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1,8-Diazabicyclo[5.4.0]undec-7-ene Catalyzed Synthesis of Some New 7-Alkyl-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles

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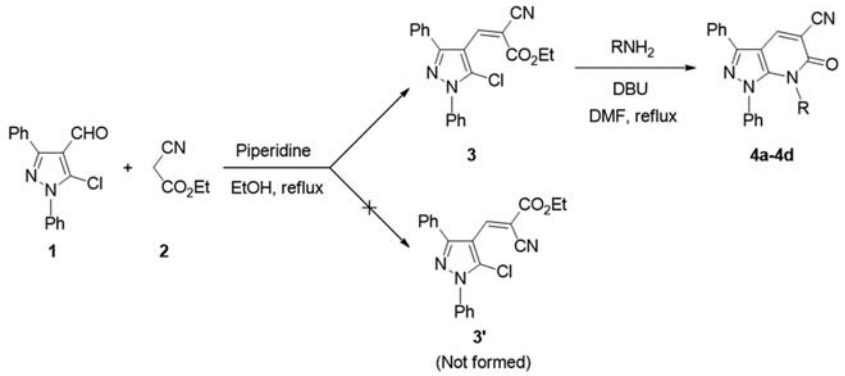
ABSTRACT Starting from 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde, the synthesis of some new bicyclic 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is described. Knoevenagel condensation reaction of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with ethyl cyanoacetate in refluxing ethanol containing a few drops of piperidine afforded the (Z)-ethyl 3-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)-2-cyanoacrylate. Treatment of this compound with primary alkyl amines in the presence of DBU as a catalyst in dimethylformamide at reflux temperature gave new 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles in high yields. All synthetic compounds were characterized on the basis of their spectral and microanalytical data. The correct stereoisomer of the Knoevenagel product was confirmed with comparison of the experimental and calculated ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR chemical shifts using density functional theory calculations at the B3LYP/6-31+G(d,p) level of theory.



KEY WORDS 5-Chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde, Ethyl cyanoacetate, Pyrazolo[3,4-*b*]pyridine, 1,8-Diazabicyclo[5.4.0]undec-7-ene.

INTRODUCTION

In the last few decades, the chemistry of pyrazoles and pyridines has received considerable attention due to their synthetic and effective biological importance. Literature reports had already established that certain pyrazoles exhibit significant biological properties such as antimicrobial,[1] anti-inflammatory,[2] antiviral,[3] antitumor,[4] and antimalarial[5] activities. The success of cyclooxygenase-2 inhibitors containing a pyrazole moiety

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has highlighted the importance of this motif in medicinal chemistry.[6,7] A number of these compounds are also used as potential inhibitors of 5α-reductase,[8] tumor necrosis factor-alpha,[9] interleukin 1 beta,[9] and hMAO-B.[10] On the other hand, the pyridine nucleus can be found in a broad variety of anti-inflammatory,[11] antimicrobial,[12] antiproliferative,[13] antioxidant,[14] anticancer,[14] and some others agents. Some of them have also inhibitory activities against multidrug-resistant tuberculosis,[15] AKT kinase,[16] and IRAK4.[17] Due to the importance of these heterocycles, we became interested in the synthesis of some new heterocyclic compounds containing pyrazole and pyridine scaffolds.

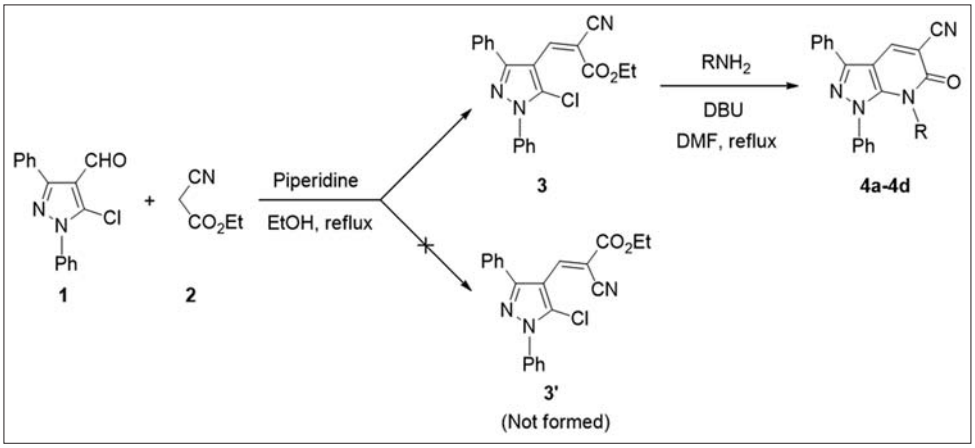
Among various pyrazolopyridine scaffolds, pyrazolo[3,4-*b*]pyridines have been relatively of more interest because of reported interesting biological properties such as antimicrobial,[18] antiplatelet,[19] antiviral,[20] and anticancer[21] activities. Furthermore, a number of these compounds are known as potential inhibitors of c-Met,[22] cyclin-dependent kinase-1,[23] and fibroblast growth factor receptor kinase.[24] A number of methods have been reported for the synthesis of pyrazolo[3,4-*b*]pyridines starting from pyrazole or pyridine moiety.[25-31]

In light of these findings and due to our interest in the synthesis of new heterocyclic compounds,[32-39] in this paper, we wish to report the synthesis of some new 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbonitriles **4a-4d** from the Knoevenagel condensation reaction of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1** with ethyl cyanoacetate **2** followed by reaction with primary alkyl amines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst **[Scheme 1]**.

RESULTS AND DISCUSSION

The starting material 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1** was prepared according to the literature method.[40] Initially, the condensation of this compound with ethyl cyanoacetate **2** was performed in refluxing EtOH containing a few drops of piperidine as catalyst. Monitoring of the reaction with thin-layer chromatography (TLC) showed the formation of a product which was isolated from the reaction mixture as described in experimental section. The ^{1}H nuclear magnetic resonance (NMR) spectrum of the isolated compound in $CDCl_3$ showed a triplet and a quartet at δ = 1.43 and 4.41 ppm with coupling constant (*J* value) of 7.1 Hz for OCH_2 and CH_3 groups, respectively, a sharp singlet at δ = 8.26 ppm belonging to the olefinic proton, and the characteristic signals at δ = 7.48–7.72 ppm for the aromatic protons, confirming the condensation reaction. The appearance of absorption bands for CN and conjugated esteric carbonyl group at 2224, and 1721 cm^{-1}, respectively, is also in accord with the successful Knoevenagel condensation reaction. Furthermore, the ^{13}C NMR spectrum showed the characteristic signals at δ = 14.17, 62.83, 106.81, 111.75, 114.76, 125.39, 128.15, 129.06, 129.31, 129.34, 129.48, 129.67, 131.36, 137.44, 145.62, 153.01, and 162.09 ppm for the aliphatic as well as the SP^2 carbons. Furthermore, the isolated compound gave satisfactory elemental analysis data corresponding to the molecular formula $C_{21}H_{16}ClN_3O_2$. In accord with these data, two stereoisomers **3** (Z) and **3'** (E) are possible for the isolated product **[Scheme 1]**. Unfortunately, however, with the presented above data, the specific stereoisomer cannot be assigned.

To identify the correct isolated stereoisomer, the experimental ^{1}H NMR and ^{13}C NMR chemical shifts of the isolated stereoisomer were compared with the calculated ones for the stereoisomers **3** (Z) and **3'** (E). Calculations have been performed using the density functional theory (DFT) methods as implemented in the Gaussian 03 program package.[41] The B3LYP/6-311+G(d,p) level of theory[42] was used. Initially, the geometries of the stereoisomers **3** (Z) and **3'** (E) were fully optimized that confirmed to have no imaginary frequency of the Hessian. Then, the optimized geometries, as shown in **Figure 1**, were employed for computing the chemical shifts. ^{1}H and ^{13}C NMR chemical shifts were predicted with respect to tetramethylsilane (TMS), where the gauge-independent atomic orbital method was used.[43] The obtained results are given in **Table 1**, where the atoms' positions are numbered as in **Figure 1**. As can be seen, the experimental chemical shifts are closer to the calculated values for the compound **3** (Z) than the **3'** (E). Based on the good consistency and less deviation between the experimental and DFT chemical shifts of the



Scheme 1: Synthesis of new 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles

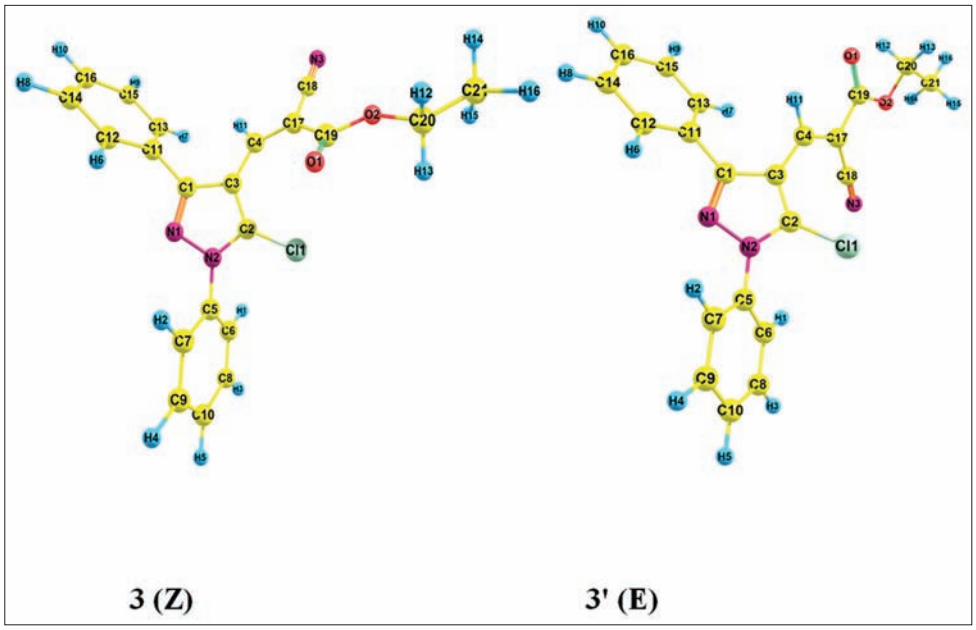


Figure 1: Optimized geometries for compounds 3 (Z) and 3' (E)

Table 1: The comparison of calculated ^{1}H and ^{13}C NMR chemical shifts data (δ, ppm) with those obtained from the experimental spectroscopy

Compound	Position of H		^{1}H NMR		Deviation $\lvert\delta_{exp} - \delta_{cal}\rvert$	Position of C		^{13}C NMR		Deviation $\lvert\delta_{exp} - \delta_{cal}\rvert$
			Calculated	Experimental				Calculated	Experimental	
3 (Z)	H1–H10	arom-H	7.76–8.18	7.48–7.72	0.28–0.46	C1–C18	C-SP^2	102.08–150.48	106.81–153.01	2.53–4.73
3' (E)	H1–H10	arom-H	7.84–8.49		0.36–0.77	C1–C18	C-SP^2	99.76–149.67		3.34–7.05
3 (Z)	H11	CH=C	8.59	8.26	0.33	C19	C=O	159.42	162.09	2.67
3' (E)	H11	CH=C	9.00		0.74	C19	C=O	158.60		3.49
3 (Z)	H12–H13	CH_2	4.41	4.41	0.00	C20	CH_2	62.80	62.83	0.03
3' (E)	H12–H13	CH_2	4.59		0.18	C20	CH_2	63.32		0.49
3 (Z)	H14–H16	CH_3	1.57	1.43	0.14	C21	CH_3	12.80	14.17	1.37
3' (E)	H14–H16	CH_3	1.70		0.27	C21	CH_3	12.98		1.19

NMR: Nuclear magnetic resonance

stereoisomer **3** (Z), it seems that the isolated stereoisomer is similar to compound **3** (Z) not to **3'** (E).

The compound **3** was then allowed to react with primary alkyl amines in refluxing EtOH in the absence of catalyst. Little conversion was observed under these conditions and a large amount of the starting material was recovered. Next, the reaction was investigated in the presence of a base as a catalyst. Among the various tested catalyst-solvent systems, the reaction was efficiently proceeded using DBU as a catalyst in dimethylformamide (DMF) as solvent at reflux temperature. The spectral and microanalytical data are in accordance with the inclusion of the ester moiety in the cyclization process, leading to high yields of the products which were identified as 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **4a-4d**. The inclusion of the ester moiety in the cyclization process is another proof that the isolated stereoisomer in the first reaction is **3** (Z) and not **3'** (E) **[Scheme 1]**. In the stereoisomer **3'** (E), the esteric carbonyl group has no proper orientation for the involvement in the cyclization process.

^{1}H and ^{13}C NMR and Fourier-transform infrared (FT-IR) spectral data along with elemental analysis were used to confirm the structure of the products **4a-4d**. For example, as shown in **Figure 2**, the ^{1}H NMR spectrum of compound **4a** showed the disappearance of the triplet and quartet signals belonging to OEt moiety of the precursor **3** at δ = 1.43 and 4.41 ppm and the appearance of a singlet for new methyl group at δ = 3.28 ppm. The sharp signal at δ = 8.26 ppm belonging to the olefinic proton in compound **3** has shifted to δ = 8.39 ppm for the CH in pyridine ring of the product **4a**. Two phenyl groups have also been appeared at δ = 7.50–7.82 ppm with a slight shift in compared with the precursor **3**. The IR spectrum showed the absorption bands at 2226 and 1651 cm^{-1} for CN and amidic carbonyl groups, respectively, confirming the formation of the product **4a**. Furthermore, this compound gave satisfactory ^{13}C NMR spectrum and elemental analysis data corresponding to the molecular

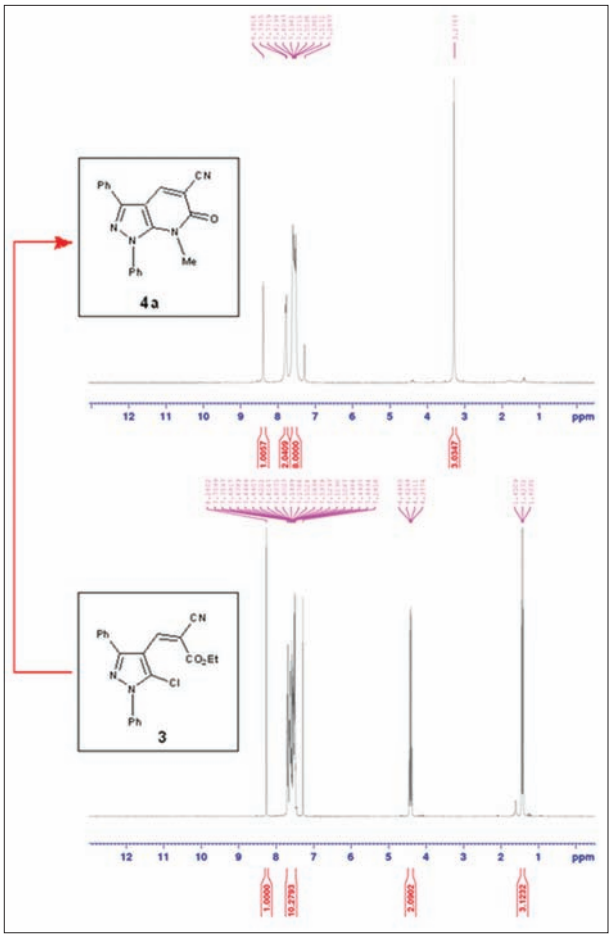


Figure 2: The ^{1}H nuclear magnetic resonance spectra of compounds 3 and 4a in $CDCl_3$

formula $C_{20}H_{14}N_4O$ (experimental section and supporting information).

EXPERIMENTAL SECTION

Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained with KBr disks using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 FT spectrometer in $CDCl_3$ as a solvent and using TMS as internal standard. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

Synthesis of (Z)-ethyl 3-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)-2-cyanoacrylate 3

A mixture of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1** (1.0 mmol) and ethyl cyanoacetate **2** (1.0 mmol) in ethanol (5 mL) in the presence of a few drops of piperidine was heated under reflux for 2 h. The reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature, and the precipitate was filtered off. The crude product was recrystallized from ethanol to give the pure compound **3** as white crystals: Yield 98%, mp 137–138°C; FT-IR (KBr disk, cm^{-1}): υ 2224 (CN), 1721 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.43 (3 H, t, J = 7.1 Hz, CH_3), 4.41 (2 H, q, J = 7.1 Hz, CH_2), 7.48–7.72 (10 H, m, arom-H), 8.26 (1 H, s, olefinic CH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.17, 62.83, 106.81, 111.75, 114.76, 125.39, 128.15, 129.06, 129.31, 129.34, 129.48, 129.67, 131.36, 137.44, 145.62, 153.01, 162.09. Anal. Calcd for $C_{21}H_{16}ClN_3O_2$: C 66.76, H 4.27, N 11.12, found: C 66.98, H 4.39, N 10.97.

General procedure for the synthesis of 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbonitriles 4a-4d

A mixture of (Z)-ethyl 3-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)-2-cyanoacrylate **3** (1.0 mmol) and a primary alkyl amine (1.2 mmol) in DMF (5 mL) in the presence of a few drops of DBU as catalyst was heated under reflux for 3–4 h. On completion of the process, according to TLC, the mixture was cooled to room temperature and the mixture was poured onto cold water (5 mL). The precipitate was collected, washed with water and diethyl ether, and recrystallized from ethanol to give compounds **4a-4d** in high yields.

7-Methyl-6-oxo-1,3-diphenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (4a)

Yellow crystals, yield 90%, mp 288–290°C; FT-IR (KBr disk, cm^{-1}): υ 2226 (CN), 1651 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.28 (3 H, s, NCH_3), 7.50–7.82 (10 H, m, arom-H), 8.39 (1 H, s, olefinic CH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 32.08, 99.29, 104.30, 116.17, 127.73, 127.78, 129.25, 129.62, 129.86, 130.40, 130.54, 138.44, 140.92, 144.77, 148.13, 159.80. Anal. Calcd for $C_{20}H_{14}N_4O$: C 73.61, H 4.32, N 17.17, found: C 73.86, H 4.22, N 17.30.

7-Benzyl-6-oxo-1,3-diphenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (4b)

Yellow crystals, yield 85%, mp 248–249°C; FT-IR (KBr disk, cm^{-1}): υ 2229 (CN), 1658 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.15 (2 H, s, NCH_2), 6.40–7.80 (15 H, m, arom-H), 8.38 (1 H, s, olefinic CH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 46.35, 99.39, 104.53, 116.15, 125.52, 127.62, 127.77, 127.89, 128.00, 128.62, 129.16, 129.26, 129.89, 130.37, 134.10, 138.00, 141.42, 144.17, 148.15, 159.86. Anal. Calcd for $C_{26}H_{18}N_4O$: C 77.59, H 4.51, N 13.92, found: C 77.36, H 4.62, N 14.06.

6-Oxo-7-phenethyl-1,3-diphenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (4c)

Yellow crystals, yield 88%, mp 258–260°C; FT-IR (KBr disk, cm^{-1}): υ 2227 (CN), 1653 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.75 (2 H, t, J = 8.3 Hz, CH_2), 4.11 (2 H, t, J = 8.3 Hz, NCH_2), 6.71–7.76 (2 H, m, arom-H), 7.17–7.21 (3 H, m, arom-H), 7.517.80 (10 H, m, arom-H), 8.41 (1 H, s, olefinic CH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 33.83, 45.02, 99.58, 104.52, 116.10, 126.92, 127.78, 128.08, 128.54, 129.28, 129.90, 130.00, 130.31, 130.83, 136.60, 138.80, 140.86, 144.29, 148.27, 159.68. Anal. Calcd for $C_{27}H_{20}N_4O$: C 77.87, H 4.84, N 13.45, found: C 77.60, H 4.71, N 13.59.

7-Octyl-6-oxo-1,3-diphenyl-6,7-dihydro-1H-pyrazolo[3,4-b] pyridine-5-carbonitrile (4d)

Yellow crystals, yield 80%, mp 142–144°C; FT-IR (KBr disk, cm^{-1}): υ 2223 (CN), 1656 (C=O); ^{1}H NMR (300 MHz,

$CDCl_3$, ppm): δ 0.78 (2 H, sex, J = 6.9 Hz, CH_2), 0.89 (3 H, t, J = 7.1 Hz, CH_3), 1.01–1.49 (10 H, m, $5CH_2$), 3.83 (2 H, t, J = 8.0 Hz, NCH_2), 7.50–7.81 (10 H, m, arom-H), 8.37 (1 H, s, olefinic CH); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.09, 22.57, 26.23, 27.96, 28.86, 29.00, 31.65, 43.55, 99.49, 104.41, 116.21, 127.75, 128.06, 129.24, 129.67, 129.82, 130.38, 130.74, 138.70, 140.65, 144.37, 148.09, 159.53. Anal. Calcd for $C_{27}H_{28}N_4O$: C 76.39, H 6.65, N 13.20, found: C 76.61, H 6.77, N 13.05.

CONCLUSION

In summary, Knoevenagel condensation reaction of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **1** with ethyl cyanoacetate **2** in the presence of piperidine in ethanol at reflux temperature gave ethyl 3-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)-2-cyanoacrylate **3**. Reaction of this compound with primary alkyl amines in the presence of DBU as a catalyst in refluxing DMF afforded new 7-alkyl-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **4a-4d** in high yields. The structure of the products was confirmed by FT-IR, ^{1}H, and^{13}C NMR spectra and microanalytical data. The comparison of experimental and theoretical ^{1}H and ^{13}C NMR chemical shifts confirmed that the isolated stereoisomer in the first reaction had Z-configuration.

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