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Synthesis and Reactivity of Cyanomethyl 2-Amino-4-methylthiazolyl Ketone. A Facile Synthesis of Novel Pyrazolo[5,1-c]1,2,4-triazine, 1,2,4-Triazolo[5,1-c]1,2,4-triazine, 1,2,4-Triazino[4,3-a]benzimidazole, Pyridazine-6-imine and 6-Oxopyridazinone Derivatives

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ABSTRACT: *The novel and versatile cyanomethyl 2-amino-4-methylthiazolyl ketone* **(5)** *was prepared by treatment of bromomethyl 2-amino-4-methyl thiazolyl ketone* **(4)** *with potassium cyanide. Reaction of* **5** *with heterocyclic diazonium salts* **6a,b** *and* **10** *afforded the corresponding hydrazones* **7a,b** *and* **11,** *respectively. Refluxing of the hydrazones in pyridine afforded the corresponding pyrazolo[5,1-c]-1,2,4-triazine, 1,2,4-triazolo[5,1-c]-1,2,4-triazine, and 1,2,4-triazolo[4,3-a]benzimidazole derivatives* **8a,b** *and* **12,** *respectively, via intramolecular cyclization. Compound* **5** *coupled also with benzenediazonium chloride to afford the corresponding hydrazone* **14,** *which is an excellent precursor for the synthesis of pyridazine-6-imine* **17a** *and pyridazinone* **17b.** *The pyridazine derivatives* **17a,b** *were also prepared by an independent route, that is, the condensation with malononitriles and coupling with benzenediazonium chloride, followed by intramolecular cyclization.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 385–390, 1999

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INTRODUCTION

A lot of compounds containing the thiazole ring system are of considerable importance because of their anti-inflammatory [1] and antibacterial activity [2]. Thiazole derivatives have also found wide pharmaceutical importance and phytosanitary uses [3]. This represents a part of our program aimed at developing simple and efficient synthetic approaches for fused ring systems with bridgehead nitrogen atoms [4–6] utilizing inexpensive and readily obtainable starting materials. In conjunction with this work, we report here the synthesis of the versatile, hitherto unreported cyanomethyl 2-amino-4-methylthiazolyl ketone **(5)** as a readily obtainable precursor for the synthesis of several new heterocycles in which the thiazole moiety is incorporated.

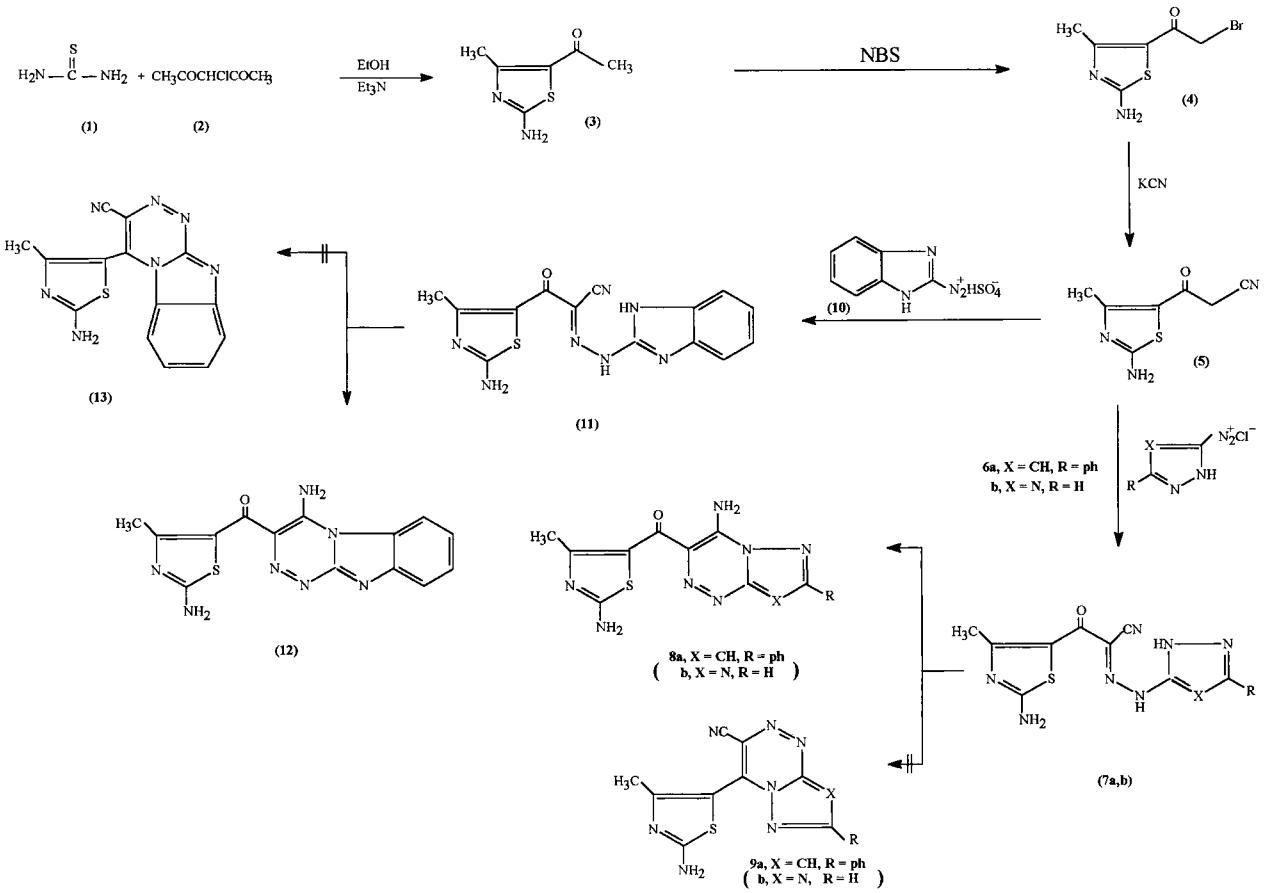
The starting material 5-acetyl-2-amino-4-methylthiazole **(3)** could be prepared by the reaction of thiourea **(1)** with 3-chloroacetylacetone **(2)**. Reaction of N-bromosuccinimide with compound **3** afforded bromomethyl 2-amino-4-methylthiazolyl ketone **(4)**. Reaction of **4** with ethanolic potassium cyanide solution gave the desired cyanomethyl 2-

amino-4-methylthiazolyl ketone **5**. Assignment of the structures of compounds **4** and **5** was based on their spectroscopic data and elemental analyses (see Experimental) (Scheme 1).

For example, the ^{1}H NMR spectra of **4** and **5** revealed the presence of a singlet peak at δ = 2.15–2.23 due to the methyl protons and another one at δ = 4.45–4.56 due to the active methylene protons, in addition to a broad singlet peak at δ = 8.51–8.53 due to the NH_2 protons. The IR spectra clearly indicate the presence of an amino, a cyano, and a carbonyl group.

Coupling of **5** with 3-phenylpyrazole-5-diazonium chloride **(6a)** in ethanol afforded the 4-amino-3-(2-amino-4-methylthiazol-5-yl)carbonyl-7-phenylpyrazolo[5,1-c]-1,2,4-triazine **(8a)** in high yield. The formation of **8a** is assumed to proceed via the isolable intermediate hydrazone **7a**, which undergoes intramolecular cyclization when boiled in pyridine to give the final product **8a**. The structure of 3-(2-amino-4-methylthiazol-5-yl)-3-oxo-2-(3-phenyl-1H-pyrazol-5-ylhydrazono)propanenitrile **(7a)** was established on the basis of its elemental analyses and spectral data. The ^{1}H NMR spectrum of **7a** displayed a singlet peak at δ = 6.35 due to a pyrazolo H-4, another broad one at δ = 9.53 due to the pyrazole NH peak, and the hydrazone NH peak at δ = 11.05 in addition to the amino and methyl protons. Their IR spectra showed conjugated carbonyl, cyano, amino, and hydrazone NH absorption bands near 1660, 2213, and 3350–3315 cm^{-1}, respectively. The IR spectrum of the isolated **8a** showed the lack of a cyano group absorption band and revealed a carbonyl absorption band at 1648 cm^{-1} (Scheme 1).

Similar to its behaviour toward **6a**, compound **5** coupled also with 1,2,4-triazole-5-diazonium chloride **(6b)** or 1H-benzimidazole-2-diazonium sulfate **(10)** to afford the corresponding hydrazones **7b** and **11**, respectively. The hydrazones **7b** and **11** were readily cyclized intramolecularly when boiled in pyridine to give the 1,2,4-triazolo[5,1-c]-1,2,4-triazine **(8b)** and 1,2,4-triazino[4,3-a]benzimidazole **(12)** derivatives, respectively. Assignment of the structures of compounds **8b** and **12** was based on their spectroscopic data. The amino and carbonyl groups in both **8b** and **12** appeared in the IR spectra at 3356–



SCHEME 1

3310, 3180, and 1656 cm^{-1}. Based on the previous IR data, the other possible structures **9b** and **13** were readily ruled out because of the lack of a cyano absorption band (Scheme 1).

Coupling of **5** with benzenediazonium chloride afforded the corresponding hydrazone **14**, the structure of which was established based on elemental and spectral analyses. The ^1H NMR spectrum of **14** revealed a singlet signal at $\delta = 2.15$ due to the methyl protons, a multiplet signal at $\delta = 7.15–8.52$ due to the phenyl and amino protons, in addition to a broad singlet signal due to the hydrazone NH. Treatment of the hydrazone **14** with malononitrile **(15a)** in the presence of ammonium acetate at 200°C for 1 hour afforded the product that can be formulated as **16a** or the isomeric **17a**. Structure **16a** was readily ruled out based on the stability of the reaction product under such conditions as to effect cyclization of arylhydrazononitriles of similar structure [7–9]. For example, the product of reaction of **14** and **15a** was recovered unchanged on long reflux with acetic acid or pyridine. The IR spectrum of **17a** revealed the C=N absorption band at 1660 cm^{-1} similar to that reported for pyridazine-6-imine [8,9]. Similarly, compound **14** condensed with ethyl cyanoacetate **(15b)** to yield the pyridazinone **17b** (Scheme 2).

3-Oxopropanenitrile undergoes the Knoevenagel condensation with malononitrile [9] to yield the condensation product that was converted into a variety of readily accessible polyfunctional heterocycles. We have been interested in determining whether such Knoevenagel condensations can be effected with **5**, as the condensation product appeared to be potentially very useful in heterocyclic synthesis. It has been found that 3-(thiazol-5-yl)-3-oxopropanenitrile **(5)** reacts with **15a** when refluxed in dimethylformamide containing a catalytic amount of piperidine to yield the condensation product **18a**. The structure of **18a** was established based on its elemental and spectral analyses (experimental part) and its chemical reactivity. Thus, **18a** coupled with benzendiazonium chloride to yield the corresponding hydrazone **19a**, which readily cyclized on reflux in pyridine for 2 hours to yield the pyridazine-6-imine **(17a)** (Scheme 2). Similarly, when **5** was treated with ethyl cyanoacetate, the condensation product **18b** was obtained. The compound **18b** undergoes coupling with benzenediazonium chloride followed by refluxing in pyridine, to yield the pyridazinone **17b**.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded in KBr disks on a Pye-Unicam SP 3-300 infrared spectrophotometer. The ^1H NMR spectra were recorded in deuterated chloroform or DMSO-d_6 on a Varian Gemini 200 NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer at 70 eV. Microanalyses were carried out at the Microanalytical Center, University of Cairo, Giza, Egypt. 3-Chloroacetylacetone **2** [10] and heterocyclic diazonium salts **6a,b** [11], **10** [12] were prepared according to literature procedures.

Methyl 2-Amino-4-methyl-5-thiazolyl Ketone (**3**)

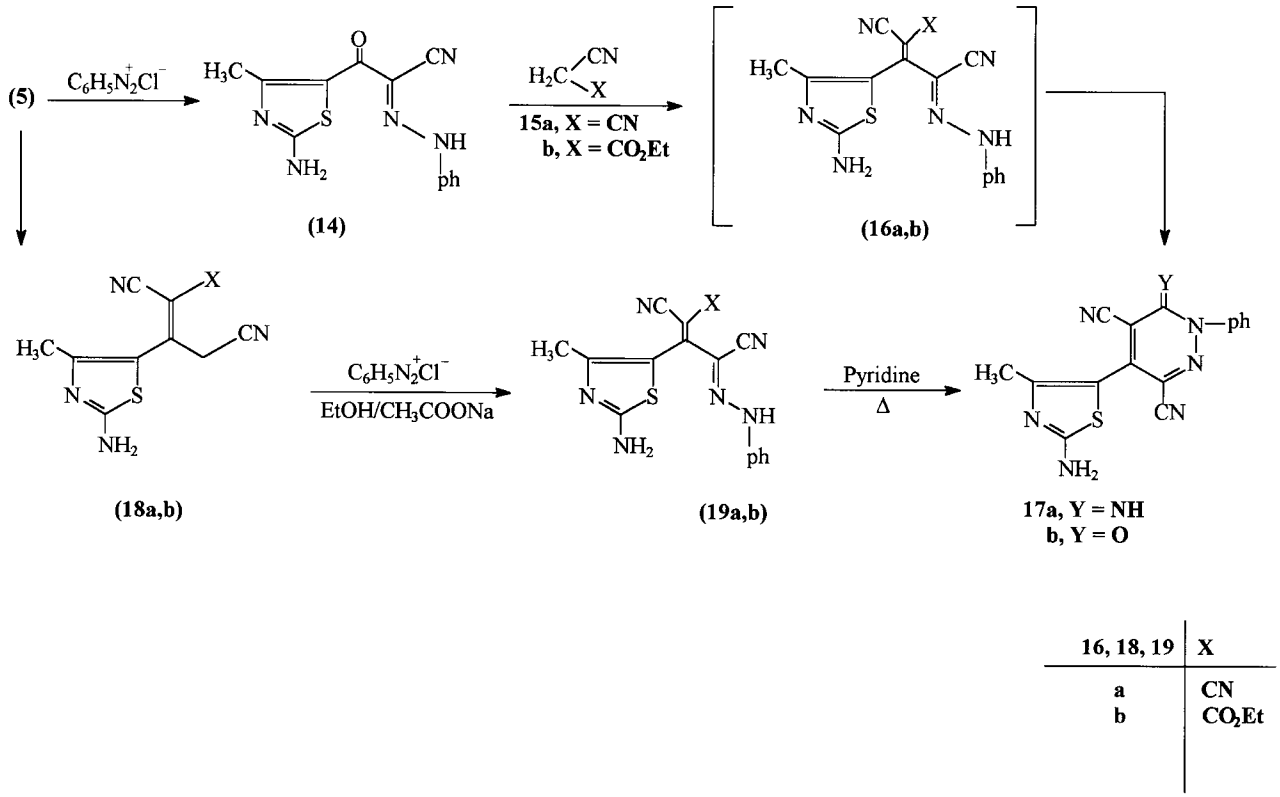
To a stirred solution of thiourea **(1)** (15.2 g, 0.2 mol) in absolute ethanol (75 mL) containing a catalytic amount of triethylamine was added dropwise a solution of 3-chloroacetylacetone (26.9 g, 0.2 mol) in 10 mL of absolute ethanol. After complete addition, the mixture was stirred at room temperature for 30 minutes and then refluxed for 5 hours. The reaction mixture was cooled, a solid filtered off, washed with cold ethanol, dried, and finally recrystallized from DMF to afford compound **3** in 70% yield; m.p. 275°C; IR (KBr): ν 3426, 3260 (NH_2), 1711 (C=O) cm^{-1}; ^1H NMR [DMSO-d_6]: $\delta = 2.35$ (s, 3H), 2.78 (s, 3H), 8.48 (br, 2H); Calcd for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.95; S, 20.50%. Found: C, 46.10; H, 5.12; N, 17.88; S, 20.46%.

Bromomethyl 2-Amino-4-methylthiazolyl Ketone (**4**)

A mixture of **3** (3.12 g, 0.02 mol) and *N*-bromosuccinimide (3.52 g, 0.02 mole) in 50 mL of chloroform was refluxed for 5 hours then allowed to cool. The precipitate was filtered off, washed with water, dried, and finally recrystallized from ethanol to afford 3.8 g (80.9%) of compound **4**; m.p. 240°C; IR (KBr): ν 3385, 3210 (NH_2), 1695 (C=O) cm^{-1}; ^1H NMR [DMSO-d_6]: $\delta = 2.15$ (s, 3H), 4.45 (s, 2H), 8.51 (br, 2H). Calcd for $C_6H_7N_2OSBr$: C, 30.65; H, 3.00; N, 11.92; S, 13.64; Br, 33.99%. Found: C, 30.61; H, 2.98; N, 11.90; S, 13.61; Br, 33.92%.

Cyanomethyl 2-Amino-4-methylthiazolyl Ketone (**5**)

To a solution of 5-bromoacetylthiazole **(4)** (4.7 g, 0.02 mol) in absolute ethanol (50 mL) was added a solution of potassium cyanide (1.3 g, 0.02 mol in 10 mL water) with stirring. The reaction mixture was heated on a boiling water bath. The reaction mixture was left at room temperature for 24 hours, with stirring, then diluted with water. The solid that precipitated was filtered off, washed with water, dried, and finally recrystallized from ethanol to afford 2.9 g



SCHEME 2

(80.1%) of compound **5**; m.p. 214°C; IR (KBr): ν 3330, 3225 (NH_2), 2240 (C≡N), 1703 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.19 (s, 3H), 4.51 (s, 2H), 8.53 (br, 2H). Calcd for $C_7H_7N_3OS$: C, 46.39; H, 3.89; N, 23.20; S, 17.67%. Found: C, 46.41; H, 3.85; N, 23.15; S, 17.65%.

Reaction of **5** *with Heterocyclic Diazonium Salts* **6a,b** *and* **10**

General Procedure. A cold solution of heterocyclic diazonium salt (20 mmol) **6a,b** or **10** was added to a cold solution of thiazolylacetonitrile (3.62 g, 20 mmol) in ethanol (50 mL) containing sodium acetate (3 g) portionwise with stirring at 0–5°C over a period of 30 minutes. After complete addition, the reaction mixture was stirred for a further 5 hours, then kept in an ice chest for 24 hours, and finally diluted with cold water, and the solid product so formed was collected by filtration, washed with water, dried, and finally recrystallized from pyridine to afford the corresponding hydrazones **7a,b** and **11**, respectively.

7a. Yield, 79%; m.p. 281–282°C; IR (KBr): ν 3350–3315, 3250 (NH_2 and 2NH), 2213 (C≡N), 1660 (C=O), 1607 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 2.31 (s, 3H), 6.35 (s, 1H, pyrazol H-4), 7.11–7.9 (m, 5H), 8.43 (br, 2H), 9.53 (br, 1H), 11.05 (br, 1H). Calcd. for $C_{16}H_{13}N_7OS$: C, 54.69; H, 3.73; N, 27.90; S, 9.13%. Found: C, 54.65; H, 3.69; N, 27.88; S, 9.03%.

7b. Yield, 80%; m.p. 268–269°C; IR (KBr) ν 3356–3230, 3210 (NH_2 and 2NH), 2219 (C≡N), 1668 (C=O), 1601 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 2.38 (s, 3H), 6.11 (s, 1H, triazole H-5), 8.56 (br, 2H), 10.2 (br, 1H), 10.98 (br, 1H). Calcd. for $C_9H_8N_8OS$: C, 39.12; H, 2.92; N, 40.56; S, 11.61%. Found: C, 39.0; H, 2.89; N, 40.51; S, 11.58%.

11. Yield, 82%; m.p. 286–288°C; IR (KBr) ν 3345–3285, 3180 (NH_2 and 2NH), 2205 (C≡N), 1665 (C=O), 1600 (C=O) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 2.3 (s, 3H), 7.2–8 (m, 4H), 8.45 (br, 2H), 10.1 (br, 1H), 11.82 (br, 1H). Calcd. for $C_{14}H_{11}N_7OS$: C, 51.68; H, 3.41; N, 30.14; S, 9.86%. Found: C, 51.61; H, 3.39; N, 30.09; S, 9.81%.

Cyclization of the Heterocyclic Hydrazones **7a,b** *and* **11**

Route A. A solution of the appropriate hydrazone **7a,b** or **11** (2 mmol) in pyridine (25 mL) was

refluxed for 4 hours, left to cool to room temperature, then poured into H_2O containing HCl. The solid product so formed was collected by filtration and recrystallized from dimethylformamide to afford the corresponding fused-ring system **8a,b** and **12**, respectively. ^{1}H NMR spectra were not obtained for these product due to their insolubility in common NMR solvents.

Route B. In a sand bath, an appropriate hydrazone **7a,b** or **11** (2 mmol) was heated for 1/2 hour. The solid product, formed upon trituration with ethanol, was collected by filtration, washed with ethanol, dried, and finally recrystallized from dimethylformamide to afford the corresponding fused-ring system **8a,b** and **12**, respectively, identical in all respects (mp., mixed mp. and spectral data) with that obtained by route A.

8a. Yield, 80%; mp. > 300°C; IR (KBr): ν 3371, 3210(NH_2), 1648(C=O), 1602(C=N) cm^{-1}; Calcd. For $C_{16}H_{13}N_7OS$: C, 54.69, H, 3.73; N, 27.90; S, 9.13%. Found: C, 54.65; H, 3.71; N, 27.88; S, 9.11%.

8b. Yield, 82%; mp >300°C; IR (KBr); v 3350, 3190(NH_2), 1658(C=O), 1605 (C=N) cm^{-1}; Calcd. for $C_9H_8N_8OS$: C, 39.12; H, 2.92; N, 40.56; S, 11.61%. Found: C, 39.10; H, 2.89; N, 40.51; S, 11.59%.

12. Yield, 86%; mp >300°C; IR (KBr); v 3380, 3195(NH_2), 1650(C=O), 1612 (C=N) cm^{-1}; MS, m/z (%) 325(M^+, 93.6), 297(61.3), 270(19.2), 230(53.3), 141(80), 77(82); Calcd. for $C_{14}H_{11}N_7OS$: C, 51.68; H, 3.41; N, 30.14; S, 9.86%. Found: C, 51.65; H, 3.40; N, 30.10; S, 9.85%.

2-Phenylhydrazono-3-amino-4-methylthiazol-5-yl)-3-oxopropanenitrile 14

A cold benzenediazonium chloride (20 mmol) solution was added portionwise with stirring to a cold solution (0–5°C) of cyanomethyl 2-amino-4-methylthiazolyl ketone (**5**, 3.62 g, 20 mmol) in ethanol (50 mL) in the presence of sodium acetate trihydrate (2 g) over a period of 30 minutes. The reaction mixture was stirred for a furthur 2 hours at 0–10°C, then it was kept in an ice box for 12 hours. The precipitated product was filtered off, washed with water, and dried. Crystallization from dioxane afforded the hydrazone **14**; m.p. 205–206°C; IR (KBr): ν 3390, 3250, 3199 (NH_2 and NH), 2219 (C≡N), 1703 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.15 (s, 3H), 7.15–8.52 (m, 7H), 12.93 (br, 1H). Calcd. for $C_{13}H_{11}N_5OS$: C, 54.72; H, 3.89; N, 24.55; S, 11.24%. Found: C, 54.66; H, 3.85; N, 24.49; S, 11.21%.

1,6-Dihydro-6-imino(Oxo)-1-phenyl-4-(2-amino-4-methylthiazol-5-yl)pyridazine-3,5-dicarbonitriles **17a,b**

General Procedure. A mixture of **14** (2.85 g, 0.01 mol) and malononitrile **15a** (0.67 g, 0.01 mol) or ethyl cyanoacetate **15b** (1.13 g, 0.01 mol) and ammonium acetate (1.7 g, 0.02 mol) was heated at 200°C for 30 minutes. During this time, ammonia and ethanol (in the case of **15b**) were liberated, and the reaction mixture gradually solidified. After cooling, the solid was treated with ethanol, and the precipitated solid was filtered off, dried, and finally recrystallized from dimethylformamide to afford the corresponding pyridazineimine **17a** and pyridazinone **17b**.

17a. Yield, 78%; m.p. 223–225°C; IR (KBr) ν 3450, 3330, 3190 (NH_2 and NH), 2220–2205 (2CN), 1670 (C=N) cm^{-1}; ^{1}H NMR [DMSO-d_6]: δ = 2.15 (s, 3H), 7.36–8.42 (m, 7H), 10.04 (br, 1H). Calcd. for $C_{16}H_{11}N_7S$: C, 57.64; H, 3.33; N, 29.41; S, 9.62%. Found: C, 57.61; H, 3.30; N, 29.39; S, 9.61%.

17b. Yield, 62%; m.p. 245–246°C; IR (KBr) ν 3350 (NH_2), 2220–2210 (2C≡N), 1690 (C=O), 1630 (C=N) cm^{-1}; ^{1}H NMR [DMSO-d_6] δ = 2.33 (s, 3H), 7.25–8.46 (m, 7H). Calcd. for $C_{16}H_{10}N_6OS$: C, 57.47; H, 3.01; N, 25.14; S, 9.59%. Found: C, 57.42; H, 3.0; N, 25.11; S, 9.58%.

2-(2-Amino-4-methylthiazol-5-yl)propen-1,1,3-tricarbonitrile **18a**

To a solution of **5** (1.81 g, 0.01 mol) in dimethylformamide (30 mL) containing a catalytic amount of piperidine, malononitrile (0.67 g, 0.01 mol) was added. The reaction mixture was refluxed for 4 hours. The solid product, formed upon trituration with water containing a few drops of concentrated hydrochloric acid (37.5%), was collected by filtration and recrystallized from dimethylformamide to afford 1.63 g (71%, yield) of **18a**; m.p. 263°C; IR (KBr); ν 3240 (NH_2), 2899 (CH_2), 2226–2210 (3C≡N), 1650 (C=C) cm^{-1}; ^{1}HNMR [DMSO-d_6]: δ = 2.31 (s, 3H), 4.38 (s, 2H), 8.52 (br, 2H). Calcd. for $C_{10}H_7N_5S$: C, 52.39; H, 3.08; N, 30.55; S, 13.99%. Found: C, 52.32; H, 3.10; N, 30.51; S, 13.91%.

2-(2-Amino-4-methylthiazol-5-yl)propen-1-ethoxycarbonyl-1,3-dicarbonitrile **18b**

To 1.81 g (0.01 mol) of **5**, piperdine (0.5 mL) and ethyl cyanoacetate (1.13 g, 0.01 mol) were added. The mixture was heated at 200°C for 1/2 hour. The solid product, formed upon trituration with ethanol,

was collected by filtration and recrystallized from dimethylformamide to afford 2 g (73%) of **18b**; m.p. 230– 232°C; IR (KBr): ν 3265 (NH_2), 2990, 2895 (CH_3, CH_2), 2225–2215 (2C≡N), 1693 (C=O), 1642 (C=C) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 1.35 (t, 3H), 2.31 (s, 3H), 3.86 (s, 2H), 4.49 (q, 2H), 8.42 (br, 2H). Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28; S, 11.60%. Found: C, 52.11; H, 4.34; N, 20.15; S, 11.58%.

3-Phenylhydrazono-2-(2-amino-4-methylthiazol-5-yl)propene Derivatives **19a,b**

To a stirred cold solution of **18a,b** (20 mmol) in pyridine was added benzenediazonium chloride (20 mmol) portionwise over a period of 30 minutes at 0–5°C. After complete addition, the reaction mixture was stirred for a further 4 hours at 0–5°C. The solid that precipitated was collected, washed with water, and dried. Recrystallization from dioxane afforded the corresponding hydrazones **19a,b**, respectively.

19a. Yield, 73%; m.p. 292–293°C; IR (KBr); ν 3410, 3320, 3250 (NH_2 and NH), 2225, 2210 (3C≡N), 1615 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ = 2.15 (s, 3H), 7.5–8.45 (m, 7H), 13.4 (br, 1H). Calcd. for $C_{16}H_{11}N_7S$: C, 57.64; H, 3.33; N, 29.41; S, 9.62%. Found: C, 57.58; H, 3.31; N, 29.38; S, 9.57%.

19b. Yield, 70%; m.p. 288–289°C; IR (KBr); ν 3380, 3150, 3210 (NH_2 and NH), 2218, 2205 (2C≡N), 1710 (C=O), 1605 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]; δ = 1.36 (t, 3H), 2.30 (s, 3H), 4.46 (q, 2H), 7.1–8.46 (m, 7H), 12.43 (br, 1H). Calcd. for $C_{18}H_{16}N_6O_2S$: C, 56.83; H, 4.24; N, 22.09; S, 8.43%. Found: C, 56.79; H, 4.18; N, 22.00; S, 8.39%.

Cyclization of the Hydrazones **19a,b**

A solution of **19a,b** (1 mmol) in pyridine (15 mL) was heated under reflux for 3 hours, then it was left to cool and was diluted with water (15 mL). The separated solid was collected by filtration, washed with cold water, and dried. Crystallization from DMF afforded **17a,b**, respectively (m.p., mixed m.p., and spectral data).

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