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Synthesis and some reactions of 5-carbmethoxymethylidene-4-oxo-1,3-thiazol-2-ylguanidine

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Dedicated to Prof. Girolamo Cirrincione in recognition of his outstanding contributions to the fields of organic and medicinal chemistry

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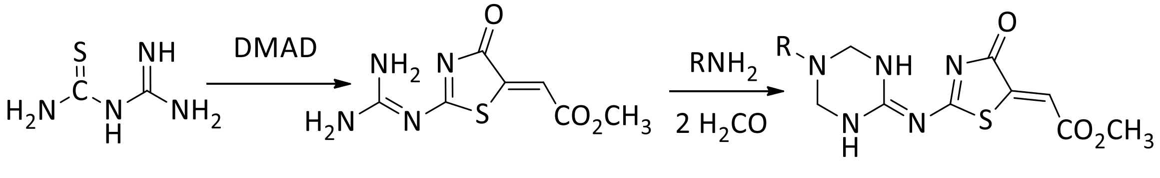
Abstract

Methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate was obtained by the reaction of *N*-amidinothiourea and dimethyl acetylenedicarboxylate (DMAD) under various conditions: methanol, ethanol, acetonitrile, ethyl acetate, dioxane, acetic acid, ethanol/TsOH. The structure of the product has been proven by X-ray diffraction analysis. A series of new *N*-(5-*R*-1,3,5-triazinan-2-ylidene)-*N*-1,3-thiazol-2-amines was obtained as a result of the multicomponent condensation of methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate with alkylamines and formaldehyde.



Keywords: *N*-Amidinothiourea, 1,3-thiazol-2-ylguanidine, *N*-1,3,5-triazinan-2-ylidene-*N*-1,3-thiazol-2-amine, dimethyl acetylenedicarboxylate, 1,3,5-triazine

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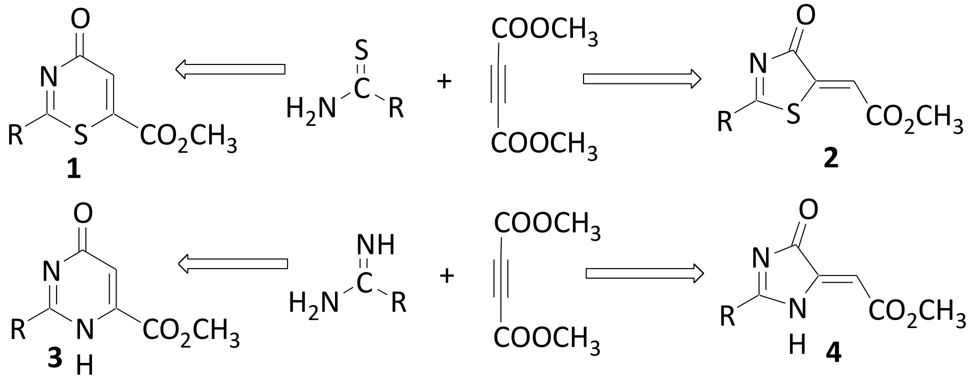
Introduction

Among the derivatives of 1,3-thiazole, compounds have been found that have antioxidant[1], antifungal[2-3], antitumor,[3-5] antiproliferative,[6] and antibacterial,[1-3.7-9] properties including those effective against bacterial biofilms.[10-11] Thieno[2,3-d]thiazole-6-carboxylic acid derivatives are potential inducers of systemic resistance in plants.[12] In this regard, the synthesis of new thiazole derivatives, including those with additional reactive groups in their structure, is an important task.

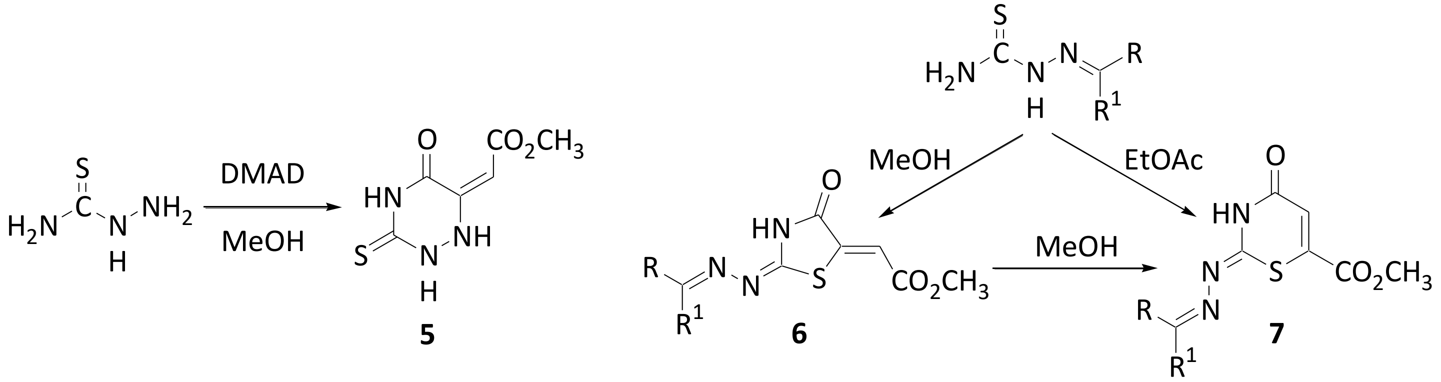
Another urgent task in organic chemistry is to study the reactions of polynucleophilic compounds with polyelectrophiles which, depending on the reaction conditions utilized, can lead to the formation of various heterocyclic systems.[13-16] In this regard, amidinothiourea is a polynucleophilic substrate that, depending on the structure of the electrophile, behaves like a 1,3-*N*,*S*-,[17-19] 1,3-*N*,*N*-[19-20] or 1,5-*N*,*N*-[21]binucleophile. In addition, imethylacetylene dicarboxylate is widely used in organic synthesis for the construction of five-, six-, and seven-membered heterocyclic systems.[22-23] Substituted 1,3-thiazinones **1** or 1,3-thiazolones **2** are formed in reactions of 1,3-*S*,*N*-binucleophiles with substituted thioacetamides, thioureas, 2-mercapto(benzo)imidazole, 2-mercapto-1,2,4-triazole, etc., along with DMAD (Scheme 1). In most cases, the formation of 1,3-thiazole cycle occurs. In this case, sulfur is attached to an activated multiple bond, and nitrogen attacks the ester group.[22-25] At the same time, in the case of unsubstituted thiourea and *N*-alkylthiourea, a six-membered ring is formed.[27]

The reactions of various 1,3-*N*,*N*-binucleophiles, including those with DMAD, lead to the formation of substituted pyrimidinones **3** or imidazolones **4** (Scheme 1).[22-23.28-33] In the case of disubstituted guanidines, a five-membered cycle (**4**)[26] is formed and in the case of 2-amino(benzo)imidazole, a six-membered cycle (**3**) is formed.[28-29] In addition, the reaction of DMAD with diaminomethylene hydrazones leads to the formation of a mixture of **3** and **4**.[30]



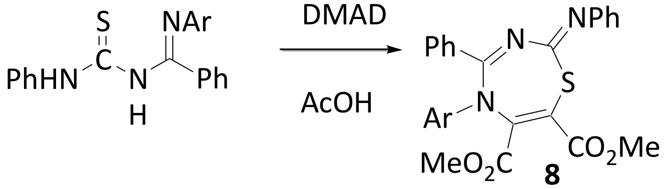
Scheme 1. Directions of reactions of DMAD with 1,3-*S*,*N*- and 1,3-*N*,*N*-binucleophiles.

However, for polynucleophilic compounds, the reaction is not so straightforward. For example, unsubstituted thiosemicarbazide reacts with DMAD as 1,4-*N*,*N*-binucleophile to form 1,2,4-triazine-3-thione **5**.[27] Thiosemicarbazones, depending on the conditions, form thiazolones **6** or thiazinones **7**, and compounds **6** can transform into **7** upon heating (Scheme 2).[32]



Scheme 2. Reactions of thiosemicarbazide and its derivatives with DMAD.

N-imidoylthioureas, which are closest in chemical structure to amidinothioureas, react with DMAD when heated in acetic acid as 1,5-N,S-binucleophiles to form 1,3,5-thiadiazepines **8** (Scheme 3).[34]

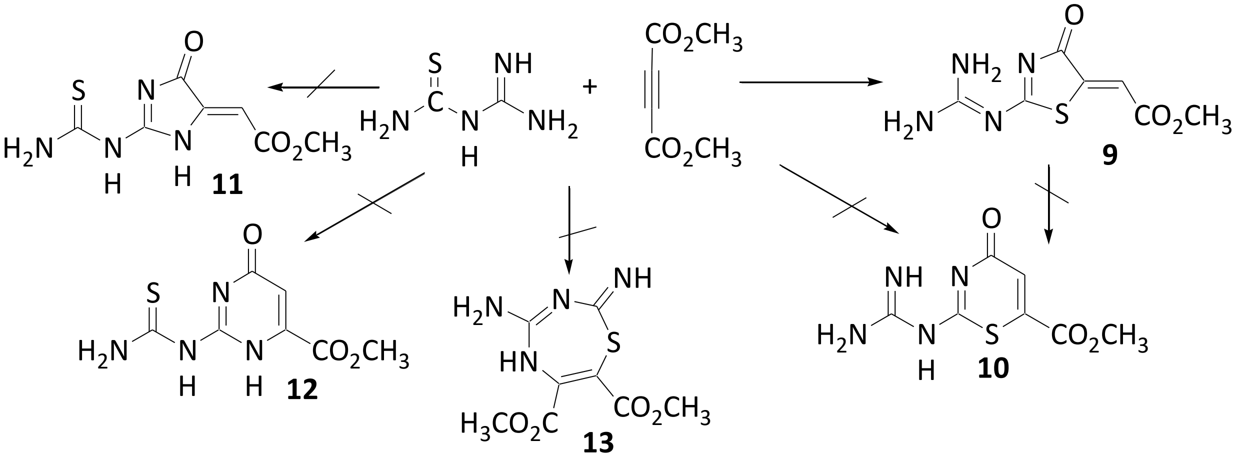


Scheme 3. Reaction of *N*-imidoylthioureas with DMAD.

Earlier, some authors[34] showed that the interaction of amidinothiourea and DMAD leads to the formation of 1,3-thiazinone, when the reaction is carried out in ethanol in the presence of *p*-TsOH as a catalyst. In this present work, we investigated the reaction of amidinothiourea and DMAD under various conditions. It was found that under all the conditions that were studied, a single product is formed, namely methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate. A series of new *N*-1,3,5-triazinan-2-ylidene-*N*-1,3-thiazol-2-amines was obtained as a result of the multicomponent condensation of methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate with alkylamines and formaldehyde.

Results and Discussion

Based on the literature data, the formation of compounds **9-13** during the interaction of amidinothiourea with DMAD can be assumed (Scheme 4).



Scheme 4. Possible reaction products of *N*-amidinothiourea with DMAD.

As noted above, there are reports in the literature[34] on the formation of 1,3-thiazinone **10** in an ethanol/*p*-TsOH medium. We carried out this reaction under the same conditions and obtained a product with characteristics (melting point) and spectral analysis data identical to those described by El-Shaieb *et al*.[34] However, by X-ray diffraction analysis (Figure 1) we proved the actual formation of 1,3-thiazole **9**. This suggests an error was made by the authors[34] in the structure of the reaction product of *N*-amidinothiourea with DMAD.

The structure of compound **9** was also confirmed by further ^{1}H NMR spectroscopic analysis. The spectrum contains a methyl group singlet at 3.76 ppm, a CH-proton singlet at 6.61 ppm, and two broadened amino group singlets at 7.58 and 8.59 ppm. The ^{13}C NMR spectrum shows signals of the carbon of the methyl group at 52.63 ppm, CH at 113.84 ppm, as well as signals of 5 carbon atoms for the carbonyl and imino groups in the range of 149.36-181.09 ppm. It should be noted that one cannot assume that **9** or **10** has been be formed based on the spectral data alone.

X-ray diffraction analysis showed that 1,3-thiazole **9** forms a solvate with a solvent molecule, DMF. A detailed description of the X-ray structural analysis data is presented in the Supplementary Material.

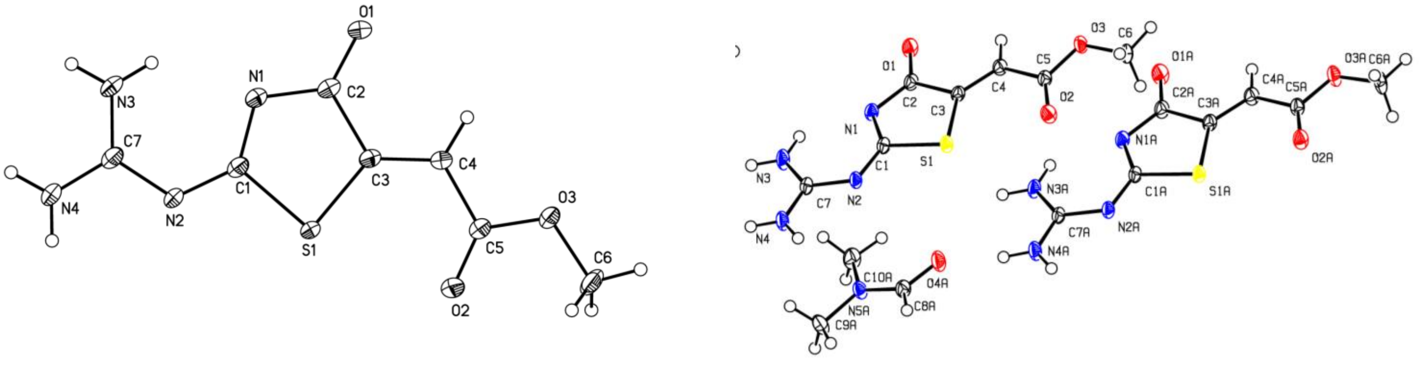


Figure 1. General view of structure **9** (CDCC: 2131042)

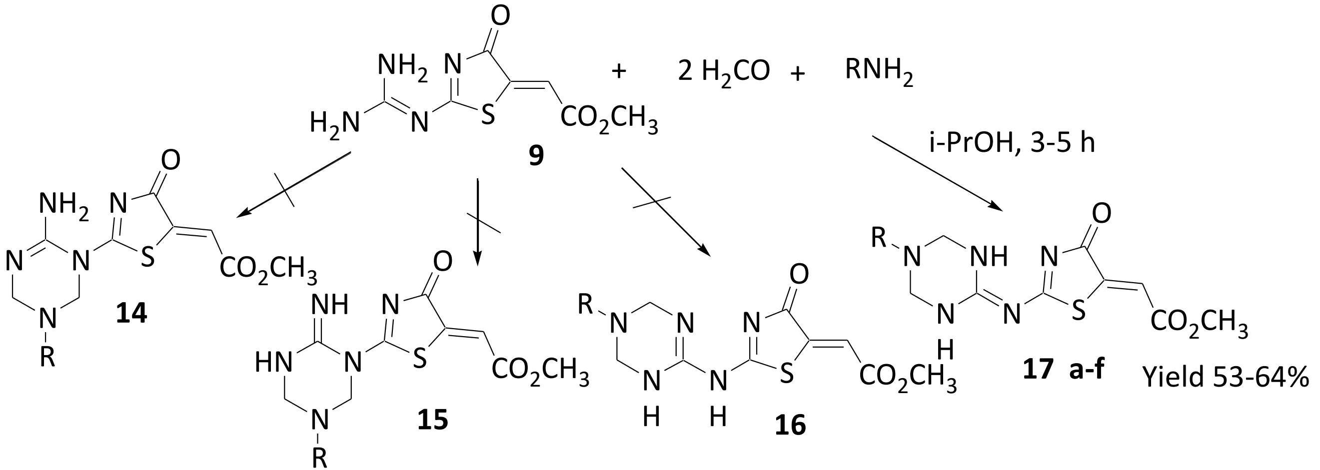
In order to study the possibility of obtaining alternative products **10-13**, we also studied the interaction of *N*-amidinothiourea and DMAD under other catalytic and non-catalytic conditions, which are presented in Table 1. A complex of physicochemical methods of analysis (^{1}H NMR spectroscopy, HPLC-MS) established that regardless of the reaction conditions, methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate **9** is formed as the main product.

Table 1. Conditions for the reaction of *N*-amidinothiourea with DMAD and yields of product **9**

Solvent	Time, min.	Yield, %	Solvent	Time, min.	Yield, %
MeOH (r.t.)	120	78	MeCN (reflux)	45	68
MeOH (reflux)	45	75	AcOH (reflux)	30	65
EtOH (TsOH, 5 mol%) (reflux)	120	85	Dioxane (reflux)	30	75

There are known examples of isomerization of 1,3-thiazoles similar in structure to compound **9** to the corresponding 1,3-thiazines upon heating in methanol[27] or in an aqueous solution of NaOH.[35] Our attempts to extend these reactions to guanidine **9** were unsuccessful. In both cases, only the starting 1,3-thiazolone **9** was isolated.

Methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5-(4*H*)-ylidene]acetate **9** is a convenient substrate for the preparation of new heterocyclic compounds. This is due to the presence of nucleophilic (guanidine fragment) and electrophilic (carbonyl and carbmethoxy groups) centers in its structure. In this work, we studied the condensation of **9** with both alkylamines and formaldehyde (Scheme 5). It is known that such reactions with 1,3-*N*,*N*-binucleophiles lead to the formation of hydrogenated 1,3,5-triazines.[36-38]



17	R	**17**	R
a	i-C_3H_7	d	4-$CH_3OC_6H_4CH_2$
b	C_4H_9	e	2$CH_3OC_6H_4CH_2$
c	C_5H_{11}	f	cyclohexyl

Scheme 5. Reactions of (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5-(4*H*)-ylidene]acetate **9** with alkylamines and formaldehyde.

1,3,5-Triazinanes **17 a-f** with exocyclic multiple bonds are formed as a result of reaction **9** with primary aliphatic amines and formaldehyde. The formation of products **14-16** can be excluded based on ^{1}H NMR and ^{13}C NMR spectroscopy data. Thus, in the ^{1}H NMR spectra, two CH_2-groups and two NH-groups are seen as singlets in the range of 4.27-4.41 and 9.01-9.14 ppm, respectively. This is due to the fact that the protons of the two NH groups and the two CH2 groups are magnetically equivalent. In the ^{13}C NMR spectra, both carbons of the CH_2 groups of the triazine ring are seen as one signal at 57.5-60.6 ppm. For alternative regioisomers **14-15** and tautomers **16**, the form of the spectra would be different. Thus, for compound **14**, the signals of the protons of methylene groups should have the form of two singletons. For compounds **15** and **16**, the signals of the protons of secondary amino groups and CH_2 groups should have an even more complex character. The ester and carbonyl groups do not react with amines. This is proved by the presence of a methoxy group singlet in the 3.71-3.75 ppm region in the ^1H NMR. Additionally, the structure of products of **17** is supported by the LCMS and IR spectroscopy.

Conclusions

We have established that the thioamide fragment is involved in the reaction of *N*-amidinothiourea with DMAD and methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate is formed. Multicomponent condensation of the latter with aliphatic amines and formaldehyde yielded a series of new series of new *N*-1,3,5-triazinan-2-ylidene-*N*-1,3-thiazol-2-amines, which are of interest as potential physiologically active compounds.

Experimental Section

General. IR spectra were registered on a Vertex 70 Fourier transform spectrometer. ^1H and ^{13}C NMR spectra were acquired on a Bruker DRX-500 spectrometer (500 and 125 MHz, respectively) in DMSO-*d*6 at 30°C with TMS as internal standard. High resolution mass spectra were recorded on an Agilent Technologies LCMS 6230B spectrometer (electrospray ionization). Melting points were determined on a Stuart SMP30 apparatus. Assaying of the purity of the starting materials and the synthesized compounds, as well as the analysis of reaction mixtures was done by TLC on Merck TLC Silica gel 60 F_{254} plates; eluents: MeOH, $CHCl_3$, and their mixtures in different ratios. Visualization of TLC plates was done under UV light or in iodine vapor. *N*-amidinothiourea, dimethyl acetylenedicarboxylate and alkylamine were supplied by Acros.

Methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene]acetate (9). A mixture of equimolar amounts of *N*-amidinothiourea (118 mg, 1.00 mmol) and dimethyl acetylenedicarboxylate (142 mg, 1.00 mmol) in the presence of a catalytic amount of *p*-TsOH (8.6 mg, 5 mol%) was refluxed in absolute ethanol (20 mL) for 2 h.[30] The resulting precipitate obtained after cooling was filtered off, dried, and recrystallized from ethanol to give (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene)acetate **9** as a yellow powder (193 mg, 0.85 mmol, 85%); mp 260-262 °C (EtOH) (lit. mp. 250-252 °C[34]); IR (cm^{-1}): 3481, 3294, 3084 (NH), 1689 (C=O, ester), 1656 (C=O, oxothiazol), 1641 (C=C), 1244, 1170 (C-O, ester); ^1H NMR (500 MHz, $(CD_3)_2SO$): δ_H 3.37 (3H, s, CH_3), 6.60 (1H, s, CH), 7.6 (2H, s, NH_2), 8.39 (s, 2H, 2NH); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_C 52.6, 113.8, 149.3, 160.9, 166.8, 179.1, 181.1; Found, *m/z*: 229.0403 $[M+H]^+$. $C_7H_8N_4O_3S$. Calculated, *m/z*: 229.0390.

General procedure for the preparation of compounds (**17**). A mixture of methyl (2*Z*)-[2[(diaminomethylene)amino]-4-oxothiazol-5(4*H*)-ylidene)acetate **9** (228 mg, 1.00 mmol), primary aliphatic amine (1 mmol), and formaldehyde (37%) (1.46 mL, 2.00 mmol) was heated in isopropyl alcohl (20 mL) for 3-5 h. The precipitate formed upon cooling to room temperature was filtered and dried.

Methyl (2*Z*)-[2-[(5-isopropyl-1,3,5-triazinan-2-ylidene)amino]-4-oxo-1,3-thiazol-5(4*H*)-ylidene]acetate (17a). Yield: 164 mg (53%); white powder; mp 210-212 °C (i-PrOH); IR (cm^{-1}): 3253, 3172 (NH), 2972, 2918 (C-H, aliphatic), 1689 (C=O, ester), 1612 (C=O, oxothiazol), 1589 (C=C), 1244, 1164 (C-O, ester), 1014 (C-NH); ^1H NMR

(500 MHz, $(CD_3)_2SO$): δ_H 1.09 (6H, d, *J* 6.3, 2xCH_3 isopropyl), 2.88-2.93 (1H, m, CH isopropyl), 3.74 (3H, s, CH_3), 4.41 (4H, s, 2CH_2), 6.59 (1H, s, CH), 9.02 (2H, s, 2NH); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_C 21.4, 48.1, 52.6, 58.3, 113.6, 149.6, 156.1, 166.9, 179.1, 179.6; Found, *m/z*: 312.1118 $[M+H]^+$. $C_{12}H_{17}N_5O_3S$. Calculated, *m/z*: 312.1126.

Methyl (2*Z*)-[2-[(5-butyl-1,3,5-triazinan-2-ylidene)amino]-4-oxo-1,3-thiazol-5(4*H*)-ylidene]acetate (17b). Yield: 188 mg (58%); white powder; mp 220-222 °C (i-PrOH); IR (cm-1): 3242, 3170 (NH), 2952, 2871 (C-H, aliphatic), 1687 (C=O, ester), 1616 (C=O, oxothiazol), 1585 (C=C), 1242, 1168 (C-O, ester), 1012 (C-NH); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H 0.85 (3H, t, *J* 7.3, CH_3 butyl), 1.22-1.24 (2H, m, CH_2 butyl), 1.38-1.44 (2H, m, CH_2 butyl), 2.52 (2H, t, *J* 7.32, CH_2N), 3.72 (3H, s, CH_3), 4.30 (4H, s, 2xCH_2 triazine), 6.58 (1H, s, CH), 9.05 (2H, s, NH); ^{13}C NMR (125 MHz, (CD3)$_2$SO): δ_C 14.2 (CH_3 butyl), 20.1, 29.8, 49.9, 52.6, 60.5, 113.6, 149.6, 155.6 , 166.9, 179.0, 179.5; Found, *m/z*: 326.1290 $[M+H]^+$. $C_{13}H_{19}N_5O_3S$. Calculated, *m/z*: 326.1282.

Methyl (2*Z*)-[4-oxo-2-[(5-pentyl-1,3,5-triazinan-2-ylidene)amino]-1,3-thiazol-5(4*H*)-ylidene]acetate (17c). Yield: 203 mg (60%); white powder; mp 215-217 °C (i-PrOH); IR (cm^{-1}): 3236, 3155 (NH), 2952, 2848 (C-H, aliphatic), 1689 (C=O, ester), 1612 (C=O, oxothiazol), 1589 (C=C), 1242, 1168 (C-O, ester), 1022 (C-NH); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H 0.87 (3H, t, *J* 6.3, CH_3 pentyl), 1.24-1.41 (4H, m, 2xCH_2 pentyl), 1.46-1.50 (2H, m, CH_2 pentyl), 2.56-2.59 (2H, m, CH_2N), 3.75 (3H, s, CH_3), 4.31 (4H, s, 2xCH_2 triazine), 6.60 (1H, s, CH), 9.00 (2H, s, NH); ^{13}C NMR (125 MHz, (CD3)$_2$SO): δ_C 13.9, 22.0, 26.9, 28.8, 49.8, 52.2, 60.1, 113.2, 149.2, 155.2, 166.5, 178.7, 179.2; Found, *m/z*: 340.1439 $[M+H]^+$. $C_{14}H_{21}N_5O_3S$. Calculated, *m/z*: 340.1438.

Methyl (2*Z*)-[2-{[5-(4-methoxybenzyl)-1,3,5-triazinan-2-ylidene]amino}-4-oxo-1,3-thiazol-5(4*H*)-ylidene]-acetate (17d). Yield: 206 mg (53%); white powder; mp 218-220 °C (i-PrOH); IR (cm^{-1}): 3234, 3149 (NH), 2866 ($COCH_3$), 1689 (C=O, ester), 1612 (C=O, oxothiazol), 1589 (C=C), 1460 (arom), 1244, 1168 (C-O, ester), 1020 (C-NH); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H 3.70 (2H, s, CH_2N), 3.72 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 4.27 (4H, s, 2CH_2 triazine), 6.59 (1H, s, CH), 6.89 (2H, d, *J* 8.6, 2CH aryl), 7.25 (2H, d, *J* 8.6, 2CH aryl), 9.09 (2H, s, NH); ^{13}C NMR (125 MHz, (CD3)$_2$SO): δ_C 52.6, 53.8, 55.5, 59.9, 113.6, 114.2, 129.7, 130.6, 149.7, 155.7, 159.1, 166.9, 179.1, 179.5; Found, *m/z*: 390.1240 $[M+H]^+$. $C_{17}H_{19}N_5O_4S$. Calculated, *m/z*: 390.1231.

Methyl (2*Z*)-[2-{[5-(2-methoxybenzyl)-1,3,5-triazinan-2-ylidene]amino}-4-oxo-1,3-thiazol-5(4*H*)-ylidene]-acetate (17e). Yield: 249 mg (64%); white powder; mp 225-227 °C (i-PrOH); IR (cm^{-1}): 3234, 3157 (NH), 2869 ($COCH_3$), 1687 (C=O, ester), 1614 (C=O, oxothiazol), 1587 (C=C), 1450 (arom), 1247, 1168 (C-O, ester), 1029 (C-NH); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H 3.71 (2H, s, CH_2N), 3.73 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 4.30 (4H, s, 2CH_2 triazine), 6.59 (1H, s, CH), 6.90-6.96 (2H, m, 2xCH aryl), 6.99-7.31 (2H, m, 2CH aryl), 9.14 (2H, s, NH); ^{13}C NMR (125 MHz, (CD3)$_2$SO): δ_C 48.7, 52.6, 55.7, 60.6, 111.2, 113.7, 120.7, 125.7, 129.1, 130.0, 149.7, 155.6, 157.7, 166.9, 179.1, 179.6; Found, *m/z*: 390.1290 $[M+H]^+$. $C_{17}H_{19}N_5O_4S$. Calculated, *m/z*: 390.1231.

Methyl (2*Z*)-[2-[(5-cyclohexyl-1,3,5-triazinan-2-ylidene)amino]-4-oxo-1,3-thiazol-5(4*H*)-ylidene]acetate (17f). Yield: 207 g (59%); white powder; mp 216-218 °C (i-PrOH); IR (cm^{-1}): 3261, 3190 (NH), 2927, 2860 (C-H, aliphatic), 1687 (C=O, ester), 1608 (C=O, oxothiazol), 1581 (C=C), 1236, 1180 (C-O, ester), 1012 (C-NH); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H 1.10-1.26 (5H, m, 2xCH_2+CH cyclohexyl), 1.55-1.57 (1H, m, CH cyclohexyl), 1.69-1.75 (2H, m, CH_2 cyclohexyl), 1.87-1.91 (2H, m, CH_2 cyclohexyl), 2.49-2.52 (1H, m, CHN), 3.73 (3H, s, CH_3), 4.11 (4H, s, 2xCH_2 triazine), 6.61 (1H, s, CH), 9.02 (2H, s, NH); ^{13}C NMR (125 MHz, (CD3)$_2$SO): δ_C 24.5, 25.4, 30.6, 52.2, 55.5, 57.5, 113.2, 149.2, 155.7, 166.5, 178.7, 179.1; Found, *m/z*: 340.1440 $[M+H]^+$. $C_{15}H_{21}N_5O_3S$. Calculated, *m/z*: 352.1439.

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Supplementary Material

IR, ^{1}H and ^{13}C NMR spectra and data LCMS for compounds **9, 17a-f** can be found via the "Supplementary Content" section of this article's webpage. A detailed description of the X-ray structural analysis data of compound **9** is presented in the Supplementary Material and structural data has been deposited as CDCC: 2131042.

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