REACTION OF ISOTHIOCYANATES WITH AZOIMIDE AND TRIMETHYLSILYL AZIDE

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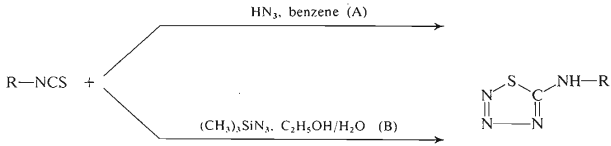
Reaction of ethyl 2-isothiocyanatocarboxylates, phenyl isothiocyanate and benzyl isothiocyanate with azoimide or trimethylsilyl azide afforded 5-(substituted amino)-1,2,3,4-thiatriazoles. Rate constants for the formation of 5-ethoxycarbonylmethylamino-1,2,3,4-thiatriazole in the reaction of trimethylsilyl azide with ethyl 2-isothiocyanatoacetate in 80% aqueous methanol at 35°C, as well as the rate constants of the thermal decomposition of this product in dioxane at 60°C, were determined. IR, UV and mass spectra of the prepared 5-(substituted amino)-1,2,3,4-thiatriazoles are discussed.

In our previous paper[1,2] we studied the potentialities of isothiocyanates as precursors of five-membered heterocyclic rings containing several heteroatoms. Isothiocyanates can be used also in the preparation of 5-(substituted amino)-1,2,3,4-thiatriazoles. These compounds have been hitherto prepared mainly by reaction of thiosemicarbazides with nitrous acid[3]. They can be also synthesised from azoimide and isothiocyanates[4]. In the case of easily available isothiocyanates the disadvantage of work with poisonous and explosive azoimide is outweighed by saving one synthetic step – the preparation of thiosemicarbazides[5] from isothiocyanates and hydrazine. The reaction of trimethylsilyl azide with isothiocyanates has not been described as yet. Formation of 5-(substituted thio)-1,2,3,4-thiatriazoles as intermediates in the reaction of trimethylsilyl azide with O-arylmonothiocarbonyl chlorides or with S-aryldithiocarbonyl chlorides was assumed by Kricheldorf[6].

This paper concerns the reaction of phenyl isothiocyanate, benzyl isothiocyanate and ethyl 2-isothiocyanatocarboxylates with azoimide (method *A*) or trimethylsilyl azide (method *B*) which affords 5-(substituted amino)-1,2,3,4-thiatriazoles (Scheme 1).

The preparation of the compound *I* by reaction of phenyl isothiocyanate[5] with azoimide, generated *in situ* from sodium azide and sulphuric acid, gave unsatisfactory results. We used therefore solutions of known concentration of azoimide in anhydrous benzene. The yields listed in Table I were achieved only after long reaction times, N-(ethoxycarbonylmethyl)cyanamide being obtained as a side-product. Its structure was proved by spectral methods as well as by comparison with the



SCHEME 1

R = C_6H_5 (*I*), $C_6H_5CH_2$ (*II*), $CH_2CO_2C_2H_5$ (*III*), $CH_3CH(CO_2C_2H_5)$ (*IV*), $C_2H_5CH(CO_2C_2H_5)$ (*V*), *i*-$C_3H_7CH(CO_2C_2H_5)$ (*VI*), *n*-$C_4H_9CH(CO_2C_2H_5)$ (*VII*), *i*-$C_4H_9CH(CO_2C_2H_5)$ (*VIII*), $C_6H_5CH_2CH(CO_2C_2H_5)$ (*IX*)

TABLE I

(5-Substituted amino)-1,2,3,4-thiatriazoles

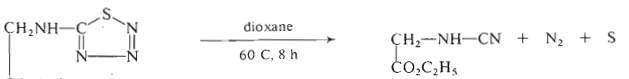
No	Formula (mol. w.)	M.p.[a], °C	Calculated/Found % C	% H	% N	Time[b], days yield, % *A*	*B*
I	$C_7H_6N_4S$ (178·2)	142·5[c]	47·17	3·93	31·44	14	2
			47·45	3·89	31·58	55	60
II	$C_8H_8N_4S$ (192·2)	80—81[d]	49·99	4·19	29·15	14	2
			49·82	4·05	29·08	45	20
III	$C_5H_8N_4O_2S$ (188·2)	69·0—69·5[e]	31·91	4·28	29·77	8	2
			31·70	3·91	29·55	60	65
IV	$C_6H_{10}N_4O_2S$ (202·2)	84·5—86·0	35·53	4·98	27·77	24	—
			35·74	4·66	27·98	63	—
V	$C_7H_{12}N_4O_2S$ (216·3)	64·5—65·5	33·87	5·59	25·91	17	2
			33·95	5·82	26·05	45	62
VI	$C_8H_{14}N_4O_2S$ (230·3)	63·5—64·0	41·72	6·13	24·33	2	—
			41·90	6·20	24·42	70	—
VII	$C_9H_{16}N_4O_2S$ (244·3)	37·0—38·0	44·24	6·60	22·93	21	—
			44·45	6·76	23·09	55	—
VIII	$C_9H_{16}N_4O_2S$ (244·3)	61·0—62·0	44·24	6·60	22·93	21	—
			44·38	6·75	23·09	58	—
IX	$C_{12}H_{14}N_4O_2S$ (278·3)	97·5—98·0	51·78	5·07	20·10	21	2
			51·80	4·87	4·87	85	80

[a] Compounds *I* and *II* were crystallised from ethanol, *III*—*IX* from an ethanol–light petroleum mixture; [b] *A* reaction with azoimide, *B* reaction with trimethylsilyl azide; [c] ref.[5] reports 142 to 143°C; [d] ref.[5] reports 80·5—81·0°C; [e] ref. reports 69·0—69·5°C.

compound obtained by thermal decomposition of the compound *III* in dioxane. The reaction of isothiocyanates with trimethylsilyl azide was perfomed in 80% aqueous ethanol at 20°C. The data in Table I show clearly that the preparation according to method *B* is much faster than that according to method *A*. The yields are approximately the same and the work with the dangerous azoimide is excluded. Trimethylsilyl azide is easily accessible[7] and can be handled safely. Hexamethyldisiloxane which is formed as a side-product, can be separated well from the main product by distillation under diminished pressure.

We determined the rate constant k' of the reaction of trimethylsilyl azide with ethyl 2-isothiocyanatoacetate ($k' = 1{\cdot}76 \cdot 10^{-4}\ s^{-1}$, $t_{1/2} = 3918$ s) at 35°C. The UV spectrum of trimethylsilyl azide (λ_{max} 213·5, log ε 2·44; λ_{max} 263, log ε 1·59) did not change during the reaction. It follows from the stability of trimethylsilyl azide and from the linearity of the dependence of log ΔE on time that the rate determining step is the formation of 5-(ethoxycarbonylmethylamino)-1,2,3,4-thiatriazole (*III*). The first step is the cycloaddition of trimethylsilyl azide to isothiocyanate leading to a 1 : 1 cycloadduct which in an aqueous-methanolic medium decomposes into the compound *III* and hexamethyldisiloxane.

Compounds *III*–*IX* are well soluble in cold chloroform, dioxane and tetrahydrofuran, insoluble in light petroleum and n-hexane. They melt with decomposition, however, their thermal stability is much greater than that of 5-aryl or 5-alkyl substituted 1,2,3,4-thiatriazoles[8]. We determined the rate constant for decomposition of the compound *III* to N-(ethoxycarbonylmethyl)cyanamide (Scheme 2) ($k' = 9{\cdot}1 \cdot 10^{-5}\ s^{-1}$; $t_{1/2} = 7{\cdot}8 \cdot 10^{3}$ s). The decomposition product was isolated and its structure confirmed by IR and ^{1}H-NMR spectroscopy.



SCHEME 2

IR spectra of 5-(substituted amino)-1,2,3,4-thiatriazoles (Table II) exhibit very strong absorption bands in the region 1548 ± 12 cm^{-1} (ε^a 324–128) due to interaction of stretching vibrations ν(C=N) and ν(N=N) of the heteroaromatic ring[9,10]. The bands in the regions 930 ± 10 cm^{-1}, 926 ± 5 cm^{-1} and 1088 ± 8 cm^{-1} belong to skeletal vibrations of the 1,2,3,4-thiatriazole ring[9,10]. The wavenumbers of the strong bands ν(C=O) at 1743 ± 4 cm^{-1} (ε^a = 378–328) are lower than

in the case of 2-isothiocyanatocarboxylic acids[11] and indicate a smaller electron-acceptor effect of the 1,2,3,4-thiatriazole ring as compared with the NCS groups. UV-absorption spectra of the compounds *III*–*IX* (Table II) exhibit a single band, λ_{max} 270 ± 2 nm, log ε 3·8 ± 0·1. Comparison of the UV spectra of our compounds with those of 5-alkylamino-1,2,3,4-thiatriazole[12] shows a small bathochromic shift due to substitution of the proton of the amino group by ethoxycarbonyl group. The higher log ε values are due to a more pronounced conjugation in the whole conjugated system.

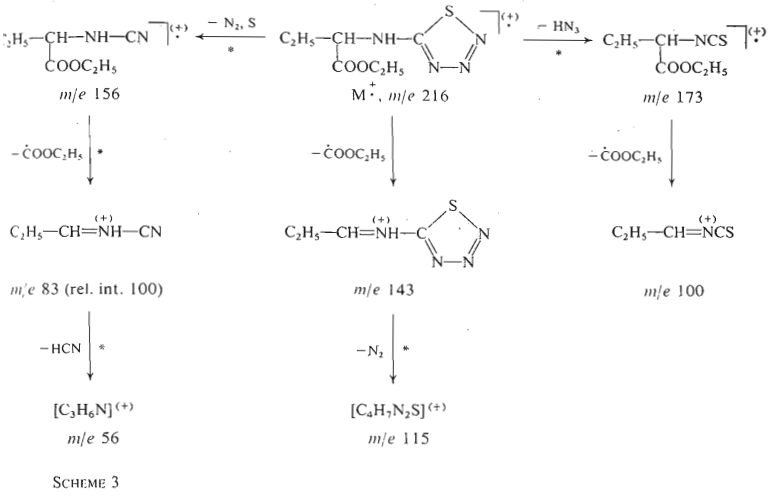
Mass spectra of 5-substituted 1,2,3,4-thiatriazoles were studied by Jensen and coworkers[13] who compared fragmentation of these compounds with their thermal decomposition. In this paper we investigated mass spectra of the compounds *III*–*IX*. In general, these spectra exhibit low relative intensities of molecular ions which decrease with an increasing number of carbons in the alkyl R and with its branching. Thus, *e.g.* for the compound *V* the relative intensity of the molecular ion is 6·1% whereas for *VIII* it is only 0·3%. The base peaks in the spectra of *III*–*V* and *VII* are due to the fragment ions $(M - N_2S{-}COOC_2H_5)^+$.

TABLE II

UV and IR Data for 5-(Substituted amino)-1,2,3,4-thiatriazoles

Compound	UV-Spectrum[a] λ_{max} (log ε^a)	IR-Spectrum[a] ν(NH)	(ε^a)	ν(C=O)	(ε^a)	ν(C=N)	(ε^a)	Other bands[b]
III	269·5 (3·91)	3 405	(113)	1 748	(370)	1 551[c] 1 540	(307) (227)	920, 1 021, 1 086
IV	269·9 (3·85)	3 397	(101)	1 744	(328)	1 541	(232)	927, 1 018, 1 088
V	272·2 (3·84)	3 398	(86)	1 742	(333)	1 540	(314)	934, 1 022, 1 094
VI	272·3 (3·78)	3 390	(74)	1 739	(366)	1 548	(325)	935, 1 022, 1 084
VII	272·3 (3·81)	3 393	(81)	1 741	(348)	1 540	(293)	940, 1 025, 1 085
VIII	272·3 (3·88)	3 396	(69)	1 741	(338)	1 551 1 537	(222) (222)	935, 1 027, 1 080
IX	268·8 (3·72)	3 395	(110	1 744	(366)	1 560	(128)	940, 1 031, 1 097

[a] ν (cm^{-1}), ε^a ($l\,mol^{-1}\,cm^{-1}$); [b] bands: 920–940 cm^{-1} weak, 1 018–1 031 cm^{-1} medium, 1 080–1 088 cm^{-1} medium, 1 097 cm^{+1} strong; [c] ref. reports 1 550 cm^{-1}; λ_{max} (log ε) for *I* and *II* were in accord with data in ref.[12].



SCHEME 3

Fig. 1 shows mass spectra of the compounds *III* and *V*. Only peaks of relative intensity greater than 4% are given. The principal fragmentation paths of the molecular ion of the compound *V* are depicted in Scheme 3. The elemental composition

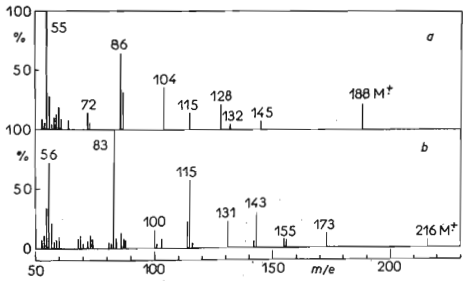


FIG. 1

Mass Spectra of *a* 5-(Ethoxycarbonylmethylamino)-1,2,3,4-thiatriazole (*III*), *b* 5-[1-(Ethoxycarbonyl)propylamino]-1,2,3,4-thiatriazole (*V*)

of the single ions was confirmed by high resolution measurements (Table III) and their formation was verified by detection of metastable transitions using the high voltage scan technique. Particular attention was paid to the fragment ion $(M - N_2S)^+$ since this ion could be the product of a thermal decomposition occuring during the mass spectral measurement. However, we proved unequivocally the metastable transition m/e 216 → m/e 156. Fragmentation of molecular ions of other studied compounds is similar to that of *V*. In the mass spectral study of these compounds one must avoid higher temperature in the inlet system and in the ion source. Even a negligible thermal decomposition during the measurement manifests itself by the presence of peaks m/e 32 (S^+), m/e 64 (S_2^+), m/e 96 (S_3^+), ... m/e 256 (S_8^+).

TABLE III

Composition of Some Ions in the Mass Spectrum of the Compound *V*

Ion	Mol. Weight		Composition
	found	calculated	
$M - NH_3$	173·0496	173·0510	$C_7H_{11}NO_2S$
$M - N_2, S$	156·0898	156·0898	$C_7H_{12}N_2O_2$
$M - COOC_2H_5$	143·0406	143·0391	$C_4H_7N_4S$
$M - NH_3—COOC_2H_4$	100·0236	100·0221	C_4H_6NS
$M - N_2,S—COOC_2H_5$	83·0613	83·0609	$C_4H_7N_2$
$M - N_2, S—COOC_2H_5—HCN$	56·0514	56·0500	C_3H_6N

EXPERIMENTAL

Benzene solution of azoimide (0·075 g NH_3/1 ml) was prepared according to ref.[14], trimethylsilyl azide was synthesized from trimethylsilyl chloride and sodium azide in boiling quinoline[7], and isothiocyanates were obtained by the thiophosgene method (ref.[11]).

5-Anilino-1,2,3,4-thiatriazole

Dilute (4M) hydrochloric acid (25 ml) was added at 0°C to a mixture of phenyl isothiocyanate (13·5 g; 0·01 mol) and sodium azide (6·5 g; 0·1 mol) in the course of 30 min. The mixture was heated on a steam bath for 30 min and cooled with ice, yielding 1·26 (7%) of 5-anilino-1,2,3,4-thiatriazole, m.p. 140—142°C, and 9·6 g of the unreacted phenyl isothiocyanate.

5-(Substituted amino)-1,2,3,4-thiatriazoles

A) The corresponding isothiocyanate (0·01 mol) was shaken with a benzene solution of azoimide (0·013 mol) at room temperature. After the reaction time, specified in Table I, the benzene

and the unreacted azoimide were removed under diminished pressure at low temperature and the solid residue was crystallized from benzene–light petroleum or ether–light petroleum at room temperature. Small amounts of sulphur were obtained in all experiments (m.p. 109–111°C).

B) The corresponding isothiocyanate (0·01 mol) was mixed with trimethylsilyl azide (0·011 mol) and 8% (vol.) aqueous ethanol (15 ml). The mixture was shaken for 48 h and the liquid portion was distilled at 20°C *in vacuo* into a receiver cooled with dry ice. According to gas–liquid chromatography (comparison with an authentic sample) the distillate contained hexamethyldisiloxane as a side product. The solid residue was crystallized three times from mixtures of solvents of various polarity.

N-(Ethoxycarbonylmethyl)cyanamide

A solution of the derivative *III* (0·200 g; 0·001 mol) in dioxane was heated to 60°C for 8 hours. The mixture became gradually turbid due to colloid sulphur. The end of the reaction was determined by UV spectrophotometry (λ_{max} 269·5 nm). Dioxane was distilled off *in vacuo* at 10°C, the residue dissolved in methanol and the sulphur removed by filtration with charcoal. (This procedure afforded 0·129 g (94·8%) of a liquid which turned brown on exposure to air. IR spectrum (cm^{-1}): ν(N—H) 3380, ν(C≡N) 2254, ν(C=O) 1757. ^{1}H-NMR spectrum (δ, ppm): 1·297, t, 3 H; 4·250, q, 2 H; $J_{CH_2-CH_3}$ = 7 Hz; 3·824, d, 2 H; 5·275, s, 1 H, (25°C); 5·162, s, 1 H (45°C).

Methods

The IR absorption spectra were taken at room temperature in chloroform on a double-beam UR-20 spectrophotometer in NaCl cells of 0·609 mm thickness; calibration with a polystyrene foil, accuracy ±1·0 cm^{-1}. The ε^a values were determined by the baseline method. ^{1}H-NMR spectra were measured on a Tesla BS-487C instrument (80 MHz) in deuteriochloroform, using hexamethyldisiloxane as internal standard. Gas–liquid chromatography was performed on a Hewlett Packard 7620A chromatograph at 100°C, column packed with 10% UCW-98 on Diatoport (80/100 mesh), length 1·8 m, diameter 2 mm. Temperature of the evaporation chamber and detector 230°C, nitrogen pressure 162·1 kPa. Mass spectra were measured on an MS 902 S A.E.I. Manchester spectrometer, using direct inlet technique, electron energy 70 eV, trap current 100 μA, ion chamber temperature 50°C. Exact mass measurements were made at the resolving power 25000 (10% valley definition) using the "peak matching" technique (heptacosafluorotributylamine as standard). The metastable transitions in the first field free region were detected by high voltage scan technique[15]. UV absorption spectra of 5-(substituted amino)-1,2,3,4-thiatriazoles, as well as kinetic measurements, were measured on a Specord UV-VIS (Zeiss, Jena) instrument.

The reaction of trimethylsilyl azide with ethyl 2-isothiocyanatoacetate in aqueous methanol was followed spectrophotometrically and the reaction rates were determined from the decrease of the extinction of the band at 269·5 nm (35 ± 0·2°C).

The reaction mixture contained an at least twentyfold excess of trimethylsilyl azide and the reaction was therefore regarded as a first-order process. The end extinction was constant over five half-lives of the reaction. The kinetic studies were performed in a reaction mixture consisting of 1 . 10^{-2}M methanolic ethyl 2-isothiocyanatoacetate (0·02 ml), 1 . 10^{-2}M methanolic trimethylsilyl azide (4 ml), water (2 ml) and methanol (4 ml). The rate constants k' (s^{-1}) were calculated from the linear relation log $\Delta E = -0{\cdot}0046t + 2{\cdot}7158$ (correlation coefficient r = = 0·9989 ± 0·01), using the equation for a first-order reaction.

The kinetics of the decomposition of *III* was measured in dioxane at 60 ± 0·2°C, starting concentration 1 . 10^{-4}M. The concentration decrease of *III* was followed at λ_{max} 269·5 nm. The

rate constant k' was calculated from the linear relation $\log \Delta E = -0{\cdot}00237t + 2{\cdot}7083$ ($r = 0{\cdot}998 \pm 0{\cdot}007$), using the equation for a first-order reaction.

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