

# Addition-Cyclization Reactions of Hexa-2,4-dienoyl Isothiocyanate with Amines and Sodium Hydrogen Sulfide

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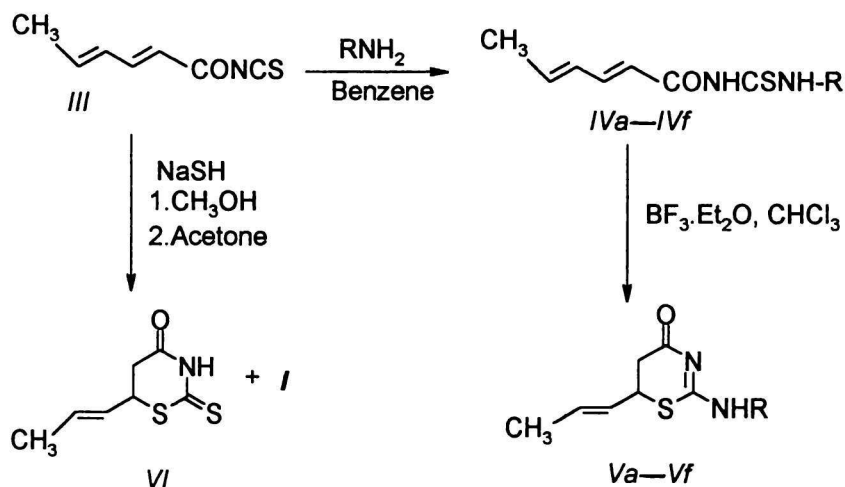
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1,3-Thiazin-4-one derivatives were synthesized by boron trifluoride-catalyzed intramolecular cyclization of *N*-substituted *N'*-(hexa-2,4-dienoyl)thioureas and by the reaction of hexa-2,4-dienoyl isothiocyanate with sodium hydrogen sulfide. The structure of the prepared compounds was confirmed by their IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra.

In our previous papers we have studied the synthesis of 1,3-thiazine derivatives by addition-cyclization reactions of  $\alpha,\beta$ -unsaturated acyl isothiocyanates with amines [1, 2] and sodium hydrogen sulfide [3, 4], under various reaction conditions. The present work describes the study of the above reactions of hexa-2,4-dienoyl isothiocyanate with the formation of corresponding 6-(propen-1-yl)-1,3-thiazin-4-one derivatives (*Va*–*Vf*, Scheme 1).

Hexa-2,4-dienoic acid (*I*) was selected as a starting compound which was transformed *via* hexa-2,4-dienoyl chloride (*II*) to hexa-2,4-dienoyl isothiocyanate (*III*). According to the literature data, chloride *II* can be obtained by the action of thionyl chloride in benzene [5], phosphorous trichloride [6, 7], or phosphorous pentachloride [8] on acid *I*, in 50–60 % yield. The preparation of isothiocyanate *III*, by treatment of hexa-2,4-dienoyl bromide with lead(II) thio-



R = C<sub>6</sub>H<sub>5</sub> (a), C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>-4 (b), C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-4 (c),  
C<sub>6</sub>H<sub>4</sub>Cl-4 (d), C<sub>6</sub>H<sub>4</sub>COCH<sub>3</sub>-4 (e), CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> (f)

Scheme 1

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**Table 1.** Characterization of Compounds *IVa–IVf*, *Va–Vf*, and *VI*

Compound	Formula $M_r$	M.p./°C Yield/%	$w_i$ (calc.)/% $w_i$ (found)/%		
			C	H	N
<i>IVa</i>	$C_{13}H_{14}N_2OS$	129–132	63.38	5.73	11.37
	246.3	89	63.56	5.86	11.49
<i>IVb</i>	$C_{14}H_{16}N_2OS$	148–149	64.59	6.19	10.76
	260.4	82	64.92	6.28	10.93
<i>IVc</i>	$C_{14}H_{16}N_2O_2S$	163.5–165.5	60.85	5.48	10.14
	276.3	85	61.02	5.63	10.31
<i>IVd</i>	$C_{13}H_{13}N_2ClOS$	157–159	55.61	4.67	9.98
	280.8	79	55.83	4.78	10.09
<i>IVe</i>	$C_{15}H_{16}N_2O_2S$	197–199	62.48	5.59	9.71
	288.4	88	62.57	5.71	9.92
<i>IVf</i>	$C_{14}H_{17}N_3OS$	147–149	64.59	6.19	10.76
	276.4	92	64.83	6.32	10.87
<i>Va</i>	$C_{13}H_{14}N_2OS$	86–87	63.38	5.73	11.37
	246.3	57	63.64	5.91	11.62
<i>Vb</i>	$C_{14}H_{16}N_2OS$	101–103	64.59	6.19	10.76
	260.4	62	64.73	6.31	10.98
<i>Vc</i>	$C_{14}H_{16}N_2O_2S$	54–56	60.85	5.48	10.14
	276.3	68	60.99	5.61	10.29
<i>Vd</i>	$C_{13}H_{13}N_2ClOS$	110–112	55.61	4.67	9.98
	280.8	55	55.84	4.71	9.99
<i>Ve</i>	$C_{15}H_{16}N_2O_2S$	100–102	62.48	5.59	9.71
	288.4	54	62.63	5.70	9.89
<i>Vf</i>	$C_{14}H_{16}N_2OS$	153–155	64.56	6.19	10.76
	260.4	66	64.81	6.28	10.91
<i>VI</i>	$C_7H_9NOS_2$	83–84	44.89	4.85	7.48
	187.3	37	44.99	4.92	7.68

**Table 2.** IR Spectral Data of Compounds *I–III*, *IVa–IVf*, *Va–Vf*, and *VI*

Compound	$\tilde{\nu}/\text{cm}^{-1}$				
	$\delta(\text{CH-trans})$	NHCS	C=C	C=O	NH
<i>I</i>	992	–	1605, 1629	1671	–
<i>II</i>	1002	–	1594, 1638	1740	–
<i>III</i>	1003	–	1504, 1640	1687	–
<i>IVa</i>	1007	1145, 1350, 1515	1592, 1632	1673	3415
<i>IVb</i>	1000	1140, 1340, 1515	1592, 1635	1677	3412
<i>IVc</i>	995	1135, 1335, 1515	1598, 1627	1670	3415
<i>IVd</i>	1003	1140, 1342, 1520	1590, 1635	1680	3413
<i>IVe</i>	960	1145, 1345, 1520	1597, 1625	1677	3412
<i>IVf</i>	1005	1160, 1340, 1530	1615, 1638	1681	3418
<i>Va</i>	978	–	1615	1694	3361
<i>Vb</i>	970	–	1625	1703	3370
<i>Vc</i>	957	–	1605	1690	3372
<i>Vd</i>	965	–	1615	1698	3370
<i>Ve</i>	955	–	1615	1675, 1695	3368
<i>Vf</i>	968	–	1622	1695	3373, 3420
<i>VI</i>	960	1420	1605	1710	3348

cyanate in pentan-3-one at 60°C in 70 % yield was also described [9]. We have found that chloride *II* can be effectively prepared in the higher yield (92 %) by refluxing of acid *I* with 2 equivalents of thionyl chloride without solvent. Subsequent reaction of *II* with potassium thiocyanate in anhydrous acetone in 25 min at room temperature afforded 79 % yield of isothiocyanate *III*.  $\alpha,\beta$ -Unsaturated acyl isothio-

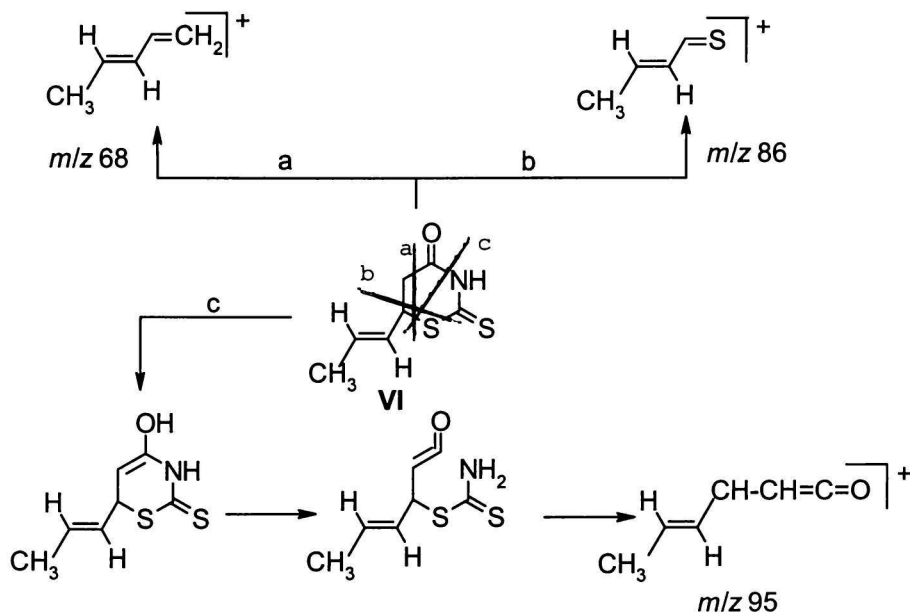
cyanates readily react with primary and secondary amines with the formation of stable thioureas [1, 2, 10–15], which are suitable intermediates in the synthesis of 1,3-thiazines [1, 2, 10, 11], thiouracils [10, 12], thiazolines [13], and benzothiazoles [13–15]. Treatment of isothiocyanate *III* with amines in benzene or acetone for 15–20 min afforded the corresponding *N*-substituted *N'*-(hexa-2,4-dienoyl)thioureas (in the for-

**Table 3.**  $^1\text{H}$  NMR Spectral Data of Compounds *I–III*, *IVa–IVf*, *Va–Vf*, and *VI*

Compound	$\delta$						
	$\text{CH}_3$	$\text{CH}_2$	$\text{CH}$	$\text{CH}=\text{CH}$	$\text{H}_{\text{arom}}$	$\text{NH}$	Other
<i>I</i>	1.87 (d, $J = 5.0$ Hz)	–	–	5.78 (d, $J = 15.0$ Hz); 6.10–7.35 (m, 3H)	–	–	11.27 (s, 1H, OH)
<i>II</i>	1.92 (d, $J = 5.2$ Hz)	–	–	6.00 (d, $J = 15.1$ Hz); 6.17–7.45 (m, 3H)	–	–	–
<i>III</i>	1.96 (d, $J = 4.4$ Hz)	–	–	5.95 (d, $J = 15.0$ Hz); 6.23–7.46 (m, 3H)	–	–	–
<i>IVa</i>	1.94 (d, $J = 5.0$ Hz)	–	–	5.98 (d, $J = 14.4$ Hz); 6.31–7.52 (m, 3H)	7.35–7.85 (m, 5H)	9.35 (s) and 11.73 (s)	–
<i>IVb</i>	1.89 (d, $J = 5.1$ Hz)	–	–	5.84 (d, $J = 14.4$ Hz); 6.24–7.50 (m, 3H)	7.10–7.60 (m, 4H)	9.03 (s) and 12.50 (s)	2.36 (s, 3H, $\text{CH}_3$ )
<i>IVc</i>	1.88 (d, $J = 4.9$ Hz)	–	–	5.88 (d, $J = 14.6$ Hz); 6.26–7.50 (m, 3H)	6.88–7.65 (m, 4H)	9.36 (s) and 12.48 (s)	3.82 (s, 3H, $\text{OCH}_3$ )
<i>IVd</i>	1.89 (d, $J = 4.7$ Hz)	–	–	6.21 (d, $J = 14.8$ Hz); 6.25–7.52 (m, 3H)	7.20–7.80 (m, 4H)	8.10 (s) and 11.30 (s)	–
<i>IVe</i>	1.88 (d, $J = 5.0$ Hz)	–	–	6.25 (d, $J = 14.9$ Hz); 6.40–7.50 (m, 3H)	7.20–8.15 (m, 4H)	8.45 (s) and 11.61 (s)	2.57 (s, 3H, $\text{CH}_3\text{CO}$ )
<i>IVf</i>	1.88 (d, $J = 5.1$ Hz)	–	–	5.82 (d, $J = 14.4$ Hz); 6.18–7.32 (m, 3H)	7.04–7.63 (m, 5H)	9.20 (s) and 11.20 (s)	4.88 (d, $J = 5.1$ Hz, $\text{CH}_2$ )
<i>Va</i>	1.63 (d, $J = 6.4$ Hz)	2.82 (m)	4.18 (m)	5.58 (m, 2H)	6.70–7.48 (m, 5H)	11.10 (s)	–
<i>Vb</i>	1.69 (d, $J = 6.1$ Hz)	2.95 (m)	3.91 (m)	5.57 (m, 2H)	6.75–7.25 (m, 4H)	11.90 (s)	2.35 (s, 3H, $\text{CH}_3$ )
<i>Vc</i>	1.67 (d, $J = 5.9$ Hz)	2.89 (m)	3.99 (m)	5.55 (m, 2H)	6.75–7.10 (m, 4H)	11.88 (s)	3.79 (s, 3H, $\text{OCH}_3$ )
<i>Vd</i>	1.68 (d, $J = 6.3$ Hz)	2.90 (m)	3.90 (m)	5.56 (m, 2H)	6.75–7.43 (m, 4H)	10.70 (s)	–
<i>Ve</i>	1.69 (d, $J = 6.2$ Hz)	2.91 (m)	3.91 (m)	5.55 (m, 2H)	6.85–8.05 (m, 4H)	11.01 (s)	2.56 (s, 3H, $\text{CH}_3\text{CO}$ )
<i>Vf</i>	1.71 (d, $J = 6.1$ Hz)	2.75 (m)	3.97 (m)	5.58 (m, 2H)	6.85–7.75 (m, 5H)	10.60 (s)	4.61 (d, $J = 5.0$ Hz, $\text{CH}_2$ )
<i>VI</i>	1.75 (d, $J = 6.0$ Hz)	2.97 (m)	4.13 (m)	5.63 (m, 2H)	–	9.65 (s)	–

**Table 4.**  $^{13}\text{C}$  NMR Spectral Data of Compounds *I–III*, *IVa*, *Va*, and *VI*

Compound	$\delta$				
	$\text{CH}_3$	$\text{CH}_2$	$\text{CH}$	$\text{C}=\text{O}$	Other
<i>I</i>	18.7	–	118.3, 129.8, 140.6, 147.3	172.9	–
<i>II</i>	19.1	–	123.2, 129.3, 145.2, 151.2	166.0	–
<i>III</i>	19.0	–	121.2, 129.5, 144.1, 149.7	160.9	146.6 (NCS)
<i>IVa</i>	18.8	–	119.1, 129.6, 142.2, 146.8	166.5	124.3, 126.8, 128.8, 137.9 ( $\text{C}_{\text{arom}}$ ), 178.9 ( $\text{C}=\text{S}$ )
<i>Va</i>	17.7	40.1	40.7	169.9	121.6, 124.5, 126.8, 128.9, 130.8, 146.9 ( $\text{C}_{\text{arom}}$ , $\text{CH}=\text{CH}$ ), 151.0 ( $\text{C}=\text{N}$ )
<i>VI</i>	17.8	38.0	44.5, 125.5, 132.0	167.1	198.8 ( $\text{C}=\text{S}$ )



mer case *IVa*–*IVd* and *IVf*, in the latter one *IVe*) in 79–92 % yield (Scheme 1, Table 1).

Boron trifluoride-catalyzed cyclization of thioureas *IVa*–*IVf* in chloroform resulted exclusively in the formation of the 2-substituted 6-(propen-1-yl)-5,6-dihydro-4*H*-1,3-thiazin-4-ones (*Va*–*Vf*, Scheme 1, Table 1). The IR and  $^1\text{H}$  NMR spectra of compounds *I*–*III*, *IVa*–*IVf*, and *Va*–*Vf* (Tables 2 and 3) as well as  $^{13}\text{C}$  NMR spectra of compounds *I*–*III*, *IVa*, and *Va* (Table 4) are in full accord with the proposed structures of synthesized products.

Five- and six-membered heterocycles containing sulfur and nitrogen atoms easily undergo the Dimroth rearrangement by treatment with acids or bases [16, 17]. We have examined the reaction of thiazine *Vf* with 2 M sodium hydroxide solution in water. It was found that instead of rearrangement, the hydrolysis took place with benzylthiourea and hexa-2,4-dienoic acid (*I*) being the only reaction products. Monitoring of the reaction by t.l.c. revealed that in the first step thiazine ring of *Vf* was opened with transient formation of thiourea derivative *IVf*, which was subsequently hydrolyzed to final products. This assumption was confirmed by the reaction of thiourea *IVf* with 2 M-NaOH, resulting in the formation of benzylthiourea and hexa-2,4-dienoic acid (*I*).

Addition-cyclization reaction of  $\alpha,\beta$ -unsaturated isothiocyanates with sodium hydrogen sulfide represents a useful method for the preparation of 6-substituted 2-thioxotetrahydro-4*H*-1,3-thiazin-4-ones [3, 4]. Nucleophilic addition of sodium hydrogen sulfide to hexa-2,4-dienoyl isothiocyanate afforded two products, namely 6-(propen-1-yl)-2-thioxotetrahydro-4*H*-1,3-thiazin-4-one (*VI*) and hexa-2,4-dienoic acid (*I*), separable by column chromatography on silica gel.

The reaction was studied in methanol and acetone as solvents, with respective 37 % and 29 % yields of thiazine *VI*. The formation of acid *I* can be explained by partial hydrolysis of transiently formed sodium *N*-(hexa-2,4-dienoyl)dithiocarbamate. The structure of compound *VI* was confirmed by elemental analysis, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (Tables 1–4) as well as by mass spectrum. The main patterns of the fragmentation of molecular ion are shown in Scheme 2.

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Infrared spectra were recorded on an IR-75 (Zeiss, Jena) spectrometer in chloroform in the  $\bar{\nu}$  region 400–4000  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR spectra were measured on Tesla BS 487 (80 MHz) in deuteriochloroform solutions (*I*–*III*, *IVa*–*IVd*, *IVf*, *Vb*–*Vf*, *VI*) and DMSO solution (*IVe*, *Va*).  $^{13}\text{C}$  NMR spectra were measured on BS 567 (25.15 MHz) in deuteriochloroform solutions (*I*–*III*, *IVa*, *Va*, *VI*). Chemical shifts are given as  $\delta$  values with reference to tetramethylsilane. The mass spectrum of compound *VI* was recorded on a JMS-100 D spectrometer (Jeol) at ionization energy 70 eV. The reaction course was monitored by t.l.c. on silufol plates (Kavalier, Czech Republic). Hexa-2,4-dienoic acid (*I*) was used as commercial chemical (Aldrich).

### Hexa-2,4-dienoyl Chloride (*II*)

A mixture of 22.4 g (0.2 mol) of hexa-2,4-dienoic acid (*I*) and thionyl chloride (47.6 g, 29  $\text{cm}^3$ , 0.4 mol) was heated under reflux for 1 h. Hexa-2,4-dienoyl chloride was isolated by distillation under reduced pres-

sure. Yield 24.1 g (92 %), b.p.(800 Pa) = 50°C.

### Hexa-2,4-dienoyl Isothiocyanate (III)

A solution of KSCN (9.70 g; 0.1 mol) in dry acetone (100 cm<sup>3</sup>) was added in 5 min to hexa-2,4-dienoyl chloride (13.06 g; 0.1 mol). The mixture was stirred for 20 min at room temperature, diluted with benzene (60 cm<sup>3</sup>), filtered, solvent evaporated and the oily residue was distilled under reduced pressure. Yield 12.1 g (79 %), b.p.(667 Pa) = 84 °C.

### N-Substituted N'-Hexa-2,4-dienoylthioureas (IVa—IVf)

The solution of corresponding amine (5 mmol) in dry benzene (5 cm<sup>3</sup>) was added dropwise to a stirred solution of hexa-2,4-dienoyl isothiocyanate (0.77 g; 5 mmol) in dry benzene (5 cm<sup>3</sup>) and stirring was continued for 1 h at room temperature. The formed precipitate was filtered off, dried and crystallized from ethanol.

### 2-Substituted 6-(Propen-1-yl)-5,6-dihydro-4H-1,3-thiazin-4-ones (Va—Vf)

Boron trifluoride etherate (0.42 g, 0.37 cm<sup>3</sup>, 3 mmol) was added dropwise to a solution of corresponding thiourea IVa—IVf (1.5 mmol) in chloroform (5 cm<sup>3</sup>). After standing for 30 min at room temperature the reaction mixture was diluted with chloroform (10 cm<sup>3</sup>), washed with a 4 % solution of sodium hydrogen carbonate (10 cm<sup>3</sup>), the chloroform layer was separated and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue crystallized from ethanol.

### 6-(Propen-1-yl)-2-thioxotetrahydro-4H-1,3-thiazin-4-one (VI)

A solution of sodium hydroxide (0.12 g; 3 mmol) in acetone (15 cm<sup>3</sup>) was saturated with hydrogen sulfide (0.10 g; 3 mmol). Then a solution of hexa-2,4-dienoyl

isothiocyanate (0.31 g; 2 mmol) in acetone (15 cm<sup>3</sup>) was added portionwise with stirring and water cooling. The mixture was diluted with water (60 cm<sup>3</sup>), formed precipitate was filtered off, dried and chromatographed on silica gel (benzene—acetone,  $\varphi_r = 7/1$ ), to yield 140 mg (37 %) of VI and 70 mg (31 %) of I. Mass spectrum,  $m/z$  ( $I_r/\%$ ): 187 ( $M^+$ , 78), 95 (100), 86 (62), 68 (48).

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