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SYNTHESIS OF 4-AMINO-5-(4,6-DIPHENYL-2-PYRIMIDINYL)-3,4-DIHYDRO-2H-1,2,4-TRIAZOLE-3-THIONE AND ITS REACTIONS WITH C-ELECTROPHILES

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4-Amino-5-(4,6-diphenyl-2-pyrimidinyl)-3,4-dihydro-2H-1,2,4-trazole-3-thione is formed from the reaction of 4,6-diphenylpyrimidinecarboxylic acid or its ethyl ester with thiocarbonyl hydrazide. Alkylation of the product leads to S-alkyl derivaties or 6-substituted 3-(4,6-diphenyl-2-pyriimidinyl)-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine. Acetylation of 4-amino-5-(4,6-diphenyl-2-pyrimidinyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione gave under different conditions monoacetyl-, diacetyl, and triacetyl derivatives at the at the amino group and the $N_{(2)}$ atom, whereas benzoylation gave a benzoyl group at the amino group and 3-(4,6-diphenyl-2-pyrimidinyl)-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole.

Keywords: 4-amino-5-(4,6-diphenyl-2-pyrimidinyl)-3,4-dihydro-2H-1,2,4-trazol-3-thione, alkylation, acylation, heterocyclization.

5-Substituted 4-amino-1,2,4-triazole-3-thiones and their S-alkylated and condensed derivatives possess antimicrobial [1-6] and anti-inflammatory activity [7-9]. 5-(4,6-Diphenyl-2-pyrimidinyl))-3,4-dihydro-2H-1,2,4-triazole-3-thione and its 4-phenyl derivative, which we synthesized earlier, show anti-inflammatory activity [10, 11]. In a continuation of our investigation of a series of pyrimidinyltriazole, we describe in this paper the synthesis of 4-amino-5-(4,6-diphenyl-2-pyrimidinyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (**1**) and its reactions with C-electrophiles.

We previously prepared thione **1** from 5-(4,6-diphenyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione [11] and hydrazine hydrate in boiling absolute butanol in 60% yield [12]. In the present work we studied a shorter method for the synthesis of **1** by fusing 4,6-diphenyl-2-pyrimidinecarboxylic acid with thiocarbohydrazide [13] at the melting point of the acid or the reaction of ethyl 4,6-diphenyl-2-pyrimidinecarboxylate [14] and thiocarbohydrazide in boiling absolute methanol in the presence of sodium methoxide. However, the yields of the desired product were lower in both cases (42 and 33% respectively).

Reaction of thione **1** with iodomethane in absolute ethanol gave the methylsulfanyl derivative **2**. Reaction of thione **1** with ω-bromoacetophenone and ethyl 4-chloroacetate was apparently accompanied by cyclocondensation of the S-alkylated intermediate with the formation of 6-substituted 3-(4,6-diphenyl-2-pyrimidinyl)-7H-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **3a,b**.

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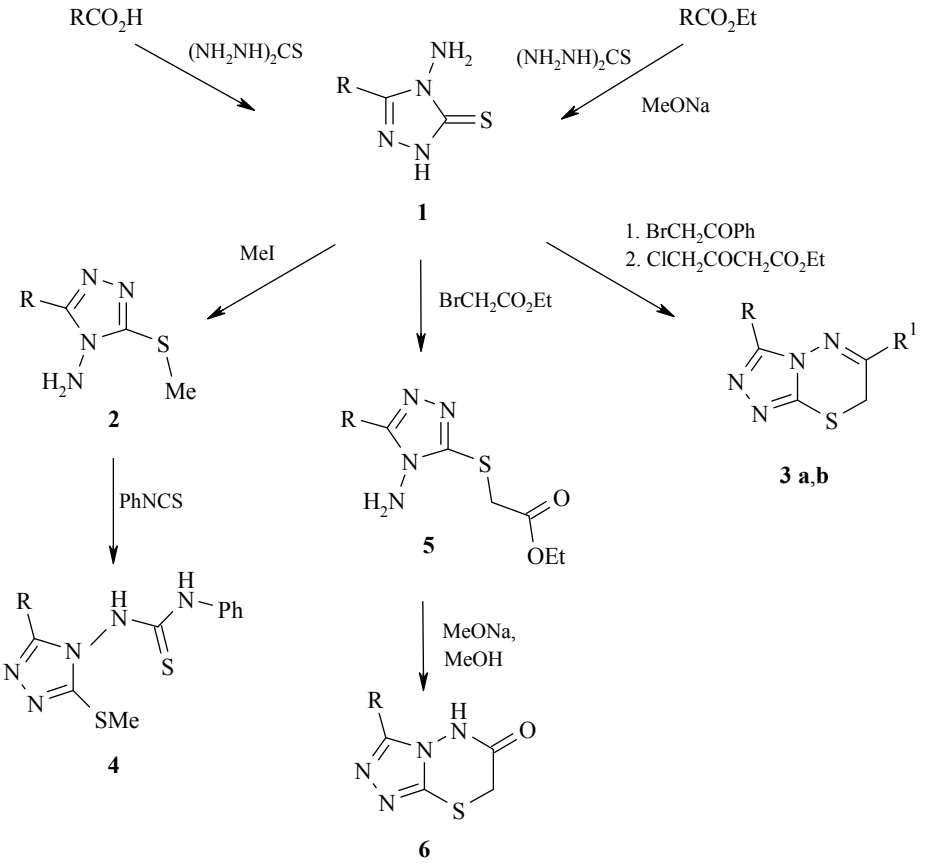
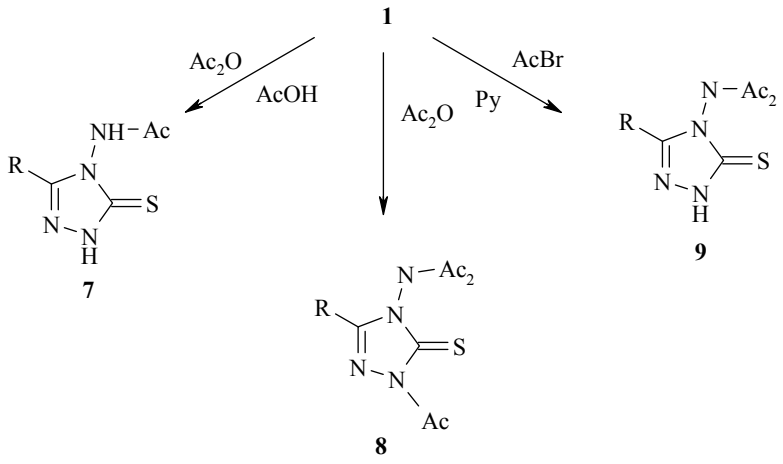


R = 4,6-diphenyl-2-pyrimidinyl; **3 a** R^1 = Ph, **b** R^1 = CH_2CO_2Et

Compound **2** reacts with phenyl isothiocyanate in absolute pyridine at room temperature to give the N-thioureido derivative **4**. Compound **5**, the product of S-alkylation of thione **1** with ethyl bromoacetate, cyclized to 1,2,4-triazolo[3,4-*b*]thiadiazin-6-one **6** on treatment with sodium methoxide in boiling methanol.



R = 4,6-diphenyl-2-pyrimidinyl

Table 1. Characteristics of the Compounds Synthesized, **2-12**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2	$C_{19}H_{16}N_6S$	63.22 / 63.31	4.22 / 4.47	23.21 / 23.32	242-243	65
3a	$C_{26}H_{18}N_6S$	70.20 / 69.94	4.25 / 4.06	19.05 / 18.82	260.0-261.5	63
3b	$C_{24}H_{20}N_6O_2S$	63.41 / 63.14	4.66 / 4.42	18.32 / 18.41	178.0-178.5	47
4	$C_{26}H_{21}N_7S_2$	62.92 / 63.01	4.46 / 4.27	19.70 / 19.78	161-162	71
5	$C_{22}H_{20}N_6O_2S$	61.36 / 61.10	4.66 / 4.66	19.65 / 19.43	179-180	87
6	$C_{20}H_{14}N_6OS$	62.50 / 62.16	3.64 / 3.65	21.66 / 21.75	272-273	46
7	$C_{20}H_{16}N_6OS$	61.25 / 61.84	4.27 / 4.15	21.78 / 21.63	182 (dec.)	51
8	$C_{24}H_{20}N_6O_3S$	61.26 / 61.00	4.17 / 4.27	17.90 / 17.79	231-232	70
9	$C_{22}H_{18}N_6O_2S$	61.70 / 61.38	4.36 / 4.21	19.48 / 19.52	158-159	27
10	$C_{25}H_{18}N_6OS$	66.39 / 66.65	3.88 / 4.03	18.54 / 18.65	>300 (dec.)	51
11	$C_{25}H_{16}N_6S$	69.33 / 69.42	3.98 / 3.73	19.67 / 19.43	>300 (dec.)	66
12	$C_{21}H_{18}N_6OS$	62.68 / 62.67	4.67 / 4.51	20.82 / 20.88	159-160	35

* Solvent: MeOH (compound **2**), MeCN (compounds **3a, 5, 8**), EtOH (compounds **3b, 7, 10, 12**), dioxan (compounds **6, 9**), DMF (compound **11**).

Acetylation of thione **1** with acetic anhydride and acetyl bromide proceeded with participation of the amino group and the $N_{(2)}$ atom of the triazole ring.

An equivalent amount of acetic anhydride selectively acylated the amino group to form the monoacetyl derivative **7**; an excess of acetic anhydride acylated the amino group and the atom $N_{(2)}$ of the triazole ring to give the triacetyl derivative **8**. On boiling equivalent amounts of the thione **1** and acetyl bromide in absolute pyridine for 1 h, the diacetyl derivative **9** was isolated.

When thione **1** was boiled for a short time (0.5 h) with benzoic acid in the presence of phosphorus oxychloride the (**10)** benzoyl derivative was formed. When the reaction time was increased to 5 h the 1,2,4-triazolo[4,3-*b*]-1,3,4- thiadiazole heterocyclic system **11** was produced.

When thione **1** was boiled with ethyl orthoformate the ethoxymethylenamine derivative **12** was formed. According to the ^{1}H NMR spectra a mixture of two geometric isomers in the ratio 7:1 was formed.

The structures of the compounds synthesized were confirmed by the results of elemental analysis (Table 1) and IR and ^{1}H NMR spectroscopic (Table 2).

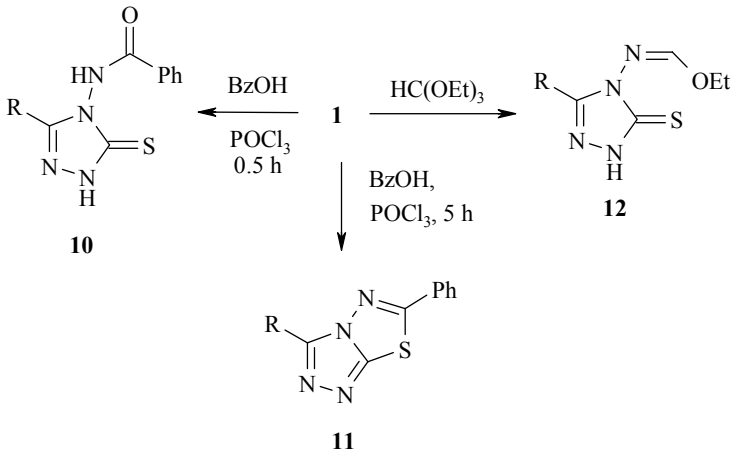
In the IR spectra absorption bands of the C=O of esters are present of alkylated compounds **3b** and **5** at 1721 and 1728, the amide group of the condensed thiadiazinone **6** at 1703, and the acyl groups of monoacetyl (**7)** and benzoyl (**10)** derivatives at 1691 and 1692, triacetyl (**8)** and diacetyl (**9)** derivatives at 1753, 1728, and 1742 cm^{-1} respectively. The absorptions in derivatives **7-10**, **12** in the 1244-1270 cm^{-1} region are characteristic of the C=S bond in the triazole ring. In the spectra of the S-alkyl derivatives **2**, **4**, **5** and the condensed compounds **3a**,**b** and **6** these bands are absent, but the C=S group in the thioureido derivative is observed at 1317 cm^{-1}.

Table 2. IR and ^{1}H NMR Spectral Data for Compounds **2-12**

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*,Hz)*
2	3336 (NH), 1584 (C=C), 1572 (C=N)	2.70 (3H, s, CH_3); 6.53 (2H, s, NH_2); 7.63-7.65 (6H, m, 3-, 4-, 5-CH, C_6H_5); 8.47-8.51 (4H, m, 2-, 6-CH, C_6H_5); 8.71 (1H, s, CH pyrim.)
3a	1585 (C=C), 1574 (C=N)	4.57 (2H, s, CH_2); 7.53-7.63 (9H, m, 3-, 4-, 5-CH, C_6H_5, 3'-, 4'-, 5'-CH, C_6H_5); 8.08 (2H, d, *J* = 7.0, 2'-, 6'-CHC_6H_5); 8.48 (4H, d, *J* = 8.1, 2-,6-CH, C_6H_5); 8.76 (1H, s, CH pyrim.)
3b	1728 (C=O), 1584 (C=C), 1573 (C=N)	1.90 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 3.89 (2H, s, CH_2); 4.09 (2H, s, SCH_2); 4.16 (2H, q, *J* = 7.0, $\underline{CH_2}$Me); 7.61-7.64 (6H, m, C_6H_5); 8.44-8.46 (4H, m, C_6H_5); 8.74 (1H, s, CH pyrim.)
4	3444, 3201 (NH), 1586 (C=C), 1574 (C=N), 1317 (C=S)	2.75 (3H, s, CH_3); 7.12-7.57 (11H, m, 3-, 4-, 5-CH, C_6H_5, 3'-, 4'-, 5'-CH, C_6H_5); 8.47-8.66 (4H, m, 2-, 6-CH, C_6H_5); 8.71 (1H, s, CH pyrim.); 10.9 (1H, s, NH); 11.03 (1H, s, NH)
5	3425 (NH), 1721 (C=O), 1584 (C=C), 1574 (C=N)	1.24 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 4.17 (2H, q, *J* = 7.0, $\underline{CH_2}$Me); 4.20 (2H, s, SCH_2); 6.57 (2H, s, NH_2); 7.63-7.65 (6H, m, 3-, 4-, 5-CH, C_6H_5); 8.47-8.50 (4H, m, 2-, 6-CH, C_6H_5); 8.70 (1H, s, CH pyrim.)
6	3389 (NH), 1703 (C=O), 1585 (C=C), 1574 (C=N)	3.98 (2H, s, CH_2); 7.64-7.66 (6H, m, 3-, 4-, 5-CH, C_6H_5); 8.46-8.49 (4H, m, 2-, 6-CH, C_6H_5); 8.73 (1H, s, CH pyrim.); 12.40 (1H, br. s, NH)
7	3448, 3158 (NH), 1691 (C=O), 1264 (C=S)	1.99 (3H, s, CH_3); 7.63-7.65 (6H, m, 3-, 4-, 5-CH, C_6H_5); 8.46-8.49 (4H, d, *J* = 9, 2-, 6-CH, C_6H_5); 8.74 (1H, s, CH pyrim.); 11.63 (1H, s, $\underline{NH}$COMe); 14.43 (1H, br. s, NH triazole)
8	1753, 1728 (C=O), 1576 (C=C), (C=N), 1270 (C=S)	2.78 (6H, s, CH_3); 3.09 (3H, s, CH_3); 7.82 (4H, t, *J* = 9.0, 3-, 5-CH, C_6H_5); 7.96 (2H, t, *J* = 9.0, 4-CH, C_6H_5); 8.21 (4H, d, *J* = 7.0, 2-, 6-CH, C_6H_5); 8,75 (1H, s, CH pyrim.)
9	3459 (NH), 1742 (C=O), 1588 (C=C), 1576 (C=N), 1244 (C=S)	2.45 (6H, s, CH_3); 7.63-7.65 (6H, m, 3-, 4-, 5-CH, C_6H_5); 8.33-8.37 (4H, d, *J* = 12, 2-, 6-CH, C_6H_5); 8.74 (1H, s, CH pyrim.); 14.92 (1H, s, NH triazole)
10	3369, 3154 (NH), 1692 (C=O), 1587 (C=C), 1575 (C=N), 1263 (C=S)	7.43-7.67 (9H, m, 3-, 4-, 5-CH, C_6H_5); 8.04 (2H, d, *J* = 7.0, 2'-, 6'-CH, C_6H_5); 8.34 (4H, d, *J* = 7.5, 2-, 6-CH, C_6H_5); 8.70 (1H, s, CH pyrim.); 12.25 (1H, s, $\underline{NH}COC_6H_5$); 14.57 (1H, s, NH triazole)
11	1582 (C=C), 1573 (C=N)	7.68-7.78 (9H, m, 3-, 4-, 5-CH, C_6H_5, 3'-, 4'-, 5'-CH, C_6H_5); 8.14-8.17 (2H, m, 2'-, 6'-CH, C_6H_5); 8.63-8.66 (4H, m, 2-, 6-CH, C_6H_5); 8.82 (1H, s, CH pyrim.)
12	3300 (NH), 1587 (C=C), 1576 (C=N), 1262 (C=S)	0.95, 1.29 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 4.15, 4.37 (2H, q, *J* = 7.0, $\underline{CH_2}$Me); 7.63-7.65 (6H, m, 3-, 4-, 5-CH, C_6H_5); 8.48-8.51 (4H, m, 2-, 6-CH, C_6H_5); 8.7 (1H, s, CH pyrim.); 8.77, 8.81 (1H, s, N=CH); 14.37 (1H, s, NH triazole)

* H pyrim. – proton of the pyrimidine unit. H triazole – proton of the triazole ring.

The signal of the H-5 proton of the pyrimidine ring is present at 8.70-8.82 ppm in the ^{1}H NMR spectra of compounds **2-12** and the phenyl group of pyrimidine in the intervals 7.12-7.67 and 8.33-8.66 ppm. In the spectra of compounds **7**, **9**, **10**, and **12** the signal of the proton of the NH group of the triazole ring is observed in the range 14.37-14.92, while in stronger field the signal of the NH protons of the thioureido derivative **4** (10.9 and 11.03) and the acylated compounds **7** and **10** are observed (11.63 and 12.25 ppm).



R = 4,6-diphenyl-2-pyrimidyl

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions (compound **8** in CF_3COOD) with TMS as internal standard were recorded with Varian Unity Inova (300 MHz) spectrometer. IR spectra of KBr disks were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer. The course of reaction and the purity of compounds **2-6** were monitored by TLC on Silufol UV-254 (Kavalier) plates with eluents: ethyl acetate (for **2,4**), 1:3 ethyl acetate–ether (for **3b**, **5**, **6**), 1:2 ethyl acetate–ether (for **12**), and 1:1 ethyl acetate–ethanol (for **3a**). Alugram® SIL G/UV-254 (Macherey-Nagel) plates were used for compounds **7-10**, eluent 4:1 ethyl acetate-methanol (for compound **10** 2:1 chloroform-ether).

4-Amino-5-(4,6-diphenyl-2-pyrimidinyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (1). A. A mixture of 4,6-diphenylpyrimidine-2-carboxylic acid (2.76 g, 10 mmol) and thiocarbohydrazide (1.06 g, 10 mmol) was heated on a Wood's metal bath at 165-170°C for 30 min. After cooling the reaction mass was triturated and treated with boiling ethanol (10×12 ml). The residue of product **1** was dried and recrystallized. Yield 1.45 g (42%); mp 244-245°C (DMF-H_2O); 244-245°C (DMF-H_2O) [11].

B. Thiocarbohydrazide (0.74 g, 6.98 mmol) was added to sodium methoxide (from metallic sodium, 0.107 g, 4.65 mmol) in methanol (10 ml). The suspension was boiled for 15 min, then ethyl 4,6-diphenyl-pyrimidine-2-carboxylate (1.42 g, 4.65 mmol) was added, and the mixture was boiled for 3 h. Water (10 ml) was added to the cooled mixture at room temperature and the mixture was acidified to pH 4 with 10% HCl. The residue of product **1** was filtered off, washed with water, treated with boiling ethanol, dried and recrystallized. Yield 0.53 g (33 %); mp 244-245°C (DMF-H_2O); 244-245°C (DMF-H_2O) [11].

5-(4,6-Diphenyl-2-pyrimidinyl)-3-methylsulfanyl-4H-1,2,4-triazole-4-amine (2). Iodomethane (0.25 g, 0.34 ml, 1.728 mmol) was added dropwise and with stirring to a suspension of thione **1** (0.6 g, 1.728 mmol) in absolute ethanole (40 ml). The reaction mixture was boiled with stirring for 3 h. The solvent was removed with a rotary evaporator, the solid product was treated with stiring with 10% KOH (15 ml). The solid product **2** was filtered off, washed with water to neutral reaction with a small amount of methanol, dried and recrystallized.

Ethyl [4-Amino-5-(4,6-diphenyl-2-pyrimidinyl)-4H-1,2,4-triazo-3-ylsulfanyl]acetate (5). Triethyl-amine (0.15 g, 0.2 ml, 1.443 mmol) was added to a boiling suspension of thione **1** (0.5 g, 1.443 mmol) in absolute ethanol (10 ml), the mixture was boiled for 5 min and then ethyl bromoacetate (0.24 g, 0.16 ml, 1.443 mmol) was added. The mixture was boiled with stirring for 2 h. The separated product **5** was filtered off and recrystallized.

3-(4,6-Diphenyl-2-pyrimidinyl)-6-phenyl-7H-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (3a). A mixture of thione **1** (0.25 g, 0.721 mmol) and ω-bromoacetophenone (0.14 g, 0.721 mmol) in absolute ethanol (5 ml) was boiled with stirring for 2 h. The hot solution was filtered, the crystals of product **3a** were washed with ethanol and ether, dried and crystallized. An additional amount of the product was obtained by evaporation of the filtrate.

Ethyl [3-(4,6-Diphenyl-2-pyrimidinyl)-7H-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (3b). Ethyl 4-chloro-acetoacetate (0.24 g, 0.2 ml, 1.443 mmol) was added to a boiling suspension of thione **1** (0.5 g, 1.443 mmol) and triethylamine (0.15 g, 0.2 ml, 1.443 mmol) in absolute ethanol (40 ml) and the mixture was boiled for 9 h. The hot solution was filtered, the filtrate was evaporated to 10 ml and cooled. The solid residue of **3b** was filtered off and recrystallized.

N^1-[5-(4,6-Diphenyl-2-pyrimidinyl)-3-methylsulfanyl-4H-1,2,4-triazol-4-yl]-N^2-phenylthiocarbamide (4). Compound **2** (0.2 g, 0.333 mmol) was dissolved with stirring in absolute pyridine (4 ml). Phenyl isothiocyanate (0.054 g, 0.3995 mmol) was added dropwise and the mixture was stirred at room temperature for 4 days. The reaction mixture was poured into ice water (15 ml) and kept for 1 day. Crystals of **4** were filtered off, washed with water, dried and recrystallized.

3-(4,6-Diphenyl-2-pyrimidinyl)-6,7-dihydro-5H-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadazin-6-one (6). A mixture of compound **5** (0.54 g, 1.25 mml) and sodium methoxide (from 0.03g, 1.25 mmol, sodium) in methanol (20 ml) was boiled with stirring for 5 h. The reaction mixture was neutralized with dilute HCl (1:1). The precipitate of product **6** was filtered off, washed with ether, dried, and recrystallized.

N-[5-(4,6-Diphenyl-2-pyrimidinyl)-3-thioxo-1,2,4-triazol-4-yl]acetamide (7). Freshly distilled acetic anhydride (0.088 g, 0.082 ml, 0.866 mmol) was added with stirring to a suspension of thione **1** (0.3 g, 0.866 mmol) in glacial acetic acid (11 ml) and the mixture was boiled for 18 h. The crystals of compound **7** formed were filtered off and recrystallized.

N-[2-Acetyl-5-(4,6-diphenyl-2-pyrimidinyl)-3-thioxo-3,4-dihydro-2H-1,2,4-triazol-4-yl]diacetamide (8). A mixture of thione **3** (0.2 g, 0.577 mmol) and freshly distilled acetic anhydride (2.16 g, 2.0 ml, 21.2 mmol) was boiled with stirring for 1 h. After cooling the reaction mixture the precipitated crystals of product **8** were filtered off, washed with ether, dried, and recrystallized.

N-5-(4,6-Diphenyl-2-pyrimidinyl)-3-thioxo-3,4-dihydro-2H-1,2,4-triazol-4-yl]diacetamide (9). Thione **1** (3 g, 0.866 mmol) was dissolved on heating in absolute pyridine (11 ml). Acetyl bromide (0.11 g, 0.065 ml, 0.866 mmol) was added dropwise to the cooled solution at room temperature and the mixture was boiled with stirring for 1 h. The solution was cooled and the precipitate of pyridinium bromide was filtered off. The filtrate was poured onto crushed ice and kept for one day. The precipitate of product **9** was filtered off, washed with water, dried, and recrystallized.

N-[5-(4,6-Diphenyl-2-pyrimidinyl)-3-thioxo-3,4-dihydro-2H-1,2,4-triazol-4-yl]benzamide (10). A mixture of thione **1** (0.3 g, 0.866 mmol), benzoic acid (0.11 g, 0.866 mmol), and freshly distilled phosphorus oxychloride (1 ml) was boiled for 30 min. The reaction mixture was cooled, poured onto crushed ice, and neutralized with potash. The solid residue of compound **10** was filtered of, washed with water, and recrystallized.

6-Phenyl-3-(4,6-diphenyl-2-pyrimidinyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (11) was synthesized analogously to compound **10**, with the difference that the reaction mixture was boiled for 5 h. The cooled solution was poured onto crushed ice. The precipitate of product **11** was filtered off, washed with 1.25% KOH solution, water, methanol, and ether, dried, and recrystallized.

4-Ethoxymethylendenamino-5-(4,6-diphenyl-2-pyrimidinyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (12). A suspension of thione **1** (0.25 g, 0.722 mmol) in ethyl orthoformate (2 ml) was boiled for 1 h. The reaction mixture was cooled. Crystals of product **12** were filtered off, washed, and recrystallized.

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