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Synthesis of Novel 1,3,5-Dithiazine Derivatives

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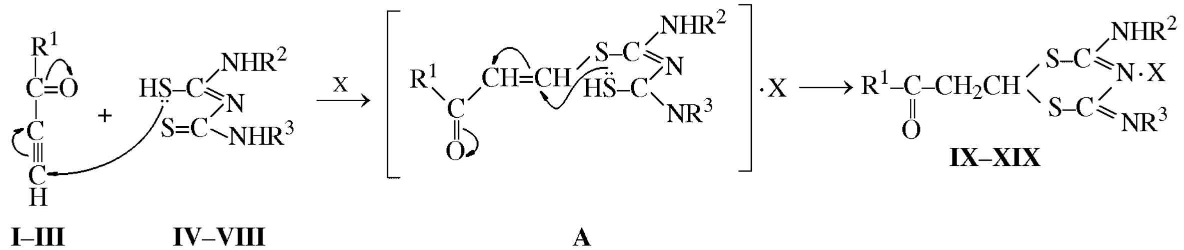
Abstract—The reactions of benzoylacetylene, propiolic acid, and methyl propiolate with 2,4-dithiobiuret and 1-substituted and 1,5-disubstituted 2,4-dithiobiurets in glacial AcOH in the presence of $HClO_4$ or $BF_3 \cdot Et_2O$ were used to obtain 2-substituted 4-amino-6-imino-1,3,5-dithiazinium perchlorates or trifluoroborates, respectively.

It is known that phenyl isocyanide dichloride reacts with 1-aryl-2,4-dithiobiurets in benzene under reflux to give 5-aryl-4-phenylimino-1,3,5-triazines [1], whereas the reactions with 1,3,5-trisubstituted 2,4-dithiobiurets in similar conditions afford substituted 1,3,5-dithiazines [2]. 1-Alkyl(aryl)-2,4-dithiobiurets were reacted with aldehydes and ketones in the presence of dry HCl [3] or ethyl chloroformate [4] to obtain hexahydro-1,3,5-triazine-4,6-dithiones, whereas 1-aroyl-2-bromoacetylenes with 2,4-dithiobiuret in benzene or AcOH form 2-acylmethylene-4,6-diimino-5,6-dihydro-1,3,5-dithiazines [5].

In the present work we studied reactions of activated acetylenes with sulfur- and nitrogen-containing ambident nucleophiles as a potentially convenient synthetic route to N,S-containing heterocyclic compounds.

It was found that propiolic acid (**I**), its methyl ester (**II**), and benzoylacetylene (**III**) react with 2,4-dithiobiuret (**IV**), 1-methyl(phenyl)-2,4-dithiobiurets (**V, VI**), 1-methyl-5-phenyl-2,4-dithiobiuret (**VII**), and 1,5-diphenyl-2,4-dithiobiuret (**VIII**) in glacial AcOH at 20°C in the presence of equimolar amounts of $HClO_4$ or $BF_3 \cdot Et_2O$, giving perchlorates **IX**–**XVI** and trifluoroborates **XVII**–**XIX** of 2-substituted 4-R'-amino-6-R^2-imino-1,3,5-dithiaziniums in good yields [scheme (1)]. The reaction presumably involves intermediate formation of ketovinyl sulfide **A** via addition of the mercapto group to the electron-deficient β-carbon atom of the starting activated acetylenes **I**–**III**. The attack of the mercapto group on the conjugated C=C bond in intermediate **A** is accompanied by intramolecular cyclization and produces 1,3,5-dithiazinium salts **IX**–**XIX**.



(1)

R^1 = OH (**I, IX, X**), MeO (**II, XI**), Ph (**III, XII–XIX**); R^2 = H (**IV, IX, XI, XII**), Me (**V, VII, XIII, XV, XVII**), Ph (**VI, VIII, X, XIV, XVI, XVIII, XIX**); R^3 = H (**IV–VI, IX–XIV, XVII, XVIII**), Ph (**VII, VIII, XV, XVI, XIX**); X = $HClO_4$ (**IX–XVI**); BF_3 (**XVII–XIX**).

The composition and structure of compounds **IX**–**XIX** were proved by elemental analysis (Table 1) and ^1H and ^{13}C NMR and IR spectroscopy (Table 2). The IR spectra of compounds **IX**–**XIX** show an absorption band at 1680–1720 cm^{-1} due to unconjugated C=O group, and stretching absorption of the NH groups appears as a group of bands at 3050–3450 cm^{-1} depending on the nature of substituents R^1 and R^2.

The ^1H NMR spectra of compounds **IX**–**XIX** show a characteristic A_2X pattern of $CH_2CH=$ protons. Protons of the methylene group α to the C=O group

Table 1. 1,3,5-Dithiazinium perchlorates **IX**–**XVI** and trifluoroborates **XVII**–**XIX**

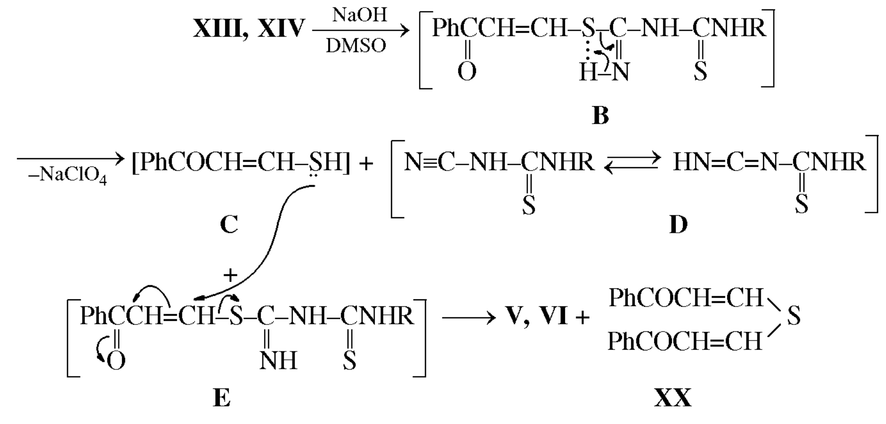
Comp. no.	Yield, %	mp, °C	Found, %					Formula	Calculated, %				
			C	H	Cl (F)	N	S		C	H	Cl (F)	N	S
IX	70	163–165	20.01	2.37	11.87	14.01	21.20	$C_5H_8ClN_3O_6S_2$	19.64	2.62	11.62	13.75	20.95
X	72	172–174	34.27	3.22	9.12	11.26	16.57	$C_{11}H_{12}ClN_3O_6S_2$	34.65	3.15	9.32	11.02	16.80
XI	72.5	104–106	22.57	3.08	11.45	13.08	20.18	$C_6H_{10}ClN_3O_6S_2$	22.53	3.13	11.11	13.14	20.03
XII	90	200–202	35.95	3.21	9.36	11.23	17.15	$C_{11}H_{12}ClN_3O_5S_2$	36.11	3.28	9.71	11.49	17.51
XIII	82	196–198	37.62	3.66	9.24	10.94	16.68	$C_{12}H_{14}ClN_3O_5S_2$	37.94	3.69	9.35	11.07	16.86
XIV	85	96–98	46.47	3.94	8.35	9.78	14.92	$C_{17}H_{16}ClN_3O_5S_2$	46.21	3.62	8.04	9.51	14.50
XV	96	96–97	47.32	4.22	7.64	9.08	14.11	$C_{18}H_{18}ClN_3O_5S_2$	47.42	3.95	7.79	9.22	14.05
XVI	92	166–168	53.69	3.76	7.07	8.39	12.36	$C_{23}H_{20}ClN_3O_5S_2$	53.33	3.86	6.86	8.12	12.37
XVII	82	198–200	41.41	3.84	(16.51)	12.07	18.31	$C_{12}H_{13}BF_3N_3OS_2$	41.50	3.75	(16.42)	12.10	18.44
XVIII	83	97–98	49.63	3.84	(14.02)	9.98	15.33	$C_{17}H_{15}BF_3N_3OS_2$	49.88	3.67	(13.94)	10.27	15.65
XIX	70	170–172	56.63	3.78	(11.41)	8.44	13.02	$C_{23}H_{19}BF_3N_3OS_2$	56.91	3.92	(11.75)	8.66	13.19

give a doublet at 2.97–4.07 ppm ($^3J_{AX}$ 6.8 Hz). The methylene proton signal is split into a triplet and absorbs at 5.28–5.69 ppm. The chemical shifts of $CH_2CH=$ protons depend on the nature of substituent R^1. Thus, along the series R = OH, MeO, Ph, the CH_2 proton signals shift downfield by 0.9 ppm, and the CH proton signals, by 0.2 ppm.

The ^{13}C NMR spectra were assigned on the basis of the spectra of the starting biurets and published data. The CH carbon absorbs upfield compared with the CH_2 carbon, probably, under the effect of two adjacent sulfur atoms. Substituents R^1 affect only the CH_2 carbon signals, shifting them downfield by 4.5 ppm along the series R^1 = OH, MeO, Ph.

Substituted 1,3,5-dithiazines **IX**–**XIX** are crystals or powders. They melt with decomposition and are stable only as salts. Treatment of salts **XIII** and **XIV** with a 1 N solution of NaOH in DMSO, aiming at obtaining free bases from the reaction mixture gave bis(benzoylvinyl) sulfide (**XX**), 2,4-dithiobiurets **V** and **VI**, and an unidentified compound whose IR spectrum contains a well-defined absorption band at 2130–2150 cm^{-1}.

Probably, bis(benzoylvinyl) sulfide (**XX**) is formed by scheme (2).



(2)

R = Me (**XIII**), Ph (**XIV**).

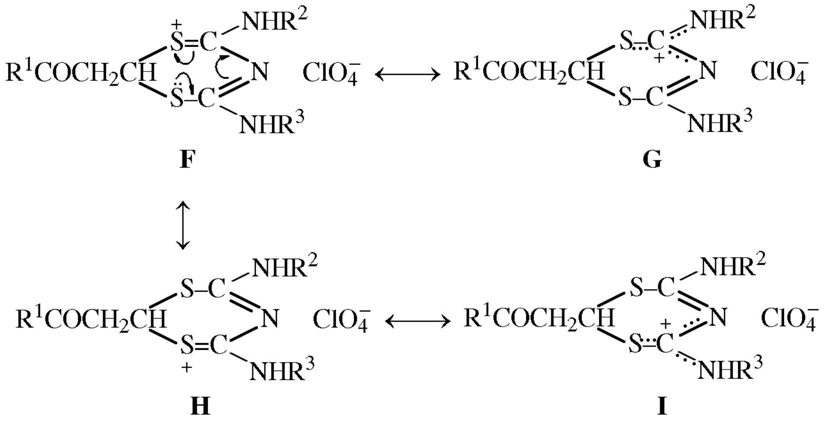
Under the action of bases, the 1,3,5-dithiazine ring in salts **XIII** and **XIV** is cleaved to form a cyclic transition complex **B** whose thioamide C–C bond is readily cleaved, affording vinylthiol **C**. The latter, in its turn, attacks the electron-deficient β-carbon atom in intermediate **E**, forming bis(benzoylvinyl) sulfide

Table 2. Spectral characteristics of 1,3,5-dithiazinium perchlorates **IX**–**XVI** and trifluoroborates **XVII**–**XIX**

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm	^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm
IX	3195, 3290, 3390 (NH_2, $=N^+H_2$), 1725 (C=O), 1610 (NH), 1510 (C=N), 1030–1120 (ClO_4^-)	2.97 d (2H, CH_2), 5.28 t (1H, CH), 9.77 s (2H, NH_2), 10.00 s (2H, $=N^+H_2$), 12.87 br.s (1H, OH)	38.74 (CH), 41.41 (CH_2), 169.03, 169.89 (C^4 and C^6), 181.72 (C=O)
X	3205, 3300, 3390 (NH, N^+H_2), 1720 (C=O), 1630 (NH), 1510–1560 (C=C, C=N), 1040–1110 (ClO_4^-)	3.08 d (2H, CH_2), 5.40 t (1H, CH), 7.28–7.73 m (5H, Ph), 10.39 d (2H, $=N^+H_2$), 12.00 s (1H, NHPh), 12.90 br.s (1H, OH)	39.18 (CH), 41.30 (CH_2), 123.47–136.97 (4C, Ph), 163.84, 170.04 (C^4 and C^6), 181.53 (C=O)
XI	3200, 3300, 3395 (NH_2), 1730 (C=O), 1620 (NH), 1520 (C=N), 1050–1110 (ClO_4^-)	3.14 d (2H, CH_2), 3.70 s (3H, CH_3), 5.41 t (1H, CH), 9.86 s (2H, NH_2), 9.92 s (2H, NH_2)	39.07 (CH), 41.60 (CH_2), 52.67 (CH_3), 163.95, 170.35 (C^4 and C^6), 185.15 (C=O)
XII	3200, 3300–3450 (NH_2), 1680 (C=O), 1620 (NH), 1500–1600 (C=C, C=N), 1060–1110 (ClO_4^-)	3.88 d (2H, CH_2, ^3J 6.8 Hz), 5.47 t (1H, CH, ^3J 6.8 Hz), 7.52–7.98 m (5H, C_6H_5), 9.85 s (2H, NH_2), 9.97 s (2H, NH_2)	38.23 (CH), 45.50 (CH_2), 128.53–135.66 (4C, C_6H_5), 169.58, 170.60 (C^4 and C^6), 195.46 (C=O)
XIII	3195, 3290, 3380 (NH, NH_2), 1690 (C=O), 1625 (NH), 1520–1580 (C=C, C=N), 1050–1100 (ClO_4^-)	3.06 s (3H, C*H*$_3$NH), 3.88, 3.84 d (2H, CH_2, ^2J 18.5 Hz, ^3J 7.0 Hz), 5.45 t (1H, CH, ^3J 7.0 Hz), 7.51–7.99 m (5H, C_6H_5, *J* 7.6 Hz), 10.03, 10.00 s (1H, NH, N*H*CH$_3$), 10.36 s (1H, N^+H)	29.82 (CH_3), 38.42 (CH), 45.18 (CH_2), 128.23–135.40 (4C, C_6H_5), 165.56, 169.42 (C^4 and C^6), 195.14 (C=O)
XIV	3100–3300 (NH, $=N^+H_2$), 1680 (C=O), 1640 (NH), 1490–1570 (C=C, C=N), 1050–1100 (ClO_4^-)	3.98 d (2H, CH_2, ^2J 6.8 Hz), 5.60 t (1H, CH, *J* 6.8 Hz), 7.28–8.02 m (10H, 2C_6H_5, *J* 7.8 Hz), 10.30 s (1H, =NH), 10.35 s (1H, N^+H), 11.95 s (1H, NHPh)	38.59 (CH), 45.26 (CH_2), 123.41–137.03 (8C, 2Ph), 164.07, 170.39 (C^4 and C^6), 195.34 (C=O)
XV	3150–3380 (NH, $=N^+H$), 1690 (C=O), 1610 (NH), 1500–1550 (C=C, C=N), 1070–1130 (ClO_4^-)	3.04 s (3H, C*H*$_3$NH), 3.98 d (2H, CH_2, ^3J 6.9 Hz), 5.60 t (1H, CH, ^3J 6.9 Hz), 7.32–8.03 m (10H, 2C_6H_5, *J* 7.8 Hz), 10.78 s (1H, N*H*CH$_3$), 12.10 s (1H, NHPh)	30.34 (CH_3), 38.65 (CH), 45.12 (CH_2), 122.91–136.47 (8C, 2Ph), 164.46, 166.32 (C^4 and C^6), 195.16 (C=O)
XVI	3020–3280 (NH, N^+H), 1690 (C=O), 1610 (NH), 1450–1560 (C=C, C=N), 1050–1120 (ClO_4^-)	4.07 d (2H, CH_2, *J* 6.9 Hz), 5.69 t (1H, CH, *J* 6.9 Hz), 7.29–8.05 m (15H, 3C_6H_5), 12.24 br.s (2H, 2 NH Ph)	39.02 (CH), 45.61 (CH_2), 124.48–136.72 (8C, Ph + 2 PhNH), 165.79, 169.92 (C^4 and C^6), 195.67 (C=O)
XVII	3210–3370 (NH, =NH), 1690 (C=O), 1625 (NH), 1510–1580 (C=C, C=N), 1000–1100 br ($[BF_3]^-$)	3.07 d (3H, C*H*$_3$NH), 3.86 d (2H, CH_2), 5.47 t (1H, CH), 7.52–7.98 m (5H, Ph), 10.03 s (1H, =NH), 10.38 s (1H, N*H*CH$_3$)	29.94 (CH_3), 38.53 (CH), 45.31 (CH_2), 128.36–135.52 (4C, Ph), 165.68, 169.54 (C^4 and C^6), 195.28 (C=O)
XVIII	3219–3386 (NH, =NH), 1677 (C=O), 1640 (NH), 1510–1597 (C=C, C=N), 1055 br ($[BF_3]^-$)	3.96 d (2H, CH_2, ^3J 6.8 Hz), 5.61 t (1H, CH, ^3J 6.8 Hz), 7.27–8.02 m (10H, 2 C_6H_5), 10.32 s (1H, NH), 11.96 br.s (1H, NHPh)	38.56 (CH), 45.27 (CH_2), 123.38–137.07 (8C, 2 Ph), 164.01, 170.34 (C^4 and C^6), 195.36 (C=O)
XIX	3250 br (NH), 1680 (C=O), 1450–1560 (C=C, C=N), 1000–1100 br ($[BF_3]^-$)	4.05 d (2H, CH_2, *J* 6.8 Hz), 5.68 t (1H, CH, *J* 6.8 Hz), 7.28–8.05 m (15H, 3 Ph), 12.00 br.s (1H, NH)	39.04 (CH), 45.30 (CH_2), 124.19–136.46 (8C, Ph + 2 PhN), 165.40, 169.40 (C^4 and C^6), 195.31 (C=O)

(**XX**) and 2,4-dithiobiurets **V** and **VI**. The unidentified reaction product is, probably, carbodiimide **D** or its polycondensation products.

The instability of the 1,3,5-thiadiazines free bases can be explained considering the structure of 2,4-dithiobiuret as a combination of ambident species tending to electron delocalization. In this case, the structure of 1,3,5-dithiazinium perchlorates **IX**–**XVI** can be represented by a combination of mesomeric structures **F**–**I**, i.e. as a “pseudoaromatic” cation stabilized by the ClO_4^- counter ion. Binding the bases



with an acid violates the coplanarity of the 1,3,5-ditiazine ring, enhancing its strain and, as a result, leading to its cleavage.

In a similar way, the stability of 1,3,5-dithiazinium trifluoroborates **XVII**–**XIX** can be explained in terms of the formation of a stable donor-acceptor complex involving delocalized lone electron pairs of the heteroatoms and the vacant orbital of the boron atom.

EXPERIMENTAL

The IR spectra were measured on a Specord IR-75 instrument in KBr. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker-DPX spectrometer 400 [400.13 MHz (^{1}H) and 100.61 MHz (^{13}C)] in DMSO-d_6.

1-Substituted and 1,5-disubstituted 2,4-dithiobiurets were synthesized by the procedures described in [6, 7].

2-Substituted 4-amino-6-imino-1,3,5-dithiazinium salts IX–**XIX.** To a suspension of 0.01 mol of 2,4-dithiobiuret **IV**–**VIII** in 20 ml of glacial AcOH, a solution of 0.01 mol of compound **I**–**III** in 15 ml of AcOH and a solution of 1.93 ml of 40% $HClO_4$ in 10 ml of glacial AcOH were added with stirring, after which the reaction mixture was stirred for 3 h at 20°C. The oily yellow solution was poured into 100 ml of absolute diethyl ether, the mixture was stirred for 1 h, and the precipitate that formed was filtered off and dried in a vacuum.

Reaction of 1,3,5-thidiazinium salts XIII and XIV with sodium hydroxide. To a solution of 0.38 g of perchlorate **XIII** in 5 ml of DMSO, cooled to 10–12°C, we added 3 ml of 1 N aqueous NaOH. The mixture was stirred at 20°C for 1 h, poured into 50 ml of cold water, and the precipitate that formed was filtered off and dried in a vacuum to obtain 0.13 g (88%) of sulfide **XX** as an amorphous light yellow powder, mp 142–143°C (from MeOH), *E,Z* isomer (mp 143–144°C [8]). IR spectrum, ν, cm^{-1}: 3053 (CH=), 1639 (C=O), 1539–1596 (C=C). ^{13}C NMR spectrum (δ_C, ppm, DMSO-d_6): 188.56, 186.31 (2C=O), 118.44, 122.53 (2 CO–*C*H=), 128.08–148.91 (2Ph, 2 S*C*H=). Found, %: C 73.24; H 4.56; S 10.62. $C_{18}H_{14}O_2S$. Calculated, %: C 73.46; H 4.76; S 10.88.

The filtrate was acidified with 0.1 N HCl to pH 6.5–7.0, the precipitate that formed was filtered off, washed with water, and dried in a vacuum to obtain 0.12 g of a dark yellow powder. It was stirred with 5 ml of MeOH at 20°C for 0.5 h, and the undissolved material was filtered off and recrystallized from MeOH to obtain 0.06 g (81%) of dithiobiuret **V**, mp 156°C (mp 157°C [6]). The methanolic solution was slowly evaporated to dryness, the residue was ground in petroleum ether (fraction with bp 40–60°C) to obtain 0.05 g of an unidentified light brown compound, mp 96–98°C.

In a similar way, from perchlorate **XIV** we obtained 62% of sulfide **XX**, 15% of 1-phenyl-2,4-dithiobiuret (**VI**), mp 178–180°C (mp 180°C [6]), and 12% of an unidentified reaction product, mp 79–82°C.

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