Preparation and reactions of 2-isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene

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2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene was prepared by the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene with thiophosgene in the presence of calcium carbonate in dichloromethane at room temperature. The product reacted with secondary amines in the mixture of dichloromethane and petroleum ether at room temperature giving five 3,3-disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thioureas.

Реакцией 2-амино-3-циано-4,5,6,7-тетрагидробензо[*b*]тиофена с тиофосгеном в дихлорметане при комнатной температуре в присутствии карбоната кальция был получен 2-изотиоцианато-3-циано-4,5,6,7-тетрагидробензо[*b*]тиофен. Продукт взаимодействовал со вторичными аминами в смеси дихлорметана с петролейным эфиром при комнатной температуре с образованием пяти 3,3-дизамещенных 1-(3-циано-4,5,6,7-тетрагидробензо[*b*]тиен-2-ил)тиомочевин.

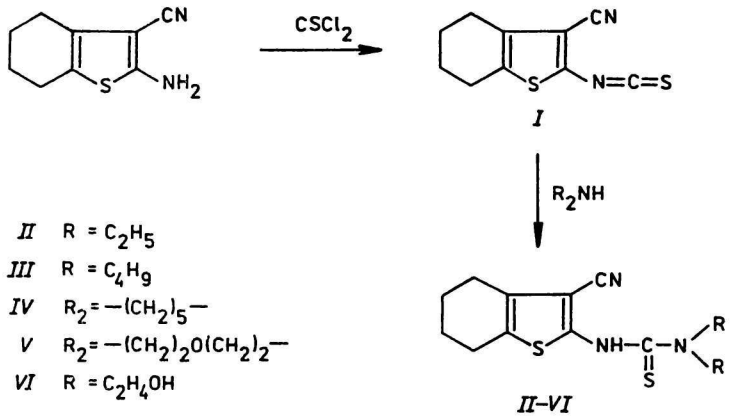
Substituted 4,5,6,7-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines find more and more their application in either medicine as cardiovascular drugs and bactericides or in agriculture as growth stimulators.

3-Substituted or 3,3-disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]-thien-2-yl)thioureas, which can be prepared by the addition of various amines to 2-isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (*I*), serve as intermediates for their preparation.

The aim of our work was the synthesis of compound *I* and its reaction with secondary amines leading to 3,3-disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thioureas (Scheme 1).

Experimental

Melting points were measured on a Kofler hot-stage instrument, Wägetechnik Rapido 79-2106.



Scheme 1

The progress of the reactions and the purity of the synthesized compounds were followed by TLC on Silufol UV 254 (Kavalier, Votice). The chromatograms were detected with Fluotest Universal (Quarzlampen, Hanau) and their elution provided with benzene, chloroform, diisopropyl ether, diethyl ether, and acetonitrile in a container saturated with vapours of the used solvent.

Elemental analyses were established on C. Erba CHN analyzer, Model 1102 and agreed with the calculated values.

IR spectra were measured with Unicam SP 1000 in KBr pellets, ^{1}H NMR spectra were recorded with Tesla BS 567 apparatus (100 MHz), compounds *III*—*V* in hexadeuteroacetone (internal standard TMS) and compounds *II* and *VI* in hexadeuterodimethyl sulfoxide (internal standard HMDSO).

2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene was prepared by the reaction of cyclohexanone with malondinitrile and sulfur under morpholine catalysis in ethanol [1, 2].

2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (I)

Suspension of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (36.7 g; 0.20 mol) in dichloromethane (300 cm^3) was under vigorous stirring at room temperature added during 20 min into suspension of finely ground calcium carbonate (50 g; 0.5 mol) and thiophosgene (28.7 g; 0.25 mol) in dichloromethane (50 cm^3). After 40 min stirring the solid was filtered off, washed with anhydrous dichloromethane. Then the solvent and unreacted thiophosgene were distilled off on a rotary evaporator and the rest was recrystallized from the mixture benzene—cyclohexane ($\varphi_r = 1:1$). Yield = 38.2 g (86.7 %) of light-brown crystals, m.p. = 68—70 °C, R_f(chloroform) = 0.77; R_f(diethyl ether) = 0.95. IR spectrum, $\tilde{\nu}$/cm^{-1}: 2225 ν(CN), 2000 ν(N=C=S), 1565 ν(C=C), 2950,

2870 ν(CH). ^{1}H NMR spectrum (deuterochloroform, TMS), δ/ppm: 2.49—2.76 (m, 4H, CH_2), 1.71—1.95 (m, 4H, CH_2).

3,3-Disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thien-2-yl)thioureas II—VI

A secondary amine (0.05 mol) was dropwise added into the solution of *I* (11.0 g; 0.05 mol) in the mixture of dichloromethane—petroleum ether (φ_r = 1 : 1) (75 cm^3) at room temperature. After 90 min the product of the reaction (*II—VI*) was filtered off, washed with dichloromethane and crystallized. The yields of the light-yellow crystals of the compounds *II—VI* and their other characteristics are given in Table 1, IR and ^{1}H NMR spectral characteristics are given in Tables 2 and 3.

Results and discussion

One of the possibilities how to synthesize aromatic and heterocyclic isothiocyanates is the reaction of primary amino derivatives with thiophosgene in either aqueous medium or in a two-phase system of water and an organic solvent (1,2-dichloroethane, chloroform, *etc.*). The intermediate is thiocarbamoyl chloride. This undergoes a decomposition to substituted isothiocyanate and hydrogen chloride which is often neutralized by the addition of a base into the reaction mixture (*e.g.* sodium hydrogencarbonate, calcium carbonate, triethylamine, *etc.*) [3].

Our first attempt of preparation of *I* was carried out in the mixture of dichloromethane—water by the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene with thiophosgene similarly as we did it in the case of the synthesis of 2-isothiocyanatobenzonitrile [4].

In order to suppress a possibility of the formation of 1,3-bis(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thiourea by the interaction of compound *I* with unreacted starting amino derivative, we carried out the reaction in an excess of thiophosgene and the suspension of amine was added into the mixture of thiophosgene, dichloromethane, and water.

A great deal of polar compounds besides *I* was formed during the reaction. We evaporated the dry organic layer after the reaction to the oily consistence and repeatedly extracted it with boiling mixture benzene—cyclohexane (φ_r = 1 : 1) so that we could get rid of the mentioned polar side products. After filtration the extract was concentrated to crystallization. The way of preparation mentioned above led to compound *I* in a 20 % yield only. As we learnt the compound is very sensitive to water and decomposes to the starting amino derivative (it was proved by TLC using standard). This can then enter into

Table 1

Characteristics of synthesized compounds *II*—*VI*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p./°C (Solvent)	R_f (Diethyl ether)
			C	H	N	%		
II	$C_{14}H_{19}N_3S$	261.38	64.33 64.25	7.33 7.26	16.08 19.01	92	100—101 (Ethanol)	0.50
III	$C_{18}H_{27}N_3S_2$	349.55	61.85 61.80	7.79 7.70	12.02 11.99	77	78—79 (Cyclohexane)	0.78
IV	$C_{15}H_{19}N_3S_2$	305.46	59.00 58.90	6.27 6.18	13.76 13.70	91	151—153	0.69
V	$C_{14}H_{17}N_3OS_2$	307.43	54.70 54.65	5.57 5.50	13.67 13.61	92	169—170	0.27
VI	$C_{14}H_{19}N_3OS_2$	309.46	54.34 54.29	6.19 6.00	13.58 13.50	89	126—129	0.28

Table 2

IR spectral characteristics of 3,3-disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thioureas *II*—*VI*

Compound	$\tilde{\nu}$/cm^{-1}							
	ν(CN)	ν(NH)	ν(NHCS)	ν(C=C)	ν(CH)	ν(COC)	ν(C—O)	ν(OH)
II	2210	3300	1480, 1240	1590	2950, 2890, 2860			
III	2210	3300	1480, 1250	1590	2950; 2900, 2880			
IV	2200	3400	1480, 1240	1590	2920, 2860			
V	2200	3250	1475, 1230	1580	2900, 2870	1120		
VI	2210	3350	1490, 1260	1600	2930, 2850		1050	3550

Table 3

^{1}H NMR spectral characteristics of 3,3-disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thioureas *II*—*VI*

Compound	δ/ppm		
II	8.56 (s, 1H, NH),	1.60—1.88 (m, 4H, CH_2), 2.40—2.72 (m, 4H, CH_2)	1.16 (t, 6H, CH_3, J = 7.0 Hz), 3.76 (q, 4H, CH_2, J = 7.0 Hz)
III	8.58 (s, 1H, NH),	1.60—1.88 (m, 4H, CH_2), 2.48—2.75 (m, 4H, CH_2),	1.00 (t, 6H, CH_3, J = 6.5 Hz), 3.73 (t, 4H, N—CH_2, J = 7.0 Hz) 1.12—1.60 (m, 8H, CH_2)
IV	8.46 (s, 1H, NH),	1.55—1.95 (m, 10H, CH_2), 2.42—2.75 (m, 4H, CH_2)	3.82—4.08 (m, 4H, N—CH_2)
V	8.50 (s, 1H, NH),	1.70—1.95 (m, 4H, CH_2), 2.42—2.80 (m, 4H, CH_2)	3.70—4.15 (m, 8H, CH_2)
VI	8.50 (s, 1H, NH),	1.45—1.83 (m, 4H, CH_2), 2.38—2.75 (m, 4H, CH_2)	3.30—3.65 (m, 8H, CH_2), 4.00 (s, 2H, OH)

reaction with *I* as was mentioned above. A decomposition was observed also during recrystallization from methanol even if methanol was properly dried [5]. But an identification of the polar products was not carried out due to very difficult separation.

In order to suppress unwanted presence of water in the reaction mixture we carried out the reaction in dried dichloromethane and as a base was used sodium hydrogencarbonate. The water formed during the reaction of sodium hydrogencarbonate with hydrogen chloride should have been removed by anhydrous sodium sulfate. Supposing the bonding of water was not perfect, we succeeded in increasing the yield of reaction to 56—60 %.

The other experiment carried out was done with calcium carbonate and the calcium chloride formed during reaction worked as the drying agent. The yield of the reaction carried out in this way increased to 86.7 %, as given in Experimental.

The purity of *I* was proved by TLC and elemental analysis, the structure by IR and ^{1}H NMR spectroscopies. In the IR spectrum the presence of cyano group, —N=C=S and —CH_2— groups of the thiophene skeleton was observed, in the ^{1}H NMR spectrum the signals of —CH_2— groups of cyclohexane ring appeared.

The following part of the work deals with the preparation of 3,3-disubstituted 1-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thioureas by the addition of secondary amines to compound *I* (Scheme 1). The reaction was carried out with diethylamine, dibutylamine, bis(2-hydroxyethyl)amine, piperidine, morpholine, and *N*-butylaniline in methanol at room temperature. The formation of compounds *II*—*VI* was accompanied by the decomposition of *I*. Unwanted by-products made complications during the isolation of pure compounds *II*—*VI*. Their recrystallization from organic solvents (ethanol, toluene with silica gel) did not lead to a good separation and so the repeated crystallization decreased the yield of the reaction. *N*-Butylaniline did not react under the mentioned conditions.

Therefore we decided to carry out the reaction in benzene at room temperature. In this medium no decomposition of *I* was observed and the only 3,3-disubstituted thioureas *II*—*VI* were formed. An exception was again *N*-butylaniline which even under extended reaction time (from 2 to 48 h) did not react. The reason for it seems to be a steric hindrance of butyl group. Compounds *II*—*VI* crystallized from this medium in pure state (proved by TLC) but yields due to their high solubility in benzene were about 30 %. An isolation by either concentration of the mother liquors or precipitating with petroleum ether led only to a tar product and further crystallizations decreased the yield (60—70 %).

Finally we decided to carry out the addition of amines in the mixture

dichloromethane—petroleum ether ($\varphi_r = 1:1$) at room temperature to avoid the previous complications. Bis(2-hydroxyethyl)amine, which did not dissolve in the used solvent mixture, was added into solution of *I* in methanolic solution. Products *II* and *III* were after isolation crystallized from solvents (Table 1), compounds *IV*—*VI* precipitated from the reaction mixture in a pure crystalline form and there was no need to purify them. The yields were over 90 %. An exception was 3,3-dibutyl derivative *III* the yield of which (77 %) is given by its solubility in the reaction mixture and by the loss during crystallization.

The purity of *II*—*VI* was checked by TLC in a number of solvents mentioned in Experimental and by elemental analysis. In the IR spectrum we found vibration of cyano group ($\tilde{\nu} = 2200$—$2210\ cm^{-1}$), stretching vibration N—H ($\tilde{\nu} = 3250$—$3400\ cm^{-1}$), vibration of thiocarbamic group ($\tilde{\nu} = 1475$—$1490\ cm^{-1}$ and 1230—$1260\ cm^{-1}$), and vibration of thiophene skeleton ($\tilde{\nu} = 1580$—$1600\ cm^{-1}$) the values of which are given in Table 2. In the ^1H NMR spectrum we found signals of protons of N—H, —CH_2— groups of cyclohexane ring and signals of alkyl substituents (Table 3).

Compounds *II*—*VI* are supposed to exhibit activity as pesticides, which is under screening.

References

1. Gewald, K., *Z. Chem. 2*, 305 (1962).
2. Gewald, K., Schinke, E., and Bötcher, H., *Chem. Ber. 99*, 94 (1966).
3. Hartmann, A., in Houben—Weyl, *Methoden der Organischen Chemie*. Extension and supplement to 4th Edition. (Hagemann, H., Editor.) Vol. *E4*, p. 834. G. Thieme Verlag, Stuttgart, 1983.
4. Pazdera, P., Nováček, E., and Ondráček, D., *Chem. Papers 43*, 465 (1989).
5. Pitra, J., Veselý, Z., and Kavka, F., *Laboratorní úprava chemikálií a pomocných látek*. (Laboratory Modification of Chemicals and Auxiliary Compounds.) P. 74, method *b*. Nakladatelství technické literatury (Publishers of Technical Literature), Prague, 1969.

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