ADDITION-CYCLIZATION REACTIONS OF ETHYL ISOTHIOCYANATOACETATE WITH CARBOXYLIC ACID HYDRAZIDES

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Ethyl (3-substituted 5-thioxo-1,2,4-triazolin-4-yl)acetates were prepared by addition-cyclization reaction of ethyl isothiocyanatoacetate with carboxylic acid hydrazides in the presence of sodium ethoxide. Thermal cyclization of the adduct in dimethylformamide afforded 1-acetamido-2--thiohydantoin. The effect of substituents on the cyclization course and the thione–thiol tautomerism are discussed.

Numerous 5-thioxo-1,2,4-triazoline derivatives are known to be antibacterially, antimycotically and antivirostatically active[1]. Their synthesis and biological activity have well been examined[2] especially with compounds bearing an alkyl, aryl and heterocyclic substituents at $N_{(4)}$ of the triazoline ring[2,3]. Reported was also the synthesis of 4-amino and 4-ethoxycarbonyl-5-thioxo-1,2,4-triazolines[4–6].

This project was aimed to synthesize 5-thioxo-1,2,4-triazolines bearing an acetate residue at $N_{(4)}$. Methods so far described for the preparation of this type of substances from halogen acetates or amidrazones are not selective enough and furnished a mixture of compounds or a disubstituted derivative[2,7]. Therefore a base-catalyzed or thermal cyclization of 1-acyl-3-thiosemicarbazides[8,9] was employed for the preparation of ethyl (3-substituted 5-thioxo-1,2,4-triazolin-4-yl)acetates, ethyl isothiocyanatoacetate (*I*) (ref.[10]) being the precursor of the acetate grouping. Addition of carboxylic acid hydrazides *IIa–IIh* to the heterocumulene grouping of acetate *I* led to 1-acyl-4-ethoxycarbonylmethyl-3-thiosemicarbazides *IIIa–IIIh* in very good yields (Table I). The IR spectra of these derivatives are dominated by absorption bands of an ester-group carbonyl at 1 748–1 724 cm^{-1} and a C—O—C grouping at 1 228–1 206 cm^{-1}.

To learn about the cyclization reaction conditions of thiosemicarbazides *IIIa–IIIh*, 4-ethoxycarbonylmethyl-3-thiosemicarbazides *IIIb,g* were chosen as model compounds. After a 3 h-reflux in toluene or 1,4-dichlorobenzene the starting material remained unchanged as monitored by thin-layer chromatography. Cyclization of the thiosemicarbazide *IIIb* took place in dimethylformamide; after a 1 h-reflux, 1-acetamido-2-thiohydantoin (*V*) was obtained in 31% yield instead of the expected ethyl (3-methyl-5-thioxo-1,2,4-triazolin-4-yl)acetate (*IVb*). Its structure was evidenced

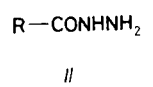
from spectral data: the ^{1}H NMR spectrum lacked proton signals of the ethyl moiety of the ester group, the ^{13}C NMR spectrum displayed signals of two C=O groups at δ 168·72 and 169·93 ppm, respectively. Diagnostic of the thiohydantoin *V* was the signal of carbon in a thioureide grouping of the ring at 183·93 ppm. Further argument for the structure *V* was the peak of molecular radical ion at *m/z* 173 in the mass spectrum. Thermal cyclization of the thiosemicarbazide *IIIg* in dimethylformamide furnished a mixture of inseparable products.

Dimethylformamide proved unsuitable for the proposed cyclization and therefore, it was replaced by sodium ethoxide in boiling ethanol. Acidification and chromatographic separation of the reaction mixture afforded ethyl (3-methyl-5-thioxo-1,2,4-triazolin-4-yl)acetate (*IVb*) in 54% yield and the corresponding acid *VIIb* in a 3 : 1 mass ratio in favour of *IVb*. Formation of acid *VIIb* could be rationalized by a partial hydrolysis of the ester *IVb* by water freed during the cyclization. To eliminate the aqueous acid solutions during the work-up of the mixture and to inhibit the consequential hydrolysis, the solution after reaction was acidified with cation exchanger Dowex 50 W in H^+ form.

TABLE I

1-Acyl-4-ethoxycarbonylmethyl-3-thiosemicarbazides *III*

Compound R	Formula (M_r)	Calculated/found			M.p., °C (Yield, %)	ν(C=O) cm^{-1}
		% C	% H	% N		
IIIa	$C_6H_{11}N_3O_3S$	35·11	5·40	20·47	136–138	1 739
H	(205·2)	35·14	5·61	20·52	(90)	1 682
IIIb	$C_7H_{13}N_3O_3S$	38·34	5·98	19·16	132–134	1 733
CH_3	(219·3)	38·28	6·04	19·14	(82)	1 694
IIIc	$C_{10}H_{19}N_3O_3S$	45·96	7·33	16·08	136–138	1 748
$(CH_3)_3C$	(261·3)	45·82	7·39	16·04	(81)	1 670
IIId	$C_{12}H_{21}N_3O_3S$	50·33	7·03	14·67	162–164	1 724
c-C_6H_{11}	(286·4)	50·21	7·12	14·61	(79)	1 672
IIIe	$C_6H_{17}N_3O_3S$	52·86	5·80	14·23	138–140	1 728
$C_6H_5CH_2$	(295·4)	52·88	5·81	14·23	(96)	1 688
IIIf	$C_{12}H_{15}N_3O_3S$	51·23	5·37	14·94	168–170	1 740
C_6H_5	(281·3)	51·24	5·37	14·89	(80)	1 664
IIIg	$C_{10}H_{13}N_3O_4S$	44·27	4·83	15·49	179–161	1 741
2-Furyl	(271·3)	44·29	4·84	15·41	(91)	1 676
IIIh	$C_{10}H_{13}N_3O_3S_2$	41·79	4·56	14·62	174–176	1 743
2-Tienyl	(287·4)	41·62	4·62	14·60	(79)	1 655



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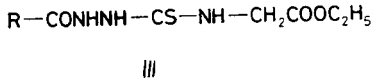
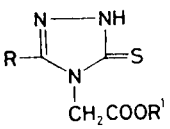
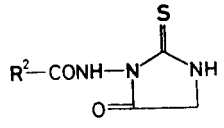


III

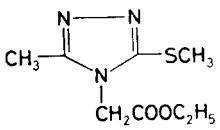


IV, $R^1 = C_2H_5$
VII, $R^1 = H$

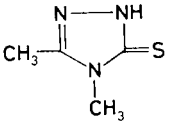


V, $R^2 = CH_3$
VI, $R^2 = C_6H_5$

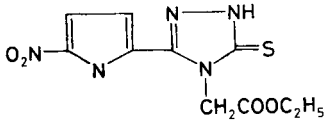
In formulae *II*–*VII* *a*, R = H; *b*, R = CH_3; *c*, R = $(CH_3)_3C$; *d*, R = c-C_6H_{11}; *e*, R = $C_6H_5CH_2$; *f*, R = C_6H_5; *g*, R = 2-furyl; *h*, R = 2-thienyl



VIII



X



IX

The unequivocal assignment of the thione structure of compound *IVb* was backed by comparison of ^{13}C NMR spectra of 1,2,4-triazole derivatives *X*, *IVb* and *VIII* with alternated peripheral groups. Compound *X* was prepared according to[16], substance *VIII* was obtained by treatment of *IVb* with methyl iodide in acetone in the presence of triethylamine. The ^{13}C chemical shift values of the triazole ring of *X* and *IVb* (δ 166·35 and 167·85 ppm, respectively) proved the thioxo structure; the thiol form would give rise to the proper signal at a considerably lower value, this being indicated by the $C_{(5)}$ chemical shift value of the methylthio derivative *VIII* at δ 152·94 ppm. This conclusion is in line with the reported values for analogous derivatives[12,13]. Change in the double bond arrangements in the triazoline derivative after S-methylation becomes also evident from a significant hypso and hypochromic

shifts of the UV absorption band from 256 nm (log ε 3·97) for compound *IVb* to 244 nm (log ε 3·26) for compound *VIII*. The characteristic absorption maximum of the 5-membered heterocyclic compounds with a thioxo grouping between two nitrogen atoms observed at 250–270 nm ref.[14,15] is in accordance with that of compounds listed in Table II.

Also thiosemicarbazides *IIIa,c–IIIh* were cyclized with sodium ethoxide in boiling ethanol. A remarkable dependence of the yield of the product on the acyl substituent was observed at a 30-min reaction time and molar ratio of the reactants. Data listed in Table III show the one-order decrease in yields when replacing aliphatic substituents for aromatic or heterocyclic. This phenomenon can be explained by the change in reactivity of the centre for cyclization of the starting thiosemicarbazide *III*, the bulky and electron-donating substituents of which lower the reactivity of the hydrazine carbonyl and $N_{(4)}$ of the thiosemicarbazide *III*, and consequently, the conversion of the reaction.

TABLE II

Ethyl (3-substituted 5-thioxo-1,2,4-triazolin-4-yl)acetates *IV*

Compound R	Formula (M_r)	Calculated/found % C	% H	% N	m.p., °C (Yield, %)	λ_{max}, nm (log ε)	ν(C=O) cm^{-1}
IVa H	$C_6H_9N_3O_2S$ (187·2)	38·49 38·41	4·84 4·92	22·44 22·47	80–82 (74)[a]	—	1 720
IVb CH_3	$C_7H_{11}N_3O_2S$ (201·3)	41·78 41·69	5·51 5·63	20·88 20·82	174–176 (54)[a]	256 (2·97)	1 738
IVc $(CH_3)_3C$	$C_{10}H_{17}N_3O_2S$ (243·3)	49·36 49·28	7·04 7·08	17·27 17·24	131–133 (22)[b]	—	1 758
IVd c-C_6H_{11}	$C_{12}H_{19}N_3O_2S$ (269·4)	53·51 53·54	7·11 7·13	15·60 15·40	146–148 (25)[b]	254 (3·28)	1 740
IVe $C_6H_5CH_2$	$C_{13}H_{15}N_3O_2S$ (277·3)	56·30 56·32	5·45 5·48	15·15 15·18	147–149 (40)[a]	255 (3·25)	1 736
IVf C_6H_5	$C_{12}H_{13}N_3O_2S$ (263·3)	54·74 54·78	4·98 4·91	15·96 15·94	136–138 (6)[a]	—	1 735
IVg 2-Furyl	$C_{10}H_{11}N_3O_3S$ (253·3)	47·42 47·40	4·38 4·44	16·59 16·61	160–162 (78)[c]	259 (3·10)	1 741
IVh 2-Tienyl	$C_{10}H_{11}N_3O_2S$ (269·3)	44·59 44·62	4·12 4·14	15·60 15·67	160–162 (67)[c]	256 (3·29)	1 744

Reaction time: [a] 0·5 h; [b] 4 h; [c] 24 h.

This relationship follows from contrasting the NMR and IR spectral data of reaction centers and neighbouring groups of the selected thiosemicarbazides *III* (Table III). The corresponding (3-substituted 5-thioxo-1,2,4-triazolin-4-yl)acetic acids *VIIb,c,e,g* were obtained by hydrolysis of ethyl esters *IV* with aqueous potassium hydroxide at room temperature.

A characteristic feature of 1,2,4-triazoles is the stability of the ring reflecting its aromatic character[2]. This nature was evidenced by nitration of *IVg* with fuming nitric acid to yield the 5-nitro-2-furyl derivative *IX*, the triazole ring of which remained unchanged under the given reaction conditions.

EXPERIMENTAL

The melting points were determined on a Kofler micro hot-stage, the IR (KBr) and UV (methanol) spectra were measured with Perkin–Elmer, model 457 and Perkin–Elmer Hitachi, model 240 UV-VIS spectrophotometers, respectively. The ^{1}H and ^{13}C NMR spectra of deuterioacetone solutions recorded with Jeol FX-100 apparatus are relative to tetramethylsilane.

The starting ethyl isothiocyanatoacetate (*I*) was prepared by pyrolysis of ethyl ethoxycarbonylmethyldithiocarbamate[10], carboxylic acid hydrazides *IIa—IIh* were synthesized from the respective ethyl esters and hydrazine hydrate according to[11].

1-Acyl-4-ethoxycarbonylmethyl-3-thiosemicarbazides *IIIa—IIIh*

1-Acylhydrazine (20 mmol) and ethoxycarbonylmethyl isothiocyanate (*I*) (20 mmol) in ethanol (30 ml) were refluxed for 90 min. The crystalline product was filtered off, washed with ether and crystallized from ethanol. Physicochemical data are listed in Table I.

Ethyl (3-Substituted 5-Thioxo-1,2,4-triazolin-4-yl)acetates *IVa—IVh*

1-Acyl-4-ethoxycarbonylmethyl-3-thiosemicarbazide (0·1 mol) in ethanol (450 ml) was refluxed with sodium ethoxide (2·53 g of sodium in 50 ml of ethanol). The necessary reaction times are

TABLE III

Yields of cyclization and diagnostic spectral data of thiosemicarbazides *IIIa,b,e,f,g*

Compound	Yields of *IV* %	^{13}C NMR, ppm[a]		^{1}H NMR, ppm[a]		ν(C=O) amide, cm^{-1}
		CONH	CH_2NH	$NHCH_2$	CH_2NH	
IIIa	74·3	167·31	61·47	7·70	4·34	1 682
IIIb	54·0	170·36	61·49	8·01	4·33	1 694
IIIe	40	169·31	60·30	7·95	4·31	1 688
IIIf	6	165·90	60·30	8·38	3·9—4·20	1 664
IIIg	3·2	157·43	60·17	8·37	3·9—4·06	1 676

[a] In hexadeuteriodimethyl sulfoxide.

given in Table II. The solution was cooled, the pH value was adjusted to 2 using Dowex 50 W (H^+). Chromatography through a silica gel-packed column with benzene–acetone (9 : 1) afforded ester *IVg*, with cyclohexane–ethyl acetate (3 : 2) esters *IVa,f,g*. The physicochemical data lists Table II. Further elution in the experiment leading to *IVf* yielded the starting compound *IIIf* in 11% and benzamido-2-thiohydantoin (*VI*) in 19% yields, m.p. 242–246°C. For $C_{10}H_9N_3O_2S$ (235·3) calculated: 51·05% C, 3·86% H, 17·86% N; found: 51·70% C, 3·84% H, 17·71% N. ^{1}H NMR spectrum, δ, ppm: 4·39 (s, 2 H, CH_2), 7·53–7·99 (m, 5 H, C_6H_5), 10·48 (s, 1 H, NH), 11·18 (s, 1 H, NH). ^{13}C NMR spectrum, δ, ppm: 47·40 (CH_2), 128·71 (C_6H_5), 164·81 (C=O), 169·78 (C=O), 182·25 (C=S)

(3-Substituted 5-Thioxo-1,2,4-triazolin-4-yl)acetic Acids *VIIb,c,e,g*

A solution of ethyl (3-substituted 5-thioxo-1,2,4-triazolin-4-yl) acetate (10 mmol) and potassium hydroxide (40 mmol) in water (25 ml) were stirred at room temperature for 24 h. The mixture was acidified and the product separated after standing was crystallized from ethanol–water. The characteristic data of acids *VIIb,c,e,g* are presented in Table IV.

Ethyl (3-Methyl-5-methylmercapto-1,2,4-triazol-4-yl)acetate (*VIII*)

A solution of *IVb* (2·01 g, 10 mmol), triethylamine (1·11 g, 11 mmol) and methyl iodide (1·55 g, 11 mmol) in acetone (30 ml) was stirred at an ambient temperature for 16 h. The solvent was removed under reduced pressure, the residue was dissolved in chloroform (50 ml) and extracted with water (30 ml). The chloroformic layer was dried with sodium sulfate, the solvent was distilled off under diminished pressure and the residue was chromatographed through a silica gel column with chloroform as eluent. The third fraction afforded the oily *III* (1·02 g, 47%). For $C_8H_{13}N_3O_2S$ (215·3) calculated: 44·63% C, 6·09% H, 19·52% N; found 44·21% C, 5·83% H, 19·30% N. UV spectrum: λ_{max}, nm, (log ε): 244 (2·26).

TABLE IV

3-Substituted (5-thioxo-1,2,4-triazolin-4-yl)acetic acids *VII*

Compound R	Formula (M_r)	Calculated/found % C	% H	% N	ν(C=O) cm^{-1}	M.p., °C (Yield, %)
VIIg	$C_8H_7N_3O_3S$	42·66	3·13	18·66	1 740	229–231
2-Furyl	(225·2)	42·81	3·19	18·52		(44)
VIIb	$C_5H_7N_3O_2S$	34·68	4·07	24·26	1 731	236–238
CH_3	(173·2)	34·78	4·03	24·32		(75)
VIIc	$C_8H_{13}N_3O_2S$	44·64	6·09	19·52	1 710	252–254
$(CH_3)_3C$	(215·3)	44·52	6·12	19·49		(46)
VIIe	$C_{11}H_{11}N_3O_2S$	53·00	4·45	16·86	1 717	175–177
$C_6H_5CH_2$	(249·3)	52·91	4·49	16·87		(57)

1-Acetamido-2-thiohydantoin (*V*)

A mixture of 1-acetyl-4-ethoxycarbonylmethyl-3-thiosemicarbazide (0·55 g, 2·5 mmol) and dimethylformamide (10 ml) was refluxed for 1 h, the solvent was distilled off *in vacuo* and the residue was purified by chromatography through silica gel with chloroform–acetone (1 : 2). Crystallization from ethanol afforded 0·12 g of the title product (31%). M.p. 175—177°C. ^{1}H NMR spectrum, δ, ppm: 2·08 (s, 3 H, CH_3), 4·27 (s, 2 H, CH_2), 9·16 (bs, 1 H, NH), 9·63 (bs, 1 H, NH). ^{13}C NMR spectrum, δ, ppm: 20·54 (CH_3), 47·98 (CH_2), 168·72 (C=O), 169·74 (C=O), 183·93 (C=S).

Ethyl (3-(5-Nitro-2-furyl)-5-thioxo-1,2,4-triazolin-4-yl)acetate (*IX*)

A mixture of nitric (4·5 ml) and sulfuric (17·9 ml) acids was added to the solution of ester *IV* (1·8 g, 7 mmol) in sulfuric acid (41 ml) at 13°C. The mixture was stirred at room temperature for 20 min, poured on ice and crystallized from ethyl acetate. Yield 1·79 g (86%), m.p. 140—141°C. For $C_{10}H_{10}N_4O_5S$ (298·3) calculated: 40·27% C, 3·38% H, 18·78% N; found: 40·9% C, 3·45% H, 18·84% N. UV spectrum: λ_{max}, nm, (log ε): 258 (3·22). IR spectrum, $\tilde{\nu}$, cm^{-1}: 1 728, 1 501, 1 343. ^{1}H NMR spectrum, δ, ppm (hexadeuteriodimethyl sulfoxide): 1·23 (t, 3 H, CH_3), 4·21 (q, 2 H, CH_2), 5·17 (s, 2 H, CH_2), 7·49, 7·89 (d, 2 H, Fu-H_3, H_4), 14·59 (s, 1 H, NH).

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Note added in proof: In formula *IX* ⟩O⟨ should be placed instead of ⟩N⟨.