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SYNTHESIS OF NEW BENZOTHIAZOLYL-PHENOTHIAZINE DERIVATIVES

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ABSTRACT. A series containing 1-, 2-, 3- and 4-(benzothiazol-2yl)-10*H*phenothiazine derivatives was advantageously prepared by the condensation of each corresponding phenothiazine-carbaldehyde regioisomer with 2-amino-benzenethiol. The reaction conditions were optimized and the structures of the new compounds were unambiguously assigned based on high resolution nuclear magnetic resonance spectroscopy and mass spectrometry.

***Key words**: phenothiazine, benzothiazole, NMR*

INTRODUCTION

Benzothiazole derivatives consisting of a cumulative structural motif formed by the 5-membered heteroaromatic ring, the fused benzene unit and diverse substituents attached in various positions (especially mercapto groups) already found important industrial applications in anti-oxidant formulations, components in metal finishing liquors [1], vulcanization accelerators in the rubber industry [2] and fungicides [3]. Various 2-substituted benzothiazoles (2-aryl benzothiazole) received much attention due to potential uses as imagining agents [4] and anticancer agents [5].

Several procedures were developed for the synthesis of benzothiazoles (scheme 1). One method involves the condensation of 2-aminothiophenols with carboxylic acids [6] or aldehydes [7, 8] respectively, under oxidative conditions (reported oxidants: bromine, iodine, quinine, metal salts). Another method involves the transition-metal-catalyzed intramolecular cyclization of thioanilides [9]. Most

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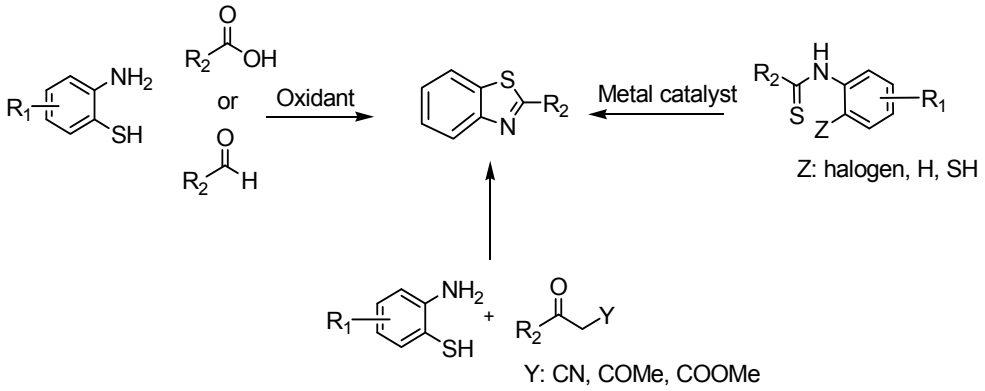
efforts were focused on noble metal catalysts, such as Ru, Rh, Pd, but the iron-catalysed [10] synthesis may benefit from the low toxicity and large availability of iron derivatives. Metal-free methods starting from alkyl amines [11] or aryl ketones [12] at high temperature under oxidative conditions were also reported. The third method involves the condensation of 2-aminothiophenols with β-ketonitriles [13], β-ketoesters [14] or β-diketones [15] under microwave activation at high temperature or in the presence of catalytic ammounts of Bronsted acids.

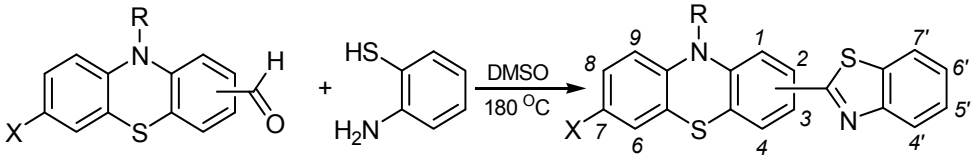


Scheme 1

Continuing our investigations dedicated to the synthesis of new polyheteroaromatic structures containing phenothiazine and thiazole units assembled in the same molecular structure [16], in this work we described an advantageous procedure for the synthesis of new derivatives with joint phenothiazine and thiazole units.

RESULTS AND DISCUSSIONS

The synthetic strategy applied in this work is based on the condensation of aldehydes with o-aminobenzenethiols under thermal activation conditions. A series of benzothiazolyl-phenothiazine derivatives was prepared starting with a phenothiazine-carbaldehyde derivative (10*H*-phenothiazin-1-carbaldehyde, 10-methyl-10*H*-phenothiazin-1-, 2-, 3-, and 4-carbaldehyde regioisomers, 10-methyl-7-bromo-10*H*-phenothiazin-3-carbaldehyde and 10-methyl-10*H*-phenothiazin-3,7-dicarbaldehyde respectively) and *ortho*-aminobenzenethiol which were severely heated in DMSO solvent (Scheme 2). No other oxidant was required when working-up in the presence of atmospheric oxygen.



R = -H, -CH_3
X = -H, -CHO, -Br

1 *1*-thiazolyl, R=H, x= H
2 *1*-thiazolyl, R=CH_3, x= H
3 *2*-thiazolyl, R=CH_3, x= H
4 *3*-thiazolyl, R=CH_3, x= H
5 *4*-thiazolyl, R=CH_3, x= H
6 *3*-thiazolyl, R=CH_3, x= Br
7 *3*-thiazolyl, R=CH_3, x=thiazolyl

Scheme 2

This convenient procedure gave satisfactory yields even in the case of sterically hindered substrates such as 10-methyl-10*H*-phenothiazin-1-carbaldehyde or 10*H*-phenothiazin-1-carbaldehyde Best yields were obtained in the preparation of 2-benzotiazolyl-phenothiazine. The products are stable crystalline compounds with a yellow colour.

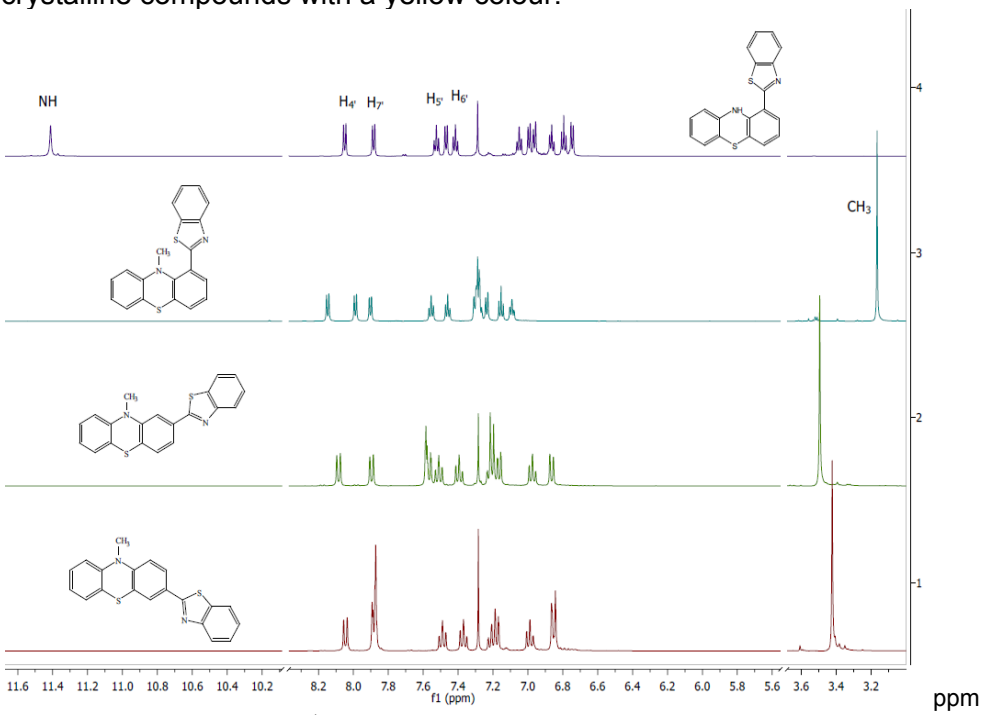


Figure 1. 600 MHz ^{1}H-NMR spectra of benzothiazol-2yl-phenothiazine regioisomers in $CDCl_3$

The structures of the new compounds were unambiguously assigned based on HRMS and NMR spectroscopic data. 2D-NMR 1H-1H homocorrelation and ^{1}H-^{13}C-heterocorrelation experiments were performed in order to completely assign the signals of the nuclei present in the two heterocyclic units. As it may be seen from figure 1 which collectively presents the ^{1}H-NMR spectra of the series of regioisomers **1-5**, the benzothiazolyl moiety is responsible for generating the most deshielded signals, accompanied by the protons of the phenothiazine unit situated in the closest neighboring position. An inspection of the chemical shifts recorded in the case of sterically hindered structures **1** and **2** suggest a preferred bisectional orientation of the benzothiazolyl substituent in respect to the aromatic ring of the phenothiazine unit. The ring current of the benzothiazolyl unit induces a magnetic anisotropy observable in the chemical shifts of the substituents situated in the *peri* position (a deshielding of the NH signals in **1** and a shielding of $-CH_3$ signals in **2** respectively).

CONCLUSIONS

A convenient procedure for the preparation of new heteroaromatic compounds with joint phenothiazine and thiazole units was developed based on thermal activated condensation of *ortho*-aminobenzenethiol with phenothiazine carbaldehydes.

EXPERIMENTAL SECTION

HRMS spectra were recorded using Thermo LTQ *Orbitrap XL* mass spectrometer.

NMR spectra were recorded at room temperature on 400 or 600 MHz Bruker Avance instruments. Chemical shifts are expressed in δ (ppm) relative to standard tetramethylsilane (TMS).

O-amino-benzenethiol was purchased from Sigma_Aldrich.

Phenothiazine carbaldehydes were prepared according to previously reported procedures.

General procedure for the synthesis of benzothiazol-2yl-phenothiazine derivatives

Ortho-Aminobenzenethiol (4mmol, 0.5g) and the corresponding phenothiazinyl aldehyde (4mmol) dissolved in 50 ml DMSO were heated at 180 ^{o}C on oil bath for 6 h. After cooling down to room temperature, the mixture was poured in water and extracted with ethyl acetate. The

organic phase was dried over Mg_2SO_4 and the solvent was removed under vacuum. The residue was purified by recrystallisation from ethanol or by column chromatography (eluent toluene).

1-(benzo[d]thiazol-2-yl)-10H-phenothiazine (1)
Purification by flash chromatography, gave 0.9 g, 68 % as orange solid.

HRMS (ESI+): $[M+H^+]$ found 333.0454, $C_{13}H_{13}N_2S$ requires 333.0515.

^{1}H-NMR (600MHz, $CDCl_3$): δ (ppm) = 6.72 (d, 1H, H_9, ^3J =7.62Hz), 6.76 (t, 1H, H_7, ^3J = 7.8 Hz), 6.83 (t, 1H, H_8, ^3J = 7.2 Hz), 6.93 (d, 1H, H_4, ^3J = 7.62Hz), 6.96 (d, 1H, H_6, ^3J =7.44 Hz), 7.02 (td, 1H, H_3, ^3J = 7.8 Hz, ^4J = 0.9 Hz), 7.39 (t, 1H, $H_{6'}$, ^3J = 7.44 Hz), 7.44 (dd, 1H, H_2, ^3J =7.86Hz, ^4J = 0.66Hz), 7.49 (t, 1H, $H_{5'}$, ^3J = 7.32 Hz), 7.85 (d, 1H, $H_{7'}$, ^3J =8.1 Hz), 8.01 (d, 1H, $H_{4'}$, ^3J =8.1 Hz), 11.38 (s, 1H, NH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 115.5 (C_q, C_1), 115.8 (C_H, C_7), 117.7 (C_q, C_{4a}), 120 (C_q, C_{5a}), 121.1 (C_H, $C_{4'}$), 121.3 (C_H, C_7), 122.6 (C_H, $C_{7'}$), 123 (C_H, C_8), 125.5 (C_H, C_6), 126.4 (C_H, $C_{6'}$), 127.5 (C_H, C_2), 128.2 (C_H, C_6), 128.5 (C_q, C_3), 133.2 (C_q, $C_{7a'}$), 140.8 (C_q, C_{9a}), 141.7 (C_q, C_{10a}), 153 (C_q, $C_{4a'}$), 168.3 (C_q, $C_{2'}$);

1-(benzo[d]thiazol-2-yl)-10-methyl-10H-phenothiazine (2)
Purification by recrystallisation, gave (0.8g, 58 %) as orange solid.

HRMS (ESI+): $[M+H^+]$ found 347.0611, $C_{13}H_{13}N_2S$ requires 347.0671.

^{1}H-NMR (600MHz, $CDCl_3$): δ (ppm) = 3.16 (s, 3H, N-CH_3), 7.09 (td, 1H, H_4,^3J = 8 Hz, ^4J = 1.74 Hz), 7.15 (t, 1H, H_3, ^3J = 7.7 Hz), 7.23 (d, 1H, H_9, ^3J =7.56Hz), 7.26-7.31 (m, 3H, H_8, H_7, H_6), 7.45 (t, 1H, $H_{6'}$, ^3J = 7.5 Hz), 7.55 (t, 1H, $H_{5'}$, ^3J = 7.5 Hz), 7.90 (dd, 1H, H_2, ^3J = 7.68 Hz, ^4J = 1 Hz), 7.99 (d, 1H, $H_{7'}$, ^3J = 8 Hz), 8.15 (d, 1H, $H_{4'}$, ^3J = 8.1 Hz);

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 43.3 (CH_3, **C_a**), 121 (C_H, **C_7**), 121.6 (C_H, **$C_{7'}$**), 123.3 (C_H, **$C_{4'}$**), 124.3 (C_H, **C_3**), 124.6 (C_H, **C_4**), 125.4 (C_H, **$C_{6'}$**), 126.2 (C_H, **$C_{5'}$**), 126.9 (C_H, **C_9**), 127 (C_q, **C_{4a}**), 127.7 (C_H, **C_8**), 128.7 (C_H, **C_6**), 128.8 (C_q, **C_{5a}**), 129.8 (C_H, **C_2**), 132.8 (C_q, **C_1**); 136.4 (C_q, **$C_{7a'}$**), 144 (C_q, **C_{9a}**), 147 (C_q, **C_{10a}**), 152.8 (C_q, **$C_{4a'}$**), 165.5 (C_q, **$C_{2'}$**);

2-(benzo[d]thiazol-2-yl)-10-methyl-10*H*-phenothiazine (3)
Purification by recrystallisation, gave 1.1 g, 81 % as yellow solid.

HRMS (ESI+): $[M+H^+]$ found 347.0616, $C_{13}H_{13}N_2S$ requires 347.0671.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 3.47 (s, 3H, N-CH_3), 6.84 (d, 1H, H_9, ^3J = 7.8 Hz), 6.95 (td, 1H, H_3, ^3J = 7.48 Hz, ^4J = 0.8 Hz), 7.14 (dd, 1H, H_6, ^3J = 7.6 Hz, ^4J = 1.3 Hz), 7.17-7.21 (m, 2H, H_4, H_8), 7.37 (td, 1H, $H_{6'}$, ^3J = 8 Hz, ^4J = 0.9 Hz), 7.48 (td, 1H, $H_{5'}$, ^3J = 8.2 Hz, ^4J = 1 Hz), 7.53-7.56 (m, 2H, H_1, H_7), 7.87 (d, 1H, $H_{7'}$, ^3J = 8 Hz), 8.06 (d, 1H, $H_{4'}$, ^3J = 8.2 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 35.6 (CH_3, C_a), 112.2 (C_H, C_1), 114.4 (C_H, C_9), 121.6 (C_H, $C_{7'}$), 122 (C_H, C_7), 122.6 (C_H, C_{4a}), 122.8 (C_H, C_3), 123.1 (C_H, $C_{4'}$), 125.3 (C_H, $C_{5'}$), 126.4 (C_H, $C_{6'}$), 127.2 (C_H, C_1), 127.3 (C_H, C_6), 127.5 (C_q, C_{5a}), 127.8 (C_H, C_8), 132.9 (C_q, C_2), 135 (C_q, $C_{7a'}$), 145.3 (C_q, C_{9a}), 146.4 (C_q, C_{10a}), 154.1 (C_q, $C_{4a'}$), 167.8 (C_q, $C_{2'}$);

3-(benzo[d]thiazol-2-yl)-10-methyl-10H-phenothiazine (4)

Purification by recrystallisation, gave 0.9 g, 65 % as yellow solid (m.p. = 160-161^{o}C).

HRMS (ESI+): [M+H$^+$] found 347.0610, $C_{13}H_{13}N_2S$ requires 347.0671.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 3.39 (s, 3H, N-CH_3), 6.82 (d, 2H, H_9, H_1,^3J = 8.2 Hz), 6.95 (td, 1H, H_7, ^3J = 7.4 Hz, ^4J = 0.8 Hz), 7.14-7.20 (m, 2H, H_8, H_6), 7.34 (td, 1H, $H_{6'}$, ^3J = 8 Hz, ^4J = 0.84 Hz), 7.46 td, 1H, $H_{5'}$, ^3J = 8.2 Hz, ^4J = 1 Hz), 7.84-7.86 (m, 3H, $H_{7'}$, H_2, H_4), 8.02 (d, 1H, $H_{4'}$, ^3J = 8 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 35.6 (CH_3, C_a), 114.1 (C_H, C_1), 114.5 (C_H, C_9), 121.6 (C_H, $C_{7'}$), 122,7 (C_q, C_{4a}), 122.9 (C_H, C_7), 123.1 (C_H, $C_{4'}$), 124.2 (C_q, C_{5a}), 124.9 (C_H, C_2), 125.96 (C_H, $C_{5'}$), 126.4 (C_H, $C_{6'}$), 127.1 (C_H, C_1), 127.36 (C_H, C_6); 127.7 (C_H, C_8), 128 (C_q, C_3), 134.9 (C_q, $C_{7a'}$), 144.8 (C_q, C_{9a}), 148.2 (C_q, C_{10a}), 154.2 (C_q, $C_{4a'}$), 167.1 (C_q, $C_{2'}$);

4-(benzo[d]thiazol-2-yl)-10-methyl-10*H*-phenothiazine (5)

Purification by recrystallisation, gave 0.8 g, 60 % as yellow solid.

HRMS (ESI+): [M+H$^+$] found 347.0615, $C_{13}H_{13}N_2S$ requires 347.0671.

^{1}H-NMR (400MHz, $CDCl_3$, ppm): δ (ppm) = 3.15 (s, 3H, N-CH_3), 6.57 (d, 1H, H_9, ^3J = 8 Hz), 6.63 (t, 1H, H_7, ^3J = 7.5 Hz), 6.68 (d, 1H, H_1, ^3J = 8.04 Hz), 6.8 (d, 1H, H_6, ^3J = 7.3 Hz), 6.92 (m, 1H, H_8), 7.01 (t, 1H, H_2, ^3J = 8 Hz), 7.18 (m, 2H, $H_{6'}$, H_3), 7.29 (m, 1H, $H_{5'}$), 7.7 (d, 1H, $H_{7'}$, ^3J = 7.92 Hz), 7.89 (d, 1H, $H_{4'}$, ^3J = 8.08 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 35.3 (CH_3, C_a), 113.5 (C_H, C_9), 115.5 (C_H, C_1), 121 (C_H, $C_{7'}$), 122 (C_H, C_7), 122.9 (C_H, $C_{4'}$), 123.2 (C_q, C_{4a}), 123.7 (C_H, $C_{6'}$), 124.9 (C_q, C_{5a}), 125.7 (C_H, C_3), 126.5 (C_H, $C_{5'}$), 127.2 (C_H, C_6), 127.6 (C_H, C_2); 128.4 (C_H, C_8), 131 (C_q, $C_{7a'}$), 135 (C_q, C_4), 145.9 (C_q, C_{9a}), 145.95 (C_q, C_{10a}), 152.8 (C_q, $C_{3a'}$), 164.8 (C_q, $C_{2'}$);

3-(benzo[d]thiazol-2-yl)-7-bromo-10-methyl-10H-phenothiazine (6)

Purification by recrystallisation, gave 1.1 g, 68 % as greenish-yellow solid.

HRMS (APCI$^+$): [M+H$^+$] found 426.9755, $C_{20}H_{14}N_2S_2Br$ requires 424.9776.

^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) = 3.38 (s, 3H, N-CH_3), 6.71 (d, 1H, H_9, ^3J = 9.24 Hz), 6.89 (d, 1H, H_1, ^3J = 8.5 Hz), 7.23-7.26 (m, 2H, H_6, H_8), 7.36 (t, 1H, $H_{6'}$, ^3J = 6.24 Hz), 7.47 (t, 1H, $H_{5'}$, ^3J = 7.3 Hz), 7.81-7.85 (m, 2H, H_2, H_4), 7.87 (d, 1H, $H_{7'}$,^3J = 8.2 Hz), 8.02 (d, 1H, $H_{4'}$,^3J = 8.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 35.7 (CH_3), 114.3 (C_H, C_1), 115.4 (C_q, C_7), 115.6 (C_H, C_9), 121.6 (C_H, $C_{7'}$), 123 (C_H, $C_{4'}$), 125 (C_q, C_{4a}), 125.1 (C_H, $C_{6'}$), 126 (C_H, C_4), 126.4 (C_H, $C_{5'}$), 127.3 (C_H, C_2), 128.4 (C_q, C_{5a}), 129.5 (C_H, C_6); 130.4 (C_H, C_8), 134.9 (C_q, C_3), 144.1 (C_q, $C_{7a'}$), 147.7 (C_q, C_{9a}), 154.2 (C_q, $C_{3a'}$), 166.9 (C_q, $C_{2'}$);

3,7-bis(benzo[d]thiazol-2-yl)-10-methyl-10*H*phenothiazine (7)
Purification by recrystallisation, gave 0.6 g, 63 % as yellow solid.

HRMS (APCI$^+$): [M+H$^+$] found 480.0653, $C_{27}H_{18}N_3S3$ requires 480.0653.

^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 3.42 (s, 3H, N-CH_3), 6.93 (d, 2H, H_1, H_9, ^3J = 8.32 Hz), 7.36 (t, 2H, $H_{6'}$, ^3J = 7.6 Hz), 7.48 (t, 2H, $H_{5'}$, ^3J = 7.6 Hz), 7.81-7.86 (m, 4H, H_2, H_4), 7.88 (d, 2H, $H_{7'}$, ^3J = 8.2 Hz), 8.03 (d, 2H, $H_{4'}$, ^3J = 8.2 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 35.5 (CH_3, C_a), 114.9 (C_H, C_9), 121.5 (C_H, C_a), 122.8 (C_H, $C_{7'}$), 123.9 (C_H, C_7), 124.9 (C_q, C_{4a}), 126 (C_H, $C_{4'}$), 126.3 (C_H, $C_{5'}$), 126.9 (C_H, $C_{6'}$), 128.3 (C_q, C_3), 134.7 (C_q, $C_{7a'}$), 145.9 (C_q, C_{9a}), 154 (C_q, $C_{3a'}$), 166.7 (C_q, $C_{2'}$).

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