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STRUCTURE OF PRODUCTS OF REACTION BETWEEN BENZOYLACETYLENE AND 1,5-DIPHENYLDITHIOBIURET

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Reaction of benzoylacetylene with 1,5-diphenyldithiobiuret in glacial AcOH in the presence of equimolar amounts of $HClO_4$ leads exclusively to 2-benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazinium perchlorate. In MeOH, benzene, and MeCN medium, the reaction proceeds nonselectively and a mixture is formed that includes 2-benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazine, 2-benzoylmethyl-4-benzoylvinylthio-3-phenyl-6-phenylimino-1,3,5-thiadiazine, 2-benzoylmethyl-4,6-di-(thiocarbonyl)-1,3-diphenyl-1,3,5-triazine, and N-benzoylvinyl-N'-phenylthiourea.

Keywords: benzoylacetylene, N-benzoylvinyl-N'-phenylthiourea, 1,5-diphenyldithiobiuret, heterocyclization, substituted 1,3,5-dithiazines, 1,3,5-thiadiazines, 1,3,5-triazines.

This report is devoted to the study of the reaction of activated acetylenes with sulfur- and nitrogen-containing nucleophilic reagents, which is a convenient method for synthesis of N,S-containing heterocyclic compounds. In this scheme, dithiobiurets are interesting objects of investigation, since they are polyfunctional systems in which there is a mesomeric interaction between the reaction centers.

Treatment of dithiobiurets with aldehydes and ketones in the presence of dry HCl [1] or ethyl chloroformate [2] leads to formation of 4,6-di(thiocarbonyl)hexahydro-1,3,5-triazines. On reaction of phenyl isocyanide dichloride with monosubstituted [3] and 1,3,5-trisubstituted dithiobiurets [4] in boiling benzene, unstable 1,3,5-dithiazines are formed which may be isomerized to the corresponding 2,6-di(thiocarbonyl)-1,3,5-triazines [3], while stable spiro-linked S,N-heterocycles are obtained by reaction of 4,4-dibromo-1,3-substituted pyrazolin-5-ones and 5,5-dibromobarbituric acid with monosubstituted 2,4-dithiobiurets under analogous conditions [5].

We have studied the reaction of benzoylacetylene (**1**) with 1,5-diphenyldithiobiuret (**2**) in AcOH, MeOH, benzene, and MeCN medium, with cooling (0°C) and at 20°C (ratio of reagents **1**:**2** equal to 1:1 and 2:1).

When carrying out the reaction in glacial AcOH in the presence of equimolar amounts of $HClO_4$, 2-benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazinium perchlorate (**5**) is formed exclusively. The latter, when treated with 0.1 N NaOH solution in DMSO, is converted to the free base: 2-benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazine (**6**) (Scheme 1).

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* Dedicated to Academician of the Russian Academy of Sciences M. G. Voronkov on his birthday.

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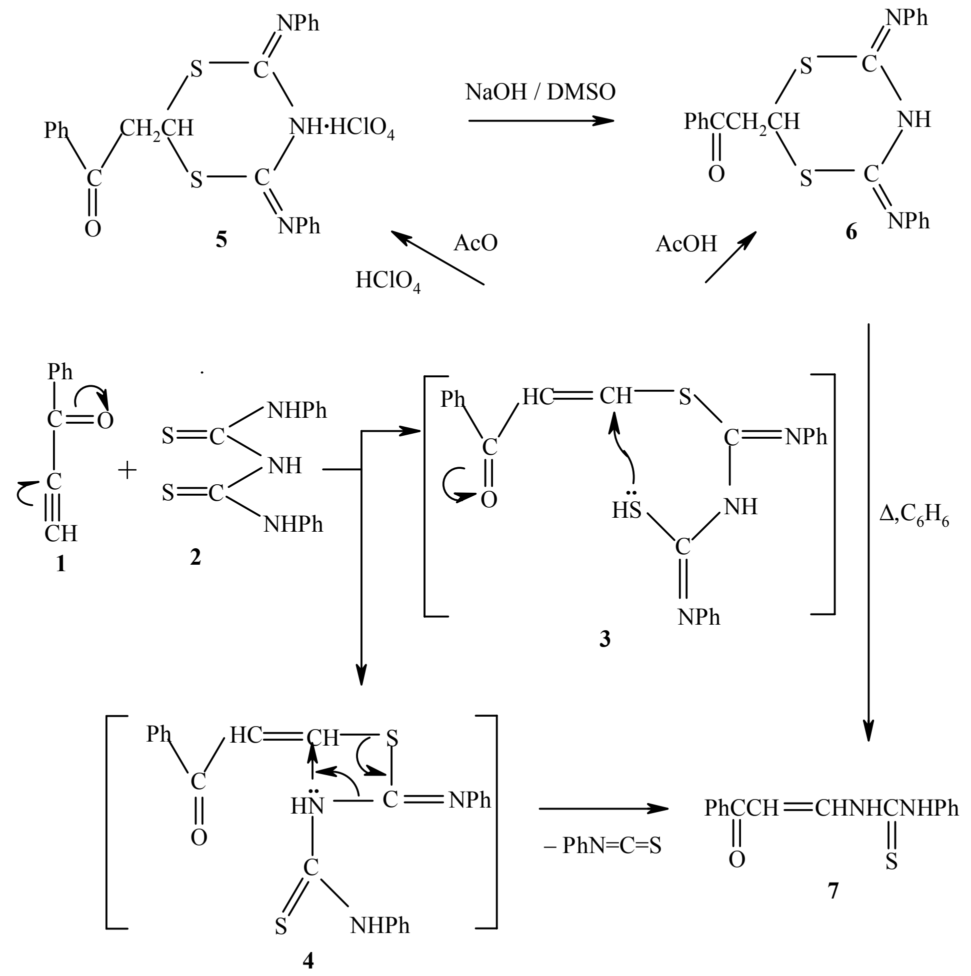
Scheme 1



The reaction of ketone **1** with dithiobiuret **2** in AcOH, benzene, or MeCN medium at 20°C and in MeOH at 0°C proceeds nonselectively to form a mixture of 2-benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazine (**6**), N-benzoylvinyl-N'-phenylthiourea (**7**), 2-benzoylmethyl-4-benzoylvinylthio-3-phenyl-6-phenylimino-1,3,5-thiadiazine (**9**), and 2-benzoylmethyl-4,6-di(thiocarbonyl)-1,3-diphenyl-1,3,5-triazine (**12**).

The end of the reaction was determined by TLC on Silufol plates using 3:1 benzene–ether mixture as the eluent, from the disappearance of the benzoylacetylene spot on the chromatogram of reaction mixture.

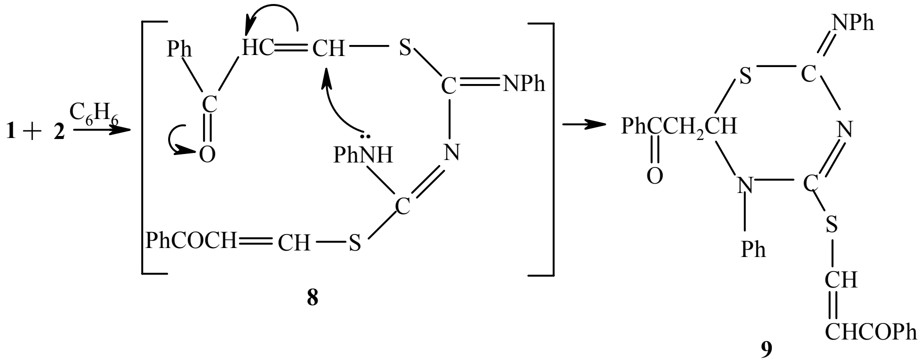
The individual compounds **6, 7, 9, 12** were isolated from the reaction mixtures by fractional crystallization. The composition of each reaction mixture was estimated from the integrated curve of its ^{1}H NMR spectrum by comparing with the ^{1}H NMR spectra of the individual compounds. Analysis of the results obtained allows us to draw the following preliminary conclusions.

The reaction of benzoylacetylene (**1**) with 1,5-diphenyldithiobiuret (**2**) in glacial AcOH leads to formation of the corresponding derivatives of 1,3,5-dithiazine and 1,3,5-triazine **6** and **12** respectively, with preferential predominance of compound **6** (according to ^{1}H NMR, the **6:12** ratio is ~5:1). In benzene and MeCN at 20°C, a mixture is formed consisting of 1,3,5-thiadiazine **9**, 1,3,5-triazine **12**, and β-benzoylvinylthiourea **7** (**9:12:7** ~ 2:2:1), and when the reaction is conducted in benzene with a ratio of **1:2** equal to 2:1, the absolute yield of 1,3,5-thiadiazine **9** is increased. In MeOH at 0°C, the reaction mixture contains compounds **6, 9,** and **11** (1:1:1) and a fairly small impurity (~5%) of substituted thiourea **7**.

Formation of 1,3,5-dithiazine derivatives **5** and **6** and thiourea derivative **7** probably occurs *via* an S-acylvinyl intermediate in which, depending on the spatial arrangement of the thiobiuret moiety (**3** or **4**), the electron-deficient β carbon atom is attacked by the free electron pair of the second sulfur atom, with either closure of the 1,3,5-dithiazine ring in compounds **5** or **6**, or attack by the free electron pair of the central nitrogen atom; and through cyclic transition complex **4**, it is accompanied by rupture of bonds in the molecule with liberation of phenyl isothiocyanate (detected by TLC, R_f 0.94) and formation of thiourea derivative **7**.

When heated in benzene for 1 h, compound **6** is almost quantitatively converted to substituted thiourea **7** (Scheme 1).

2-Benzoylmethyl-4-(β-benzoylvinylthio)-3-phenyl-6-phenylimino-1,3,5-thiadiazine (**9**) is obviously formed from intermediate S,S'-di(benzoylvinyl)isodithiobiuret **8**



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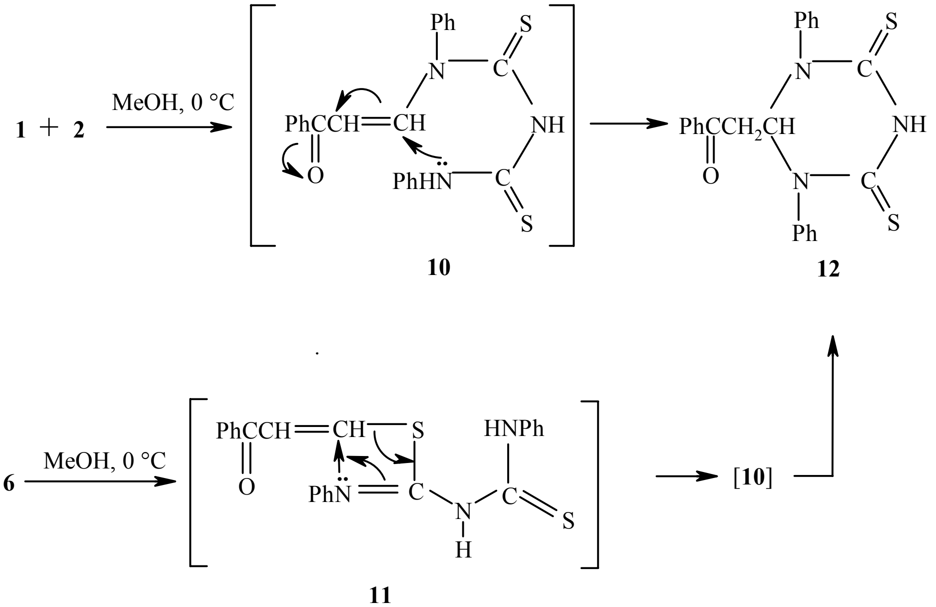
Based on available data, it is not yet possible to verify the possibility that 1,3,5-triazine **12** is formed as a result of intramolecular cyclization of intermediate adduct **10** or by opening of the 1,3,5-thiadiazine ring of compound **6** and its subsequent recyclization through intermediates **11** and **10** to 1,3,5-triazine **12**, as reported in the literature [3]. In any case, the second route cannot be excluded, since it has been observed that in the precipitate falling out during recrystallization of compound **6** from AcOH, according to ^{1}H NMR data, the content of substituted 1,3,5-triazine **12** increased approximately up to 30%, compared with 15%-17% in the unrecrystallized product **6**.



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12

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The composition and structure of the reaction products were confirmed by elemental analysis, IR spectra, and ^{1}H and ^{13}C NMR.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 for KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 (400.13 MHz for ^{1}H; 100.61 MHz for ^{13}C) spectrometer in DMSO-d$_6$ solutions.

1,5-Diphenyldithiobiuret (2) was obtained by the familiar procedure [6].

2-Benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazinium perchlorate (5). Solution of benzoylacetylene (**1**) (0.65 g, 5 mmol) and 40% $HClO_4$ (1 ml) in glacial AcOH (10 ml) was added to suspension of compound **2** (1.43 g, 5 mmol) in glacial AcOH (20 ml) under stirring. The reaction mixture was stirred for 1 h at 20°C and cooled down to 0°C. The precipitate was filtered off, washed on the filter with ether, and dried under vacuum. Obtained 2.38 g (92%) of compound **5** as colorless needles; mp 166-168°C (AcOH). IR spectrum, ν, cm^{-1}: 3020-3280 (NH, N^+H); 1690 (C=O); 1610 (NH bend); 1450-1560 (C=C, C=N); 1050-1120 (ClO_4^-). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 4.07 (2H, d, ^3J = 6.83, CH_2); 5.69 (1H, t, ^3J = 6.83, CH); 7.29-8.05 (15H, m, 3 Ph); 12.24 (2H, br. s, NH, N^+H). ^{13}C NMR spectrum, δ, ppm: 39.02 (CH); 45.61 (CH_2); 124.48-136.72 (Ph); 165.79 ($C_{(4)}$ and $C_{(6)}$); 195.67 (C=O). Found, %: C 53.69; H 3.76; Cl 7.07; N 8.39; S 12.36. $C_{23}H_{20}ClN_3O_5S_2$. Calculated, %: C 53.33; H 3.86; Cl 6.86; N 8.12; S 12.37.

2-Benzoylmethyl-4,6-di(phenylimino)-1,3,5-dithiazine (6). 0.1 N solution of NaOH (26 ml) was added to solution of perchlorate **5** (1.33 g, 2.5 mmol) in DMSO (5 ml) with stirring and cooling down to 0°C. The precipitate was filtered off, washed on the filter with water, and dried under vacuum over $CaCl_2$. Obtained 1.05 g (98%) of dithiazine **6** as white powder; mp 164-166°C. IR spectrum, ν, cm^{-1}: 3120 (NH); 1682 (C=O); 1597 (NH bend); 1445-1566 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 4.08 (2H, d, ^3J = 6.8, CH_2); 5.69 (1H, t, ^3J = 6.8, CH); 12.82 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 38.4 (CH); 45.32 (CH_2); 123.27-136.33 (Ph); 165.51 ($C_{(4)}$ and $C_{(6)}$); 195.27 (C=O). Found, %: C 66.08; H 4.35; N 9.98; S 15.44. $C_{23}H_{19}N_3OS_2$. Calculated, %: C 66.16; H 4.59; N 10.06; S 15.36.

N-(β-Benzoylvinyl)-N'-phenylthiourea (7). Dithiazine **6** (0.42 g, 1 mmol) was boiled in benzene (10 ml) for 1 h. The solution was cooled and held for 8 h at 20°C. The precipitate was filtered off, washed with a moderate amount of cold benzene, and dried under vacuum. Obtained 0.24 g (86%) of compound **7** as whitish needles; mp 171-172°C (benzene). IR spectrum, ν, cm^{-1}: 3100, 3170 (NH, NHPh); 1640 (C=O); 1600 (NH bend); 1540 (C=C). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 6.51 (1H, d, $J_{\alpha\beta}$ = 8.5, COCH=, *cis*-isomer); 8.29 (1H, t, HN–C$\underline{H}$=); 7.24-8.00 (10H, m, 2 Ph); 11.50 (1H, s, NHPh); 12.33 (1H, d, ^3J = 10.4, N$\underline{H}$–CH=). ^{13}C NMR spectrum, δ, ppm: 98.80 (CO–$\underline{C}$H); 143.36 (N–CH=); 179.20 (C=S); 190.82 (C=O); 123.97-138.34 (2 Ph). Found, %: C 68.25; H 4.81; N 9.95; S 11.68. $C_{16}H_{14}N_2OS$. Calculated, %: C 68.06; H 5.00; N 9.92; S 11.36.

2-Benzoylmethyl-4-(β-benzoylvinyl)-3-phenyl-6-phenylimino-1,3,5-thiadiazine (9). 1,5-Diphenyldithiobiuret (**2**) (0.72 g, 2.5 mmol) was added slowly with stirring and cooling (5-8°C) to solution of benzoylacetylene **1** (0.65 g, 5 mmol) in benzene (20 ml). The mixture was stirred at the same temperature for 2 h. The precipitate was filtered off and dried under vacuum. Obtained 0.72 g (53%) of thiadiazine **9** as liqht yellow powder; mp 156-158°C. IR spectrum, ν, cm^{-1}: 1680 ($\underline{CO}$CH$_2$=); 1652 ($\underline{CO}$CH$_2$); 1493-1592 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 3.58 (1H, dd, ^2J = 18.0, ^3J = 10.1, CH_2); 4.04 (1H, dd, ^2J = 18.0, ^3J = 3.6, CH_2); 5.84 (1H, dd, ^3J = 10.1, ^3J = 3.6, CH); 5.88 (1H, d, $J_{\alpha\beta}$ = 13.8, COCH=, *trans*-isomer); 7.05-7.90 (20H, m, 4 Ph); 9.46 (1H, d, $J_{\alpha\beta}$ = 13.8, SCH=). ^{13}C NMR spectrum, δ, ppm: 41.94 (CH_2); 65.81 (CH); 118.57 (CO$\underline{C}$H=); 124.69-141.02 (4 Ph); 145.88 (S$\underline{C}$H=); 158.12 (C=N); 168.81 (C=NPh); 190.55 ($\underline{C}$OCH=); 195.57 ($\underline{C}$OCH$_2$). Found, %: C 69.98; H 4.63; N 7.45; S 11.34. $C_{32}H_{25}N_3O_2S_2$. Calculated, %: C 70.18; H 4.60; N 7.67; S 11.71.

2-Benzoylmethyl-1,3-diphenyl-4,6-dithiono-1,3,5-triazine (12). 1,5-Diphenyldithiobiuret (1.2 g, 4.2 mmol) was added in portions with stirring to solution of benzoylacetylene **1** (0.54 g, 4.2 mmol) in MeOH (20 ml), cooled down to 0°C. The mixture was stirred for 1 h, cooled down to -8°C, and held at that temperature for 24 h. The precipitate was filtered off, washed on the filter with a moderate amount of cold MeOH, and dried under vacuum. Obtained 0.56 g (32%) of triazine **12** as white powder; mp 200-201°C (DMSO). IR spectrum, ν, cm^{-1}: 3120 (NH); 1680 (C=O); 1600 (NH bend); 1440-1510 (C=C); 1210 (C=S). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 4.04 (2H, d, $^3J = 5.6$, CH_2); 5.84 (1H, t, $^3J = 5.6$, CH); 7.44-7.91 (15H, m, 3 Ph); 12.24 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm : 42.07 (CH_2); 75.79 (CH); 124.42-141.91 (Ph); 174.47 (C=S); 195.40 (C=O). Found, %: C 66.28; H 4.35; N 10.18; S 15.02. $C_{23}H_{19}N_3OS_2$. Calculated, %: C 66.16; H 4.59; N 10.06; S 15.36.

The mother liquor, after separation of compound **12**, was evaporated down to 1/3 volume in air at 20°C and benzene (10 ml) was added to the residue. The mass was stirred and held at 5-8°C for 24 h. The precipitate was filtered off, washed with 2 ml of cold benzene, and dried under vacuum. Obtained 0.34 g (30%) of thiadiazine **9** as yellow powder; mp 157-158°C.

The mother liquor, after separation of compound **9**, was evaporated down in air to the consistency of a viscous oil and triturated with petroleum ether (fraction with bp 40-60°C). The residue was filtered off and dissolved in DMSO (5 ml). The solution was added to 20 ml of water. The precipitate was filtered off, washed with water, and dried under vacuum over $CaCl_2$. Obtained 0.51 g (29%) of dithiazine **6**.

Reaction of benzoylacetylene with 1,5-diphenyldithiobiuret. A. 1,5-Diphenyldithiobiuret (**2**) (1.43 g, 5 mmol) was added all at once with stirring to solution of benzoylacetylene **1** (0.65 g, 5 mmol) in glacial AcOH (20 ml). The mixture was stirred for 1 h at 20°C. The precipitate was filtered off, washed with ether, and dried under vacuum. Obtained 1.34 g (64%) of dithiazine **6** as colorless crystals; mp 165-166°C. The residue (a viscous mass) was washed three times by decantation with ether in 50 ml portions and triturated in petroleum ether (fraction with bp 40-60°C) until a light yellow, powdery residue was formed. The latter was dissolved in DMSO (5 ml) at 40-45°C and the solution was held for 3 h at 20°C. The precipitate was filtered off, washed with water, and dried under vacuum above $CaCl_2$. Obtained 0.32 g (15%) of triazine **12** as white powder; mp 199-201°C.

B. Solution of benzoylacetylene **1** (0.65 g, 5 mmol) in benzene (10 ml) was added with stirring to suspension of 1,5-diphenyldithiobiuret (**2**) (1.43 g, 5 mmol) in benzene (20 ml). The mixture was stirred for 2 h and then held for 2 days at 20°C. The precipitate was filtered off, washed with a moderate amount of cold benzene, and dried under vacuum. Obtained 0.43 g (32%) of thiadiazine **9** as yellow powder; mp 157-159°C.

The mother liquor was evaporated down to 1/2 volume at 20°C and held for 5 h at 5-8°C. The residue was filtered off, washed with a moderate amount of cold benzene, and dried under vacuum. Obtained 0.24 g (17%) of N-benzoylvinyl-N'-phenylthiourea (**7**) as white needles; mp 170-172°C.

After separation of products **9** and **7**, the mother liquor was treated as described in procedure A. Obtained 0.71 g (34%) of triazine **12**; mp 198-200°C.

C. The reaction and isolation of the individual compounds was conducted as described in procedure B, using MeCN as the solvent. Obtained 0.44 g (33%) of thiadiazine **9**, 0.21 g (15%) of thiourea derivative **7**, and 0.67 g (32%) of triazine **12**.

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