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RESEARCH ARTICLE

Tandem regioselective 1,5-electrocyclizations of *bis*-nitrilimines – a new convenient synthesis of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles

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Starting from *bis*(substituted methylene)carbonothioic dihydrazides, two series of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole derivatives were synthesized *via* their oxidative cyclization. The mechanism and regioselectivity of the reactions studied were discussed. The structures of the compounds prepared were elucidated on the basis of their analyses, spectral data, alternative synthesis, and comparison with authentic samples of their isomers.

Keywords: Hydrazones; 1,5-Electrocyclization; Nitrilimines; Heterocycles

1. Introduction

Since the 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole ring system was first reported by Kanaoka [1], much attention has been devoted to the chemistry of 3,6-disubstituted derivatives of this class of heterocycles because many of them possess various biological activity. For example, some of such derivatives were reported to have antibacterial [2–4], analgesic [5], anti-inflammatory [5] and fungicidal activity [3, 6] as well as interesting CNS depressant action [7], whereas others exhibit moderate antimalarial and antitumor activity [8].

At present, there are only two synthetic strategies for preparation of the target ring system. The first synthetic strategy depends on the use of 4-amino-s-triazole-3-thiols [9] and constructing the 1,3,4-thiadiazole ring using carboxylic acids, acetic anhydride, acid chlorides, aldehydes, aryl isothiocyanates, cyanogen bromide, carbon disulfide [10]. In the second strategy, 2-hydrazino-1,3,4-thiadiazoles, usually prepared from 2-amino-1,3,4-thiadiazole [3, 11] were used as thiadiazole precursors on which the triazole ring was formed by cyclocondensation with ortho esters, cyanogen bromide, carbon disulfide and aryl isothiocyanates [10]. Each of the foregoing strategies comprises at least three steps for synthesis of the target ring system [10, 11].

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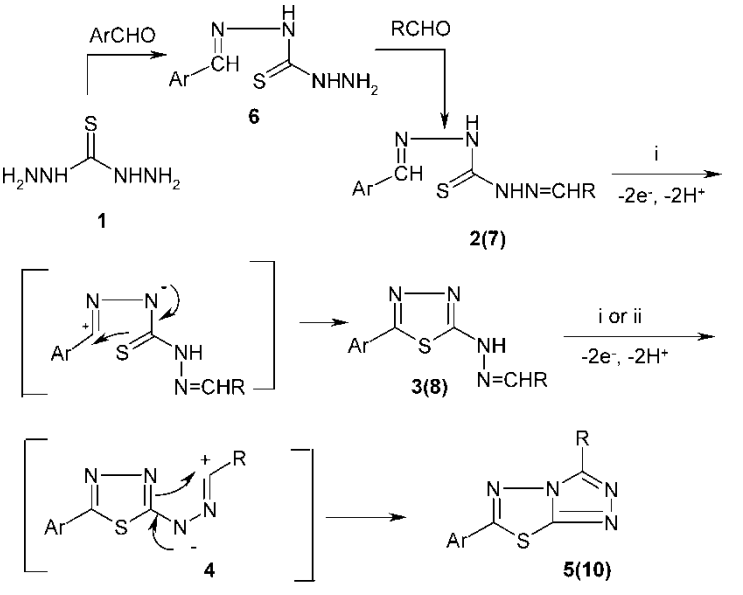


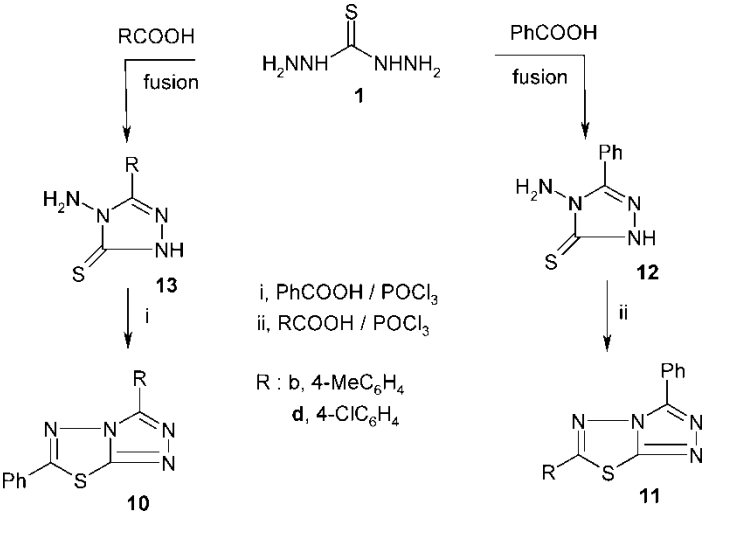
Reagents: i. $FeCl_3$ / EtOH; ii, Br_2 / AcOH / AcONa

For **2**, **3**, & **5** : Ar = R For **6**, **7**, **8**, **10** : Ar = Ph

R: **a**, 4-$MeOC_6H_4$; **b**, 4-MeC_6H_4; **c**, C_6H_5; **d**, 4-ClC_6H_4 ; **e**, 2-ClC_6H_4; **f**, 2-furanyl; **g**, 2-thienyl; **h**, 3-pyridinyl; **i**, 2-pyridinyl

SCHEME 1

Motivated by the above mentioned facts and in continuation of our research program to explore the potential synthetic utility of nitrilimine precursors [12–16], we studied the oxidative cyclization of symmetrical 2,2'-*bis*(arylmethylene)carbonothioic dihydrazides **2** (scheme 1) and their asymmetric analogs **7** (scheme 2) with two objectives in mind. First, we would like



SCHEME 2

to develop a new convenient synthetic route towards the title ring system and second, we wished to explore the regioselectivity in the oxidative cyclization of asymetric *bis*-hydrazones of type **7** (scheme 2). This is because oxidative cyclization of **7** can lead to the formation of **8** and/or **9** which upon further oxidation will afford **10** and/or **11**, respectively (scheme 2). It should be pointed out that a literature search has revealed that the oxidative cyclization of *bis*-hydrazones reported herein has not been explored hitherto although the oxidative cyclization of aldehyde N-heteroarylhydrazones has been frequently used to prepare s-triazolo[3,2-c]-s-triazole [17], oxazolo[2,3-c]-s-triazole [18], thiazolo[2,3-c]-s-triazole [18], 1H-s-triazolo[4,3-d]tetrazole [19] and 3H-1,2,4-triazolo[4,3-d]tetrazole [19] derivatives.

2. Results and discussion

The required *bis*-hydrazones **2** and **7** were prepared by condensation of carbonothioic dihydrazide **1** with the appropriate aldehydes (schemes 1 and 2). Some of these *bis*-hydrazones namely **2a–d** are known [20], whereas the other hydrazones **2e–h** and **7a,c–i** have not yet been reported. The structures of the new derivatives were confirmed by their elemental analyses and spectral data (MS, IR and ^{1}H NMR, see Experimental section). For example, the ^{1}H NMR spectra of **2** in DMSO-d_6 exhibited, in each case, two characteristic signals in the regions δ 8.54–8.96 and 11.48–11.89 corresponding to the −N=CH−and hydrazone −NH−N=C protons, respectively. The ^{1}H NMR spectra of **7** in DMSO-d_6 revealed in each case four characteristic signals at δ 8.02–8.60, 8.10–8.62, 10.40–11.95 and 10.8–12.30 due to the protons of the two differently substituted hydrazone moities (−NH−N=CH−).

Treatment of each of the *bis*-hydrazones **2** with one equivalent of ferric chloride in ethanol for 30 min gave in each case one crystalline product. Elemental analyses and mass spectra revealed that each of the isolated products has two hydrogen less than the respective *bis*-hydrazone **2**. Their ^{1}H NMR spectra showed that each has one methine proton −N=CH−and one hydrazone (−NHN=C) proton whose signals appeared at δ 7.89–8.49 and 11.76–12.80, respectively. On the basis of these findings, the isolated oxidation products were assigned the structure of aldehyde N-[5-aryl-1,3,4-thiadiazol-2-yl]hydrazone **3**.

In addition, the oxidative cyclization of the asymmetric *bis*-hydrazones **7** was examined in order to shed light on the regiochemistry of their 1,5-electrocyclization (Scheme 2). The treatment of compounds **7** with ferric chloride refluxing in ethanol yielded, in each case as evidenced by tlc chromatography, one product that was identified as aldehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone **8** (scheme 2). In no case was the other isomeric hydrazone derivative **9** produced. The structures of the products **8** were evidenced by using their spectral data (MS, ^{1}H NMR) and elemental analyses as well as through chemical transformations outlined in the following section. Like compounds **3**, the ^{1}H NMR spectra of **8** revealed, in each case, two singlet signals in the regions δ 7.89 − 8.74 and 11.04 − 12.65, assignable to −N=CH−and NHN=C−protons, respectively. The foregoing two conversions namely **2** → **3** and **7** → **8** are analogous to the oxidative cyclization of aldehyde thiosemicarbazones with ethanolic ferric chloride which was reported to give 1,3,4-thiadiazoline derivatives [21].

Treatment of hydrazones **3** with ferric chloride in ethanol or with bromine in acetic acid in the presence of anhydrous sodium acetate afforded the respective s-triazolo[3,4-b][1,3,4]thiadiazoles **5**, whose structures were consistent with their spectra (MS, IR and 1H NMR) and elemental analyses. Similarly, oxidation of **8** with bromine in acetic acid in the presence of sodium acetate afforded the respective s-triazolo[3,4-b][1,3,4]thiadiazoles **10** (scheme 2).

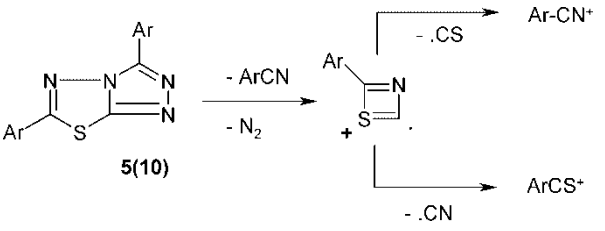
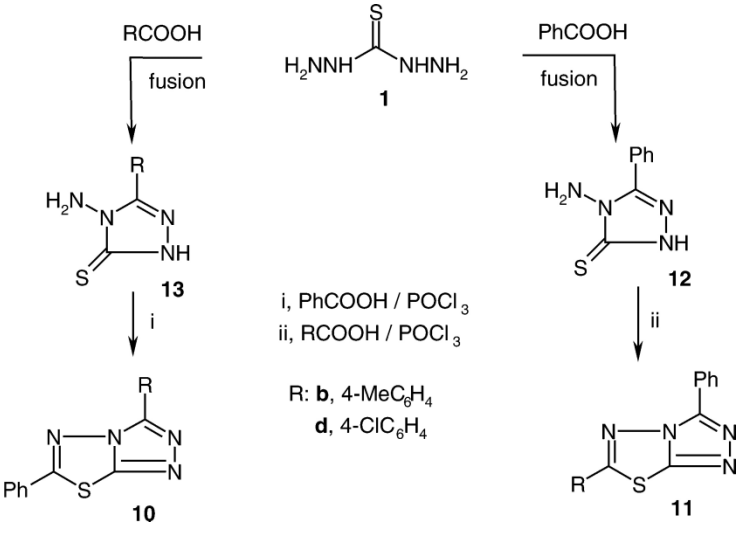


CHART 1

The assigned structures **10** and in turn the regioselectivity observed in the oxidative cyclization of compounds **7** were confirmed by an alternative synthesis and by comparison with authentic samples of their isomers namely **11** (scheme 3). For example, following a literature procedure, fusion of p-toluic acid and p-chlorobenzoic acid each with carbonothioic dihydrazide **1** gave **13b** and **13d**, respectively. The treatment of the latter triazolethiones with benzoic acid in the presence of $POCl_3$ afforded **10b** and **10d** (scheme 3), which were found identical in all respects with **10b** and **10d**, respectively and which were obtained above *via* the sequence **7** → **8** → **10** (scheme 2). On the other hand, fusion of the carbonothioic dihydrazide **1** with benzoic acid afforded **12** [23]. The heating of the latter with each of p-toluic acid and p-chlorobenzoic acid in the presence of $POCl_3$ afforded **11b** and **11d**, respectively (scheme 2). The latter products were found to be different in all respects from their isomers **10b** and **10d** that were showed in scheme 2.



SCHEME 3

The mass spectral data of compounds of both series **5** and **10** were consistent with their structures. They showed common peaks at m/z values characteristic to ArCNCS, ArCS and ArCN ion fragments. Such peaks indicate that the fragmentation of the molecular ion peaks follows the pattern outlined in chart 1. In some cases the peak of the thioacyl ArCS cation is the base peak. The IR spectra of compounds **5** and **10** exhibit in all cases three common absorption bands at 690–705, 1254–1285 and 1608–1624 cm^{-1}. These bands correspond to the bending vibrations of C-S-C and −N−N=C residues and the stretching vibration of the

C=N bond, respectively. The ^{1}H NMR spectra of the title compounds **5a–h** and **10a–i** reveal the signals due to resonances of the aromatic and heterocyclic proton in the expected regions of δ values. Details of these observations are summarized in the Experimental section.

Regarding the mechanisms of the studied oxidative cyclization reactions **2** → **3** → **5** and **7** → **8** → **10**, it is reasonable to suggest each cyclization reaction proceeds *via* the intermediacy of a nitrilimine which undergoes *in situ* 1,5-electrocyclization as depicted in scheme 1. This suggested pathway is reminiscent of other related oxidative cyclization of aldehyde thiosemicarbazones [21] and aldehyde N-heteroaryl hydrazones reported recently by Shawali *et al*. [22] and by others [17–19].

In conclusion, the regioselective oxidative cyclization of 2,2'-(substituted methylene)-carbonothioic dihydrazides has proven to be of general utility for synthesis of 2-(substituted methylene)hydrazino-5-substituted-1,3,4-thiadiazoles allowing easier preparation of 3,6-diaryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles. In addition, the method described herein has the advantages of higher overall yields, shorter reaction time and utilization of save and easily handled chemicals (aldehydes and $FeCl_3$).

3. Experimental section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using KBr disks. ^{1}H NMR spectra were recorded in DMSO-d_6 at 300 MHz and referenced to TMS. Mass spectra were measured at 70 eV using GC-MS. Elemental analyses were provided by the Microanalytical Laboratory at University of Cairo, Giza, Egypt. The starting carbonothioic dihydrazide **1** [24], 5-phenyl-2-hydrazino-1,3,4-thiadiazole [11] and 2-phenylmethylene carbonothioic dihydrazide **6** [20] and the compounds **12** [25], **13b** [25] and **13c** [26] were prepared as previously described.

3.1 *Synthesis of 2,2'-Bis(arylmethylene) carbonothioic dihydrazides (2). General procedure*

To a solution of carbonothioic dihydrazide **1** (1.06 g, 0.01 mole) in ethanol (20 ml) was added the appropriate aldehyde (0.02 mole) and the mixture was refluxed for 30 min then cooled to room temperature. The solid that precipitated was filtered off and crystallized from ethanol to give the respective N,N-bis(arylmethylene) carbonothioic dihydrazide **2**. The physical properties of the compounds **2a–d** are similar to those reported in literature [20]. The physical constants of the new derivatives **2e–h** prepared are listed below.

3.1.1 2,2'-*Bis*(2-chlorophenylmethylene) carbonothioic dihydrazide (2e). White crystals, yield 87%, Mp. 226–227 °C (EtOH), IR(KBr) ν 3417, 1612 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.44–7.88 (m, 8H), 8.68 (s, 2H), 11.80 (s, 2H); MS m/z (%) 353 (M^++2, 2), 352 (M^++1, 5), 351 (M^+, 5), 196 (40), 154 (24), 140 (31), 138 (59), 124 (20), 111 (95), 90 (100), 77 (16); Anal. Calcd for $C_{15}H_{12}Cl_2N_4S$ (351.2): C, 51.29; H, 3.44; N, 15.95. Found: C, 51.32; H, 3.39; N, 15.93%.

3.1.2 2,2'-*Bis*(2-furanylmethylene) carbonothioic dihydrazide (2f). Dark yellow crystals, yield 80%, Mp. 195–196 °C (EtOH), IR(KBr) ν 3448, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.13–7.69 (m, 6H), 8.54 (s, 2H), 11.51 (s, 2H); MS, m/z (%) 263 (M^++1, 7), 262 (M^+, 38),

188 (13), 152 (26), 109 (20), 94 (59), 80 (31), 79 (11), 52 (100); Anal. Calcd for $C_{11}H_{10}N_4O_2S$ (262.29): C, 50.37; H, 3.84; N, 21.36. Found: C, 50.26; H, 3.86; N, 21.33%.

3.1.3 2,2'-*Bis*(2-thienylmethylene) carbonothioic dihydrazide (2g). Yellow crystals, yield 81%, Mp. 211–212 °C (EtOH), IR(KBr) ν 3448, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.13–7.68 (m, 6H), 8.54 (s, 2H), 11.48 (s, 2H); MS, m/z (%) 296 (M^++2, 1), 295 (M^++1, 19), 294 (M^+, 20), 292 (14), 183 (19), 168 (89), 127 (18), 110 (100), 99 (27), 84 (43); Anal. Calcd for $C_{11}H_{10}N_4S_3$ (294.42): C, 44.88; H, 3.42; N, 19.05. Found: C, 44.81; H, 3.41; N, 19.12%.

3.1.4 2,2'-*Bis*(3-pyridinylmethylene) carbonothioic dihydrazide (2h). White solid, yield 82%, Mp. 227–228 °C (EtOH), IR(KBr) ν 3425, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.48–8.23 (m, 8H), 8.96 (s, 2H), 11.89 (s, 2H); MS, m/z (%) 285 (M^++1, 1), 284 (M^+, 4), 163 (14), 120 (27), 105 (33), 79 (21), 51 (100); Anal. Calcd for $C_{13}H_{12}N_6S$ (284.34): C, 54.91; H, 4.25; N, 29.56. Found: C, 54.89; H, 4.24; N, 29.50%.

3.2 *Synthesis of 2'-(arylmethylene)-2-(phenylmethylene)-carbonothioic dihydrazides (7)*

Repetition of the above procedure used for synthesis of **2**, using **6** (1.94 g, 0.01 mol) *in lieu* **1** and the appropriate aldehyde (0.01 ml) and work up the reaction mixture as above yielded the respective 2'-(arylmethylene)-2-(phenylmethylene)-carbonothioic dihydrazides **7**. The physical properties of the compounds **7a–i** prepared are listed below.

3.2.1 2'-(4-Methoxyphenylmethylene)-2-(phenylmethylene)-carbonothioic dihydrazide (7a). Yellow crystals, yield 70%, Mp. 230 °C (EtOH), IR(KBr) ν 3442, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.81 (s, 3H), 7.01–7.96 (m, 9H), 8.24 (s, 1H), 8.62 (s, 1H), 11.65 (s, 1H), 11.75 (s, 1H); MS m/z (%) 313 (M^++1, 1), 312 (M^+, 2), 268 (6), 238 (4), 192 (56), 150 (34), 134 (49), 120 (19), 107 (21), 104 (13), 93 (10), 77 (100); Anal. Calcd for $C_{16}H_{16}N_4OS$ (312.40): C, 61.52; H, 5.16; N, 17.93. Found: C, 61.75; H, 5.18; N, 17.84%.

3.2.2 2-(4-Methylphenylmethylene)-2'-(Phenylmethylene)-carbonothioic dihydrazide (7b). Pale yellow crystals, yield 75%, Mp. 165 °C (EtOH), (Lit. mp. 164–166 °C) [20], IR(KBr) ν 3440, 1604 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.36 (s, 3H), 7.07 (d, J = 9 Hz, 2H), 7.40–7.53 (m, 5H), 8.07 (d, J = 9 Hz, 2H), 8.10 (s, 1H), 8.49 (s, 1H), 10.40 (s, 1H), 10.80 (s, 1H); MS m/z (%) 297 (M^++1, 2), 296 (M^+, 5), 260 (19), 240 (12), 223 (23), 194 (22), 169 (15), 127 (15), 107 (13), 98 (21), 91 (100), 77 (59); Anal. Calcd for $C_{16}H_{16}N_4S$ (296.40): C, 64.84; H, 5.44; N, 18.90. Found: C, 64.70; H, 5.54; N, 18.73%.

3.2.3 2'-(4-Chlorophenylmethylene)-2-(phenylmethylene)-carbonothioic dihydrazide (7d). White solid, yield 70%, Mp. 265 °C (EtOH), IR(KBr) ν 3441, 1604 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.50–7.53 (m, 5H), 7.66 (d, J = 8 Hz, 2H), 7.83 (d, J = 8 Hz, 2H), 8.20 (s, 1H), 8.33 (s, 1H), 11.57 (s, 1H), 11.95 (s, 1H); MS m/z (%) 318 (M^++2, 3), 317 (M^++1, 2), 316 (M^+, 6), 198 (16), 196 (46), 156 (23), 154 (64), 137 (18), 127 (19), 113 (33), 102 (48), 89 (63), 77 (63), 75 (100); Anal. Calcd for $C_{15}H_{13}ClN_4S$ (316.81): C, 56.87; H, 4.14; N, 17.68. Found: C, 56.64; H, 4.08; N, 17.52%.

3.2.4 2-(2-Chlorophenylmethylene)-2'-(phenylmethylene)-carbonothioic dihydrazide (7e). Pale yellow solid, yield 75%, Mp. 222 °C (EtOH), IR(KBr) ν 3425, 1589 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.36–8.84 (m, 9H), 8.02 (s, 1H), 8.44 (s, 1H), 11.42 (s, 1H), 11.63 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 191.0, 150.9, 136.5, 132.8, 132.0, 131.8, 131.3, 131.0, 130.9, 130.2, 129.5, 129.3, 127.6; MS m/z (%) 318 (M^++2, 3), 317 (M^++1, 2), 316 (M^+, 5), 181 (11), 141 (31), 139 (100), 119 (10), 113 (19), 91 (31), 77 (58), 75 (21); Anal. Calcd for $C_{15}H_{13}N_4ClS$ (316.81): C, 56.87; H, 4.14; N, 17.68. Found: C, 56.82; H, 4.11; N, 17.60%.

3.2.5 2-(2-Furanylmethylene)-2'-(phenylmethylene)-carbonothioic dihydrazide (7f). Yellow solid, yield 65%, Mp. 192 °C (EtOH), IR(KBr) ν 3417, 1589 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.46–7.83 (m, 8H), 8.17 (s, 1H), 8.59 (s, 1H), 11.26 (s, 1H), 11.85 (s, 1H); MS m/z (%) 273 (M^++1, 0.5), 272 (M^+, 0.6), 157 (100), 126 (21), 86 (13), 84 (64), 77 (4); Anal. Calcd for $C_{13}H_{12}N_4OS$ (272.33): C, 57.34; H, 4.44; N, 20.57. Found: C, 57.32; H, 4.41; N, 20.51%.

3.2.6 2-(Phenylmethylene)2'-(2-thienylmethylene)-carbonothioic dihydrazide (7g). Dark yellow solid, yield 72%, Mp. 200 °C (EtOH), IR(KBr) ν 3442, 1596 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.08–8.01 (m, 8H), 8.21 (s, 1H), 8.35 (s, 1H), 11.39 (s, 1H), 11.50 (s, 1H); MS m/z (%) 289 (M^++1, 3), 288 (M^+, 8), 287 (37), 259 (69), 163 (48), 136 (40), 122 (62), 105 (16), 91 (19), 90 (100), 77 (24); Anal. Calcd for $C_{13}H_{12}N_4S_2$ (288.40): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.19; H, 4.01; N, 19.51%.

3.2.7 2-(Phenylmethylene)-2'-(3-pyridinylmethylene)-carbonothioic dihydrazide (7h). Pale yellow solid, yield 70%, Mp. 212 °C (EtOH), IR(KBr) ν 3433, 1585 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38–8.04 (m, 9H), 8.40 (s, 1H), 8.60 (s, 1H), 11.43 (s, 1H), 11.59 (s, 1H); MS m/z (%) 284 (M^++1, 16), 283 (M^+, 15), 163 (31), 121 (38), 119 (15), 104 (33), 91 (18), 77 (58), 51 (100); Anal. Calcd for $C_{14}H_{13}N_5S$ (283.36): C, 59.34; H, 4.62; N, 24.72. Found: C, 59.30; H, 4.59; N, 24.71%.

3.2.8 2-(Phenylmethylene)-2'-(2-pyridinylmethylene)-carbonothioic dihydrazide (7i). Pale brown solid, yield 68%, Mp. 195 °C (EtOH), IR(KBr) ν 3442, 1594 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.42–8.26 (m, 9H), 8.60 (s, 1H), 8.62 (s, 1H), 11.95 (s, 1H), 12.30 (s, 1H); MS m/z (%) 284 (M^++1, 11), 283 (M^+, 14), 178 (11), 146 (36), 119 (24), 120 (74), 104 (40), 92 (71), 91 (19), 77 (92), 51 (100); Anal. Calcd for $C_{14}H_{13}N_5S$ (283.36): C, 59.34; H, 4.62; N, 24.72. Found: C, 59.32; H, 4.68; N, 24.61%.

3.3 *Synthesis of aldehyde N-(5-aryl-1,3,4-thiadiazol-2-yl)hydrazones (3d–h and 8a–i).*

To a solution of the appropriate compound **2** (14 mmoles) in ethanol (40 ml) was added a solution of iron(III) chloride in ethanol (5 ml, 5M). The reaction mixture was refluxed for 30 min and then left while being stirred overnight at room temperature. The excess solvent was distilled under reduced pressure and the solid residue left was collected and washed with water several times, dried and finally crystallized from the proper solvent to give the respective compound **3**.

Repitition of the above procedure using **7a–i** each in lieu of **2** afforded the respective aldehyde N-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazone **8**. The physical constants of the products **3a–c** are identical to those reported in literature [27]. The physical constants of the new products **3d–h** and **8a–i** are listed below.

3.3.1 4-Chlorobenzaldehyde N-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]-hydrazone (3d). Pale yellow crystals, yield 62%, Mp. 219–220 °C (acetonitrile) (Lit. mp. 218–220 °C [27], IR(KBr) ν 3433, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.48–7.89 (4d, 8H), 8.12 (s, 1H), 12.60 (s, 1H); MS m/z (%) 351 (M^++2, 2), 350 (M^++1, 1.7), 349 (M^+, 3), 213 (23), 155 (62), 152 (100), 137 (30), 89 (80), 77 (6), 75 (45); Anal. Calcd for $C_{15}H_{10}Cl_2N_4S$ (349.24): C, 51.59; H, 2.89; N, 16.04. Found: C, 51.56; H, 2.88; N, 16.06%.

3.3.2 2-Chlorobenzaldehyde N-[5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl]-hydrazone (3e). Pale yellow crystals, yield 57%, Mp. 265–266 °C (acetonitrile), IR(KBr) ν 3417, 1589 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.40–8.09 (m, 8H), 8.49 (s, 1H), 12.80 (s, 1H); MS m/z (%) 351 (M^++2, 1.2), 350 (M^++1, 6), 349 (M^+, 3), 313 (30), 211 (63), 157 (22), 152 (100), 139 (15), 124 (41), 111 (23), 89 (80), 77 (7), 75 (55); Anal. Calcd for $C_{15}H_{10}Cl_2N_4S$ (349.24): C, 51.59; H, 2.89; N, 16.04. Found: C, 51.66; H, 2.81; N, 15.91%.

3.3.3 2-Furanaldehyde N-(5-(2-furanayl)-1,3,4-thiadiazol-2-yl]hydrazone (3f). Dark yellow crystals, yield 38%, Mp. 200–201 °C (acetonitrile), IR(KBr) ν 3417, 1589 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.27–7.87 (m, 6H), 7.89 (s, 1H), 12.06 (s, 1H); MS m/z (%) 261 (M^++1, 3), 260 (M^+, 30), 163 (21), 149 (54), 122 (31), 117 (13), 103 (26), 90 (57), 76 (100); Anal. Calcd for $C_{11}H_8N_4O_2S$ (260.28): C, 50.76; H, 3.10; N, 21.53. Found: C, 50.77; H, 3.92; N, 21.52%.

3.3.4 2-Thiophenealdehyde N-[5-(2-thienyl)-1,3,4-thiadiazol-2-yl]hydrazone (3g). Dark yellow crystals, yield 42%, Mp. 180–181 °C (acetonitrile), IR(KBr) ν 3409, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.50–7.83 (m, 6H), 8.33 (s, 1H), 11.76 (s, 1H); MS m/z (%) 293 (M^++1, 3), 292 (M^+, 10), 191 (45), 190 (55), 173 (100), 145 (45), 137 (76), 119 (99), 117 (19), 91 (64), 65 (52); Anal. Calcd for $C_{11}H_8N_4S_3$ (292.41): C, 45.18; H, 2.76; N, 19.16. Found: C, 45.16; H, 2.73; N, 19.47%.

3.3.5 3-Pyridinealdehyde N-[5-(3-pyridinyl)-1,3,4-thiadiazol-2-yl]hydrazone (3h). Pale green crystals, yield 70%, Mp. 280–282 °C (acetonitrile), IR(KBr) ν 3425, 1635 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.38–7.87 (m, 8H), 8.15 (s, 1H), 12.47 (s, 1H); MS m/z (%) 282 (M^++1, 1), 281 (M^+, 2), 178 (14), 104 (100), 77 (64), 76 (22), 51 (33); Anal. Calcd for $C_{13}H_{10}N_6S$ (282.33): C, 55.31; H, 3.57; N, 29.77. Found: C, 55.21; H, 3.61; N, 29.73%.

3.3.6 4-Methoxybenzaldehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8a). Pale brown crystals, yield 65%, Mp. 200 °C (EtOH), IR(KBr) ν 3413, 1607 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H), 7.38–7.51 (m. 5H), 7.60 (d, J = 7 Hz, 2H), 7.85 (d, J = 7 Hz, 2H), 8.20 (s, 1H), 12.45 (s, 1H); MS m/z (%) 311(M^++1, 2), 310 (M^+, 6), 176 (33), 145 (18), 120 (34), 118 (45), 106 (22), 104 (43), 91 (97), 77 (100), 65 (78); Anal. Calcd for $C_{16}H_{14}N_4OS$ (310.38): C, 61.92; H, 4.55; N, 18.05. Found: C, 61.96; H, 4.28; N, 17.98%.

3.3.7 4-Methylbenzaldehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8b). Pale brown crystals, yield 60%, Mp. 195 °C (EtOH), IR(KBr) ν 3424, 1605 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H), 7.40–7.45 (m. 5H), 7.89 (d, J = 7 Hz, 2H), 8.17 (d, J = 7 Hz, 2H), 8.19 (s, 1H), 11.55 (s, 1H); MS m/z (%) 295 (M^++1, 19), 294 (M^+, 20), 183 (19), 168 (89), 125 (24), 111 (37), 110 (100), 97 (36), 84 (43), 83 (50), 76 (26), 77 (6), 65 (78); Anal.

Calcd for $C_{16}H_{14}N_4S$ (294.38): C, 65.28; H, 4.79; N, 19.03. Found: C, 65.63; H, 4.64; N, 19.11%.

3.3.8 4-Chlorobenzaldehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8d). Pale brown crystals, yield 70%, Mp. 275 °C (EtOH), IR(KBr) ν 3422, 1600 cm^{-1}, ^1H NMR (DMSO-d_6) δ 7.01–7.44 (m, 9H), 8.28 (s, 1H), 12.50 (s, 1H), MS m/z (%) 316 (M^++2, 23), 315 (M^++1, 23), 314 (M^+ 46), 228 (45), 207 (12), 197 (25), 196 (36), 163 (20), 161 (78), 140 (36), 138 (80), 124 (14), 104 (43), 91 (24), 89 (68), 77 (80), 76 (50), 75 (100), 65 (78); Anal. Calcd for $C_{15}H_{11}ClN_4S$ (314.80): C, 57.23; H, 3.52; N, 17.80. Found: C, 57.13; H, 3.74; N, 17.67%.

3.3.9 2-Chlorobenzaldehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8e). Yellow crystals, yield 55%, Mp. 250 °C (EtOH), IR(KBr) ν 3409, 1595 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.35–8.26 (m, 9H), 8.40 (s, 1H), 11.50 (s, 1H); MS m/z (%) 316 (M^++2, 2), 315 (M^++1, 3), 314 (M^+ 8), 228 (15), 207 (10), 197 (15), 196 (40), 163 (15), 161 (60), 140 (30), 138 (75), 124 (11), 104 (40), 91 (21), 89 (33), 77 (65), 76 (45), 75 (100); Anal. Calcd for $C_{15}H_{11}ClN_4S$ (314.80): C, 57.23; H, 3.52; N, 17.80. Found: C, 57.20; H, 3.48; N, 17.76%.

3.3.10 2-Furanaldehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8f). Dark yellow crystals, yield 55%, Mp. 215 °C (EtOH), IR(KBr) ν 3410, 1604 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.12–8.24 (m, 8H), 8.74 (s, 1H), 11.04 (s, 1H); MS m/z (%) 271 (M^++1, 4), 270 (M^+, 21), 108 (36), 107 (49), 93 (100), 92 (44), 78 (14), 65 (64); Anal. Calcd for $C_{13}H_{10}N_4OS$ (270.31): C, 57.76; H, 3.73; N, 20.73. Found: C, 57.71; H, 3.69; N, 20.68%.

3.3.11 2-Thiophenealdehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8g). Dark yellow crystals, yield 55%, Mp. 215 °C (EtOH), IR(KBr) ν 3426, 1582 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.21–7.87 (m, 8H), 7.89 (s, 1H), 12.06 (s, 1H); MS m/z (%) 287 (M^++1, 11), 286 (M^+, 55), 280 (5), 279 (10), 183 (18), 177 (38), 124 (19), 121 (33), 96 (100), 90 (48), 77 (35); Anal. Calcd for $C_{13}H_{10}N_4S_2$ (286.38): C, 54.52; H, 3.52; N, 19.56. Found: C, 54.74; H, 3.82; N, 19.45%.

3.3.12 3-Pyridinealdehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8h). Dark yellow crystals, yield 50%, Mp. >300 °C (EtOH/DMF), IR(KBr) ν 3417, 1589 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.13–7.68 (m, 9H), 8.54 (s, 1H), 11.48 (s, 1H); MS m/z (%) 282 (M^++1, 22), 281 (M^+, 36), 280 (5), 179 (38), 177 (22), 121 (26), 104 (95), 90 (48), 77 (31), 74 (40), 51 (100); Anal. Calcd for $C_{14}H_{11}N_5S$ (281.34): C, 59.77; H, 3.94; N, 24.89. Found: C, 59.71; H, 3.88; N, 24.84%.

3.3.13 2-Pyridinealdehyde N-[5-phenyl-1,3,4-thiadiazol-2-yl]hydrazone (8i). Dark yellow crystals, yield 50%, Mp. 280 °C (EtOH), IR(KBr) ν 3411, 1555 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.47–7.97 (m, 9H), 8.12 (s, 1H), 12.65 (s, 1H); MS m/z (%) 282 (M^++1, 1), 281 (M^+, 4), 280 (9), 177 (26), 121 (23), 118 (33), 115 (26), 104 (45), 91 (24), 90 (100), 77 (88), 76 (31), 59 (44); Anal. Calcd for $C_{14}H_{11}N_5S$ (281.34): C, 59.77; H, 3.94; N, 24.89. Found: C, 59.21; H, 3.99; N, 24.73%.

3.4 *Synthesis of 3,6-disubstituted–1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles (5 and 10)*

Method A: To a stirred solution of the appropriate **3** (5 mmoles) in glacial acetic acid containing anhydrous sodium acetate (1.2 g, 15 mmoles) was added dropwise a solution of bromine (0.44 g, 5 mmoles) in acetic acid (5 ml) at room temperature. After the addition was completed, the reaction mixture was stirred for further 12 hr at room temperature. The mixture was poured into ice-cold water while being stirred. The solid precipitate was filtered off and washed with aqueous solution of sodium bicarbonate (5%), then with water, dried and finally crystallized from the appropriate solvent to give the respective compound **5**.

Method B: To a solution of the appropriate **3** (14 mmoles) in ethanol (40 ml) was added a solution of iron(III) chloride in ethanol (5 ml, 5M). The reaction mixture was refluxed for 30 min and then left while being stirred overnight at room temperature. The excess solvent was distilled under reduced pressure and the solid residue left was collected and washed with water several times, dried and finally crystallized from the proper solvent to give the respective compound **5**.

Repetition of each of the above mentioned two procedures using **8** in place of **3** afforded the respective **10**. The physical properties of the products **5b–d,f,g**, [25, 28–31] and **10a,b,e–g** [29–31], are similar to those of reported in literature. The physical properties of the new compounds **5a,e,h** and **10d,h,i** are listed below.

3.4.1 3,6-Di(4-methoxyphenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (5a). Pale yellow crystals, yield 40%, Mp. 200–201 °C (EtOH), IR(KBr) ν 1604, 1258, 686 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 6H), 7.01–8.55 (4d J = 8 Hz, 8H); MS m/z (%) 339 (M^++1, 31), 338 (M^+, 81), 337 (57), 283 (14), 281 (24), 236 (12), 203 (11), 186 (12), 172 (23), 151 (13), 140 (67), 116 (20), 111 (100), 104 (13), 77 (32); Anal. Calcd for $C_{17}H_{14}N_4O_2S$ (338.39): C, 60.34; H, 4.17; N, 16.56. Found: C, 60.26; H, 4.26; N, 16.61%.

3.4.2 3,6-Di(2-chlorophenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (5e). Yellow crystals, yield 41%, Mp. 300 °C (EtOH), IR(KBr) ν 1610, 1260, 705 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 7.66–8.31 (m. ArH); MS m/z (%) 349 (M^++2, 1), 348 (M^++1, 1), 347 (M^+, 1), 157 (0.3), 156 (0.2), 129 (0.3), 128 (0.1), 77 (100); Anal. Calcd for $C_{15}H_8Cl_2N_4S$ (347.2): C, 51.89; H, 2.32; N, 16.14. Found: C, 51.87; H, 2.35; N, 16.13%.

3.4.3 3,6-Di(3-pyridyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (5h). dark Yellow crystals, yield 40%, Mp. >300 °C (EtOH), IR(KBr) ν 1620, 1261, 695 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 7.40–8.19 (m. ArH); MS m/z (%) 281 (M^++1, 1), 280 (M^+, 10), 163 (15), 149 (78), 122 (27), 118 (10), 105 (13), 91 (17), 77 (15), 76 (100), 63 (48); Anal. Calcd for $C_{13}H_8N_6S$ (280.3): C, 55.70; H, 2.88; N, 29.98. Found: C, 55.69; H, 2.87; N, 29.97%.

3.4.4 3-(4-Chlorophenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (10d). Dark yellow crystals, yield 70%, Mp. 205 °C (EtOH), IR(KBr) ν 1608, 1285, 689 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 7.54–7.95 (m, 5H), 8.08 (d, J = 8 Hz, 2H), 8.30 (d, J = 8 Hz, 2H); MS m/z (%)314 (M^+ + 2, 35), 313 (M^++1, 43), 312 (M^+, 15), 277 (38), 271 (22), 153 (23), 151 (27), 141 (19), 139 (55), 138 (100), 125 (34), 111 (57), 103 (18), 102 (45), 92 (35), 91 (23), 83 (23), 82 (15), 78 (23), 77 (45); Anal. Calcd for $C_{15}H_9ClN_4S$ (312.78): C, 56.60; H, 2.90; N, 17.91. Found: C, 57.40; H, 2.75; N, 18.01%.

3.4.5 6-Phenyl-3-(3-pyridinyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (10h). Dark yellow crystals, yield 50%, Mp. 220 °C (EtOH), IR(KBr) ν 1601, 1273, 704 cm^{-1}, ^1H NMR (DMSO-d_6) δ 7.34–8.29 (m, ArH); MS m/z (%) 280 (M^++1, 13), 279 (M^+, 27), 213 (29), 203 (10), 177 (26), 157 (25), 139 (17), 137 (36), 124 (42), 118 (39), 103 (21), 102 (33), 91 (12), 90 (72), 89 (100), 77 (42), 75 (54); Anal. Calcd for $C_{14}H_9N_5S$ (279.33): C, 60.20; H, 3.25; N, 25.07. Found: C, 60.18; H, 3.14; N, 24.95%.

3.4.6 6-Phenyl-3-(2-pyridinyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (10i). Dark yellow crystals, yield 55%, Mp. 248°C (EtOH), IR(KBr) ν 1604, 1297, 686 cm^{-1}, ^1H NMR (DMSO-d_6) δ 7.44–7.79 (m, ArH); MS m/z (%) 280 (M^++1, 11), 279 (M^+, 2), 177 (18), 145 (10), 121 (37), 118 (34), 105 (23), 104 (69), 103 (58), 91 (18), 90 (94), 89 (35), 77 (84), 51 (100); Anal. Calcd for $C_{14}H_9N_5S$ (279.33): C, 60.20; H, 3.25; N, 25.07. Found: C, 60.58; H, 3.11; N, 24.99%.

3.5 *Alternate synthesis of 10b,d and their isomers 11b,d.*

A mixture of each of the appropriate 4-amino-3-mercapto-5-aryl-1,2,4-triazole **13b** or **13d** (5 mmole), benzoic acid (5 mmole) and $POCl_3$ (25 ml) was refluxed for 6 h, then the excess $POCl_3$ was distilled under reduced pressure. The resulting residue was poured into ice-cold water with stirring, basicified by adding potassium hydroxide solution and the resulting solid was filtered off. The crude solid was crystallized from ethanol to give the respective s-triazolo[3,4-b][1,3,4]thiadiazoles **10b,d**, respectively. The latter products proved identical in all respects with the ones obtained above from oxidative cyclization of **8b** and **8d**, respectively.

Repetition of the above procedure using 3-mercapto-5-phenyl-1,2,4-triazole **12** *in lieu* of **13b** or **13d** with p-toluic acid and p-chlorobenzoic acid afforded the products **11b** and **11d**, respectively. The physical constants of compound **11d** were found to be identical with those of the ones reported in literature [7].

3.5.1 6-(4-Methylphenyl)-3-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (11b). Dark yellow crystals, yield 57%, Mp. 162°C (EtOH), IR(KBr) ν 1604, 1258, 690 cm^{-1}, ^1H NMR (DMSO-d_6) δ 2.44 (s, 3H), 7.31 (d, J = 8 Hz, 2H), 7.45–7.53 (m, 5H), 7.88 (d, J = 8 Hz, 2H); MS m/z (%) 293 (M^++1, 15), 292 (M^+, 67), 291 (5), 147 (10), 135 (100), 134 (11), 117 (6), 103 (45), 91 (14), 77 (13), 76 (22); Anal. Calcd for $C_{16}H_{12}N_4S$ (292.36): C, 65.73; H, 4.14; N, 19.16. Found: C, 65.63; H, 4.30; N, 19.23%.

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