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Synthesis and Characterization of [1,4]benzothiazino[2,3-b]phenothiazine Derivatives

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ABSTRACT

New heterocyclic derivatives of [1,4]benzothiazino[2,3-b]phenothiazines 4(a-d) are prepared by refluxing 3H-phenothiazin-3-one 3(a-d) intermediates with substituted ortho-aminothiophenols (2a-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.

Keywords: 3*H*-phenothiazin-3-one, *Ortho*-aminothiophenol, Condensation, Spectral data.

INTRODUCTION

[1,4]Benzothiazino[2,3-*b*]phenothiazines (or) triphenodithiazines which are part of the family of phenothiazines are polycyclic aromatic compounds containing phenothiazine moiety and it is a linear pentacyclic system that consists of two thiazine rings with alternating double bonds resulted from quinone coupling. [1,4]Benzothiazino[2,3-*b*] phenothiazines are excellent chromogenic molecules and have been used as dye stuffs for cotton and other materials such as paper, rubber, plastic and lacquers in different shades [1-4]. These compounds possess significant antifungal [5] and antimicrobial [6] activities. A number of [1,4]Benzothiazino[2,3-*b*]phenothiazine derivatives have been reported for their wide range of applications. Heda et al. [6] have synthesized 1,3,4,8,10,11-hexachloro-6,13-dibromo-[1,4] benzothiazino[2,3-*b*]phenothiazine from bromanil by two methods (a) by reacting 4,6,7-trichlorobenzo[*d*]thiazol-2-amine in two steps with bromanil and (b) by the reaction of 2,4,5-trichloroaniline and thiocyanic acid with bromanil in three steps. Mital and Jain [7] have synthesized substituted 6,13-dihalo-[1,4] benzothiazino[2,3-*b*]phenothiazines by condensation of substituted 1,2,4-trihalo-3*H*-phenothiazin-3-ones with substituted *ortho*-aminothiophenols in ethanol and also by condensing zinc salt of substituted 2-aminobenzenethiols with substituted 1,2,4-trihalo-3*H*-phenothiazin-3-ones. Substituted 6,13-dihalo-[1,4] benzothiazino [2,3-*b*] phenothiazines were prepared by Ojha et al. [8,9] by condensation of chloranil or bromanil in presence of anhydrous sodium acetate in ethanol by two methods. The first method which involves the condensation of chloranil or bromanil with substituted *ortho*-aminothiophenol in 1:1 molar ratio afforded substituted 1,2,4-trihalo-3*H*-phenothiazin-3-ones and the resulting 3*H*-phenothiazin-3-ones were further condensed with same or different substituted *ortho*-aminothiophenols to get substituted 6,13-dihalo-[1,4] benzothiazino[2,3-*b*]phenothiazines. The second method is a single step reaction involving condensation of substituted *ortho*-aminothiophenols with chloranil or bromanil in 2:1 molar ratio and it afforded symmetric 6,13-dihalo-[1,4] benzothiazino[2,3-*b*]phenothiazine derivatives. Nishi et al. [10,11] have obtained 3,10-disubstituted 6,13-dihalo-[1,4] benzothiazino[2,3-*b*]phenothiazines by the reaction of two equivalents of zinc salts of substituted 2-aminobenzenethiols with tetrahalo-1,4-benzoquinones in acetic acid and substituted 6,13-bis(arylamino)-[1,4]benzothiazino[2,3-*b*] phenothiazines by the reaction of 2,5-dichloro-3,6-bis(arylamino)-1,4-benzoquinones with two equivalents of the zinc salts of 2-aminobenzenethiols in 2-methoxyethanol in the presence of sodium ethoxide. Sudhakar et al. [12] have synthesized 2-bromo-1,4-dimethoxy-3*H*-phenothiazin-3-one derivatives 3(a-d) by refluxing 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone (1) with substituted *ortho*-aminothiophenols 2(a-d) in 1:1 molar ratio in the presence of anhydrous sodium acetate in ethanol. The present research paper deals with the synthesis and characterization new heterocyclic derivatives of [1,4]benzothiazino[2,3-*b*]phenothiazines 4(a-d). [1,4]Benzothiazino[2,3-*b*]phenothiazine

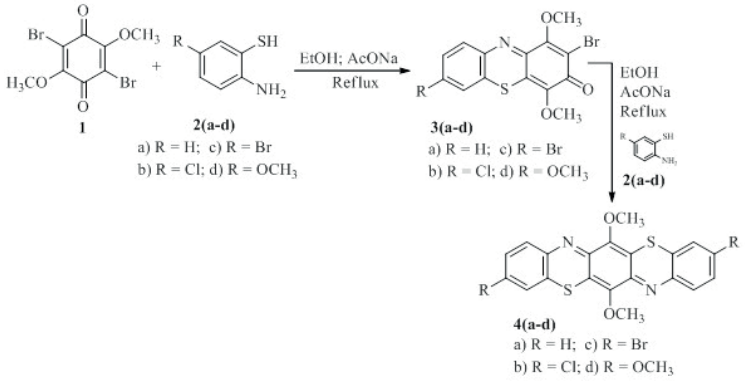
derivatives 4(a-d) are prepared by refluxing 3*H*-phenothiazin-3-one 3(a-d) intermediates with substituted *ortho*-aminothiophenols (2a-d) in ethanolic solution of fused sodium acetate.

MATERIALS AND METHODS

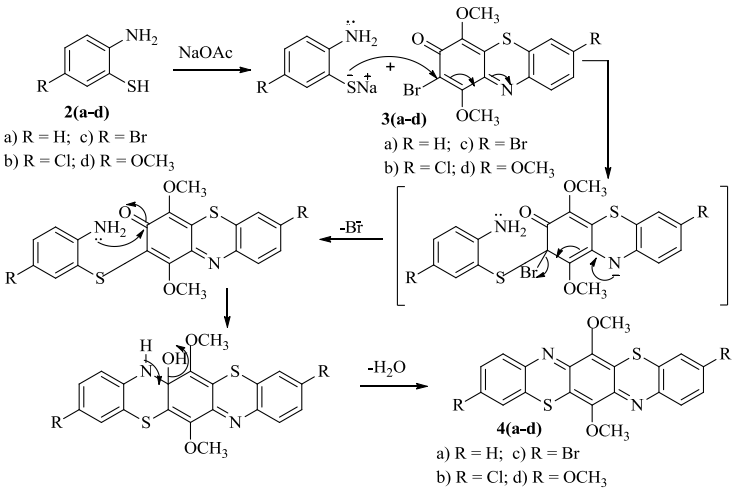
Experimental Procedure

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.

General procedure for the synthesis of [1,4]benzothiazino[2,3-*b*]phenothiazine derivatives (4a-d): Substituted 2-bromo-1,4-dimethoxy-3*H*-phenothiazin-3-ones 3(a-d) 1.42 mmol were added portion wise to the stirred suspension of substituted *ortho*-aminothiophenols 2(a-d) (1.42 mmol) and anhydrous sodium acetate (1.42 mmol) in ethanol (15 ml) at room temperature. The reaction mixture was stirred for 15 minutes followed by reflux for 6-8 hours. The progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mixture was cooled to room temperature, poured into water and extracted with three 15 ml portions of EtOAc [13-15]. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and filtered. The organic layers were concentrated to obtain the crude solid. The crude product was purified by silica gel column chromatography using variants of ethyl acetate-petroleum ether mixture to afford the compounds 4(a-d). Formation of 4(a-d) was confirmed by their spectral analysis (**Schemes 1 and 2**).



Scheme 1: Formation of [1,4]benzothiazino[2,3-b]phenothiazine derivatives.



Scheme 2: Plausible reaction mechanism.

6,13-Dimethoxy-[1,4]benzothiazino[2,3-*b*]phenothiazine (4a): Yield 0.40 g, 74%, dark brown colour solid, mp>300^{0}C. IR (KBr) ν_{max} cm^{-1}:1614 (C=N), 1238, 1027 (C-O-C), 708 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10-7.67 (8H, m, Ar-H), 3.86 (6H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 146.4, 139.6, 130.7, 127.0, 126.3, 124.9, 124.8, 123.7, 119.9, 60.80. ESI-MS, m/z 379 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_2O_2S_2$; C, 63.39; H, 3.66; N, 7.38. Found C, 63.26; H, 2.96; N, 7.42.

3,10-Dichloro-6,13-dimethoxy-[1,4]benzothiazino[2,3-*b*]phenothiazine (4b): Yield 0.42 g, 66%, pale brown colour solid, mp>300°C. IR (KBr) ν_{max} cm^{-1}: 1618 (C=N), 1241, 1028 (C-O-C), 712 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.76 (6H, m, Ar-H), 3.88 (6H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 146.3, 139.5, 131.5, 130.4, 129.5, 124.2, 123.1, 119.7, 119.0, 60.9. ESI-MS, m/z 447 $[M+H]^+$. Anal. Calcd for $C_{20}H_{12}Cl_2N_2O_2S_2$; C, 53.55; H, 2.68; N, 6.82. Found C, 53.92; H, 2.63; N, 6.71.

3,10-Dibromo-6,13-dimethoxy-[1,4]benzothiazino[2,3-*b*]phenothiazine (4c): Yield 0.49 g, 64%, pale brown colour solid, mp>300°C. IR (KBr) ν_{max} cm^{-1}: 1615 (C=N), 1239, 1026 (C-O-C), 710 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.88 (6H, m, Ar-H), 3.87 (6H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) 146.2, 139.3, 129.2, 129.0, 126.2, 125.7, 124.3, 119.8, 117.8, 60.6. ESI-MS, m/z 535 $[M+H]^+$. Anal. Calcd for $C_{20}H_{12}Br_2N_2O_2S_2$; C, 45.02; H, 2.21; N, 5.31. Found C, 44.97; H, 2.32; N, 5.27.

3,6,10,13-Tetramethoxy-[1,4]benzothiazino[2,3-*b*]phenothiazine (4d): Yield 0.47 g, 76%, thick brown colour solid, mp>300°C. IR (KBr) ν_{max} cm^{-1}: 1610 (C=N), 1235, 1024 (C-O-C), 705 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77-7.51 (6H, m, Ar-H), 3.82 (6H, s, OCH_3), 3.80 (6H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), 146.2, 139.4, 132.3, 127.8, 124.8, 123.9, 119.6, 114.5, 113.0, 60.70, 55.8. ESI-MS, m/z 439 $[M+H]^+$. Anal. Calcd for $C_{22}H_{18}N_2O_4S_2$; C, 50.12; H, 4.31; N, 6.19. Found C, 50.28; H, 4.26; N, 6.22. Acidic nature of thiol group paves way for the formation of sodium salt and strong nucleophilic character of 2-aminobenzenethiolate results in attack through sulphur on carbon bearing bromine of 3*H*-phenothiazin-3-one due to polarization of C=N which is in conjugation and elimination of bromide ion results in C-S-C linkage. NH_2 part of 2-aminobenzenethiolate attacks the carbonyl carbon of 3*H*-phenothiazin-3-one as expected and elimination of H_2O result the formation of the 6,13-dimethoxy-[1,4]benzothiazino[2,3-*b*] phenothiazine product.

RESULTS AND DISCUSSION

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

The absorption bands at 1614 cm^{-1} (C=N), 1238 cm^{-1}, 1027 cm^{-1} (C-O-C) and 708 cm^{-1} (C-S-C) observed in the infrared spectrum of the compound 4a corroborate the structure. The main difference of this spectrum from that of its parent compound is the disappearance of thiazin-3-one carbonyl (C=O) frequency band and this confirming the structure proposed. A multiplet at δ 7.10-7.67 in the ^{1}H NMR spectrum of the compound 4a accounting for eight protons (H-2, H-9; H-3, H-10; H-1, H-8; H-4, H-11) in the aromatic region is in conformity with the structure. A singlet appearing at δ 3.86 shows the presence of six protons of two methoxy groups confirm the formation of the compound 4a. ^{13}C NMR spectrum of the compound 4a showed the peaks corresponding to C-OCH_3, imine (-N=C<), C-S-C, aromatic and methoxy carbons. The peaks recorded at δ 146.4, 139.6, 130.7 and δ 60.8 belong to C-OCH_3 (C-6,13), imine (C-6a,13a), C-S-C (C-5a,12a) and methoxy carbons respectively. Rest of the peaks between δ 119.9-127.0 are for belong to aromatic carbons. The ESI mass spectrum of the compound 4a shows evidence for weight with a molecular peak at m/z 379 $[M+H]^+$. The IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data fit the structure proposed indicating the formation of the compound 6,13-Dimethoxy-[1,4]benzothiazino[2,3-*b*]phenothiazine 4a in the reaction as expected.

CONCLUSION

All the reactions were carried out in ethanol in the presence of fused sodium acetate at reflux temperature. 6,13-Dimethoxy-[1,4]benzothiazino[2,3-*b*]phenothiazine derivatives 4(a-d) are successfully synthesized by the condensation of substituted 2-bromo-1,4-dimethoxy-3*H*-phenothiazin-3-ones 3(a-d) with substituted *ortho*-aminothiophenols 2(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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