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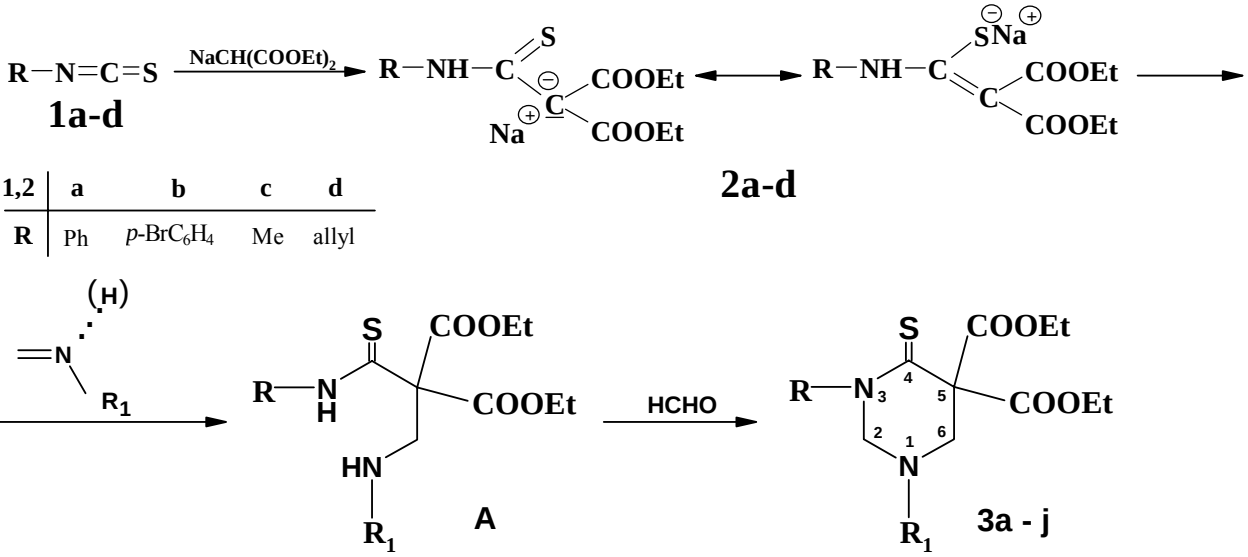
A NOVEL CONVENIENT SYNTHESIS OF 1,3,5,5-TETRASUBSTITUTED HEXAHYDROPYRIMIDINE-4-THIONES

Juraj Bernát,[a] Pavol Kristian,[a*] Janka Guspanová,[b] and Igor Chomča[a]

[a] Department of Organic Chemistry, P. J. Šafárik University, 04167 Košice, Slovakia
[b] Organisch-chemisches Institut der Universität Zürich, CH-8057 Zürich, Schweiz

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.[1] In spite of this fact, only two papers are known up to date dealing with the synthesis of hexyhydropyrimidine-4-thiones.[2,3] The compound 1-methyl-5-phenyl-5-pyridin-2-yl-hexahydropyrimidine-4-thione was prepared from the corresponding thioacetamide by cyclocondensation with $MeNH_2$ and HCHO,[2] 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.[3] In our previous works we used for the synthesis of dihydropyrimidine-4-thiones condensation reaction of acylisothiocyanates with enamines.[4]



1,2	a	b	c	d
R	Ph	*p*-BrC_6H_4	Me	allyl

3	a	b	c	d	e	f	g	h	i	j
R	Ph	Ph	Ph	Ph	Ph	Ph	Ph	*p*-Br C_6H_4	Me	allyl
R_1	Me	Et	cHex	*p* -MeC_6H_4	*p*-$MeOC_6H_4$	Bn	acridin-9-ylmethyl	acridin-9-ylmethyl	Me	Me

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}H, ^{13}C, and MS data (see EXPERIMENTAL).

EXPERIMENTAL

Elemental analyses were performed on a Perkin-Elmer CHN 2400 analyzer. ^{1}H and ^{13}C NMR spectra (δ, 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 $CaCl_2$ 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 ^{o}C; yield 79%. Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.01; H, 6.30; N, 7.91. ^{1}H NMR : 7.50-7.26 (m, 5H, ArH), 4.31 (q, J=7.1 Hz, 4H, OCH_2), 4.23 (s, 2H, 2-CH_2), 3.56 (s, 2H, 6-CH_2), 2.46 (s, 3H, NCH_3), 1.32 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR: 13.8 ($OCH_2\underline{C}H_3$), 41.9 (NCH_3), 56.8 (6-CH_2), 62.2 ($O\underline{C}H_2CH_3$) 68.4 (5-C), 75.7 (2-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 ^{o}C; yield 82%. Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.01; H, 6.60; N, 7.59. ^{1}H NMR : 7.48-7.25 (m, 5H, ArH), 4.28 (q, J=7.1 Hz, 4H, OCH_2), 4.27 (s, 2H, 2-CH_2), 3.56 (s, 2H, 6-CH_2), 2.61 (q, J=7.1 Hz, 2H, NCH_2), 1.29 (t, J=7.1 Hz, 6H, CH_3), 1.09 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR: 11.8 ($NCH_2\underline{C}H_3$), 13.6 ($OCH_2\underline{C}H_3$), 48.0 ($N\underline{C}H_2CH_3$), 53.9 (6-CH_2), 62.1 ($O\underline{C}H_2CH_3$), 74.4 (2-

CH_2), 68.5 (5-C), 74.4 (2-CH_2), 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 $C_{22}H_{30}N_2O_4S$: C, 63.13; H, 7.22; N, 6.69. Found: C, 62.97; H, 7.20; N, 6.61. ^{1}H NMR : 7.49-7.25 (m, 5H, ArH), 4.39 (s, 2H, 2-CH_2), 4.30 and 4.28 (q, J=7.2 Hz, 4H, OCH_2), 3.58 (s, 2H, 6-CH_2), 2.49-2.47 (m, 1H, NCH), 1.90-1.07 (m, 10H, cyclohexyl-CH_2), 1.32 (t, J=7.2 Hz, 6H, CH_3). ^{13}C NMR: 13.9 ($OCH_2\underline{C}H_3$), 25.4, 25.8, 28.8 (cyclohexyl-CH_2), 50.8 (6-CH_2), 61.6 (NCH) 62.0 ($O\underline{C}H_2CH_3$), 68.4 (5-C), 72.5 (2-CH_2), 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 ^{o}C; yield 78%. Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.77; H, 6.14; N, 6.57. Found: C, 64.71; H, 6.09; N, 6.55. ^{1}H NMR : 7.35-6.85 (m, 9H, ArH), 4.73 (s, 2H, 2-CH_2), 4.47 (s, 2H, 6-CH_2) 4.06 and 4.03 (q, J=7.2 Hz, 4H, OCH_2), 2.27 (s, 3H, tolyl-CH_3), 1.19 (t, J=7.2 Hz, 6H, CH_3). ^{13}C NMR: 13.7 ($OCH_2\underline{C}H_3$), 20.4 (tolyl-CH_3), 52.8 (6-CH_2), 55.6 (2-CH_2), 62.0 ($O\underline{C}H_2CH_3$), 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 ^{o}C; yield 81%. Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.17; H, 5.90; N, 6.29. ^{1}H NMR : 7.35-6.81 (m, 9H, ArH), 4.71 (s, 2H, 2-CH_2), 4.44 (s, 2H, 6-CH_2) 4.07 and 4.02 (q, J=7.1 Hz, 4H, OCH_2), 3.76 (s, 3H, OCH_3), 1.20 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR: 13.7 ($OCH_2\underline{C}H_3$), 53.7 (6-CH_2), 55.5 (OCH_3), 56.3 (2-CH_2), 62.0 ($O\underline{C}H_2CH_3$), 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 ^{o}C; yield 80%. Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.77; H, 6.14; N, 6.57. Found: C, 64.27; H, 6.08; N, 6.54. ^{1}H NMR : 7.47-7.24 (m, 10H, ArH), 4.31 and 4.24 (q, J=7.2 Hz, 4H, OCH_2), 4.29 (s, 2H, 2-CH_2), 3.75 (s, 2H, NCH_2), 3.63 (s, 2H, 6-CH_2), 1.28 (t, J=7.2 Hz, 6H, CH_3). ^{13}C NMR: 13.8 ($OCH_2\underline{C}H_3$), 54.7 (6-CH_2), 58.6 (NCH_2), 62.1 ($O\underline{C}H_2CH_3$), 68.4 (5-C), 74.1 (2-CH_2), 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 ^{o}C; yield 67%. Anal. Calcd for $C_{30}H_{29}N_3O_4S$: C, 68.29; H, 5.54; N, 7.96. Found: C, 68.08; H, 5.49; N, 7.89. ^{1}H NMR : 8.42-6.90 (m, 13H, ArH), 4.87 (s, 2H, NCH_2), 4.36 and 4.35 (q, J=7.2 Hz, 4H, OCH_2), 4.28 (s, 2H, 2-CH_2), 3.99 (s, 2H, 6-CH_2), 1.34 (t, J=7.2 Hz, 6H, CH_3). ^{13}C NMR: 13.9 ($OCH_2\underline{C}H_3$), 47.4 (NCH_2), 55.7 (6-CH_2), 58.7 (2-CH_2), 68.4 (5-C), 62.1 ($O\underline{C}H_2CH_3$), 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^++1).

Diethyl 1-(acridin-9-ylmethyl)-3-(*p*-bromophenyl)-4-thioxohexahydropyrimidine-5,5-dicarboxylate (3h): mp 152-154 ^{o}C; yield 69%. Anal. Calcd for $C_{30}H_{28}N_3O_4BrS$: C, 59.41; H, 4.65; N, 6.93. Found: C, 59.28; H, 4.60; N, 6.89. ^{1}H NMR : 8.39-6.79 (m, 12H, ArH), 4.85 (s, 2H, NCH_2), 4.35 and 4.32 (q, J=7.1 Hz, 4H, OCH_2), 4.27 (s, 2H, 2-CH_2), 4.00 (s, 2H, 6-CH_2), 1.34 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR: 13.9 ($OCH_2\underline{C}H_3$), 47.4 (NCH_2), 55.7 (6-CH_2), 58.7 (2-CH_2), 68.4 (5-C), 62.1 ($O\underline{C}H_2CH_3$),

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 ^oC; 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-NCH_3), 3.35 (s, 2H, 6-CH_2), 2.39 (s, 3H, 1-NCH_3), 1.30 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR: 13.8 ($OCH_2\underline{C}H_3$), 40.5, 41.7 (1,3-NCH_3), 56.3 (6-CH_2), 62.0 ($O\underline{C}H_2CH_3$), 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 ^oC; 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, NCH_3), 1.29 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR: 13.8 ($OCH_2\underline{C}H_3$), 41.8 (NCH_3), 54.0 (allyl-CH_2), 56.5 (6-CH_2), 62.0 ($O\underline{C}H_2CH_3$), 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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