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Synthesis of novel pyrazolo[3,4-*b*]pyridine derivatives in aqueous medium

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This paper is dedicated to Gordon Gribble on his retirement – indole chemist par excellence and delightful collaborator. A true gentleman and fine chemist.

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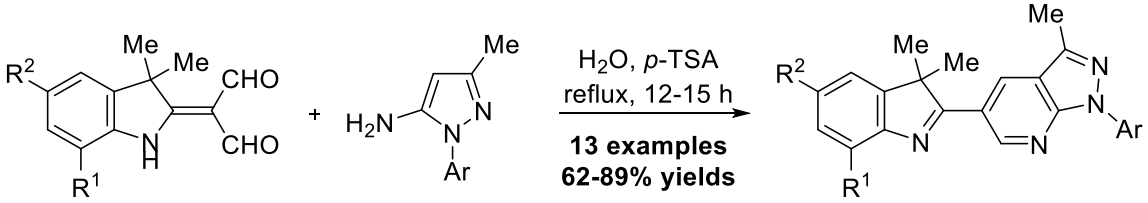
Abstract

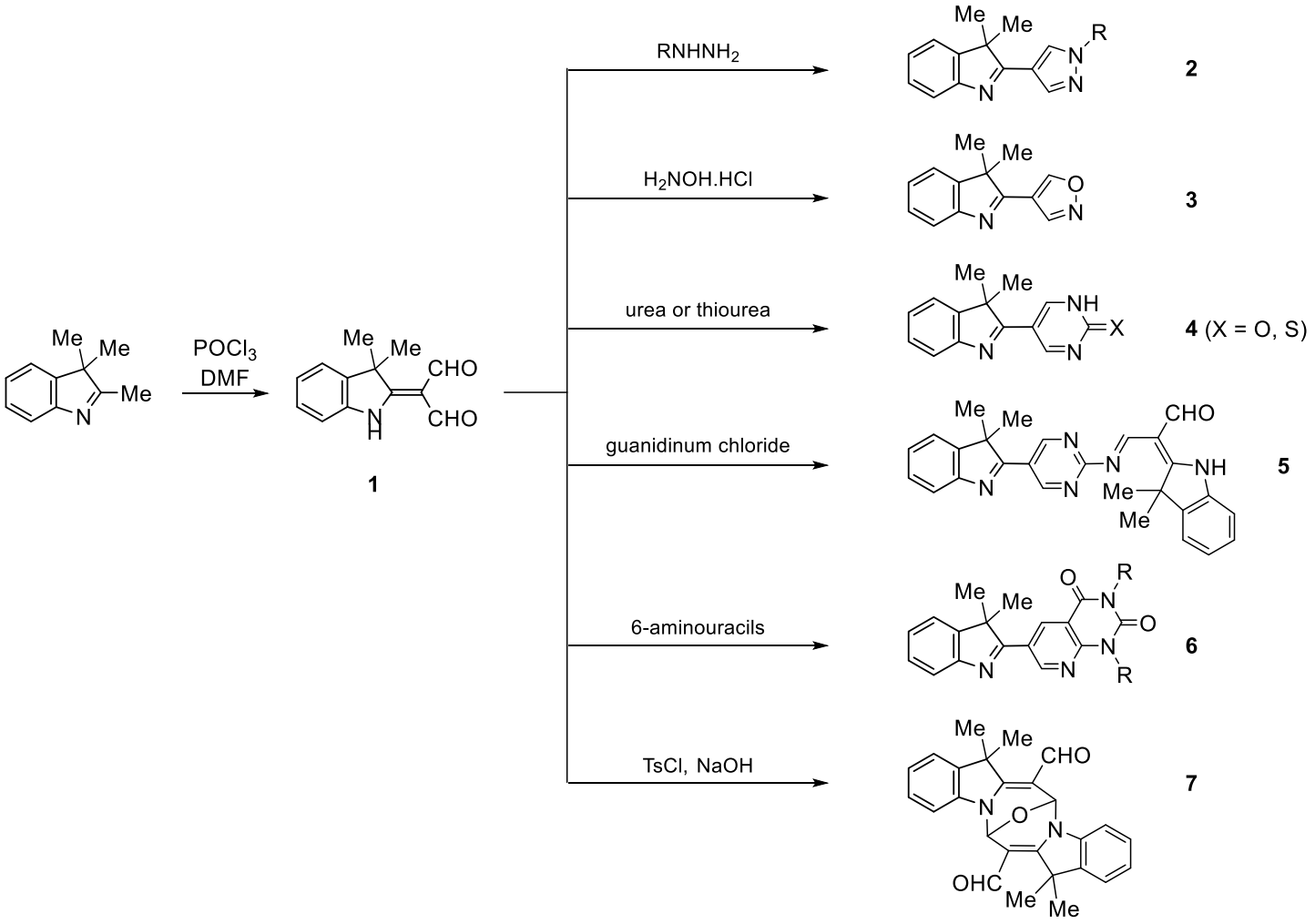
A synthesis of 5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridines by the reaction of variously substituted aminomethylene malondialdehydes [2-(3,3-dimethyl-3*H*-indol-2-ylidene)malondialdehydes] with 5-amino-1-aryl-3-methylpyrazoles in the presence of *p*-toluenesulfonic acid in water is described.



Keywords: Indolenine, aminomethylene malondialdehydes, aminopyrazole, pyrazolopyridine, water

Introduction

The indole moiety is a well-known heterocycle, an important feature of many natural products and medicinal agents,[1] and has been of continuing interest throughout the research work of the Dedicatee. Many methods are available for the construction and modification of indoles.[2] Indole derivatives, such as indolenines (3*H*-indoles), have received considerable attention due to their wide application in synthesis, especially for photoswitchable compounds, such as spiropyrans,[3] spirooxazines[3,4] and cyanine dyes.[5,6] In recent years, our research group has been developing a project centered on the synthesis of novel indolenines and bisindolenines, and reactions of them with the Vilsmeier reagent to produce aminomethylene malondialdehydes.[7-14] These malondialdehydes, as 1,3-dicarbonyl compounds, can be used to produce new heterocyclic systems, illustrated in Scheme 1 using the simplest example, malondialdehyde **1**, leading to: pyrazoles **2**,[8-13] isoxazole **3**,[12] pyrimidines **4** and **5**,[12,13] pyridopyrimidinedione **6**[14] and in work by others, oxygen-bridged diazocine **7**.[15]



Scheme 1. Previous examples of the use of 2-(3,3-dimethyl-3*H*-indol-2-ylidene)malondialdehydes for heterocycle construction.[6-15]

Fused heterocycles containing pyrazolopyridine systems have been associated with several biological and medicinal activities.[16,17] Substituted pyrazolo[3,4-*b*]pyridines represent a very important building block in

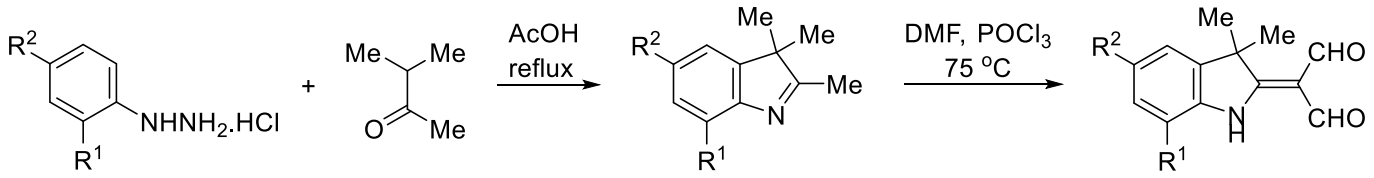
organic synthesis and numerous studies have been reported due to their well-documented biological activity.[18,19]

The use of water as a solvent in organic chemistry was 'rediscovered' in the 1980s by Breslow[20] who showed that hydrophobic effects can strongly enhance the rate of organic reactions. The unique properties of aqueous reaction media are associated with the high dielectric constant and cohesive energy density of water, that can result in extraordinary effects on reaction rates.[21] Moreover, the cost-effectiveness, abundance, non-inflammability and non-toxic nature of water encourage its use.[22-24]

Herein, we report the synthesis of new pyrazolo[3,4-*b*]pyridines **12a-m** by the reaction of malondialdehydes **10a-c** and electron-rich aminopyrazoles **11a-e** in the presence of *p*-toluenesulfonic acid in water as a green solvent.

Results and Discussion

2,3,3-Trimethyl-3*H*-indoles (indolenines) **9a-c** were synthesized by the reaction of the relevant phenylhydrazine hydrochloride **8a-c** with isopropyl methyl ketone in a Fischer reaction[25] (Scheme 2). Each of the indolenines **9a-c** was then reacted with the Vilsmeier reagent to afford indole-malonaldehydes **10a-c** in excellent yields, according to our prior protocol.[7-14] The malondialdehyde **10c** is a new example and its structure rests on the observation of two ^{1}H NMR one-hydrogen singlets at δ_H 9.75 and 9.78 corresponding to the aldehyde protons and a one-hydrogen signal for the N-hydrogen appearing at δ_H 13.60.

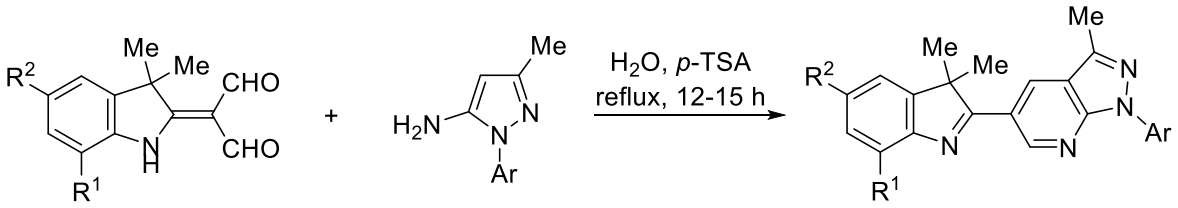


8a R^1=R^2=H
8b R^1=Cl, R^2=H
8c R^1=H, R^2=Br

9a-c **10a-c**

Scheme 2. Synthesis of 2-(3,3-dimethyl-3*H*-indol-2-ylidene)malondialdehydes.

After some preliminary experiments, it was found that a mixture of aminomethylene malondialdehyde **10a** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **11a**[26] in the presence of *p*-TSA, in refluxing water for 12 hours, afforded 5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **12a** in 85% yield (Scheme 3). It should be mentioned that when the reaction of aminomethylene **10a** with aminopyrazole **11a** was attempted in the absence of acid for 12 hours under reflux in water, the yield of product **12a** was less than 10%. We also examined these cyclizing condensations in ethanol as solvent or cosolvent: **12a** was formed in 80% yield in refluxing ethanol after two days and in 50% yield in refluxing ethanol/water (1:1) after four days.



10a R^1=R^2=H
10b R^1=Cl, R^2=H
10c R^1=H, R^2=Br

11a Ar = Ph
11b Ar = 2-ClC_6H_4
11c Ar = 3-ClC_6H_4
11d Ar = 4-ClC_6H_4
11e Ar = 4-BrC_6H_4

12a-m

Yields **12a-g** (%)	R^1	R^2	Ar	Yields **12h-m** (%)	R^1	R^2	Ar
a (85)	H	H	Ph	**h** (62)	Cl	H	3-ClC_6H_4
b (70)	H	H	2-ClC_6H_4	**i** (89)	H	Br	Ph
c (80)	H	H	3-ClC_6H_4	**j** (80)	H	Br	2-ClC_6H_4
d (81)	H	H	4-ClC_6H_4	**k** (73)	H	Br	3-ClC_6H_4
e (73)	H	H	4-BrC_6H_4	**l** (79)	H	Br	4-ClC_6H_4
f (67)	Cl	H	Ph	**m** (81)	H	Br	4-BrC_6H_4
g (69)	Cl	H	2-ClC_6H_4				

Scheme 3. Reaction of 2-(3,3-dimethyl-3*H*-indol-2-ylidene)malondialdehydes **10** with 3-methyl-1-phenyl-1*H*-pyrazol-5-amines **11** producing 5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines **12**.

Encouraged by this success, we extended this process to other aminomethylene malondialdehydes **10b** and **10c** and 5-aminopyrazoles **11b** and **11e**[26] under similar conditions (*p*-TSA/H_2O at reflux), furnishing the respective compounds **12b-m** in high yields (Scheme 3).

Each of the pyrazolo[3,4-*b*]pyridines **12a-m** showed three-hydrogen singlets for the methyl protons in the range δ_H 1.65-2.76 and aromatic proton signals between δ_H 7.18 and 9.39. For example, for compound **12a**, there was a six-hydrogen singlet for the geminal methyl groups at δ_H 1.68, and a three-hydrogen singlet at 2.74 for the pyrazole methyl protons. The signals between δ_H 7.32 and 9.38 were evidence for the aromatic-protons, and two one-hydrogen singlets at δ_H 8.94 and 9.38 characterized the newly-formed pyridine ring. The ^{13}C NMR spectrum of compound **12a** showed 20 signals in agreement with the structure.

Conclusions

An examination of *p*-TSA catalyzed cyclocondensations of (3*H*-indol-2-ylidene)malondialdehydes and various 5-aminopyrazoles in boiling water afforded pyrazolo[3,4-*b*]pyridines. The cyclocondensation reactions were clean and the new crystalline 5-(3,3-dimethyl-3*H*-indol-2-yl)pyrazolo[3,4-*b*]pyridines **12a-m** were obtained in high yields.

Experimental Section

General. Melting points were recorded on an Electrothermal Engineering LTD 16218 (Bibby Scientific Limited, Staffordshire, UK). ^{1}H and ^{13}C NMR spectra were recorded on an Avance AQS 300 MHz spectrometer (Brucker, Karlsruhe, Germany) at 300 and 75 MHz, respectively. Chemical shifts δ are in parts per million (ppm) measured in $CDCl_3$ as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a Nexus 670 FT-IR instrument (Thermonicolet, USA). Microanalyses were performed on a Perkin Elmer series II 2400 Analyzer (Perkin Elmer, USA).

5-Bromo-2,3,3-trimethyl-3*H*-indole (9c). A mixture of 4-bromophenylhydrazine hydrochloride **8c** (0.010 mol, 2.23 g) and isopropyl methyl ketone (0.011 mol, 1.18 mL) was refluxed in acetic acid (25 mL) for 6 h and then cooled, diluted with cold water (50 mL), and neutralized with NaOH (2 M), then extracted with EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4) and solvent was evaporated to give **9c** as a viscous oil, which was crystallized from EtOH/H_2O (1:1). Red crystals; (1.78 g, 75%); mp 35-36 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3059, 2954, 2926, 1583, 1462, 1381, 1197, 1076, 1012, 817; ^{1}H NMR ($CDCl_3$): δ_H 1.29 (s, 6H), 2.26 (s, 3H), 7.39-7.41 (m, 3H); ^{13}C NMR ($CDCl_3$): δ_C 15.4, 22.9, 54.1, 118.9, 121.2, 124.9, 130.7, 147.8, 152.6, 188.5; Found: C, 55.39; H, 5.01; N, 6.02. $C_{11}H_{12}BrN$ requires: C, 55.48; H, 5.08; N, 5.88%.

2-(5-Bromo-3,3-dimethyl-3*H*-indol-2-ylidene)malonaldehyde (10c). To *N,N*-dimethylformamide (0.3 mol, 23 mL) cooled in an ice bath was added dropwise $POCl_3$ (0.15 mol, 13.7 mL) with stirring at below 5 °C. After this addition, a solution of 5-bromo-2,3,3-trimethyl-3*H*-indole (**9c**) (0.05 mol, 11.90 g) in DMF (0.15 mol, 11 mL) was added dropwise. The cooling bath was removed and the reaction mixture was stirred at 75 °C for 12 h. The resulting solution was added to ice-cooled water and made alkaline with aq NaOH solution. The resulting precipitate was collected by filtration after 12 h, dried and recrystallized from EtOH, to give the title compound **10c**. Light brown crystals;(13.52 g, 92%); mp 114-117 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3215, 3086, 2969, 2929, 2867, 2768, 1656, 1607, 1525, 1465, 1365, 1196, 1159, 815; ^{1}H NMR ($CDCl_3$): δ_H 1.75 (s, 6H), 7.07 (d, *J* 8.4 Hz, 1H), 7.43-7.45(m, 2H), 9.75 (s, 1H), 9.78 (s, 1H), 13.60 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ_C 23.3, 51.5, 109.5, 113.9, 118.8, 125.8, 131.3, 138.4, 142.8, 162.3, 179.0, 187.6; Found: C, 53.16; H, 4.04; N, 4.69. $C_{13}H_{12}BrNO_2$ requires: C, 53.08; H, 4.11; N, 4.76%.

General procedure for synthesis of pyrazolo[3,4-*b*]pyridines 12a-m. *p*-TSA (0.086 g, 0.5 mmol) was added to a mixture of an aminomethylene malondialdehyde **10a-c** (1 mmol) and 5-aminopyrazole **11a-e** (1 mmol) in H_2O (25 mL), and the mixture was heated with stirring at reflux for 12-15 h. After this time, there was no trace of either of the starting materials in the crude product; the crude product showed just one spot on TLC. The mixture was cooled, and the resulting precipitate was collected by filtration, dried and recrystallized from EtOH to afford the product (**12a-m**).

5-(3,3-Dimethyl-3*H*-indol-2-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (12a). Yellow crystals; (0.30 g, 85%); mp 80-82 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3059, 2965, 2873, 1598, 1502, 1443, 1268, 1110, 759, 689; ^{1}H NMR ($CDCl_3$): δ_H 1.68 (s, 6H), 2.74 (s, 3H), 7.33 (d, *J* 6.0 Hz, 2H), 7.40 (d, *J* 7.2 Hz, 2H), 7.55 (t, *J* 7.8 Hz, 2H), 7.73 (d, *J* 8.1 Hz, 1H), 8.28 (d, *J* 8.1 Hz, 2H), 8.94 (s, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 13.6, 24.2, 54.0, 117.4, 119.9, 122.0, 123.0, 125.0, 126.9, 128.2, 128.7, 129.1, 130.1, 131.0, 147.6, 148.1, 149.8, 150.3, 152.8, 181.5; Found: C, 78.28; H, 5.68; N, 15.81. $C_{23}H_{20}N_4$ requires: C, 78.38; H, 5.72; N, 15.90%.

1-(2-Chlorophenyl)-5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12b). Yellow crystals; (0.27 g, 70%); mp 99-100 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3058, 2962, 2933, 1716, 1596, 1504, 1456, 1252, 1094, 1038, 759, 603; ^{1}H NMR ($CDCl_3$): δ_H 1.66 (s, 6H), 2.75 (s, 3H), 7.32 (d, *J* 6.6 Hz, 1H), 7.39 (d, *J* 7.8 Hz, 2H), 7.43-7.48 (m, 2H), 7.55-7.64 (m, 2H), 7.73 (d, *J* 6.9 Hz, 1H), 8.98 (s, 1H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.7,

24.8, 53.6, 116.0, 120.8, 121.0, 123.1, 126.1, 127.6, 128.0, 129.8, 130.3, 130.7, 132.2, 135.6, 144.6, 147.2, 149.4, 151.9, 152.8, 162.3, 181.2; Found: C, 71.24; H, 4.88; N, 14.62. $C_{23}H_{19}ClN_4$ requires: C, 71.40; H, 4.95; N, 14.48%.

1-(3-Chlorophenyl)-5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12c). Orange crystals; (0.32 g, 82%); mp 71-73 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3065, 2962, 2928, 1590, 1479, 1324, 1227, 1161, 1100, 1013, 876, 764, 678, 566; ^{1}H NMR ($CDCl_3$): δ_H 1.67 (s, 6H), 2.71 (s, 3H), 7.32 (d, *J* 4.8 Hz, 1H), 7.38-7.47 (m, 4H), 7.73 (d, *J* 6.3 Hz, 1H), 8.30 (d, *J* 7.5 Hz, 1H), 8.42 (s, 1H), 8.92 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 24.8, 53.6, 117.6, 118.3, 120.5, 120.9, 121.0, 123.4, 125.6, 126.2, 128.0, 130.1, 134.8, 140.3, 144.6, 147.3, 149.0, 151.0, 152.9, 162.3, 181.0; Found: C, 71.45; H, 4.89; N, 14.61. $C_{23}H_{19}ClN_4$ requires: C, 71.40; H, 4.95; N, 14.48%.

1-(4-Chlorophenyl)-5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12d). Orange crystals; (0.31 g, 81%); mp 150-151 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3069, 2967, 2928, 1709, 1594, 1495, 1449, 1399, 1266, 1087, 940, 818, 759; ^{1}H NMR ($CDCl_3$): δ_H 1.67 (s, 6H), 2.72 (s, 3H), 7.33 (d, *J* 6.3 Hz, 1H), 7.39 (d, *J* 6.6 Hz, 2H), 7.49 (d, *J* 7.2 Hz, 2H), 7.73 (d, *J* 6.9 Hz, 1H), 8.30 (d, *J* 7.2 Hz, 2H), 8.92 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 23.7, 53.6, 117.5, 119.8, 120.7, 122.1, 122.9, 123.3, 125.2, 127.0, 128.0, 129.1, 130.2, 131.1, 144.5, 147.7, 148.1, 150.3, 181.1; Found: C, 71.33; H, 4.88; N, 14.53. $C_{23}H_{19}ClN_4$ requires: C, 71.40; H, 4.95; N, 14.48%.

1-(4-Bromophenyl)-5-(3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12e). Yellow crystals; (0.314 g, 73%); mp 139-140 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3067, 2963, 2871, 1590, 1492, 1453, 1390, 1266, 1076, 1015, 817, 761, 570; ^{1}H NMR ($CDCl_3$): δ_H 1.67 (s, 6H), 2.71 (s, 3H), 7.33-7.39 (m, 3H), 7.57-7.71 (m, 3H), 8.23 (d, *J* 7.2 Hz, 2H), 8.92 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 24.8, 53.6, 117.5, 118.9, 120.8, 121.0, 122.0, 123.3, 126.2, 128.0, 129.8, 131.4, 132.1, 138.3, 144.5, 147.2, 149.0, 152.8, 181.1; Found: C, 63.92; H, 4.35; N, 12.86. $C_{23}H_{19}BrN_4$ requires: C, 64.05; H, 4.44; N, 12.99%.

5-(7-Chloro-3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (12f). Yellow crystals; (0.26 g, 67%); mp 96-98 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3060, 2963, 2928, 1598, 1502, 1438, 1295, 1215, 1106, 757, 683; ^{1}H NMR ($CDCl_3$): δ_H 1.68 (s, 6H), 2.75 (s, 3H), 7.29-7.38 (m, 3H), 7.53-7.58 (m, 3H), 8.29 (d, *J* 7.8 Hz, 2H), 9.01 (s, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.7, 24.8, 54.9, 117.3, 119.4, 121.0, 122.7, 125.1, 125.9, 127.1, 128.0, 128.5, 129.2, 130.4, 139.1, 144.2, 149.0, 149.7, 150.9, 182.2; Found: C, 71.45; H, 4.91; N, 14.61. $C_{23}H_{19}ClN_4$ requires: C, 71.40; H, 4.95; N, 14.48%.

5-(7-Chloro-3,3-dimethyl-3*H*-indol-2-yl)-1-(2-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12g). Orange crystals; (0.29 g, 69%); mp 106-107 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3063, 2959, 2927, 2868, 1601, 1513, 1454, 1292, 1162, 1102, 757; ^{1}H NMR ($CDCl_3$): δ_H 1.66 (s, 6H), 2.76 (s, 3H), 7.18-7.26 (m, 2H), 7.37-7.49 (m, 3H), 7.58-7.65 (m, 2H), 9.04 (s, 1H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.8, 24.8, 54.9, 116.0, 119.4, 120.4, 122.8, 125.9, 126.6, 127.1, 127.6, 128.2, 128.5, 129.7, 130.3, 130.7, 132.2, 135.6, 144.7, 149.2, 162.3, 182.2; Found: C, 65.48; H, 4.25; N, 13.44. $C_{23}H_{18}Cl_2N_4$ requires: C, 65.57; H, 4.31; N, 13.30%.

5-(7-Chloro-3,3-dimethyl-3*H*-indol-2-yl)-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12h). Orange crystals; (0.26 g, 62%); mp 97-99 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3077, 2963, 2930, 1591, 1481, 1270, 1095, 774, 679, 579; ^{1}H NMR ($CDCl_3$): δ_H 1.69 (s, 6H), 2.74 (s, 3H), 7.22-7.25 (m, 2H), 7.39-7.49 (m, 3H), 8.31 (d, *J* 7.2 Hz, 1H), 8.45 (s, 1H), 9.00 (s, 1H), 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.7, 24.7, 54.9, 117.6, 118.4, 119.4, 120.6, 123.0, 124.8, 125.1, 125.7, 127.2, 128.5, 130.0, 130.1, 134.8, 140.3, 144.8, 149.2, 149.7, 151.1, 182.0; Found: C, 65.63; H, 4.27; N, 13.19. $C_{23}H_{18}Cl_2N_4$ requires: C, 65.57; H, 4.31; N, 13.30%.

5-(5-Bromo-3,3-dimethyl-3*H*-indol-2-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (12i). Light brown crystals; (0.38 g, 89%); mp 151-152 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3068, 2967, 2937, 1598, 1505, 1439, 1255, 1172, 1102, 823, 762; ^{1}H NMR ($CDCl_3$): δ_H 1.67 (s, 6H), 2.73 (s, 3H), 7.33 (t, *J* 7.2 Hz, 1H), 7.51-7.60 (m, 5H), 8.26 (d, *J* 7.8 Hz, 2H), 8.90 (s, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 24.7, 54.0, 117.3, 119.8, 121.1, 122.1, 122.6, 124.6, 126.1, 129.2, 129.9, 131.1, 139.1, 144.1, 149.0, 149.3, 150.8, 151.8, 181.5; Found: C, 63.93; H, 4.37; N, 13.12. $C_{23}H_{19}BrN_4$ requires: C, 64.05; H, 4.44; N, 12.99%.

5-(5-Bromo-3,3-dimethyl-3*H*-indol-2-yl)-1-(2-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12j). Light brown crystals; (0.37 g, 80%); mp 190-191 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3066, 2927, 2937, 1710, 1601, 1505, 1448, 1321, 1244, 1091, 1035, 880, 762, 607; ^{1}H NMR ($CDCl_3$): δ_H 1.65 (s, 6H), 2.75 (s, 3H), 7.46-7.55 (m, 4H), 7.57-7.67 (m, 3H), 8.95 (s, 1H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.7, 24.7, 54.0, 116.0, 119.8, 122.1, 122.7, 124.6, 127.7, 129.7, 130.1, 130.3, 130.7, 131.1, 132.2, 135.5, 144.6, 149.3, 149.4, 151.8, 152.0, 181.5; Found: C, 59.18; H, 3.83; N, 11.91. $C_{23}H_{18}BrClN_4$ requires: C, 59.31; H, 3.90; N, 12.03%.

5-(5-Bromo-3,3-dimethyl-3*H*-indol-2-yl)-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12k). Light brown crystals; (0.34 g, 73%); mp 110-111 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3066, 2964, 2929, 1589, 1477, 1323, 1252, 1163, 1091, 828, 776, 738, 676; ^{1}H NMR ($CDCl_3$): δ_H 1.68 (s, 6H), 2.73 (s, 3H), 7.34 (d, *J* 6.3 Hz, 1H), 7.37-7.49 (m, 3H), 7.73 (d, *J* 7.8 Hz, 1H), 8.31 (d, *J* 8.1 Hz, 1H), 8.43 (s, 1H), 8.94 (s, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 24.8, 54.0, 117.6, 118.4, 119.9, 120.6, 122.2, 123.0, 124.6, 125.8, 130.0, 130.1, 131.2, 134.8, 140.2, 144.7, 149.0, 149.3, 151.0, 151.8, 181.3; Found: C, 59.36; H, 3.81; N, 12.16. $C_{23}H_{18}BrClN_4$ requires: C, 59.31; H, 3.90; N, 12.03%.

5-(5-Bromo-3,3-dimethyl-3*H*-indol-2-yl)-1-(4-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12l). Light brown crystals; (0.36 g, 79%); mp 201-203 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3072, 2960, 2922, 2868, 1600, 1499, 1446, 1407, 1322, 1251, 1092, 821; ^{1}H NMR ($CDCl_3$): δ_H 1.67 (s, 6H), 2.72 (s, 3H), 7.48-7.56 (m, 5H), 8.30 (d, *J* 8.4 Hz, 2H), 8.89 (s, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 24.7, 54.0, 117.4, 119.9, 121.8, 122.2, 122.8, 124.6, 129.2, 129.9, 131.2, 137.8, 144.4, 148.9, 149.3, 150.8, 151.9, 162.3, 181.3; Found: C, 59.24; H, 3.96; N, 12.08. $C_{23}H_{18}BrClN_4$ requires: C, 59.31; H, 3.90; N, 12.03%.

5-(5-Bromo-3,3-dimethyl-3*H*-indol-2-yl)-1-(4-bromophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (12m). Light brown crystals; (0.41 g, 81%); mp 127-129 °C; FT-IR (KBr) ν_{max}/cm^{-1}: 3083, 2964, 2929, 1594, 1495, 1452, 1323, 1265, 1074, 1014, 825; ^{1}H NMR ($CDCl_3$): δ_H 1.67 (s, 6H), 2.72 (s, 3H), 7.51-7.60 (m, 3H), 7.65 (d, *J* 8.4 Hz, 2H), 8.25 (d, *J* 8.4 Hz, 2H), 8.89 (s, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$): δ_C 12.6, 24.7, 54.0, 117.5, 119.0, 119.9, 122.1, 122.2, 122.9, 124.6, 131.2, 132.2, 138.3, 144.5, 149.3, 150.9, 151.8, 162.3, 167.2, 181.3; Found: C, 54.03; H, 3.50; N, 11.16. $C_{23}H_{18}Br_2N_4$ requires: C, 54.14; H, 3.56; N, 10.98%.

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Supplemental Data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra of all the products) associated with this article can be found in the online version.

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