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Effective Synthesis of *N*-Substituted 1,3,5-Dithiazinanes by Reactions of *N*-Methyl-1,3,5-dithiazinane and 1,3,5-Trithiane with Aromatic Amines

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Abstract—A novel procedure has been developed for selective synthesis of *N*-aryl-1,3,5-dithiazinanes, 1,2,6,7-tetrahydro-3,5,1,7-benzodithiadiazonine, and 6,7-dihydro-1,3,5,7-benzotrithiazonine by reactions of aniline derivatives with *N*-methyl-1,3,5-dithiazinane or 1,3,5-trithiane in the presence of transition and rare earth metal salts and complexes.

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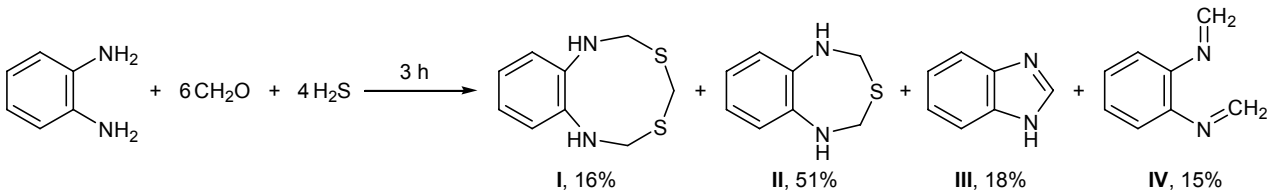
N-Substituted 1,3,5-dithiazinanes are widely used as selective sorbents for noble and rare metals [1], fungicides [2], biocides [3, 4], and food additives [5, 6]; a popular method of their synthesis is based on cyclothiomethylation of primary amines with formaldehyde–hydrogen sulfide [7]. This reaction was studied in detail with the use of various aliphatic and aromatic amines [8]. Its considerable disadvantage is the necessity of using gaseous hydrogen sulfide and aqueous formaldehyde. Moreover, most reactions are characterized by low selectivity. For example, the condensation of *o*-phenylenediamine with H_2S–CH_2O (Scheme 1) gives a mixture of compounds **I**–**IV** which are difficult to separate [9]. Analogous reaction with *m*-phenylenediamine gives rise to a mixture of various macroheterocyclic compounds, whereas *p*-phenylenediamine failed to react with H_2S–CH_2O under similar conditions [8].

With a view to develop an ecologically safe and efficient procedure for the synthesis of *N*-substituted 1,3,5-dithiazinanes we examined reactions of isomeric phenylenediamines, aminophenols, and aminobenzenethiols with *N*-methyl-1,3,5-dithiazinane and 1,3,5-trithianes as synthetic equivalents of H_2S and CH_2O. Preliminary experiments showed that, among Fe, Co, Ti, Zr, Ni, Pd, Sm, and Yb salts and complexes used as catalysts, the most efficient in the reactions of aromatic amines with *N*-methyl-1,3,5-ditihazinane were $CoCl_2$ and $Sm(NO_3)_3 \cdot 6H_2O$. Therefore, all subsequent experiments were carried out in the presence of these catalysts.

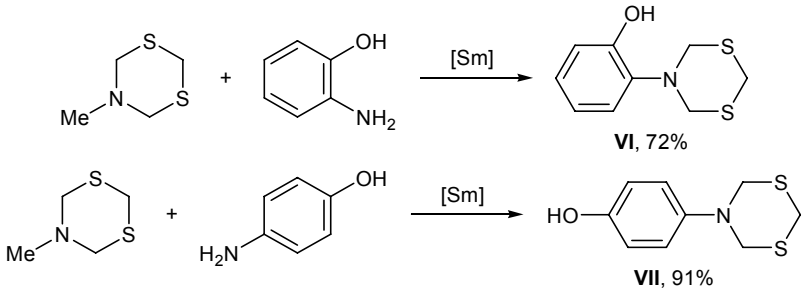
o-Phenylenediamine reacted with an equimolar amount of *N*-methyl-1,3,5-ditihazinane in the presence of 5 mol % of $CoCl_2$ ($CHCl_3$, 20°C, 3 h) to produce 1,2,6,7-tetrahydro-3,5,1,7-benzodithiadiazonine (**I**) with high selectivity (yield 75%). The reaction of *p*-phenylenediamine with *N*-methyl-1,3,5-dithiazinane, catalyzed by $Sm(NO_3)_3 \cdot 6H_2O$ (DMF, 60°C, 3 h), involved only one amino group with formation of 4-(1,3,5-dithiazinan-5-yl)aniline (**V**) in 70% yield. Analogous reaction with *m*-phenylenediamine resulted in the formation of poorly soluble substances. The

Scheme 1.

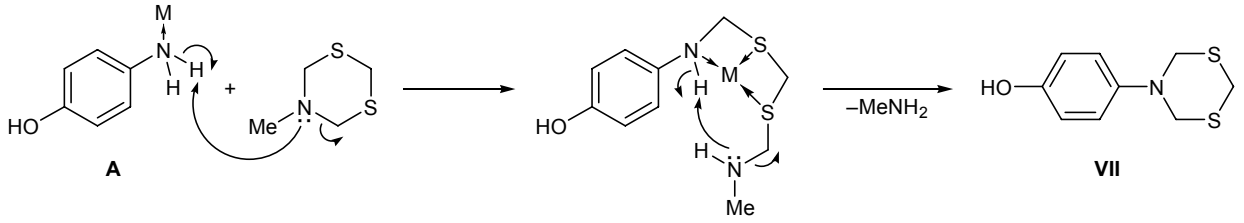


I, 16% **II**, 51% **III**, 18% **IV**, 15%

Scheme 2.



Scheme 3.



yield of heterocyclic compounds **I** and **V** in the absence of a catalyst did not exceed 10%.

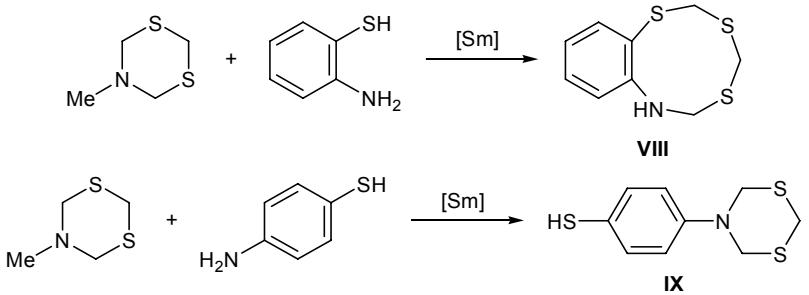
In the ^{1}H NMR spectrum of **V**, methylene protons in the 1,3,5-dithiazinane ring resonated as broadened singlets at δ 4.25 (SCH_2S) and 4.97 ppm (SCH_2N). Signals from aromatic protons were observed in the region δ 6.7–7.7 ppm. Triplet signals at δ_C 34.30 and 55.40 ppm in the ^{13}C NMR spectrum of **V** were assigned to the methylene carbon atoms in the 1,3,5-dithiazinane ring located, respectively, between two sulfur atoms and between sulfur and nitrogen atoms.

Isomeric *o*- and *p*-aminophenols reacted with *N*-methyl-1,3,5-dithiazinane in the presence of 5 mol % of $Sm(NO_3)_3\cdot 6H_2O$ (EtOH–$CHCl_3$, 60°C, 3 h) to give 2- and 4-(1,3,5-dithiazinan-5-yl)phenols **VI** and **VII** in 72 and 91% yield, respectively (Scheme 2).

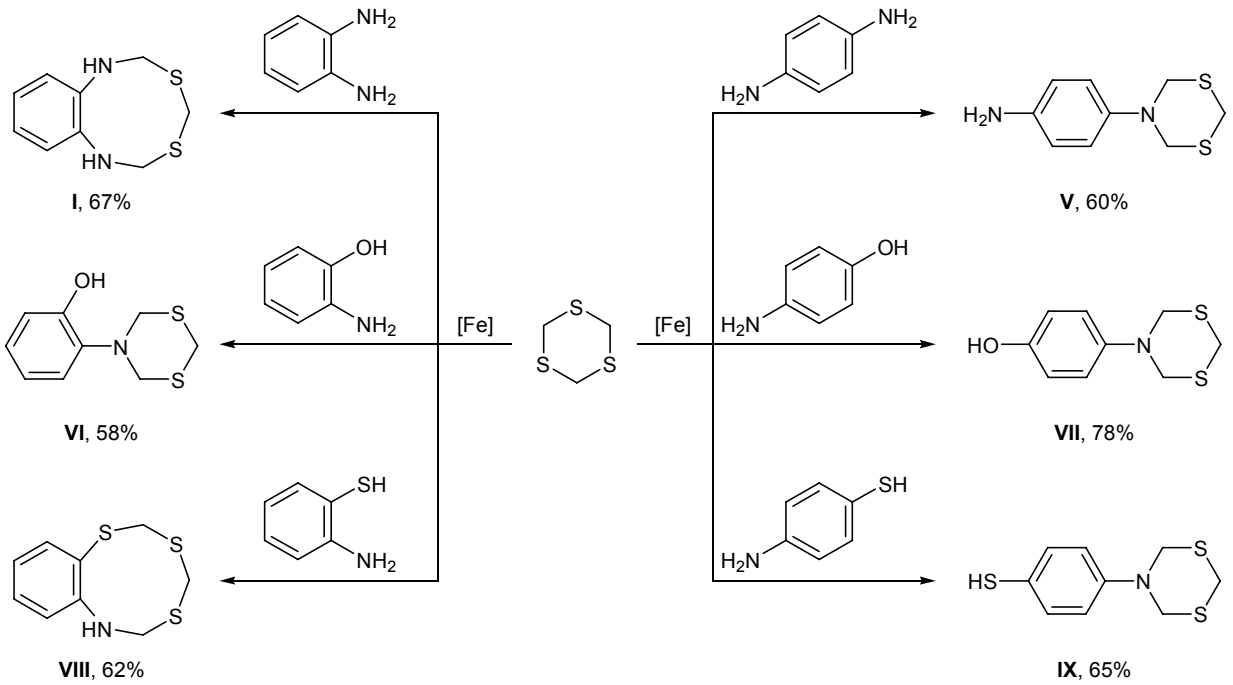
Presumably, the above reactions catalyzed by samarium complex involve coordination of the substrate to the metal ion, which enhances mobility of NH hydrogen atoms in the aromatic amine molecule and favors activation of the C–S bond in the *N*-methyl-1,3,5-dithiazinane molecule [10–12]. As a result, the reaction of *N*-methyl-1,3,5-dithiazinane with arylamine with formation of *N*-aryl-1,3,5-dithiazinane occurs more readily (Scheme 3). In fact, in the ^{13}C NMR spectra we observed upfield shift ($\Delta\delta_C$ = –0.84 ppm) of the signal from the carbon atom linked to the coordinated nitrogen atom in complex **A** relative to the corresponding signal of *p*-aminophenol. No analogous shift of the C–N carbon signal was observed in the ^{13}C NMR spectrum for *N*-methyl-1,3,5-dithiazinane.

Cyclothiomethylation of *o*- and *p*-aminophenols with H_2S–CH_2O yields 1,3,5-dithiazinanes in a mixture with 1,2,4-trithiolane [13]. Chemoselectivity of this reaction is determined by the reactant concentrations in the initial three-component mixture. Under these conditions, supply of a required amount of gaseous hydrogen sulfide is fairly difficult to control; as a result, 1,2,4-trithiolane is obtained as by-product. Likewise, 1,2,4-trithiolane is formed together with the target products in the reactions of *o*- and *p*-aminobenzenethiols with CH_2O–H_2S.

Scheme 4.



Scheme 5.



However, 6,7-dihydro-1,3,5,7-benzotrithiazonine (**VIII**) and 4-(1,3,5-dithiazinan-5-yl)benzenethiol (**IX**) were synthesized with high selectivity in 70 and 75% yield, respectively, by reactions of *o*- and *p*-aminobenzenethiols with *N*-methyl-1,3,5-dithiazinane (Scheme 4) in the presence of $Sm(NO_3)_3 \cdot 6H_2O$ as catalyst (EtOH–$CHCl_3$, 60°C, 3 h).

The IR spectrum of compound **VIII** contained an absorption band at 1580 cm^{-1} due to N–H bending vibrations in the secondary amino group, whereas no absorption at 2550–2600 cm^{-1}, typical of SH group was present. Compound **VIII** displayed in the ^1H NMR spectrum three broadened singlets with equal intensities at δ 3.86, 4.56, and 4.85 ppm due to methylene protons located between two sulfur atoms and between nitrogen and sulfur atoms, respectively. In the ^{13}C NMR spectrum of **VIII** we observed two signals at δ_C 33.10 and 50.56 ppm (SCH_2S) and one signal at δ_C 55.73 ppm (NCH_2S). Aromatic carbon nuclei resonated at δ_C 108.65, 119.98, 122.06, 125.25, 127.40, and 145.57 ppm. These findings allowed us to assign the structure of 6,7-dihydro-1,3,5,7-benzotrithiazonine to compound **VIII**.

Compound **IX** showed in the IR spectrum strong absorption bands at 720, 1100, 1600, and 2900 cm^{-1}, which correspond to stretching vibrations of the C–S, C–N, C=C_{arom}, and C–H (CH_2) bonds, and a weak band at 2600 cm^{-1}, typical of S–H bond, was present. In the ^1H NMR spectrum of **IX**, the broadened singlet at δ 4.25 ppm was assigned to protons in the methylene group linked to two sulfur atoms. Protons in the two NCH_2S groups in the dithiazinane ring gave rise to a broadened singlet at δ δ 4.93 ppm. Signals at δ_C 33.23 and 55.02 ppm in the ^{13}C NMR spectrum of **IX** originated from C^2 and C^4/C^6 in the dithiazinane ring, respectively.

Our results obtained by studying reactions of aromatic amines with *N*-methyl-1,3,5-dithiazinane, as well as the possibility for replacement of the latter by more commercially accessible 1,3,5-trithiane, stimulated our study on the reactions of 1,3,5-trithiane with isomeric phenylenediamines, aminophenols, and aminobenzenethiols in the presence of the above listed transition metal salts and complexes.

Isomeric phenylenediamines, aminophenols, and aminobenzenethiols reacted with an equimolar amount of 1,3,5-trithiane to give 1,2,6,7-tetrahydro-3,5,1,7-benzodithiadiazonine (**I**), 4-(1,3,5-dithiazinan-5-yl)-aniline (**V**), 2- and 4-(1,3,5-dithiazinan-5-yl)phenols **VI** and **VII**, 6,7-dihydro-1,3,5,7-benzotrithiazonine (**VIII**), and 4-(1,3,5-dithiazinan-5-yl)benzenethiol (**IX**) with high selectivity (Scheme 5). In these reactions, $FeCl_3 \cdot 6H_2O$ showed the highest catalytic activity. The presence of 5 mol % of that catalyst ensured 58–78% yield of heterocycles **I** and **V**–**IX** in acetonitrile at 60°C (reaction time 6 h).

Presumably, as in *N*-methyl-1,3,5-dithiazinane, the nitrogen atom in aromatic amine molecule is coordinated to the central metal ion of the catalyst ($FeCl_3 \cdot 6H_2O$), which enhances lability of the N–H bond in the initial arylamine and favors [10] hydrogen transfer from aromatic amine to activated trithiane with formation of compounds **I** and **V**–**IX** (Scheme 3).

Thus catalytic reaction of *N*-methyl-1,3,5-dithiazinane or 1,3,5-trithiane with *o*- and *p*-phenylenediamines, aminophenols, and aminobenzenethiols ensures selective preparation of N-substituted 1,3,5-dithiazinanes, 1,2,6,7-tetrahydro-3,5,1,7-benzodithiadiazonine, and 6,7-dihydro-1,3,5,7-benzotrithiazonine in high yields without using gaseous hydrogen sulfide and aqueous formaldehyde.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The mass spectrum of **V** was obtained on a Bruker Autoflex III MALDI-TOF/TOF mass spectrometer. The ^1H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ on a Bruker Avance 400 spectrometer at 400.13 and 100.62 MHz, respectively, using Bruker standard pulse sequences. The progress of reactions was monitored by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor. The products were analyzed by HPLC on an Altex-330 chromatograph (USA) equipped with a UV detector (λ 340 nm). Gas chromatographic–mass spectrometric analysis of compounds **VIII** and **IX** was performed on Finnigan 4021 (glass capillary column, 50000 × 0.25 mm, stationary phase HP-5, 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) and Shimadzu QP-2010Plus instruments (Supelco PTE-5 capillary column, 30 m × 0.25 mm). Silica gel KSK (100–200 μm) was used for column chromatography.

***N*-Methyl-1,3,5-dithiazinane.** Hydrogen sulfide (prepared by treatment of 40 mmol of sodium sulfide with hydrochloric acid) was bubbled through 60 mmol of a 37% aqueous formaldehyde solution over a period of ~30 min. A solution of 20 mmol of methylamine hydrochloride in water was then added dropwise, the mixture was stirred for 3 h at 80°C, neutralized to pH 7 with a dilute solution of sodium hydroxide, and extracted with chloroform, and the extract was evaporated. Yield 40%. ^1H NMR spectrum, δ, ppm: 2.54 br.s (3H, CH_3), 4.12 br.s (2H, 2-H), 4.42 br.s (4H, 4-H, 6-H). ^{13}C NMR spectrum, δ_C, ppm: 32.00 q (CH_3), 37.63 t (C^2), 59.38 t (C^4, C^6).

Cyclothiomethylation of aromatic amines with *N*-methyl-1,3,5-dithiazinane (*general procedure*). A Schlenk flask equipped with a magnetic stirrer was charged under argon with 11 mmol of *N*-methyl-1,3,5-dithiazinane in 5 ml of chloroform, 0.5 mmol of the catalyst [$Sm(NO_3)_3 \cdot 6H_2O$ or $CoCl_2$], and 10 mmol of the corresponding arylamine in 5 ml of $CHCl_3$, DMF, or EtOH. The mixture was stirred for 3 h at a required temperature (20 or 60°C). Compounds **I**, **VI**, and **VII** were identified by comparing with authentic samples [9, 13].

4-(1,3,5-Dithiazinan-5-yl)aniline (V). R_f 0.6 (benzene–ethanol, 9 : 1). IR spectrum, ν, cm^{-1}: 3300, 2900, 1650, 1600, 1100, 720. ^1H NMR spectrum, δ, ppm: 4.25 br.s (2H, 2-H), 4.97 br.s (4H, 4-H, 6-H), 6.70 d (2H, 8-H, 12-H), 7.70 d (2H, 9-H, 11-H). ^{13}C NMR spectrum, δ_C, ppm: 34.3 t (C^2), 55.4 t (C^4, C^6), 115.4 d (C^8, C^{12}), 116.6 d (C^9, C^{11}). Mass spectrum: *m*/*z* 213.379 $[M + H]^+$. $C_9H_{12}N_2S_2$. *M* 212.3371.

6,7-Dihydro-1,3,5,7-benzotrithiazonine (VIII). R_f 0.4 (benzene–ethyl acetate, 5 : 1). IR spectrum, ν, cm^{-1}: 3400, 2900, 1620, 1580, 1110, 720. ^1H NMR spectrum, δ, ppm: 3.86 br.s (2H, 2-H), 4.56 br.s (2H, 9-H), 4.85 br.s (2H, 4-H), 6.59–7.12 m (4H, 10-H, 11-H, 12-H, 13-H). ^{13}C NMR spectrum, δ_C, ppm: 33.10 t (C^2), 50.56 t (C^9), 55.73 t (C^4), 108.65 d (C^{10}), 119.98 d (C^{12}), 122.06 d (C^{11}), 125.25 d (C^{13}), 127.40 s (C^7), 145.57 s (C^6). Mass spectrum, *m*/*z* (I_{rel}, %): 197 (35) $[M - S]^+$, 169 (20) $[M - CH_2SCH_2]^+$, 137 (10) $[M - CH_2SCH_2S]^+$, 136 (100) $[M - CH_3SCH_2S]^+$, 109 (35) $[M - SPh]^+$. Found, %: C 47.25; H 4.90; N 6.15; S 41.70. $C_9H_{11}NS_3$. Calculated, %: C 47.12; H 4.83; N 6.11; S 41.94. *M* 229.

4-(1,3,5-Dithiazinan-5-yl)benzenethiol (IX). R_f 0.5 (chloroform–benzene–ethyl acetate, 1 : 5 : 1). IR spectrum, ν, cm^{-1}: 3300, 2900, 2600, 1600, 1100, 720. ^1H NMR spectrum, δ, ppm: 4.25 br.s (2H, 2-H), 4.93 br.s (4H, 4-H, 6-H), 6.66–7.49 m (4H, 8-H, 9-H, 11-H, 12-H). ^{13}C NMR spectrum, δ_C, ppm: 33.23 t (C^2), 55.02 t (C^4, C^6), 114.70 d (C^8, C^{12}), 118.03 d (C^9, C^{11}), 131.96 s (C^{10}), 137.72 s (C^7). Mass spectrum, *m*/*z* (I_{rel}, %): 197 (35) $[M - S]^+$, 136 (100) $[M - CH_3SCH_2S]^+$, 109 (35) $[M - SPh]^+$. Found, %: C 46.80; H 4.65; N 5.95; S 41.91. $C_9H_{11}NS_3$. Calculated, %: C 47.12; H 4.83; N 6.11; S 41.94. *M* 229.

Cyclothiomethylation of arylamines with 1,3,5-trithiane (*general procedure*). A Schlenk flask

equipped with a magnetic stirrer was charged under argon with 11 mmol of 1,3,5-trithiane, 0.5 mmol of $FeCl_3 \cdot 6H_2O$ as catalyst, and 10 mmol of the corresponding arylamine in 5 ml of acetonitrile. The mixture was stirred for 6 h at 60°C, and the products (compounds **I** and **V**–**IX**) were purified by column chromatography and identified by comparing with authentic samples [9, 13, 14].

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