

**A NOVEL CONVENIENT SYNTHESIS OF 1,3,5,5-TETRASUBSTITUTED HEXAHYDROPYRIMIDINE-4-THIONES**

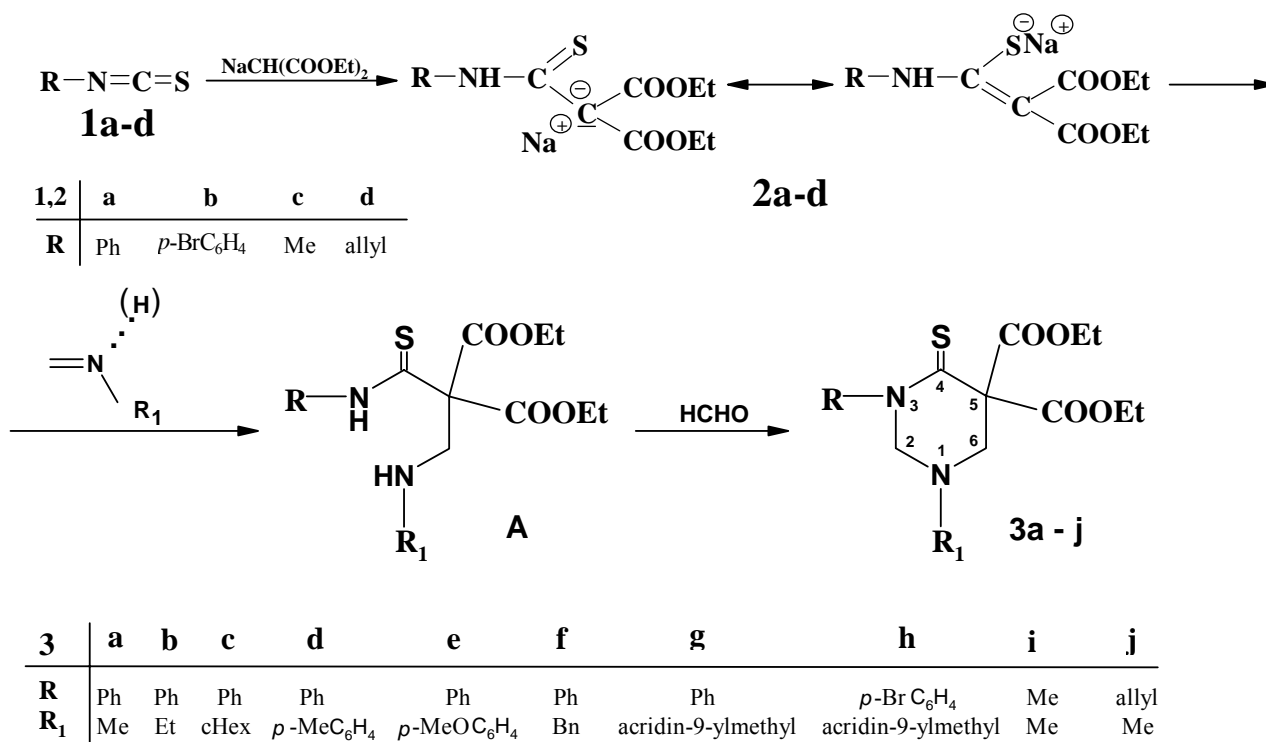
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**Abstract** – Sodium salts of (2-substituted thiocarbamoyl)malonic acid diethyl esters (**2a-d**) obtained *via* reaction of isothiocyanates (**1a-d**) with sodium diethyl malonate afforded with formaldehyde and amine sulfate in water medium diethyl 1,3-disubstituted 4-thioxohexahydropyrimidine-5,5-dicarboxylates (**3a-j**). Reaction represents the simple and convenient way to synthesize the title compounds.

Considering the specific properties of pyrimidine derivatives it is not surprising a great number of publications concerning this interesting topic of chemistry.<sup>1</sup> In spite of this fact, only two papers are known up to date dealing with the synthesis of hexahydropyrimidine-4-thiones.<sup>2,3</sup> The compound 1-methyl-5-phenyl-5-pyridin-2-yl-hexahydropyrimidine-4-thione was prepared from the corresponding thioacetamide by cyclocondensation with MeNH<sub>2</sub> and HCHO,<sup>2</sup> some 1,2,3,5,6-pentasubstituted hexahydropyrimidine-4-thiones were obtained by the reaction of the thioketenes with the azomethines as 1:2 cycloadducts.<sup>3</sup> In our previous works we used for the synthesis of dihydropyrimidine-4-thiones condensation reaction of acylisothiocyanates with enamines.<sup>4</sup>



**Scheme 1**

The aim of this work was to elaborate a new efficient method for the preparation of functionalized hexahydropyrimidine-4-thiones (**3a-j**). The synthesis was carried out by the reaction of isothiocyanates (**1a-d**) with sodium diethyl malonate and subsequent cyclization of the intermediates (**2a-d**) obtained with formaldehyde and corresponding amine sulfate or hydrochloride in water medium (Scheme 1).

We assume that the reaction of **2a-d** starts with imine (or iminium), which is formed in situ from formaldehyde and amine sulfate or hydrochloride to give intermediate (**A**). The subsequent reaction of **A** with another molecule of formaldehyde affords the final product (**3a-j**) (see Scheme 1).

The structure of the synthesized compounds was confirmed by their  $^1\text{H}$ ,  $^{13}\text{C}$ , and MS data (see EXPERIMENTAL).

## EXPERIMENTAL

Elemental analyses were performed on a Perkin-Elmer CHN 2400 analyzer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\delta$ , ppm) were measured on Bruker ARX (300 MHz) instrument. Chemical shifts are expressed in ppm relative to TMS as internal standard. MS spectra were taken on an Finnigan MAT 90 (70eV).

### General procedure for the preparation of diethyl 1,3-disubstituted 4-thioxohexahydropyrimidine-5,5-dicarboxylates (**3a-j**).

To a suspension of sodium diethyl malonate (0.2 g, 1.1 mmol) in dry ether (30-40 mL), prepared by the reaction of diethyl malonate with powdered sodium, the corresponding isothiocyanate (**1a-d**) (1 mmol) was added dropwise. The reaction mixture was intensively stirred at rt for 5-10 h until isothiocyanate has disappeared (monitored by TLC, eluent cyclohexane-ethyl acetate 5:2. UV detection at 254 nm). The precipitate was collected by filtration and washed with dry ether (20 mL).

The obtained sodium salt of addition product (**3**) was dissolved in water (100 mL) and an excess of 35% formaldehyde (0.26 mL, 3 mmol) and a solution of amine sulfate (**a-f**) or amine hydrochloride (**g-j**) (1.5 mmol) in water (10 mL) was added to keep the reaction pH in the range of 6-7. The crude product received in oil or solid form was extracted into chloroform, and extract was dried over  $\text{CaCl}_2$  and concentrated *in vacuo*. After addition of ether the final product was obtained in oil **3c** or solid **3a,b, d-j** form, sufficiently pure for spectra measurements.

**Diethyl 1-methyl-3-phenyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3a)**: mp 88-90 °C; yield 79%. Anal. Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$  : C, 58.27; H, 6.33; N, 7.99. Found: C, 58.01; H, 6.30; N, 7.91.  $^1\text{H}$  NMR : 7.50-7.26 (m, 5H, ArH), 4.31 (q,  $J=7.1$  Hz, 4H,  $\text{OCH}_2$ ), 4.23 (s, 2H, 2- $\text{CH}_2$ ), 3.56 (s, 2H, 6- $\text{CH}_2$ ), 2.46 (s, 3H,  $\text{NCH}_3$ ), 1.32 (t,  $J=7.1$  Hz, 6H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR: 13.8 ( $\text{OCH}_2\text{CH}_3$ ), 41.9 ( $\text{NCH}_3$ ), 56.8 (6- $\text{CH}_2$ ), 62.2 ( $\text{OCH}_2\text{CH}_3$ ) 68.4 (5-C), 75.7 (2- $\text{CH}_2$ ), 126.6, 128.3, 129.8 (aromatic CH), 144.1 (aromatic C), 167.3 (CO), 193.9 (CS).

**Diethyl 1-ethyl-3-phenyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3b)**: mp 110-112 °C; yield 82%. Anal. Calcd for  $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$  : C, 59.32; H, 6.64; N, 7.69. Found: C, 59.01; H, 6.60; N, 7.59.  $^1\text{H}$  NMR : 7.48-7.25 (m, 5H, ArH), 4.28 (q,  $J=7.1$  Hz, 4H,  $\text{OCH}_2$ ), 4.27 (s, 2H, 2- $\text{CH}_2$ ), 3.56 (s, 2H, 6- $\text{CH}_2$ ), 2.61 (q,  $J=7.1$  Hz, 2H,  $\text{NCH}_2$ ), 1.29 (t,  $J=7.1$  Hz, 6H,  $\text{CH}_3$ ), 1.09 (t,  $J=7.1$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR: 11.8 ( $\text{NCH}_2\text{CH}_3$ ), 13.6 ( $\text{OCH}_2\text{CH}_3$ ), 48.0 ( $\text{NCH}_2\text{CH}_3$ ), 53.9 (6- $\text{CH}_2$ ), 62.1 ( $\text{OCH}_2\text{CH}_3$ ), 74.4 (2-

CH<sub>2</sub>), 68.5 (5-C), 74.4 (2-CH<sub>2</sub>), 126.9, 127.3, 128.3 (aromatic CH), 144.1 (aromatic C), 167.3 (CO), 194.1 (CS).

**Diethyl 1-cyclohexyl-3-phenyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3c):** oil; yield 80%. Anal. Calcd for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>S : C, 63.13; H, 7.22; N, 6.69. Found: C, 62.97; H, 7.20; N, 6.61. <sup>1</sup>H NMR : 7.49-7.25 (m, 5H, ArH), 4.39 (s, 2H, 2-CH<sub>2</sub>), 4.30 and 4.28 (q, J=7.2 Hz, 4H, OCH<sub>2</sub>), 3.58 (s, 2H, 6-CH<sub>2</sub>), 2.49-2.47 (m, 1H, NCH), 1.90-1.07 (m, 10H, cyclohexyl-CH<sub>2</sub>), 1.32 (t, J=7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 13.9 (OCH<sub>2</sub>CH<sub>3</sub>), 25.4, 25.8, 28.8 (cyclohexyl-CH<sub>2</sub>), 50.8 (6-CH<sub>2</sub>), 61.6 (NCH) 62.0 (OCH<sub>2</sub>CH<sub>3</sub>), 68.4 (5-C), 72.5 (2-CH<sub>2</sub>), 126.9, 128.3, 128.8 (aromatic CH), 144.1 (aromatic C), 167.3 (CO), 194.3 (CS).

**Diethyl 3-phenyl-1-(p-tolyl)-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3d):** mp 109-110 °C; yield 78%. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S : C, 64.77; H, 6.14; N, 6.57. Found: C, 64.71; H, 6.09; N, 6.55. <sup>1</sup>H NMR : 7.35-6.85 (m, 9H, ArH), 4.73 (s, 2H, 2-CH<sub>2</sub>), 4.47 (s, 2H, 6-CH<sub>2</sub>) 4.06 and 4.03 (q, J=7.2 Hz, 4H, OCH<sub>2</sub>), 2.27 (s, 3H, tolyl-CH<sub>3</sub>), 1.19 (t, J=7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 13.7 (OCH<sub>2</sub>CH<sub>3</sub>), 20.4 (tolyl-CH<sub>3</sub>), 52.8 (6-CH<sub>2</sub>), 55.6 (2-CH<sub>2</sub>), 62.0 (OCH<sub>2</sub>CH<sub>3</sub>), 62.3 (5-C), 117.8, 119.7, 124.6, 128.7, 129.4 (aromatic CH), 130.7, 144.1, 148.8 (aromatic C), 167.6 (CO), 194.7 (CS).

**Diethyl 1-(p-methoxyphenyl)-3-phenyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3e):** mp 94-97 °C; yield 81%. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S : C, 62.42; H, 5.92; N, 6.33. Found: C, 62.17; H, 5.90; N, 6.29. <sup>1</sup>H NMR : 7.35-6.81 (m, 9H, ArH), 4.71 (s, 2H, 2-CH<sub>2</sub>), 4.44 (s, 2H, 6-CH<sub>2</sub>) 4.07 and 4.02 (q, J=7.1 Hz, 4H, OCH<sub>2</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 1.20 (t, J=7.1 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 13.7 (OCH<sub>2</sub>CH<sub>3</sub>), 53.7 (6-CH<sub>2</sub>), 55.5 (OCH<sub>3</sub>), 56.3 (2-CH<sub>2</sub>), 62.0 (OCH<sub>2</sub>CH<sub>3</sub>), 62.0 (5-C), 114.2, 119.7, 119.8, 124.6, 128.7 (aromatic CH), 140.6, 148.8, 154.7 (aromatic C), 167.6 (CO), 194.8 (CS).

**Diethyl 1-benzyl-3-phenyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3f):** mp 93-95 °C; yield 80%. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S : C, 64.77; H, 6.14; N, 6.57. Found: C, 64.27; H, 6.08; N, 6.54. <sup>1</sup>H NMR : 7.47-7.24 (m, 10H, ArH), 4.31 and 4.24 (q, J=7.2 Hz, 4H, OCH<sub>2</sub>), 4.29 (s, 2H, 2-CH<sub>2</sub>), 3.75 (s, 2H, NCH<sub>2</sub>), 3.63 (s, 2H, 6-CH<sub>2</sub>), 1.28 (t, J=7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 13.8 (OCH<sub>2</sub>CH<sub>3</sub>), 54.7 (6-CH<sub>2</sub>), 58.6 (NCH<sub>2</sub>), 62.1 (OCH<sub>2</sub>CH<sub>3</sub>), 68.4 (5-C), 74.1 (2-CH<sub>2</sub>), 126.6, 127.8, 128.3, 128.5, 128.8, 129.9 (aromatic CH), 135.8, 144.0 (aromatic C), 167.3 (CO), 194.1 (CS).

**Diethyl 1-(acridin-9-ylmethyl)-3-phenyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3g):** mp 142-146 °C; yield 67%. Anal. Calcd for C<sub>30</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>S : C, 68.29; H, 5.54; N, 7.96. Found: C, 68.08; H, 5.49; N, 7.89. <sup>1</sup>H NMR : 8.42-6.90 (m, 13H, ArH), 4.87 (s, 2H, NCH<sub>2</sub>), 4.36 and 4.35 (q, J=7.2 Hz, 4H, OCH<sub>2</sub>), 4.28 (s, 2H, 2-CH<sub>2</sub>), 3.99 (s, 2H, 6-CH<sub>2</sub>), 1.34 (t, J=7.2 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 13.9 (OCH<sub>2</sub>CH<sub>3</sub>), 47.4 (NCH<sub>2</sub>), 55.7 (6-CH<sub>2</sub>), 58.7 (2-CH<sub>2</sub>), 68.4 (5-C), 62.1 (OCH<sub>2</sub>CH<sub>3</sub>), 119.7, 124.21, 126.7, 128.7, 130.8 (aromatic CH), 125.8, 129.2, 147.6, 148.1 (aromatic C), 168.2 (CO), 194.1 (CS). MS, *m/z* (%): 528 (100, M<sup>+</sup>+1).

**Diethyl 1-(acridin-9-ylmethyl)-3-(p-bromophenyl)-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3h):** mp 152-154 °C; yield 69%. Anal. Calcd for C<sub>30</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub>BrS : C, 59.41; H, 4.65; N, 6.93. Found: C, 59.28; H, 4.60; N, 6.89. <sup>1</sup>H NMR : 8.39-6.79 (m, 12H, ArH), 4.85 (s, 2H, NCH<sub>2</sub>), 4.35 and 4.32 (q, J=7.1 Hz, 4H, OCH<sub>2</sub>), 4.27 (s, 2H, 2-CH<sub>2</sub>), 4.00 (s, 2H, 6-CH<sub>2</sub>), 1.34 (t, J=7.1 Hz, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 13.9 (OCH<sub>2</sub>CH<sub>3</sub>), 47.4 (NCH<sub>2</sub>), 55.7 (6-CH<sub>2</sub>), 58.7 (2-CH<sub>2</sub>), 68.4 (5-C), 62.1 (OCH<sub>2</sub>CH<sub>3</sub>),

121.5, 124.1, 126.6, 131.8 (aromatic CH), 125.8, 129.9, 130.2, 147.6, 148.1 (aromatic C), 168.1 (CO), 193.9 (CS). MS,  $m/z$  (%): 608 (100,  $M^+ + 2$ ).

**Diethyl 1,3-dimethyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3i):** mp 88-90 °C; yield 85%. Anal. Calcd for  $C_{12}H_{20}N_2O_4S$  : C, 49.98; H, 6.99; N, 9.71. Found: C, 49.27; H, 6.98; N, 9.69.  $^1H$  NMR : 4.27 and 4.26 (q,  $J=7.1$  Hz, 4H,  $OCH_2$ ), 4.01 (s, 2H, 2- $CH_2$ ), 3.39 (s, 3H, 3-N $CH_3$ ), 3.35 (s, 2H, 6- $CH_2$ ), 2.39 (s, 3H, 1-N $CH_3$ ), 1.30 (t,  $J=7.1$  Hz, 6H,  $CH_3$ ).  $^{13}C$  NMR: 13.8 ( $OCH_2CH_3$ ), 40.5, 41.7 (1,3-N $CH_3$ ), 56.3 (6- $CH_2$ ), 62.0 ( $OCH_2CH_3$ ), 68.4 (5-C), 74.4 (2- $CH_2$ ), 167.2 (CO), 191.2 (CS).

**Diethyl 3-allyl-1-methyl-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3j):** mp 64-66 °C; yield 87%. Anal. Calcd for  $C_{14}H_{22}N_2O_4S$  : C, 53.48; H, 7.05; N, 8.91. Found: C, 53.28; H, 6.99; N, 8.85.  $^1H$  NMR : 5.87 (ddt,  $J=17.3$ , 10.3, and 5.5 Hz, 1H,  $CH=$ ), 5.33 (ddt,  $J=17.3$ , 1.5, and 1.5 Hz, 1H, H-*trans*), 5.23 (ddt,  $J=10.3$ , 1.5, and 1.4 Hz, 1H, H-*cis*), 4.59 (ddd,  $J=5.5$ , 1.5, and 1.4 Hz, 2H, allyl- $CH_2$ ), 4.27 and 4.27 (q,  $J=7.1$  Hz, 4H,  $OCH_2$ ), 3.97 (s, 2H, 2- $CH_2$ ), 3.35 (s, 2H, 6- $CH_2$ ), 2.38 (s, 3H, N $CH_3$ ), 1.29 (t,  $J=7.1$  Hz, 6H,  $CH_3$ ).  $^{13}C$  NMR: 13.8 ( $OCH_2CH_3$ ), 41.8 (N $CH_3$ ), 54.0 (allyl- $CH_2$ ), 56.5 (6- $CH_2$ ), 62.0 ( $OCH_2CH_3$ ), 68.5 (5-C), 72.2 (2- $CH_2$ ), 118.3 ( $=CH_2$ ), 129.5( $=C$ ), 167.2 (CO), 191.4 (CS).

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