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Mahmoud Mahmoud

Chemistry Department, Faculty of Science, Ain Shams University, 11566 Cairo, Egypt.

Manal El-Shahawi

Chemistry Department, Faculty of Science, Ain Shams University, 11566 Cairo, Egypt.

Fatma Abu El-Azm

Chemistry Department, Faculty of Science, Ain Shams University, 11566 Cairo, Egypt.

Mohamed Abdeen

Chemistry Department, Faculty of Science, Ain Shams University, 11566 Cairo, Egypt.

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SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLIC COMPOUNDS DERIVED FROM 5-CINNAMOYLAMINO-2-CYANOMETHYL-1,3,4-THIADIAZOLE

MAHMOUD REFAEE MAHMOUD, MANAL MOHAMED EL-SHAHAWI*, FATMA SABER ABU EL-AZM, MOHAMED ABDEEN

Chemistry Department, Faculty of Science, Ain Shams University, 11566 Cairo, Egypt.

ABSTRACT

*Cinnamoyl isothiocyanate **1** was reacted with 2-cyanoethanoic acid hydrazide **2** to afford 1-cyanoacetyl-4-substituted thiosemicarbazide **3** which on treatment with a mixture of glacial acetic acid and acetic anhydride gave the desired 5-cinnamoylamino-2-cyanomethyl-1,3,4-thiadiazole **4**. Compound **4** was subjected to react with aromatic aldehydes, phenylisothiocyanate, carbon disulphide and arylidene malononitrile to give coumarin **5**, thiazolidines **8,9** and 1,3,4-thiadiazolo[3,2-a]pyridine **13** derivatives. The structures of all synthesized compounds were ascertained by spectral and analytical data.*

INTRODUCTION

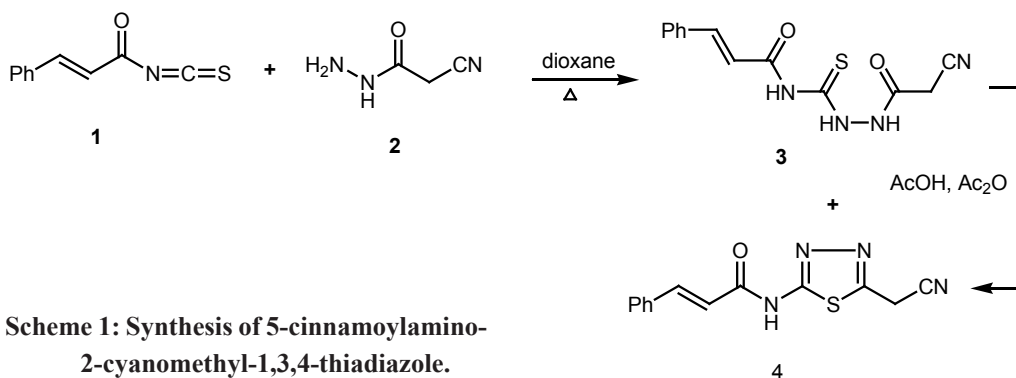
Aroyl and acyl isothiocyanates are important reagents which can be transformed to variety of heterocyclic derivatives on reacting with polyfunctional molecules, either *via* addition followed by cyclization or *via* cycloaddition[1]. Treatment of aroyl and/or acyl isothiocyanates with acid hydrazids yields substituted thiosemicarbazides which undergo cyclization to different heterocyclic compounds depending on the reaction conditions. Under basic conditions, substituted thiosemicarbazides undergo cyclization to 1,2,4-triazole-3-thione derivatives[2-10]. On the other hand, under acidic conditions substituted thiosemicarbazides undergo dehydrative cyclization to 1,3,4-thiadiazole derivatives.[4,7-13].

The 1,3,4-thiadiazole moiety is one of those compounds at the apex of chemists attention owing to its biological and pharmaceutical importance. A literature survey shows that 1,3,4-thiadiazole derivatives exhibit antimicrobial [14-18], anti-inflammatory [18,19], antitumor [20-23], antihyperlipidemic [24], anticonvulsant [25,26], antiviral [27], antioxidant [28], antifungal [29,30], antitubercular [31,32] and antide-

pressant activities [33]. In addition, 1,3,4-thiadiazole have important technological uses as corrosion and oxidation inhibitors [34], metal complexation agents [35,36] and in analytical fields [37]. In view of these fascinating and encouraging results and in continuation of our work on biologically active nitrogen and sulfur heterocycles [38-40], we have synthesized some 2,5-disubstituted 1,3,4-thiadiazoles by adopting a different methodology.

RESULTS AND DISCUSSION

In this investigation, the nucleophilic addition of 2-cyanoacetohydrazide **2** to cinnamoyl isothiocyanate **1** in refluxing dioxane afforded a mixture of two products which were easily separated by fractional crystallization. The soluble fraction in methanol was identified as 5-cinnamoylamino-2-cyanomethyl-1,3,4-thiadiazole (63%) **4** and the insoluble fraction recrystallized from dioxane and was identified as 4-cinnamoyl-1-(2-cyanoacetyl)thiosemicarbazide (17%) **3**. Compound **3** readily cyclized to the corresponding 1,3,4-thiadiazole derivative **4** using a mixture of acetic anhydride and glacial acetic acid (**Scheme 1**).

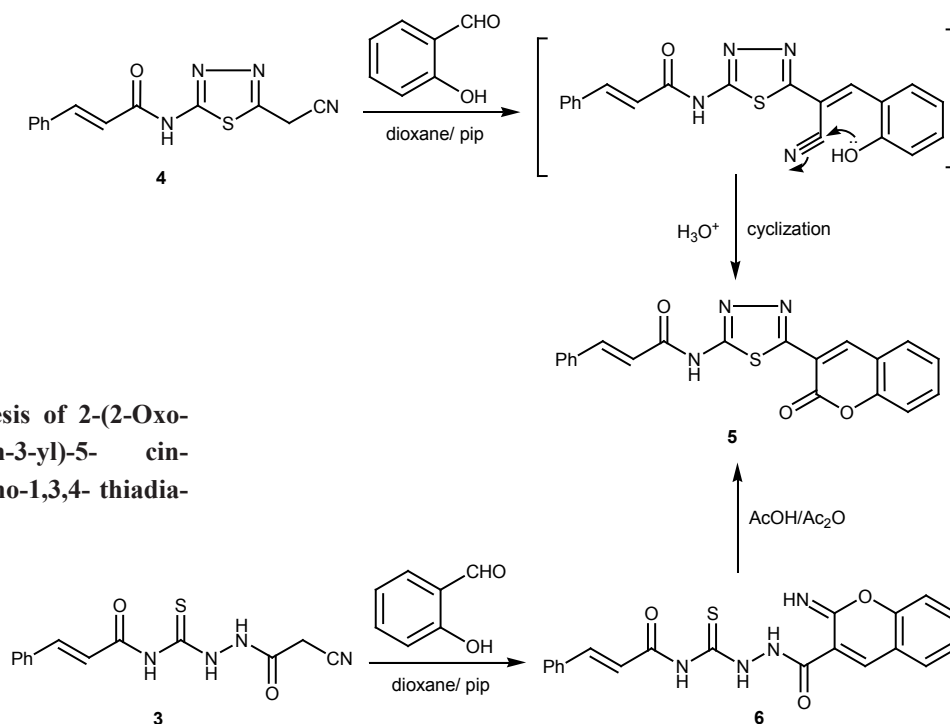


Scheme 1: Synthesis of 5-cinnamoylamino-2-cyanomethyl-1,3,4-thiadiazole.

The structure of the acyclic product **3** was deduced from appropriate analytical and spectroscopic data. Thus, $^1\text{H-NMR}$ spectrum (DM-SO-d_6) disclosed downfield three singlets each integrating for 1H (NH) at δ 12.5, 11.7 and 11.21 ppm, aromatic protons (5H) as a multiplet at δ 7.78-7.46 ppm together with two doublets each integrating for one hydrogen at δ 7.03 and 6.98 ppm with coupling constant $J=15$. Hz characteristic of trans olefinic protons. The cyanomethylene protons (2H) of the cyanoacetamide group appeared upfield at δ 3.86 ppm. Complete evidence for the acyclic structure **3** was forthcoming from the mass spectrum which showed the correct molecular ion peak at $m/z = 288$ (74.2%). In addition, the base peak at $m/z = 131$ attributable to the cinnamoyl cation $\text{PhCH}=\text{CHCO}^+$ is in harmony with the assigned structure **3**. Cyclization of the thiosemicarbazide derivative **3** us-

ing a mixture of glacial acetic acid and acetic anhydride afforded the 1,3,4-thiadiazole derivative **4** as the sole product (**Scheme 1**). The structure of compound **4** was deduced from its spectroscopic and analytical data.

The proclivity of compound **4** towards electrophilic reagents such as aromatic aldehydes, carbon disulfide, phenyl isothiocyanate and nucleophilic reagents such as hydrazine hydrate and hydrazides were investigated. Thus, the reaction of **4** with salicylaldehyde in refluxing dioxane in the presence of a catalytic amount of piperidine afforded the coumarin derivative **5**. On the other hand, treatment of the acyclic product **3** with salicylaldehyde under the same conditions affords **6** which on treatment with a mixture of freshly distilled acetic anhydride and glacial acetic acid yielded coumarin derivative **5** (**Scheme 2**).

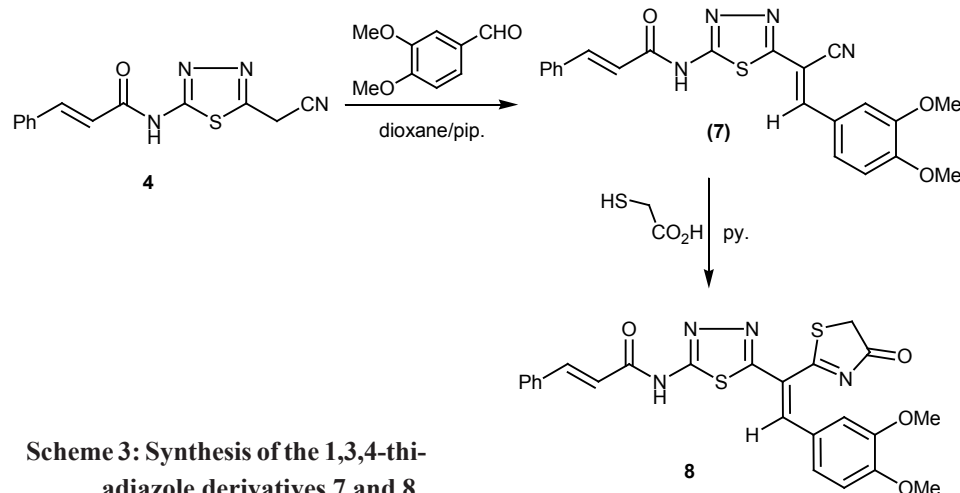


Scheme 2: Synthesis of 2-(2-Oxo-2H-chromen-3-yl)-5-cinnamoylamino-1,3,4-thiadiazole

The structure of coumarin derivative **5** was verified with microanalytical data and was confirmed by spectroscopic data. Therefore, the IR spectrum of **5** revealed the absence of a stretching band for the nitrile group and the presence of an oxo-coumarin band at 1712 cm^{-1} . Moreover, the $^1\text{H-NMR}$ spectrum of compound **5** displayed signals characteristic of the NH proton at δ 10.92 ppm as a broad singlet that disappeared with D_2O , a singlet for the $\text{C}_4\text{-H}$ coumarin proton at δ 8.50 ppm, a multiplet for aromatic protons (9H) at δ 7.87-7.37 ppm and two doublets for the trans-olefinic protons at δ 7.0 and 6.90 ppm which are in accord with the proposed structure **5**. Furthermore, the highest recorded peak in the mass spectrum of **5** at $m/z = 375$ (9.7%) repre-

sents the molecular ion peak which upon loss of cinnamoyl radical yielded the base peak at $m/z = 245$ (100%).

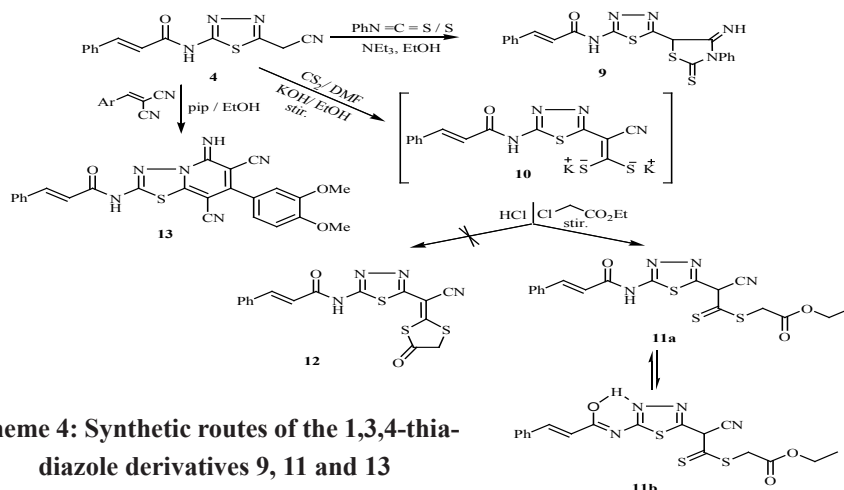
On the other hand, treatment of 1,3,4-thiadiazole derivative **4** with 3,4-dimethoxybenzaldehyde in dioxane and in the presence of a catalytic amount of piperidine afforded the corresponding arylidene derivative **7** (**Scheme 3**). The structure of **7** was confirmed by the analytical and spectroscopic data. Thus, the IR spectrum of **7** showed one weak absorption band of NH at 3198 cm^{-1} , $\nu_{\text{C}\equiv\text{N}}$ (conjugated) at 2201 cm^{-1} and $\nu_{\text{C}=\text{O}}$ at 1670 cm^{-1} . The strong clue for the structure **7** was forthcoming from the study of its mass and $^1\text{H-NMR}$ spectra which is compatible with the proposed structure.



Scheme 3: Synthesis of the 1,3,4-thiadiazole derivatives 7 and 8.

The reaction of the arylidene derivative **7** with mercaptoacetic acid in refluxing pyridine yielded the thiazolidinone derivative **8** (**Scheme 3**). The IR spectrum of **8** revealed the absence of stretching band of the nitrile group and retained carbonyl stretching band at 1695 cm^{-1} . Location of a new $\nu_{\text{C}=\text{N}}$ at 1630 cm^{-1} is in harmony with the assigned structure. The structure of **8** was further supported by mass spectroscopy as the molecular weight inferred the incorporation of one mercaptoacetic acid molecule in the reaction product.

Treatment of compound **4** with phenylisothiocyanate and elemental sulfur in presence of a catalytic amount of triethylamine in ethanol yielded the thiazole-2-thione derivative **9** (**Scheme 4**). The IR spectrum of compound **9** revealed the absence of the stretching band of the nitrile group and retained three weak bands of NH at 3453 , 3277 , 3142 cm^{-1} together with carbonyl stretching band at 1674 cm^{-1} . Moreover, the $^1\text{H-NMR}$ spectrum of compound **9** revealed signals characteristic for three types of protons which are consistent with the proposed structure **9**.

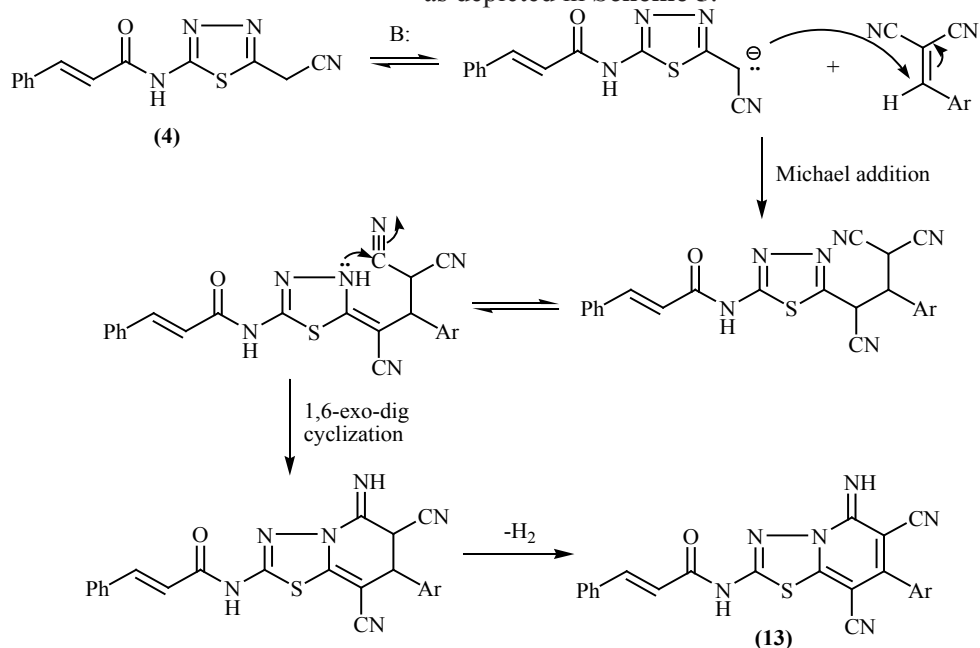


Scheme 4: Synthetic routes of the 1,3,4-thiadiazole derivatives 9, 11 and 13

Stirring compound **4** with carbon disulphide in ethanolic potassium hydroxide (10%) and dimethyl formamide for three hours yielded the dipotassium disulphide salt **10** which *in situ* added to ethyl chloroacetate followed by acidification with cold dilute hydrochloric acid gave the uncyclized product **11** (**Scheme 4**). No evidence was detected for the cyclized product **12** since the IR spectrum of the product obtained exhibited broad band at 3439 cm^{-1} (bonded OH, NH), $\nu_{\text{C}=\text{N}}$ at 2202 cm^{-1} , $\nu_{\text{C}=\text{O}}$ (ester) at 1727 cm^{-1} , $\nu_{\text{C}=\text{O}}$ (α,β -unsaturated amide) at 1677 cm^{-1} and $\nu_{\text{C}=\text{N}}$ at 1624 cm^{-1} .

Furthermore, when 1,3,4-thiadiazole derivative **4** was subjected to react with 3,4-dimethoxy benzyldiene malononitrile in refluxing ethanol in presence of a catalytic amount of piperidine,

the 1,3,4-thiadiazolo[3,2-a]pyridine derivative **13** was obtained (**Scheme 4**). The structure **13** was substantiated from the microanalytical and spectroscopic data. Thus, the IR spectrum of **13** displayed ν_{NH} at 3245 (w) and 3224 (w), 3170 cm^{-1} , $\nu_{\text{C}=\text{N}}$ (conjugated) at 2216 cm^{-1} , $\nu_{\text{C}=\text{O}}$ at 1687 cm^{-1} and $\nu_{\text{C}=\text{N}}$ at 1628 cm^{-1} which are agree well with the assigned structure. The $^1\text{H-NMR}$ spectrum of **13** revealed the presence of a singlet downfield integrating for one proton (NH) at δ 11.01 ppm which is exchangeable with D_2O , a broad singlet for 1H (=NH) at 8.18 ppm, a multiplet involved the aromatic and olefinic protons at δ 7.68-6.98 ppm integrating for 10H, and two singlets each integrating for 3H corresponding to the two methoxyl protons at δ 3.87 and 3.84 ppm. The formation of **13** could be formulated as depicted in **Scheme 5**.



Scheme 5

Experimental

The melting points were measured on a Galenkamp melting point apparatus. The FTIR spectra were recorded on a Pye Unicam SP-3-300 spectrometer. ¹H-NMR spectra were run on a Varian Mercury VX-300 NMR 300 MHz spectrometer. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70e.V. Elemental analysis was performed by Vario EL-III elemental analysis.

Synthesis of (3) and (4)

Ammonium thiocyanate (1 g, 0.01 mol) was added to a solution of cinnamoyl chloride (1.66 g, 0.01 mol) in dioxane (10 ml) and then the reaction mixture was stirred for 10 minutes. The reaction mixture was filtrated off and the filtrate was added to a solution of cyanoacetylhydrazide (1 g, 0.01 mol) in dioxane (10 ml) and then the reaction mixture was heated under reflux for 15 minutes. The formed solid (two spots on TLC) was collected by filtration, dried, and fractionally crystallized from methanol to give **4** (63%), while the residue was crystallized from dioxane to afford the **3** (17%).

4-Cinnamoyl-1-(2-cyanoacetyl)thiosemicarbazide (3)

white crystals, Yield: 17%, mp: 235-236°C; ¹H-NMR (DMSO-d₆) δ (ppm): 12.50 (s, 1H, NH, exchangeable with D₂O), 11.71 (s, 1H, NH, exchangeable with D₂O), 11.21 (s, 1H, NH, exchangeable with D₂O), 7.78-7.46 (m, 5H_{arom.}), 7.03 (d, H, PhCH=, J = 15.4Hz) 6.98 (d, 1H, PhCH=CH, J = 15.4Hz) 3.86 (s, 2H, CH₂CN); IR (KBr) v : 3297, 3221 (NH), 2267 (CN), 1680, 1666 (C=O); MS m/z (%): 288 (M⁺; 74), 270 (21), 204 (24), 131 (100), 103 (90), 77 (89); Anal. Calcd. for C₁₃H₁₂N₄O₂S (288.315): C, 54.16; H, 4.19; N, 19.43; S, 11.12. Found: C, 54.10; H, 4.08; N, 19.39; S, 11.08.

5-Cinnamoylamino-2-cyanomethyl-1,3,4-thiadiazole (4)

white crystals, Yield: 63%, mp: 218- 220 °C; ¹H-NMR (DMSO-d₆) δ (ppm): 11.72 (s, 1H, NH, exchangeable with D₂O), 7.78-7.45 (m, 5H_{arom.}), 7.03(d, 1H, PhCH=, J= 15.7Hz), 6.98 (d, 1H, PhCH=CH, J= 15.7Hz), 3.86 (s, 2H, CH₂CN); IR (KBr) v: 3158 (NH), 2252 (CN), 1691 (C=O),

1634 (C=N); MS m/z (%): 270 (M⁺; 21), 202 (20), 131 (6), 76 (46), 69 (100). Anal. Calcd. for C₁₃H₁₀N₄OS (270.302): C, 57.77; H, 3.73; N, 20.73; S, 11.86. Found: C, 57.80; H, 3.70; N, 20.68; S, 11.80.

Cyclization of (3)

Thiosemicarbazide derivative **3** (1 g), freshly distilled acetic anhydride (10 ml) and glacial acetic acid (10 ml) was heated under reflux for 2hrs. The reaction mixture was concentrated and then poured into ice/cold water. The yielded solid was separated by filtration, washed with water, dried, and recrystallized from methanol to give **4** (identity M.P., mixed M.P., IR and TLC comparison).

2-(2-Oxo-2H-chromen-3-yl)-5- cinnamoylamino-1,3,4-thiadiazole (5).

A mixture of thiadiazole **4** (2.7 g, 0.01 mol), salicylaldehyde (1.23 ml, 0.01 mol) and piperidine (0.5 ml) in dioxane (20 ml) was refluxed for 2 hrs. The reaction mixture was concentrated and then poured into ice/cold water and acidified with concentrated hydrochloric acid. The yielded solid was separated by filtration, washed with water, dried, and recrystallized from ethanol/ dioxane mixture (7:3) to give **5** as yellow crystals, Yield: 51%, mp: 228-230°C; ¹H-NMR (DMSO-d₆) δ (ppm): 10.92 (s, 1H, NH, exchangeable with D₂O), 8.50 (s, 1H, C₄-H coumarin), 7.87-7.37 (m, 9H_{arom.}), 6.92 (d, 1H, PhCH=, J= 15.4Hz), 6.54 (d, 1H, PhCH=CH, J= 15.4Hz). IR (KBr) v: 3190 (NH), 1712, 1689 (C=O), 1636 (C=N); MS m/z (%): 375 (M⁺; 10), 245 (100), 172 (79), 146 (71), 131 (90), 103 (98), 77 (78). Anal. Calcd. for C₂₀H₁₃N₃O₃S (375.392): C, 63.99; H, 3.49; N, 11.19; S, 8.54. Found: C, 63.92; H, 3.52; N, 11.10; S, 8.58.

4-Cinnamoyl-1-(2-imino-2H-chromene-3-carbonyl)thiosemicarbazide (6).

To a solution of compound **3** (2.88 g, 0.01 mol) in dioxane (20 ml), salicylaldehyde (1.23 ml, 0.01 mol) was added with piperidine (0.2 ml), and then the reaction mixture was refluxed for 3hrs. After evaporation of excess solvent and acidification with dilute cold hydrochloric acid the solid separated was collected by filtration, washed with water, dried, and then recrystal-

lized from dioxane to give **6**, yellowish- white crystals, Yield: 43%, mp: 208-210°C; IR (KBr) ν : 3254, 3158 (NH), 1691 (C=O), 1634 (C=N); MS m/z (%): 392 (M^+ ; 14), 245 (79), 206 (40), 173 (41), 146 (92), 131 (100), 103 (89), 77 (99). Anal. Calcd. for $C_{20}H_{16}N_4O_3S$ (392.419): C, 61.22; H, 4.11; N, 14.28; S, 8.17. Found: 61.18; H, 4.17; N, 14.32; S, 8.10.

Cyclization of (6)

Thiosemicarbazide derivative **6** (1 g), acetic anhydride (10ml) and glacial acetic acid (10 ml) was heated under reflux for 2hrs. The reaction mixture was concentrated and then poured into ice/cold water. The yielded solid was collected by filtration, washed with water, dried, and recrystallized from dioxane to give **5** (identity M.p., mixed M.p., IR and TLC comparison).

2-[1-Cyano-2-(3,4-dimethoxyphenyl)vinyl]-5-cinnamoylamino-1,3,4-thiadiazole (**7**).

A mixture of thiadiazole **4** (2.7 g, 0.01 mol), 3,4-dimethoxybenzaldehyde (1.66 g, 0.01 mol) and piperidine (0.5 ml) in ethanol (20 ml) was refluxed for 1 hr. The produced solid on hot was separated by filtration, dried, and recrystallized from dioxane to give **7** as yellow crystals, Yield: 48%, mp: 160-162°C; 1H -NMR (DMSO- d_6) δ (ppm): 11.68 (s, 1H, NH, exchangeable with D_2O), 8.20 (s, 1H, $\underline{CH=}$), 7.78-7.73 (m, 3H_{arom.}), 7.71-7.47 (m, 5H_{arom.}), 7.20 (d, 1H, PhCH=, J= 15.2 Hz), 7.04 (d, 1H, PhCH=CH, J= 15.2 Hz), 3.88 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃); IR (KBr) ν : 3189 (NH), 2201 (C \equiv N), 1670 (C=O), 1618 (C=N); MS m/z (%): 418 (M^+ ; 23.9), 288 (23), 151 (54), 131 (100), 103 (99), 77 (55). Anal. Calcd. for $C_{22}H_{18}N_4O_3S$ (418.455): C, 63.15; H, 4.33; N, 13.39; S, 7.66. Found: C, 63.20; H, 4.29; N, 13.35; S, 7.70.

2-[2-(3,4-Dimethoxyphenyl)-1-(4-oxo-4,5-dihydrothiazol-2-yl)vinyl]-5-cinnamoylamino-1,3,4-thiadiazole (**8**).

A mixture of arylidene derivative **7** (2.1 g, 0.005 mol) and mercaptoacetic acid (0.46 g, 0.005 mol) and in pyridine (15 ml) was heated under reflux for 7 hrs. The reaction mixture was concentrated and then poured into ice/cold water and acidified with concentrated hydrochloric acid. The yielded solid was separated by filtra-

tion, washed with water, dried, and recrystallized from methanol to give **8**, pale yellow crystals, Yield: 47%, mp: 270-272°C; IR (KBr) ν : 3196 (NH), 1695 (C=O), 1630 (C=N); MS m/z (%): 492 (M^+ ; 1), 459 (2), 287 (11), 260 (11), 216 (21), 151 (100), 131 (64), 103 (36), 77 (55). Anal. Calcd. for $C_{24}H_{20}N_4O_4S_2$ (492.556): C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.48; H, 3.99; N, 11.42; S, 13.08.

2-(4-Imino-3-phenyl-2-thioxothiazolidin-5-yl)-5-cinnamoylamino-1,3,4-thiadiazole (**9**).

A mixture of arylidene derivative **7** (2.1 g, 0.005 mol), phenylisothiocyanate (0.65 ml, 0.005 mol), elemental sulfur (0.16 g, 0.005 mol) and triethylamine (0.5 ml) in ethanol (20 ml) was heated under reflux for 4 hrs. The produced solid after cooling was separated by filtration, dried, and recrystallized from dioxane to give **9** as yellow crystals, Yield: 47%, mp: 270-272°C; 1H -NMR (DMSO- d_6) δ (ppm): 11.28 (s, 1H, =NH, exchangeable with D_2O), 10.36 (s, 1H, NH, exchangeable with D_2O), 7.44-7.35 (m, 12H, 10H_{arom.} + 2H olefinic protons), 4.92 (s, 1H, C₅-H of thiazole ring); IR (KBr) ν : 3453, 3277, 3142 (NH), 1674 (C=O), 1280 (C=S); MS m/z (%): 437 (M^+ ; 9), 307 (10), 208 (70), 131 (91), 103 (92), 77 (90). Anal. Calcd. for $C_{20}H_{15}N_5OS_3$ (437.552): C, 54.90; H, 3.45; N, 16.00; S, 21.99. Found: C, 54.95; H, 3.40; N, 16.05; S, 21.92.

2-[Ethyl 2-(2-cyanoethanethioylthio)acetate]-5-cinnamoylamino-1,3,4-thiadiazole (**11**).

The thiadiazole **4** (2.7 g, 0.01 mol) was added to a cold suspension of finally deviated potassium hydroxide (0.56 g, 0.01 mol) in dry dimethyl formamide (20ml) and then the reaction mixture was stirred for 15 minutes. Carbon disulphide (0.76 ml, 0.01 mol) was added drop wise and the reaction mixture was allowed to stand for 3 hrs. The reaction mixture was cooled to 0°C and stirred with ethyl chloroacetate (1.23 ml, 0.01 mol) at room temperature for 3hrs and then allow to stand overnight. The reaction mixture was poured into ice/cold water and acidified with concentrated hydrochloric acid. The obtained solid was separated by filtration, washed with water, dried, and recrystallized from methanol to give **11** as pale yellow crystals, Yield: 75%,

mp:180-182°C; ¹H-NMR (DMSO-d₆) δ (ppm): 10.28 (s, 1H, NH, exchangeable with D₂O), 7.64-7.48 (m, 5H_{arom}), 7.06 (d, 1H, PhCH=, J= 15.4 Hz), 6.96 (d, 1H, PhCH=CH, J= 15.4 Hz), 4.23 (s, 1H, CHCN), 4.207 (q, 2H, CH₂CH₃, J= 7.2 Hz), 4.21 (s, 2H, S-CH₂CO), 1.22 (t, 3H, CH₂CH₃, J= 7.2 Hz); IR (KBr) v: 3439 (NH), 2202 (C≡N), 1727, 1677 (C=O), 1624 (C=N); MS m/z (%): 432 (M⁺, 11), 386 (11), 358 (2), 267 (4), 229 (6), 131 (17), 103 (8), 77 (11). Anal. Calcd. for C₁₈H₁₆N₄O₃S₃ (432.528): C, 49.98; H, 3.72; N, 12.95; S, 22.24. Found: 49.92; H, 3.68; N, 13.05; S, 22.30.

2- Cinnamoylamino -6,8-dicyano-7-(3,4-dimethoxyphenyl)-5-imino-5H-1,3,4-thiadiazolo[3,2-a]pyridine (13).

A mixture of thiadiazole **4** (2.7g, 0.01 mol), 3,4-dimethoxybenzylidene malononitrile (2.2 g, 0.01 mol) and piperidine (0.5 ml) in ethanol (20 ml) was refluxed for 6 hrs. The solid formed after concentration was separated by filtration, dried, and recrystallized from dioxane to give **13** as light brown crystals, Yield:48%, mp: 270-272°C; ¹H-NMR (DMSO-d₆) δ (ppm): 11.01 (s, 1H, NH, exchangeable with D₂O), 8.18 (s, 1H, =NH, exchangeable with D₂O), 7.68-6.98 (m, 10H, 8H_{arom}+2H olefinic proton), 3.87 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃); IR (KBr) v: 3245, 3224, 3170 (NH), 2216 (C≡N), 1687 (C=O), 1628 (C=N); MS m/z (%): 456 (M⁺-CN; 28), 441 (98), 417 (50), 247 (20), 131 (100), 103 (89), 77 (54). Anal. Calcd. for C₂₅H₁₈N₆O₃S (482.500): C, 62.23; H, 3.73; N, 17.42; S, 6.65. Found: 62.23; H, 3.46; N, 17.46; S, 6.70.

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