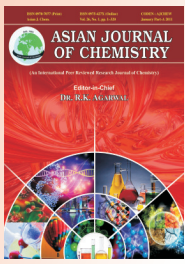
Asian Journal of Chemistry; Vol. 26, No. 21 (2014), 7457-7459

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.17429



Synthesis, Characterization, Crystal Structure and Free Radical Scavenging Activities of 2-(2-Butylamine)-6-[(2-butylamine)amino]- 5-nitro-1H-benzo[de]-isoquinoline-1,3(2H)-dione

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Received: 20 February 2014; *Accepted*: 5 May 2014; *Published online*: 30 September 2014; AJC-16161

2-(2-Butylamine)-6-[(2-butylamine)amino]-5-nitro-1H-benzo[de]-isoquinoline-1,3(2H)-dione (**2**) was synthesized and then characterized by FT-IR, NMR and elemental analysis. The crystal structure of compound **2** was investigated using X-ray diffraction and SHELXTL97 software and the result indicated that compound **2** crystallized in the monoclinic system, space group C2/c with a = 32.1094 (19), b = 7.1888 (4), c = 16.7750 (9) Å, V = 3827.2 (4) Å^3; Z = 8. The free radical scavenging activity screening results showed that compound **2** exhibited good scavenging activity against 2,2-diphenyl-1-picrylhydrazyl radical (DPPH$^•$), with IC_{50} of 214.7 μM.

Keywords: Naphthalimides, Synthesis, Crystal, Free radical scavenging activity.

INTRODUCTION

Previous work showed that naphthalimides exhibited good inhibition activity toward multifarious murine and human tumor cells[1,2]. Two compounds of this kind derivatives, amonifide and mitonafide, had been even reported as undergoing clinical trials[2]. Therefore, the synthesis of naphthalimides derivatives has recently been the subject of many chemists.

The importance of free radicals and reactive oxygen species in the pathogenesis of multifarious diseases[3-5] has prompted chemists to the synthesis for screening for efficient new free radical scavenging agents. Continuing our research program on the synthesis of radical scavenger effective[6-8], naphthalimide skeleton is chosen in the present work as active structural core and butyl and nitro groups are introduced to explore its radical scavenging activity. The present study was to synthesize and characterize a naphthalimide derivative (**2**) and to evaluate the free radical activity.

EXPERIMENTAL

2,6-Diter-butyl-4-toluene (BHT) and 1,1-diphenyl-2-picrylhydrazyl radical (DPPH$^•$) were purchased from Sigma Chemicals Co. (St. Louis, MO, USA). Other chemicals were purchased from China National Medicine Group Shanghai Corporation (Shanghai, China). All chemicals and solvents used were of analytical grade. Infrared spectra were recorded on a PE Spectrum One FI-IR spectrometer as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 500 spectrometer in $CDCl_3$. Mass spectra were recorded on BRUKER ESQUIRE HCT or VG ZAB-HS spectrometer. All elemental analyse were performed by PE 2400II analyzer. The data of single crystal were collected in a Rigaku Mercury CCD Area Detector.

Synthesis: Compound **2** was synthesized as outlined in Fig. 1. 4-bromo-1,8-naphthalic anhydride (BNA) was treated with the mixture of potassium nitrate and sulphuric acid to offer 3-nitro-4-bromo-1,8-naphthalic anhydride in good yield, according to the literature[6]. The mixture of butylamine (2.1 mmol), dimethylfomamide (DMF, 10 mL) and 4-bromo-3-nitro-1,8-naphthalic anhydride (1 mmol) was refluxed at 100 ºC for 7 h. Once cooled to room temperature, red crystals of compound **2** were obtained in 82 % yields. Compound **2** was then characterized by FT-IR, NMR and elemental analysis: m.p. 236.5-236.7 °C (from DMF). IR (KBr, ν_{max}, cm^{-1}): 3462, 3060, 2958, 2929, 2873, 1698, 1649, 1606, 1577, 1538; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H, NH), 9.32 (s, 1H), 8.68 (dd, *J* = 7.4 and 8.5 Hz, 2H), 7.71 (t, *J* = 7.8 Hz, 1H), 4.18 (t, *J* = 7.5 Hz, 2H), 3.99 (t, *J* = 5.5 Hz, 2H), 1.45-1.88 (m, 8H), 1 (s, 6H, CH_3); ^{13}C NMR (125 MHz): 14, 14.2, 19.9, 20.2, 30.1, 32.1, 49.2, 110, 122.8, 123.8, 126.7, 129.5, 129.8, 131.4, 133.1, 133.5, 149.4, 162.5, 163.5; MS (ESI) *m/z*: 368 (M^+-1); Anal. (%) Calcd. for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.16; H, 6.47; N, 11.24.

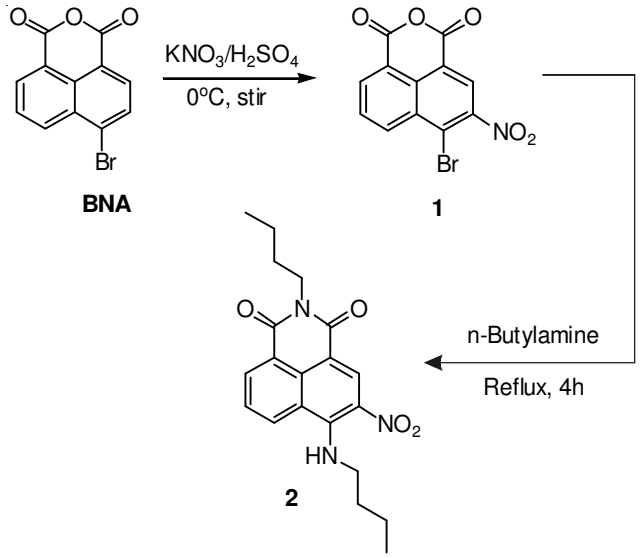

Fig. 1. Synthetic route of naphthalimides (**2**)

X-ray crystallography: An orange bar crystal of compound **2** grown in DMF with dimensions of 0.56 mm × 0.19 mm × 0.12 mm was used for structural determination. Diffraction data were collected on a Rigaku Mercury CCD Area 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 F2 by full-matrix least-squares method with SHELXL-97. All non-hydrogen atoms were refined anisotropically.

Scavenging activity: Compound **2** was reacted with a stable free radical, 1,1-diphenyl-2-picrylhydrazyl radical (DPPH•) according to the literature[8] with a little modification. Briefly, each scavenger solution (0.1 mL) in DMF at different concentrations was added to solution [3.9 mL, 0.004 % (w/v)] of DPPH• in ethanol. The reaction mixture was incubated at 37 ºC. The scavenging activity on DPPH• radical was determined by measuring the absorbance at 517 nm after 0.5 h. The scavenging activity was expressed as a percentage of scavenging activity on DPPH• radical: SC % = $[(A_{control} - A_{test})/A_{control})] \times 100$ %, where $A_{control}$ is the absorbance of the control (DPPH• solution without test sample) and A_{test} is the absorbance of the test sample (DPPH• solution plus scavenger). The control contains all reagents except the scavenger.

RESULTS AND DISCUSSION

The crystal configuration of compound **2** 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 **2** were selected and listed in Table-2. The molecular structure of the title compound **2** is shown in Fig. 2. The molecular geometry is well comparable with that of 2-(2-hydroxyethyl)-6-[(2-hydroxyethyl)amino]-5-nitro-1H-benzo[de]-isoquinoline-1,3(2H)-dione[9], apart from the hydroxyethyl substituent replacing with butyl group. It features a six-membered imide ring in which two acyls are coordinated by N atom [C-N-C= 123.8 (5) Å]. All the atoms of 1,8-naphthalimide unit are almost in a coplanar. In the crystal packing of the title compound **2** (Fig. 3), there are π-π stacking interactions, which makes the stabilization of the crystal structure and the centroid-to-centroid distance within the stacks being 3.4402 Å.

TABLE-1
CRYSTALLOGRAPHIC DATA FOR COMPOUND **2**

Chemical formula	$C_{20}H_{23}N_3O_4$
Formula weight	369.41
Crystal system, space group	Monoclinic, C2/c
Unit Cell Dimensions	a = 32.1094 (19) Å, α = 90°
	b = 7.1888 (4) Å, β = 98.742 (4)°
	c= 16.7750 (9) Å, γ = 90°
Volume (Å^3)	3827.2 (4)
Crystal size (mm^3)	0.56 × 0.19 × 0.12
Temp (K)	296 (2)
Z	8
D_{calc} (g cm^{-3})	1.282
θ range for data collection	2.5 to 25.6°
$\mu_{Absorp.}$ (mm^{-1})	0.09
Max. and min. Transmission	phi and ω scans
Limiting indices	$-41 \le h \le 39$, $-9 \le k \le 9$, $-21 \le l \le 21$
F (000)	1568
Reflections collected/unique	18548/4392 [R(int) = 0.038]
Data/restraint/parameters	4392/0/246
R [I>2σ (I)]	$R_1 = 0.068$, $\omega R_2 = 0.219$
Goodness-of-fit on F^2	1.06
Largest diff. peak/hole(e/Å^3)	0.49 and –0.39

TABLE-2
SELECTED GEOMETRIC PARAMETERS FOR COMPOUND **2**

Bond	Dist. (Å)	Angle	Data (º)
N1–C5	1.391 (3)	C5–N1–C15	123.8 (2)
N1–C15	1.400 (3)	C5–N1–C4	118.1 (2)
N1–C4	1.465 (4)	C15–N1–C4	118.1 (2)
N2–C9	1.340 (3)	C9–N2–C17	130.7 (2)
N2–C17	1.463 (3)	O3–N3–O4	121.2 (2)
N3–O3	1.227 (3)	O3–N3–C8	119.0 (2)
N3–O4	1.242 (3)	O4–N3–C8	119.8 (2)
N3–C8	1.440 (3)	C3–C2–C1	95.1 (11)
O1–C15	1.219 (3)	C2–C3–C4	102.5 (12)
O2–C5	1.220 (3)	N1–C4–C3	105.8 (3)
C1–C2	1.798 (14)	O2–C5–N1	120.0 (2)
C2–C3	1.103 (14)	O2–C5–C6	122.7 (2)
C3–C4	1.717 (11)	N1–C5–C6	117.3 (2)
C5–C6	1.462 (4)	C7–C6–C16	119.0 (2)
C6–C7	1.357 (3)	C7–C6–C5	119.7 (2)

Free radical scavenging activity of compound **2** was determined against DPPH radical, according to the literatures[8]. The values of IC_{50}, the effective concentration at which 50 % of the radicals were scavenged, were calculated to evaluate the free radical scavenging activity. A lower IC_{50} value indicated greater antioxidant activity. IC_{50} values of lower than 10 mg/mL usually implied effective activities in antioxidant properties[10]. The IC_{50} of commercial antioxidant BHT was also determined for comparison. The results showed that IC_{50} of compound **2** was 214.7 μM, which was equivalent to 0.079 mg/mL and was clearly lower than 10 mg/mL[10], indicating good radical scavenging activity of compound **2**. It is pity that compound **2** displayed lower radical scavenging activity than BHT (65.8 μM).

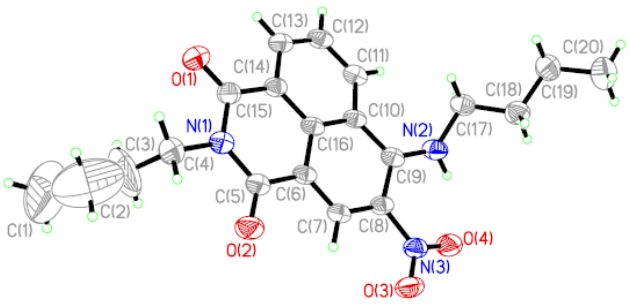

Fig. 2. General appearance of compound **2** with the atoms represented by thermal vibration ellipsoids of 50 % probability

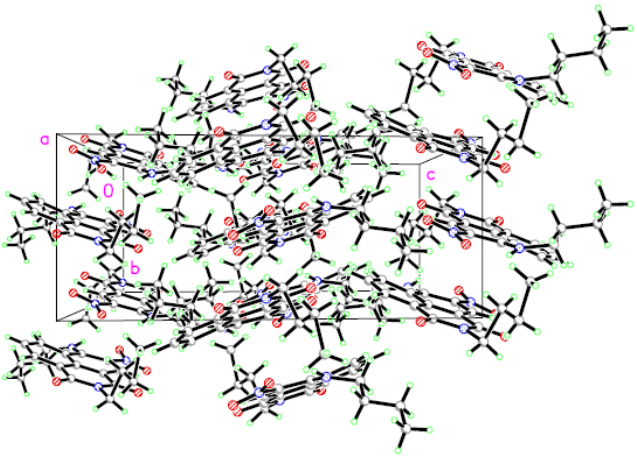

Fig. 3. Packing diagram for compound **2**

ACKNOWLEDGEMENTS

This study was supported by the Fund of Guangxi Key Laboratory of Functional Phytochemicals Research and Utilization (No. FPRU2011-6; FPRU2013-6), the Guilin Scientific Research and Technological Development Project (20120108-6; 20110106-2), the Program for Excellent Talents in University of Guangxi Zhuang Automous Region (No. 2011104), the Guangxi Natural Science Foundation (No. 2014GXNSFBA-118050) and Guangxi Department of Education Research Project (No. 2013YB283; 2013YB284).

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