Synthesis R. S. Alekseyev et al. Paper

# Preparation of 2,3-Disubstituted 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine Framework by Fischer Cyclization

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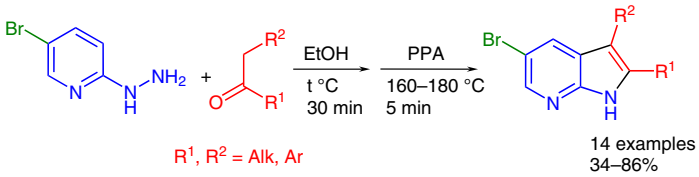


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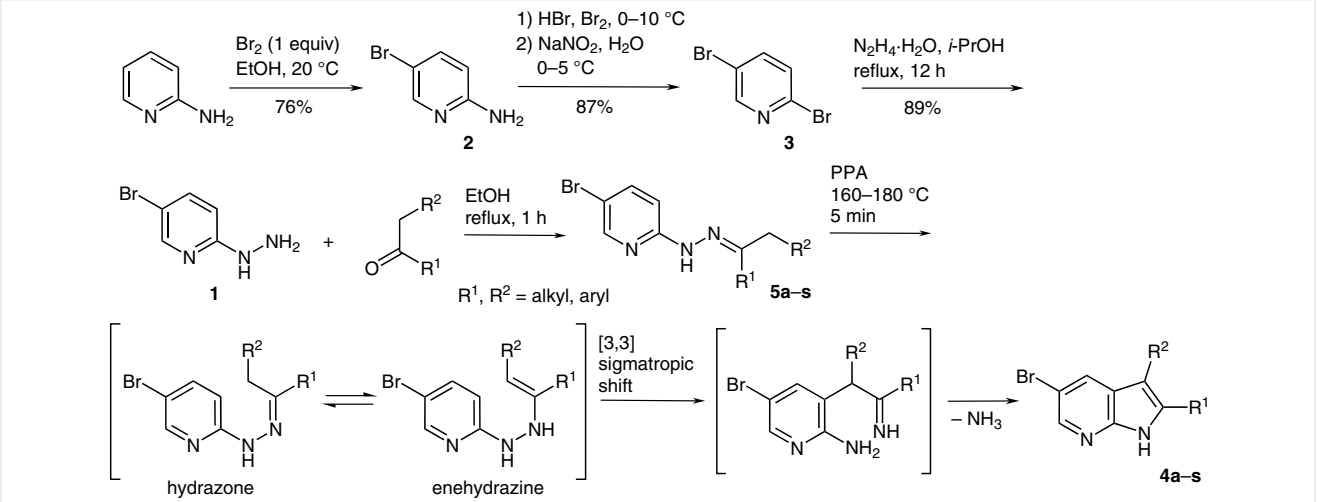
**Abstract** A simple synthesis of some hard-to-reach heterocycles containing 2,3-disubstituted 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine framework by Fischer indole cyclization in polyphosphoric acid has been developed. A particularly valuable feature of this synthetic route is the possibility to build a 5-bromo-7-azaindole scaffold with alkyl or aryl substituents at positions 2 and 3 from available starting materials.

**Key words** heterocycles, fused-ring systems, pyridines, pyrroles, cyclization, hydrazones

1*H*-Pyrrolo[2,3-*b*]pyridines (more commonly named as 7-azaindoles) and their derivatives exhibit significant physicochemical and biological activities, and the use of this framework has contributed to the generation of new therapeutic agents.[1] Rarely found in nature,[2] 7-azaindoles and other isomers are interesting in terms of drug optimization strategies and have been recognized as privileged structures in biological process modulation, medicinal chemistry, and drug discovery.[3,4] One of the nitrogen atoms in 7-azaindole moiety is part of a π-electron-rich five-membered pyrrole ring and the other nitrogen atom is the electron-deficient six-membered pyridine ring, thus 7-azaindoles may be excellent bioisosters of indole and purine systems.

A frequently employed strategy for the synthesis of azaindoles is to start with substituted pyridines and build up a pyrrole ring, but the electron-deficient nature of the pyridine ring makes it difficult for the most classical methods of indole preparation to be used. Currently, the common routes for the synthesis of 7-azaindoles are various modifications of Madelung and Reissert syntheses,[5] as well as palladium-catalyzed processes based on 2-amino-3-halopyridines,[6] and annulation of pyridine ring to pyrrole moiety.[7] The Fischer reaction discovered in 1883 remains one of the most useful methods for indole synthesis at pres-




**Scheme 1**

ent, but only a few examples exist for the preparative synthesis of 1*H*-pyrrolo[2,3-*b*]pyridines (or 7-azaindoles) by Fischer cyclization using various 2-pyridylhydrazones.[8] It should be noted that the acid-catalyzed (aq $H_2SO_4$) Fischer reaction has been recently successfully used for the preparation of 4- and 6-azaindoles with electron-donating substituents on the pyridine ring, but attempts to extend this approach to the synthesis of 7-azaindole moiety were ineffective under themal conditions or had little effect under microwave irradiation.[9]

The 5-bromo-7-azaindole framework is in demand as starting material for the synthesis of biologically active compounds and potential drugs, especially as substrate in palladium-catalyzed coupling processes, for example, for the preparation of different potent kinase inhibitors[10] or melatonin analogues.[11]

At present, there are few examples, presented mostly in patents,[12] for the preparation of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine moiety by the Fischer synthesis under thermal conditions or microwave irradiation in moderate yields. Our work is the first example of a successful application of the Fischer reaction to the synthesis of 2,3-disubstituted 5-bromo-7-azaindole moiety with alkyl and aryl substituents in acidic medium (polyphosphoric acid in our case). It should be noted the 5-bromo-7-azaindole framework may be synthesized via direct bromination of 7-azaindole derivatives[13] or by annulation of pyrrole ring to 5-bromo-2-aminopyridines by palladium-catalyzed processes.[14]

**Table 1** 5-Bromo-7-azaindoles Prepared from Appropriate Ketones

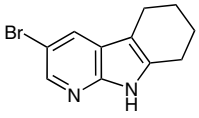
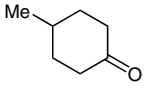
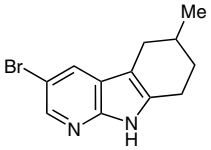
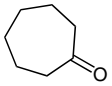
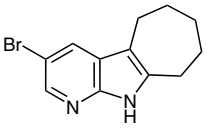
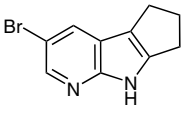
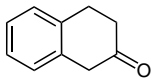
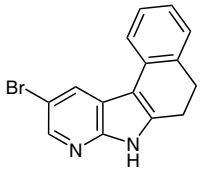
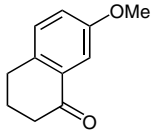
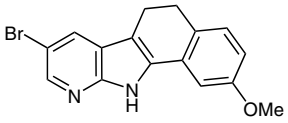
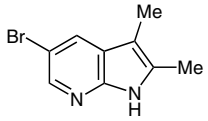
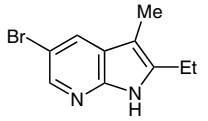
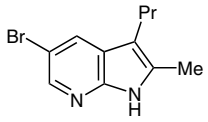
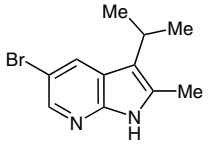
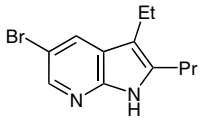
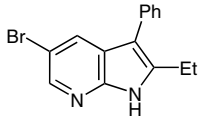
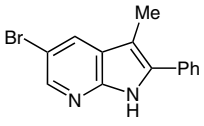
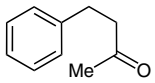
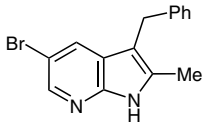
| Starting ketone | Product | Yield (%)[a] |
|---|---|---|
|  | **4a**  | 78 |
|  | **4b**  | 84 |
|  | **4c**  | 56 |
|  | **4d**  | 34 |

Table 1 (continued)

| Starting ketone | Product | Yield (%)[a] |
|---|---|---|
|  | **4e**  | 52 |
|  | **4f**  | 56 |
|  | **4g**  | 65 |
|  | **4h**  | 53 |
|  | **4i**  | 75 |
|  | **4j**  | 62 |
|  | **4k**  | 54 |
|  | **4l**  | 86 |
|  | **4m**  | 38 |
|  | **4n**  | 44 |

[a] All yields are based on the starting 5-bromo-2-hydrazinopyridine (**1**).

The starting 5-bromo-2-hydrazinopyridine (**1**) was prepared from commercially available and cheap 2-aminopyridine by a known synthetic route, used previously by us for unsubstituted 2-hydrazinopyridine synthesis.[8d] This route involves its bromination to 2-amino-5-bromopyridine (**2**), substitution of the amino group with bromine atom by diazotization, and further nucleophilic substitution of the bromine atom at position 2 of the formed 2,5-dibromopyridine (**3**) with hydrazine fragment (Scheme 1).

The 2,3-disubstituted 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridines **4a**–**n** were obtained from (5-bromopyridin-2-yl)hydrazones **5a**–**n**, which were initially prepared by refluxing the hydrazine **1** with one equivalent of the appropriate carbonyl compound (ketone). The cyclization of the hydrazones **5a**–**n** was achieved by heating in polyphosphoric acid (PPA) for five minutes at 160–180 °C, leading to the required 5-bromo-7-azaindole derivatives **4a**–**n** in moderate to good yields (Scheme 1, Table 1). All final 5-bromo-7-azaindole derivatives **4a**–**n** were characterized by appropriate spectroscopic ($^1$H and $^{13}$C NMR, IR, and MS) and physical data (melting point and elemental analysis).

In this procedure, most of the hydrazones **5** were obtained as a viscous liquid, and all of them were used without isolation (under reaction conditions they are of sufficient purity to be used for further transformations without additional purification), but their formation and purity was controlled by NMR spectra. The $^1$H and $^{13}$C NMR spectral data of viscous hydrazones are presented in Table 2. The solid hydrazones **5c**,**d**,**f**,**k**,**p**,**q**,**r**,**s** were isolated from the reaction mixture as individual compounds by recrystallization, and appropriate spectroscopic and physical data for them are presented in Table 3 and Table 4.

Fischer indolization via [3,3] sigmatropic rearrangement involves an enehydrazine form of the starting hydrazone as intermediate, and the cyclization should be facilitated by the ease of formation of this enehydrazine (Scheme 2). An earlier study[15] of 7-azaindole synthesis by Fischer reaction suggested that a higher degree of enolization of the starting ketone correlated with the rate of Fischer cyclization of the respective hydrazone, and this relationship is applied both to cyclic as well as aliphatic ketones.

**Table 2** $^1$H and $^{13}$C NMR Data for Viscous Hydrazones **5**

| Hydrazone | $^1$H NMR ($CDCl_3$): δ | $^{13}$C NMR ($CDCl_3$): δ |
|---|---|---|
| **5a** | 1.62–1.75 (m, 6 H, 3,4,5-$CH_2$), 2.30–2.38 (m, 4 H, 2,6-$CH_2$), 7.14 (d, $J$ = 8.9 Hz, 1 H, H-3 Py), 7.61 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 7.90 (br s, 1 H, NH), 8.10 (d, $J$ = 2.3 Hz, 1 H, H-6 Py) | 25.7, 25.9, 27.1, 35.5, 42.0, 108.9, 109.0, 140.6, 147.6, 153.2, 156.3 |
| **5b** | 0.97 (d, $J$ = 6.6 Hz, 3 H, $CH_3$), 1.10–1.28 (m, 2 H, 3,5-$CH_2$), 1.67–1.73 (m, 1 H, 4-CH), 1.87–1.93 (m, 3 H, 2,3,5,6-$CH_2$), 2.24 (dt, $J_1$ = 13.7 Hz, $J_2$ = 4.8 Hz, 1 H, 2,6-$CH_2$), 2.50 (d, $J$ = 14.6 Hz, 1 H, 2,6-$CH_2$), 2.69–2.75 (m, 1 H, 2,6-$CH_2$), 7.13 (d, $J$ = 8.9 Hz, H-3 Py), 7.61 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 7.82 (br s, 1 H, NH), 8.12 (d, $J$ = 2.3 Hz, 1 H, H-6 Py) | 21.6, 25.0, 31.9, 33.7, 34.7, 35.1, 108.9, 109.0, 140.5, 147.8, 152.8, 156.3 |
| **5e** | 2.53 (t, $J$ = 6.6 Hz, 2 H, 4-$CH_2$), 2.97 (t, $J$ = 6.6 Hz, 2 H, 3-$CH_2$), 3.65 (s, 2 H, 1-$CH_2$), 7.18 (d, $J$ = 8.9 Hz, 1 H, H-3 Py), 7.19–7.22 (m, 4 H, $C_6H_4$), 7.65 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 7.66 (br s, 1 H, NH), 8.14 (d, $J$ = 2.3 Hz, 1 H, H-6 Py) | 25.2, 27.7, 38.3, 108.8, 109.7, 126.7, 126.9, 127.1, 127.4, 135.6, 137.7, 140.4, 148.2, 150.0, 156.0 |
| **5g** | 1.14 (t, $J$ = 7.3 Hz, 3 H, $CH_3CH_2$), 1.86 (s, 3 H, $CH_3C$=N), 2.32 (q, $J$ = 7.3 Hz, 2 H, Me$CH_2$), 7.15 (d, $J$ = 8.8 Hz, 1 H, H-3 Py), 7.62 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.2 Hz, 1 H, H-4 Py), 7.76 (br s, 1 H, NH), 8.12 (d, $J$ = 2.2 Hz, 1 H, H-6 Py) | 10.9, 14.7, 32.1, 109.0, 109.2, 140.4, 148.0, 1503, 156.3 |
| **5h** | 1.12 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 1.14 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 2.26 (q, $J$ = 7.3 Hz, 2 H, $CH_2$), 2.32 (q, $J$ = 7.3 Hz, 2 H, $CH_2$), 7.16 (d, $J$ = 8.9 Hz, 1 H, H-3 Py), 7.61 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.4 Hz, 1 H, H-4 Py), 7.87 (br s, 1 H, NH), 8.11 (d, $J$ = 2.4 Hz, 1 H, H-6 Py) | 9.7, 10.8, 21.9, 29.7, 108.9, 109.1, 140.4, 148.1, 154.6, 156.4 |
| **5i** | 0.92 (t, $J$ = 7.3 Hz, 3 H, $CH_3CH_2$), 1.35 (sext, $J$ = 7.3 Hz, 2 H, 5-$CH_2$), 1.50–1.58 (m, 2 H, 4-$CH_2$), 1.85 (s, 3 H, $CH_3C$=O), 2.29 (t, $J$ = 7.5 Hz, 2 H, 3-$CH_2$), 7.14 (d, $J$ = 9.0 Hz, 1 H, H-3 Py), 7.61 (dd, $J_1$ = 9.0 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 7.93 (br s, 1 H, NH), 8.09 (d, $J$ = 2.3 Hz, 1 H, H-6 Py) | 14.0, 14.8, 22.4, 28.6, 38.6, 108.8, 109.0, 140.5, 147.7, 149.8, 156.2 |
| **5j** | 0.94 [d, $J$ = 6.6 Hz, 6 H, $(CH_3)_2CH$], 1.85 (s, 3 H, $CH_3C$=N), 1.97–2.03 (m, 1 H, CH), 2.18 (d, $J$ = 7.2 Hz, 2 H, $CH_2$), 7.15 (d, $J$ = 8.9 Hz, 1 H, H-3 Py), 7.62 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.4 Hz, 1 H, H-4 Py), 7.72 (br s, 1 H, NH), 8.12 (d, $J$ = 2.4 Hz, 1 H, H-6 Py) | 15.0, 22.5, 26.1, 48.0, 108.8, 109.0, 140.5, 147.9, 149.0, 156.2 |
| **5l**[a] | 1.02 (t, $J$ = 7.7 Hz, 1.5 H) and 1.18 (t, $J$ = 7.4 Hz, 1.5 H, $CH_3$), 2.22 (q, $J$ = 7.7 Hz, 1 H) and 2.38 (q, $J$ = 7.4 Hz, 1 H, $CH_2$Me), 3.63 (s, 1 H) and 3.66 (s, 1 H, $CH_2$Ph), 7.17–7.34 (m, 6 H, H-3 Py, $C_6H_5$), 7.62–7.66 (m, 1 H, H-4 Py), 7.93 (br s, 0.5 H) and 7.96 (s, 0.5 H, NH), 8.10 (d, $J$ = 2.4 Hz, 0.5 H) and 8.14 (d, $J$ = 2.4 Hz, 0.5 H, H-6 Py) | 9.6, 10.8, 21.3, 31.0, 35.3, 43.4, 109.0, 109.5, 126.7, 127.0, 128.3, 128.6, 129.1, 134.9, 137.6, 140.3, 140.4, 148.2, 151.0, 152.3, 156.2, 156.3 |
| **5m**[b] | 1.23 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 2.74 (q, $J$ = 7.3 Hz, 1.2 H) and 3.01 (q, $J$ = 7.3 Hz, 0.8 H, $CH_2$), 7.33–7.48 (m, 4 H, H-3 Py, H-3,4,5 $C_6H_5$), 7.54 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz, 1 H, H-4 Py), 7.79 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.5 Hz, 1.2 H) and 7.97 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.5 Hz, 0.8 H, H-2,6 $C_6H_5$), 8.15 (d, $J$ = 2.4 Hz, 1 H, H-6 Py), 8.33 (s, 0.5 H, NH) | 10.3, 11.1, 19.2, 31.5, 108.8, 109.3, 110.0, 125.8, 127.3, 128.5, 128.6, 129.2, 129.6, 137.5, 140.4, 140.6, 148.1, 148.2, 148.6, 155.8, 155.9 |
| **5n** | 1.91 (s, 3 H, $CH_3$), 2.66 (t, $J$ = 7.9 Hz, 2 H, $CH_2C$=N), 2.96 (t, $J$ = 7.9 Hz, 2 H, $CH_2$Ph), 7.17 (d, $J$ = 8.8 Hz, 1 H, H-3 Py), 7.23–7.27 (m, 3 H, H-3,4,5 $C_6H_5$), 7.33 (t, $J$ = 7.3 Hz, 2 H, H-2,6 $C_6H_5$), 7.66 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 7.82 (br s, 1 H, NH), 8.16 (d, $J$ = 2.3 Hz, 1 H, H-6 Py). | 15.3, 32.7, 40.6, 109.0, 109.4, 126.0, 128.4, 128.5, 140.5, 141.6, 148.0, 148.3, 156.2 |

[a] A 1:1 mixture of two diastereomers (by $^1$H NMR analysis).
[b] A 3:2 mixture of two diastereomers (by $^1$H NMR analysis).

**Table 3** Physical Data for Solid Hydrazones **5c**,**d**,**f**,**k**,**o**–**s** Prepared

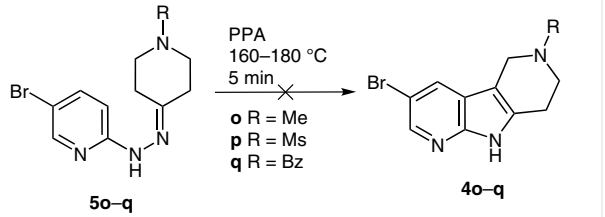
| Hydra zone | Yield (%) | Mp (°C) (solvent) | Elemental analysis | MS (EI, 70 eV), *m*/*z* (%) | IR (KBr), $cm^{-1}$ |
|---|---|---|---|---|---|
| **5c** | 95 | 75–76 (hexane)<br>$R_f$ = 0.7[a] | Anal. Calcd for $C_{12}H_{16}BrN_3$: C, 51.08; H, 5.72; N, 14.89. Found: C, 50.97; H, 5.80; N, 14.81 | 283 (49, [M ($^{81}$Br)]$^+$), 281 (47, [M ($^{79}$Br)]$^+$), 240 (60), 238 (62), 226 (100), 224 (100), 213 (38), 211 (38), 174 (29), 172 (28), 92 (53) | 3257, 2925, 2910, 2848, 1585, 1495, 1441, 1082, 1053 |
| **5d**[a] | 96 | 121–122 (hexane)<br>$R_f$ = 0.65[a] | Anal. Calcd for $C_{10}H_{12}BrN_3$: C, 47.26; H, 4.76; N, 16.54. Found: C, 47.35; H, 4.64; N, 16.62 | 255 (23, [M ($^{81}$Br)]$^+$), 253 (24, [M ($^{79}$Br)]$^+$), 226 (94), 224 (100), 214 (48), 212 (49), 173 (21), 171 (20), 92 (21) | 3199, 2966, 2943, 2870, 1585, 1508, 1442, 1080 |
| **5f** | 83 | 115–116 (MeOH)<br>$R_f$ = 0.5[b] | Anal. Calcd for $C_{16}H_{16}BrN_3O$: C, 55.51; H, 4.66; N, 12.14. Found: C, 55.55; H, 4.54; N, 12.12 | 347 (55, [M ($^{81}$Br)]$^+$), 345 (61, [M ($^{79}$Br)]$^+$), 318 (86), 316 (100), 266 (11), 226 (16), 224 (18), 201 (17), 199 (19), 173 (94), 158 (34), 146 (66), 115 (35), 103 (20) | 3350, 2949, 2916, 2858, 1579, 1502, 1086, 1027 |
| **5k** | 93 | 44–45 (hexane)<br>$R_f$ = 0.7[b] | Anal. Calcd for $C_{12}H_{18}BrN_3$: C, 50.71; H, 6.38; N, 14.79. Found: C, 50.76; H, 6.24; N, 14.83 | 285 (7, [M ($^{81}$Br)]$^+$), 283 (24, [M ($^{79}$Br)]$^+$), 242 (98), 240 (100), 173 (13), 92 (11) | 3194, 2960, 2931, 2871, 1589, 1504, 1076 |
| **5o** | 93 | 67–68 (hexane)<br>$R_f$ = 0.2[c] | Anal. Calcd for $C_{11}H_{15}BrN_4$: C, 46.66; H, 5.34; N, 19.79. Found: C, 46.79; H, 5.20; N, 19.82. | 284 (19, [M ($^{81}$Br)]$^+$), 282 (19, [M ($^{79}$Br)]$^+$), 213 (14), 211 (14), 172 (9), 111 (100), 70 (15) | 3228, 2939, 2792, 1589, 1506, 1448, 1128, 1082, 1063 |
| **5p** | 57 | 154–155 (MeOH)<br>$R_f$ = 0.55[b] | Anal. Calcd for $C_{11}H_{15}BrN_4O_2S$: C, 38.05; H, 4.35; N, 16.14; S, 9.23. Found: C, 37.97; H, 4.26; N, 16.18; S, 9.26 | 348 (22, [M ($^{81}$Br)]$^+$), 346 (22, [M ($^{79}$Br)]$^+$), 269 (39), 267 (43), 226 (52), 224 (55), 213 (96), 211 (100), 172 (14), 79 (25) | 3294, 2924, 2866, 1585, 1315, 1149, 1035 |
| **5q**[b] | 82 | 169–170 (EtOH)<br>$R_f$ = 0.5[b] | Anal. Calcd for $C_{17}H_{17}BrN_4O$: C, 54.70; H, 4.59; N, 15.01. Found: C, 54.82; H, 4.46; N, 15.05 | 374 (15, [M($^{81}$Br)]$^+$), 372 (16, [M ($^{79}$Br)]$^+$), 253 (51), 226 (19), 224 (18), 201 (23), 172 (11), 105 (100), 77 (58) | 3236, 3045, 2956, 2894, 1614, 1579, 1504, 1442, 1064 |
| **5r** | 67 | 77–78 (acetone)<br>$R_f$ = 0.65[a] | Anal. Calcd for $C_8H_{10}BrN_3$: C, 42.13; H, 4.42; N, 18.42. Found: C, 42.20; H, 4.29; N, 18.43 | 229 (17, [M ($^{81}$Br)]$^+$), 227 (17, [M ($^{79}$Br)]$^+$), 214 (100), 212 (99), 171 (24), 144 (8), 92 (18), 28 (66) | 3226, 2935, 2908, 1587, 1502, 1444, 1086, 1034 |
| **5s** | 89 | 124–125 (acetone)<br>$R_f$ = 0.5[a] | Anal. Calcd for $C_{13}H_{12}BrN_3$: C, 53.81; H, 4.17; N, 14.48. Found: C, 53.72; H, 4.29; N, 14.42 | 291 (25, [M ($^{81}$Br)]$^+$), 289 (26, [M ($^{79}$Br)]$^+$), 276 (99), 274 (100), 214 (45), 212 (46), 173 (18), 171 (16), 103 (15), 77 (48) | 3330, 2922, 1583, 1506, 1387, 1138, 1070 |

[a] Eluent: EtOAc–$CHCl_3$ (1:1).
[b] Eluent: EtOAc.
[c] Eluent: EtOAc–MeOH (2:1).

We established that Fischer cyclization of cyclic ketone hydrazones **5a**–**d** led to the corresponding tricyclic 5-bromo-7-azaindole derivatives **4a**–**d**, while the cyclization product yields depended mainly on the aliphatic ring size in the starting hydrazone and the degree of enolization of the starting ketone. The best results were observed for six-membered ketones (1.18% of enol form for cyclohexanone) and the worst for five-membered cyclopentanone (0.09% of enol form). Cycloheptanone has an intermediate level of enolization (0.56%).[15] The yields of azaindoles **4a**–**d** are in full agreement with this hypothesis.

Use of β-tetralone and 7-methoxy-α-tetralone as carbonyl compounds gave tetracyclic 7-azaindole derivatives **4e**,**f** in 52 and 56% yield, respectively; however, the hydrazones **5e**,**f** should have produced **4e**,**f** in higher yields compared to the cyclohexanone hydrazone **5a** due to their increased tendency to form the enehydrazine tautomeric form owing to the conjugation with benzene ring.

Surprisingly, the Fischer cyclization of hydrazones of *N*-substituted piperidin-4-ones **5o**–**q** under the general reaction conditions (PPA, 160–180 °C, 5 min) could not be achieved (Scheme 2). The cyclization of *N*-methyl-substituted hydrazone **5o** gave back the starting material in 96% yield instead of the expected tricyclic 7-azaindole derivative **4o**. Cyclization of *N*-mesyl- and *N*-benzoyl-substituted hydrazones **5p**,**q** led to tarring of the reaction mixtures. In the case of hydrazone **5q**, benzoic acid sublimed out of the reaction mixture as white crystals under heating.




**5o–q** **4o–q**

**Scheme 2**

**Table 4** $^{1}H$ and $^{13}C$ NMR Data for Solid Hydrazones **5c**,**d**,**f**,**k**,**o**–**s** Prepared

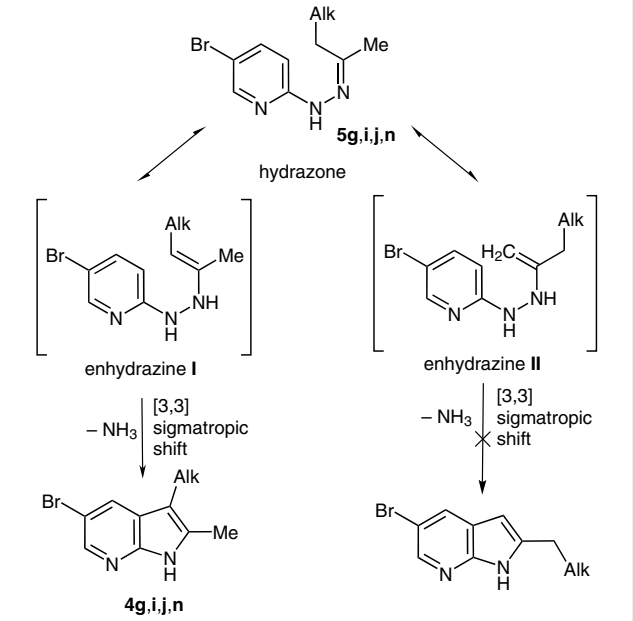
| Hydrazone | $^{1}H$ NMR ($CDCl_3$): δ | $^{13}C$ NMR ($CDCl_3$): δ |
|---|---|---|
| **5c** | 1.61–1.66 (m, 6 H, 3 × $CH_2$), 1.76–1.79 (m, 2 H, $CH_2$), 2.38 (t, *J* = 5.8 Hz, 2 H, $CH_2$), 2.52 (t, *J* = 5.8 Hz, 2 H, $CH_2$), 7.15 (d, *J* = 8.8 Hz, 1 H, H-3 Py), 7.62 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.2 Hz, 1 H, H-4 Py), 7.71 (br s, 1 H, NH), 8.12 (d, *J* = 2.2 Hz, 1 H, H-6 Py) | 24.6, 28.1, 30.0, 30.5, 30.6, 37.2, 108.9, 109.3, 140.4, 148.1, 155.4, 156.2 |
| **5d**[a] | 1.69 (quint, *J* = 7.0 Hz, 2 H, $CH_2$), 1.79 (quint, *J* = 7.0 Hz, 2 H, $CH_2$), 2.30 (quint, *J* = 7.0 Hz, 2 H, $CH_2$), 2.35 (quint, *J* = 7.0 Hz, 2 H, $CH_2$), 6.98 (d, *J* = 8.9 Hz, 1 H, H-3 Py), 7.53 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 8.03 (d, *J* = 2.3 Hz, 1 H, H-6 Py), 8.76 (br s, 1 H, NH) | 24.3, 24.4, 27.2, 32.7, 107.5, 108.1, 139.3, 147.3, 156.1, 159.1 |
| **5f** | 1.97 (quint, *J* = 6.6 Hz, 2 H, 3-$CH_2$), 2.57 (t, *J* = 6.6 Hz, 2 H, 4-$CH_2$), 2.72 (t, *J* = 6.6 Hz, 2 H, 2-$CH_2$), 3.87 (s, 3 H, $CH_3O$), 6.83 (dd, $J_1$ = 8.3 Hz, $J_2$ = 2.8 Hz, 1 H, H-6 Ar), 7.06 (d, *J* = 8.3 Hz, 1 H, H-5 Ar), 7.34 (d, *J* = 8.9 Hz, 1 H, H-3 Py), 7.66 (d, *J* = 2.8 Hz, 1 H, H-8 Ar), 7.69 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 8.13 (br s, 1 H, NH), 8.18 (d, *J* = 2.3 Hz, 1 H, H-6 Py) | 21.9, 24.6, 28.7, 55.5, 108.3, 109.1, 110.0, 115.3, 129.5, 131.7, 133.8, 140.6, 144.1, 148.3, 155.8, 158.3 |
| **5k** | 0.97 (t, *J* = 7.4 Hz, 3 H, $CH_3$), 1.00 (t, *J* = 7.4 Hz, 3 H, $CH_3$), 1.53–1.67 (m, 4 H, $CH_2$), 2.21 (t, *J* = 7.4 Hz, 2 H, $CH_2$), 2.26 (t, *J* = 7.4 Hz, 2 H, $CH_2$), 7.15 (d, *J* = 8.8 Hz, 1 H, H-3 Py), 7.62 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz, 1 H, H-4 Py), 7.86 (br s, 1 H, NH), 8.11 (d, *J* = 2.4 Hz, 1 H, H-6 Py) | 14.0, 14.5, 18.8, 19.8, 31.0, 39.2, 108.9, 109.1, 140.5, 147.9, 153.0, 156.3 |
| **5o** | 2.33 (s, 3 H, $CH_3$), 2.43–2.57 (m, 8 H, 2 × $CH_2CH_2$), 7.12 (d, *J* = 8.9 Hz, 1 H, H-3 Py), 7.61 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.3 Hz, H-4 Py), 7.91 (br s, 1 H, NH), 8.10 (d, *J* = 2.3 Hz, 1 H, H-6 Py) | 25.6, 34.5, 45.9, 54.3, 56.0, 108.7, 109.4, 140.4, 148.1, 148.5, 156.2 |
| **5p** | 2.67 (t, *J* = 6.0 Hz, 2 H, $CH_2$), 2.64 (t, *J* = 6.0 Hz, 2 H, $CH_2$), 2.85 (s, 3 H, $CH_3$), 3.41–3.48 (m, 4 H, 2 × $CH_2$), 7.14 (d, *J* = 8.9 Hz, 1 H, H-3 Py), 7.66 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.2 Hz, 1 H, H-4 Py), 7.85 (br s, 1 H, NH), 8.15 (d, *J* = 2.2 Hz, 1 H, H-6 Py) | 26.1, 34.3, 36.0, 44.6, 46.4, 109.4, 141.3, 146.6, 146.7, 155.5 |
| **5q**[b] | 2.40–2.66 (m, 4 H, 2 × $CH_2$), 3.59 (br s, 2 H, $CH_2$), 3.89 (br s, 2 H, $CH_2$), 7.12–7.16 (m, 1 H, H-3 Py), 7.43 (br s, 5 H, $C_6H_5$), 7.64 (d, *J* = 7.6 Hz, 1 H, H-4 Py), 7.94 (br s, 0.5 H) and 8.06 (br s, 0.5 H, NH), 8.13 (s, 1 H, H-6 Py) | 25.7, 26.7, 33.0, 34.6, 40.4, 43.7, 44.9, 47.7, 108.8, 109.7, 126.9, 128.6, 130.0, 135.6, 140.5, 146.6, 148.0, 155.9, 170.8 |
| **5r** | 1.90 (s, 3 H, $CH_3$), 2.05 (s, 3 H, $CH_3$), 7.14 (d, *J* = 8.8 Hz, 1 H, H-3 Py), 7.62–7.64 (m, 2 H, NH, H-4 Py), 8.13 (d, *J* = 2.2 Hz, 1 H, H-6 Py). | 16.1, 25.4, 109.0, 109.2, 140.7, 147.4, 147.7, 156.7 |
| **5s** | 2.28 (s, 3 H, $CH_3$), 7.33–7.42 (m, 4 H, H-3 Py, H-3,4,5 $C_6H_5$), 7.69 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.3 Hz, 1 H, H-4 Py), 7.79 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.2 Hz, 2 H, H-2,6 $C_6H_5$), 8.09 (br s, 1 H, NH), 8.19 (d, *J* = 2.3 Hz, 1 H, H-6 Py). | 12.4, 109.3, 110.1, 125.8, 128.5, 128.6, 138.5, 140.6, 143.9, 148.2, 155.8 |

[a] $^{1}H$ and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$.
[b] A 1:1 mixture of two rotamers (by $^{1}H$ NMR analysis).

In contrast to cycloalkanones, acyclic ketones are usually characterized by lower degree of enolization.[12] Fischer cyclization of hydrazones of **5g**–**n** resulted in the formation of 2,3-disubstituted 1*H*-pyrrolo[2,3-*b*]pyridines **4g**–**n** in moderate to good yields (Table 1). Indolization of methyl alkyl ketone hydrazones **5g**,**i**,**j** led to only one of the two possible regioisomers, that is, to the corresponding 2,3-disubstituted azaindoles **4g**,**i**,**j**, thus the reaction proceeded exclusively through the formation of thermodynamically stable enehydrazine form **I** with the disubstituted double bond (Scheme 3).

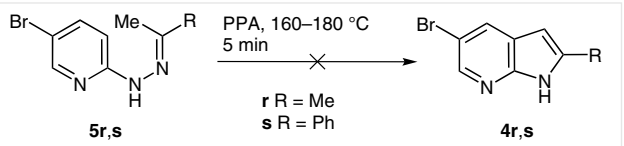
A similar pattern was observed for the cyclization of benzyl ethyl ketone hydrazone **5l**, which occurred in a high yield (86%), leading to only 5-bromo-2-ethyl-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**4l**). This reaction proceeded solely through the formation of enehydrazine at the benzyl group due to its stabilization by conjugation of the double bond with benzene ring. A lower content of enehydrazine form for hydrazones **5m** and **5n** should be expected and lower yields of azaindoles **4m**,**n** were the result (38 and 44%, respectively).

It should be noted that in the case of hydrazones obtained from methyl ketones (acetone **5r** or acetophenone **5s**) only 2-substituted 7-azaindoles **4r**,**s** would be formed; however, the respective 5-bromo-7-azaindoles **4r**,**s** were not formed under the reaction conditions: the acetone and acetophenone hydrazones **5r**,**s** were isolated unchanged (Scheme 4). This acetophenone inertness is in agreement




**Scheme 3**

with the attempt to synthesize the corresponding 4-azaindole in aqueous $H_2SO_4$ by Suzenet et al.[9]




**Scheme 4**

The lack of cyclization in the case of methyl ketone hydrazones **5r**,**s** can be explained by the very low ability of these substrates to proceed into the enehydrazine form involving the methyl group, necessary for [3,3] sigmatropic rearrangement under used conditions, while the content of enehydrazine form is higher for different alkyl ketone hydrazones **5g**–**n**, leading to the formation of the corresponding 5-bromo-7-azaindole derivatives.

Previously, we have reported on the synthesis of 2,3-disubstituted 7-azaindole derivatives from unsubstituted 2-hydrazinopyridine via aza-Fischer reaction in PPA under the same conditions (10 examples).[8d] If we compare the yields of final cyclization products, the azaindole yields are slightly higher for 5-bromo-substituted hydrazones of cyclic ketones whereas significantly higher yields of the 7-azaindole derivatives are observed for unsubstituted hydrazones of alkyl ketones. Thus, it is not possible to make an unambiguous conclusion about the impact of a weak π-donating bromine group on the formation of azaindole derivatives under the reaction conditions. However, the presence of the bromine atom on the pyridine ring facilitates the resinification with increasing reaction time or temperature.

In conclusion, we have developed a simple and cheap synthesis of some heterocycles containing 2,3-disubstituted 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine moiety by Fischer indole cyclization in polyphosphoric acid. This procedure is quite general for different alkyl or aryl ketones and the observed yields are generally high, but it has some exception: these conditions are not suitable for methyl ketones and N-substituted piperidin-4-ones.

$^1$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 ppm and 2.51 ppm for $^1$H, 77.1 ppm and 39.5 ppm for $^{13}$C). 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 are not corrected. TLC were run on precoated silica gel plates (Merck 60 $F_{254}$) and the spots were visualized using a UV lamp. Commercially available reagents from Acros, Sigma-Aldrich, Fluka, Merck, Alfa Aesar, and Fischer Scientific were used. *N*-Mesyl- and *N*-benzoylpiperidin-4-ones were prepared according to reported procedure.[16]

**2-Amino-5-bromopyridine (2)**

To a solution of 2-aminopyridine (9.40 g, 0.1 mol) in EtOH (100 mL) was added dropwise $Br_2$ (5.8 mL, 0.11 mol) maintaining the temperature below 20 °C. When the addition of bromine was completed, the mixture was stirred for 1 h. After removal of EtOH, the residue was made alkaline with a solution of NaOH (5.0 g, 0.13 mol) in $H_2O$ (50 mL) and cooled (10 °C). The solid was collected by filtration, slurry-washed with cold $H_2O$ (10 mL), and then washed with boiling heptane (3 × 20 mL) to remove the 2-amino-3,5-dibromoaminopyridine, followed by air-drying to constant weight; yield: 13.15 g (76%); off-white fine crystals; mp 135–136 °C (Lit.[17] mp 132–135 °C); $R_f$ = 0.4 ($CHCl_3$–EtOAc).

IR (KBr): 3452, 3292, 3153, 2924, 2852, 1628, 1587, 1550, 1481, 1387, 1088, 999 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 4.57 (br s, 2 H, $NH_2$), 6.41 (d, *J* = 8.8 Hz, 1 H, H-3), 7.48 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz, 1 H, H-4), 8.09 (d, *J* = 2.4 Hz, 1 H, H-6).

$^{13}$C NMR ($CDCl_3$): δ = 108.3, 110.1, 140.2, 148.7, 157.1.

MS (EI, 70 eV): *m*/*z* (%) = 174 (88, [M ($^{81}$Br)]$^+$), 172 (100, [M ($^{79}$Br)]$^+$), 147 (46), 145 (49), 92 (97), 65 (67), 64 (60), 50 (49).

Anal. Calcd for $C_5H_5BrN_2$: C, 34.71; H, 2.91; N, 16.19. Found: C, 34.59; H, 3.01; N, 16.10.

**2-Amino-3,5-dibromoaminopyridine**

Evaporation of the heptane filtrate from the above workup and further recrystallization of the residue from hexane gave 2-amino-3,5-dibromoaminopyridine as yellow needles; yield 3.10 g (12%); mp 105–106 °C (EtOH–$H_2O$, 3:1) (Lit.[18] mp 104–105 °C); $R_f$ = 0.65 ($CHCl_3$–EtOAc).

IR (KBr): 3462, 3280, 3147, 2922, 2852, 1626, 1568, 1466, 1387, 1024 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 5.14 (br s, 2 H, $NH_2$), 7.75 (d, *J* = 2.0 Hz, 1 H, H-4), 8.03 (d, *J* = 2.0 Hz, 1 H, H-6).

$^{13}$C NMR ($CDCl_3$): δ = 104.6, 107.1, 141.9, 147.6, 154.5.

MS (EI, 70 eV): *m*/*z* (%) = 254 (51, [M ($^{81}$Br, $^{81}$Br)]$^+$), 252 (100, [M ($^{79}$Br, $^{81}$Br)]$^+$), 250 (59, [M ($^{79}$Br, $^{79}$Br)]$^+$), 173 (22), 171 (22), 144 (15), 92 (65), 65 (32), 64 (31).

Anal. Calcd for $C_5H_4Br_2N_2$: C, 23.84; H, 1.60; N, 11.12. Found: C, 23.91; H, 1.43; N, 11.15.

**2,5-Dibromopyridine (3)**

2-Amino-5-bromopyridine (**2**; 13.0 g, 75.1 mmol) was added over 10 min to a cold (10 °C) aq 47% HBr (37 mL, 0.33 mol). $Br_2$ (11 mL, 0.21 mol) was added, keeping the temperature below 10 °C. Then, a solution of $NaNO_2$ (16.1 g, 0.19 mol) in $H_2O$ (19 mL) was added dropwise, maintaining the temperature at 0–5 °C. The reaction mixture was stirred for an additional 30 min, then treated with a solution of NaOH (28.0 g, 0.70 mol) in $H_2O$ (30 mL) at such a rate that the temperature did not exceed 20–25 °C. The mixture was extracted with $Et_2O$ (3 × 40 mL) and the combined organic layers were dried ($Na_2SO_4$). The solvent was evaporated under vacuum, the residue was suspended in hexane (10 mL), and the solid formed was collected by filtration to afford a pale brown powder; yield: 15.49 g (87%); mp 94–95 °C (Lit.[19] mp 96–97 °C); $R_f$ = 0.55 ($CHCl_3$).

IR (KBr): 3411, 3022, 2924, 2852, 1549, 1437, 1356, 1090, 997 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 1 H, H-3), 7.67 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.5 Hz, 1 H, H-4), 8.45 (d, *J* = 2.4 Hz, 1 H, H-6).

$^{13}$C NMR ($CDCl_3$): δ = 120.1, 129.5, 140.4, 141.2, 151.3.

MS (EI, 70 eV): *m*/*z* (%) = 239 (36, [M ($^{81}$Br, $^{81}$Br)]$^+$), 237 (71, [M ($^{79}$Br, $^{81}$Br)]$^+$), 235 (35, [M ($^{79}$Br, $^{79}$Br)]$^+$), 158 (85), 156 (85), 81 (57), 76 (78), 50 (100).

Anal. Calcd for $C_5H_3Br_2N$: C, 25.35; H, 1.28; N, 5.91. Found: C, 25.46; H, 1.13; N, 5.95.

### 5-Bromo-2-hydrazinopyridine (1)

A mixture of 2,5-dibromopyridine (**3**; 15.4 g, 65.0 mmol), hydrazine hydrate (30 mL), and propan-2-ol (30 mL) was refluxed for 12 h, and the excess hydrazine hydrate was removed under vacuum. The residue was suspended in cold $H_2O$ (50 mL), and the precipitate formed was collected by filtration and washed with ice cold $H_2O$ (2 × 15 mL). The obtained precipitate was recrystallized from EtOH to give off-white or pale beige crystals; yield: 10.89 g (89%); mp 134–135 °C (EtOH) (Lit.[20] mp 134–136 °C); $R_f$ = 0.6 ($CHCl_3$–EtOAc).

IR (KBr): 3294, 3248, 3172, 2925, 2854, 1595, 1504, 1477, 989, 808 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 3.80 (br s, 2 H, $NH_2$), 5.95 (br s, 1 H, NH), 6.67 (d, *J* = 8.8 Hz, 1 H, H-3), 7.55 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.2 Hz, 1 H, H-4), 8.15 (d, *J* = 2.2 Hz, 1 H, H-6).

$^{13}$C NMR ($CDCl_3$): δ = 107.8, 108.6, 139.5, 147.5, 159.6.

MS (EI, 70 eV): *m*/*z* (%) = 189 (96, [M ($^{81}$Br)]$^+$), 187 (100, [M ($^{79}$Br)]$^+$), 159 (35), 157 (35), 117 (11), 92 (16), 78 (71), 64 (55), 51 (65), 50 (57).

Anal. Calcd for $C_5H_6BrN_3$: C, 31.94; H, 3.22; N, 22.35. Found: C, 32.06; H, 3.13; N, 22.46.

### 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridines 4a–n; General Procedure

To a solution of 5-bromo-2-hydrazinopyridine (**1**; 0.56 g, 3.0 mmol) in EtOH (5 mL) was added a solution of the corresponding carbonyl compound (3.0 mmol) in EtOH (5 mL) in one portion. The reaction mixture was refluxed for 30 min, evaporated under vacuum to a constant mass to give the corresponding hydrazone **5** (solid hydrazones **5c**,**d**,**f**,**k**,**o**–**r** were recrystallized from appropriate solvent, isolated, and characterized by spectroscopical and physical data). Freshly prepared[21] polyphosphoric acid (5.0 g) was added to the residue, the mixture was heated with stirring to 160 °C and maintained for 5 min at 160–180 °C. After cooling to 20–30 °C, the reaction mixture was treated with $H_2O$ (25–30 mL). The obtained solution (or suspension) was cooled to 0 °C and adjusted to basic pH with 25% aq ammonia. The precipitate that formed was collected by filtration, washed with ice water (10 mL), $H_2O$–MeOH mixture (1:5, 1 mL), and air-dried. In case, if the product separated as an oil, the reaction mixture was extracted with $CH_2Cl_2$ (3 × 20 mL), the combined extracts were dried ($Na_2SO_4$), and evaporated to dryness. The obtained precipitate was recrystallized from appropriate solvent or washed with $H_2O$–MeOH mixture (1:5, 1 mL) (Table 1).

### 3-Bromo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (4a)

After washing the precipitate with ice cold $H_2O$ (10 mL), **4a** was obtained as an off-white powder; yield: 0.59 g (78%); mp 209–210 °C ($H_2O$); $R_f$ = 0.3 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3427, 3143, 3047, 2931, 2837, 1572, 1485, 1404, 1282, 1070, 997 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.77–1.89 (m, 4 H, 6,7-$CH_2$), 2.57 (t, *J* = 5.6 Hz, 2 H, 5-$CH_2$), 2.73 (t, *J* = 5.7 Hz, 2 H, 8-$CH_2$), 7.76 (d, *J* = 1.7 Hz, 1 H, H-4), 8.11 (d, *J* = 1.7 Hz, 1 H, H-2), 10.10 (br s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 20.1, 22.4, 22.5, 22.6, 106.9, 110.0, 121.4, 126.8, 137.6, 140.7, 146.8.

MS (EI, 70 eV): *m*/*z* (%) = 252 (53, [M ($^{81}$Br)]$^+$), 250 (57, [M ($^{79}$Br)]$^+$), 224 (96), 222 (100), 183 (10), 181 (11), 169 (16), 143 (15), 116 (13), 102 (11).

Anal. Calcd for $C_{11}H_{11}BrN_2$: C, 52.61; H, 4.42; N, 11.16. Found: C, 52.72; H, 4.30; N, 11.11.

### 3-Bromo-6-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (4b)

After washing the precipitate with ice cold $H_2O$–MeOH mixture (1:5, 1 mL), **4b** was obtained as a pale beige powder; yield: 0.67 g (84%); mp 200–201 °C (MeOH–$H_2O$); $R_f$ = 0.3 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3427, 3141, 3051, 2920, 1573, 1488, 1406, 1284, 1076, 978 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 1.08 (d, *J* = 6.5 Hz, 3 H, $CH_3$), 1.43–1.53 (m, 1 H, 7-$CH_B$), 1.85–1.93 (m, 2 H, 6-CH, 7-$CH_A$), 2.13–2.19 (m, 1 H, 5-$CH_B$), 2.73–2.75 (m, 3 H, 5-$CH_A$, 8-$CH_2$), 7.93 (d, *J* = 2.2 Hz, 1 H, H-4), 8.10 (d, *J* = 2.2 Hz, 1 H, H-2), 11.43 (br s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 21.5, 22.3, 28.5, 28.8, 30.5, 106.7, 110.0, 121.4, 126.8, 137.4, 140.7, 147.0.

MS (EI, 70 eV): *m*/*z* (%) = 266 (56, [M ($^{81}$Br)]$^+$), 264 (57, [M ($^{79}$Br)]$^+$), 224 (100), 222 (98), 183 (16), 181 (12), 143 (12).

Anal. Calcd for $C_{12}H_{13}BrN_2$: C, 54.36; H, 4.94; N, 10.57. Found: C, 54.47; H, 2.79; N, 10.60.

### 3-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[4,5]pyrrolo[2,3-*b*]pyridine (4c)

After washing the precipitate with ice cold $H_2O$–MeOH mixture (1:5, 1 mL), **4c** was obtained as a pale grey powder; yield: 0.45 g (56%); mp 197–198 °C (MeOH–$H_2O$); $R_f$ = 0.35 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3433, 3141, 3045, 2921, 2844, 1570, 1489, 1402, 1273, 1070, 937 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 1.62–1.72 (m, 4 H, 7-$CH_2$, 8-$CH_2$), 1.81–1.85 (m, 2 H, 6-$CH_2$), 2.71 (t, *J* = 5.6 Hz, 2 H, 5-$CH_2$), 2.84 (t, *J* = 5.6 Hz, 2 H, 9-$CH_2$), 8.00 (d, *J* = 1.8 Hz, 1 H, H-4), 8.10 (d, *J* = 1.8 Hz, 1 H, H-2), 11.48 (br s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 23.9, 26.8, 28.3, 28.4, 31.3, 110.1, 110.7, 122.8, 126.9, 140.5, 141.2, 145.3.

MS (EI, 70 eV): *m*/*z* (%) = 266 (96, [M ($^{81}$Br)]$^+$), 264 (100, [M ($^{79}$Br)]$^+$), 235 (76), 224 (36), 212 (22), 210 (26), 185 (15), 183 (15), 156 (39), 130 (14), 116 (11), 102 (20).

Anal. Calcd for $C_{12}H_{13}BrN_2$: C, 54.36; H, 4.94; N, 10.57. Found: C, 54.29; H, 4.99; N, 10.55.

### 3-Bromo-5,6,7,8-tetrahydrocyclopenta[4,5]pyrrolo[2,3-*b*]pyridine (4d)

After washing the precipitate with ice cold MeOH (1 mL), **4d** was obtained as a pale brown powder; yield: 0.24 g (34%); mp 170–171 °C (MeOH) [Lit.[13] mp 214–215 °C (hexane–$CH_2Cl_2$)]; $R_f$ = 0.25 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3431, 3128, 3037, 2927, 2850, 1570, 1486, 1412, 1279, 1066, 964 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 2.42 (quint, *J* = 7.0 Hz, 2 H, 6-$CH_2$), 2.74 (t, *J* = 7.0 Hz, 2 H, 5-$CH_2$), 2.87 (t, *J* = 7.0 Hz, 2 H, 7-$CH_2$), 7.94 (d, *J* = 2.0 Hz, 1 H, H-4), 8.10 (d, *J* = 2.0 Hz, 1 H, H-2), 11.68 (br s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 24.2, 25.7, 27.2, 110.4, 111.1, 119.8, 127.3, 138.4, 140.0, 148.4.

MS (EI, 70 eV): *m*/*z* (%) = 238 (84, [M (81Br)]+), 236 (100, [M (79Br)]+), 209 (17), 156 (32), 131 (11), 129 (14), 117 (11), 102 (22).

Anal. Calcd for $C_{10}H_9BrN_2$: C, 50.66; H, 3.83; N, 11.82. Found: C, 50.78; H, 3.69; N, 11.90.

**10-Bromo-6,7-dihydro-5*H*-benzo[*e*]pyrido[2,3-*b*]indole (4e)**

After washing the precipitate with ice cold MeOH (1.5 mL), **4e** was obtained as a pale brown powder; yield: 0.47 g (52%); mp 252–253 °C (MeOH); $R_f$ = 0.4 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3116, 3024, 2929, 2829, 1562, 1502, 1446, 1412, 1267, 1022, 968 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 2.97–3.03 (m, 4 H, 6-$CH_2$, 7-$CH_2$), 7.08 (t, *J* = 7.3 Hz, 1 H, H-3), 7.24–7.28 (m, 2 H, H-2, H-4), 7.76 (d, *J* = 7.6 Hz, 1 H, H-1), 8.25 (d, *J* = 1.9 Hz, 1 H, H-11), 8.52 (d, *J* = 1.9 Hz, 1 H, H-9), 12.12 (br s, 1 H, NH).

$^{13}C$ NMR (DMSO-$d_6$): δ = 21.5, 28.2, 107.3, 111.5, 118.3, 122.1, 124.7, 127.0, 128.1, 128.3, 132.0, 132.9, 138.9, 141.4, 147.1.

MS (EI, 70 eV): *m*/*z* (%) = 300 (70, [M (81Br)]+), 298 (82, [M (79Br)]+), 218 (100), 190 (29), 163 (16), 143 (13), 109 (29).

Anal. Calcd for $C_{15}H_{11}BrN_2$: C, 60.22; H, 3.71; N, 9.36. Found: C, 60.28; H, 3.62; N, 9.39.

**8-Bromo-2-methoxy-6,11-dihydro-5*H*-benzo[*g*]pyrido[2,3-*b*]indole (4f)**

After washing the precipitate with ice cold MeOH (2 mL), **4f** was obtained as a dark grey powder; yield: 0.55 g (56%); mp 270–271 °C (MeOH); $R_f$ = 0.4 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3155, 3130, 2924, 2835, 1574, 1477, 1280, 1222, 1049, 953 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 2.85–2.94 (m, 4 H, 5-$CH_2$, 6-$CH_2$), 3.80 (s, 3 H, $CH_3$), 6.80 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1.7 Hz, 1 H, H-3), 7.22 (d, *J* = 8.1 Hz, 1 H, H-4), 7.43 (d, *J* = 1.7 Hz, 1 H, H-1), 8.16 (s, 1 H, H-7), 8.22 (s, 1 H, H-9), 12.25 (br s, 1 H, NH).

$^{13}C$ NMR (DMSO-$d_6$): δ = 19.0, 27.6, 55.2, 107.9, 109.2, 110.8, 113.0, 121.0, 128.2, 128.3, 128.7, 129.3, 135.4, 142.4, 147.9, 158.3.

MS (EI, 70 eV): *m*/*z* (%) = 330 (81, [M (81Br)]+), 328 (100, [M (79Br)]+), 285 (28), 283 (25), 248 (87), 205 (93), 177 (23), 164 (17), 125 (24), 103 (46).

Anal. Calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.29; H, 4.08; N, 8.41.

**5-Bromo-2,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (4g)**

After washing the precipitate with ice cold MeOH (1 mL), **4g** was obtained as an off-white powder; yield: 0.44 g (65%); mp 233–234 °C (MeOH); $R_f$ = 0.3 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3396, 3153, 2918, 2856, 1589, 1496, 1383, 1284, 1086, 916 $cm^{-1}$.

$^1H$ NMR (DMSO-$d_6$): δ = 2.13 (s, 3 H, 3-$CH_3$), 2.32 (s, 3 H, 2-$CH_3$), 7.98 (d, *J* = 1.8 Hz, 1 H, H-4), 8.10 (d, *J* = 1.8 Hz, 1 H, H-6), 11.44 (br s, 1 H, NH).

$^{13}C$ NMR (DMSO-$d_6$): δ = 7.9, 11.2, 104.0, 109.0, 123.0, 127.0, 134.7, 140.7, 146.2.

MS (EI, 70 eV): *m*/*z* (%) = 226 (97, [M (81Br)]+), 224 (100, [M (79Br)]+), 211 (48), 209 (50), 144 (20).

Anal. Calcd for $C_9H_9BrN_2$: C, 48.02; H, 4.03; N, 12.45. Found: C, 48.10; H, 3.89; N, 12.49.

**5-Bromo-2-ethyl-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4h)**

After extraction and recrystallization from benzene–hexane mixture (1:1), **4h** was obtained as a pale brown powder; yield 0.38 g (53%); mp 176–177 °C (benzene–hexane); $R_f$ = 0.65 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3454, 3149, 3055, 2966, 2852, 1571, 1487, 1404, 1279, 1078, 914 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.36 (t, *J* = 7.6 Hz, 3 H, 2-$CH_3$), 2.21 (s, 3 H, 3-$CH_3$), 2.83 (q, *J* = 7.6 Hz, 2 H, $CH_2$), 7.90 (d, *J* = 2.0 Hz, 1 H, H-4), 8.21 (d, *J* = 2.0 Hz, 1 H, H-6), 10.46 (br s, 1 H, NH).

$^{13}C$ NMR ($CDCl_3$): δ = 8.2, 13.9, 19.7, 104.2, 110.7, 124.1, 128.3, 140.0, 140.9, 146.8.

MS (EI, 70 eV): *m*/*z* (%) = 240 (80, [M (81Br)]+), 238 (74, [M (79Br)]+), 225 (97), 223 (100), 209 (13), 144 (21).

Anal. Calcd for $C_{10}H_{11}BrN_2$: C, 50.23; H, 4.64; N, 11.72. Found: C, 50.34; H, 4.55; N, 11.77.

**5-Bromo-2-methyl-3-propyl-1*H*-pyrrolo[2,3-*b*]pyridine (4i)**

After extraction and recrystallization from MeOH, **4i** was obtained as a beige powder; yield: 0.57 g (75%); mp 147–148 °C (MeOH); $R_f$ = 0.3 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3429, 3140, 3047, 2952, 2858, 1572, 1491, 1406, 1284, 1074, 943 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, 3-$CH_3$), 1.63 (sext, *J* = 7.4 Hz, 2 H, $CH_2$Me), 2.46 (s, 3 H, 2-$CH_3$), 2.62 (t, *J* = 7.4 Hz, 2 H, $CH_2$Et), 7.90 (d, *J* = 1.7 Hz, 1 H, H-4), 8.20 (d, *J* = 1.7 Hz, 1 H, H-6), 10.91 (br s, 1 H, NH).

$^{13}C$ NMR ($CDCl_3$): δ = 12.0, 14.0, 23.9, 25.9, 110.3, 110.7, 123.6, 128.3, 134.2, 140.8, 146.7.

MS (EI, 70 eV): *m*/*z* (%) = 254 (29, [M (81Br)]+), 252 (31, [M (79Br)]+), 225 (100), 223 (99), 144 (31), 103 (7).

Anal. Calcd for $C_{11}H_{13}BrN_2$: C, 52.19; H, 5.18; N, 11.07. Found: C, 52.30; H, 5.07; N, 11.12.

**5-Bromo-3-isopropyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4j)**

After extraction and recrystallization from MeOH, **4j** was obtained as beige crystalline needles; yield: 0.47 g (62%); mp 188–189 °C (MeOH); $R_f$ = 0.45 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3417, 3140, 3035, 2960, 2864, 1562, 1489, 1404, 1275, 1066, 937 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.38 [d, *J* = 7.1 Hz, 6 H, $(CH_3)_2CH$], 2.47 (s, 3 H, 2-$CH_3$), 3.14 [sept, *J* = 7.1 Hz, 1 H, $(CH_3)_2CH$], 8.05 (d, *J* = 1.8 Hz, 1 H, H-4), 8.19 (d, *J* = 1.8 Hz, 1 H, H-6), 10.71 (br s, 1 H, NH).

$^{13}C$ NMR ($CDCl_3$): δ = 12.3, 23.2, 25.8, 110.4, 116.0, 122.0, 129.4, 132.8, 140.3, 146.8.

MS (EI, 70 eV): *m*/*z* (%) = 254 (28, [M (81Br)]+), 252 (27, [M (79Br)]+), 239 (97), 237 (100), 158 (28).

Anal. Calcd for $C_{11}H_{13}BrN_2$: C, 52.19; H, 5.18; N, 11.07. Found: C, 52.27; H, 5.12; N, 11.00.

**5-Bromo-3-ethyl-2-propyl-1*H*-pyrrolo[2,3-*b*]pyridine (4k)**

After extraction and recrystallization from MeOH, **4k** was obtained as a yellowish powder; yield: 0.43 g (54%); mp 122–123 °C (MeOH); $R_f$ = 0.75 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3147, 3045, 2958, 2864, 1573, 1489, 1404, 1282, 1055, 935 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.02 (t, *J* = 7.4 Hz, 3 H, 2-$CH_3$), 1.23 (t, *J* = 7.6 Hz, 3 H, 3-$CH_3$), 1.79 (sext, *J* = 7.4 Hz, 2 H, 2-C$H_2$Me), 2.68 (q, *J* = 7.6 Hz, 2 H, 3-C$H_2$Me), 2.79 (t, *J* = 7.4 Hz, 2 H, 2-C$H_2$Et), 7.94 (d, *J* = 1.8 Hz, 1 H, H-4), 8.19 (d, *J* = 1.8 Hz, 1 H, H-6), 10.92 (br s, 1 H, NH).

$^{13}$C NMR ($CDCl_3$): δ = 14.0, 15.8, 17.2, 23.0, 28.3, 110.7, 112.0, 123.1, 128.5, 138.0, 140.9, 146.9.

MS (EI, 70 eV): *m*/*z* (%) = 268 (35, [M ($^{81}$Br)]$^+$), 266 (39, [M ($^{79}$Br)]$^+$), 253 (57), 251 (60), 239 (45), 237 (52), 224 (23), 222 (21), 172 (28), 158 (36), 117 (24), 76 (22), 41 (36), 29 (100).

Anal. Calcd for $C_{12}H_{15}BrN_2$: C, 53.95; H, 5.66; N, 10.49. Found: C, 54.06; H, 5.58; N, 10.42.

### 5-Bromo-2-ethyl-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (4l)

After washing the precipitate with ice cold MeOH (1 mL), **4l** was obtained as an off-white powder; yield: 0.78 g (86%); mp 225–226 °C (MeOH); $R_f$ = 0.65 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3429, 3138, 3030, 2924, 2848, 1599, 1564, 1500, 1450, 1402, 1275, 1078, 933 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 1.29 (t, *J* = 7.6 Hz, 3 H, $CH_3$), 2.82 (q, *J* = 7.6 Hz, 2 H, $CH_2$), 7.24 (t, *J* = 7.6 Hz, 1 H, H-4 $C_6H_5$), 7.34–7.42 (m, 4 H, H-2,3,5,6 $C_6H_5$), 7.85 (d, *J* = 1.7 Hz, 1 H, H-4), 8.12 (d, *J* = 1.7 Hz, 1 H, H-6), 11.63 (br s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 14.0, 19.4, 110.3, 111.0, 121.1, 126.2, 127.5, 128.9, 129.1, 133.7, 140.9, 141.8, 146.5.

MS (EI, 70 eV): *m*/*z* (%) = 302 (93, [M ($^{81}$Br)]$^+$), 300 (100, [M ($^{79}$Br)]$^+$), 287 (42), 285 (49), 219 (13), 206 (96), 164 (10).

Anal. Calcd for $C_{15}H_{13}BrN_2$: C, 59.82; H, 4.35; N, 9.30. Found: C, 59.70; H, 4.46; N, 9.20.

### 5-Bromo-3-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (4m)

After washing the precipitate with ice cold $Et_2O$ (1 mL), **4m** was obtained as an off-white powder; yield: 0.33 g (38%); mp 207–208 °C (MeOH); $R_f$ = 0.60 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3431, 3130, 3045, 2922, 2854, 1570, 1477, 1398, 1277, 1080, 914 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 2.36 (s, 3 H, $CH_3$), 7.32 (t, *J* = 7.3 Hz, 1 H, H-4 $C_6H_5$), 7.44 (t, *J* = 7.3 Hz, 2 H, H-3,5 $C_6H_5$), 7.63 (d, *J* = 7.3 Hz, 2 H, H-2,6 $C_6H_5$), 7.94 (d, *J* = 2.1 Hz, 1 H, H-4), 8.16 (d, *J* = 2.1 Hz, 1 H, H-6), 11.70 (br s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 9.6, 105.5, 110.5, 123.6, 127.9, 128.0, 128.5, 128.8, 131.8, 136.2, 142.7, 146.8.

MS (EI, 70 eV): *m*/*z* (%) = 288 (94, [M ($^{81}$Br)]$^+$), 286 (100, [M ($^{79}$Br)]$^+$), 211 (28), 209 (29), 205 (47), 103 (21).

Anal. Calcd for $C_{14}H_{11}BrN_2$: C, 58.56; H, 3.86; N, 9.76. Found: C, 58.63; H, 3.77; N, 9.81.

### 3-Benzyl-5-bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4n)

After extraction and recrystallization from toluene, **4n** was obtained as a pale brown powder; yield: 0.40 g (44%); mp 184–185 °C (toluene); $R_f$ = 0.65 ($CHCl_3$–MeOH, 20:1).

IR (KBr): 3429, 3145, 3051, 2952, 2864, 1581, 1489, 1394, 1277, 1074, 904 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.48 (s, 3 H, $CH_3$), 4.03 (s, 2 H, $CH_2$), 7.17–7.21 (m, 3 H, H-2,4,6 $C_6H_5$), 7.26–7.30 (m, 2 H, H-3,5 $C_6H_5$), 7.74 (d, *J* = 2.0 Hz, 1 H, H-4), 8.21 (d, *J* = 2.0 Hz, 1 H, H-6), 10.20 (br s, 1 H, NH).

$^{13}$C NMR ($CDCl_3$): δ = 12.1, 30.0, 108.8, 111.2, 123.5, 126.2, 128.2, 128.55, 128.59, 134.9, 140.7, 141.3, 146.8.

MS (EI, 70 eV): *m*/*z* (%) = 302 (62, [M ($^{81}$Br)]$^+$), 300 (67, [M ($^{79}$Br)]$^+$), 287 (30), 285 (33), 225 (98), 223 (100), 212 (19), 178 (14), 144 (25), 110 (42), 103 (32).

Anal. Calcd for $C_{15}H_{13}BrN_2$: C, 59.82; H, 4.35; N, 9.30. Found: C, 59.91; H, 4.23; N, 9.37.

### Attempted Preparation of 5-Bromo-7-azaindoles 4o–s, Following the General Procedure for 4a–n

When *N*-methylpiperidin-4-one was used as the carbonyl compound, after reaction with PPA, and extraction with $CH_2Cl_2$ from reaction mixture and purification by flash chromatography ($CH_2Cl_2$–MeOH, 20:1), 1-methylpiperidin-4-one (5-bromopyridin-2-yl)hydrazone (**5o**) was obtained as a red-orange oil that crystallized upon storage; yield 0.79 g (93%). No cyclization to **4o** was detected. All necessary physical and spectral data for **5o** are given in Tables 3 and 4.

In the cases of *N*-methylsulfonyl- and *N*-benzoylpiperidin-4-ones, the reaction with PPA, followed by basification with aqueous ammonia furnished dark brown tars. None of the corresponding cyclized product **4p** or **4q** was obtained. The intermediate hydrazones **5p**,**q** were isolated and characterized (Tables 3 and 4).

Cyclization of acetone (5-bromopyridin-2-yl)hydrazone (**5r**) under conditions indicated in the general procedure gave the starting material as a beige solid; yield: 0.62 g (91%).

Similarly, the same result was obtained in the case of acetophenone (5-bromopyridin-2-yl)hydrazone (**5s**), which was isolated after the cyclization reaction as an off-white solid; yield: 0.83 g (95%).

All data for compounds **5r** and **5s** are presented in Tables 3 and 4.

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381040.

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