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AN ALTERNATIVE PREPARATION OF PYRAZOLO-PYRIDINE DERIVATIVES IN IONIC LIQUID AND COMPARISON STUDY ON THE REACTIVITY OF THIOAMIDE AND AMIDE GROUP

Xin-Ying Zhang, Xiao-Yan Li, Xue-Sen Fan,* Xia Wang, Gui-Rong Qu* and Jian-Ji Wang

School of Chemical and Environmental Sciences, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, P. R. China. E-mail: xuesen.fan@yahoo.com; quguir@sina.com

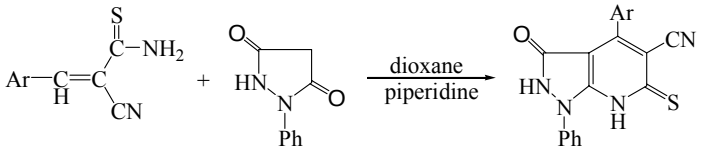
Abstract – A novel and efficient preparation of pyrazolo[3,4-*b*]pyridine (**5**) and pyrazolo[3,4-*b*]pyridin-6-one (**8**) derivatives from the condensation of arylidenecyanothioacetamide (**1**) or arylidenecyanoacetamide (**7**) with 5-amino-3-methyl-1-phenylpyrazole (**4**) in [bmim]BF_4 is reported for the first time. The mechanism for the formation of **5** from **1** and **4**, or **8** from **7** and **4**, and the comparison between the reactivity of thioamide group *versus* amide group are briefly discussed.

Room temperature ionic liquids (RTILs) have gained wide popularity for their increasing use in two important fields of chemistry-synthetic and biochemical as greener reaction media due to their unique properties such as non-volatility, non-flammability, excellent chemical and thermal stability, and recyclability. Many chemical transformations have been carried out successfully by employing ionic liquids as "green" substitutes for traditional organic solvents.[1] However, greener technology is generally not enough to justify a new process. For this reason, a goal of ionic liquids is to identify the additional advantages they have over organic solvent. In this regards, how to use RTILs to promote the selectivity of various organic reactions and to dramatically influence the outcome of chemical reactions has also attracted much attention.[2]

In view of the rapidly increasing importance of imidazolium based ionic liquids as novel reaction media, we have been working to explore the use of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) as a recyclable solvent and promoter for greener organic synthesis, especially for the preparation of biologically important heterocyclic compounds from multi-component reactions.[3]

In the meantime, there has been an increasing recognition of the thioamide group as a useful moiety in organic synthesis and comprehensive reviews of the use of thioamides have been published. Thioamides with active α hydrogen atoms, such as 2-cyanothioacetamide, can be condensed with aldehydes to give

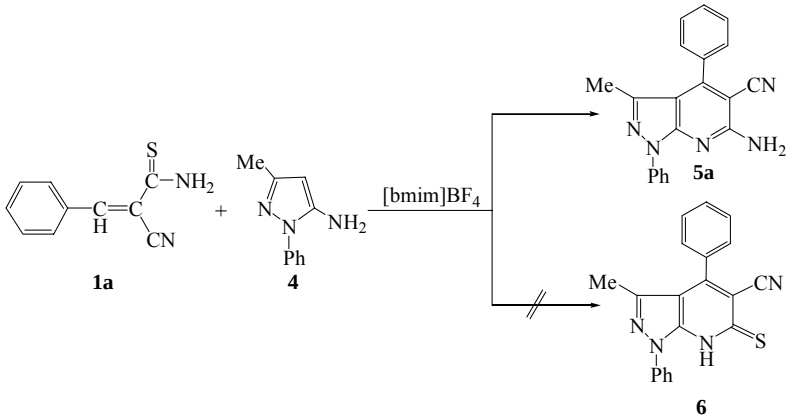
2-cyano-2-enethioamide, which acts as good Michael addition receptor to undergo addition-cyclization reactions to afford the corresponding heterocyclic frameworks.[4] In this regard, Ghattas et al. reported a novel preparation of pyrazolo[3,4-*b*]pyridine-thiones (**3**, Scheme 1) from the reaction of arylidenecyanothioacetamide (**1**) with 1-phenylpyrazolidine-3,5-dione (**2**).[5] This prompted us to develop a new and efficient methodology to obtain another kind of pyrazolo[3,4-*b*]pyridine-thione derivative (**6**, Scheme 2) from benzylidenecyanothioacetamide and 5-amino-3-methyl-1-phenylpyrazole (**4**) by using [bmim]BF_4 as reaction medium and promoter.



1 **2** **3**

Scheme 1

Thus, a mixture of **1a** and **4** was treated with [bmim]BF_4 without any added catalyst. It turned out that at room temperature, the reaction was very reluctant to take place. However, at elevated temperature, TLC analysis showed that a new substance could be formed. It was then observed that when the reaction was run at 80 ºC, all the starting materials were consumed in 6 h and a solid product was formed. It was collected by suction and submitted to identification. It turned out that this product is a pyrazolo[3,4-*b*]pyridine derivative (**5a**, Scheme 2), instead of the expected pyrazolo[3,4-*b*]pyridine-thione (**6**). The structure of **5a** was established on the basis of its spectroscopic data. The ^{1}H NMR spectrum showed a broad singlet at 7.21 ppm (2 protons) most likely due to the NH_2 protons. In addition, ESI MS showed that the molecular weight of this product is 325 rather than 342 for **6**. Finally, the structure of **5a** was proved beyond doubt by comparison with the authentic compound prepared with known procedure.[6]

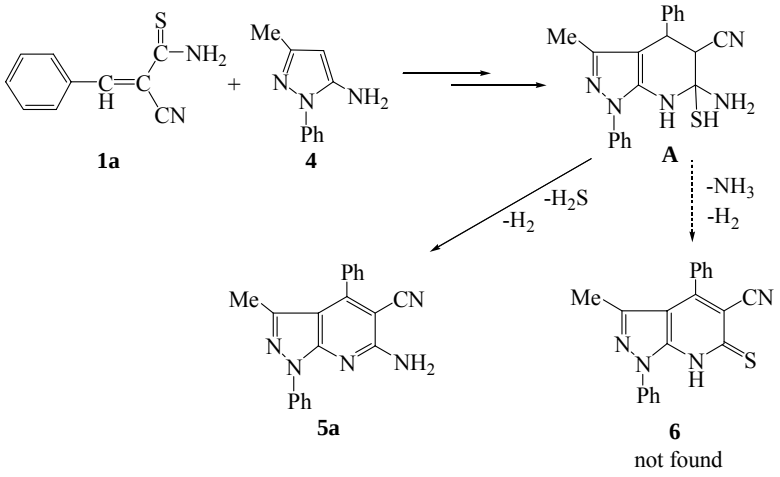


1a **4** **5a** **6**

Scheme 2

A mechanism to account for the formation of **5a** is proposed and outlined in Scheme 3. The reaction was initiated with the Michael addition reaction between **1a** and **4** and then an intramolecular cyclization was followed to give the key intermediate **A**. From intermediate **A**, **5a** is formed by loss of H_2S and

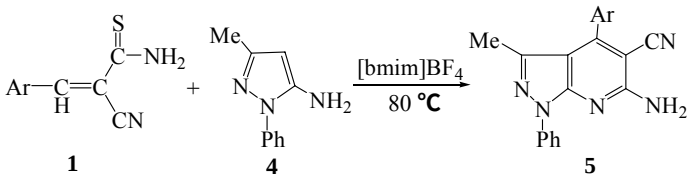
subsequent aromatization through loss of H_2. On the other hand, although loss of NH_3 from **A** and then aromatization to give **6** was theoretically possible, only **5a** was obtained from the process described above, indicating that it is easier for H_2S to be eliminated than NH_3 from intermediate **A**. This is probably due to that anion HS^- is much less basic than H_2N^- and therefore acting as a better leaving group.



Scheme 3

Although the expected pyrazolo[3,4-*b*]pyridine-thione (**6**) was not obtained, the mild condition, high efficiency and green nature of the above procedure make it potentially suitable as a novel alternative for the preparation of pyrazolo[3,4-*b*]pyridine, a very interesting heterocyclic framework with numerous biological activities. Actually, it has been reported that pyridine and fused pyridine moieties present in numerous natural product. In particular, pyrazolo-pyridine derivatives have been found of interest for their various applications as good vasodilators, hypotensive, hypoglycemic, anti-inflammatory, analgesic and antipyretic agents.[7] Pyrazolo[3,4-*b*]pyridine derivatives were usually obtained through condensation and cyclization of aminopyrazole and compounds with active methylene group or α,β-unsaturated compounds.[6,8] However, with those methods, either a combination of several additives and catalysts was employed or volatile solvents were used for the reaction to complete.

Therefore, further efforts were then made to investigate the scope and generality of this process by screening a series of substrates with different substituents on the aryl ring (Scheme 4). The results were listed in Table 1.



Scheme 4

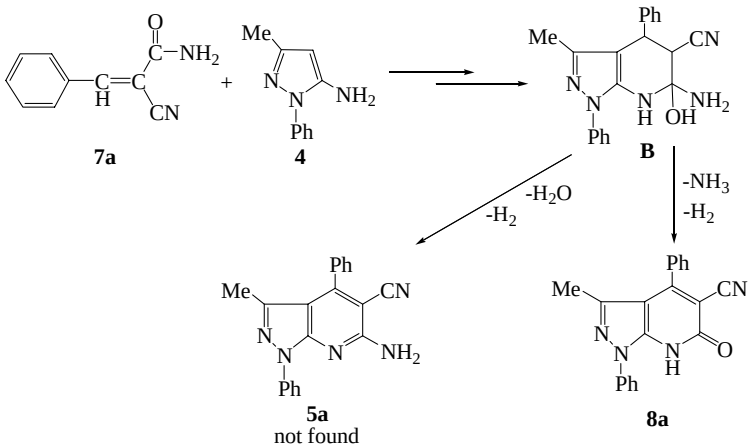
It turned out that various arylidenecyanothioacetamide reacted smoothly with **4** to give product **5** in good to excellent yields. In the mean time, substrates with electron-withdrawing groups usually gave relatively

higher yields in shorter reaction time compared with substrates with electron-donating groups. It should be noted that compared with the reported methodologies, this procedure is of remarkable interest since no added catalysts or volatile organic compounds (VOCs) were needed and the yields are generally good to excellent. All these merits make it a potential alternative for the synthesis of this class of important N-containing heterocyclic compounds.

Table 1. Preparation of compound **5** in [bmim][BF_4]

Entry	Ar	Product	Reaction Time (h)	Temperature (°C)	Yield (%)
1	C_6H_5	**5a**	6	80	84
2	*p*-MeC_6H_4	**5b**	6	80	78
3	*p*-ClC_6H_4	**5c**	6	80	86
4	*p*-BrC_6H_4	**5d**	6	80	85
5	*p*-$NO_2C_6H_4$	**5e**	5	80	92
6	*o*-$NO_2C_6H_4$	**5f**	6	80	79
7	*m*-$NO_2C_6H_4$	**5g**	5	80	89
8	4-pyridyl	**5h**	8	80	80
9	3-pyridyl	**5i**	8	80	78

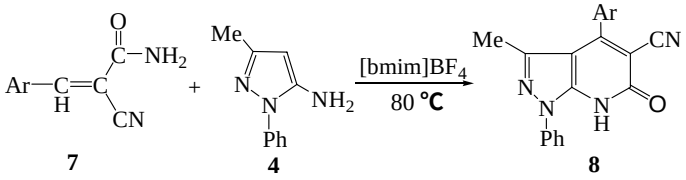
With the above results in hand, we were then interested in the study of the behavior of arylidenecyanoacetamide (**7**) toward **4** in [bmim]BF_4. As shown in Scheme 5, it is reasonable to suggest that if **7a**, instead of **1a**, was treated with **4** under similar condition, intermediate **B** should be formed in the first place. From **B**, there are also two possible routes for the reaction to go further. If it resembles the reaction mode of intermediate **A** shown in Scheme 3, intermediate **B** will dispose a H_2O molecule and then aromatize to give **5a**. On the other hand, it is also possible for intermediate **B** to eliminate an NH_3 molecule and aromatize to afford a pyrazolo[3,4-*b*]pyridin-6-one compound **8a**.



Scheme 5

In order to elucidate this equivocal problem, a mixture of **7a** and **4** was treated with [bmim]BF_4 at 80 °C and monitored by TLC. It turned out that after being stirred for 8 h, the reaction completed and gave a solid product, which was conveniently obtained by suction. Further structural analysis turned out that it is not **5a**, but **8a**. The evidence behind this conclusion is its spectroscopic data and their consistence with that of the authentic sample prepared separately according to literature reference.[6] It should be noted here that by giving **8a** as the final product, the amide group in **7a** demonstrated a different reaction mode as compared to the thioamide group in **1a**. In other words, an NH_3 rather than a H_2O molecule is eliminated from intermediate **B**. The reason behind this observation is most likely that compared with H_2O, NH_3 is a gas and it is much easier for NH_3 to escape from the reaction system and thus drives the reaction to go further in the direction of forming **8a**.

Considering that the above procedure can be developed as a novel approach to pyrazolo[3,4-b]pyridin-6-ones, it was then investigated with regard to the scope and generality of the substrates. Thus, a series of substrates were studied and the results were listed in Table 2.



Scheme 6

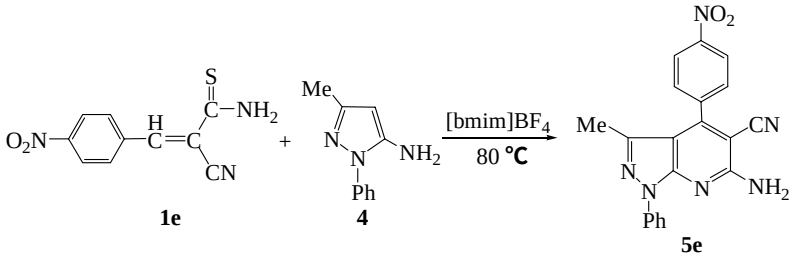
Table 2. Preparation of compound 8 in [bmim][BF_4]

Entry	Ar	Product	Reaction Time (h)	Temperature (°C)	Yield (%)
1	C_6H_5	**8a**	8	80	82
2	*p*-MeC_6H_4	**8b**	10	80	80
3	*p*-$MeOC_6H_4$	**8c**	12	80	78
4	*p*-BrC_6H_4	**8d**	8	80	83
5	*p*-ClC_6H_4	**8e**	8	80	83
6	*p*-$NO_2C_6H_4$	**8f**	7	80	88
7	*m*-$NO_2C_6H_4$	**8g**	7	80	84
8	4-pyridyl	**8h**	10	80	79

As shown in Table 2, under our reaction conditions, substrates bearing either electron-donating substituents or electron-withdrawing substituents underwent the above process smoothly and gave the corresponding product with high yields. Taking its high efficiency, simple operational process, no use of

added catalysts and VOCs, this procedure is advantageous for the preparation of pyrazolo[3,4-*b*]pyridin-6-ones over the literature methods.

On the other hand, as mentioned earlier, one of the goals in ionic liquids is to identify the additional advantages they have over organic solvent besides a greener nature. In this regard, it has been documented that compared with classical organic solvents, reactions carried out in ionic liquids possess the advantages of offering simpler operational process and/or enhanced reactivity and better yields. This was indeed demonstrated by comparing [bmim]BF_4 with several conventional volatile organic solvents including ethanol, toluene and THF. The following is the results (shown in Table 3) of investigations by using **1e** and **4** as model substrates for the preparation of **5e** (Scheme 7).



Scheme 7

Table 3. Preparation of **5e** in different solvents

Entry	Solvent	Temperature (°C)	Product	Reaction Time (h)	Yield (%)
1	[bmim][BF_4]	80	**5e**	5	92
2	EtOH	reflux	**5e**	8	35
3	toluene	80	**5e**	8	20
4	THF	reflux	**5e**	8	40

It is shown in Table 3 that of the four solvents studied, [bmim][BF_4] gave the best result in terms of both reaction time and yield. Moreover, using [bmim][BF_4] as reaction medium made the separation process much easier since in [bmim][BF_4] **5e** is in solid state and can be obtained with high purity through suction. On the other hand, with ethanol, toluene or THF as the reaction medium, it usually gave mixtures and **5e** could only be obtained through column chromatography.

In summary, a novel preparation of pyrazolo-pyridine derivatives has been achieved from the condensation of arylidenecyanothioacetamide or arylidenecyanoacetamide with 5-amino-3-methyl-1-phenylpyrazole in [bmim]BF_4. Compared with the reported methods, the notable features of the procedures presented here include high efficiency, mild conditions, cleaner reaction profiles, simple operation process. In addition, a brief study of the comparison between the reactivity of thioamide group

versus amide group was also conducted. Currently, the search for new applications of thioacetamide and/or acetamide compounds in organic synthesis is under way in our laboratory.

EXPERIMENTAL

Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. ^{1}H NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO-d_6 solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants *J* were given in Hz. Mass spectra were recorded on a Bruker Esquire 3000 mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

General procedure for the preparation of 6-amino-4-aryl-5-cyano-3-methyl-1-phenylpyrazolo-[3,4-*b*]pyridine (5)

To 1 mL of [bmim][BF_4] were added benzylidenecyanothioacetamide (**1**, 1 mmol) and 5-amino-3-methyl-1-phenylpyrazole (**4**, 1 mmol). The reaction mixture was stirred at 80 °C for a certain period of time to complete the reaction (monitored by TLC). Upon completion, the mixture was cooled to rt and 2 mL of 50% EtOH was added. The solid precipitated was collected by suction and rinsed with water and EtOH, and then dried to give **5** with high purity. The ionic liquid layer was dried at 100 °C under reduced pressure to recover the ionic liquid.

General procedure for the preparation of 4-aryl-5-cyano-3-methyl-1-phenyl-7*H*-pyrazolo-[3,4-*b*]pyridin-6-one (8)

To 1 mL of [bmim][BF_4] were added arylidenecyanoacetamide (**7**, 1 mmol) and 5-amino-3-methyl-1-phenylpyrazole (**4**, 1 mmol). The reaction mixture was stirred at 80 °C for a certain period of time to complete the reaction (monitored by TLC). Upon completion, the mixture was cooled to rt and 2 mL of 50% EtOH was added. The solid precipitated was collected by suction and rinsed with water and EtOH, and then dried to give **8** with high purity. The ionic liquid layer was dried at 100 °C under reduced pressure to recover the ionic liquid.

6-Amino-5-cyano-3-methyl-1, 4-diphenyl-pyrazolo[3,4-*b*]pyridine (5a)

White solid. mp 207-208 °C (Lit.,[6] mp 208 °C); ^{1}H NMR (DMSO-d_6): 1.83 (s, 3H, Me); 7.21 (br s, 2H, NH_2); 7.26 (t, 1H, J = 7.2 Hz, Ar-H); 7.45-7.56 (m, 7H, Ar-H); 8.15 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): 14.3, 88.0, 108.1, 116.5, 120.5, 125.6, 128.5, 128.6, 129.0, 129.7, 134.2, 138.9, 143.8, 151.1, 152.6, 159.3; MS (ESI): *m/z* 348 (M^++Na).

6-Amino-5-cyano-3-methyl-4-(4-methylphenyl)-1-phenylpyrazolo[3,4-*b*]pyridine (5b)

White solid. mp 199-201 °C; ^{1}H NMR (DMSO-d_6): 1.86 (s, 3H, Me); 2.40 (s, 3H, Me); 7.16 (br s, 2H, NH_2); 7.26 (t, 1H, J = 7.2 Hz, Ar-H); 7.34-7.40 (m, 4H, Ar-H); 7.47 (t, 2H, J = 8.0 Hz, Ar-H); 8.15 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): 14.4, 21.0, 88.1, 108.1, 116.6, 120.5, 125.6, 128.6, 129.0, 131.3, 139.0, 139.3, 143.9, 151.2, 152.8, 159.3; MS (ESI): *m/z* 362 (M^++Na); Anal. Calcd for $C_{21}H_{17}N_5$: C 74.32, H 5.05, N 20.63; Found C 74.40, H 5.06, N 20.54.

6-Amino-4-(4-chlorophenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine (5c)

White solid. mp 193-194 °C (Lit.,[6] mp 195 °C); ^{1}H NMR (DMSO-d_6): 1.86 (s, 3H, Me); 7.25-7.28 (m, 3H, Ar-H, NH_2); 7.47 (t, 2H, J = 8.0 Hz, Ar-H); 7.56（d, 2H, J = 8.4 Hz, Ar-H); 7.63 (d, 2H, J = 8.4 Hz, Ar-H); 8.14 (d, 2H, J = 7.6 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): 14.4, 88.0, 108.0, 116.4, 120.5, 125.7, 128.7, 129.1, 130.7, 133.0, 134.6, 138.9, 143.7, 151.2, 151.3, 159.3; MS (ESI): *m/z* 382, 384 (M^++Na).

6-Amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine (5d)

White solid. mp 210-213 °C (Lit.,[8d] mp 222-223 °C); ^{1}H NMR (DMSO-d_6): 1.87 (s, 3H, Me); 7.26-7.28 (m, 3H, Ar-H, NH_2); 7.46-7.50 (m, 4H, Ar-H); 7.77 (d, 2H, J = 8.0 Hz, Ar-H); 8.14 (d, 2H, J = 7.6 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): 14.4, 87.9, 107.9, 116.4, 120.6, 123.3, 125.7, 129.1, 130.9, 131.6, 133.4, 138.9, 143.7, 151.2, 151.3, 159.3; MS (ESI): *m/z* 426, 428 (M^++Na).

6-Amino-5-cyano-3-methyl-4-(4-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine (5e)

Yellow solid. mp 216-219 °C (Lit.,[8d] mp 221-223 °C); ^{1}H NMR (DMSO-d_6): 1.82 (s, 3H, Me); 7.27 (t, 1H, J = 7.6 Hz, Ar-H); 7.34 (br s, 2H, NH_2); 7.48 (t, 2H, J = 7.6 Hz, Ar-H); 7.85 (d, 2H, J = 8.8 Hz, Ar-H); 8.14 (d, 2H, J = 7.6 Hz, Ar-H); 8.39 (d, 2H, J = 8.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): 14.3, 87.7, 107.7, 116.1, 120.6, 123.7, 125.7, 129.1, 130.5, 138.8, 140.7, 143.5, 148.4, 150.2, 151.1, 159.2; MS (ESI): *m/z* 393 (M^++Na).

6-Amino-5-cyano-3-methyl-4-(2-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine (5f)

Pale yellow solid. mp 196-197 °C; ^{1}H NMR (DMSO-d_6): 1.76 (s, 3H, Me); 7.30 (t, 1H, J = 6.8 Hz, Ar-H); 7.38 (br s, 2H, NH_2); 7.51 (t, 2H, J = 8.0Hz, Ar-H); 7.75 (d, 1H, J = 7.2 Hz, Ar-H); 7.88-8.01 (m, 2H, Ar-H); 8.17 (d, 2H, J = 7.6 Hz, Ar-H); 8.36 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): 13.5, 87.9, 108.0, 116.1, 120.9, 125.5, 126.2, 129.2, 129.5, 131.8, 132.0, 135.0, 139.2, 143.6, 147.6, 149.4, 151.5, 159.4; MS (ESI): *m/z* 393 (M^++Na); Anal. Calcd for $C_{20}H_{14}N_6O_2$: C 64.86, H 3.81, N 22.69. Found C 64.93, H 3.73, N 22.66.

6-Amino-5-cyano-3-methyl-4-(3-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine (5g)

Pale yellow solid. mp 151-153 °C; ^{1}H NMR (DMSO-d_6): 1.84 (s, 3H, Me); 7.28 (t, 1H, J = 7.6 Hz, Ar-H); 7.31 (br s, 2H, NH_2); 7.49 (t, 2H, J = 8.0 Hz, Ar-H); 7.88 (t, 1H, J = 8.0 Hz, Ar-H); 8.04 (d, 1H, J = 7.2 Hz, Ar-H); 8.15 (d, 2H, J = 8.0 Hz, Ar-H); 8.41-8.43 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): 14.4, 88.1, 108.0, 116.2, 120.6, 123.7, 124.6, 125.7, 129.1, 130.4, 135.4, 135.7, 138.8, 143.5, 147.7, 149.9, 151.2,

159.2; MS (ESI): *m/z* 393 (M^++Na); Anal. Calcd for $C_{20}H_{14}N_6O_2$: C 64.86, H 3.81, N 22.69. Found C 64.97, H 3.75, N 22.61.

6-Amino-5-cyano-3-methyl-4-(pyridin-4-yl)-1-phenylpyrazolo[3,4-*b*]pyridine (5h)

Pale yellow solid. mp 295-296 °C; ^{1}H NMR (DMSO-d_6): 1.86 (s, 3H, Me); 7.29 (t, 1H, J = 7.2 Hz, Ar-H); 7.40 (br s, 2H, NH_2); 7.50 (t, 2H, J = 8.0 Hz, Ar-H); 7.61 (d, 2H, J = 5.6 Hz, C_5H_4N); 8.15 (d, 2H, J = 8.0 Hz, Ar-H); 8.80 (d, 2H, J = 5.6 Hz, C_5H_4N); ^{13}C NMR (DMSO-d_6): 14.6, 87.8, 107.7, 116.4, 120.9, 123.8, 126.2, 129.5, 139.1, 142.4, 143.9, 150.0, 150.3, 151.5, 159.5; MS (ESI): *m/z* 349 (M^++Na); Anal. Calcd for $C_{19}H_{14}N_6$: C 69.92, H 4.32, N 25.75. Found C 69.81, H 4.33, N 25.86.

6-Amino-5-cyano-3-methyl-4-(pyridin-3-yl)-1-phenylpyrazolo[3,4-*b*]pyridine (5i)

White solid. mp 194-196 °C; ^{1}H NMR (DMSO-d_6): 1.88 (s, 3H, Me); 7.30 (t, 1H, J = 7.2 Hz, Ar-H); 7.38 (br s, 2H, NH_2); 7.51 (t, 2H, J = 7.6 Hz, Ar-H); 7.62-7.65 (m, 1H, C_5H_4N); 8.06 (d, 1H, J = 7.6 Hz, C_5H_4N); 8.17 (d, J = 8.0 Hz, 2H, Ar-H); 8.78-8.79 (m, 2H, C_5H_4N); ^{13}C NMR (DMSO-d_6): 14.8, 88.7, 108.5, 116.7, 120.9, 123.8, 126.1, 129.5, 130.6, 137.0, 139.2, 144.1, 149.1, 149.5, 151.2, 151.5, 159.6; MS (ESI): *m/z* 349 (M^++Na); Anal. Calcd for $C_{19}H_{14}N_6$: C 69.92, H 4.32, N 25.75. Found C 69.98, H 4.25, N 25.76.

5-Cyano-3-methyl -1,4-diphenyl-7*H*-pyrazolo[3,4-*b*]pyridin-6-one (8a)

White solid. mp 134-136 °C (Lit.,[6] mp 183 °C); ^{1}H NMR ($CDCl_3$): 1.54 (s, 3H, Me); 5.41 (br s, 1H, NH); 7.29 (t, J = 7.6 Hz, 1H, Ar-H); 7.44-7.55 (m, 7H, Ar-H); 8.10 (d, J = 8.8 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): 14.2, 94.2, 106.5, 118.7, 121.8, 125.0, 127.8, 128.0, 128.2, 128.6, 135.1, 139.2, 143.8, 152.3, 152.5, 169.9; MS (ESI): *m/z* 349 (M^++Na).

5-Cyano-3-methyl-4-(4- methylphenyl)-1-phenyl-7*H*-pyrazolo[3,4-*b*]pyridin-6-one (8b)

Pale yellow solid. mp 298-300 °C; ^{1}H NMR (DMSO-d_6): 1.93 (s, 3H, Me); 2.40 (s, 3H, Me); 7.33 (t, J = 7.2 Hz, 1H, Ar-H); 7.38 (d, J = 8.0 Hz, 2H, Ar-H); 7.43 (d, J = 8.0 Hz, 2H, Ar-H); 7.52 (t, J = 8.0 Hz, 2H, Ar-H); 8.05(d, J = 7.6 Hz, 2H, Ar-H); 13.05 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.5, 21.1, 109.6, 115.9, 121.4, 126.5, 128.7, 129.1, 129.2, 130.7, 138.3, 139.6, 144.1, 154.1, 163.9; MS (ESI): *m/z* 363 (M^++Na); Anal. Calcd for $C_{21}H_{16}N_4O$: C 74.10, H 4.74, N 16.46. Found C 74.18, H 4.58, N 16.50.

5-Cyano-3-methyl-4-(4-methoxyphenyl)-1-phenyl-7*H*-pyrazolo[3,4-*b*]pyridin-6-one (8c)

white solid. mp 295-297 °C; ^{1}H NMR (DMSO-d_6): 2.00 (s, 3H, Me); 3.86 (s, 3H, OMe); 7.14 (d, J = 8.4 Hz, 2H, Ar-H); 7.36 (t, J = 7.2 Hz, 1H, Ar-H); 7.51-7.57 (m, 4H, Ar-H); 8.08 (d, J = 7.6 Hz, 2H, Ar-H); 13.02 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 17.2, 58.0, 93.9, 112.3, 116.5, 118.5, 124.0, 128.2, 129.1, 131.8, 133.0, 140.9, 146.7, 151.6, 156.5, 163.1, 166.5; MS (ESI): *m/z* 379 (M^++Na); Anal. Calcd for $C_{21}H_{16}N_4O_2$: C 70.77, H 4.53, N 15.72. Found C 70.88, H 4.40, N 15.77.

4-(4-Bromophenyl)-5-cyano-3-methyl-1-phenyl-7*H*- pyrazolo[3,4-*b*]pyridin-6-one (8d)

Pale yellow solid. mp 281-283 °C; ^{1}H NMR (DMSO-d_6) : 1.93 (s, 3H, Me); 7.33 (t, J = 7.2 Hz, 1H, Ar-H); 7.50-7.53 (m, 4H, Ar-H); 7.79 (d, J = 8.4 Hz, 2H, Ar-H); 8.05 (d, J = 8.0 Hz, 2H, Ar-H); 13.15 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.4, 91.3, 109.4, 115.7, 121.4, 123.6, 126.6, 129.2, 130.9, 131.6, 132.8, 138.2, 144.0, 149.1, 152.5, 163.8; MS (ESI): *m/z* 427, 429 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}BrN_4O$: C 59.30, H 3.23, N 13.80. Found C 59.21, H 3.30, N 13.85.

4-(4-Chlorophenyl)-5-cyano-3-methyl-1-phenyl-7*H*- pyrazolo[3,4-*b*]pyridin-6-one (8e)

White solid. mp 276-277 °C (Lit.,[6] mp 278 °C); ^{1}H NMR (DMSO-d_6): 1.93 (s, 3H, Me); 7.33 (t, J = 7.2 Hz, 1H, Ar-H); 7.52 (t, J = 8.0 Hz, 2H, Ar-H); 7.59 (d, J = 8.4 Hz, 2H, Ar-H); 7.65 (d, J = 8.4 Hz, 2H, Ar-H); 8.04 (d, J = 7.6 Hz, 2H, Ar-H); 13.15 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.4, 91.4, 109.5, 115.6, 121.4, 126.6, 128.7, 129.2, 130.7, 132.5, 134.9, 138.2, 144.0, 149.1, 152.5, 163.8; MS (ESI): *m/z* 383, 385 (M^+ +Na).

5-Cyano-3-methyl-4-(4-nitrophenyl)-1-phenyl-7*H*-pyrazolo[3,4-*b*]pyridin-6-one (8f)

Pale yellow solid. mp 291-294 °C (Lit.,[6] mp 308 °C); ^{1}H NMR (DMSO-d_6): 1.91 (s, 3H, Me); 7.35 (t, J = 7.6 Hz, 1H, Ar-H); 7.53 (t, J = 8.0 Hz, 2H, Ar-H); 7.89 (d, J = 8.4 Hz, 2H, Ar-H); 8.05 (d, J = 8.0 Hz, 2H, Ar-H); 8.42 (d, J = 8.4 Hz, 2H, Ar-H); 13.28 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) : 14.4, 88.5, 109.2, 115.4, 121.5, 123.7, 126.7, 129.3, 130.5, 138.2, 140.0, 143.8, 148.5, 151.3, 163.8; MS (ESI): *m/z* 394 (M^+ +Na).

5-Cyano-3-methyl-4-(3-nitrophenyl)-1-phenyl-7*H*-pyrazolo[3,4-*b*]pyridin-6-one (8g)

yellow solid. mp 300-302 °C; ^{1}H NMR (DMSO-d_6): 1.90 (s, 3H, Me); 7.34 (t, J = 7.2 Hz, 1H, Ar-H); 7.53 (t, J = 7.6 Hz, 2H, Ar-H); 7.90 (t, J = 7.6 Hz, 1H, Ar-H); 8.05-8.06 (m, 3H, Ar-H); 8.43-8.47 (m, 2H, Ar-H); 13.25 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.4, 91.5, 109.6, 115.5, 121.4, 123.7, 124.8, 126.6, 129.3, 130.5, 135.1, 135.4, 138.2, 143.8, 147.7, 149.2, 151.0, 163.8; MS (ESI): *m/z* 394 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}N_5O_3$: C 64.69, H 3.53, N 18.86. Found C 64.79, H 3.40, N 18.90.

5-Cyano-3-methyl-1-phenyl-4-(pyridin-4-yl)-7*H*- pyrazolo[3,4-*b*]pyridin-6-one) (8h)

white solid. mp 329-331°C; ^{1}H NMR (DMSO-d_6): 1.94 (s, 3H, Me); 7.37 (t, J = 7.6 Hz, 1H, Ar-H); 7.55 (t, J = 7.6 Hz, 2H, Ar-H); 7.63 (d, J = 4.8 Hz, 2H, C_5H_4N); 8.07 (d, J = 8.0 Hz, 2H, Ar-H); 8.83 (d, J = 4.8 Hz, 2H, C_5H_4N); 13.26 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.6, 91.4, 109.3, 115.7, 121.9, 123.7, 127.0, 129.6, 138.5, 141.9, 144.1, 149.5, 150.4, 151.2, 164.1; MS (ESI): *m/z* 350 (M^+ +Na); Anal. Calcd for $C_{19}H_{13}N_5O$: C 69.71, H 4.00, N 21.39. Found C 69.66, H 4.10, N 21.40.

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