SYNTHESIS OF SOME *o*-AMINOPHENOL DERIVATIVES AND ANTIOXIDANT ACTIVITIES

Nguyen Thi Ngoc Mai[1], Trinh Thi Huan[1], Pham Van Tuan[2], Tran Thi Thu Trang[3], Ha Thi Hien[4]

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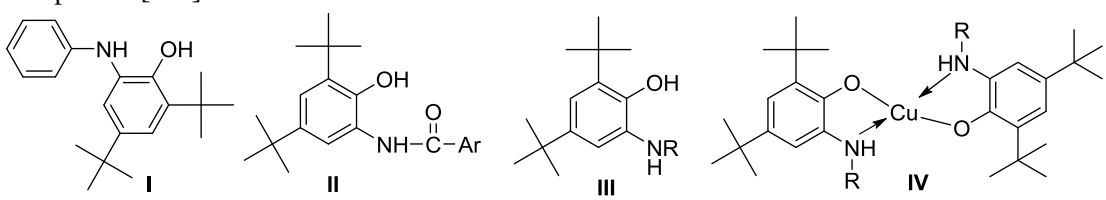
Abstract: *o-Amino phenol derivatives are well-known reagents in organic synthesis. Two o-aminophenol **6a, 6b** were synthesized successfully from corresponding o-nitrophenol derivatives in 75% over the yield in 5 steps. Two steps were promoted with microwave irradiation for 4-6 minutes in high yield. Conversion of nitro to amino group was reduced with $Na_2S_2O_4$ in ethanol in 75% yield. Structures of them were elucidated carefully by IR and NMR methods. Two compounds **6a**, **6b** were exhibited antioxidant activity with SC_{50} = 12.23 μg/mL and 22.96 μg/mL.*

Keywords: *o-aminophenol derivatives, microwave, antioxidant.*

1. Introduction

o-Aminophenol is a useful reagent for the synthesis of dyes and heterocyclic compounds. Due to the adjacency of the amino and hydroxyl groups, *o*-aminophenol readily forms heterocycles. These heterocycles, such as benzoxazoles, can be biologically active and useful in the pharmaceutical industry [1]. *o*-Aminophenol derivatives exhibit wide range of bioactivities. Butaminophen **(I)** is an antibacterial reagent for treating a herpetic of skin and mucosa [2]. *N*-acyl **(II)**, *N*-aryl **(III)** of 4,6-di-*tert*-butyl-*o*-aminophenol exhibit not only anti bacteria but also anti oxidant properties [3]. Moreover, *o*-aminophenol derivatives could be easily coordinated with metallic ions to form complexes [4-6].



In order to explore the structures of new *o*-aminophenol derivatives, we further study the synthesis of two kinds of *o*-aminophenol derivatives. The methodology was quite short because of microwave promoted technique using domestic microwave oven. IR and NMR spectroscopies provided spectral data associated with expected compounds.

[1] Faculty of Natural Sciences, Hong Duc University; Email: nguyenthingocmai@hdu.edu.vn
[2] Nguyen Thi Loi High School, Sam Son City, Thanh Hoa Province
[3] Thanh Hoa University of Culture, Sports and Tourism, Thanh Hoa Province
[4] Quang Xuong 4 High School, Thanh Hoa Province

2. Content

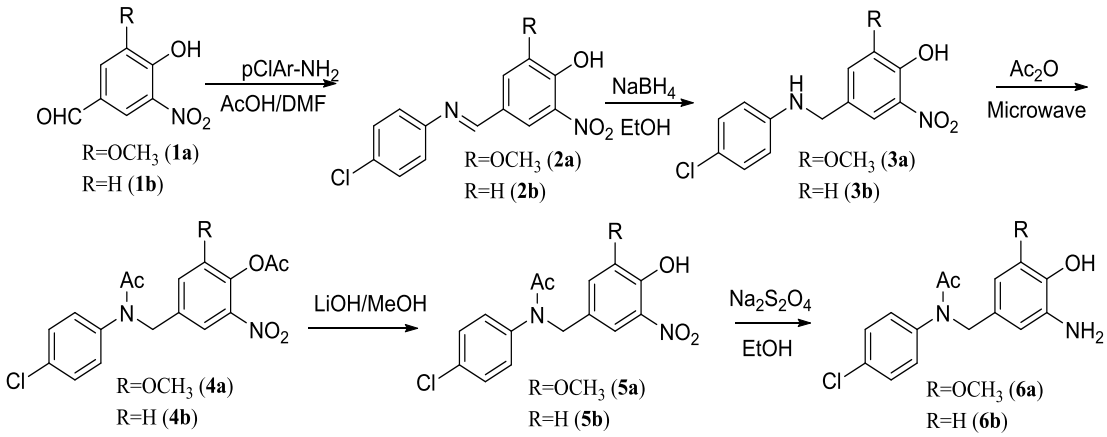
2.1. The Experimental

2.1.1. Chemicals and equipment

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck Corp, Aladdin, Vietnam or other China's companies were used as received, unless indicated in detail. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (500 and 125 MHz) using deuterated solvents and tetramethyl silane (TMS) as internal standard. MS spectra were recorded on SCIEX X500 QTOF system. Melting points were measured using a Gallenkamp melting point apparatus. A domestic Electrolux 800w (2015, Vietnam) microwave oven was used to carry out the reactions.

2.1.2. Synthesis

Scheme 1 shows the route for synthesizing the *o*-aminophenol derivatives based on our work [7-10][11]. The reduction was followed by Siddiqui *et. al* [12].



***Scheme 1**. Synthesis of o-aminophenol derivatives*

*4-((E)-(4-chlorophenylimino)methyl)-2-methoxy-6-nitrophenol (**2a**)*

A solution of 5-nitrovanillin **1a** (0.40g, 2 mmol) and *p*-chloroaniline (0.32g, 2.5 mmol) in DMF (10 mL) was added acetic acid (5 drops). The resulting mixture was irradiated with the microwave oven at 400 watt for 4 min. The progress of reaction was monitored by TLC. The product was re-crystallized in 96 ethanol to obtain a brown needle crystal of **2a** (0.49 g, 80%, mp. = 196 ^{o}C).

*4-((E)-(4-Chlorophenylimino)methyl)-2-nitrophenol (**2b**)*

Following the procedure of **2a**: the product **2b** was obtained from 3-nitro-4-hydroxybenzaldehyde **1b** (0.334 g, 2 mmol), *p*-chloroaniline (0.32 g, 2.5 mmol), DMF (10 mL) and acetic acid (5 drops) as a brown needle crystal of **2b** (0.44 g, 82%, mp. = 187^{o}C).

*4-((4-chlorophenylamino)methyl)-2-methoxy-6-nitrophenol (**3a**)*

To a solution of **2a** (0.306 g, 1mmol) in ethanol (20 mL) in a 100 mL erlenmeyer was added a portion of $NaBH_4$ (0.3 g, 8.0 mmol) in 10 min then stood at room temperature for 15 min. The reaction mixture was added ice water (50mL). The mixture was neutralized with 5% HCl until pH= 5-6. The precipitate was filtered and washed to yield an orange solid of **3a** (0.28 g, 90%, mp.= 186 ^oC); ^1H NMR (δ (ppm), J (Hz)): OH (10.3, br., 1H); NH (6.4, br., 1H); H2 (7.2, d, J=1.5, 1H); H6 (7.39, d, J = 2.0, 1H); H7 (3.8, s, 3H); H8 (4.2, s, 2H); H11 and H13 (7.0, d, J=7.0, 2H); H10 and H14 (6.5, d, J=7.0; 2H); ^{13}C NMR (δ (ppm)): C1 (130.7); C2 (115.6); C3 (149.5); C4 (141.5); C5 (135.7); C6 (113.8); C7 (56.6); C8 (45.6); C9 (147.2); C10/C14 (113.9); C12 (119.4); C11/C13 (128.6).

*4-((4-chlorophenylamino)methyl)-2-nitrophenol (**3b**)*

Following the procedure of **3a**: the product **3b** was obtained from (**2b,** 1mmol, 0.276 g), ethanol (20 mL), $NaBH_4$ (0.3 g, 8.0 mmol). The title product was yielded as an orange solid (0.25 g, 90%, mp.= 183 ^oC)

*4-((N-(4-chlorophenyl)acetamido)methyl)-2-methoxy-6-nitrophenyl acetate (**4a**)*

To a solution of **3a** (0.308 g, 1mmol) and anhydride acetic (2ml) in a 100 mL beaker was irradiated for 7 min. The progress of reaction was monitored by TLC. The precipitate was re-crystallized in 96^0 ethanol to form a cubic pale yellow crystal **4a** (0.37 g, 95%, mp.= 196 ^oC). ^1H NMR (δ (ppm), J (Hz)): H2 (7.04, d, J =1.5), 1H); H6 (7.48, m, 1H); H7 (3.80, s, 3H), H8 (4.81, s, 2H); H10 (1.8, s, 3H); H13 and H15 (7.45, m, 2H); H12 and H14 (7.26, m, 2H); H18 (2.3, s, 3H); ^{13}C NMR; δ (ppm): C1 (137.7); C2 (117.72); C3 (152.6); C4 (132.74); C5 (142.8); C6 (115.4); C7 (57.3); C8 (51.4); C9 (170.2); C10 (20.1); C11 (141.6); C12 (128.4); C13 (130.4); C14 (129.9); C15 (130.16); C16 (128.4); C17 (168.1); C18 (22.8).

*4-((N-(4-chlorophenyl)acetamido)methyl)-2-nitrophenyl acetate (**4b**)*

Following the procedure of **3a**: the product 4**b** was obtained from **3b** (0.278 g, 1mmol) and anhydride acetic (2ml). The precipitate was re-crystallized in 96^0 ethanol to form a cubic pale yellow crystal **4b** (0.34 g, 95%, mp.= 193 ^oC). ^1H NMR; δ (ppm); J (Hz): H2 (7.9, d, J=2.0, 1H); H5 (7.3, d, J=8.0, 1H); H6 (7.6, d, J=6.5, 1H); H7 (4.9, s, 2H); H9 (1.86, s, 3H); H11 and H15 (7.31, d, J=8.5; 2H); H12/H14 (7.45, d, J=8.5, 2H); H17 (2.31, s, 3H); ^{13}C NMR; δ (ppm): C1(136.5); C2 (122.6); C3 (141.1); C4 (150.8); C5 (121.4); C6 (134.4); C7 (50.6); C8 (170.4); C9 (20.17); C10 (139.8); C11 and C15 (129.7); C12 and C14 (129.8); C13 (130.2); C16 (168.3); C17 (22.1).

*N-(4-hydroxy-3-methoxy-5-nitrobenzyl)-N-(4-chlorophenyl)acetamide (**5a**)*

To a solution of **4a** (0.078g, 0.2 mmol), LiOH (0.048g, 2 mmol) in methanol/H_2O (4/1, 10 mL) was refluxed for 30 min. The progress of reaction was monitored by TLC. The mixture was neutralized by 5% HCl solution until pH = 5 ÷ 6. The precipitate was re-crystallized in ethanol/H_2O (1/2) as a needle crystal of **5a** (0.33 g, 92%, mp.= 196 ^oC); ^1H NMR (δ (ppm), J (Hz)): H2 (7.00, d, J=1.5, 1H); H6 (7.22, d, J=1.5, 1H); H7 (3.79, s, 3H); H8 (4.8, s, 2H); H10 (1.8, s, 3H); H13 and H15 (7.40, d, J=8.5, 2H); H12 and H16 (7.25, dd, J=8.5, 2.0, 2H); ^{13}C NMR (δ (ppm)): C1 (127.5); C2 (115.7); C3 (149.6); C4 (142.5); C5 (136.3); C6 (115.2); C7 (56.4); C8 (50.5); C9 (169.3); C10 (22.4); C11 (141.1); C12 and C16 (129.3); C13 and C15 (129.9); C14 (132.2).

*N-(4-hydroxy-3-nitrobenzyl)-N-(4-chlorophenyl)acetamide (**5b**)*

Following the procedure of **3a**: the product **3b** was obtained from **4b** (0.072 g, 0.2 mmol), LiOH (0.048g 2 mmol) and methanol/H_2O (4/1, 10 mL). The title compound was re-crystallized in ethanol/H_2O (1/2) to obtain compound **3b** as pale yellow needle crystal of **5b** (0.30 g, 92%, mp.= 193 ^oC); ^1H NMR (δ (ppm), *J* (Hz)): OH (10.88, br., 1H); H2 (7.6, d, *J*=2.5, 1H); H5 (7.05, d, *J*=8.5, 1H); H6 (7.33, dd, *J* = 8.5, 1.5, 1H); H7 (4.80, s, 2H); H9 (1.80, s, 3H); H11 and H15 (7.20, dd, *J*=8.5, 2.5, 2H); H12 and H14 (7.40, d, *J*=9.0, 2H); ^{13}C NMR (δ (ppm)): C1 (136.3); C2 (124.4); C3 (128.5); C4 (151.2); C5 (119.1); C6 (135.0); C7 (50.2); C8 (169.3); C9 (22.3); C10 (141.1); C11 and C15 (129.8); C12 and C14 (129.4); C13 (132.1).

*N-(3-amino-4-hydroxy-5-methoxybenzyl)-N-(4-chlorophenyl)acetamide (**6a**)*

A solution of **5a** (0.351g, 1 mol) and absolute ethanol (10 mL) was refluxed and added in portion of $Na_2S_2O_4$ (1.1g, 6 mmol) until the color of **5a** disappearing (8-10h). The progress of reaction was monitored with TLC. The mixture was concentrated to one-third then cooled down. Filtration gave compound **6a**, (0.24 g, 75%, mp.= 186 ^oC);^1H NMR (δ (ppm), *J* (Hz)): OH (7.97, br., 1H); NH2 (4.52, br., 2H); H2 (6.01, s, 1H); H6 (6.13, s, 1H); H7 (3.64, s, 3H); H8 (4.63, s, 2H); H10 (1.81, s, 3H); H12 and H16 (7.19, d, *J*=8.0, 2H); H13 and H15 (7.4, d, *J*=8.5, 2H); ^{13}C NMR; δ (ppm): C1 (127.85); C2 (100.9); C3 (147.4); C4 (131.38); C5 (136.8); C6 (108.0); C7 (55.5); C8 (51.5); C9 (168.8); C10 (22.4); C11 (9141.5); C12 (129.9); C13 (129.1); C14 (131.8); C15 (129.1); C16 (129.9).

*N-(3-amino-4-hydroxybenzyl)-N-(4-chlorophenyl)acetamide (**6b**).*

Following the procedure of **6a**: the product **6b** was obtained from **5a** (0.321 g, 1 mol), absolute ethanol (20 mL) and $Na_2S_2O_4$ (1.1g, 6 mmol) in (0.21 g, 75%, mp.= 183 ^oC); ^1H NMR; δ (ppm); *J* (Hz): OH (10.68, br., 1H); NH2 (4.56, br., 2H); H2 (7.62, d, *J*=2.5, 1H); H5 (7.08, d, *J*=8.5, 1H); H6 (7.34, dd, *J* = 8.5, 1.5, 1H); H7 (4.81, s, 2H); H9 (1.82, s, 3H); H11 and H15 (7.20, dd, *J*=8.5, 2.5, 2H); H12 and H14 (7.40, d, *J*=9.0, 2H); ^{13}C NMR (δ (ppm)): C1 (136.3); C2 (124.4); C3 (128.5); C4 (151.2); C5 (136.8); C6 (135.0); C7 (50.2); C8 (169.3); C9 (22.3); C10 (141.1); C11 and C15 (129.8); C12 and C14 (129.4); C13 (132.1).

2.2. Results and discussion

2.2.1. Synthesis

Synthetic route was accelerated by using a domestic microwave oven. The condensation of amines and aldehyde and acylation were completed after 4-6 min.

The reduction of NO_2 group to NH_2 group in acidic conditions such as Fe/HCl; Zn/NH_4Cl; or basic condition $Na_2S_2O_4$/NaOH, however, gave some drawbacks. For instance, Fe/HCl gave salt of amine, even; ion was indicated in the product. Meanwhile, $Na_2S_2O_4$/NaOH disturbed the product by observation of aniline black problem [10], [12]. Compound **5a** was converted to **6a** by $Na_2S_2O_4$ in ethanol in 90% yield. This method gave some advantages: neutral and mild condition; good visualization; inexpensive reagent; high yield simple; work up and no by-product and by reactions.

2.2.2. Structure

Structures of new compounds **3a, 4a, 4b, 5a, 5b, 6a** and **6b** were analyzed based on IR, ^{1}H NMR, ^{13}C NMR, HMBC spectra [13]. Structures of compounds **3a, 4a, 4b, 5a, 5b** were also compared to the known analog [8-10]. Spectral analysis of compound **6a** was selected to present, spectral date of the other were presented in the experimental section.

IR spectrum of **6a** showed vibrations of N-H bond at 3448 and 3371 cm^{-1} as sharp bands and O-H in range of 2500-3600 cm^{-1} as a broad peak due to hydrogen bonding. It's clear that the reduction of nitro group by sodium dithionite was happened. Moreover, the stretching vibration of carbonyl group absorbed at 1650 and 1612 cm^{-1} due to existence of two conformers of tertiary amide.

^{1}H MNR spectrum of **6a** showed a peak at δ = 1.81 ppm assigned to three protons of H10; a peak at δ = 3.64 ppm indicated to three protons of H7; a single peak at δ = 4.63 ppm with intensity of 2 protons was for H8. Two single peaks at δ = 6.01 and δ = 6.13 ppm was for H2 and H6, respectively. A doublet signal at δ = 7.19 ppm with ^{2}J = 8.0 Hz was good for interaction of 2 protons in *ortho* position which was suitable for a pair of identical protons H12 and H16; similarly, a doublet peak at δ = 7.4 ppm with splitting constant of ^{2}J = 8.5 Hz must be for H13 and H15. Exchangeable protons of OH and NH_2 groups were assigned as two broad peaks at δ = 7.97 ppm and δ = 4.52 ppm, respectively (Fig.1).

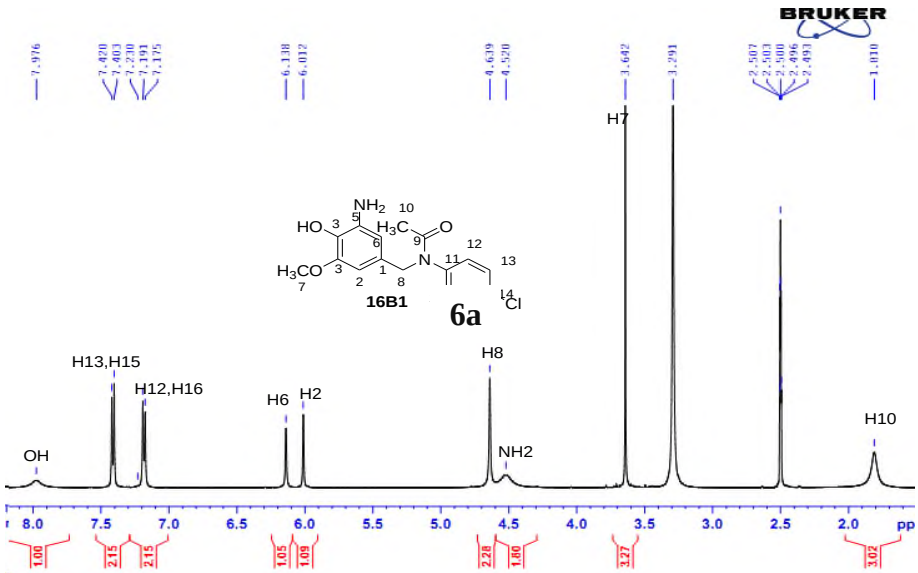


Fig.1. *^{1}H NMR spectrum of **6a***

The above results were combined with HSQC and HMBC to ensure and assign the other carbons. Fig.2 showed 7 correlation peaks that indicated 7 interactions of 8 C-H bond groups (except the peak of solvent δ = 2.5 ppm) resulting assignment of all carbons bearing hydrogen such as C2 (100.9 ppm); C6 (108.0 ppm); C7 (55.5 ppm); C8 (51.5 ppm); C10 (22.4 ppm); C12/C16 (129.9 ppm); C13/C15 (129.19 ppm), respectively.

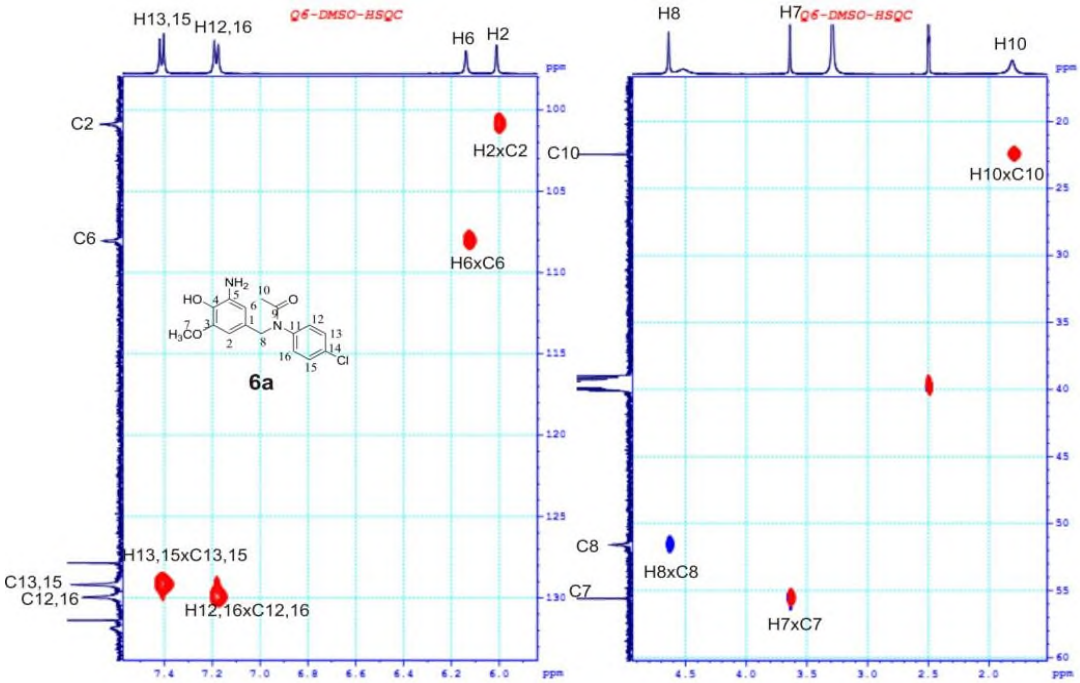


Fig.2**. HSQC spectrum of **6a

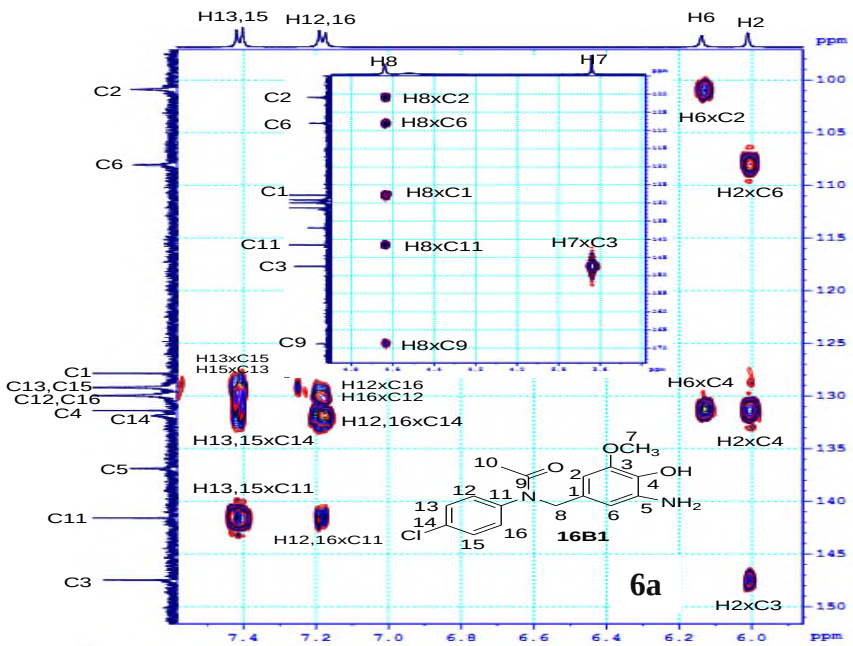


Fig.3**. HMBC spectrum of **6a

In order to ensure quaternary carbons and carbons without bearing protons were assigned further on HMBC spectrum, Fig.3. For instance, the correlation peak of H7 indicated C3 at 147.4 ppm. In the same manner, H8 indicated C1 at 127.8 ppm; C9 at

168.8 ppm; C11 at 141.5 ppm which also had a cross peak with H12/H16 and H13/H15; H2 indicated C4 at 131.3 ppm which had a cross peak with H6 indicating C2 at 100.9 ppm; H12/H16 indicated C14 at 131.8 ppm.

2.2.3. Antioxidant activities of o-aminophenol derivatives

Two *o*-aminophenol derivatives **6a** and **6b** were tested for antioxidant activities. The test results are presented in Table 1.

Table 1. *Antioxidant activities*

N^o	Sample	SC (%)	SC_{50} (μg/ml)
	Acid ascorbic	87.53±0.3	11.5
	DPPH*	0±0	-
1	6a	83.92 ± 0.7	12.23
2	6b	88.52 ± 0.5	22.96
SC (%): Percent of inhibition and scavenging at 100 mg mL^{-1}; SC_{50} is defined as the concentration sufficient to obtain 50% of a maximum scavenging capacity; *DPPH: 2,2-diphenyl-1-picrylhydrazyl.			

Test results showed that, two compounds **6a, 6b** exhibited good antioxidant activity with SC_{50} = 12.23 and 22.96 μg/mL comparing to 11.5 μg/mL of ascorbic acid.

3. Conclusion

Seven new compounds **3a, 4a, 4b, 5a, 5b, 6a** and **6b** were synthesized in which two *o*-aminophenol derivatives **6a** and **6b** were synthesized from *o*-nitrophenols in 5 steps in 85% over yield. Two out of 5 steps were shortened by irradiating with a domestic microwave oven. The sequence of synthesis was close to green synthesis. Structures of new compounds were confirmed IR, ^{1}H NMR, ^{13}C NMR, HSQC, HMBC spectra. Compounds **6a**, **6b** were exhibited antioxidant activity with SC_{50} = 12.23 μg/mL and 22.96 μg/Ml.

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