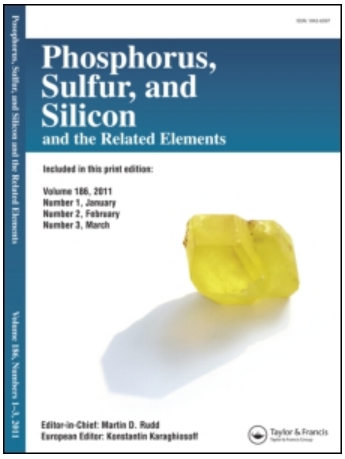

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Nitriles in Organic Synthesis: Synthesis of Some New 2-Heterocyclic Benzothiazole Derivatives

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Nitriles in Organic Synthesis: Synthesis of Some New 2-Heterocyclic Benzothiazole Derivatives

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*2-Cyanomethylbenzothiazole (**1**) was utilized for the synthesis of several new 2-heteryl benzothiazole derivatives as pyrazolyl, thienyl, pyridyl, benzoimidazolyl, and benzothiazolyl derivatives.*

Keywords 2-cyanomethylbenzothiazole; benzothiazole; pyrazole

INTRODUCTION

In recent times there have been broad developments in investigations of both the synthesis and the study of the chemical properties of benzothiazole derivatives which have valuable pharmacological activity.[1–3] Several lines of evidence support the hypothesis that 2-cyanomethylbenzothiazole (**1**) has resulted in much interest in their synthesis and chemistry. For the past decade, we have been exploring the synthetic potential, scope, and limitations of activated nitriles in heterocyclic synthesis.[4–6] Several new approaches for the synthesis of five members, six members and their fused heterocyclic derivatives have been developed during the work for this article.

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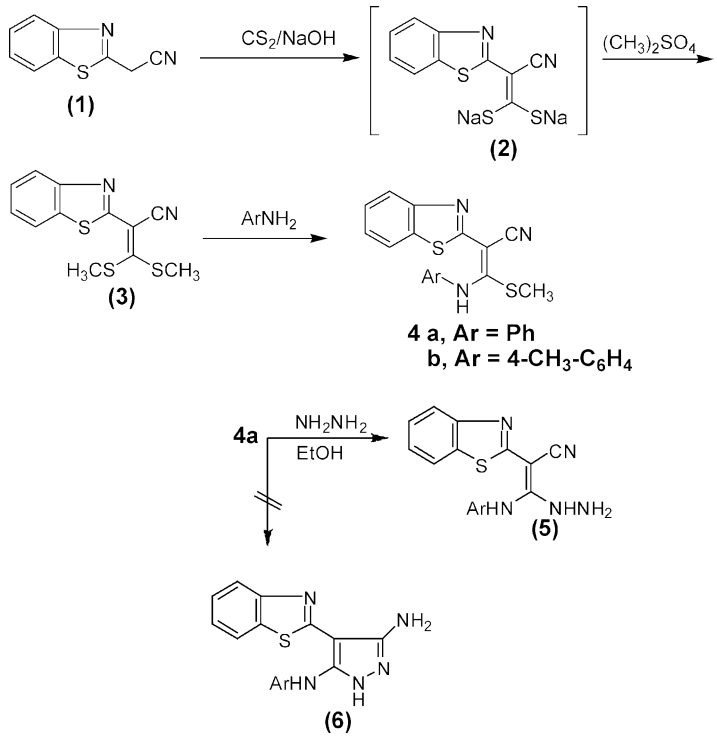
RESULTS AND DISCUSSION

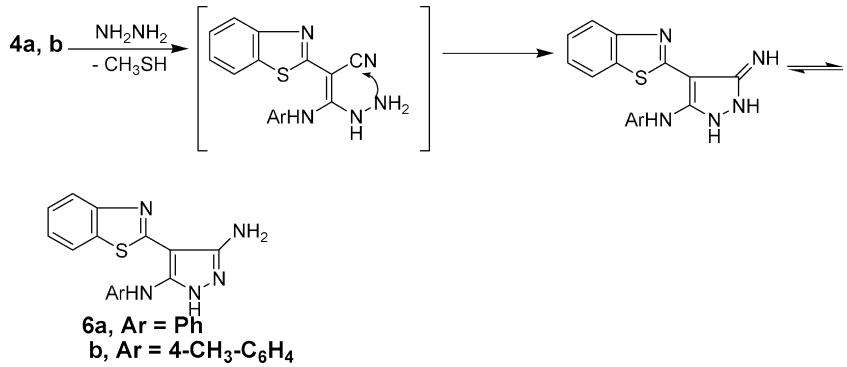
As an extension of this work, and in continuation of our interest in the synthesis of new heterocycles incorporating a benzothiazole nucleus, we report here the behavior of **1** towards some reactive bifunctional reagents as a facile and convenient route to some heterocyclic derivatives containing a benzothiazole moiety.

As a part of this investigation, the reactions of α-, β-unsaturated nitriles (**4a**,**b**)[6] and certain activated bifunctional reagents have been investigated. The resulting benzothiazole derivatives have latent functional substituents, which have potential for further chemical transformations and new routes for the preparation of substituted benzothiazole derivatives in excellent yields with possible biological activity.

Thus, it has been found that **4a** with hydrazine hydrate in boiling ethanol afforded β-hydrazino-β-arylamino-α-2-benzothiazolylacrylonitrile (**5**)—not the expected aminopyrazole derivative (**6**) (Scheme 1).



SCHEME 1



SCHEME 2

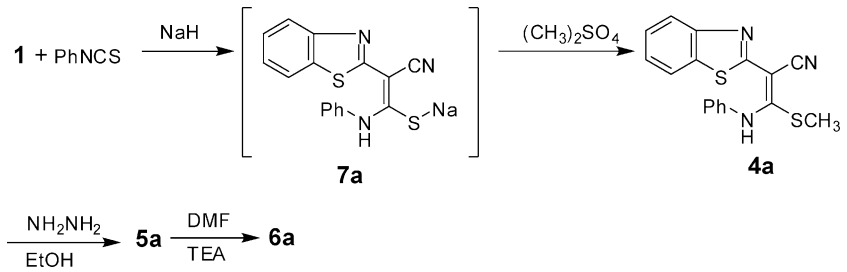
Structure **5** was proved by IR spectrum which revealed stretching frequencies of CN at 2216 cm,$^{-1}$ NH_2 at 3418, 3581 cm^{-1}, and 3347 cm^{-1} due to NH. The ^{1}H NMR (DMSO-d_6) for compound **5** showed multiplet bands at δ 6.9–8.1 ppm for (aromatic protons) and broad band at δ 9.0–9.5 ppm (-$NHNH_2$ and NH). On the other hand, treatment of the key intermediate 4a,b with hydrazine hydrate in DMF gave a single product, which analyzed correctly for $C_{16}H_{13}N_5S$ (**6a**) and $C_{17}H_{15}N_5S$ (**6b**) (Scheme 2).

The structure of **6** was inferred from its spectral data. Thus, the infrared spectrum of (**6b**) showed bands at 3189, 3229, and 3419 cm^{-1}, corresponding to the NH and NH_2 groups, respectively, and was avoid a band due to the cyano group. The ^{1}H NMR spectra revealed a singlet at δ 2.3, assigned for the methyl protons, a broad band located at δ 6.48, assignable to amino group, and a multiplet at δ 7.0–8.2, assigned for aromatic protons. The NH protons appeared at δ 10 and 12 ppm. The formation of **6a**,**b** is assumed to proceed via the replacement of the SCH_3 group by the hydrazine moiety to give the intermediates **5a**,**b**, which then cyclized via the cyano group to afford the final isolable products **6a**,**b**.

In fact, the structures of **6a**,**b** were further confirmed by alternative synthesis. Thus, it has been found that, treatment of **7a** with hydrazine hydrate in boiling ethanol for a long period of time produced the intermediate **5a**. Refluxing **5a** in DMF led to the formation of a product identical in all respects (m.p., mixed m.p., and IR, ^{1}H NMR) with **6a** (Scheme 3).

Moreover, structure **6a** was also proved by mass spectroscopy which gave the fragments m/z 307, 291, 261, 199, 173, 108.

The aminopyrazole derivative **9** was prepared by reaction of **3** with hydrazine hydrate in DMF/TEA to yield the intermediate **8**, which



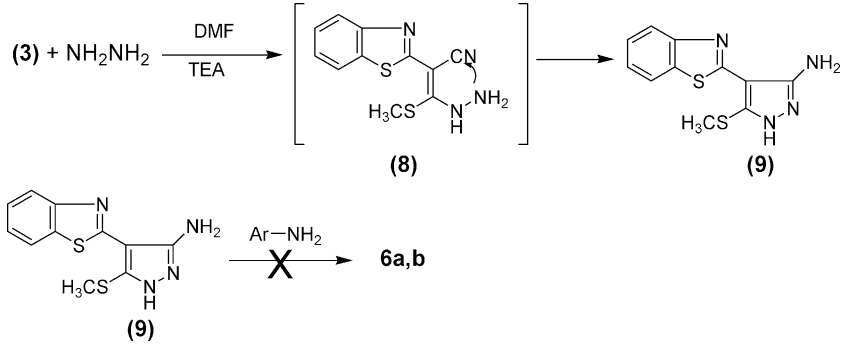
SCHEME 3

undergoes intramolecular nucleophilic cycloaddition reaction affording compound **9**.

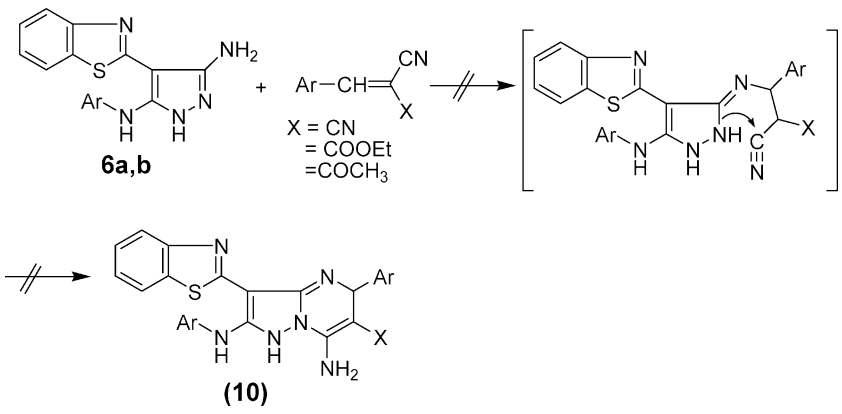
All attempts to prepare 3-amino-5-arylamino-4-[2-benzothiazolyl]-pyrrazole (**6a**,**b**) by reaction of 3-amino-5-methylthio-4-[2-benzot hazolyl]-pyrazole (**9**) with the appropriate aryl amines in DMF/TEA, EtOH/TEA or fusion failed (Scheme 4).

The structure of (**9**) was established by IR spectrum, which showed no absorption bands in the region 2150–2300 cm,$^{-1}$ indicating the absence of cyano group which involved in the cyclization process, in addition to the presence of 3396, 3338 cm^{-1} (NH_2), 3296 cm^{-1} (NH), 1623 cm^{-1} (C=N), and 1601 cm^{-1} (C=C). The ^{1}H NMR (DMSO-d_6) spectrum of this product showed singlet signal at δ 2.7 (CH_3S-), multiplet signal for aromatic protons, and two amino protons at δ 7.3 - 8.1 and singlet signal at δ 8.25 ppm due to (NH) proton. The mass spectrum of structure (**9**) showed m/z 262 (M^+, 100%), 261, 247, 246, 216, 215, 200, 199, 174, 108, 107.

All attempts to use the amino-imino tautomeric character in **6a**,**b** in the synthesis of pyrrazolo[2,3-a]pyrimidine derivatives by reaction



SCHEME 4

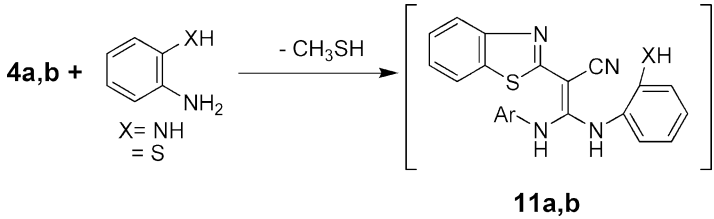


SCHEME 5

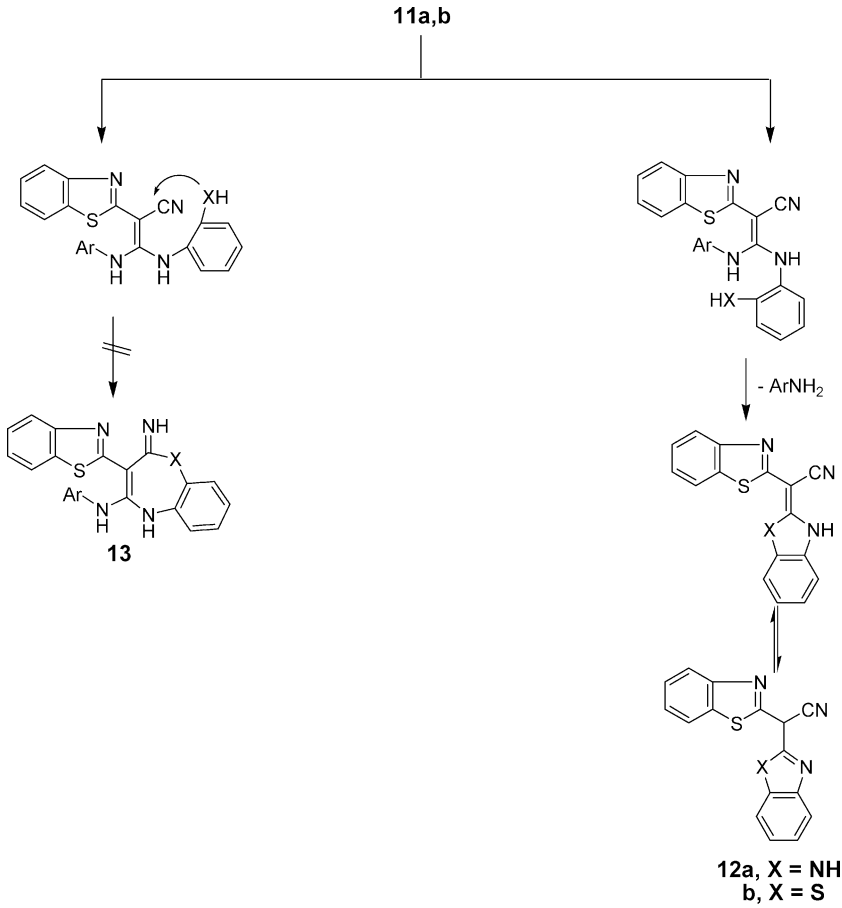
with arylidene of activated nitriles (e.g., arylidene of malonitrile, ethyl cyanoacetate, ... etc), in boiling ethanol and in presence of a base such as piperidine, triethylamine, sodium hydride or sodium ethoxide failed (Scheme 5).

Moreover, it has been found the adduct (**4a**,**b**) behaved differently towards o-phenylenediamine and o-aminothiophenol when compared with their reaction with ethylenediamine and ethanolamine[5]. Thus, when (**4a**,**b**) reacted with o-phenylenediamine and/or o-aminothiophenol in DMF and in presence of triethylamine afforded the intermediate **11** (Scheme 6). The formation of **11** from **4** is assumed to proceed via replacement of the SCH_3 group with aromatic amines which then cyclized by loss of the aryl amine fragment affording the final product **12a**,**b** (Scheme 7).

The formation of α-[benzothiazole-2-yl]α-[2-benzimidazolyl] acetonitrile (**12a**) and α,α-di[2-benzothiazolyl]acetonitrile (**12b**), instead of the expected benzo[b]diazepine and benzo[b]oxazepine derivatives (**13a**,**b**) were confirmed by their IR spectra which showed for compound (**12a**,**b**) absorption band at 2188, 2198 cm^{-1} respectively, due to (C≡N) and this



SCHEME 6



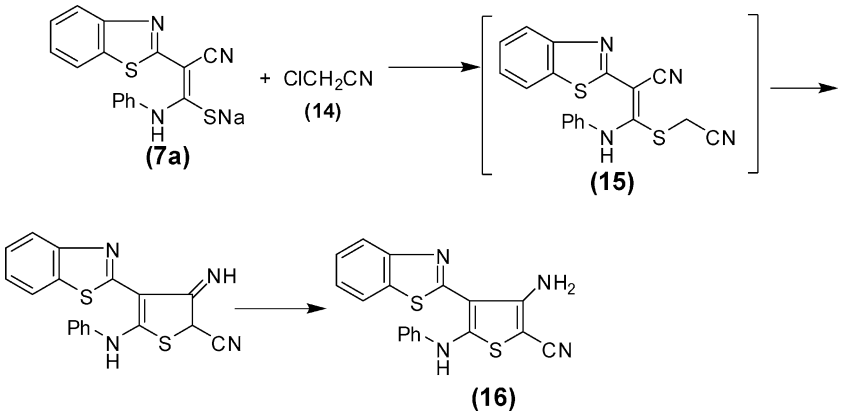
SCHEME 7

confirm that cyano group not involved in the cyclization, in addition compound **12a** showed band at 3153 cm^{-1} (NH) and no spectrum band for NH_2 group has been observed for both compounds **12a** and **12b**. Mass spectrum of **12a** showed m/e 290 (M^+, 100%), 289, 288, 262, 199, 182, 173.

Melting points and spectral data of compounds **12a**,**b**, were in agreement with that prepared by Augstin and Dolling.[7]

Continuing our interest in thiophene chemistry, and with a view directed towards preparing biological active heterocycles, we wish to broaden the scope of the Gewald reaction utilizing heterocyclic cyanomethylenes as candidates for facile synthetic route to heterocyclic thiophenes. The work resulted in the formation of some

new aminothiophene derivative. Thus, 3-amino-4-[2-benzothiazolyl]-2-cyano-5-phenylaminothiophene (**16**) was prepared by action of chloroacetonitrile on the sodium salt derivative **7a** to form the intermediate β-cyanomethylthio-β-phenylamino-α-2-benzothiazolyl acrylonitrile (**15**), which undergoes intramolecular cyclization by nucleophilic addition of active methylene group to the cyano group affording the amino-imino tautomeric form **(16)** (Scheme 8).

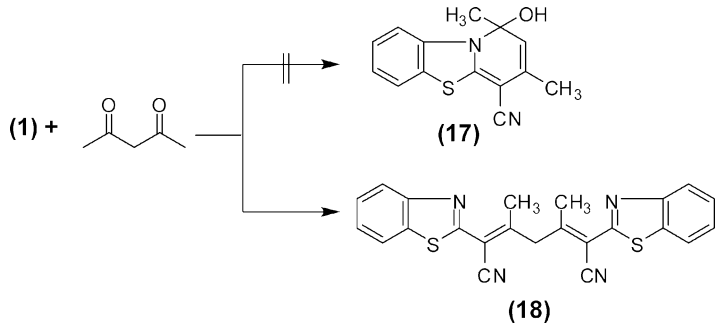


SCHEME 8

The structure of compound **16** was established by both elemental and spectral data. The IR spectrum showed absorption bands at 3399, 3328 cm^{-1} (NH_2 group), 3227 cm^{-1} (NH), 2180 cm^{-1} (CN), and 1637 cm^{-1} (—C=N). While its ^1H NMR (DMSO-d6) spectrum revealed multiplet band at δ 6.9–8.0 ppm due to nine aromatic protons and NH_2, a singlet signal at δ11.6 ppm (NH).The NH_2 and NH protons disappeared on the addition of few drops of deuterium oxide. The mass spectrum showed m/z 348 (M^+ base peak 100%), 347, 320, 315, 288, 245, 238, 180, 174, 135, 108, 77.

In attempts to prepare pyridobenzothiazole through the reaction of **1** with β-diketone as reported with benzimidazolylacetonitrile by Chuiguk and Volovenko[8] and Kuz'menho et al.,[9] the reaction of **1** with acetyl acetone yielded the unexpected single product (as examined by TLC) which analyzed correctly for $C_{23}H_{16}N_4S_2$ and its mass spectrum exhibited a molecular ion peak at m/e 412 (M^+ 20%). These data indicated that one mole of acetylacetone was condensed with two moles of **1** to give **18**. This product was formulated as 1,5-di[benzothiazol-2-yl]-1,5-dicyano-2,4-dimethyl-1,4-pentadiene **(18)** (Scheme 9).

The structure of **18** was confirmed on the basis of elemental analysis, IR, and mass spectrum. Its IR spectrum showed the complete



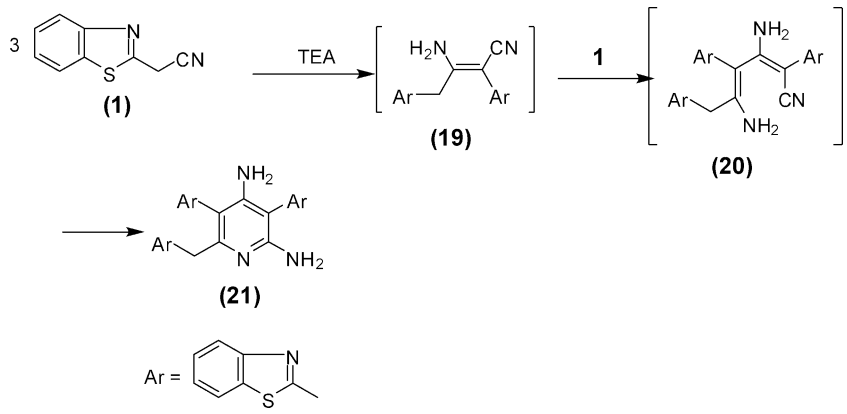
SCHEME 9

disappearance of CO band (or its enolic band) already present in the parent compound (acetyl acetone), also the IR spectrum showed band at 2192 cm^{-1} due to CN group. Moreover, its mass spectrum showed a molecular ion peak at m/e 412 (M^+ 20%), in addition to the following fragments 397, 359, 213, 173 (100%) and 134.

Finally, we found that heating 2-cyanomethylbenzothiazole (**1)** in absolute ethanol in presence of a few drops of TEA, a product of molecular formula $C_{27}H_{18}N_6S_3$ was obtained **21**. Structure **21** was proposed for the reaction product based on IR spectrum which revealed the presence of two amino stretching bands at 3450-3200 cm^{-1}, three C=N stretching bands at 1600-1630 cm^{-1}. A mass spectrum measurement gave an additional evidence for trimerization of **1** which showed $M^+ = 522$. In addition ^1H NMR showed singlet signal at δ 5.1 for methylene group, two broad bands at δ 6.1 and 6.7 (D_2O exchangeable) due to two NH_2 group and multiplet band at δ 7.0–8.2 for twelve aromatic protons. A logical mechanism for this reaction is based on first dimerization of **1** in the basic medium to give compound **19**, the latter in turn reacts with a third molecule of **1** to give **20** which spontaneously cyclized directly to afford 2,4-diamino-3,5-di(benzothiazol-2-yl)-6-[(benzothiazol-2-yl)-methyl]pyridine (**21)** (Scheme 10). Such pyridine formation finds parallels with the reported literature.[10]

EXPERIMENTAL

Melting points were uncorrected. Elemental analysis was carried out in the Microanalytical Unit Faculty of Science, Cairo University. IR spectra were recorded on Pye Unicam SP-1000cm^{-1} spectrometer using KBr wafer technique. ^1H NMR spectra were determined on Varian Gemini 200 MHz NMR spectrometers using TMS as an internal standard with



SCHEME 10

(δ = 0 ppm). Mass spectra were determined on GC-MS.QP-100 EX. Schimadzye (Japan).

Synthesis of β-Hydrazino-β-phenylamino-α-2-benzothiazolylacrylo-nitrile (5)

A mixture of **4a** (1.615 g, 0.005 mol) and hydrazine hydrate (0.25 ml, 0.005 mol) in 20 ml of absolute ethanol was refluxed until the evolution of methyl thiol was ceased (2–3 h). The reaction mixture was concentrated to its half volume and left to cool at room temperature and the resulting material recrystallized from ethanol to give (**5**).

Compound 5. white crystals; yield (65%); m.p. 197°C; IR(cm^{-1}) (KBr) at 2216 (CN), 3418, 3581 (NH_2), and 3347 (NH); ^{1}H NMR: (DMSO-d_6): δ = 6.9–8.1 (m, 9H, aromatic protons) and 9.0–9.5 (m (br), 4H, $NHNH_2$ and NH); MS: m/z 307 (M^+); Anal. calcd. For $C_{16}H_{13}N_5S$: C, 62.52; H, 4.26; N, 22.78; S, 10.43. Found: C, 62.34; H, 4.30; N, 22.76; S, 10.39.

Synthesis of 3-Amino-5-arylamino-4-[2-benzothiazolyl]-pyrazole (6a,b)—

Method A

A mixture of **4a**,**b** (0.01 mol) and hydrazine hydrate (0.01 mol) in dimethylformamide was refluxed for 8 h. The reaction mixture was cooled to room temperature and then poured onto ice cold water (100 ml). The precipitated solid material was filtered off, dried well, and

recrystallized from dimethylformamide-ethanol mixture (1:3) to give (**6a**,**b**).

Method B

A solution of **5** (0.01 mol) in dimethylformamide (20 ml) containing a catalytic amount of triethylamine (4 drops) was refluxed for 4 h and then cooled to room temperature. The reaction mixture was poured onto ice cold water (100 ml). The precipitated solid material was filtered off, dried well, and recrystallized from dimethylformamide-ethanol (1:3) to give(**6a**,**b**)

Compound 6a. white crystals; yield (74%); m.p. > 300°C; IR(cm^{-1}) (KBr) 3217 (NH), 3325, 3465 (NH_2); ^1H NMR: (DMSO-d_6): $\delta = 6.2$ (broad, 2H, NH_2), 7.0–7.9 (m, 10H, aromatic protons and NH), and 8.9(s, 1H, NH) ; MS 307(M^+); Anal. calcd. For $C_{16}H_{13}N_5S$: C, 62.52; H, 4.26; N, 22.78; S, 10.43. Found: C, 62.54; H, 4.19; N, 22.57; S, 10.42.

Compound 6b. Page crystals; yield (71%); m.p. > 300°C; IR(cm^{-1}) (KBr) 3189 (NH), 3229, 3419 (NH_2); ^1H NMR: (DMSO-d_6): $\delta = 2.3$ (s, 3H, CH_3), 6.48 (broad, 2H, NH_2), 7.0–8.2 (m, 8H, aromatic protons), 10.0 (s, 1H, NH), 12.0(s, 1H, NH); MS 321(M^+); Anal. calcd. For $C_{17}H_{15}N_5S$: C, 63.53; H, 4.70; N, 21.79; S, 9.98. Found: C, 63.49; H, 4.69; N, 21.82; S, 9.97.

Synthesis of 3-Amino-5-methylthio-4-[2-benzothiazolyl]-pyrazole (9)

To a solution of (**3**) (0.01 mol) in dimethylformamide (20 ml) was added hydrazine hydrate (0.32 ml, 0.01 mol). The reaction mixture was refluxed for six h, then left to cool at room temperature. The reaction mixture was then poured onto ice cold water (100 ml). The precipitated solid material was filtered off, dried well, and recrystallized from ethanol to give (**9**).

Compound 9. Yellow crystals; yield (62%); m.p. 190°C; IR(cm^{-1}) (KBr) 1623 (C=N), 3296 (NH), 3338, 3396 (NH_2); ^1H NMR: (DMSO-d_6): $\delta = 2.7$(s, 3H, SCH_3), 7.3-8.1 (m, 6H, aromatic protons and NH_2), and 8.25(s, 1H, NH); MS 262 (M^+); Anal. calcd. For $C_{11}H_{10}N_4S_2$: C, 50.36; H, 3.84; N, 21.36; S, 24.44. Found: C, 50.31; H, 3.89; N, 21.40; S, 24.42.

Synthesis of α-[benzothiazole-2-yl]- α-[2-benzimidazolyl]-acetonitrile (12a) and di[benzothiazol-2-yl]acetonitrile (12b):

A mixture of (**4a**,**b**, 0.01 mol) and o-phenylenediamine or o-aminothiophenol (0.01 mol) in dimethylformamide (25 ml) was refluxed for 12 h. After cooling, the reaction mixture was poured onto ice cold water (100 ml). The resulting, solid product was collected by filtration, dried well, and recrystallized from dimethylformamide-ethanol (1:3) to obtain (**12a**,**b**).

Compound 12a. Yellow crystals; yield (81%); m.p. > 300°C; IR(cm^{-1}) (KBr) 2188(CN), 3153(NH); ^{1}H NMR: (DMSO-d_6): $\delta = 4.38$ (s, 1H, CH), 7.2–8.0 (m, 8H, aromatic protons), and 8.8(s, 1H, NH); MS 290 (M^+); Anal. calcd. For $C_{16}H_{10}N_4S$: C, 66.19; H, 3.47; N, 19.30; S, 11.04. Found: C, 66.12; H, 3.50; N, 19.26; S, 11.02.

Compound 12b. Yellow crystals; yield (65%); m.p. 290°C; IR(cm^{-1}) (KBr) 2198 (CN); ^{1}H NMR: (DMSO-d_6): $\delta = 4.40$ (s, 1H, CH), 7.2–8.0 (m, 8H, aromatic protons); MS 307 (M^+); Anal. calcd. For $C_{16}H_9N_3S_2$: C, 62.52; H, 2.95; N, 13.67; S, 20.86. Found: C, 62.50; H, 3.01; N, 13.65; S, 20.85.

Synthesis of 3-Amino-4-[2-benzothiazolyl]-2-cyano-5-phenylamino-thiophene (16)

To a well stirred solution of (**1**, 0.01 mol) in absolute ethanol (25 ml) containing sodium ethoxide (0.015 mol) was added phenyl isothiocyanate (1.2 ml, 0.01 mol). The reaction mixture was stirred for one hour at room temperature. To the above reaction mixture, chloroacetonitrile (0.01 mol) was added and refluxed for 8 h. The reaction mixture was poured onto ice cold water (100 ml) and acidified by 2N HCl. The precipitated product was collected by filtration, washed with water several times, and recrystallized from dimethylformamide-ethanol to obtain (**16**).

Compound 16. Yellow crystals; yield (89%); m.p. 196°C; IR(cm^{-1}) (KBr) 2180 (CN), 3227 (NH) and 3399, 3328 (NH_2); ^{1}H NMR: (DMSO-d_6): 6.9–8.0 (m, 11H, aromatic protons and NH_2) and 11.6(s, 1H, NH) ; MS 348 (M^+); Anal. calcd. For $C_{18}H_{12}N_4S_2$: C, 62.05; H, 3.47; N, 16.08; S, 18.40. Found: C, 62.04; H, 3.45; N, 16.10; S, 18.38.

Synthesis of 1,5-Di[benzothiazol-2-yl]-1,5-dicyano-2,4-dimethyl-1,3-pentadiene (18)

A mixture of (**1**, 0.01 mol) and acetyl acetone (0.01 mol) in dry dimethylformamide (20 ml) containing a catalytic amount of triethylamine

(3 drops) was heated under reflux for 6 h. The reaction mixture was poured onto ice cold water. The separated solid product was filtered off and recrystallized from dimethylformamide-ethanol (1:5) to give **(18)**.

Compound 18. Yellow crystals; yield (68%); m.p. 192°C; IR(cm^{-1}) (KBr) 2192 (CN); ^{1}H NMR: (DMSO-d_6): $\delta = 1.8$ (s, 6H, $2CH_3$), 2.7(s, 2H, CH_2), and 7.2–8.2 (m, 8H, aromatic protons); MS 412 (M^+); Anal. calcd. For $C_{23}H_{16}N_4S_2$: C, 66.96; H, 3.91; N, 13.58; S, 15.55. Found: C, 66.93; H, 3.94; N, 13.60; S, 15.54.

Synthesis of 2,4-Diamino-3,5-di[benzothiazol-2-yl]-6-[(benzothiazol-2-yl)methyl]pyridine (21)

2-Cyanomethylbenzothiazole (**1**) (0.01 mole) was dissolved in ethanol (20 ml), a few drops of triethylamine (4 drops) were added; then the solution was refluxed for 6 h. The solid product obtained after cooling was collected by filtration and recrystallized from ethanol-DMF (1:3) to give (**21**).

Compound 21. Yellow crystals; yield (68%); m.p. 226°C; IR(cm^{-1})(KBr) 3200–3450 (two NH_2).; ^{1}H NMR: (DMSO-d_6): $\delta =$ 5.1 (s, 2H, CH_2), 6.1(s, 2H, NH_2), 6.7(s, 2H, NH_2), and 7.0–8.2 (m, 12H, aromatic protons); MS 522 (M^+); Anal. calcd. For $C_{27}H_{18}N_6S_3$: C, 62.05; H, 3.47; N, 16.08; S, 18.40. Found: C, 62.06; H, 3.46; N, 16.10; S, 18.41.

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