

Reactions of 2-cyano-3-phenylpropenoyl isothiocyanate with amines

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Dedicated to Professor RNDr. V. Sutoris, CSc., in honour of his 60th birthday

The reactions of 2-cyano-3-phenylpropenoyl isothiocyanate with aniline and secondary amines, respectively, have been studied. It has been found that stable thiourea, which in alkali medium cyclizes to the mixture of *cis*- and *trans*-2-thiouracils, was formed only from aniline. Secondary amines provided the mixture of the corresponding isomeric 1,3-thiazines directly. The data of elemental analysis as well as of ¹H NMR and IR spectra proved the structures of the synthesized compounds.

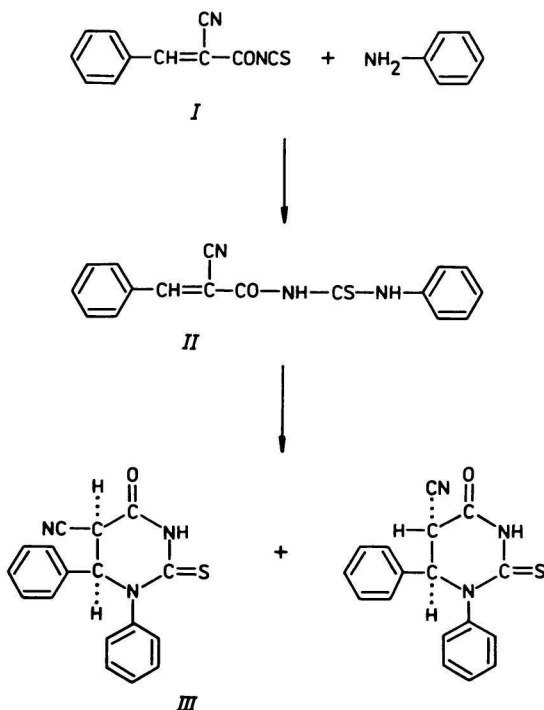
Изучены реакции 2-циано-3-фенилпропеноилизотиоцианата с анилином или вторичными аминами. Обнаружено, что устойчивая тиомочевина, циклизирующаяся в щелочной среде с образованием *цис*- и *транс*-2-тиоурацилов, образовывалась только в реакции с анилином. Реакция со вторичными аминами приводила прямо к смеси соответствующих изомерных 1,3-тиазинов. Результаты элементарного анализа, а также ¹H ЯМР и ИК-спектры подтверждают строение синтезированных соединений.

There are several papers in the literature dealing with synthesis and biological activity of 1,3-thiazine skeletons [1—3]. In our previous works we followed the intramolecular cyclization of α,β -unsaturated acylthioureas, formed in the reaction of α,β -unsaturated acyl isothiocyanates and amines [4, 5].

In the present work we attempted to activate the C=C bond by introduction of an electron-accepting substituent into the α -position of the 3-phenylpropenoyl residue. We chose the cyano group as the electron-accepting substituent and 2-cyano-3-phenylpropenoyl isothiocyanate (*I*) as the starting compound for the reaction with amines.

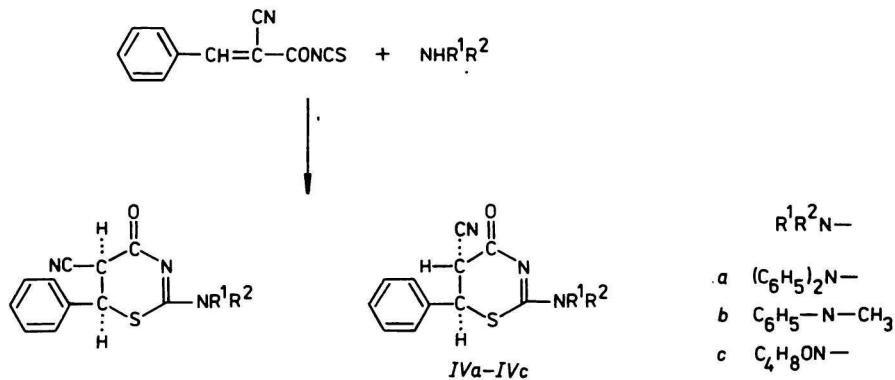
When preparing thioureas from the respective isothiocyanate we found that stable thiourea was formed from aniline only. Cyclization of thiourea (*II*) in ethanolic NaOH, aqueous solution of NaOH, chloroform, and benzene in the presence of triethylamine resulted in the mixture of *cis*- and *trans*-isomers of 2-thiouracils (*III*; Scheme 1). As indicated by the IR and ¹H NMR spectra the isomeric thiouracils (*III*) bound the solvent (benzene or ethanol) on crystallization. The presence of one solvent molecule per one molecule of the product in the

crystalline sample was proved unambiguously by thermal analysis. Decomposition of the compound began at 65 °C as an endothermic process, reaching the optimum on the DTA curve at 93 °C. The amount of benzene released (77.10 mg/mmol) was in good agreement with the theoretical amount of 78.11 mg/mmol. In the case of ethanol, decomposition started at 55 °C as an endothermic process, reaching the optimum on the DTA curve at 85 °C. The amount of ethanol released was 47.72 mg/mmol (theoretical amount 46.07 mg/mmol). When attempting to prepare the respective 1,3-thiazine derivative from thiourea *II* it was found that on heating the compound in benzene, toluene, and xylene cyclization had not occurred.



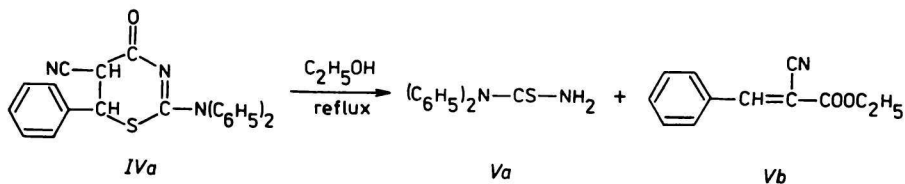
Scheme 1

In the case of the secondary amines (diphenylamine, *N*-methylaniline, morpholine), which can provide only 1,3-thiazine systems (*IVa*—*IVc*; Scheme 2), it was found that these skeletons were formed directly by the reaction with 2-cyano-3-phenylpropenyl isothiocyanate, *i.e.* the respective thioureas could not have been isolated. Chromatography and crystallization of the formed mixtures of *cis*- and *trans*-isomers have not led to their separation. On crystallization



Scheme 2

of 1,3-thiazine (*IVa*) from ethanol ring opening took place, while *N,N*-diphenylthiourea (*Va*) and ethyl 2-cyano-3-phenylpropenoate (*Vb*) were isolated from the reaction mixture, as proved by IR and ^1H NMR spectra (Scheme 3). The derivatives (*Vb*, *Vc*) did not decompose on ethanolysis.



Scheme 3

^1H NMR spectroscopy was used to study the *cis-trans* isomerism. On the basis of vicinal coupling constants $^3J_{\text{AB}}$ it is possible to ascribe the isomers the respective configuration, since the vicinal coupling constants of *trans*-isomers of cyclic compounds are higher than those of *cis*-isomers [6]. From the precisely measured $^3J_{\text{AB}}$ values (INDOR technique in the CW regime) (Table 1) it follows that the derivatives with higher coupling constants are *trans*-isomers and those with lower ones are *cis*-isomers. Correctness of this assignment of configuration can be supported also by the coupling constants reported by *Giordano* [7] for the synthesized *trans*-2-phenyl-5,6-dimethyl-5,6-dihydro-4*H*-1,3-thiazine (8.4 Hz) and for the *cis*-isomer (3.3 Hz). The ratio of geometric isomers in the synthesized crystallized mixtures (*III*, *IVa-IVc*) was established on the basis of integrated intensities of -CH-CH- doublets in their ^1H NMR spectra (Table 1).

Table 1

Chemical shifts, coupling constants of the AB system, and assignment of configuration (α) of 2-thiouracil (III) and 1,3-thiazine (IV) derivatives

Compound	δ_A	δ_B	$^3J_{AB}/\text{Hz}$	$\alpha^a/\%$
	ppm	ppm		
III <i>cis</i>	4.31	5.50	3.3	38
III <i>trans</i>	5.28	5.38	6.5	62
IVa <i>cis</i>	3.94	4.73	3.4	41
IVa <i>trans</i>	4.00	4.70	12.0	59
IVb <i>cis</i>	4.26	4.91	4.3	20
IVb <i>trans</i>	4.39	4.79	12.0	80
IVc <i>cis</i>	4.01	4.79	3.2	37
IVc <i>trans</i>	4.00	4.74	12.2	63

a) Relative abundance of the individual diastereoisomers.

Experimental

The *E*-isomer of 2-cyano-3-phenylpropenoyl isothiocyanate (*I*) was prepared according to [8]. IR spectra were measured on an IR-75 (Zeiss, Jena) spectrophotometer. ^1H NMR spectra (80 MHz) were taken on a Tesla BS 487 A apparatus using tetramethylsilane as internal standard. Thermal decomposition of the derivative *III* was performed under dynamic conditions in argon atmosphere on a MOM-OD 102 Derivatograph using aluminium(III) oxide as standard, heating rate 3°C min^{-1} .

N-Phenyl-*N'*-(2-cyano-3-phenylpropenoyl)thiourea (*II*)

Into the solution of 2-cyano-3-phenylpropenoyl isothiocyanate (1.07 g; 5 mmol) in benzene (10 cm^3) aniline (0.46 cm^3 ; 5 mmol) was added dropwise with stirring. A yellow solid compound precipitated which after 30 min was sucked, washed with hexane, dried, and crystallized. Yield = 1.24 g (81 %), m.p. = $138.5\text{--}140^\circ\text{C}$ (chloroform—petroleum ether).

For $\text{C}_{17}\text{H}_{13}\text{N}_3\text{OS}$ ($M_r = 307.4$) $w_i(\text{calc.})$: 66.43 % C, 4.26 % H, 13.67 % N; $w_i(\text{found})$: 66.56 % C, 4.15 % H, 13.69 % N. IR (CHCl_3), $\tilde{\nu}/\text{cm}^{-1}$: (NH) 3377, (C \equiv N) 2210, (C=O) 1675, (C=C) 1580. ^1H NMR (CDCl_3), δ/ppm : 7.64 (m, C_6H_5), 8.40 (s, CH), 9.10 and 12.20 (s, NH).

Mixture of *cis*- and *trans*-1,6-diphenyl-5-cyano-2-thiouracils (*III*)

N-Phenyl-*N'*-(2-cyano-3-phenylpropenoyl)thiourea (1.1 g; 3.5 mmol) was dissolved in chloroform (15 cm^3) and triethylamine (1 cm^3) was added. After 2 h reflux the solvent

was distilled off and the oily residue was crystallized. Yield = 0.68 g (62 %), m.p. = 178—180 °C (chloroform—petroleum ether).

For $C_{17}H_{13}N_3OS$ ($M_r = 307.4$) $w_i(\text{calc.})$: 66.43 % C, 4.26 % H, 13.67 % N; $w_i(\text{found})$: 66.24 % C, 4.17 % H, 13.59 % N. IR (KBr), $\bar{\nu}/\text{cm}^{-1}$: (C≡N) 2250, (C=O) 1707, (NHCS) 1485. $^1\text{H NMR}$ (CDCl_3 - d_6 —DMSO), δ/ppm : 7.27 (m, C_6H_5), 11.91 and 12.05 (s, NH).

Mixture of cis- and trans-2-diphenylamino-6-phenyl-5-cyano-5,6-dihydro-4H-1,3-thiazin-4-ones (IVa)

2-Cyano-3-phenylpropenoyl isothiocyanate (1.07 g; 5 mmol) was dissolved in benzene (15 cm^3) and diphenylamine (0.84 g; 5 mmol) in benzene (2 cm^3) was added dropwise. The precipitate was after 30 min stirring sucked, washed with petroleum ether, and dried. Yield = 1.58 g (82.5 %), m.p. = 165—166.5 °C (benzene).

For $C_{23}H_{17}N_3OS$ ($M_r = 383.5$) $w_i(\text{calc.})$: 72.04 % C, 4.47 % H, 10.96 % N; $w_i(\text{found})$: 72.12 % C, 4.35 % H, 10.87 % N. IR (CHCl_3), $\bar{\nu}/\text{cm}^{-1}$: (C≡N) 2250, (C=O) 1678, (—N=C—S—) 1592. $^1\text{H NMR}$ (CDCl_3), δ/ppm : 7.34 (m, C_6H_5).

Mixture of cis- and trans-2-(N-methylanilino)-6-phenyl-5-cyano-5,6-dihydro-4H-1,3-thiazin-4-ones (IVb)

Into the solution of 2-cyano-3-phenylpropenoyl isothiocyanate (1.07 g; 5 mmol) in benzene (30 cm^3) *N*-methylaniline (0.54 cm^3 ; 5 mmol) in benzene (10 cm^3) was added. The mixture was refluxed for 90 min, then ice-cooled and the precipitate was sucked, washed with *n*-hexane, and dried. Yield = 1.05 g (65.4 %), m.p. = 179.5—181 °C (benzene).

For $C_{18}H_{15}N_3OS$ ($M_r = 321.4$) $w_i(\text{calc.})$: 67.27 % C, 4.70 % H, 13.07 % N; $w_i(\text{found})$: 67.18 % C, 4.81 % H, 13.02 % N. IR (CHCl_3), $\bar{\nu}/\text{cm}^{-1}$: (C≡N) 2243, (C=O) 1670, (—N=C—S—) 1578. $^1\text{H NMR}$ (CDCl_3), δ/ppm : 3.56 (d, CH_3), 7.31 (m, C_6H_5).

Mixture of cis- and trans-2-morpholino-6-phenyl-5-cyano-5,6-dihydro-4H-1,3-thiazin-4-ones (IVc)

2-Cyano-3-phenylpropenoyl isothiocyanate (0.65 g; 3 mmol) was dissolved in cyclohexane (200 cm^3) and morpholine (0.26 cm^3 ; 3 mmol) was added slowly. The formed light-yellow precipitate was sucked and dried. Yield = 0.82 g (90 %), m.p. = 152—154 °C (ethanol).

For $C_{15}H_{15}N_3O_2S$ ($M_r = 301.4$) $w_i(\text{calc.})$: 59.78 % C, 5.02 % H, 13.95 % N; $w_i(\text{found})$: 59.64 % C, 4.98 % H, 13.78 % N. IR (CHCl_3), $\bar{\nu}/\text{cm}^{-1}$: (C≡N) 2232, (C=O) 1658, (—N=C—S—) 1589. $^1\text{H NMR}$ (CDCl_3), δ/ppm : 3.75 (m, $C_4H_8\text{ON}$), 7.43 (m, C_6H_5).

Ethanolysis of the mixture of cis- and trans-2-diphenylamino-6-phenyl-5-cyano-5,6-dihydro-4H-1,3-thiazin-4-ones (IVa)

The mixture of *cis*- and *trans*-1,3-thiazine *IVa* (3.84 g; 10 mmol) was refluxed in ethanol (100 cm^3) for 20 min. After cooling the mixture *Va* crystallized. It was sucked,

dried, and recrystallized from ethanol. The solvent from the filtrate was distilled off and the residue was distilled *in vacuo* to give *Vb*.

N,N'-Diphenylthiourea (*Va*): yield = 2.18 g (95.8 %), m.p. = 225—226 °C (ethanol) [9]. IR (CHCl₃), $\bar{\nu}/\text{cm}^{-1}$: (as, s NH) 3509 and 3392, (=C—H) 2971, (C=C_{arom}) 1579.

Ethyl 2-cyano-3-phenylpropenoate (*Vb*): yield = 1.77 g (88.2 %), b.p. = 120—122 °C (53.3 Pa) [10]. IR (CHCl₃), $\bar{\nu}/\text{cm}^{-1}$: (C≡N) 2210, (C=O) 1741, (CH=CH) 1624. ¹H NMR (CDCl₃), δ/ppm : 1.35 (t, CH₃), 4.34 (q, CH₂), 7.44 (m, C₆H₅), 8.20 (s, CH).

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