Reactions of trichloromethylarenes with hydrazine derivatives. Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles

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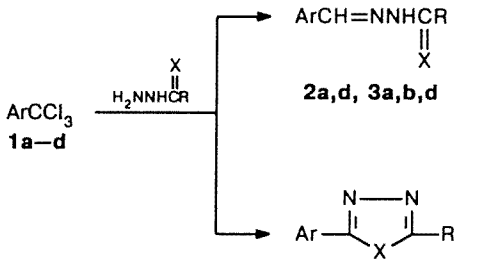
The effect of the solvent on the course of the reaction between trichloromethylarenes and thioacylhydrazines or acylhydrazines has been considered. In alcohols as solvents, alkyl arenecarboxylates form as a result of alcoholysis, while 2,5-disubstituted 1,3,4-thiadiazoles (1,3,4-oxadiazoles) form as minor products. In pyridine solutions, the major or sole products are those of reductive condensation, *i.e.*, the corresponding *N*-substituted hydrazones of arenecarbaldehydes. 1,3,4-Thiadiazole or 1,3,4-oxadiazole derivatives are obtained in good yield when the reaction is carried out in a pyridine—alkanol mixture.

Key words: trichloromethylarenes; acylhydrazines; thioacylhydrazines; 1,3,4-oxadiazoles; 1,3,4-thiadiazoles.

Recently we have found that, in the interaction of trichloromethylarenes (TCMA) with hydrazines or hydroxylamine in pyridine solution, an unusual reductive condensation takes place that leads to derivatives of the respective aldehydes, *i.e.*, aldazines, hydrazones and oximes as well as nitriles (the latter being formed by dehydration of the oximes under the reaction conditions).[1,2] Hydroxylamine or hydrazines were supposed by us to be true reducing reagents. The same role was given by the authors of Ref. 3 to thiosemicarbazide in the transformation of 4-trichloromethylpyridine into 4-pyridinecarbaldehyde thiosemicarbazone, which took place upon prolonged refluxing in pyridine solution and was probably the first known example of the reductive condensation.

Later it was found that the actual reducing agent in the reductive condensation is not hydroxylamine or hydrazines, but pyridine[4] (we considered the reaction mechanism previously[5]). In the context of this paper it is important to note that reactions of benzotrichloride with hydroxylamine and hydrazine yielded not only products of reductive condensation, but also, in low yields, 3,5-diphenyl-1,2,4-oxadiazole and 2,5-diphenyl-1,3,4-oxadiazole, respectively, which don't require reduction to form.

Scheme 1



1—7: Ar = Ph (**a**), 2,4-$Me_2C_6H_3$ (**b**), 2,4,5-$Me_3C_6H_2$ (**c**), 2,4,6-$Me_3C_6H_2$ (**d**)

2, 4: X = O, R = NH_2

3, 6: X = S, R = NH_2

5: Ar = 2,4,5-$Me_3C_6H_2$, X = O, R = 2-HOC_6H_4

7: X = S, R = Ph

Results and Discussion

The aim of this work was the investigation of factors controlling preferential realization of one of the competing reactions (Scheme 1) of TCMAs **1a—d**, *i.e.*, reductive condensation, leading to products of the types **2** and **3**, or heterocyclization with the formation of substituted 1,3,4-oxadiazoles **4, 5** and 1,3,4-thiadiazoles **6, 7**.

As became evident[6] 2,5-diaryl-1,3,4-oxadiazoles are obtained in very low yields (<20 %) when their preparation is carried out in alcohol solutions in the presence of sodium carbonate, *i.e.*, under conditions offered in Ref. 7. We failed also to prepare 2-amino-5-phenyl-1,3,4-thiadiazole (**6a**) from benzotrichloride and thiosemi-

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Table 1. Effect of solvent on yields of products (R = NH_2) of reductive condensation (**2, 3**) and heterocyclization (**4, 5**)

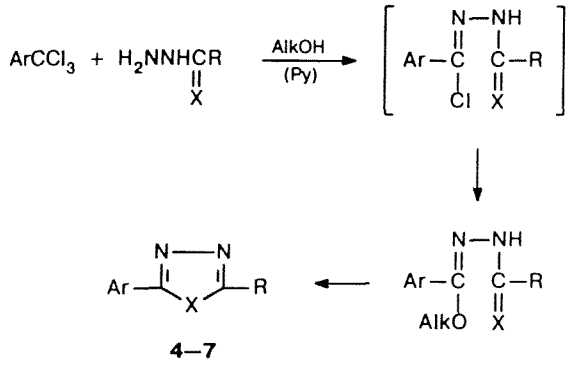
TCMA	Ar	X	Yield (%)			
			in Py		in MeOH—Py	
			2, 3	**4, 6**	**2, 3**	**4, 6**
1a	Ph	O	16	26	—	63
1d	2,4,6-$Me_3C_6H_2$	O	78	—	60	—
1a	Ph	S	10	30	—	60
1b	2,4-$Me_2C_6H_3$	S	18	15	5	30
1d	2,4,6-$Me_3C_6H_2$	S	70	—	55	—

carbazide in ethanol in the presence of sodium carbonate according to Ref. 8, whereas using methanol as the solvent isolated product **6a** in ~5 % yield. Similar results were obtained using morpholine or piperidine as bases in methanol solution in the reaction of 2,4,5-trimethylbenzotrichloride with 2-hydroxybenzhydrazide: the yields of the respective diaryl-1,3,4-oxadiazole **5** varied in the range of 10—20 %. In all cases the main products were the corresponding alkyl benzoates. Proceeding the heterocyclization of TCMAs with acylhydrazines in triethylamine in the absence of an alcohol,[6] the desired 2,5-disubstituted 1,3,4-oxadiazoles were also isolated in low yields.

When pyridine was used as a solvent in reactions with semicarbazide or thiosemicarbazide, semicarbazones **2** and thiosemicarbazones **3** were obtained in pronounced quantities or even turned out to be practically the only products, whereas the yields of 2-amino-5-aryl-1,3,4-oxadiazoles **4** or respective thiadiazoles **5** were low or negligible (Table 1). Taking into account the fact that the use of methanol—pyridine or ethanol—pyridine mixtures as solvents made it possible to transform TCMAs **1a—c** to 2,5-diaryl-, 5-alkyl-2-aryl-, and 5-aryl-2-hetaryl-1,3,4-oxadiazoles in 65—95 % yields,[6] we extended the procedure to the synthesis of 2-amino-5-aryl-1,3,4-oxa- and -thiadiazoles, as well as 2,5-diaryl-1,3,4-thiadiazoles.

In interaction of TCMAs **1a,b** with semicarbazide or thiosemicarbazide in a methanol—pyridine mixture, 2-amino-5-aryl-1,3,4-oxadiazoles **4** or 2-amino-5-aryl-1,3,4-thiadiazoles **6** were obtained, respectively. Under similar conditions TCMAs **1a** and **1b** were transformed to diaryl-1,3,4-thiadiazoles **7** in 50—65 % yields (see Scheme 1) after they reacted with thiobenzhydrazide, the latter being prepared from benzotrichloride analogously to the procedure given in Ref. 3.

Scheme 2



4—7

The only exception is the behavior of *o,o'*-disubstituted TCMA's, which readily undergo both alcoholysis and reductive condensation. Thus, in the case of mesitotrichloride **1d** the only products isolated were those of the latter reaction (see Table 1).

The probable mechanism of heterocyclization is presented in Scheme 2, TCMA possibly being activated by the formation of pyridinium salt.

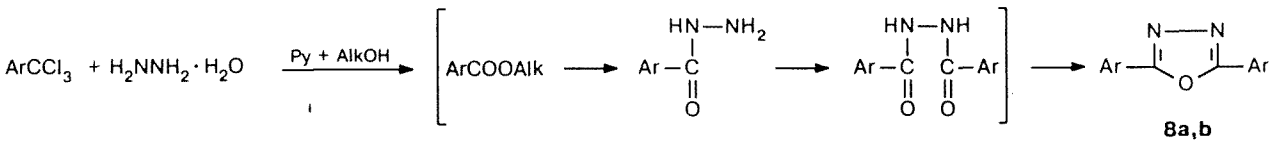
We also studied the reaction of TCMAs with hydrazine hydrate in a pyridine—methanol mixture. Symmetrically substituted 2,5-diaryl-1,3,4-oxadiazoles **8a,b** were obtained, although in low yields (~20 %). The mechanism of the reaction can involve as the first step the interaction of TCMA with hydrazine hydrate, to give the corresponding hydrazonoyl chloride (cf. Ref. 2). However, the isolation of methyl benzoate and benzhydrazide from the reaction mixture allow an alternative mechanism to be supposed as more probable: 1) hydrazine-catalyzed alcoholysis of TCMA with the formation of alkyl benzoate; 2) transformation of the latter to aroylhydrazine; 3) the interaction of aroylhydrazine with unreacted TCMA (Scheme 3).

To conclude, transformations described above make a good basis for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles starting from available trichloromethylarenes and acyl- or thioacylhydrazines, respectively.

Experimental

The ^1H NMR spectra were recorded on a Bruker WM-250 radiospectrometer (250 MHz) in $CDCl_3$ and DMSO-d_6. The mass spectra were obtained on a Varian MAT CH-6 instrument

Scheme 3



8a,b

Ar = Ph (**a**), 2,4-$Me_2C_6H_3$ (**b**)

with direct introduction of the sample into the ionic source, using an ionizing voltage of 70 eV and an emission current of 0.1 mA. The melting points were measured on a Boetius microscope stage and were not corrected.

Commercial samples of benzotrichloride (**1a**), semicarbazide, thiosemicarbazide, and hydrazine hydrate were used. 2-Hydroxybenzhydrazide, as in Ref. 6, was obtained by interaction of ethyl salicylate with hydrazine hydrate. 2,4-Dimethylbenzotrichloride (**1b**) and 2,4,5-trimethylbenzotrichloride (**1c**) were obtained by electrophilic trichloromethylation, as described in Ref. 9.[1] 2,4,6-Trimethylbenzotrichloride (**1d**) was prepared in a similar way according to Ref. 10.[1]

Thiobenzhydrazide. Benzotrichloride **1a** (13.9 mL, 0.1 mol) was added dropwise with stirring to a solution of sodium hydrosulfide (22.4 g, 0.4 mol) in ethanol (100 mL). The resulting mixture was boiled 10 h, the precipitate of sodium chloride was filtered off, the filtrate was partially evaporated, 70 mL of water and 70 mL of chloroform were added, the mixture was stirred vigorously, the aqueous layer was separated and evaporated *in vacuo*, and the residue was dried in a dessicator over P_2O_5. The resulting sodium dithiobenzoate was dissolved in 50 % ethanol (80 mL), and hydrazine hydrate (10 mL, 0.2 mol) was added to the solution. The mixture was boiled for 9 h, the solvent was removed on a rotary evaporator, methanol (30 mL) was added, the solvent was evaporated, the residue was dissolved in a minimal quantity of water, and the aqueous solution was acidified with hydrochloric acid to pH 4.5—5.0, filtered and evaporated *in vacuo*. The residue was recrystallized twice from ethanol to give thiobenzhydrazide (10.65 g, 70 %), m.p. 72—73 °C (*cf.* Ref. 11).

Reaction of 2,4,5-trimethylbenzotrichloride 1c with 2-hydroxybenzhydrazide. Trichloride **1c** (0.70 g, 2.95 mmol) was added to the solution of salicylhydrazide (0.45 g, 2.95 mmol) in 6 mL of methanol and 1 mL of morpholine. The mixture was boiled for 6 h, after cooling and partial evaporation 2-(2-hydroxyphenyl)-5-(2,4,5-trimethylphenyl)-1,3,4-oxadiazole (0.18 g, 22 %) was filtered off, m.p. 164—166 °C (*cf.* Ref. 6), from the filtrate methyl 2,4,5-trimethylbenzoate (0.29 g, 56 %), n_D^{20} 1.5040 (*cf.* Ref. 12), was obtained. An analogous experiment with piperidine instead of morpholine gave the same products and yields 12 % and 63 %, respectively.

Reaction of trichloromethylarenes 1a,d with semicarbazide hydrochloride. Trichloride **1a** or **1d** (7 mmol) was added to the suspension of semicarbazide hydrochloride (14 mmol) in 10 mL of pyridine or methanol—pyridine (1 : 1) solution. The mixture was boiled for 3—7 h, cooled, the precipitate (2-amino-5-aryl-1,3,4-oxadiazole **4**) was filtered off and recrystallized from ethanol. After partial evaporation, the corresponding substituted benzaldehyde semicarbazone **2** was precipitated from the filtrate, then filtered off and recrystallized. The yields of products **2** and **4** are presented in Table 1. **2-Amino-5-phenyl-1,3,4-oxadiazole (4a)**, m.p. 241—243 °C (*cf.* Ref. 13), $[M]^+$ 161. **Benzaldehyde semicarbazone (2a)**, m.p. 220—222 °C (*cf.* Ref. 14), $[M]^+$ 163. **2,4,6-Trimethylbenzaldehyde semicarbazone (2d)**, m.p. 184—186 °C (*cf.* Ref. 15).

Reaction of trichloromethylarenes 1a,b,d with thiosemicarbazide hydrochloride. *A.* In conditions similar to that of preceding experiment from trichlorides **1a**, **1b** or **1d** (3.5 mmol), thiosemicarbazide (3.5 mmol) in 10 mL of pyridine or in 10 mL of pyridine and 1.7 mL of methanol after 8—15 h boiling 2-amino-5-aryl-1,3,4-thiadiazoles **6** and respective substituted benzaldehyde thiosemicarbazones **3** were obtained. The yields of products **3** and **6** are presented in Table 1. **2-Amino-5-phenyl-1,3,4-thiadiazole (6a)**, m.p. 221—223 °C (*cf.* Ref. 3), $[M]^+$ 177. **Benzaldehyde thiosemicarbazone (3a)**, m.p. 160—162 °C (*cf.* Ref. 16), $[M]^+$ 179. **2-Amino-5-(2,4-dimethylphenyl)-1,3,4-thiadiazole (6b)**, m.p. 182—184 °C, $[M]^+$ 205. ^{1}H NMR (DMSO-d_6), δ: 2.31 (s, 3 H, 4-Me); 2.40 (s, 3 H, 2-Me); 7.12 (br.d, 1 H, H(5)); 7.16 (br.s, 1 H, H(3)); 7.48 (d, 1 H, H(6), J = 8.2 Hz); 13.52 and 13.63 (br.s, 2 H, NH). **2,4-Dimethylbenzaldehyde thiosemicarbazone (3b)**, m.p. 208—210 °C, (*cf.* Ref. 17), $[M]^+$ 207. ^{1}H NMR (DMSO-d_6), δ: 2.26 (s, 3 H, 4-Me); 2.33 (s, 3 H, 2-Me); 7.02 (br.s, 1 H, H(3)); 7.03 (br.d, 1 H, H(5)); 7.83 (br.s, 1 H, NH); 7.92 (d, 1 H, H(6) , J = 8.2 Hz); 8.16 (br.s, 1 H, NH); 8.35 (s, 1 H, CH=N); 11.28 (s, 1 H, NHN). **2,4,6-Trimethylbenzaldehyde thiosemicarbazone (3d)**, m.p. 231—232 °C (*cf.* Ref. 18), $[M]^+$ 221. ^{1}H NMR (DMSO-d_6), δ: 2.22 (s, 3 H, 4-Me); 2.35 (s, 6 H, 2- and 6-Me); 6.88 (s, 2 H, H(3), H(5)); 7.33 (br.s, 1 H, NH); 8.16 (br.s, 1 H, NH); 8.43 (s, 1 H, CH=N); 11.28 (s, 1 H, NHN).

B. The mixture of benzotrichloride **1a** (2.8 mL, 20 mmol), thiosemicarbazide (1.82 g, 20 mmol), and anhydrous Na_2CO_3 (4.14 g, 4 mmol) in 30 mL of methanol was refluxed for 6 h. The precipitate resulting from cooling was filtered off and washed with methanol (the residue, a mixture of sodium carbonate and chloride, 3.13 g). The filtrate was evaporated, the residual oily crystals were treated with chloroform, then a mixture (0.75 g) of inorganic salts with thiosemicarbazide was filtered off, the latter (0.1 g, m.p. 180—182 °C) being isolated after washing the precipitate with water. Evaporation of the chloroform solution gave the product **6a**, (0.2 g, yield 5.6 %) m.p. 223—227 °C.

Reactions of trichloromethylarenes 1a,b with thiobenzhydrazide. Trichloride **1a** or **1b** (4.6 mmol) was added to the solution of thiobenzhydrazide (4.6 mmol) in 5 mL of methanol and 1.5 mL of dry pyridine. The mixture was boiled for 8—10 h, partially evaporated, cooled, the precipitate was filtered off, washed with aqueous ethanol and recrystallized from ethanol. From the mother liquor, after evaporation and crystallization of the residue an additional amount of the product **7a** or **7b** was obtained. **2,5-Diphenyl-1,3,4-thiadiazole (7a)**, yield 65 %, m.p. 140—143 °C (*cf.* Ref. 19). **2-(2,4-Dimethylphenyl)-5-phenyl-1,3,4-thiadiazole (7b)**, yield 50 %, m.p. 106—108 °C, $[M]^+$ 266. ^{1}H NMR ($CDCl_3$), δ: 2.35 (s, 3 H, 4-Me); 2.70 (s, 3 H, 2-Me); 7.10 (d, 1 H, 5-H); 7.12 (s, 1 H, H(3)); 7.49 (m, 3 H, H(3), H(4), H(5) Ph); 7.82 (d, 1 H, H(6)); 8.02 (m, 2 H, H(2), H(6) Ph, J = 8 Hz). Found (%): C, 72.01; H, 7.39; N, 10.44; S, 12.21. $C_{16}H_{14}N_2S$. Calculated (%): C, 72.15; H, 7.30; N, 10.52; S, 12.03.

Reactions of trichloromethylarenes 1a,b with hydrazine hydrate. Trichloride **1a** or **1b** (5.5 mmol) was added to the solution of hydrazine hydrate (0.14 mL, 2.75 mmol) in 3.5 mL of methanol and 1.8 mL of dry pyridine. After treatment analogous to that described above the following products were obtained. **2,5-Diphenyl-1,3,4-oxadiazole (8a)**, yield 17 %, m.p. 139—140 °C (*cf.* Ref. 1); **benzhydrazide**, yield 8 %, m.p. 111—114 °C (from hexane) and **methyl benzoate**, yield 43 %, n_D^{20} 1.5134 (isolated by column chromatography on silica gel, ethyl acetate—hexane, 1 : 3 as eluent). **2,5-Di(2,4-dimethylphenyl)-1,3,4-oxadiazole (8b)**, yield 25 %, m.p. 111—112 °C, $[M]^+$ 278. ^{1}H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, 4-Me); 2.76 (s, 3 H, 2-Me); 7.16 (br.d, 1 H, H(5)); 7.18 (br.s, 1 H, H(3)); 7.93 (d, 1 H, H(6), J = 8 Hz). ^{13}C NMR ($CDCl_3$), δ: 21.45 and 22.21 (2- and 4-Me); 120.33 (C(1)); 126.98 (C(5)); 128.91 (C(6)); 132.59 (C(3)); 138.29 (C(2)); 141.51 (C(4)); 164.31 (C of the heterocycle). Found (%): C, 77.37; H, 6.60; N, 10.13. $C_{18}H_{18}N_2O$. Calculated (%): C, 77.67; H, 6.52; N, 10.07.

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