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Facile Synthesis of Novel Polysubstituted Thiophene and 1,3,4-Thiadiazole Derivatives

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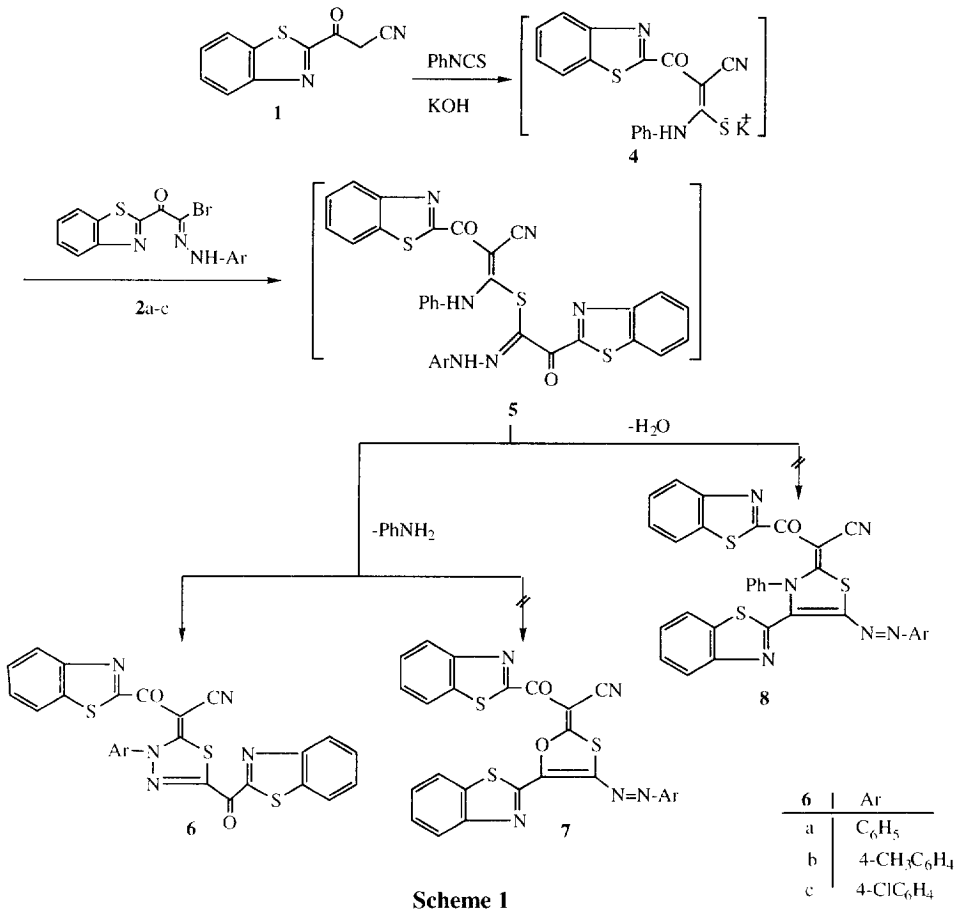
Abstract: 3-(Benzothiazol-2-yl)-3-oxopropanenitrile (**1**) reacts with phenylisothiocyanate in the presence of potassium hydroxide followed by addition of the hydrazonoyl bromides **2a-c** to afford the novel 1,3,4-thiadiazole derivatives **6a-c** via the intermediate **4**. Reaction of **4** with 2-bromoacetylbenzothiazole (**3**) furnished the new polysubstituted thiophene **13**. Treatment of the latter product with aromatic diazonium salts resulted in the formation of 2-arylazothiophene derivatives **16a-c**. A suggested mechanisms of the investigated reactions were presented. Copyright © 1996 Elsevier Science Ltd

In continuation of our studies on the chemistry of 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**1**),[1,2] N-aryl-α-oxo-2-benzothiazoleethanehydrazonoyl bromides **2a-c**[2,3] and 2-bromoacetylbenzothiazole (**3**),[3] and as part of our program directed towards developing new approaches to a variety of heterocycles incorporating benzothiazole moiety[1-5] of expected potential biological activity, we report here on the utility of the highly versatile, multifunctional intermediates **1**, **2**, and **3** as building blocks for the synthesis of the title compounds.

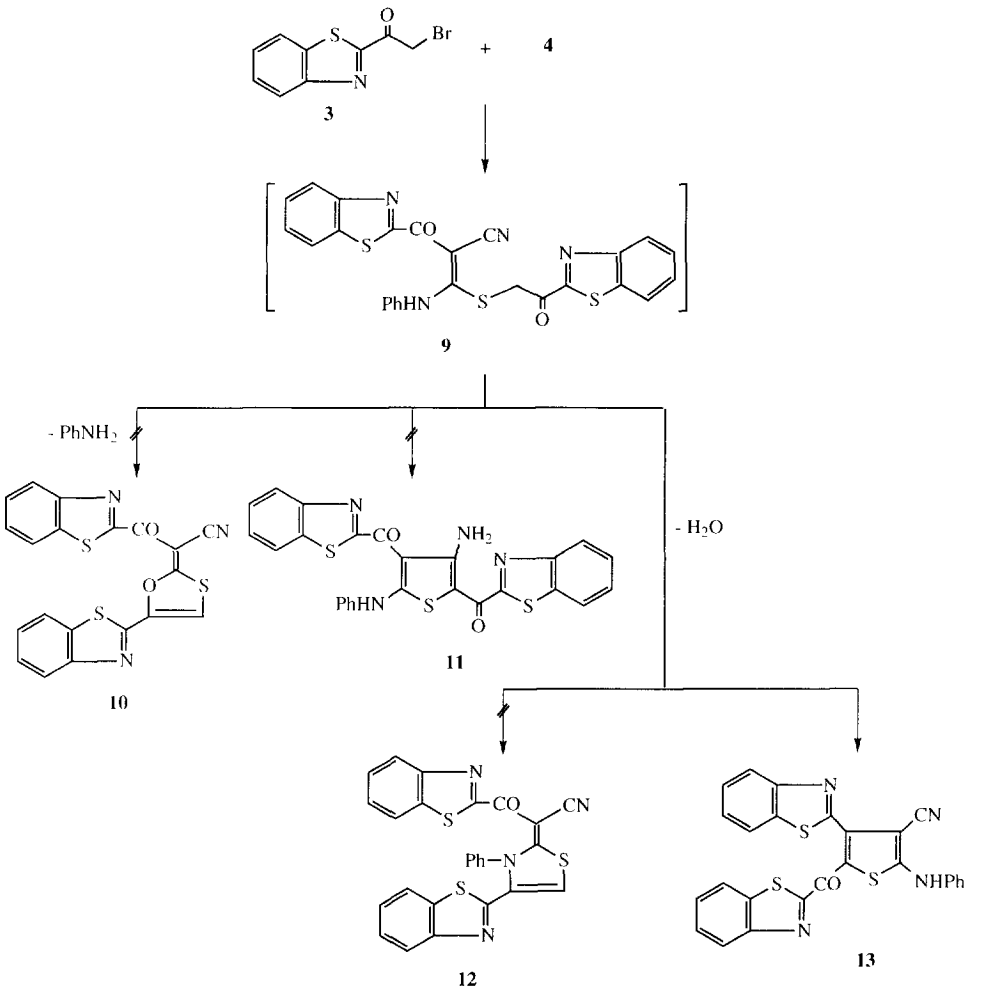
Thus, treatment of a solution of the 3-oxopropanenitrile **1** in dimethylformamide with phenylisothiocyanate, in the presence of potassium hydroxide, at room temperature followed by the addition of an equimolar amount of the appropriate hydrazonoyl bromide **2a-c** furnished in each case, only one isolable product (as tested by TLC analysis). Scheme 1 depicts all the possible structures proposed for the reaction products. However, of these structures, only the 3-aryl-5-(benzothiazol-2-yl)carbonyl-2-(benzothiazol-2-yl)carbonylcyanomethylene-2,3-dihydro-1,3,4-thiadiazole structure **6** manifested to be the reasonable one as confirmed by the elemental analyses, IR, ^{1}H NMR and mass spectra of the isolated products (see Experimental part). For example, the IR spectra of **6a-c** revealed in each case, absorption bands near 2200, 1670 and 1640 cm^{-1} corresponding to a nitrile and two conjugated carbonyl groups, respectively. Also, the ^{1}H NMR spectrum of **6b**, for example, displayed a singlet signal at δ 2.38 ppm and a multiplet at δ 7.4-8.32 ppm due to methyl and aromatic protons, respectively. Moreover, the mass spectrum of **6c** exhibited a molecular ion peak at m/z 558. These results indicate that the reaction of the non-isolable intermediate **4** with hydrazonoyl bromides **2a-c** proceeds in each case,*via* loss of potassium bromide followed by elimination of aniline molecule from the non-isolable intermediate **5**, respectively.



Scheme 1

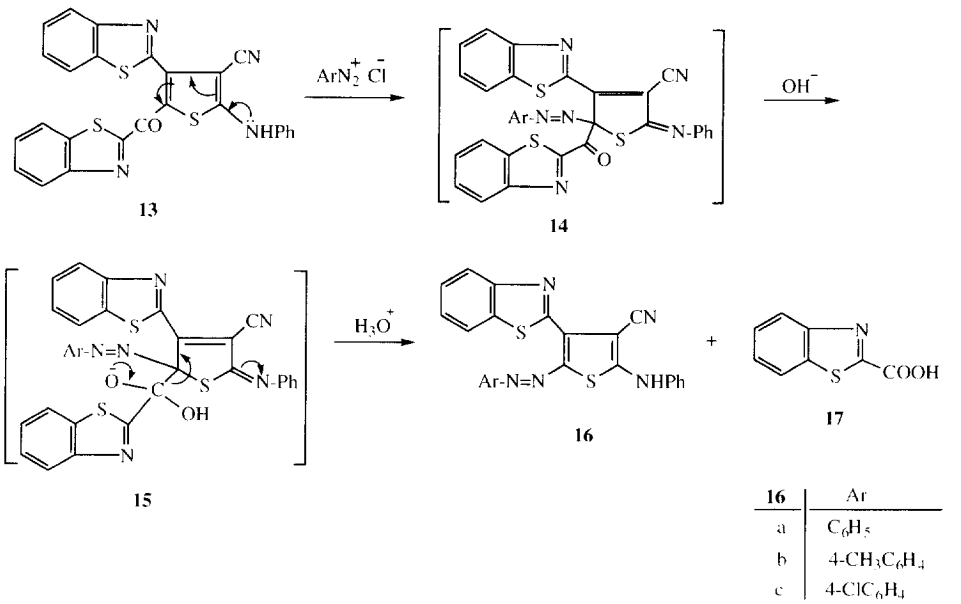
Similarly, 2-bromoacetylbenzothiazole (**3**) reacts with the intermediate **4**, formed *in situ* under the same reaction conditions, to afford a single product for which the four proposed structures **10-13** depicted in scheme 2 seemed possible. However, the elemental analyses and spectral data of the reaction product were compatible only with the thiophene structure **13**. This assignment was supported by the appearance of NH, nitrile and carbonyl absorption bands at 3194, 2219 and 1671 cm^{-1}, respectively, in the IR spectrum of the isolated product. Moreover, its ^1H NMR spectrum revealed a broad signal at δ 8.5 ppm (exchangeable with deuterium oxide) due to NH proton, in addition to a multiplet at δ 7.4-8.35 ppm due to aromatic protons.

Treatment of the 2-(benzothiazol-2-yl)carbonylthiophene derivative **13** with benzene diazonium chloride in a cold mixture of pyridine and dimethylformamide followed by dilution with water afforded two isolable products (as tested by TLC analysis) none of them was the starting thiophene derivative **13**. Elemental analysis and mass spectrum of one of the reaction products were compatible with the molecular formula $C_{24}H_{15}N_5S_2$. The IR spectrum of this product revealed absorption bands at 3210 and 2220 cm^{-1} assignable to imine and nitrile functions, respectively, and showed no bands in the region 1640-1800 cm^{-1} due to carbonyl absorption. Its mass spectrum exhibited, in addition to the molecular ion peak at m/z 437, a fragment at m/z 332 corresponding to



Scheme 2

[M - PhN=N]$^+$. The other product was identified as 2-benzothiazolecarboxylic acid (**17**) which was found to be identical in all respects with an authentic sample prepared by an independent method[6]. Based on the forgoing results, it was assumed that the benzothiazol-2-ylcarbonyl residue at the 2-position of the thiophene ring was replaced by the phenylazo group in a manner similar to Japp-Klingmann acyl cleavage.[7] Therefore, the reaction product was assigned the 3-(benzothiazol-2-yl)-4-cyano-2-phenylazo-5-(N-phenylamino)thiophene structure **16a**. A suggested mechanism for the formation of **16a** is depicted in scheme 3. Prompted by these interesting results and in order to generalize this phenomenon, the reaction of **13** with other diazotized aromatic amines under the same reaction conditions was examined. The reaction products were found to be the 2-arylazothiophene derivatives **16b,c**, respectively. The structures of the latter products were supported by their elemental analyses and spectral data (see Experimental part).



16	Ar
a	C_6H_5
b	$4\text{-}CH_3C_6H_4$
c	$4\text{-}ClC_6H_4$

Scheme 3

EXPERIMENTAL

Melting points were recorded on a Gallenkamp melting point apparatus. IR spectra were measured as KBr pellets on a Pye-Unicam SP 3-300 spectrophotometer. ^1H NMR spectra were recorded on deuterated dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 3-(Benzothiazol-2-yl)-3-oxopropanenitrile **(1)**,[1] N-aryl-α-oxo-2-benzothiazoleethanehydrazonoyl bromides **2a-c**[3] and 2-bromoacetylbenzothiazole **(3)**[8] were prepared according to literature procedures.

3-Aryl-5-(benzothiazol-2-yl)carbonyl-2-(benzothiazol-2-yl)carbonylcyanomethylene-2,3-dihydro-1,3,4-thiadiazoles 6a-c. General procedure:

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 ml) was added the 3-oxopropanenitrile **1** (0.404 g, 2 mmol). After stirring for 30 min, phenylisothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6h, then the appropriate hydrazonoyl bromide **2a-c** (2 mmol) was added portionwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for further 12h, during which the hydrazonoyl bromide **2** dissolved and a yellowish-red coloured product precipitated. The solid product was filtered off, washed with water and dried. Recrystallization from dimethylforamide afforded the corresponding 1,3,4-thiadiazole derivatives **6a-c** in 80-85% yields.

6a: Yield (81%); mp. 332-4°C; IR (KBr) ν 2212 (C≡N), 1665 (C=O), 1645 (C=O), 1605 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.48-8.39 (m, ArH's); MS, m/z (%) 523 (M^+, 8.9), 361 (5.0), 335 (14.8), 253 (4.6), 162 (85.3), 134 (100), 77 (51.6); (Calcd. for $C_{26}H_{13}N_5O_2S_3$: C, 59.63; H, 2.51; N, 13.37; S, 18.37. Found: C, 59.60; H, 2.43; N, 13.50; S, 18.43).

6b: Yield (80%); mp. 326-8°C; IR (KBr) ν 2208 (C≡N), 1667 (C=O), 1646 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 7.36-8.35 (m, 12H, ArH's); (Calcd. for $C_{27}H_{15}N_5O_2S_3$: C, 60.31; H, 2.81; N, 13.02; S, 17.89. Found : C, 59.96; H, 2.66; N, 13.10; S, 17.66).

6c: Yield (85%); mp. > 350°C; IR (KBr) ν 2220 (C≡N), 1670 (C=O), 1650 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (this product is insufficiently soluble in the usual NMR solvents); MS, m/z (%) 559 (M^++1, 17.0), 558 (M^+, 10.2), 557 (25.6), 423 (12.0), 369 (29.5), 287 (12.0), 162 (100), 134 (82.6), 90 (16.5); (Calcd. for $C_{26}H_{12}ClN_5O_2S_3$: C, 55.95; H, 2.16; N, 12.55; S, 17.23. Found : C, 55.78; H, 2.21; N, 12.45; S, 17.10).

2-(Benzothiazol-2-yl)carbonyl-3-(benzothiazol-2-yl)-4-cyano-5-(N-phenylamino)thiophene (13).

This compound was prepared by the same procedure described above using 2-bromoacetylbenzothiazole (**3**) instead of the hydrazonoyl bromides **2a-c**. Yield (85%); mp 280-2°C; IR (KBr) ν 3194 (NH), 2219 (C≡N), 1671 (C=O), 1599 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.4-8.35 (m, 13H, ArH's), 8.5 (br.s, 1H, NH) ppm; MS, m/z (%) 494 (M^+, 32.3), 360 (18.8), 316 (16.3), 229 (27.2), 185 (100), 134 (27.0), 77 (83.3); (Calcd. for $C_{26}H_{14}N_4OS_3$: C, 63.13; H, 2.85; N, 11.32; S, 19.59. Found : C, 63.20; H, 2.80; N, 11.26; S, 19.62).

2-Arylazo-3-(benzothiazol-2-yl)-4-cyano-5-(N-phenylamino)thiophenes 16a-c.

To a cold solution of 2-(benzothiazol-2-yl)carbonylthiophene derivative **13** (0.494 g, 1 mmol) in pyridine (30 ml) and dimethylformamide (20 ml), was added the appropriate arene diazonium chloride solution (1 mmol) with stirring over a period of 30 min. The reaction mixture was stirred at 0-5°C for further 4h, and left in the refrigerator for 12h then diluted with water. The solid that precipitated was collected by filtration, washed with water and dried. Recrystallization from dimethylformamide afforded the corresponding 2-arylazothiophene derivatives **16a-c** in 57-65% yields.

16a: Yield (60%); mp. 270-2°C; IR (KBr) ν 3210 (NH), 2220 (C≡N), 1600 (C=N), 1330 (azo-N=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.26-8.33 (m, 14H, ArH's), 10.85 (br.s, 1H, NH) ppm; MS, m/z (%) 437 (M^+, 45.7), 408 (27.7), 332 ([M - PhN=N]$^+$, 21.1), 305 (10.4), 229 (2.12), 185 (55.9), 77 (100); (Calcd. for $C_{24}H_{15}N_5S_2$: C, 65.88; H, 3.45; N, 16.00; S, 14.65. Found : C, 65.69; H, 3.38; N, 15.74; S, 14.71).

16b: Yield (57%); mp. 273-5°C; IR (KBr) ν 3181 (NH), 2213 (C≡N), 1596 (C=N), 1309 (azo-N=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 7.31-8.22 (m, 13H, ArH's), 11.0 (br.s, 1H, NH) ppm; (Calcd. for $C_{25}H_{17}N_5S_2$: C, 66.49; H, 3.79; N, 15.51; S, 14.20. Found: C, 66.72; H, 3.92; N, 15.46; S, 14.23).

16c: Yield (65%); mp. 291-3°C; IR (KBr) ν 3186 (NH), 2220 (C≡N), 1602 (C=N), 1335 (azo-N=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.51-8.39 (m, 13H, ArH's), 8.48 (br.s, 1H, NH) ppm; MS, m/z (%) 473 (M^++ 2, 45.6), 472 (M^++ 1, 33.9), 471 (M^+, 82.3), 442 (28.1), 409 (11.6), 349 (14.4), 333 (48.0), 305 (19.6), 229 (37.9), 185 (82.9), 139 (16.8), 111 (100), 77 (69.1); (Calcd. for $C_{24}H_{14}ClN_5S_2$: C, 61.07; H, 2.98; N, 14.84; S, 13.58. Found: C, 61.13; H, 2.90; N, 14.69; S, 13.62).

When the mother liquor of the reaction mixture was acidified with concentrated hydrochloric acid, a white precipitate was formed which was filtered off, washed with water and dried. Recrystallization from dilute ethanol afforded 2-benzothiazolecarboxylic acid (**17**) mp. 108°C identical in all respects (mp., mixed mp. and IR spectra) with an authentic sample prepared according to literature procedures[6].

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