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STUDIES WITH 2-BENZOTHAZOLYLACETONITRILE: SYNTHESIS OF NEW 2-THIENYLBENZOTHAZOLES AND N-THIENYL MALEIMIDE DERIVATIVES

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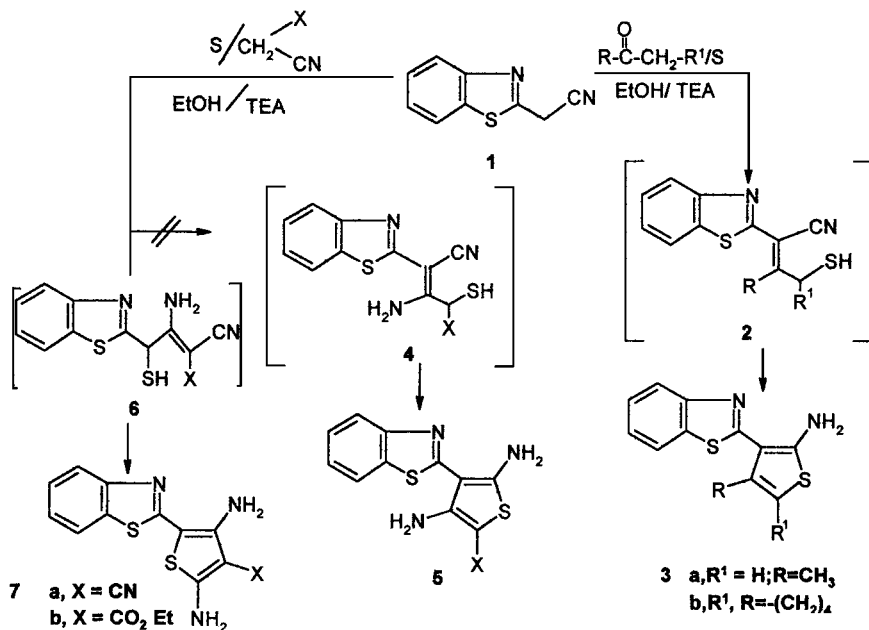
*The synthesis of new 2-thienylbenzothiazoles and N-thienyl maleimide derivatives utilizing 2-benzothiazolyl acetonitrile **1** as starting component.*

Keywords: 2-benzothiazolylacetonitrile; maleic anhydride; thiophene

Azolyl acetonitriles are readily obtainable compounds that have been extensively utilized as intermediates in heterocyclic synthesis^{1–3} which are of potential biological activity.^{4,5} Thiazole and its derivatives are long known for their antibacterial⁶ activity and their use as hypoglycemic,⁷ fungicidal⁸ and herbicidal⁹ agents. In conjunction with our previous work^{10,11} we report here the results of our further work exploring the synthetic potential of 2-benzothiazolylacetonitrile **1**. Thus, it has been found that **1** reacts with acetone in the presence of sulfur and triethylamine in boiling ethanol solution to yield a product that is assigned the structure **3a** based on analytical and spectral data. The IR spectrum of this product revealed the absence of the CN signal and the appearance of the NH₂ signal as required by structure **3**. The formation of **3** is assumed to proceed via the nonisolated intermediate mercapto derivative **2** that cyclizes and then aromatized readily under the reaction condition to give **3**. Similarly, compound **1** reacts with cyclohexanone to yield the thienyl benzothiazole derivative **3b**. Furthermore, a mixture of malononitrile and sulfur reacted with compound **1** to yield either **5a** or **7a**. The formation of **7a** is assumed to proceed via addition of CH₂ group of the malononitrile to the CN

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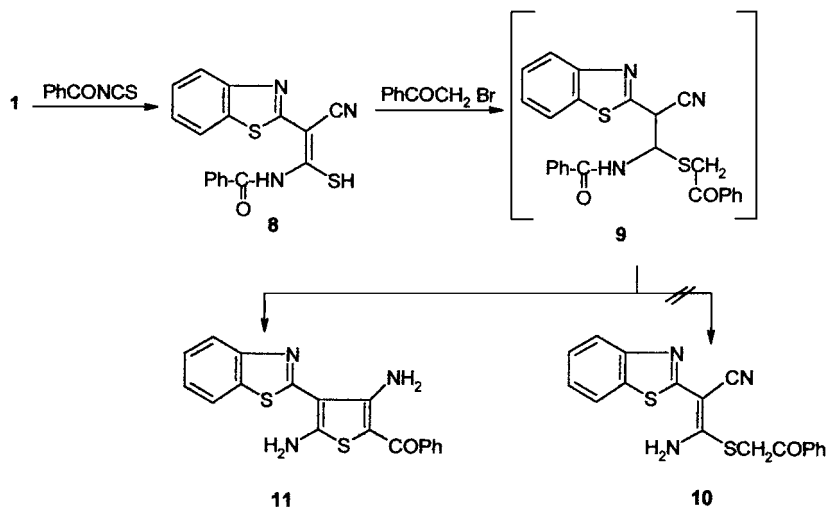
function in **1** followed by reaction with sulfur to yield **6a** which was cyclized into **7a**. Alternatively CH_2 of **1** may added to the CN function of malononitrile and then reacted with sulfur to give the intermediate **4**, which was cyclized to **5**. Structure **7a** is preferred over possible **5a** based on the IR spectrum which showed a CN signal at 2250 cm^{-1} . Alternative **5a** is expected to show a CN signal at a lower frequency.¹² Similar to malononitrile, ethyl cyanoacetate yields **7b** (cf. Scheme 1).



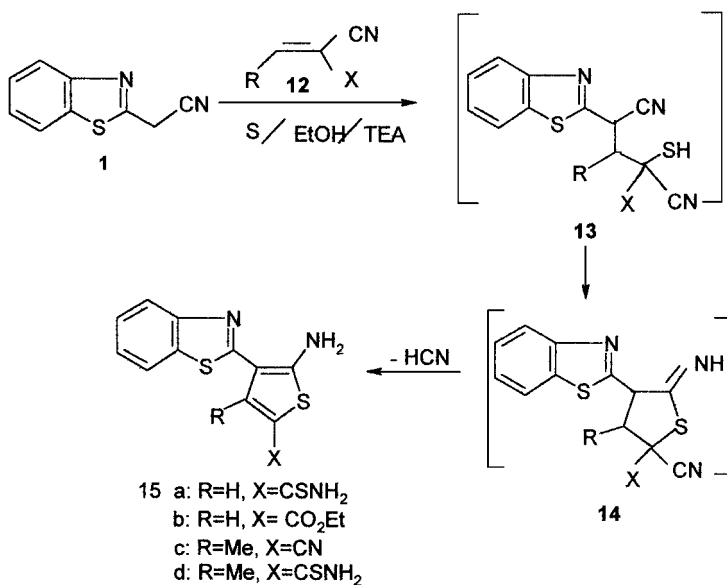
SCHEME 1

In other trials to prepare thienylbenzothiazole derivative with di-amino substituent as a good dyestuff, compound **1** reacted with benzoylisothiocyanate to yield a 1:1 adduct which may be formulated as **8**. Structure **8** was established for the reaction product based on ^1H NMR which revealed the absence of the CH_2 function and the presence of NH as well as SH function. Compound **8** reacted with phenacyl bromide to yield a product which was formulated as **10** rather than isomeric **11**.¹³ Compound **11** was established based on the IR spectrum, which showed signals for two NH_2 groups and disappearance of cyano group. Compound **11** is believed to be formed via the nonisolated intermediate **9**, which undergoes cyclization under the reaction condition to give the final isolated product. (cf. Scheme 2).

Furthermore, compound **1** reacts with methyldine derivative **12** and sulfur in the presence of ethanolic triethylamine to give



SCHEME 2

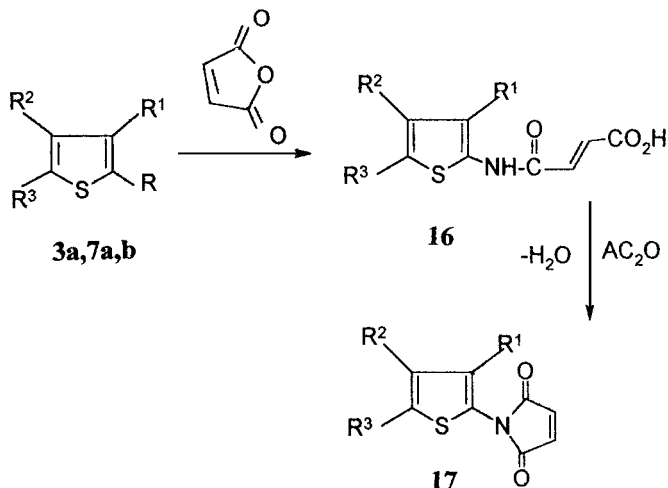


SCHEME 3

thienyl derivatives **15a-d** through the nonisolated intermediate **13** and **14**.

Compounds **3a**, **7a**, and **7b** reacted with maleic anhydride to give the thienylamidomaleic acid derivatives **16a-c**, which readily cyclized

to give N-thienylmaleimide derivatives **17a-c** via elimination of H₂O when heated in acetic anhydride (cf. Scheme 4).



- 17 a:** R=NH₂, R¹=2-benzothiazolyl, R²=Me, R³=H
b: R=NH₂, R¹=CN, R²=NH₂, R³=2-benzothiazolyl
c: R=NH₂, R¹=CO₂Et, R²=NH₂, R³=2-benzothiazolyl

SCHEME 4

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were obtained on a Shimadzu 408 spectrophotometer. The ¹H NMR were measured in DMSO[d₆] on a Varian EM-390 MHz spectrometer using TMS as internal reference and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Analytical Data Unit at Cairo University, Egypt.

General Procedure for the Synthesis of 2-Thienylbenzothiazole Derivatives (3a,b and 7a,b)

A solution of **1** (0.01 mol) in ethanol (30 ml) was treated with the appropriate amount of active methylene reagents (0.01 mol) and sulfur (0.01 mol) with catalytic amount of triethylamine (2 ml). The reaction mixture was heated under reflux for 5 h. The solvent was removed under reduced pressure and the residue was triturated with water and neutralized with conc. HCl. The solid product so formed was collected by filtration and recrystallized from DMF.

2-[3-(2-amino-4-methyl)thienyl]benzothiazole (3a)

Compound **3a** was obtained as yellow crystals (65%) from DMF; m.p. 127°C; IR: 3400–3100 (br. NH₂), 2990 (CH₃), 1600 (C=N) cm⁻¹. ¹H NMR: δ 2.2 (s, 3H, CH₃), 6.9–8.2 (m, 7H, aromatic and NH₂) ppm. Anal. requires for C₁₂H₁₀N₂S₂ (246.34): C, 58.5; H, 4.08, N, 11.37; S, 26.01. Found: C, 58.8; H, 4.1; N, 11.5; S, 26.2.

2-[3-(2-aminocyclohexa[*b*]thienyl]benzothiazole (3b)

Compound **3b** was obtained as yellow crystals (68%) from DMF; m.p. 142°C; IR: 3400–3150 (br. NH₂), 1620 (C=N) cm⁻¹. ¹H NMR: δ 2.6 (t, 4H, 2CH₂); 3.6 (m, 4H, 2CH₂); 6.9–8.3 (m, 6H, aromatic and NH₂). Anal. requires for C₁₅H₁₄N₂S₂ (286.40): C 62.90; H, 4.92, N, 9.78; S, 22.39. Found: C, 63.0; H, 4.4; N, 9.91; S, 22.7.

2-[2-(3,5-diamino-4-cyanothienyl]benzothiazole (7a)

Compound **7a** was obtained as yellow crystals (60%) from DMF; m.p. 146°C; IR: 3400–3150 (br. NH₂), 2250 (CN), 1620 (C=N) cm⁻¹. ¹H NMR: δ 7.2–7.9 (m, 8H, aromatic and NH₂ protons). Anal. requires for C₁₂H₈N₄S₂ (272.34): 52.92; H, 2.95; N, 20.57; S, 23.54. Found: C 53.2; H, 3.3; N, 20.8; S, 23.8.

2-[2-(3,5-diamino-4-ethoxycarbonyl]benzothiazole (7b)

Compound **7b** was obtained as yellow crystals (70%) from DMF; m.p. 162°C; IR: 3450–3150 (br. NH₂), 1700–1680 (CO) cm⁻¹. ¹H NMR: δ 1.3 (t, 3H, CH₃); 4.2 (q, 2H, CH₂); 7.1–7.5 (m, 8H, aromatic and NH₂ protons). Anal. requires for C₁₄H₁₃N₃O₂S₂ (319.3) C, 52.66; H, 4.07; N, 13.16; S, 20.06. Found: C 52.9; H, 4.1; N, 13.5; S, 20.3.

Reaction of Compound 1 with Benzoylisothiocyanate

A solution of benzoylisothiocyanate (0.01 mol) in acetone (30 ml) was treated with compound **1** (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was triturated with water. The solid product formed was collected by filtration and recrystallized from ethanol.

2-benzamido-1-benzothiazolyl-1-cyano-2-mercaptoethene (8)

Compound **8** was obtained as brown crystals (65%) from ethanol; m.p. 175°C; IR: 3150 (NH); 2200 (CN), 1680 (C=O); 1600 (C=N) cm⁻¹. ¹H NMR: δ 7.3–8.3 (m, 10H, aromatic and NH protons); 10.6 (s, 1H, SH). Anal. requires for C₁₇H₁₁N₃OS₂ (337.39) C, 60.51; H, 3.28; N, 12.45; S, 19.0. Found: C, 60.8; H, 3.5; N, 12.7; S, 19.4.

Synthesis of Diaminothiophene Derivative (11)

A solution of compound **8** (0.01 mol) in dioxane (40 ml) was treated with phenacyl bromide (0.01 mol) and triethylamine (2 ml). The reaction mixture was heated under reflux for 4 h. The solvent was then evaporated under reduced pressure and the residue was triturated with water. The solid product formed was collected by filtration and recrystallized from DMF.

2-[3-(2,4-Diamino-5-benzoyl)thienyl]benzothiazole (11)

Compound **11** was obtained as yellow crystals (58%) from DMF; m.p. 210°C; IR: 3300 (br. 2NH₂); 1680 (CO), 1600 (C=N) cm⁻¹. ¹H NMR: δ 7.3–7.9 (m, 9H, aromatic protons); 8.2 (br, 4H, 2NH₂). Anal. requires for C₁₈H₁₃N₃OS₂ (351.4): C, 61.52; H, 3.72; N, 11.95; S, 18.2 Found: C, 61.8; H, 3.5; N, 11.6; S, 17.9.

General Procedure for the Synthesis of Thienyl Derivatives (15a–d)

A solution of the appropriate methyldine derivatives **12a–d** (0.01 mol) [prepared in situ from the reaction of the corresponding aldehyde and active methylene in ethanol in the presence of a catalytic amount of triethylamine] and sulfur element (0.01 mol) were added to compound **1** (0.01 mol). The reaction mixture was heated under reflux for 4 h. The solid product so formed was collected by filtration and recrystallized from DMF.

2-[3-(2-amino-5-thiamido)thienyl]benzothiazole (15a)

Compound **15a** was obtained as brown crystals (67%) from DMF; m.p. 276°C; IR: 3400–3100 (NH₂) cm⁻¹. ¹H NMR: δ 5.4 (br, 2H, NH₂); 7.1–8.3 ppm (m, 7H, aromatic, thiophene-H and NH₂ protons). Anal. requires for C₁₂H₉N₃S₃ (291.38): C 49.46; H, 3.10; N, 14.41; S, 33.02. Found: C, 49.6; H, 3.2; N, 14.8; S, 33.4.

2-[3-(2-amino-5-ethoxycarbonyl)thienyl]benzothiazole (15b)

Compound **15b** was obtained as brown crystals (71%) from DMF; m.p. 291°C; IR: 3350 (NH₂), 1700 (ester CO) cm⁻¹. ¹H NMR: δ 1.3 (t, 3H, CH₃); 4.2 (q, 2H, CH₂); 7.1–8.2 (m, 7H, aromatic, thiophene-H and NH₂ protons). Anal. requires for C₁₄H₁₂N₂O₂S₂ (304.34): C, 55.25; H, 3.96; N, 9.20; S, 21.06. Found: C, 55.6; H, 3.6; N, 9.5; S, 21.3.

2-[3-(2-amino-5-cyano-4-methyl)thienyl]benzothiazole (15c)

Compound **15c** was obtained as yellow crystals (68%) from DMF; m.p. 298°C; IR: 3200–3100 (NH₂), 2210 (CN) cm⁻¹. ¹H NMR: δ 1.7 (s, 3H, CH₃); 7.1–8.2 (m, 6H, aromatic and NH₂ protons). Anal. requires for C₁₃H₉N₃S₂ (271.33): C 57.54; H, 3.33; N, 15.48; S, 23.63. Found: C, 57.6; H, 3.6; N, 15.8; S, 23.7.

2-[3-(2-amino-4-methyl-5-thiamido)thienyl]benzothiazole (15d)

Compound **15d** was obtained as yellow crystals (65%) from DMF; m.p. 283°C; IR: 3400–3100 (NH₂) cm⁻¹. ¹H NMR: δ 1.7 (s, 3H, CH₃), 4.2 (br, 2H, NH₂), 7.1–8.2 (m, 6H, aromatic and NH₂). Anal. requires for C₁₃H₁₁N₃S₃ (305.4): C, 51.12; H, 3.62; N, 13.75; S, 31.49. Found: C, 51.4; H, 3.8; N, 13.9; S, 31.6.

Reaction of 3a, 7a, and 7b with Maleic Anhydride

A solution of compounds **3a**, **7a**, and **7b** (0.01 mol) in DMF (40 ml) was treated with maleic anhydride (0.01 mol) and the reaction mixture was heated under reflux for 5 h. The solvent was then evaporated in vacuo and the residue was treated with ice and water; the solid product formed on standing was collected by filtration and recrystallized from DMF.

Compound **16a** was obtained as yellow crystals (61%) from DMF; m.p. 243°C; IR: 3380–3350 (NH, OH), 1730, 1670 (2CO) cm⁻¹. ¹H NMR: δ 5.4, 5.6 (2d, 2H, 2CH), 1.7 (s, 3H, CH₃), 7.1–8.2 (m, 4H, aromatic protons) 10.12 (s, 1H, OH), 13.2 (br, 1H, NH). Anal. requires for C₁₆H₁₂N₂O₃S₂ (344.35): C, 55.80; H, 3.50; N, 8.13; S, 18.62. Found: C, 55.6; H, 3.6; N, 8.4; S, 18.7.

Compound **16b** was obtained as yellow crystals (68%) from DMF; m.p. 233°C; IR: 3400–3350 (OH, NH), 2210 (CN), 1740, 1665 (CO) cm⁻¹. ¹H NMR: δ 5.4, 5.6 (2d, 2H, 2CH), 7.1–8.1 (m, 6H, aromatic protons and NH₂); 10.10 (s, 1H, OH); 13.10 (br, 1H, NH). Anal. requires for C₁₆H₁₀N₄O₃S₂ (370.35): C, 51.88; H, 2.71; N, 15.12; S, 17.31. Found: C, 51.4; H, 2.6; N, 15.6; S, 17.7.

Compound **16c** was obtained as yellow crystals (68%) from DMF; m.p. 213°C; IR: 3400–3100 (OH, NH), 1740–1670 (CO), 1735 (CO) cm⁻¹. ¹H NMR: δ 1.3 (t, 3H, CH₃); 4.2 (q, 2H, CH₂); 8.2 (br, 4H, 2NH₂), 7.1–7.6 (m, 4H, aromatic protons), 10.0 (s, 1H, OH); 13.10 (br, 1H, NH). Anal. requires for C₁₈H₁₅N₃O₅S₂ (417.37): C, 51.79; H, 3.61; N, 10.06; S, 15.36. Found: C, 51.6; H, 3.4; N, 10.4; S, 15.4.

Synthesis of N-thienylmaleimide Derivatives (17a–c)

A solution of **16a–c** (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 2 h. The reaction mixture was treated with ice and water; the solid product formed on standing was collected by filtration and recrystallized from absolute ethanol.

Compound **17a** was obtained as yellow crystals (50%) from EtOH; m.p. 280°C; IR: 1680 (CO) cm^{-1} . ^1H NMR: δ 1.7 (s, 3H, CH_3), 6.4, 6.8 (2d, 2H, 2CH), 7.1–8.2 (m, 4H, aromatic protons). Anal. requires for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2\text{S}_2$ (326.35): C, 58.88; H, 3.08; N, 8.58; S, 19.64. Found: C, 58.6; H, 3.2; N, 8.4; S, 19.7.

Compound **17b** was obtained as yellow crystals (48%) from EtOH; m.p. 250°C; IR: 3400–3100 (NH_2), 2210 (CN), 1680 (CO) cm^{-1} . ^1H NMR: δ 6.4, 6.8 (2d, 2H, 2CH), 7.1–8.1 (m, 6H, aromatic-protons, and NH_2). Anal. requires for $\text{C}_{16}\text{H}_8\text{N}_4\text{O}_2\text{S}_2$ (352.35): C, 54.53; H, 2.28; N, 15.89; S, 18.19. Found: C, 54.4; H, 2.6; N, 15.6; S, 18.4.

Compound **17c** was obtained as yellow crystals (45%) from EtOH; m.p. 220°C; IR: 3400–3100 (NH_2), 1675 (CO), 1735 (CO) cm^{-1} . ^1H NMR: δ 1.3 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 7.1–8.1 (m, 6H, aromatic protons, and NH_2). Anal. requires for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_4\text{S}_2$ (399.37): C, 54.13; H, 3.27; N, 10.51; S, 16.05. Found: C, 54.4; H, 3.4; N, 10.4; S, 16.4

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