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Reaction of *N*-(Carbamimidoyl)thiourea with 1-Benzoyl-2-phenylacetylene

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Abstract—1-Benzoyl-2-phenylacetylene reacted with *N*-(carbamimidoyl)thiourea in glacial acetic acid saturated with 20% HBr to give (4,6-diphenyl-2*H*-1,3-thazin-2-ylidene)guanidine hydrobromide. The reaction of the same compounds in anhydrous ethanol in the presence of sodium ethoxide led to the formation of *N*-(4,6-diphenylpyrimidin-2-yl)thiourea. Bis(3-oxo-1,3-diphenylprop-1-en-1-yl) sulfide and 1-benzoyl-2-ethylsulfanyl-2-phenylethylene were isolated in the reactions of 1-benzoyl-2-phenylacetylene with *N*-(carbamimidoyl)thiourea and *N*-(carbamimidoyl)-S-ethylisothiuronium bromide, respectively, in anhydrous methanol.

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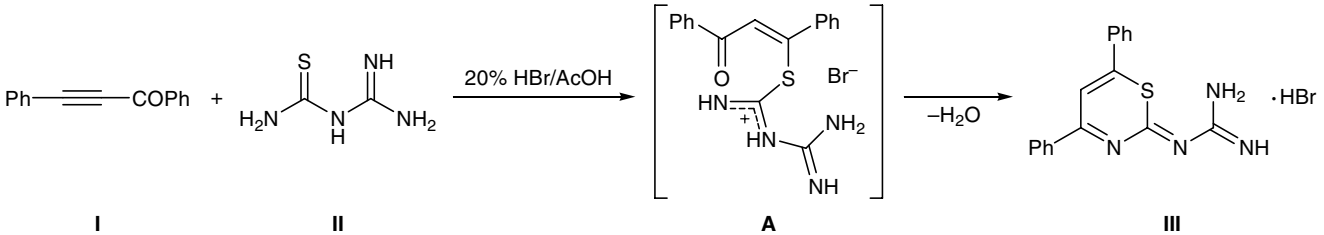
Reactions of sulfur- and nitrogen-containing ambident nucleophiles, including *N*-(carbamimidoyl)thiourea, with α-acetylenic ketones can take different pathways, depending on the conditions and substituents in the reactants. Therefore, such reactions may be used for selective synthesis of various heterocycles which attract interest as potential biologically active substances, dyes, extractants for noble metals, and rubber vulcanizing agents. *N*-(Carbamimidoyl)thiourea is known to react with α-halo ketones, 2-acylcycloalkanones, and thiophosgene to give functionally substituted derivatives of thiazole [1, 2], pyrimidine [3], and 1,3,5-thiadiazine [4], some of which are important from the viewpoint of application in medicine and agriculture; it also seems to be promising to use *N*-(carbamimidoyl)thiourea as N,N- or S,N-ligand in complex formation with metals [5].

In continuation of our studies on reactions of α-acetylenic ketones with S,N-centered ambident nucleophiles [6–9], in the present work we examined reactions of 1-benzoyl-2-phenylacetylene with *N*-(carbamimidoyl)thiourea and *N*-(carbamimidoyl)-*S*-ethylisothiuronium bromide in AcOH, EtOH, MeOH under acidic (HBr) and basic (EtONa, Et_3N) conditions. 1-Benzoyl-2-phenylacetylene (**I**) reacted with *N*-(carbamimidoyl)thiourea (**II**) at 20°C in glacial acetic acid saturated with 20% HBr to give (4,6-diphenyl-2*H*-1,3-thia-zin-2-ylidene)guanidine hydrobromide (**III**) with high chemoselectivity (yield 91%, Scheme 1). Presumably, the reaction begins with nucleophilic attack by the sulfur atom of thiourea on the electron-deficient β-carbon atom in activated acetylene **I**. The subsequent attack by the nitrogen atom on the carbonyl carbon atom in intermediate isothiuronium salt **A** is accompanied by closure of 1,3-thiazine ring and elimination of water molecule.

Molecule **II** may be regarded as a composition of thiourea and guanidine fragments. It is known that thiourea reacts with α,β-unsaturated carbonyl compounds under acidic conditions to form isothiourea

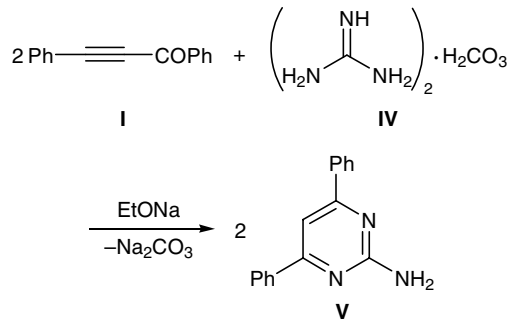
Scheme 1.



I **II** **A** **III**

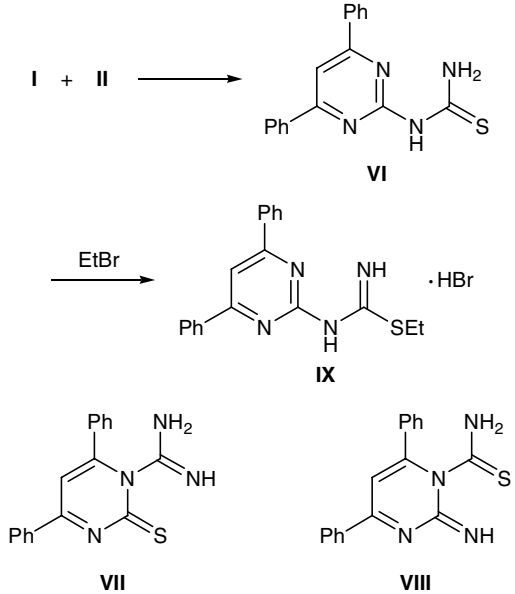
derivatives due to the ability of thiourea to undergo isomerization to isothiuronium salts in acid medium [10–12]. Therefore, the formation of intermediate **A** in the first stage of the acid-catalyzed reaction of 1-benzoyl-2-phenylacetylene (**I**) with *N*-(carbamimidoyl)thiourea (**II**) (Scheme 1) seems to be quite reasonable. The dehydration stage is also catalyzed by acid which favors formation of mesomeric carbenium–oxonium ion possessing an enhanced affinity for the nucleophilic partner [13].

Scheme 2.



Baddar et al. [14] reported on the synthesis of pyrimidine-2-thione derivatives from 1-aroyl-2-phenylacetylenes and thiourea or *N*-monosubstituted thiourea on heating in ethanol in the presence of sodium ethoxide. We have found that the reaction of acetylenic ketone **I** with diguanidine dihydrogen carbonate (**IV**) in the system EtONa–EtOH leads to the formation of 82% of 4,6-diphenylpyrimidin-2-amine (**V**) (Scheme 2). Thus, the formation of several alternative products, namely pyrimidine derivatives **VI–VIII**, may be expected in base-catalyzed reactions of thiourea **II** with unsaturated ketone **I** (Scheme 3).

Scheme 3.

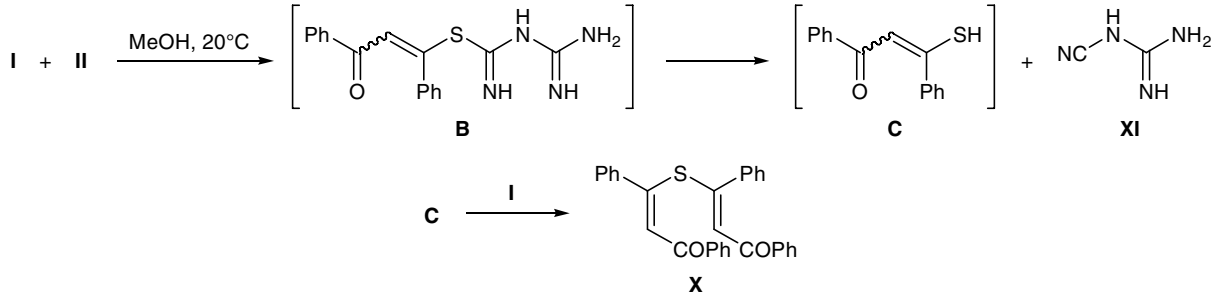


In the reaction of acetylene **I** with thiourea **II** in anhydrous ethanol in the presence of sodium ethoxide (heating under argon) we isolated 55% of *N*-(4,6-diphenylpyrimidin-2-yl)thiourea (**VI**) as the only product (Scheme 3). Its structure was established on the basis of the ^{1}H, ^{13}C, and ^{15}N NMR data, as well as by chemical transformation. The ^{1}H NMR spectrum of the product contained only two multiplet signals belonging to protons of two phenyl rings in positions *4* and *6* of the heteroring. The shape of these signals indicated that both phenyl rings are equivalent and hence that the pyrimidine ring is substituted in a symmetric mode. Likewise, only one set of narrow peaks was observed in the aromatic region of the ^{13}C NMR spectrum. The signals were assigned using two-dimensional C–H correlation technique. From the inverse HSQC ^{15}N–^{1}H spectrum we determined the chemical shifts of the nitrogen atoms in the thiourea fragment, for these atoms are directly linked to protons: δ_N (relative to $MeNO_2$) –256.3 (NH_2) and –235.3 ppm (NH). The two-dimensional HMBC ^{15}N–^{1}H spectrum contained only one cross peak between the CH= proton and nitrogen atoms in the pyrimidine ring (δ_N –135.6 ppm), which also confirmed complete equivalence of the ring nitrogen atoms.

After isolation of pyrimidine **VI**, the residue was a complex mixture of unidentifiable products which were likely to be formed via polycondensation of the carbamimidoylthiourea fragments resulting from hydrolysis and alkaline cleavage. By heating compound **VI** with ethyl bromide in ethanol we obtained the corresponding *S*-ethyl derivative **IX** (Scheme 3); this result allowed us to rule out alternative structure **VII** for the condensation product of compounds **I** and **II**.

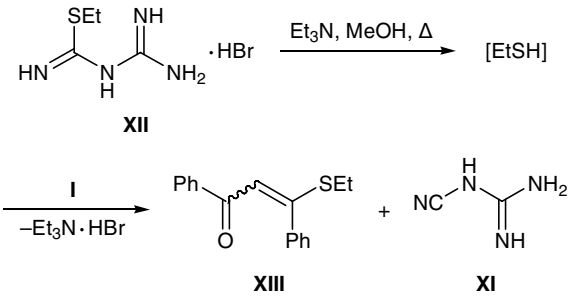
When the reaction of benzoylacetylene **I** with an equimolar amount of thiourea **II** was performed in anhydrous methanol at 20°C, the major product was (*E*,*Z*)-3,3'-thiobis(1,3-diphenylprop-2-en-1-one) (**X**); it was isolated in 50% yield (Scheme 4). The process is likely to include nucleophilic addition to give intermediate sulfide **B**, and dissociation of the C–S bond in the latter leads to thiol **C** and cyanoguanidine **XI**; thiol **C** then reacts with another molecule of acetylene **I**, yielding sulfide **X**. The ^{13}C NMR spectrum of the reaction mixture after separation of sulfide **X** showed the presence of only unreacted initial thiourea **II** and cyanoguanidine **XI** in approximately equal amounts.

Scheme 4.



With a view to obtain heterocyclization products at the amidine fragment, we tried to react compound **I** with *N*-(carbamimidoyl)-*S*-ethylisothiuronium bromide (**XII**) in anhydrous methanol. However, no reaction occurred even at the boiling point, whereas the reaction performed in the presence of an equimolar amount of triethylamine on heating led to the formation of 3-ethylsulfanyl-1,3-diphenylprop-2-en-1-one (**XIII**) (yield 61%) and cyanoguanidine (**XI**) (Scheme 5). This result may be rationalized assuming facile base-catalyzed decomposition of isothiuronium salt **XII** to cyanoguanidine and ethanethiol which adds to acetylene **I** to give compound **XIII**.

Scheme 5.



Taking into account the available published data, we can conclude that the behavior of *N*-(carbamimidoyl)thiourea and *N*-(carbamimidoyl)-*S*-ethylisothiourea in reactions with 1-benzoyl-2-phenylacetylene under the above conditions is similar to the behavior of thiourea [15] and *S*-benzylisothiourea [14] in reactions with aroyl(phenyl)acetylenes, where products of sulfur addition to the latter were also formed.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Bruker IFS-25 instrument. The ^{1}H, ^{13}C, and ^{15}N NMR spectra were obtained on a Bruker DPX-400 spectrometer at 400.13 (^{1}H) and 100.61 MHz (^{13}C) using DMSO-d_6 as solvent.

(4,6-Diphenyl-2*H*-1,3-thiazin-2-ylidene)guanidine hydrobromide (III). *N*-(Carbamimidoyl)thiourea (**II**), 1.18 g (10 mmol), was added in portions under stirring to a solution of 2.06 g (10 mmol) of 1-benzoyl-2-phenylacetylene (**I**) in 30 ml of glacial acetic acid saturated with 20% HBr. The mixture was stirred for 1 h at 20°C, the precipitate was filtered off and dispersed in a mixture of 20 ml of ethanol and 10 ml of diethyl ether, the suspension was stirred for 1 h, and the precipitate was filtered off, washed with 20 ml of diethyl ether, and dried under reduced pressure. Yield 3.53 g (91%), yellow crystals, mp 232–234°C. IR spectrum, ν, cm^{-1}: 3110, 3300, 3405 (NH_2, H_2N^+); 1630 ($C{=}N_{guan}$); 1460–1550 (C=C, C=N), 680 (C–S). ^{1}H NMR spectrum, δ, ppm: 7.62–7.73 m (6H, *m*-H, *p*-H), 8.01 d (2H, *o*-H), 8.32 d (2H, *o*-H), 8.08 s (1H, 5-H), 8.34 br.s (2H, NH_2), 8.58 br.s (2H, H_2N^+). ^{13}C NMR spectrum, δ_C, ppm: 110.44 (C^5); 127.30, 129.17, 129.35, 129.73, 133.03, 133.83, 134.02, 136.20 (C_{arom}); 160.35 (C^6); 162.87 (C_{guan}); 165.90 (C^4); 169.41 (C^2). Found, %: C 52.91; H 3.76; Br 20.32; N 14.49; S 7.95. $C_{17}H_{14}N_4S\cdot HBr$. Calculated, %: C 52.72; H 3.90; Br 20.63; N 14.46; S 8.28.

4,6-Diphenylpyrimidin-2-amine (V). A mixture of 1.03 g (5 mmol) of 1-benzoyl-2-phenylacetylene (**I**) and 0.34 g (5 mmol) of sodium ethoxide in 20 ml of anhydrous ethanol was added while stirring under argon to a suspension of 0.45 g (2.5 mmol) of diguanidine dihydrogen carbonate (**IV**) in 5 ml of anhydrous ethanol. The mixture was heated to the boiling point, stirred for 4 h at that temperature under argon, cooled, poured into 100 ml of water, and acidified with acetic acid to pH 6–7. The precipitate was filtered off and dried under reduced pressure. Yield 1.01 g (82%), colorless needles, mp 133–134°C (from MeCN); published data [16]: mp 135–137°C (from toluene). IR spectrum, ν, cm^{-1}: 3430, 3290 (NH_2); 1500–1620 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 6.76 s (2H, NH_2), 7.51–8.22 m (10H, H_{arom}), 7.70 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 101.96 (C^5); 127.07,

128.69, 130.51, 137.46 (C_{arom}); 164.14 (C^2); 164.99 (C^4, C^6). Found, %: C 77.56; H 5.56; N 17.23. $C_{16}H_{13}N_3$. Calculated, %: C 77.71; H 5.30; N 16.99.

***N*-(4,6-Diphenylpyrimidin-2-yl)thiourea (VI).** A mixture of 1.03 g (5 mmol) of 1-benzoyl-2-phenylacetylene (**I**) and 0.34 g (5 mmol) of sodium ethoxide in 20 ml of anhydrous ethanol was added while stirring under argon to a suspension of 0.59 g (5 mmol) of compound **II** in 5 ml of anhydrous ethanol. The mixture was heated to the boiling point, stirred for 4 h at that temperatue under argon, and kept for 12 h at 5–8°C. The precipitate was filtered off, washed with 5 ml of cold ethanol, and dried under reduced pressure. Yield 0.84 g (55%), colorless crystals, mp 222–224°C (from EtOH). IR spectrum, ν, cm^{-1}: 3150, 3300, 3390 (NH, NH_2); 1490–1585 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 8.22 s (1H, 5-H), 8.27 d (4H, *o*-H), 7.55–7.59 m (6H, *m*-H, *p*-H), 9.22 and 10.39 (2H, NH_2), 10.56 (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 107.46 (C^5); 127.59, 129.20, 131.75, 135.96 (C_{arom}); 158.11 (C^2); 165.24 (C^4, C^6); 181.18 (C=S). Found, %: C 66.45; H 4.48; N 18.35; S 10.24. $C_{17}H_{14}N_4S$. Calculated, %: C 66.64; H 4.60; N 18.28; S 10.46.

***N*-(4,6-Diphenylpyrimidin-2-yl)-*S*-ethylisothiuronium bromide (IX).** A mixture of 0.306 g (1 mmol) of compound **VI** and 5 ml of ethyl bromide in 20 ml of anhydrous ethanol was stirred for 12 h at 40°C. The solution was evaporated under reduced pressure, the residue was ground with 20 ml of water, and the precipitate was filtered off and dried under reduced pressure over $CaCl_2$. Yield 0.3 g (72%), colorless powder, mp 169–170°C. IR spectrum, ν, cm^{-1}: 2800–3100 (HN, H_2N^+), 1500–1600 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, CH_3), 3.34 q (2H, CH_2), 7.58–8.28 m (10H, H_{arom}), 8.41 s (1H, 5-H), 11.5 br.s (2H, HN, HN=). ^{13}C NMR spectrum, δ_C, ppm: 13.99 (CH_3); 25.79 (CH_2); 110.24 (C^5); 128.09, 129.56, 132.46, 135.51 (C_{arom}); 157.89 (C^2); 165.91 (C^4, C^6); 170.19 (C–S). Found, %: C 55.12; H 4.48; Br 19.01; N 13.35; S 7.58. $C_{19}H_{18}N_4S \cdot HBr$. Calculated, %: C 54.94; H 4.61; Br 19.23; N 13.48; S 7.72.

3,3'-Thiobis(1,3-diphenylprop-2-en-1-one) (X). 1-Benzoyl-2-phenylacetylene (**I**), 1.03 g (5 mmol), was added in small portions under stirring to a suspension of 0.59 g (5 mmol) of thiourea **II** in 20 ml of anhydrous methanol. The mixture was stirred for 3 h at 20°C, and the precipitate was filtered off, washed with methanol, and dried under reduced pressure. Yield 0.56 g (50%), yellow crystals, mp 134–136°C (*E*,*Z*-isomer); published data: mp 139°C [15], 135–136°C [17]. ^{13}C NMR spectrum, δ_C, ppm: 125.79, 125.95 (CH=); 128.33–139.78 (C_{arom}); 153.56, 154.38 (S–C=); 189.07, 189.24 (C=O). Found, %: C 80.42; H 4.86; S 7.16. $C_{30}H_{22}O_2S$. Calculated, %: C 80.69; N 4.96; S 7.18.

The filtrate was evaporated to dryness, the residue was ground with diethyl ether, and the precipitate was filtered off to isolate 0.42 g of a colorless crystalline substance which (according to the ^{13}C NMR data) was an approximately equimolar mixture of initial *N*-(carbamimidoyl)thiourea (**II**) and cyanoguanidine (**XI**). ^{13}C NMR spectrum, δ_C, ppm: **II**: 188.11 (C=S), 161.90 (C=NH); **XI**: 118.89 (C≡N), 163.08 (C=NH).

3-Ethylsulfanyl-1,3-diphenylprop-2-en-1-one (XIII). 1-Benzoyl-2-phenylacetylene (**I**), 1.03 g (5 mmol), was dissolved in 20 ml of anhydrous methanol, 1.14 g (5 mmol) of *N*-(carbamimidoyl)-*S*-ethylisothiuronium bromide (**XII**) and 0.505 g (5 mmol) of triethylamine were added, and the mixture was stirred for 3 h under reflux. The solvent was distilled off, the residue was ground with 40 ml of diethyl ether, and the precipitate was filtered off. The ether extract was evaporated to dryness to obtain 0.82 g (61%) of compound **XIII** as a thick oily substance which crystallized on storage, mp 92°C (bright yellow crystals from EtOH). IR spectrum, ν, cm^{-1}: 1620 (C=O), 1480–1510 (C=C), 700 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 2.38 q (2H, CH_2), 7.10 s (1H, CH=), 7.46–7.91 m (10H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.89 (CH_3); 26.08 (CH_2); 120.22 (C^2); 127.49, 127.64, 128.18, 128.27, 128.53, 131.92, 138.02, 138.28 (C_{arom}); 160.94 (C^3); 187.32 (C=O). Found, %: C 76.27; H 5.86; S 12.12. $C_{17}H_{16}OS$. Calculated, %: C 76.08; H 6.00; S 11.95.

The material insoluble in ether was recrystallized from 20 ml of water to obtain 0.13 g (31%) of cyanoguanidine (**XI**) as colorless crystals with mp 201–202°C; published data [18]: mp 206–208°C. IR spectrum, ν, cm^{-1}: 3151–3427 (NH, NH_2), 2162–2207 (C≡N). ^{13}C NMR spectrum, δ_C, ppm: 118.91 (C≡N), 163.10 (C=NH). Found, %: C 28.59; H 5.03; N 66.83. $C_2H_4N_4$. Calculated, %: C 28.57; H 4.76; N 66.67.

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