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MANNICH REACTION IN THE SYNTHESIS OF N,S-CONTAINING HETEROCYCLES. 13*. ONE-POT METHOD FOR PREPARING PYRIMIDO[4,3-*b*]-[1,3,5]THIADIAZINES BY REACTION OF ALDEHYDES, CYANOTHIOACETAMIDE, FORMALDEHYDE, AND PRIMARY AMINES

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Successive reaction of cyanothioacetamide with aliphatic or aromatic aldehydes, formaldehyde, and primary amines gives the corresponding 3,7-disubstituted 3,4,7,8-tetrahydro-2H,6H-pyrimido-[4,3-b][1,3,5]thiadiazine-9-carbonitriles.

Keywords: cyanothioacetamide, pyrimido[4,3-*b*][1,3,5]thiadiazines, aminomethylation, Mannich reaction, multicomponent condensation.

The double aminomethylation of different N,S-dinucleophiles including dithiocarbamates, primary thioamides, and 2-mercaptoazoles(azines) can be deservedly considered as one of the most simple and convenient methods for constructing the 1,3,5-thiadiazine system [2-4]. This route was used successfully in the synthesis of condensed thiadiazines including substituted bis(pyrido[2,1-*b*][1,3,5]thiadiazin-7-yl)methanes [5], 1,2,4-triazolo[3,4-*b*][1,3,5]thiadiazines [6], imidazo[2,1-*b*][1,3,5]thiadiazines [7-16], 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazines [15], thiazolo[3',4':1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines [17], 1,3,5-thiadiazino[3,2-a]benzimidazoles [18], cyclopenta[*g*]pyrido[2,1-*b*][1,3,5]thiadiazines [19], pyrimido[2,1-*b*][1,3,5]thiadiazines [20], and pyrido[2,1-*b*][1,3,5]thiadiazines [21].

We have previously reported the preparation of 8-aryl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*]-[1,3,5]thiadiazine-9-carbonitriles **1** by treatment of 3-aryl-2-cyanoprop-2-enethioamides **2** with primary amines and HCHO [22] (method A), by recyclization of 4*H*-thiopyrans **3** under the Mannich reaction conditions [23] (method B), or by the aminomethylation of tetrahydropyridine-2-thiolates **4** [24] (method C). The said methods are not free from limitations and drawbacks. Method A allows preparation of pyrimidothiadiazines **1** with acceptable yields (up to 65%) but is limited to a range of products consisting only of 8-aryl derivatives of compound **1** since the 3-alkyl analogs of the starting α,β-unsaturated thioamides **2** are unknown at this time.

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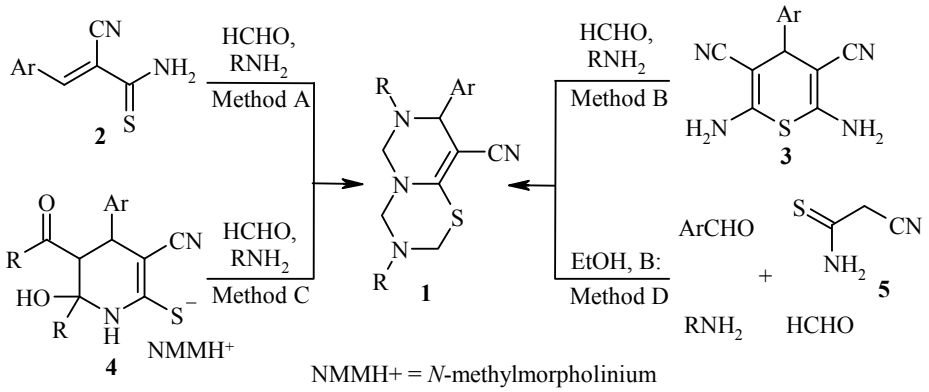
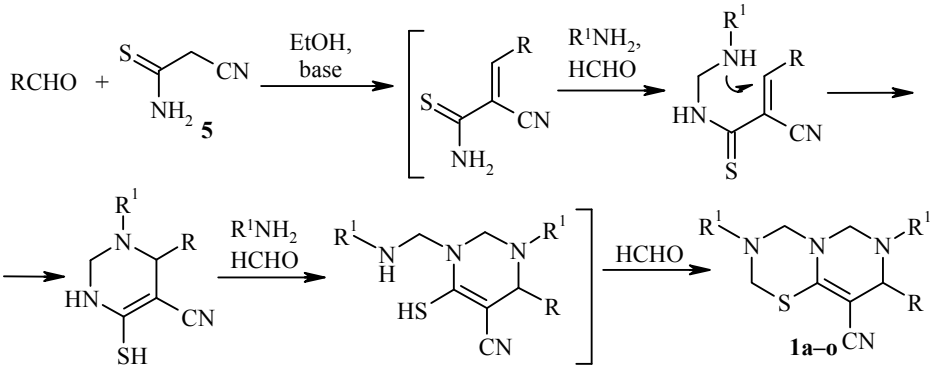
This limitation is removed with the preparation of thiadiazines **1** by the aminomethylation of 4*H*-thiopyrans **3** using method B, but, in this case, the yields of the target products are lower and the route itself is atom inefficient. Method C gives the lowest yields of thiadiazines **1** (up to 28%) and seems the least rational.

In the earlier study [23], we declared the possible preparation of pyrimido[4,3-*b*][1,3,5]thiadiazines **1** by a multicomponent condensation of aromatic aldehydes, cyanothioacetamide **5**, *p*-toluidine, and HCHO (method D). In searches for the optimum approach to the pyrimido[4,3-*b*][1,3,5]thiadiazines **1** synthesis, we have studied and summerized in the present work the overall possibilities for a multicomponent approach and, in particular, the possibility of varying the substituents in the 8 position of the pyrimido[4,3-*b*][1,3,5]thiadiazine system **1** and the introduction of aliphatic aldehydes into this reaction.



NMMH+ = *N*-methylmorpholinium

It was found that successive reaction of cyanothioacetamide (**5**) with aldehydes, primary amines, and formaldehyde occurs under mild conditions (short term heating in aqueous EtOH in the presence of catalytic amounts of base) and leads to the pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitriles **1a-o** in 11-70% yield (Table 1). Both aromatic and aliphatic aldehydes can be used in the reaction.



a R = Et; **b–e** R = *i*-Pr, **f–h** R = 3,4-(OCH$_2$O)C$_6$H$_3$CH$_2$CH(Me), **i–k** R = 4-MeC$_6$H$_4$, **l** R = 2-ClC$_6$H$_4$, **m** R = 4-Me$_2$NC$_6$H$_4$, **n** R = 4-O$_2$NC$_6$H$_4$, **o** R = 3-O$_2$NC$_6$H$_4$; **a**,**c**,**g**,**k–o** R^1 = 4-MeC$_6$H$_4$, **b** R^1 = Ph, **d** R^1 = 4-AcNHC$_6$H$_4$, **e**,**f** R^1 = 4-MeOC$_6$H$_4$, **h**,**j** R^1 = Bn, **i** R^1 = 3-MeC$_6$H$_4$

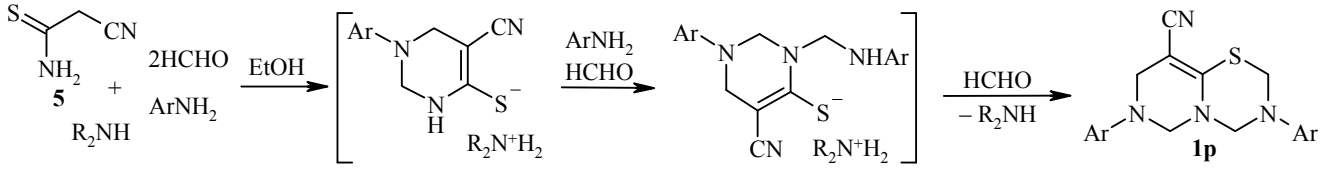
In the latter case, the previously unknown 8-alkylpyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitriles **1a-g** are formed in low yields (up to 40%). The use of aromatic aldehydes in this reaction usually gives higher yields of the target products **1i-o** when compared with yields using aliphatic aldehydes. Compound **1h** could not be prepared in a pure state. In this case, synthesis by the general method gives an uncrystallizable oil which contains about 73% of the target product according to HPLC-MS and ^{1}H NMR spectroscopy. Attempts to purify the

TABLE 1. Physicochemical and Spectroscopic Characteristics of Compounds **1a-p**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N			
1a	$C_{23}H_{26}N_4S$	70.65 / 70.73	6.75 / 6.71	14.50 / 14.35	175-176 (decomp.) (Me_2CO)	2165 (C≡N)	17
1b	$C_{22}H_{24}N_4S$	69.88 / 70.18	6.39 / 6.42	14.99 / 14.88	140-142 (decomp.) (Me_2CO-EtOH)	2173 (C≡N)	29
1c	$C_{24}H_{28}N_4S$	71.08 / 71.25	7.09 / 6.98	14.00 / 13.85	171-173 (decomp.) (Me_2CO)	2164 (C≡N)	39
1d	$C_{26}H_{30}N_6O_2S$	63.23 / 63.65	6.20 / 6.16	17.26 / 17.13	169-171 (decomp.) (Me_2CO)	2167 (C≡N) 1675 (C=O) 3300 (NH)	19
1e	$C_{24}H_{28}N_4O_2S$	65.65 / 66.03	6.52 / 6.46	12.53 / 12.38	152-153 (decomp.) (Me_2CO-EtOH)	2172 (C≡N)	26
1f	$C_{31}H_{32}N_4O_4S$	66.40 / 66.89	5.81 / 5.79	10.14 / 10.06	164-165 (decomp.) (DMF-Me_2CO)	2167 (C≡N)	30
1g	$C_{31}H_{32}N_4O_2S$	70.53 / 70.96	6.18 / 6.15	10.79 / 10.68	185-187 (decomp.) (Me_2CO)	2170 (C≡N)	37
1h	—	—	—	—	—	2170 (C≡N)	-
1i	$C_{28}H_{28}N_4S$	74.03 / 74.30	6.28 / 6.24	12.49 / 12.38	177-179 (DMF-EtOH)	2176 (C≡N)	62
1j	$C_{28}H_{28}N_4S$	74.14 / 74.30	6.22 / 6.24	12.50 / 12.38	128-131 (DMF) (125-128 [22])	2176 (C≡N)	65
1k	$C_{28}H_{28}N_4S$	74.16 / 74.30	6.25 / 6.24	12.53 / 12.38	177-176 (DMF-EtOH) (178-181 [22])	2172 (C≡N)	70
1l	$C_{27}H_{25}ClN_4S$	68.32 / 68.56	5.27 / 5.33	12.01 / 11.84	210-212 (DMF-EtOH) (210-211 [22])	2167 (C≡N)	66
1m	$C_{29}H_{31}N_5S$	72.11 / 72.32	6.50 / 6.49	14.73 / 14.54	165-167 (decomp.) (DMF-Me_2CO)	2165 (C≡N)	26
1n	$C_{27}H_{25}N_5O_2S$	66.75 / 67.06	5.25 / 5.21	14.69 / 14.48	213-215 (decomp.) (DMF-EtOH)	2167 (C≡N)	36
1o	$C_{27}H_{25}N_5O_2S$	66.88 / 67.06	5.22 / 5.21	14.65 / 14.48	205-207 (decomp.) (DMF-EtOH)	2168 (C≡N)	33
1p	$C_{21}H_{22}N_4S$	69.37 / 69.58	6.15 / 6.12	15.55 / 15.46	195-197 (decomp.) (DMF-Me_2CO)	2158 (C≡N)	11 (A) 13 (B)

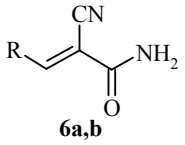
compound **1h** or to separate it from the mixture using column chromatography were unsuccessful. In the case of aliphatic aldehydes it was found that morpholine is preferred to tertiary amine catalysts such as *N*-methylmorpholine or triethylamine.

A very unexpected result was obtained in the condensation of acetaldehyde, thioamide **5**, *p*-toluidine, and formaldehyde. Instead of the expected 8-methyl-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido-[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile its 8-unsubstituted analog **1p** was formed. Compound **1p** was also found as an admixture (up to 20% according to ^{1}H NMR data) in unpurified samples of compounds **1a,c**. Clearly formation of the pyrimidothiadiazine system precedes the *N*-aminomethylation and retro-Knoevenagel reaction. A possible reason for the anomalous reaction course is the ease of the retro-reaction and the comparable rate of the reaction of the cyanothioacetamide with formaldehyde and aliphatic aldehydes. Compound **1p** was also obtained by the direct aminomethylation of the cyanothioacetamide (**5**).

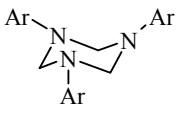


Ar = 4-MeC_6H_4; R_2NH = morpholine

Finally, attempts to broaden the boundaries of the use of this route and to exchange the cyanothioacetamide (**5**) in this reaction for cyanoacetamide or to introduce into the reaction 3-aryl-2-cyanoprop-2-enamides **6a,b** in place of compounds **2** were not successful. Hence under the said conditions only the perhydro-1,3,5-triazine **7** (a known product of *p*-toluidine condensation with formaldehyde [25]) was isolated in place of the 3-(2-chlorophenyl)-2-cyanoprop-2-enamide (**6a**) aminomethylation products. Polycomponent condensation of furfural, cyanoacetamide, HCHO, and *p*-toluidine gives a mixture of the unsaturated amide **6b** (R = 2-furyl) and the perhydro-1,3,5-triazine **7**.



6a,b



7

6 a R = 2-ClC_6H_4, **b** 2-furyl; 7 Ar = 4-MeC_6H_4

Hence the 3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitriles can be successfully prepared by condensation of cyanothioacetamide with aliphatic or aromatic aldehydes, formaldehyde, and primary amines. A similar route, in contrast to other methods, allows the preparation of pyrimido[4,3-b]-[1,3,5]thiadiazines unsubstituted in position 8 or with alkyl substituents in this position in acceptable yields. Cyanoacetamide and its arylmethylidene derivatives do not take part in a Mannich reaction under these conditions.

EXPERIMENTAL

IR spectra were recorded on an IKS-29 spectrophotometer in nujol. ^{1}H NMR spectra were recorded on Varian Unity Plus (400 MHz) and Bruker DRX-500 (500 MHz) spectrometers and ^{13}C NMR spectra on a Bruker DRX-500 (125 MHz) using DMSO-d_6 with TMS as internal standard. HPLC-MS analysis was carried out on an Agilent 1100 liquid chromatograph with DAD and Sedex 75 ELSD detectors combined with an Agilent LC/MSD VL mass spectrometer in electrospray ionization mode. Elemental analysis was performed on a Carlo-Erba 1106 Elemental Analyzer with an accuracy of measurement of ± 0.25%. Monitoring of the purity of the compounds obtained was carried out by TLC using Silufol UV-254 plates with acetone–hexane (1:1) as eluent and visualized by UV light or iodine vapor. Melting points for the prepared compounds were determined on a Kofler hot bench and are not corrected.

The starting cyanothioacetamide (**5**) was prepared by a known method [26].

3,4,7,8-Tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitriles (1a-o) (General Method). The base (2-3 drops, morpholine in the case of the aliphatic aldehydes, *N*-methylmorpholine or Et_3N in the case of aromatic aldehydes) was added to a mixture of cyanothioacetamide (**5**) (0.5 g, 5.0 mmol) and the corresponding aldehyde (5.0 mmol) in EtOH (15-20 ml). The product was stirred for 10-20 min at 20ºC and the corresponding amine (10.5 mmol) and 37% formalin, free from paraformaldehyde admixture (2.5-3.0 ml, 34-40 mmol) were added. The mixture was then refluxed with vigorous stirring for 1-3 min, a further 15 ml of EtOH added, and stirring continued for 3-5 h at 20ºC. The precipitate formed after 24 h was filtered off (in the case of tar formation the solution was decanted) and immediately recrystallized from acetone, a mixture of acetone–EtOH (1: 1), or dissolved in hot DMF with subsequent reprecipitation using EtOH or acetone.

8-Ethyl-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1a). Colorless crystals. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.00 (3H, t, ^3J = 7.3, $CH_2C\underline{H}_3$); 1.62-1.75 (2H, m, $C\underline{H}_2CH_3$); 2.25 (3H, s, CH_3); 2.26 (3H, s, CH_3); 3.70 (1H, dd, ^3J = 9.1, ^3J = 9.1, H-8); 4.39 (1H, d, ^2J = 12.9) and 4.62 (1H, d, ^2J = 12.9, NCH_2N); 4.75 (1H, d, ^2J = 12.9) and 4.88 (1H, d,

^2J = 12.9, NCH_2N); 4.99 (1H, d, ^2J = 12.6) and 5.17 (1H, d, ^2J = 12.6, SCH_2N); 6.80 (2H, d, ^3J = 7.9, H Ar); 6.95 (2H, d, ^3J = 8.2, H Ar); 6.96 (2H, d, ^3J = 7.9, H Ar); 7.00 (2H, d, ^3J = 8.2, H Ar).

8-Isopropyl-3,7-diphenyl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1b). Beige powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.01 (3H, d, ^3J = 6.2, CH_3); 1.09 (3H, d, ^3J = 6.2, CH_3); 1.94-1.96 (1H, m, C<u>H</u>$(CH_3)_2$); 3.45 (1H, d, ^3J = 9.1, H-8); 4.48 (1H, d, ^2J = 12.9) and 4.74 (1H, d, ^2J = 12.9, NCH_2N); 4.82 (1H, d, ^2J = 12.9) and 5.07 (1H, d, ^2J = 12.9, NCH_2N); 5.03 (1H, d, ^2J = 12.6) and 5.25 (1H, d, ^2J = 12.6, SCH_2N); 6.83-7.26 (10H, m, H Ph).

8-Isopropyl-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1c). Colorless crystals. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.00 (3H, d, ^3J = 6.3, CH_3); 1.07 (3H, d, ^3J = 6.3, CH_3); 1.83-1.87 (1H, m, C<u>H</u>$(CH_3)_2$); 2.25 (6H, br. s, $2ArCH_3$); 3.30 (1H, d, ^3J = 8.6, H-8); 4.40 (1H, d, ^2J = 13.0) and 4.56 (1H, d, ^2J = 13.0, NCH_2N); 4.72 (1H, d, ^2J = 13.5) and 4.82 (1H, d, ^2J = 13.5, NCH_2N); 4.92 (1H, d, ^2J = 13.1) and 5.16 (1H, d, ^2J = 13.1, SCH_2N); 6.70–6.94 (8H, m, H Ar).

3,7-Di(4-acetamidophenyl)-8-isopropyl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1d). Colorless amorphous powder. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 0.99 (3H, d, ^3J = 6.2, CH_3); 1.06 (3H, d, ^3J = 6.2, CH_3); 1.90-1.95 (1H, m, C<u>H</u>$(CH_3)_2$); 2.02 (3H, s, $NHCOC\underline{H}_3$); 2.04 (3H, s, $NHCOC\underline{H}_3$); 3.42 (1H, br. d, ^3J = 9.3, H-8); 4.47 (1H, d, ^2J = 13.2) and 4.67 (1H, d, ^2J = 13.2, NCH_2N); 4.79 (1H, d, ^2J = 12.7) and 4.98 (1H, d, ^2J = 12.7, NCH_2N); 5.09 (1H, d, ^2J = 12.7) and 5.25 (1H, d, ^2J = 12.7, SCH_2N); 6.85 (2H, d, ^3J = 8.8, H Ar); 7.10 (2H, d, ^3J = 8.8, H Ar); 7.36 (2H, d, ^3J = 8.8, H Ar); 7.47 (2H, d, ^3J = 8.8, H Ar); 9.75 (1H, s, NHAc); 9.82 (1H, s, NHAc).

8-Isopropyl-3,7-di(4-methoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1e). White amorphous powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.00 (3H, d, ^3J = 6.6, CH_3); 1.07 (3H, d, ^3J = 6.6, CH_3); 1.84-1.88 (1H, m, $CH(CH_3)_2$); 3.20 (1H, d, ^3J = 9.4, H-8); 3.71 (3H, s, OCH_3); 3.74 (3H, s, OCH_3); 4.43 (1H, d, ^2J = 13.2) and 4.47 (1H, d, ^2J = 13.2, NCH_2N); 4.74-4.76 (2H, m, NCH_2N); 4.93 (1H, d, ^2J = 12.6) and 5.21 (1H, d, ^2J = 12.6, SCH_2N); 6.68-6.98 (8H, m, H Ar).

8-[2-(1,3-Benzodioxol-5-yl)-1-methylethyl]-3,7-di(4-methoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1f). White amorphous powder. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz) (ratio of main and minor diastereomers 3:1): 0.81 (2.25H, d, ^3J = 6.4, $CHC\underline{H}_3$); 0.89 (0.75H, d, ^3J = 6.8, $CHC\underline{H}_3$)*; 1.97-2.05 (1H, m, $CHC\underline{H}_3$)*[2]; 2.18-2.26 (1H, m)*[2], 2.99 (0.75H, dd, ^2J = 13.2, ^3J = 3.4), and 3.05 (0.25H, dd, ^2J = 13.1, ^3J = 3.0, $ArC\underline{H}_2CH$)*; 3.41 (0.25H, d, ^3J = 8.8, H-8)*; 3.46 (0.75H, d, ^3J = 8.3, H-8); 3.71 (2.25H, s, OCH_3); 3.72 (0.75H, s, OCH_3)*; 3.73 (0.75H, s, OCH_3)*; 3.74 (2.25H, s, OCH_3); 4.51 (0.75H, d, ^2J = 13.2) and 4.55 (0.75H, d, ^2J = 13.2, NCH_2N); 4.63 (0.5H, dd, ^2J = 13.2, ^2J = 13.2, NCH_2N)*; 4.79-4.88 (2H, m, NCH_2N)*[2]; 5.00 (0.25H, d, ^2J = 12.7)* and 5.27 (0.25H, d, ^2J = 12.7, NCH_2S)*; 5.04 (0.75H, d, ^2J = 12.7) and 5.29 (0.75H, d, ^2J = 12.7, NCH_2S); 5.98 (1.5H, s, OCH_2O); 5.99 (0.5H, s, OCH_2O)*; 6.60-7.05 (11H, m, H Ar)*[2]. ^{13}C NMR spectrum, δ, ppm: 16.0 ($CH\underline{C}H_3$)*; 16.2 ($CH\underline{C}H_3$); 38.8 ($\underline{C}HCH_3$); 39.0 ($\underline{C}HCH_3$)* 42.8 ($ArCH_2$); 43.4 ($ArCH_2$)*; 53.4 ($ArOCH_3$)*; 55.7 ($ArOCH_3$); 61.9 (C-8)*; 62.3 (C-8); 64.0 (NCH_2N)*; 61.1 (NCH_2N); 64.5 (NCH_2N); 64.6 (NCH_2N)*; 73.6 (SCH_2N); 73.7 (SCH_2N)*; 101.1 (OCH_2O); 108.5; 109.6 (C-9); 109.8 (C-9)*; 114.6 (C≡N); 114.7 (C≡N)*; 119.6 (C Ar)*; 119.9 (C Ar); 120.7 (C Ar)*; 120.9 (C Ar); 121.5 (C Ar); 122.3 (C Ar); 122.5 (C Ar)*; 134.9 (C Ar); 135.0 (C Ar)*; 139.1 (C Ar); 143.9 (C Ar); 145.7 (C Ar); 151.7 (C-9a)*; 151.9 (C-9a); 154.3 (C Ar)*; 154.6 (C Ar)*[2].

8-[2-(1,3-Benzodioxol-5-yl)-1-methylethyl]-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1g). White amorphous powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz) (ratio of main and minor diastereomers 10:1): 0.86 (2.73H, d, ^3J = 6.4, $CHC\underline{H}_3$); 0.95 (0.27H, d, ^3J = 6.7, $CHC\underline{H}_3$)*; 1.93-2.03 (1H, m, $C\underline{H}CH_3$)*[2]; 2.18-2.24 (1H, m, $ArC\underline{H}_2CH$)*[2]; 2.28 (3H, s, $ArCH_3$)*[2]; 2.30 (3H, s, $ArCH_3$)*[2]; 2.96-3.04 (1H, m, $ArC\underline{H}_2CH$)*[2]; 3.47 (0.09H, d, ^3J = 7.7, H-8)*; 3.52 (0.91H, d, ^3J = 8.1, H-8); 4.46 (1H, d, ^2J = 12.9)*[2] and 4.54 (1H, d, ^2J = 12.9, NCH_2N)*[2]; 4.77-4.79 (2H, m, NCH_2N)*[2]; 4.96 (1H, d, ^2J = 12.6)*[2] and 5.19 (1H, d, ^2J = 12.6, NCH_2S)*[2]; 5.92 (0.18H, s, OCH_2O)*; 5.93 (1.82H, s, OCH_2O); 6.57

(1H, d, ^3J = 7.6, H Ar)*[2]; 6.64-6.68 (2H, m, H Ar)*[2]; 6.76 (2H, d, ^3J = 8.0, H Ar)*[2]; 6.90-6.95 (4H, m, H Ar)*[2]; 6.99 (2H, d, ^3J = 8.4, H Ar)*[2].

8-[2-(1,3-Benzodioxol-5-yl)-1-methylethyl]-3,7-dibenzyl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*]-[1,3,5]thiadiazine-9-carbonitrile (1h). Yellow tar, glassifies on prolonged standing. According to HPLC-MS and ^{1}H NMR data the content of the main material is about 73%. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz) (ratio of main and minor diastereomers 10:9): 0.72 (1.41H, d, ^3J = 6.3, CHC$\underline{H}_3$)*; 0.81 (1.59H, d, ^3J = 6.8, CHC$\underline{H}_3$); 1.90-2.12 (2H, m, C$\underline{H}$CH$_3$, ArC$\underline{H}$HCH)*[2]; 2.93-2.97 (0.47H, m, ArCH$\underline{H}$CH)*; 3.08-3.12 (0.53H, m, ArCH$\underline{H}$CH); 3.33-3.39 (4H, m, 2CH$_2$Ph)*[2]; 3.43-4.87 (7H, m, H-8, 2NCH$_2$N, NCH$_2$S)*[2]; 5.92-5.97 (2H, m, OCH$_2$O)*[2]; 6.53-7.42 (13H, m, H Ar)*[2]. Mass spectrum (ESI), *m/z* (I_{rel}, %): 525 [M+H]$^+$ (37), 406 [M+H-PhCH$_2$N=CH$_2$]$^+$ (100), 120 [PhCH$_2$NH=CH$_2$]$^+$ (16).

3,7-Di(3-methylphenyl)-8-(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1i). Pale-yellow amorphous powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.30 (6H, br. s, 2 CH$_3$); 2.36 (3H, s, CH$_3$); 4.14 (1H, d, ^2J = 13.0) and 4.63 (1H, d, ^2J = 13.0, NCH$_2$N); 4.81 (1H, d, ^2J = 13.0) and 4.97 (1H, d, ^2J = 13.0, NCH$_2$N); 5.13 (1H, s, H-8); 5.08 (1H, d, ^2J = 12.9) and 5.27 (1H, d, ^2J = 12.9, SCH$_2$N); 6.69-7.28 (12H, m, H Ar).

3,7-Dibenzyl-8-(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1j). Beige amorphous powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.30 (3H, s, CH$_3$); 3.49 (1H, d, ^2J = 12.3) and 3.70 (1H, d, ^2J = 12.3, NCH$_2$N); 3.90 (2H, br. s, PhCH$_2$); 4.00 (1H, d, ^2J = 12.4) and 4.11 (1H, d, ^2J = 12.4, NCH$_2$N); 4.19 (2H, br. s, PhCH$_2$); 4.23 (1H, s, H-8); 4.51 (1H, d, ^2J = 12.1) and 4.74 (1H, d, ^2J = 12.1, SCH$_2$N); 7.09-7.45 (14H, m, H Ar).

3,7,8-Tri(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1k). White finely crystalline powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.25 (3H, s, CH$_3$); 2.28 (3H, s, CH$_3$); 2.30 (3H, s, CH$_3$); 4.28 (1H, d, ^2J = 13.0) and 4.53 (1H, d, ^2J = 13.0, NCH$_2$N); 4.87 (1H, d, ^2J = 12.7) and 4.94 (1H, d, ^2J = 12.7, NCH$_2$N); 5.12 (1H, s, H-8); 5.10 (1H, d, ^2J = 12.5) and 5.32 (1H, d, ^2J = 12.5, SCH$_2$N); 7.00-7.20 (12H, m, H Ar).

8-(2-Chlorophenyl)-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1l). White finely crystalline powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.27 (3H, s, CH$_3$); 2.31 (3H, s, CH$_3$); 4.20 (1H, d, ^2J = 13.0) and 4.49 (1H, d, ^2J = 13.0, NCH$_2$N); 4.68 (1H, d, ^2J = 13.1) and 4.94 (1H, d, ^2J = 13.1, NCH$_2$N); 5.12 (1H, d, ^2J = 12.6) and 5.23 (1H, d, ^2J = 12.6, SCH$_2$N); 5.28 (1H, s, H-8); 6.80-7.20 (8H, m, H Ar); 7.25-7.45 (4H, m, 2-ClC$_6$H$_4$).

8-(4-Dimethylaminophenyl)-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]-thiadiazine-9-carbonitrile (1m). Bright-yellow crystals. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.31 (3H, s, ArCH$_3$); 2.32 (3H, s, ArCH$_3$); 2.95 (6H, s, (CH$_3$)$_2$N); 4.15 (1H, d, ^2J = 12.6) and 4.46 (1H, d, ^2J = 12.6, NCH$_2$N); 4.77-4.78 (2H, m, NCH$_2$N); 4.94 (1H, s, H-8); 5.01 (1H, d, ^2J = 12.5) and 5.21 (1H, d, ^2J = 12.5, SCH$_2$N); 6.64 (2H, d, ^3J = 8.1, H Ar); 6.90-7.02 (8H, m, 2MeC$_6$H$_4$); 7.09 (2H, d, ^3J = 8.1, H Ar).

3,7-Di(4-methylphenyl)-8-(4-nitrophenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-b][1,3,5]thiadiazine-9-carbonitrile (1n). Bright-yellow crystals. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.27 (3H, s, CH$_3$); 2.28 (3H, s, CH$_3$); 4.03 (1H, d, ^2J = 13.2) and 4.68 (1H, d, ^2J = 13.2, NCH$_2$N); 4.89 (1H, d, ^2J = 12.7) and 4.95 (1H, d, ^2J = 12.7, NCH$_2$N); 5.15 (1H, d, ^2J = 12.2) and 5.31 (1H, d, ^2J = 12.2, SCH$_2$N); 5.37 (1H, s, H-8); 7.00-7.05 (8H, m, 2MeC$_6$H$_4$); 7.60 (2H, d, ^3J = 8.1, H Ar); 8.25 (2H, d, ^3J = 8.1, H Ar).

3,7-Di(4-methylphenyl)-8-(3-nitrophenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1o). Bright-yellow crystals. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.26 (3H, s, CH$_3$); 2.27 (3H, s, CH$_3$); 4.05 (1H, d, ^2J = 12.9) and 4.68 (1H, d, ^2J = 12.9, NCH$_2$N); 4.87 (1H, d, ^2J = 13.3) and 4.94 (1H, d, ^2J = 13.3, NCH$_2$N); 5.14 (1H, d, ^2J = 12.5) and 5.32 (1H, d, ^2J = 12.5, SCH$_2$N); 5.37 (1H, s, H-8);

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* Signals of the minor diastereomers.

*[2] Overlapping of the signals of the main and minor diastereomers.

6.97 (2H, d, ^3J = 7.9, H Ar); 7.03 (2H, d, ^3J =7.9, H Ar); 7.04-7.08 (4H, m, H Ar); 7.71 (1H, dd, ^3J = 7.5, ^3J = 7.9, H-5'); 7.80 (1H, d, ^3J = 7.5, H-6'); 8.18 (1H, s, H-2'); 8.22 (2H, d, ^3J = 7.9, H-4').

3,7-Di(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (1p). A. Obtained by condensation of acetaldehyde, thioamide **5**, *p*-toluidine, and HCHO. A mixture of cyanothioacetamide (**5**) (0.5 g, 5.0 mmol), acetaldehyde (0.5 ml, 8.9 mmol) and *N*-methylmorpholine (3 drops) was stirred in EtOH (15-20 ml) for 30 min at 20ºC. *p*-Toluidine (1.1 g, 10.3 mmol) and 37% formalin free from paraformaldehyde (3.0 ml, 40.0 mmol) were added. The mixture was refluxed for 2-3 min and then stirred at 20ºC. The precipitate formed after 24 h was filtered off, washed with EtOH, and immediately recrystallized from a mixture of acetone and DMF (1:1). Compound **1p** (200 mg, 11%) was obtained as a light-yellow, finely crystalline powder.

B. Obtained from thioamide **5**, formalin, and toluidine. A mixture of the cyanothioacetamide (**5**) (1.00 g, 10.0 mmol), *p*-toluidine (1.38 g, 12.9 mmol), and 37% formalin (3.0 ml, 40.0 mmol) was refluxed for 2-3 min in EtOH (30 ml) with stirring. After 24 h the precipitate was filtered off and recrystallized from a mixture of ethanol and DMF (1:1). Yield 480 mg (13%). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.25 (3H, s, CH_3); 2.27 (3H, s, CH_3); 3.96 (2H, br. s, 8-CH_2); 4.65 (2H, br. s) and 4.78 (2H, br. s, 4,6-CH_2); 5.08 (2H, br. s, SCH_2N); 6.87-6.91 (4H, m, 2H-3',5'); 6.98 (4H, d, ^3J = 7.6, 2H-2',6'). Mass spectrum (ESI), *m/z* (I_{rel}, %): 364 $[M+H]^+$ (100), 245 $[M+H\text{-}ArN{=}CH_2]^+$ (76), 120 $[ArNH{=}CH_2]^+$ (81).

1,3,5-Tri(4-methylphenyl)-1,3,5-perhydrotriazine (7). 3-(2-Chlorophenyl)-2-cyanoacrylamide (**6a**) (0.564 g, 2.73 mmol), *p*-toluidine (0.658 g, 6.14 mmol), and 37% HCHO (2.5 ml, 33.30 mmol) were refluxed in DMF (4 ml) for 3-4 min and then held for 72 h at 20ºC. Yield 205 mg (28%). Colorless needle like crystals; mp 125ºC (mp 127.9ºC [25], 126-127ºC [27]), R_f = 0.81 (acetone–hexane, 1:1). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.21 (9H, s, $3CH_3$); 4.77 (6H, br. s, $3CH_2$); 7.05 (12H, dd, ^3J = 8.1, ^3J = 8.1, H Ar). Found, %: C 80.56; H 7.65; N 11.79. $C_{24}H_{27}N_3$. Calculated, %: C 80.63; H 7.61; N 11.75.

Multicomponent Condensation of Furfural, Cyanoacetamide, Formalin, and *p*-Toluidine. A mixture of cyanoacetamide (0.5 g, 6.0 mmol), furfural (0.5 ml, 6.0 mmol), and morpholine (1 drop) was stirred in EtOH (20-25 ml) for 30 min at 20ºC. *p*-Toluidine (0.71 g, 6.6 mmol) and 37% formalin free from an admixture of paraformaldehyde (2.0 ml, 26.6 mmol,) were added. The mixture was refluxed for 2-3 min, filtered through a plaited filter, and held for 48 h at 20ºC. The precipitate formed was filtered off and washed with EtOH to give the sandy-gray product (0.34 g). According to ^{1}H NMR data (400 MHz) this product is the (*E*)-2-cyano-3-(2-furyl)prop-2-enamide (**6b**) (35% yield) with an admixture of about 2% of the perhydrotriazine **7**. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 6.70 (1H, dd, ^3J = 3.4, ^3J = 1.6, H-4 furyl); 7.33 (1H, br. d, ^3J = 3.4, H-3 furyl); 7.47 (1H, br. s) and 7.56 (1H, br. s, $CONH_2$); 7.92 (1H, d, ^3J = 1.6, H-5 furyl); 7.96 (1H, s, –CH=). Proton signals of the perhydrotriazine **7**: 2.23 (9H, s, $3CH_3$); 4.72 (6H, br. s, $3CH_2$); 6.90 (12H, dd, ^3J = 8.1, ^3J = 8.1, H Ar).

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