J Chem Crystallogr (2012) 42:508–512
DOI 10.1007/s10870-011-9996-7

ORIGINAL PAPER

Structural and Spectral Analyses of 2-[(2-Benzothiazolylmethyl) thio]-benzenamine and 2-[(2-Benzothiazolylmethyl)thio]-benzenamine hydrobromide

Dustin W. Demoin · Charles L. Barnes ·
Timothy J. Hoffman · Silvia S. Jurisson

Received: 18 August 2010 / Accepted: 14 January 2011 / Published online: 4 February 2011

Abstract 2-[2-benzothiazoylmethyl)thio]-benzenamine, which was first reported in 1898, was isolated from the reaction of bromoacetyl bromide and 2-aminothiophenol [1]. The product crystallized from an aqueous methanol solution of the reaction mixture to which nickel(II) acetate had been added. 2-[(2-benzothiazolylmethyl)thio]-benzenamine crystallized in the monoclinic system, in space group $C2/c$, with cell dimensions of $a = 27.392$ (19) Å, $b = 4.730$ (3) Å, and $c = 23.686$ (16) Å, $\beta = 122.465$ (6)°, $V = 2589(3)$ Å^3, $Z = 8$ and refined to $R = 0.0343$ and $R_w = 0.0844$. Crystallization from methanol yielded the product as the hydrobromide salt in the monoclinic space group Cc, with cell dimensions of $a = 10.488$ (3) Å, $b = 33.404$ (9) Å, $c = 5.2578$ (14) Å, $\beta = 116.769(2)°$, $V = 1644.7(8)$ Å^3, $Z = 4$ and refined to $R = 0.0296$ and $R_w = 0.0600$. Mass spectral and NMR analyses confirmed that the bulk and crystalline compound were all 2-[(2-benzothiazolylmethyl)thio]-benzenamine.

Keywords 2-[(2-Benzothiazolylmethyl)thio]-benzenamine · 2-[(2-Benzothiazolylmethyl)thio]-benzenamine hydrobromide · Crystal structure · Mass spectrum · 2-(2′-Aminophenylthio)methylbenzthiazole · Nuclear magnetic resonance

Introduction

2-[(2-benzothiazolylmethyl)thio]-benzenamine was originally prepared by Unger et al. in an attempt to understand the chemistry of α-brominated acids reacted with 2-aminothiophenol [1]. Further analysis of this compound was reported by Cymerman-Craig, et al. as a potential anti-parasitic agent that would expel parasitic worms from mice [2]. Both Unger and Cymerman-Craig cited the melting point (89–90 °C) and elemental analysis as characterization of 2-[(2-benzothiazolylmethyl)thio]-benzenamine.

2-[(2-benzothiazolylmethyl)thio]-benzenamine was isolated and fully characterized as the primary product in an attempted facile synthesis of *N*-(2-mercaptophenyl)-2-((2-mercaptophenyl)amino)acetamide. The approach used was to prepare *N*-(2-mercaptophenyl)-2-((2-mercaptophenyl) amino)acetamide through the direct reaction of bromoacetyl bromide and 2-aminothiophenol without thiol protection. Prior research has shown that tetradentate N_2S_2 dithiol ligands are excellent chelates for stabilizing both oxorhenium (V) and oxotechnetium (V) for potential use in radiopharmaceuticals [3–6]. Kung, et al. showed that monoamide, monoamine dithiols are particularly good as possible oxotechnetium (V) chelates [7]. Here we report the synthesis and full characterization of 2-[(2-benzothiazolylmethyl)thio]-benzenamine.

D. W. Demoin · C. L. Barnes · T. J. Hoffman ·
S. S. Jurisson (✉)
Department of Chemistry, University of Missouri,
125 Chemistry Building, 601 S. College Avenue,
Columbia, MO 65211, USA
e-mail: JurissonS@missouri.edu

T. J. Hoffman
Department of Internal Medicine, University of Missouri,
Columbia, MO 65211, USA

T. J. Hoffman
Harry S Truman VA Hospital, Columbia, MO 65211, USA

Experimental

Materials

Bromoacetyl bromide and 2-aminothiophenol were obtained from Aldrich and used without purification. All solvents were reagent grade and used as received.

Physical Measurements

^{1}H- and ^{13}C-NMR spectra were obtained in d_4-MeOD and referenced to the MeOH solvent signal at 3.30 ppm using a Bruker DRX 500 MHz Spectrometer. Electrospray ionization mass spectrometry (ESI–MS) was performed at the University of Missouri using a Finnigan TSQ7000 triple-quadrupole mass spectrometer in the positive ion mode.

2-[(2-Benzothiazolylmethyl)thio]-benzenamine

Bromoacetyl bromide (0.87 mL, 10 mmol) was added to 20 mL of dichloromethane with stirring and cooled to −78 °C. 2-Aminothiophenol (2.2 mL, 21 mmol) was diluted with 20 mL of dichloromethane, and then added dropwise to the bromoacetyl bromide solution. During addition, a white precipitate formed immediately. The reaction mixture was continuously stirred for 30 min at −78 °C and then warmed overnight to room temperature. The resultant mixture contained green-yellow solids, which were filtered and washed with dichloromethane to yield a white precipitate and an orange-brown filtrate. Yield: 2.3549 g (87%). ESI–MS (m/z): 272.88 (calc. 273.05 $[M + H]^+$).

Method 1: Free Base [**1**]

The uncharacterized white solid (0.2749 g) was added to 10 mL of methanol and stirred to yield a clear, pale-yellow solution. Nickel(II) acetate tetrahydrate (0.1521 g, 0.6112 mmol) dissolved in about 4 mL of deionized water (clear, pale green solution) was added to the pale-yellow solution, which became noticeably cloudy upon addition. The mixture was allowed to stir for about 45 min at room temperature, filtered, and the filtrate collected. The filtrate was heated and mixture remained slightly cloudy. The mixture was allowed to cool to room temperature, capped, and placed in the freezer for 1 week. The light green mother liquor was decanted and crystals of [**1**] were harvested from the sides of the vial and analyzed by X-ray crystallography. ^{1}H-NMR ($CDCl_3$, 500 MHz, δ (ppm)): 7.94 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.43 (t, $J = 7.3$ Hz, 1H), 7.4-7.29 (overlapped m, 2H), 7.12 (br s, 1H), 6.68 (br s, 1H), 6.59 (br s, 1H) 4.33 (s, 2H), 4.09 (br s, 2H). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ (ppm)): 168.8, 152.9, 148.1, 136.1, 135.6, 130.5, 125.9, 125.0, 122.8, 121.5, 118.7, 116.0, 115.3, 36.8.

Method 2: Hydrobromide Salt [**2**]

Alternatively, the uncharacterized white solid (0.9914 g) was dissolved in 5 mL of hot methanol. The clear yellow solution was allowed to cool to room temperature. Small white needles of [**2**] were filtered via gravity filtration, washed with methanol and analyzed by NMR and X-ray crystallography. ^{1}H-NMR (d_4-MeOD, 500 MHz, δ (ppm)): 7.95 (d, $J = 1.4$ Hz, 1H), 7.93 (d, $J = 1.6$ Hz, 1H), 7.71 (dd, $J = 1$, 8.0 Hz, 1H), 7.52 (dt, $J = 1$, 7.9 Hz, 1H), 7.48–7.41 (overlapped m, 3H), 7.37 (dt, $J = 2$, 7.5 Hz, 1H), 3.34 (s, 2H). ^{13}C-NMR (d_4-MeOD, 500 MHz, δ (ppm)): 170.2, 153.2, 137.4, 136.7, 135.5, 131.9, 130.4, 128.9, 127.7, 127.0, 124.4, 123.4, 123.1. ^{13}C-NMR (d_6-DMSO, 500 MHz, δ (ppm)): 168.8, 152.3, 135.2, 134.8, 134.2, 131.1, 129.6, 126.2, 125.3, 122.4, 122.3, 35.7.

X-ray Diffraction Analysis

The crystal of [**1**] was approximately 0.55 × 0.25 × 0.05 mm; [**2**] approximately 0.50 × 0.20 × 0.05 mm. Intensity data were obtained on a Bruker APEXII using the ω-scan mode with Mo $K\alpha$ radiation from a graphite monochromator ($\lambda = 0.71073$ Å). Important information regarding the crystal data and structure refinement are listed in Table 1. Lattice constants for the crystal of [**1**] were obtained from 2,968 centered reflections ($1.76° \leq \theta \leq 27.57°$); [**2**] 3,698 centered reflections ($2.26° \leq \theta \leq 27.55°$). The structures were solved by direct methods and refined with full-matrix least-squares techniques, employing the SHELX programs and X-Seed [8, 9]. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were placed at calculated positions and included in the refinement using a riding model, with fixed isotropic U. The final least-squares cycle for the crystal of [**1**] was calculated with 18 atoms and 165 parameters and afforded $R = 0.0343$, $R_w = 0.0844$. The final least-squares cycle for the crystal of [**2**] was calculated with 21 atoms and 195 parameters and afforded $R = 0.0296$, $R_w = 0.0599$. The polarity of the structure of [**2**] was determined by refinement of the Flack parameter, 0.012 (5). Final difference maps of both structures had no features of chemical significance.

Results and Discussion

The previously reported 2-[(2-benzothiazolylmethyl)thio]-benzenamine was inadvertently synthesized during a procedure to synthesize a new N_2S_2 ligand. The product was

Table 1 Crystal data and structure refinement for 2-[(2-benzothiazolylmethyl) thio]-benzenamine and 2-[(2-benzothiazolylmethyl) thio]-benzenamine hydrobromide

	[1]	[2]
CCDC Number	789463	789462
Empirical formula	$C_{14}H_{12}N_2S_2$	$C_{15}H_{17}BrN_2OS_2$
Formula weight	272.38	385.34
Temperature (K)	173 (2)	173 (2)
Wavelength (Å)	0.71073	0.71073
Crystal system, space group	Monoclinic, $C_{2/c}$	Monoclinic, C_c
Unit cell dimensions		
a (Å)	27.392 (19)	10.488 (3)
b (Å)	4.730 (3)	33.404 (9)
c (Å)	23.686 (16)	5.2578 (14)
α (°)	90	90
β (°)	122.465 (6)	116.769 (2)
γ (°)	90	90
Volume (Å^3)	2589 (3)	1644.7(8)
Z	8	4
Calculated density (mg/m^3)	1.398	1.556
Absorption coefficient (mm^{-1})	0.393	2.753
F(000)	1136	784
Crystal size	0.55 × 0.25 × 0.05 mm	0.50 × 0.20 × 0.05 mm
Theta range for data collection	1.76–27.57°	2.26–27.55°
Range of h,k,l	±35, ±6, ±30	±13, ±43, ±6
Reflections collected/unique	13885/2968 [R(int) = 0.0284]	8833/3698 [R(int) = 0.0287]
Completeness to theta = 27.57	99.2%	99.8%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.84	0.87 and 0.70
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2968/0/165	3698/2/195
Goodness-of-fit on F^2	1.060	0.926
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0295$, $wR2 = 0.0809$	$R1 = 0.0265$, $wR2 = 0.0589$
R indices (all data)	$R1 = 0.0343$, $wR2 = 0.0844$	$R1 = 0.0296$, $wR2 = 0.0600$
Largest diff. peak and hole (e^{-1} Å^{-3})	0.314 and −0.209	0.643 and −0.251

crystallized as the free base [**1**] and the hydrobromide salt [**2**], and analyzed via X-ray crystallography, mass spectroscopy, and nuclear magnetic resonance spectroscopy.

The ^{1}H-NMR and ESI–MS of the isolated product were not those expected for the desired N_2S_2 ligand. In order to correctly identify the product, it was reacted with nickel(II) acetate expecting to form a Ni(N_2S_2) complex that could be isolated and characterized. The X-ray crystal structure showed that a condensation side-product of the desired ligand had formed, [**1**]. The thiol group on the 2-aminothiophenol is more reactive than the amine toward alkylation by the bromoacetyl bromide, and reacted first. The close proximity of the thioester oxygen to the amine on the aromatic ring facilitated the condensation reaction, forming a cyclic imine.

The ESI–MS shows a large peak at m/z = 272.88, which corresponds to the calculated mass of a protonated 2-[(2-benzothiazolylmethyl)thio]-benzenamine. Eight aromatic protons and two non-aromatic protons are observed by ^{1}H-NMR spectroscopy, which corresponds to the structure obtained via X-ray crystallography. The ^{13}C-NMR spectrum in d_4-MeOD showed 13 unique aromatic carbon signals, with the CH_2 protons overlapping with the solvent peaks. The ^{13}C-dept135 NMR (in d_4-MeOD) experiment showed eight aromatic CH carbons. The ^{13}C-NMR spectrum in DMSO showed 12 unique carbon signals, 11 aromatic carbons and the CH_2 carbon signal. The ^{13}C-dept135 NMR (in d_6-DMSO) experiment showed both the eight aromatic CH carbons and the CH_2 carbon. Two of the quaternary carbon signals are likely absent in the DMSO experiment since the sensitivity for their detection is lower.

Two different forms of 2-[(2-benzothiazolylmethyl) thio]-benzenamine were isolated; the free base [**1**] crystallized in the presence of nickel(II) acetate from methanol/H_2O and the hydrobromide salt [**2**] crystallized from methanol. Crystal structure and refinement details are presented in Table 1. Selected bond lengths and angles for the structures are given in Table 2.

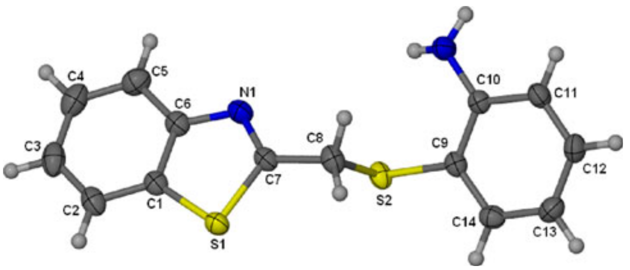

Fig. 1 ORTEP representation of 2-[(2-benzothiazolylmethyl)thio]-benzenamine [**1**] with 50% probability ellipsoids (CCDC 789463)

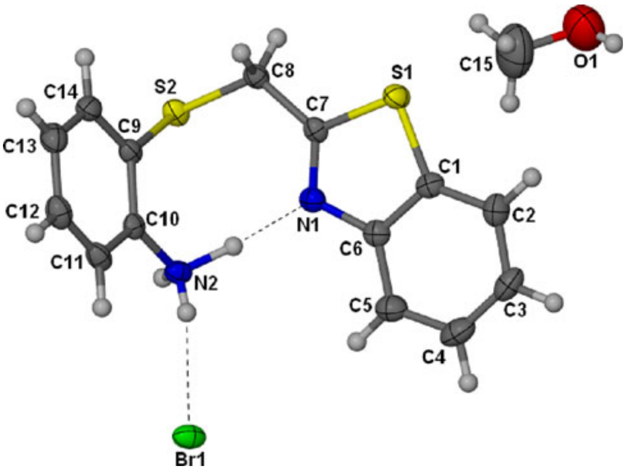

Fig. 2 ORTEP representation of 2-[(2-benzothiazolylmethyl)thio]-benzenamine hydrobromide [**2**] with 50% probability ellipsoids (CCDC 789462)

Table 2 Selected bond lengths [Å] and angles [°]

	[1]	[2]
S(1)–C(1)	1.7309 (17)	1.737 (3)
S(1)–C(7)	1.7464 (19)	1.743 (3)
N(1)–C(7)	1.2980 (19)	1.295 (3)
N(1)–C(6)	1.3902 (18)	1.390 (3)
S(2)–C(9)	1.7736 (15)	1.782 (3)
S(2)–C(8)	1.8306 (16)	1.811 (3)
N(2)–C(10)	1.3790 (19)	1.453 (4)
N(2)–H(1 N)	0.8520	0.8604
N(2)–H(2 N)	0.8528	0.8261
C(7)–C(8)	1.4911 (19)	1.501 (4)
O(1)–C(15)	–	1.377 (5)
O(1)–H(1)	–	0.8400
N(1)–N(2)	–	2.811 (3)
N(2)–Br(1)	–	3.287 (3)
C(1)–S(1)–C(7)	89.28 (6)	89.12 (13)
C(7)–N(1)–C(6)	110.65 (12)	111.3 (2)
C(2)–C(1)–S(1)	129.43(11)	128.9 (2)
C(6)–C(1)–S(1)	109.18 (10)	109.4 (2)
C(9)–S(2)–C(8)	99.34 (7)	100.14 (12)
N(1)–C(6)–C(5)	125.16 (13)	126.4 (2)
N(1)–C(6)–C(1)	115.00 (13)	114.3 (2)
N(1)–C(7)–C(8)	123.14 (13)	126.1 (2)
N(1)–C(7)–S(1)	115.87 (10)	115.9 (2)
C(8)–C(7)–S(1)	120.99 (11)	117.94 (19)
C(7)–C(8)–S(2)	108.52 (10)	116.29 (18)
C(14)–C(9)–S(2)	119.80 (11)	120.7 (2)
C(10)–C(9)–S(2)	120.05 (11)	120.9 (2)
N(2)–C(10)–C(11)	119.60 (12)	119.5 (2)
N(2)–C(10)–C(9)	122.50 (12)	119.6 (2)
C(15)–O(1)–H(1)	–	109.5

The N1–C7 bond lengths of 1.2980 (19) [**1**] and 1.295 (3) Å [**2**] and the N1–C6 bond lengths of 1.3902 (18) Å [**1**] and 1.390 (3) Å [**2**] indicate that the N1-C7 bond is an imine and the N1–C6 bond is an amine. Recently, Mike, et al. reported the syntheses and crystal structures for numerous disubstituted benzenamines, which had an average C=N length of 1.292 Å and C–N length of 1.396 Å and are comparable to those observed here [10]. Additionally, the bond angles around C7 [N1–C7–S1 115.87 (10)°, S1–C7–C8 120.99 (11)°, and N1–C7–C8 123.14 (13)° for [**1**]; 115.9 (2)°, 117.94 (19)°, 126.1 (2)° for [**2**]] sum to 360.00 (34)° for [**1**] and 359.94 (59)° for [**2**], consistent with the expected geometry of an sp^2 hybridized carbon (planar) (Figs. 1, 2).

The crystal structure of [**1**] shows intermolecular hydrogen bonding interactions between molecules within the lattice framework, which correspond to the solid phase crystal packing of the compound. The crystal structure of [**2**] differs from [**1**] in that it is present as the hydrobromide salt and includes a solvent molecule for every 2-[(2-benzothiazolylmethyl)thio]-benzenaminium bromide. The ammonium group intramolecularly hydrogen bonds to the amide nitrogen and to two bromides (dotted lines in Fig. 2). The N(1)–N(2) interatomic distance of 2.811(3) Å is within published values for hydrogen bonding between two nitrogen atoms [11]. The hydrogen bonding interactions between the ammonium group and two bromide anions give an infinite chain of –Br–N–Br–N– linkages along the c-axis (only one hydrogen bond of this nature is shown by the dotted line in Fig. 2), as evidenced by their relatively short interatomic distances of 3.288(3) and 3.308(3) Å; these are well within the established interatomic distances for a reasonable hydrogen bonding interaction to a bromide anion [12].

Conclusions

The synthesis of 2-[(2-benzothiazolylmethyl)thio]-benzenamine was previously reported, but full characterization utilizing today's technology was impossible at that time [1, 2]. After inadvertently preparing this compound, the analysis herein provides the necessary data for identification.

Acknowledgments The authors acknowledge the University of Missouri Mass Spectroscopy Facility; National Science Foundation grant NSF-CHE-89-08304 for the use of the NMR facility, and NSF-CHE-9011804 for the use of the X-ray facility; Dr. Wei Wycoff for assistance with the 500 MHz NMR; and NIBIB Training Grant NIBIB 5 T32 EB004822 (D.W.D.). The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre (CCDC).

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