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Hydrazines in the Synthesis of *N*-Substituted 1,5,3-Dithiazocan-3-amines Catalyzed by Ti and Cu Compounds

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Abstract—Efficient preparation method was developed for *N*-aryl(benzyl, alkyl)-1,5,3-dithiazocan-3-amines consisting in the transamination of 3-*tert*-butyl-1,5,3-dithiazocane with aryl(benzyl)hydrazines, and also in the reaction of N^1,N^1,N^7,N^7-tetramethyl-2,6-dithiaheptane-1,7-diamine with aryl(benzyl, alkyl)hydrazines in the presence of catalytic amounts of Ti and Cu compounds.

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Recently [1] we developed a selective method of the synthesis of *N*-aryl-1,5,3-dithiazocanes capable of exhibiting fungicidal activity [2]consisting in the transamination of 3-*tert*-butyl-1,5,3-dithiazocane with primary arylamines in the presence of Sm and Co complexes.

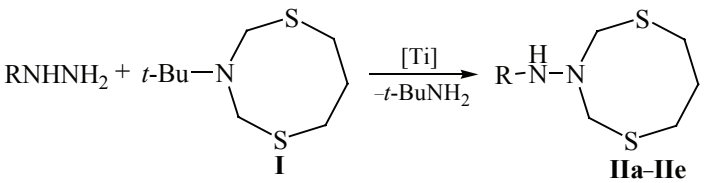
In extension of the previous research and also aiming at the efficient procedure of the synthesis of *N*-substituted 1,5,3-dithiazocan-3-amines we studied the transamination of 3-*tert*-butyl-1,5,3-dithiazocane by substituted hydrazines in the presence of catalysts based on transition metals [1]. Among the tested in this reaction catalysts based on salts and complexes of Fe, Cu, V, Pd, Co, Zr, Hf, Ti Cp_2TiCl_2 exhibited the highest activity. The initial hydrazines involved into the reaction were phenylhydrazine, 4-nitrophenylhydrazine, 2,4-dinitrophenylhydrazine, 4-methylphenylhydrazine, benzylhydrazine, methylhydrazine, and *tert*-butylhydrazine.

In the presence of catalytic quantities of Cp_2TiCl_2 the reaction of aryl(benzyl)hydrazines with 3-*tert*-butyl-1,5,3-dithiazocane (**I**) [molar ratio aryl(benzyl)-hydrazine–(**I**)–Cp_2TiCl_2 1 : 1 : 0.05, solvent acetonitrile, 20°C, 0.5 h] proceeds selectively to afford *N*-aryl(benzyl)-1,5,3-dithiazocan-3-amines **IIa–IIe** in 68–80% yields (Scheme 1).

Without catalyst the yield of compounds **IIa–IIe** was less than 40% after 24–48 h; without catalyst prevailing formation of oligomeric compounds was observed, and the yield of amines **II** did not exceed 30%.

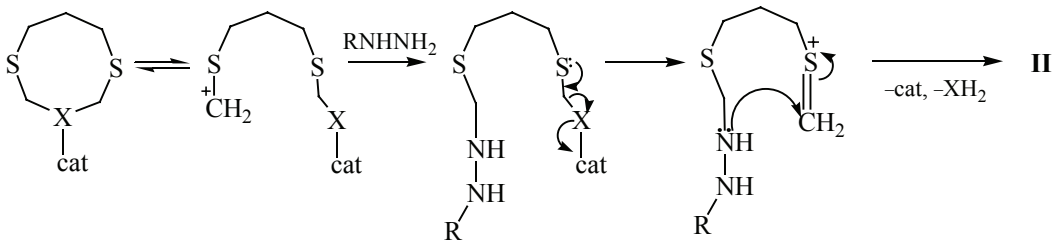
It is presumable that the catalytic transamination of 3-*tert*-butyl-1,5,3-dithiazocane (**I**) by the substituted hydrazines includes a stage of the heterocycle opening under the action of the catalyst, the nucleophilic addition

Scheme 1.

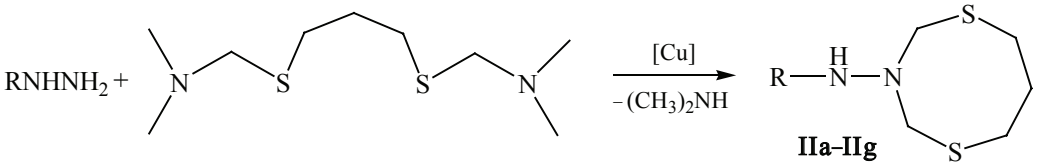


R = Ph (**a**), 4-$NO_2C_6H_4$ (**b**), 2,4-$NO_2C_6H_3$ (**c**), 4-$CH_3C_6H_4$ (**d**), $C_6H_5CH_2$ (**e**).

Scheme 2.



Scheme 3.



R = Ph (**a**), 4-$NO_2C_6H_4$ (**b**), 2,4-$NO_2C_6H_3$ (**c**), 4-$CH_3C_6H_4$ (**d**), $C_6H_5CH_2$ (**e**), CH_3 (f), $(CH_3)_3C$ (**g**).

of the hydrazine to the carbocation followed by intramolecular cyclization with the formation of *N*-substituted 1,5,3-dithiazocan-3-amine **II** (Scheme 2).

We failed to bring into the reaction under the chosen conditions the *N*-alkylhydrazines (methyl-, *tert*-butylhydrazine) for the preparation of the corresponding *N*-alkyl-substituted 1,5,3-dithiazocan-3-amines.

In order to develop the preparation procedure for *N*-alkyl-substituted 1,5,3-dithiazocan-3-amines we carried out under the catalysis with the complexes of transition metals the reaction of cyclothiomethylation of alkylhydrazines with *N*^{1},*N*^{1},*N*^{7},*N*^{7}-tetramethyl-2,6-dithiaheptane-1,7-diamine [3] similarly to the reaction of the cyclothiomethylation of carboxylic acids hydrazides [4]. In the reaction of *N*^{1},*N*^{1},*N*^{7},*N*^{7}-tetramethyl-2,6- dithiaheptane-1,7-diamine with methylhydrazine without catalyst (60°C, $CHCl_3$, 1 h) the yield of *N*-methyl-1,5,3-dithiazocan-3-amine (**IIf**) did not exceed 15%, and in the presence of 5 mol% of $CuCl_2$ the yield of amine **IIf** attained 74%. Under the developed conditions (60°C, $CHCl_3$, 5 mol% $CuCl_2$, 1 h) from *N*^{1},*N*^{1},*N*^{7},*N*^{7}-tetramethyl-2,6-dithiaheptane-1,7-diamine and *tert*-butylhydrazine we obtained *N*-*tert*-butyl-1,5,3-dithiazocan-3-amine (**IIg**) in ~70% yield.

In the subsequent experiments we applied the developed method of alkylhydrazines cyclothiomethylation with the use of *N*^{1},*N*^{1},*N*^{7},*N*^{7}-tetramethyl-2,6-dithiaheptane-1,7-diamine to the synthesis of *N*-aryl(benzyl)-1,5,3-dithiazocanes **II** and we obtained them in the yields of 79–85% (Scheme 3).

The structure of *N*-aryl(benzyl, alkyl)-1,5,3-dithiazocan-3-amines was confirmed by ^{13}C and ^1H NMR spectra and the other physicochemical methods.

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 a UV detector at the wavelength 340 nm. ^{13}C and ^1H NMR spectra were registered on a spectrometer Bruker Avance 400 (100.62 and 400.13 MHz respectively), solvent $CDCl_3$. GC-MS measurements were carried out on instruments Finnigan-4021 (glass capillary column 5000 × 0.25 mm, stationary phase HP-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, 70 eV) and Shimadzu QP-2010 Plus (capillary column Supelco PTE-5 30 m × 0.25 mm). For column chromatography silica gel KSK (100–200 μm) was utilized.

***N*-Aryl(benzyl)-1,5,3-dithiazocan-3-amines**. *a*. In a Schlenk vessel was placed 10 mmol of 3-*tert*-butyl-1,5,3-dithiazocinane [1] and 0.5 mmol of catalyst Cp_2TiCl_2, the mixture was stirred for 15–30 min, 5 ml of acetonitrile and 10 mmol of an appropriate aryl(benzyl)hydrazine, was added, the reaction mixture was stirred for 3 h at 20°C.

The reaction products were passed through a thin bed of SiO_2, the solvent was distilled off on the rotary evaporator.

b. In a Schlenk vessel was placed 10 mmol of *N*[1],*N*[1],*N*[7],*N*[7]-tetramethyl-2,6-dithiaheptane-1,7-diamine, 10 mmol of aryl(benzyl, alkyl)hydrazine, 5 ml of chloroform, 0.5 mmol of catalyst $CuCl_2$, the mixture was stirred for 1 h at 60°C. The reaction products were passed through a thin bed of SiO_2, the solvent was distilled off on the rotary evaporator. Amines **II** are brown oily fluids, well soluble in the most organic solvents .

***N*-Phenyl-1,5,3-dithiazocan-3-amine (IIa)**. Yield 71% (*a*), 79% (*b*), R_f 0.55, oily fluids. ^{1}H NMR spectrum, δ, ppm: 1.87 s (2H, CH_2), 2.80 s (2H, CH_2), 4.51 s (2H, CH_2), 6.80–7.33 m (5H, CH). ^{13}C NMR spectrum, δ, ppm: 29.01 (C[7]), 35.07 (C[6,8]), 59.74 (C[4,2]), 119.20 (C[10,14]), 120.28 (C[12]), 125.75 (C[11,13]), 145.64 (C[9]). Mass spectrum, *m/z* (I_{rel}, %): 240 $[M]^+$ (60); 147 $[C_4H_7N_2S_2]^+$ (50), 120 $[C_3H_6NS_2]^+$ (100), 106 $[C_6H_6N_2]^+$ (15), 91 $[C_6H_5N]^+$ (35), 77 $[C_6H_5]^+$ (23), 75 $[CH_3N_2S]^+$ (25), 60 $[CH_2NS]^+$ (25), 51 $[CNCN]^+$ (50), 46 $[CH_2S]^+$ (10). M_{calc} 240.39.

***N*-(4-Nitrophenyl)-1,5,3-dithiazocan-3-amine (IIb)**. Yield 68% (*a*), 83% (*b*), mp 198–200°C. ^{1}H NMR spectrum, δ, ppm: 1.74 s (2H, CH_2), 2.55 s (2H, CH_2), 4.83 s (2H, CH_2), 6.54 d (2H, CH, *J* 4 Hz), 7.02 d (2H, CH, *J* 4 Hz). ^{13}C NMR spectrum, δ, ppm: 28.92 (C[7]), 33.81 (C[6,8]), 58.66 (C[4,2]), 118.19 (C[10,14]), 122.59 (C[11,13]), 140.09 (C[12]), 147.71 (C[9]). Mass spectrum, *m/z* (I_{rel}, %): 285 $[M]^+$ (40), 198 $[C_7H_8N_3O_2S]^+$ (15), 226 $[C_9H_{12}N_3O_2S]^+$ (100), 272 $[C_{10}H_{14}N_3O_2S_2]^+$ (20), 92 $[CH_2SCH_2S]^+$ (20), 78 $[C_6H_6]^+$ (15), 46 $[CH_2S]^+$ (65). M_{calc} 285.38.

***N*-(2,4-Dinitrophenyl)-1,5,3-dithiazocan-3-amine (IIc)**. Yield 75% (*a*), 80% (*b*), mp 203–205°C. ^{1}H NMR spectrum, δ, ppm: 1.91 s (2H, CH_2), 2.70 s (2H, CH_2), 4.56 s (2H, CH_2), 6.90–7.13 m (3H, CH). ^{13}C NMR spectrum, δ, ppm: 27.50 (C[7]), 36.00 (C[6,8]), 60.10 (C[2,4]), 113.41 (C[14]), 119.24 (C[11]), 123.13 (C[12]), 139.69 (C[10]), 145.00 (C[9]). Mass spectrum, *m/z* (I_{rel}, %): 330 $[M]^+$ (40), 287 $[C_{10}H_{13}N_4O_4S]^+$ (40), 272 $[C_9H_{11}N_4O_4S]^+$ (20), 244 $[C_7H_7N_4O_4S]^+$ (50), 92 $[CH_2SCH_2S]^+$ (10), 46 $[CH_2S]^+$ (100). M_{calc} 330.39.

***N*-(4-Methylphenyl)-1,5,3-dithiazocan-3-amine (IId)**. Yield 78% (*a*), 85% (*b*), R_f 0.67, oily fluids. ^{1}H NMR spectrum, δ, ppm: 1.50 s (3H, CH_3), 2.00 s (2H, CH_2), 2.95 s (2H, CH_2), 4.69 s (2H, CH_2), 6.97–7.35 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 19.23 (C[15]), 29.32 (C[7]), 32.92 (C[6,8]), 59.43 (C[2,4]), 112.41 (C[10,14]), 119.15 (C[11,13]), 145.59 (C[9]). Mass spectrum, *m/z* (I_{rel}, %): 254 $[M]^+$ (100), 209 $[C_{11}H_{17}N_2S]^+$ (50), 152 $[C_8H_{10}NS]^+$ (30), 121 $[C_7H_9N_2]^+$ (70), 92 $[CH_2SCH_2S]^+$ (20), 46 $[CH_2S]^+$ (50). M_{calc} 254.41.

***N*-Benzyl-1,5,3-dithiazocan-3-amine (IIe).** Yield 80% (*a*), 81% (*b*), R_f 0.43, oily fluids. ^{1}H NMR spectrum, δ, ppm: 1.93 s (2H, CH_2), 2.68 s (2H, CH_2), 4.55 s (2H, CH_2), 4.69 s (2H, CH_2), 6.88–7.55 m (5H, CH). ^{13}C NMR spectrum, δ, ppm: 29.13 (C[7]), 33.69 (C[6,8]), 59.41 (C[2,4]), 69.20 (C[9]), 125.27 (C[13]), 127.92 (C[11,15]), 129.30 (C[12,14]), 143.80 (C[10]). Mass spectrum, *m/z* (I_{rel}, %): 254 $[M]^+$ (100), 182 $[C_9H_{14}N_2S]^+$ (40), 135 $[C_8H_{12}N_2]^+$ (80), 92 $[CH_2SCH_2S]^+$ (15), 46 $[CH_2S]^+$ (100). M_{calc} 254.42.

***N*-Methyl-1,5,3-dithiazocan-3-amine (IIf).** Yield 74% (*b*), R_f 0.47, oily fluids. ^{1}H NMR spectrum, δ, ppm: 1.81 s (2H, CH_2), 4.35 s (3H, CH_3), 2.43 s (2H, CH_2), 4.01 s (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 29.03 (C[7]), 37.85 (C[6,8]), 59.56 (C[2,4]), 45.24 (C[9]). Mass spectrum, *m/z* (I_{rel}, %): 178 $[M]^+$ (70), 233 $[C_5H_{13}N_2S]^+$ (20), 105 $[C_3H_9N_2S]^+$ (50), 45 $[CH_5N_2]^+$ (70). M_{calc} 178.32.

***N*-*tert*-Butyl-1,5,3-dithiazocan-3-amine (IIg)**. Yield 74% (*b*), R_f 0.53, oily fluids. ^{1}H NMR spectrum, δ, ppm: 1.13 s (9H, CH_3), 1.77 s (2H, CH_2), 2.85 s (2H, CH_2), 4.15 s (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 28.32 (C[7]), 35.44 (C[6,8]), 50.35 (C[11–13]), 58.46 (C[2,4]), 45.24 (C[10]). Mass spectrum, *m/z* (I_{rel}, %): 220 $[M]^+$ (50), 161 $[C_7H_{17}N_2S]^+$ (50), 133 $[C_5H_{13}N_2S]^+$ (70), 87 $[C_4H_{11}N_2]^+$ (100). M_{calc} 220.40.

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