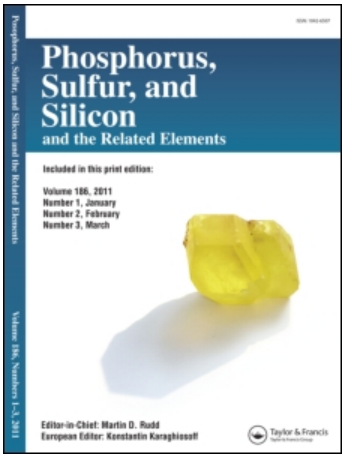

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Studies on Azolylacetonitriles: The Reactivity of Thiazole-2-yl, Thiadiazol-2-yl Acetonitriles Toward Electrophilic Reagents

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STUDIES ON AZOLYLACETONITRILES: THE REACTIVITY OF THIAZOLE-2-YL, THIADIAZOL-2-YL ACETONITRILES TOWARD ELECTROPHILIC REAGENTS

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5-Acetyl-2-cyanomethyl-4-methylthiazole, 2-aminothiazole, and 5-N-benzoylamino-1,3,4-thiadiazole-2-yl-acetonitrile react with acetone, and malononitrile derivatives in the presence of sulfur to yield the corresponding thiophene derivatives. Also, 4-furylmethylene-2-phenyl-2-oxazolin-5-ones react with thiophenol, and/or thionaphthol to give the thiolester derivatives in one-pot synthesis. The structures of the products were based on IR, ^1H NMR, and elemental analysis.

Keywords: 2-Aminothiophenes; spectra; synthesis; thiadiazole; thiazole; thiolester

Azolylacetonitriles are readily obtainable starting compounds that have been extensively utilized in the heterocyclic synthesis.[1–7] In continuation of our interest to prepare new heterocycles with possible biological activity,[8–12] we report here on the susceptibility of 5-acetyl-2-cyanomethyl-4-methylthiazole **1**, 2-aminothiazols **13**, 5-N-benzoylamino-1,3,4-thiadiazole-2-yl-acetonitrile **16**, and 4-furylmethylene-2-phenyl-2-oxazolin-5-ones **19** toward different reagents. Thus, compound **1** reacts with acetone **2** in the presence of sulfur in refluxing dioxane /triethylamine to yield the thiophene derivative **5**. It is assumed that mixing acetone with compound **1** results in the formation of the intermediate **3** which remains in equilibrium with its constituents. In fact, equilibrium lies heavily in the reverse direction. The adduct **3** then reacts with sulfur to form irreversibly the thiophene derivative **5**

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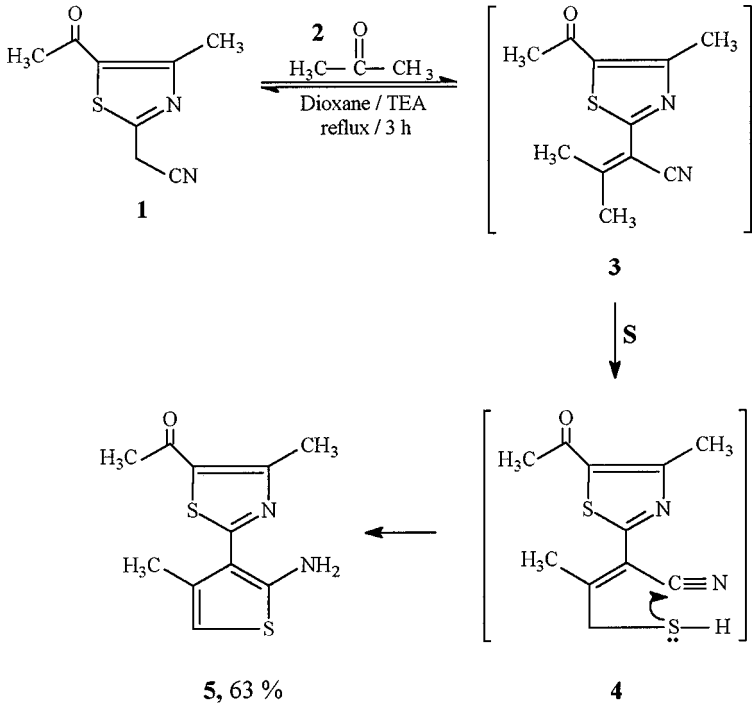
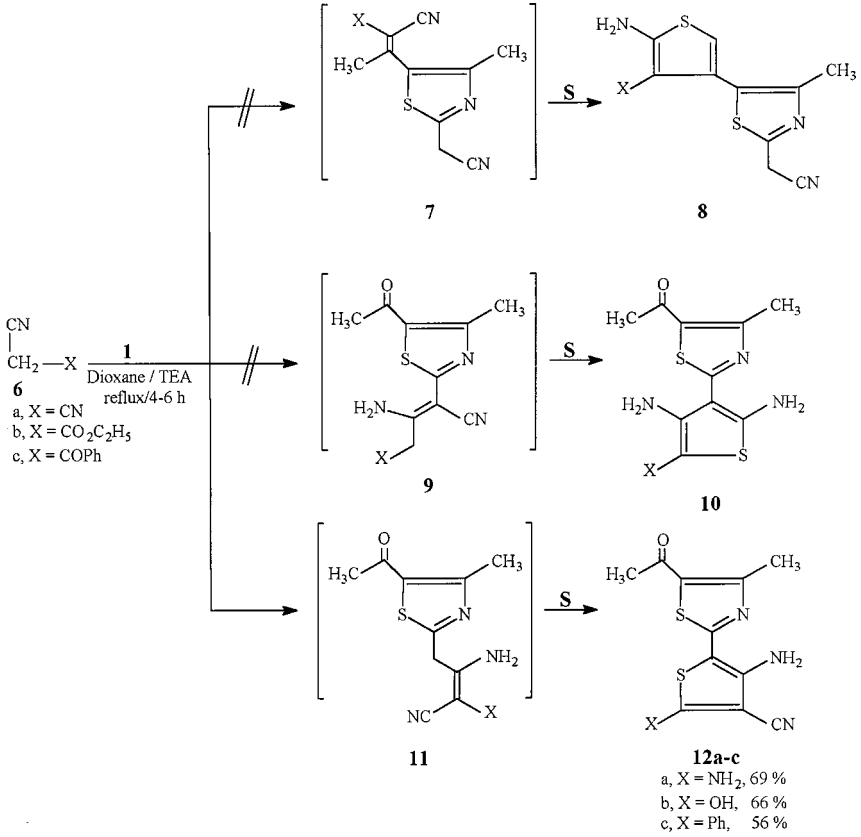


SCHEME 1

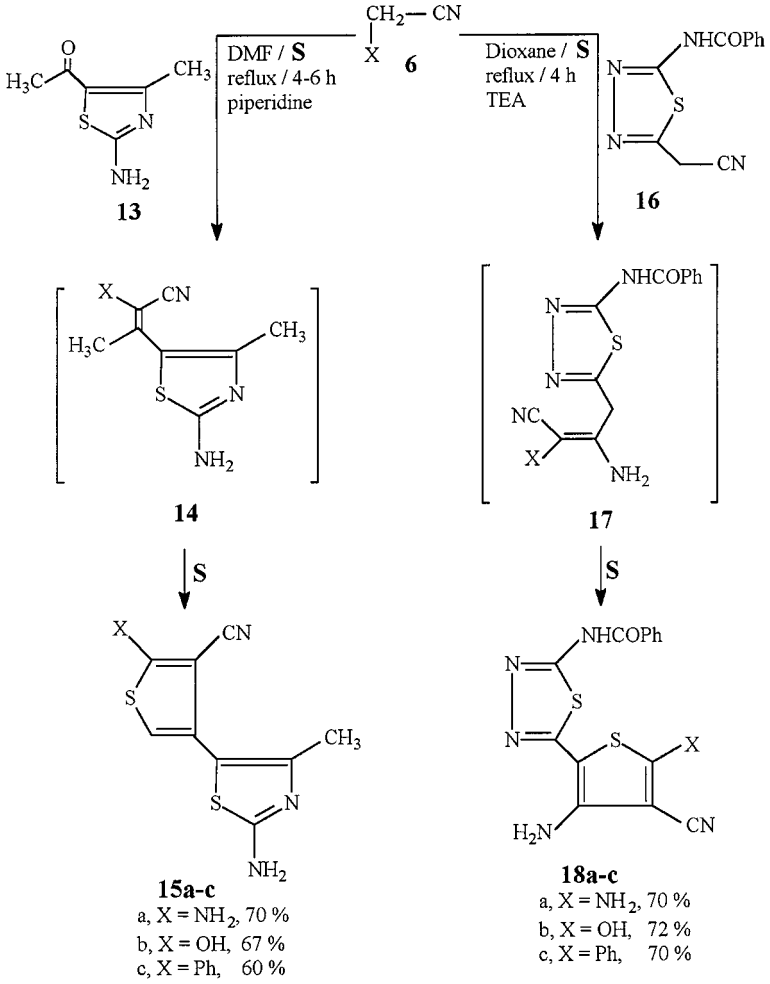
(Scheme 1). The IR (KBr) analysis reveals the absence of the cyano function and the presence of an amino function at $\nu = 3200–3300\ cm^{-1}$. The ^1H NMR ($CDCl_3$) analysis reveals signals at δ 2.2, 2.3, 2.9 due for three methyl groups, 5.3 for amino, and 7.2 ppm for one proton of the thiophene ring.

On the other hand, compound **1** react directly with malononitrile **6a**, ethyl cyano-acetate **6b** and benzoylacetonitrile **6c** in the presence of sulfur to yield the thiophene derivatives **12a**,**b**. Two isomeric structures **8**,**10** were also considered. Formation of **8** assumed to proceed by the condensation of malononitrile derivatives **6** with the carbonyl of the acetyl of **1** to yield the intermediate **7**, which then would react with sulfur to give **8**. Alternatively, the active methylene of **1** may add to the cyano function of malononitrile **6** forming **9**, which leads to compound **10**. In contrast, the active methylene of malononitrile **6** added to the cyano function of **1** to yield **12** via the intermediate **11** (Scheme 2). The structure **12** is preferred based on its IR data which revealed characteristic absorption band at $\nu = 2220\ cm^{-1}$ (CN), and its ^1H NMR ($CDCl_3$) showed the absence of the methylene which would be



SCHEME 2

present in structure **8**. Similarly, 5-acetyl-2-amino-4-methylthiazole **13** reacted with **6a–c** at reflux temperature of DMF/piperidine solution in the presence of sulfur to yield the thiophene derivatives **15a–c** via the formation of the intermediate **14**. The structures were based on spectral and elemental analysis. However, 2-cyanomethyl-1,3,4-thiadiazole **16** reacts easily with malononitrile derivatives **6a–c** in the presence of sulfur at reflux in dioxane/triethylamine for 4 h to afford the 4-aminothiophene derivatives **18a–c** in good yields (70–72%) (Scheme 3). The IR (KBr) spectrum of **18a** revealed bands at $\nu = 3400–3200$ (NH, NH_2), 2220 (CN), and 1660 cm^{-1} (C=O). The ^1H NMR ($CDCl_3$) spectra of **18a** showed signals at δ 7.9–8.4 ppm assigned for NH_2, NH. Finally, treatment of 4-furylmethylene-2-phenyl-2-oxazolin-5-ones **19** with thiophenol and thionaphthol **20a**,**b** under fusion conditions in oil bath (200°C) lead to rearrange into the oxazole

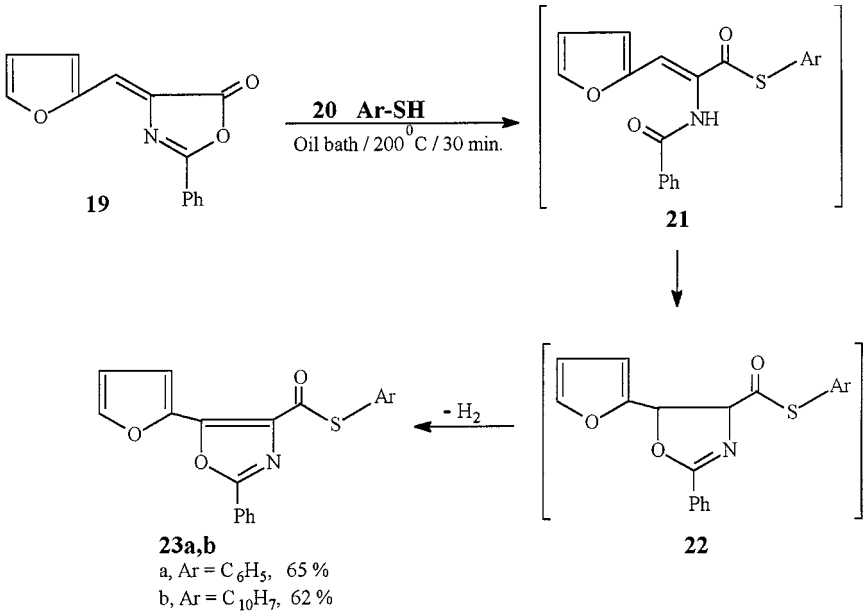


SCHEME 3

thiolester derivatives **23a**,**b** via the intermediates **21** and **22** (Scheme 4). The IR (KBr) spectra of **23a**,**b** revealed absorption bands at $\nu = 1725$, 1730 cm^{-1} assigned for the carbonyl group.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded (KBr, $\nu = cm^{-1}$) on a Perkin-Elmer FT IR (1650) Spectrophotometer. The ^1H NMR spectra were measured ($CDCl_3$, DMSO-d_6, $\delta = ppm$) on a



SCHEME 4

Varian EM 390 90 MHz spectrometer and TMS was used as internal reference. Elemental analysis were carried out at Microanalytical Center, Cairo University, Egypt.

5-Acetyl-4-methyl-2-(2-amino-4-methylthiophene-2-yl)-thiazole (5)

A mixture of **1** (1.8 g, 0.01 mol) and acetone **2** (0.6 g, 0.01 mol) in 40 ml dioxane was refluxed for 3 h in the presence of 0.32 g of sulfur (0.01 mol) and 1 ml of triethylamine. The solvent was evaporated under reduce pressure and the residue was triturated with water and neutralized with conc. HCl. The solid product so formed was filtered and recrystallized from DMF.

Compound 5

Yield 63%, m.p. >300°C (DMF); IR: $\nu = 3300–3200$ (NH_2), 1660 cm^{-1} (C=O). ^1H NMR: $\delta = 2.2$ (s, 3H, CH_3), 2.3 (s, 1H, CH_3), 2.9 (s, 3H, CH_3), 5.3 (br, 2H, NH_2), 7.2 (s, 1H, thiophene-H). $C_{11}H_{12}N_2OS_2$ (252.35); Found C 52.40, H 4.8, N 11.01, S 25.40; requires, C 52.36, H 4.79, N 11.10, S 25.41%.

Reaction of Malononitrile Derivatives (6a–c) with Thiazole (1)

General procedure. A mixture of **1** (1.8 g, 0.01 mol) and malononitrile **6a** (0.66 g, 0.01 mol) in 30 ml dioxane was refluxed for 4 h in the presence of 0.32 g of sulfur (0.01 mol) and 1 ml of triethylamine. The solvent was evaporated under reduce pressure and the residue was triturated with water and neutralized with conc. HCl. The solid product so formed was filtered and recrystallized from DMF into **12a**. In analogy, compound **1** reacted with **6b** or **6c** (each 0.01 mol) under the same reaction conditions to afford **12b**,**c**.

5-Acetyl-4-methyl-2-(4-cyano-3-diaminothiophene-2-yl)-thiazole (12a)

Yield 69%; m.p. 200°C (DMF); IR: $\nu = 3410–3350$ (NH_2), 2820 (CH_3), 2200 (CN), 1660 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 7.8–8.2 (br, 4H, $2NH_2$); $C_{11}H_{10}N_4OS_2$ (278.35), Found, C 47.35, H 3.48, N 20.02, S 23.11; requires C 47.47, H 3.62, N 20.13, S 23.04%.

5-Acetyl-4-methyl-2-(3-amino-4-cyano-5-hydroxythiophene-2-yl)thiazole (12b)

Yield 66%; m.p. 280°C (DMF); IR: $\nu = 3545–3195$ (OH, NH_2), 2965 (CH_3), 2200 (CN), 1660 cm^{-1} (C=O); $C_{11}H_9N_3O_2S_2$ (279.33), Found C 47.17, H 3.48, N 20.02, S 23.11; requires C 47.30, H 3.25, N 15.04, S 22.95%.

5-Acetyl-4-methyl-2-(3-amino-4-cyano-5-phenylthiophene-2-yl)thiazole (12c)

Yield 56%; m.p. 245°C (DMF); IR: $\nu = 3310$ (NH_2), 2905 (CH_3), 2210 (CN), 1670 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 7.2–7.5 (m, 5H, Ar–H); $C_{17}H_{13}N_3OS_2$ (339.43) Found, C 60.04, H 3.73, N 12.24, S 18.77; requires C 60.16, H 3.86, N 12.38, S 18.89%.

Reaction of Malononitrile Derivatives (6a–c) with 2-Aminothiazole (13) and with 2-Cyanomethylthiadiazole (16)

General procedure. A mixture of **13** (1.6 g, 0.01 mol) and malononitrile **6a** (0.66 g, 0.01 mol) in 30 ml DMF was refluxed for 4 h in the presence of 0.32 g of sulfur (0.01 mol) and 1 ml of piperidine. The solvent was evaporated under reduce pressure and the residue was triturated with water and neutralized with conc. HCl. The solid product so formed was filtered and recrystallized from DMF into **15a**.

Similarly, thiazole **13** reacted with **6b** or **6c** (each 0.01 mol) under the same reaction conditions to afford **15b**,**c**. In analogy, thiadiazole **16** (2.4 g, 0.01 mol) reacted with malononitrile derivatives **6a–c** (0.01 mol) and sulfur (0.32 g) in reflux dioxane in the presence of 0.1 ml of triethylamine for 4 h to give the corresponding 2-aminothiophene derivatives **18a–c**.

2-Amino-4-methyl-5-(2-amino-3-cyanothiophene-4-yl)-thiazole (15a)

Yield 70%; m.p. 295 (DMF); IR: $\nu = 3320–3139$ (NH, NH_2), 2927 (CH_3), 2203 $cm^{-}1$ (CN); $C_9H_8N_4S_2$ (236.31), Found, C 45.61, H 3.26, N 23.55, S 27.02; requires C 45.74, H 3.41, N 23.71, S 27.13%.

2-Amino-4-methyl-5-(3-cyano-2-hydroxythiophene-4-yl)-thiazole (15b)

Yield 67%; m.p. 130 (DMF); IR: $\nu = 3360–3306$ (OH, NH_2), 2200 (CN), 1667 cm^{-1} (C=O); $C_9H_7N_3OS_2$ (237.30), Found, C 45.43, H 2.85, N 17.60, S 27.12; requires C 45.55, H 2.97, N 17.71, S 27.02%.

2-Amino-4-methyl-5-(3-cyano-2-phenylthiophene-4-yl)-thiazole (15c)

Yield 60%; m.p. 110 (DMF); IR: $\nu = 3354–3325$ (NH_2), 2211 cm^{-1} (CN); $C_{15}H_{11}N_3S_2$ (297.39), Found, C 60.71, H 3.62, N 14.02, S 21.43; requires C 60.58, H 3.73, N 14.13, S 21.56%.

2-Bnzamido-5-(2,4-diamino-3-cyanothiophene-5-yl)-thiadiazole (18a)

Yield 70%; m.p. 254–255°C (DMF); IR: $\nu = 3400–3200$ (NH, NH_2), 2220 (CN), 1665 cm^{-1} (CO); ^{1}H NMR: (DMSO-d_6): δ 7.4–7.8 (m, 5H, Ar–H), 7.9–8.4 (br, 5H, $2NH_2$ and NH); $C_{14}H_{10}N_6OS_2$ (342.40); Found C 49.24, H 2.84, N 24.37, S 18.58; requires C 49.11, H 2.94, N 24.54, S 18.73%.

Compound 18b

Yield 72%; m.p. 160–162°C (DMF); IR: $\nu = 3450–3200$ (NH, NH_2), 2220 (CN), 1680 cm^{-1} (CO); ^{1}H NMR: (DMSO-d_6): δ 7.4–7.7 (m, 5H, Ar–H), 7.9–8.7 (m, 4H, OH, NH_2 and NH); $C_{14}H_9N_5O_2S_2$ (343.40); Found C 48.83, H 2.51, N 20.25, S 18.52; requires C 48.97, H 2.64, N 20.40, S 18.67%.

Compound 18c

Yield 70%; m.p. 207–209°C (CHC_3); IR: $\nu = 3400–3200$ (NH, NH_2), 2220 (CN), 1680 cm^{-1} (CO); ^{1}H NMR: (DMSO-d_6) δ 7.4–8.2 (m, 13H,

Ar—H and NH_2); $C_{20}H_{13}N_5OS_2$ (403.48); Found C 59.40, H 3.12, N 17.22, S 18.75; requires C 59.53, H 3.25, N 17.36, S 18.89%.

Reaction of (19) with Thiophenol (20a) and Thionaphthol (20b)

General Procedure

A mixture of 4-furylmethylene-2-phenyl-2-oxazolin-5-ones **19** (2.4 g, 0.01 mol) and thiophenol **20a** (1.1 g, 0.01 mol) was fused for **30** min at 200°C over an oil bath. The mixture cooled at room temperature, then triturated with ethanol and the solid product so formed was collected by filtration and recrystallized from dioxane into thiolester **23a**. Similarly, compound **19** reacted with thionaphthol **20b** (1.6 g, 0.01 mol) under the same reaction conditions to yield **23b**.

Compound 23a

Yield 65%; m.p. 146–147°C (dioxane); IR: $\nu = 1725$ cm^{-1} (C=O); $C_{20}H_{13}NO_3S$ (347.39); Found C 69.03, H 3.64, N 4.16, S 9.11; requires C 69.15, H 3.77, N 4.03, S 9.23%.

Compound 23b

Yield 62%; m.p. 150–152°C (DMF); IR: $\nu = 1730$ cm^{-1} (C=O); $C_{24}H_{15}NO_3S$ (397.45); Found C 72.40, H 3.64, N 3.36, S 8.19; requires C 72.53, H 3.80, N 3.52, S 8.07%.

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