Asian Journal of Chemistry; Vol. 26, No. 22 (2014), 7766-7768

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.17765

Synthesis, Characterization and Crystal Structure of *N*-(4-(4-Fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide

JIA-YING XU[1,*], WEI-HUA CHENG[2], XUN ZHU[2], HUAN-LING WU[2] and KAI WANG[3]

[1]College of Chemical and Biological Engineering, Yancheng Institute of Technology, Yancheng 224051, Jiangsu Province, P.R. China
[2]Department of Light Chemical Engineering, Yancheng Institute of Industry Technology, Yancheng 224051, Jiangsu Province, P.R. China
[3]High Technology Research Institute of Nanjing University, Changzhou, 213162, Jiangsu Province, P.R. China

*Corresponding author: E-mail: xujiaying-1984@163.com

Received: 5 April 2014; *Accepted*: 9 June 2014; *Published online*: 6 November 2014; AJC-16231

N-[4-(4-Fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethane sulfonamide (**I**), an important intermediate to synthesize rosuvastatin, an HMG-CoA reductase inhibitor. It was prepared from methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylamino)pyrimidine-5-carboxylate (**1**) *via* mesylation by mesyl chloride and sodium *tert*-pentoxide, then reduction by DIBAL/HCl. The product was characterized by NMR and LC-MS. The crystal structure of compound **I** was investigated using X-ray diffraction and SHELXTL-97 software. The result indicated that compound **I** crystallized in the monoclinic system, space group C2/C with a = 29.683(6), b = 7.6290 (15), c = 18.215(4) Å, V = 3451.1 (16) Å^3; Z 8.

Keywords: Rosuvastatin, Synthesis, Characterization, Crystal structure.

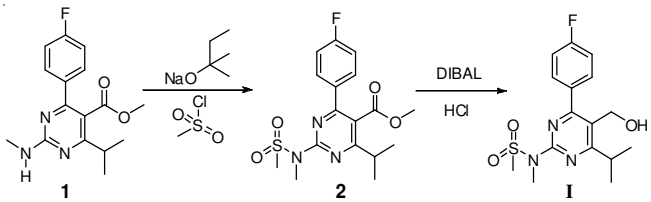
INTRODUCTION

Pyrimidine derivatives are known as pharmaceutical active ingredients or as precursors for the preparation. An important pyrimidine derivative is rosuvastatin, an HMG-CoA reductase inhibitor[1], that is to say an inhibitor of cholesterol biosynthesis, which is used in the treatment of hyperlipoprote-inaemia and arteriosclerosis. It was proved to be a kind of long duration, good tolerance and high security drug to treat hyperlipidemia and high cholesterol statins, which have a broad market prospect.

N-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropyl-pyrimidin-2-yl]-*N*-methylmethane sulfonamide (**I**) is widely concerned as the most important intermediate to synthesize rosuvastatin. Now some synthetic routes are reported about (**I**) in the literatures[2-9], such as, (I) could be prepared from methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylthio)-pyrimidine-5-carboxylate by *m*-CPBA, then through reduction by DIBAL. The disadvantage of this route is that there are too much multi-products, the final product is difficult to separate from the reaction system.

In other literatures, the compound **I** was prepared by methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylthio) pyrimidine-5-carboxylate through hydrolysis by LiOH and then reduction by $NaBH_4/BF_3{\cdot}Et_2O$. The disadvantage of this route is that the $BF_3{\cdot}Et_2O$ is toxic and it is not friendly to the environment.

Herein, we report the synthesis of (**I**) from compound **1** with an overall yield of about 78 %. Meanwhile, the crystal structure of (**I**) also was investigated (CCDC NO. 895525). The synthetic route of compound **I** was presented as **Scheme-I**.



Scheme-I: Route for the synthesis of compound **I**

EXPERIMENTAL

Methyl 4-(4-fluorophenyl)-6-isopropyl-2-(methylamino) pyrimidine-5-carboxylate (**1**) was supplied by Well Chemical Co. Ltd. of Jiangsu (Yancheng, People's Republic of China), its mass content is 98.5 % determined by LC. DIBAL solution, mesyl chloride and sodium *tert*-pentoxide was supplied by Sinopharm Chemical Reagent Co. Ltd. of China. All other chemicals were of reagent grade and used without purification as received.

^{1}H NMR spectrum was obtained with Bruker AV-300 spectrometer at 300.13 MHz and measured in $CDCl_3$ solution at 25 ± 0.5 °C. The sample was dissolved in a 5 mm diameter tube at a concentration of 20 mg/mL. X-ray diffraction was

performed on a Bruker APEXII CCD diffractometer. Mass spectrum of (**I**) was analyzed using Trace DSQ LC/MS (Thermo Electron Co., USA).

Synthesis of compound 2: In a 1 L four-necked flask, sodium *tert*-pentoxide (11.2 g, 0.1 mol) is added into dimethoxyethane (130 mL) under argon and the compound **1** (15.1 g, 0.05 mol) is then added. Stirring is carried out at room temperature for 1.5 h, cooling to -10 °C is then carried out and mesyl chloride (11.5 g, 0.2 mol) is added. Stirring is carried out at that temperature for a further 1 h and the reaction mixture is then added to 150 mL of water. The mixture is diluted with ether and the organic phase is separated off. The organic phase is washed twice with water and then dried using Na_2SO_4. The salt mixture is filtered off and the filtrate is concentrated by evaporation. The residue is suspended in a mixture of hexane/acetone (6:1, 35mL). The yellow powder is filtered off and dried. In this manner, 15 g of compound **2** (78 %) are obtained.

Synthesis of compound I: In a 1 L four-necked flask, DIBAL solution (1 M in hexane, 135 mL, 0.135 mol) is added dropwise at -10 °C to a solution of the compound **2** (14.5 g, 0.038 mol) in toluene (130 mL). The mixture is subsequently stirred at -10 °C for a further 1.5 h. After adding 1 mL of methanol, the mixture is warmed to room temperature and is added dropwise to a warm solution of HCl (37 %, 50 mL) and water (60 mL). Stirring is carried out at 45 °C for 0.5 h, followed by cooling to room temperature, separating off the organic phase and drying. The salt mixture is filtered off and the filtrate is concentrated by evaporation. The residue is concentrated by evaporation. In this manner, 13.5 g (m.p. 145-146 °C) of the compound **I** are obtained in the form of a yellow oil which crystallizes at room temperature.

Crystals of (**I**) that suitable for X-ray diffraction were obtained by slow evaporation of 1,2-dichloroethane solution of compound **I**.

X-ray crystallography: A colorless block-like crystal of compound **I** grown in 1,2-dichloroethane with dimensions of 0.30 mm × 0.20 mm × 0.20 mm was used for structural determination. Diffraction data were collected on a Bruker APEX-II CCD diffractometer by using graphite monochromated MoK_α radiation (λ = 0.71073 Å). The structure was solved by direct methods with SHELXS-97 and refined on the F^2 by full-matrix least-squares method with SHELXL-97. All non-hydrogen atoms were refined anisotropically[10-13].

RESULTS AND DISCUSSION

In the ^{1}H NMR of compound **I**, the peak at 1.34 ppm was ascribed to the proton of isopropyl group. The other data was described as below, ^{1}H NMR ($CDCl_3$): δ 1.34 (6H, d, *J* = 6.0 Hz), 1.74 (1H, s), 3.48(3H, s), 3.46-3.53 (1H, m), 3.56 (3H, s), 4.66 (2H, s), 7.14-7.20 (2H, m), 7.78-7.85 (2H, m). In the LC spectrum peak at 5.304 min ascribed to the compound **I**. In the MS spectrum, the existence of the peaks at right end showed the compound **I**, *m/z* 353.90 was ascribed to molecular ion peak (M^+).

The crystal configuration of compound **I** was confirmed by X-ray structural analysis. Experimental details for X-ray data collection were presented in Table-1 and the geometric parameters for compound **I** were listed in Table-2. Molecular structure and packing plot of compound **I** were showed in Figs. 1 and 2, respectively.

According to the data from X-ray crystallographic analysis, compound **I** crystallized in a C2/C space group of the monoclinic system. All H atoms were positioned geometrically and constrained to ride on their parent atoms, with C-H = 0.93 Å for aromatic H. Other H atoms were positioned geometrically and refined using a riding model, with C-H = 0.96 Å for alkyl H, with Uiso(H) =1.2Ueq(C) for aromatic H and Uiso(H) =1.5Ueq(C) for other H. There are C-H···O, C-H···N intramolecular and O-H···O intermolecular hydrogen bonds in the structure, hydrogen-bond geometry for compound **I** was listed in Table-3. Unit cell parameters: a = 29.683(6), b = 7.629 (15), c = 18.215(4) Å, V = 3451.1(16) Å^3; Z = 8.

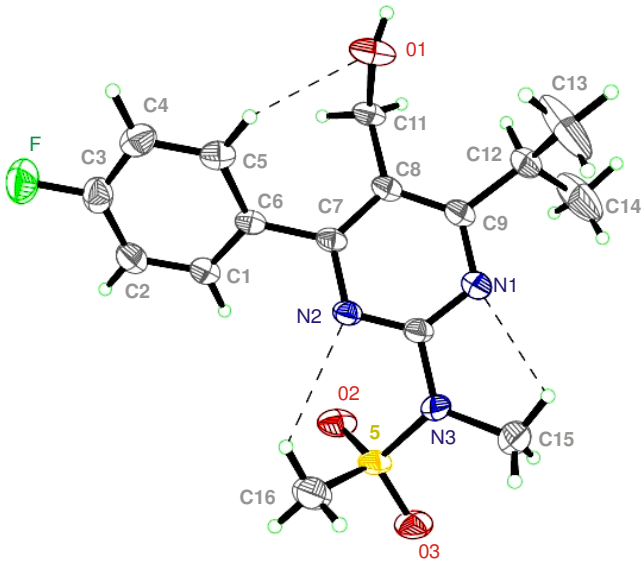


Fig. 1. General appearance of compound **I** with the atoms represented by thermal vibration ellipsoids of 50% probability

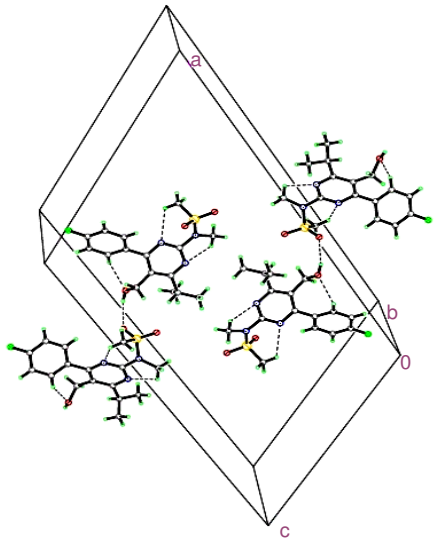


Fig. 2. Packing diagram for compound **I**

ACKNOWLEDGEMENTS

The authors will gratefully acknowledge the support of Nanjing University and Changzhou University in analysis.

TABLE-1
CRYSTALLOGRAPHIC DATA FOR COMPOUND **I**

ITEM	Data or description
m.f.	$C_{16}H_{20}N_3O_3SF$
m.w.	353.41
Temperature (K)	293 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C2/C
a (Å)	29.683(6)
b (Å)	7.629 (15)
c (Å)	18.215(4)
Volume (Å^3)	3451.1(16)
Z	8
Calculated density (g/cm^3)	1.360
Absorption coefficient (mm^{-1})	0.22
F(000)	1488
Crystal size (mm)	0.30 × 0.20 × 0.20
Theta range for data collection (°)	1.64 to 25.38
Reflections collected/unique	3170/2123 [$R_{(int)}$ = 0.0538]
Completeness to theta = 25.38 (%)	99.9
Max. and min. transmission	0.621 and 0.779
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2123/0/218
Goodness-of-fit on F^2	1.001
Final R indices [I > 2σ(I)]	R1 = 0.0538, wR2 = 0.1709
R indices (all data)	R1 = 0.0848, wR2 = 0.1527
Largest diff. peak and hole (e. Å^{-3})	0.37 and -0.25

TABLE-2
GEOMETRIC PARAMETERS FOR COMPOUND (**I**)

Bond	Dist. (Å)	Bond	Dist. (Å)
S—O3	1.426 (2)	C6—C7	1.484 (4)
S—O2	1.436 (2)	C7—C8	1.398 (4)
S—N3	1.635 (3)	C8—C9	1.394 (4)
S—C16	1.745 (4)	C8—C11	1.506 (4)
F—C3	1.349 (4)	C9—C12	1.522 (4)
N1—C10	1.329 (4)	C11—H11A	0.9700
N1—C9	1.341 (4)	C11—H11B	0.9700
C1—C2	1.373 (4)	C12—C14	1.470(7)
C1—C6	1.391 (8)	C12—C13	1.485(8)
C1—H1C	0.9300	C12—H12A	0.9800
N2—C10	1.314 (4)	C13—H13A	0.9600
N2—C7	1.348(8)	C13—H13B	0.9600
O1—C11	1.432 (3)	C13—H13C	0.9600
O1—H1B	0.8200	C14—H14A	0.9600
C2—C3	1.368(7)	C14—H14B	0.9600
N3—C10	1.420(7)	C15—H15A	0.9600
N3—C15	1.474(8)	C15—H15B	0.9600
C3—C4	1.369 (5)	C15—H15C	0.9600
C4—C5	1.377(8)	C16—H16A	0.9600
C4—H4B	0.9300	C16—H16B	0.9600
C5—C6	1.392 (4)	C16—H16C	0.9600
C5—H5A	0.9300	—	—
Angle	**Data (°)**	**Angle**	**Data (°)**
O3—S—O2	118.19 (4)	N2—C10—N1	128.1
O3—S—N3	106.35 (5)	N2—C10—N3	117.0
O2—S—N3	109.05	N1—C10—N3	114.9 (5)
O3—S—C16	108.11	O1—C11—C8	111.6 (5)
O2—S—C16	108.63	O1—C11—H11A	109.3 (5)
N3—S—C16	105.85	C8—C11—H11A	109.3 (5)
C10—N1—C9	115.6	O2—C11—H11B	109.3 (5)
C2—C1—C6	121.0	C8—C11—H11B	109.3 (5)
C2—C1—H1C	119.5	H11A—C11—H11B	108.0 (5)
C6—C1—H1C	119.5	C14—C12—C13	111.5 (5)
C10—N2—C7	116.0	C14—C12—C9	114.0 (5)
C11—O1—H1B	109.5	C13—C12—C9	109.3(5)
C3—C2—C1	119.1	C14—C12—H12A	107.2(5)
C3—C2—H2C	120.5	C13—C12—H12A	107.2
C1—C2—H2C	120.5	C9—C12—H12A	107.2
C10—N3—C15	119.1	C12—C13—H13A	109.5
C10—N3—S	121.2	C12—C13—H13B	109.5
C15—N3—S	119.6	H13A—C13—H13C	109.5
F—C3—C2	119.2	C12—C13—H13C	109.5
F—C3—C4	118.8(5)	H13A—C13—H13C	109.5
C2—C3—C4	122.0(5)	H13B—C13—H13C	109.5
C3—C4—C5	118.6(5)	C12—C14—H14A	109.5
C3—C4—H4B	120.7(5)	C12—C14—H14B	109.5
C5—C4—H4B	120.7(5)	H14A—C14—H14B	109.5
C4—C5—C6	121.2(5)	C12—C14—H14C	109.5
C4—C5—H5A	119.4(5)	H14A—C14—H14C	109.5
C6—C5—H5A	119.4	H14B—C14—H14C	109.5
C1—C6—C5	118.1	N3—C15—H15A	109.5
C1—C6—C7	119.1(6)	N3—C15—H15B	109.5
C5—C6—C7	122.8	H15A—C15—H15B	109.5
N2—C7—C8	121.1	N3—C15—H15C	109.5
N2—C7—C6	114.2(6)	H15A—C15—H15C	109.5
C8—C7—C6	124.7	H15B—C15—H15C	109.5
C9—C8—C7	116.8	S—C16—H16A	109.5
C9—C8—C11	121.4(5)	S—C16—H16B	108.0
C7—C8—C11	121.6(7)	H16A—C16—H16B	109.5
N1—C9—C8	121.7(7)	S—C16—H16C	109.5
N1—C9—C12	114.9(8)	H16A—C16—H16C	109.5
C8—C9—C12	123.3(5)	H16B—C16—H16V	109.5
C6—C1—C2—C3	-0.6	C6—C7—C8—C9	175.0(9)
O3—S—N3—C10	165.9	N2—C7—C8—C11	168.8(8)
O2—S—N3—C10	37.5	C6—C7—C8—C11	-10.0(6)
C16—S—N3—C10	-79.3(5)	C10—N1—C9—C8	-0.1(7)
O3—S—N3—C15	-16.6(5)	C10—N1—C9—C12	179.6(7)
O2—S—N3—C15	-145.1(8)	C7—C8—C9—N1	6.2(6)
C16—S—N3—Cl5	98.2(9)	C11—C8—C9—N1	-168.9(8)
C1—C2—C3—F	179.7(10)	C7—C8—C9—C12	-173.5(5)
C1—C2—C3—C4	0.2(10)	C11—C8—C9—C12	11.4(9)
F—C3—C4—C5	-180.0(9)	C7—N2—C10—N1	6.8(10)
C2—C3—C4—C5	-0.4(5)	C7—N2—C10—N3	-174.2(5)
C3—C4—C5—C6	1.1(5)	C9—N1—C10—N2	-7.0(9)
C2—C1—C6—C5	1.3(8)	C9—N1—C10—N3	174.0(5)
C2—C1—C6—C7	179.0(8)	C15—N3—C10—N2	-151.4(9)
C4—C5—C6—C1	-1.6(5)	S—N3—C10—N2	26.1(5)
C4—C5—C6—C7	-179.1(5)	C15—N3—C10—N1	27.7(9)
C10—N2—C7—C8	0.4(7)	S—N3—C10—N1	-154.8(5)
C10—N2—C7—C6	179.2(8)	C9—C8—C11—O1	-86.8(6)
C1—C6—C7—N2	-37.2 (3)	C7—C8—C11—O1	98.4 (3)
C5—C6—C7—N2	140.3 (3)	N1—C9—C12—C14	35.7 (5)
C1—C6—C7—C8	141.6 (3)	C8—C9—C12—C14	-144.7(4)
C5—C6—C7—C8	-40.8 (4)	N1—C9—C12—C13	-89.9 (4)
N1—C7—C8—C9	-6.3 (4)	C8—C9—C12—C13	89.9 (5)

Symmetry code: (i) –x+1/2, y+3/2 ,-z-1/2

TABLE-3
HYDROGEN-BOND GEOMETRY FOR COMPOUND (**I**)

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1B···O2	0.82 Å	2.22 Å	2.977 (4) Å	153°
C5—H5A···O1	0.93 Å	2.48 Å	3.225 (5) Å	137°
C15—H15A···N1	0.96 Å	2.33 Å	2.764 (4) Å	107°
C16—H16B···N2	0.96 Å	2.62 Å	3.194 (5) Å	119°

REFERENCES

1. M. Vasudevan, J. Ravi, S. Ravisankar and B. Suresh, *J. Pharm. Biomed. Anal.*, **25**, 77 (2001).
2. E. Nicole and R. Yvonne, WO Patent 2004103977 (2004).
3. C. Zdenko and S. Damjan, WO Patent 2012013325 (2012).
4. Q. Jeremy, T. Mark and K. Peter, *News Analysis*, **2**, 769 (2003).
5. L. Wenqing, Z. Hongjie and P. Yang, US Patent 20130143908 (2013).
6. D. Šterk, Z. Casar, M. Jukic and J. Košmrlj, *Tetrahedron*, **68**, 2155 (2012).
7. L. Jing-lin and H. Hua-rong, CN Patent 201010245642 (2010).
8. H. Zhong-bin, D. Lian-hua and H. Yong, CN Patent 200810146732 (2008).
9. L. Kai-Chao, CN Patent 201210069448 (2012).
10. F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, S1 (1987).
11. J. Folkman, *Sci. Am.*, **275**, 150 (1996).
12. A.C.T. North, D.C. Phillips and F.S. Mathews, *Acta Crystallogr. A*, **24**, 351 (1968).
13. G.M. Sheldrick, *Acta Crystallogr. A*, **64**, 112 (2008).