Synthesis of 1,3-thiazoline derivatives by the reaction of thioureas with 2-propynyl bromide

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Dedicated to Professor P. Kristian, DrSc., in honour of his 60th birthday

2-Propynyl bromide enters the reaction with lithium or sodium salts of *N,N'*-bis(4-bromophenyl)-, *N*-benzoyl-*N'*-benzyl-, *N*-benzoyl-*N'*-phenyl-, and *N*-(3-phenylpropenoyl)-*N'*-phenylthiourea in dimethylformamide under formation of the respective *S*-(2-propynyl)isothioureas. These may be either isolated from the reaction mixture or cyclized *in situ* by addition of lithium or sodium hydride to the corresponding 2-imino-4-methyl-1,3-thiazolines substituted on exocyclic nitrogen and in the position 3.

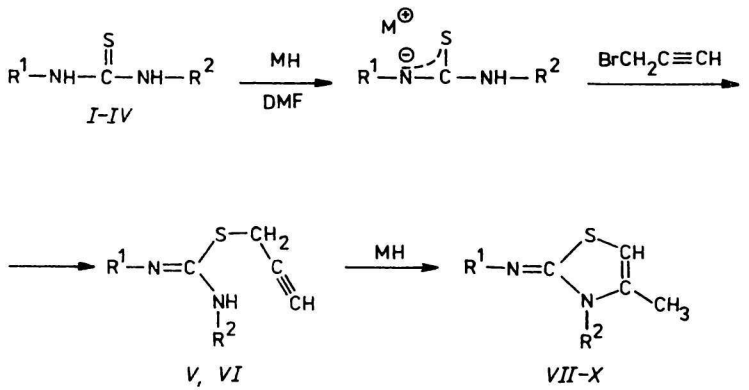
2-Пропинилбромид вступает в реакцию с литиевыми или натриевыми солями *N,N'*-бис(4-бромфенил)-, *N*-бензоил-*N'*-бензил-, *N*-бензоил-*N'*-фенил- и *N*-(3-фенилпропеноил)-*N'*-фенилтиомочевины в диметилформамиде с образованием соответствующих *S*-(2-пропинил)изотиомочевин. Последние могут быть выделены из реакционной смеси, либо зациклизованы *in situ* посредством прибавки гидрида лития или натрия в соответствующие 2-имино-4-метил-1,3-тиазолины, замещенные по экзоциклическому азоту и в положении 3.

There are several papers in the literature dealing with synthesis of five-membered heterocycles from 2-propynyl derivatives [1—3]. However, only little attention has been paid to reactions of thiourea with 2-propynyl bromide and its derivatives, yielding heterocyclic compounds with 1,3-thiazole skeleton [4, 5].

In this work we have studied the reactions of derivatives of thiourea with 2-propynyl bromide in order to verify the possibilities of their utilization for synthesis of 1,3-thiazoline heterocycles. We found that the reaction proceeded rather well in aprotic dipolar solvents, best in dimethylformamide. 2-Propynyl bromide reacts with lithium or sodium salts of thioureas which can be generated advantageously by treating the respective thioureas with lithium or sodium hydride in commercial or dry dimethylformamide. After complete alkylation (monitored by thin-layer chromatography) of *N*-benzoyl-*N'*-benzylthiourea (*II*) and *N*-benzoyl-*N'*-phenylthiourea (*III*) the respective *S*-(2-propynyl)isothioureas *V* and *VI* were isolated. These are the intermediates of the studied conversion of thioureas to 1,3-thiazolines. When after complete alkylation of *I*

and *II* another portion of lithium hydride (in the case of *III* and *IV* sodium hydride) is added into the reaction mixture, *N*-anion is formed which enters the intramolecular nucleophilic addition with the C≡C bond under formation of 1,3-thiazoline derivatives *VII*—*X* (Scheme 1, Table 1). It is probable that in consequence of high concentration of the anionic intermediate after addition to the triple bond a rearrangement [3] to a more stable *C*-anion occurs and the respective derivative of 4-methyl-1,3-thiazoline with an endocyclic C=C bond is formed as the final product. With thioureas *III* and *IV* it is necessary to use sodium hydride as the reaction with lithium hydride proceeds very slowly at room temperature, while at elevated temperature decomposition takes place. Though alkylation of *N*-benzoyl-*N'*-phenylthiourea (*III*) can be accomplished in the presence of lithium hydride, cyclization proceeds only under the action of sodium hydride. The reaction of *N*,*N'*-dicyclohexylthiourea or *N*,*N'*-diphenylthiourea with 2-propynyl bromide in the presence of lithium or sodium hydride resulted in a complicated mixture of compounds, the analysis of which was unsuccessful.

The structures of the products were proved by IR, ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectra of *S*-(2-propynyl)isothioureas *V* and *VI* showed signals of acetylene protons at $\delta = 2.15$ and 2.24 ppm. In the IR spectrum of compound *VI* the absorption band ν(C=O) was shifted to the region below



I–*IV* *V*, *VI* *VII*–*X*

M = Li (*I*, *II*), Na (*III*, *IV*)
I, *VII* $R^1 = R^2 = 4\text{-}BrC_6H_4$
II, *V*, *VIII* $R^1 = C_6H_5CO$, $R^2 = C_6H_5CH_2$
III, *VI*, *IX* $R^1 = C_6H_5CO$, $R^2 = C_6H_5$
IV, *X* $R^1 = C_6H_5CH{=}CHCO$, $R^2 = C_6H_5$

Scheme 1

Table 1

Physicochemical constants of derivatives *VII—X*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C Solvent
			C	H	N		
VII	$C_{16}H_{12}Br_2N_2S$	424.2	45.30	2.86	6.60	67	135—137
			45.09	3.01	6.77		Acetone + water
VIII	$C_{18}H_{16}N_2OS$	308.4	70.10	5.23	9.08	38	125—127
			70.34	5.12	9.24		Hexane
IX	$C_{17}H_{14}N_2OS$	294.4	69.38	4.79	9.52	65	155—157
			69.59	4.52	9.67		Heptane
X	$C_{19}H_{16}N_2OS$	320.4	71.31	5.03	8.75	26	211—213
			71.06	5.28	8.97		Ethanol

$\tilde{\nu} = 1600\,cm^{-1}$ as a consequence of conjugation in the system O=C—N=C. The ^{13}C NMR spectrum of the compound *VI* displayed the signal of the C=N carbon atom instead of the thiocarbonyl carbon signal. The IR spectra of substituted 4-methyl-1,3-thiazolines *VII—X* revealed the absorption bands characteristic of the C=N bond (*VII*) and of the O=C—N=C grouping (*VIII—X*). The ^1H and ^{13}C NMR spectra proved unambiguously the presence of methyl groups and endocyclic C=C bond (Table 2).

Experimental

N,N'-Dicyclohexylthiourea [6], *N,N'*-bis(4-bromophenyl)thiourea (*I*) [7], *N*-benzoyl-*N'*-benzylthiourea (*II*) [8], *N*-benzoyl-*N'*-phenylthiourea (*III*) [8], *N*-(3-phenylpropenoyl)-*N'*-phenylthiourea (*IV*) [9], and 2-propynyl bromide [10] were prepared according to the respective literature. *N,N'*-Diphenylthiourea was a commercial preparation (Lachema, Brno). The reaction course was monitored by thin-layer chromatography on Silufol plates (Kavalier, Votice).

IR absorption spectra of the prepared compound were measured in chloroform with an IR-75 (Zeiss, Jena) spectrophotometer. ^1H and ^{13}C NMR spectra were measured in deuterochloroform with Tesla BS 487 A (80 MHz) and Tesla BS 567 (25.25 MHz) spectrometers, respectively, using tetramethylsilane as internal standard.

N-Benzoyl-N'-benzyl-S-(2-propynyl)isothiourea (V)

To the suspension of lithium hydride (24 mg; 3 mmol) in dimethylformamide (10 cm^3) *N*-benzoyl-*N'*-benzylthiourea (*II*; 540 mg; 2 mmol) was added and the mixture was

Table 2

Spectral data of derivatives *VII*—*X*

Compound	IR, $\tilde{\nu}$/cm^{-1}		^{1}H NMR, δ/ppm			^{13}C NMR, δ/ppm			
	ν(C═C)	ν(O═C—N═C)	CH_3[a]	HC═[b]	H_{arom}	CH_3	HC═	C═N	C═O
VII	1620	1570[c]	1.85	5.70	6.79—7.67	15.35	94.10	150.50	—
VIII	1615	1560	2.17	6.05	7.25—8.35	14.93	104.37	170.06	174.24
IX	1616	1550	2.02	6.10	7.30—8.00	14.26	104.66	169.62	174.10
X	1635	1570	1.98	6.33	7.10—7.67	—	—	—	—

a) Doublet, J = 2 Hz; *b*) quartet, J = 2 Hz; *c*) ν(C═N).

stirred at room temperature until complete evolution of hydrogen (30 min). Then 2--propynyl bromide (476 mg; 0.3 cm^3; 4 mmol) was added and stirring was continued for 2 h. The reaction mixture was poured into cold water (500 cm^3), the solution became turbid and an oily compound precipitated. This was extracted with ether (5 × 70 cm^3), the extract was dried with anhydrous sodium sulfate and ether was evaporated. The oily residue could not be converted to solid state by cooling, addition of various solvents or filtration through a silica gel column. When distillation was attempted, decomposition occurred. Therefore, the crude product (0.31 g; 50 %) was used for ^{1}H NMR measurements.

^{1}H NMR spectrum, δ/ppm: 2.24 (t, J = 3 Hz, 1H, ≡CH), 4.05 (d, J = 3 Hz, 2H, —CH_2C≡), 4.50 (d, J = 5 Hz, 2H, NH—CH_2), 7.32—8.20 (m, 10H, C_6H_5CO, and C_6H_5), 11.50 (s, 1H, —NH—).

N-Benzoyl-N'-phenyl-S-(2-propynyl)isothiourea (VI)

The procedure was similar as with *V* but in this case the product precipitated after pouring the reaction mixture into water. The precipitate was sucked, dried, and crystallized from the mixture of tetrachloromethane—hexane.

Yield = 68 %, m.p. = 117—119 °C. For $C_{17}H_{14}N_2OS$ (M_r = 294.4) w_i(calc.): 69.36 % C, 4.80 % H, 9.52 % N; w_i(found): 69.51 % C, 4.62 % H, 9.73 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3310 ν(≡C—H), 1590 ν(O=C—N=C). ^{1}H NMR spectrum, δ/ppm: 2.15 (t, J = 3 Hz, 1H, ≡CH), 4.02 (d, J = 3 Hz, 2H, —CH_2C≡), 7.40—7.84 (m, 10H, C_6H_5CO and C_6H_5), 12.75 (s, 1H, —NH—). ^{13}C NMR spectrum, δ/ppm: 20.11 (t, —CH_2—), 71.40 (d, ≡CH), 79.98 (s, ≡C—), 126.17, 128.11, 129.38, 129.87, 132.14, 136.24, and 137.29 (d, d, d, d, d, s, s, C_6H_5CO and C_6H_5), 171.15 (s, C=N), 176.59 (s, C=O).

2-R^1-Imino-3-R^2-4-methyl-1,3-thiazolines (VII—X)

To the suspension of lithium hydride (24 mg; 3 mmol) in dimethylformamide (10 cm^3) thiourea *I* or *II* (2 mmol) was added, or to the suspension of sodium hydride (72 mg; 3 mmol) in dry dimethylformamide (10 cm^3) thiourea *III* or *IV* (2 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. 2-Propynyl bromide (476 mg; 0.3 cm^3; 4 mmol) was added and the mixture was stirred for 2 h (*I*, *II*) or 30 min (*III*, *IV*). Then another portion of lithium hydride (*I*, *II*; 3 mmol) or sodium hydride (*III*, *IV*; 3 mmol) was added and stirring was continued for 40 min (*I*, *II*), 3 h (*III*), and 5 min (*IV*). The reaction mixture was slowly poured under stirring into ice water (200 cm^3) and allowed to stand overnight at 0 °C. The precipitate was sucked, dried, and purified on silica gel 100/160 μm (130 g) using the mixture of benzene—acetone (φ_r = 7 : 1) as eluent. The products obtained (*VII—IX*) are characterized in Tables 1 and 2.

In preparation of *X* only a small amount of precipitate was formed after pouring the mixture into water. Therefore, the supernatant was diluted with water to 800 cm^3 and extracted with ether (5 × 60 cm^3). The extract was dried with magnesium sulfate and ether

was evaporated. The combined portions of the crude product *X* were purified similarly as the derivatives *VII—IX*.

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