SYNTHESIS OF ISOTHIOCYANATES FROM NON-AROMATIC NITROGEN-CONTAINING HETEROCYCLES

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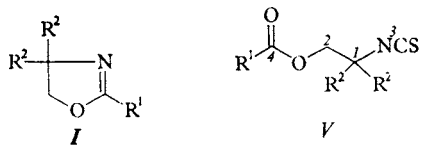
Investigation of the reaction of thiophosgene with Δ^2-oxazolines *I*, Δ^3-thiazolines *II*, 4*H*-benzo[*d*][1,3]thiazines *III*, 2-methoxypentahydro-Δ^1-azepine *IV*, theophylline and caffeine showed that only compounds *I* and *IV* reacted to give 2-acyloxyethyl isothiocyanates and methyl 6-isothiocyanatohexanoate. The structure of these products was corroborated by IR, ^{1}H NMR, ^{13}C NMR and mass spectral methods. The suitability of the above-mentioned compounds to react is discussed.

Our preceding papers[1,2] dealt with the synthesis of 2-(S-aryloxycarbonylthio)ethyl isothiocyanates and some of their derivatives from 2-aryloxy-Δ^2-thiazolines; this paper is directed towards generalization of this method of isothiocyanate preparations, its limitation and scope. Since reactions of thiophosgene with aromatic nitrogen-containing heterocycles have already been studied[3,4], our attention was paid to non-aromatic heterocycles characterized by a C=N bond, as *e.g.* substituted Δ^2-oxazolines *I*, Δ^3-thiazolines *II*, 4*H*-benzo[*d*][1,3]thiazines *III*, and 2-methoxypentahydro-Δ^1-azepine *IV*.

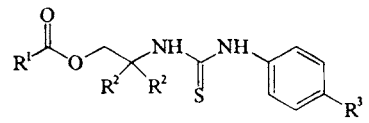
Δ^2-Oxazolines *I* react with thiophosgene in chloroform or dichloromethane in the presence of a weak base, as *e.g.* calcium carbonate at room temperature to afford 2-acyloxyethyl isothiocyanates *V* (Scheme 1, Table I). The IR, ^{1}H and ^{13}C NMR spectra, the molecular and fragment ions are in accord with the structure of isothiocyanates *V* (Table II).

Although isothiocyanates *V* possess two electrophilic centres CO, NCS, they react with amines (*p*-toluidine, *p*-bromoaniline) to yield exclusively thioureas *VI* (Table III). The reaction with oxazolines *I* proceeds *via* an addition intermediate of thiophosgene to the C=N double bond furnishing 2-chlorothiocarbamoyl chloride *VII* (ref.[1]) which underwent decomposition in alkaline medium to the corresponding isothiocyanate. Hydrolysis of the thiocarbamoyl group can be the concurrent reaction leading to liberation of the original heterocyclic compound (Scheme 2).

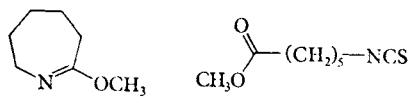
As found, this method of isothiocyanate preparation is of no general use, since attempts to obtain isothiocyanates from Δ^3-thiazolines and 4*H*-benzo[*d*][1,3]thiazines failed. Success of this reaction depends on *1*) the sufficient basicity of nitrogen



I *V*



VI



VIII *IX*

SCHEME 1

TABLE I

2-Acetoxyethyl isothiocyanates *Va*—*Vh*

Compound	R^1 R^2	B.p. (°C, 0·2 kPa) (yield, %)	Formula (M_r)	Calculated/Found			
				% C	% H	% N	% S
Va	CH_3	59—61[a]	$C_5H_7NO_2S$	41·37	4·86	9·65	22·04
	H	(46)	(145·1)	41·33	5·01	9·32	21·98
Vb	C_6H_5	122—124[a]	$C_{10}H_9NO_2S$	57·59	4·38	6·76	15·44
	H	(50)	(207·2)	57·45	4·37	6·61	15·57
Vc	H	54—55	$C_6H_9NO_2S$	45·27	4·70	8·80	20·09
	CH_3	(50)	(159·2)	45·32	4·64	8·57	19·89
Vd	CH_3	52—53	$C_7H_{11}NO_2S$	48·53	6·40	8·09	18·48
	CH_3	(40)	(173·2)	58·46	6·54	8·11	18·36
Ve	C_2H_5	62—64	$C_8H_{13}NO_2S$	51·31	7·00	7·48	17·08
	CH_3	(69)	(187·2)	51·42	7·07	7·53	17·09
Vf	n-C_3H_7	97—98	$C_9H_{15}NO_2S$	53·70	7·51	6·96	15·89
	CH_3	(55)	(201·2)	53·66	7·59	6·90	15·92
Vg	i-C_3H_7	98—99	$C_9H_{15}NO_2S$	53·70	7·51	6·96	15·89
	CH_3	(68)	(201·2)	53·69	7·54	6·93	15·90
Vh	$C_6H_5CH_2$	105—110	$C_{13}H_{15}NO_2S$	62·62	6·06	6·52	12·83
	CH_3	(30)	(249·3)	62·54	6·03	6·66	12·91

[a] At 1·3 kPa.

of the C=N bond of the heterocycle required for the reaction with thiophosgene; thus, *e.g.* imidazole, the p*Ka* value of which is 6·96, afforded by this method 1,2--diisothiocyanatoethene[4]; nonetheless we found that caffeine and theophylline (p*Ka* ~ 1, ref.[5]) do not react at all; 2) on the higher reactivity of carbon atom of the C=N bond of intermediate *VII* in relation with that of S=C—Cl grouping towards OH^- ions. In the opposite case only hydrolysis of the primarily formed thiocarbamoyl chloride or thiophosgene takes place (Scheme 2). On the other hand, this method was employed for preparation of methyl 6-isothiocyanatohexanoate *IX* from 2-methoxypentahydro-Δ^1-azepine *VIII* (Scheme 1). The heterocyclic compounds, affording the appropriate isothiocyanates with thiophosgene, could be considered cyclic imino ethers, and therefore, it was of interest to examine also their acyclic, analogues. N-Ethyl-O-methyl acetimidate reacts with thiophosgene to give ethyl

TABLE II

Spectral data for 2-acyloxyethyl isothiocyanates *Va*—*Vh*

Compound	R^1 / R^2	^{1}H NMR δ, ppm (C^2HCl_3)		IR ν, cm^{-1} ($CHCl_3$)	
		R^1/R^2	CH_2	ν(C=O)	ν(N=C=S)
Va[a]	CH_3	2·1 s	4·28 t	1 736	2 100
	H	3·75 t			
Vb	C_6H_5	7·7 s	4·50 t	1 720	2 100
	H	3·85 t			
Vc[b]	H	2·12 s	4·12 s	1 730	2 070
	CH_3	1·44 s			
Vd	CH_3	2·12 s	4·05 s	1 740	2 060
	CH_3	1·44 s			
Ve[c]	$CH_3^xCH_2^y$	x = 1·2 t;	y = 2·4 q	4·05 s	1 740	2 065
	CH_3	1·43 s			
Vf[d]	$CH_3^xCH_2^yCH_2^z$		x = 0·95 t	4·05 s	1 735	2 070
		y = 1·7 m;	z = 2·4 t		
	CH_3	1·43 s			
Vg	CH_3^x CH_2^y	x = 1·2 d;	y = 2·65 m	4·05 s	1 730	2 075
	CH_3	1·33 s			

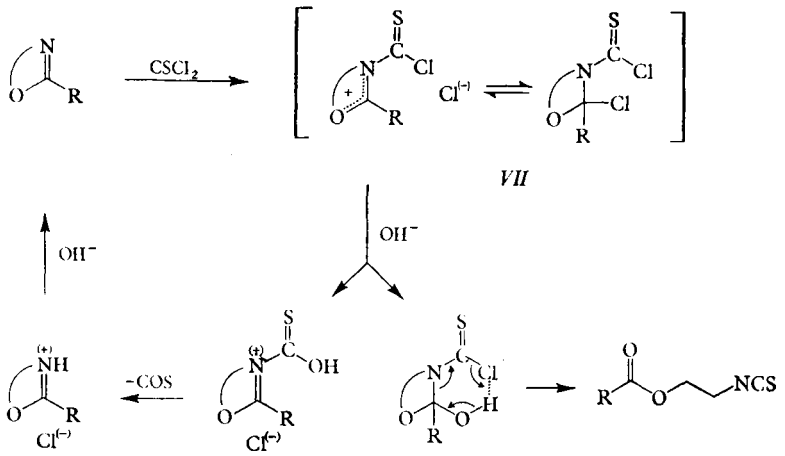
[a] ^{13}C NMR spectrum (C^2HCl_3), δ, ppm: 20·68 C_R1, 44·35 $C_{(1)}$, 61·96 $C_{(2)}$, 133·85 $C_{(3)}$, 170·36 $C_{(4)}$. [b] Mass spectrum, *m/z* (relat. intensity, %); 159, M^+ (15), 100, $M-HCO_2CH_2^+$ (100), 73, $M-HCO_2CH_2-HCN^+$ (42), 55, $M-HCO_2H-NCS^+$ (92), 99, $M-HCO_2CH_3^+$ (67). [c] Mass spectrum, *m/z* (relat. intensity, %); 187, M^+ (7), 158, $M-C_2H_5^+$ (9), 130, $M-C_2H_5CO^+$ (28), 100, $M-C_2H_5CO_2CH_2^+$ (36), 57, $C_2H_5CO^+$ (100). [d] ^{13}C NMR spectrum, δ, ppm; 13·66 C_{Rz}^1, 18·36 C_{Ry}^1, 25·98 C_R2, 35·98 C_{Rz}^1, 60·17 $C_{(1)}$, 69·88 $C_{(2)}$, 134·6 $C_{(3)}$, 172·82 $C_{(4)}$.

TABLE III

N-Aryl-N'-2-acyloxyethyl thioureas *VIa*—*VIh*

Compound	R^2 R^3	M.p., °C yield, %	Formula (M_r)	Calculated/Found % C	% H	% N	ν(CO)[a] ν(NH)	
VIa	H	73·5—75	$C_{12}H_{16}N_2O_2S$	57·12	6·39	11·10	1 735	
CH_3	CH_3	93	(252·3)	57·03	6·38	10·96	3 400	
VIb	H	132—134	$C_{17}H_{18}N_2O_2S$	64·96	5·77	8·91	1 720	
C_6H_5	CH_3	95	(314·3)	64·87	5·72	9·03	3 400	
VIc	CH_3	86—87	$C_{12}H_{15}BrN_2O_2S$	43·51	4·56	8·66	1 720	
H	Br	76	(331·2)	43·56	4·53	8·50	3 380	
VId	CH_3	91—93	$C_{14}H_{20}N_2O_2S$	59·97	7·19	9·99	1 735	
CH_3	CH_3	89	(280·3)	60·08	7·20	9·83	3 375	3 415
VIe	CH_3	113—115	$C_{14}H_{19}BrN_2O_2S$	46·80	5·33	7·80	1 730	
C_2H_5	Br	85	(359·2)	46·90	5·29	7·86	3 400	
VIf	CH_3	122—124	$C_{15}H_{21}BrN_2O_2S$	48·26	5·67	7·50	1 725	
n-C_3H_7	Br	72	(373·2)	48·20	5·74	7·45	3 400	
VIg	CH_3	118—121	$C_{16}H_{24}N_2O_2S$	62·31	7·84	9·08	1 725	
i-C_3H_7	CH_3	93	(308·3)	62·45	7·84	9·12	3 375	3 420
VIh	CH_3	120—122	$C_{19}H_{21}BrN_2O_2S$	54·14	5·02	6·65	1 730	
$C_6H_5CH_2$	Br	92	(421·3)	54·20	5·10	6·63	3 395	

[a] ln cm^{-1}.



SCHEME 2

isothiocyanate, what evidences that it is not decisive whether the C=N bond is embodied in the heterocyclic ring or not. Similar procedure was employed for the preparation of phenyl isothiocyanate from benzalaniline and 4-nitrobenzalaniline. Isothiocyanates *V* are analogues of natural mustard oils of glucosinolate type[6] characteristic of a considerable antimicrobial activity prevalently against yiests and moulds (*Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger*; MIC $1 . 10^{-4}$ to $1 . 10^{-5}$ mol l^{-1}).

EXPERIMENTAL

Spectral Measurements

The IR spectra of chloroform solutions were measured with a Specord 75 IR Zeiss, Jena spectrophotometer, ^1H and ^{13}C NMR spectra of deuteriochloroform solutions were recorded with Tesla BS 487 A (80 MHz) and Tesla BS 567 (25·12 MHz) instruments, respectively, tetramethylsilane being the internal reference. The multiplicity of ^{13}C NMR resonance signals was determined by the ^1H off-resonance technique. Mass spectra were taken with a Mat, model 111, apparatus at 200°C and 80 eV ionization energy.

Δ^2-Oxazolines *Ia*—*Ih*

The title compounds were synthesized from ethanolamine[7] or 2-methyl-2-amino-1-propanol[8,9] and the appropriate carboxylic acids.

2-Acyloxyethyl Isothiocyanates *Va*—*Vh*

Thiophosgene (2·87 g, 25 mmol) in dichloromethane (30 ml) was added to a suspension of $CaCO_3$ (5 g) in water (60 ml). The oxazoline derivative (20 mmol) dissolved in dichloromethane (20 ml) was successively added to this suspension with stirring at room temperature. After a 4 h-stirring the organic layer was separated, dried with $MgSO_4$, the solvent was evaporated and the residue was purified by distillation under reduced pressure.

N-Aryl-N-(2-acyloxyethyl)thioureas *VIa*—*VIh*

Arylamine (10 mmol) in ether (20 ml) was added to the solution of the respective isothiocyanates *Va*—*Vh* (10 mmol) in ether (10 ml). The mixture was left to stand overnight at an ambient temperature, the solvent was removed and the residue was crystallized (*VIa*, *VIb* from ether–tetrachloromethane, *VIc*—*VIh* from chloroform–hexane).

Methyl 6-Isothiocyanatohexanoate *IX*

A solution of thiophosgene (17·25 g) in chloroform (50 ml) and the suspension of $CaCO_3$ (15 g) in water (100 ml) were added to the solution of 2-methoxypentahydro-Δ^1-azepine (12·7 g, 0·1 mol) in chloroform (50 ml) and the mixture was stirred at room temperature for 3 h. The chloroform solution was then separated, dried and worked up. The residue distilled at 101—104°C/1·3 kPa, yield 56%. IR spectrum ν_{max}, cm^{-1}: 1 730 (CO), 2 100 (NCS).

Ethyl Isothiocyanate from N-Ethyl-O-methyl Acetimidate

N-Ethyl-O-methyl acetimidate[10] (5 g, 50 mmol) was added within 10 min to a stirred suspension of $CaCO_3$ (6 g) in water (100 ml) and thiophosgene (5·75 g, 50 mmol) in dichloromethane (100 ml). The unreacted calcium carbonate was filtered off after 1 h, the organic layer was separated, dried with $MgSO_4$, the solvent was distilled off and the residue was fractionated at atmospheric pressure. B.p. 130–132°C (130–131°C/101 kPa, ref.[11]). Yield 40%. IR spectrum ν_{max}, cm^{-1}: 2 120 (NCS). ^1H NMR spectrum δ, ppm: 1·35, t, (CH_3), 3·52, q, (CH_2).

Phenyl Isothiocyanate from Benzalaniline and 4-Nitrobenzalaniline

Benzalaniline (3 g, 16 mmol), or 4-nitrobenzalaniline (3·6 g, 16 mmol) in dichloromethane (50 ml) was added to a stirred suspension of $CaCO_3$ (5 g) in water (100 ml) and thiophosgene (1·84 g, 16 mmol) in dichloromethane (50 ml). The mixture was stirred for 6 h, $CaCO_3$ was filtered off, the organic layer was separated, dried with $MgSO_4$ and the solvent was evaporated. The residue was fractionated *in vacuo*; b.p. 95°C/1·6 kPa (120–121°C/4·6 kPa, ref.[12]), yield 63% per benzalaniline, 42% per 4-nitrobenzalaniline. IR spectrum ν_{max}, cm^{-1}: 2 180 (NCS).

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