Synthesis of Pyrazolo[3,4-*b*]pyridines Using Ammonium Acetate as Green Reagent in Multi-component Reactions

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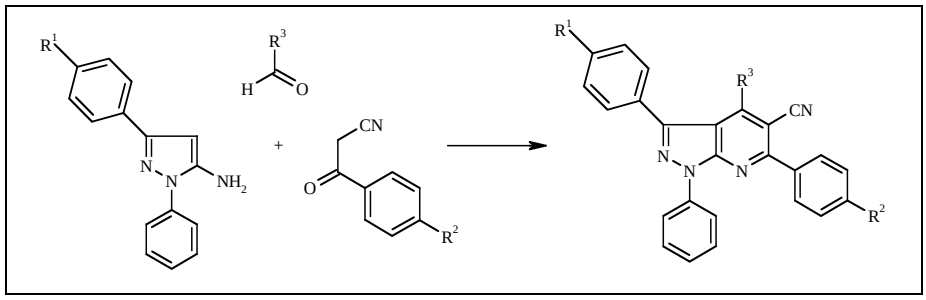

Several new pyrazolo[3,4-*b*]pyridine derivatives were synthesized by one pot cyclocondensation of the components; 5-amino-3-aryl-1*H*-phenylpyrazoles, *p*-substituted benzoylacetonitriles and some aldehydes. The condensations were most effective by using ammonium acetate as the base catalyst; triethylamine was also studied as a catalyst.

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INTRODUCTION

Multi-component reactions (MCRs) are of increasing importance in organic and medicinal chemistry. MCR strategies offer significant advantages over conventional linear type synthesis [1]. Ugi reported a three component condensation with heterocyclic amine, various aldehydes and nitriles or isocynate [2] and *Tsai et al*. reported that this condensation speeds up in a sealed vessel under microwave heating [3].

Today chemists are in search of environmentally friendly reagents to furnish clean reactions with high yield of a single product and easy to work up. Previously [6] we have successfully synthesized pyranofused quinolines, coumarins/pyridones by using cyclic β-ketoesters and 4-hydroxy quinoline/coumarin/pyridones with ammonium acetate. We have also synthesed fused pyrimidines [7] by fusion of 2-aminoheterocycles and β-ketoester in ammonium acetate at 120 °C. The pyrazolo[3,4-*b*]-pyridine derivatives show promising biological activities [8-13]. These reports prompted us to study the synthesis of pyrazolo[3,4-*b*]pyridines using multicomponent reactions.

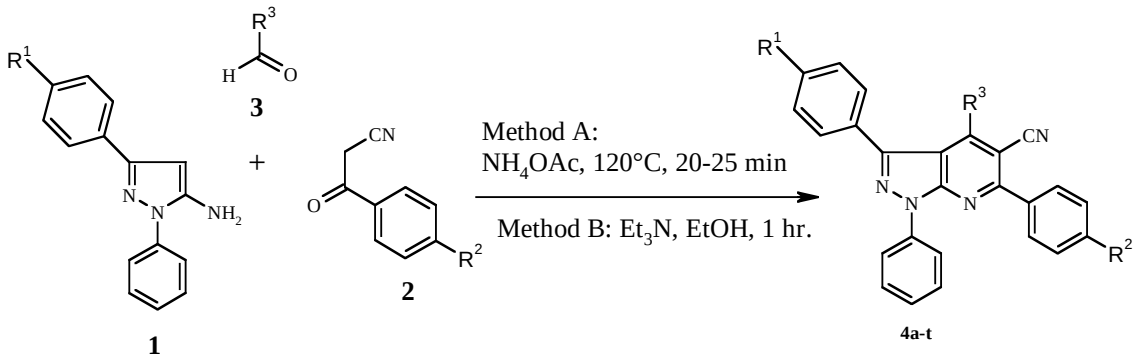
RESULTS AND DISCUSSION

Synthesis of pyrazolo[3,4-*b*]pyridine derivatives has been reported by J. Quiroga and coworker [14,15] using 5-amino-3-methyl/phenyl-1-phenyl/H-1*H*-pyrazole and chalcone of benzoylacetonitrile/malanonitrile with aromatic aldehydes. The title compounds could be synthesized in one pot in which the synthesis of chalcone is not required. A literature survey showed few reports on the synthesis of pyrazolo[3,4-*b*]pyridines using Michael addition [14,15] however with substitution patterns different from ours. As 5-amino-3-aryl-1-phenyl-1*H*-pyrazole was already in hand [16] we performed the one pot synthesis of the title compounds. Thus cyclocondensation of 5-amino-3-aryl-1-phenyl-1*H*-pyrazole **1**, *p*-substituted benzoylacetonitriles **2** and aryl/H aldehydes **3** on fusion in ammonium acetate at 120 °C gave pyrazolo[3,4-*b*]pyridine derivatives **4** in 80-85 % yield (Scheme 1). This reaction did not require any solvent and the aqueous work up of the reaction allowed for the isolation of 100 % of the product. During heating, the acetate ion serves as the base in this condensation reaction and the condensation products were obtained in pure state without the need for further purification. Compounds **4** were also synthesized by using solvent and catalyst, however low yields of products were obtained and further purification was necessary.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting points apparatus in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Varian XL-300 MHz spectrometer and chemical shifts are expressed in ppm with reference to TMS as an internal standard. IR spectra were obtained on Shimadzu IR-408 as potassium bromide pellets unless otherwise stated. Elemental analyses were determined on Hosli C, H Analyzer. The reactions were checked with thin layer chromatography

Scheme 1



Product				Color & Physical State (Crystallization Solvent)	Mp (°C)	Yield (%)	
	R^1	R^2	R^3			Method A	Method B
4a	Cl	Cl	*p*-FC_6H_4	Colorless (DMF)	280-281	82	72
4b	Cl	Br	*p*-FC_6H_4	Colorless (DMF)	284-285	85	74
4c	Cl	Br	*p*-CNC_6H_4	Colorless (DMF)	326-327	81	69
4d	Cl	Cl	*p*-ClC_6H_4	Colorless (DMF)	280-281	79	66
4e	CH_3	CH_3	H	Colorless (DMF)	235-237	80	70
4f	CH_3	CH_3	*p*-FC_6H_4	Colorless (DMF)	234-235	82	71
4g	CH_3	Cl	*p*-ClC_6H_4	Colorless (DMF)	258-259	81	69
4h	CH_3	CH_3	C_4H_3S (2-Thienyl)	Colorless (DMF)	221-222	84	73
4i	CH_3	CH_3	C_4H_3 (Furyl)	Colorless (DMF)	238-239	82	71
4j	CH_3	CH_3	$C_{15}H_{10}ClN_2$ (4-{3-(4-chlorophenyl) pyrazoyl}	Colorless (DMF)	244-245	83	70
4k	Cl	Br	*p*-ClC_6H_4	Colorless (DMF)	263-264	88	77
4l	Br	Br	*p*-ClC_6H_4	Yellow (ethanol /DMF)	315-316	82	73
4m	Br	Cl	*p*-ClC_6H_4	Yellow (ethanol /DMF)	302-303	86	75
4n	Br	Cl	*p*-CNC_6H_4	Colorless (DMF)	331-332	79	78
4o	Cl	Br	*p*-BrC_6H_4	Colorless (DMF)	289-290	89	76
4p	Br	Cl	*p*-$OMeC_6H_4$	Yellow (ethanol /DMF)	245-247	83	67
4q	Br	Cl	*m*-$OMeC_6H_4$	Yellow (ethanol /DMF)	234-235	78	68
4r	Br	Cl	*p*-MeC_6H_4	Yellow (ethanol /DMF)	270-272	77	72
4s	Br	Br	C_6H_5	Yellow (ethanol /DMF)	245-246	88	71
4t	Cl	CH_3	$C_{15}H_{10}ClN_2$ (4-{3-(4-chlorophenyl) pyrazoyl}	Colorless (DMF)	278-279	85	73

using UV light. All Compounds were synthesized by both, methods A and B.

General Procedure Synthesis of 3,4 6-triaryl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4).

Method-A. A mixture of 5-aminopyrazole **1** (2 mmole), aroylacetonitrile **2** (2 mmole) and aryl/H aldehyde **3** (2 mmole) and ammonium acetate (5 mole) was placed in a reaction flask with a short condenser or vigreaux column attached to the flask. The reaction mixture was heated in an oil bath at 120° C for 20-25 minutes (TLC Check). Reaction mixture after cooling was stirred in 100 mL cold water to remove excess of ammonium acetate and impurities formed during the reaction. The solid obtained was collected by filtration washed with water, dried and recrystallized from a suitable solvent to furnish the compounds **4** in good yield.

Method-B. A mixture of 5-aminopyrazole **1** (2 mmole), aroylacetonitrile **2** (2 mmole) and aryl/H aldehyde **3** (2 mmole) was refluxed in ethanol (10 mL) in presence of catalytic amount of triethylamine (1 mL) for one hour. The solid obtained was collected by filtration, washed with ethanol, dried and recrystallized from a suitable solvent to furnish the compounds **4** in good yield.

3,6-Bis(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4a). ir: (Potassium bromide): 2221, 1453, 1520, 1166 864, 843, 731cm^{-1}; ^{1}H nmr: ($CDCl_3$) δ 7.02-7.50 (m, 9H, Ar-H), 7.62 (d, 2H, J = 8.4 Hz, Ar-H), 7.76 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 2H, J = 8.7 Hz, Ar-H); *Anal.* Calcd. for $C_{31}H_{17}Cl_2FN_4$: C, 69.54; H, 3.20; N, 10.46. Found: C, 69.70; H, 3.45; N, 10.58.

6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4b). ir: (Potassium bromide): 2223,1453, 1520, 1166 cm^{-1}; ^{1}H nmr: ($CDCl_3$) δ 7.02-7.63 (m, 11H, Ar-H), 7.74 (d, 2H, J = 8.7 Hz, Ar-H), 7.94 (d, 2H, J = 8.4 Hz, Ar-H), 8.35 (d, 2H, J = 8.7 Hz, Ar-H), 8.42 (d, 2H, Ar-H); *Anal.* Calcd. for $C_{31}H_{17}BrClFN_4$: C, 64.21; H, 2.95; N, 9.66 Found: C, 64.38; H, 2.67; N, 9.79.

6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(4-cyanophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4c). ir: (Potassium bromide): 2219, 1453, 1515, 1169 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 7.03-7.14 (m, 4H, Ar-H), 7.39-7.74 (m, 8H, Ar-H), 7.89-8.24(m, 5H, Ar-H); *Anal.* Calcd. for $C_{32}H_{17}BrClN_5$: C, 65.49; H, 2.92; N, 11.93 Found: C, 65.71; H, 3.17; N, 12.18.

3,4,6-Tri(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (4d). ir: (Potassium bromide): 2220,1453, 1515, 1169 cm^{-1}; ^1H nmr: (DMSO-d_6), δ 7.15-7.74 (m, 11H, Ar-H), 7.84-8.24 (m, 6H, Ar-H); *Anal.* Calcd. for $C_{31}H_{17}Cl_3N_4$: C,67.47; H, 3.10; N, 10.15 Found: C, 67.65; H, 3.27; N, 10.36.

3,6-Bis(4-Methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (4e). ir: (Potassium bromide): 2227,1453, 1519, 1170 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.54 (s, 6H, $2CH_3$), 7.39 (m, 5H, Ar-H), 7.55 (m, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.42 (d, 2H, J = 8.4 Hz, Ar-H), 8.83 (s, 1H, C_4H); *Anal.* Calcd. for $C_{21}H_{17}ClN_2O_2$: C,80.97; H, 5.03; N, 13.99 Found: C, 80..98; H, 5.24; N, 14.23.

3,6-Bis(4-Methylphenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4f). ir: (Potassium bromide): 2224,1453, 1519, 1170 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.56 (s, 6H, $2CH_3$), 7.39-7.51 (m, 9H, Ar-H), 7.55 (m, 2H, Ar-H), 7.74 (d, 2H, J = 8.4 Hz, Ar-H), 7.95 (d, 2H, J = 8.4 Hz, Ar-H), 8.42 (d, 2H, J = 8.6 Hz, Ar-H); *Anal.* Calcd. for $C_{33}H_{23}FN_4$: C,80.14; H, 4.69; N, 11.33 Found: C, 80.11; H, 4.67; N, 11.48

4,6-Bis(4-Chlorophenyl)-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4g). ir: (Potassium bromide): 2223,1453, 1519, 1170 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 7.02-7.63 (m, 11H, Ar-H), 7.74 (d, 2H, J = 8.4 Hz, Ar-H), 7.94 (d, 2H, J = 8.7 Hz, Ar-H), 8.35 (d, 2H, J = 8.4 Hz, Ar-H); *Anal*. Calcd. for $C_{32}H_{20}Cl_2N_4$: C,72.32; H, 3.79; N,8.07. Found: C, 72.5; H, 3.97; N, 8.22.

3,6-Bis(4-Methylphenyl)-1-phenyl-4-thien-2-yl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4h). ir: (Potassium bromide): 2219,1453, 1519, 1170 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.47 (s, 6H, $2CH_3$), 6.99-7.56 (m, 12H, Ar-H), 7.92 (d, 2H, J = 8.4 Hz, Ar-H), 8.32 (d, 2H, J = 8.4 Hz, Ar-H); *Anal.* Calcd. for $C_{31}H_{22}N_4S$: C, 77.15; H, 4.59; N,11.61 Found: C, 77.34; H, 4.68; N,11.68.

3,6-Bis(4-Methylphenyl)-4-(2-furyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4i). ir: (Potassium bromide): 2218,1453, 1519, 1170 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.49 (s, 6H, $2CH_3$), 6.54 (m, 1H, Ar-H), 7.10 (m, 1H, Ar-H), 7.17-7.55 (m, 8H, Ar-H), 7.67 (d, 2H, J = 8.4 Hz, Ar-H), 7.85 (d, 2H, J = 8.6 Hz, Ar-H), 8.25 (d, 2H, J = 8.3 Hz, ArH); *Anal.* Calcd. for $C_{31}H_{22}N_4O$: C,79.81; H, 4.75; N,12.01 Found: C, 79.94; H, 4.85; N, 12.08.

3,6-Bis(4-Methylphenyl)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4j). ir: (Potassium bromide): 2218,1453, 1519, 1170 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.41 (s, 6H, $2CH_3$), 6.97 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H), 7.12-7.57 (m, 14H, Ar-H), 7.67 (d, 2H, J = 8.4 Hz, Ar-H), 7.84 (m, 3H, Ar-H), 8.31 (d, 2H, J = 8.4 Hz, Ar-H); *Anal.* Calcd. for $C_{42}H_{29}ClN_6$: C,77.23; H, 4.47; N,12.87 Found: C, 77.43; H, 4.64; N,12.94.

6-(4-Bromophenyl)-3,4-bis(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4k). ir: (Potassium bromide): 2214,1453, 1519, 1170 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.02 (d, 2H, J = 8.7 Hz, Ar-H), 7.12 (d, 2H, J = 8.4 Hz, Ar-H), 7.21 (m, 4H, Ar-H), 7.36 (t, 1H, J = 7.2 Hz, Ar-H), 7.53 (m, 4H, Ar-H), 7.96 (d, 2H, J = 8.4 Hz, Ar-H), 8.29 (d, 2H, J = 7.8 Hz, Ar-H); *Anal.* Calcd. for $C_{21}H_{17}BrCl_2N_4$: C,62.44; H, 2.87; N,9.40. Found: C, 62.52; H, 2.91; N, 9.36.

3,6-Bis(4-bromophenyl)-4-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4l).; ir: (Potassium bromide): 2230,1462, 1520, 1167 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.01 (d, 2H, J = 8.7 Hz, Ar-H), 7.11 (d, 2H, J = 8.4 Hz, Ar-H), 7.20 (m, 4H, Ar-H), 7.29 (t, 1H, J = 7.2 Hz, Ar-H), 7.52 (m, 4H, Ar-H), 7.95 (d, 2H, J = 8.4 Hz, Ar-H), 8.28 (d, 2H, J = 7.8 Hz, Ar-H); *Anal*. Calcd. for $C_{21}H_{17}Br_2ClN_4$: C,58.11; H, 2.67; N, 8.74. Found: C, 58.22; H, 2.58; N, 8.70.

3-(4-Bromophenyl)-4,6-bis(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4m). ir: (Potassium bromide): 2232,1462, 1512, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.01 (d, 2H, J = 8.7 Hz, Ar-H), 7.13 (d, 2H, J = 8.4 Hz, Ar-H), 7.20 (m, 4H, Ar-H), 7.36 (t, 1H, J = 7.2 Hz, ArH), 7.53 (m, 4H, Ar-H), 7.98 (d, 2H, J = 8.4 Hz, Ar-H), 8.29 (d, 2H, J = 7.8 Hz, Ar-H); *Anal.* Calcd. for $C_{21}H_{17}BrCl_2N_4$: C, 62.44; H, 2.87; N, 9.40. Found: C, 62.55; H, 2.92; N, 9.39.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-4-(4-cyanophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4n). ir: (Potassium bromide): 2230,1462, 1596, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.07 (d, 2H, J = 8.4 Hz, Ar-H), 7.11 (d, 2H, J = 8.7 Hz, Ar-H), 7.30 (t, 1H, Ar-H), 7.41 (d, 2H, J = 8.4 Hz, Ar-H), 7.70 (d, 2H, J = 8.4 Hz, Ar-H), 7.54 (m, 4H, Ar-H), 7.89 (d, 2H, J = 8.7 Hz, Ar-H), 8.29 (d, 2H, J = 7.8 Hz, Ar-H); *Anal.* Calcd. for $C_{32}H_{17}BrClN_5$: C, 65.49; H, 2.92; N, 11.93 Found: C, 65.26; H, 2.88; N, 11.96.

4,6-Bis(4-bromophenyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4o). ir: (Potassium bromide): 2230,1462, 1596, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.01 (d, 2H, J = 8.4 Hz, Ar-H), 7.11 (d, 2H, J = 8.7 Hz, Ar-H), 7.20 (m, 4H, Ar-H), 7.37 (t, 1H, J = 7.2 Hz, Ar-H), 7.52 (m, 4H, Ar-H), 7.98 (d, 2H, J = 8.7 Hz, Ar-H), 8.28 (d, 2H, J = 7.8 Hz, Ar-H); *Anal*. Calcd. for $C_{21}H_{17}Br_2ClN_4$: C,58.11; H, 2.67; N, 8.74. Found: C, 58.30; H, 2.70; N, 8.78.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-4-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4p). ir: (Potassium bromide): 2231,1462, 1596, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.22 (s, 3H, OCH_3), 7.04 (d, 2H, J = 8.4 Hz, Ar-H), 7.15 (d, 2H, J = 8.7 Hz, Ar-H), 7.22 (m, 4H, ArH), 7.37 (t, 1H, J = 7.2 Hz, Ar-H), 7.52 (m, 4H, Ar-H), 7.99 (d, 2H, J = 8.7 Hz, Ar-H), 8.30 (d, 2H, J = 7.8 Hz, Ar-H); *Anal.*Calcd. for $C_{32}H_{20}BrClN_4O$: C, 64.94; H, 3.41; N, 9.47. Found: C, 65.10; H, 3.70; N, 9.78.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-4-(3-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4q). ir: (Potassium bromide): 2231,1462, 1596, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.26 (s, 3H, OCH_3) 7.06 (d, 2H, J = 8.4 Hz, ArH), 7.17 (d, 2H, J = 8.7 Hz, ArH), 7.23 (m, 4H, ArH), 7.38 (t, 1H, J = 7.2 Hz, ArH), 7.50 (m, 4H, ArH), 7.99 (d, 2H, J = 8.7 Hz, ArH), 8.32 (d, 2H, J = 7.8 Hz, ArH); *Anal.* Calcd. for $C_{32}H_{20}BrClN_4O$: C, 64.94; H, 3.41; N, 9.47. Found: C, 65.17; H, 3.21; N, 9.17.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-1-phenyl-4-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4r). ir: (Potassium bromide): 2238, 1462, 1596, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.9 (s, 3H, CH_3), 7.03 (d, 2H, J = 8.4 Hz, Ar-H), 7.18 (d, 2H, J = 8.7 Hz, Ar-H), 7.25 (m, 4H, Ar-H), 7.40 (t, 1H, J = 7.2 Hz, Ar-H), 7.50 (m, 4H, Ar-H), 7.99 (d, 2H, J = 8.7 Hz, Ar-H), 8.26 (d, 2H, J = 7.8 Hz, Ar-H); *Anal.* Calcd. for $C_{32}H_{20}BrClN_4$: C, 66.74; H, 3.50; N, 9.73. Found: C, 66.46; H, 3.21; N, 9.52.

3,6-Bis(4-bromophenyl)-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (4s). ir: (Potassium bromide): 2236, 1462, 1596, 1157 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.03 (d, 2H, J = 8.4 Hz, Ar-H), 7.18 (d, 2H, J = 8.7 Hz, Ar-H), 7.25 (m, 4H, Ar-H), 7.40 (t, 1H, J = 7.2 Hz, Ar-H), 7.50 (m, 5H, Ar-H), 7.99 (d, 2H, J = 8.7 Hz, Ar-H), 8.26 (d, 2H, J = 7.8 Hz, Ar-H); *Anal.* Calcd. for $C_{31}H_{18}Br_2N_4$: C, 61.41; H, 2.99; N, 9.24. Found: C, 61.31; H, 2.71; N, 9.52.

3-(4-Chlorophenyl-6-(4-Methylphenyl)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4t). ir: (Potassium bromide): 2221,1453, 1569, 1160 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.41 (s, 6H, $2CH_3$), 6.97 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H), 7.12-7.57 (m, 14H, Ar-H), 7.67 (d, 2H, J = 8.4 Hz, Ar-H), 7.84 (m, 3H, Ar-H), 8.31 (d, 2H, J = 8.4 Hz, Ar-H); *Anal.* Calcd. for $C_{41}H_{26}Cl_2N_6$: C,73.11; H, 3.89; N, 12.48. Found: C, 73.26; H, 3.96; N, 12.64.

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