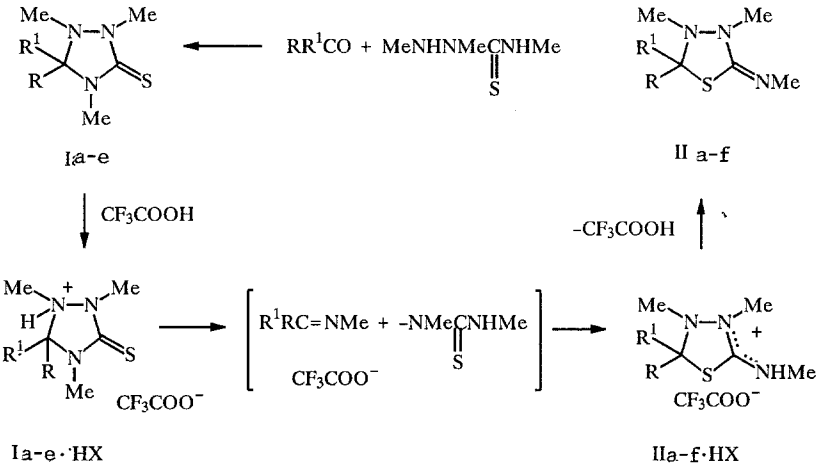
1,2,4-TRIMETHYL-1,2,4-TRIAZOLIDINE-3-THIONES AND 3,4-DIMETHYL-2-METHYLIMINO-1,3,4-THIADIAZOLIDINES

K. N. Zelenin, O. B. Kuznetsova and V. V. Alekseev

The reaction of aldehydes and ketones with 1,2,4-trimethylthiosemicarbazide in chloroform in the presence of CF_3COOH gives the corresponding 1,2,4-triazolidine-3-thiones, which in an excess of trifluoroacetic acid irreversibly and quantitatively recyclize to 2-imino-1,3,4-thiadiazolidine derivatives.

The reaction of monocarbonyl compounds with 1-substituted thiosemicarbazides can in principle proceed by an alternative cyclization to 1,2,4-triazolidine or 1,3,4-thiadiazolidine derivatives, but little is known about this reaction. An earlier report asserted that the reaction of acet- and benzaldehydes with such thiosemicarbazides was amenable to the method of synthesis of the corresponding 2-imino-1,3,4-thiadiazolidines [1], but this has not been demonstrated, while the product of reaction of benzaldehyde with 1-substituted thiosemicarbazide was proposed to have a bicyclic structure [2]. The condensation of 1,4-diphenylthiosemicarbazide with formaldehyde gave a mixture of thiadiazolidine and triazolidine isomers [3], the structures of which were established by their chemical transformations. It has recently been shown [4] that in neutral medium 1,2-dimethylthiosemicarbazide and benzaldehyde react to form the corresponding 1,2,4-triazolidine-3-thione, which, like the reaction products of aldehydes and ketones with thiosemicarbazides of other substitution types, recyclize in acid medium to the salt of 2-imino-1,3,4-thiadiazolidine.

Guided by these results, we examined the reaction of carbonyl compounds (acetic and anisic aldehyde, acetone, methyl ethyl ketone, and acetophenone) with 1,2,4-trimethylthiosemicarbazide.



I, II HX = CF_3COOH, [a] R = H, $R^1 = CH_3$; b R = H, R^1 = 4-CH_3O—C_6H_4; c R = $R^1 = CH_3$; d R = CH, $R^1 = C_2H_5$; e R = CH_3, $R^1 = C_6H_5$; f R = H, $R^1 = C_6H_5$

If this reaction is conducted in a low-polarity solvent such as chloroform in the presence of equimolar quantities of CF_3COOH, the sole products of condensation are formed in 60-80% yield. The exception was the reaction involving acetaldehyde, which the PMR spectrum showed to be a mixture of two isomers. However, attempts to separate them either by recrystallization or by preparative TLC resulted in the complete loss of the minor isomer probably by hydrolysis, since in its stead the starting 1,2,4-trimethylthiosemicarbazide was detected in the product of such treatment. Thus in every case we isolated individual compounds, which are 1,2,4-triazolidine-3-thiones Ia-e. Their structural assignments follow not so much from the similarity of the spectral characteristics of compound Ic (Tables 1 and 2) with those in the ^1H and ^{13}C NMR spectra of 2,4,5,5-tetramethyl-1,2,4-triazolidine-3-thione obtained from acetone and 2,4-trimethylthiosemicarbazide [4], nor even from the C=S signal at 176.1-179.5 ppm in the carbon spectra (Table 2), but principally from their subsequent chemical transformations.

S. M. Kirov Military Medicine Academy, Saint Petersburg, 194175. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 403-407, March, 1992. Original article submitted May 21, 1991.

 0009-3122/92/2802-0340$12.50

TABLE 1. Characteristics of 1,2,4-Triazolidine-3-thiones I and 3-Thio-1,2,4-triazolidinium salts I·HX

Compound	Elemental formula	T_{mp}, °C	R_f, ether	PMR spectrum in $CDCl_3$(I) or in CF_3COOH–$CDCl_3$ 1:1 (I·HX), ppm (J, Hz)				
				CH_3–N(1) (3H)	CH_3–N (3H, s)	CH_3–N(4) (3H, s)	R	R^1
Ia	$C_6H_{13}N_3S$	51...52	0,34	2,48 s	3,17	3,00	1,20 (3H, d, 6,0)	4,19 (1H, g, 6,0)
IaHX		*	*	2,90 br	3,06	2,79	1,34 (3H, d, 6,0)	4,71 (1H, g, 6,0)
Ib	$C_{12}H_{17}N_3OS$	60...62	0,89	2,48 s	3,18	2,76	3,69 (3H, s, OCH_3); 6,84 (2H, d, 9,0); 7,24 (2H, d, 9,0)	4,71 (1H, s)
Ib·HX		*	*	2,82	3,12	2,66	3,47 (3H, s OCH_3); 6,68 (2H, d, 8,5); 7,05 (2H, d, 8,5)	5,52 (1H, s)
Ic	$C_7H_{15}N_3S$	97...98	0,39	2,37s	3,26	2,98	1,28 (6H,s)	
IcHX		*	*	2,85br	3,08	2,79	1,36 (6H, s)	
Id	$C_8H_{17}N_3S$	36...38	0,66	2,39 s	3,24	3,00	1,32 (3H,s)	0,78 (3H, t, 7,0); 1,40...1,65 (2H, m)
IdHX		*	*	2,85 br	3,04	2,71	1,23 (3H, s)	0,55 (3H, t, 7,0); 1,54 (2H, m)
Ie	$C_{12}H_{17}N_3S$	Oil	0,74	2,23 s	3,18	2,94	1,65 (3H,s)	7,28 (5H, s)
Ie·HX		*	*	2,72 br	3,10	2,54	1,85 (3H,s)	6,96...7,26 (5H,m)

*Not preparatively isolated.

1,2,4-Triazolidine-3-thiones Ia-e are very weak bases and are not protonated on addition of an equivalent quantity of CF_3COOH in $CDCl_3$ solution, as shown by the absence of any change in their spectra. The acid thus serves in their synthesis only as a catalyst. Dissolution of compounds I in a large excess of trifluoroacetic acid leads to formation of their salts Ia-e·HX (HX = CF_3COOH), which cannot be isolated in pure form since removal of the CF_3COOH under vacuum leads to their deprotonation.

The large downfield shift of the $N_{(1)}$—CH_3 signal and those of the substituents R and R^1 (especially the methine proton signal for derivatives Ia, b) in the PMR spectra, along with the absence of a change expected with protonation of the thioamide fragment, localize this proton to the 1-position. In support of this is the broadening of the $N_{(1)}$—CH_3 signal as well as those of the methine protons on $C_{(5)}$ in compounds Ia-b, resulting from spin—spin coupling with the $N_{(1)}H$ proton. Cooling to —30°C results in still greater broadening of these signals in the spectrum of a solution of salt Ib, although their definitive resolution into doublets is not seen, probably due to intermolecular exchange.

Salts Ia-e·HX are unstable and within a few hours isomerize irreversibly and quantitatively. The position of the $C_{(5)}$ signal in their ^{13}C NMR spectra is evidence of the cyclic structure of the isomers (Table 2). The N_{exo}—CH_3 doublet (Table 3) indicates the localization of the proton on this atom, while the disappearance of the C=S absorption in the carbon spectra in the interval 176.1-179.5 ppm replaces the new one, more silicon signals, in the region 171.5-174.0 corresponding to the C=N carbon indicates that these isomers have the structures of 2-imino-1,3,4-thiadiazolidinium salts of IIa-e·HX. Thus the recyclization I·HX → II·HX is completely analogous to the previously studied transformations of the products of condensation of 2,4-dimethylthiosemicarbazide with acetone [4].

Treatment of a solution of the salts II·HX with an excess of pyridine-d_5 yields the free bases of 2-methylimino-3,4-dimethyl-1,3,4-thiadiazolidines IIa-e, which were characterized by ^1H and ^{13}C NMR (Tables 2 and 3). These compounds are very readily hydrolyzed and could be isolated in pure form from solution neither by preparative TLC nor by removal of the solvent under

TABLE 2. ^{13}C NMR Spectra of Compounds I and II and Their Salts I·HX and II·HX, ppm

Compound	Solvent	C=S (I), C=N (II)	$C_{(5)}$	R, R^1	CH3—N
Ia	$CDCl_3$	177,1	80,1	17,4	31,5; 34,5; 40,9
Ia·HX	$CDCl_3$—CF_3COOH, 1:1	179,5	85,1	13,5	31,9; 34,4; 39,7
IIa·HX	$CDCl_3$—CF_3COOH, 1:1	174,0	81,7	18,4	30,1; 36,4; 42,5
Ic	$CDCl_3$	177,2	81,2	20,8	29,2; 33,6; 35,4
Ic·HX	$CDCl_3$—CF_3COOH, 1:1	177,1	82,1	19,8	29,0; 33,4; 34,5
IIc·HX	$CDCl_3$—CF_3COOH, 1:1	171,9	84,0	26,0	35,1; 35,3; 35,5
Id	$CDCl_3$	176,1	83,3	7,2; 16,7; 29,0	28,4; 33,3; 35,4
Id·HX	$CDCl_3$—CF_3COOH, 1:1	176,7	84,4	6,7; 16,2; 28,9	28,0; 34,0; 34,8
IId	$CDCl_3$—Py-D_5, 1:1	172,4	89,0	9,9; 21,6; 36,0	34,3; 36,3; 36,8
IIdHX	$CDCl_3$—CF_3COOH, 1:1	171,7	88,9	8,2; 20,2; 34,0	32,9; 34,8; 35,1
IIf	$CDCl_3$	170,1	78,3	126,1; 128,9; 129,4; 135,7	34,5; 36,1; 39,8
If·HX	CF_3COOH—C_6D_6, 1:1	171,5	79,4	126,5; 129,3; 130.2: 135.5	33,6; 35,8; 39,2

TABLE 3. PMR Spectra of 2-Imino-1,3,4-thiadiazolidines II in a Mixture of $CDCl_3$-D_5, 1:1, and Their Salts II·HX in a Mixture of CF_3COOH—$CDCl_3$, 1:1, ppm (J, Hz)

Compound	CH_3—N(4) (3H, s)	CH_3—N (3H, s)	CH_3—N exo (3H)	R	R^1
IIa	2,55	3,34	3,02 (s)	1,45 (3H, d, 6,5)	4,98 (1H, q, 6,5)
IIa·HX	2,32	2,92	2,78 (d, 4,5)	1,23 (3H, d, 6,5)	4,61 (1H, q, 6,5)
IIb	2,76	3,41	3,06 (s)	3,72 (3H, s, OCH_3); 6,82 (2H, d, 9,0); 7,28 (2H, d, 9,0)	6,07 (1H, s)
IIb·HX	2,44	3,00	2,76 (d, 5,0)	3,43 (3H, s, OCH_3); 6,58 (2H, d, 9,0); 6,97 (2H, d, 9,0)	5,67 (1H, s)
IIc	2,53	3,40	3,05 (s)	1,61 (6H, s)	
IIc·HX	2,28	2,95	2,75 (d, 5,0)	1,36 (6H, s)	
IId	2,53	3,38	3,03 (s)	1,56 (3H, s)	0,92 (3H, t, 7,0); 1,86 (2H, q, 7,0)
IId·HX	2,26	2,93	2,73 (d, 5,0)	1,29 (3H, s)	0,63 (3H, t, 7,0); 1,60 (2H, q, 7,0)
IIe	2,67	3,38	3,08 (s)	1,86 (3H, s)	7,06...7,30 (5H, m)
IIe·HX	2,37	2,98	2,73 (d, 5,0)	1,57 (3H, s)	6,98...7,26 (5H, m)
IIf*	2,81	3,40	3,08 (s)	7,34 (5H, s)	5,94 (1H, s)
IIf·HX	2,51	3,03	2,80 (d, 5,0)	7,02 (5H, s)	5,72 (1H, s)

*In $CDCl_3$.

vacuum. In all cases they were heavily contaminated with hydrolysis products: 1,2,4-trimethylthiosemicarbazide and carbonyl compounds as well as their reaction products, the corresponding 1,2,4-thiadiazolidine-3-thione I.

Nonetheless, the isolation in principle of 2-imino-1,3,4-trimethylthiosemicarbazide was specially demonstrated using the example of the reaction between benzaldehyde and 1,2,4-trimethylthiosemicarbazide, which we carried out in CF_3COOH. This immediately gave salt IIf·HX, from whose solution, by removal of the acid under vacuum to constant weight, was isolated 2-methylamino-3,4-dimethyl-1,3,4-thiadiazolidine (IIf) (see Tables 2 and 3).

Thus the conditions have been found for a directed synthesis of isomeric derivatives of triazolidine and thiadiazolidine in the reaction of 1-substituted thiosemicarbazides with aldehydes and ketones.

These data and the discovery of recyclization call for a critical evaluation of the available information on the structure of compounds that formally correspond to products of such condensation but were obtained by other means. In particular this

applies to products of the reaction of 1-substituted thiosemicarbazides with bromoacetylenic ketones [5], 1-substituted thiosemicarbazides [6] and thiosemicarbazides [7] with acetylenic ketones, and to data on the Grignard reaction with oxidized thiosemicarbazones [8], where the authors state without proof that they have obtained 1,3,4-thiadiazolidine derivatives. In contrast, the authors of [9] consider that the reaction of α-chlorocarbamoyl chlorides with hydrazines furnishes 1,2,4-triazolidine derivatives, for which there is equally little proof.

Finally, our results will serve as useful orientation to the investigation of alternative cyclizations involving the thioamide group: in neutral or weakly acid medium the nitrogen atom is expected to be involved, while in strongly acid medium, cyclization at the sulfur atom is more probable.

EXPERIMENTAL

PMR spectra were taken on a Tesla-BS-497 (100 MHz) instrument with HMDS as internal standard. ^{13}C NMR spectra were recorded on a Gemini-200 (50.29 MHz) instrument with 10% solutions. All spectral measurements were conducted in completely anhydrous solvents with precautions to exclude contact with moist air. TLC was performed on Silufol-UV_254 plates.

Results of elemental analysis for C, H, N, S corresponded to calculated values.

1,2,4-Trimethylthiosemicarbazide was obtained by the method of [10].

1,2,4-Triazolidine-3-thiones Ib-e were synthesized in 70-80% yield by reaction of 0.01 mole of 1,2,4-trimethylthiosemicarbazide with 0.012 mole of carbonyl compound in the presence of equivalent quantities of trifluoroacetic acid. For aldehydes the mixture was left overnight and for ketones it was refluxed for 3 h. The solvent was removed under vacuum and the residue recrystallized from a mixture of benzene—hexane. Compounds Ib, e were separated from the admixture with starting carbonyl compounds by column chromatography on Al_2O_3 with ether elution. Condensation with acetaldehyde gave a mixture of two isomers Ia and IIa. Attempts to separate this mixture by crystallization or chromatography led to the isolation of 1,2,4,5-tetramethyl-1,2,4-triazolidine-3-thione Ia (yield 55%) and the starting 1,2,4-trimethylthiosemicarbazide due to the complete hydrolysis of IIa.

2-Methylimino-3,4-dimethyl-5-phenyl-1,3,4-thiadiazolidine (IIf, $C_{11}H_{15}N_3S$) was obtained by reaction of 0.01 mole of benzaldehyde with 0.01 mole of 1,2,4-trimethylthiosemicarbazide in 30 ml of trifluoroacetic acid. After 1 h the acid was removed to constant weight under vacuum. The residue was a yellow oil. The PMR and ^{13}C NMR spectra are given in Tables 2 and 3.

LITERATURE CITED

1. M. Busch and H. Ridder, *Ber.*, **30**, 849 (1897).
2. M. Busch, E. Opfermann, and H. Walter, *Ber.*, **37**, 2318 (1904).
3. G. W. Evans and B. Milligan, *Aust. J. Chem.*, **20**, 1783 (1967).
4. K. N. Zelenin, V. V. Alekseev, O. V. Solod, O. B. Kuznetsova, and V. N. Torocheshnikov, *Dokl. Akad. Nauk SSSR*, 286, 1133 (1987).
5. A. S. Nakhmanovich, T. E. Glotova, T. N. Komarova, M. V. Sigalov, and L. S. Romanenko, *Khim. Geterotsikl. Soedin.*, No. 10, 1421 (1990).
6. A. S. Nakhmanovich, T. E. Glotova, M. V. Sigalov, and V. Yu. Vitkovskii, *Khim. Geterotsikl. Soedin.*, No. 5, 703 (1984).
7. Yu. B. Pisarskii, T. N. Komarova, and L. B. Medvezhonkova, *Khim.-farm. Zh.*, **23**, 1442 (1989).
8. I. Yamamoto, I. Abe, M. Nozawa, M. Kotani, J. Motoyoshiya, H. Gotoh, and K. Matsuzaki, *J. Chem. Soc. Perkin Trans.*, No. 10, 2297 (1983).
9. A. Martvon, M. Uher, and S. Stankovsky, *Collect. Czech. Chem. Commun.*, **42**, 745 (1977).
10. K. A. Jensen, U. Anthony, B. Kägi, C. Larsen, and C. T. Pederson, *Acta Chem. Scand.*, **22**, 1 (1968).