Synthesis and Reactivity of 2-(2,2-Dicyano-1-methylvinyl)benzothiazole in Heterocyclic Synthesis: Convenient Route to Some Pyridazinone, Hydrazonoethyl, Thiophene, Phathalic Anhydride and Benzene Derivatives Incorporating a Benzothiazole Moiety

Maghraby A. Selim[b], Mohamed A. Raslan[a]*, Mohamed A. Khalil[a] and Samia M. Sayed[a]
[a]*Department of Chemistry, Faculty of Science, South Valley University, Aswan, Egypt*
[b]*Department of Chemistry, Faculty of Science, South Valley University, Qena, Egypt*

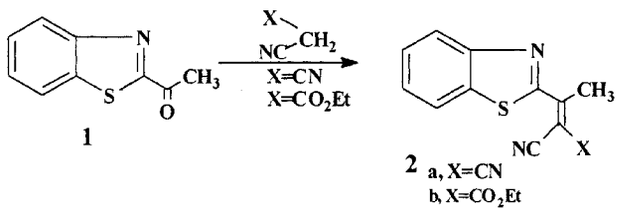
A facile route to some pyridazinone, hydrazonoethyl, thiophene, phathalic anhydride and benzene derivatives incorporating a benzothiazole moiety is reported.

INTRODUCTION

Benzothiazole derivatives have attracted a great deal of interest due to their antiviral,[1] antibacterial,[2] antimicrobial[3] and fungicidal activites.[4] They are also useful as antiallergic,[5] anti-inflammatory[6] and anthelmintic[7] agents and as appetite depressants,[8] intermediates for dyes,[9] plant protectants,[10] histamine H_2 antagonists[11] and photographic sensitizers.[12] In continuation of our interest in the synthesis of heterocycles containing a benzothiazole moiety,[13-15] we report here on a facile route to synthesis of some new benzothiazole derivatives.

As a part of a programme aimed at the synthesis of novel benzothiazole derivatives which could be useful for biological and pharmacological screening, we have investigated the possible utility of crotonitrile derivatives **2a,b** for synthesis of title products. Thus, we have found that 2-acetylbenzothiazole **1** condensed with malononitrile in boiling benzene containing ammonium acetate and acetic acid using a Dean-Stark water separator afforded the 2-(2,2-dicyano-1-methylvinyl)benzothiazole (**2a**) (Scheme I).

Scheme I

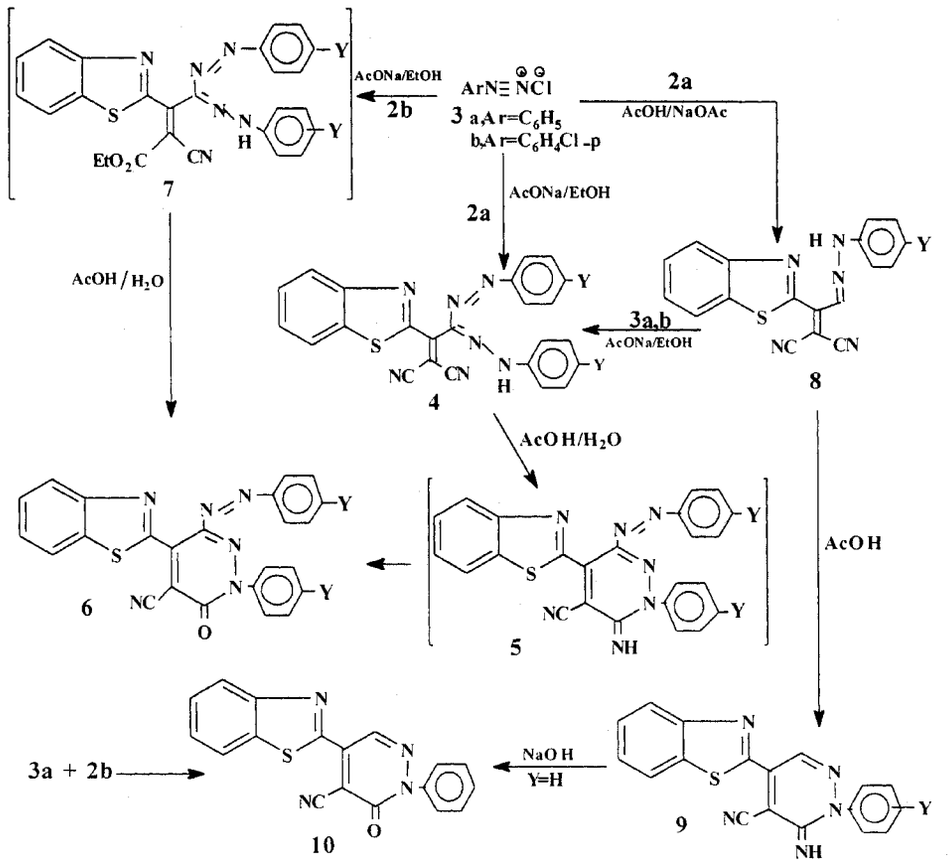


The coupling products were found to be dependent on the different applied coupling reaction conditions. Acetic acid-sodium acetate and ethanolic sodium acetate were selected as media that fulfil requirements. The first medium affords weak basic conditions while the second allows more basic conditions. Thus, coupling of **2a** with areneiazonium salts **3a,b** in an ethanolic sodium acetate solution yields the corresponding coupling product (structures **4**, **5** and **6**). The pyridazine structure **5** and **6** were readily ruled out based on the ^{13}C NMR which revealed signals for two cyano groups at δ 114.6 and 119.8 and ^1H NMR which displayed D_2O-exchangeable broad singlet signals around δ_H 9.72-9.41 due to the NH proton. The absence of any CH signals in the ^1H NMR spectra of compounds **4a,b** excludes the presence of the azo tautomers and indicates that they exist almost entirely in the hydrazone form. Also, the structure of the hydrazones **4a** and **4b** were established based on recovering changed on refluxing under conditions reported to effect cyclization of arylhydrazononitriles of similar structures.[16] Pyridazines **6a,b** are assumed to be formed via the non-isolable intermediate pyridazinimins **5a,b** which undergo spontaneous hydrolysis of C=NH into C=O under the reaction conditions to give the final products **6a,b**. Attempted isolation of the imines **5a,b** were unsuccessful.

The proposed structures **6a,b** were supported by their independent synthesis from coupling of **2b** with arenediazonium salts **3a,b** under the same conditions. Also the formation of **6a,b** was assumed to be formed via the non-isolable hydrazones **7a,b** which undergo intramolecular cyclization via ethanol elimination on refluxing in acetic acid to give the final products **6a,b** (Scheme II).

In contrast to the behaviour of **2a** towards arenediazonium salts in an ethanolic sodium acetate solution, **2a** coupled with arenediazonium salts in acetic acid-sodium acetate afforded the hydrazone **8** which yielded the pyridazinimine **9** on refluxing in acetic acid. The exocyclic imino group present in **9** is converted into C=O function by boiling in an ethanolic sodium hydroxide solution to afford the pyridazinone **10**. The hydrazone **8** could be converted into **4a,b** on coupling with

Scheme II



arenediazonium salts in an ethanolic sodium acetate solution.

The reactivity of the methyl group in **2a** towards arenediazonium chloride finds a parallelism and contravention with the earlier report[17] on the reactivity of the methyl function towards the same reagents.

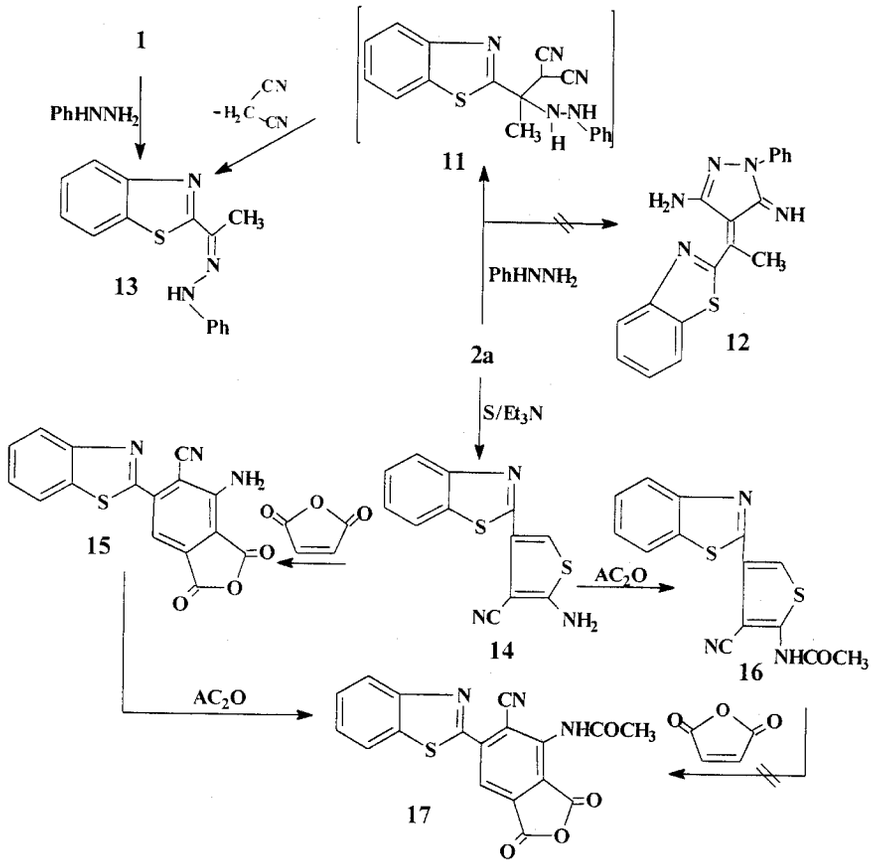
Treatment of 2-(2,2-dicyano-1-methylvinyl)benzothiazole (**2a**) with phenylhydrazine in boiling ethanol furnished one isolable product for which structures **11**, **12** and **13** seemed possible (Scheme III). The IR spectra of the isolated product showed a lack of CN absorption bands and the presence of NH absorption band between 3280 and 3430 cm^{-1}. The ^1H NMR spectra revealed a broad singlet signal (D_2O-exchangeable) near δ_H 9.4 ppm due to the NH proton. These findings provide firm support for structure **13** and exclude the anticipated pyrazoline derivative **12**.[18] The structure for **13** was supported by its independent synthesis from refluxing of 2-acetyltbenzothiazole with phenylhydrazine in boiling ethanol.

2-(2,2-Dicyano-1-methylvinyl)benzothiazole (**2a**) readily reacts with elemental sulphur to yield the thiophene derivative **14**. Evidence for the structure **14** is provided by spectral data. The formation of **14** from reaction of **2a** with elemental sulphur is an application of reported earlier.[19] Interaction of **14** with maleic anhydride afforded benzofuran derivatives **15**. The formation of **15** is assumed to proceed via an intermediate [4+2] cycloadduct which is aromatised by liberation of hydrogen sulphide to yield the isolable final product **15**. Acetylation of **15** afforded **17**.

Acetylation of **14** afforded the corresponding acylated compound **16**. The IR of **16** showed absorption bands in the region 2220 cm^{-1} and 1680 cm^{-1} due to cyano and carbonyl groups, respectively. Compound **16** does not react with dienophiles under conditions utilised to effect facile addition to the amino derivatives **14**. Acylation of the amino function reduces its electron donating mesomeric effects, and thus the double bond system becomes inert as a diene.

Reactions of nucleophiles with α,β-unsaturated nitriles take place at the β-carbon. Thus, it has been found that **2a** reacts with 2-cyano-3-arylpropenenitrile derivatives **18a-c** in ethanol containing a catalytic amount of triethylamine to yield 2-(3-amino-2,4-dicyano-5-arylphenyl)benzothiazoles **21a-c** (Scheme III). The formation of **21a-c** are assumed to proceed

Scheme III



via addition C-1 of the nucleophile **2a** to the β-carbon atom in **18a-c** forming the Michael adduct **19** with subsequent cyclization, yielding **20**. The latter undergoes aromatization via the loss of hydrogen cyanid to the isolable product **21a-c**. In contrast to the anticipated enaminoesters **24d-f**, the reaction of **2a** with **18d-f** afforded **21a-c**, presumably via elimination of ethyl formate from the intermediate **23** (Scheme IV).

EXPERIMENTAL

Mps are uncorrected. IR spectra were measured as KBr pellets on a Pye-Unicam SP 1000 spectrophotometer. ^{1}H NMR spectra were recorded in deuterated dimethylsulfoxide or deuterated chloroform at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. ^{13}C NMR spectra were measured in DMSO [d6] on a Bruker spectrometer 300 MHz and chemical shifts are expressed as δ. Mass spectra were obtained on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 2-Acetylbenzothiazole[20] (**1**), 2-(2-ethoxycarbonyl-2-cyano-1-methylvinyl)benzothiazole[14] (**2b**) and the arenediazonium salts (**3a,b**) were prepared as described in the literature.[21]

2-(2,2-Dicyano-1-methylvinyl)benzothiazole (2a)

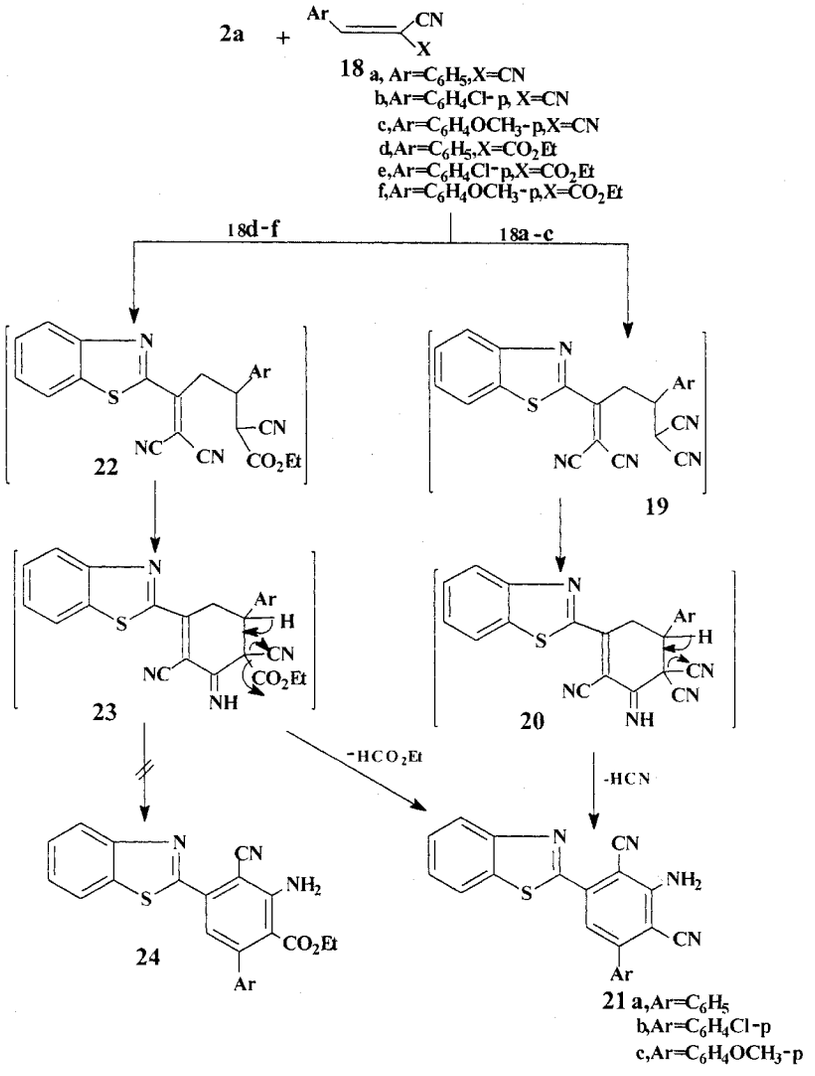
To a solution of 2-acetylbenzothiazole (**1**) (17.7 g, 0.1 mol) in dry benzene (100 mL) was added malononitrile (6.66 g, 0.1 mol), ammonium acetate (2 g) and acetic acid (5 mL). The reaction mixture was heated under reflux using a Dean-Stark water separator until water ceased to be collected. The solid product obtained was crystallized from ethanol to give **2a** (82% yield), mp 175 °C; IR (KBr, cm^{-1}) 2985 (CH_3), 2220, 2200 (CN), 1640 (C=C), 1600 (C=N); ^{1}H NMR (DMSO, 200 MHz) δ 2.73 (3H, s), 7.1-8.23 (4H, m); *m/z* 225 (M^+) (Found: C, 63.92; H, 3.09; N, 18.58; S, 14.21. $C_{12}H_7N_3S$ requires C, 63.98; H, 3.13; N, 18.65; S, 14.23%).

3-Arylazo-3-arylhydrazono-2-(benzothiazol-2-yl)propene-1,1-dicarbonitrile (4a,b)

General procedure - Method A

To a cold solution of **2a** (2.25 g, 0.01 mol) in ethanol (30 mL) containing sodium acetate (5 g) was added the appropriate arenediazonium salt solution **3a,b** (0.02 mol) portionwise over 30 minutes with constant stirring. After complete addi-

Scheme IV



tion, the reaction mixture was stirred for a further 3 h at 0-5 °C and then left to stand in an ice box for 12 h, then diluted with water. The formed solid was collected by filtration, washed with water, dried and finally recrystallized from ethanol to afford the corresponding **4a,b** in 64-68% yield, **4a** (64% yield), brown crystals, mp 145 °C; IR (KBr, cm^{-1}) 3240 (NH), 2220, 2200 (CN), 1595 (C=N); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.41 (1H, br), 7.21-8.22 (14H, m); *m/z* 433 (M^+); ^{13}C NMR (DMSO, 300 MHz) δ 93.2 (C-l), 139.1 (C-2), 152.8 (C-3), 129-131 (aromatic carbons), 114.6, 119.8 (2CN), 158 (benzothiazole C-2), 122-126 (benzothiazole C4-7), 133.2 (benzothiazole C-8), 154.6 (benzothiazole C-9) (Found: C, 66.34; H, 3.52; N, 22.56; S, 7.31. $C_{24}H_{15}N_7S$ requires C, 66.49; H, 3.49; N, 22.62; S, 7.39%). **4b** (68% yield), brown crystals, mp > 300 °C; IR (KBr, cm^{-1}) 3280 (NH), 2222, 2195 (CN), 1599 (C=N); ^1H NMR (DMSO, 200 MHz) δ 9.72 (1H, br), 7.22-8.28 (12H, m); *m/z* 502 (M^+) (Found: C, 57.34; H, 2.52; N, 19.56; S, 6.31; Cl, 14.23. $C_{24}H_{13}N_7SCl_2$ requires C, 57.38; H, 2.61; N, 19.52; S, 6.38; Cl, 14.11%).

Method B

To a cold solution of **8a,b** (10 mmol) in ethanol (30 mL) containing sodium acetate (5 g) was added the appropriate arenediazonium salt solution **3a,b** (10 mmol) portionwise over 30 minutes with constant stirring. After complete addition, the reaction mixture was stirred for a further 3 h at 0-5 °C and then left to stand in an ice box for 12 h, then diluted with water. The formed solid was collected by filtration, washed with water, dried and finally recrystallized from ethanol to afford a product identical in all respects (mp, mixed mp and spectra) with compounds **4a,b** prepared by method A.

1-Aryl-3-arylazo-4-(benzothiazol-2-yl)-6-oxo-1,6-dihydropyridazin-5-carbonitrile (6a,b)

General procedure - Method A

A solution of either **4a** or **4b** (0.01 mol) in aqueous acetic acid (30 mL; 70%) was refluxed for 4 h and then left to cool. The solid products so formed were collected by filtration and crystallized from DMF to afford the corresponding **6a,b** in 60-63% yield. **6a** (60% yield), brown crystals, mp 255 °C; IR (KBr, cm^{-1}) 2220 (CN), 1690 (C=O), 1650 (C=N); ^1H NMR (DMSO, 200 MHz) δ 7.14-8.13 (14H, m); *m/z* 434 (M^+) (Found: C, 66.32; H, 3.32; N, 19.56; S, 7.31. $C_{24}H_{14}N_6SO$ requires C, 66.35; H, 3.25; N, 19.34; S, 7.38%). **6b** (63% yield), brown crystals, mp 285 °C; IR (KBr, cm^{-1}) 2215 (CN), 1695 (C=O), 1640 (C=N); ^1H NMR (DMSO, 200 MHz) δ 7.12-8.36 (12H, m); *m/z* 503 (M^+) (Found: C, 57.31; H, 2.50; N, 16.56; S, 6.31; Cl, 14.13. $C_{24}H_{12}N_6SOCl_2$ requires C, 57.27; H, 2.40; N, 16.69; S, 6.37; Cl, 14.09%).

Method B

The appropriate heterocyclic diazonium salt **3a,b** (20 mmol) was added portionwise with stirring to a cold solution (0-5 °C) of the corresponding **2b** (10 mmol) in ethanol (50 mL) in the presence of sodium acetate (5 g) over a period of 30 minutes. The reaction mixture was stirred for a further 2 h at 0-10 °C then kept in an ice box for 12 h. The precipitated products formed were refluxed in acetic acid (25 mL) for 30 min. and the reaction mixture was collected by filtration and crystallized from DMF to afford products identical (TLC, mp, mixed mp and spectra) with compounds **6a,b**, respectively.

3-Arylhydrazono-2-(benzothiazol-2-yl)propene-1,1-dicarbonitrile (8a,b)

General procedure

The same experimental procedure described for the synthesis of **4a,b** was adopted except for the use of acetic acid instead of ethanol. **8a** (62% yield), brown crystals, mp 220 °C; IR (KBr, cm^{-1}) 3335 (NH), 2225, 2210 (CN), 1635 (C=N); ^1H NMR (DMSO, 200 MHz) δ 9.32 (1H, br), 6.73 (1H, s), 7.21-8.33 (9H, m); *m/z* 329 (M^+) (Found: C, 65.54; H, 3.57; N, 21.46; S, 9.63. $C_{18}H_{11}N_5S$ requires C, 65.64; H, 3.37; N, 21.26; S, 9.73%). **8b** (66% yield), brown crystals, mp 195 °C; IR (KBr, cm^{-1}) 3210 (NH), 2220, 2210 (CN), 1650 (C=N); ^1H NMR (DMSO, 200 MHz) δ 9.41 (1H, br), 6.63 (1H, s), 7.12-8.19 (8H, m); *m/z* 363 (M^+) (Found: C, 59.64; H, 2.45; N, 19.49; S, 8.61; Cl, 9.59. $C_{18}H_{10}N_5SCl$ requires C, 59.42; H, 2.77; N, 19.25; S, 8.81; Cl, 9.74%).

1-Aryl-4-(benzothiazol-2-yl)-6-imino-1,6-dihydropyridazin-5-carbonitrile (9a,b)

Method A

A solution of either **8a,b** (1 mmol) in acetic acid (20 mL) was heated under reflux for 2-4 h then left to cool, then diluted with water (20 mL). The separated solid was collected by filtration, washed with water and dried. Crystallization from DMF afforded **9a,b**, respectively. **9a** (53% yield), brown crystals, mp 175 °C; IR (KBr, cm^{-1}) 3280-3320 (NH), 2220 (CN), 1670 (C=N); ^1H NMR (DMSO, 200 MHz) δ 7.32-8.18 (10H, m); 10.2 (1H, br); *m/z* 329 (M^+) (Found: C, 65.32; H, 3.32; N, 21.46; S, 9.31. $C_{18}H_{11}N_5S$ requires C, 65.64; H, 3.37; N, 21.26; S, 9.73%). **9b** (56% yield), brown crystals, mp 160 °C, IR (KBr, cm^{-1}) 3280 (NH), 2225 (CN), 1665 (C=N); ^1H NMR (DMSO, 200 MHz) δ 7.12-8.31 (9H, m) 10.41 (1H, br); *m/z* 363 (M^+) (Found: C, 59.31; H, 2.57; N, 19.26; S, 8.71; Cl, 9.74. $C_{18}H_{10}N_5SCl$ requires C, 59.42; H, 2.77; N, 19.25; S, 8.81; Cl, 9.74%).

Method B

Compound **8a,b** (10 mmol) was heated at 220 °C (bath temperature) for 15 min., then left to cool to room temperature. The products so formed were triturated with methanol, collected by filtration and crystallized from DMF afforded products identical (TLC, mp, mixed mp and spectra) with compound **9a,b**.

1-Phenyl-4-(benzothiazol-2-yl)-6-oxo-1,6-dihydropyridazin-5-carbonitrile (10)

Method A

A solution of **9a** (3.29 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (2 mL, 0.01 mol) was heated under reflux for 4 h. The solid product formed upon dilution with water containing a few drops of hydrochloric acid was collected by filtration; crystallization from dioxane afforded the pyridazinone **10** in 68% yield, brown crystals, mp 210 °C; IR (KBr, cm^{-1}) 2220 (CN), 1690 (C=O); ^1H NMR (DMSO, 200 MHz) δ 7.12-8.26 (10H, m); *m/z* 330 (M^+) (Found: C, 65.32; H, 3.12; N, 16.84; S, 9.63. $C_{18}H_{10}N_4OS$ requires C, 65.44; H, 3.05; N, 16.96; S, 9.7%).

Method B

The same experimental procedure described for the synthesis **6a,b** was adopted except for the use of acetic acid instead of ethanol.

2-[1-(phenylhydrazonoethyl)]benzothiazole (13)

A mixture of **1** or **2a** (0.01 mol) and phenylhydrazine (0.012 mol) in ethanol (30 mL) was refluxed for 3 h and then cooled. The solid that precipitated was filtered off, washed with ether and dried. Recrystallization from ethanol afforded **13** in 69% yield, brown crystals, mp 140-142 °C; IR (KBr, cm^{-1}) 3280-3340 (NH), 1650 (C=N); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.46 (3H, s), 7.32 -8.46, (9H, m), 9.43 (D_2O-exchangeable, 1H, br); *m/z* 267 (M^+); (Found: C, 67.32; H, 4.52; N, 15.46; S, 11.93. $C_{15}H_{13}N_38$ requires C, 67.39; H,

4.90; N, 15.72; S, 11.99%).

2-Amino-4-benzothiazol-2-yl-3-cyanothiophene (14)

To a solution of **2a** (2.25 g, 0.01 mol) in ethanol (30 mL), elemental sulphur (0.3 g, 0.01 mol) and a catalytic amount of triethylamine were added. The reaction mixture was heated at reflux for 4 h. The solid product formed on dilution with water, was collected by filtration, crystallized from dioxane afforded **14** in 62% yield, brown crystals, mp 160 °C; IR (KBr, cm^{-1}) 3410, 3310 (NH_2), 2210 (CN), 1630 (C=C); ^{1}H NMR (DMSO, 200 MHz) δ 7.1-8.56 (7H, m); *m/z* 257 (M^+); (Found: C, 56.12; H, 2.52; N, 15.96; S, 24.87. $C_{12}H_7N_3S_2$ requires C, 56.01; H, 2.74; N, 16.33; S, 24.92%).

3-Amino-5-(benzothiazol-2-yl)-4-cyanophathalic anhydride (15)

Equimolar amounts of **14** (2.57 g, 0.01 mol) and maleic anhydride (1 g, 0.01 mol) were heated at (bath temperature) for 1 h. The resulting solid product was washed several times with water and crystallized from DMF afforded **15** in 45% yield, brown crystals, mp 185 °C; (KBr, cm^{-1}) 3400, 3320 (NH_2), 2210 (CN), 1780, 1765 (CO), 1635 (C=N), 1601 (C=C); ^{1}H NMR (DMSO, 200 MHz) δ 5.96 (D_2O-exchangeable, 2H, br), 7.32-8.61 (5H, m); *m/z* 321 (M^+); (Found: C, 59.72; H, 2.25; N, 13.20; S, 9.57. $C_{16}H_7N_3SO_3$ requires C, 59.81; H, 2.19; N, 13.08; S, 9.98%).

2-Acetamido-3-(benzothiazol-2-yl)-3-cyanothiophene (16)

A solution of **14** (2.57 g, 0.01 mol) in acetic anhydride (20 mL) was heated at reflux for 2 h. The solid product was collected by filtration and recrystallized from DMF to afford **16** in 56% yield, brown crystals, mp 275 °C; (KBr, cm^{-1}) 3460-3290 (OH and NH), 2225 (CN), 1680 (CO), 1650 (C=N); ^{1}H NMR (DMSO, 200 MHz) δ 3.58 (3H, s), 7.14-8.53 (5H, m), 9.65 (1H, br); *m/z* 299 (M^+); (Found: C, 56.22; H, 3.12; N, 14.16; S, 21.57. $C_{14}H_9N_3S_2O$ requires C, 56.17; H, 3.03; N, 14.04; S, 21.42%).

3-Acetamido-5-(benzothiazol-2-yl)-4-cyanophathalic anhydride (17)

The same experimental procedure described for the synthesis **16** was adopted except for the use of **15** instead of **14**. **17** in 45% yield, brown crystals, mp > 300 °C; (KBr, cm^{-1}) 3320-3350 (NH), 2220 (CN), 1830, 1710 (CO), 1640 (C=N); ^{1}H NMR spectra were not obtained for this product owing to low solubility in the common NMR solvents; *m/z* 363 (M^+) (Found: C, 59.58; H, 2.39; N, 11.52; S, 8.77. $C_{18}H_9N_3SO_4$ requires C, 59.5; H, 2.49; N, 11.56; S, 8.82%).

Reaction of 2a with cinnamonitrile derivatives (18a-f)

To a solution of **2a** (2.25 g, 0.01 mol) in ethanol (30 mL), benzylidenemalononitrile derivatives (0.01 mol) and a catalytic amount of triethylamine were added. The reaction mixture was heated at reflux for 3-5 h (TLC control). The precipitate formed on cooling was collected by filtration. Recrystallization from ethanol afforded **21a-c** in (62-65%) yield, **21a** (62% yield), brown crystals, mp 200 °C; (KBr, cm^{-1}) 3430, 3320 (NH_2), 2230, 2220 (CN), 1640 (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.56 (D_2O-exchangeable, 2H, br), 7.15-8.63 (9H, m) (Found: C, 71.57; H, 3.43; N, 15.89; S, 9.12. $C_{21}H_{12}N_4S$ requires C, 71.57; H, 3.43; N, 15.89; S, 9.09%). **21b** (65% yield), brown crystals, mp 135 °C; (KBr, cm^{-1}) 3450, 3320 (NH_2), 2225, 2220 (CN), 1640 (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.56 (D_2O-exchangeable, 2H, br), 7.15-8.63 (9H, m) (Found: C, 65.27; H, 2.86; N, 14.38; S, 8.15; Cl, 9.36. $C_{21}H_{11}N_4SCl$ requires C, 65.20; H, 2.87; N, 14.48; S, 8.28; Cl, 9.19%). **21c** (64% yield), brown crystals, mp 225 °C, ν_{max}/cm^{-1} (KBr) 3430, 3350 (NH_2), 2235, 2220 (CN), 1650 (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.48 (3H, s), 5.62 (D_2O-exchangeable, 2H, br), 7.16-8.81 (9H, m) (Found: C, 69.31; H, 3.58; N, 14. 59; S, 8.29. $C_{22}H_{14}N_4OS$ requires C, 69.19; H, 3.69; N, 14.67; S, 8.39%).

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Key Words

2-Acetylbenzothiazole; Areneiazonium salts; Cinnamonitriles.

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