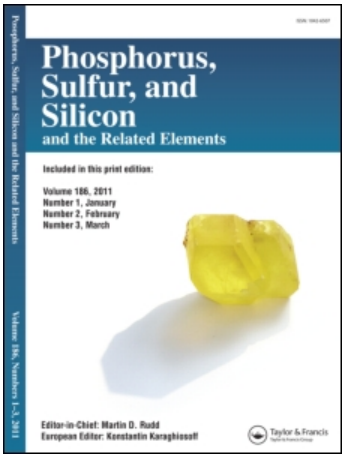

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A Novel Synthetic Route to New 2-Aryl-6-methyl[1,3,5]triazino[1,2-d] [1,3,4]thiadiazine-4,7(6H,9H)-dithiones

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A NOVEL SYNTHETIC ROUTE TO NEW 2-ARYL-6-METHYL[1,3,5]TRIAZINO[1,2-d] [1,3,4]THIADIAZINE-4,7(6H,9H)-DITHIONES

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The synthesis of some new 2-aryl-6-methyl[1,3,5]triazino[1,2-d] [1,3,4]thiadiazine-4,7(6H,9H)dithiones ***5*** *has been achieved by cyclocondesation reaction of the N′-(3-methyl-2-thioxo-l,3,4-thiadiazin-5-yl)-arylcarboximidamide* ***4*** *with carbon disulfide in ethanolic potassium hydroxide.*

Keywords: Carbon disulfide; cyclocondensation; novel synthetic route; triazinothiadiazines

Triazinothiadiazines are of chemical and pharmacological interest because of their structural assignment to the 2-phenylnaphthalene ring system which is an important moiety in many biological active compounds.[1] However there are very few reports on the synthesis and chemical properties of triazinothiadiazines.[2–8] Inspired by these facts and owing to our interest in the synthesis of heterocyclic compounds with potential biological activities,[9] we deemed it interesting to look for specific routes to new derivatives of triazinothiadiazines.

We report a novel method for preparation of some new 2-aryl-6-methyl[1,3,5]triazino[1,2-d][1,3,4]thiadiazine-4,7(6H,9H)dithiones **5** in synthetically useful yields. Our approach is based on the cyclocondesation reaction of the *N′*-(3-methyl-2-thioxo-l,3,4-thiadiazin-5-yl)arylcarboximidamide **4** with carbon disulfide in ethanolic potassium hydroxide. As shown in Scheme 1, the starting 5-amino-3-methyl-3, 6-dihydro-2H-1,3,4-thiadiazine-2-thione **3** was prepared by the base catalyzed heterocyclization of cyanomethyl-l-methyl-hydrazinecarbodithioate **1**. It is noteworthy that acid catalyzed heterocyclization of

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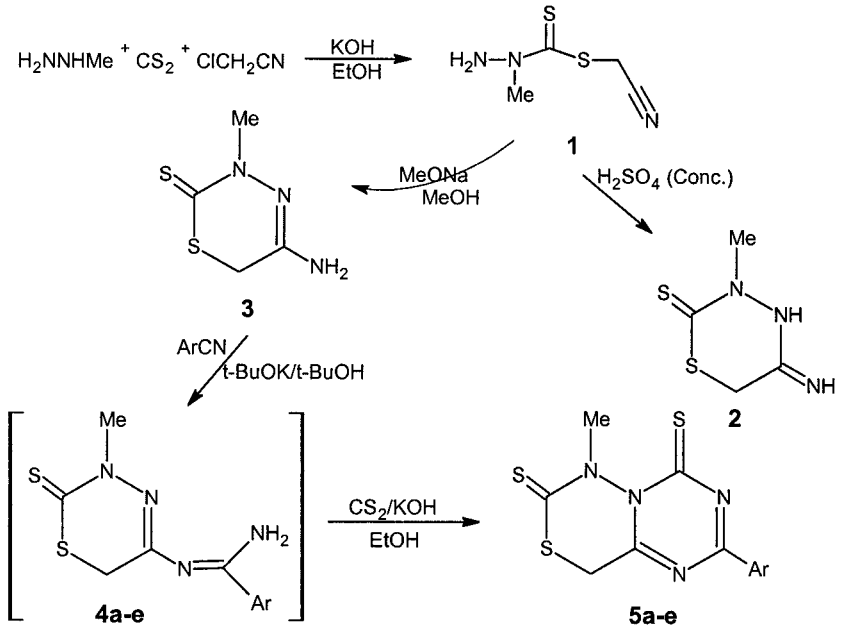

Ar = a: 4-F-C_6H_4; b: 4-Cl-C_6H_4-;
c: 3, 5 - $(MeO)_2$-C_6H_3-; d: 2-Thiophene;
e: 2-Pyridyl

SCHEME 1

compound **1** afforded the imino derivative **2** which was subsequently converted to its amino derivative **3** on treatment with base. The structure assigned to compound **3** was substantiated by its spectral data. In the ^{1}H NMR spectrum of compound **3** the sharp singlets at δ 3.45 and 3.59 ppm are assignable to the thiadiazine ring protons and N-Me group, respectively, and the relatively broad singlet at δ 6.65 assignable to NH_2 protons. The IR spectrum of compound **3** is devoid of the CN absorption band of its precursor at 2250 cm^{-1}, but instead shows two bands at 3400–3250 cm^{-1} indicative of NH_2 group on the thiadiazine ring.

Further treatment of compounds **2** and **3** with aromatic nitriles in the presence of potassium t-butoxide in t-butanol under reflux gave products identified as N′-(3-methyl-2-thioxo-3,6-dihydro-2H-1,3,4-thiadiazin-5-yl) aryl-2-carboximidamide **4**. When compounds **4** were heated under reflux with carbon disulfide in the presence of potassium hydroxide in ethanol, cyclization occurred and gave the expected

[1,3,5]triazino[l,2-d][1,3,4] thiadiazinedithiones **5**. Assignment of the structures **5** was supported by their spectral data (Table I). The ^{1}H NMR spectra of these compounds were devoid of the signal for NH_2 group of the precursors **4** and showed further downfield shifts for NCH_3, SCH_2, and aromatic protons, indicating the construction of an triazine ring around positions 4 and 5 of the [1,3,5]triazines. Mass spectra show the expected molecular ion peak and the fragmentation pattern is according with the proposed structure.

In summary, some new 2-aryl-6-methyl [1,3,5]triazino[1,2-d][1,3,4] thiadiazine-4,7(6H,9H)dithiones have been synthesized by a novel synthetic route and their structures were established by their spectral data.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on Bruker AC 100 Spectrometer. Mass spectra were obtained from Varian CH-7 at 70 eV.

Preparation of Cyanomethyl 1-methylhydrazinecarbodithioate 1

A mixture of methyl hydrazine (0.1 mmol, 3.5 ml), carbon disulfide (0.1 mmol, 6.0 ml), chloroacetonitrile (0.1 mmol, 6.3 ml), and potassium hydroxide (0.1 mmol, 5.6 g) in ethanol (15 ml) was stirred at room temperature for 1 h. The precipitate was filtered off and recrystallized from ethanol as white crystals to yield the required product (12.9 g, 80% yield), m.p. 106–107°C.

Preparation of 5-Imino-3-methyl-1,3,4-thiadiazine-2-thione 2

The foregoing compound 1 (0.01 mmol, 1.61 g) in conc. H_2SO_4 (5.0 ml) was stirred at room temperature for 3 h. The solution was then neutralized by slow addition of ammonia with gradual cooling. The solid was filtered off and crystallized from ethanol to yield the required product as white crystals (1.2 g, 75% yield), m.p. 165–166°C.

Preparation of 5-Amino-3-methyl-3, 6-dihydro-2H-1,3,4-thiadiazine-2-thione 3

A mixture of compound 1 (0.01 mmol, 1.61 g) in methanolic solution (0.23 g sodium in 25 ml methanol) was heated under reflux for 6 h. The

TABLE I Physical and Spectral Data of Cyanomethyl 1-methylhydrazine-carbodithioate 1,5-imino-3-methyl-1,3,4-thiadiazinane-2-thione 2, 5-amino-3-methyl-3, 6-dihydro-2H-1,3,4-thiadiazine-2-thione 3, N′-(3-methyl-2-thioxo-3, 6-dihydro-2H-1,3,4-thiadiazin-5-yl)arylcarboximidamide, **4a–e**, and 2-Aryl-6-methyl[1,3,5]triazino[1,2-d][1,3,4]thiadiazine-4,7(6H,9H)-dithione **5a–e**

Entry	Reaction time (h)	Yield (%)	m.p. (°C)	Spectral data
1	1	80	106–107	^{1}H NMR: (DMSO-d_6) δ, 5.80 (s, 2H, NH_2), 4.04 (s, 2H, S-CH_2), 3.57(s, 3H, NCH_3), IR(KBr disk): v, NH_2, 3400 cm^{-1}, CN, 2230 cm^{-1}, m/z, 161
2	3	75	165–166	^{1}H NMR: (DMSO-d_6) δ, 7.69 (br, H, NH), 7.33 (br, H, NH), 3.90 (s, 2H, S-CH_2) 3.75(s, 3H, NCH_3), IR(KBr disk): v, 2NH, 3150–3300 cm^{-1}, m/z, 161
3	6	60	134–135	^{1}H NMR: (DMSO-d_6) δ, 6.65 (s, 2H, NH_2), 3.58 (s, 2H, S-CH_2): v, 3.45 (s, 3H, NCH_3), IR(KBr disk): NH_2, 3250 cm^{-1}, m/z, 161
4a	5	70	129–130	^{1}H NMR: ($CDCl_3$) δ, 7.07–7.91 (tt, 4H, aromatic), 6.4 (br, 2H, NH_2), 3.83 (s, 5H, S-CH_2, NCH_3), IR(KBr disk): v, NH_2, 3350 cm^{-1}, m/z, 282
4b	3	65	235–236	^{1}H NMR: ($CDCl_3$) δ, 7.37–7.80 (dd, 4H, aromatic), 6.06 (s, 2H, NH_2), 3.82 (s, 5H, S-CH_2, NCH_3), IR(KBr disk): v, NH_2, 3300 cm^{-1}, m/z, 298
4c	4	72	210–211	^{1}H NMR: ($CDCl_3$) δ, 6.58–6.94 (m, 3H, aromatic), 5.85 (br, 2H, NH_2), 3.77 (s, 5H, S-CH_2, NCH_3), 3.67 (s, 6H, 2OCH_3), IR(KBr disk): v, NH_2, 3400 cm^{-1}, m/z, 324
4d	3	75	231–232	^{1}H NMR: (DMSO-d_6) δ, 7.70–7.75 (m, 3H, thiophen), 7.60 (br, 2H, NH_2), 3.7(s, 2H, S-CH_2) 3.52(s, 3H, NCH_3), IR(KBr disk): v NH_2, 3330 cm^{-1}, m/z, 270
4e	3	67	246–247	^{1}H NMR: (DMSO-d_6) δ, 7.54–8.77 (m, 4H, pyridin), 6.07 (br, 2H, NH_2), 4.05–4.09 (d, 5H, S-CH_2, NCH_3), IR(KBr disk): v, NH_2, 3200 cm^{-1}, m/z, 265
5a	6	65	155–156	^{1}H NMR: (DMSO-d_6) δ, 7.20–8.03 (tt, 4H, aromatic), 3.77(s, 5H, S-CH_2, NCH_3) m/z, 324
5b	4	60	204–205	^{1}H NMR: (CD_3COCD_3) δ, 7.60–7.93 (dd, 4H, aromatic), 3.99 (s, 2H, S-CH_2), 3.81 (s, 3H, NCH_3), m/z, 340

(Continued)

TABLE I Physical and Spectral Data of Cyanomethyl 1-methylhydrazine-carbodithioate 1, 5-imino-3-methyl-1,3,4-thiadiazinane-2-thione 2, 5-amino-3-methyl-3, 6-dihydro-2H-1,3,4-thiadiazine-2-thione 3, N′-(3-methyl-2-thioxo-3, 6-dihydro-2H-1,3,4-thiadiazin-5-yl)arylcarboximidamide, **4a–e**, and 2-Aryl-6-methyl[1,3,5]triazino[1,2-d][1,3,4]thiadiazine-4,7(6H,9H)-dithione **5a–e**

Entry	Reaction time (h)	Yield (%)	m.p. (°C)	Spectral data
5c	5	63	185–186	^{1}H NMR: (DMSO-d_6) δ, 6.62–7.04 (m, 3H, aromatic), 3.91(s, 5H, S-CH_2, NCH_3) 3.75 (s, 6H, 2OCH_3), m/z, 366
5d	6	60	198–199	^{1}H NMR: ($CDCl_3$) δ, 7.20–8.03 (m, 3H, thiophen), 3.85 (s, 2H, S-CH_2) 3.67(s, 3H, NCH_3), m/z, 312
5e	7	55	170–171	^{1}H NMR: ($CDCl_3$) δ, 7.70–8.97 (m, 4H, pyridin), 4.23 (s, 2H, S-CH_2) 3.67 (s, 3H, NCH_3), m/z, 307

mixture was cooled and the precipitated solid filtered off and crystallized from ethanol to give the require product as white crystals (0.966 g, 60% yield), m.p. 134–135°C.

General Procedure for the Preparation of N′-(3-methyl-2-thioxo-3,6-dihydro-2H-1,3,4-thiadiazin-5-yl)arylcarboximidamide 4a–e

A mixture of the foregoing compound **3** (0.01 mmol, 1.61 g), aryl cyanide (0.01 mmol), and potassium t-butoxide [from potassium (0.78 g, 0.02 mmol) in t-BuOH (15 ml)] was heated under reflux for the indicated time (Table I). After the reaction was complete, the mixture was then neutralized with dilute HCl. The precipitate was collected and crystallized from ethanol as white crystals (data in Table I).

General Procedure for the Preparation of 2-Aryl-6-methyl[1,3,5]triazino[1,2-d][1,3,4]thiadiazine-4,7(6H,9H)-dithione 5a–e

A mixture of the foregoing compound **4a–e** (0.01 mmol), carbon disulfide (0.01 mmol), and potassium hydroxide (1.12, g, 0.02 mol) in ethanol (10 ml) was heated under reflux for the indicated time (Table I). After the reaction was complete, the mixture was then neutralized with dilute HCl. The precipitate was collected and crystallized from ethanol as white to pale yellow crystals (data in Table I).

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