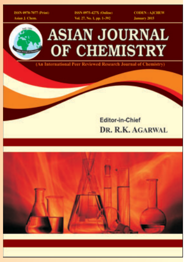
*Asian Journal of Chemistry; Vol. 27, No. 7 (2015), 2647-2650*

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18745



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

KAI WANG[1], XIU-QIN ZHANG[1], JIAN ZHU[1], QIANG CHEN[1], ZHONG-QIANG ZHANG[3] and LI FAN[2,*]

[1]High Technology Research Institute of Nanjing University, Changzhou 213162, Jiangsu Province, P.R. China
[2]Gastroenterology Department Nanjing Medical University Affiliated Changzhou No. 2 Hospital, Changzhou 213000, Jiangsu Province, P.R. China
[3]School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210000, Jiangsu Province, P.R. China

*Corresponding author: E-mail: wkcoool@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 $K_2CO_3$. Finally, the product was obtained by nitration reaction with $HNO_3$. The product was characterized by $^1$H 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) Å$^3$; Z 4.

**Keywords: Vandetanid, Synthesis, Characterization, Crystal structure.**

## INTRODUCTION

Vandetanib[1-5] 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

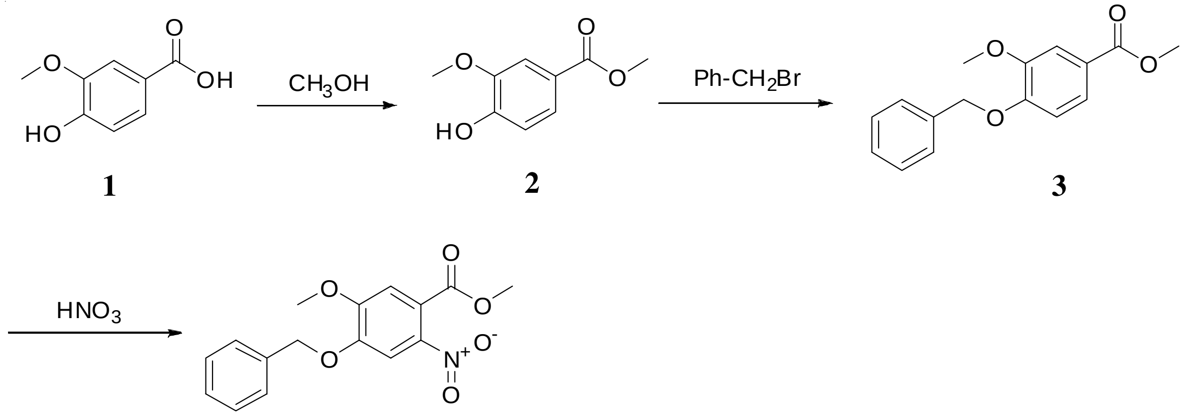
4-Hydroxy-3-methoxybenzoic acid was supplied by Well Chemical Co. Ltd of Jiangsu (Changzhou, People's Republic of China), its mass content is 99 % determined by GC. Benzyl bromide was purchased from Sinopharm Chemical Reagent Co. Ltd of China. All other chemicals were of reagent grade and used without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

$^1$H NMR spectrum was obtained with Bruker AV-500 spectrometer at 500.13 MHz and measured in $CDCl_3$ 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 $CH_3COOH$ (50 mL) and then added into a 250 mL, round-bottomed flask with a stirring bar. Then $HNO_3$ (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 obtained[6-8] (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$_\alpha$ radiation ($\lambda$ = 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.

## RESULTS AND DISCUSSION

**Identification of resonance in the spectra:** In the $^1$H 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, $^1$H NMR (CDCl$_3$): 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.

TABLE-1
CRYSTALLOGRAPHIC DATA FOR COMPOUND (I)

| 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 |

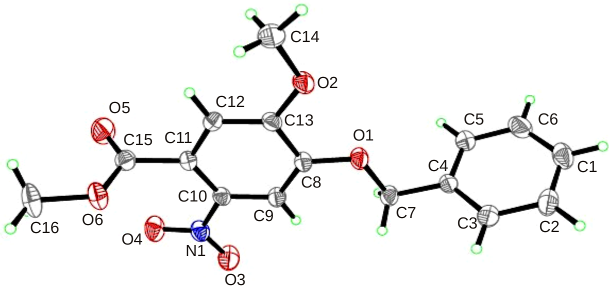


Fig. 1. General appearance of compound I with the atoms represented by thermal vibration ellipsoids of 50 % probability

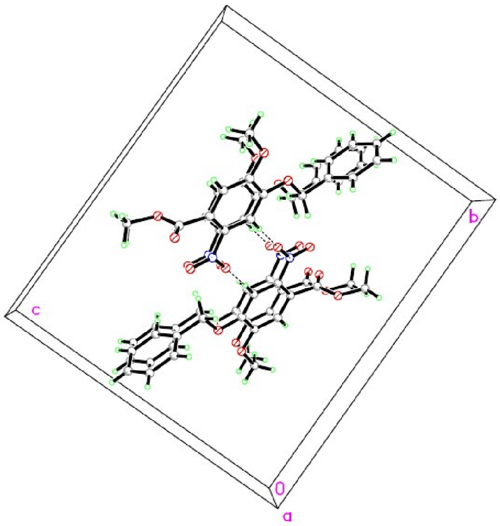


Fig. 2. Packing diagram for compound **I**

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-N1-03 | 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 Uiso(H) =1.2Ueq(C) for aromatic H and Uiso(H) =1.5Ueq(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) Å$^{3}$; 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).