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Reaction of heterocyclic thioamides with dimethyl acetylenedicarboxylate. Synthesis of novel 2-azolyl-5-methoxycarbonylmethylene thiazolin-4-ones

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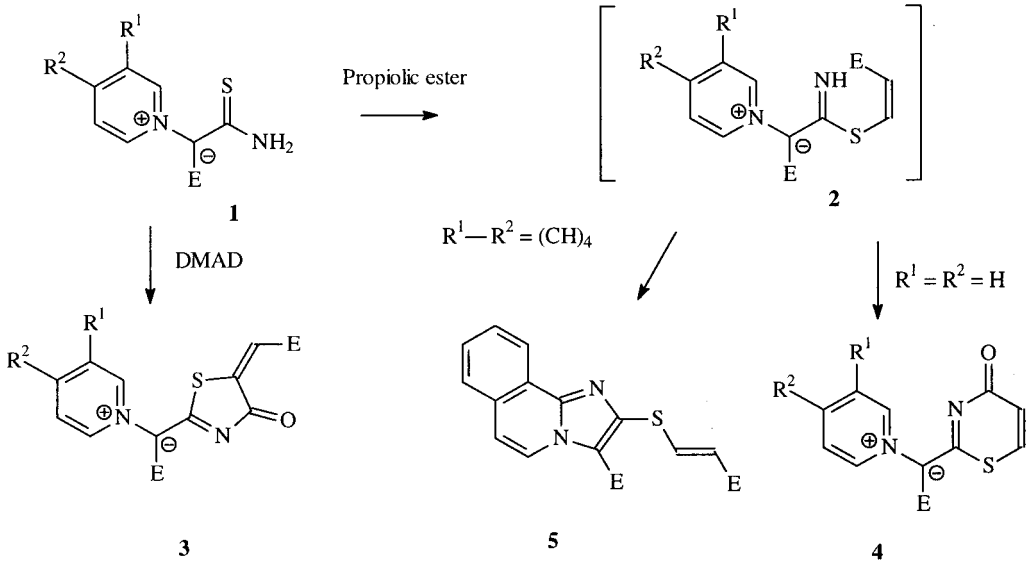
Abstract—A systematic study of the reactions of dimethyl acetylenedicarboxylate (DMAD) with heterocyclic thioamides has been carried out and a number of new 2-isoxazolyl-(**8**), imidazolyl-(**13a**,**b** and **17a**), 1,2,3-triazolyl-(**13d**,**e**) and 1,2,3-thiadiazolyl (**17b**) thiazolines have been prepared. The higher reactivity of the thioamide group in comparison with the amino group in these reactions has been established.

The reaction of thioureas and thiosemicarbazide derivatives with dimethyl acetylene dicarboxylate (DMAD) is known as a convenient and effective method to prepare 2-imino-5-methoxycarbonylthiazolidin-4-ones.[1–4] The reactions of thioamides with DMAD are studied to a lesser extent,[2,5,6] and a general strategy to prepare thiazoline derivatives based on this reaction was not developed before our work on the subject.[7] Earlier we have shown that the reaction of thiocarbamoyl pyridinium and isoquinolinium ylides **1** with esters of acetylenecarboxylic acids, depending on the nature of the acetylene, leads to formation of five- or six-membered rings to give ylides containing thiazolinone **3** and thiazinone moieties **4**.[6] The proof that the first step of the overall process includes addition of the sulfur atom onto the



Scheme 1.

Keywords: dimethyl acetylene dicarboxylate; thioamides; thiazoline.
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Table 1. ^{1}H Chemical shifts, δ (ppm)

No.	Solvent	^{1}H Chemical shifts
8	$CDCl_3$	2.97 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 7.04 (1H ,s, =CH), 7.5–7.6 (5H, m)
12g	DMSO-d_6	2.52 (3H, s, CH_3), 7.85 (1H, s, = CH)
13a	DMSO-d_6	1.32 (3H, t, CH_3); 3.25 (2H, q, CH_2); 3.80 (3H, s, OCH_3); 6.85 (1H, s, = CH); 8.15 (1H, s, = CH)
13b	DMSO-d_6	3.8 (3H, s, OCH_3), 4.53 (2H, q, CH_2); 6.87 (1H, s, = CH), 7.2–7.5(5H, m, ArH), 8.2 (1H, s, =CH)
13e	$CDCl_3$	2.7 (3H, s, SCH_3), 3.9 (3H, s, OCH_3), 4.2 (3H, s, NCH_3), 7.2 (1H, s, = CH)
13f	DMSO-d_6	2.58 (3H, s, SCH_3), 3.84 (3H, s, OCH_3), 5.83 (2H, s, CH_2), 7.04 (1H, s, =CH), 7.25–7.45 (5H, m, ArH)
15	DMSO-d_6	3.97 (3H, s, OCH_3), 6.66 (1H, s, =CH), 8.6 (1H, s, =CH), 7.40 (2H, d br, NH)
16d	DMSO-d_6	3.78 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 5.40 (1H, s, NH), 5.65 (1H, s, =CH), 6.89 (1H, s, NH), 14.84 (1H, s, NH)
16e	DMSO-d_6	2.80 (3H, d br, NCH_3), 3.71 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.57 (1H, s, =CH), 7.80 (1H, s br, NH)
17a	DMSO-d_6	3.78 (3H, s, OCH_3); 6.68 (1H, s, =CH); 7.56 (1H, s, =CH); 7.78 (2H, s, NH_2)
17b	DMSO-d_6	3.84 (3H, s, OCH_3); 6.97 (1H, s, =CH); 9.15 (2H, s, NH_2)

acetylene triple bond comes from the study of this type of ylides with ethyl propiolate. The intermediate product of type **2**, generated in the reaction of isoquinoline ylide and ethyl propiolate undergoes 1,5-electrocyclization to give, after oxidation, vinyl sulfide of type **5** (Scheme 1).

The formation of 2-substituted thiazolin-4-ones was also observed in the reaction of both benzothioamide[2] and conjugated enaminothioamides[5] with DMAD. In previous work, we have shown that novel 2,5-dimethylenethiazolidin-4-one derivatives can be prepared by the reaction of malonthioamide derivatives with DMAD.[7] The thioamides of heteroaromatic carboxylic acids have not been studied in the reaction with DMAD so far. In order to find a general approach to bis-heterocyclic compounds containing the thiazoline moiety, we have studied the reactions of azolecarbothioamides with DMAD, using isoxazoles **6**, imidazoles **12a**,**b** and **14a**, 1,2,3-triazoles **12d**–**g**, and 1,2,3-thiadiazole **14b**.

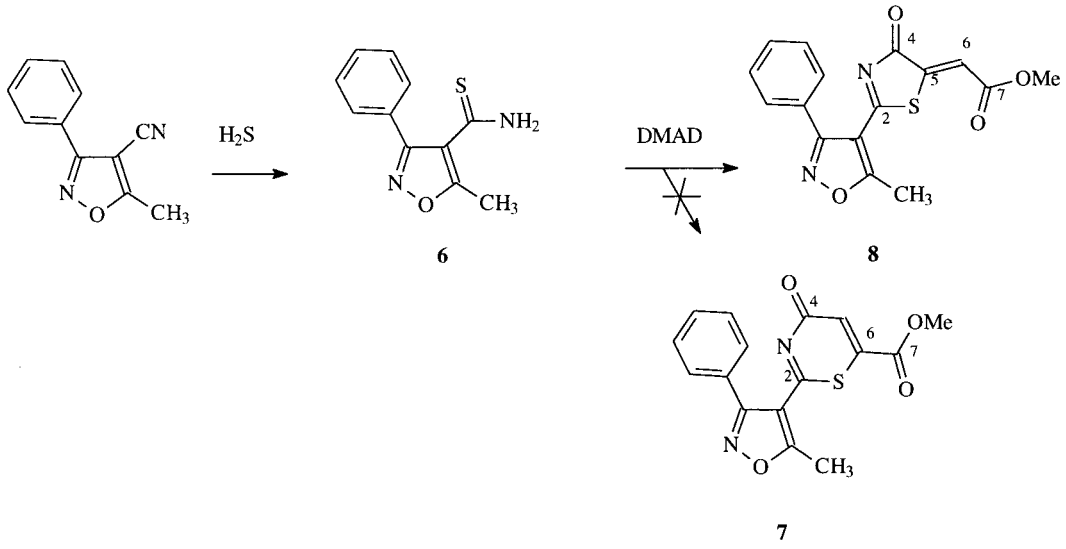
5-Methyl-3-phenylisoxazol-4-carbothioamide **6** was prepared in 50% yield by the treatment of the corresponding nitrile derivative with hydrogen sulfide. Reaction of 3-phenyl derivative **6** with DMAD in principle could give either thiazinone **7** or thiazoline **8** derivatives. We have found that this reaction in ethanol at room temperature results in the exclusive formation of bis-heterocycle **8**, containing a thiazolin-4-one ring.

The structure of product **8** was identified as a thiazolin-4-one by ^{1}H and ^{13}C NMR spectroscopy (Tables 1 and 2). The signal of the methine group resonates at a characteristic value of 7.04 ppm in the ^{1}H NMR spectrum.[7] The ^{1}H coupled ^{13}C spectrum of **8** shows a doublet signal at 122.6 ppm with a coupling constant of 173.0 Hz, which is typical for a C=CH fragment. Moreover, the signals of C_4 and C_7 at 180.8 and 165.7 ppm are more in agreement with the thiazoline rather than with the thiazinone structure.[7] In the case of the thiazinone structure one could expect the doublet signal at 108–112 ppm and the signals for C_4 and C_7 should be upfield at 165–160 and 158–161 ppm, respectively.[1,2] A final decision in favor of the thiazolinone structure can be made after considering the magnitudes of the ^{13}C–^{1}H coupling constants in the ^{13}C NMR spectrum.[7] The C_7 signal in the coupled spectrum of **8** is found as a doublet with a $^2J_{CH}$ coupling constant of 1.0 Hz, caused by the vinyl proton. This shows the presence of the exocyclic double bond in the structures of thiazoline. Furthermore, the constant $^3J_{C(4)H(6)}$ of 4.0 Hz clearly demonstrates the *Z*-configuration of the double bond C_5=C_6. In conclusion, the NMR spectra are in full agreement with the thiazoline structure for **8** and reject the thiazinone structure **7** (Scheme 2).

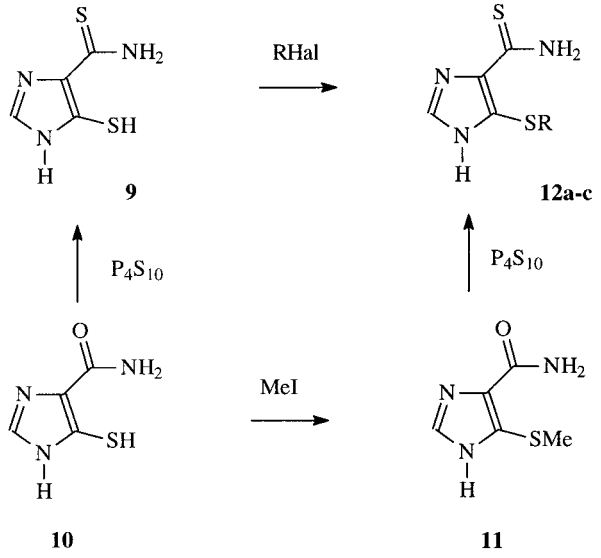
The 5(4)-mercaptoimidazol-4(5)-carbothioamide **9** contains two sulfur atoms which each may react with the triple bond of DMAD. To avoid the formation of the addition product of the acetylene function with the mercapto group, we first alkylated compound **9**, leading to sulfides **12a**–**c**. Compound **12c** was also obtained by thionation of 5(4)-methylthioimidazol-4(5)-carboxamide **11** with P_4S_{10} in boiling dioxane. This alternative synthesis proved the structure of compounds **12a**–**c** as 5-alkylmercaptoimidazole-5-carbothioamides (Scheme 3).

Table 2. ^{13}C Chemical shifts δ (ppm, solvent) and J_{C-H} (Hz)

No.	Solvent	^{13}C Chemical shifts δ								
		C_2	C_4	C_5	C_6	C_7	$^1J_{C6-H6}$	$^2J_{C5-H6}$	$^2J_{C7-H6}$	$^3J_{C4—H6}$
8	$CDCl_3$	183.2 (s)	180.8 (d)	142.2 (d)	122.6	165.7		1.0	<1.0	4.0
13b	DMSO-d_6		180.7	144.6	119.3	165.8				
13e	$CDCl_3$	182.2	181.8	142.9	123.0 (d)	165.8	167.0		<1.0	5.0
15	DMSO-d_6									
13f	DMSO-d_6	181.8	182.3	142.8	123.0	165.7				
17a	DMSO-d_6	173.2	179.6	146.5	114.9 (d)	166.3	170.0			
17b	DMSO-d_6	168.8	180.2 (d)	143.4 (d)	120.0	165.6	172.0	2.0		4.5



Scheme 2.

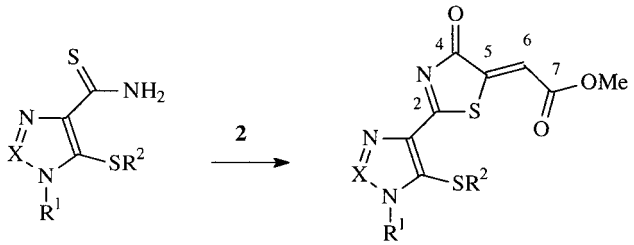


Scheme 3.

We have found that 5(4)-mercaptosubstituted imidazol-5(4)-carbothioamides **12a**,**b** also react smoothly with DMAD in chloroform to form 2-imidazolylthiazinones **13a**,**b** in good yield. The ^{1}H and ^{13}C NMR spectral data are, again in accordance with their structures as thiazolin-4-ones (Tables 1 and 2, Scheme 4).

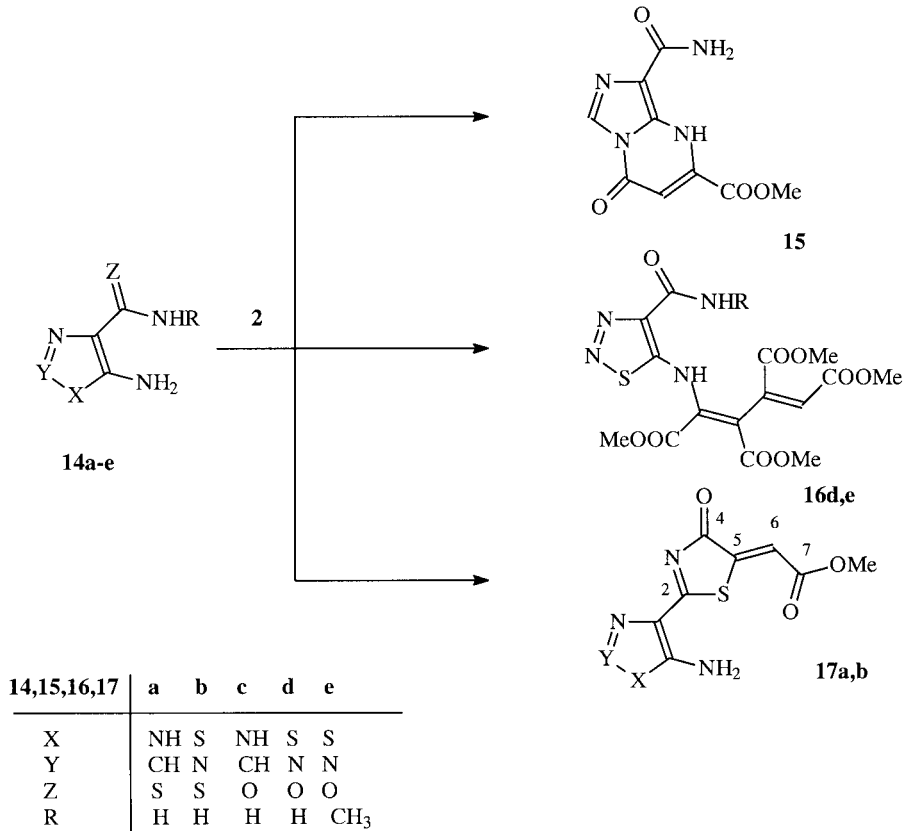
In contrast to imidazoles **12a**,**b**, 1,2,3-triazole-4-carbothioamides **12d**,**e** are unreactive towards DMAD. Only in the case of *N*-alkylated triazole **12f**,**g** we could obtain the thiazolin-4-ones **13f**,**g** in moderate yield. The lesser reactivity of the triazolecarbothioamides **12d**–**g** in comparison with the imidazolyl derivatives **12a**,**b** may be due to the inductive effect of the extra nitrogen atom on the thioamide functionality.

In the reaction of the 5-aminoimidazole-4-carbo(thio)-amides **14a**–**e** with DMAD one could expect the formation of various compounds, because both the (thio)amide group and the 5-amino group are able to react with DMAD.[8] It was found that the thioamides **14a**,**b** react exclusively with the



12, 13	a	b	d	e	f	g
X	CH	CH	N	N	N	N
R^1	H	H	Ph	Ph	Me	CH_2Ph
R^2	Et	CH_2Ph	CH_2Ph	Me	Me	Me

Scheme 4.



Scheme 5.

thioamide function to afford thiazolines **17a**,**b**. On the contrary, the reaction of 5-aminoimidazole-4-carboxamide **14c** with DMAD involves both the amino group and NH moiety of imidazole ring to give imidazo[1,5-*a*]pyrimidinone **15** in good yield.

On the other hand, reaction of 5-amino-1,2,3-thiadiazoles **14d**,**e** with DMAD took place to the amino group only, to furnish adducts with two moles of DMAD of type **16d**,**e**. The ^{1}H NMR spectra of these compounds contain four signals for the methoxycarbonyl groups at 3.70–3.96 ppm and a single methine signal at 5.6 ppm. In the ^{13}C NMR spectra of compounds **16d**,**e** four signals, due to the methoxycarbonyl groups at 51.5–53.4 ppm and five signals due to carbonyl atoms at 160.4–166.4 ppm were observed. The mass spectral data also confirm the structure of compounds **16d**,**e** as bearing a substituted butadiene moiety (Scheme 5).

On the other hand, we have found that the reactions of thioamides **14a**,**b** with DMAD occur selectively with the participation of the thioamide groups. Amino groups at position 5 do not take part in the process and these reactions lead to thiazolin-4-ones **17a**,**b** as single products. This experiment confirms the higher reactivity of the thioamide group in these reactions in comparison with the amino functionalities. The structures of these compounds are in a good agreement with their NMR spectra (Tables 1 and 2).

In conclusion, we have shown that reactions of heterocyclic thioamides with DMAD take place selectively with participation of the thioamide group to form novel conjugated bisheterocycles incorporating a thiazolinone ring.

1. Experimental

1.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AMX 400 with TMS as internal reference in DMSO-d_6 and $CDCl_3$ solutions. The products were analyzed by TLC on DC-Plastikfolen Kieselgel 60 F 254. The melting points were uncorrected. The mass spectra were recorded in a Varian-311A mass spectrometer under standard conditions.

Compounds **7**, **9**, **10**, **12c**–**f**, **14a**,**b**,**d**,**e** have been synthesized according to the literature.[9–11]

1.1.1. 5-Methyl-3-phenylisoxazol-4-carbothioamide (6). 5-Methyl-3-phenylisoxazol-4-carbonitrile **7** (0.01 mol) was added to a solution of sodium (0.005 mol) in ethanol (150 ml). The mixture was saturated by H_2S at 0°C. Then the mixture was heated at 75°C in a closed ampoule for 5 h. The precipitate formed after cooling was filtered off and recrystallized from ethanol, mp 173–175°C. Yield 50%. Found: N 13.0; S 14.97. Calcd for $C_{11}H_{10}N_2OS$. N 12.83; S 14.7%.

1.1.2. 3-Phenyl-4-(4-oxo-5-methoxycarbonylmethylene-thiazolin-2-yl)-5-methylisoxazole (8). DMAD (0.001 mol)

was added to a solution of carbothioamide **6** (0.001 mol) in ethanol. The mixture was stirred at room temperature for 2 h. Filtration gave compound **8** as yellow crystals, mp 228–231°C (from acetone). Yield 36%. Found: N 8.76; S 10.20. Calcd for $C_{16}H_{12}O_4N_2S$; N 8.54; S 9.76%.

1.1.3. 5(4)-Methylmercaptoimidazole-4(5)carboxamide (11). 5(4)-Mercaptoimidazol-4(5)-carboxamide **10** (0.01 mol) was added to a sodium methylate solution made of sodium (0.01 mol) and methanol (5 ml). After 30 min methyl iodide (0.012 mol) was added. The mixture was stirred at room temperature for 2 h. Filtration gave compound **11** as yellow crystals, mp 193–196°C (from ethanol). Yield 49%. Found: N 20.22; S 26.33. Calcd for $C_5H_7N_3OS$; N 20.40; S 26.73%.

1.1.4. 5(4)-Ethylmercaptoimidazole-4(5)carbothioamide (12a). The compound was obtained by analogy with **11** in ethanol as colourless crystals, mp 165–167°C (from ethanol). Yield 57%. Found: N 22.36; S 34.07. Calcd for $C_6H_9N_3S_2$; N 22.46; S 34.27%.

1.1.5. 5(4)-Benzylmercaptoimidazole-4(5)carbothioamide (12b). The compound was obtained by analogy with **11** in ethanol as colourless crystals, mp 155–157°C (from ethanol). Yield 46%. Found: N 16.63; S 26.16. Calcd for $C_{11}H_{11}N_3S_2$; N 16.87; S 25.70%.

1.1.6. 5(4)-Methylmercaptoimidazole-4(5)carbothioamide (12c). *Procedure 1*. The compound was obtained from carbothioamide **9** by analogy with **11** as yellow crystals, mp 200–203°C (from ethanol). Yield 85%. Found: N 24.23; S 36.96. Calcd for $C_5H_7N_3S_2$; N 24.7; S 37.0%. *Procedure 2*. P_4S_{10} (0.015 mol) was added to carboxamide **10** (0.01 mol) in dry dioxane (50 ml) at 60°C with stirring. The mixture was boiled for 4 h and, after cooling, filtered off. The precipitate was dissolved in 100 ml of boiling water and treated with charcoal. The water phase was concentrated in vacuum. Yellow crystals, mp 200–202°C (from water). Yield 40%.

1.1.7. 2-(5-Ethylmercaptoimidazol-4-yl)-5-methoxycarbonylmethylenethiazolin-4-on (13a). The compound was obtained by analogy with **8** in chloroform as yellow crystals, mp 250–252°C (from ethanol). Yield 50%. Found: N 14.32; S 22.0. Calcd for $C_{11}H_{11}N_3O_3S_2$; N 14.13; S 21.56%.

1.1.8. 2-(5-Benzylmercaptoimidazol-4-yl)-5-methoxycarbonylmethylenethiazolin-4-on (13b). The compound was obtained by analogy with **8** in chloroform as yellow crystals, mp 232°C (decomp., ethanol). Yield 71%. Found: N 11.46; S 18.10. Calcd for $C_{16}H_{14}N_3O_3S_2$; N 11.67, S 17.78%.

1.1.9. 5-Methylmercapto-1-methyl-4-(4-oxo-5-methoxycarbonylmethylenethiazolin-2-yl)-1,2,3-triazole (13f). The compound was obtained by analogy with **8** in ethanol as yellow crystals, mp 169–172°C (from ethanol). Yield 45%. Found: N 19.18, S 21.12. Calcd for $C_{10}H_{10}N_4O_3S_2$; N 18.78, S 21.0%.

1.1.10. 1-Benzyl-5-methylmercapto-4-(4-oxo-5-methoxycarbonylmethylenethiazolin-2-yl)-1,2,3-triazole (13g). The compound was obtained by analogy with **8** in ethanol as yellow crystals, mp 159–161°C (from ethanol). Yield 37%. Found: N 15.32, S 17.46. Calcd for $C_{16}H_{14}N_4O_3S_2$; N 14.96, S 17.09%.

1.1.11. 8-Carbamoyl-4-oxo-1,4-dihydroimidazo[1,5-*a*]-pyrimidine-2-carboxylic acid methyl ester (15). To a solution of 5-amino-4-imidazolecarboxamide hydrochloride **14c** (0.001 mol) in ethanol (50 ml), DMAD (0.0015 mol) was added. The reaction mixture was refluxed for 3 h. Filtration gave compound **15** as yellow crystals, mp 172–175°C (decomp., ethanol). Yield 45%. Found: N 23,67, C 46.12%, H 3.67. Calcd for $C_9H_8N_4O_4$; N 23.72, C 45.77, H 3.41%. ^{13}C NMR (DMSO): 165.0 (*C*OOEt), 160.7 (CO), 158.2 (CO), 135.0 (C_2 imidaz.), 134.4 (C_4 imidaz.), 135.0 (C_6 pyrim.), 113.0 (C_5 pyrim.)

1.1.12. 2-(4-Carbamoyl-[1,2,3]thiadiazol-5-yl)-amino-3,4-bis(methoxycarbonyl)hexa-2,4-dienedioic acid dimethyl ester (16d). To a solution of 5-amino-1,2,3-thiadiazol-4-carboxamide **14d** (0.001 mol) in ethanol (50 ml), DMAD (0.002 mol) was added. The reaction mixture was refluxed for 4 h. Filtration gave compound **16d** as red crystals (from ethanol), mp 205–208°C, Yield 32%.$C_{15}H_{16}N_4O_9S$. M^+ 428.

1.1.13. 2-(4-Methylcarbamoyl-[1,2,3]thiadiazol-5-yl)-amino-3,4-bis-methoxycarbonyl-hexa-2,4-dienedioic acid dimethyl ester (16e). The compound was obtained by analogy with **16d** as red crystals, mp 172–175°C (from ethanol). Yield 35%. $C_{16}H_{18}N_4O_9S$. M^+ 442.

1.1.14. 2-(5-Aminoimidazol-4-yl)-5-methoxycarbonylmethylenethiazolin-4-on (17a). The compound was obtained by analogy with **8** as brown crystals, mp 225°C (decomp., ethanol). Yield 47%. Found: N 21.95, S 12.69. Calcd for $C_9H_8N_4O_3S$; N 22.21, S 12.70%.

1.1.15. 4-(4-Oxo-5-methoxycarbonylmethylenethiazolin-2-yl)-1,2,3-thiadiazol-5-amine (17b). The compound was obtained by analogy with **8** as yellow crystals, mp 213–216°C (from ethanol). Yield 41%. Found: N 20.63, S 24.12. Calcd for $C_8H_6N_4O_3S_2$; N 20.73, S 23.72%.

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