FACILE SYNTHESIS OF NOVEL POLYSUBSTITUTED THIOPHENE AND BENZO[g]THIAZO [3,2-a]PYRIDINE

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Abstract: 2-cyanomethylbenzothiazole 1 reacts with acetone derivatives **2a-d**, or acetonitrile derivative 6a-d in the presence of sulfiur and triethylamine afforded the novel polysubstituted thiophene. Treatment of 1 with alkylidenemalononitrile derivatives **IIa-h** resulted in the formation of benzo[g]thiazo[3,2-a]pyridines in high yield.

Introduction:

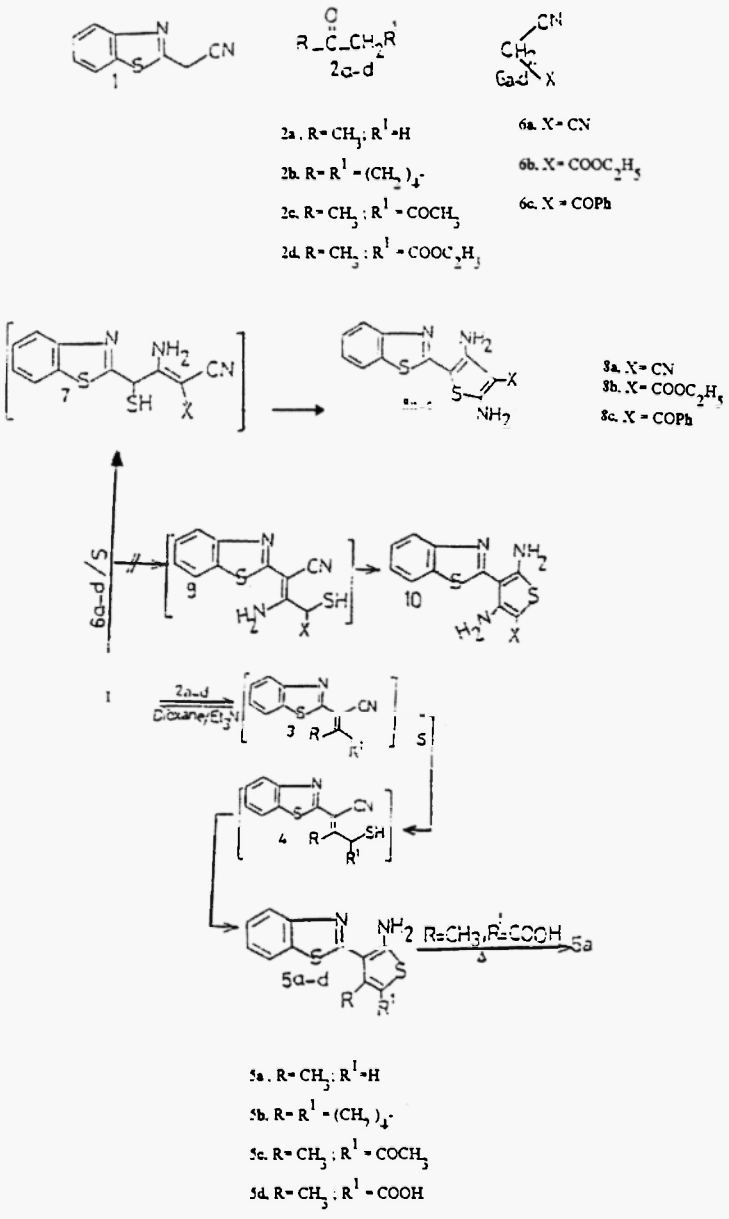
Benzothiazole derivatives have attracted a great deal of interest due to their biological and commerical importance. They have been found to have their antiviral(1); antibacterial(2) and fungicidal(3) activites. They are also useful as anti-allergic(4), an theliminic(5) agent and histamine H_2 antagonists(6) and appetite depressants(7), intermediates for dyes(8) and photographic sensitizers(9).

Results and Discussion:

As part of our program amining to synthesis of heterocycles containing benzothiazole moiety (10-13). We report here on a facile route to several new benzothiazol-2-yl thiophene and benzo[g] thiazo[3,2-a]pyridines. Alkyl functions in alkylheteroaromatics are in contract to alkylaromatic hydrocarbons active toward electroplulic reagents(14,15). This activity is enhanced by both acidic and basic catalysts(16,17). This extra activity has been extensively utilized in synthesis of heterocycles(18,19). In previous work from our laboratories we have shown that the cyanomethyl function in several azoles are active toward electrophilic reagents which enabled synthesis of several condensed azole(20,21). Thus, it has been found that 2-cyanomethyl benzothiazole 1 reacts with acetone **2a** in the presence of sulfur in refluxing dioxane-triethylamine to yield the thiophene derivative **3a**. It is assumed that mixing 1 and **2a** results in the formation of **3** which remains in equilibrium with its constituents. In fact the equilibrium lies heavily in the reverse direction. Compound **3a** then reacts with sulphur to form the mercapto derivative **4a** that cyclizes readily into irreversibly the thiophene derivative **5a**. The structure assigned for the reaction product was established based on analytical and spectral data. Thus IR spectrum of the reaction product reveals the absence of a cyano function and the presence of amino function at ν=3220 cm^{-1}. Moreovers, ^1H NMR analysis of the reaction product reveals the absence of methylene function which indicates the involvement of the methylene function in 1 in the reaction. The behaviour of 1, thus resembles other active methylene nitrile and to our knowledge this is the first reported use of 1as active methylene in the Gewald reaction. Compound 1and cyclohexanone, acetylacetone or ethyl acetoacetate **2b-d** reacted similarly to yield the thienylbenzothiazole derivatives **5b-d** The proposed structure **5a** was supported by its independent synthesis from decarboxylation of **5d** via heating above their melting point (mp and mixed mp).

Malononitrile and sulfur reacted with 1 to yield either **8a** or **10a**. The formation of **8a** is assumed to procced via addition of methylene group of malononitrile to cyano function in 1 followed by reaction with sulfur to yield **7a** which was then cyclized into **8a**. Alternately methylene of 1 may add to the cyano of malononitrile, react with sulfur and then cyclize to **10a**. Structure of **8a** is

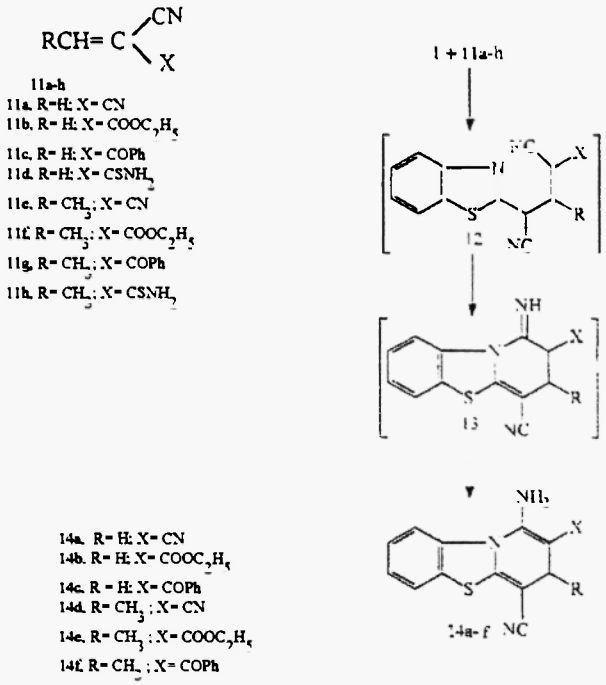
preferred over possible **10a** based on the IR spectrum which showed a cyano signal at ν 2250 cm^{-1}. Alternative **10a** is expected to show a CN signal at lower frequency(22). Similar to malononitrile ethyl cyanoacetate and/or benzoylactonitrile yield **8b,c**. Similarly compound **1** reacted with 2-cyanoethanethioamide and sulfur to yield a product identical (mp, mixed mp and spectra) with **8a** (Scheme 1).



Scheme-1

Cyanomethylazoles have been extensively uitilized for the synthesis of condensed pyridines (23)bv reaction with arylidenemalononitriles derivatives. The reaction of 2- cyanomethyl-lH-benzimidazole with alkylidenemalononitriles has been reported by us(24). We report here the reaction of **1** with alkylidenemalononitrile derivatives **11a-h** and to our knowledge this is the first reported use of cyanomethylbenzothiazole with alkylidenemalononitriles derivatives. Thus compound **1** reacts with mixture of formaldehyde and malonitrile to yield compound **14a**. Structure **14a** was confirmed based on the ^1H NMR spectrum band which

reavled an amino function at δ= 8.1 ppm and absorption band at δ = 4.9 ppm which was assigned for pyridine CH_2-4. The proposed structure **14a** was supported by its independent synthesis from **1** and **11 d** via elimination of hydrogen sulfide (mp and mixed mp). Similarly, compound **1** reacts with **11h-h** affording **14b-f** . Also the proposed structure **14d** was supported by its independent synthesis from **1** and **11h** via elimination of hydrogen sulfide (mp and mixed mp) (Scheme 2).



Scheme - 2

Experimental:

Melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Data Unit at Cairo University. IR spectra (KBr) were measured on a Shimadzu IR 440 spectrophotometer. The ^1H NMR were measured in DMSO [d6] on a Varian EM-390 90 MHZ spectrometer using TMS as internal refrence and chemical shifts are expressed as δ ppm and mass spectra on a Shimadzu GC-MS-QP 1000 EX spectrometer using a direct-inlet system.

Synthesis of benzothiozolo-2-ylthiophene derivatives 5a-d and 8a-c. (General procedure): A solution of **1** (0.01 mol) in dioxane (30 ml) was treated with the appropriate active methylene reagent **2a-d** or **6a-d** (0.01mol) and sulfur (0.01 mol) with catalytic amount of triethylamine (0.5ml). The reaction mixture was heated under reflux for 4-6h (TLC control). The solvent was removed under reduced pressure and the residue was triturated with ice/water and neutralized with acetic acid. The solid product so formed was collected by filteration and recrystallized from the proper solvent.

5a: Yield 81%; m-p. 260-2°C from DMF. ν max/cm^{-1} (KBr) 3410-3200 (NH_2),3010(CH_3), 1610(C=N). δ_H (DMSO) 2.15 (3H,s), 7.3-8.1 (7H,m). (Found): C, 58.34; H, 4.12; N, 11.25; S, 25.92. $C_{12}H_{10}N_2S_2$ requires C, 58.51; H, 4.09; N, 11.37; S, 26.03 % (M^+= 246).

5b: Yield 71%; mp. 290-2°C from dioxane. νmax/cm^{-1} (KBr) 3280. (NH_2),1620 (C=N). δ_H (DMSO) 2.5 (4H,t), 3.8 (4H,m), 6.7-8.1 (6H,m). (Found: C, 62.7; H, 4.71; N, 9.52; S, 22.15.$C_{15}H_{14}N_2S_2$ requires C, 62.9; H, 4.93; N, 9.78; S, 22.39%).

5c: Yield 72%; mp. 300°C from DMF, ν max/cm^{-1} (KBr) 3250 (NH_2), 2990 (CH_3), 1690 (CO), 1610 (C=N). δ_H (DMSO) 2.26 (3H,s), 2.5 (3H,s), 7.2-8.15 (6H,m). (Found: C, 58.15; H, 4.15; N, 9.55; S, 22.1. $C_{14}H_{12}N_2OS_2$, requires C, 58.31; H, 4.19; N, 9.72; S, 22.24 %).

5d: Yield 63%; mp. >300°C from DMF, νmax/cm^{-1} (KBr) 3450-3100 (OH,NH_2), 2990 (CH_3), 1735 (CO), 1615 (C=N), δ_H (DMSO) 2.21 (3H,s), 10.4 (lH,s). (Found: C, 53.55; H, 3.52; N, 9.57; S, 22. 1. $C_{13}H_{10}N_2O_2S_2$. requires C, 53.78; H, 3.47; N, 9.64; S, 22.08% (M^+ = 290).

Conversion of 5d into 5a: 2 gm of **5d** was heated above their melting point for few min. The solid product was then triturated with ethanol and the resulting solid product was collected by filteration and crystallized from DMF.

8a: Yield 65%; mp. >300°C from DMF, νmax/cm^{-1} (KBr) 3370-3200 (NH_2), 2250 (CN), 1620 (C=N). δ_H (DMSO) 7.0-8.1 (8H,m). (Found: C, 52.7; H, 2.8; N, 20.35; S, 23.32. $C_{12}H_8N_4S_2$. requires C, 52.92; H, 2.96; N, 20.57; S, 23.54% (M^+= 272).

8b: Yield 69%; mp. 295°C from DMF, νmax/cm^{-1} (KBr) 3420-3210 (NH_2), 1710 (CO), 1610 (C=N). δ_H (DMSO) 1.41 (3H,t), 4.4 (2H,q), 7.0-7.9 (8H,m). (Found: C, 52.54; H, 4.0; N, 13.12; S, 20.1. $C_{14}H_{13}N_3O_2S_2$. requires C,52.64; H, 4.10; N, 13.16; S, 20.08%).

8c: Yield 55%; mp. >300°C from DMF, νmax/cm^{-1} (KBr) 3350-3150 (NH_2), 1690 (CO), 1620 (C=N). δ_H (DMSO) 6.9-7.9 (13H,m). (Found: C, 61.4; H, 3.51; N, 11.72; S, 18.15.$C_{18}H_{13}N_3OS_2$. requires C, 61.51; H, 3.73; N, 11.96; S, 18.25%).

Synthesis of benzo[g]thiazo[3,2-a]pyridine derivatives 14a-f (General procedure). A solution of the appropriate alkylidenemalononitrile derivative **11a-h** (0.01 mol), prepared in situ from the reaction of the corresponding aldehyde and active methylene in ethanol in the presence of piperidine was added to compound **1** (0.01mol). The reaction mixture was heated under reflux for 4-6h. The solvent was then evaporated under reduced pressure. The solid product so formed, was collected by filteration and crystallized from the proper solvent.

14a: Yield 62%; mp. 255°C from dioxane. νmax/cm^{-1} (KBr) 3250 (NH_2), 2230, 2210 (2CN). δH (DMSO) 4.2 (2H,s), 6.9-8.1 (6H,m). (Found: C, 61.65; H, 3.12; N; 22.12; S, 12.5. $C_{13}H_8N_4S$. requires C, 61.89; H, 3.20; N, 22.12; S, 12.71% (M^+ = 252).

14b: Yield 61%; mp. 273°C from DMF, νmax/cm^{-1} (KBr) 3200 (NH_2), 2220 (CN), 1700 (CO). δH (DMSO), 1.4 (3H,t), 4.2(2H,q), 4.4 (2H,s), 7.1-7.9 (6H,m), (Found: C, 60.13; H, 4.21; N, 14.0; S, 10.5. $C_{15}H_{13}N_3O_2S$, requires C, 60.18; H, 4.38; N, 14.02; S, 10.71%).

14c: Yield 56%; mp. 262-3°C from DMF, νmax/cm^{-1} (KBr) 3240 (NH_2),2230(CN),1710 (CO). (Found: C, 68.62; H, 3.72; N, 12.62; S, 9.52. $C_{19}H_{13}N_3OS$. requires C, 68.86; H, 3.95; N, 12.68; S, 9.67% (M^+ = 331).

14d: Yield 69%; mp. >300°C from DMF, νmax/cm^{-1} (KBr) 3300-3200 (NH_2), 2240-2220 (2CN). δH (DMSO) 2.8 (3H,s), 4.1 (lH,s). 7.1-7.9 (6H,m), (Found: C, 63.15; H, 3.62; N, 21.15; S, 12.10. $C_{14}H_{10}N_4S$. requires C, 63.14; H, 3.79; N, 21.04; S, 12.04% (M^+ = 266).

14e: Yield 62%; mp. >300°C from DMF, νmax/cm^{-1} (KBr) 3230 (NH_2), 2215 (CN), 1710 (ester CO). δH (DMSO), 1.3 (3H,t), 2.63 (2H,s), 4.1 (2H,q), 4.43 (lH,s), 6.9-9.1 (6H,m). (Found: C, 61.21; H, 4.62; N, 13.15; S, 10.1. $C_{16}H_{15}N_3O_2S$, requires C, 61.32; H, 4.83; N,13.41; S,10.23%).

14f: Yield 57%; mp. 296°C from DMF, vmax/cm^{-1} (KBr) 3210 (NH_2), 2210 (CN), 1695 (CO).(Found: C, 69.32; H, 4.25; N, 12.1 ; S, 9.13. $C_{20}H_{15}N_3OS$. requires C, 69.54; H, 4.38; N, 12.17; S, 9.28% (M^+= 345).

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