SYNTHESIS, CHARACTERIZATION AND CRYSTAL STRUCTURES OF BENZOHYDRAZONE COMPOUNDS DERIVED FROM 5-METHYLSALICYLALDEHYDE

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ABSTRACT

A series of three new benzohydrazone derivatives, *N'*-(2-hydroxy-5-methylbenzylidene)-4-methylbenzohydrazide (1), *N'*-(2-hydroxy-5-methylbenzylidene)-4-hydroxybenzohydrazide (2), and *N'*-(2-hydroxy-5-methylbenzylidene)-4-dimethylaminobenzohydrazide (3), were prepared and characterized by elemental analysis, ¹H and ¹³C NMR, and single crystal X-ray diffraction. Compound (1) crystallizes in the monoclinic space group *C2/c* with unit cell dimensions *a* = 27.421(1) Å, *b* = 9.9843(4) Å, *c* = 24.302(1) Å, β = 119.416(2)°, *V* = 5795.7(5) Å³, *Z* = 16, *R*₁ = 0.0520, and *wR*₂ = 0.1172. Compound (2) crystallizes in the orthorhombic space group *Pna2₁* with unit cell dimensions *a* = 9.511(2) Å, *b* = 9.866(2) Å, *c* = 13.871(3) Å, *V* = 1301.6(5) Å³, *Z* = 4, *R*₁ = 0.0342, and *wR*₂ = 0.0912. Compound (3) crystallizes in the monoclinic space group *C2/c* with unit cell dimensions *a* = 26.957(2) Å, *b* = 10.0612(9) Å, *c* = 25.526(2) Å, β = 114.405(3)°, *V* = 6304.5(10) Å³, *Z* = 16, *R*₁ = 0.0532, and *wR*₂ = 0.1079. X-ray diffraction indicated that the benzohydrazone molecules of the compounds display *trans* configuration with respect to the C=N double bonds. The crystal structures of the compounds are stabilized by hydrogen bonds and weak $\pi \cdots \pi$ interactions.

Keywords Benzohydrazone · 5-methylsalicylaldehyde · X-ray diffraction · hydrogen bonding · $\pi \cdots \pi$ interaction

INTRODUCTION

Benzohydrazone derivatives with the typical functional groups –CH=N–NH–C(O)– are a kind of important compounds in biological and medical chemistry [1–3]. The compounds are usually synthesized from the condensation reaction between benzohydrazides and carbonyl-containing compounds. In the past decade, a number of benzohydrazone derivatives have been synthesized and investigated for their structures and biological applications [4–6]. Detailed study on the crystal structures seems to be essential for the understanding of the activities and applications of the compounds. However, to the best of our knowledge, benzohydrazone compounds derived from 5-methylsalicylaldehyde have seldom been reported. In this paper, the author reports the synthesis, characterization, and crystal structures of three new benzohydrazone derivatives, *N'*-(2-hydroxy-5-methylbenzylidene)-4-methylbenzohydrazide (1), *N'*-(2-hydroxy-5-methylbenzylidene)-4-hydroxybenzohydrazide (2), and *N'*-(2-hydroxy-5-methylbenzylidene)-4-dimethylaminobenzohydrazide (3), from the reaction of 5-methylsalicylaldehyde with various substituted benzohydrazides.

EXPERIMENTAL

Materials and Measurements

5-Methylsalicylaldehyde, 4-methylbenzohydrazide, 4-hydroxybenzohydrazide, and 4-dimethylaminobenzohydrazide were purchased from Aldrich. Methanol was commercially available and used without further purification. Elemental analyses (C, H and N) were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer. ¹H and ¹³C NMR spectra were obtained from solution in DMSO-*d*₆ with Me₄Si as internal standard using a Bruker AVANCE 500 MHz analyzer.

Synthesis of (1)

5-Methylsalicylaldehyde (1.0 mmol, 0.136 g) and 4-methylbenzohydrazide (1.0 mmol, 0.150 g) were dissolved in methanol (20 mL). The mixture was stirred at room temperature for 30 min to give colorless solution. After keeping the solution in air for a few days, colorless block-shaped single crystals, suitable for X-ray diffraction, were formed. The crystals were isolated by filtration, washed with methanol and dried in air. Yield 0.18 g (67%). ¹H NMR (ppm): δ : 2.32–2.35 (d, 6H), 6.92 (d, 1H), 7.09 (d, 1H), 7.41–7.53 (m, 3H), 7.93 (d, 2H), 8.72 (s, 1H), 10.62 (s, 1H), 12.23 (s, 1H). ¹³C NMR (ppm): δ : 21.5, 116.7, 118.6, 127.3, 129.2, 129.7, 130.7, 131.2, 133.0, 140.9, 145.8, 159.0, 162.9.

Synthesis of (2)

Using 5-methylsalicylaldehyde and 4-hydroxybenzohydrazide (1.0 mmol, 0.152 g), and following exactly the same procedure as that described for (1), colorless block-shaped single crystals of (2) were obtained. Yield 0.22 g (81%). ¹H NMR (ppm): δ : 2.33 (s, 3H), 6.85–6.92 (m, 3H), 7.09 (d, 1H), 7.45 (s, 1H), 7.87 (d, 2H), 8.73 (s, 1H), 10.55 (s, 1H), 10.73 (s, 1H), 11.87 (s, 1H). ¹³C NMR (ppm): δ : 21.5, 115.8, 116.7, 118.6, 125.1, 128.8, 130.7, 131.6, 133.0, 145.8,

158.7, 161.2, 163.0.

Synthesis of (3)

Using 5-methylsalicylaldehyde and 4-dimethylaminobenzohydrazide (1.0 mmol, 0.179 g), and following exactly the same procedure as that described for (1), colorless block-shaped single crystals of (3) were obtained. Yield 0.23 g (75%). ¹H NMR (ppm): δ : 2.33 (s, 3H), 3.07 (s, 6H), 6.89–6.95 (m, 3H), 7.09 (d, 1H), 7.46 (s, 1H), 7.62 (d, 2H), 8.73 (s, 1H), 10.67 (s, 1H), 12.05 (s, 1H). ¹³C NMR (ppm): δ : 21.5, 42.2, 111.3, 116.7, 118.6, 121.9, 130.5, 131.6, 133.0, 145.8, 153.7, 163.0.

X-ray crystallography

Suitable single crystals were carefully selected under a microscope. Crystal data for the compounds were collected on a Bruker SMART APEX II-CCD diffractometer at 298(2) K using graphite monochromated Mo K α radiation (λ = 0.71073 Å). Cell parameters were obtained by the global refinement of the positions of all collected reflections. An empirical absorption correction was applied. The structures were solved by direct method and refined by full-matrix least-squares on *F*² using the SHELXL-97 software [7]. All the non-hydrogen atoms were refined anisotropically. The amino H atoms in the compounds were located from difference Fourier maps and refined isotropically, with N–H distances restrained to 0.90(1) Å. The remaining H atoms were added theoretically. Some relevant crystallographic data and structure determination parameters are summarized in Table 1. Selected bond lengths and angles for the compounds are given in Tables 2.

RESULTS AND DISCUSSION

The compounds were readily prepared by the reaction of equimolar quantities of 5-methylsalicylaldehyde with 4-methylbenzohydrazide, 4-hydroxybenzohydrazide, and 4-dimethylaminobenzohydrazide, respectively, in methanol. The elemental analyses are in agreement with the empirical formulae given by the single crystal X-ray determination (Table 3). Single crystals of the compounds can easily be formed by slow evaporation of their methanol solutions. All the compounds are soluble in methanol, ethanol, acetonitrile, dichloromethane, and chloroform.

Crystal structure description of the compounds

Figs. 1, 2, and 3 give the perspective views of (1), (2), and (3), respectively, with the atomic labeling system. The asymmetric units of compounds (1) and (3) contain two molecules, while that of compound (2) contains only one molecule. All the bond lengths in the compounds are within normal ranges [8], and are comparable to those of the similar benzohydrazone compounds [9–11]. The bond lengths of C7–N1 and C23–N3 (for (1)), C8–N1 (for (2) and (3)), and C25–N4 (for (3)) confirm them as double bonds. The bond lengths of C8–N2 and C24–N4 (for (1)), C9–N2 (for (2) and (3)), C26–N5 (for (3)), and N1–N2 (for all the compounds), N3–N4 (for (1)), and N4–N5 (for (3)) are relatively short, suggesting some degree of delocalization in the acetohydrazide systems.

The dihedral angles between the two benzene rings are 30.3(3)° (molecule A) and 13.6(3)° (molecule B) for (1), 41.1(3)° for (2), and 17.0(3)° (molecule A) and 27.0(3)° (molecule B) for (3). All the molecules of the compounds exist in *trans* configuration with respect to the C=N double bonds of the central methyldene units.

Table 1. Crystal data for the compounds.

Compounds	(1)	(2)	(3)
Color/shape	colorless/block	colorless/block	colorless/block
Empirical formula	C ₁₆ H ₁₆ N ₂ O ₂	C ₁₅ H ₁₄ N ₂ O ₃	C ₁₇ H ₁₉ N ₃ O ₂
Formula weight	268.31	270.28	297.35
Temperature, K	298(2)	298(2)	298(2)
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	C2/c	Pna2 ₁	C2/c
Unit cell dimensions			
<i>a</i> , Å	27.421(1)	9.511(2)	26.957(2)
<i>b</i> , Å	9.9843(4)	9.866(2)	10.0612(9)
<i>c</i> , Å	24.302(1)	13.871(3)	25.526(2)
β , °	119.416(2)		114.045(3)
Volume, Å ³	5795.7(5)	1301.6(5)	6304.5(10)
<i>Z</i>	16	4	16
Density (calculated), g/cm ³	1.230	1.379	1.253
Absorption coefficient, mm ⁻¹	0.082	0.098	0.084
<i>F</i> (000)	2272	568	2528
Crystal size, mm ³	0.27 × 0.25 × 0.23	0.17 × 0.13 × 0.13	0.23 × 0.21 × 0.20
Theta range for data collection, °	2.57–25.50	2.94 – 26.49	2.48 – 25.50
Limiting indices	–33 ≤ <i>h</i> ≤ 33, –11 ≤ <i>k</i> ≤ 12, –29 ≤ <i>l</i> ≤ 29	–11 ≤ <i>h</i> ≤ 11, –12 ≤ <i>k</i> ≤ 12, –15 ≤ <i>l</i> ≤ 17	–32 ≤ <i>h</i> ≤ 31, –12 ≤ <i>k</i> ≤ 11, –30 ≤ <i>l</i> ≤ 30
Reflections collected	119145	9350	33689
Observed reflections [<i>I</i> ≥ 2σ(<i>I</i>)]	5383	2479	5875
Data/restraints/parameters	4421/2/372	2365/2/186	2994/2/410
<i>R</i> _{int}	0.0320	0.0205	0.0885
Goodness-of-fit on <i>F</i> ²	1.171	1.146	1.008
Final <i>R</i> indices [<i>I</i> ≥ 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0520, <i>wR</i> ₂ = 0.1172	<i>R</i> ₁ = 0.0342, <i>wR</i> ₂ = 0.0912	<i>R</i> ₁ = 0.0532, <i>wR</i> ₂ = 0.1079
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0684, <i>wR</i> ₂ = 0.1366	<i>R</i> ₁ = 0.0372, <i>wR</i> ₂ = 0.1021	<i>R</i> ₁ = 0.1411, <i>wR</i> ₂ = 0.1368
Largest diff. peak and hole	0.221, –0.153	0.193, –0.338	0.167, –0.147

In the crystal structure of (1), molecules are linked through intermolecular N–H⋯O and C–H⋯O hydrogen bonds (Table 4), to form 1D chains (Fig. 4). In the crystal structure of (2), molecules are linked through intermolecular O–H⋯O and N–H⋯O hydrogen bonds (Table 4), to form 1D chains (Fig. 5). In the crystal structure of (3), molecules are linked through intermolecular N–H⋯O and C–H⋯O hydrogen bonds (Table 4), to form 1D chains (Fig. 6). Moreover, there are also π -electron ring– π -electron ring interactions in the packing structures of the compounds that are specified in Table 5.

Table 2. Selected bond lengths (Å) and angles (°) for the compounds.

(1)			
Bond distances			
C7-N1	1.275(3)	N1-N2	1.377(2)
N2-C8	1.350(3)	C8-O2	1.226(2)
C23-N3	1.279(2)	N3-N4	1.369(2)
N4-C24	1.352(2)	C24-O4	1.229(2)
Bond angles			
C7-N1-N2	117.8(2)	N1-N2-C8	118.7(2)
N2-C8-O2	122.7(2)	N2-C8-C9	114.1(2)
C23-N3-N4	118.6(2)	N3-N4-C24	118.2(2)
N4-C24-O4	120.9(2)	N4-C24-C25	116.6(2)
(2)			
Bond distances			
C8-N1	1.279(2)	N1-N2	1.376(2)
N2-C9	1.352(2)	C9-O2	1.241(2)
Bond angles			
C8-N1-N2	118.2(1)	N1-N2-C9	118.2(1)
N2-C9-O2	120.9(2)	N2-C9-C10	116.7(2)
(3)			
Bond distances			
C8-N1	1.278(3)	N1-N2	1.372(2)
N2-C9	1.361(3)	C9-O2	1.232(3)
C25-N4	1.276(3)	N4-N5	1.379(2)
N5-C26	1.360(3)	C26-O4	1.231(3)
Bond angles			
C8-N1-N2	117.8(2)	N1-N2-C9	118.7(2)
N2-C9-O2	120.6(2)	N2-C9-C10	115.5(2)
C25-N4-N5	117.3(2)	N4-N5-C26	118.3(2)
N5-C26-O4	122.1(2)	N5-C26-C27	114.5(2)

Table 3. Elemental analysis (%) for the compounds.

	C		H		N	
	Calcd	Found	Calcd	Found	Calcd	Found
(1)	71.6	71.7	6.0	6.0	10.4	10.5
(2)	66.7	66.5	5.2	5.3	10.4	10.2
(3)	68.7	68.5	6.4	6.3	14.1	14.2

Table 4. Hydrogen-bond geometry (Å, °) of the compounds

<i>D</i> –H... <i>A</i>	<i>d</i> (<i>D</i> –H) (Å)	<i>d</i> (H... <i>A</i>) (Å)	<i>d</i> (<i>D</i> ... <i>A</i>) (Å)	Angle(<i>D</i> – H... <i>A</i>) (°)
(1)				
N4–H4...O2 ⁱ	0.90(1)	2.15(1)	3.025(2)	165(2)
N2–H2...O4 ⁱⁱ	0.90(1)	1.99(1)	2.869(2)	168(2)
O1–H1...N1	0.82	1.88	2.598(2)	145
O3–H3...N3	0.82	1.86	2.581(2)	146
C13–H13...O1 ⁱⁱⁱ	0.93	2.51	3.351(2)	151
C23–H23...O2 ⁱ	0.93	2.58	3.374(2)	143
(2)				
O1–H1...N1	0.82	1.90	2.616(2)	145
O3–H3...O2 ^{iv}	0.82	2.01	2.764(2)	154
N2–H2...O2 ^v	0.90(1)	2.16(1)	3.046(2)	168(3)
(3)				
N5–H5...O2 ⁱ	0.90(1)	2.03(1)	2.925(3)	170(2)
N2–H2...O4 ^{vi}	0.90(1)	2.23(1)	3.102(2)	163(2)
O3–H3...N4	0.82	1.90	2.611(3)	145
O1–H1...N1	0.82	1.87	2.588(3)	146
C8–H8...O4 ^{vi}	0.93	2.59	3.396(3)	146
C23–H23...O1 ⁱ	0.93	2.55	3.448	164

Symmetry codes: i) $-1+x, y, z$; ii) $1+x, 1+y, z$; iii) $2-x, y, 1/2-z$; iv) $2-x, 1-y, -z$; v) $-1/2+x, 1/2-y, z$; vi) $1+x, -1+y, z$.

Table 5. π - π Interactions (Å) of compounds.

(1)			
<i>Cg</i> 1... <i>Cg</i> 3 ^{vii}	4.675(3)	<i>Cg</i> 2... <i>Cg</i> 2 ^{viii}	4.918(3)
<i>Cg</i> 3... <i>Cg</i> 3 ^{ix}	4.784(3)		
(2)			
<i>Cg</i> 4... <i>Cg</i> 5 ^x	4.774(3)	<i>Cg</i> 5... <i>Cg</i> 4 ^{xi}	4.975(3)
(3)			
<i>Cg</i> 6... <i>Cg</i> 6 ^{ix}	3.782(3)	<i>Cg</i> 7... <i>Cg</i> 6 ^{ix}	4.738(3)

*Cg*1, *Cg*2 and *Cg*3 are the centroids of the C9–C14, C17–C22 and C25–C30 benzene rings, respectively, in (1). *Cg*4 and *Cg*5 are the centroids of the C1–C6 and C10–C15 benzene rings, respectively, in (2). *Cg*6 and *Cg*7 are the centroids of the C10–C15 and C27–C32 benzene rings, respectively, in (3). Symmetry codes: vii) $1/2+x, 1/2+y, z$; viii) $-x, 1-y, -z$; ix) $-x, y, 1/2-z$; x) $-x, 2-y, -1/2+z$; xi) $1/2-x, -1/2+y, 1/2+z$.

Fig. 1. Molecular structure of (1) showing 30% probability displacement ellipsoids. Intramolecular hydrogen bonds are drawn as dashed lines.

Fig. 2. Molecular structure of (2) showing 30% probability displacement ellipsoids. Intramolecular hydrogen bond is drawn as a dashed line.

Fig. 3. Molecular structure of (3) showing 30% probability displacement ellipsoids. Hydrogen bonds are drawn as dashed lines.

Fig. 4. Molecular packing of (1). Hydrogen bonds are shown as dashed.

Fig. 5. Molecular packing of (2). Hydrogen bonds are shown as dashed lines.

Fig. 6. Molecular packing of (3). Hydrogen bonds are shown as dashed lines.

Fig. 7. IR spectrum of (1).

Fig. 8. IR spectrum of (2).

Fig. 9. IR spectrum of (3).

IR spectra

IR spectra of the compounds (1), (2) and (3) are shown in Figures 7, 8 and 9, respectively. The characteristic intense bands in the range 1648 cm⁻¹ for (1) and (2), and 1605 cm⁻¹ for (3) were generated by the $\nu(\text{C}(\text{O})-\text{NH}-\text{C}=\text{N})$ vibrations. In the spectra of the compounds, there were broad absorptions in the range 3350–3470 cm⁻¹, which can be attributed to the hydrogen-bonded phenol groups. The sharp bands at 3209 cm⁻¹ for (1), 3215 cm⁻¹ for (2), and 3227 cm⁻¹ for (3) were assigned to the $\nu(\text{N}-\text{H})$ vibrations.

Supplementary material

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 965347 (1), 965348 (2), and 965349 (3). Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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