SYNTHESIS, GROWTH AND CHARACTERIZATION OF NEW 1,3,4 -THIADIAZOLE-5-(*N*-SUBSTITUTED)-SULFONAMIDES CRYSTALS

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Abstract

New 1,3,4-thiadiazole-5-(N-substituted)-sulfonamide derivatives incorporating N-cyclohexyl, N-benzyl and N-[sec-butyl] moieties, carbonic anhydrase inhibitors, have been obtained by an optimized synthesis. Single crystals of these sulfonamides have been successfully grown up to suitable dimensions for X-ray diffraction measurements by slow evaporation of solvent at room temperature. Structural data for these monoclinic compounds are compared with those of related phases. The sulfonyl moiety presents a distorted tetrahedral arrangement around the S atom. The different groups introduced cause no observable modifications of the 1,3,4-thiadiazole ring structure. Thermal analysis show total sample degradation at temperatures higher than that of the melting point of the three phases. The FTIR spectra confirm the compounds formation and provide a first insight on the modes of NH…N hydrogen bond in these sulfonamides.

Resumen

Nuevas 1,3,4-tiadiazol-5-(N-substituidas)-sulfonamidas, inhibidores de anhidrasa carbónica, fueron obtenidas incorporando los grupos N-ciclohexil, N-benzil and N-[sec-butil], por una síntesis optimizada y monocristales de las mismas fueron crecidos desde alcohol absoluto por evaporación lenta a temperatura ambiente hasta dimensiones adecuadas para medidas de DRX. Los datos estructurales de estos compuestos monoclínicos son comparados con los de otras fases relacionadas. El grupo sulfonil presenta una geometría tetraédrica distorsionada alrededor del átomo de S. Los diferentes sustituyentes introducidos no producen modificaciones en la estructura del anillo 1,3,4-tiadiazol. El análisis térmico de las tres fases muestra descomposición total a temperaturas por encima del punto de fusión. Los espectros FTIR confirman la formación de los compuestos y es el

primer aporte sobre el conocimiento de la unión puente hidrógeno NH...N en estas sulfonamidas.

Introduction

Since Davenport reported that thiophene-2-sulfonamide is a carbonic anhydrase inhibitor 40 times more active than other sulfonamides [1], many compounds of this type with heterocyclic rings have been prepared and studied [2,3]. Some of them are currently used in medical prevention and treatment of several diseases such as glaucoma and epilepsy, and also as diuretics and antibiotics. Acetazolamide, the best investigated sulfonamide of this pharmacological agents family, incorporates the 1,3,4-thiadiazole ring in its structure. This ring constitutes a very important moiety for the development of therapeutic compounds because it admits different organic substituents at C(2) and C(5) [4]. Following the method proposed by Young et al. [5], we have obtained several 1,3,4-thiadiazole sulfonamides and determined their crystal structures [6,7,8]. Some of them show a remarkable increase in the CA inhibitory ability and exhibit anticonvulsant action [9]. On the other hand, the presence of diverse donor atoms allows these substituted sulfonamides to behave as versatile ligands for metallic ions chelation [10, 11].

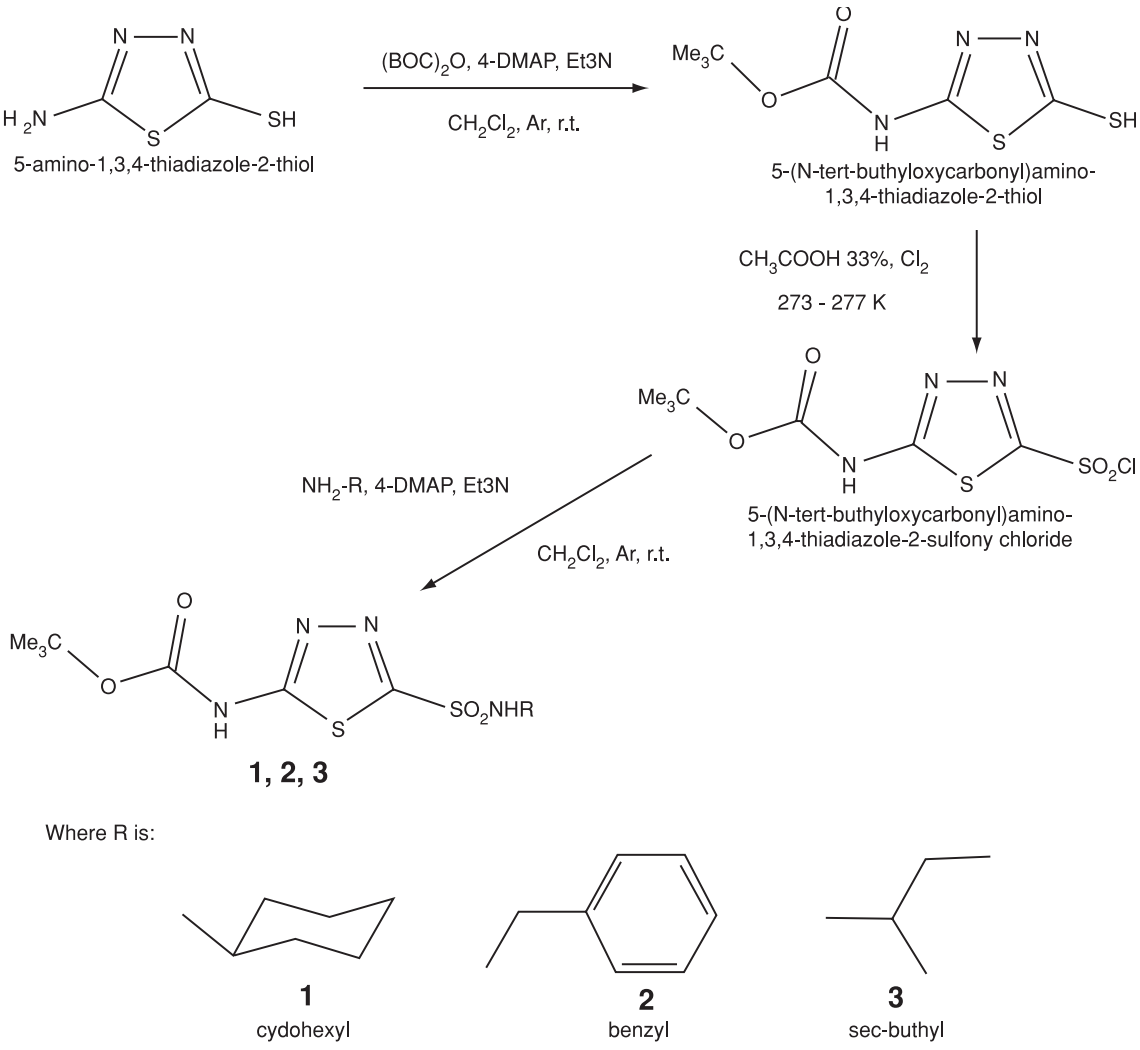
The synthesis employed in such previous works by protection of the C(5) amino group, chlorosulfonation of C(2) thiol and subsequent amidation of the sulfonyl chloride, implied laborious purifications at each step, with performances to be improved upon. Furthermore, low yield crystallization renders imperfect crystals difficult to isolate. Based on such investigations, it was of our interest not only to synthesize 1,3,4-thiadiazole-5-(N-substituted)-sulfonamide derivatives using more convenient routes, but also to grow suitable single crystals to determinate their structures by X-ray diffraction. In addition, as far as we know, information on monosubstituted sulfonamides structurally related to acetazolamide is scarce.

The present paper reports an optimized synthetic route that was achieved by the combination of previously published methods [5,12]. The new route produces better yields and high purity final products so that better crystals for further spectroscopic and structural characterization can be grown. The crystal structures have been determined and an unique polimorphic form has been found at room temperature in studies carried out with other solvents. A structural comparison with related compounds has been made. An assignment of the FTIR spectra has also been carried out.

Experimental

Scheme 1 shows the synthesis of 1,3,4 -thiadiazole-5-(*N*-substituted)-sulfonamides. In the first step (amino group protection), the initial reagent (5-amino-1,3,4-thiadiazole-2-thiol, 2 g, 15.04 mmol) was suspended in 50 ml CH_2Cl_2, followed by addition of 4-dimethylaminopyridine (4-DMAP, 100 mg, 4.6 mmol) and triethylamine (Et_3N, 2.5 mL, 17.89 mmol) as catalysts, and finally di-tert-butyldicarbonate ($(BOC)_2O$, 3.70 g, 17 mmol), all in the given order and with permanent stirring at room temperature under argon atmosphere. The reaction was monitored by thin-layer chromatography (TLC). After 18 hours, the solvent was removed by vacuum. The reaction product, 5-(N-tert-butyloxycarbonyl)amino-1,3,4-thiadiazole-2-thiol, was thus obtained and purified by liquid chromatography using ethylacetate/hexane (2:1) mixture, yielding 3.15 g (90%, melting point 436-438 K). In the second step, 0.35 g (1.5 mmol) of 5-(N-tert-butyloxycarbonyl)amino-1,3,4-thiadiazole-2-thiol were dissolved in acetic acid 33% V/V (100

mL) and the solution was bubbled with Cl_2 at 273-278 K (ice bath) for 15 min with permanent stirring [13]. The obtained reaction product 5-(N-tert-butyloxycarbonyl)amino-1,3,4-thiadiazole-2-sulfonyl chloride was then filtered and washed with distilled water (3-4 times) and hexane (3-4 times), yielding 0.36 g (80%). Finally, the third step was an aminolysis of 5-(N-tert-butyloxycarbonyl)amino-1,3,4-thiadiazole-2-sulfonyl chloride using aliphatic or aromatic primary amines: 4-DMAP (100 mg, 4.6 mmol), Et_3N (1.5 mL, 10.7 mmol) and 4 mmol of R-NH_2 (where R is: *N*-cyclohexyl, *N*-benzyl and *N*-[*s*ec-butyl] were added to 50 mL of CH_2Cl_2 and with permanent stirring at room temperature under an argon atmosphere. Under these conditions, 1.2 g (4 mmol) of 5-(N-tert-butyloxycarbonyl)amino-1,3,4-thiadiazole-2-sulfonyl chloride dissolved in CH_2Cl_2 (10 mL) were added to the above solution. The reaction was followed by TLC. After 12 hours the solvent was removed by vacuum. The products were obtained and purified by liquid chromatography using ethylacetate/hexane (2:1) mixture.



***Scheme 1**. Synthesis of 1,3,4 -thiadiazole-5-(N-substituted)-sulfonamides.*

Single crystals growing was performed using the evaporative crystallization technique by dissolution of each final microcrystalline product in absolute ethanol which was left to evaporate very slowly at room temperature. ID names, ID numbers, and several physical properties of all studied compounds are showed in Table 1, the size of the obtained crystals are showed in Table 2.

Table 1. *Monosubstituted sulfonamides obtained from 5-amino-1,3,4-thiadiazole-2-thiol.*

Compound	**I.D. Number**	**Solid characteristics**	**Yield % (media)**	**M.P. (K) (DTA)**
5-[*N*-(*tert*-butyloxycarbonyl)amino]-*N*-cyclohexyl-1,3,4-thiadiazole-2-sulfonamide	**1**	colorless plate prismatic crystals	83.7	437.05 (d)
N-benzyl-5-[*N*-(*tert*-butyloxycarbonyl)amino]-1,3,4-thiadiazole-2-sulfonamide	**2**	colorless needlelike crystals	74.6	439.25 (d)
N-[*sec*-butyl]-5-[*N*-(*tert*-butyloxycarbonyl)amino]-1,3,4-thiadiazole-2-sulfonamide	**3**	colorless prismatic crystals	95.3	449.77 (d)

(d) decomposition

Single-crystals suitable for X-ray diffraction studies were mounted on a glass fiber and transferred to the diffractometer (Nonius CAD-4). Crystal data are summarized in Table 2. Unit cell parameters were determined from a least-squares fit of ca. 30 accurately centred reflections ($9 < 2\theta < 25$). The structures were solved by direct methods and refined anisotropically on F^2 (SHELX97 program)[14]. For compound **1**, two methyl groups of the tert-butyl moiety are disordered over two sites. Amino groups hydrogen atoms were located in a difference Fourier synthesis and refined with restrained N-H bond length. The remaining hydrogen atoms were included using a riding model. For compound **2**, amino groups hydrogen atoms were located in a difference Fourier synthesis and refined with restrained N-H bond length. The remaining hydrogen atoms were included as rigid methyl groups or using riding model. For compound **3**, two molecules were found in the asymmetric unit. Both, the amino group corresponding to N(4A) and the sulfone oxygen atom O(2A) are disordered over two sites. The amino group hydrogen atom corresponding to N(4A) was not considered, other amino groups hydrogen atoms were located in a difference Fourier synthesis and refined with restrained N-H bond length. Other hydrogen atoms were included using a riding model. The programs use the neutral atom scattering factors, Δf' and Δf" and absorption coefficients from International Tables for Crystallography [15].

FTIR spectra were recorded on a Nicolet Protégé 460 in the 4000 to 225 cm^{-1} range, using the KBr pellets technique for the solid samples. Spectral resolution was better than 4 cm^{-1} between 4000 and 2000 cm^{-1}, and better than 2 cm^{-1} in the remaining ranges.

Table 2. Crystal data for compoun **1**, **2** and **3**

Compound	**1**	**2**	**3**
Formula	$C_{13}H_{22}N_4O_4S_2$	$C_{14}H_{18}N_4O_4S_2$	$C_{11}H_{20}N_4O_4S_2$
Formula weight	362.47	370.44	336.43
Crystal size (mm)	0.64 x 0.19 x 0.08	0.54 x 0.48 x 0.23	0.68 x 0.25 x 0.12
Crystal habit	Colourless lath	Pale yellow prism	Colourless lath
Unit cell constants			
a (Å)	15.885(3)	5.5262(4)	13.653(4)
b (Å)	6.1794(12)	23.2521(16)	11.894(2)
c (Å)	19.611(4)	13.5985(10)	21.729(3)
α (°)	90	90	90
β (°)	110.50(3)	98.213(7)	104.99(2)
γ (°)	90	90	90
V ($Å^3$)	1803.1(6)	1729.4(2)	3408.4(11)
Z	4	4	8
λ (Å)	0.71073	0.71073	0.71073
T (K)	293(2)	293(2)	293(2)
Radiation	MoKα	MoKα	MoKα
Monochromator	Graphite	Graphite	Graphite
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)/n	P2(1)/c	P2(1)/n
μ (mm^{-1})	0.318	0.334	0.331
Diffractometer	Nonius CAD4	Nonius CAD4	Nonius CAD4
Scan method	ω	ω	ω
2 θ range	3.12-24.98°	3.03-25.97°	2.03-25.97°
hkl range	±h, -k, ±1	-h, +k, ±1	±h, -k, +1
Reflections collected	6230	4859	7798
Independent			
reflections	3165	3385	6661
R_{int}	0.2769	0.0311	0.0241
Parameters refined	212	226	385
$R_1[I>2\sigma(I)]$[a]	0.0708	0.0508	0.0650
wR2 all reflections[b]	0.1929	0.12190	0.1878
Max./min. Δρ ($eÅ^{-3}$)	0.332/–0.366	0.256/–0.307	0.687/–0.411
Max. shift (Δ/σ)	0.007	0.001	0.001

[a] $R_1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$. [b] $wR_2 = [\Sigma\omega(F_o^2-F_c^2)^2 / \Sigma\omega(F_o^2)^2]^{1/2}$; $w^{-1} = \sigma^2(F^2) + (aP)^2 + bP$, where $P = (2F_c^2 + F_o^2)/3$ and a and b are constants set by the program.

TG-DTA measurements were made with a Shimadzu TGA-51 and DTA-50 equipments from room temperature to 1273 K and to 773 K respectively, using platinum pan, 20 mL/min. $N_{2\,(g)}$ purge and 50 mL/min air flux at a heating rate of 10ºC/min.

Results and Discussion

This new route of synthesis employed not only achieves better yields and high purity final products but it is also adequate for growing crystals, suitable for crystallographic structure determinations.

X-ray diffraction studies were performed on suitable single crystals. Table 2 shows crystal data and Table 3 reports relevant bond distances and angles. The structure of the compounds under investigation are displayed in Fig. 1. Interaction between monomeric units occurs through a 3-D network of hydrogen bonds that give rise to sulfonamide structures. The 3-D crystal structure of these sulfonamides is stabilized by ($N_{sulfonamide}$-H…$N(1)_{thiadiazole}$ and N_{amino}-H…$N(2)_{thiadiazole}$.

1,3,4-thiadiazole ring: The 1,3,4-thiadiazole ring is planar within the experimental error, such as in other compounds presenting this annular system [6,13,16-18]. The C-S, N-N and C-N bond distances are shorter than the corresponding single bonds. This fact suggests multiple order bonds and confers aromaticity to the ring. The C-S bond distances involve carbon atoms with sp^2 hybridization [16,17]. Our results are similar to those found for thiophene semicarbazole (1.722 Å)[19,20], acetazolamide (1.724 (2) Å) [17], and other compounds with this ring [6,13,18]. The N-N endocyclic bond distance is shorter than the corresponding to the simple N-N bond (1.40 Å). Similar values are found in compounds such as 5-aminotetrazole monohydrate (1.381 and 1.382 Å) and pyrazole (1.366 Å) [20]. The C-N endocyclic bond distances present double bond characteristics. The values found for **1**, **2** and **3** are supported by previous reports from Allen and al. [20] who informed $C(sp^2)$=N media bond distances of 1.302 (21) Å for -S-C=N- and 1.314 (11) Å for imidazole. Deviation of the bond angles to 120º in the 1,3,4-thiadiazole ring is a common feature in five-membered rings. The bond angles measured for **1**, **2** and **3** are similar to those in related compounds [6,13,16-18]

Sulfonamide group: The exocyclic C-S bond distances measured for **1**, **2** and **3** are 1.784 (5) Å, 1.775 (3) Å and 1.773 (4) Å, respectively. These values were also found in sulfonamides such as α-sulfanilamide (1.74 (1) Å), β-sulfanilamide (1.750 (2) Å), sulfathiazole III, (1.745 (5) Å and 1.769 (6) Å) and 1.759 (13) Å in many other sulfonamides [20]. As expected, the C-S exocyclic bond distance is longer than the corresponding C-S endocyclic bond for the three compounds under study. The S-N and O=S=O sulfonamide bond distances are comparable to those in related compounds [6,17,18]. Nevertheless, a slight difference was observed between both S=O bond distances within the molecule due to intermolecular H-bond interactions for all three sulfonamides. According to the bond angles informed in Table 3, it can be noted that the sulfonyl group presents a distorted tetrahedral arrangement around the S atom.

Carbonamide group: In the protected C(5) amino group, the found C-N exocyclic bond distances are typically of a $C(sp^2)$-N single bond. Moreover, the found bond distances for C=O and C-O-C are typically of $C(sp^2)$-O and $C(sp^3)$-O bonds distances respectively, similar to esters [20].

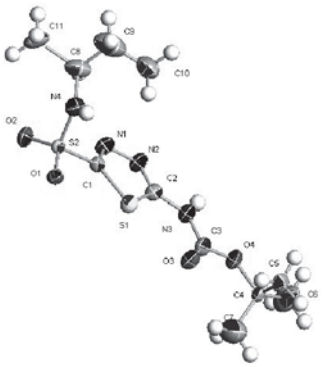
Table 3. *Bond lengths (Å) and angles (º) for compounds* ***1****,* ***2*** *and* ***3****.*

Lengths	Compound 1	Compound 2	Compound 3
Thiadiazole ring			
S(1)-C(1)	1.713 (5)	1.718 (3)	1.720 (4)
S(1)-C(2)	1.724 (5)	1.717 (3)	1.730 (4)
N(1)-C(1)	1.281 (6)	1.286 (4)	1.292 (5)
N(2)-C(2)	1.317 (7)	1.305 (4)	1.298 (5)
N(1)-N(2)	1.384 (6)	1.380 (3)	1.380 (4)
C1 Substituents			
C(1)-S(2)	1.784 (5)	1.775 (3)	1.773 (4)
S(2)-O(1)	1.439 (4)	1.429 (2)	1.424 (3)
S(2)-O(2)	1.409 (4)	1.419 (2)	1.406 (3)
S(2)-N(4)	1.591 (4)	1.587 (3)	1.583 (4)
N(4)-C(8)	1.487 (7)	1.461 (4)	1.463 (6)
C2 Substituents			
C(2)-N(3)	1.350 (7)	1.367 (4)	1.363 (5)
N(3)-C(3)	1.361 (7)	1.371 (4)	1.366 (5)
C(3)-O(3)	1.209 (6)	1.204 (3)	1.200 (5)
C(3)-O(4)	1.333 (6)	1.318 (3)	1.331 (5)
O(4)-C(4)	1.444 (7)	1.488 (3)	1.469 (5)
C(4)-C(5)	1.482 (12)	1.512 (4)	1.505 (7)
C(4)-C(6)	1.522 (8)	1.507 (5)	1.504 (6)
C(4)-C(7)	1.487 (11)	1.510 (4)	1.501 (7)
Angles			
Thiadiazole ring			
C(1)-S(1)-C(2)	85.5 (2)	85.66 (14)	85.22 (18)
S(1)-C(1)-N(1)	117.0 (4)	116.2 (2)	116.3 (3)
C(1)-N(1)-N(2)	111.1 (4)	111.3 (2)	111.2 (3)
N(1)-N(2)-C(2)	111.6 (4)	112.0 (2)	112.1 (3)
N(2)-C(2)-S(1)	114.7 (4)	114.9 (2)	115.1 (3)
C1 Substituents			
S(1)-C(1)-S(2)	122.2 (3)	121.98 (17)	122.9 (2)
N(1)-C(1)-S(2)	120.8 (4)	121.8 (2)	120.7 (3)
C(1)-S(2)-O(1)	107.7 (2)	105.41 (14)	104.58 (18)
C(1)-S(2)-O(2)	102.7 (3)	106.64 (15)	106.77 (19)
C(1)-S(2)-N(4)	107.4 (2)	107.43 (14)	106.5 (4)
S(2)-N(4)-C(8)	120.1 (3)	123.9 (2)	122.4 (3)
O(1)-S(2)-O(2)	121.2 (3)	119.64 (15)	121.5 (2)
O(1)-S(2)-N(4)	109.0 (2)	108.42 (16)	107.37 (19)
O(2)-S(2)-N(4)	108.0 (2)	108.69 (15)	109.1 (2)
C2 Substituents			
S(1)-C(2)-N(3)	124.7 (4)	123.9 (2)	124.0 (3)
N(2)-C(2)-N(3)	120.6 (4)	121.2 (3)	120.9 (3)
C(2)-N(3)-C(3)	124.1 (5)	122.4 (2)	123.4 (3)
N(3)-C(3)-O(3)	124.0 (5)	122.5 (3)	123.8 (4)
N(3)-C(3)-O(4)	108.0 (5)	109.3 (2)	107.6 (3)
O(3)-C(3)-O(4)	127.9 (5)	128.2 (3)	128.6 (4)
C(3)-O(4)-C(4)	122.2 (5)	121.1 (2)	121.9 (3)
O(4)-C(4)-C(5)	104.0 (8)	101.2 (2)	107.8 (4)
O(4)-C(4)-C(6)	102.1 (5)	109.1 (3)	101.9 (4)
O(4)-C(4)-C(7)	116.3 (8)	111.2 (3)	111.1 (4)
C(5)-C(4)-C(6)	105.0 (8)	111.4 (3)	112.5 (5)
C(6)-C(4)-C(7)	117.3 (9)	112.5 (3)	111.5 (5)
C(5)-C(4)-C(7)	110.6 (14)	111.0 (3)	111.7 (5)

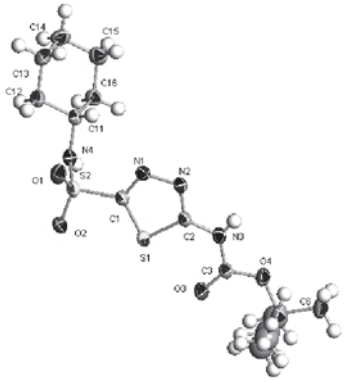
Table 4. *Assignation of FTIR spectra of substituted sulfonamides* ***1****,* ***2*** *and* ***3****.*

Assignation	1	2	3
$\nu NH_{Sulfonamide}$	3273 (m)	3343 (s)	3284 (s)
νNH_{amido}	3165 (w)	3141 (m)	3161 (m)
N-H…N bond	2857 (w) 2789 (w)	2782 (w) 2677 (w)	2840 (sh) 2791 (w)
ρNH	1088 (m) 1052 (w)	1090 (m) 1060 (m)	1088 (m) 1034 (w)
νCN 1,3,4-TDZ	1571 (s) 1452 (m)	1552 (s) 1424 (m)	1564 (s) 1433 (m)
νN-N	1160 (s)	1160 (s)	1161 (s)
νC-S	767 (w) 656 (m)	782 (w) 679 (m)	769 (w) 652 (m)
Ring bending	610 (m)	603 (s)	610 (m)
νC=O	1717 (s)	1724 (s)	1724 (s)
$\nu_{as}SO_2$ $\nu_{s}SO_2$ wag SO_2	1355 (m) 1127 (m) 582 (m)	1367 (m) 1110 (w) 588 (s)	1362 (m) 1127 (w) 584 (m)
νSN	886 (m)	872 (m)	881 (m)
νC-C *t*-butyl	1273-1247 (d, m)	1273-1245 (t, m)	1272-1248 (t, m)
νCH	2934 (m)	3028 (sh) 2937 (m)	2973 (m) 2935 (w)
δCH	1431 (m) 1394 (w) 1315 (s)	1496 (w) 1475 (w) 1443 (sh) 1391 (w) 1322 (m)	1458 (w) 1394 (w) 1315 (s)
ρCH	839 (vw) 818 (w) 682 (vw)	841 (m) 812 (m) 765 (w) 680 (vw)	816 (w) 678 (vw)

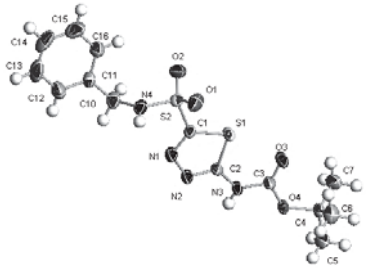
s: strong; m: media; w: weak; vw: very weak; sh: shoulder.
d: doublet; t: triplet; *t*-bu: *tert*-butyl; 1,3,4-TDZ: 1,3,4-thiadiazole ring; Sulf.: sulfonamide group
ν: stretching; δ: deformation; ρ: rocking; wag.: wagging.
s: symmetric; as: asymmetric.



(a) Compound 1



(b) Compound 2



(c) Compound 3

Figure 1*. The molecular structure of (a) compound* ***1****, (b) compound* ***2*** *and (c) compound* ***3*** *showing the atom-numbering scheme and probability displacement ellipsoids.*

Dihedral angles: Finally, the analysis of the dihedral angles led to the conclusion that the 5-amido group and the thiadiazole ring are coplanar within experimental error both being involved in an important electronic delocalization. Thus, the amide nitrogen has a planar triangular geometry as result of the N(sp^2) hybridization. It is worth noting that this electronic delocalization aids in the formation of intermolecular H-bonds.

The assignment of the FTIR spectra corresponding to **1**, **2** and **3** is shown in Table 4. Analysis of the spectra was based on general and particular bibliography [21]. Our results are in agreement with the theoretical spectrum obtained by quantum chemical calculations for a related sulfonamide: 5-amino-1,3,4-thiadiazole-2-sulfonamide [21]. For the molecules under study, the main fundamental vibrations are $\nu NH_{sulfonamide}$, νNH_{amide}, νC=O, $\nu_{as}SO_2$ and ν_sSO_2, νS-N and 1,3,4-thiadiazole ring modes.

N-H group modes: The $NH_{sulfonamide}$ modes were assigned at 3340-3270 cm^{-1}; they appear at lower frequencies than those expected for the free amine group (3422 and 3318 cm^{-1}) [22] due to the presence of the hydrogen bonds indeed observed in the crystalline package of these molecules ($N_{sulfonamide}$-H…$N(1)_{thiadiazole}$). The band located at lower frequencies (3170-3130 cm^{-1}) than that corresponding to the sulfonamido group is attributed to the νNH_{amido} mode. Other bands at lower frequencies (2875-2675 cm^{-1}) correspond to H-bond type N_{amido}-H…$N(2)_{thiadiazole}$ modes that form the framework and overlap with some overtones. These H-bond modes are important in monitoring complexation reactions with metallic ions.

Carbonyl mode: This mode appears at 1725 – 1700 cm^{-1} in agreement with the C=O modes of other sulfonamide compounds with similar C-O distances (1.20(9)Å), indicating the presence of a double bond [23].

SO_2 modes: Asymmetric and symmetric stretching vibrations of the SO_2 group were assigned. In these compounds, the presence of the $\nu_{as}SO_2$ (1375-1350 cm^{-1}) and ν_sSO_2 (1130-1105 cm^{-1}) modes are used as fingerprints to unequivocally identify the intermediate and final products in the second and third synthetic steps.

S-N mode: the νS-N of all monosubstituted sulfonamides in study shifted to lower frequencies, as compared to other reported sulfonamides [18, 21, 23]. The actual S-N distance, however, remained unchanged with respect to unsubstituted sulfonamides. This vibrational mode is also very useful for identification of the final synthetic products.

1,3,4-thiadiazole ring: Because of the rigidity of the ring, the vibrational spectra cannot be interpreted in terms of localized vibrations, since many atoms of the ring are involved in several vibrational modes [24]. Our assignments for the 1,3,4-thiadiazole ring modes were thus done in agreement with those reported by Edwards et al. [25] as well as with results from our previous work on related sulfonamides [23,26].

The assignment in the 500 – 250 cm^{-1} range is difficult to perform due to the presence of several bands of low intensity associated with librational and lattice modes, most of them strongly overlapped.

The TG-DTA diagrams corresponding to **1**, **2** and **3** are shown in Figures 2, 3 and 4. The DTA curve for **1** exhibits a peak before the melting point at 328 K indicating a reversible solid-solid transformation. On the other hand, it was observed total sample degradation at temperatures higher than that of the melting point for the three sulfonamides under investigation. No residual product was left after the complete heating process in which the temperature reached 1073 K.

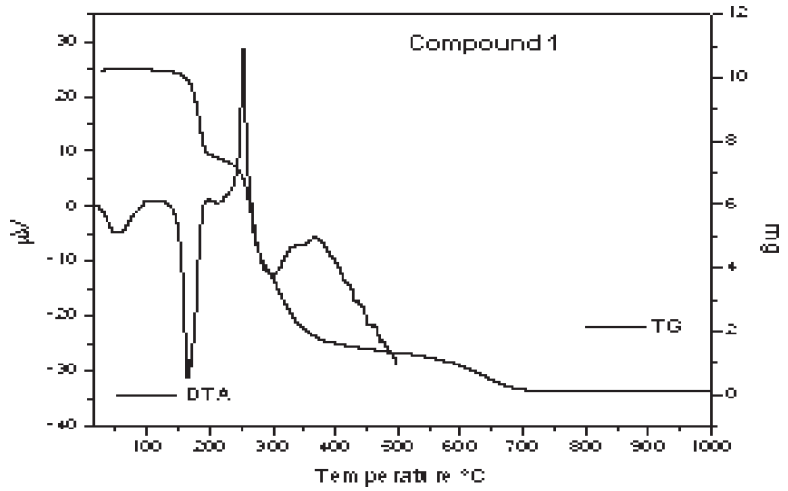


Figure 2. *TG-DTA curve of compound* ***1***

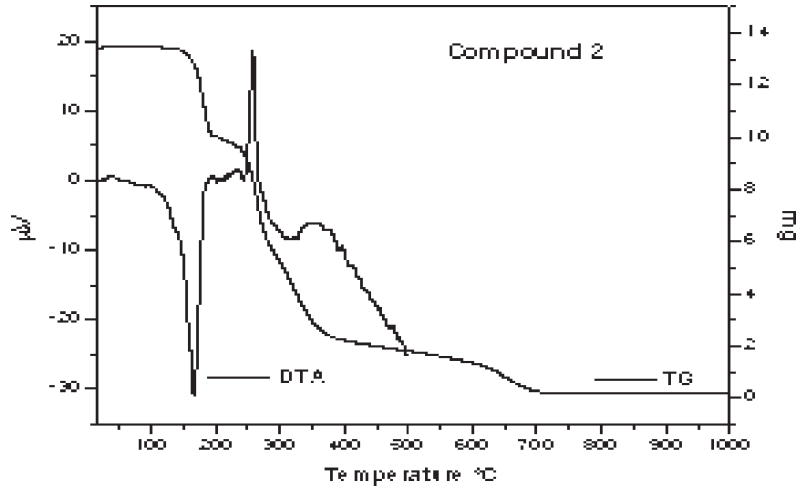


Figure 3. *TG-DTA curve of compound* ***2***

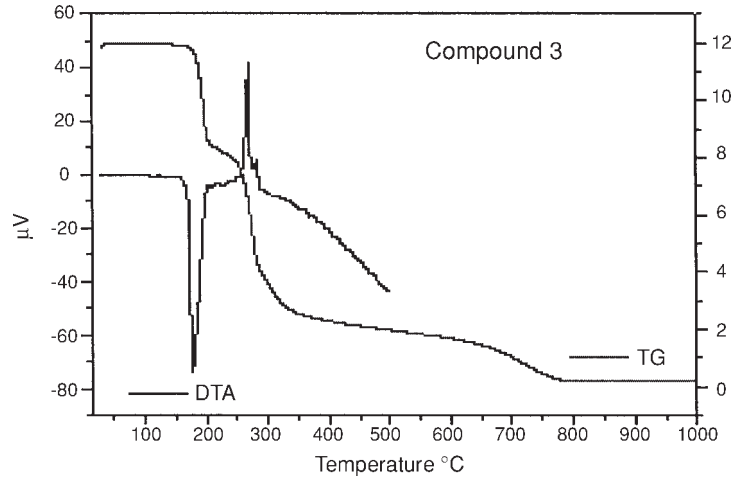


Figure 4*. TG-DTA curve of compound* ***3***

Conclusions

Single crystals of three novel 1,3,4-thiadiazole-5-(N-substituted)-sulfonamide derivatives have been spectroscopic and structurally characterized. As a result of the present research, we developed an optimized synthetic route that let us grow single crystals suitable for FTIR and X-ray diffraction measurements, thereby adding important information to the body of scientific knowledge on 1,3,4-thiadiazole ring compounds. According to our experimental results, it can be concluded that the substituents assayed do not modify the ring structure. The FTIR spectra provide a first insight on modes of NH…N hydrogen bond in these compounds. The high purity and excellent quality of the crystals obtained for the first time are promising in the sense that the methodology here reported can be used for the synthesis of these and other compounds of this class of sulfonamides for applications as pharmacological agents.

Supplementary material

Supplementary material has been sent in electronic format to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK as cif file Nº CCDC 216052 (compound **1**: $C_{13}H_{22}N_4O_4S_2$), 216053 (compound **2**: $C_{14}H_{18}N_4O_4S_2$) and 216051 (compound **3**: $C_{11}H_{20}N_4O_4S_2$), and can be obtained by contacting the CCDC. Final positional and thermal parameters, anisotropic thermal parameters, hydrogen-atoms parameters, distances and angles involving hydrogen atoms of these sulfonamides are also available from the authors on request.

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