



Synthesis, Characterization and Crystal Structure of Methyl 4-(Benzyloxy)-5-methoxy-2-nitrobenzoate

KAI WANG¹, XIU-QIN ZHANG¹, JIAN ZHU¹, QIANG CHEN¹, ZHONG-QIANG ZHANG³ and LI FAN^{2,*}

¹High Technology Research Institute of Nanjing University, Changzhou 213162, Jiangsu Province, P.R. China

²Gastroenterology Department Nanjing Medical University Affiliated Changzhou No. 2 Hospital, Changzhou 213000, Jiangsu Province, P.R. China

³School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210000, Jiangsu Province, P.R. China

*Corresponding author: E-mail: wkcool@163.com

Received: 13 September 2014;

Accepted: 8 October 2014;

Published online: 30 March 2015;

AJC-17097

Methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate was synthesized from 4-hydroxy-3-methoxybenzoic acid. Firstly, 4-hydroxy-3-methoxybenzoic acid reacted with methanol in the presence of concentrated sulfuric acid at reflux temperature, then the product of the first step was transformed into benzyl bromide by the process of substitution reaction by using K₂CO₃. Finally, the product was obtained by nitration reaction with HNO₃. The product was characterized by ¹H NMR and LC-MS. The crystal structure of compound **I** was investigated using X-ray diffraction and SHELXTL-97 software. The results indicated that compound **I** crystallized in the monoclinic system, space group P2(1)/c with a = 5.590(2), b = 17.591 (7), c = 15.427(6) Å, V = 1516.9 (10) Å³; Z 4.

Keywords: Vandetanib, Synthesis, Characterization, Crystal structure.

INTRODUCTION

Vandetanib¹⁻⁵ is an orally active antagonist of vascular endothelial growth factor (VEGF) receptor-2 (VEGFR-2), epidermal growth factor receptor (EGFR) and RET kinase. It was approved for the treatment of metastatic medullary thyroid cancer (MTC) by U.S. Food and Drug Administration (FDA) on June 4, 2011.

Methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate (**I**) is a key intermediate compound for vandetanib. It was synthesized from 4-hydroxy-3-methoxybenzoic acid through a three-steps reaction.

Herein, we introduce a synthetic method of methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate (**I**) from compound **1** by methylation, substitution and nitration reactions (**Scheme-I**), with an overall yield of about 79.5 %. Meanwhile, the crystal structure of methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate (**I**) was also investigated.

EXPERIMENTAL

4-Hydroxy-3-methoxybenzoic acid was supplied by Well Chemical Co. Ltd of Jiangsu (Changzhou, People's Republic of China), its mass content is 99 % determined by GC. Benzyl bromide was purchased from Sinopharm Chemical Reagent Co. Ltd of China. All other chemicals were of reagent grade and used without purification as received.

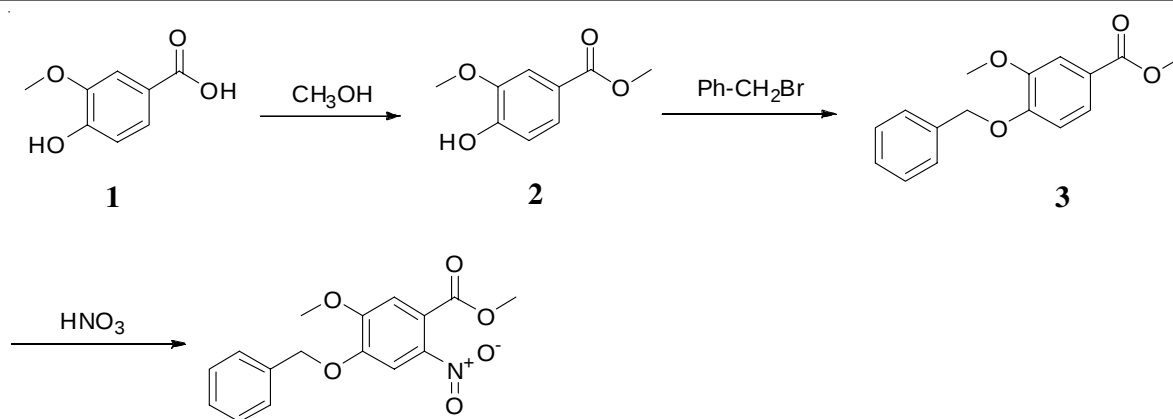
¹H NMR spectrum was obtained with Bruker AV-500 spectrometer at 500.13 MHz and measured in CDCl₃ solution

at 30 ± 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 I: A 250 mL, round-bottomed flask with a stirring bar, a solution of 4-hydroxy-3-methoxybenzoic acid (20 g, 118.94 mmol) was added slowly to a solution of methanol (100 mL) and concentrated sulfuric acid (10 mL). After being stirred for 12 h at reflux, saturated solution of sodium bicarbonate was added to adjust the pH to 7. Dichloromethane was added and the mixture was then filtered and the organic phase evaporated on a rotary evaporator and to obtain the compound **2** (20.37 g, 94 %).

Compound **2** (20.4 g, 111.98 mmol) was added into a 500 mL, round-bottomed flask with a stirring bar, then benzyl bromide (18 mL), potassium carbonate (22 g, 156.8 mmol), DMF (200 mL) were added. It was stirred for 6 h at 80 °C. Then the reaction system was poured into right amount of water, white solid (**3**) was obtained by filtration (28.97 g, 95 %).

Compound **3** (16.54 g, 60.74 mmol) was dissolved in CH₃COOH (50 mL) and then added into a 250 mL, round-bottomed flask with a stirring bar. Then HNO₃ (25 mL) was added in to the system slowly to keep the temperature of the reaction above 5 °C. The reaction temperature was raised to 50 °C and kept for another 2 h. After that the system was poured

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

into water and pale yellow solid (**I**) was obtained⁶⁻⁸ (18.3 g, 95 %, m.p.: 134-135 °C).

Crystals of **I** that suitable for X-ray diffraction were obtained by slow evaporation of dichloromethane solution of **I**.

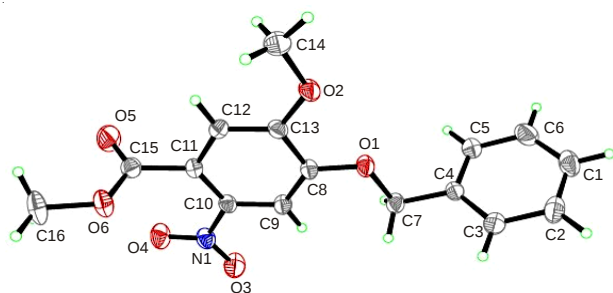
X-Ray crystallography: A colourless block-like crystal of compound **I** grown in dichloromethane with dimensions of 0.35 mm × 0.25 mm × 0.16 mm was used for structural determination. Diffraction data were collected on a Bruker APEXII CCD diffractometer by using graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods with SHELXS-97 and refined on the F² by full-matrix least-squares method with SHELXL-97. All non-hydrogen atoms were refined anisotropically.

RESULTS AND DISCUSSION

Identification of resonance in the spectra: In the ¹H NMR of compound **I**, the peak at 5.20 ppm was ascribed to the proton of methylene which was substituted by phenyl group. The other data was described as below, ¹H NMR (CDCl₃): δ 3.91 (3H, s), 3.98 (3H, s), 5.20 (2H, s), 7.08 (1H, s), 7.26-7.46 (5H, m), 7.52 (1H, s).

In the LC spectrum peak at 4.930 min. ascribed to the compound **I**. In the MS spectrum, the existence of the peaks at right end showed the compound **I**, m/z 317.15 was ascribed to molecular ion peak (M⁺), m/z 339.95 was ascribed to M+Na peak.

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.

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

ITEM	Data or description
Formula	C ₁₆ H ₁₅ NO ₆
Formula weight	317.29
Temperature (K)	296 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P2(1)/c
a (Å)	5.590(2)
b (Å)	17.591(7)
c (Å)	15.427(6)
Volume (Å ³)	1516.9(10)
Z	4
Calculated density (g/cm ³)	1.389
Absorption coefficient (mm ⁻¹)	0.11
F(000)	664
Crystal size (mm)	0.30 × 0.25 × 0.16
Theta range for data collection (°)	1.8 to 25.0
Reflections collected/unique	2671/1410 [R _{int} = 0.089]
Completeness to theta = 25.38 (%)	99.7
Max. and min. transmission	0.968 and 0.983
Refinement method	Full-matrix least-squares on F ²
Data/restraints/parameters	2671/0/196
Goodness-of-fit on F ²	1.01
Final R indices [I > 2σ(I)]	R1 = 0.0987, wR2 = 0.1191
R indices (all data)	R1 = 0.0547, wR2 = 0.1140
Largest diff. peak and hole (e. Å ⁻³)	0.21 and -0.23

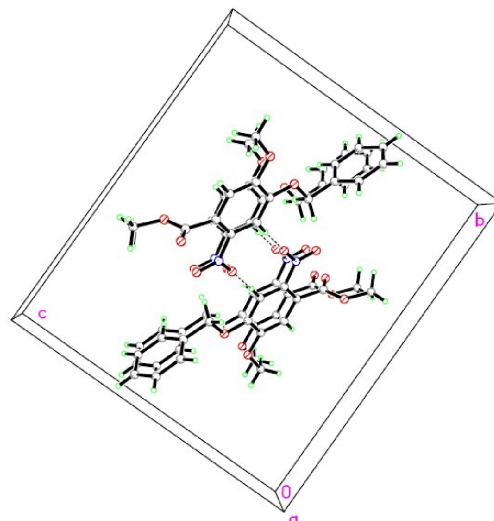
Fig. 2. Packing diagram for compound **I**

TABLE-2
GEOMETRIC PARAMETERS FOR COMPOUND I

Bond	Dist. (Å)	Bond	Dist. (Å)
C1-C2	1.3900	C10-C11	1.378(3)
C1-C6	1.3900	C10-N1	1.456(3)
C1-H1	0.9300	C11-C12	1.385(3)
C2-C3	1.3900	C11-C15	1.501(4)
C2-H2	0.9300	C12-C13	1.379(4)
C3-C4	1.3900	C12-H12	0.9300
C3-H3	0.9300	C13-O2	1.350(3)
C4-C5	1.3900	C14-O2	1.431(3)
C4-C7	1.4926	C14-H14A	0.9600
C5-C6	1.3900	C14-H14B	0.9600
C5-H5	0.9300	C14-H14C	0.9600
C6-H6	0.9300	C15-O5	1.192(3)
C7-O1	1.442(2)	C15-O6	1.305(4)
C7-H7A	0.9700	C16-O6	1.446(3)
C7-H7B	0.9700	C16-H16A	0.9600
C8-O1	1.356(3)	C16-H16B	0.9600
C8-C9	1.360(3)	C16-H16C	0.9600
C8-C13	1.408(3)	N1-O4	1.220(3)
C9-C10	1.386(3)	N1-O3	1.220(3)
C9-H9	0.9300		
Angle	Data (°)	Angle	Data (°)
C2-C1-C6	120.0	C9-C10-N1	117.9(2)
C2-C1-H1	120.0	C10-C11-C12	118.0(2)
C6-C1-H1	120.0	C10-C11-C15	124.7(2)
C3-C2-C1	120.0	C12-C11-C15	117.2(2)
C3-C2-H2	120.0	C13-C12-C11	121.1(2)
C1-C2-H2	120.0	C13-C12-H12	119.4
C4-C3-C2	120.0	C11-C12-H12	119.4
C4-C3-H3	120.0	O2-C13-C12	124.8(2)
C2-C3-H3	120.0	O2-C13-C8	115.6(2)
C5-C4-C3	120.0	C12-C13-C8	119.7(3)
C5-C4-C7	119.0	O2-C14-H14A	109.5
C3-C4-C7	120.9	O2-C14-H14B	109.5
C4-C5-C6	120.0	H14A-C14-H14B	109.5
C4-C5-H5	120.0	O2-C14-H14C	109.5
C6-C5-H5	120.0	H14-C14-H14C	109.5
C5-C6-C1	120.0	H14B-C14-H14C	109.5
C5-C6-H6	120.0	O5-C15-O6	125.0(3)
C1-C6-H6	120.0	O5-C15-C11	124.3(3)
O1-C7-C4	106.81(11)	O6-C15-C11	110.4(3)
O1-C7-H7A	110.4	O6-C16-H16A	109.5
C4-C7-H7A	110.4	O6-C16-H16B	109.5
O1-C7-H7B	110.4	H16A-C16-H16B	109.5
C4-C7-H7B	110.4	O6-C16-H16C	109.5
H7A-C7-H7B	108.6	H16A-C16-H16C	109.5
O1-C8-C9	125.9(2)	H16B-C16-H16C	109.5
O1-C8-C13	114.7(2)	O4-N1-O3	123.2(2)
C9-C8-C13	119.4(2)	O4-N1-C10	118.9(2)
C8-C9-C10	120.0(2)	O3-N1-C10	117.9(2)
C8-C9-H9	120.0	C8-O1-C7	116.97(18)
C10-C9-H9	120.0	C13-O2-C14	118.6(2)
C11-C10-C9	121.8(2)	C15-O6-C16	116.4(3)
C11-C10-N1	120.3(2)	C11-C12-C13-C8	1.5(4)
C6-C1-C2-C3	0.0	O1-C8-C13-O2	-0.2(4)
C1-C2-C3-C4	0.0	C9-C8-C13-O2	179.4(3)
C2-C3-C4-C5	0.0	O1-C8-C13-C12	-179.8(3)
C2-C3-C4-C7	-177.0	C9-C8-C13-C12	-0.2(4)
C3-C4-C5-C6	0.0	C10-C11-C15-O5	-108.8(4)
C7-C4-C5-C6	177.1	C12-C11-C15-O5	75.2(4)
C4-C5-C6-C1	0.0	C10-C11-C15-O6	77.4(4)
C2-C1-C6-C5	0.0	C12-C11-C15-O6	-98.6(3)
C5-C4-C7-O1	-70.11(16)	C11-C10-N1-O4	3.2(4)
C3-C4-C7-O1	106.96(16)	C9-C10-N1-O4	-175.4(3)
O1-C8-C9-C10	179.2(3)	C11-C10-N1-O3	-179.4(3)
C13-C8-C9-C10	-0.4(4)	C9-C10-N1-O3	2.0(4)

C8-C9-C10-C11	-0.4(5)	C9-C8-O1-C7	1.4(4)
C8-C9-C10-N1	178.2(3)	C13-C8-O1-C7	-179.0(2)
C9-C10-C11-C12	1.6(4)	C4-C7-O1-C8	178.08(19)
N1-C10-C11-C12	-176.9(3)	C12-C13-O2-C14	5.6(4)
C9-C10-C11-C15	-174.3(3)	C8-C13-O2-C14	-174.0(3)
N1-C10-C11-C15	7.2(5)	O5-C15-O6-C16	6.1(5)
C10-C11-C12-C13	-2.2(4)	C11-C15-O6-C16	179.9(3)
C15-C11-C12-C13	174.0(3)		
C11-C12-C13-O2	-178.1(3)		

Symmetry code: (i) x, y, z (ii) $-x, 1/2 + y, 1/2 - z$

According to the data from X-ray crystallographic analysis, compound **I** crystallized in a $P2(1)/c$ space group of the triclinic 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 $U_{iso}(H) = 1.2U_{eq}(C)$ for aromatic H and $U_{iso}(H) = 1.5U_{eq}(C)$ for other H. There are no intramolecular hydrogen bonds in the structure. There is one intermolecular hydrogen bonds in the structure and the hydrogen-bond geometry for compound (**I**) was listed in Table-3. Unit cell parameters: $a = 5.590(2)$, $b = 17.591(7)$, $c = 15.427(6)$ Å, $V = 1516.9(10)$ Å³; Z 4.

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

D-H...A	D-H	H...A	D...A	D-H...A
C9-H9...O3	0.93 Å	2.45 Å	3.371 (4) Å	171°

ACKNOWLEDGEMENTS

This work was financially supported by the Science and Technology Research Project of Changzhou City-Technology Support Program (Industry) (CE20140028).

REFERENCES

1. H. Takeda, N. Takigawa, K. Ohashi, D. Minami, I. Kataoka, E. Ichihara, N. Ochi, M. Tanimoto and K. Kiura, *Exp. Cell Res.*, **319**, 417 (2013).
2. L.F. Hennequin, E.S.E. Stokes, A.P. Thomas, C. Johnstone, P.A. Plé, D.J. Ogilvie, M. Dukes, S.R. Wedge, J. Kendrew and J.O. Curwen, *J. Med. Chem.*, **45**, 1300 (2002).
3. D. Zampieri, M. Grazia Mamolo, E. Laurini, C. Zanette, C. Florio, S. Collina, D. Rossi, O. Azzolina and L. Vio, *Eur. J. Med. Chem.*, **44**, 124 (2009).
4. Y. Seimbille, M.E. Phelps, J. Czernin and D.H.S. Silverman, *J. Label. Comp. Radiopharm.*, **48**, 829 (2005).
5. S. Tasler, O. Muller, T. Wieber, T. Herz, S. Pegoraro, W. Saeb, M. Lang, R. Krauss, F. Totzke, U. Zirrgiebel, J.E. Ehlert, M.H.G. Kubbutat and C. Schächtele, *Bioorg. Med. Chem.*, **17**, 6728 (2009).
6. T. Wang, A.S. Lui and I.S. Cloudsdale, *Org. Lett.*, **1**, 1835 (1999).
7. A. Kamal, N. Markandeya, N. Shankaraiah, C.R. Reddy, S. Prabhakar, C.S. Reddy, M.N. Eberlin and L. Silva Santos, *Chem. Eur. J.*, **15**, 7215 (2009).
8. L.F. Hennequin, A.P. Thomas, C. Johnstone, E.S.E. Stokes, P.A. Plé, J.-J.M. Lohmann, D.J. Ogilvie, M. Dukes, S.R. Wedge, J.O. Curwen, J. Kendrew and C. Lambert-van der Brempt, *J. Med. Chem.*, **42**, 5369 (1999).