Thiocarbamoylation of amine-containing compounds

6.* Reactions of tetramethylthiuram disulfide with hydrazones of aromatic aldehydes

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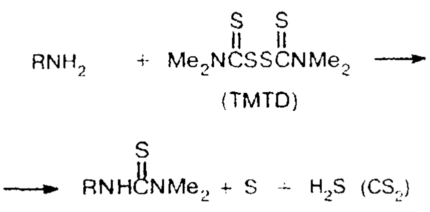
Thiocarbamoylation of hydrazones of aromatic aldehydes with tetramethylthiuram disulfide (TMTD) afforded diarylaldazines, 4,4-dimethylthiosemicarbazide, and 5-dimethylamino-1,3,4-thiadiazole-2-thiol. In addition, the reaction of TMTD with salicylaldehyde hydrazone yielded symmetrical thiocarbonyldihydrazone of salicylaldehyde, whereas the reactions with *p*-bromobenzaldehyde and *m*-nitrobenzaldehyde hydrazones afforded *p*-bromo-*N*,*N*-dimethyl- and *N*,*N*-dimethyl-*m*-nitrothiobenzamides, respectively. Possible pathways of formation of the resulting products are discussed.

Key words: tetramethylthiuram disulfide, hydrazones of aromatic aldehydes, diarylaldazines, *N*,*N*-dimethylthiosemicarbazones, 4,4-dimethylthiosemicarbazide, 5-dimethylamino-1,3,4-thiadiazole-2-thiol, *N*,*N*-dimethylthiobenzamides, thiocarbonyldihydrazone of salicylaldehyde.

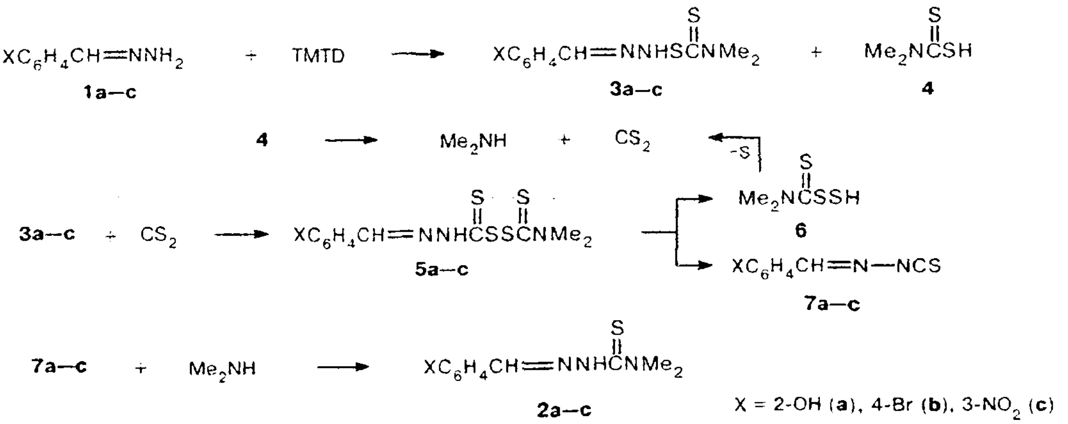
Previously,[1—7] we have demonstrated that the reactions of alkyl-, aryl-, and hetarylamines with tetramethylthiuram disulfide (TMTD) afforded *N*'-aryl(hetaryl)-*N*,*N*-dimethylthioureas (Scheme 1).

Scheme 1



These reactions can serve as a good preparative procedure for the insertion of a thiocarbonyl group into amine-containing compounds. This procedure is characterized by simplicity and high yields of the products. Thiocarbonyl compounds prepared according to this procedure serve as readily available starting material in organic synthesis. The use of arylthioureas in the synthesis of other classes of compounds, in particular, for the preparation of difficultly accessible aryl isothiocyanates, has been considered previously.[8,9] In the present work, we attempted to carry out direct thiocarbamoylation of hydrazones of aromatic aldehydes (**1a—c**) with TMTD with the aim of performing the one-stage synthesis of *N*,*N*-dimethylthiosemicarbazones of aromatic aldehydes (**2a—c**). The process would be expected to occur according to the general mechanism suggested by us previously[1,2] for the reactions of amines with TMTD (Scheme 2).

Scheme 2



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* For Part 5, see Ref. 1.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 2, pp. 343—346, February, 2000.

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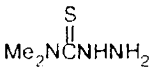
According to the suggested scheme, the reactions of hydrazones **1a—c** with TMTD should afford *N'*-(*N,N*-dimethylthiocarbamoylthio)hydrazones (**3a—c**) and dimethyldithiocarbamic acid (**4**). The latter readily decomposes to produce dimethylamine and CS_2, which can convert hydrazones **3a—c** into *N*-aminothiuram disulfides (**5a—c**) as a result of the insertion reaction. Due to the presence of the H atom at the N atom bound to the disulfide group, *N*-benzylideneaminothiuram disulfides **5a—c** can be readily converted into thiocarbohydrazones (**7a—c**). The reactions of the latter with dimethylamine should yield the final products (**2a—c**).[9]

Contrary to our expectations, the reactions of **1a—c** with TMTD taken in a ratio of 1 : 1 afforded azines (**8a—c**), 4,4-dimethylthiosemicarbazide (**9**), and 5-dimethylamino-1,3,4-thiadiazole-2-thiol (**10**) as the final products. In the case of hydrazone **1a**, thiocarbonyldihydrazone of salicylaldehyde (**11**) was formed along with the above-mentioned products. The reactions with hydrazones **1b,c** gave *p*-bromo-*N,N*-dimethylthiobenzamide and *N,N*-dimethyl-*m*-nitrothiobenzamide (**12b** and **12c**, respectively). Note that when the reagents were taken in an equimolar ratio, small amounts of carbon disulfide and dimethylammonium dimethyldithiocarbamate were additionally obtained.

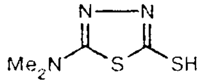
$XC_6H_4—CH=N—N=CH—C_6H_4X$

8a—c



$Me_2N\overset{S}{\overset{\|}{C}}NHNH_2$

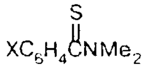
9



10

$(2\text{-}HOC_6H_4—CH=NNH)_2C=S$

11



$XC_6H_4\overset{S}{\overset{\|}{C}}NMe_2$

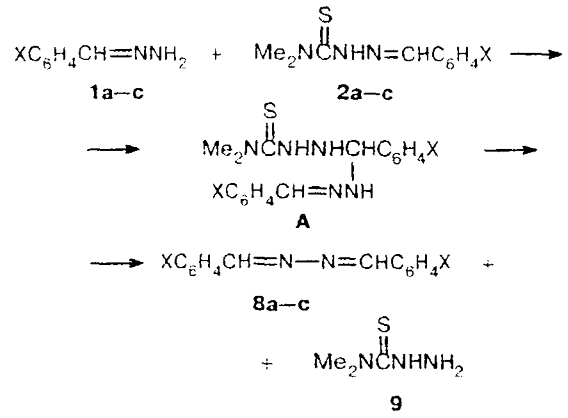
12b,c

TLC control demonstrated that the desired thiosemicarbazones **2a—c** were also formed. The absence of these compounds in the mixture of the products is attributable to the fact that they entered into the nucleophilic addition reactions with hydrazones **1a—c** to give intermediates (**A**). Under the reaction conditions, the latter decomposed to give azines **8a—c** and thiosemicarbazide **9**. Analogous reactions were described in the literature[10] (Scheme 3).

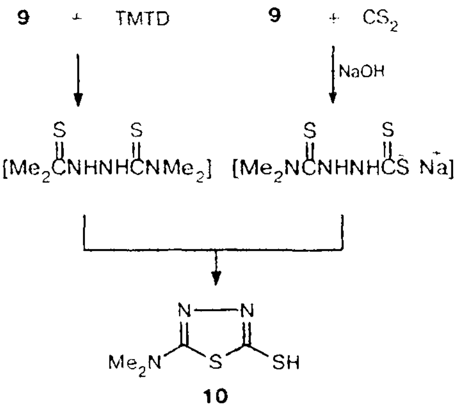
It is not inconceivable that intermediates **A** were also formed as a result of thiocarbamoylation of condensation products of two molecules of hydrazones **1a—c** [10] with TMTD, which was present in the mixture.

According to Scheme 3, the amount of the resulting compounds **8a—c** and **9** should correspond to the stoichiometric ratio (1 : 1). However, the yield of 4,4-dimethylthiosemicarbazide **9** (~4%) does not correlate with the yields of azines **8a—c** (75%). Apparently, compound **9** undergoes further conversion in the reaction with TMTD or carbon disulfide, which is a decomposition product of dithiocarbamic acid **4** (see Scheme 2). This conversion affords 5-dimethylamino-1,3,4-thiadiazole-2-thiol **10**. The reaction of thiosemicarbazide **9** with carbon disulfide is known as one of the classical procedures[11] for the preparation of derivatives of thiadiazole **10**. We confirmed the formation of the latter in the reaction of compound **9** with TMTD by independent synthesis (Scheme 4).

Scheme 3



Scheme 4



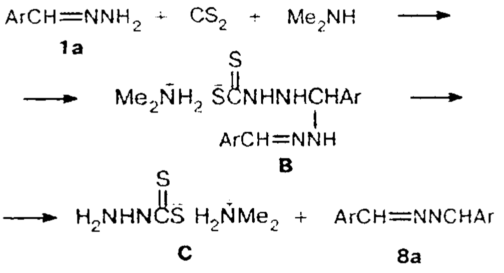
When the reagents were taken in equimolar ratio, TMTD was virtually completely consumed. On this basis, the yield of sulfur should correlate with the yields of azines **8a—c** (~75%). However, the amount of sulfur eliminated was only ~60% of the theoretical value. Consequently, azines **8a—c** were also formed in other processes without elimination of sulfur. One such process may involve the reaction of two molecules of hydrazones **1a—c** in the presence of carbon disulfide and dimethylamine. This suggestion was confirmed by independent synthesis, *viz*., by mixing of the latter compounds with hydrazone **1a** in a molar ratio of 1 : 1 : 1. Heating in anhydrous dioxane afforded compounds **8a** and **10** in 78 and 31% yields, respectively (Scheme 5). Apparently, the reaction of hydrazone **1a** with CS_2 and dimethylamine, like the reactions with primary amines, initially afforded an intermediate (**B**), which was decomposed upon heating to produce azine **8a** and a salt (**C**).

Table 1. Reaction products of TMTD with hydrazones **1a—c** and their physicochemical characteristics

Hydrazone	Ratio TMTD : **1**	*T* /°C	*t* /h	Product	Yield (%)	M.p. /°C	Found/Calculated (%) C	H	N	Molecular formula	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
1a	1 : 1	80	1	**8a**	75	214—215 (213—214)[18]					6.95 (m, Ar); 7.45 (m, Ar); 7.75 (s, CH)
				10	30	176—177					
				11a	24	204—206	57.48 57.31	4.56 4.49	17.93 17.82	$C_{15}H_{14}N_4O_2S$	7.05 (m, Ar); 7.90 (s, =CH); 8.55 (br.s, NH); 11.85 (br.s, OH)
1b	1 : 1	80	1	**8b**	22	209—210 (209.5—210)[19]					7.40 (d, Ar, *J* = 11.2); 8.00 (d, Ar, *J* = 11.2); 8.55 (s, =CH)
				10	25	176—177					
				12b	21	123—124	45.07 44.28	4.27 4.13	5.43 5.74	$C_9H_{10}BrNS$	3.17 (s, 3 H, Me); 3.51 (s, 3 H, Me); 7.46 (d, 2 H, Ar, *J* = 11.5); 8.05 (d, 2 H, Ar, *J* = 11.5)
1c	1 : 1	80	1	**8c**	13	191—193 (193)[17]					7.80 (m, Ar); 8.30 (m, Ar); 8.75 (s, Ar); 8.89 (s, =CH)
				10	19	176—177					
				12c	57	131—132	52.14 51.41	4.92 4.79	13.67 13.32	$C_9H_{10}N_2O_2S$	3.19 (s, 3 H, Me); 3.56 (s, 3 H, Me); 7.94 (m, 4 H, Ar)
1a	1 : 2	60—95	3	**8a**	40	214—215					
				10	10	176—177					
				11a	18	204—206					
1b	1 : 2	60—95	3	**8b**	23	209.5—210					
				10	12	176—178					
				12b	13	123—124					
1c	1 : 2	60—95	3	**8c**	7	191—193					
				10	3	176—177					3.06* (s, 6 H, Me_2N); 11.3* (s, 1 H, =N—SH)
				12c	36	131—132					

* In $CDCl_3$.

Scheme 5


$ArCH{=}NNH_2 + CS_2 + Me_2NH \longrightarrow Me_2\overset{+}{N}H_2\ \overset{-}{S}\overset{S}{\overset{\|}{C}}NHNHCHAr(ArCH{=}NNH) \longrightarrow H_2NHN\overset{S}{\overset{\|}{C}}\overset{-}{S}\ H_2\overset{+}{N}Me_2 + ArCH{=}NNCHAr$

The conversion of salt **C** into thiosemicarbazide **9** and then into **10** proceeded analogously to Schemes 3 and 4.

The suggestions as to the pathways of formation of azines **8a—c** are also confirmed by the fact that hydrazone **1c** possesses low basicity, as result of which it reacts difficultly with carbon disulfide, its reaction with thiosemicarbazide **2c** is hindered, and the yield of 3,3′-dinitrobenzaldazine **8c** is no higher than 12%.

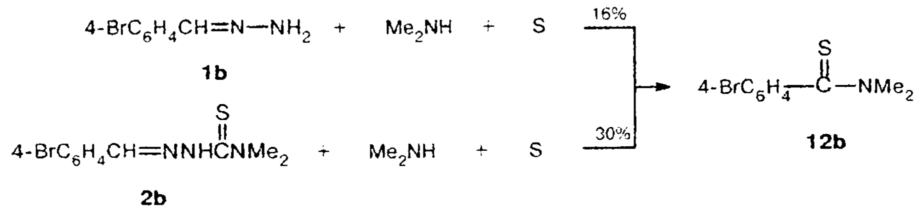
Apparently, thiocarbonylhydrazone **11** was formed as a result of condensation of hydrazone **1a** with intermediate isothiocyanate **7a**.

Evidently, thioamides **12b,c** were formed as a result of the reactions of hydrazones **1b,c** or thiosemicarbazides **2b,c** with the available sulfur and dimethylamine according to a reaction of the Willgerodt—Kindler type.[12] This suggestion was confirmed by the results of independent synthesis. Thus heating of equimolar amounts of hydrazone **1b** (or thiosemicarbazone **2b**), sulfur, and dimethylamine in dioxane afforded thioamides **12b** in 16% (30%) yield (Scheme 6) (see the Experimental section).

Experimental

The ^{1}H NMR spectra were recorded on a Bruker AM-250 instrument. The chemical shifts were measured relative to Me_4Si. TLC was carried out on Silufol UV-254 plates; the

Scheme 6


$4\text{-}BrC_6H_4CH{=}N{-}NH_2 + Me_2NH + S \xrightarrow{16\%} 4\text{-}BrC_6H_4{-}\overset{S}{\overset{\|}{C}}{-}NMe_2$

$4\text{-}BrC_6H_4CH{=}NNH\overset{S}{\overset{\|}{C}}NMe_2 + Me_2NH + S \xrightarrow{30\%} 4\text{-}BrC_6H_4{-}\overset{S}{\overset{\|}{C}}{-}NMe_2$

spots were visualized with UV light. The mass spectra were obtained on an INCOS-50 instrument (EI, 70 eV).

A sample of TMTD was recrystallized from $CHCl_3$, m.p. 154—156 °C (*cf.* the literature data[13]: m.p. 156 °C).

We used freshly prepared hydrazones* **1a—c**, which were synthesized from the corresponding aromatic aldehydes according to procedures reported previously.[15,16] Their purity was checked by chromatography on Silufol plates. **1a**, m.p. 95—96 °C (*cf.* the literature data[15]: m.p. 96 °C); **1b**, m.p. 71—72 °C; **1c**, m.p. 107—108 °C (*cf.* the literature data[16]: m.p. 107 °C).

Reactions of TMTD with hydrazones 1a—c. *A.* A solution of hydrazone **1a** (1.36 g, 10 mmol) and TMTD (2.40 g, 10 mmol) in anhydrous dioxane (4 mL) was heated at 80 °C for 1 h. The solvent was distilled off (carbon disulfide was distilled off together with the solvent) and the residue was washed with water, dried, and chromatographed on a column with silica gel. Salicylaldazine **8a** was eluted with a 1 : 2 benzene—hexane mixture in a yield of 0.90 g (75%). Traces of TMTD were eluted with benzene. Thiocarbonyldihydrazone **11** and thiadiazole **10** were eluted with 9 : 1 and 1 : 1 benzene—acetone mixtures in yields of 0.37 g (23.6%) and 0.48 g (29.8%), respectively.

Salicylaldehyde *N,N*-dimethylthiosemicarbazone **2a** was synthesized from salicylaldehyde and *N,N*-dimethylthiosemicarbazide, m.p. 198—199 °C (*cf.* the literature data[17]: m.p. 199—200 °C).

The reactions with hydrazones **1b,c** were carried out analogously.

B. A solution of hydrazone **1a** (1.36 g, 10 mmol) and TMTD (1.20 g, 5 mmol) in anhydrous dioxane (4 mL) was heated at 60 °C for 1 h and then on a boiling water bath for 2 h. After removal of the solvent, the residue was worked up as described in procedure *A*.

The yields and selected physicochemical characteristics of the synthesized compounds are given in Table 1.

5-Dimethylamino-1,3,4-thiadiazole-2-thiol (10). A solution of 4,4-dimethylthiosemicarbazide hydrochloride **9** (0.62 g, 4 mmol), TMTD (0.96 g, 4 mmol), and KOH (0.23 g) in EtOH (4 mL) was heated at 90 °C for 2 h. After removal of the solvent, the residue was shaken with an aqueous solution of KOH (0.22 g, 4 mL). The precipitate was filtered off. The filtrate was acidified with AcOH and the precipitate that formed was filtered off. Thiadiazole **10** was obtained in a yield of 0.54 g (85%), R_f 0.31 (benzene—ethyl acetate mixture, 4 : 1), m.p. 176—177 °C.

Reaction of hydrazone 1a with CS_2 and Me_2NH. A solution of hydrazone **1a** (1.36 g, 10 mmol), CS_2 (0.83 g, 11 mmol), and Me_2NH (0.5 g, 11 mmol) in anhydrous dioxane (4 mL) was heated at 80 °C for 3 h. After cooling, the precipitate that formed was filtered off. Azine **8a** was obtained in a yield of 0.93 g (78%), m.p. 214—215 °C.

After evaporation of the solvent, thiadiazole **10** was isolated from the filtrate in a yield of 0.5 g (31%), m.p. 176—177 °C.

Reaction of hydrazone 1b with S and Me_2NH. A mixture of hydrazone **1b** (10 mmol), S (10 mg-at.), and Me_2NH (15 mmol) in anhydrous dioxane (6 mL) was heated in a sealed tube on a boiling water bath for 1.5 h. Unconsumed sulfur was filtered off and the filtrate was cooled. The precipitate that formed was worked up as described above. Compound **12b** was obtained in a yield of 0.39 g (~16%).

The reaction with thiosemicarbazone **2b** was performed analogously. Compound **12b** was obtained in a yield of 0.73 g (~30%).

We thank N. N. Makhova and O. V. Lebedev for assistance in studies and helpful discussion.

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Received June 28, 1999;
in revised form August 26, 1999

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* Recently,[14] a convenient procedure for the preparation of hydrazones of aromatic ketones and aldehydes was described.