Synthesis of 2,3-Disubstituted 5-Iodo-1*H*-Pyrrolo[2,3-*b*]pyridines *via* Fischer Cyclization

Roman S. Alekseyev,[a]* Sabina S. Amirova,[b] and Vladimir I. Terenin[a]

[a]Chemistry Department, M. V. Lomonosov Moscow State University, Leninskiye Gory 1/3, Moscow 119991, Russian Federation

[b]Chemistry Department, M. V. Lomonosov Moscow State University, Baku Branch, Universitetskaya St. 1, Khojasan, Binagadi, AZ 1144 Baku, Azerbaijan

*E-mail: alros@hotmail.ru

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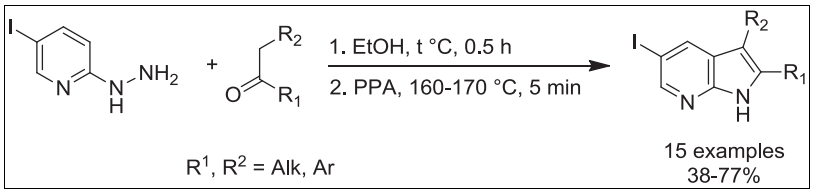

A simple and convenient procedure for the preparation of some unknown 2,3-disubstituted 5-iodo-1*H*-pyrrolo[2,3-*b*]pyridines from readily available starting materials by Fischer indole cyclization in polyphosphoric acid is described. The present methodology provides an alternative synthetic approach to the synthesis of 5-iodo-7-azaindole scaffold. All synthesized compounds were characterized by IR, MS, ^{1}H and ^{13}C NMR, and elemental analysis.

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INTRODUCTION

1*H*-Pyrrolo[2,3-*b*]pyridines (also known as 7-azaindoles) and their derivatives possess more favorable bioactive utilities than the corresponding indole moieties because of their significant physicochemical properties that are caused by additional nitrogen atom in six-membered ring [1]. 7-Azaindoles are widely used as key frameworks in a variety of drug candidates in medicinal chemistry and drug discovery [2,3]. The iodine-containing 7-azaindole scaffold may be useful in the synthesis of biological active compounds and potential drug candidates, first of all as substrate in palladium-catalyzed cross-coupling [4] or in metallation and further metal exchange processes [5].

There are many different methods for the preparation of 7-azaindoles, which have been considered in details in reviews [6–9]. However, only a few number of synthetic approaches to the synthesis of 5-iodo-7-azaindole frameworks have been developed previously. The first classical approach to 5-iodo-7-azaindole scaffold is based on electrophilic iodination of pyridine ring in 7-azaindole moiety in the presence of iodine chloride [10] or *N*-iodosuccinimide (NIS) [11]. The second one deals with metal-catalyzed nucleophilic substitution of halogen to iodine atom (Finkelstein reaction) [12,13]. And the last one includes lithiation of 7-azaindole moiety and further lithium/iodine exchange by electrophilic substitution [14,15]. Thus, all known strategies for the synthesis of 5-iodo-7-azaindole moiety propose iodination of starting 1*H*-pyrrolo[2,3-*b*]pyridine.

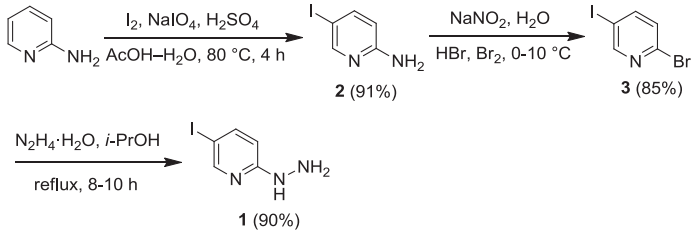
The Fischer reaction widely used for indole synthesis may be applied for the preparative synthesis of 7-azaindole framework in polyphosphoric acid (PPA) at 160–180°C, as we have demonstrated previously for unsaturated [16] and bromo-substituted derivatives [17]. The main purpose of present work is to extend the field of application of the Fischer indole synthesis under thermal conditions for the preparation of 2,3-disubstituted 5-iodo-7-azaindole moiety and to explore the influence of iodine atom in pyridine ring on the yields of the final products.

RESULTS AND DISCUSSION

The starting 2-hydrazino-5-iodopyridine (**1**) was prepared from commercially available and cheap 2-aminopyridine by the synthetic route, formerly used by us [16,17], which involves its electrophilic iodination to 2-amino-5-iodopyridine (2), and its further transformation to 2-bromo-5-iodopyridine (**3**) (Scheme 1).

The final 2,3-disubstituted 5-iodo-1*H*-pyrrolo[2,3-*b*] pyridines **4a–p** were obtained in moderate to good yields by cyclization of the (5-iodopyridin-2-yl)hydrazones **5a–p** in PPA at 160–170°C for 5 min, which were initially prepared by refluxing the hydrazine **1** with the appropriate ketone (1 equiv) (Scheme 2, Table 1). All data of MS, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis for synthesized 5-iodo-7-azaindoles **4a–p** are shown in the Experimental section.

Scheme 1. Synthesis of 2-hydrazino-5-iodopyridine (**1**).



Scheme 2. Synthesis of 5-iodo-7-azaindoles **4a–p** and estimated mechanism of their formation.

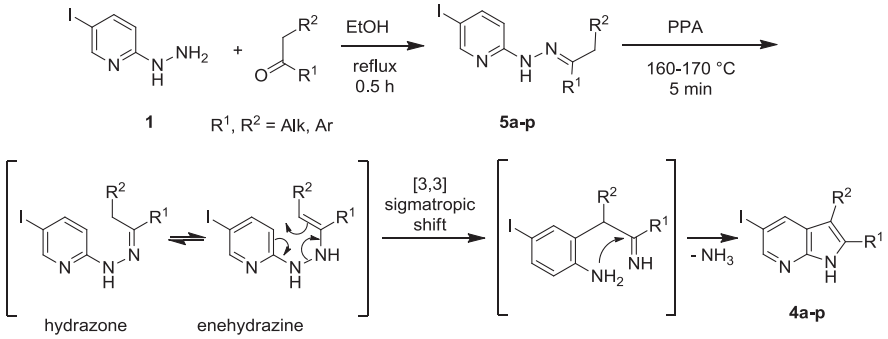
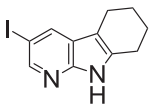
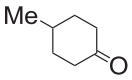
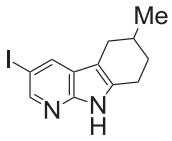
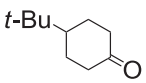
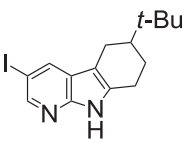
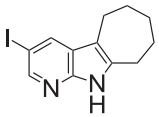
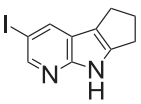


Table 1

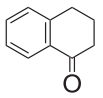
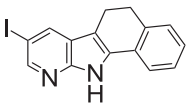
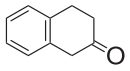
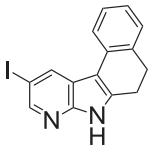
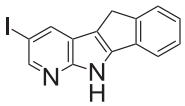
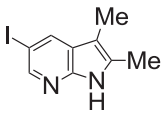
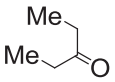
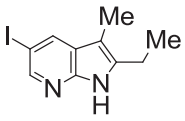
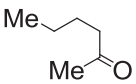
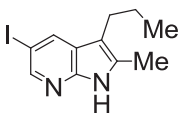
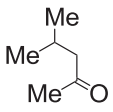
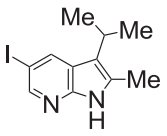
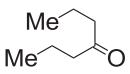
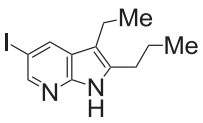
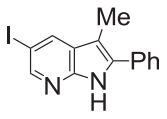
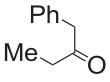
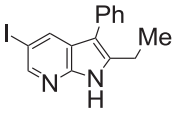
Synthesis of 5-iodo-7-azaindoles **4a–p.**

Entry	Starting ketone		Product	Yield, %[a]
1		**4a**		69
2		**4b**		71
3		**4c**		77
4		**4d**		53
5		**4e**		49

(*Continued*)

Table 1

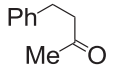
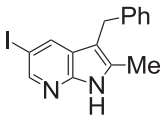
(*Continued*)

Entry	Starting ketone		Product	Yield, %[a]
6		**4f**		57
7		**4g**		52
8		**4h**		0[b]
9		**4i**		53
10		**4j**		51
11		**4k**		59
12		**4l**		38
13		**4m**		46
14		**4n**		43
15		**4o**		63

(*Continued*)

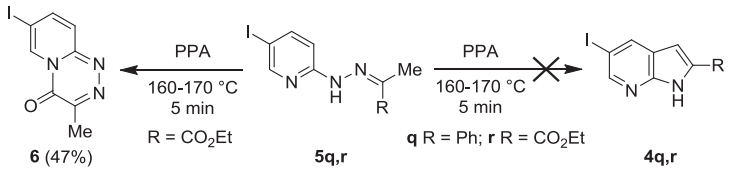
Table 1

(*Continued*)

Entry	Starting ketone		Product	Yield, %[a]
16		**4p**		42

[a]Isolated yields based on the starting hydrazine **1**.
[b]Starting hydrazone **5h** was isolated in unchanged form.

Scheme 3. Cyclization of methyl ketone hydrazones **5q,r.**



It should be noted that hydrazones **5a–p** were used without isolation and additional purification (spectral data for them are presented in the Supporting Information). In contrast to 5-bromo- and unsubstituted 7-azaindoles, 5-iodo-derivatives are sensitive to overheating: the temperature must be carefully controlled and kept below 170–175°C during the Fischer indolization; otherwise, decomposition occurs with elimination of iodine. Increased reaction time also provides resinification of the reaction mixture under this conditions and leads to lower yields of the target 5-iodo-7-azaindoles **4a–p**.

Fischer cyclization proceeds via [3] sigmatropic shift, which involves an enehydrazine form of the starting hydrazone **5a–p** as intermediate (Scheme 2), and the indolization rate depends on the ease of enhydrazine formation, which correlates with a degree of enolization of the starting ketone [16]. The best results (yields 69%–77%) were observed for cyclic six-membered ketones (entries 1–3) and several acyclic ketones, including aliphatic (entries 9–11) and benzyl ones (entry 15). However, no traces of the corresponding 5-iododerivative **4h** were detected, and only starting hydrazone **5h** was isolated unchanged for indan-1-one (entry 8). It may be explained by the very low ability of this substrate to transform into the enehydrazine form.

The same results were observed in the case of methyl ketone hydrazones **5q,r** (Scheme 3): instead of the respective 5-iodo-7-azaindoles **4q,r**, the starting hydrazone **5q** (R = Ph) or the hitherto unknown triazinone **6** (R═COOEt) were isolated. The structure of compound **6** was offered on the basis of the analysis of spectral data set for this one.

We have previously reported on the synthesis of 5-bromo-7-azaindole derivatives by the Fischer reaction in PPA under the same conditions [17]. If we compare the yields of 5-iodo- and 5-bromo-derivatives, the azaindole yields are similar or slightly lower for 5-iodo-substituted ones. It can be explained by lower thermodynamic stability of 5-iodo-substituted hydrazones (decomposition above 170–175°C in PPA). Comparison with the yields of unsubstituted 1*H*-pyrrolo[2,3-*b*] pyridines [16] shows the absence of definite correlations between the yields of 5-iodo- and unsubstituted 7-azaindoles from the presence of the iodine atom on the pyridine ring, which promotes the resinification with increasing temperature or reaction time.

CONCLUSIONS

In summary, we have proposed a simple and efficient synthesis of some previously unknown 2,3-disubstituted 5-iodo-7-azaindole derivatives via aza-Fischer reaction in polyphosphoric acid under thermal conditions, leading to the required fused-ring heterocycles in moderate to good yields. This procedure is common for various alkyl and aryl ketones, and also useful for the preparation of 5-iodo-7-azaindoles at multigram scale level, but these reaction conditions are not appropriate for methyl ketones.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance-400 spectrometer (400 and 100 MHz,

respectively) in $CDCl_3$ or DMSO-d_6, with residual solvent protons as internal standard (7.27 and 2.51 ppm for ^1H nuclei, 77.1 and 39.5 ppm for ^{13}C nuclei). Mass spectra were recorded on a Finnigan MAT ITD-700 instrument, EI ionization (70 eV), *m/z* range 45–400. IR spectra were recorded on a Thermo Nicolet IR200 FTIR spectrometer. Elemental analysis was performed on a EURO EA CHNS-analyzer. Melting points were determined in open capillaries and were not corrected. TLC were run on pre-coated silica gel plates (Merck $60F_{254}$), and the spots were visualized using a UV lamp. Commercially available reagents from Acros, Sigma-Aldrich, Merck, Alfa Aesar, Fischer Scientific and Reakhim were used in this work.

2-Amino-5-iodopyridine (2). 2-Aminopyridine (25.0 g, 0.27 mol), $NaIO_4$ (12.0 g, 56.1 mmol), and iodine (27.7 g, 109.1 mmol) were added to a mixture of AcOH (200 mL), H_2O (30 mL), and H_2SO_4 (5 mL), and the final reaction mixture was heated at 80°C for 4 h. After cooling, Na_2SO_3 (0.5–1.0 g) was added for decoloration, and the solvent was evaporated under vacuum. The residue was suspended in H_2O (30 mL) and neutralized with saturated aqueous solution of K_2CO_3 (~50 mL). The solid was filtered off, washed with cold water (3 × 30 mL), and air-dried to constant weight. The solid was washed with boiling heptane (20 mL) to remove traces of 2-amino-3,5-diiodopyridine; off-white fine crystals; yield 53.2 g (91%); m.p. 127–128°C (heptane) (lit. m.p. 128–129°C [18]); R_f = 0.7 ($CHCl_3$–EtOAc, 1:1). IR (KBr) ν, cm^{-1}: 3395, 3300, 3139, 1634, 1582, 1482, 1381, 1258, 1142, 822. ^1H NMR ($CDCl_3$): δ = 4.48 (br s, 2H, NH_2), 6.36 (d, J = 8.7 Hz, 1H, H-3), 7.63 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H, H-4), 8.22 (d, J = 2.1 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ = 77.8, 110.9, 145.3, 153.8, 157.4. MS (EI, 70 eV) *m/z* (%): 220 $[M]^+$ (100), 193 (12), 127 $[I]^+$ (10), 93 (5), 66 (11). *Anal.* Calcd for $C_5H_5IN_2$: C, 27.30; H, 2.29; N, 12.73. Found: C, 27.44; H, 2.13; N, 12.69.

2-Bromo-5-iodopyridine (3). 2-Amino-5-iodopyridine (**2**) (22.0 g, 0.1 mol) was added over 10 min to a cold (10°C) aq 48% HBr (50 mL, 0.6 mol), then the mixture was heated until all solid was dissolved, and cooled to 0–10°C. Bromine (15 mL, 0.3 mol) was added drop by drop, keeping the temperature below 10°C. Then, a solution of $NaNO_2$ (20.0 g, 0.2 mol) in water (25 mL) was added dropwise for 1 h, maintaining the temperature at 0–5°C. The reaction mixture was stirred for additional 30 min, then treated with a solution of NaOH (35.0 g, 0.9 mol) in water (40 mL) at such a rate that temperature did not exceed 20–25°C. The solid was filtered off, slurry-washed with cold water (3 × 10 mL), and air-dried to afford a pale yellowish powder; yield 24.1 g (85%); m. p. 116–117°C (hexane) (lit. m.p. 117–119°C (EtOH) [19]); R_f = 0.6 ($CHCl_3$). IR (KBr) ν, cm^{-1}: 3090, 3020, 1547, 1439, 1354, 1085, 994, 828. ^1H NMR ($CDCl_3$) δ, ppm: 7.29 (d, J = 8.3 Hz, 1H, H-3), 7.82 (dd, J_1 = 8.3 Hz, J_2 = 2.3 Hz, 1H, H-4), 8.59 (d, J = 2.3 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ, ppm: 91.7, 130.0, 141.5, 146.6, 156.2. MS (EI, 70 eV) *m/z* (%): 285 $[M(^{81}Br)]^+$ (93), 283 $[M(^{79}Br)]^+$ (100), 204 (47), 127 $[I]^+$ (51), 77 (16), 76 (16), 50 (30). *Anal.* Calcd for C_5H_3BrIN: C, 21.15; H, 1.07; N, 4.93. Found: C, 21.04; H, 1.14; N, 4.89.

2-Hydrazino-5-iodopyridine (1). A mixture of 2-bromo-5-iodopyridine (**3**) (22.6 g, 79.6 mmol), hydrazine hydrate (30 mL, 0.6 mol), and 2-propanol (30 mL) was refluxed for 8–10 h, and the excess hydrazine hydrate and 2-propanol were evaporated under vacuum. The residue was suspended in cold H_2O (30 mL), and the precipitate formed was filtered off, washed with ice cold H_2O (2 × 5 mL), and air-dried to constant mass. The obtained precipitate was recrystallized from EtOH to give off-white crystals; yield 16.8 g (90%); m.p. 124–125°C (EtOH); R_f = 0.5 ($CHCl_3$–EtOAc, 1:1). IR (KBr) ν, cm^{-1}: 3249, 3171, 3047, 1590, 1506, 1476, 1375, 1135, 984, 809. ^1H NMR ($CDCl_3$) δ, ppm: 4.16 (br s, 2H, NH_2), 6.62 (d, J = 8.8 Hz, 1H, H-3), 7.64 (br s, 1H, NH), 7.68 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H, H-4), 8.12 (d, J = 2.3 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$) δ, ppm: 76.0, 108.9, 144.1, 152.5, 160.8. MS (EI, 70 eV) *m/z* (%): 235 $[M]^+$ (100); 205 (15); 168 (12); 127 $[I]^+$ (12); 91 (8); 78 (12). *Anal.* Calcd for $C_5H_6IN_3$: C, 25.55; H, 2.57; N, 17.88. Found: C, 25.67; H, 2.44; N, 17.82.

Preparation of 5-iodo-1*H*-pyrrolo[2,3-*b*]pyridines 4; general procedure. A solution of the corresponding carbonyl compound (3.0 mmol) in EtOH (5 mL) was added drop by drop to a solution of 2-hydrazino-5-iodopyridine (**1**; 705 mg, 3.0 mmol) in EtOH (5 mL). The reaction mixture was refluxed for 30 min, evaporated under vacuum to constant mass to give corresponding hydrazone **5** as a solid or viscous liquid. Polyphosphoric acid freshly prepared by solving P_2O_5 (2.0 g) in H_3PO_4 (85%, 1 mL) under heating on water bath for 3 h was added to the residue. The reaction mixture was heated to 160°C (carefully!) and maintained at 160–170°C for 5 min (temperature should be below 170–175°C). After cooling to 40–50°C, the reaction mixture was suspended with H_2O (25–30 mL), cooled to ~0°C, and alkalified with aq 25% ammonia. The precipitate that formed was filtered off, washed with cold water (10 mL, 0°C) and MeOH (1 mL, 0°C), and air-dried.

3-Iodo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (4a). An off-white powder; yield 0.62 g (69%); m.p. 223–224°C (MeOH); R_f = 0.5 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3139, 3032, 2932, 2832, 1568, 1407, 1281, 1226, 996, 905, 874, 768. ^1H NMR ($CDCl_3$) δ, ppm: 1.78–1.81 (m, 4H, 6,7-CH_2), 2.57 (t, J = 5.1 Hz, 2H, 5-CH_2), 2.70 (t, J = 5.1 Hz, 2H, 8-CH_2), 8.07 (s, 1H, H-4), 8.21 (s, 1H, H-2), 11.38 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ,

ppm: 20.1, 22.4, 22.5, 22.6, 81.8, 106.6, 122.5, 132.4, 137.0, 145.5, 146.8. MS (EI, 70 eV) *m/z* (%): 298 $[M]^+$ (100); 270 (79); 171 (11); 143 (10); 127 (8); 89 (4). *Anal.* Calcd for $C_{11}H_{11}IN_2$: C, 44.32; H, 3.72; N, 9.40. Found: C, 44.27; H, 3.60; N, 9.59.

3-Iodo-6-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (4b). A pale gravel powder; yield 0.66 g (71%); m.p. 209–210°C (MeOH); R_f = 0.55 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3131, 3045, 2924, 2867, 1570, 1488, 1409, 1281, 975, 875, 769. ^{1}H NMR (DMSO-d_6) δ, ppm: 1.06 (d, J = 6.6 Hz, 3H, Me), 1.42–1.51 (m, 1H, 7-CH_B), 1.85–1.93 (m, 2H, 6-CH, 7-CH_A), 2.13 (dd, J_1 = 15.6 Hz, J_2 = 9.7 Hz, 1H, 5-CH_B), 2.71–2.74 (m, 3H, 5-CH_A, 8-CH_2), 8.05 (d, J = 2.0 Hz, 1H, H-4), 8.21 (d, J = 2.0 Hz, 1H, H-2), 11.39 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 21.5, 22.2, 28.5, 28.9, 30.5, 81.8, 106.5, 122.4, 132.4, 136.7, 145.5, 147.1. MS (EI, 70 eV) *m/z* (%): 312 $[M]^+$ (93); 308 (13); 270 (100); 186 (11); 144 (16); 127 $[I]^+$ (6); 89 (3). *Anal.* Calcd for $C_{12}H_{13}IN_2$: C, 46.17; H, 4.20; N, 8.97. Found: C, 46.25; H, 4.25; N, 8.89.

6-*tert*-Butyl-3-iodo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (4c). A pale gravel powder; yield 0.82 g (77%); m.p. 208–209°C (MeOH); R_f = 0.6 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3140, 3046, 2947, 2863, 1568, 1468, 1406, 1363, 876. ^{1}H NMR (DMSO-d_6) δ, ppm: 0.95 (s, 9H, *t*-Bu), 1.36–1.47 (m, 2H, 7-CH_2), 2.03–2.06 (m, 1H, 5-CH_B), 2.23–2.34 (m, 1H, 6-CH), 2.69–2.80 (m, 3H, 5-CH_A, 8-CH_2), 8.10 (d, J = 2.2 Hz, 1H, H-4), 8.21 (d, J = 2.2 Hz, 1H, H-2), 11.37 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 21.5, 23.5, 24.0, 27.3 (3C), 32.3, 44.6, 81.7, 107.0, 122.7, 132.4, 137.0, 145.4, 147.2. MS (EI, 70 eV) *m/z* (%): 354 $[M]^+$ (83); 297 (9); 270 (100); 169 (11); 144 (15); 116 (4); 57 (12); 41 (12). *Anal.* Calcd for $C_{15}H_{19}IN_2$: C, 50.86; H, 5.41; N, 7.91. Found: C, 50.75; H, 5.64; N, 7.87.

3-Iodo-5,6,7,8,9,10-hexahydrocyclohepta[4,5]pyrrolo[2,3-*b*]pyridine (4d). A gravel powder; yield 0.50 g (53%); m.p. 191–192°C (MeOH); R_f = 0.5 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3134, 3042, 2918, 2844, 1566, 1489, 1403, 1272, 934, 872, 769, 661. ^{1}H NMR (DMSO-d_6) δ, ppm: 1.63–1.69 (m, 4H, 7-CH_2, 8-CH_2), 1.81–1.85 (m, 2H, 6-CH_2), 2.69 (t, J = 5.0 Hz, 2H, 5-CH_2), 2.83 (t, J = 5.0 Hz, 2H, 9-CH_2), 8.13 (d, J = 1.8 Hz, 1H, H-4), 8.20 (d, J = 1.8 Hz, 1H, H-2), 11.43 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 23.9, 26.8, 28.2, 28.3, 31.3, 81.9, 110.4, 123.7, 124.7, 132.4, 140.5, 145.3. MS (EI, 70 eV) *m/z* (%): 312 $[M]^+$ (100); 283 (40); 270 (22); 258 (13); 185 (18); 156 (14); 127 $[I]^+$ (16); 103 (6). *Anal.* Calcd for $C_{12}H_{13}IN_2$: C, 46.17; H, 4.20; N, 8.97. Found: C, 46.09; H, 4.34; N, 8.90.

3-Iodo-5,6,7,8-tetrahydrocyclopenta[4,5]pyrrolo[2,3-*b*]pyridine (4e). A brown powder; yield 0.42 g (49%); m.p. 225–226°C (MeOH); R_f = 0.45 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3141, 3043, 2929, 2845, 1580, 1443, 1411, 1274, 876, 769. ^{1}H NMR (DMSO-d_6) δ, ppm: 2.42 (quin, J = 7.1 Hz, 2H, 6-CH_2), 2.73 (t, J = 7.1 Hz, 2H, 5-CH_2), 2.86 (t, J = 7.1 Hz, 2H, 7-CH_2), 8.07 (d, J = 1.8 Hz, 1H, H-4), 8.19 (d, J = 1.8 Hz, 1H, H-2), 11.60 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 24.2, 25.7, 27.3, 82.4, 110.8, 119.8, 132.9, 144.9, 146.3, 151.1. MS (EI, 70 eV) *m/z* (%): 284 $[M]^+$ (100); 257 (13); 220 (22); 157 (19); 155 (15); 127 $[I]^+$ (21); 75 (6). *Anal.* Calcd for $C_{10}H_9IN_2$: C, 42.28; H, 3.19; N, 9.86. Found: C, 42.17; H, 3.30; N, 9.91.

8-Iodo-6,11-dihydro-5*H*-benzo[*g*]pyrido[2,3-*b*]indole (4f). A dark gray powder; yield 0.59 g (57%); m.p. 294–295°C (EtOH); R_f = 0.55 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3149, 3058, 2926, 2832, 1566, 1473, 1442, 1275, 930, 804, 764, 665. ^{1}H NMR (DMSO-d_6) δ, ppm: 2.85–2.89 (m, 2H, 5-CH_2), 2.96–3.01 (m, 2H, 6-CH_2), 7.20–7.31 (m, 2H, H-2,3), 7.59–7.77 (m, 2H, H-1,4), 8.27 (s, 1H, H-7), 8.32 (s, 1H, H-9), 12.22 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 18.7, 28.5, 82.7, 120.5, 121.9, 122.4, 126.8, 127.6, 127.9, 128.4, 133.8, 134.6, 136.3, 147.1, 149.9. MS (EI, 70 eV) *m/z* (%): 346 $[M]^+$ (100); 345 (75); 344 (78); 218 (59); 190 (24); 163 (10); 127 (9); 109 (9). *Anal.* Calcd for $C_{15}H_{11}IN_2$ C, 52.04; H, 3.20; N, 8.09. Found: C, 51.96; H, 3.36; N, 8.05.

10-Iodo-6,7-dihydro-5*H*-benzo[*e*]pyrido[2,3-*b*]indole (4g). A pale brown powder; yield 0.54 g (52%); m.p. 275–276°C (MeOH); R_f = 0.6 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3096, 3023, 2822, 2716, 1559, 1501, 1410, 1265, 963, 758. ^{1}H NMR (DMSO-d_6) δ, ppm: 2.97–3.02 (m, 4H, 6-CH_2, 7-CH_2), 7.07 (t, J = 7.4 Hz, 1H, H-3), 7.23–7.27 (m, 2H, H-2, H-4), 7.73 (d, J = 7.2 Hz, 1H, H-1), 8.34 (s, 1H, H-11), 8.63 (s, 1H, H-9), 12.06 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 21.4, 28.2, 83.6, 107.0, 119.3, 122.1, 124.6, 126.9, 127.5, 128.0, 132.1, 133.8, 136.6, 146.2, 147.2. MS (EI, 70 eV) *m/z* (%): 346 $[M]^+$ (100); 345 (36); 344 (71); 218 (30); 190 (14); 163 (8); 109 (7). *Anal.* Calcd for $C_{15}H_{11}IN_2$: C, 52.04; H, 3.20; N, 8.09. Found: C, 52.14; H, 3.04 ; N, 8.01.

5-Iodo-2,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (4i). An off-white powder; yield 0.43 g (53%); m.p. 181–182°C (MeOH); R_f = 0.5 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3136, 3043, 2940, 2858, 1567, 1486, 1404, 1281, 909, 874, 770, 673. ^{1}H NMR (DMSO-d_6) δ, ppm: 2.13 (s, 3H, 3-Me), 2.32 (s, 3H, 2-Me), 8.11 (s, 1H, H-4), 8.21 (s, 1H, H-6), 11.40 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 7.9, 11.2, 81.7, 103.7, 124.1, 132.6, 134.0, 145.5, 146.3. MS (EI, 70 eV) *m/z* (%): 272 $[M]^+$ (100); 257 (17); 145 (12); 127 (11); 103 (4); 76 (5). *Anal.* Calcd for $C_9H_9IN_2$: C, 39.73; H, 3.33; N, 10.30. Found: C, 39.69; H, 3.45; N, 10.24.

2-Ethyl-5-iodo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4j). A beige powder; yield 0.44 g (51%); m.p. 193–194°C

(MeOH); R_f = 0.6 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3145, 3048, 2965, 2851, 1569, 1487, 1404, 1276, 908, 872, 768, 657. ^1H NMR (DMSO-d_6) δ, ppm: 1.21 (t, J = 7.6 Hz, 3H, 2-Me), 2.13 (s, 3H, 3-Me), 2.69 (q, J = 7.6 Hz, 2H, CH_2), 8.11 (d, J = 2.0 Hz, 1H, H-4), 8.22 (d, J = 2.0 Hz, 1H, H-6), 11.42 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6), δ, ppm: 7.9, 13.9, 18.8, 81.8, 102.9, 124.1, 132.9, 139.7, 145.7, 146.4. MS (EI, 70 eV) *m/z* (%): 286 $[M]^+$ (100); 271 (74); 257 (7); 159 (19); 144 (22); 127 (26); 103 (6); 76 (7). *Anal.* Calcd for $C_{10}H_{11}IN_2$: C, 41.98; H, 3.88; N, 9.79. Found: C, 42.03; H, 3.75; N, 9.85.

5-Iodo-2-methyl-3-propyl-1*H*-pyrrolo[2,3-*b*]pyridine (4k). A beige powder; yield 0.53 g (59%); m.p. 164–165°C (MeOH); R_f = 0.65 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3133, 3037, 2954, 2925, 2852, 1568, 1488, 1404, 1282, 1217, 940, 891, 876, 770, 676. ^1H NMR ($CDCl_3$) δ, ppm: 0.87 (t, J = 7.3 Hz, 3H, 3-Me), 1.53 (sext, J = 7.3 Hz, 2H, CH_2Me), 2.32 (s, 3H, 2-Me), 2.57 (t, J = 7.3 Hz, 2H, CH_2Et), 8.12 (d, J = 1.6 Hz, 1H, H-4), 8.20 (d, J = 1.6 Hz, 1H, H-6), 11.42 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 11.2, 13.7, 23.5, 25.0, 81.8, 108.8, 123.5, 132.6, 134.1, 145.4, 146.3. MS (EI, 70 eV) *m/z* (%): 300 $[M]^+$ (68); 271 (100); 144 (15); 127 (3). *Anal.* Calcd for $C_{11}H_{13}IN_2$: C, 44.02; H, 4.37; N, 9.33. Found: C, 44.15; H, 4.23; N, 9.27.

5-Iodo-3-isopropyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4l). Off-white needle crystals; yield 0.34 g (38%); m.p. 182–183°C (hexane); R_f = 0.55 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3132, 3029, 2956, 2864, 1560, 1463, 1401, 1275, 931, 869, 674. ^1H NMR ($CDCl_3$) δ, ppm: 1.37 (d, J = 7.1 Hz, 6H, Me_2CH), 2.46 (s, 3H, 2-Me), 3.13 (sept, J = 7.1 Hz, 1H, $CHMe_2$), 8.22 (s, 1H, H-4), 8.31 (s, 1H, H-6), 10.68 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ, ppm: 12.2, 23.2 (2C), 25.8, 81.1, 115.9, 123.1, 132.1, 135.0, 145.2, 146.8. MS (EI, 70 eV) *m/z* (%): 300 $[M]^+$ (56); 285 (100); 158 (20); 127 (10); 89 (3). *Anal.* Calcd for $C_{11}H_{13}IN_2$: C, 44.02; H, 4.37; N, 9.33. Found: C, 44.08; H, 4.42; N, 9.25.

3-Ethyl-5-iodo-2-propyl-1*H*-pyrrolo[2,3-*b*]pyridine (4m). A gravel powder; yield 0.43 g (46%); m.p. 104–105°C (hexane); R_f = 0.65 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3141, 3045, 2952, 2864, 1567, 1453, 1403, 1255, 930, 874. ^1H NMR (DMSO-d_6) δ, ppm: 0.89 (t, J = 7.2 Hz, 3H, 2-Me), 1.13 (t, J = 7.3 Hz, 3H, 3-Me), 1.65 (sext, J = 7.2 Hz, 2H, 2-CH_2Me), 2.59–2.67 (m, 4H, 3-CH_2Me and 2-CH_2Et), 8.15 (s, 1H, H-4), 8.22 (s, 1H, H-6), 11.40 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: = 13.6, 15.8, 16.4, 22.5, 27.3, 81.7, 110.6, 123.0, 132.8, 137.6, 145.6, 146.5. MS (EI, 70 eV) *m/z* (%): 314 $[M]^+$ (100); 299 (71); 285 (39); 270 (12); 172 (9); 157 (8); 29 (24). *Anal.* Calcd for $C_{12}H_{15}IN_2$: C, 45.88; H, 4.81; N, 8.92. Found: C, 45.80; H, 4.88; N, 8.90.

5-Iodo-3-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (4n). An off-white powder; yield 0.43 g (43%); m.p. 220–221°C (MeOH); R_f = 0.6 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3124, 3046, 2924, 2857, 1475, 1398, 1275, 1072, 909, 879, 767, 698, 673. ^1H NMR (DMSO-d_6) δ, ppm: 2.38 (s, 3H, Me), 7.41 (t, J = 7.4 Hz, 1H, H-4 Ph), 7.52 (t, J = 7.4 Hz, 2H, H-3,5 Ph), 7.71 (d, J = 7.4 Hz, 2H, H-2,6 Ph), 8.33 (s, 1H, H-4), 8.36 (s, 1H, H-6), 11.95 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 9.5, 82.3, 105.2, 124.5, 127.8, 128.0 (2C), 128.7 (2C), 131.8, 134.1, 135.5, 146.9, 147.4. MS (EI, 70 eV) *m/z* (%): 334 $[M]^+$ (100); 257 (10); 205 (11); 127 (4); 103 (7); 77 (6). *Anal.* Calcd for $C_{14}H_{11}IN_2$: C, 50.32; H, 3.32; N, 8.38. Found: C, 50.43; H, 3.19; N, 8.42.

2-Ethyl-5-iodo-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (4o). A light brown powder; yield 0.66 g (63%); m.p. 209–210°C (MeOH); R_f = 0.65 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3134, 3026, 2970, 2932, 2872, 1599, 1500, 1448, 1401, 1267, 930, 759, 704. ^1H NMR (DMSO-d_6) δ, ppm: 1.29 (t, J = 7.4 Hz, 3H, Me), 2.83 (q, J = 7.4 Hz, 2H, CH_2), 7.31–7.48 (m, 5H, Ph), 8.11 (s, 1H, H-4), 8.34 (s, 1H, H-6), 11.95 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ, ppm: 14.1, 19.3, 82.9, 110.1, 122.1, 126.2, 128.8 (2C), 128.9 (2C), 133.1, 133.8, 140.3, 146.5, 146.6. MS (EI, 70 eV) *m/z* (%): = 348 $[M]^+$ (100); 333 (24); 221 (7); 206 (20); 127 $[I]^+$ (4); 103 (4). *Anal.* Calcd for $C_{15}H_{13}IN_2$: C, 51.74; H, 3.76; N, 8.05. Found: C, 51.71; H, 3.65; N, 8.11.

3-Benzyl-5-iodo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4p). A pale brown powder; yield 0.44 g (42%); m.p. 205–206°C (toluene); R_f = 0.6 ($CHCl_3$–MeOH, 20:1). IR (KBr) ν, cm^{-1}: 3129, 3025, 2927, 2843, 2745, 1569, 1491, 1403, 1275, 875, 698. ^1H NMR ($CDCl_3$) δ, ppm: 2.39 (s, 3H, Me), 3.97 (s, 2H, CH_2), 7.14 (t, J = 7.3 Hz, 1H, H-4 Ph), 7.19–7.27 (m, 4H, H-2,3,5,6 Ph), 8.1 (s, 1H, H-4), 8.21 (s, 1H, H-6), 11.55 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ, ppm: 11.4, 29.0, 82.1, 107.9, 123.4, 125.7, 128.1 (2C), 128.3 (2C), 132.8, 134.7, 141.4, 145.7, 146.4. MS (EI, 70 eV) *m/z* (%): 348 $[M]^+$ (100); 333 (23); 271 (67); 258 (11); 221 (12); 205 (11); 178 (10); 144 (23); 127 (13); 103 (11); 77 (15); 51 (15); 42 (15). *Anal.* Calcd for $C_{15}H_{13}IN_2$: C, 51.74; H, 3.76; N, 8.05. Found: C, 51.63; H, 3.90; N, 7.98.

7-Iodo-3-methyl-4*H*-pyrido[2,1-c][1,2,4]triazin-4-one (6). If ethyl pyruvate was used as a carbonyl compound, the only triazine-4-one **6** was isolated as a pale gray powder from reaction mixture after alkalization and washing with cold water; yield 0.38 g (47%); m.p. 228–229°C (decomp); R_f = 0.42 (EtOAc). IR (KBr) ν, cm^{-1}: 3352, 3097, 3081, 3024, 1679, 1541, 1499, 1462, 1436, 1377, 1289, 1153, 1095, 1066, 829, 748. ^1H NMR ($CDCl_3$) δ, ppm: 2.57 (s, 3H, Me), 7.44 (d, J = 9.3 Hz, 1H, H-9), 7.76 (d, J = 9.3 Hz, 1H, H-8), 8.89 (s, 1H, H-6). ^{13}C NMR

($CDCl_3$) δ, ppm: 17.7, 82.7, 125.2, 129.0, 142.6, 145.6, 146.9, 149.2. MS (EI, 70 eV) *m/z* (%): 287 $[M]^+$ (76); 259 (100); 218 (46); 204 (9); 191 (9); 127 $[I]^+$ (19); 91 (34); 77 (15); 64 (24). *Anal.* Calcd for $C_8H_6IN_3O$: C, 33.47; H, 2.11; N, 14.64. Found: C, 33.56; H, 1.99; N, 2.09.

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