Synthesis and cyclization reactions of novel benzo[a]phenazine- and phenoxazine-5-ones derivatives

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In the present study we reported the cyclization reactions of 2-(alkylthio)-1,4-naphthoquinones to 6-(alkylthio)benzo[a]phenazine- and phenoxazine-5-ones derivatives 5a-c and 7b-c, respectively and their structural studies. The reactions of 2-(alkylthio)-3-chloro-1,4-naphthoquinone 3a-c with phenyl-1,2-diamine 4 and 2-aminophenol 6 in ethanol in the presence of sodium carbonate (Na$_2$CO$_3$) were investigated. All new compounds were characterized on the basis of nuclear magnetic resonance spectroscopy (1H- and 13C-NMR), mass spectrometry (MS), and fourier transform infrared spectroscopy (FT-IR). A probable mechanism for the formation of all reaction products was presented and detailed spectroscopic data of all compounds were given.

**Keywords** Phenazine; Phenoxazine; Phenyl-1,2-diamine; 2-Aminophenol; Quinones

**INTRODUCTION**

Quinone imines are useful for medicine, dyestuffs and others in the wide of industries. Some phenoxazone and phenothiazine derivatives containing stable quinone imine systems have been synthesized to study the biological and pharmaceutical activities, e.g. antitumor activities, and to obtain the useful pigments [1-3]. Quinones are well known in biological systems as reactive centers of transporting both electrons and protons across biological membranes. The evaluation of the redox chemistry and electrochemical properties of quinones are a useful way for identifying their biological evolutions. Most of the reported methods for the synthesis of phenoxazones [4-6] from quinones and o-aminophenols involve the initial attack of the amino group of the o-aminophenol on the quinone substituent (OH, OCH$_3$, Cl, etc.) and subsequent ring closure. An o-aminophenol exchange reaction or a rearrangement leads finally to the phenoxazone system.

In this work, we synthesized novel 6-(alkylthio) benzo[a]phenazine-5(7H)-ones (compounds 5a-c) and 6-(alkylthio)-5H-benzo[a]phenoxazine-5-ones (compounds 7b-c) by the condensation of phenyl-1,2-diamine 4 or 2-aminophenol 6 with 2-(alkylthio)-3-chloro-1,4-naphthoquinone compounds (3a-c). The condensations between 3a-c and 4 or 6 were carried out in ethanol in the presence of sodium carbonate (Na$_2$CO$_3$). The conversion of the substituents of the resulting products, the reduction and the dehalogenation were carried out. Their structures were characterized by using micro analysis, FT-IR, 1H-NMR, 13C-NMR, MS spectroscopy.

**EXPERIMENTAL**

**Reagents and apparatus**

Micro analyses were performed on a Thermo Finnigan Flash EA 1112 Elemental analyser. Infrared (FT-IR) spectra were recorded in KBr pellets in Nujol mulls on a Perkin Elmer Precisely Spectrum One FTIR spectrometry. 1H- and 13C NMR spectra were recorded on VarianUNITYINova operating at 500 MHz. Chemical shifts δ (ppm) were reported relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. 1H- and 13C NMR spectra in CDCl$_3$ refer to the solvent signal center at δ = 7.26 and δ = 77.0 ppm, respectively. Mass spectra were obtained on a Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer using an ESI probe. Products were isolated by column chromatography on Silica gel (Fluka Silica gel 60, particle size 63-200 µm). Melting points were measured on a Buchi B-540 melting point apparatus.

Analytical thin layer chromatography (TLC) was purchased from Merck KGaA (silica gel 60 F254) based on Merck DC-plates (aluminum based). Visualization of the chromatogram was performed by UV light (254 nm). Moisture was excluded from the glass apparatus using CaCl$_2$ drying tubes.

Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use, and all

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other chemicals (reagent grade) were used without further purification.

**General procedure for the synthesis of 2-(alkylthio)-3-chloro-1,4-naphthoquinone compounds as a starting material (3a-c)**

2-(Ethylthio)-3-chloro-1,4-naphthoquinone (3a) [7], 2-(hexadecylthio)-3-chloro-1,4-naphthoquinone (3b) [8] and 2-(octadecylthio)-3-chloro-1,4-naphthoquinone (3c) [9] were synthesized from the reactions of compound 1 with 2a-c for using as a starting material according to the literatures [7-9].

**General procedure for the synthesis of new phenazine and phenoxazine compounds (5a-c and 7b-c)**

Sodium carbonate was dissolved in ethanol (50 mL), and equimolar amounts of 2-(alkylthio)-3-chloro-1,4-naphthoquinone (3a-c) and nucleophiles (4 and 6) were added slowly. The mixture was heated at 40°C and stirred in a single reaction vessel for 18 h. The color of the solution quickly changed (from yellow to red color), and the extent of the reaction was monitored by TLC. Chloroform (30 mL) was added to the reaction mixture. The organic layer was separated, washed with water (4 × 30 mL), and dried with Na2SO4. After the solvent was evaporated, the residue was purified by column chromatography on silica gel.

6-(Ethylthio)benz[a]phenazine-5(7H)-one (5a)

Compound 5a was synthesized from reaction of 2-(ethylthio)-3-chloro-1,4-naphthoquinone (3a) (0.5 g, 1.978 mmol) with phenyl-1,2-diamine 4 (0.213 g, 1.978 mmol) according to the general procedure.

Orange solid. Yield: 18.4% (0.111 g). m.p.: 86.1-88.5°C. Rf [PET/CHCl3(3:1)]: 0.52. FT-IR (KBr): ν (cm⁻¹)= 2925-2853 (C=H-aromatic), 3018 (CH-aromatic), 1600 (C=N), 1588 (C=O), 1522 (C=C), 3295 (N-H). ¹H-NMR (499.74 MHz, CDCl₃): δ = 7.09-7.23 ppm (m, 10H, benzene ring), 7.18-7.24 ppm (m, 2H, CH=CH), 7.19-7.24 ppm (m, 2H, CH=CH), 7.18-7.21 ppm (m, 2H, CH=CH), 7.46-7.48, 7.27-7.29 ppm (m, 2H, CH=CH), 7.73-7.78 ppm (m, 2H, CH=CH), 8.29-8.33 ppm (m, 2H, CH=CH). ¹³C-NMR (125.66 MHz, CDCl₃): δ = 135 (-CH₃), 28.8 (SC₂H₆), 118.6 (SC₂H₆), 118.6 (SC₂H₆), 131.6, 131.4, 131.9, 132.5 (SC₂H₆), 134.0, 135.1 (SC₂H₆), 118.7, 127.9, 128.1, 129.3 (SC₂H₆), 135.2 (N=SC₂H₆), 142.0 (NH=SC₂H₆), 178.5 (C=O), 142.1 (C=N). MS [+ESI]: m/z = 307.1 [M+H]⁺. Micro analysis: C₁₈H₁₄N₂OS, (Mₐ= 306.38 g/mol). Calculated: C, 70.56; H, 4.61; N, 9.14; S, 10.46% Found: C, 70.83; H, 4.92; N, 9.17; S, 10.45%.

6-(Hexadecylthio)benz[a]phenazine-5(7H)-one (5b)

Compound 5b was synthesized from reaction of 2-(hexadecylthio)-3-chloro-1,4-naphthoquinone (3b) (0.2 g, 0.445 mmol) with phenyl-1,2-diamine 4 (0.048 g, 0.445 mmol) according to the general procedure.

Red solid. Yield: 10.4% (0.023 g). m.p.: 112.1-113.9°C. Rf [PET/CHCl₃(5:2)]: 0.60. FT-IR (KBr): ν (cm⁻¹)= 2926-2854 (C=H-aromatic), 3019 (C=H-aromatic), 1601 (C=N), 1590 (C=O), 1525 (C=C), 3335 (N-H). ¹H-NMR (499.74 MHz, CDCl₃): δ = 0.78-0.82 ppm (t, 3H, J = 7.11 Hz, CH₃), 1.11-1.54 ppm (m, 28H, CH₂), 2.97-3.00 ppm (t, 2H, J = 7.31 Hz, S-CH₂), 2.84 ppm (bs, H, -NH), 7.74-7.84 ppm (m, 2H, CH=CH₂), 8.23-8.28 ppm (m, 2H, CH=CH₂), 8.30-8.36 ppm (m, 2H, CH=naph), 9.32-9.34 ppm (m, 2H, CH=naph). ¹³C-NMR (125.66 MHz, CDCl₃): δ = 14.1 (+CH₃), 22.7-31.9 (+CH₂), 35.2 (SCH₂), 123.8 (S-C₇H₈), 142.7 (NH=CH₂), 129.2, 129.5, 129.9, (CH=naph), 130.0, 131.8 (CH=naph), 123.9, 125.5, 128.8, 129.3 (CH=CH₂), 140.0 (N=CH₂), 144.0 (NH=CH₂), 174.4, (C=O), 140.1 (C=N). MS [+ESI]: m/z = 503.5 [M+H]⁺. Micro analysis: C₂₄H₂₃N₂OS, (Mₐ= 502.75 g/mol). Calculated: C, 76.45; H, 8.42; N, 5.57; S, 6.38%; Found: C, 76.63; H, 9.01; N, 5.62; S, 6.35%.

6-(Octadecylthio)benz[a]phenazine-5(7H)-one (5c)

Compound 5c was synthesized from reaction of 2-(octadecylthio)-3-chloro-1,4-naphthoquinone (3c) (0.4 g, 0.838 mmol) with phenyl-1,2-diamine 4 (0.090 g, 0.838 mmol) according to the general procedure.

Dark orange solid. Yield: 9.3 (0.041 g)%. m.p.: 117.6-118.4°C. Rf [PET/CHCl₃(5:2)]: 0.58. FT-IR (KBr): ν (cm⁻¹)= 2920-2850 (C=H-aromatic), 2957 (C=H-aromatic), 1649 (C=N), 1727 (C=O), 1591 (C=C), 3355 (N-H). ¹H-NMR (499.74 MHz, CDCl₃): δ = 0.81-0.84 ppm (t, 3H, J = 7.46 Hz, CH₃), 1.13-1.61 ppm (m, 31H, CH₂), 3.21 ppm (bs, H, -NH), 3.37-3.42 ppm (t, 2H, J = 7.32 Hz, S-CH₂), 7.82-7.87 ppm (m, 2H, CH=naph), 7.87-7.91 ppm (m, 2H, CH=naph), 8.30-8.35 ppm (m, 2H, CH=naph), 9.28-9.32 ppm (m, 2H, CH=naph). ¹³C-NMR (125.66 MHz, CDCl₃): δ = 14.1 (+CH₃), 22.8-31.9 (+CH₂), 38.7 (S=CH₂), 125.7 (S=CH₂), 143.1 (NH=CH₂), 129.5, 130.5, 130.7, 130.9 (CH=naph), 131.5, 132.5 (CH=naph), 123.2, 125.9, 128.8, 129.8 (CH=CH₂), 141.6 (N=CH₂), 144.8 (NH=CH₂), 167.8 (C=O), 141.9 (C=N). MS [+ESI]: m/z = 553.3 [M+Na]⁺. Micro analysis: C₂₆H₂₄N₂O₃S, (Mₐ= 530.33 g/mol). Calculated: C, 76.93; H, 8.74; N, 5.28; S, 6.04%; Found: C, 77.05; H, 8.99; N, 5.33; S, 6.01%.
6-(Hexadecylthio)-5H-benzo[a]phenoxazine-5-one (7b)

Compound 7b was synthesized from reaction of 2-(hexadecylthio)-3-chloro-1,4-naphthoquinone (3b) (0.4 g, 0.890 mmol) with aminophenol 6 (0.097 g, 0.880 mmol) according to the general procedure.

Red solid. Yield: 13.7% (0.061 g), m.p.: 80.6-81.9°C. Rf [PET/CHCl₃(3:1)]; 0.61. FT-IR (KBr): ν (cm⁻¹)= 2924-2852 (C-H_aliph), 3018 (C-H_arom), 1595 (C=N), 1633 (C=O), 1542 (C=C). ¹H-NMR (499.74 MHz, CDCl₃); δ = 0.89-0.91 (t, 3H, J = 7.09 Hz, CH₃), 1.21-1.68 (m, 28H, CH₂), 3.12-3.17 (t, 2H, J = 7.48 Hz, S-CH₂), 7.38-7.47 (m, 2H, CH_arom), 7.52-7.84 (m, 2H, CH_arom), 7.71-7.81 (m, 2H, CH_naph), 8.35-8.75 ppm (m, 2H, CH_naph). ¹³C-NMR (125.66 MHz, CDCl₃); δ = 14.1 (-CH₃), 22.7-32.0 (-CH₂-), 33.4 (S-CH₂-), 117.2 (S-C_naph), 146.5 (O-C_naph), 128.7, 129.6, 131.1, 131.8 (CH_naph), 132.1, 132.4 (C_naph), 115.9, 124.3, 125.7, 127.0 (CH_arom), 133.0 (N-C_arom), 150.2 (O-C_arom), 183.0 (C=O), 144.0 (C=N). MS [+ESI]: m/z = 504.84 [M+H⁺]. Micro analysis: C₃₂H₂₆NO₂S_Ma = 503.74 g/mol. Calculated: C, 76.30; H, 8.20; N, 2.78; S, 6.37% Found: C, 76.72; H, 8.77; N, 2.84; S, 6.30%.

6-(Octadecylthio)-5H-benzo[a]phenoxazine-5-one (7c)

Compound 7c was synthesized from reaction of 2-(octadecylthio)-3-chloro-1,4-naphthoquinone (3c) (0.4 g, 0.838 mmol) with aminophenol 6 (0.091 g, 0.838 mmol) according to the general procedure.

Red solid. Yield: 11.9% (0.053 g), m.p.: 88-89°C. Rf [PET/CHCl₃(3:1)]; 0.62. FT-IR (KBr): ν (cm⁻¹)= 2918-2849 (C-H_aliph), 3019 (C-H_arom), 1596 (C=N), 1628 (C=O), 1541 (C=C). ¹H-NMR (499.74 MHz, CDCl₃); δ = 0.87-0.91 (t, 3H, J = 7.09 Hz, CH₃), 1.21-1.68 (m, 32H, CH₂), 3.12-3.17 (t, 2H, J = 7.39 Hz, S-CH₂), 7.38-7.48 ppm (m, 2H, CH_arom), 7.52-7.89 (m, 2H, CH_arom), 7.73-7.82 (m, 2H, CH_naph), 8.35-8.75 ppm (m, 2H, CH_naph). ¹³C-NMR (125.66 MHz, CDCl₃); δ = 14.1 (-CH₃), 22.7-32.0 (-CH₂-), 33.4 (S-CH₂-), 116.1 (S-C_naph), 146.3 (O-C_naph), 129.6, 131.0, 131.5, 131.9 (CH_naph), 132.1, 132.2 (C_naph), 115.9, 124.7, 125.5, 126.5 (CH_arom), 132.8 (N-C_arom), 150.4 (O-C_arom), 183.4 (C=O), 144.4 ppm (C=N). MS [+ESI]: m/z = 532.5 [M+H⁺]. Micro analysis: C₃₄H₂₉NO₂S_Ma = 531.79 g/mol. Calculated: C, 76.79; H, 8.53; N, 2.63; S, 6.03% Found: C, 76.95; H, 8.84; N, 2.66; S, 5.98%.

RESULTS AND DISCUSSION

The aim of this work, the novel 6-(alkylthio) benzo[a]phenazine-5(7H)-ones (compounds 5a-c) and 6-(alkylthio)-5H-benzo[a]phenoxazine-5-ones (compounds 7b-c) were synthesized by the condensation reactions of phenyl-1,2-diamine 4 or 2-aminophenol 6 with 2-(alkylthio)-3-chloro-1,4-naphthoquinone compounds (3a-c), respectively. As shown in Scheme 1, the condensations between 3a-c and 4 or 6 were carried out in ethanol in the presence of sodium carbonate (Na₂CO₃) at 40°C about 18 h.

The known compounds 2-(ethylthio)-3-chloro-1,4-naphthoquinone (3a), 2-(hexadecylthio)-3-chloro-1,4-naphthoquinone (3b) and 2-(octadecylthio)-3-chloro-1,4-naphthoquinone (3c) were synthesized according to published literatures [7-9]. These compounds were used for starting materials. All these new compounds were separated and purified by column chromatography and structures were established by micro analysis, FT-IR, ¹H- and ¹³C-NMR, and mass spectra, chemical reactions, or comparison with authentic samples.

We assume that the reactions of 3a-c and 4 or 6 in ethanol in the presence of sodium carbonate start with nucleophilic attack of the amino group of 4 or 6 on the halogen atom of 3a-c with the elimination of hydrogen chloride to give B and D in schemes 2 and 3, respectively. In the formations of B and D, addition of the amino or hydroxyl group to the quinone carbonyl group in equilibrium reaction lead to the formation of the hemiketal, isetherified to the ketal. In addition to this, the open forms (B, D) and a hemiketal/ketal of B and D could not be isolated.

The formation of A and C in from the reactions of 3a-c with 4 or 6 did not obtain reasonable because amino- and hydroxy-phenazines and phenoxazines were highly unstable [10]. These proposed mechanisms in schemes 2 and 3 were agree well with the mechanism of the synthesis of similar compounds [5].

The ¹H spectrum of the products in CDCl₃ displayed distinct signals with appropriate multiplets. ¹H NMR signal of the hydrogen atoms of the adjacent to the nitrogen atom (-NH) in compounds 5a-c were shifted to a higher field and displayed singlet at 2.87, 2.84 and 3.21 ppm as single broad, respectively. The ¹³C NMR spectra of compounds 5a-c and 7b-c gave just one carbonyl signals (C=O) at 178.5, 174.4 167.8, 183.0 and 181.2 ppm, respectively, in the naphthoquinone units of 5a-c and 7b-c. The carbonyl signals (C=O) in ¹³C-NMR spectra of 5a-c and 7b-c are in close agreement with the spectral characteristic of analogous heterocycles [11-14]. In the ¹³C-NMR spectra of compounds 5a-c and 7b-c carbon signals of (C=O) group appeared around at 144 ppm.
Scheme 1. The synthesis of phenazines and phenoxazines derivatives (5a-c, 7b-c)

Scheme 2. Proposed mechanism of the synthesis of phenazine compounds (5a-c)

Scheme 3. Proposed mechanism of the synthesis of phenoxazine compounds (7b-c)
CONCLUSION

In continuation of our investigations of quinone [11-16] chemistry, we have studied the reactions of naphthoquinones with phenyl-1,2-diamine 4 and 2-aminophenol 6. The aim of this study was to the investigation of the cyclization reactions of 2-(alkylthio)-3-chloro-1,4-naphthoquinones 3a-c with nitrogen- and oxygen-containing nucleophiles (4, 6) and obtain to highly functionalized heterocyclic new compounds (5a-c, 7b-c). The condensations between 3a-c and compounds 4 or 6 were carried out in ethanol in the presence of sodium carbonate (Na₂CO₃). These reactions of 3a-c and 4 or 6 proceeded at 40°C. A probable mechanisms for the formation of all reaction products was presented and detailed spectroscopic data of all compounds were given. All synthesized new compounds 5a-c and 7b-c were purified by the column chromatography. Their structures of new synthesized compounds were determined by micro analysis, FT-IR, ¹H-NMR, ¹³C-NMR and MS.

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REFERENCES