

# Facile and efficient synthesis of 4'-thioxo-1',3,3',4,4',6'-hexahydro-1*H*,2'*H*-spiro(naphthalene-2,5'-pyrimidin)-1-ones in a three-component Mannich-type reaction

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DOI: <http://dx.doi.org/10.3998/ark.5550190.p007.912>

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## Abstract

Spirohexahydropyrimidines were obtained in the one-pot three-component reaction of the tetralone-derived thioamides, amines and formaldehyde with alcoholic hydrogen chloride as the catalyst.

**Keywords:** Mannich reaction, thioamides, spirohexahydropyrimidines

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## Introduction

Although thioamides are known almost since the very dawn of organic chemistry, their synthetic applicability gained a wide recognition only a few decades ago. High reactivity of the thioamide group towards both electro- and nucleophilic agents, often in conjunction with that of other reactive centers in the molecule, made thioamides handy building blocks of particular importance in the synthesis of heterocyclic systems by inter- and intramolecular cyclization.<sup>1-5</sup> Saturated or partially saturated heterocyclic compounds with a thioamide group were found to be of interest as potential ionic liquid media.<sup>6</sup> Bogdanowicz-Szwed and co-workers reported the base-catalyzed reaction of  $\beta$ -ketothioamides with (*E*)- $\beta$ -nitrostyrenes which yielded spiro(indane-1,3'-thiophenes).<sup>7,8</sup>

On the other hand, the hexahydropyrimidine fragment is present in several natural products and in pharmaceutical agents of various biological activity.<sup>9-12</sup> Some derivatives of hexahydropyrimidine are used as stabilizers of polymers.<sup>13</sup> Owing to their facile cleavage in mild acidic medium, hexahydropyrimidines have been employed in organic synthesis as protective groups in the selective acylation and addition of 1,3-diamines.<sup>18</sup>

The classic synthetic route leading to this type of heterocyclic compounds involves the condensation of substituted propane-1,3-diamines with aldehydes and ketones.<sup>14-17</sup> Liang and co-

workers recently synthesized 1,3-diaryl-5-spirohexahydropyrimidines *via* the proline-catalyzed one-pot condensation of anilines, formaldehyde, and cyclohexanones in the Mannich-type reaction,<sup>19</sup> which as a powerful C-C bond formation process is widely applied to the preparation of diverse aminoalkyl derivatives.<sup>20-23</sup>

In recent years multicomponent reactions (MCRs) have attracted the attention of organic chemists because of their numerous advantages over conventional multistep syntheses.<sup>24-26</sup> Thus, Mukhopadhyay and co-workers<sup>27</sup> reported a multicomponent synthesis of 1,3-diarylhexahydropyrimidines in the one-pot reaction of 1,3-dicarbonyl compounds, aromatic amines and formaldehyde catalyzed by iron(III) chloride. T. B. Shah and co-workers<sup>28</sup> described their results of the synthesis and *in vitro* biological screening of a series of *N*-Mannich bases obtained from 3,4-dihydropyrimidine-2-(1*H*)-thiones; those with morpholine as the heterocyclic secondary amino component showed a promising activity against both bacterial and fungal microorganisms.<sup>28</sup>

In our earlier papers we have described the reactions of intramolecular cyclization of *N*-allylthioamides derived from cyclic ketones and  $\beta$ -diketones,<sup>29</sup> the reactions of  $\beta$ -keto thioamides with carboxylic esters,<sup>30</sup> as well as the reactions of  $\beta$ -keto thioamides with  $\alpha,\beta$ -unsaturated aldehydes.<sup>31</sup>

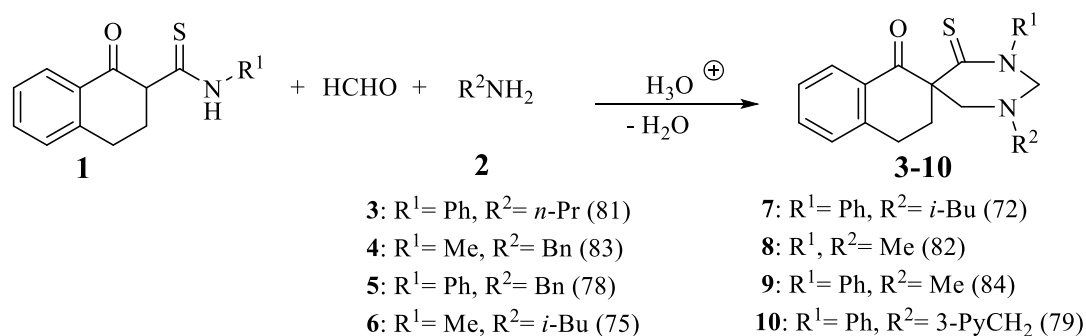
## Results and Discussion

Continuing our studies on the application of  $\beta$ -keto thioamides to the synthesis of heterocyclic compounds we report in the present paper a facile and efficient synthesis of 4'-thioxo-1',3,3',4,4',6'-hexahydro-1*H*,2'*H*-spiro(naphthalene-2,5'-pyrimidin)-1-ones in a three-component Mannich-type reaction.

Neither room nor elevated (approx. 40 °C) temperature conditions were found effective when the reaction of 2-tetralone derivatives **1** with secondary amines (dimethylamine, morpholine) was carried out according to the classic Mannich procedure. However, when primary aliphatic amines **2** were used under analogous conditions at room or slightly elevated (approx. 40 °C) temperatures, spiroheterocyclic compounds **3-10** were readily formed in good yields (Scheme 1), although aromatic amines failed to react as shown in the experiments with the 2-tetralone-derived thioamides **1** or 1,3-indanedione **11**. Methanol, ethanol or THF containing a catalytic amount of hydrochloric acid served as the reaction medium. The failure with secondary and aromatic amines may be due to steric hindrance, though no experiments have been made to substantiate that assumption.

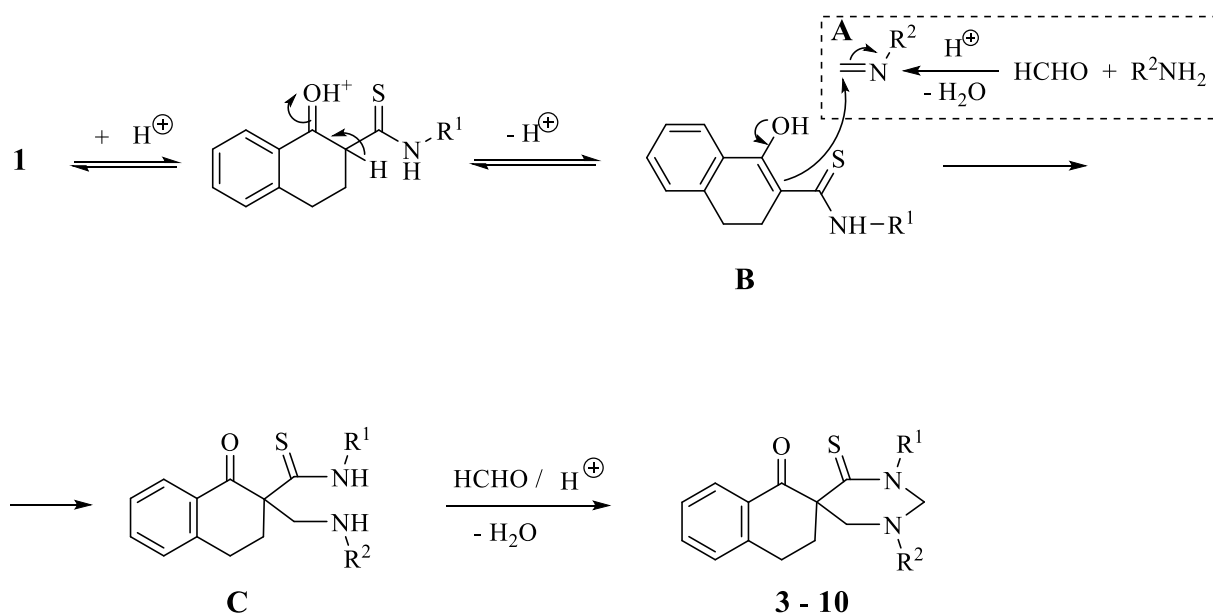
In the earlier studies on the three-component reactions of amines and formaldehyde with  $\beta$ -diketones or  $\beta$ -keto esters, double aminomethylation was observed to occur at the  $\alpha$  carbon atom.<sup>27</sup> Six molecules of reactants were involved and six new covalent bonds were formed in this one-pot three-component reaction; the highest yields of hexahydropyrimidines were obtained when the 1,3-carbonyl compound : amine : formaldehyde molar ratio was 1 : 2 : 3. An analogous

reaction course was reported in the case of the proline-catalyzed aminomethylation of cyclohexanone.<sup>19</sup>



**Scheme 1.** Synthesis of (+/-)-1',3'-disubstituted-4'-thioxo-1',3,3',4,4',6'-hexahydro-1H,2'H-spiro(naphthalene-2,5'-pyrimidin)-1-ones.

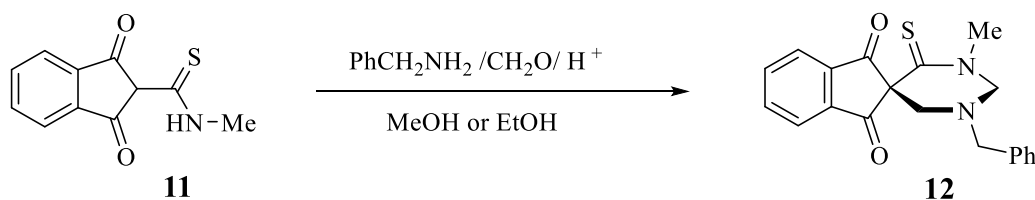
Our results indicate that the thioamide-group nitrogen atom takes part in the formation of the pyrimidine ring. Furthermore, in comparison with similar reactions of ketones<sup>19,27</sup> the molar ratio of reagents is much different, in our case. In the preparative procedures both the amine and formaldehyde were used in an excess in order to optimize the yield of the hexahydropyrimidines. In contrast to the reported reactions of (2-substituted thiocarbamoyl)malonic acid diethyl esters<sup>32</sup> no advance generation of the thioamide anion is required.



**Scheme 2.** Proposed mechanism for the reaction.

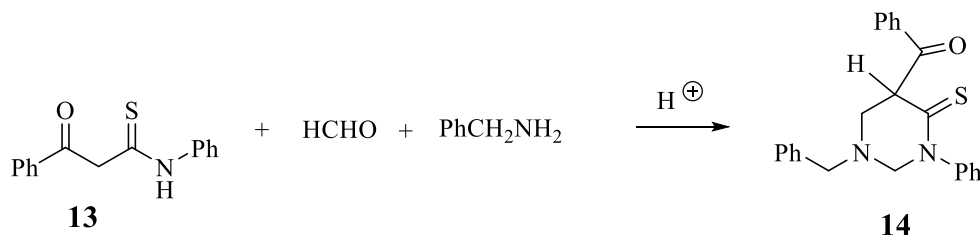
The suggested mechanistic explanation of this reaction assumes that the electrophilic imine **A** attacks the enol form **B** of the thioamide at both its sides to produce two enantiomeric amino thioamides **C** which subsequently condense with another molecule of formaldehyde to yield ultimately the racemic mixtures of (*R,S*)-1',3'-disubstituted-4'-thioxo-1',3,3',4,4',6'-hexahydro-1*H*,2'*H*-spiro(naphthalene-2,5'-pyrimidin)-1-ones **3-10** (Scheme 2). The reaction yield was roughly independent of the substituent attached to the thioamide nitrogen atom.

Thioamides derived from cyclic  $\beta$ -ketodiketones were found to react similarly. For example, 1,3-dioxindane-2-carbothioic *N*-methylamide (**11**) with benzylamine yielded the spirocyclic compound **12** (Scheme 3).



**Scheme 3.** Synthesis of 1'-benzyl-3'-methyl-4'-thioxo-2',3',4',6'-tetrahydro-1'H-spiro(indene-2,5'-pyrimidine)-1,3-dione.

In our preliminary experiments on the reactions of linear  $\beta$ -ketothiomides, 3-oxo-3,*N*-diphenylthiopropionamide (**13**) readily reacted with benzylamine and formaldehyde to give in high yield (88%) the racemic hexahydropyrimidines (**14**). Detailed results will be shortly published in full.



**Scheme 4.** Synthesis of (1-benzyl-3-phenyl-4-thioxohexahydropyrimidin-5-yl)phenylmethanone.

## Conclusions

Aminomethylation of the thioamides with an acidic hydrogen atom at the  $\alpha$  carbon atom has to be considered as a general reaction. Its substrates are easily available and the products are formed at room or slightly elevated temperatures in usually high yields. A proper choice of the starting thioamides and amines makes it possible to use this reaction in order to synthesize

several new and potentially useful hexahydropyrimidine derivatives, for example biologically active compounds.

## Experimental Section

**General.** Melting points were determined in a Boëtius hot-stage apparatus and are uncorrected. The NMR spectra were recorded with a Bruker DPX (400 MHz and 100 MHz for  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR, respectively) spectrometer in deuteriochloroform with tetramethylsilane as internal standard. The IR spectra were taken with Specord M80 instruments in potassium bromide pellets or nujol. Purity and molecular mass determinations were carried out by gas chromatography-mass spectrometry (GC/MS) with a Hewlett-Packard instrument model HP 6890 equipped with a mass detector HP 5973 (**8** only, other compounds decomposed); the analytical procedure was developed for a 30-m long capillary column, 0.2 mm in diameter, with methylsiloxane modified with phenyl groups (5% Ph, Me siloxane) in the 0.25  $\mu\text{m}$  thick active phase layer. Elemental analyses were performed on EuroEA 3000series Euro Vector CHNS-O. All compounds gave satisfactory elemental analysis results (C, H, N, S). The starting thioamides **1** were prepared as described earlier.<sup>8,33</sup>

### Synthesis of compounds **3-10**, **14**

A mixture of thioamide **1** or **13** (1 mmol), alkylamine **2** (3 mmol), formaldehyde (6 mmol, 37% aqueous solution) in 20 mL of EtOH or MeOH containing few drops of conc. HCl was stirred at room temperature for 1 h and then left overnight. The reaction progress was monitored by TLC (silufol /chloroform or hexane : ethyl acetate 1:1). After the completion of the reaction (1-24 hours), the solvent was removed by evaporation. An aqueous sodium carbonate solution (5%) was added and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried with  $\text{MgSO}_4$ , and passed under reduced pressure through a short column (8 · 1.5 cm) packed with  $\text{Al}_2\text{O}_3$  (Brockmann I, neutral, standard) using ethyl acetate as the eluent; reduced pressure was applied to make this operation less time-consuming. Upon evaporation of the solvent, the residue was recrystallized from EtOH or  $n\text{-C}_6\text{H}_{14}/\text{EtOH}$ . Samples used in elemental analyses were chromatographed in a silica gel packed column with chloroform or a hexane/ethyl acetate (1 : 1 or 2 : 1) mixture as the eluent and finally recrystallized again from an appropriate solvent.

**3'-Phenyl-1'-propyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (3)** White powder, yield 81%; m.p. 69-71 °C ( $n\text{-C}_6\text{H}_{14}/\text{EtOH}$ ); IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1678 (C=O).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  0.91 (3H, t,  $J$  7.3 Hz,  $\text{CH}_3$ ), 1.50 (2H, q,  $J$  7.3 Hz,  $\text{CH}_3\text{CH}_2$ ), 2.32-2.44 (2H, m,  $\text{CH}_2\text{CHHC}$ ,  $\text{NCHH}$ ), 2.56 (2H, t,  $J$  7.1 Hz,  $\text{NCH}_2\text{CH}_2$ ), 2.95-3.07 (1H, m,  $\text{CHHCH}_2\text{C}$ ), 3.08-3.37 (3H, m,  $\text{CHHCH}_2\text{C}$ ,  $\text{CH}_2\text{CHHC}$ ,  $\text{NCHH}$ ), 4.27-4.40 (2H, m,  $\text{NCH}_2\text{N}$ ), 7.09-7.19 (1H, m, Ph), 7.20-7.28 (1H, m, Ph), 7.29-7.41 (3H, m, Ph), 7.43-7.53 (3H, m, Ph), 8.07 (1H, d,  $J$  7.8 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  11.6 (q,  $\text{CH}_3$ ), 20.2 (t,  $\text{CH}_3\text{CH}_2\text{CH}_2$ ), 25.4 ((t,

$\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 35.7 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 55.6 (t,  $\text{NCH}_2$ ), 55.8 (t,  $\text{CH}_3\text{CH}_2\underline{\text{C}}\text{H}_2$ ), 59.0 (s,  $\underline{\text{C}}\text{H}_2\text{CH}_2\underline{\text{C}}$ ), 75.0 (t,  $\text{NCH}_2\text{N}$ ), 127.0, 127.1, 128.3, 128.3, 128.6, 129.9, 132.2, 133.6, 142.8, 144.7 (12C, Ph) 196.7 (s,  $\text{C}=\text{O}$ ), 202.8 (s,  $\text{C}=\text{S}$ ). Anal. Calcd. for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{OS}$  (364.50): C, 72.49; H, 6.64; N, 7.69; S, 8.80. Found: C, 72.40; H, 7.03; N, 7.56; S, 8.37%.

**1'-Benzyl-3'-methyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (4).** Yellowish powder, yield 83%, mp 93-95 °C (EtOH); IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1678 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.28 (1H, dt,  $J$  13.7, 5.0 Hz,  $\text{CH}_2\text{CHHC}$ ), 2.63-2.76 (1H, m,  $\text{CHHCH}_2\text{C}$ ), 2.93 (1H, d,  $J$  12.7 Hz,  $\text{NCHH}$ ), 2.97-3.11 (2H, m,  $\text{NCHH}$ ,  $\text{CHHCH}_2\text{C}$ ), 3.12-3.22 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 3.40 (3H, s,  $\text{CH}_3$ ), 3.60 (1H, d,  $J$  =13.1 Hz,  $\text{CHHPh}$ ), 3.76 (1H, d,  $J$  13.1 Hz,  $\text{CHHPh}$ ), 4.10 (1H, d,  $J$  10.4 Hz,  $\text{NCHHN}$ ), 4.17 (1H, d,  $J$  10.4 Hz,  $\text{NCHHN}$ ), 7.16 (1H, d,  $J$  7.6 Hz, Ph), 7.21-7.35 (6H, m, Ph), 7.39-7.47 (1H, m, Ph), 8.03 (1H, d,  $J$  7.9 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  25.2 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 35.2 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 40.9 (q,  $\text{CH}_3$ ), 54.7 (q,  $\text{CH}_3$ ), 58.5 (t,  $\underline{\text{C}}\text{H}_2\text{Ph}$ ), 59.6 (s,  $\underline{\text{C}}\text{H}_2\text{CH}_2\underline{\text{C}}$ ), 73.1 (t,  $\text{NCH}_2\text{N}$ ), 126.8, 127.8, 128.3, 128.5, 128.6, 128.7, 132.3, 133.5, 136.3, 142.8 (12C, Ph), 196.6 (s,  $\text{C}=\text{O}$ ), 200.2 (s,  $\text{C}=\text{S}$ ). Anal. Calcd. for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{OS}$  (350.48): C, 71.97; H, 6.33; N, 7.99; S, 9.15. Found: C, 72.04; H, 5.54; N, 7.99; S, 9.20%.

**1'-Benzyl-3'-phenyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (5).** Yellowish powder, yield 78%, mp 143-146 °C (EtOH); IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1672 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.32-2.43 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 2.72-2.85 (1H, m,  $\text{CHHCH}_2\text{C}$ ), 3.03-3.17 (2H, m,  $\text{CHHCH}_2\text{C}$ ,  $\text{NCHH}$ ), 3.24 (1H, d,  $J$  13.2 Hz,  $\text{NCHH}$ ), 3.26-3.37 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 3.71 (1H, d,  $J$  13.2 Hz,  $\text{CHHPh}$ ), 3.86 (1H, d,  $J$  13.2 Hz,  $\text{CHHPh}$ ), 4.35 (1H, d,  $J$  10.6 Hz,  $\text{NCHHN}$ ), 4.42 (1H, d,  $J$  10.6 Hz,  $\text{NCHHN}$ ), 7.18 (1H, d,  $J$  7.6 Hz, Ph), 7.21-7.40 (9H, m, Ph), 7.41-7.50 (3H, m, Ph), 8.05 (1H, d,  $J$  7.8 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  25.2 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 35.5 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 55.0 (t,  $\text{NCH}_2$ ), 58.3 (t,  $\underline{\text{C}}\text{H}_2\text{Ph}$ ), 59.3 (s,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 74.7 (t,  $\text{NCH}_2\text{N}$ ), 126.9, 127.1, 127.8, 128.3, 128.4, 128.5, 128.6, 128.7, 129.9, 132.2, 133.5, 136.4, 142.8, 144.5 (18C, Ph), 196.6 (s,  $\text{C}=\text{O}$ ), 203.0 (s,  $\text{C}=\text{S}$ ); Anal. Calcd. for  $\text{C}_{26}\text{H}_{24}\text{N}_2\text{OS}$  (412.55): C, 75.70; H, 5.86; N, 6.79; S, 7.77. Found: C, 75.31; H, 5.95; N, 6.82; S, 7.66%.

**1'-Isobutyl-3'-methyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (6).** White powder, yield 75%, mp 114-116 °C; IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1676 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  0.89 (6H, q,  $J$  6.6 Hz, 2  $\text{CH}_3$ ), 1.64-1.77 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.23 (2H, d,  $J$  7.4 Hz,  $\underline{\text{C}}\text{H}_2\text{CH}$ ), 2.27-2.36 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 2.88-3.04 (3H, m,  $\text{CHHCH}_2\text{C}$ ,  $\text{NCHH}$ ), 3.09-3.25 (2H, m,  $\text{CH}_2\text{CHHC}$ ,  $\text{NCHH}$ ), 3.42 (3H, s,  $\text{CH}_3$ ), 4.03 (1H, d,  $J$  10.4 Hz,  $\text{NCHHN}$ ), 4.11 (1H, d,  $J$  10.4 Hz,  $\text{NCHHN}$ ), 7.23 (1H, d,  $J$  7.6 Hz, Ph), 7.31 (1H, t,  $J$  7.4 Hz, Ph), 7.47 (1H, td,  $J$  7.4, 1.4 Hz, Ph), 8.04 (1H, dd,  $J$  7.8, 1.21 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  20.5 (q,  $\text{CH}_3$ ), 20.6 (q,  $\text{CH}_3$ ), 25.4 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 25.8 (d,  $\underline{\text{C}}\text{H}(\text{CH}_3)_2$ ), 35.1 (t,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{C}$ ), 40.8 (q,  $\text{N}-\text{CH}_3$ ), 55.3 (t,  $\text{NCH}_2$ ), 59.6 (s,  $\underline{\text{C}}\text{H}_2\text{CH}_2\underline{\text{C}}$ ), 62.2 (t,  $\underline{\text{C}}\text{H}_2\text{CH}(\text{CH}_3)_2$ ), 73.8 (t,  $\text{NCH}_2\text{N}$ ), 126.9, 128.3, 128.5, 132.3, 133.5, 142.7 (6C, Ph), 196.5 (s,  $\text{C}=\text{O}$ ), 199.9 (s,  $\text{C}=\text{S}$ ). Anal. Calcd. For  $\text{C}_{18}\text{H}_{24}\text{N}_2\text{OS}$  (316.46): C, 68.32; H, 7.64; N, 8.85; S, 10.13. Found: C, 68.01; H, 7.79; N, 8.83; S, 10.09%.

**1'-Isobutyl-3'-phenyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (7).** White powder, yield 72%, mp 86-88 °C (n- $\text{C}_6\text{H}_{14}$ /EtOH). IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1676 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  0.91 (6H, q,  $J$  6.6 Hz, 2  $\text{CH}_3$ ), 1.63-1.83 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ),

2.35 (2H, dd,  $J$  7.2, 2.8 Hz,  $\text{CH}_2\text{CH}$ ), 2.37-2.46 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 2.96-3.06 (1H, m,  $\text{CHHCH}_2\text{C}$ ), 3.09-3.27 (3H, m,  $\text{CHHCH}_2\text{C}$ ,  $\text{NCHH}$ ), 3.29-3.38 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 4.29 (1H, d,  $J$  10.6 Hz,  $\text{NCHHN}$ ), 4.32 (1H, d,  $J$  10.6 Hz,  $\text{NCHHN}$ ), 7.24 (1H, d,  $J$  7.7 Hz, Ph), 7.29-7.35 (3H, m, Ph), 7.36-7.42 (1H, m, Ph), 7.44-7.53 (3H, m, Ph), 8.07 (1H, dd,  $J$  7.8, 0.8 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  20.5 (q,  $\text{CH}_3$ ), 20.6 (q,  $\text{CH}_3$ ), 25.4 (t,  $\text{CH}_2\text{CH}_2\text{C}$ ), 26.0 (d,  $\text{CH}(\text{CH}_3)_2$ ), 35.6 (t,  $\text{CH}_2\text{CH}_2\text{C}$ ), 55.9 (t,  $\text{NCH}_2$ ), 59.1 (s,  $\text{CH}_2\text{CH}_2\text{C}$ ), 62.1 (t,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 75.3 (t,  $\text{NCH}_2\text{N}$ ), 126.9, 127.0, 128.3, 128.4, 128.5, 129.9, 132.3, 133.5, 142.8, 144.6 (12C, Ph), 196.3 (s,  $\text{C}=\text{O}$ ), 202.8 (s,  $\text{C}=\text{S}$ ). Anal. Calcd. For  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{OS}$  (378.53): C, 72.98; H, 6.92; N, 7.40; S, 8.47. Found: C, 72.40; H, 7.34; N, 7.30; S, 8.39%.

**1',3'-Dimethyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (8).** Yellowish powder, yield 82%, mp 124-127 °C (EtOH); IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1674 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.25 (1H, dt,  $J$  13.7, 4.4 Hz,  $\text{CH}_2\text{CHHC}$ ), 2.38 (3H, s,  $\text{CH}_3$ ), 2.83 (1H, d,  $J$  11.9 Hz,  $\text{CHHCH}_2\text{C}$ ), 2.90-3.01 (1H, m,  $\text{NCHH}$ ), 3.06 (1H, d,  $J$  11.9 Hz,  $\text{CHHCH}_2\text{C}$ ), 3.09-3.19 (1H, m,  $\text{NCHH}$ ), 3.21-3.33 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 3.43 (3H, s,  $\text{CH}_3$ ), 3.93-4.11 (2H, m,  $\text{NCH}_2\text{N}$ ), 7.20-7.36 (2H, m, Ph), 7.48 (1H, t,  $J$  7.4 Hz, Ph), 8.05 (1H, d,  $J$  7.8 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  25.4 (t,  $\text{CH}_2\text{CH}_2\text{C}$ ), 35.4 (t,  $\text{CH}_2\text{CH}_2\text{C}$ ), 41.0 (q,  $\text{S}=\text{CNCH}_3$ ), 42.4 (q,  $\text{CH}_2\text{NCH}_3$ ), 57.7 (t,  $\text{N-CH}_2$ ), 59.3 (s,  $\text{CH}_2\text{CH}_2\text{C}$ ), 74.5 (t,  $\text{NCH}_2\text{N}$ ), 126.9, 128.4, 128.5, 132.0, 133.5, 142.7 (6C, Ph), 196.3 (s,  $\text{C}=\text{O}$ ), 199.5 (s,  $\text{C}=\text{S}$ ). MS,  $m/z$  (%) = 274 ( $\text{M}^+$ , 76), 256 (31), 241 (61) 200 (35), 184 (31), 155 (27), 128 (47), 116 (44), 90 (42), 58 (88), 42 (100). Anal. Calcd. For  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{OS}$  (274.38): C, 65.66; H, 6.61; N, 10.21; S, 11.69. Found: C, 65.30; H, 6.88; N, 10.17; S, 11.98%.

**1'-Methyl-3'-phenyl-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (9).** White powder, yield 84%; mp 130-132 °C (EtOH); IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1674 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.23-2.32 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 2.37 (3H, s,  $\text{CH}_3$ ), 2.82-2.99 (2H, m,  $\text{CHHCH}_2\text{C}$ ,  $\text{NCHH}$ ), 3.00-3.14 (1H, m,  $\text{CHHCH}_2\text{C}$ ), 3.19 (1H, d,  $J$  12.2 Hz,  $\text{NCHH}$ ), 3.24-3.38 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 4.10-4.25 (2H, m,  $\text{NCH}_2\text{N}$ ), 7.01-7.12 (1H, m, Ph), 7.16 (2H, d,  $J$  7.0 Hz, Ph), 7.23 (2H, d,  $J$  7.0 Hz, Ph), 7.26-7.33 (1H, m, Ph), 7.34-7.44 (2H, m, Ph), 8.00 (1H, d,  $J$  7.7 Hz, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  25.4 (t,  $\text{CH}_2\text{CH}_2\text{C}$ ), 35.7 (t,  $\text{CH}_2\text{CH}_2\text{C}$ ), 42.3 (q,  $\text{S}=\text{CNCH}_3$ ), 58.1 (t,  $\text{N-CH}_2$ ), 59.0 (s,  $\text{CH}_2\text{CH}_2\text{C}$ ), 76.2 (t,  $\text{NCH}_2\text{N}$ ), 127.0, 128.3, 128.4, 128.5, 128.6, 129.1, 130.0, 132.0, 133.6, 142.8, 144.7 (12C, Ph), 196.4 (s,  $\text{C}=\text{O}$ ), 202.3 (s,  $\text{C}=\text{S}$ ); Anal. Calcd. for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{OS}$  (336.45): C, 71.40; H, 5.99; N, 8.33; S, 9.53. Found: C, 71.13; H, 6.08; N, 8.29; S, 9.65%.

**3'-Phenyl-1'-(pyridin-3-ylmethyl)-4'-thioxo-2',3,3',4,4',6'-hexahydro-1H,1'H-spiro(naphthalene-2,5'-pyrimidin)-1-one (10).** White powder, yield 79%, mp 198-200 °C (EtOH); IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1666 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.25-2.36 (1H, m,  $\text{CH}_2\text{CHHC}$ ), 2.73-2.87 (1H, m,  $\text{CHHCH}_2\text{C}$ ), 3.03-3.19 (2H, m,  $\text{CHHCH}_2\text{C}$ ,  $\text{NCHH}$ ), 3.22-3.36 (2H, m,  $\text{CH}_2\text{CHHC}$ ,  $\text{NCHH}$ ), 3.77 (1H, d,  $J$  13.6 Hz,  $\text{CHH-Pyr}$ ), 3.86 (1H, d,  $J$  13.6 Hz,  $\text{CHH-Pyr}$ ), 4.37 (1H, d,  $J$  10.7 Hz,  $\text{NCHHN}$ ), 4.44 (1H, d,  $J$  10.7 Hz,  $\text{NCHHN}$ ), 7.17 (1H, d,  $J$  7.6 Hz, Ph), 7.19-7.26 (1H, m, Ph), 7.27-7.32 (3H, m, Ph, Pyr), 7.33-7.39 (1H, m, Ph), 7.41-7.50 (3H, m, Ph), 7.64-7.71 (1H, m, Pyr), 8.04 (1H, dd,  $J$  7.9, 1.22 Hz, Ph), 8.50 (1H, dd,  $J$  4.8, 1.6 Hz, Pyr), 8.56 (1H, s, Pyr).  $^{13}\text{C}$

NMR (CDCl<sub>3</sub>):  $\delta_C$  25.2 (t, CH<sub>2</sub>CH<sub>2</sub>C), 35.7 (t, CH<sub>2</sub>CH<sub>2</sub>C), 55.2 (t, CH<sub>2</sub>-Pyr), 55.5 (t, NCH<sub>2</sub>), 58.9 (s, CH<sub>2</sub>CH<sub>2</sub>C), 74.5 (t, NCH<sub>2</sub>N), 123.6, 127.0, 128.3, 128.4, 128.6, 130.0, 132.0, 132.1, 133.6, 136.4, 142.7, 144.4, 149.4, 150.1 (17C, Ph, Pyr), 196.4 (s, C=O), 202.7 (s, C=S). Anal. Calcd. for C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>OS (413.53): C, 72.61; H, 5.61; N, 10.16; S, 7.75. Found: C, 72.72; H, 5.71; N, 10.27; S, 7.85%.

**(1-Benzyl-3-phenyl-4-thioxohexahydropyrimidin-5-yl)phenylmethanone (14).** Yellowish powder, yield 88%, mp 186-188 °C; IR ( $\nu_{\max}$ , cm<sup>-1</sup>): 1660, 1672 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta_H$  3.39 (3H, s, CH<sub>3</sub>), 3.42 (2H, s, CH<sub>2</sub>N), 3.98 (2H, s, CH<sub>2</sub>Ph), 4.46 (2H, s, NCH<sub>2</sub>N), 7.23-7.31 (1H, m, Ph), 7.34 (2H, t, *J* 7.2 Hz, Ph), 7.41 (2H, d, *J* 7.2 Hz, Ph), 7.77-7.88 (2H, m, Ph), 7.96-8.08 (2H, m, Ph). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta_C$  40.6 (q, CH<sub>3</sub>), 53.2 (t, NCH<sub>2</sub>), 56.9 (t, CH<sub>2</sub>Ph), 65.7 (2, C-C=S), 71.6 (t, NCH<sub>2</sub>N), 124.3, 127.8, 128.6, 129.1, 135.7, 136.9, 143.4 (12C, Ph), 190.1 (s, C=O), 197.1 (s, C=S). Anal. Calcd. for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>OS (386.15): C, 74.58; H, 5.74; N, 7.25; S, 8.30. Found: C, 74.33; H, 5.69; N, 7.18; S, 8.26%.

**Synthesis of 1'-benzyl-3'-methyl-4'-thioxo-2',3',4',6'-tetrahydro-1'H-spiro(indene-2,5'-pyrimidine)-1,3-dione (12).** To a solution of benzylamine (3 mmol, 0.32 g) and formaldehyde (6 mmol; 0.49 g, a 37% solution in water) in 15 mL of EtOH, 1,3-dioxindane-2-carbothioic *N*-methylamide (1 mmol, 0.219 g) **11** and 1 mL of acetic acid as catalyst were added under stirring. The reaction mixture was stirred at room temperature for 1 hour and then left for 2-3 days. The crude crystals were separated by filtration and purified by crystallization from EtOH. The product formed as a white powder, yield 65%, mp 143-145 °C; IR ( $\nu_{\max}$ , cm<sup>-1</sup>): 1666, 1702 (C=O). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta_H$  3.29-3.42 (1H, m, CHHCH), 3.54 (1H, dd, *J* 13.5, 8.9 Hz, CHHCH), 4.00 (2H, dd, *J* 20.0, 13.3 Hz, CH<sub>2</sub>Ph), 4.37 (1H, dd, *J* 12.3, 1.9 Hz, NCH<sub>2</sub>HN), 4.80 (1H, d, *J* 12.5 Hz, CHC=O), 5.28-5.41 (1H, m, NCH<sub>2</sub>HN), 7.23-7.32 (3H, m, Ph), 7.33-7.42 (5H, m, Ph), 7.43-7.52 (4H, m, Ph), 7.54-7.62 (1H, m, Ph), 8.01-8.10 (2H, m, Ph). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta_C$  51.7 (t, NCH<sub>2</sub>), 52.8 (d, CH-C=S), 56.8 (t, CH<sub>2</sub>Ph), 73.7 (t, NCH<sub>2</sub>N), 126.7, 128.0, 128.3, 128.7, 128.8, 129.3, 129.9, 133.5, 136.6, 136.8, 144.0 (18C, Ph), 196.7 (s, C=O), 197.9 (s, C=S); Anal. Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S (350.43): C, 68.55; H, 5.18; N, 7.99; S, 9.15. Found: C, 68.28; H, 5.28; N, 7.91; S, 9.35%.

## Acknowledgements

We express our thanks to Professor Jerzy Lange of the Warsaw University of Technology for helpful discussions and assistance with the manuscript.



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