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Synthesis and Crystal Structure of [2-Chloro-4-(methylsulfonyl)phenyl]methanol

XIA YUAN, FEI LI, YU JIANG, CHUAN ZHANG* and LEI JIN*

Department of Science for Identifying Chinese Materia Medica, School of Pharmacy, Second Military Medical University, Shanghai 200433, P.R. China

*Corresponding authors: Fax: +86 21 81871359; Tel: +86 21 81871358; E-mail: zhangchuan@smmu.edu.cn; jinl_2001@126.com

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The crystal structure of the [2-chloro-4-(methylsulfonyl)phenyl]methanol has been determined by single crystal X-ray diffraction method. The crystal belongs to monoclinic, space group P2(1)/c, with a = 8.208(4), b = 4.870 (2), c = 23.349 (10) Å, α = 90, β = 97.160 (6), γ = 90°, V = 926.0 (7)Å^3, Z = 4, D_x = 1.583 Mg/m^3, λ(MoKα) = 0.71073, F(000) = 456, μ(MoKα) = 0.607 mm^{-1}, R = 0.0506 and wR = 0.1231 for 0.1263 reflections with I > 2σ (I). The S atom has a distorted tetrahedral geometry with bond angles ranging from 103.03 (12)° to 118.13 (13)°. The crystal structure is stabilized by intermolecular hydrogen bonds and π-π stacking interactions.

Keywords: Synthesis, Crystal structure, [2-Chloro-4-(methylsulfonyl)phenyl]methanol.

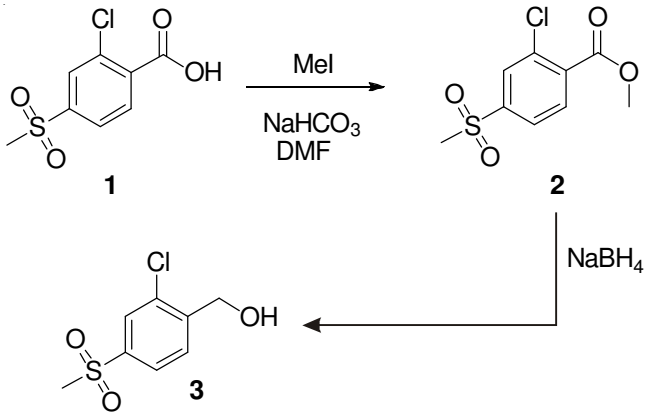
INTRODUCTION

p-Methylsulfonyl toluene has been widely incorporated into a variety of biologically active compounds. The *p*-methylsulfonyl toluene moiety has been identified as an important molecular component in various classes of cyclooxygenase-2 (COX-2) inhibitors[1-3], anticancer drugs[4], human leukocyte elastase inhibitors[5], analgesics[6], vascular adhesion protein-1 (VAP-1) inhibitors[7] and allosteric glucokinase activators[8]. More and more *p*-methylsulfonyl toluene derivatives have been developed in recent years[4]. Inspired by their research work, we also synthesized the compound [2-chloro-4-(methylsulfonyl) phenyl]methanol. In order to confirm its structure, a single crystal of this compound was obtained from a solvent mixture of MeOH and water (3:1), and the molecular structure was determined by X-ray diffraction.

EXPERIMENTAL

The melting point was determined on a Yamato MP-21 melting point apparatus and the thermometer was uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-300P Instrument (300 MHz) with $CDCl_3$ as the solvent. ESI mass spectra were performed on an API-3000 LC-MS spectrometer. The single-crystal structure was determined on a Rigaku Saturn CCD area detector. All the reagents were of analytical-reagent grade.

Synthesis and characterization: The [2-chloro-4-(methylsulfonyl)phenyl]methanol (**3**) was prepared as follows (**Scheme-I**):



Scheme-I: Procedure of preparing the title compound (**3**)

Preparation of compound 2: A mixture of 2-chloro-4-(methylsulfonyl)benzoic acid (**1**) (20 g, 100 mmol), $NaHCO_3$ (16.8 g, 200 mmol) in DMF (450 mL) was added CH_3I (71 g, 31 mL) dropwise at 0 °C under N_2, after addition, the mixture was stirred at room temperature overnight. After the completion of reaction the reaction mixture was added water (1 L) and extracted with EtOAc (500 mL × 3). The extract was washed with saturated brine (500 mL) succesively. The organic layer was dried over Na_2SO_4, then concentrated to afford the methyl 2-chloro-4-(methylsulfonyl)benzoate (**2**) which used into next step directly. (20 g), Yield: 95 % white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 1.2 Hz, 1H, Ar-H), 7.92-7.84 (m, 2H, Ar-H), 4.01 (s, 3H, OCH_3), 3.31 (s, 3H, SCH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 165.62, 144.59, 141.83, 136.72, 129.35,

128.41, 126.79, 50.21, 45.37. MS(ESI) *m/z* calcd. for $C_9H_9ClO_4S$ 248.68, found $[M - H]^+$ 247.3.

Synthesis of compound 3: A mixture of methyl 2-chloro-4-(methylsulfonyl)benzoate (2) (6.8 g, 27.6 mmol) in EtOH (200 mL) was added $NaBH_4$ (6 g, 157.9 mmol) in portions over 15 min at 0 °C under N_2, after addition, the mixture was stirred at room temperature for 1 h. After the completion of reaction the reaction mixture was quenched with water (100 mL) and removed the EtOH, then extracted with EtOAc (50 mL × 3). The extract was washed with saturated brine (150 mL) succesively. The organic layer was dried over Na_2SO_4, then concentrated to afford the [2-chloro-4-(methylsulfonyl)phenyl]methanol (**3**). (5 g), Yield: 80 %, white solid; m.p. 115.3-117.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.82-7.74 (m, 2H, Ar-H), 4.84 (s, 2H, CH_2), 3.05 (s, 3H, CH_3), 2.47 (br, 1H, OH). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 144.82, 140.38, 132.99, 128.62, 127.91, 125.74, 61.89, 44.49. MS(ESI) *m/z* calcd. for $C_8H_9ClO_3S$ 220.67, found $[M - H]^+$ 218.9.

Crystallographic studies: The title compound was dissolved in 10 mL a solvent mixture of MeOH and water (3:1) and colorless transparent crystals suitable for X-ray analysis grew over a period of two week when the solution was exposed to air at room temperature. The crystal having approximate dimensions of 0.15 × 0.12 × 0.10 mm was mounted on the top of a glass fiber in a random orientation. The data were collected by a Bruker SMART 1000 CCD area detector diffractometer equipped with a graphite-monochromatized MoKaradiation radiation (λ = 0.71073 Å) by using a φ-ω scan mode at 293 K. A total of 7790 reflections were collected in the range of 1.43 < θ < 25.01°, of which 3457 were independent (R_{int} = 0.1239) and 2378 were observed with I > 2σ (I).

The data collection and procession were performed with program SMART and SHELXTL[9]. The structure was solved by direct methods and refined by fullmatrix least-squares/difference Fourier techniques with SHELXS-97 and SHELXL-97 programs[10]. All non-hydrogen atoms were refined with anisotropic displacement parameters. After that, all hydrogen atoms were located theoretically and refined with riding model position parameters and fixed isotropic thermal parameters. The final R = 0.1083, wR = 0.3062 ($w = 1/[\sigma^2(F_o^2) + (0.2P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$), $(\Delta/\sigma)_{max}$ = 0.004, S = 1.104, $(\Delta\rho)_{max}$ = 1.032 and $(\Delta\rho)_{min}$ = -0.470 e/Å^{-3}.

RESULTS AND DISCUSSION

The title compound was prepared according to (**Scheme-I**). The ^{1}H NMR, ^{13}C NMR, MS and melting point for the product are in good agreement with the title compound. In order to confirm the configuration of the product, a single crystal of the title compound was cultured for X-ray diffraction analysis. The crystal belongs to monoclinic with space group P2(1)/c. The molecular structure and perspective view of the crystal packing in a unit cell of the title compound are shown in Figs. 1 and 2, respectively. The selected bond lengths are listed in Table-1 and the bond angles in Table-2. The hydrogen bond lengths and bond angles are listed in Table-3.

In the compound, the bond lengths and bond angles in the phenyl ring are generally normal. The bond lengths of O(2)-IS(1) (1.4329(19)Å) and O(3)-S(1) (1.4329(19)Å) are in agreement with those of similar structures (O-S, 1.430(2) Å and 1.431(2)[11]. The S atom exhibits significant deviation from a regular tetrahedron, with the largest deviations being seen for the O(3)-S(1)-O(2) [118.13 (13)°] and C(7)-S(1)-C(4) [103.74(12)°] angles. The widening of the angles may be due to repulsive interactions between the two short S=O bonds, similar to what is observed in related structures[12].

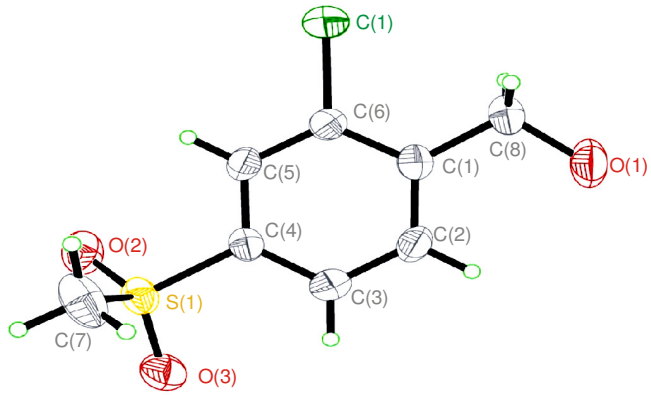


Fig. 1. Molecular structure of the title compound

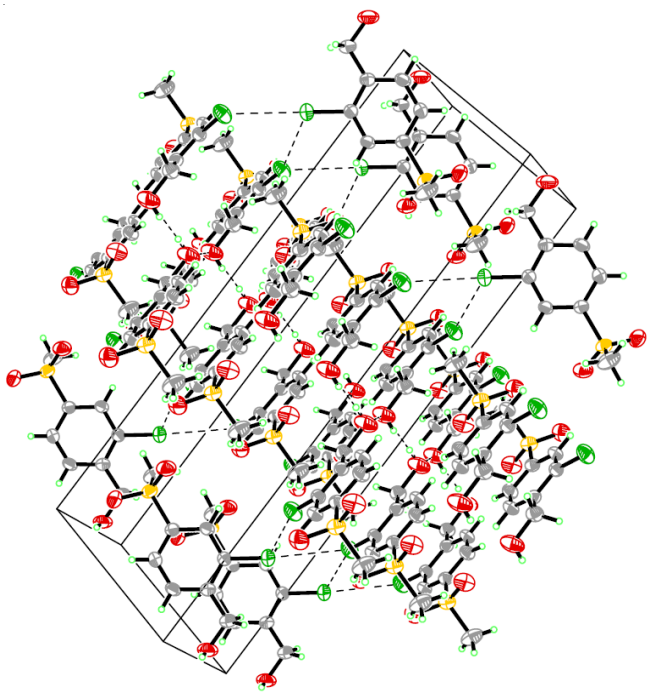


Fig. 2. Crystal packing of the title compound

TABLE-1
SELECTED BOND LENGTHS (Å) FOR THE TITLE COMPOUND

Bond	Dist.	Bond	Dist.
O(1)-C(8)	1.408(3)	C(3)-C(4)	1.385(3)
O(1)-H(1A)	0.78(2)	C(3)-H(3)	0.9300
O(2)-S(1)	1.4329(19)	C(4)-C(5)	1.383(3)
O(3)-S(1)	1.4320(18)	C(5)-C(6)	1.377(3)
S(1)-C(7)	1.746(3)	C(5)-H(5)	0.9300
S(1)-C(4)	1.763(2)	C(6)-C1(1)	1.737(2)
C(1)-C(2)	1.390(3)	C(7)-H(7A)	0.9600
C(1)-C(6)	1.394(3)	C(7)-H(7B)	0.9600
C(1)-C(8)	1.501(3)	C(7)-H(7C)	0.9600
C(2)-C(3)	1.381(3)	C(8)-H(8A)	0.9700
C(2)-H(2)	0.9300	C(8)-H(8B)	0.9700

TABLE-2
SELECTED BOND ANGLES (°) FOR THE TITLE COMPOUND

Angles	(°)	Angles	(°)	Angles	(°)
C(8)-O(1)-H(1A)	109(3)	C(2)-C(3)-C(4)	119.7(2)	S(1)-C(7)-H(7A)	109.5
O(3)-S(1)-O(2)	118.13(12)	C(2)-C(3)-H(3)	120.1	S(1)-C(7)-H(7B)	109.5
O(3)-S(1)-C(7)	109.04(14)	C(4)-C(3)-H(3)	120.1	H(7A)-C(7)-H(7B)	109.5
O(2)-S(1)-C(7)	107.89(14)	C(5)-C(4)-C(3)	121.0(2)	S(1)-C(7)-H(7C)	109.5
O(3)-S(1)-C(4)	107.98(11)	C(5)-C(4)-S(1)	119.28(17)	H(7A)-C(7)-H(7C)	109.5
O(2)-S(1)-C(4)	109.12(11)	C(3)-C(4)-S(1)	119.59(17)	H(7B)-C(7)-H(7C)	109.5
C(7)-S(1)-C(4)	103.74(12)	C(6)-C(5)-C(4)	118.1(2)	O(1)-C(8)-C(1)	112.6(2)
C(2)-C(1)-C(6)	117.4(2)	C(6)-C(5)-H(5)	120.9	O(1)-C(8)-H(8A)	109.1
C(2)-C(1)-C(8)	122.2(2)	C(4)-C(5)-H(5)	120.9	C(1)-C(8)-H(8A)	109.1
C(6)-C(1)-C(8)	120.4(2)	C(5)-C(6)-C(1)	122.8(2)	0(1)-C(8)-H(8B)	109.1
C(3)-C(2)-C(1)	121.0(2)	C(5)-C(6)-C1(1)	118.43(17)	C(1)-C(8)-H(8B)	109.1
C(3)-C(2)-H(2)	119.5	C(1)-C(6)-C1(1)	118.78(17)	H(8A)-C(8)-H(8B)	107.8
C(1)-C(2)-H(2)	119.5	C(7)-C(12)-C(11)	119.4(4)	C(24)-C(25)-C(26)	118.9(4)
C(6)-C(5)-S(1)	129.5(3)	–	–	–	–

TABLE-3
HYDROGEN BOND LENGTHS (Å) AND BOND ANGLES (º)

D-H···A	d(D-H)	d(H···A)	d(D···A)	∠(DH···A) (º)	Symmetry code
O(1)-H(1A)···O(1)#1	0.78(2)	2.07(3)	2.840(4)	168(4)	-x + 2, -y + 1, -z

In the solid state of this construction, the crystal structure is stabilized by an efficient three-dimensional network formed by C-H···O intermolecular interaction hydrogen bonds and π-π stacking interactions as shown in Table-3 and Fig. 2.

Conclusion

In conclusion, the compound (2-chloro-4-(methylsulfonyl)phenyl)methanol, was synthesized and characterized by means of ^{1}H NMR, ^{13}C NMR, MS and X-ray diffraction. The crystal belongs to monoclinic with space group P2(1)/n and the crystal structure is stabilized by intermolecular hydrogen bonds and π-π stacking interactions.

Supplementary material

The full crystallographic information has been deposited with the Cambridge Crystallographic Data Center, CCDC No. 937306. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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REFERENCES

1. P.G. De Benedetti, U. Folli, D. Iarossi and C. Frassineti, *J. Chem. Soc. Perkin Trans. II*, 1527 (1985).
2. D. Dubé, C. Brideau, D. Deschênes, R. Fortin, R.W. Friesen, R. Gordon, Y. Girard, D. Riendeau, C. Savoie and C.-C. Chan, *Bioorg. Med. Chem. Lett*., **9**, 1715 (1999).
3. F. Wuest, X. Tang, T. Kniess, J. Pietzsch and M. Suresh, *Bioorg. Med. Chem. Lett*., **17**, 1146 (2009).
4. S. Ovais, K. Javed, S. Yaseen, R. Bashir, P. Rathore, R. Yaseen, A.D. Hameed and M. Samim, *Eur. J. Med. Chem*., **67**, 352 (2013).
5. A.G. Romero, W.H. Darlington, M.F. Piercey and R.A. Lahti, *Bioorg. Med. Chem. Lett*., **2**, 1703 (1992).
6. G. Gonzalez-Martin, C. Lyndon and C. Sunkel, *Eur. J. Pharm. Biopharm*., **46**, 293 (1998).
7. T. Inoue, M. Morita, T. Tojo, A. Nagashima, A. Moritomo, K. Imai and H. Miyake, *Bioorg. Med. Chem. Lett*., **21**, 2478 (2013).
8. T. Iino, D. Tsukahara, K. Kamata, K. Sasaki, S. Ohyama, H. Hosaka, T. Hasegawa, M. Chiba, Y. Nagata, J. Eiki and T. Nishimura, *Bioorg. Med. Chem. Lett*., **17**, 2733 (2009).
9. G.M. Sheldrick, Programs SMART and SHELXTL, Bruker AXS, Inc., Madison, WI, USA (2003).
10. G.M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures and SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany (1997).
11. U. Sankar, V. Sabari, S. Mahalakshmi *et al*., *Acta Crystallogr*., **E69**, o1387 (2013).
12. G. Chakkaravarthi, V. Dhayalan, A.K. Mohanakrishnan *et al*., *Acta Crystallogr*., **E64**, o542 (2008).