Microwave-Assistant Synthesis, Crystal Structure and Fungicidal Activity of 3-Chloro-2-hydrazinylpyridine

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A pyridine derivative *i.e.*, 3-chloro-2-hydrazinylpyridine (C₅H₆N₃Cl) was synthesized under microwave irradiation and its structure was studied by X-ray diffraction and ¹H NMR. The crystals are monoclinic, space group *p*2₁/*c* with *a* = 11.6276 (14), *b* = 3.8924 (5), *c* = 13.9558 (17) Å, α = 90.00, β = 103.447 (6), γ = 90.00°, *V* = 614.31(13) Å³, *Z* = 4, *F*₍₀₀₀₎ = 296, *D*_c = 1.552 g/cm³, μ = 0.52 cm⁻¹, the final *R* = 0.0623 and *wR* = 0.1897. A total of 7008 reflections were collected, of which 1406 were independent (*R*_{int} = 0.0544). The fungicidal activity of this compound was also studied.

Key Words: Microwave assistant synthesis, Crystal structure, Biological activity.

INTRODUCTION

In recent years, heterocyclic compounds had received considerable attentions because of their important biological activity¹. So the synthesis of broader spectrum and highly bioactive compounds becomes the mainstream in the medicinal and agriculture chemistry field². Pyridine derivatives also exhibited excellent property, such as nicotinate mononucleotide adenylyltransferase inhibitor³, antifungal activity⁴, antiinflammatory activity⁵, antimicrobial activities⁶, anticancer activity⁷, antiviral activity⁸, cholesterol absorption inhibitors⁹. Microwave technique has been widely used for a variety of organic reactions, such as Claisen, heterocyclic synthesis, oxidation, hydrolysis, esterification, etherification, *etc.*

In order to search for new compounds with good biological activity, a pyridine compound was synthesized under microwave irradiation. Their structures are confirmed by ¹H NMR and single crystal. The preliminary biological tests show that these compounds had moderate fungicidal activity.

EXPERIMENTAL

Melting points determined by a Yanaco MP-241 apparatus and uncorrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as KBr tablets. ¹H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as internal standard and CDCl₃ as solvent. Crystallographic data of the compound collected on a BRUCKER CCD SMART diffractometer. All chemicals were of AR grade.

Crystal structure determination: The crystal of 3-chloro-2-hydrazinylpyridine with dimensions of 0.12 mm × 0.08 mm × 0.06 mm was mounted on a Rigaku Saturn CCD area-detector diffractometer with a graphite-monochromated MoK α radiation (λ = 0.71073 Å) by using a phi and scan modes at 294(2) K in the range of 3.1° ≤ θ ≤ 27.7°. The crystal belongs to monoclinic system with space group *P*2₁/*C* and crystal parameters of *a* = 11.6276(14) Å, *b* = 3.8924(5) Å, *c* = 13.9558(17) Å, α = 90° β = 103.447(6)°, γ = 90°, *V* = 614.31(13) Å³ *D*_c = 1.552 g/cm³. The absorption coefficient μ = 0.520 mm⁻¹ and *Z* = 4. The structure was solved by direct methods with SHELXS-97 and refined by the full-matrix least squares method on *F*² data using SHELXL-97. The empirical absorption corrections were applied to all intensity data. H atom of N-H was initially located in a difference Fourier map and were refined with the restraint *U*iso(H) = 1.2 *U*eq(N). Other H atoms were positioned geometrically and refined using a riding model, with *d*(C-H) = 0.93-0.97 Å and *U*iso(H) = 1.2 *U*eq(C) or 1.5 *U*eq(Cmethyl). The final full-matrix least squares refinement gave *R* = 0.0623 and *wR* = 0.1897.

Synthesis: A modified two-phase procedure was applied. 2,3-Dichloropyridine (0.2 mol), hydrazine hydrate (85 %, 1 mol) were put in a sealed vial, then refluxed at 100°C for 0.5 h under microwave irradiation. The product was obtained after filtrated. ¹H NMR (CDCl₃, 400 MHz): 3.97 (br. s, 2H, NH₂), 6.21 (br. s, 1H, NH), 6.64 (m, 1H, pyridyl-H), 7.47 (d, 1H, *J* = 7.6 Hz, pyridyl-H), 8.09 (d, 1H, *J* = 4.9 Hz, pyridyl-H).

Scheme-I: Synthesis route of 3-chloro-2-hydrazinylpyridine

RESULTS AND DISCUSSION

Synthesis and spectroscopic properties: The title compound was synthesized under conventional and microwave irradiation condition. If the title compound was synthesized under refluxing, it should react with ethanolic solution of NH_2NH_2 for 72 h. Surprisingly, it was synthesized for 0.5 h under microwave irradiation. ^1H NMR spectrum of the title compound tested shows 3.97 and 6.21 is the peak of NH_2 and NH , respectively. The 6.647.478.09 can be assigned to the three CH of pyridine. The melting point is according to the reference.

Structure of the title compound: Crystallographic and refinement parameters are given in Table-1. The selected bond lengths and bond angles listed in Tables 2-4, respectively. The structure was solved by direct methods. Anisotropic displacement parameters were applied to all nonhydrogen atoms in full-matrix least-square refinements based on F^2 . The hydrogen atoms were set in calculated positions with a common fixed isotropic thermal parameter.

TABLE-1
CRYSTAL DATA AND STRUCTURE
REFINEMENT FOR THE TITLE COMPOUND

Items	Values
Empirical formula	$\text{C}_5\text{H}_6\text{N}_3\text{Cl}$
Formula weight	143.58
Crystal system	monoclinic
Space group	$p2_1/c$
Unit cell dimensions	
a (Å)	11.6276(14)
b (Å)	3.8924(5)
c (Å)	13.9558(17)
Unit cell angles (°)	
α	90
β	103.447(6)
γ	90
Volume (Å ³)	614.31(13)
Z	4
Temperature (K)	296(2)
Wavelength (Å)	0.71073
Calculated density (g/cm ³)	1.552
Absorption coefficient (mm ⁻¹)	0.520
$F_{(000)}$	296
Theta range for data collection (°)	1.80-27.72
Reflections collected	7008
Independent reflections	1406 [$R_{\text{int}} = 0.0544$]
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0623$, $wR_2 = 0.1897$

The molecular structure and atom labels are shown in Fig. 1. The one-dimensional linework of hydrogen bonds (dashed lines) is illustrated in Fig. 2, respectively.

In Table-3, the results indicate that the lengths of three C-N bond C5-N3, C1-N2 and N3-C1 are 1.348(5), 1.365(4) and 1.335(4) Å, respectively, which are all longer than those in the single heterocycle ring. However, the C5-N3, C1-N2

TABLE-2
SELECTED BOND LENGTHS [Å] FOR THE TITLE COMPOUND

Bond lengths	X-Ray crystal	Bond lengths	X-Ray crystal
C(1)-C(2)	1.740(3)	N(2)-H(2A)	0.86
N(3)-C(1)	1.335(4)	C(2)-C(3)	1.357(5)
N(3)-C(5)	1.348(5)	C(4)-C(5)	1.369(6)
N(1)-N(2)	1.403(4)	C(4)-C(3)	1.389(6)
N(1)-H(1A)	0.86	C(4)-H(4A)	0.93
N(1)-H(1B)	0.86	C(5)-H(5A)	0.93
C(1)-N(2)	1.365(4)	C(3)-H(3A)	0.93
C(1)-C(2)	1.412(4)	—	—

TABLE-3
SELECTED BOND ANGLES [°] FOR THE TITLE COMPOUND

Bond angles	X-Ray crystal	Bond angles	X-Ray crystal
C(1)-N(3)-C(5)	118.1(3)	C(3)-C(2)-Cl(1)	120.9(3)
N(2)-N(1)-H(1A)	120	C(1)-C(2)-Cl(1)	118.6(2)
N(2)-N(1)-H(1B)	120	C(5)-C(4)-C(3)	118.4(3)
H(1A)-N(1)-H(1B)	120	C(5)-C(4)-H(4A)	120.8
N(3)-C(1)-N(2)	118.4(3)	C(3)-C(4)-H(4A)	120.8
N(3)-C(1)-C(2)	120.7(3)	N(3)-C(5)-C(4)	123.8(3)
N(2)-C(1)-C(2)	121.0(3)	N(3)-C(5)-H(5A)	118.1
C(1)-N(2)-N(1)	121.5(3)	C(4)-C(5)-H(5A)	118.1
C(1)-N(2)-H(2A)	119.3	C(2)-C(3)-C(4)	118.6(3)
N(1)-N(2)-H(2A)	119.3	C(2)-C(3)-H(3A)	120.7
C(3)-C(2)-C(1)	120.5(3)	C(4)-C(3)-H(3A)	120.7

TABLE-4
SELECTED BOND ANGLES [°] TORSIONAL
ANGLES (°) FOR THE TITLE COMPOUND

Bond angles	X-Ray crystal
C(5)-N(3)-C(1)-N(2)	-177.6(3)
C(5)-N(3)-C(1)-C(2)	0.4(5)
N(3)-C(1)-N(2)-N(1)	-9.2(5)
C(2)-C(1)-N(2)-N(1)	172.8(3)
N(3)-C(1)-C(2)-C(3)	-0.3(5)
N(2)-C(1)-C(2)-C(3)	177.7(3)
N(3)-C(1)-C(2)-Cl(1)	178.4(3)
N(2)-C(1)-C(2)-Cl(1)	-3.6(5)
C(1)-N(3)-C(5)-C(4)	-0.1(5)
C(3)-C(4)-C(5)-N(3)	-0.3(6)
C(1)-C(2)-C(3)-C(4)	-0.2(6)
Cl(1)-C(2)-C(3)-C(4)	-178.8(3)
C(5)-C(4)-C(3)-C(2)	0.5(6)

Fig. 1. Molecular structure of 3-chloro-2-hydrazinylpyridine

Fig. 2. The two-dimensional network of hydrogen bonds (dashed lines)

and N3-C1 are longer than the general C=N double bond length of 1.27 Å. The N1-N2 bond lengths is 1.403(4) Å. The bond angles of pyridine ring vary from 118.4(3) to 121.5(3)° with the average of 120°.

The title compound has an extensive network of hydrogen bonding involving the two acceptor atoms N. In the ac plane, they are linked together by N(1)-H(1C)···N(2)# 2, N(1)-H(1B)···N(3)# 2 hydrogen bonds. This hydrogen-bonding sequence is repeated to form a ring. The ring has two N atoms at the vertices, leading to a hydrogen-bond network defining cyclic motifs denoted $R_2^2(6)$. The vertices are shared with neighbouring decagon to form an infinite two-dimensional network of hydrogen bonds in the ac plane.

Bioassay of fungicidal activities: Fungicidal activity of title compounds against *Gibberella zeae* (Schwein.) Petch., *Alternaria solani* (Ellis et Martin) Jones et Grout., *Cercospora arachidicola*, *Botryosphaeria berengeriana* f.sp. *piricola* (Nose) koganezawa et Sakuma, *Fusarium oxysporum* f.sp. *cucumerinum*, were determined according the reference. At the dose of 50 µg/mL, the title compounds display moderate fungicidal activity against *Gibberella zeae* (Schwein.) Petch. (32 %), *Alternaria solani* (Ellis et Martin) Jones et Grout. (44 %), *Cercospora arachidicola* (18 %), *Botryosphaeria berengeriana* f.sp. *piricola* (Nose) koganezawa et Sakuma (51 %), *Fusarium oxysporum* f.sp. *cucumerinum* (21 %), respectively.

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