Synthesis of [1,2,4]Triazolo[3,4-*b*][1,3]thiazine-5-carboxylates *via* One-Pot Reaction of *N*-Substituted-hydrazino-carbothioamides with Diethyl Maleate

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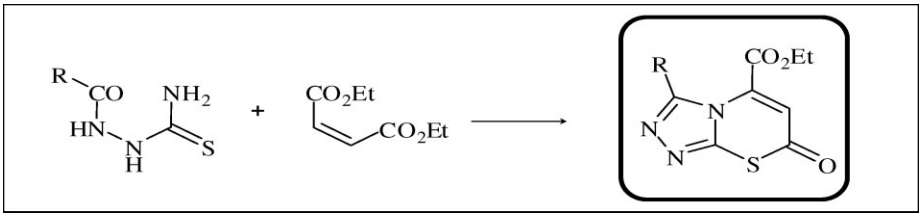

Diethyl maleate reacts with *N*-substituted-hydrazino-carbothioamides to form ethyl [1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates. Reaction proceeds *via* bicyclization and oxidation processes.

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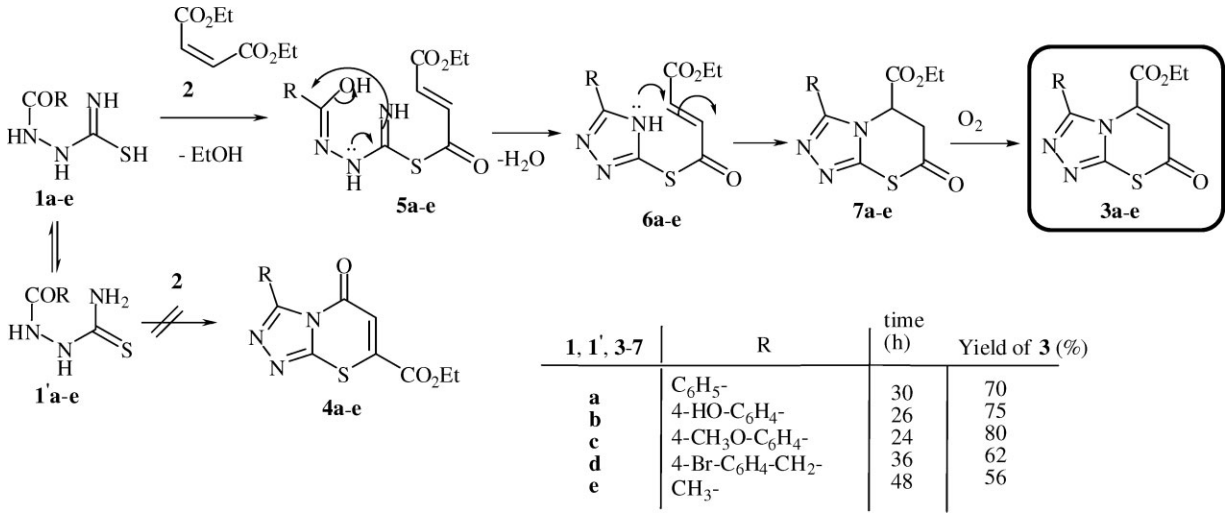
INTRODUCTION

Thioamides and their derivatives occupy a special place among *N*,*S*-containing compounds used in the synthesis of heterocyclic systems, due to their accessibility and the ability to act as difunctional nucleophiles. Reaction of acetylenecarboxylic acid derivatives with *N*,*S*-dinucleophiles provides the general approach for the construction of 1,3-thiazolidine and 1,3-thiazine systems, which are of great interest [1,2]. [1,2,4]Triazepine-3-thiones have been obtained during the reactions of *N*-substituted-hydrazino-carbothioamides with dimethyl acetylene-dicarboxylate and dibenzoyl acetylene under microwave irradiation [3]. The proton-coupled ^{15}N-NMR spectra of hydrazine-carbothioamides have been taken at the natural-abundance level in neutral, basic and acidic solutions at 25°C. The *N*-H proton-exchange reactions of the hydrazino-NH_2 groups in both compounds were found to be very rapid in the presence of acid, but quite slow in the presence of base [4]. Recent report has shown that various *N*-ethyl hydrazine-carbothioamides can undergo different cyclization reactions to give five member heterocycles, which showed a general stimulation effect on B-cells' response [5]. Recently Aly *et al*. [6] investigated the reaction between 2,3-diphenylcyclopropenone and ylidene-*N*-phenylhydrazine-carbothioamides. 1,3-Thiazines have shown wide biological activities. For example, they have shown potential CNS activity [7], potential analgesic, anti-inflammatory, activities [8], and activity as chemotherapeutic agents (i.e., leishmanicides) [9], in addition to their antifungal activity [10]. Our synthetic program has been concerned with the preparation of novel heterocycles efficiently [11–13]. On the basis of the aforementioned encouraging results, we have investigated the reaction of *N*-substituted-hydrazino-carbothioamides **1a**-**e** [14] with diethyl maleate (**2**) to synthesize heterocyclic systems, which might give prospective biological and/or pharmaceutical activities.

RESULTS AND DISCUSSION

Now we have reacted *N*-substituted-hydrazino-carbothioamides **1a**-**e** [14] with diethyl maleate (**2**); the reactions gave mainly the corresponding ethyl 7-oxo-3-substituted-7*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates **3a-e** (Scheme 1). We chose compounds **1a-d** having aryl groups, whereas we used the methyl derivative **1e** to generalize the idea beyond benzenoid aromatics, to alkyl-substituted starting materials. The structural proof of **3a**-**e** was based upon the mass, ^{1}H-NMR, ^{13}C-NMR and IR spectra, and elemental analyses. The IR and ^{13}C-NMR spectra of **3a**-**e** supported the disappearance of any thione and/or NH group. Mass spectrometry and elemental analysis of **3a** proved its molecular formula to be $C_{14}H_{11}N_3O_3S$. The ^{1}H-NMR spectrum of **3a** showed three multiplets for the aromatic phenyl. Besides, the ester-ethyl protons appeared at δ_H 4.12 (q, 2 H, J = 6.8 Hz, CH_2) and 1.25 (t, 3 H, J = 6.8 Hz, CH_3). The H-6 proton in the ^{1}H-NMR spectrum of **3a** resonated at δ_H 6.82, whereas CH-6 appeared at δ_C 124.2. The ^{13}C-NMR spectrum supported the ^{1}H-NMR spectroscopic data by the distinctive appearance of the

Scheme 1. Reaction of *N*-substituted-hydrazino-carbothioamides **1a-e** with diethyl maleate (**2**). Condition: AcOH, reflux, 1-3d.



1, 1', 3-7	R	time (h)	Yield of **3** (%)
a	C_6H_5-	30	70
b	4-HO-C_6H_4-	26	75
c	4-CH_3O-C_6H_4-	24	80
d	4-Br-C_6H_4-CH_2-	36	62
e	CH_3-	48	56

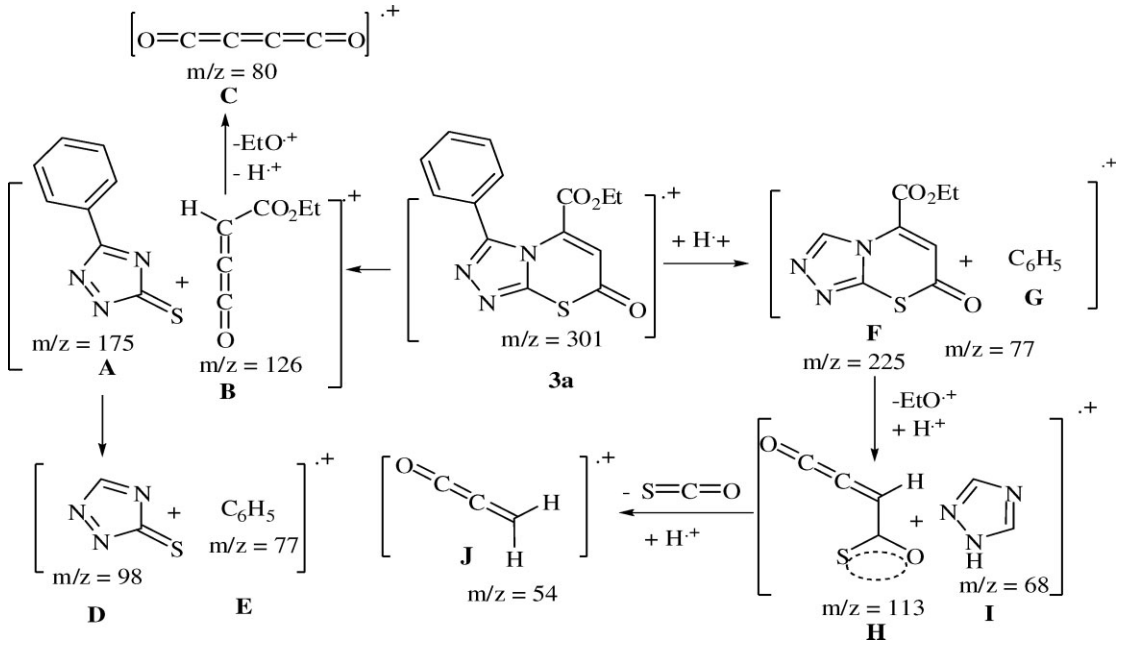
carbon signals representing the ethyl triazolo-thiazine-5-ester skeleton at δ_C 184.0 (C-7), 166.4 (CO-ester), 158.0 (C-3), 150.8 (C-8a), 131.0 (C-5) and 124.2 (CH-6). In **3b**, the mass spectrometry and elemental analysis proved the molecular formula to be $C_{14}H_{11}N_3O_4S$. The IR spectrum did not reveal any absorption due to C=S and/or NH groups, but an absorption band at ν_{max} 3490 cm^{-1} was assigned to the OH stretching. In the ^{1}H-NMR spectrum of **3b**, the OH proton absorbed at δ_H 9.20. Distinctive ^{13}C-NMR signals of **3b** appeared at δ_C 184.2 (C-7), 158.4 (C-3), 150.6 (C-8a), 149.0 (OH-Ar-C), 134.0 (Ar-C-1′), 131.6 (C-5), 128.6 (*ortho*-Ar CH), 120.6 (*meta*-Ar CH), 124.6 (CH-6). The ester carbon signals appeared at δ_C 166.1 (CO), 59.6 (CH_2), and 13.0 (CH_3). In the ^{13}C-NMR of **3d**, characteristic carbon signals appeared at δ_C 183.2, 166.2, 158.3, 150.6, 134.8, 132.0, 129.2, 126.8, 124.4, 122.2, 33.6, and 24.2, which were assigned to C-7, CO-ester, C-3, C-8a, Br-Ar-C, C-5, Ar-C-1′, *ortho*-Ar CH, CH-6, *meta*-Ar CH, 60.2 CH_2-ester, benzyl-CH_2 and CH_3-ester, respectively (Experimental part). The reaction of **1e** with **2** took the longest time of refluxing (2d) compared with other substituents. The ^{1}H-NMR spectrum of **3e** revealed the proton signals at δ_H 6.82 (s, 1 H, H-6), 4.17 (q, 2 H, J = 6.7 Hz, CH_2-ester), 2.20 (s, 3 H, C-3-CH_3), 1.21 (t, 3 H, J = 6.7, CH_3-ester), whereas the carbon signals appeared at δ_C 184.2 (C-7), 166.6 (CO-ester), 158.4 (C-3), 151.2 (C-8a), 132.0 (C-5), 124.2 (CH-6), 59.8 (CH_2-ester), 22.2 (CH_3), 24.4 (CH_3-ester).

The yield percentages of the obtained products increase in the presence of aromatic moiety. On the other hand, the methyl derivative **1e** gives a lower yield and the reaction requires more time than the other derivatives **1a-d**.

The reaction mechanism proceeds *via* the HN=C—SH tautomer **1** instead of the H_2N—C=S tautomer **1′**. Evidently attack by the SH group is faster than attack by the amine [6]. Accordingly, the reaction of **1a-e** with **2** can be described as due to nucleophilic attack of the thiol group to the ester carbon accompanied by elimination of one molecule of ethanol to form the intermediate **5** (Scheme 1). Thereafter, amidine-like nucleophilic attack on the amide is accompanied by water elimination to give **6** (Scheme 1). Nucleophilic attack of the terminal NH on the π-deficient double-bond produces the corresponding triazolo-dihydrothiazines **7** (Scheme 1). Ultimately, we propose that aerial oxidation of **7** gives the stable heterocyclic compounds **3** (Scheme 1). In HMBC studies of **3a-c**, the aromatic protons showed a correlation with the carbonyl ester, but not with the carbonyl in position-7. In methyl derivative **3e**, the methyl revealed a medium correlation with the carbonyl-ester, whereas no correlation was indicated with C-7. In an NOE experiment, irradiation of the methyl protons in **3e** (δ_H 2.20) showed enhancement the CH_2-ester protons. These data unambiguously exclude the formation of isomers **4a-e** (Scheme 1).

The 70-eV EI mass spectra of compounds **3a-e** are illustrated in the experimental section. All compounds **3a-e** exhibit the molecular peaks as intense base ion peaks. Most indicative is the appearance of the triazolethiones$^+$ and ethyl 4-oxobuta-2,3-dienoate$^+$ (Scheme 2). For example, the fragmentation pattern of **3a** showed ion peaks for $\mathbf{A}^+$ and $\mathbf{B}^+$ at m/z 175 (50) and 126 (28), respectively. An abundant peak resulting from loss of ethanol from $\mathbf{B}^+$ leads to $\mathbf{C}^+$, whereas loss of phenyl group gave species $\mathbf{D}^+$ and $\mathbf{E}^+$ (Scheme 2). The ion peak $\mathbf{H}^+$ shows that it fragmented primarily *via* the loss of carbonoxysulfide from $\mathbf{H}^+$ to give $\mathbf{J}^+$ at m/z 54. Other species **F**-$\mathbf{J}^+$ of **3a** appeared as shown in Scheme 2.

Scheme 2. Fragmentation patterns of compound **3a**.



CONCLUSION

In conclusion, *N*-substituted-hydrazino-carbothioamides react with diethyl maleate *via* initial *S*-acylation followed by cyclizative conjugate addition to the unsaturated ester. A second cyclization forms a triazole ring, and aerial oxidation occurs to afford the [1,2,4]triazolo-[3,4-*b*][1,3]thiazine-5-carboxylate products.

EXPERIMENTAL

Melting points are uncorrected values. ^{1}H-NMR and ^{13}C-NMR spectra (Bruker AM 400, ^{1}H: 400.13 MHz, ^{13}C: 100.6 MHz) were obtained from deuterio-chloroform and deuterio-DMSO solutions; the chemical shifts are given relative to internal standard TMS. For preparative thin layer chromatography (PLC), glass plates (20 × 48 cm) were covered with slurry of silica gel Merck PF_{254} and air-dried using the solvents listed for development. Zones are detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in Assiut Microanalysis Center of Assiut University. Mass spectroscopy was performed at 70 eV with a Finnigan Mat 8430 spectrometer at the Institute of Organic Chemistry, TU-Braunschweig. Germany. The IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets.

Starting materials. *N*-Substituted-hydrazino-carbothioamides **1a-e** were prepared according to literature [14].

General procedure. To a 250 cm^3 two-necked round bottom flask containing a solution of **1a-e** (2 mmol) in glacial acetic acid (50 mL), a solution of **2** (0.344 g, 2 mmol) in glacial acetic acid (10 mL) was added dropwise with stirring. The mixture was refluxed for 1-2 d (the reaction was monitored by TLC). The solvent was evaporated under vacuum, and the solid residue was dissolved in dry acetone (30 mL), and the solution was chromatographed on thin layer plates (silica gel) using toluene. All zones were extracted and the obtained products were recrystallized from the stated solvents.

Ethyl 3-phenyl-7-oxo-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3] thiazine-5-carboxylate (3a). Yellow crystals 0.42 (70%), mp 212°C (ethanol); ^{1}H-NMR (400 MHz, deuterio-chloroform): δ_H 7.90-7.80 (m, 2 H, Ar-H), 7.60-7.50 (m, 2 H, Ar-H), 7.46-7.41 (m, 1 H, Ar-H), 6.82 (s, 1 H, H-6), 4.12 (q, 2 H, J = 6.8 Hz, CH_2-ester), 1.25 (t, 3 H, J = 6.8 Hz, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 184.0 (C-7), 166.4 (CO-ester), 158.0 (C-3), 150.8 (C-8a), 131.4 (Ar-C-1′), 131.0 (C-5), 130.0 (*para*-Ar CH), 127.8 (*ortho*-Ar CH), 127.2, (*meta*-Ar CH), 124.2 (C-6), 60.0 (CH_2-ester), 24.2 (CH_3-ester); IR (KBr): ν_{max} 3086-3008 (w, Ar-CH), 1720 (s, CO-ester), 1700 (s, CO), 1625 (s, C=N), 1590 (m, C=C) cm^{-1}; λ_{max} (CH_3CN, nm, lg ε): 400 (3.8); ms (EI): m/z 301 [M$^+$] (100), 286 (14), 272 (18), 256 (38), 228 (22), 225 (30), 175 (50), 152 (24), 126 (28), 113 (32), 98 (20), 80 (16), 77 (34), 68 (24), 54 (22). *Anal*. Calcd for $C_{14}H_{11}N_3O_3S$ (301.33): C, 55.81; H, 3.68; N, 13.95; S, 10.64. Found: C, 56.00; H, 3.60; N, 13.86; S, 10.70.

Ethyl 3-(4′-hydroxyphenyl)-7-oxo-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3]thiazine-5- carboxylate (3b). Yellow plates 0.47 g (75%), mp 234°C (ethanol); ^{1}H-NMR (400 MHz, deuterio-chloroform): δ_H 9.20 (s, 1 H, OH), 7.53-7.29 (m, 4 H, Ar-H), 6.74 (s, 1 H, H-6), 4.14 (q, 2 H, J = 7.0 Hz, CH_2-ester), 1.22 (t, 3 H, J = 7.0 Hz, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 184.2 (C-7), 166.1 (CO-ester), 158.4 (C-3), 150.6 (C-8a), 149.0 (Ar-C-OH), 134.0 (Ar-C-1′), 131.6 (C-5), 128.6 (*ortho*-Ar CH), 126.6, (*meta*-Ar CH), 124.6 (CH-6), 59.6 (CH_2-ester), 24.6 (CH_3-ester); IR (KBr): ν_{max} 3490 (s, OH), 3090-3010 (m, Ar-CH), 1724 (CO-ester), 1702 (CO), 1628 (s, C=N), 1596 (m, C=C) cm^{-1}; λ_{max} (CH_3CN, nm, lg

ε): 410 (4.0); ms (EI): m/z 317 [M^+] (100), 300 (22), 286 (24), 256 (14), 234 (26), 225 (34), 190 (24), 175 (22), 160 (42), 152 (32), 126 (30), 113 (40), 98 (20), 94 (40), 80 (26), 77 (32), 68 (26), 54 (20). *Anal*. Calcd for $C_{14}H_{11}N_3O_4S$ (317.33): C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: C, 52.78; H, 3.40; N,13.10; S, 10.06.

Ethyl 3-(4′-methoxyphenyl)-7-oxo-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3]thiazine-5-carboxylate (3c). Yellow crystals 0.53 g (80%), mp 298°C (acetonitrile); ^{1}H-NMR (400 MHz, deuterio-chloroform): δ_H 7.49-7.28 (m, 4 H, Ar-H), 6.80 (s, 1 H, H-6), 4.10 (q, 2 H, J = 6.9 Hz, CH_2-ester), 3.90 (s, 3 H, OCH_3), 1.25 (t, 3 H, J = 6.9 Hz, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 185.0 (C-7), 165.9 (CO-ester), 158.6 (C-3), 156.0 (CH_3O-C), 150.8 (C-8a), 134.2 (Ar-C-1′), 131.6 (C-5), 130.2 (*meta*-Ar CH), 125.2 (CH-6), 123.0 (*ortho*-Ar CH), 60.0 (CH_2-ester), 58.8 (OCH_3), 24.3 (CH_3-ester); IR (KBr): ν_{max} 3060-3007 (w, Ar-CH), 2996-2886 (aliph.-CH), 1722 (s, CO-ester), 1700 (s, CO), 1632 (s, C=N), 1590 (m, C=C) cm^{-1}; λ_{max} (CH_3CN, nm, lg ε): 418 (4.1); ms (EI): m/z 331 [M^+] (100), 316 (18), 300 (22), 286 (32), 258 (28), 226 (34), 205 (16), 174 (40), 126 (34), 113 (42), 108 (32), 99 (20), 80 (24), 77 (26), 68 (26), 54 (24). *Anal*. Calcd for $C_{15}H_{13}N_3O_4S$ (331.35): C, 54.37; H, 3.95; N, 12.68; S, 9.68. Found: C, 54.30; H, 3.98; N, 12.62; S, 9.72.

Ethyl 3-(4′-bromobenzyl)-7-oxo-7*H*-1,2,4-triazolo[3,4-*b*][1,3]thiazine-5-carboxylate (3d). Yellow crystals 0.47 g (62%), mp 290°C (ethyl acetate). ^{1}H-NMR (400 MHz, deuterio-DMSO): δ_H 7.46-7.10 (m, 4 H, Ar-H), 6.70 (s, 1 H, H-6), 4.07 (s, 2H, benzyl-CH_2), 4.14 (q, 2 H, J = 6.9 Hz, CH_2-ester), 1.21 (t, 3 H, J = 6.9, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-DMSO): δ_C 183.2 (C-7), 166.2 (CO-ester), 158.3 (C-3), 150.6 (C-8a), 134.8 (Br-C), 132.0 (C-5), 129.2 (Ar-C-1′), 126.8 (*ortho*-Ar CH), 124.4 (CH-6), 122.2 (*meta*-Ar CH), 60.2 (CH_2-ester), 33.6 (benzyl-CH_2), 24.2 (CH_3-ester); IR (KBr): ν_{max} 3082-3015 (w, Ar-CH), 2980-2880 (m, aliph.-CH), 1726 (s, CO-ester), 1700 (s, CO), 1612 (br, s, C=N), 1588 (m, C=C), 1112 (m, C—O) cm^{-1}; λ_{max} (CH_3CN, lg ε, nm): 388 (4.0); ms (EI): m/z 395 [M+1] (94), 393 [M-1] (100) 313 (32), 268 (28), 240 (26), 224 (45), 212 (28), 172 (40), 170 (55), 126 (18), 113 (24), 98 (30), 80 (22), 77 (40), 68 (22), 80 (22), 54 (18). *Anal*. Calcd for $C_{15}H_{12}BrN_3O_3S$ (394.24): C, 45.70; H, 3.07; Br, 20.27; N, 10.66; S, 8.13. Found: C, 45.60; H, 3.00; Br, 20.37; N, 10.50; S, 8.20.

Ethyl 3-methyl-7-oxo-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3]thiazine-5-carboxylate (3e). Pale yellow crystals 0.27 g (56%), mp 170°C (ethanol); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 6.82 (s, 1 H, H-6), 4.17 (q, 2 H, J = 6.7 Hz, CH_2-ester), 2.20 (s, 3 H, C-3-CH_3), 1.21 (t, 3 H, J = 6.7, CH_3-ester); ^{13}C-NMR (100.6 MHz, deuterio-chloroform): δ_C 184.2 (C-7), 166.6 (CO-ester), 158.4 (C-3), 151.2 (C-8a), 132.0 (C-5), 124.2 (CH-6), 59.8 (CH_2-ester), 22.2 (C-3-CH_3), 24.4 (CH_3-ester); IR (KBr): ν_{max} 3078-3000 (w, Ar-CH), 2980-2860 (m, aliph.-CH), 1718 (s, CO-ester), 1700 (s, CO), 1622 (s, C=N), 1590 (s, C=C) cm^{-1}; λ_{max} (CH_3CN, nm, lg ε): 390 (3.2); ms (EI): m/z 239 [M^+] (100), 194 (24), 166 (24), 151 (18), 126 (22), 113 (56), 80 (16), 64 (16), 54 (18). *Anal*. Calcd for $C_9H_9N_3O_3S$ (239.25): C, 45.18; H, 3.79; N, 17.56; S, 13.40. Found; C, 45.04; H, 3.70; N, 17.40; S, 13.40.

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