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SHORT COMMUNICATIONS

Cyclocondensation of Hydrazine, Formaldehyde, and Hydrogen Sulfide in the Presence of Acids and Bases

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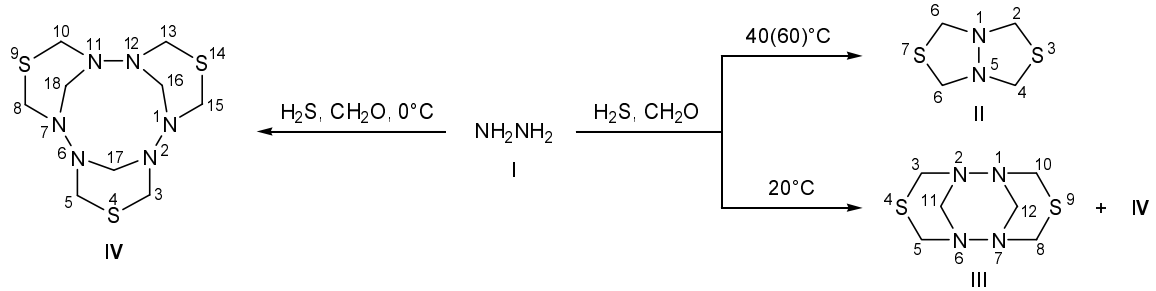
We recently synthesized fused bi-, tri-, and tetracyclic nitrogen- and sulfur-containing heterocycles **II**–**IV** by condensation of hydrazine with hydrogen sulfide and formaldehyde [1] (Scheme 1). Taking into account prospects in the development of this procedure for building up various heterocyclic compounds, we continued studies on multicomponent condensations of compounds having labile hydrogen atoms with hydrogen sulfide and formaldehyde and examined the effect of reaction conditions (pH, temperature, and reactant concentration) on the structure and yield of heterocyclic products with a view to devise effective methods for controlling the selectivity of the reaction of hydrazine with H_2S and CH_2O.

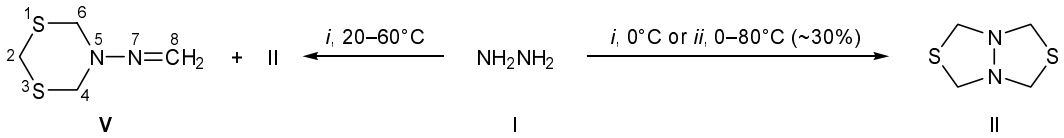
When the condensation of hydrazine with H_2S and CH_2O was carried out in water in the presence of a BuONa–BuOH buffer (pH 10.75–11.5), the reaction direction changed. Unlike our previous results [1], the major product was *N*-methylidene-4*H*-1,3,5-dithiazin-5(6*H*)-amine (**V**) (Scheme 2). The best yield of **V** was achieved at a NH_2NH_2–CH_2O–H_2S–BuONa ratio of 1:4:2:4 at ~20°C. The reaction temperature strongly affects the direction of hydrazine condensation with hydrogen sulfide and formaldehyde. At ~20°C, the product was a mixture of compounds with the general formula $C_4H_8N_2S_2$, which consisted of [1,3,4]thiadiazolo[3.4-*c*][1,3,4]thiadiazole (**II**) and *N*-methylidene-4*H*-1,3,5-dithiazin-5(6*H*)-amine (**V**). Compounds **II** and **V** were isolated as individual substances by column chromatography in 23 and 56% yield, respectively. Raising the temperature to 60°C strongly decreases the fraction of dithiazine derivative **V** (Table 1), whereas the reaction at reduced temperature (0–5°C) afforded exclusively bicyclic thiadiazole **II** (yield ~80%). As follows from the data in Table 1, compound **II** is also formed in a low yield (10–22%) by reaction of hydrazine dihydrogen sulfate (or hydrochloride) with CH_2O and H_2S at a **I**·H_2SO_4–CH_2O–H_2S ratio of 2:4:2 ((pH 0.75–0.8).

Reactant ratio is also an important factor affecting the condensation direction. Increase in the fractions of CH_2O and H_2S in the reaction with hydrazine (CH_2O–

Scheme 1.



Scheme 2.



i: BuONa–CH_2O–H_2S, 4:4:2; *ii*: **I**·H_2SO_4–CH_2O–H_2S, 2:4:2.

H_2S–NH_2NH_2 ratio 6:4:1) in the presence of BuONa leads to formation, in addition to previously described fused S,N-heterocycles **II**–**IV**, of perhydro-*N*-(1,3,5-dithiazin-5-yl)-1,3,5-dithiazine (**VI**), perhydro-*N*-(1,3-thiazet-3-yl)-1,3,5-dithiazine (**VII**), and 3,5,9-trithia-1,7-diazabicyclo[5.3.0]decane (**VIII**) in an overall yield of ~20% (Table 2). The structure of compounds **VI**–**VIII** was determined from the GC–MS data.

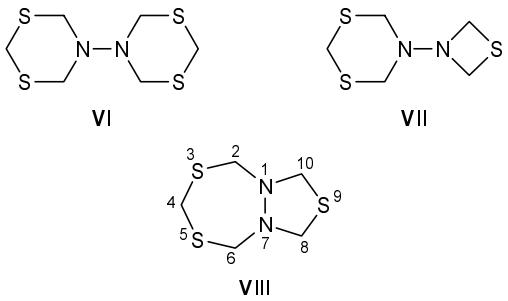


Table 1. Effect of temperature and pH on the yield of cyclocondensation products of hydrazine (**I**) with formaldehyde and hydrogen sulfide at a ratio of 1:4:2

Temperature, °C	pH	Yield, %	
		II	**V**
0	0.75–0.8	10	–
20	H_2SO_4	22	–
40	(2 equiv)	23	–
60	–	10	–
0	10.75–11.5	80	
20	BuONa	23	56
40	(4 equiv)	16	4
60	–	32	17

Table 2. Effect of temperature on the yield of cyclocondensation products of hydrazine (**I**) with formaldehyde and hydrogen sulfide at a ratio of 1:6:4 in the presence of BuONa

Temperature, °C	pH	Yield, %					
		II	**III**	**IV**	**VI**	**VII**	**VIII**
0	10.5–11.25	12	8	33	5	5	7
20	BuONa	37	28	8	5	6	7
40	(4 equiv)	16	10	4	5	6	9

The condensation of hydrazine with hydrogen sulfide and formaldehyde in the presence of other bases (such as NaOH, K_2CO_3, Et_3N, MeONa, and EtONa) was characterized by appreciably lower selectivity. The use of sodium sulfide instead of H_2S (CH_2O–Na_2S–NH_2NH_2 ratio 4:2:1) favored formation of 1,2,4-trithiolane and compound **II** (overall yield ~25%).

All the obtained compounds displayed molecular ion peaks in the mass spectra, and we observed a distinct correlation between the number of sulfur atoms (4% of ^{34}S) and the relative intensity of $[M + 2]^+$ ion peaks with respect to $[M]^+$ [2]. The mass spectra of isomeric compounds **II** and **V**, *m*/*z* 148 $[M]^+$, were characterized by similar fragmentation patterns but different intensities of the molecular ion peaks. The main decomposition pathway of the molecular ions of **II** and **V** includes successive elimination of thiomethylene fragments CH_2S.

The ^{13}C NMR spectrum of dithiazine **V** contained three triplets at δ_C 33.82 (C^2), 53.92 (C^4, C^6), and 131.71 ppm (C^8) with an intensity ratio of 1:2:1. In the ^1H NMR spectrum of **V**, signals from methylene protons in the dithiazine ring appeared as two singlets at δ 4.11 and 4.80 ppm (intensity ratio 1:2). Protons of the exocyclic methylene group gave rise to two doublets in the olefinic region, at δ 6.49 and 6.79 ppm ($^2J_{HH}$ = 10.2 Hz) [3].

Thus the direction of cyclocondensation of hydrazine with formaldehyde and hydrogen sulfide is determined by the acidity of the medium (pH), temperature, and reactant concentration and ratio. We were the first to synthesize *N*-methylidene-4*H*-1,3,5-dithiazin-5(6*H*)-amine (**V**) in ~56% yield by reaction of hydrazine with CH_2O and H_2S in the presence of BuONa (NH_2NH_2–BuONa–CH_2O–H_2S ratio 1:4:4:2) at 20°C. The condensation in the presence of mineral acids (H_2SO_4, HCl) in the temperature range from 0 to 80°C selectively afforded [1,3,4]thiadiazolo[3.4-*c*][1,3,4]thiadiazole (**II**).

Condensation of hydrazine with hydrogen sulfide and formaldehyde. *a*. A three-necked flask equipped with a stirrer, reflux condenser, and gas-inlet

tube and maintained at a constant temperature (20°C) was charged with 14.7 ml (0.2 mol) of a 37% formaldehyde solution. The solution was saturated with hydrogen sulfide over a period of 30 min (0.1 mol), and a mixture of 2.66 ml (0.05 mol) of 60% hydrazine and 0.2 mol of BuONa in BuOH was added dropwise. The mixture was stirred for 3 h at 20°C and neutralized with 10% hydrochloric acid. The organic phase was separated and evaporated to isolate a mixture of compounds **II** and **V** which were separated by column chromatography on silica gel using chloroform–petroleum ether (1:1) as eluent.

***N*-Methylidene-4*H*-1,3,5-dithiazin-5(6*H*)-amine (V).** Yield 4.12 g (56%), mp 74–76°C, R_f 0.22. IR spectrum, ν, cm^{-1}: 690, 920, 1090, 1380, 1450, 1590, 2840, 2900. ^1H NMR spectrum, δ, ppm: 4.11 s (2H, 2-H), 4.80 s (4H, 4-H, 6-H), 6.49 d and 6.79 d (1H each, 8-H, ^2J = 10.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 33.82 t (C^2), 53.92 t (C^4, C^6), 131.71 t (C^8). Mass spectrum, *m*/*z* (I_{rel}, %): 148 (64) $[M]^+$, 116 (48) $[M-S]^+$, 102 (42) $[M-CH_2S]^+$, 70 (26) $[M-SCH_2S]^+$, 56 (100) $[M-CH_2SCH_2S]^+$, 42 (98) $[CH_2=N-N]^+$. Found, %: C 32.70; H 5.60; N 18.53; S 43.17. $C_4H_8N_2S_2$. Calculated, %: C 32.43; H 5.41; N 18.92; S 43.24.

[1,3,4]Thiadiazolo[3.4-*c*][1,3,4]thiadiazole (II). Yield 1.72 g (23.3%), mp 56–58°C, R_f 0.36. The IR, ^1H and ^{13}C NMR, and mass spectra and the melting point were identical to those reported in [1].

b. Following an analogous procedure, the ratio NH_2NH_2–BuONa–CH_2O–H_2S being 1:4:6:4, we obtained a mixture of compounds **II** (yield 37%, R_f 0.53), **III**, **IV**, and **VI**–**VIII** which were separated by column chromatography on silica gel using hexane–ethyl acetate–chloroform (1.5:1:1) as eluent.

4,9-Dithia-1,2,6,7-tetraazatricyclo[5.3.1.$1^{2,6}$]dodecane (III). Yield 2.5 g (28%), R_f 0.22. The IR, ^1H and ^{13}C NMR, and mass spectra and the melting point were identical to those reported in [1].

4,9,14-Trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.$1^{2,6}$.$1^{7,11}$]octadecane (IV). Yield 0.7 g (8%), R_f 0.14. The IR, ^1H and ^{13}C NMR, and mass spectra and the melting point of compound **IV** coincided with those reported in [1].

Perhydro-*N*-(1,3,5-dithiazin-5-yl)-1,3,5-dithiazine (VI). Mass spectrum, *m*/*z* (I_{rel}, %): 240 (39) $[M]^+$, 148 (13) $[M-2CH_2S]^+$, 102 (64) $[M-3CH_2S)^+$, 101 (47) $[M-C_3H_7S_3]^+$, 70 (47) $[M-C_3H_6S_4]^+$, 57 (51) $[M-C_2H_5N_2]^+$, 56 (20) $[M-4CH_2S]^+$, 46 (60) $[CH_2S]^+$, 45 (61) $[CHS]^+$, 42 (100) $[CH_2=N-N]^+$.

Perhydro-*N*-(1,3-thiazet-3-yl)-1,3,5-dithiazine (VII). Mass spectrum, *m*/*z* (I_{rel}, %): 194 (16) $[M]^+$, 148 (46) $[M-CH_2S]^+$, 102 (100) $[M-CH_2SCH_2S]^+$, 101 (52) $[M-CHSCH_2S]^+$, 70 (32) $[M-C_2H_4S_3]^+$, 57 (95) $[C_2H_5N_2]^+$, 56 (48) $[M-3CH_2S]^+$, 46 (73) $[CH_2S]^+$, 45 (82) $[CHS]^+$, 42 (84) $[CH_2=N-N]^+$.

3,5,9-Trithia-1,7-diazabicyclo[5.3.0]decane (VIII). Mass spectrum, *m*/*z* (I_{rel}, %): 194 (20) $[M]^+$, 148 (19) $[M-CH_2S]^+$, 115 (19) $[M-SCH_2S]^+$, 102 (26) $[M-CH_2SCH_2S]^+$, 92 (43) $[CH_2SCH_2S]^+$, 70 (90) $[M-C_2H_4S_3]^+$, 57 (72) $[C_2H_5N_2]^+$, 56 (33) $[M-3CH_2S]^+$, 46 (89) $[CH_2S]^+$, 45 (89) $[CHS]^+$, 42 (100) $[CH_2=N-N]^+$.

c. Following an analogous procedure, from 3 ml (0.04 mol) of a 37% formaldehyde solution saturated with 0.02 mol of hydrogen sulfide and 1.3 g (0.01 mol) of hydrazine dihydrogen sulfate at 0, 20, 40, or 60°C, we obtained compound **II** (after neutralization with a solution of potassium hydroxide).

The ^1H NMR spectra were recorded on a Tesla BS-487 spectrometer at 80 MHz; the ^{13}C NMR spectra were measured on a Jeol FX 90Q instrument at 22.50 MHz; tetramethylsilane was used as internal reference, and chloroform-*d*, as solvent. The IR spectra were obtained on a Specord 75IR spectrometer from samples dispersed in mineral oil. Gas chromatographic–mass spectrometric analyses were performed on a Finigan 4021 GC–MS system (50000 × 0.25-mm HP-5 glass capillary column; carrier gas helium; oven temperature programming from 50 to 300°C at a rate of 5 deg/min; injector temperature 280°C; ion source temperature 250°C; electron impact, 70 eV). The acidity of reaction solutions was measured using a pH-340 pH-meter. The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates using chloroform–petroleum ether (1:1) as eluent for compounds **II** and **V** or hexane–ethyl acetate–chloroform (1.5:1:1) for compounds **III**, **IV**, and **VI**–**VIII**; development with iodine vapor.

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