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4-((5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-thiadiazol-2-yl)amino)benzenesulfonic acid: unexpected synthesis, structure elucidation and antimicrobial activity

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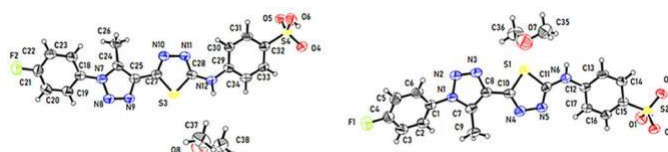
ABSTRACT

Unexpected ring closure of 2-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-N-phenylhydrazine-1-carbothioamide (3) on exposure to sulfuric acid at room temperature for an extended duration (12 h) gave 4-((5-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-thiadiazol-2-yl)amino)benzenesulfonic acid (4) in 75% yield. The use of sulfuric acid led to sulfonation at the para-position of the benzene ring in phenyl isothiocyanate. The crystal structure comprises two independent types of molecules of 4 and two disordered ether solvent molecules. The synthesized benzenesulfonic acid inhibits the growth of both *Listeria monocytogenes* and *Escherichia coli* and its activity was comparable to those obtained for ampicillin and vancomycin.

KEYWORDS

4-(1,3,4-Thiadiazol-2-yl)amino)benzenesulfonic acid; phenyl isothiocyanate; 1,2,3-triazole; antimicrobial activity; X-ray crystallography

GRAPHICAL ABSTRACT



Introduction

Heterocycles containing the 1,2,3-triazole moiety^[1] represent a pivotal pharmacophore system since they exhibit a variety of biological activities (e.g., antibacterial, antitubercular, and antiviral).^[2–6] In addition, 1,3,4-thiadiazole-containing heterocycles^[7] have shown activities against microbes.^[8–10] Sulfonation is a reaction that is highly applicable in the manufacture of a range of important products, including pharmaceuticals, pigments, and pesticide intermediates.^[11–13] The synthesis of novel heterocycles with a combination of the properties of both 1,2,3-triazole and sulfonic acid moieties is an interesting prospect in the generation of new potentially biologically active materials. Here, we report the unexpected synthesis of 4-((5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-thiadiazol-2-yl)amino)benzenesulfonic acid using a simple procedure, in continuation of our long-term interest in the synthesis of bioactive molecules.^[14–17]

Results and discussion

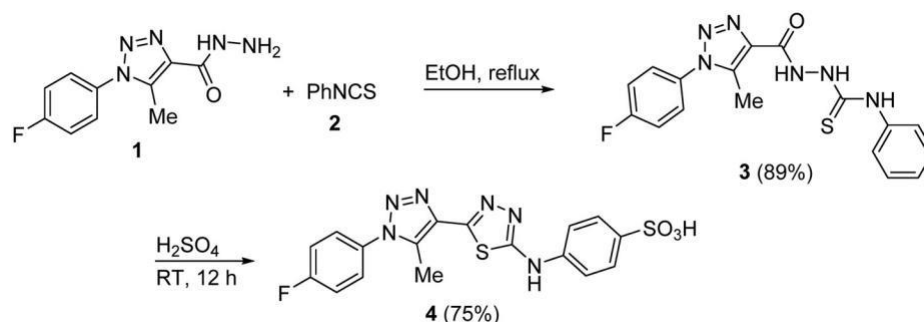
Chemistry

Abdel-Wahab et al^[18] have reported the synthesis of 2-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-

N-phenylhydrazine-1-carbothioamide (3) from reaction of 1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (1) with phenyl isothiocyanate (2) in ethanol under refluxing conditions (Scheme 1). Ring closure of 3 was achieved on treatment with concentrated sulfuric acid (H₂SO₄) at room temperature for 12 h to give an unexpected product, 4-((5-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-thiadiazol-2-yl)amino)benzenesulfonic acid (4), in 75% yield (Scheme 1). The use of H₂SO₄ led to sulfonation at the para-position of the benzene ring in phenyl isothiocyanate.

The chemical structure of 4 was confirmed by the NMR spectral data and by single crystal X-ray crystallography. The ¹H NMR spectrum of 4 shows two exchangeable singlet signals at 8.35 and 10.88 ppm that correspond to the SO₃H and NH protons, respectively.

The crystal structure comprises two independent molecules (M₁ and M₂) of 4 and two disordered ether solvent molecules (Figure 1). The molecule of 4 includes four rings (A–D), namely; an aryl (M₁A: C1–C6 and M₂A: C18–C23), a triazolyl (M₁B: C7, C8, N1–N3, and M₂B: C24, C25, N7–N9), a thiadiazolyl (M₁C: C10, C11, N4, N5, S1 and M₂C: C27, C28, N10, N11, S3), and a second aryl (M₁D: C12–C17, S2 and M₂D: C29–C34) rings.



Scheme 1. Synthesis of benzenesulfonic acid 4.

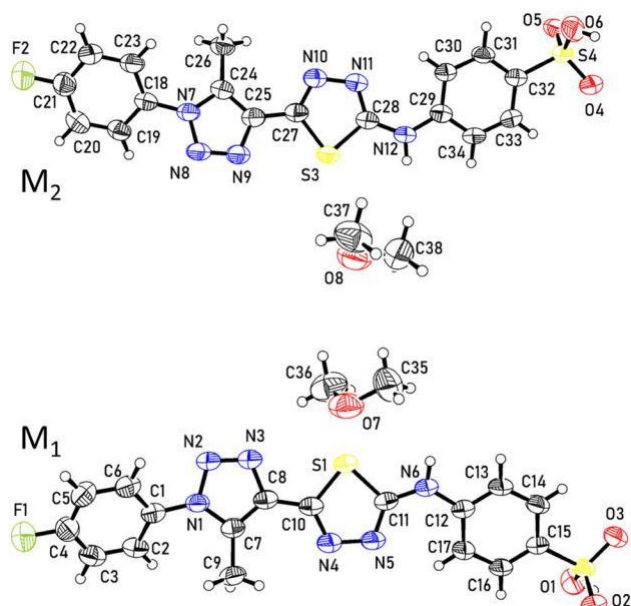


Figure 1. Ortep representation of the asymmetric unit of the crystal structure of 4 with 50% probability ellipsoids showing the major component of the disordered ether solvent.

The conformations of the two independent molecules of 4 are similar in the crystal structure. Rings B D are almost coplanar with twist angles M₁B/M₁C ¼ 9.76(28) and M₂B/M₂C ¼ 14.09(20); M₁C/M₁D ¼ 14.31(24) and M₂C/M₂D ¼ 13.71(24). The angles between rings A and B are greater: M₁A/M₁B ¼ 40.47(17) and M₂A/M₂B ¼ 40.58(17). The ether solvent molecules are disordered and occupy channels in the crystal structure [Figure 2(a)]. The channels are created between columns of molecules of 4 which are stacked parallel to the c-axis. Stacking is associated with p ... p type interactions illustrated by the shortest contacts between the thiadiazolyl groups of neighboring molecules [shown in Figure 2(b)] with centroid-to-centroid distances of M₁C ... M₁C ¼ 3.719 Å and M₁C ... M₂C ¼ 3.667 Å. The stacks are linked by N-H...O hydrogen bonding with geometry [distance D...A, angle D-H ... A]: N(6)-H(6A) ... O(5), [2.843(6) Å, 173.8°], N(12) ... H(12) ... O(2), [2.793(5) Å, 170.6°]. The sulfonic acid group interacts with the solvent molecules with geometry: O(1) H(1) ... O(7), [2.745(11) Å, 134.9°], O(6) H(6B) ... O(8), [2.673(11) Å, 171.8°]. Bond lengths and angles are shown in Table S1 (Supplemental Materials) and are consistent with other heterocycles containing the 1,3,4-thiadiazole moiety.^[19–21]

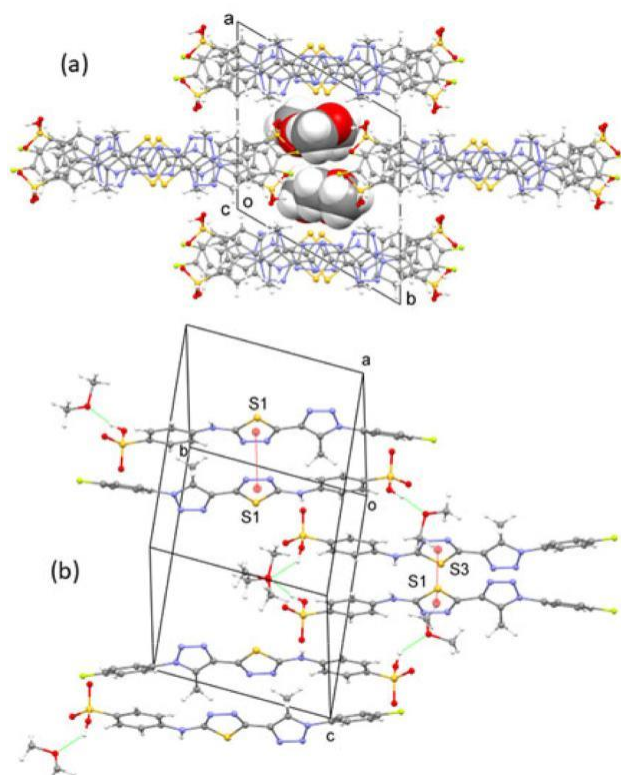


Figure 2. (a) A view of the crystal structure of 4 down the c axis with the ether solvent molecules highlighted by space-fill representation. (b) A segment of the crystal structure showing hydrogen bonding (green dashed lines) and p ... p (red dashed lines) contacts.

Antimicrobial activity

The antimicrobial activity of the new compound 4 was determined against some targeted pathogenic microorganisms obtained from the American Type Culture Collection (ATCC; Rockville, MD, USA). The organisms used in the test were *Staphylococcus aureus* ATCC-47077 (*S. aureus*), *Listeria monocytogenes* ATCC-35152 (*L. monocytogenes*), *Escherichia coli* ATCC-25922 (*E. coli*), *Salmonella typhi* ATCC-15566, and *Candida albicans* ATCC-10231 (*C. albicans*). Ampicillin and vancomycin were used as reference antibiotics for comparison.

Compound 4 showed good activity against *L. monocytogenes* and *E. coli* with performance comparable to those of ampicillin and vancomycin (Table 1). Conversely, no activity was observed against *S. aureus*, *S. typhimurium*, and *C. albicans*. The minimal inhibitory concentration (MIC) of

Table 1. Antimicrobial activity of compound 4.

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungi
	<i>S. aureus</i>	<i>L. monocytogenes</i>	<i>E. coli</i>	<i>S. typhi</i>	<i>C. albicans</i>
4	—	15	11	—	—
Ampicillin	15	20	16	19	19
Vancomycin	14	15	15	17	15

compound 4 was also investigated. The results indicated that the concentrations of 4 needed to kill *L. monocytogenes* and *E. coli* were of 70 and 85 lg/mL, respectively. In comparison, ampicillin has a wide range of MIC for *E. coli* (1–128 lg/mL) and *L. monocytogenes* (25–50 lg/mL). The average MIC for vancomycin against *E. coli* and *L. monocytogenes* are in the ranges of 0.4–3.0 and 20–40 lg/mL, respectively.

Experimental

General

The melting point was determined using an Electrothermal (variable heater) melting point apparatus. The IR spectrum (KBr disc) of 4 was recorded on Bruker Tensor 27 FTIR Spectrometer. The NMR spectra were measured with a JEOLNMR 500 MHz spectrometer. ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in deuterated dimethyl sulfoxide (DMSO- d_6) using tetramethylsilane as a standard. The chemical shift (δ) was reported in ppm and the coupling constant (J) was reported in Hz. Compounds 1^[22] and 3^[18] were prepared based on literature procedures. The Supplemental Materials contain the FTIR, ^1H , ^{13}C NMR spectra (Figures S1–S3), and bond lengths and angles for compound 4 (Table S1).

Synthesis of benzenesulfonic acid 4

A suspension of 3 (0.74 g, 2.0 mmol) in concentrated sulfuric acid (8 mL) was stirred overnight (16 h) at room temperature. The mixture was poured into ice-water (50 mL) and the solid obtained was removed by filtration, washed with water, dried, and recrystallized from DMF/ether to give 4 as a colorless solid (75%). mp > 300 C. IR (max, cm^{-1}): 3080 (NH), 1619 (C $\frac{1}{4}$ N), 1582 (C $\frac{1}{4}$ C), 1348 (SO_3H). ^1H NMR: 2.37 (s, 3H, CH₃), 7.46–7.70 (m, 8H, Ar), 8.35 (s, exch., 1H, SO_3H), 10.88 (s, exch., 1H, NH). ^{13}C NMR: 10.2, 117.2 (d, J_{C-F} $\frac{1}{4}$ 32.2 Hz), 127.2 (d, J_{C-F} $\frac{1}{4}$ 143.0 Hz), 128.3, 132.2, 133.7, 137.0, 141.3, 142.0 (d, J_{C-F} $\frac{1}{4}$ 84.5 Hz), 151.4, 162.1, 163.7 (d, J_{C-F} $\frac{1}{4}$ 48.6 Hz), 164.1. Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{FN}_6\text{O}_3\text{S}_2$ (432.05): C, 47.22; H, 3.03; N, 19.43, Found: C 47.35, H 3.12, N 19.55%.

Determination of antimicrobial activity

The agar well diffusion procedure was employed to investigate the antimicrobial activities of compound 4.^[23,24] The antimicrobial activities of ampicillin and vancomycin against the tested microorganism were also assessed for comparison. Bacterial (70 mL) and yeast (106 CFU/mL) cells were spread on plates containing nutrient agar. The wells (6 mm diameter) were excavated on the injected agar plates, then each sample (100 mg) in DMSO

Table 2. Crystal data and structure refinement for compound 4.

Compound	4
Empirical Formula	$\text{C}_{17}\text{H}_{13}\text{FN}_6\text{O}_3\text{S}_2 \cdot \text{C}_2\text{H}_6\text{O}$
Formula Weight	478.52
Wavelength (Å)	1.54184
Crystal System	Triclinic
Space Group	$P\bar{1}$
a / Å	12.9497(8)
b / Å	14.2197(10)
c / Å	14.9407(8)
a / °	113.699(6)
b / °	92.651(5)
c / °	116.407(7)
V/Å ³	2169.9(3)
Z	4
D calc (mg/m ³)	1.465
ρ (mm ⁻¹)	2.657
Crystal size (mm)	0.362 0.066 0.021
Temp (K)	293(2)
F(000)	992
Reflections collected	13339
Independent reflections	8497
R(int)	0.0704
Goodness of fit on F ²	0.877
R1 ($I > 2\sigma(I)$)	0.0824
wR2 ($I > 2\sigma(I)$)	0.1924
Largest difference peak/hole (e.Å ⁻³)	0.894 and 0.393

(1 mL) was added. The reference antibiotics disks (10 and 30 lg/ disks of ampicillin and vancomycin, respectively) were introduced on the surface of agar inoculated plates. The plates were kept at 4 C for 2 h before incubation to permit diffusion to occur. The plates were kept at 37 C for 24 h except yeast strain which was incubated at 28 C for 24 h. The diameter of the inhibition zone (mm) was measured. The tests were replicated five times and the averages were calculated.

Determination of minimum inhibition concentration (MIC)

The MIC is the concentration of microorganism that does not present visible growth with regard to the positive control. The MIC was determined for compound 4 based on a reported procedure.^[25] Serial dilutions were made from the solution containing solutions of 4 in DMSO. A double strength Mueller Hinton broth medium (150 mL) was loaded in each well of a plate containing 96 wells followed up by a 2-fold of appropriate concentration (150 mg/mL) of sample and mixed well to give the final concentration. Broth cultures of the screened microorganism were prepared as an inoculum of 5% by volume (optical density $\frac{1}{4}$ 0.5 McFarland standard) and inoculated into the wells. The same size of each test strain was inoculated without 4 as a positive growth control. DMSO was tested as a negative control. The plates were incubated at 37 C for 24 h. The prepared solution (30 IL; 0.18%) in DMSO was added to each well to act as an electron acceptor. The inhibition of bacterial growth was indicated by dark blue coloration and growth by red, pink, or purple color.

Crystal structure determination

Single-crystal XRD data were collected at room temperature on an Agilent SuperNova Dual Atlas diffractometer with a

mirror monochromator using Cu radiation. The crystal structure was solved by SHELXS^[26] and refined using SHELXL.^[27] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions, and a riding model was used with Uiso set at 1.2 or 1.5 times the value of Ueq for the atom to which they are bonded. The two independent solv-ent locations are occupied by disordered molecules with two components of occupancies (0.544(19)/0.456(19), and (0.509(16)/0.491(16)). The X-ray crystallographic data for **4** have been deposited at the Cambridge Crystallographic Data Center with CCDC reference number 2141414. Structure solution and refinement data of **4** are shown in Table 2.

Conclusions

A novel 1,3,4-thiadiazole containing sulfonic acid and a 1,2,3-triazole moiety has been synthesized using a simple procedure and characterized. The newly synthesized hetero-cycle showed activities against both *Listeria monocytogenes* and *Escherichia coli*.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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