h . Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.168 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred at room temperature for additional 6 h. The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product.

Compound **3a**: White solid, yield: 82%, mp 162 °C, IR (KBr): 3445 (m), 3335 (m), 2980 (w), 1745 (s), 1698 (vs), 1612 (s), 1584 (m), 1515 (s), 1460 (m), 1364 (m), 1257 (s), 1181 (s), 1027 (m), 773 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.38 (d, J=7.9 Hz, 2H, ArH), 7.20 (t, J=6.8 Hz, 1H, ArH), 7.03 (t, J=6.5 Hz, 1H, ArH), 6.99 (t, J=9.5 Hz, 2H, ArH), 6.91 (d, J=8.0 Hz, 2H, CH), 6.23 (d, J=7.2 Hz, 1H, CH), 5.98 (s, 1H, NH), 5.68 (s, 1H, CH), 5.63 (s, 1H, NH), 5.36 (d, J=7.2 Hz, 1H, CH), 4.49 (d, J=8.6 Hz, 1H, CH), 4.33 (d, J=8.6 Hz, 1H, CH), 4.21–4.18 (m, 2H, CH_2), 3.81 (s, 3H, CH_3O), 1.23 (t, J=6.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 165.9, 160.0, 134.6, 133.3, 132.6, 129.7, 129.3, 126.0, 125.9, 125.6, 125.1, 124.9, 117.7, 114.8, 114.4, 99.8, 69.2, 69.1, 64.0, 61.9, 55.3, 53.5, 14.1. MS (m/z): 418.67 ($[M+1]^+$, 100%). Anal. Calcd for $C_{24}H_{23}N_3O_4$: C 69.05, H 5.55, N 10.07. Found: C 68.72, H 5.76, N 9.80.

Compound **3b**: White solid, yield: 76%, mp 148–150 °C, IR (KBr): 3176 (m), 2900 (w), 1742 (m), 1698 (s), 1615 (m), 1458 (w), 1380 (m), 1344 (w), 1263 (w), 1211 (s), 763 (w). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.44–7.43 (m, 2H, ArH), 7.39–7.34 (m, 3H, ArH), 7.20 (t, J=7.4 Hz, 1H, ArH), 7.03–6.96 (m, 3H, ArH), 6.24 (d, J=7.6 Hz, 1H, CH), 6.07 (s, 1H, NH), 6.02 (s, 1H, NH), 5.66 (s, 1H, CH), 5.35 (d, J=7.6 Hz, 1H, CH), 4.54 (d, J=8.5 Hz, 1H, CH), 4.37 (d, J=8.5 Hz, 1H, CH), 4.17 (q, 2H, CH_2), 1.20 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 165.8, 134.6, 134.0, 132.6, 129.4, 129.0, 128.9, 128.5, 126.0, 125.9, 125.0, 117.6, 99.8, 69.3, 69.2, 64.0, 61.9, 53.9, 14.1. MS (m/z): 388.88 ($[M+1]^+$, 100%). Anal. Calcd for $C_{23}H_{21}N_3O_3$: C 71.30, H 5.46, N 10.85. Found: C 71.26, H 5.80, N 10.53.

Compound **3c**: White solid, yield: 68%, mp 160–162 °C, IR (KBr): 3186 (m), 2989 (w), 1744 (s), 1698 (vs), 1627 (m), 1491 (w), 1424 (m), 1380 (m), 1199 (s), 1110 (w), 764 (w). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.43 (s, 1H, ArH), 7.36–7.32 (m, 3H, ArH), 7.22 (t, J=7.3 Hz, 1H, ArH), 7.06–6.97 (m, 3H, ArH), 6.24 (d, J=7.3 Hz, 1H, CH), 6.03 (s, 1H, NH), 5.73 (s, 1H, NH), 5.63 (s, 1H, CH), 5.39 (d, J=7.4 Hz, 1H, CH), 4.50 (d, J=8.5 Hz, 1H, CH), 4.38 (d, J=8.4 Hz, 1H, CH), 4.23–4.20 (m, 2H, CH_2), 1.24 (t, J=6.2 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 165.5, 136.2, 134.9, 134.5, 132.5, 130.3, 129.5, 129.2, 128.8, 126.6, 126.1, 126.0, 125.1, 124.8, 117.3, 100.1, 69.5, 69.2, 63.9, 62.1, 53.3, 14.1. MS (m/z): 422.60 ($[M+1]^+$, 100%), 424.81 ($[M+3]^+$, 27%). Anal. Calcd for $C_{23}H_{20}ClN_3O_3$: C 65.48, H 4.78, N 9.96. Found: C 65.17, H 5.12, N 9.47.

Compound **3d**: White solid, yield: 80%, mp 166 °C, IR (KBr): 3184 (m), 2987 (w), 1745 (s), 1691 (vs), 1625 (m), 1531 (s), 1490 (w), 1347 (s), 1305 (m), 1207 (m), 796 (m), 698 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.32 (s, 1H, ArH), 8.23 (d, J=8.1 Hz, 1H, ArH), 7.81 (d, J=7.7 Hz, 1H, ArH), 7.59 (t, J=8.0 Hz, 1H, ArH), 7.23 (t, J=7.5 Hz, 1H, ArH), 7.06–7.01 (m, 2H, ArH), 6.97 (d, J=7.6 Hz, 1H, ArH), 6.27 (d, J=7.6 Hz, 1H, CH), 6.10 (s, 2H, NH), 5.62 (s, 1H, CH), 5.41 (d, J=7.6 Hz, 1H, CH), 4.57 (d, J=8.5 Hz, 1H, CH), 4.54 (d, J=8.5 Hz, 1H, CH), 4.22–4.19 (m, 2H, CH_2), 1.23 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 165.1, 148.1, 136.5, 134.6, 134.5, 132.4, 130.2, 129.6, 126.2, 126.0, 125.2, 124.6, 123.9, 123.5, 117.1, 100.3, 69.7, 69.2, 63.8, 62.3, 53.0, 14.1. MS (m/z): 433.77 ($[M+1]^+$, 100%). Anal. Calcd for $C_{23}H_{20}N_4O_5$: C 63.88, H 4.66, N 12.96. Found: C 63.65, H 4.83, N 12.67.

3.6. General procedure for the preparation of tetrahydropyrrolo[2,1-*a*]isoquinolines 3e–g

In nitrogen atmosphere a mixture of *p*-nitrobenzyl bromide (2.2 mmol, 0.475 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was heated at 50 °C for about 4 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.168 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred at 50 °C for additional 8–12 h . The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product for analysis.

Compound **3e**: Yellow solid, yield: 63%, mp 130 °C, IR (KBr): 2962 (w), 1703 (m), 1668 (s), 1632 (m), 1599 (m), 1524 (s), 1460 (w), 1349 (vs), 937 (w), 854 (w), 770 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.14 (d, J=8.7 Hz, 1H, ArH), 7.41–7.37 (m, 6H, ArH), 7.23 (t, J=7.6 Hz, 1H, ArH), 7.06 (t, J=7.4 Hz, 1H, ArH), 7.03–7.00 (m, 2H, ArH), 6.10 (d, J=7.5 Hz, 1H, CH), 5.99 (s, 1H, NH), 5.89 (s, 1H, CH), 5.66 (s, 1H, NH), 5.38 (d, J=7.5 Hz, 1H, CH), 5.20 (d, J=9.7 Hz, 1H, CH), 3.92 (d, J=9.7 Hz, 1H, CH), 1.32 (s, 9H, $(CH_3)_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 134.2, 132.3, 129.4, 128.4, 128.2, 127.6, 127.4, 127.0, 126.8, 126.7, 126.2, 126.0, 125.9, 125.1, 124.7, 124.1, 107.1, 99.7, 74.7, 70.3, 68.9, 64.3, 59.1, 57.1, 34.7, 34.6, 31.3, 31.2. MS (m/z): 493.69 ($[M+1]^+$, 100%). Anal. Calcd for $C_{30}H_{28}N_4O_3$: C 73.15, H 5.73, N 11.37. Found: C 72.84, H 5.85, N 11.13.

Compound **3f**: Yellow solid, yield: 73%, mp 158 °C, IR (KBr): 3057 (w), 1696 (s), 1629 (m), 1589 (m), 1518 (m), 1493 (m), 1461 (w), 1347 (vs), 1109 (w), 937 (w), 764 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.15 (d, J=8.7 Hz, 1H, ArH), 7.55 (d, J=8.5 Hz, 2H, ArH), 7.38–7.35 (m, 4H, ArH), 7.24 (d, J=7.6 Hz, 1H, ArH), 7.08 (t, J=7.4 Hz, 1H, ArH), 7.03 (d, J=7.5 Hz, 1H, ArH), 6.98 (d, J=7.6 Hz, 1H, ArH), 6.08 (d, J=7.5 Hz, 1H, CH), 6.03 (s, 1H, NH), 5.86 (s, 1H, CH), 5.67 (s, 1H, NH), 5.39 (d, J=7.5 Hz, 1H, CH), 5.16 (d, J=9.7 Hz, 1H, CH), 3.93 (d, J=9.7 Hz, 1H, CH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 148.3, 146.2, 139.9, 134.7, 132.6, 132.5, 132.4, 130.5, 129.3, 127.9, 127.8, 127.5, 126.8, 126.7, 126.6, 124.8, 124.3, 122.5, 122.2, 107.5, 74.7, 70.1, 57.1. MS (m/z): 515.69 ($[M+1]^+$, 100%), 517.08 ($[M+3]^+$, 36%). Anal. Calcd for $C_{26}H_{19}BrN_4O_3$: C 60.59, H 3.72, N 10.87. Found: C 60.34, H 4.23, N 10.30.

Compound **3g**: Yellow solid, yield: 82%, mp 142–144 °C, IR (KBr): 3163 (w), 2853 (vw), 1703 (vs), 1620 (m), 1521 (m), 1459 (w), 1347 (s), 1109 (w), 856 (w), 769 (m). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.16 (d, J=8.5 Hz, 2H, ArH), 7.44 (s, 1H, ArH), 7.39–7.36 (m, 5H, ArH), 7.24 (d, J=7.5 Hz, 1H, ArH), 7.08 (t, J=7.4 Hz, 1H, ArH), 7.03 (d, J=7.5 Hz, 1H, ArH), 6.99 (d, J=7.5 Hz, 1H, ArH), 6.10 (d, J=7.5 Hz, 1H, CH), 6.06 (s, 1H, NH), 5.85 (s, 1H, CH), 5.77 (s, 1H, NH), 5.40 (d,

J=7.5 Hz, 1H, CH), 5.18 (d, J=9.6 Hz, 1H, CH), 3.94 (d, J=9.6 Hz, 1H, CH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 148.3, 146.7, 143.1, 135.2, 134.7, 132.6, 130.7, 128.5, 128.0, 127.8, 127.6, 127.5, 127.4, 126.9, 126.8, 126.7, 126.6, 125.8, 124.8, 124.3, 122.5, 121.1, 107.6, 74.6, 70.0, 57.2. MS (m/z): 471.50 ([M+1]$^+$, 100%), 473.51 ([M+3]$^+$, 20%). Anal. Calcd for $C_{26}H_{19}ClN_4O_3$: C 66.31, H 4.07, N 11.90. Found: C 66.21, H 4.38, N 11.83.

3.7. General procedure for the preparation of dihydropyrrolo [2,1-*a*]isoquinoline 2a–f

A mixture of ethyl α-bromoacetate (2.2 mmol, 0.367 g) and isoquinoline (3.0 mmol, 0.388 g) in 10 mL of ethanol was stirred at room temperature about 4 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.186 g), and triethylamine (4.0 mmol, 0.404 g) were added to it. The solution was stirred at room temperature for additional 6 h . Then the DDQ (2.0 mmol, 0.454 g) was added. The resulting mixture was stirred at room temperature for 2–4 h . The resulting precipitates were collected by filtration and washed with cold alcohol. The crude product was recrystallized in chloroform/ethanol to give the pure product.

Compound **2a**: Yellow solid, yield: 65%, mp 162–164 °C, IR (KBr): 2966 (w), 2170 (s), 1741 (m), 1692 (w), 1630 (m), 1552 (s), 1512 (m), 1247 (s), 1205 (m), 1177 (m), 1031 (m), 781 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (d, J=8.0 Hz, 1H, ArH), 7.52 (t, J=7.3 Hz, 1H, ArH), 7.38 (t, J=7.46 Hz, 1H, ArH), 7.35 (d, J=7.7 Hz, 1H, ArH), 7.27 (s, 2H, ArH), 6.90 (d, J=8.1 Hz, 2H, ArH), 6.68 (d, J=7.1 Hz, 1H, ArH), 6.15 (d, J=7.0 Hz, 1H, ArH), 4.59 (d, J=4.7 Hz, 1H, CH), 4.48 (d, J=4.4 Hz, 1H, CH), 4.38–4.26 (m, 2H, CH_2), 3.80 (s, 3H, CH_3O), 1.35 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 159.3, 151.7, 134.8, 133.5, 132.0, 131.3, 129.5, 129.2, 128.6, 128.3, 127.2, 126.5, 112.7, 121.4, 114.5, 113.3, 106.2, 71.7, 71.1, 62.5, 55.3, 50.5, 14.2. MS (m/z): 373.58 ([M+1]$^+$, 100%). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C 74.18, H 5.41, N 7.52. Found: C 73.89, H 5.93, N 7.28.

Compound **2b**: Yellow solid, yield: 68%, mp 144–146 °C, IR (KBr): 3157 (s), 2784 (w), 2218 (m), 1694 (vs), 1591 (vs), 1506 (w), 1371 (s), 1213 (m), 1181 (m), 819 (m), 791 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (d, J=7.8 Hz, 1H, ArH), 7.52 (t, J=6.7 Hz, 1H, ArH), 7.38 (t, J=6.9 Hz, 1H, ArH), 7.35 (d, J=7.4 Hz, 1H, ArH), 7.24 (d, J=6.8 Hz, 2H, ArH), 7.18 (d, J=7.2 Hz, 2H, ArH), 6.68 (d, J=6.1 Hz, 1H, CH), 6.15 (d, J=6.2 Hz, 1H, CH), 4.61 (s, 1H, CH), 4.48 (s, 1H, CH), 4.36–4.27 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.34 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 151.8, 138.4, 137.7, 134.8, 132.1, 129.8, 129.2, 127.2, 127.1, 126.5, 126.4, 122.7, 121.3, 106.2, 77.2, 71.6, 71.0, 62.5, 50.8, 21.1, 14.2. MS (m/z): 359.45 ([M+1]$^+$, 100%). Anal. Calcd for $C_{23}H_{20}N_2O_2$: C 77.51, H 5.66, N 7.86. Found: C 77.29, H 5.94, N 7.66.

Compound **2c**: Yellow solid, yield: 60%, mp 158–160 °C, IR (KBr): 3046, 2166 (s), 1741 (s), 1631 (m), 1567 (vs), 1489 (w), 1463 (w), 1391 (m), 1329 (w), 1224 (m), 786 (w), 769 (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (d, J=7.9 Hz, 1H, ArH), 7.52 (t, J=7.4 Hz, 1H, ArH), 7.40–7.36 (m, 6H, ArH), 7.30 (d, J=5.0 Hz, 1H, ArH), 6.7 (d, J=7.0 Hz, 1H, CH), 6.16 (d, J=7.0 Hz, 1H, CH), 4.64 (d, J=4.5 Hz, 1H, CH), 4.53 (d, J=4.3 Hz, 1H, CH), 4.37–4.27 (m, 2H, CH_2), 1.35 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 151.9, 141.3, 134.8, 132.2, 129.2, 128.0, 127.2, 127.1, 126.5, 126.4, 122.7, 121.3, 106.3, 71.5, 70.7, 62.6, 51.1, 46.0, 14.2. MS (m/z): 343.74 ([M+1]$^+$, 100%). Anal. Calcd for $C_{22}H_{18}N_2O_2$: C 77.17, H 5.30, N 8.18. Found: C 77.42, H 5.56, N 7.95.

Compound **2d**: Yellow solid, yield: 60%, mp 142 °C, IR (KBr): 3022 (w), 2219 (m), 1621 (s), 1519 (m), 1393 (m), 1372 (m), 1347 (s), 1292 (w), 1247 (s), 895 (m), 800 (m), 736 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.62 (d, J=8.1 Hz, 1H, ArH), 7.53 (t, J=7.5 Hz, 1H, ArH), 7.49 (d, J=8.2 Hz, 2H, ArH), 7.39–7.35 (m, 2H, ArH), 7.23 (d, J=8.2 Hz, 2H, ArH), 6.70 (d, J=7.2 Hz, 1H, CH), 6.17 (d, J=7.2 Hz, 1H, CH), 4.59 (d, J=5.3 Hz, 1H, CH), 4.50 (d, J=5.3 Hz, 1H, CH), 4.36–4.26 (m, 2H, CH_2), 1.33 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 152.1, 140.3, 134.8, 132.3, 129.1, 129.0, 127.3, 126.6, 126.4, 122.5, 121.9, 121.0, 106.5, 71.3, 70.1, 62.7, 50.5, 14.2. MS (m/z): 423.84 ([M+1]$^+$, 100%), 421.93 ([M+3]$^+$, 39%). Anal. Calcd for $C_{22}H_{17}BrN_2O_2$: C 62.72, H 4.07, N 6.65. Found: C 62.50, H 4.39, N 6.51.

Compound **2e**: Yellow solid, yield: 54%, mp 138 °C, IR (KBr): 2982 (w), 2165 (s), 1745 (s), 1631 (m), 1553 (vs), 1468 (w), 1392 (w), 1313 (w), 1246 (m), 1202 (m), 874 (w), 785 (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (d, J=8.1 Hz, 1H, ArH), 7.54 (t, J=7.5 Hz, 1H, ArH), 7.40–7.36 (m, 2H, ArH), 7.33 (s, 1H, ArH), 7.32–7.24 (m, 3H, ArH), 6.71 (d, J=7.2 Hz, 1H, CH), 6.18 (d, J=7.2 Hz, 1H, CH), 4.61 (d, J=5.0 Hz, 1H, CH), 4.51 (d, J=5.0 Hz, 1H, CH), 4.37–4.27 (m, 2H, CH_2), 1.34 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 152.2, 143.4, 135.0, 134.8, 132.3, 130.5, 129.1, 128.3, 127.4, 127.3, 126.6, 126.5, 125.5, 122.5, 121.0, 106.6, 71.3, 69.9, 62.7, 50.6, 14.2. MS (m/z): 377.66 ([M+1]$^+$, 100%), 380.49 ([M+3]$^+$, 36%). Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C 70.12, H 4.55, N 7.43. Found: C 69.85, H 4.68, N 7.29.

Compound **2f**: Yellow solid, yield: 65%, mp 150 °C, IR (KBr): 2987 (w), 2168 (s), 1748 (m), 1631 (m), 1553 (vs), 1538 (vs), 1488 (w), 1348 (m), 1321 (m), 1239 (m), 1210 (m), 810 (m), 783 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (d, J=8.1 Hz, 1H, ArH), 8.23 (s, 1H, ArH), 8.18 (d, J=8.1 Hz, 1H, ArH), 7.73 (d, J=7.6 Hz, 1H, ArH), 7.59–7.55 (m, 2H, ArH), 7.44–7.39 (m, 2H, ArH), 6.76 (d, J=7.2 Hz, 1H, CH), 6.24 (d, J=7.2 Hz, 1H, CH), 4.68 (q, J=5.5 Hz, 2H, CH), 4.40–4.30 (m, 2H, CH_2), 1.37 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 152.6, 148.8, 143.4, 134.8, 133.7, 132.6, 130.3, 128.9, 127.4, 126.7, 126.5, 123.1, 122.5, 122.3, 120.8, 107.1, 71.0, 69.4, 63.0, 50.6, 14.2. MS (m/z): 388.78 ([M+1]$^+$, 100%). Anal. Calcd for $C_{22}H_{17}N_3O_4$: C 68.85, H 4.42, N 10.85. Found: C 68.76, H 4.77, N 10.45.

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Supplementary data

Experimental details and characterization data including ^{1}H and ^{13}C NMR spectra for new compounds are available free of charge via the internet. Crystallographic data (**1b**: CCDC 785001; **2b**: CCDC 785003; **3g**: CCDC 785002; **4d**: CCDC 785005; **4i**: CCDC 785004) have been deposited via the Cambridge Crystallographic Database Centre and is available on request (http://www.ccdc.cam.ac.uk/). Supplementary data associated with this article can be found online at doi:10.1016/j.tet.2011.01.046.

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