A new knowledge about the synthesis of 1-phenyl--3-(2-cyanophenyl)thiourea

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The addition of 2-aminobenzonitrile to phenyl isothiocyanate reproducing the procedure described in literature [1] did not lead to 1-phenyl--3-(2-cyanophenyl)thiourea but to the product of its cyclization, *i.e.* 3--phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione. This was the only product of the addition, even under varied conditions.

The reaction of 2-aminobenzonitrile with 4-nitrophenyl isothiocyanate under various conditions was studied. The only product formed was 4-imino-3-(4-nitrophenyl)-1,2,3,4-tetrahydroquinazoline-2-thione.

1-Phenyl-3-(2-cyanophenyl)thiourea was prepared by the addition of aniline to 2-isothiocyanatobenzonitrile at room temperature in the mixture dichloromethane—petroleum ether. So far unknown 2-isothiocyanatobenzonitrile was prepared by the reaction of thiophosgene with 2-aminobenzonitrile in the mixture dichloromethane—water.

Посредством присоединения 2-аминобензонитрила к фенилизотиоцианату по методике, известной из литературы [1], была получена не 1-фенил-3-(2-цианофенил)тиомочевина, а продукт ее циклизации, то есть, 3-фенил-4-имино-1,2,3,4-тетрагидрохиназолин-2-тион. Этот продукт был получен в качестве единственного продукта реакции присоединения также и после модификации условий эксперимента.

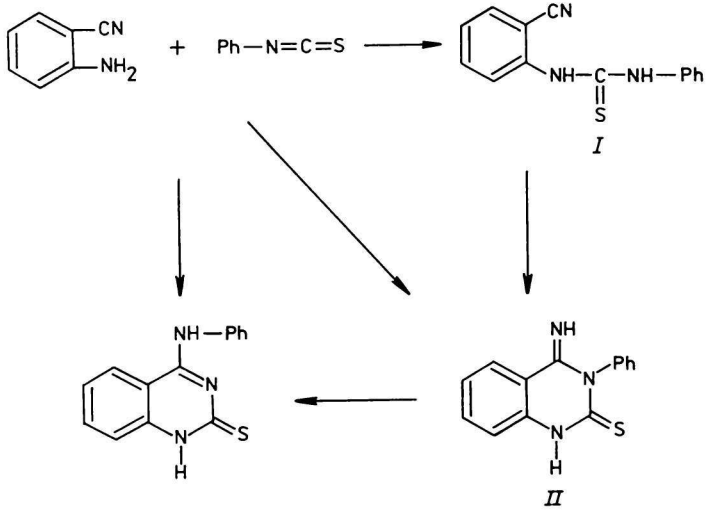
Исследована реакция 2-аминобензонитрила с 4-нитрофенилизотиоцианатом в разных условиях. Продуктом присоединения был исключительно 4-имино-3-(4-нитрофенил)-1,2,3,4-тетрагидрохиназолин-2-тион.

1-Фенил-3-(2-цианофенил)тиомочевина была получена путем присоединения анилина к 2-изотиоцианатобензонитрилу при лабораторной температуре в смеси дихлорметана с петролейным эфиром. До сих пор неописанный в литературе 2-изотиоцианатобензонитрил был получен реакцией тиофосгена с 2-аминобензонитрилом в смеси дихлорметана с водой.

The synthesis of 1-phenyl-3-(2-cyanophenyl)thiourea (*I*) was at first described by *Taylor* and *Ravindranathan* [1] as a result of the reaction of 2-aminobenzonitrile with phenyl isothiocyanate in the absence of solvent at the

temperature of (50 ± 2) °C (Scheme 1). The time of the reaction was 20 h, yield = 85 %. The only characteristic given was m.p. = 165—168 °C.

When the addition of 2-aminobenzonitrile to phenyl isothiocyanate was carried out boiling both components in benzene for 20 h, 3-phenyl-4-imino--1,2,3,4-tetrahydroquinazoline-2-thione (*II*) was formed (yield = 53 %). The same product was obtained by the cyclization of compound *I* boiling in methanol for 10 min (yield = 95 %).



Scheme 1

When the reaction of addition proceeded by smelting both components at the temperature of 100 °C, 4-phenylamino-1,2-dihydroquinazoline-2-thione was isolated in 97 % yield. This compound was identical with the product that was obtained by the rearrangement of quinazoline derivative *II* boiling in the mixture dimethylformamide—water (Scheme 1). The mechanism is similar to the Dimroth rearrangement of pyrimidine derivatives.

Experimental

Melting points of the synthesized compounds were measured on a Kofler hot stage (Rapido 79-2106, Wägetechnik). TLC was carried out on Silufol UV 254 (Kavalier, Votice), chloroform, benzene, ethyl acetate, and ether were the eluents. Chromatograms were detected with the instrument Fluotest Universal (Quarzlampen, Hanau). Infrared spectra were measured on a Unicam SP 1000 apparatus in KBr pellets. ^{1}H NMR spectra of compounds were taken with spectrophotometer Tesla BS 567 (100 MHz) in saturated

hexadeuteroacetone solution with TMS as internal standard or in hexadeuterodimethyl sulfoxide with HMDSO as internal standard. UV spectra were recorded with spectrophotometer Unicam SP 1800 in acetonitrile solution of compounds [2] in concentration 1×10^{-4} mol dm^{-3}

4-Nitrophenyl isothiocyanate was prepared according to Ref. [3]. M.p. = 114—116 °C (acetic acid), Ref. [3] gives m.p. = 112 °C. IR spectrum, $\tilde{\nu}$/cm^{-1} 2050 (ν(N=C=S)), 1525, 1340 (ν(NO_2)), 1605, 1590, 1490 (ν(C=C)).

2-Isothiocyanatobenzonitrile

The solution of 2-aminobenzonitrile (23.6 g; 0.20 mol) in 50 cm^3 of dichloromethane was dropwise added into the solution of thiophosgene (28.7 g; 0.25 mol) in dichloromethane (30 cm^3) and water (70 cm^3) during 10 min. The mixture was stirred for 120—180 min at room temperature. The reaction was followed by TLC on Silufol (eluent chloroform).

When 2-aminobenzonitrile disappeared, the organic layer was separated, washed with water to neutral reaction and dried with anhydrous sodium sulfate. The solvent and unreacted thiophosgene were distilled off. After crystallization from petroleum ether (with silica gel) 28.3 g (88.4 %) of product was obtained. M.p. = 60—61 °C, R_f(chloroform) = 0.83. IR spectrum, $\tilde{\nu}$/cm^{-1}: 2240 (ν(C≡N)), 2070 (ν(N=C=S)), 1595, 1495, 1450 (ν(C=C)).

Addition of 2-aminobenzonitrile to phenyl isothiocyanate

a) The reaction was carried out following literature [1]. From the reaction mixture 3-phenyl-4-imino-1,2,3,4-tetrahydroquinazoline-2-thione (*II*) was isolated in the yield of 95 %. M.p. = 196—198 °C (methanol), Ref. [1] gives m.p. = 195—198 °C. R_f(chloroform) = 0.03; R_f(diethyl ether) = 0.34. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3190, 3280 (ν(NH)), 1635 (ν(C=N)), 1510 (ν(NHCS)), 1595, 1530, 1490 (ν(C=C)). UV spectrum, λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 235 (4.225), 293 (4.305). ^{1}H NMR spectrum (DMSO-d_6), δ/ppm: 9.50 (s, 2H, N—H), 7.20—8.32 (m, 9H, H_{arom}).

b) The reaction was carried out following procedure in [1] at the temperature of (40 ± 1) °C in nitrogen atmosphere, reaction time 50 h. Compound *II* was isolated in 88 % yield, m.p. = 195—198 °C.

c) 2-Aminobenzonitrile (0.12 g; 1 mmol) and fresh distilled phenyl isothiocyanate (0.14 g; 1 mmol) were dissolved in dichloromethane (20 cm^3). The mixture was left in a tightly closed tube for 30 d at the temperature of 5—10 °C. The product so formed was filtered off and washed with dichloromethane. Yield = 0.095 g (36 %) of *II*, m.p. = = 195—197 °C.

Addition of 2-aminobenzonitrile to 4-nitrophenyl isothiocyanate

a) 2-Aminobenzonitrile (1.2 g; 0.01 mol) and 4-nitrophenyl isothiocyanate (1.8 g; 0.01 mol) were heated at an oil bath for 8 h at the temperature of 80 °C till the mixture

got stiff. The product so formed was rubbed in ether and crystallized from acetic acid. Yield = 2.9 g (96.7 %) of 4-imino-3-(4-nitrophenyl)-1,2,3,4-tetrahydroquinazoline-2--thione, m.p. = 270—272 °C. R_f(chloroform) = 0.03, R_f(diethyl ether) = 0.42. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3100, 3290 (ν(NH)), 1625 (ν(C═N)), 1520 (ν(NHCS)), 1530, 1340 (ν(NO_2)), 1590, 1490, 1460 (ν(C═C)). ^{1}H NMR spectrum (DMSO-d_6), δ/ppm: 11.00 (s, 1H, N—H), 9.62 (s, 1H, N—H), 7.25—8.55 (m, 8H, H_{arom}).

b) The reaction was carried out similarly as in *a*) in ethanol or benzene boiling for 3 h. Crystallization from acetic acid gave the same compound in yield of 80 % or 85 %, m.p. = 270—272 °C.

c) The reaction was carried out similarly as in *a*) in either ethanolic or benzene solution at room temperature, the reaction time 17 or 20 h. The yields of the cyclic product like in *a*) were 76 % or 80 %.

1-Phenyl-3-(2-cyanophenyl)thiourea (I)

Aniline (18.6 g; 0.2 mol) dissolved in dichloromethane (50 cm^3) was dropwise added into solution of 2-isothiocyanatobenzonitrile (32 g; 0.2 mol) in 150 cm^3 of the mixture dichloromethane—petroleum ether (φ_r = 1 1). The reaction mixture was stirred at room temperature for 1 h. Then the product was filtered off, washed with dichloromethane and petroleum ether and dried in vacuum at room temperature. Yield = 50 g (98 %), m.p. = = 184—186 °C. R_f(chloroform) = 0.32, R_f(diethyl ether) = 0.73. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3380, 3250 (ν(NH)), 2230 (ν(CN)), 1550, 1235 (ν(NHCS)), 1610, 1595, 1490, 1450 (ν(C═C)). ^{1}H NMR spectrum (hexadeuteroacetone), δ/ppm: 9.56 (s, 1H, N—H), 9.16 (s, 1H, N—H), 7.20—8.00 (m, 9H, H_{arom}). UV spectrum, λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 231 (4.209), 273 (4.086).

Results and discussion

The aim of our work was the synthesis of 1-phenyl-3-(2-cyanophenyl)thiourea (*I*) and its transformation to substituted 2-cyanophenylguanidines the properties of which were to be examined.

We tried to prepare *I* by the procedure mentioned above [1], that is addition of 2-aminobenzonitrile to phenyl isothiocyanate smelting at the temperature of 50 °C. The reaction was followed by TLC, the reaction products were identified by IR and ^{1}H NMR spectroscopy. We found that only 3-phenyl-4-imino--1,2,3,4-tetrahydroquinazoline-2-thione (*II*) was formed.

The formation of *I* was not proved, not even under modification of the reaction conditions (decreasing temperature of the reaction from 50 °C to 40 °C and at the same time extending the reaction time, changing the employed solvent — reaction carried out in ethanol or benzene at room temperature or boiling, in dichloromethane at the temperature of 5—10 °C). In all cases we have proved in the reaction mixture the starting compounds and compound *II* only.

No band of the cyano group vibration in the region $\tilde{\nu} = 2210$—$2260\,cm^{-1}$ was observed in IR spectrum of *II*. On the other hand, we found there the band at $\tilde{\nu} = 1635\,cm^{-1}$ which belongs to the vibration of the imino group (ν(C=N)).

We also followed the addition of 2-aminobenzonitrile to 4-nitrophenyl isothiocyanate. The reaction was carried out smelting both components at the temperature of 80 °C. From the reaction mixture we isolated again the cyclic product, *i.e.* 4-imino-3-(4-nitrophenyl)-1,2,3,4-tetrahydroquinazoline-2-thione in the yield of 96.7 %. That happened in spite of the fact that the nitro group that increases the reactivity in the addition reaction at the same time decreases the nucleophility of the nitrogen atom attacking cyano group during the cyclization and so making the cyclization more difficult.

In the IR spectrum of 4-imino-3-(4-nitrophenyl)-1,2,3,4-tetrahydroquinazoline-2-thione we have not found any nitrile band, the band of vibration of C=N bond we found at $\tilde{\nu} = 1625\,cm^{-1}$

The reaction of 2-aminobenzonitrile with 4-nitrophenyl isothiocyanate in either ethanol or benzene boiling or at room temperatures gave the same results. The yields of quinazoline derivative were from 76 % to 85 %. The formation of 1-(4-nitrophenyl)-3-(2-cyanophenyl)thiourea was not proved even by TLC in the reaction mixtures.

The results obtained led us to the conclusion that 1-phenyl substituted 3-(2-cyanophenyl)thioureas are so reactive that under studied conditions they immediately enter the cyclization reaction to 3-phenyl substituted 4-imino--1,2,3,4-tetrahydroquinazoline-2-thiones. It is probably due to a low activation energy of the cyclization reaction which does not differ very much from the activation energy of the addition reaction.

In order to support our conclusion we tried to prepare compound *I* by the reaction of aniline with 2-isothiocyanatobenzonitrile. Both components are in the addition more reactive systems than in the previous case. The nitrile group that in the addition reaction of 2-aminobenzonitrile to phenyl isothiocyanate decreases the nucleophility of the amino group on the other hand increases the reactivity of the isothiocyanato group in the reaction of 2-isothiocyanatobenzonitrile with aniline.

The reaction was carried out in the mixture of dichloromethane—petroleum ether at room temperature. This mixture was chosen as a solvent because compound *I* formed in the reaction precipitated from the reaction medium in a crystalline form so that its cyclization was suppressed. The reaction was followed by TLC — in the reaction only compound *I* was formed. Its purity was checked by chromatography on Silufol in many eluents. The structure of product was proved by IR and ^1H NMR spectroscopies. In the spectrum the vibration of the cyano group at $\tilde{\nu} = 2230\,cm^{-1}$ and the vibration of the NHCS group at $\tilde{\nu} =$ $= 1235$ and $1550\,cm^{-1}$ were observed.

The difference in melting points between our compound *I* and the product prepared by *Taylor* and *Ravindranathan* [1] which is about 20 °C might be explained by the fact that the authors did not prepare by their method pure 1-phenyl-3-(2-cyanophenyl)thiourea (*I*) but a mixture with compound *II*.

Compound *I* is so thermally unstable that the mere dissolving in acetone or ethanol at room temperature causes its cyclization to *II*. In ethylene glycol monomethyl ether solution the cyclization is finished at room temperature in a few minutes.

This is the reason for which compound *I* cannot be purified by the crystallization and our method seems to be the only way of preparing it in pure state.

2-Isothiocyanatobenzonitrile, so far unknown, was prepared by the reaction of 2-aminobenzonitrile with thiophosgene in the mixture water—dichloromethane following the literature [4]. Its structure was confirmed by IR spectroscopy.

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