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Synthesis and characterization of 3*H*-phenothiazin-3-one derivatives

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ABSTRACT

Heterocyclic derivatives of 3H-phenothiazin-3-one ***6(a-d)*** *are prepared by refluxing 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone* ***4*** *with substituted ortho-aminothiophenols* ***5(a-d)*** *in ethanolic solution of fused sodium acetate. The structures of newly synthesized compounds are characterized by using elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.*

Key words: 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone, *Ortho*-aminothiophenol, 3*H*-Phenothia- zin-3-one, Condensation, Spectral data.

INTRODUCTION

3*H*-Phenothiazin-3-one moieties belong to the family of phenothiazines. These compounds are useful therapeutic agents for treating allergic conditions, asthma, cardiovascular disorders and inhibitors of mammalian leukotrine biosynthesis [1]. These molecules have antiviral [2], antibacterial [3], antimicrobial [4,5], anticonvulsant, analgesic [5], antiinflammatory [5,6], antifungal [7], antitumor [8], anticancer [9] and lipoxygenase inhibitory activities [10]. A number of 3*H*-phenothiazin-3-one derivatives have been reported [11-14] for their wide range of applications. The present research paper deals with the synthesis and characterization of 3*H*-phenothiazin-3-one heterocyclic derivatives. Derivatives of 3*H*-phenothiazin-3-one **6(a-d)** are prepared in four steps starting from hydroquinone **1**. 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone **4** was prepared from hydroquinone **1** by the known literature [15-17].

MATERIALS AND METHODS

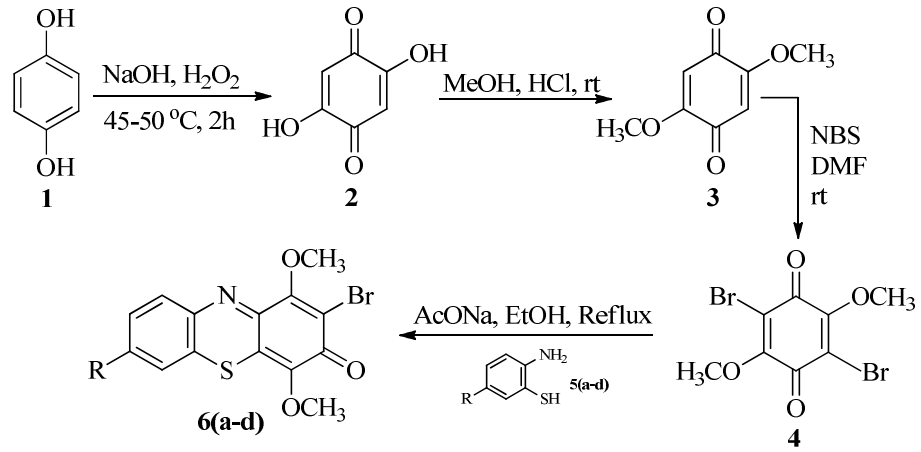
Experimental

All the reagents and solvents used are of laboratory grade. Melting points of all the compounds are determined in open capillary method and are uncorrected. All the new products are monitored by TLC using Merck brand silica gel-G plates for TLC. IR spectra are recorded in KBr pellets on Nexus 470 FTIR spectrometer. ^{1}H NMR spectra are recorded in $CDCl_3$ solvent on Varian Mercury 400 MHz spectrometer using TMS as internal standard. ^{13}C NMR spectra are recorded on Varian Mercury 75 MHz spectrometer and ESI-Mass spectra are obtained on Shimadzu mass spectrometer.

Preparation of 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone (4)

2,5-Dihydroxy-1,4-benzoquinone **2** was prepared [15] from the oxidation of hydroquinone **1** by hydrogen peroxide in alkaline solution. The two hydroxyl groups were then protected by reaction with methanol under acidic conditions

[16] to give 2,5-dimethoxy-1,4-benzoquinone **3**. Bromination of 2,5-dimethoxy-1,4-benzoquinone [17] was carried out with N-bromosuccinimide (NBS) in dimethyl formamide (DMF) solvent at room temperature to obtain 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinones **4.**



Scheme 1

General procedure for the synthesis of 3*H*-phenothiazin-3-one derivatives (6a-d)

To a stirred suspension of substituted *ortho*-aminothiophenol **5(a-d)** (6.135 mmol) and anhydrous sodium acetate (6.135 mmol) in ethanol (30 ml) was added 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone **4** (6.135 mmol) portion wise at room temperature and the mixture stirred for 15 minutes. Then the reaction mixture was refluxed for 4-6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate thrice (3x20 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate to obtain the crude product. The crude product was purified by silica gel column chromatography using variants of ethyl acetate-petroleum ether mixture and concentrated the fractions to afford the compounds **6(a-d)**. Formation of **6(a-d)** was confirmed by their spectral analysis (Scheme 1).

2-Bromo-1,4-dimethoxy-3*H*-phenothiazin-3-one (6a): Yield 1.8 g, 83%, mp 228-230 ^{0}C. IR (KBr) ν_{max} cm^{-1}: 1649 (C=O), 1601 (C=N), 1264, 1036 (C-O-C), 690 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16-7.58 (4H, m, Ar-H), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 155.7, 155.0, 139.4, 130.7, 128.5, 127.0, 126.2, 124.9, 124.8, 111.7, 60.9, 59.1. ESI-MS, m/z 352 $[M+H]^+$. Anal. Calcd for $C_{14}H_{10}BrNO_3S$; C, 47.80; H, 2.78; N, 4.07. Found C, 47.69; H, 2.83; N, 4.12.

2-Bromo-7-chloro-1,4-dimethoxy-3*H*-phenothiazin-3-one (6b): Yield 1.64 g, 69%, mp 241-243 ^{0}C. I.R (KBr) ν_{max} cm^{-1}: 1652 (C=O), 1607 (C=N), 1269, 1046 (C-O-C), 696 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26-7.72 (4H, m, Ar-H), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.5, 155.4, 155.0, 138.5, 131.9, 130.5, 125.5, 123.6, 124.7, 123.3, 117.0, 111.4, 60.7, 60.7. ESI-MS, m/z 388 $[M+H]^+$. Anal. Calcd for $C_{14}H_9BrClNO_3S$; C, 43.54; H, 2.29; N, 3.71. Found C, 43.61; H, 2.34; N, 3.72.

2,7-Dibromo-1,4-dimethoxy-3*H*-phenothiazin-3-one (6c): Yield 1.77 g, 67%, mp 259-261 ^{0}C. IR (KBr) ν_{max} cm^{-1}: 1650 (C=O), 1604 (C=N), 1266, 1044 (C-O-C), 693 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28-7.80 (3H, m, Ar-H), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 155.6, 155.1, 138.2, 130.4, 129.7, 127.7, 125.5, 124.5, 123.1, 115.1, 111.5, 60.6, 59.3. ESI-MS, m/z 432 $[M+H]^+$. Anal. Calcd for $C_{14}H_9Br_2NO_3S$; C, 38.78; H, 2.12; N, 3.98. Found C, 38.59; H, 2.09; N, 4.21.

2-Bromo-1,4,7-trimethoxy-3*H*-phenothiazin-3-one (6d): Yield 2.0 g, 88%, mp 233-235 ^{0}C. IR (KBr) ν_{max} cm^{-1}: 1647 (C=O), 1600 (C=N), 1252, 1038 (C-O-C), 672 (C-S-C). ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.03-7.55 (4H, m, Ar-

H), 3.82 (3H, S, OCH_3), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) 170.4, 155.5, 155.0, 154.0, 136.4, 133.9, 130.6, 126.0, 124.6,123.5, 123.0, 111.6, 60.8, 59.2, 55.9. ESI-MS, m/z 382 $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}BrNO_4S$; C, 48.01; H, 3.52; N, 3.01. Found C, 47.88, H, 3.38, N, 2.99.

RESULTS AND DISCUSSION

In this article, we have synthesized four new heterocyclic compounds **6(a-d)**. All reactions were carried out in ethanol in the presence of fused sodium acetate at reflux temperatures. The synthesis of **6(a-d)** has been achieved by condensation of 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone **4** with substituted *ortho*-aminothiophenols **5(a-d)**. The structures of all the newly synthesized compounds have been supported by elemental analysis, IR, ^1H NMR, ^{13}C NMR and mass spectral studies.

The infrared spectrum of the compound **6a** has C=O stretching frequency recorded at 1649 cm^{-1}, C-O-C stretching frequencies at 1264 cm^{-1}, 1036 cm^{-1} and C-S-C bands appearing at 690 cm^{-1}. They are absent in the IR spectrum of the parent compound and confirm the formation of the compound **6a** structure. The ^1H NMR spectrum of the compound **6a** shows a multiplet at δ 7.16-7.58 accounting for four protons in the aromatic region corresponding to H-6, H-7, H-8 and H-9 on the thiazine ring. Two singlets appearing at δ 3.80 and δ 3.76 shows the presence of six protons of two methoxy groups. The ^{13}C NMR spectrum of the compound **6a** showed the presence of carbonyl (C=O), C-OCH_3, imine (-N=C<), aromatic and methoxy carbons. The peak which appeared at δ 170.6 belong to carbonyl (C=O) carbon, the peaks at δ 155.7 and δ 155.0 belong to C-OCH_3 (C-1& C-4) carbons and the peaks at δ 139.4, 130.7 are due to imine (C-10a) and C-O-C (C-4a) carbons respectively. The aromatic carbon peaks appeared between δ 111.7 and 128.5 and the peaks appeared at δ 60.9 and 59.1 belong to two methoxy carbons. The data confirm the formation of 2-bromo-1,4-dimethoxy-3*H*-phenothiazin-3-one **6a**. The ESI mass spectrum of the compound **6a** shows a peak at m/z 352 $[M+H]^+$ giving evidence for the molecular weight of the compound. The IR, ^1H NMR, ^{13}C NMR and Mass spectral data fit the structure proposed indicating the formation of the compound **6a** in the reaction as expected.

CONCLUSION

All the reactions were carried out in ethanol in the presence of fused sodium acetate at reflux temperature. 3*H*-phenothiazin-3-one **6(a-d)** derivatives are successfully synthesized by the condensation of 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone **4** with substituted *ortho*-aminothiophenols **5(a-d).** All the new derivatives were obtained in good yields. Structures of new compounds are confirmed by analytical and spectral evidence.

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