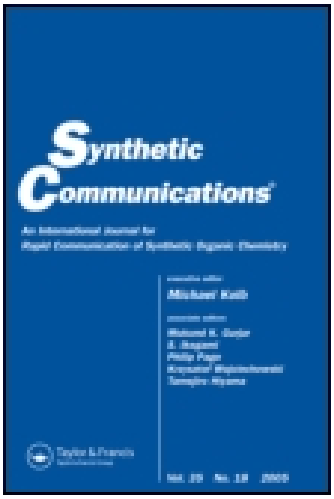

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An Efficient Synthesis of Pyrazolo[3,4-b]pyridine Derivatives in Ionic Liquid

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AN EFFICIENT SYNTHESIS OF PYRAZOLO[3,4-*b*]-PYRIDINE DERIVATIVES IN IONIC LIQUID

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A series of 3-methyl-1,4,6-triaryl-1H-pyrazolo[3,4-b]pyridines was synthesized via the reaction of 3-methyl-1-phenyl-1H-pyrazol-5-amine and α,β-unsaturated ketones in ionic liquid without any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

Keywords: Ionic liquid; pyrazolo[3,4-*b*]pyridine; synthesis

INTRODUCTION

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial, anti-inflammatory and antitumor properties.[1–4] In particular, condensed pyrazoles are known for various biological activities, e.g., pyrazolo[3,4-*b*]pyridines are useful for treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, haemorrhaged stress, drug and alcohol withdrawal symptoms, drug addition and infertility.[5] Pyrazolo[3,4-*b*]pyridine derivatives are generally prepared by reaction of 5-aminopyrazole and substituted α,β-unsaturated nitriles in organic solvent (i.e., ethanol) using triethylamine as catalyst,[6–7] but most of them suffer from drawbacks such as lower yields, and using organic solvent.

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

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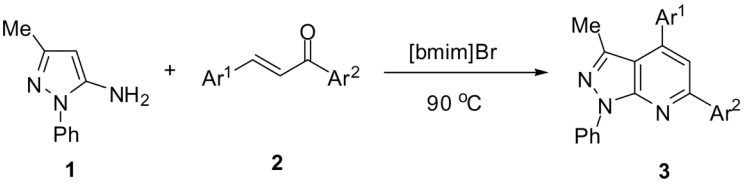


Scheme 1. The synthetic route for the pyrazolo[3,4-*b*]pyridine derivatives **3**.

condensations,[13] Biginelli reactions,[14] Beckmann rearrangements[15] and other reactions.[16] As part of our current studies on the developments of new routes to heterocyclic system in ionic liquid,[17] we herein described a facile synthesis of pyrazolo[3,4-*b*]pyridine derivatives by the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and α,β-unsaturated ketones in ionic liquid [bmim]Br without any catalyst (Scheme 1).

Choosing an appropriate solvent is of crucial important for the successful organic synthesis. To search for the optical solvent, the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** and 1-(4-chlorophenyl)-3-(4-methylphenyl)prop-2-en-1-one **2a** was examined using different solvents, respectively. The results are summarized in Table 1.

As can be seen from Table 1, the best result was obtained when the reaction was carried out in [bmim]Br at 90 °C (Table 1, entry 6). Indeed, the reaction using [bmim]Br proceeded in higher yield and shorter reaction time than that using another ionic liquids as reaction medium. [bmim]Br was chosen as the solvent for all further reactions as it is environmentally friendly and the toxic organic reagents can be avoided. Under these optimized reaction conditions, a series of pyrazolo[3,4-*b*]pyridine derivatives **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 rings of α,β-unsaturated ketones with electron-withdrawing groups (such as halide and nitro groups), but also to α,β-unsaturated ketones with electron-donating groups (such as alkyl and alkoxyl groups). Therefore, we concluded that the

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

Entry	Solvent	Reaction temperature (°C)	Reaction time (h)	Isolated yield (%)
1	acetone	reflux	25	24
2	acetonitrile	reflux	20	42
3	ethanol	reflux	17	59
4	chloroform	reflux	27	34
5	DMF	100	10	83
6	[bmim]Br	90	8.5	90
7	[bmim]BF_4	90	10	62
8	[bmim]PF_6	90	10	71
9	[bmim]Br	r.t.	33	34
10	[bmim]Br	40	23	41
11	[bmim]Br	60	15	61
12	[bmim]Br	80	12	80

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

Entry	Ar^1	Ar^2	Time (h)	Yield (%)
3a	4-$CH_3C_6H_4$	4-ClC_6H_4	8.5	90
3b	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	8	96
3c	4-ClC_6H_4	4-$CH_3OC_6H_4$	9	83
3d	4-ClC_6H_4	3-$NO_2C_6H_4$	9	91
3e	4-BrC_6H_4	4-$CH_3OC_6H_4$	9.5	87
3f	4-FC_6H_4	4-$CH_3OC_6H_4$	9	82
3g	3,4-$Cl_2C_6H_3$	4-$CH_3OC_6H_4$	9	94
3h	3,4-$OCH_2OC_6H_3$	4-ClC_6H_4	8	92
3i	4-ClC_6H_4	4-ClC_6H_4	8.5	92
3j	4-BrC_6H_4	4-ClC_6H_4	8	90
3k	4-BrC_6H_4	Naphthalen-2-yl	13	83
3l	4-$CH_3C_6H_4$	Naphthalen-2-yl	13	80
3m	4-ClC_6H_4	Naphthalen-2-yl	13	85

electronic nature of the substituents of aromatic rings of α,β-unsaturated ketones has no significant effect on this reaction.

In this study, all the products **3** were characterized by mp, IR and ^{1}H NMR spectral data as well as HRMS analysis. The structure of **3j** was further confirmed by X-ray diffraction analysis. The molecular structure of **3j** is shown in Figure 1.

Although the detailed mechanism of above reaction remains not to be fully clarified, the formation of compounds **3** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded via a reaction sequence of Michael addition, cyclization, dehydration and aromatization. First, the Michael addition reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** to α,β-unsaturated ketones **2** give the intermediate product **4**, which on intermolecular cyclization and dehydration gave rise to **5**. In the last step, the intermediate product **5** aromatized to product **3**.

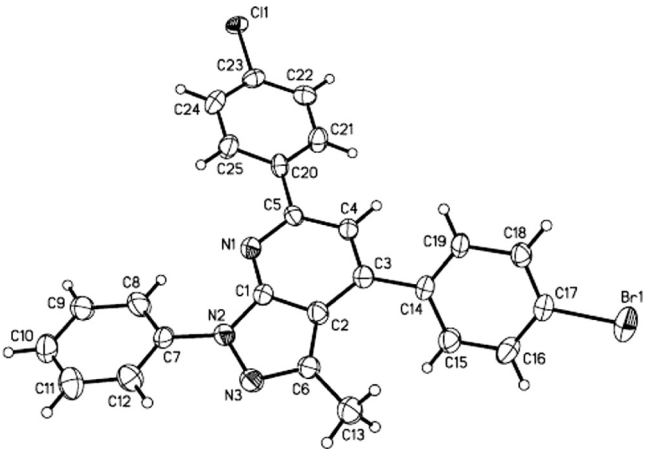
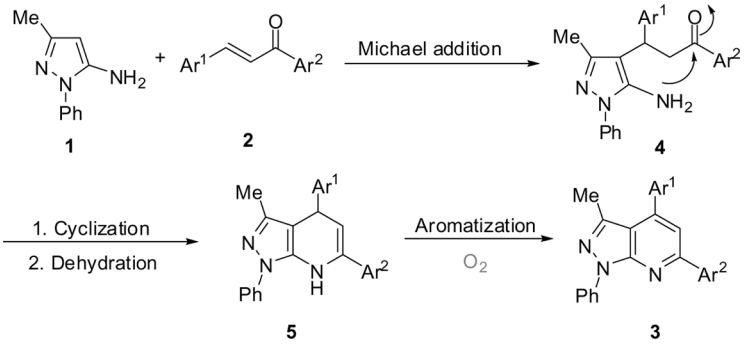


Figure 1. ORTEP diagram of **3j**.



Scheme 2. The mechanistic pathway leading to the pyrazolo[3,4-*b*]pyridine.

In conclusion, we have developed an efficient synthesis of 3-methyl-1,4,6-triaryl-1*H*-pyrazolo-[3,4-*b*]pyridines via the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and α,β-unsaturated ketones in ionic liquid without any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR was measured on a Varian-400 MHz spectrometer in DMSO-d_6 with TMS as internal standard. High resolution mass spectra were obtained using a time-of-flight mass spectrometry (TOF-MS) instrument.

General Procedure for the Preparation of 3-Methyl-1,4,6-triaryl-1*H*-pyrazolo[3,4-*b*]pyridines (3)

A dry 50 mL flask was charged with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** (1 mmol), α,β-unsaturated ketones **2** (1 mmol), and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 90 °C for 8–13 h to complete the reaction (monitored by TLC), then 50 mL H_2O was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give **3**.

SPECTRAL DATA

6-(4-Chlorophenyl)-3-methyl-1-phenyl-4-p-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine (3a)

Mp 155–157 °C; ^1H NMR (DMSO-d_6) δ: 2.27 (3H, s, CH_3), 2.43 (3H, s, CH_3), 7.30–7.40 (3H, m, ArH), 7.55–7.61 (6H, m, ArH), 7.75 (1H, s, ArH), 8.29 (2H, d, $J = 8.4$ Hz, ArH), 8.33 (2H, d, $J = 8.4$ Hz, ArH); IR (KBr) ν: 1595, 1577, 1555, 1513, 1472, 1385, 1345, 1309, 1149, 1093, 1052, 1015, 837, 819, 764, 730 cm^{-1}. HRMS calcd. for $C_{26}H_{20}{}^{35}ClN_3$, m/z: 409.1346 (M^+); Found, m/z: 409.1345.

6-(4-Methoxyphenyl)-3-methyl-1-phenyl-4-p-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine (3b)

Mp 135–136 °C; ^{1}H NMR (DMSO-d_6) δ: 2.26 (3H, s, CH_3), 2.24 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 7.10 (2H, d, $J = 8.0$ Hz, ArH), 7.34 (1H, t, $J = 7.2$ Hz, ArH), 7.40 (2H, d, $J = 7.6$ Hz, ArH), 7.55–7.62 (4H, m, ArH), 7.68 (1H, s, ArH), 8.25 (2H, d, $J = 8.4$ Hz, ArH), 8.38 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr) ν: 1598, 1506, 1475, 1413, 1387, 1349, 1307, 1243, 1173, 1147, 1031, 824, 755, 691 cm^{-1}. HRMS calcd. for $C_{27}H_{23}N_3O$, m/z: 405.1841 (M^+); Found, m/z: 405.1843.

4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3c)

Mp 134–136 °C; ^{1}H NMR (DMSO-d_6) δ: 2.24 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 7.09 (2H, d, $J = 8.4$ Hz, ArH), 7.34 (1H, t, $J = 7.2$ Hz, ArH), 7.57–7.65 (4H, m, ArH), 7.71 (3H, d, $J = 8.4$ Hz, ArH), 8.24 (2H, d, $J = 8.4$ Hz, ArH), 8.36 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr) ν: 1600, 1575, 1559, 1505, 1490, 1387, 1351, 1243, 1185, 1145, 1088, 1053, 1028, 829, 756, 686 cm^{-1}. HRMS calcd. for $C_{26}H_{20}{}^{35}ClN_3O$, m/z: 425.1295 (M^+); Found, m/z: 425.1294.

4-(4-Chlorophenyl)-3-methyl-6-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3d)

Mp 194–196 °C; ^{1}H NMR (DMSO-d_6) δ: 2.28 (3H, s, CH_3), 7.38 (1H, t, $J = 7.2$ Hz, ArH), 7.62 (2H, t, $J = 8.0$ Hz, ArH), 7.68 (2H, d, $J = 8.0$ Hz, ArH), 7.77 (2H, d, $J = 8.0$ Hz, ArH), 7.85 (1H, t, $J = 8.0$ Hz, ArH), 8.00 (1H, s, ArH), 8.32–8.36 (3H, m, ArH), 8.75 (1H, d, $J = 7.6$ Hz, ArH), 9.06 (1H, s, ArH); IR (KBr) ν: 1596, 1577, 1554, 1526, 1503, 1344, 1290, 1246, 1154, 1145, 1092, 1014, 841, 761, 690 cm^{-1}. HRMS calcd. for $C_{25}H_{17}{}^{35}ClN_4O_2$, m/z: 440.1040 (M^+); Found, m/z: 440.1053.

4-(4-Bromophenyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3e)

Mp 138–140 °C; ^{1}H NMR (DMSO-d_6) δ: 2.26 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 7.10 (2H, d, $J = 8.0$ Hz, ArH), 7.34 (1H, t, $J = 7.6$ Hz, ArH), 7.58–7.66 (4H, m, ArH), 7.74 (1H, s, ArH), 7.79 (2H, d, $J = 7.6$ Hz, ArH), 8.26 (2H, d, $J = 8.4$ Hz, ArH), 8.37 (2H, d, $J = 8.4$ Hz, ArH); IR (KBr) ν: 1598, 1574, 1555, 1506, 1474, 1414, 1350, 1239, 1253, 1173, 1035, 1011, 855, 825, 752 cm^{-1}. HRMS calcd. for $C_{26}H_{20}{}^{79}BrN_3O$, m/z: 469.0790 (M^+); Found, m/z: 469.0795.

4-(4-Fluorophenyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3f)

Mp 131–132 °C; ^{1}H NMR (DMSO-d_6) δ: 2.25 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 7.10 (2H, d, $J = 8.8$ Hz, ArH), 7.34 (1H, t, $J = 7.6$ Hz, ArH), 7.42 (2H, t, $J = 8.8$ Hz, ArH), 7.60 (2H, t, $J = 8.0$ Hz, ArH), 7.73–7.76 (3H, m, ArH), 8.26 (2H, d, $J = 8.4$ Hz, ArH), 8.37 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr) ν: 1598, 1565,

1510, 1476, 1416, 1350, 1308, 1241, 1173, 1158, 1032, 837, 756, 699 cm^{-1}. HRMS calcd. for $C_{26}H_{20}FN_3O$, m/z: 409.1590 (M^+); Found, m/z: 409.1589.

4-(3,4-Dichlorophenyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3g)

Mp 168–169 °C; ^1H NMR (DMSO-d_6) δ: 2.26 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 7.11 (2H, d, $J = 8.4$ Hz, ArH), 7.35 (1H, t, $J = 7.6$ Hz, ArH), 7.60 (2H, t, $J = 7.2$ Hz, ArH), 7.69 (1H, d, $J = 8.4$ Hz, ArH), 7.80 (1H, s, ArH), 7.84 (1H, d, $J = 8.4$ Hz, ArH), 8.03 (1H, s, ArH), 8.27 (2H, d, $J = 8.4$ Hz, ArH), 8.36 (2H, d, $J = 8.4$ Hz, ArH); IR (KBr) v: 1599, 1575, 1506, 1469, 1416, 1390, 1347, 1298, 1251, 1237, 1180, 1145, 1129, 1038, 833 cm^{-1}. HRMS calcd. for $C_{26}H_{19}{}^{35}Cl_2N_3O$, m/z: 459.0905 (M^+); Found, m/z: 459.0900.

4-(3,4-Methylenedioxylphenyl)-6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3h)

Mp 162–164 °C; ^1H NMR (DMSO-d_6) δ: 2.34 (3H, s, CH_3), 6.16 (2H, s, OCH_2O), 7.13 (1H, d, $J = 7.6$ Hz, ArH), 7.18 (1H, d, $J = 8.0$ Hz, ArH), 7.33–7.37 (2H, m, ArH), 7.58–7.62 (4H, m, ArH), 7.78 (1H, s, ArH), 8.31–8.35 (4H, m, ArH); IR (KBr) v: 1592, 1560, 1505, 1473, 1443, 1385, 1247, 1227, 1094, 1037, 1010, 837, 809, 762, 693 cm^{-1}. HRMS calcd. for $C_{26}H_{18}{}^{35}ClN_3O_2$, m/z: 439.1088 (M^+); Found, m/z: 439.1091.

4,6-Bis(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3i)

Mp 159–160 °C; ^1H NMR (DMSO-d_6) δ: 2.26 (3H, s, CH_3), 7.35 (1H, t, $J = 7.2$ Hz, ArH), 7.58–7.62 (4H, m, ArH), 7.66 (2H, d, $J = 7.6$ Hz, ArH), 7.73 (2H, d, $J = 7.2$ Hz, ArH), 7.82 (1H, s, ArH), 8.30–8.34 (4H, m, ArH); IR (KBr) v: 1596, 1552, 1497, 1403, 1342, 1309, 1089, 1052, 858, 832, 766 cm^{-1}. HRMS calcd. for $C_{25}H_{17}{}^{35}Cl_2N_3$, m/z: 429.0800 (M^+); Found, m/z: 429.0797.

4-(4-Bromophenyl)-6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3j)

Mp 167–168 °C; ^1H NMR (DMSO-d_6) δ: 2.26 (3H, s, CH_3), 7.35 (1H, t, $J = 7.2$ Hz, ArH), 7.57–7.61 (4H, m, ArH), 7.65 (2H, d, $J = 8.4$ Hz, ArH), 7.74–7.75 (1H, m, ArH), 7.77–7.80 (2H, m, ArH), 8.28–8.34 (4H, m, ArH); IR (KBr) v: 1595, 1576, 1553, 1505, 1473, 1413, 1344, 1151, 1091, 1070, 1011, 856, 823, 756 cm^{-1}. HRMS calcd. for $C_{25}H_{17}{}^{79}Br^{35}ClN_3$, m/z: 473.0294 (M^+); Found, m/z: 473.0291.

4-(4-Bromophenyl)-3-methyl-6-(naphthalen-3-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3k)

Mp 158–159 °C; ^1H NMR (DMSO-d_6) δ: 2.28 (3H, s, CH_3), 7.37 (1H, t, $J = 7.6$ Hz, ArH), 7.58–7.66 (4H, m, ArH), 7.70 (2H, d, $J = 7.6$ Hz, ArH), 7.82

(2H, d, $J = 8.4$ Hz, ArH), 7.97–8.01 (2H, m, ArH), 8.09 (2H, d, $J = 8.4$ Hz, ArH), 8.40–8.48 (3H, m, ArH), 8.88 (1H, s, ArH); IR (KBr) *v*: 1597, 1577, 1549, 1503, 1487, 1418, 1159, 1070, 1011, 857, 830, 812, 753, 691 cm^{-1}. HRMS calcd. for $C_{29}H_{20}{}^{79}BrN_3$, *m/z*: 489.0841 (M^+); Found, *m/z*: 489.0840.

3-Methyl-6-(naphthalen-3-yl)-1-phenyl-4-p-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine (3l)

Mp 172–174 °C; ^1H NMR (DMSO-d_6) δ: 2.30 (3H, s, CH_3), 2.46 (3H, s, CH_3), 7.37 (1H, t, $J = 7.6$ Hz, ArH), 7.43 (2H, d, $J = 8.0$ Hz, ArH), 7.62–7.66 (6H, m, ArH), 7.98–8.00 (2H, m, ArH), 8.08–8.11 (2H, m, ArH), 8.41–8.49 (3H, m, ArH), 8.88 (1H, s, ArH); IR (KBr) *v*: 1600, 1579, 1554, 1503, 1436, 1418, 1363, 1161, 1055, 814, 778, 751 cm^{-1}. HRMS calcd. for $C_{30}H_{23}N_3$, *m/z*: 425.1892 (M^+); Found, *m/z*: 425.1892.

4-(4-Chlorophenyl)-3-methyl-6-(naphthalen-3-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3m)

Mp 163–165 °C; ^1H NMR (DMSO-d_6) δ: 2.29 (3H, s, CH_3), 7.38 (1H, t, $J = 7.6$ Hz, ArH), 7.59–7.70 (6H, m, ArH), 7.76–7.80 (2H, m, ArH), 7.99–8.02 (2H, m, ArH), 8.08–8.11 (2H, m, ArH), 8.40–8.43 (2H, m, ArH), 8.46–8.50 (1H, m, ArH), 8.87–8.90 (1H, m, ArH); IR (KBr) *v*: 1598, 1578, 1558, 1506, 1491, 1412, 1197, 1147, 1089, 854, 834, 814, 756 743 cm^{-1}. HRMS calcd. for $C_{29}H_{20}{}^{35}ClN_3$, *m/z*: 445.1346 (M^+); Found, *m/z*: 445.1346.

Crystal Data for 3j

$C_{25}H_{17}BrClN_3$; $M = 474.78$, colorless block crystals, $0.60 \times 0.30 \times 0.20$ mm, monoclinic, space group $P2_1/c$, $a = 15.023(3)$, $b = 6.6109(10)$, $c = 21.924(4)$ Å, $\beta = 102.019(4)°$, $V = 2129.7(6)$ Å^3, $Z = 4$, $Dc = 1.481$ g cm^{-3}. $F(000) = 960$, $\mu(MoK\alpha) = 2.073$ mm^{-1}. Intensity data were collected on Rigaku Mercury diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71070$ Å) using ω scan mode with $3.02° < \theta < 25.35°$. 3786 unique reflections were measured and 3067 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.1040$ and $wR = 0.2767$.

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