Ionic Liquid as an Efficient Promoting Medium for Synthesis of Bis-pyrazolo[3,4-b:4′,3′-e]pyridines

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The preparation of a series of bis-pyrazolo[3,4-b:4′,3′-e]pyridines by the reaction of 5-aminopyrazole with aldehydes in ionic liquid [bmim]Br is described. This new method has the advantages of easier work-up, milder reaction conditions, high yields and environmental friendliness compared with other methods.

Keywords: Bis-pyrazolo[3,4-b:4′,3′-e]pyridine; 5-Aminopyrazole; Aldehyde; Ionic liquid.

INTRODUCTION

Room temperature ionic liquids, especially those based on 1-alkyl-3-methylimidazolium cations, have shown great promise as an attractive alternative to conventional organic solvents, and more attention has been currently focused on organic reactions promoted by ionic liquids.[1] They are nonvolatile, recyclable, nonexplosive, easily operable, and thermally robust.[2] There are many reports concerning the applications of ionic liquids in organic reactions, such as Friedel-Crafts reactions,[3,4] Diels-Alder reactions,[5-7] Heck reactions,[8,9] Pechmann condensations,[10] Biginelli reactions,[11] Beckmann rearrangements,[12,13] and other reactions.[14,15]

Bis-pyrazolo[3,4-b:4′,3′-e]pyridines have been attractive for physicochemical applications since they exhibit a high fluorescence in both solution and solid state under exposure to white light,[16] which makes them appropriate in the design of electroluminescent materials, like organic light emitting diodes (OLEDs).[16e-g] In addition, the pyrazole nucleus has long shown pharmacological properties, as in anti-anxiety,[17] anti-pyretic, analgesic and anti-inflammatory agents,[18] as well as for their anti-microbial properties,[19] especially anti-bacterial and anti-fungal activities.[19a,c,20]

Brack has previously reported the synthesis of bis-pyrazolo[3,4-b:4′,3′-e]pyridines, and described that when 5-amino-3-methyl-1-phenylpyrazole and (5-chloro-3-methyl-1-phenylpyrazol-4-yl)(4-aryl)methanone were treated in DMF at 240~250 °C for 2~3 hours, products were formed in 14~60% yield.[21] Gonzales et al. reported the reaction between 5-amino-1,3-dimethylpyrazole and aromatic aldehydes catalyzed by benzamide; the products were bis-pyrazolo[3,4-b:4′,3′-e]pyridines (yield of 40%) and pyrazolo-[3,4-d] pyrimidines (yield of 15%);[22] Puchala et al. reported that high yields of 42-76% were obtained in hot ethanol, but some reactions needed two steps;[23] Joshi et al. found bis-pyrazolo[3,4-b:4′,3′-e] pyridines can also be obtained when 5-amino-3-methyl-1-phenylpyrazole and 2-chlorobenzaldehyde or 2-fluorobenzaldehyde were treated in xylene and acetum;[24] Recently, Quiroga et al. described the synthesis of a series of bis-pyrazolo[3,4-b:4′,3′-e]pyridines in the reaction of amino-pyrazole and aldehydes under microwave irradiation and solvent-free conditions, with an over average yield.[25]

However, the principal drawbacks are low yields, toxic waste and the products can be difficult to separate from the reaction mixture.

In order to avoid volatility and toxicity that many organic solvents inherently have, we describe a very simple, green and efficient route to synthesize bis-pyrazolo[3,4-b:4′,3′-e]pyridines in an ionic liquid [bmim]Br.

To get bis-pyrazolo[3,4-b:4′,3′-e]pyridines **3**, we re-

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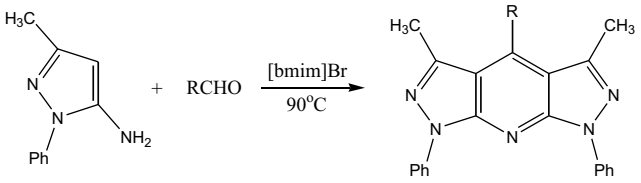
ported a facile method consisting of 5-aminopyrazole **1** and aldehydes **2** (in ratio 2:1) in an ionic liquid [bmim]Br at 90 °C for a few hours (Scheme I).

Scheme I



1 **2a-n** **3a-n**

RESULTS AND DISCUSSION

It is well-known that choosing an appropriate solvent is crucially important for an efficient organic synthesis. With the intention to search for the optimum solvent, the reaction of 5-amino-3-methyl-1-phenylpyrazole **1** and 4-chlorobenzaldehyde was examined using some ionic liquids, water and organic solvents. The corresponding results are summarized in Table 1.

It is shown in Table 1 that the ionic liquid [bmim]Br as solvent resulted in the most excellent yield and shortest reaction time. Therefore, [bmim]Br was chosen as the solvent of this reaction.

Under these optimized reaction conditions, a series of bis-pyrazolo[3,4-b:4′,3′-e]pyridines **3** were synthesized. The results are summarized in Table 2.

As shown in Table 2, this protocol could be applied not only to the aromatic aldehydes with either electron-withdrawing groups (such as halide, nitro groups) or electron-donating groups (such as alkyl, hydroxyl groups), but also to heterocyclic aldehydes, which highlighted the wide scope of this reaction. Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction.

Table 1. Solvent optimization for the synthesis of **3b**

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	[bmim]Br	90	3	93
2	[bmim]BF_4	90	4	76
3	[bmim]PF_6	90	5	69
4	EtOH	80	5	40
5	DMF	110	4	50
6	CH_3COCH_3	50	5	N. R.
7	CH_3COOEt	80	5	N. R.
8	$CHCl_3$	60	5	N. R.
9	CH_3CN	80	5	Trace
10	H_2O	100	5	N. R.

As new clean media, room temperature ionic liquids are recyclable and can be reused. The reaction between 5-amino-3-methyl-1-phenylpyrazole and 4-chlorobenzaldehyde was also investigated in the recycling reactions of ionic liquids, and the corresponding results are listed in Table 3.

From the reaction results, we found that after every recycle, reaction yields are almost the same as before.

Although we have not yet established the mechanism, a possible explanation is given in Scheme II.

In conclusion, a series of bis-pyrazolo[3,4-b:4′,3′-e]pyridines were synthesized via reactions of 5-amino-3-

Table 2. Synthesis of **3** in ionic liquid [bmim]Br

Entry	R	Time (h)	Yield (%)	m.p. (°C)	Lit. m.p. (°C)
a	4-BrC_6H_4	2	93	231-233	227-228[25]
b	4-ClC_6H_4	3	93	243-245	240-241[26]
c	4-FC_6H_4	3	94	214-216	216-218[25]
d	3,4-$(CH_3)_2C_6H_3$	2	95	246-249	
e	3-ClC_6H_4	2	97	293-295	
f	4-$NO_2C_6H_4$	3.5	88	268-270	269-271[26]
g	3,4-$(CH_3O)_2C_6H_3$	2	91	219-221	
h	3-$NO_2C_6H_4$	4	79	208-210	213-215[25]
i	4-$CH_3C_6H_4$	2	96	255-257	259-260[25]
j	3,4-$Cl_2C_6H_4$	2	85	261-264	
k	4-$CH_3OC_6H_4$	2	92	229-231	232-233[27]
l	4-HOC_6H_4	3	71	277-278	
m	3,4-$(OCH_2O)_2C_6H_3$	2.5	86	255-257	260-261[25]
n	4-$(CH_3)_2NC_6H_4$	2.5	70	242-244	244-246[27]

Table 3. Recyclation of ionic liquid

Entry	Temperature (°C)	Time (h)	Yield (%)
1	90	3	93
2	90	3	92
3	90	3	93
4	90	3	92
5	90	3	91

methyl-1-phenylpyrazole and aldehydes in ionic liquid [bmim]Br. The advantages of this method are easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer. ^{1}H NMR spectra were measured on a Bruker DPX-400 M Hz spectrometer using TMS as internal standard, DMSO-d_6 as solvent. High resolution mass spectra were obtained using a TOF-MS instrument.

General Procedure for the Synthesis of 4-Aryl-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridines (3a-n)

A dry 50 mL flask was charged with amino-pyrazole **1** (2 mmol) and the corresponding aldehyde **2** (1 mmol) and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 90 °C for 2-4 h to complete the reaction (monitored by TLC), then cooled to room temperature. The yellow solid was filtered off and washed with water. The filtrate of ionic liquid [bmim]Br was then recovered for reuse by drying at 80 °C for several hours in a vacuum. The crude product was purified by recrystallization from 95% EtOH to give **3**.

4-(4-Bromophenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3a)

IR (KBr) ν (cm^{-1}): 3070, 3050, 2985, 2955, 2911, 1597, 1578, 1510, 1498, 1487, 1458, 1437, 1412, 1379, 1328, 1239, 1113, 1091, 1068, 1029, 1012, 904, 883, 849, 821, 754, 692; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, J = 8.0 Hz, 4H, ArH), 7.85 (d, J = 8.4 Hz, 2H, ArH), 7.65-7.59 (m, 6H, ArH), 7.38-7.33 (m, 2H, ArH), 2.06 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{27}H_{20}{}^{79}BrN_5$ 493.0902, found 493.0888.

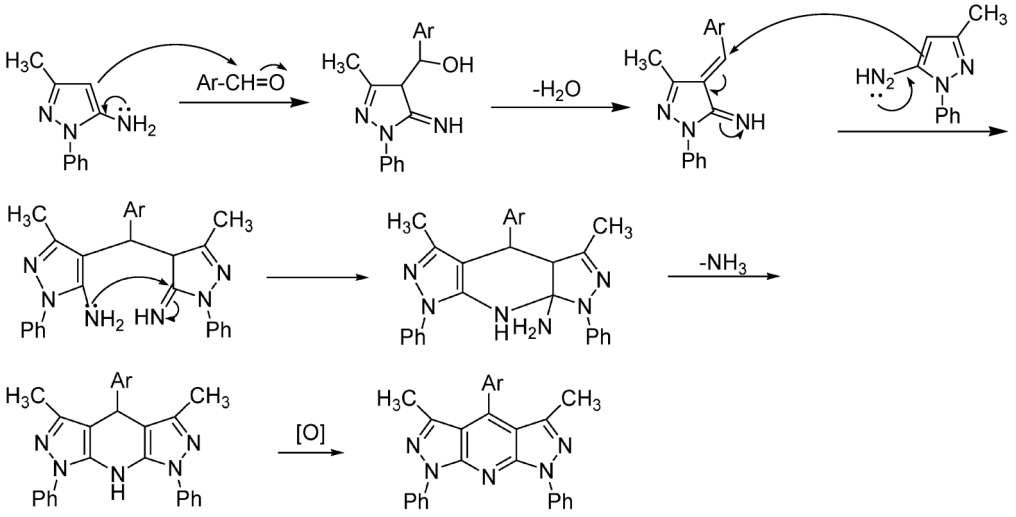
4-(4-Chlorophenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3b)

IR (KBr) ν (cm^{-1}): 3043, 2921, 1598, 1577, 1509, 1458, 1437, 1411,1378, 1327, 1276, 1239, 1175, 1091, 1015, 1006, 904, 883, 850, 823, 794, 755, 740, 694; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, J = 8.0 Hz, 4H, ArH), 7.72-7.70 (m, 4H, ArH), 7.64-7.60 (m, 4H, ArH), 7.35 (t, J = 7.2 Hz, 2H, ArH), 2.07 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{27}H_{20}{}^{35}ClN_5$ 449.1407, found 449.1425.

4-(4-Fluorophenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3c)

IR (KBr) ν (cm^{-1}): 3067, 2924, 1595, 1577, 1497, 1459, 1438, 1413, 1379, 1327, 1275, 1237, 1226, 1159, 1114, 1091, 1016, 905, 883, 857, 832, 796, 755, 692, 648; ^{1}H NMR (DMSO-d_6) δ: 8.35 (d, J = 8.4 Hz, 4H, ArH), 7.75-7.72 (m, 2H, ArH), 7.63 (t, J = 8.0 Hz, 4H, ArH), 7.49 (t, J = 8.8 Hz, 2H, ArH), 7.36 (t, J = 7.2 Hz, 2H, ArH), 2.07 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{27}H_{20}{}^{19}FN_5$ 433.1703,

Scheme II



found 433.1701.

3,5-Dimethyl-4-(3,4-dimethylphenyl)-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3d)

IR (KBr) ν (cm^{-1}): 3058, 3036, 2982, 2920, 1591, 1577, 1514, 1499, 1458, 1435, 1377, 1328, 1272, 1240, 1202, 1112, 1093, 1067, 1028, 1006, 900, 871, 820, 805, 793, 757, 738, 693, 670, 650; ^{1}H NMR (DMSO-d_6) δ: 8.35 (d, J = 8.0 Hz, 4H, ArH), 7.62 (t, J = 8.0 Hz, 4H, ArH), 7.43-7.33 (m, 5H, ArH), 2.40 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.07 (s, 6H, 2 × CH_3); ^{13}C NMR (CF_3COOD) δ: 13.93, 19.78, 19.88, 115.93, 126.75, 127.77, 129.09, 130.24, 131.92, 132.14, 133.36, 135.03, 140.59, 143.41, 150.62, 150.67, 157.77; HRMS: Calcd for $C_{29}H_{25}N_5$ 443.2110, found 443.2109.

4-(3-Chlorophenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3e)

IR (KBr) ν (cm^{-1}): 3047, 2963, 2911, 1600, 1592, 1579, 1563, 1498, 1459, 1435, 1414, 1378, 1327, 1274, 1238, 1144, 1089, 1028, 1007, 963, 868, 799, 788, 749, 731, 689; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, J = 8.0 Hz, 4H, ArH), 7.83 (s, 1H, ArH), 7.74 (d, J = 7.6 Hz, 1H, ArH), 7.70-7.60 (m, 6H, ArH), 7.36 (t, J = 7.2 Hz, 2H, ArH), 2.07 (s, 6H, 2 × CH_3); ^{13}C NMR (CF_3COOD) δ: 14.05, 115.79, 127.58, 127.72, 129.70, 132.02, 132.54, 133.36, 133.49, 133.81, 135.28, 138.24, 149.96, 151.22, 153.60; HRMS: Calcd for $C_{27}H_{20}{}^{35}ClN_5$ 449.1407, found 449.1400.

3,5-Dimethyl-4-(4-nitrophenyl)-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3f)

IR (KBr) ν (cm^{-1}): 3049, 2980, 2923, 2853, 1592, 1576, 1519, 1499, 1459, 1438, 1413, 1380, 1348, 1326, 1283, 1241, 1113, 1103, 1089, 1015, 1007, 850, 837, 756, 720, 694; ^{1}H NMR (DMSO- d_6) δ: 8.48 (d, J = 8.4 Hz, 2H, ArH), 8.34 (d, J = 8.0 Hz, 4H, ArH), 7.99 (d, J = 8.4 Hz, 2H, ArH), 7.63 (t, J = 8.0 Hz, 4H, ArH), 7.36 (t, J = 7.2 Hz, 2H, ArH), 2.04 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{27}H_{20}N_6O_2$ 460.1648, found 460.1656.

4-(3,4-Dimethoxyphenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3g)

IR (KBr) ν (cm^{-1}): 3070, 2999, 2954, 2931, 2834, 1600, 1590, 1577, 1516, 1498, 1460, 1438, 1412, 1378, 1330, 1251, 1232, 1159, 1140, 1099, 1028, 903, 851, 814, 755, 695, 670; ^{1}H NMR (DMSO-d_6) δ: 8.35 (d, J = 8.0 Hz, 4H, ArH), 7.62 (t, J = 8.0 Hz, 4H, ArH), 7.35 (t, J = 8.0 Hz, 2H, ArH), 7.25 (s, 1H, ArH), 7.22-7.14 (m, 2H, ArH), 3.90 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 2.12 (s, 6H, 2 × CH_3); ^{13}C NMR (DMSO-d_6) δ: 16.15, 56.02, 56.22, 111.54, 113.35, 113.82, 120.25, 120.37, 121.97, 125.74, 125.83, 129.63, 139.54, 144.97, 148.68, 149.84, 150.41; HRMS: Calcd for $C_{29}H_{25}N_5O_2$ 475.2008, found 475.2007.

3,5-Dimethyl-4-(3-nitrophenyl)-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3h)

IR (KBr) ν (cm^{-1}): 3050, 2963, 2911, 1592, 1580, 1535, 1498, 1460, 1437, 1378, 1348, 1326, 1270, 1238, 1110, 871, 758, 723, 712, 690, 649; ^{1}H NMR (DMSO-d_6) δ: 8.57 (s, 1H, ArH), 8.53 (d, J = 8.0 Hz, 1H, ArH), 8.35 (d, J = 8.0 Hz, 4H, ArH), 8.18 (d, J = 8.0 Hz, 1H, ArH), 7.96 (t, J = 8.0 Hz, 1H, ArH), 7.64 (t, J = 8.0 Hz, 4H, ArH), 7.37 (t, J = 7.6 Hz, 2H, ArH), 2.06 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{27}H_{20}N_6O_2$ 460.1648, found 460.1644.

3,5-Dimethyl-4-(4-methylphenyl)-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3i)

IR (KBr) ν (cm^{-1}): 3029, 2921, 1591, 1578, 1517, 1498, 1458, 1436, 1412, 1378, 1326, 1277, 1241, 1182, 1114, 1091, 1022, 1004, 898, 881, 812, 792, 755, 691, 670, 648; ^{1}H NMR (DMSO-d_6) δ: 7.35 (d, J = 8.0 Hz, 4H, ArH), 7.62 (t, J = 8.0 Hz, 4H, ArH), 7.53 (d, J = 8.0 Hz, 2H, ArH), 7.45 (d, J = 8.0 Hz, 2H, ArH), 7.35 (t, J = 7.2 Hz, 2H, ArH), 2.49 (s, 3H, CH_3), 2.06 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{28}H_{23}N_5$ 429.1953, found 429.1958.

4-(3,4-Dichlorophenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3j)

IR (KBr) ν (cm^{-1}): 3052, 2897, 1591, 1578, 1549, 1511, 1498, 1459, 1437, 1412, 1379, 1365, 1327, 1278, 1239, 1115, 1090, 1033, 1006, 869, 823, 755, 691, 670, 650; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, J = 8.0 Hz, 4H, ArH), 8.09 (d, J = 2.0 Hz, 1H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH), 7.71 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, ArH), 7.63 (t, J = 8.0 Hz, 4H, ArH), 7.36 (t, J = 7.2 Hz, 2H, ArH), 2.11 (s, 6H, 2 × CH_3); ^{13}C NMR (CF_3COOD) δ: 14.13, 115.63, 127.55, 128.68, 131.59, 131.80, 131.90, 133.18, 133.29, 135.24, 136.58, 138.73, 149.54, 151.28, 151.91; HRMS: Calcd for $C_{27}H_{19}{}^{35}Cl_2N_5$ 483.1018, found 483.1029.

4-(4-Methoxyphenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3k)

IR (KBr) ν (cm^{-1}): 3042, 2963, 2923, 2838, 1598, 1578, 1517, 1499, 1458, 1436, 1411, 1378, 1327, 1290, 1249, 1171, 1115, 1104, 1091, 1030, 1009, 901, 879, 854, 827, 794, 758, 693, 671, 649; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, J = 8.0 Hz, 4H, ArH), 7.61 (t, J = 7.6 Hz, 4H, ArH), 7.55 (d, J = 8.4 Hz, 2H, ArH), 7.34 (t, J = 7.6 Hz, 2H, ArH), 7.18 (d, J = 8.4 Hz, 2H, ArH), 3.90 (s, 3H, OCH_3), 2.06 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{28}H_{23}N_5O$ 445.1903, found

445.1924.

4-(4-Hydroxyphenyl)-3,5-dimethyl-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3l)

IR (KBr) ν (cm^{-1}): 3177, 2925, 1592, 1573, 1517, 1500, 1458, 1435, 1381, 1327, 1276, 1238, 1208, 1171, 1117, 1103, 1028, 1011, 882, 856, 830, 755, 690, 673, 648; ^{1}H NMR (DMSO-d_6) δ: 9.93 (s, 1H, OH), 8.34 (d, J = 8.0 Hz, 4H, ArH), 7.61 (t, J = 7.6 Hz, 4H, ArH), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.34 (t, J = 7.2 Hz, 2H, ArH), 7.00 (d, J = 8.4 Hz, 2H, ArH), 2.09 (s, 6H, 2 × CH_3); ^{13}C NMR (CF_3COOD) δ: 14.19, 114.71, 116.18, 117.16, 118.24, 125.27, 127.84, 131.65, 132.04, 133.47, 135.13, 150.39, 150.82; HRMS: Calcd for $C_{27}H_{21}N_5O$ 431.1746, found 431.1739.

3,5-Dimethyl-4-(3,4-methylenedioxyphenyl)-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3m)

IR (KBr) ν (cm^{-1}): 3065, 2888, 2779, 1591, 1573, 1508, 1499, 1485, 1458, 1438, 1378, 1365, 1327, 1278, 1238, 1185, 1103, 1082, 1033, 1006, 966, 934, 901, 854, 806, 791, 752, 718, 688, 651; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, J = 7.6 Hz, 4H, ArH), 7.62 (t, J = 7.6 Hz, 4H, ArH), 7.35 (t, J = 7.6 Hz, 2H, ArH), 7.27 (d, J = 1.2 Hz, 1H, ArH), 7.17 (d, J = 7.6 Hz, 1H, ArH), 7.08 (dd, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H, ArH), 6.21 (s, 2H, OCH_2O), 2.13 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{28}H_{21}N_5O_2$ 459.1695, found 459.1700.

3,5-Dimethyl-4-(4-(dimethylamino)phenyl)-1,7-diphenyl-1*H*,7*H*-bispyrazolo[3,4-*b*:4′,3′-*e*]pyridine (3n)

IR (KBr) ν (cm^{-1}): 3043, 2910, 2800, 1591, 1575, 1522, 1497, 1458, 1435, 1410, 1395, 1377, 1360, 1326, 1276, 1239, 1204, 1164, 1112, 1092, 1066, 1029, 1005, 953, 899, 876, 815, 756, 691, 649; ^{1}H NMR (DMSO-d_6) δ: 8.35 (d, J = 8.0 Hz, 4H, ArH), 7.61 (t, J = 7.6 Hz, 4H, ArH), 7.42 (d, J = 8.0 Hz, 2H, ArH), 7.34 (t, J = 7.6 Hz, 2H, ArH), 6.92 (d, J = 8.0 Hz, 2H, ArH), 3.05 (s, 6H, $N(CH_3)_2$), 2.14 (s, 6H, 2 × CH_3); HRMS: Calcd for $C_{29}H_{26}N_6$ 458.2219, found 458.2213.

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