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ORIGINAL PAPER

Synthesis, Crystal Structure and Antibacterial Activity of 5-Bromonicotinic Acid [1-(4-Chlorophenyl)methylidene] hydrazide Monohydrate Methanol Solvate

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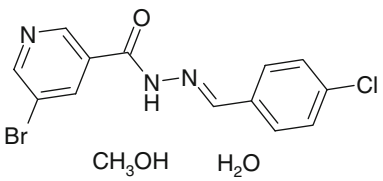
Abstract The compound 5-bromonicotinic acid [1-(4-chlorophenyl)methylidene]hydrazide monohydrate methanol solvate, derived from the condensation reaction of 5-bromonicotinic acid hydrazide with 4-chlorobenzaldehyde in a methanol solution, was synthesized and characterized by elemental analysis, IR spectrum, ^{1}H NMR and X-ray single crystal determination. The compound crystallizes in the triclinic space group $P-1$ with unit cell dimensions $a = 6.9360(14)$ Å, $b = 10.070(2)$ Å, $c = 12.267(3)$ Å, $\alpha = 84.39(3)°$, $\beta = 86.10(3)°$, $\gamma = 80.50(3)°$, $V = 839.8(3)$ Å^3, $Z = 2$, $R_1 = 0.0724$, and $wR_2 = 0.1720$. X-ray structure determination reveals that the compound has a *trans* configuration with respect to the C=N double bond or C–N single bond. In the crystal structure, molecules are linked through intermolecular O–H···N, O–H···O, and C–H···O hydrogen bonds, forming layers parallel to the *ab* plane. The preliminary biological tests show that the compound has excellent antibacterial activity.

Keywords Synthesis · Crystal structure · Schiff base · Hydrogen bonds · Antibacterial activity

Introduction

The condensation reaction of aromatic aldehydes with primary amines has been shown to offer an easy and inexpensive way of forming a variety of Schiff base compounds. These Schiff base compounds exhibit a wide range of biological activities and applications [1–4]. Hydrazones possessing the azomethine –NHN=CH– groups, have been demonstrated to possess antibacterial, anticonvulsant, antitubercular, and antitumor activities [5–7]. Recently, a pair of hydrazones derived from 3-hydroxybenzohydrazide and 3-alkoxysalicylaldehyde with antibacterial activities have been reported [8]. The results indicate that such compounds show potent antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and *Pseudomonas aeruginosa*. As a continuous work, in this paper, the author reports the synthesis, crystal structure and antibacterial activity of a new Schiff base compound, 5-bromonicotinic acid [1-(4-chlorophenyl)methylidene]hydrazide monohydrate methanol solvate (see the following Scheme).



Experimental

Materials and Measurements

All the starting materials and reagents were obtained commercially and were used as received. Elemental analyses were determined on an Elemental Vario EL III elemental analyzer. Infrared spectra were measured as KBr pellets on a Nicolet Magna 750 FT-IR spectrophotometer in the range 4,000–400 cm^{-1}. The ^{1}H NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer with tetramethylsilane as the internal reference.

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Synthesis of 5-Bromonicotinic Acid [1-(4-Chlorophenyl) methylidene]hydrazide Monohydrate Methanol Solvate

5-Bromonicotinic acid hydrazide (1.0 mmol, 216.0 mg) and 4-chlorobenzaldehyde (1.0 mmol, 140.6 mg) were dissolved in a methanol solution (80 ml). The mixture was stirred at room temperature for 10 min to give a clear yellow solution. Yellow needle-like crystals of the compound, suitable for X-ray single crystal structural determination, were formed at the bottom of the vessel on slow evaporation of the solvent in air for a week. The crystals were isolated, washed three times with methanol and dried in air. Yield 317.0 mg (81.7%). Analysis calculated for $C_{14}H_{15}BrClN_3O_3$: C, 43.27; H, 3.89; N, 10.81%; found: C, 43.03; H, 3.96; N, 10.72%. Selected IR data (KBr, cm^{-1}): 3,582 (w), 3,437 (w), 3,065 (w), 2,931 (w), 2,862 (w), 1,645 (s), 1,635 (s), 1,280 (s), 755 (s). ^1H NMR data (DMSO-d6, ppm): $\delta = 7.53$ (s, 1H), 7.55 (s, 1H), 7.78 (s, 1H), 7.93 (s, 1H), 8.42 (s, 1H), 8.49 (s, 1H), 8.92 (d, 1H), 9.03 (d, 1H), 12.11(s, 1H).

Crystallography

X-ray single crystal diffraction measurement was carried out at 298(2) K on a Bruker Smart 1000 CCD area diffractometer equipped with a graphite-monochromatic Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å) for data collection. The unit cell dimensions were obtained with the least-squares refinements and the structure was solved by direct methods with SHELXTL-97 package [9]. The final refinement was performed by full-matrix least-squares methods with anisotropic thermal parameters for the non-hydrogen atoms on F^2. Atoms H1, H2A and H2B were located in a difference Fourier map and refined isotropically, with the U_{iso}(H) values fixed at 0.08 $Å^2$, and with N–H distance restrained to 0.90(1) Å, O–H distances restrained to 0.85(1) Å, and H···H distance restrained to 1.37(2) Å. Other H atoms were placed in the calculated positions and constrained to ride on their parent atoms. Multi-scan absorption correction was applied by using the SADABS program [10]. The crystallographic data for the complex are summarized in Table 1. Selected bond lengths and bond angles are listed in Table 2. Hydrogen bonding interactions are listed in Table 3. Crystallographic data for the complex has been deposited with the Cambridge Crystallographic Data Centre (CCDC 665052).

Table 1 Crystal data and refinement parameters for the compound

CCDC	665052
Molecular formula	$C_{14}H_{15}BrClN_3O_3$
Molecular weight	388.65
Crystal system	Triclinic
Space group	$P-1$
Temperature (K)	298(2)
a (Å)	6.9360(14)
b (Å)	10.070(2)
c (Å)	12.267(3)
α (°)	84.39(3)
β (°)	86.10(3)
γ (°)	80.50(3)
V ($Å^3$)	839.8(3)
Z	2
D_{calc} (g cm^{-3})	1.537
Crystal dimensions (mm); colour	0.27 × 0.23 × 0.22; yellow
Absorption coefficient (mm^{-1})	2.621
Radiation λ	Mo Kα (0.71073 Å)
T_{min}/T_{max}	0.538/0.596
Reflections measured	6,870
Range/indices (h, k, l)	−8, 8; −12, 12; −15, 15
θ limit (°)	1.67–26.49
Total no. of unique data	3,437 [$R_{int} = 0.0479$]
No. of observed data, $I > 2\sigma(I)$	1,714
No. of variables	210
No. of restraints	4
Goodness of fit on F^2	0.916
R_1, wR_2 [$I \geq 2\sigma(I)$][a]	0.0724, 0.1720
R_1, wR_2 (all data)[a]	0.1398, 0.2069

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$

Antibacterial Tests

The bacterial subcultures for *E. coli*, *P. aeruginosa*, *S. typhi* and *S. aureus* were obtained from the Dalian Medical University. A standard inoculum was introduced onto the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 7.0 mm in diameter were sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration (5,000 μg/cm^3 in DMSO) of the compound were placed in nutrient agar medium. Solvent and growth controls were maintained. The plates were inverted and incubated for 24 h at 37 °C. Ciprofloxacin was used as a standard. The inhibition zones were measured and compared with the control. Minimum inhibitory concentration (MIC) was determined by broth dilution technique. The nutrient broth, which contained logarithmic serially twofold diluted amount of the compound and the control, was inoculated with approximately 1×10^6 CFU/cm^3 of actively dividing bacterial cells. The cultures were incubated for 24 h at 37 °C and the growth was monitored visually and spectrophotometrically.

Table 2 Bond distances (Å) and angles (°) for the compound

Bond distances			
Br1–C3	1.879(6)	Cl1–C11	1.753(6)
O1–C6	1.226(7)	O3–C14	1.363(10)
N1–C6	1.355(7)	N1–N2	1.389(6)
N2–C7	1.270(7)	N3–C4	1.327(8)
N3–C5	1.332(7)	C1–C2	1.389(8)
C1–C5	1.392(8)	C1–C6	1.496(8)
C2–C3	1.375(8)	C3–C4	1.381(8)
C7–C8	1.464(8)	C8–C9	1.389(8)
C8–C13	1.395(8)	C9–C10	1.399(8)
C10–C11	1.374(9)	C11–C12	1.349(9)
C12–C13	1.397(8)		
Bond angles			
C6–N1–N2	118.5(5)	C7–N2–N1	115.1(5)
C4–N3–C5	117.5(5)	C2–C1–C5	117.3(5)
C2–C1–C6	126.1(5)	C5–C1–C6	116.7(5)
C3–C2–C1	118.6(5)	C2–C3–C4	119.8(6)
C2–C3–Br1	121.4(5)	C4–C3–Br1	118.7(4)
N3–C4–C3	122.6(6)	N3–C5–C1	124.2(6)
O1–C6–N1	122.3(5)	O1–C6–C1	121.1(5)
N1–C6–C1	116.7(5)	N2–C7–C8	121.9(6)
C9–C8–C13	118.6(5)	C9–C8–C7	122.0(5)
C13–C8–C7	119.4(6)	C8–C9–C10	120.0(6)
C11–C10–C9	119.4(6)	C12–C11–C10	122.1(6)
C12–C11–Cl1	119.3(5)	C10–C11–Cl1	118.6(5)
C11–C12–C13	119.0(6)	C8–C13–C12	121.0(6)

Results and Discussion

The compound was obtained in high yield as air stable yellow needle-like crystals from the methanol solution. It is soluble in methanol, ethanol, acetonitrile, and DMSO, insoluble in water and chloroform.

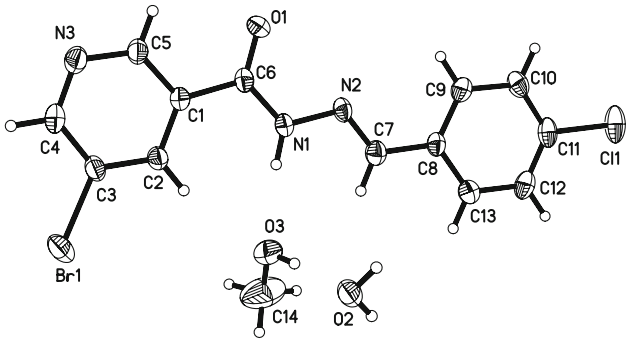

Fig. 1 Molecular structure of the compound. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii; numbering according to Table 2

Crystal Structure Description

Figure 1 gives perspective view of the compound with the atomic labeling system. The compound consists of a Schiff base molecule, a lattice methanol molecule and a lattice water molecule. The Schiff base molecule is nearly coplanar, with mean deviation from plane of 0.0323 Å. The dihedral angle between the benzene ring and the pyridine ring is 3.0(5)°. All the bond lengths in the compound are within normal ranges [11], and comparable to those of the similar compounds [8, 12, 13]. The C7=N2 bond length of 1.270(7) Å confirms it as a double bond. The C6–N1 bond length of 1.355(7) Å and the N1–N2 bond length of 1.389(6) Å are relatively short, suggesting some degree of delocalization in the acetohydrazide system. The torsion angles C8–C7–N2–N1, C7–N2–N1–C6, and N2–N1–C6–C1 are 0.4(5), 0.1(5), and 1.5(5)°, respectively.

In the crystal structure of the compound, the lattice water molecules are linked to the Schiff base molecules through the intermolecular hydrogen bonds of O2–H2A···N2, O2–H2A···O1, O2–H2B···N3 and C9–H9···O2. The methanol molecules are linked to the Schiff base molecules through the intramolecular hydrogen bonds of

Table 3 Distances (Å) and angles (°) involving hydrogen bonding of the compound

D–H···A	D(D–H) (Å)	D(H···A) (Å)	D(D···A) (Å)	∠(D–H···A) (°)
O2–H2A···N2$^{\#1}$	0.85(5)	2.37(4)	3.099(7)	145(6)
O2–H2A···O1$^{\#1}$	0.85(5)	2.19(4)	2.889(6)	139(5)
N1–H1···O3	0.90(5)	1.96(5)	2.862(7)	173(7)
O2–H2B···N3$^{\#2}$	0.85(3)	2.01(4)	2.865(7)	175(7)
O3–H3···O2	0.82	1.87	2.685(8)	173
C2–H2···O3	0.93	2.32	3.220(8)	162
C5–H5···O1	0.93	2.41	2.761(8)	102
C7–H7···O3	0.93	2.59	3.374(8)	142
C9–H9···O2$^{\#1}$	0.93	2.56	3.447(8)	159

Symmetry transformations used to generate the equivalent atoms: #1 $1 - x$, $1 - y$, $1 - z$; #2 x, $1 + y$, z

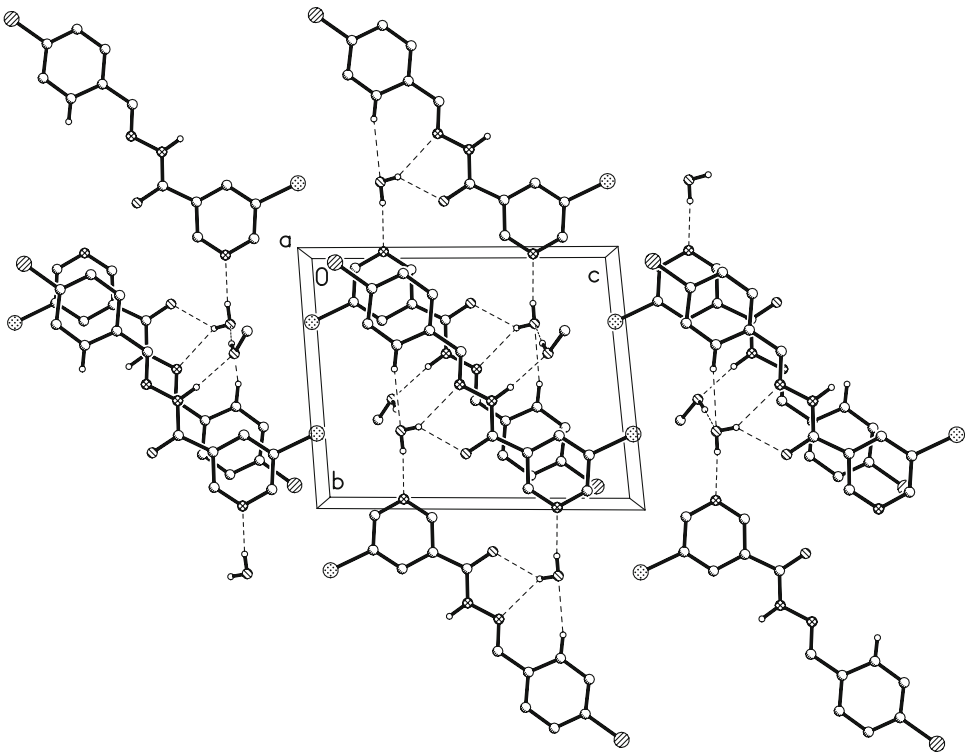

Fig. 2 Molecular packing of the compound, viewed along the *a* axis. Hydrogen bonds are shown as *dashed lines*

N1–H1···O3, C2–H2···O3 and C7–H7···O2. The lattice water and methanol molecules are linked together by intramolecular hydrogen bonds of O3–H3···O2. All the hydrogen bonds link the molecules forming layers parallel to the *ab* plane (Fig. 2).

Antibacterial Results

The preliminary antibacterial tests show that the compound exhibits excellent antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. aureus*, with the inhibition zone, respectively, of 9.3, 13.2, and 10.7 mm, but exhibits weak antibacterial activity against *S. typhi*, with the inhibition zone of 2.3 mm. It is very interesting that the compound does not affect the *S. typhi* bacteria, which do not agree with those reported in the previously reported paper [8] further work needs to be done to investigate the problem.

Supplementary Material

CCDC-665052 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge at http://www.ccdccam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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