Fused Polyaza-heterocycles and 1,3,4-Thiadiazoles *via* A Tricyano Synthon

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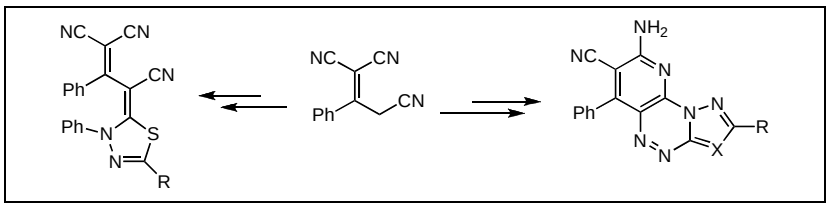

Treatment of 2-cyano-3-phenyl-2-pentenedinitrile with some heterocyclic diazonium salts afforded the corresponding heterocyclic hydrazones. Some of the latter hydrazones were converted into fused polyaza-heterocycles upon boiling in pyridine. Reaction of 2-cyano-3-phenyl-2-pentenedinitrile with phenylisothiocyanate gave a tricyano-thiole derivative which on treatment with hydrazonoyl chlorides and 1-(benzothiazol-2-yl)-2-bromoethanone furnished 1,3,4-thiadiazole and thiazole derivatives, respectively.

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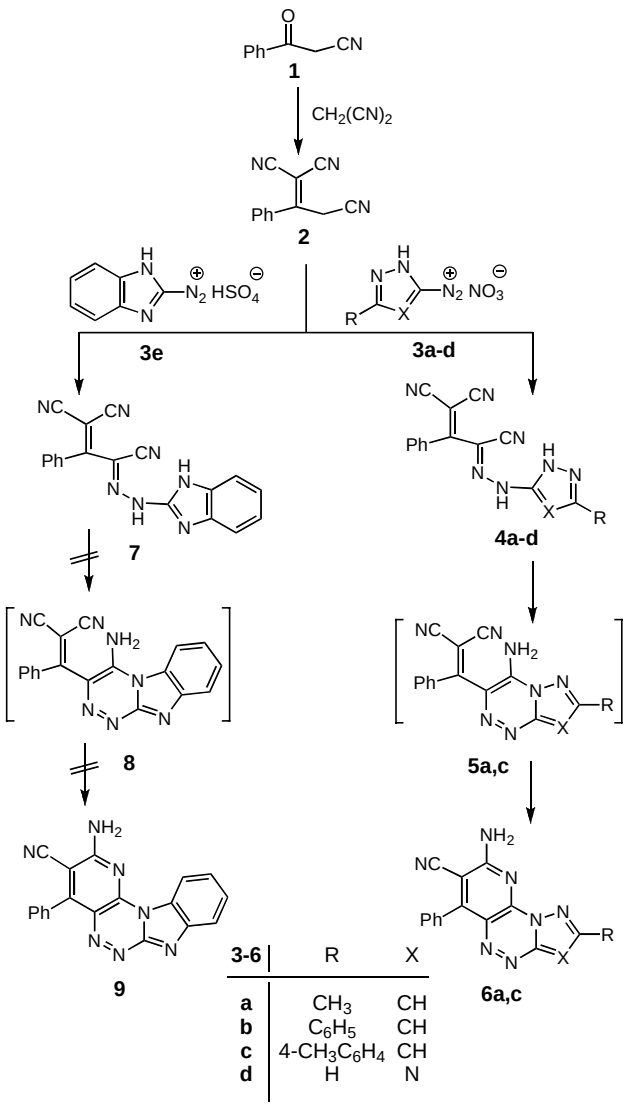
INTRODUCTION

α,β-Unsaturated nitriles are important synthetic intermediates in organic synthesis and key precursors in the synthesis of different carbocycles and heterocycles [1-4]. Heterocyclic hydrazones have remarkable wide scope of applications in the synthesis of fused heterocycles [5]. In addition, benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry [6] encompassing a diverse range of biological activities including antiarrhythmic, antiulcer, antihistamine, antifungal, antiviral and cytotoxicity [7]. Pyrazole derivatives are also attracting important applications in the field of medicinal chemistry [8,9]. Furthermore, 1,3,4-thiadiazoles were reported as highly anti-inflammatory [10], antimicrobial [11] and anticonvulsant [12] agents. 2-cyano-3-phenyl-2-pentenedinitrile (2) is known two decades ago and has been used in the synthesis of pyridazines [13,14], pyrroles [15], thiophenes [16] and some photosensitive materials [17,18], however, its use in the synthesis of polyfused heterocycles and 1,3,4-thiadiazole derivatives has not been reported so far. In continuation to our work on the synthesis of fused polyaza-heterocycles [19-24], we studied the reactivity of compound 2 with different nitrogen electrophiles as a convenient route to the entitled compounds.

RESULTS AND DISCUSSION

2-cyano-3-phenyl-2-pentenedinitrile (**2**) was prepared *via* treatment of benzoylacetonitrile (**1**) with malononitrile according to reported procedure [15]. Firstly, the reactions of 2-cyano-3-phenyl-2-pentene-dinitrile (**2**) towards several heterocyclic diazonium salts were undertaken to synthesize heterocyclic hydrazones and consequently bridgehead-nitrogen heterocycles. Thus, the reactivity of 2-cyano-3-phenyl-2-pentenedinitrile **2** with the 5-methylpyrazole diazonium salt **3a** at room temperature afforded the corresponding pyrazolylhydrazone **4a** (Scheme 1). The hydrazone **4a** was isolated in excellent yield and its structure was substantiated from its elemental analyses and spectral data (IR, MS, ^{1}H- and ^{13}C NMR). Its IR spectrum showed absorption peaks at 3367, 3218 and 2234 cm^{-1} due to NH and C≡N functions. The ^{1}H NMR spectrum also revealed two singlet signals at δ 2.35, 6.37 due to CH_3 and pyrazole-4-CH protons and two broad signals (D_2O-exchangeable) at δ 9.44 and 13.09 corresponding to pyrazole-NH and hydrazone-NH protons, respectively in addition to an aromatic multiplet in the region δ 7.64-7.74. When the latter hydrazone **4a** was refluxed in pyridine it underwent an intramolecular cyclization and afforded a dark brown solid product that was identified as 8-amino-2-methyl-6-phenylpyrazolo-[5,1-*c*]pyrido[2,3-*e*][1,2,4]triazine-7-carbonitrile (**6a**) based on its spectral data. The ^{1}H-NMR spectrum of the isolated product **6a** was free of the two broad signals at δ 9.44 and 13.09 corresponding to pyrazole-NH and hydrazone-NH protons, and exhibited instead only one signal (D_2O-exchangeable) integrated for two protons at δ 8.73 in addition to signals at δ 2.21 and 5.51 due to CH_3 and pyrazole-4-CH besides an aromatic multiplet at δ 7.41-7.53.

Scheme 1



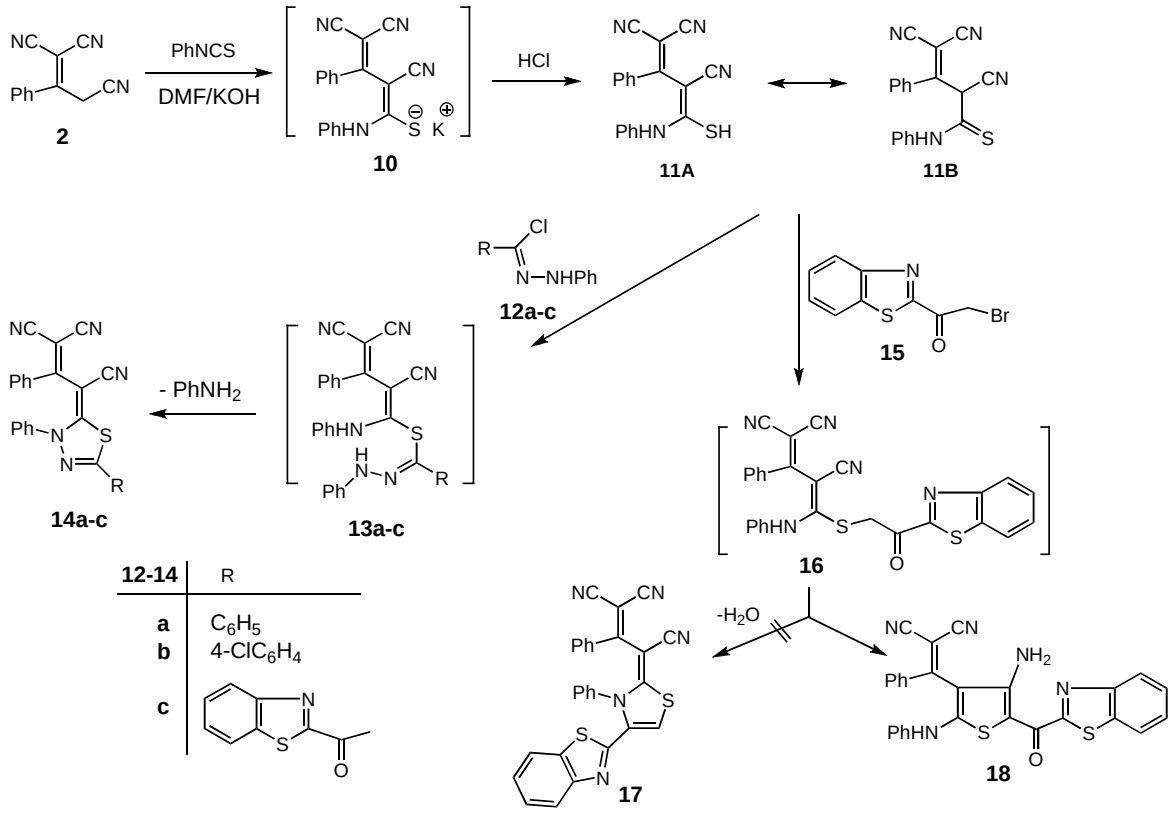
Next, the reactions of 2-cyano-3-phenyl-2-pentenedinitrile (**2**) toward further heterocyclic diazonium salts were also investigated. It was found that compound **2** couples smoothly with the diazonium salts of 5-amino-3-phenylpyrazole (**3b**), 5-amino-3-(*p*-toyl)pyrazole (**3c**), 5-amino-1,2,4-triazole (**3d**), and 2-aminobenzimidazole (**3e**) to afford the corresponding hydrazones **4b**, **4c, 4d** and **7,** respectively (Scheme 1). The IR spectra of the isolated products showed, in each case, two absorption bands in the region 3400–3100 cm^{-1} corresponding to two NH groups in addition to nitrile function around 2230 cm^{-1}, respectively. Compounds **4c** underwent an intramolecular cyclization upon boiling in pyridine to afford the corresponding fused heterocyclic system; 8-amino-6-phenyl-2-(*p*-tolyl)-pyrazolo[5,1-*c*]pyrido[2,3-*e*][1,2,4]-triazine-7-carbonitrile (**6c**) *via* the non-isolable pyrazolo-[5,1-*c*][1,2,4]triazine intermediate **5c** as depicted in Scheme 1. The polyaza fused heterocyclic system **6c** was confirmed from its ^{1}H and ^{13}C-NMR spectra. In contrast, the hydrazones **4b**, **4d** and **7** could not be converted into the corresponding fused systems **6b**, **6d** and **9** even after 30 hours of prolonged heating in pyridine and they were completely recovered without any change in their physical properties (color, mp, IR and ^{1}H NMR spectra).

Next, we turned out our attention to the reaction of 2-cyano-3-phenyl-2-pentenedinitrile (**2**) with phenyl isothiocyanate, in dimethylformamide, in the presence of potassium hydroxide, to afford the corresponding potassium salt **10** which was converted into 4-mercapto-2-phenyl-4-(phenylamino)buta-1,3-diene-1,1,3-tricarbonitrile (**11**) upon treatment with dilute hydrochloric acid (Scheme 2). ^{1}H NMR spectrum of the reaction product was free of any aliphatic protons which means that compound **11** is solely present in **11A** form instead of its tautomer **11B**. Compound **11** is a versatile multifunctional reagent and its reactivity towards hydrazonoyl chlorides **12a-c** is studied. Thus, reaction of compound **11** with *C*-phenyl-*N*-phenylhydrazonoyl chloride (**12a**) in refluxing ethanol and in the presence of triethylamine afforded the corresponding 1,3,4-thiadiazole derivative **14a**. Formation of the latter structure is assumed to proceed *via* elimination of aniline molecule from the intermediate **13a** as outlined in Scheme 2. The 1,3,4-thiadiazole structure **14a** was confirmed from the elemental analyses and spectral data of the isolated product. The IR spectrum revealed broad absorption band at 2212 cm^{-1} due to two nitrile functions. Its mass spectrum revealed a peak at *m/z* 429 corresponding to the molecular ion (M^{+}).

In a similar manner compound **11** reacted with equimolar amounts of *C*-(4-chlorophenyl)-*N*-phenyl-hydrazonoyl chloride (**12b**) and *C*-(2-benzothiazolylcar-bonyl)-*N*-phenylhydrazonoyl chloride (**12c**) and furnished in each case, only one isolable product (as tested by TLC analysis) which have the 1,3,4-thiadiazole structures **14b,c** based on their elemental and spectral analyses (see experimental part).

Similar treatment of compound **11** with 1-(benzo-thiazol-2-yl)-2-bromoethanone (**15**) in refluxing benzene in the presence of triethylamine resulted in the formation of a single product for which the thiazole **17** or thiophene **18** structures can be assumed. However, the elemental and spectral data of the reaction product were in complete accordance with the thiazole derivative **17**. ^{1}H NMR spectrum of **17** displayed a multiplet in the region 7.41-8.23 due to aromatic protons. Moreover, the mass spectrum of **17** exhibited a peak at 485 corresponding to the molecular ion (M^{+}). These results indicate that the reaction of compound **11** with **15** proceeds *via* loss of water molecule from the non-isolable intermediate **16** but not *via* the addition of active methylene to the cyano group, as shown in Scheme 2.

Scheme 2



In a similar manner compound **11** reacted with equimolar amounts of *C*-(4-chlorophenyl)-*N*-phenylhydrazonoyl chloride (**12b**) and *C*-(2-benzothiazolylcarbonyl)-*N*-phenylhydrazonoyl chloride (**12c**) and furnished in each case, only one isolable product (as tested by TLC analysis) which have the 1,3,4-thiadiazole structures **14b,c** based on their elemental and spectral analyses (see experimental part).

Similar treatment of compound **11** with 1-(benzothiazol-2-yl)-2-bromoethanone (**15**) in refluxing benzene in the presence of triethylamine resulted in the formation of a single product for which the thiazole **17** or thiophene **18** structures can be assumed. However, the elemental and spectral data of the reaction product were in complete accordance with the thiazole derivative **17**. ^{1}H NMR spectrum of **17** displayed a multiplet in the region 7.41-8.23 due to aromatic protons. Moreover, the mass spectrum of **17** exhibited a peak at 485 corresponding to the molecular ion (M^+). These results indicate that the reaction of compound **11** with **15** proceeds *via* loss of water molecule from the non-isolable intermediate **16** but not *via* the addition of active methylene to the cyano group, as shown in Scheme 2.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical center of Cairo University. 2-cyano-3-phenyl-2-pentenedinitrile (**2**) [15], heterocyclic diazonium salts **3a-e** [25-28], hydrazonyl halides **12a-c** [29,30] and 1-(benzothiazol-2-yl)-2-bromoethanone **15** [31] were prepared following the reported literature procedures.

General Procedure for the Reaction of 2-cyano-3-phenyl-2-pentenedinitrile (2) with Heterocyclic Diazonium Salts. To a cold solution of 2-cyano-3-phenyl-2-pentenedinitrile (**2**) (0.58 g, 3 mmol), in pyridine (20 ml), was added the appropriate heterocyclic diazonium salt of 5-amino-3-methylpyrazole (**3a**), 5-amino-3-phenylpyrazole (**3b**), 5-amino-3-(*p*-tolyl)pyrazole (**3c**), 3-amino-1,2,4-triazole (**3d**) or 2-aminobenzimidazole (**3e**) (3 mmol of each) that were prepared according to literature procedures. The addition was carried out portion-wise with stirring at 0–5℃ over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4h, then kept in an ice-chest for 12h, and finally diluted with water. The precipitated solid was collected, washed with water, dried and recrystallized from

ethanol/DMF to afford the corresponding heterocyclic hydrazones **4a**-**d** and **7** respectively.

3-(2-(3-Methyl-1*H*-pyrazol-5-yl)hydrazono)-2-phenylprop-1-ene-1,1,3-tricarbonitrile (4a). This compound was obtained as greenish-yellow crystals (DMF/EtOH), Yield (0.84 g, 93%); mp. 238-240 °C; ir (KBr) ν_{max}/cm^{-1}: 3367, 3218 (NH), 2234 (C≡N), 1604 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 2.35 (s, 3H, CH$_3$), 6.37 (s, 1H, pyrazole-4-CH), 7.64-7.74 (m, 5H, ArH), 9.44 (s, 1H, D$_2$O-exchangeable), 13.09 (s, 1H, D$_2$O-exchangeable); ^{13}C nmr δ 11.5, 98.3, 114.4, 114.8, 122.3, 129.6, 129.7, 129.9, 130.1, 131.5, 132.2, 141.8, 146.1, 146.3, 152.1; MS (*m/z*) 301 (M$^+$), 275, 260, 198, 180, 153, 127, 100, 77. For $C_{16}H_{11}N_7$ Calcd: C, 63.78; H, 3.68; N, 32.54%. Found: C, 63.61; H, 3.72; N, 32.18%.

3-(2-(3-Phenyl-1*H*-pyrazol-5-yl)hydrazono)-2-phenyl prop-1-ene-1,1,3-tricarbonitrile (4b). This compound was obtained as brownish-yellow crystals (DMF/EtOH), Yield (0.93 g, 86%); mp. 271-273 °C; ir (KBr) ν_{max}/cm^{-1}: 3381, 3229 (NH), 2241 (C≡N), 1629 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 7.06 (s, 1H, pyrazole-4-CH), 7.42-7.95 (m, 10H, ArH), 9.70 (s, 1H, D$_2$O-exchangeable), 13.85 (s, 1H, D$_2$O-exchangeable); MS (*m/z*) 363 (M$^+$), 337, 260, 180, 116, 77. For $C_{21}H_{13}N_7$ Calcd: C, 69.41; H, 3.61; N, 26.98%. Found: C, 69.22; H, 3.41; N, 26.59%.

3-(2-(3-*p*-Tolyl-1*H*-pyrazol-5-yl)hydrazono)-2-phenyl prop-1-ene-1,1,3-tricarbonitrile (4c). This compound was obtained as brown powder (DMF/EtOH), Yield (1.05 g, 93%); mp. 265-267 °C; ir (KBr) ν_{max}/cm^{-1}: 3386, 3175 (NH), 2221 (C≡N), 1590 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 2.37 (s, 3H, CH$_3$), 7.02 (s, 1H, pyrazole-4-CH), 7.33-7.38 (m, 3H, ArH), 7.65-7.81 (m, 6H, ArH), 9.51 (s, 1H, D$_2$O-exchangeable), 13.77 (s, 1H, D$_2$O-exchangeable); ^{13}C nmr δ 21.9, 96.2, 114.4, 114.8, 122.5, 126.4, 129.2, 129.6, 129.9, 130.6, 131.5, 132.2, 139.7, 144.7, 146, 146.1, 152.8, 159.8; MS (*m/z*) 377 (M$^+$), 328, 311, 285, 198, 156, 118, 91, 77. For $C_{22}H_{15}N_7$ Calcd: C, 70.01; H, 4.01; N, 25.98%. Found: C, 69.65; H, 3.73; N, 25.66%.

3-(2-(2*H*-1,2,4-Triazol-3-yl)hydrazono)-2-phenylprop-1-ene-1,1,3-tricarbonitrile (4d). This compound was obtained as greenish-yellow crystals (DMF/EtOH), Yield (0.75 g, 87%); mp. 286-288 °C; ir (KBr) ν_{max}/cm^{-1} 3326, 3140 (NH), 2215 (C≡N), 1605 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 6.72 (s, 1H, triazole H-5), 7.42-7.80 (m, 5H), 9.51 (br.s, 1H), 13.68 (br. s, 1H); MS (*m/z*) 288 (M$^+$), 262, 198, 179, 144, 127, 100, 84, 67. For $C_{14}H_8N_8$ Calcd: C, 58.33; H, 2.80; N, 38.87%. Found: C, 58.02; H, 2.63; N, 38.49%.

3-(2-(1*H*-Benzimidazol-2-yl)hydrazono)-2-phenylprop-1-ene-1,1,3-tricarbonitrile (7). This compound was obtained as red crystals (DMF/EtOH), Yield (0.82 g, 81%); mp. 278-279 °C; ir (KBr) ν_{max}/cm^{-1}: 3332, 3155 (NH), 2206 (C≡N), 1639 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 7.35-7.80 (m, 9H, ArH), 10.95 (s, 1H, D$_2$O-exchangeable), 13.15 (s, 1H, D$_2$O-exchangeable); MS (*m/z*) 337 (M$^+$), 312, 272, 182, 118, 90, 77. For $C_{19}H_{11}N_7$ Calcd: C, 67.65; H, 3.29; N, 29.06%. Found: C, 67.89; H, 3.41; N, 28.77%.

General Procedure for the Cyclization of the Heterocyclic Hydrazones 4a,c. A solution of the appropriate hydrazone **4a** or **4c** (1 mmol) in pyridine (10 ml) was refluxed for 12h, then left to cool. The solid that formed was collected by filtration, washed with ethanol, dried and finally recrystallized from DMF/ethanol to afford the corresponding fused heterocycles **6a** and **6c**, respectively

8-Amino-2-methyl-6-phenylpyrazolo[5,1-*c*]pyrido-[2,3-*e*]-[1,2,4]triazine-7-carbonitrile (6a). This compound was obtained as pale brown powder (DMF/EtOH), Yield (0.24 g, 79%); mp. 266-268 °C; ir (KBr) ν_{max}/cm^{-1}: 3130 (NH), 2225 (C≡N), 1589 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 2.21 (s, 3H, CH$_3$), 5.51 (s, 1H, pyrazole-4-CH), 7.41-7.53 (m, 5H, ArH), 8.73 (br.s, 2H, D$_2$O-exchangeable); For $C_{16}H_{11}N_7$ Calcd: C, 63.78; H, 3.68; N, 32.54%. Found: C, 63.59; H, 3.55; N, 32.22%.

8-Amino-6-phenyl-2-(p-tolyl)-pyrazolo[5,1-*c*]pyrido-[2,3-*e*]-[1,2,4]triazine-7-carbonitrile (6c). This compound was obtained as green amorphous (DMF/EtOH), Yield (0.31 g, 82%); mp. 257-258 °C; ir (KBr) ν_{max}/cm^{-1}: 3125 (NH), 2230 (C≡N), 1580 (C=N); ^{1}H nmr (DMSO-d$_6$) δ 2.40 (s, 3H, CH$_3$), 3.40 (br. s, 2H, D$_2$O-exchangeable), 7.07 (s, 1H, pyrazole-4-CH), 7.33-7.38 (m, 2H, ArH), 7.58-7.75 (m, 4H, ArH), 7.98-8.09 (m, 3H, ArH); ^{13}C nmr δ 21.9, 98.5, 114.8, 124.6, 126.2, 127.6, 127.8, 128.7, 129.7, 130.1, 130.9, 131.5, 132.9, 133.7, 134.9, 140.8, 141.9, 152.1, 159.8, 166.1; MS (*m/z*) 377 (M$^+$), 352, 336, 288, 233, 180, 165, 118, 91, 77, 65. For $C_{22}H_{15}N_7$ Calcd: C, 70.01; H, 4.01; N, 25.98%. Found: C, 69.65; H, 3.73; N, 25.66%.

4-Mercapto-2-phenyl-4-(phenylamino)buta-1,3-diene-1,1,3-tricarbonitrile (11). To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide (20 ml), 2-cyano-3-phenyl-2-pentenedinitrile (**2**) (1.93 g, 10 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (1.35 g, 10 mmol) was added to the resulting mixture. Stirring was continued for 6 h then poured onto crushed ice containing hydrochloric acid. The solid product so-formed was collected by filtration, washed with water, dried and finally recrystallized from EtOH/DMF to afford of 4-mercapto-2-phenyl-4-(phenylamino)buta-1,3-diene-1,1,3-tricarbonitrile (**11**) as brown powder in 2.43 g, 74% yield, mp. 240-242°C; ir (KBr) ν_{max}/cm^{-1}: 3386 (NH), 2206 (C≡N), 1589 (C=C); ^{1}H nmr (DMSO-d$_6$) δ 7.33-7.69 (m, 10H, ArH), 9.85 (s, 1H, NH, D$_2$O-exchangeable), 14.34 (s, 1H, SH, D$_2$O-exchangeable); MS (*m/z*) 328 (M$^+$), 261, 213, 160, 119, 107, 92, 66. For $C_{19}H_{12}N_4S$ Calcd: C, 69.49; H, 3.68; N, 17.06%. Found: C, 69.71; H, 3.55; N, 16.77%.

General Procedure for the Reaction of 4-Mercapto-2-phenyl-4-(phenylamino)buta-1,3-diene-1,1,3-tricarbonitrile (11) with Hydrazonoyl Chlorides 12a-c. To a solution of 11 (0.328 g, 1 mmol) in ethanol (20 ml) and the appropriate hydrazonoyl chlorides **12a-c** (1 mmol of each), triethylamine (0.5 ml) was added. The mixture was refluxed for 3h then allowed to cool. The formed solid was collected by filtration, washed with ethanol and recrystallized from dimethylformamide (DMF) to afford the corresponding 1,3,4-thiadiazole derivatives **14a-c**.

2-Phenyl-3-(3,5-diphenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-prop-1-ene-1,1,3-tricarbonitrile (14a). This compound was obtained as orange-red powder (DMF/EtOH), Yield (0.28 g, 65%); mp. 280-282 °C; ir (KBr) ν_{max}/cm^{-1}: 2212 (C≡N), 1583 (C=C); ^{1}H NMR (DMSO-d$_6$) δ 7.31-7.69 (m, ArH); MS (*m/z*) 429 (M$^+$), 381, 364, 276, 194, 173, 121, 105, 91, 77. For $C_{26}H_{15}N_5S$ Calcd: C, 72.71; H, 3.52; N, 16.31; S, 7.47%. Found: C, 72.39; H, 3.61; N, 16.02; S, 7.44%.

3-(5-(4-Chlorophenyl)-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-2-phenylprop-1-ene-1,1,3-tricarbonitrile (14b). This compound was obtained as brownish-red crystals (DMF/EtOH), Yield (0.366 g, 79%); mp. 287-289 °C; ir (KBr) ν_{max}/cm^{-1}: 2220 (C≡N); ^{1}H nmr (DMSO-d$_6$) δ 7.39-7.82 (m, ArH); MS (*m/z*) 463 (M$^+$), 327, 295, 228, 165, 91. For $C_{26}H_{14}ClN_5S$ Calcd: C, 67.31; H, 3.04; N, 15.10; S, 6.91%. Found: C, 66.94; H, 3.12; N, 14.88; S, 7.02%.

3-(5-(Benzothiazol-2-yl)carbonyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-2-phenylprop-1-ene-1,1,3-tricarbonitrile (14c): This compound was obtained as orange-red powder (DMF), Yield (0.35 g, 67%); mp. > 300°C; ir (KBr) ν_{max}/cm^{-1}: 2220 (C≡N), 1647 (C=O); ^{1}H nmr (DMSO-d_6) δ 7.51-8.20 (m, ArH); MS (*m/z*) 514 (M^+), 483, 395, 249, 162, 134, 105, 77. For $C_{28}H_{14}N_6OS_2$ Calcd: C, 65.35; H, 2.74; N, 16.33; S, 12.46%. Found: C, 65.24; H, 3.06; N, 16.10; S, 12.17%.

Reaction of Compound 11 with 1-(Benzothiazol-2-yl)-2-bromoethanone (15). To a solution of **11** (0.328 g, 1 mmol) in ethanol (20 ml) and 1-(benzothiazol-2-yl)-2-bromoethanone (**15**) (0.254 g, 1 mmol), triethylamine (0.5 ml) was added. The mixture was refluxed for 2h then allowed to cool. The formed solid was collected by filtration, washed with ethanol and recrystallized from DMF to afford 3-(4-(benzothiazol-2-yl)-3-phenylthiazol-2(3*H*)-ylidene)-2-phenylprop-1-ene-1,1,3-tricarbonitrile (**17**) as dark-brown crystals. Yield (0.306 g, 63%); mp. 250-252°C; ir (KBr) ν_{max}/cm^{-1}: 2214 (C≡N), 1596 (C=N); ^{1}H nmr (DMSO-d_6) δ 7.41-8.23 (m, ArH); MS (*m/z*) 485 (M^+), 437, 345, 303, 231, 172, 134, 77. For $C_{28}H_{15}N_5S_2$ Calcd: C, 69.26; H, 3.11; N, 14.42; S, 13.21%. Found: C, 69.39; H, 3.32; N, 14.23; S, 13.24%.

REFERENCES

[1] Lattanzi, L A.; Orelli, R.; Barone, P.; Massa, A.; Iannece, P.; Scettria, A. *Tetrahedron Lett.* **2003**, *44*, 1333.

[2] Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.

[3] (a) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Org. Lett.* **1999**, *1,* 1547; (b) Zoretic, P. A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 7213.

[4] Sharanin, Y. A.; Goncharenko, M. P.; Litvinov, V. P. *Russ. Chem. Rev.* **1998**, *67*, 442.

[5] Ciesielski, M.; Pufky, D.; M. Doering *Tetrahedron* **2005**, *61,* 5942.

[6] Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31,* 2235.

[7] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

[8] Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43,* 4934.

[9] Manna, F; Chimenti, F; Bolasco, A; Cenicola, M L; Amico, M D, *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 633.

[10] (a) Labanauskas, L.; Kalcas, V.; Udrenaite, E.; Gaidelis, P.; Brukstus, A.; Dauksas, V. *Pharmazie* **2001**, *56*, 617. (b) Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Filippelli, W.; Falcone, G.; Giordano, L.; Vitelli, M. R. *Bioorg. Med. Chem.* **2001**, *9*, 2149.

[11] Dogan, H. N.; Duran, A.; Rollas, S.; Sener, G.; Uysal, M. K.; Gulen, D. *Bioorg. Med. Chem.* **2002**, *10*, 2893.

[12] (a) Ilies, M. A.; Masereel, B.; Rolin, S.; Scozzafava, A.; Campeanu, G.; Cimpeanu, V.; Supuran, C. T. *Bioorg. Med. Chem.* **2004**, *12*, 2717. (b) Archana; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2002**, *37*, 873.

[13] Elgemeie, G. H.; Elfahham, H. A.; Elgamal, S.; Elnagdi, M. H. *Heterocycles* **1985**, *23*, 1999.

[14] Elgemeie, G. H.; Elfahham, H. A.; Ibrahim, Y. R.; Elnagdi, M. H. *Arch Pharmazie* **1989**, *322*, 535.

[15] Kandeel, Z. E.; Farag, A. M.; Abdel-Razek, F. M. *Heteroatom Chem.* **1995**, *6*, 281.

[16] Kandeel, Z. E. *Heteroatom Chem.* **1996**, *7*, 29.

[17] Andreu, R.; Cerdan, M. A.; Garin, J.; Orduna, J. *Arkivoc* **2004**, 32.

[18] Tada, J.; Ito, Y. Jpn Kokai Tokkyo 1986, 61103862; *Chem. Abstr.* **1987**, *106*, 76075.

[19] Farag, A. M.; Dawood, K. M. *Heteroatom Chem.* **1997**, *8*, 129.

[20] Sayed, S. M.; Raslan, M. A.; Khalil, M. A.; Dawood, K. M. *Heteroatom Chem.* **1999**, *10*, 385.

[21] Khalil, M. A.; Raslan, M. A.; Dawood, K. M.; Sayed, S. M. *Heterocycl. Commun.* **1999**, 463.

[22] Dawood, K. M.; Raslan, M. A.; Farag, A. M. *Synth. Commun.* **2003**, *33*, 4079.

[23] Dawood, K. M.; Ragab, E. A.; Farag, A. M. *J. Chem. Res.* **2003** *(S)*, 685 *(M),* 1151.

[24] Dawood, K. M. *Heteroatom Chem.* **2004**, *15*, 432.

[25] Elnagdy, M. H.; Elmoghayar, M. R. H.; Fleita, D. H.; Hafez; E. A. A.; Fahmy, S. M. *J. Org. Chem.* **1976**, *41,* 3781.

[26] Farag, A. M. *J. Chem. Res. (S),* **1995**, 96.

[27] Butler, R. N. *Chem. Rev.* **1975**, *75*, 241.

[28] Joshi, K. C.; Pathak, V. N.; Grag, U. *J. Heterocycl. Chem.* **1979,** *16*, 114.

[29] Wolkoff, P. *Can. J. Chem.* **1975**, *53,* 1333.

[30] Farag, A. M.; Dawood, K. M. *Heteroatom Chem.* **1997**, *8*, 45.

[31] Sawhney, S. N.; Singh, J. *Indian J. Chem.* **1970**, *8*, 882.