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Synthesis and Characterization of New Cyclic Aminobenzoquinones

Amaç Fatih Tuyun[1,] * and Mahmut Yıldız[2]

[1]Istanbul University, Engineering Faculty, Engineering Sciences Department, 34320 Avcılar, Istanbul, Turkey

[2]Gebze Technical University, Chemistry Department, Gebze, 41400, Kocaeli, Turkey

Abstract: The aim of this research is to synthesize and characterize new members of cyclic aminobenzoquinones. Mono amino substituted products, namely 2-chloro-5,6-dimethyl-3-(pyrrolidin-1-yl)-1,4-benzoquinone (**2**), 2-chloro-5,6-dimethyl-3-(piperidin-1-yl)-1,4-benzoquinone (**3**), 2-chloro-5,6-dimethyl-3-morpholino-1,4-benzoquinone (**4**), and 2-chloro-5,6-dimethyl-3-thiomorpholino-1,4-benzoquinone (**5**) have been synthesized by the nucleophilic substitution reactions between 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**1**) and cyclic secondary amines with a green methodology using water as solvent. Structure determination of the new products (**2-5**) was established on the basis of FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Keywords: Benzoquinones, secondary amine, aminoquinones.

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***Corresponding author. E-mail:**aftuyun@gmail.com

INTRODUCTION

Compounds containing quinone core exist widely in nature (plants, microorganisms, animals, *etc*.) and have been utilized by mankind during many years (1, 2). These structures could be either isolated from natural products or synthesized in the laboratories by applying various experimental methods (3-8). Plenty of molecules which belong to quinone family are particularly biologically active compounds and possess antitumor, cytotoxic, anticancer, antimalarial, and antifungal properties (9-13). These type of compounds can also find potential application as the electron-deficient compounds in heterocyclic synthesis, a generator of reactive oxygen species in photodynamic therapies, the organic electrode materials in lithium-ion batteries, a chemosensor in metal detection analyses, and the quinone oligomers in the field of DNA sensors (2, 14-21).

The reactions of quinones with a variety of amines give aminoquinone compounds (22-24). Particularly, aminoquinone structures draw interest in the literature because of the similar biological characteristics to quinone moieties (5, 23, 25-36). Although they have numerous beneficial biological activities, quinone structures including pharmacophore groups could sometimes cause possible toxic effects in *in vivo* implementations. However, Zakharova *et al.* have investigated also the cytotoxicity of new polyfluorinated 1,4-naphthoquinones and indicated that a number of synthesized structures exhibited a substantial cytotoxic effect against cancer cells compared to normal mammalian cells (36). Moreover, Khodade *et al.* have suggested that there is a good correlation between reactive oxygen species production of 2-aryl-3-amino-1,4-naphthoquinones and their DNA damage inducing ability (37). Besides that, Sharma *et al*. showed a new synthesis of 2-aryl-3-amino-1,4-naphthoquinones by using an eco-friendly, non-toxic, efficient, inexpensive, and reusable $HClO_4$-SiO_2 heterogeneous catalyst which is applied to different organic reactions (29). In a study reported by Verma *et al.* in 2015, some metal complexes of 2-chloro-3-amino-1,4-naphthoquinone derivatives with Mn, Co, Ni, Cu, and Zn metals were synthesized and characterized. The complex compounds exhibited a promising antimicrobial activity and fluorescence emission behavior and they were also found as electro active compounds (35). Nitrogen and sulfur containing quinones known also sulfanyl aminoquinones in the literature are of great importance in drug exploration researches due to their bioactive properties (13, 38-43). Recently, new sulfanyl and arylamine substituted 1,4-naphthoquinones have been synthesized and characterized (44, 45).

Encouraged by the previous studies and taking into account the well-documented quinone chemistry associated with the 1,4-benzoquinone pharmacophoric unit, it was attempted to synthesize several new cyclic aminobenzoquinone compounds. Thus, as a part of our research, aiming at the discovery of novel biologically active molecules based on 1,4-benzoquinone moiety, we have recently reported

the synthesis and characterization of cyclic aminobenzoquinones which contain a heterocyclic fragment as a key structural element.

MATERIALS AND METHODS

All reagents used were purchased from the various commercial supplier. Reactions were monitored by TLC performed on silica gel plate purchased from Merck KGaA (silica gel 60 F_{254}) based on Merck DC-plates (aluminum-based) and visualization was achieved by UV light (254 nm). Column chromatography was performed with silica gel 60 (Merck, 63–200 μm particle size, 60–230 mesh). ^{1}H NMR and ^{13}C NMR spectra (VarianUNITY INOVA spectrometers 500 MHz frequency for ^{1}H and 125 MHz frequency for ^{13}C NMR) and Fourier transform infrared (FT-IR) spectra as ATR (Thermo Scientific Nicolet 6700 spectrometer) were used to elucidate the structures of the products. Chemical shifts are expressed in parts per million (δ in ppm) and coupling constants are expressed in Hz. ^{1}H NMR spectroscopic data are used as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were recorded with either a Thermo Finnigan LCQ Advantage MAX MS/MS spectrometer equipped with ESI (electrospray ionization) sources or a BRUKER Microflex LT by MALDI (Matrix Assisted Laser Desorption Ionization)-TOF (Time of Flight) technique via addition of 1,8,9-anthracenetriol (DIT, dithranol) as matrix. The 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**1**) was prepared according to the literature reported previously and the reference cited therein (46).

General Procedure for Synthesis of the Cyclic Aminobenzoquinone Derivatives (2-5)

The mixture of 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**1**, 0.5 mmol) in water (10 mL) and cyclic secondary amines (1.1 mmol) was stirred at 50-60 ^{o}C for 6 to 18 h as stated in the literature (42). The resulting solution was extracted with 100 mL chloroform, and then was washed with water (4 x 25 mL) and dried over calcium chloride. The solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel using suitable solvents to give the products (**2-5**).

*2-Chloro-5,6-dimethyl-3-(pyrrolidin-1-yl)-1,4-benzoquinone (**2**).* Following general procedure by applying pyrrolidine (0.076 g, 1.07 mmol), the crude residue was purified by column chromatography to furnish **2** as purple oil. Yield: 71%. FTIR (ATR) υ (cm^{-1}): 2919, 2850 ($CH_{aliphatic}$), 1661 (>C=O). ^{1}H NMR (*$CDCl_3$*) δ (ppm): 1.80-1.82 (m, 4H, H10 and H10'), 1.89 (dd, *J* = 1.13 and 2.33 Hz, 3H, H8), 1.99 (dd, *J* = 1.17 and 2.37 Hz, 3H, H7), 3.78-3.81 (m, 4H, H9 and H9'). ^{13}C NMR (*$CDCl_3$*) δ (ppm): 11.4, 12.2 (C7 and C8), 24.7 (C10 and C10'), 52.7 (C9 and C9'), 107.6, 135.8, 140.8, 146.0 (C2, C3, C5, and C6), 178.2, 184.2 (C1 and C4). MS (+ESI) *m/z* (%): 240 (27, $[M+H]^+$), 238 (10, $[M-H]^+$). Calcd. for $C_{12}H_{14}ClNO_2$ (239.70).

*2-Chloro-5,6-dimethyl-3-(piperidin-1-yl)-1,4-benzoquinone (**3**).* Following general procedure by applying piperidine (0.091 g, 1.07 mmol), the crude residue was purified by column chromatography to furnish **3** as purple oil. Yield: 57%. FTIR (ATR) υ (cm^{-1}): 2934, 2853 ($CH_{aliphatic}$), 1657 (>C=O). ^{1}H NMR (*$CDCl_3$*) *δ* (ppm): 1.60-1.64 (m, 6H, H10, H10', and H11), 1.92 (m, 3H, H8), 1.98 (m, 3H, H7), 3.33-3.35 (m, 4H, H9 and H9'). ^{13}C NMR (*$CDCl_3$*) *δ* (ppm): 11.6, 12.1 (C7 and C8), 23.1, 25.8 (C10, C10', and C11), 51.6 (C9 and C9'), 117.6, 137.5, 140.2, 147.9 (C2, C3, C5, and C6), 179.1, 183.1 (C1 and C4). MS (MALDI TOF) *m/z*: 252 $[M-H]^+$. Calcd. for $C_{13}H_{16}ClNO_2$ (253.72).

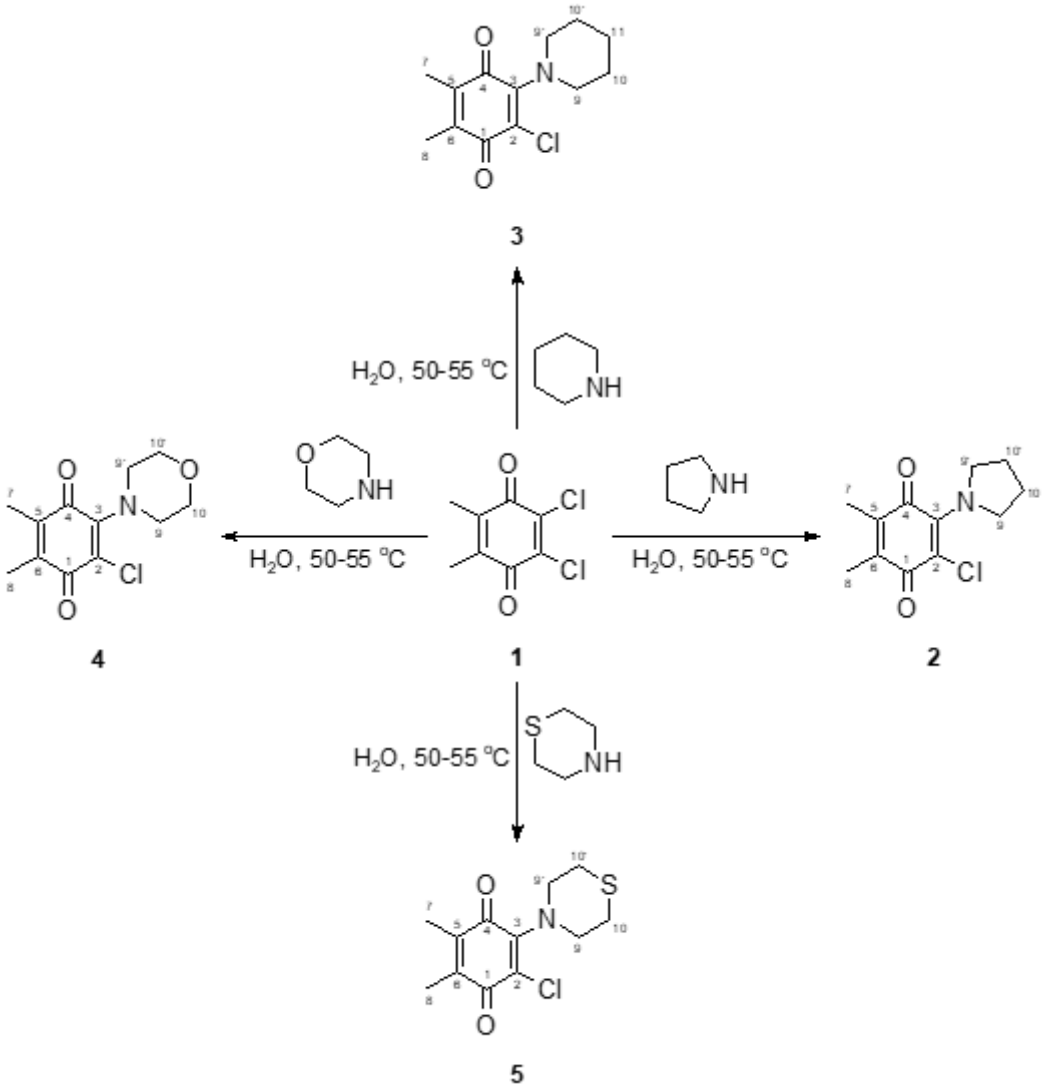
*2-Chloro-5,6-dimethyl-3-morpholino-1,4-benzoquinone (**4**).* Following general procedure by applying morpholine (0.093 g, 1.07 mmol), the crude residue was purified by column chromatography to furnish **4** as dark red oil. Yield: 29%. FTIR (ATR) υ (cm^{-1}): 2966, 2916, 2854 ($CH_{aliphatic}$), 1656 (>C=O). ^{1}H NMR (*$CDCl_3$*) *δ* (ppm): 1.93 (dd, *J* = 1.11 and 2.31 Hz, 3H, H8), 1.99 (dd, *J* = 1.10 and 2.30 Hz, 3H, H7), 3.43 (t, *J* = 4.40 Hz, 4H, H9 and H9'), 3.57 (t, *J* = 4.39 Hz, 4H, H10 and H10'). ^{13}C NMR (*$CDCl_3$*) *δ* (ppm): 11.5, 12.1 (C7 and C8), 50.5 (C9 and C9'), 66.5 (C10 and C10'), 118.8, 137.8, 140.3, 146.7 (C2, C3, C5, and C6), 179.1, 182.8 (C1 and C4). MS (MALDI TOF) *m/z*: 256 $[M+H]^+$. Calcd. for $C_{12}H_{14}ClNO_3$ (255.70).

*2-Chloro-5,6-dimethyl-3-thiomorpholino-1,4-benzoquinone (**5**).* Following general procedure by applying thiomorpholine (0.110 g, 1.07 mmol), the crude residue was purified by column chromatography to furnish **5** as a dark red oil. Yield: 61%. FTIR (ATR) υ (cm^{-1}): 2957, 2910, 2846 ($CH_{aliphatic}$), 1654 (>C=O). ^{1}H NMR (*$CDCl_3$*) *δ* (ppm): 1.93 (s, 3H, H8), 1.98 (s, 3H, H7), 2.68-2.70 (m, 4H, H10 and H10'), 3.57 (t, *J* = 4.88 Hz, 4H, H9 and H9'). ^{13}C NMR (*$CDCl_3$*) *δ* (ppm): 11.6, 12.1 (C7 and C8), 27.2 (C10 and C10'), 52.5 (C9 and C9'), 120.6, 138.0, 140.1, 147.9 (C2, C3, C5, and C6), 179.2, 182.9 (C1 and C4). MS (+ESI) *m/z* (%): 273 (13, $[M+2H]^+$), 272 (100, $[M+H]^+$). Calcd. for $C_{12}H_{14}ClNO_2S$ (271.76).

RESULTS AND DISCUSSION

It is well known the reactions of 1,4-quinones containing chlorine atoms with amine, sulfur, or oxygen nucleophiles proceed by nucleophilic substitution. Herein, when 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**1**) was stirred with different cyclic secondary amines (pyrrolidine, piperidine, morpholine, and thiomorpholine) according to the literature (42) at 50-60 °C in the absence of a base using water as solvent, mono substituted products; 2-chloro-5,6-dimethyl-3-(pyrrolidin-1-yl)-1,4-benzoquinone (**2**), 2-chloro-5,6-dimethyl-3-(piperidin-1-yl)-1,4-benzoquinone (**3**), 2-chloro-5,6-dimethyl-3-morpholino-1,4-benzoquinone (**4**), and 2-chloro-5,6-dimethyl-3-thiomorpholino-

1,4-benzoquinone (**5**) were obtained in 29-71% yield, respectively. The newly synthesized products (**2-5**) were characterized on the basis of FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry.



Scheme 1. Synthesis of cyclic aminobenzoquinones (**2-5**) from the reactions of 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**1**) with different cyclic secondary amines.

The FT-IR spectra of aminobenzoquinones (**2-5**) have showed characteristic carbonyl (>C=O) band at around 1650 cm^{-1}. The ^{1}H NMR spectra of aminobenzoquinone (**5**) exhibited two singlets at 1.93 and 1.98 ppm for the aliphatic methyl groups attached to the quinone moiety. On the other hand, aliphatic methyl protonds in aminobenzoquinones (**2** and **4**) have resonated in doublet of doublets at around 1.90 and 1.99 ppm because of the interaction of the protons in the methyl groups. In the ^{1}H NMR spectra of **4**, protons of methylene group which are adjacent to the oxygen atom have appeared as triplet at 3.57 ppm while protons of methylene group which are adjacent to the nitrogen atom have appeared as triplet at 3.43 ppm. In the ^{1}H NMR spectra of **5**, protons of methylene group

next to the sulfur atom have appeared as multiplet at between 2.68-2.70 ppm while protons in methylene group which are adjacent to the nitrogen atom have appeared as triplet at 3.57 ppm. In the ^{13}C NMR spectra of all compounds, the presence of methyl carbons could be seen as two peaks at around 11 and 12 ppm. In the ^{13}C NMR spectra of all the cyclic aminobenzoquinones (**2-5**), there are signals corresponding to the >C=O carbons at around 178 and 182 ppm as two peaks. In the mass spectrum of compounds (**2**-**5**), the accurate mass measurements of the molecular ion peaks were noticed at *m/z* 240 $[M+H]^+$, 252 $[M-H]^+$, 256 $[M+H]^+$, and 272 $[M+H]^+$, respectively.

CONCLUSION

In conclusion, the present study describes the synthesis and characterization of new cyclic aminobenzoquinones (**2-5**) by a green methodology using water as solvent according to the literature reported previously by Tandon (42). The conditions are mild and good yields are obtained in the absence of any additives. We believe that these new cyclic aminobenzoquinone compounds (**2-5**) could be biologically important because of the fact that the compounds containing quinone skeleton with heteroatoms usually have anticancer and antimicrobial activities. Since the multifaceted biologically character of the quinone moiety provides significant potential in medicinal chemistry, further extension of our research is now ongoing in our laboratory.

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