Acta Chemica Scandinavica B 30 (1976) 837—842

Reaction of Hydrazonyl Halides with Secondary and Tertiary Thioamides; Formation of 5-Amino- and 5-Alkoxy-1,3,4-thiadiazolines

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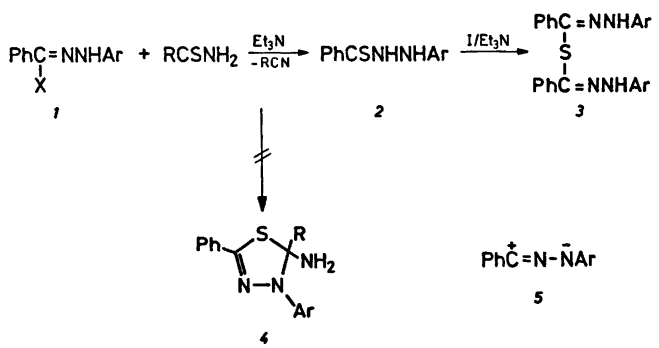
N-Arylbenzohydrazonyl bromides react with *N*-alkyl- and *N*,*N*-dialkylthiobenzamides, but not *N*-arylthiobenzamides, in the absence of base, while hydrazonyl chlorides require base (triethylamine) for reacting. Reactions with *N*-alkylthiobenzamides lead to a mixture of thiohydrazide, hydrazonyl sulfide, and 4-alkyl-1,3,5-triphenyl-1,2,4-triazolium halide. The latter is also formed when treating benzohydrazonyl halides with imidoyl halides in the presence of base. Reactions of benzohydrazonyl halides with *N*-aryl- and *N*,*N*-dialkylthiobenzamides lead to 5-anilino- and 5-dialkylamino-2,4,5-triaryl-1,3,4-thiadiazolines, respectively; alkoholysis of these compounds leads to the corresponding 5-alkoxy-1,3,4-thiadiazolines. Diphenylnitrilimine, generated by thermolysis of 2,5-diphenyltetrazole, adds to *N*-phenyl thiobenzamide to give 5-anilino-2,4,5-triphenyl-1,3,4-thiadiazoline, whereas cycloaddition of diphenylnitrilimine to *N*,*N*-dialkylthiobenzamides does not occur.

In a preceding paper [1] primary thioamides were shown to react with hydrazonyl halides (*1*) to give thiohydrazides (*2*), hydrazonyl sulfides (*3*), and nitriles by (formal) dehydrosulfurization of the thioamide. However, Huisgen and coworkers [2] have shown that tertiary thioamides, such as *N*,*N*-dimethylthiobenzamide, react differently with hydrazonyl halides, producing thiadiazolines.

We now report the results of an examination of the reactions of secondary and tertiary thioamides (*6*) with hydrazonyl halides (*1*) and diphenylnitrilimine (*5a*) (generated by thermolysis of 2,5-diphenyltetrazole [3]). This examination was undertaken to extend our knowledge of the reactions of hydrazonyl halides with the CS "double" bonds of thioacid derivatives, and to examine whether hydrazonyl halides in these systems react by a displacement mechanism or *via* 1,3-dipolar species, nitrilimines (*5*).[4]



Scheme 1.

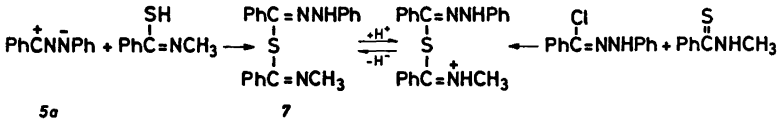
RESULTS AND DISCUSSION

The reactions of hydrazonyl halides with secondary and tertiary thioamides (Scheme 4) were found to be remarkably different, and the reactivity of the hydrazonyl halides was very dependent on the nature of the halogen atom. The reactions of *N*-alkyl- and *N,N*-dialkylthiobenzamides with hydrazonyl bromides proceed readily, whereas with hydrazonyl chlorides base (triethylamine) is required for reaction to take place; base is necessary for *N*-aryl-thiobenzamides to react in either case. It is not clear whether this difference is due to the higher relative reactivity of the hydrazonyl bromides, or if the two types of hydrazonyl halides react in part by different mechanisms.

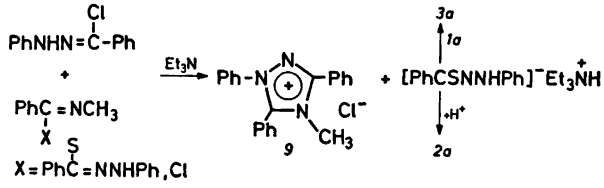
Reactions with N-*methylthiobenzamide.* Hydrazonyl halides react with *N*-methylthiobenzamide under a variety of conditions to give mixtures of thiohydrazides (*2*, detected by TLC), hydrazonyl sulfides (*3*) in yields varying from 20 to 60 %, and 4-methyl-1,3,5-triaryl-1,2,4-triazolium halides (*9*, see Scheme 3). Neither TLC nor NMR provided evidence for the formation of thiadiazolines (*cf.* Ref. 2). The reactions were sluggish and seldom went to completion. Even after prolonged periods of reaction considerable amounts of starting material were present and could be recovered. These findings may be rationalized as outlined in Schemes 2 and 3. The initial step is believed to be formation of a mixed hydrazonylimidoyl sulfide (*7*), which may arise either by displacement of the hydrazonyl halogen atom by the thioamide anion or the thioamide itself (to give a protonated form of the mixed sulfide), or by addition of the nitrilimine (*5*), formed *in situ* by dehydrohalogenation of *1*,[4] to the thiol form of the thioamide (see Scheme 2), in analogy to the reaction of nitrilimines with thiophenols.[3,5] The appearance of an absorption at 1680 cm^{-1} in the infrared spectrum of the reaction mixtures is compatible with the formation of the mixed sulfide, which may be regarded as an imidoyl pseudohalide.[6] Reaction between the hydrazonyl halide or the nitrilimine and the mixed sulfide (or its protonated form) then gives rise to the 1,2,4-triazolium ion and the thiohydrazide anion. The latter may react further with the hydrazonyl halide to produce the hydrazonyl sulfide (see Scheme 3), as discussed recently.[7] The plausibility of the above sequence of reactions is supported by our observation that imidoyl halides react with hydrazonyl halides to give 1,2,4-triazolium halides, *e.g.*, *N*-methylbenzimidoyl chloride reacts with *N*-phenylbenzohydrazonyl chloride (*1a*) and triethylamine (Scheme 3) to give 4-methyl-1,3,5-triphenyl-1,2,4-triazolium chloride. This reaction is analogous to the formation of 1,2,4-triazolines from nitrilimines and Schiff bases.[8]

Reactions with thiobenzanilide and tertiary thioamides. Thiobenzanilide and tertiary thioamides react with hydrazonyl halides in the presence of triethylamine to give 5-amino-2,4,5-triaryl-1,3,4-thiadiazolines (*10*),* which upon alcoholysis produce the corresponding 5-alkoxy-1,3,4-thiadiazolines (*11*, see Scheme 4).

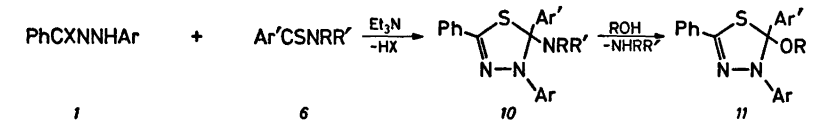
* For numbering see legend to Scheme 4.



Scheme 2.



Scheme 3.



1 6 10 11

X/Ar
a Cl/Ph
b Br/2-Cl-4-BrC_6H_3
c Br/2,4-$Br_2C_6H_3$

Ar'/R/R'
a Ph/H/CH_3
b Ph/H/Ph
c Ph/CH_3/CH_3
d 4-$CH_3OC_6H_4$/CH_3/CH_3
e Ph/-$(CH_2)_5$-
f 4-$CH_3OC_6H_4$/-$(CH_2)_5$-

Scheme 4. Individual 5-amino-thiadiazolines are designated in the text with a double index, *e.g. 10ac*, where the left index (*a*) identifies the starting hydrazonyl halide, and hence the N(4) aryl group, and the right index (*c*) identifies the starting thioamide, and hence the 5-substituents (*10ac* is 5-dimethylamino-2,4,5-triphenyl-1,3,4-thiadiazoline).

Neither thiohydrazides nor hydrazonyl sulfides were formed in these reactions.

N,N-Dimethylthiobenzamide displaces the bromine atom from hydrazonyl bromides, even in the absence of triethylamine, to give 5-dimethylaminothiadiazolines (observed by NMR); decomposition of these compounds by liberation of dimethylammonium bromide occurs in the reaction mixture, decreasing the isolated yield of *10* or, after alcoholysis, *11*.

It was not possible to isolate the 5-anilinothiadiazoline *10ab* from the reaction of thiobenzanilide; only *N'*-thiobenzoyl-*N*-benzoylphenylhydrazine [9] [PhCSNHN(COPh)Ph] was obtained. This compound is presumably formed from the 5-anilinothiadiazoline by elimination of aniline and ring opening. It has been found that the ring of 2,4,5-triaryl-1,3,4-thiadiazolium chlorides is opened by base to give thiohydrazides of the general formula ArCSNHN(COAr')-Ph;[10a] analogously, 2,4,5-triphenyl-1,3,4-oxadiazolium perchlorate reacts with sodium sulfide to give *N'*-benzoyl-*N*-thiobenzoylphenylhydrazine (PhCONHN(CSPh)Ph).[10b]

Of interest in this connection is a recent report [11] that hydrazonyl halides react with β-keto thioanilides in the presence of triethylamine, to give 5-ketonylidene-2,4-disubstituted-1,3,4-thiadiazolines by elimination of aniline from the initial ring closed product. Under more basic conditions a hydrazonyl sulfide was formed as a by-product; a thiohydrazide is most likely formed first by (formal) abstraction of hydrogen sulfide from the β-keto thioanilide; further reaction with the hydrazonyl halide then gives the sulfide (see also Ref. 8).

The 5-dimethylamino-2,4,5-triphenyl-1,3,4-thiadiazoline (*10ac*) suggested by Huisgen and coworkers [2] to be formed in the reaction of the hydrazonyl chloride *1a* with *N,N*-dimethylthiobenzamide and triethylamine was not isolated by these workers. Instead they obtained the corresponding 5-methoxythiadiazoline after methanolysis of the reaction mixture, and only indirect evidence was obtained for the intermediacy of *10*. Our results establish, in support of Huisgen's assumptions,[2] that a 5-dialkylamino group in thiadiazolines is readily replaced by an alkoxy group on treatment with alcohol (see Scheme 4), confirming that ring closure probably precedes displacement of the amino group.

Finally, the reactions of a secondary and a tertiary thioamide, thiobenzanilide and 4-methoxythiobenzpiperidide, respectively, with diphenylnitrilimine (*5a*) (generated by thermolysis of 2,5-diphenyltetrazole in refluxing bromobenzene) were examined. 1-Hexanol (10 %) was added to the bromobenzene to trap any 5-aminothiadiazoline formed. Thiobenzanilide reacts under these conditions (160 °C) to give a 60 % yield of 5-hexyloxy-2,4,5-triphenyl-1,3,4-thiadiazoline, while 4-methoxy-thiobenzpiperidide under similar conditions affords only 4-methoxythiobenzanilide in 14 % yield. The latter is presumably formed in a transamidation reaction preceded by reduction of either the tetrazole or the nitrilimine to aniline. These

results show that thiobenzanilide under these conditions acts as a good dipolarophile, in contrast to the thiobenzpiperidide.

CONCLUSION

The reaction of thioamides with hydrazonyl halides under basic conditions may be divided into those which occur by hydrogen sulfide abstraction leading initially to thiohydrazides, and those which occur by ring closure to thiadiazolines. Generally, primary thioamides,[1] including thioureas and thiosemicarbazide,[12] and certain secondary thioamides are capable of (formally) donating H_2S, and the reactions of these compounds lead to the formation of thiohydrazides and hydrazonyl sulfides. The reactions of tertiary thioamides always lead to thiadiazolines. Reactions of *N*-alkyl- and *N*,*N*-dialkylthiobenzamides deviate in two respects from those of other thioamides: they do not require base (triethylamine) to react with hydrazonyl bromides, and ring closure reactions with (thermally generated) diphenylnitrilimine to give thiadiazolines are not observed; this is also the case for primary thioamides. However, for thiobenzanilide base is required for reaction to take place, and in the reaction with diphenylnitrilimine thiadiazolines are formed.

EXPERIMENTAL

Materials. *N*-Methylthiobenzamide was prepared from carboxymethyl dithiobenzoate[13] and aqueous methylamine, m.p. 81–82 °C (ethanol) (lit.[14] m.p. 79–80 °C). *N*,*N*-Dimethyl-4-methoxythiobenzamide was prepared from carboxymethyl 4-methoxydithiobenzoate[12] and dimethylamine hydrochloride according to Huisgen *et al.*[2] in 94 % yield, m.p. 71–72 °C (abs. ethanol) (lit.[15] m.p. 68–70 °C).

The reactions of N*-methylthiobenzamide (*6a*) with* N*-aryl benzohydrazonyl halides (*1a *and* 1b*).* (i) Triethylamine (10.0 mmol) was added to a stirred solution of *1a*[16] (5.0 mmol) and *6a* (5.0 mmol) in benzene (25 ml). After 20 h the solution was filtered and the precipitate washed carefully with warm benzene, followed by evaporation of the filtrate. Addition of ethanol (5 ml) and filtration gave the sulfide *3a* (19 %), m.p. 158–160 °C (lit.[7] m.p. 158–160 °C). TLC of the residue showed the presence of unreacted *6a*.

(ii) Triethylamine (20.0 mmol) was added to a stirred solution of *1a* (10.0 mmol) and *6a* (5.0 mmol) in chloroform (50 ml). After 4 h the solvent was removed and the residue treated with boiling ethanol, leaving 58 % of the sparingly soluble sulfide *3a*. The filtrate was evaporated to dryness and taken up in ether-chloroform (4:1), filtered to remove insoluble material, and again evaporated to give an oil. An ^{1}H NMR spectrum ($CDCl_3$) of the oil showed the presence of a new compound with a singlet at δ 3.85, in addition to unreacted *6a*. The oil was redissolved in chloroform and addition of hexane caused white needles to precipitate. Recrystallization from chloroform-hexane (10:3) gave 230 mg of 4-methyl-1,3,5-triphenyl-1,2,4-triazolium chloride (*9*). This was identified by conversion to the known perchlorate: treatment of the chloride (230 mg) in ethanol (1 ml) with 4 drops of 70 % perchloric acid afforded an oil, which upon addition of ether crystallized as 4-methyl-1,3,5-triphenyl-1,2,4-triazolium perchlorate (82 %), m.p. 207–208 °C (after one crystallization from acetonitrile) (lit.[17] m.p. 206–208.5 °C).

(iii) Compound *1b*[18] (2.5 mmol) and *6a* (2.5 mmol) were dissolved together in chloroform (10 ml). After 3 days ethanol was added and the solution was taken to dryness. The solid was washed with ethanol leaving the sparingly soluble sulfide *3b* (20 %), m.p. 188–190 °C (lit.[18] m.p. 188–190 °C). TLC of the filtrate showed the presence of unreacted *6a*, but not 5-ethoxy-2,5-diphenyl-4-(2-bromo-4-chlorophenyl)-1,3,4-thiadiazoline.

(iv) In a similar experiment with triethylamine (5.0 mmol) and benzene (10 ml) as solvent the yield of *3b* was 16 %. TLC of the reaction mixture showed the presence of a small amount of the thiohydrazide *2b*.

Independent synthesis of compound 9. *N*-Methylbenzamide (10.0 mmol) and thionyl chloride (15 mmol) were refluxed together (steam bath) until no further evolution of HCl took place. The solution was evaporated under reduced pressure leaving *N*-methylbenzimidoyl chloride as an oil.[19] Triethylamine (20 mmol) and *1a* (10.0 mmol) were added to a solution of this oil in chloroform (10 ml). After 20 h the solvent was evaporated, the residue was taken up in ether-chloroform (2:1, 15 ml) and filtered to remove insoluble material. The filtrate was again taken to dryness and redissolved in ether–chloroform, filtered, followed by evaporation of the filtrate. Chloroform (5 ml) and hexane (2 ml) were added to give an oil which crystallized upon cooling. Recrystallization from chloroform–hexane (10:3) afforded 4-methyl-1,3,5-triphenyl-1,2,4-triazolium chloride. An IR spectrum was identical to that of *9*. Treatment of an ethanolic solution of the chloride with 70 % perchloric acid afforded the corresponding perchlorate salt, m.p. 207–209 °C.

*The reaction of thiobenzanilide (*6b*) with* N*-aryl benzohydrazonyl halides (*1a *and* 1c*).* (i) Triethylamine (21 mmol) was added to a solution

of *1a* (10.0 mmol) and thiobenzanilide [20] (10.0 mmol) in dry benzene (50 ml). After 2 days at room temperature the solution was filtered and evaporated *in vacuo*, leaving an oil, which crystallized by treatment with light petroleum (40 – 60 °C) and cooling (dry ice – acetone). The solid was treated with boiling ethanol to give after crystallization from ethanol 5-ethoxy-2,4,5-triphenyl-1,3,4-thiadiazoline in 91 % yield, m.p. 125 – 128 °C. Recrystallization raised the m.p. to 128 – 129 °C (lit.[2] m.p. 128.5 – 129.5 °C). Attempts to isolate *10ab* yielded small amounts of *N'*-thiobenzoyl-*N*-benzoylphenylhydrazine, m.p. 150 – 152 °C (chloroform) (lit. [9] m.p. 160 °C). MS, *m/e* 332 (M^+). (Anal. $C_{20}H_{16}N_2OS.\frac{1}{3}CHCl_3$: C, H, N, S).

(ii) Compound *1c* [21] and thiobenzanilide gave in a similar manner *5-ethoxy-2,5-diphenyl-4-(2,4-dibromophenyl)-1,3,4-thiadiazoline* in 50 % yield. Anal. $C_{22}H_{18}Br_2N_2OS$: C, H, N, S; m.p. 155 – 157 °C (ethanol-chloroform). In a similar experiment in which the triethylamine was left out no reaction was observed (NMR).

The reaction of N,N-*dimethylthiobenzamide with* N-*aryl benzohydrazonyl halide* (1b). Compound *1b* (2.5 mmol) and *N,N*-dimethylthiobenzamide [2] (2.5 mmol) were dissolved in dry chloroform (5 ml). After 20 h ethanol (5 ml) was added, followed by evaporation. Crystallization from ethanol afforded 33 % of *5-ethoxy-2,5-diphenyl-4-(2-bromo-4-chlorophenyl)-1,3,4-thiadiazoline*. Anal. $C_{22}H_{18}BrClN_2OS$: C, H, N, S; m.p. 146 – 148 °C. NMR spectra of the reaction mixture in $CDCl_3$ showed the formation of 5-dimethylaminothiadiazoline (*10bc*), δ 2.44 [$N(CH_3)_2$], together with dimethylammonium ions (identified by the addition of a few crystals of dimethylamine hydrochloride to the NMR sample).

In a similar experiment with *1a* no reaction had taken place even after 48 h (NMR).

5-Dimethylamino-2,4,5-triphenyl-1,3,4-thiadiazoline (10ac). Triethylamine (10.7 mmol) was added to a solution of *1a* (4.00 mmol) and *N,N*-dimethylthiobenzamide (4.05 mmol) in dry benzene (10 ml). After 2 days at room temperature the solution was filtered and the solvent removed *in vacuo*. TLC showed that the sulfide *3a* was not present in the reaction mixture. Crystallization was induced with light petroleum (40 – 60 °C) and cooling (dry ice-acetone). Recrystallization from light petroleum yielded the title compound as yellow crystals in 84 % yield. Anal. $C_{22}H_{21}N_3S$: C, H, N, S; m.p. 103 – 105 °C.

5-Dimethylamino-2,5-diphenyl-4-(2,4-dibromophenyl)-1,3,4-thiadiazoline (10cc) was prepared in a similar manner from *1c* and *N,N*-dimethylthiobenzamide in 81 % yield. Anal. $C_{22}H_{19}Br_2N_3S$: C, H, N, S; m.p. 128 – 138 °C (hexane).

The product from the reaction of *1a* with *N,N*-dimethyl 4-methoxythiobenzamide was not crystallized, but treated crude with ethanol to give *5-ethoxy-2,4-diphenyl-5-(4-methoxyphenyl)-1,3,4-thiadiazoline* in 83 % yield. Anal. $C_{23}H_{22}N_2O_2S$: C, H, N, S; m.p. 109 – 110 °C (ethanol).

5-Piperidino-2,4,5-triphenyl-1,3,4-thiadiazoline (10ae). Triethylamine (21 mmol) was added to a solution of *1a* (10.0 mmol) and thiobenzpiperidide [13] (10.0 mmol) in dry benzene (50 ml). After 2 days at room temperature the solution was filtered and the solvent removed *in vacuo*. The resulting oil was brought to crystallization with light petroleum (40 – 60 °C). Yield after crystallization from benzene or ethanol 82 %. (Anal. $C_{25}H_{25}N_3S$: C, H, N, S), m.p. 121 – 130 °C (ethanol). A mass spectrum showed only little contamination with the corresponding 5-ethoxy compound. Treatment with boiling propanol gave *5-propoxy-2,4,5-triphenyl-1,3,4-thiadiazoline* m.p. 113 – 115 °C. (Anal. $C_{23}H_{22}N_2OS$: C, H, N, S).

5-Piperidino-2,4-diphenyl-5-(4-methoxyphenyl)-1,3,4-thiadiazoline (10af) was prepared in a similar manner from *1a* and 4-methoxythiobenzpiperidide [13] in 80 % yield. Anal. $C_{26}H_{27}N_3OS$: C, H, N, S; m.p. 126 – 129 °C (light petroleum).

Reactions of thiobenzanilide and 4-methoxythiobenzpiperidide with 2,5-diphenyltetrazole in refluxing bromobenzene – hexanol. The thioamide (5.0 mmol) and 2,5-diphenyltetrazole [3] (5.0 mmol) were refluxed together in a mixture of bromobenzene (25 ml) and hexanol (2 ml) for 5 h. The solvent was removed and ethanol was added and the solution left for evaporation at room temperature. Thiobenzanilide gave *5-hexyloxy-2,4,5-triphenyl-1,3,4-thiadiazoline* in 58 % yield, m.p. 74 – 75 °C (ethanol). (Anal. $C_{26}H_{28}N_2OS$: C, H, N, S). In a similar experiment 4-methoxythiobenzpiperidide gave 4-methoxythiobenzanilide (14 %), m.p. 155 – 158 °C (lit.[22] m.p. 153 – 154 °C).

All 5-aminothiadiazolines decomposed on storage at room temperature. The 5-amino- and 5-alkoxythiadiazolines all exhibited an infrared absorption at 1558 cm^{-1} as described in the literature;[2] the 2,4,5-triaryl-1,3,4-thiadiazolines were further characterized by mass spectrometry.[23]

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Received March 12, 1976.