Hindawi Publishing Corporation
Journal of Chemistry
Volume 2014, Article ID 929401, 5 pages
http://dx.doi.org/10.1155/2014/929401

Research Article

Synthesis and X-Ray Structure of (1*Z*,2*Z*)-1,2-Bis(2-(phenylsulfonyl)-1-(4-tolyl)ethylidene)hydrazine

Hatem A. Abdel-Aziz,[1,2] Hazem A. Ghabbour,[1] Khalid A. Al-Rashood,[1] and Hoong-Kun Fun[1,3]

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia*
[2]*Department of Applied Organic Chemistry, National Research Center, Dokki, Cairo 12622, Egypt*
[3]*X-Ray Crystallography Unit, School of Physics, Universiti Sains Malaysia (USM), 11800 Penang, Malaysia*

Correspondence should be addressed to Hatem A. Abdel-Aziz; hatem_741@yahoo.com

Received 7 September 2014; Accepted 26 October 2014; Published 22 December 2014

Academic Editor: Hakan Arslan

The title compound (1*Z*,2*Z*)-1,2-bis(2-(phenylsulfonyl)-1-(4-tolyl)ethylidene)hydrazine (**5**) was prepared, in 78% yield, by the reaction of 2-(phenylsulfonyl)-1-(4-tolyl)ethan-1-one (**3**) with hydrazine hydrate in acetic acid at 90°C under microwave irradiation in a closed vessel with power 100 W for 3 min. The structure of the newly synthesized compound was established under the basis of its IR, mass, ^{1}H NMR, and X-ray single crystal analysis. The crystal of **5** belongs to monoclinic space group, $P2_1/c$, with $a = 5.2944\ (3)$ Å, $b = 17.5748\ (9)$ Å, $c = 15.4701\ (8)$ Å, $\beta = 105.767\ (4)^\circ$, $Z = 2$, $V = 1385.30\ (13)$ Å^3, $Dc = 1.306$ Mg m^{-3}, $\mu = 2.05$ mm^{-1}, $F(000) = 572$, $R = 0.075$, and $wR = 0.224$ for 1419 observed reflections with $I > 2\sigma(I)$. The asymmetric unit of compound **5** contains one molecule with *Z* configuration about the C7=N1 and C7A=N1A double bond. This *Z* configuration of **5** is stabilized by intramolecular hydrogen bonds C1–H1A$\cdots$N1 and C1A–H1AA$\cdots$N1A. The molecular packing in the crystal structure of **5** is stabilized by intermolecular interactions forming a three-dimensional network.

1. Introduction

Hydrazones are a very important class of compounds with effective biological activities. They are found to possess anti-HIV [1], anticonvulsant [2], and antitubercular [3] activities. Furthermore, hydrazones have been reported as active antimicrobial agents where hydrazone function is the main scaffold in several marketed antimicrobial drugs such as the potent intestinal antiseptic drug nifuroxazide [4]. In addition, (*Z*)-*N*′-(2-oxoindolin-3-ylidene)formohydrazide exhibited a good activity against *S. aureus* microbe which is almost similar to that of ciprofloxacin [5]. Moreover, hydrazone derivatives have been reported as potent anticancer agents; for example, the modulation of activity of the well-known anticancer drug doxorubicin occurred through a conjugation with fatty acyl and terphenyl hydrazones [6]. In addition, isatin-based hydrazones have been reported as active agents against multidrug-resistant cancer cells [7] whereas chromene-based hydrazones showed cytotoxicity against K562, MDA-MB-468, and HT-29 cell lines [8]. Furthermore, aroylhydrazone derivatives have been reported as inhibitors of carbonic anhydrases from the extremophilic bacteria SspCA and SazCA [9].

On the other hand, sulfones received a special interest due to their significant biological activity; for example, sulfone function is essential in the antimicrobial drug dapsone [10]. β-Keto sulfones have been reported as key intermediates in the synthesis of several biologically active compounds [11]; for example, novel celecoxib analogs were synthesized as potent anti-inflammatory agents starting from some β-keto sulfone derivatives [12].

In the light of previous research publications and in continuation of our interests in the synthesis of biologically active compounds containing hydrazone function and/or sulfone moiety [5, 7–9, 12], we have reported in this study the microwave-assisted synthesis and X-ray single crystal

analysis of the title compound which is a sulfone-based hydrazone derivative.

2. Experimental

2.1. Chemistry

2.1.1. General. Melting point was determined on a Gallenkamp melting point apparatus and it is uncorrected. Infrared (IR) spectrum was recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR spectrum was scanned in DMSO-d_6 on a Bruker NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard. Coupling constants (J) are expressed in Hz. The mass spectrum was measured on an Agilent Triple Quadrupole 6410 QQQ LC/MS equipped with an ESI (electrospray ionization) source. The microwave irradiations were carried out in an Explorer-48 microwave reactor from CEM, USA.

2.1.2. Synthesis of 2-(Phenylsulfonyl)-1-(4-tolyl)ethan-1-one (3). To a solution of 2-bromo-1-(4-tolyl)ethan-1-one (**1**) (2.13 g, 10 mmol) in absolute ethanol (50 mL), sodium benzenesulfinate (**2**) (13 mmol) was added. The mixture was refluxed for 2 h and then left to cool. The reaction mixture was poured into cold water and the solid product was filtered off, washed with water, dried, and finally recrystallized from EtOH to afford compound **3** [13].

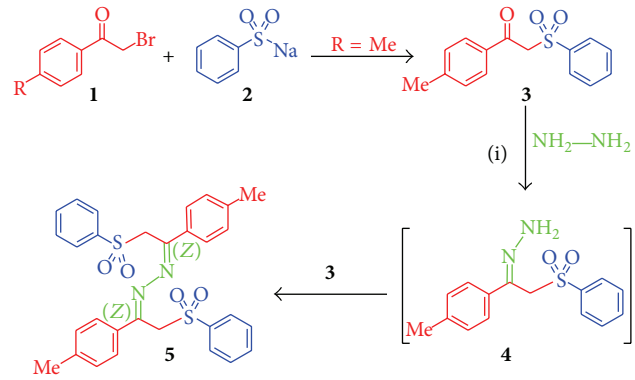
2.1.3. Synthesis of (1Z,2Z)-1,2-Bis(2-(phenylsulfonyl)-1-(4-tol-yl)ethylidene)hydrazine (5)

MWI Synthesis. A mixture of 2-(phenylsulfonyl)-1-(4-tolyl)ethan-1-one (**3**) (0.55 g, 2 mmol) and hydrazine hydrate (99%, 1.1 mmol) in glacial acetic acid (5 mL) was added to a closed vessel in a microwave reactor. The closed vessel was irradiated with microwaves at 100 W and 90°C and with 200 psi maximum pressure for 3 min (holding time). The vessel was cooled and the solid that formed was collected by filtration and washed with ethanol, dried, and finally recrystallized from AcOH to afford compound **5** in 78% yield.

Conventional Synthesis. A mixture of 2-(phenylsulfonyl)-1-(4-tolyl)ethan-1-one (**3**) (0.55 g, 2 mmol) and hydrazine hydrate (1.1 mmol) in glacial acetic acid (30 mL) was refluxed for 10 h and then left to cool. The precipitated product was filtered off, washed with ethanol, and dried. Recrystallization from AcOH afforded the corresponding compound **5** in 42% yield; m.p. 140–142°C; IR ν 1612 (C=N) cm^{-1}; ^{1}H NMR (DSMO-d_6, 500 MHz) δ 2.26 (s, 6H, $2CH_3$), 4.80 (s, 4H, $2CH_2$), 7.05-7.06 (m, 4H, ArHs), 7.47 (d, J = 8.0 Hz, 4H, ArHs), 7.58–7.61 (m, 4H, ArHs), 7.69–7.72 (m, 2H, ArHs), 7.92 (d, J = 8.0 Hz, 4H, ArHs); ^{13}C NMR (DSMO-d_6, 125 MHz) δ 20.62, 51.58, 125.11, 127.89, 128.43, 129.16, 132.14, 133.95, 135.22, 136.35, 139.50; MS (ESI) m/z 544.4 $[M]^+$.

2.2. X-Ray Crystallography

2.2.1. General. Single crystals were obtained by slow evaporation from acetic acid. A good crystal with a suitable size was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II CCD diffractometer equipped with graphite monochromatic CuK\α radiation (λ = 1.54178) at 293 (2) K. Cell refinement and data reduction were done by Bruker SAINT; program used to solve structure and refine structure is SHELXS-97 [14]. The final refinement was performed by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on F^2. All the hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Multiscan absorption correction was applied by the use of SADABS software.



Scheme 1: Synthetic pathway of compound **5**. Reagents and conditions: (i) NH_2–NH_2 (99%)/AcOH, MWI, 100 W, 90°C, 3 min, 78% yield.

2.2.2. Crystal Data of 5. Molecular formula: $C_{30}H_{28}N_2O_4S_2$, formula weight: 544.66, monoclinic, $P2_1/c$, a = 5.2944 (3) Å, b = 17.5748 (9) Å, c = 15.4701 (8) Å, β = 105.767 (4)°, V = 1385.30 (13) Å^3, and D_{calc} = 1.306 Mg m^{-3}. A total of 5664 reflections were measured, of which 2120 were independent. R_{int} = 0.037, dataset (h; k; l) = −6, 4; −20, 18; −14, 17. Refinement of F^2, against all reflections, led to $R[F^2 > 2\sigma(F^2)]$ = 0.075, $wR(F^2)$ = 0.224, S = 1.04. The labeled displacement ellipsoid plot of this molecule showing the three intramolecular interactions is shown in Figure 2.

3. Results and Discussion

3.1. Chemistry. Hydrazones can be synthesized by reacting hydrazines with carbonyl compounds in various organic solvents such as MeOH, EtOH, BuOH, THF, AcOH, or AcOH/EtOH. Also hydrazones can be synthesized by the coupling of aryldiazonium salts with active methylene compounds [15]. In this study, 2-(phenylsulfonyl)-1-(4-tolyl)ethan-1-one (**3**) [13] was synthesized by the reaction of 2-bromo-1-(4-tolyl)ethan-1-one (**1**) with sodium benzenesulfinate (**2**) (Scheme 1). The reaction of 2-(phenylsulfonyl)-1-(4-tolyl)ethan-1-one (**3**) with hydrazine hydrate in acetic acid at 90°C under microwave irradiation in a closed vessel with power 100 W for 3 min (holding time) resulted in the formation of the title compound **5**, as final isolable product, in 78% yield (Scheme 1). The conventional synthesis of **5** at refluxing temperature for 10 h afforded 42% yield. However, the

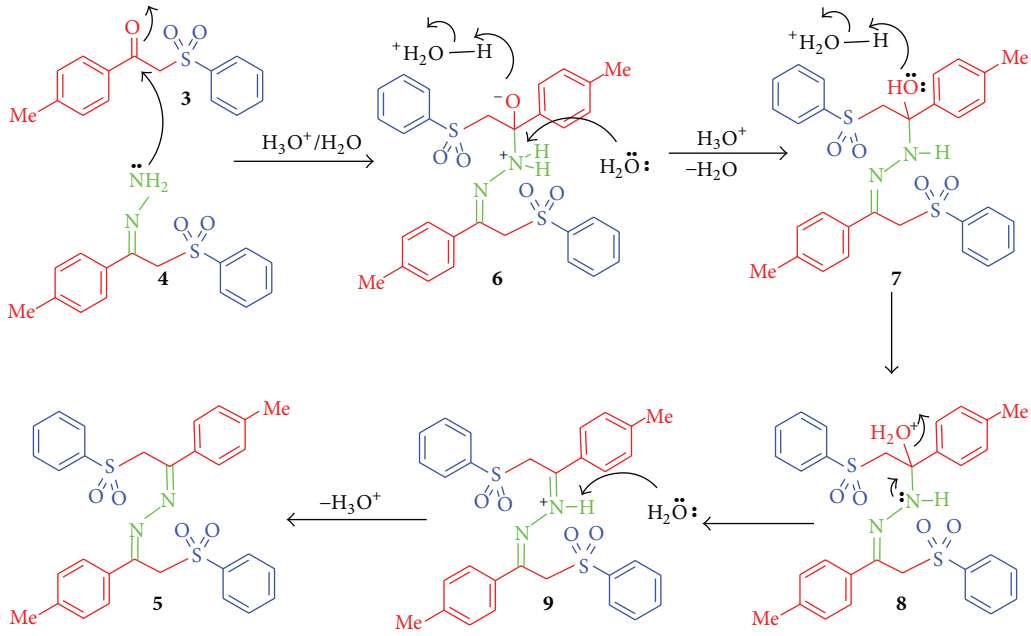


Figure 1: Mechanistic pathway of the reaction of intermediate **4** with compound **3**.

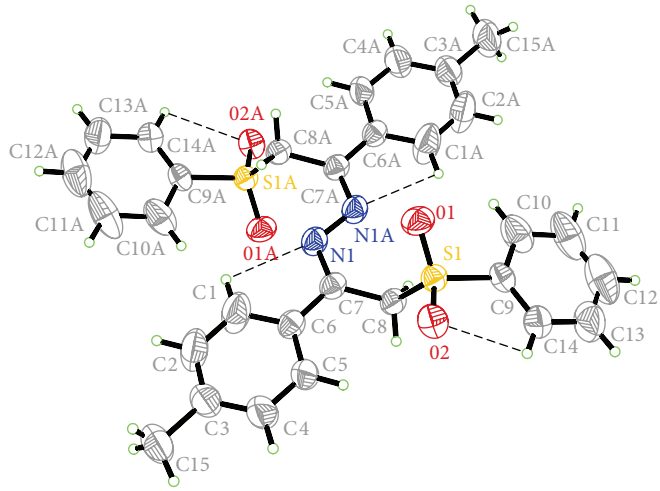


Figure 2: ORTEP diagram of compound **5** 40% probability ellipsoid, showing intramolecular hydrogen bonds.

reaction of compound **3** with hydrazine hydrate in MeOH, EtOH, BuOH, THF, or AcOH/EtOH, under the previous conditions, gave a poor yield of compound **5** whereas using of AcOH gave the highest yield of **5** (78%). Recently, we have reported the reaction of sulfone **3** (R=Cl) with hydrazine hydrate in ethanol, in the presence of catalytic amount of acetic acid, at 90°C/100 W/30 sec to give hydrazone **4** (R=Cl), in 86% yield, as final isolable product [16].

The structure of compound **5** was confirmed using spectral data and X-ray single crystal analysis (crystallographic data for the structure **5** has been deposited with the Cambridge Crystallographic Data Center (CCDC) under the numbers CCDC 943715-16. Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk/].). The ^{1}HNMR (DSMO-d_6, 500 MHz) of **5** revealed the singlet signal of methylene protons at δ 4.80 in addition to the singlet signal of methyl protons which appeared at δ 2.26. ^{13}C NMR (DSMO-d_6, 125 MHz) of compound **5** exhibited the signal of two methyl carbons at δ 20.62 while the signal of methylene carbons appeared at δ 51.58. The MS (ESI) of compound **5** revealed a pek at m/z 544.4 equal to $[M]^+$.

The condensation reaction of intermediate **4** with compound **3** through loss of water can be described as an addition-elimination reaction. In the presence of acidic medium, nucleophilic addition of the $-NH_2$ group of **4** to the C=O function of sulfone **3** was followed by the elimination of a H_2O molecule (Figure 1).

Table 1: Selected bond distances (Å), bond angles (°), and torsion angles (°) of compound **5**.

Bond distances			
S1–O1	1.419 (5)	S1–C9	1.766 (5)
S1–O2	1.424 (4)	N1–C7	1.290 (7)
S1–C8	1.792 (5)	N1–N1A	1.419 (5)
Bond angles			
O1–S1–O2	118.6 (3)	N1i–N1–C7	113.8 (4)
O1–S1–C8	108.8 (2)	N1–C7–C6	116.8 (4)
O1–S1–C9	109.0 (3)	N1–C7–C8	122.8 (4)
O2–S1–C8	108.8 (2)	S1–C8–C7	112.3 (4)
O2–S1–C9	108.4 (2)	S1–C9–C10	119.6 (5)
C8–S1–C9	101.9 (2)	S1–C9–C14	119.2 (4)
Torsion angles			
O1–S1–C8–C7	−43.1 (4)	C5–C6–C7–C8	3.8 (8)
O2–S1–C8–C7	87.4 (4)	C10–C9–C14–C13	0.2 (11)
C9–S1–C8–C7	−158.2 (4)	S1–C9–C10–C11	−177.3 (7)
C14–C9–S1–C8	−97.4 (5)	C5–C6–C7–N1	−179.3 (6)
S1–C8–C7–N1	91.7 (5)		

Symmetry code: (i) $-x-2, -y-1, -z-$.

Table 2: Hydrogen-bond geometry (Å, °) of compound **5**.

D–H$\cdots A$	D–H	H$\cdots A$	$D\cdots A$	D–H$\cdots A$
C1–H1A$\cdots$N1	0.9300	2.4200	2.744 (9)	101.00
C8–H8A$\cdots$N1i	0.9700	2.3300	2.683 (7)	100.00
C8–H8B$\cdots$O1ii	0.9700	2.5600	3.444 (7)	151.00
C14–H14A$\cdots$O2	0.9300	2.5300	2.905 (8)	105.00

Symmetry codes: (i) $-x-2, -y-1, -z-2$; (ii) $x+1, y, z$.

3.2. X-Ray Crystallography. The asymmetric unit of the titled compound **5**, $C_{30}H_{28}N_2O_4S_2$, contains one-half of a molecule. The other half of the molecule is generated by a 2_1 screw axis with symmetry operator $(-x, y+1/2, -z)$. The full molecule has a Z configuration about the C7=N1 and C7A=N1A double bond (Figure 2).

This Z configuration of compound **5** is stabilized by intramolecular hydrogen bonds C1–H1A$\cdots$N1, C1A–H1AA$\cdots$N1A, and C14–H14A$\cdots$O2.

The single bond N1–N1A is clearly characterized by the distance of 1.419 (5) Å. The double bond of C7=N1 is characterized by the distance of 1.290 (7) Å. The dihedral angle between the two benzene (C1–C6) and (C9–C14) rings is 16.89 (5)°. The hydrazine group is twisted slightly, with a C6–C7–N1–N1A torsion angle of –177.79 (2)°. The molecules packing in the crystal structure of **5** is stabilized by intermolecular interactions forming a three-dimensional network (Figure 3).

Selected bond distances (Å), bond angles (°), and torsion angles (°) of compound **5** are illustrated in Table 1. Hydrogen bonds geometry of the crystal **5** is showed in Table 2.

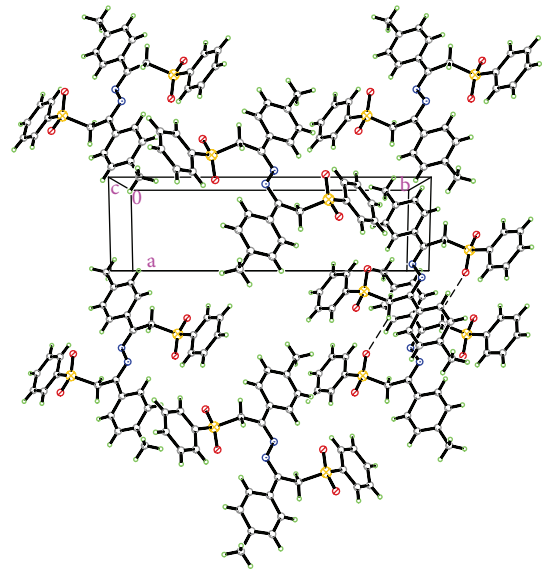


Figure 3: Crystal packing of **5** showing intermolecular hydrogen bonds as dashed lines.

4. Conclusion

In conclusion, the title compound **5** was prepared efficiently by the reaction of sulfone **3** with hydrazine hydrate in acetic acid at 90°C/MWI/100 W/3 min. The 3D structure of the newly synthesized compound **5** determined by X-ray single crystal analysis.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at the King Saud University for its funding of this research through the Research Group Project no. RGP-VPP-321.

References

[1] P. Vicini, M. Incerti, P. la Colla, and R. Loddo, "Anti-HIV evaluation of benzo[*d*]isothiazole hydrazones," *European Journal of Medicinal Chemistry*, vol. 44, no. 4, pp. 1801–1807, 2009.

[2] J. Jain, Y. Kumar, R. Sinha, R. Kumar, and J. Stables, "Menthone aryl acid hydrazones: a new class of anticonvulsants," *Medicinal Chemistry*, vol. 7, no. 1, pp. 56–61, 2011.

[3] P. Dandawate, K. Vemuri, E. M. Khan, M. Sritharan, and S. Padhye, "Synthesis, characterization and anti-tubercular activity of ferrocenyl hydrazones and their β-cyclodextrin conjugates," *Carbohydrate Polymers*, vol. 108, no. 1, pp. 135–144, 2014.

[4] C. M. C. Ernest, "Antibacterial nitrofurfurylidene derivatives and methods of using same," US Patent, 3290213 A, 1966.

[5] H. A. Abdel-Aziz, H. A. Ghabbour, W. M. Eldehna, M. M. Qabeel, and H.-K. Fun, "Synthesis, crystal structure and biological activity of *cis/trans* amide rotomers of (*Z*)-*N*′-(2-oxoindolin-3-ylidene)formohydrazide," *Journal of Chemistry*, vol. 2014, Article ID 760434, 7 pages, 2014.

[6] K. Effenberger, S. Breyer, and R. Schobert, "Modulation of doxorubicin activity in cancer cells by conjugation with fatty acyl and terpenyl hydrazones," *European Journal of Medicinal Chemistry*, vol. 45, no. 5, pp. 1947–1954, 2010.

[7] T. Aboul-Fadl, A. Kadi, and H. A. Abdel-Aziz, "Novel N, N′-Hydrazino-bis-isatin Derivatives with Selective Activity Against Multidrug-Resistant Cancer Cells," US Patent no. 20120252860, 2012.

[8] H. A. Abdel-Aziz, T. Elsaman, A. Al-Dhfyan, M. I. Attia, K. A. Al-Rashood, and A. R. M. Al-Obaid, "Synthesis and anticancer potential of certain novel 2-oxo-N'-(2-oxoindolin-3-ylidene)-2H-chromene-3-carbohydrazides," *European Journal of Medicinal Chemistry*, vol. 70, pp. 358–363, 2013.

[9] A. M. Alafeefy, H. A. Abdel-Aziz, D. Vullo et al., "Inhibition of carbonic anhydrases from the extremophilic bacteria *Sulfurihydrogenibium yellostonense* (SspCA) and *S. azorense* (SazCA) with a new series of sulfonamides incorporating aroylhydrazone-, [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazinyl- or 2-(cyanophenylmethylene)-1,3,4-thiadiazol-3(2*H*)-yl moieties," *Bioorganic & Medicinal Chemistry*, vol. 22, no. 1, pp. 141–147, 2014.

[10] G. Wozel and C. Blasum, "Dapsone in dermatology and beyond," *Archives of Dermatological Research*, vol. 306, no. 2, pp. 103–124, 2014.

[11] Y. M. Markitanov, V. M. Timoshenko, and Y. G. Shermolovich, "β-Keto sulfones: preparation and application in organic synthesis," *Journal of Sulfur Chemistry*, vol. 35, no. 2, pp. 188–236, 2014.

[12] H. A. Abdel-Aziz, K. A. Al-Rashood, K. E. H. Eltahir, and G. M. Suddek, "Synthesis of N-benzenesulfonamide-1H-pyrazoles bearing arylsulfonyl moiety: novel celecoxib analogs as potent anti-inflammatory agents," *European Journal of Medicinal Chemistry*, vol. 80, pp. 416–422, 2014.

[13] H. A. Abdel-Aziz, K. A. Al-Rashood, H. A. Ghabbour, H.-K. Fun, and T. S. Chia, "1-(4-Methylphenyl)-2-(phenylsulfonyl)ethanone," *Acta Crystallographica Section E*, vol. 68, part 4, Article ID o1033, p. o1033, 2012.

[14] G. M. Sheldrick, "A short history of SHELX," *Acta Crystallographica Section A*, vol. 64, no. 1, pp. 112–122, 2008.

[15] S. Bala, G. Uppal, A. Kajal, S. Kamboj, and V. Sharma, "Hydrazones as promising lead with diversity in bioactivity-therapeutic potential in present scenario," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 18, no. 1, pp. 65–74, 2013.

[16] H. A. Abdel-Aziz, H. A. Ghabbour, M. A. Bhat, and H.-K. Fun, "Microwave-assisted synthesis and characterization of certain oximes, hydrazones and olefins derived from β-keto sulfones," *Journal of Chemistry*, vol. 2014, Article ID 532467, 6 pages, 2014.