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Hydrazines in the Synthesis of 1,5,3-Dithiazepane and 1,5,3-Dithiazocane Derivatives in the Presence of Catalysts under the Action of *d*- and *f*-Elements

N. N. Makhmudiyarova, R. Sh. Rakhimov, A. G. Ibragimov, and U. M. Dzhemilev

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, Ufa, 450075 Russia
e-mail: ink@anrb.ru

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Abstract—A method of synthesis was developed for 1,5,3-dithiazepan(dithiazocan)-3-ylamines and 3,3'-bi-1,5,3-dithiazepane(dithiazocane) by hydrazines cyclocondensation with formaldehyde and α,ω-alkanedithiols (1,2-ethanedithiol, 1,3-propanedithiol) involving catalysts based on *d*- and *f*-elements.

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Dithiazepanes [1, 2] and dithiazocanes [3] based on hydrazines are potential fungicides [1, 2]. The hydrazine heterocyclization with 1,2-ethanedithiol and formaldehyde depending on pH of environment and reaction temperature leads to the formation of a mixture of 1,5,3-dithiazepan-3-ylamine and 3,3'-bi-1,5,3-dithiazepane in an overall yield ~90% [1].

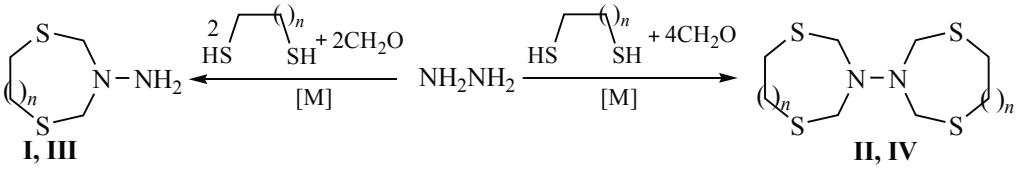
With the goal of developing a selective preparation method for *N*-substituted 1,5,3-dithiazepanes and 1,5,3-dithiazocanes and also aiming at the extension of the above method to the reactions with other substituted hydrazines and alkanedithiols we investigated the hydrazines cyclocondensation with formaldehyde and α,ω-alkanedithiols in the presence of catalysts underlain by transition and rare earth metals. The preliminary experiments showed that the reaction of hydrazine with CH_2O and 1,2-ethanedithiol at the molar ratio 1 : 2 : 1 (20°C, 2.5 h) in the presence of catalysts based on salts and complexes of Cu, Pd, Fe, Co, Sm, V, Ti, Zr, Mn led to the selective formation of 1,5,3-dithiazepan-3-ylamine (**I**) (Scheme 1).

Among the tested catalyst the highest activity was shown by Cp_2TiCl_2 in whose presence heterocycle **I** was formed in 95% yield (0.5 h, 20°C, solvent toluene) (see the table). At the ratio hydrazine–formaldehyde–1,2-ethane-dithiol 1 : 4 : 2 under the same conditions 3,3'-bi-1,5,3-dithiazepane (**II**) was formed selectively in ~100% yield.

In subsequent experiments we tried to synthesize 1,5,3-dithiazocane derivatives by the cyclocondensation of hydrazine with formaldehyde and 1,3-propanedithiol. Under the chosen conditions (0.5 h, toluene, 20°C, hydrazine–CH_2O–1,3-propanedithiol, 1 : 2 : 1) in the presence of 5 mol % of Cp_2TiCl_2 1,5,3-dithiazocan-3-ylamine (**III**) was formed in 87% yield. At the ratio hydrazine–CH_2O–1,3-propanedithiol 1 : 4 : 2 under the same conditions 3,3'-bi-1,5,3-dithiazocane (**IV**) was obtained in 80% yield. The attempts to carry out the reaction without catalyst were unsuccessful.

In the ^1H NMR spectrum of 1,5,3-dithiazocan-3-ylamine (**III**) the methylene protons SCH_2N resonate

Scheme 1.



I, III **II, IV**

n = 1 (**I**, **II**), 2 (**III**, **IV**).

The effect of catalyst nature, solvent, and reaction duration on the yield of 1,5,3-dithiazepan-3-ylamine (**I**)

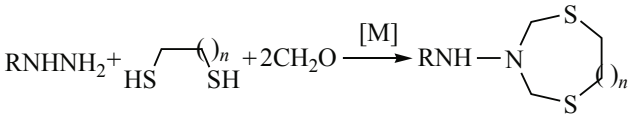
Catalyst, 5 mol %	Time, h (solvent)	Yield, %	Catalyst, 5 mol %	Time, h (solvent)	Yield, %
CuCl	0.5 (toluene)	91	Cp_2TiCl_2	0.5 (toluene)	95
CuCl	2.5 (–)	83	$Sm(NO_3)_3·6H_2O$	0.5 (toluene)	73
$CuCl_2$	0.5 (toluene)	85	$CoCl_2$	0.5 (toluene)	69
$CuCl_2$	2.5 (–)	79	Cp_2ZrCl_2	0.5 (toluene)	66
CuI	0.5 (toluene)	87	$Fe(acac)_3$	0.5 (toluene)	65
CuI	2.5 (–)	80	$Co(acac)_2$	0.5 (toluene)	64
CuBr	0.5 (toluene)	90	$MnCl_2$	0.5 (toluene)	60
CuBr	2.5 (–)	85	$VO(acac)_2$	0.5 (toluene)	50
–	0.5 (toluene)	20	$PdCl_2$	0.5 (toluene)	57

as a singlet at 4.33 ppm; a triplet at 2.73 ppm. Multiplet at 1.55–1.61 ppm correspond to the protons of the $SCH_2CH_2CH_2S$ fragment. In the ^{13}C NMR spectrum of heterocycle **III** the signals of the carbon atoms appear at 54.16, 30.29, and 26.00 ppm.

The attempts of selective thermal cyclocondensation of alkylhydrazines with formaldehyde and α,ω-alkanedithiols failed [1]. In this connection we studied this reaction in the presence of catalysts based on *d*- and *f*-elements. Methyl- and *tert*-butylhydrazines in the presence of 5 mol % of Cp_2TiCl_2 catalyst undergo the cyclocondensation with formaldehyde and 1,2-ethanedithiol (5 mol % of Cp_2TiCl_2, 0.5 h, toluene, 20°C) giving *N*-alkyl-substituted 1,5,3-dithiazepan-3-ylamines **Va, Vb** in 40 and 55% yields (Scheme 2). *N*-Methyl- and *N*-*tert*-butyl-1,5,3-dithiazepane-3-ylamines (**Va, Vb**) were obtained in higher yields at the use as catalysts of $CoCl_2$ (60 and 62%) and $Fe(acac)_3$ (59 and 63%).

By analogy with alkylhydrazines we carried out the cyclocondensation of aryl(benzyl)hydrazines with formaldehyde and 1,2-ethanedithiol (5 mol% of Cp_2TiCl_2, 0.5 h, toluene, 20°C) and obtained *N*-aryl(phenyl, 4-nitrophenyl, 2,4-nitrophenyl, 4-methylphenyl, benzyl)-1,5,3-dithiazepan-3-ylamines **Vc–Vg** in 60–77% yields. In the same conditions the cyclocondensation of methyl- and *tert*-butylhydrazines with CH_2O and 1,3-propanedithiol afforded *N*-methyl- and *N*-*tert*-butyl-1,5,3-dithiazocan-3-ylamines (**VIa, VIb**) in 53 and 49% yield respectively. In the reaction with benzyl-, phenyl-, 4-nitrophenyl-, 2,4-dinitrophenyl-, 4-methylphenylhydrazines we obtained *N*-substituted 1,5,3-dithiazocan-3-ylamines **VIc–VIg** in 59–87% yields (Scheme 2).

Scheme 2.



Va–Vg, VIa–VIg

R = CH_3 (**a**), $(CH_3)_3C$ (**b**), Ph (**c**), 4-$NO_2C_6H_4$ (**d**), 2,4-$NO_2C_6H_3$ (**e**), 4-$CH_3C_6H_4$ (**f**), $C_6H_5CH_2$ (**g**); [M] = catalyst; *n* = 1 (**V**), 2 (**VI**).

The probable mechanism of hydrazines heterocyclization in the presence of a catalyst includes a cyclocondensation of α,ω-dithiol with formaldehyde [4], the opening of the formed 1,3,7-oxadithiocane, nucleophilic addition of hydrazine to carbocation, and intramolecular cyclization furnishing the target heterocycles [5–8].

EXPERIMENTAL

The reaction progress was monitored by TLC on Silufol W-254 plates, eluent petroleum ether–EtOAc–$CHCl_3$, 5 : 1 : 1. The reaction products were analyzed by HPLC on a chromatograph Altex-330 (USA) equipped with an UV detector on the wavelength 340 nm. NMR spectra were registered on a spectrometer Bruker Avance 400 [100.62 (^{13}C) and 400.13 MHz (^{1}H)] in $CDCl_3$. GC-MS measurements were performed on instruments Finnigan 4021 (glass capillary column 50000 × 0.25 mm, stationary phase FTHP-5, carrier gas helium, ramp from 50 to 300°C at a rate 5 deg/min, vaporizer temperature 280°C, ion source temperature 250°C, EI, 70 eV) and Shimadzu QP-2010 Plus (capillary column Supelco PTE-5 30000 ×

0.25 mm). Column chromatography was performed on silica gel KSK (100–200 μm). The isolated amines **II** are oily liquids well soluble in most organic solvents. Compounds **I, II, Vc, Vg, VIa–VIg** were identified by comparing with known samples [1, 3].

1,5,3-Dithiazepan(dithiazocan)-3-ylamines, 3,3'-bi-1,5,3-dithiazepane and 3,3'-bi-1,5,3-dithiazocane. Heterocyclization of hydrazine hydrate with CH_2O and 1,2-ethanedithiol (1,3-propanedithiol). Into a Schlenk vessel placed on a magnetic stirrer was charged under an argon atmosphere 20 mmol of formaldehyde and 10 mmol of 1,2-ethanedithiol (1,3-propanedithiol) at 20°C, the mixture was stirred for 30 min, 5 mL of toluene, 0.5 mmol of an appropriate catalyst, and 10 mmol of hydrazine hydrate was added, the reaction mixture was stirred for 30 min at 20°C. The reaction products were extracted into chloroform, the extract was dried with $CaCl_2$. On distilling off the solvent the residue was chromatographed on a column.

***N*-Aryl(benzyl, alkyl)-1,5,3-dithiazepan(dithiazocan)-3-ylamines.** Heterocyclization of phenyl(benzyl, alkyl)hydrazines with CH_2O and 1,2-ethanedithiol (1,3-propanedithiol)**.** Into a Schlenk vessel placed on a magnetic stirrer was charged under an argon atmosphere 20 mmol of formaldehyde and 10 mmol of 1,2-ethanedithiol (1,3-propanedithiol) at 20°C, the mixture was stirred for 30 min, 5 ml of toluene, 0.5 mmol of catalyst, and 10 mmol of an appropriate phenyl(benzyl,alkyl)hydrazine was added, the reaction mixture was stirred for 30 min at 20°C. The reaction products were extracted into chloroform, the extract was dried with $CaCl_2$. On distilling off the solvent the residue was chromatographed on a column.

1,5,3-Dithiazocan-3-ylamine (III). Yield 87%, R_f 0.55, n_D^{20} 1.5144. ^{1}H NMR spectrum, δ, ppm: 1.55–1.61 m (2H, CH_2), 2.73 t (2H, CH_2, *J* 5.2 Hz), 3.71 s (2H, NH_2), 4.33 s (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 26.00 (C^7), 30.29 ($C^{6,8}$), 54.16 ($C^{4,2}$). Mass spectrum, *m/z* (I_{rel}, %): 164 $[M]^+$ (50), 120 $[C_4H_8S_2]^+$ (80), 73 $[N_2CH_2S]^+$ (50), 60 $[NCHS]^+$ (100), 55 $[C_2H_3N_2]^+$ (25), 27 $[NCH]^+$ (45).

3,3'-Bi-1,5,3-dithiazocane (IV). Yield 80%, R_f 0.60, n_D^{20} 1.5161. ^{1}H NMR spectrum, δ, ppm: 1.63–1.81 m (4H, CH_2), 2.45 t (4H, CH_2, *J* 6.0 Hz), 4.67 s (8H, CH_2). ^{13}C NMR spectrum, δ, ppm: 29.15 ($C^{7,13}$), 35.48 ($C^{6,8,14,12}$), 58.75 ($C^{2,4,10,16}$). Mass spectrum, *m/z* (I_{rel}, %): 296 $[M]^+$ (30), 148 $[C_5H_{10}NS_2]^+$ (70), 135 $[C_4H_9NS_2]^+$ (50), 120 $[C_4H_8S_2]^+$ (15), 60 $[NCH_2S]^+$ (80), 57 $[C_2H_4N_2]^+$ (10), 42 $[C_2H_4N]^+$ (10).

***N*-Methyl-1,5,3-dithiazepane-3-ylamine (Va)**. Yield 60%, R_f 0.58, n_D^{20} 1.5151. ^{1}H NMR spectrum, δ, ppm: 2.55 s (2H, CH_2), 3.18 c (3H, CH_3), 4.33 s (4H, CH_2). ^{13}C NMR spectrum, δ, ppm: 34.17 (C^9), 35.05 ($C^{6,7}$), 56.36 ($C^{4,2}$). Mass spectrum, *m/z* (I_{rel}, %): 164 $[M]^+$ (70), 136 $[C_3H_8N_2S_2]^+$ (10), 122 $[C_3H_7NS_2]^+$ (70), 92 $[C_2H_4S_2]^+$ (50), 45 $[CH_5N_2]^+$ (15).

***N*-*tert*-Butyl-1,5,3-dithiazepane-3-ylamine (Vb)**. Yield 62%, R_f 0.67, n_D^{20} 1.5146. ^{1}H NMR spectrum, δ, ppm: 1.13 s (9H, CH_3), 3.03 s (2H, CH_2), 4.57 s (4H, CH_2). ^{13}C NMR spectrum, δ, ppm: 30.35 (C^{10-12}), 34.98 ($C^{6,7}$), 57.00 ($C^{4,2}$), 45.76 (C^9). Mass spectrum, *m/z* (I_{rel}, %): 206 $[M]^+$ (50), 160 $[C_7H_{16}N_2S]^+$ (40), 136 $[C_3H_8N_2S_2]^+$ (50), 122 $[C_3H_7NS_2]^+$ (15), 92 $[C_2H_4S_2]^+$ (20), 45 $[CH_5N_2]^+$ (50).

***N*-(4-Nitrophenyl)-1,5,3-dithiazepane-3-ylamine (Vd)**. Yield 65%, R_f 0.59, n_D^{20} 1.5540. ^{1}H NMR spectrum, δ, ppm: 3.15 s (4H, CH_2), 4.43 s (4H, CH_2), 6.84–7.02 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 34.75 ($C^{6,7}$), 56.96 ($C^{4,2}$), 117.39 ($C^{10,14}$), 121.30 ($C^{11,12}$), 139.09 (C^{12}), 146.55 (C^9). Mass spectrum, *m/z* (I_{rel}, %): 269 $[M]^+$ (30), 225 $[C_9H_{11}N_3O_2S]^+$ (100), 92 $[C_2H_4S_2]^+$ (20), 78 $[C_6H_6]^+$ (15), 46 $[CH_2S]^+$ (65).

***N*-(2,4-Dинitrophenyl)-1,5,3-dithiazepane-3-ylamine (Ve)**. Yield 65%, R_f 0.64, n_D^{20} 1.5656. ^{1}H NMR spectrum, δ, ppm: 3.20 s (4H, CH_2), 4.38 s (4H, CH_2), 6.80–7.10 m (3H, CH). ^{13}C NMR spectrum, δ, ppm: 35.43 ($C^{6,7}$), 57.18 ($C^{4,2}$), 112.40 (C^{14}), 118.94 (C^{11}), 120.13 (C^{10}), 123.13 (C^{13}), 137.96 (C^{12}), 144.00 (C^9). Mass spectrum, *m/z* (I_{rel}, %): 316 $[M]^+$ (40), 273 $[C_9H_{11}N_4O_4S]^+$ (40), 244 $[C_7H_7N_4O_4S]^+$ (30), 92 $[CH_2SCH_2S]^+$ (100), 46 $[CH_2S]^+$ (50).

***N*-(4-Methylphenyl)-1,5,3-dithiazepane-3-ylamine (Vf)**. Yield 70%, R_f 0.66, n_D^{20} 1.5560. ^{1}H NMR spectrum, δ, ppm: 1.44 s (3H, CH_3), 3.15 s (4H, CH_2), 4.49 s (4H, CH_2), 6.87–7.25 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 26.23 (C^{15}), 34.12 ($C^{6,7}$), 58.34 ($C^{4,2}$), 114.26 ($C^{11,13}$), 121.15 ($C^{10,14}$), 145.00 (C^9), 149.77 (C^{12}). Mass spectrum, *m/z* (I_{rel}, %): 256 $[M]^+$ (70), 197 $[C_{10}H_{15}N_2S]^+$ (30), 140 $[C_7H_8NS]^+$ (15), 121 $[C_7H_9N_2]^+$ (50), 92 $[CH_2SCH_2S]^+$ (80), 46 $[CH_2S]^+$ (50).

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