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A Convenient *Mannich*-Type One-Pot Synthesis of Pyrimido[6,1-*b*][1,3,5]thiadiazines

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Summary. 3-(Het)aryl-2-cyanoprop-2-enethioamides easily reacted with primary amines and excessive formaldehyde under mild conditions to afford pyrimido[6,1-*b*][1,3,5]thiadiazine derivatives in moderate yields. Furthermore, 2-cyano-2-cyclohexylideneethanethioamide reacted in the similar *Mannich*-type manner to give spiro-conjugated pyrimido-1,3,5-thiadiazines. The structure of 3,7-dibenzyl-8-(fur-2-yl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3,5]thiadiazine-9-carbonitrile was determined by X-ray diffraction analysis.

Keywords. Heterocycles; Cyclizations; *Mannich* reaction; 3-(Het)aryl-2-cyanoprop-2-enethioamides; X-ray structure determination.

Introduction

Although the *Mannich* reaction has been described for the first time almost one hundred years ago [1], it still remains one of the most important, convenient, and powerful tools in organic chemistry [2]. Numerous examples of heterocyclic syntheses proceeding through the *Mannich*-type aminomethylation as key step have been reported over the last years. Since recent times we have been interested in the title reaction to use it as a suitable approach towards the single-step construction of the 1,3,5-thiadiazine framework starting from substituted 2-thioxo- or tautomeric 2-mercaptoazines. Thus, we have found that the multi-component condensation of certain 2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates with formaldehyde and primary amines gave pyrido[2,1-*b*][1,3,5]thiadiazines in good to excellent yields [3]. Generally, both primary and secondary thioamides, as well as their cyclic analogs, easily were reacted with amines in the presence of formaldehyde to give

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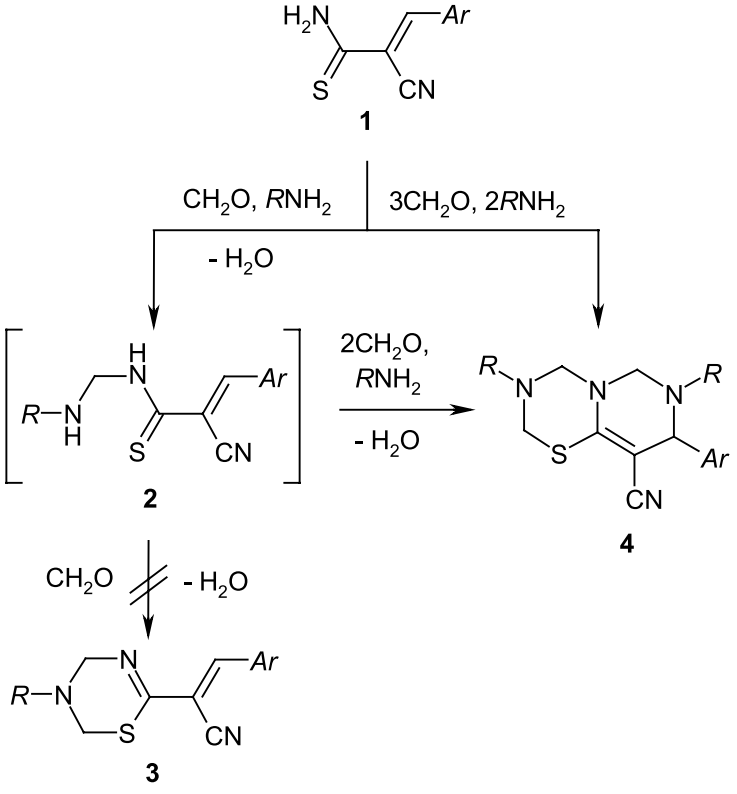
corresponding *N*-aminomethyl derivatives [2]. However, only few examples of heterocyclization based on this sort of *Mannich* reaction had been reported hitherto. First of all, the syntheses of 1,2,4-triazolo[3,4-*b*][1,3,5]thiadiazines [4], imidazo[2,1-*b*][1,3,5]thiadiazines, and 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazines [5] starting from 2-mercaptoazoles and -azines are to be mentioned. It should be noted that the practical importance of 1,3,5-thiadiazines has generated a growing interest in their synthesis in order to explore their biodynamic properties [6]. Thus, many compounds having a 1,3,5-thiadiazine moiety have a great potential in agriculture, due to the remarkable insecticidal [7], antifungal, and antimicrobal [8] activities.

In connection with our investigations related to the chemistry of cyanothioacetamide and its derivatives [9], we intended to study the aminomethylation of 3-substituted 2-cyanoprop-2-enethioamides **1**. The latter are stable solids easily accessible by condensation of cyanothioacetamide and carbonyl compounds, and suggested to be attractive precursors for heterocyclic synthesis. Following the *Mannich* strategy mentioned above an approach to synthesize functionalized 1,3,5-thiadiazines *via* a three-component condensation among primary amines, formaldehyde, and substituted 2-cyanoprop-2-enethioamides is reported herein.

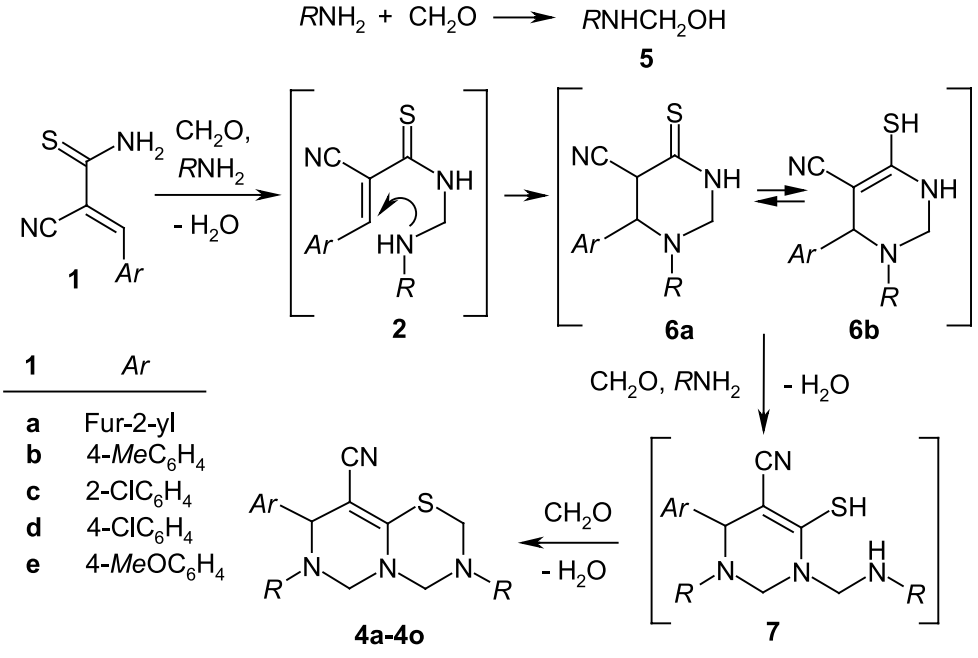
Results and Discussions

First, the reaction of unsaturated thioamides **1** and amines (taken in the molar ratio 1:1) in the presence of excessive formaldehyde was attempted with anticipation of

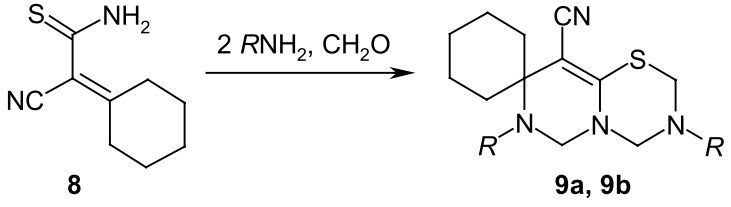


Scheme 1

formation of 2-(3,4-dihydro-2*H*-1,3,5-thiadiazin-6-yl)acrylonitrile derivatives **3** by *Mannich*-type condensation of **1** to give *N*-(aminomethyl)thioamides **2**, followed by cyclocondensation with a second mol of HCHO (Scheme 1). According to TLC data, no starting material remained after 24 h in the reaction mixture. However, no acrylonitrile derivatives **3** were obtained at all. Surprisingly, the previously unknown 3,7,8-trisubstituted 3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3,5]thiadiazine-9-carbonitriles **4** were isolated as main products, albeit with low yields



1	*Ar*
a	Fur-2-yl
b	4-*Me*C_6H_4
c	2-ClC_6H_4
d	4-ClC_6H_4
e	4-*Me*OC_6H_4



4	*Ar*	*R*	4	*Ar*	*R*
a	Fur-2-yl	CH_2Ph	**h**	2-ClC_6H_4	CH_2Ph
b	Fur-2-yl	4-*Et*C_6H_4	**i**	2-ClC_6H_4	4-*Me*C_6H_4
c	4-*Me*C_6H_4	CH_2Ph	**j**	2-ClC_6H_4	3,4-$Me_2C_6H_3$
d	4-*Me*C_6H_4	4-*Et*OC_6H_4	**k**	2-ClC_6H_4	4-FC_6H_4
e	4-*Me*C_6H_4	4-*Me*C_6H_4	**l**	4-ClC_6H_4	4-*Me*C_6H_4
f	4-*Me*C_6H_4	4-*Me*OC_6H_4	**m**	4-ClC_6H_4	4-ClC_6H_4
g	4-*Me*C_6H_4	3,4-$Me_2C_6H_3$	**n**	4-ClC_6H_4	3,4-$Me_2C_6H_3$
			o	4-*Me*OC_6H_4	4-*Me*C_6H_4

9	*R*
a	CH_2Ph
b	4-*Me*C_6H_4

Scheme 2

(10–17%). The obtained **4** belong to a new class of heterocyclic compounds and are supposed to be of a practical interest, especially when taking into account the potent insecticidal activity of the related 2,3,7,8-tetrahydro-4*H*,6*H*-pyrimido[2,1-*b*][1,3,5]thiadiazin-4-ones [10].

Following these results, we next examined the syntheses of **4** from primary amines and thioamides **1**, taken in the optimum 2 : 1 molar ratio, in presence of excess amounts of aqueous formaldehyde solution (Scheme 2). This approach gave much better results: pyrimido[6,1-*b*][1,3,5]thiadiazines **4a**–**4o** were obtained in fair to moderate yields (32–65%). Both aromatic and aliphatic amines reacted under these conditions; however, all efforts to put into reaction certain sterically hindered ones, such as *t*-butylamine, 2-ethyl-6-methylaniline, or 2,6-dimethylaniline, failed. We assumed that the formation of **4** proceeded *via* the mechanism depicted in Scheme 2. It had been suggested that formation of *N*-(aminomethyl)thioamides **2** by *Mannich* condensation of *N*-(hydroxymethyl)amines **5** and **1** took place, which could be regarded as a typical behavior for thioamides in itself [2]. Next, **2** underwent an intramolecular *Michael* addition to give non-isolated hexahydropyrimidine-4-thione **6a**, or its mercaptotautomer **6b**, followed by a further *Mannich* reaction to form the intermediate *N*-(aminomethyl)pyrimidines **7**. Finally, the latter reacted with a third mole of formaldehyde to provide the target pyrimido-1,3,5-thiadiazines **4**. The obtained pyrimido[6,1-*b*][1,3,5]thiadiazines **4** are stable, mostly white or slightly yellowish crystalline solids, soluble in acetone, *DMF*, or *DMSO*, and insoluble in alcohols.

To extend the scope of this reaction, we examined the three-component condensation of cyclohexylideneethanethioamide **8** with 2 equivalents of primary amines and an excess of formaldehyde carried out under similar conditions. We found that **8** reacted in the same way as **1a**–**1o** to furnish the spiro-conjugated pyrimidothiadiazines **9a** and **9b**, but in rather low yields (21–26%).

The structures of the obtained compounds were confirmed by means of elemental analysis, as well as IR and ^{1}H NMR data. Thus, the IR spectra of pyrimidothiadiazines **4** and **9** revealed absorption bands in the region 2180–2164 cm^{-1} due to the conjugated cyano group stretches. The ^{1}H NMR spectra showed the presence of three sets of aromatic protons. In addition, C(8)H proton appeared as a singlet resonating at $\delta =$ 4.31–5.25 ppm. The signal of the SCH_2N protons appeared as a doublet of doublets at $\delta = 3.37$–4.39 ppm with $^2J = 12.3$–13.1 Hz, whereas two doublets of doublets resonating at $\delta = 3.98$–4.88 ppm ($^2J = 12.0$–13.3 Hz), and $\delta = 4.51$–5.20 ppm ($^2J = 11.7$–12.8 Hz) were assigned to the methylene protons of both NCH_2N fragments.

For additional and unambiguous evidence the structure of **4a** was established by a single crystal X-ray diffraction (Fig. 1). Both the S(1)N(1)N(2)C(1–3) and N(2)N(3)C(2)C(4–6) heterocycles have intermediate between *half-chair* and *half-boat* conformations. Selected bond lengths (Å) and angles (°) in the molecule of **4a** have values of: S(1)–C(1) 1.849(3), S(1)–C(2) 1.764(2), N(1)–C(1) 1.434(3), N(1)–C(3) 1.440(3), N(2)–C(2) 1.365(3), N(2)–C(3) 1.471(3), N(2)–C(6) 1.478(3), N(3)–C(5) 1.467(3), N(3)–C(6) 1.439(3), C(2)–C(4) 1.356(3); C(1)S(1)C(2) 100.2(1), C(1)N(1)C(3) 110.6(2), C(2)N(2)C(3) 122.1(2), C(2)N(2)C(6) 117.3(2), C(5)N(3)C(6) 109.7(2).

In conclusion, we have demonstrated that pyrimido[6,1-*b*][1,3,5]thiadiazine derivatives could be synthesized through the novel convenient one-pot *Mannich*-

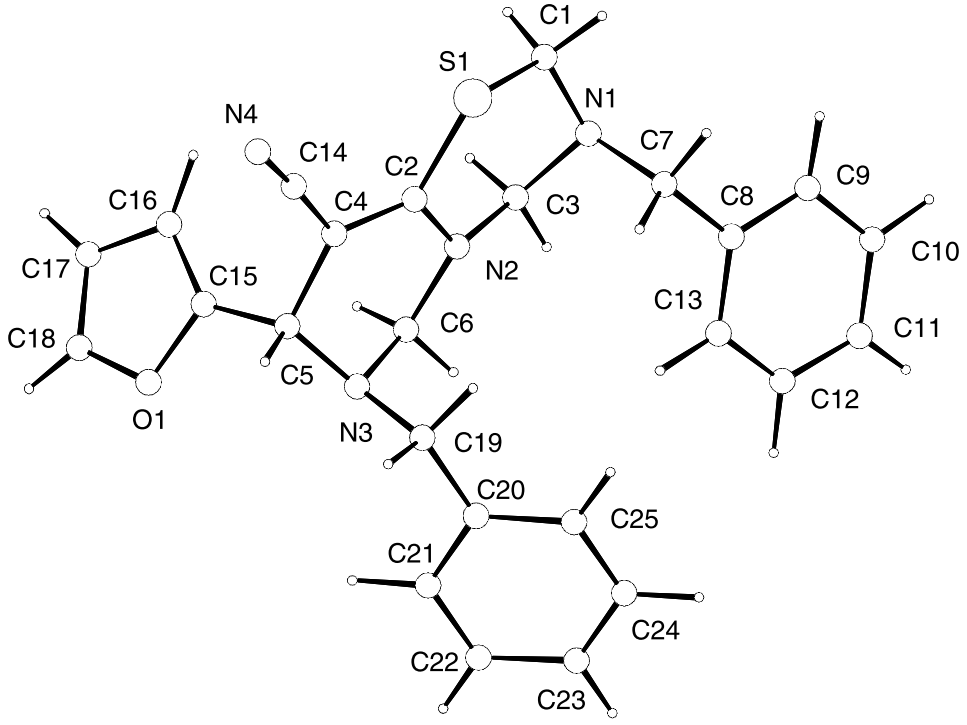


Fig. 1. A perspective view of **4a**

type condensation starting from the readily available 3-substituted 2-cyanoprop-2-enethioamides. The investigation of the scope and limitations of this reaction is in progress and will be reported elsewhere.

Experimental

Melting points were measured on a *Kofler* apparatus and are uncorrected. Elemental analyses for C, H, and N were conducted using a *Perkin-Elmer* C, H, N Analyzer; their results were found to be in good agreement with the calculated values (±0.2%). IR spectra were recorded on an IKS-29 spectrophotometer in Nujol mulls. The ^{1}H NMR spectra were performed on a Varian Gemini 200 (200 MHz) spectrometer in *DMSO*-d_6 solution with Me_4Si as the internal standard. The purity of all obtained compounds was checked by TLC on Silufol UV 254 plates in the acetone:heptane (1 : 1) system; spots were visualized with iodine vapors and UV light. 3-(Het)aryl-2-cyanoprop-2-enethioamides **1a**–**1e** were prepared according to the known general procedure [11]; their physical data were found to be identical with the ones previously described [12–14]. 2-Cyano-2-cyclohexylideneethanethioamide **8** was prepared by the method of Ref. [15].

3,7-R_2-8-(Het)aryl-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitriles (**4**) *and 3′,7′-R_2-3′,4′,6′,7′-tetrahydro-2′H-spiro[cyclohexane-1,8′-pyrimido[6,1-b][1,3,5]thiadiazine]-9′-carbonitriles* (**9**); *General procedure*

A mixture of 4.5 mmol of α,β-unsaturated thioamide **1a**–**1o** or **8**, an excess (5 cm^3, 0.06 mol) of 37% HCHO, and 10 mmol of the corresponding primary amine in 20 cm^3 *Et*OH was refluxed for 3–5 min, filtered through a paper filter, and left overnight. The precipitate was filtered off and recrystallized from an appropriate solvent to afford the corresponding pyrimido[6,1-*b*][1,3,5]thiadiazine.

3,7-Dibenzyl-8-(fur-2-yl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4a**, $C_{25}H_{24}N_4OS$)
Yield 41%; mp 155–158°C (*DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 3.47$ (d, 1H, $^2J = 12.4$ Hz, NCH_2S), 3.91 (br s, 2H, PhCH_2N), 4.02–4.09 (m, 3H, NCH_2N, overlapping with one of NCH_2S-protons), 4.17 (br s, 2H, PhCH_2N), 4.31 (s, 1H, H-8), 4.63 (dd, 2H, $^2J = 11.8$ Hz, NCH_2N), 6.35 and 6.39 (2 m, 2 × 1H, H-3 furyl and H-4 furyl), 7.29–7.45 (m, 10H, 2 Ph), 7.52 (m, 1H, H-5 furyl) ppm; IR (nujol): $\bar{\nu} = 2173$ (C≡N) cm^{-1}.

3,7-Di(4-ethylphenyl)-8-(fur-2-yl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4b**, $C_{27}H_{28}N_4OS$)
Yield 42%; mp 113–116°C (*DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 1.20$ (br t, 6H, $^3J = 7.5$ Hz, 2CH_2CH_3, overlapping), 2.55 (m, 4H, 2CH_2CH$_3$, overlapping), 4.39 (dd, 2H, $^2J = 12.4$ Hz, NCH_2S), 4.73 (dd, 2H, $^2J = 12.3$ Hz, NCH_2N), 4.97 (s, 1H, H-8), 4.99 (dd, 2H, $^2J = 12.5$ Hz, NCH_2N), 6.24 and 6.30 (2m, 2×1H, H-3 furyl and H-4 furyl), 6.83–7.02 (m, 8H, CH arom), 7.41 (m, 1H, H-5 furyl) ppm; IR (nujol): $\bar{\nu} = 2179$ (C≡N) cm^{-1}.

3,7-Dibenzyl-8-(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4c**, $C_{28}H_{28}N_4S$)
Yield 61%; mp 125–128°C (*DMF*); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.30$ (s, 3H, H_3C-Ar), 3.56 (dd, 2H, $^2J = 12.3$ Hz, NCH_2S), 3.86 (br s, 2H, PhCH_2N), 4.03 (dd, 2H, $^2J = 12.4$ Hz, NCH_2N), 4.11 (s, 2H, PhCH_2N), 4.19 (s, 1H, H-8), 4.58 (dd, 2H, $^2J = 11.9$ Hz, NCH_2N), 7.08–7.41 (m, 14H, CH arom) ppm; IR (nujol): $\bar{\nu} = 2176$ (C≡N) cm^{-1}.

3,7-Di(4-ethoxyphenyl)-8-(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4d**, $C_{30}H_{32}N_4O_2S$)
Yield 63%; mp 168–170°C (*DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 1.40$ (br t, 6H, $^3J = 7.1$ Hz, 2OCH$_2$CH_3, overlapping), 2.36 (s, 3H, H_3C-Ar), 3.99 (q, 4H, $^3J = 7.1$ Hz, 2OCH_2CH$_3$, overlapping), 4.25 (dd, 2H, $^2J = 12.6$ Hz, NCH_2S), 4.74 (dd, 2H, $^2J = 13.1$ Hz, NCH_2N), 4.90 (s, 1H, H-8), 5.10 (dd, 2H, $^2J = 12.5$ Hz, NCH_2N), 6.80 and 6.87 (2q, 2×4H, $^3J = 8.0$ Hz, 2(4-*Et*OC$_6H_4$)), 7.18 (q, 4H, $^3J = 7.9$ Hz, 4-MeC$_6H_4$), 7.41 (m, 1H, CH arom) ppm; IR (nujol): $\bar{\nu} = 2165$ (C≡N) cm^{-1}.

3,7,8-Tri(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4e**, $C_{28}H_{28}N_4S$)
Yield 35%; mp 178–181°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.24$, 2.27, and 2.31 (3s, 3×3H, H_3C-Ar), 4.34 (dd, 2H, $^2J = 12.8$ Hz, NCH_2S), 4.88 (dd, 2H, $^2J = 12.8$ Hz, NCH_2N), 5.11 (s, 1H, H-8), 5.20 (dd, 2H, $^2J = 12.3$ Hz, NCH_2N), 7.03 (m, 8H, 4-MeC$_6H_4$N-3 and 4-MeC$_6H_4$N-7), 7.19 (m, 4H, 4-MeC$_6H_4$C-8) ppm; IR (nujol): $\bar{\nu} = 2172$ (C≡N) cm^{-1}.

3,7-Di(4-methoxyphenyl)-8-(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4f**, $C_{28}H_{28}N_4O_2S$)
Yield 35%; mp 198–200°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.35$ (s, 3H, H_3C-Ar), 3.77 (br s, 6H, 2 OCH_3, overlapping), 4.26 (dd, 2H, $^2J = 12.8$ Hz, NCH_2S), 4.81 (m, 2H, NCH_2N), 4.99 (s, 1H, H-8), 5.17 (dd, 2H, $^2J = 12.2$ Hz, NCH_2N), 6.89 (br q, 8H, $^3J = 8.4$ Hz, 2(4-MeOC$_6H_4$)), 7.19 (m, 4H, 4-MeC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2180$ (C≡N) cm^{-1}.

3,7-Di(3,4-dimethylphenyl)-8-(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4g**, $C_{30}H_{32}N_4S$)
Yield 32%; mp 174–176°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.15$ (br s, 12H, 4H_3C-Ar), 2.31 (s, 3H, 4-H_3CC$_6$H$_4$C-8), 4.34 (dd, 2H, $^2J = 13.0$ Hz, NCH_2S), 4.89 (dd, 2H,

$^2J = 12.9$ Hz, NCH_2N), 5.13 (s, 1H, H-8), 5.20 (dd, 2H, $^2J = 12.5$ Hz, NCH_2N), 6.83–6.97 (m, 6H, ArN-3 and ArN-7), 7.20 (m, 4H, 4-MeC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2176$ (C≡N) cm^{-1}.

3,7-Dibenzyl-8-(2-chlorophenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4h**, $C_{27}H_{25}ClN_4S$)
Yield 57%; mp 133–135°C (*DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 3.37$ (dd, 2H, $^2J = 12.9$ Hz, NCH_2S), 3.96 (br s, 2H, PhCH_2N), 3.98 (dd, 2H, $^2J = 12.0$ Hz, NCH_2N), 4.16 (br s, 2H, PhCH_2N), 4.64 (dd, 2H, $^2J = 11.7$ Hz, NCH_2N), 4.67 (s, 1H, H-8), 7.19–7.50 (m, 14H, CH arom) ppm; IR (nujol): $\bar{\nu} = 2179$ (C≡N) cm^{-1}.

8-(2-Chlorophenyl)-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4i**, $C_{27}H_{25}ClN_4S$)
Yield 54%; mp 210–211°C (*DMF*); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 2.27$ and 2.30 (2s, 2×3H, 4-H_3CC$_6$H$_4$N-3 and 4-H_3CC$_6$H$_4$N-7), 4.33 (dd, 2H, $^2J = 12.9$ Hz, NCH_2S), 4.78 (dd, 2H, $^2J = 13.1$ Hz, NCH_2N), 5.16 (dd, 2H, $^2J = 12.4$ Hz, NCH_2N), 5.25 (s, 1H, H-8), 6.80–7.19 (m, 8H, 4-H$_3$CC$_6H_4$N-3 and 4-H$_3$CC$_6H_4$N-7), 7.25–7.44 (m, 4H, 2-ClC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2165$ (C≡N) cm^{-1}.

8-(2-Chlorophenyl)-3,7-di(3,4-dimethylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4j**, $C_{29}H_{29}ClN_4S$)
Yield 50%; mp 195–197°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 2.07$ and 2.15 (2s, 2×3H, 3-H_3C-ArN-3 and 3-H_3C-ArN-7), 2.18 (br s, 6H, 2(4-H_3C-Ar)), 4.28 (dd, 2H, $^2J = 13.1$ Hz, NCH_2S), 4.71 (dd, 2H, $^2J = 13.3$ Hz, NCH_2N), 5.08 (dd, 2H, $^2J = 12.1$ Hz, NCH_2N), 5.23 (s, 1H, H-8), 6.55–6.98 (m, 6H, ArN-3 and ArN-7), 7.22–7.37 (m, 4H, 2-ClC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2169$ (C≡N) cm^{-1}.

8-(2-Chlorophenyl)-3,7-di(4-fluorophenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4k**, $C_{25}H_{19}ClF_2N_4S$)
Yield 55%; mp 193–195°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 4.30$ (dd, 2H, $^2J = 12.9$ Hz, NCH_2S), 4.77 (dd, 2H, $^2J = 13.1$ Hz, NCH_2N), 5.14 (dd, 2H, $^2J = 12.6$ Hz, NCH_2N), 5.19 (s, 1H, H-8), 6.87–7.11 (m, 8H, 4-FC$_6H_4$N-3 and 4-FC$_6H_4$N-7), 7.31–7.38 (m, 4H, 2-ClC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2178$ (C≡N) cm^{-1}.

8-(4-Chlorophenyl)-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4l**, $C_{27}H_{25}ClN_4S$)
Yield 61%; mp 213–215°C (*Et*OH); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 2.22$ and 2.24 (2s, 2×3H, 4-H_3CC$_6$H$_4$N-3 and 4-H_3CC$_6$H$_4$N-7), 4.32 (dd, 2H, $^2J = 13.0$ Hz, NCH_2S), 4.88 (dd, 2H, $^2J = 13.2$ Hz, NCH_2N), 5.13 (s, 1H, H-8), 5.19 (dd, 2H, $^2J = 12.0$ Hz, NCH_2N), 6.95–7.06 (m, 8H, 4-H$_3$CC$_6H_4$N-3 and 4-H$_3$CC$_6H_4$N-7), 7.37 (q, 4H, $^3J = 8.5$ Hz, 4-ClC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2175$ (C≡N) cm^{-1}.

3,7,8-Tri(4-chlorophenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4m**, $C_{25}H_{19}Cl_3N_4S$)
Yield 49%; mp 221–223°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 4.32$ (dd, 2H, $^2J = 12.5$ Hz, NCH_2S), 4.84 (dd, 2H, $^2J = 13.2$ Hz, NCH_2N), 5.10 (s, 1H, H-8), 5.11 (dd, 2H, $^2J =$ 12.8 Hz, NCH_2N), 6.97–7.30 (m, 12H, CH arom) ppm; IR (nujol): $\bar{\nu} = 2175$ (C≡N) cm^{-1}.

8-(4-Chlorophenyl)-3,7-di(3,4-dimethylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4n**, $C_{29}H_{29}ClN_4S$)
Yield 56%; mp 182–185°C (*DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 2.15$ (m, 12H, 4(H_3C-Ar)), 4.26 (dd, 2H, $^2J = 12.7$ Hz, NCH_2S), 4.79 (m, 2H, NCH_2N), 5.03 (s, 1H, H-8), 5.08 (dd, 2H, $^2J = 12.8$ Hz, NCH_2N), 6.66–6.95 (m, 6H, ArN-3 and ArN-7), 7.30 (m, 4H, 4-ClC$_6H_4$) ppm; IR (nujol): $\bar{\nu} = 2175$ (C≡N) cm^{-1}.

8-(4-Methoxyphenyl)-3,7-di(4-methylphenyl)-3,4,7,8-tetrahydro-2H,6H-pyrimido[6,1-b][1,3,5]thiadiazine-9-carbonitrile (**4o**, $C_{28}H_{28}N_4OS$)
Yield 65%; mp 185–187°C (*DMF*:*Et*OH = 1:1); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.24$ and 2.26 (2s, 2×3H, 4-$H_3CC_6H_4$N-3 and 4-$H_3CC_6H_4$N-7), 3.75 (s, 3H, OCH_3), 4.33 (dd, 2H, $^2J = 12.5$ Hz,

Table 1. Crystal structure information for **4a**

Formula	$C_{25}H_{24}N_4OS$
Formula weight	428.56
Temperature/K	293
Crystal size/mm^3	$0.34 \times 0.42 \times 0.46$
Colour	brown
Shape	block
Crystal class	Orthorhombic
Cell dimensions	
a/Å	10.818(3)
b/Å	22.965(7)
c/Å	8.837(2)
α/°	89.96(2)
β/°	90.02(2)
γ/°	89.98(2)
V/Å^3	2195.6(10)
Z	4
Radiation/Wavelength	CuK_α ($\lambda = 1.541800$ Å)
d/g·cm^{-3}	1.30
μ/mm^{-1}	1.499
Cell from	22 reflections
Θ range/°	25 to 26
Standard Interval	0
Standard Count	3
Diffractometer type	MACH3
Scan type	$2\theta/\omega$
Absorption type	psi-scan
Transmission range	0.50–0.60
Reflections measured	3743
Independent reflections	3204
R_{int}	0.0002
Θ_{max}/°	64.94
Sphere segments	
H_{min}, H_{max}	−12, 12
K_{min}, K_{max}	−26, 26
L_{min}, L_{max}	−5, 10
Refinement on F	
R-factor	0.038
Weighted R-factor	0.039
Reflections used	2883
Number of parameters	280
Goodness of fit	0.984

NCH_2S), 4.87 (m, 2H, NCH_2N), 5.07 (s, 1H, H-8), 5.19 (dd, 2H, $^2J = 12.6$ Hz, NCH_2N), 6.88–7.22 (m, 12H, CH arom) ppm; IR (nujol): $\bar{\nu} = 2166$ (C≡N) cm^{-1}.

3′,7′-Dibenzyl-3′,4′,6′,7′-tetrahydro-2′H-spiro[cyclohexane-1,8′-pyrimido[6,1-b][1,3,5]thiadiazine]-9′-carbonitrile (**9a**, $C_{26}H_{30}N_4S$)
Yield 21%; mp 150°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.34$–2.07 (m, 10H, $(CH_2)_5$), 3.69 (br s, 4H, 2PhCH_2), 3.91 (br s, 2H, NCH_2S), 4.10 and 4.51 (2br s, 2×2H, 2NCH_2N), 7.26–7.31 (m, 10H, 2Ph) ppm; IR (nujol): $\bar{\nu} = 2168$ (C≡N) cm^{-1}.

3′,7′-Di(4-methylphenyl)-3′,4′,6′,7′-tetrahydro-2′H-spiro[cyclohexane-1,8′-pyrimido[6,1-b][1,3,5]thiadiazine]-9′-carbonitrile (**9b**, $C_{26}H_{30}N_4S$)
Yield 26%; mp 173–175°C (*DMF*:*Et*OH = 1:2); ^{1}H NMR (200 MHz, *DMSO*-d$_6$): $\delta = 1.27$–1.84, 2.20 (m, 10H, $(CH_2)_5$), 2.23 and 2.29 (2s, 2×3H, 2H_3C-Ar), 4.28–5.16 (m, 6H, NCH_2S, 2NCH_2N), 6.74–7.08 (m, 8H, CH arom) ppm; IR (nujol): $\bar{\nu} = 2164$ (C≡N) cm^{-1}.

X-Ray Crystallography
Crystallographic data (excluding structure factors) for the structure of **4a** reported in this paper were deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-262217 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223/336-033, e-mail: deposit@ccdc.cam.ac.uk). Other data from single crystal analysis is summarized in Table 1. The data were obtained using the automated four-circle Enraf-Nonius CAD-4 diffractometer.

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