SYNTHESIS OF 2-(S-ARYLOXYCARBONYLTHIO)ETHYL ISOTHIOCYANATES — ANALOGUES OF NATURAL MUSTARD OILS

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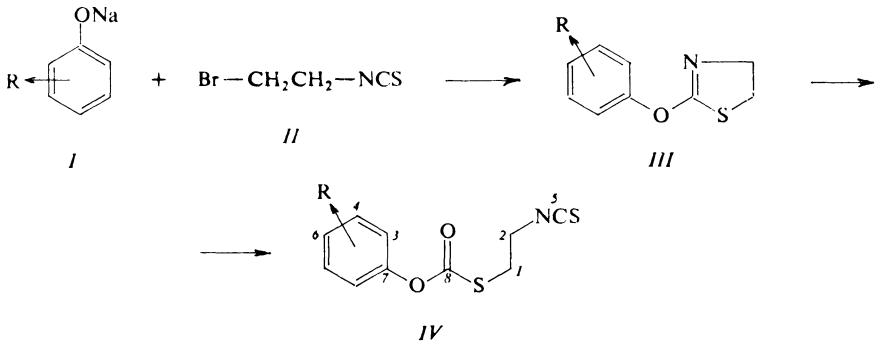
A simple reaction of 2-aryloxythiazolines with thiophosgene leads to formation of 2-(S-aryloxycarbonylthio)ethyl isothiocyanates. The starting thiazolines can easily be obtained from 2-bromoethyl isothiocyanates and phenolates. The structure of the products synthesized was evidenced by spectral methods.

Hull and coworkers[1-4] studied the reaction of thiophosgene with a C=N bond of aromatic heterocycles related to pyridine and imidazole affording isothiocyanates with the NCS group attached to an sp^2 carbon.

This paper reports a modification of this reaction for the synthesis of biologically active isothiocyanates of glucosinolate type[5] from 2-aryloxythiazolines *III*. The latter can easily be prepared from 2-bromoethyl isothiocyanate *II* with phenolates *I* in benzene according to the method for the synthesis of 2-alkoxythiazolines and 2--aminothiazolines[6,7] (Table I). The obtained thiazolines react with thiophosgene in chloroform or dichloromethane in the presence of water and a base ($CaCO_3$, $BaCO_3$, NaOH) at 0–30°C to furnish 2-(S-phenoxycarbonylthio)ethyl isothiocyanates *IV* in high yields (Table II, Scheme 1). The reaction proceeds presumably *via* an addition intermediate of thiophosgene to the C=N bond to give α-chlorothio-



SCHEME 1

carbamoyl chloride *V*. Analogous addition compounds were isolated with Schiff bases[8,9]. Decomposition of the addition product *V* in an alkaline medium is shown in Scheme 2.

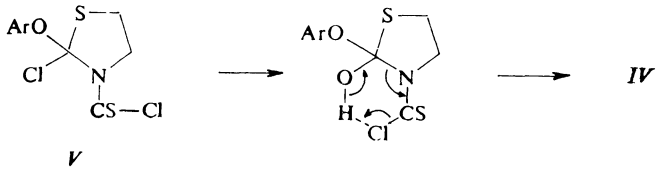
The structure of isothiocyanates *IV* was corroborated by analytical and spectral methods. The IR spectra displayed characteristic absorption bands of CO and NCS groups at 1 725 and 2 075 cm^{-1}, respectively. The mass spectrum of compound *IVa*, the ^{13}C NMR spectrum of *IVg* are in accordance with the structure anticipated (Table II).

TABLE I

2-Aryloxythiazolines *IIIa*—*IIIi*

Product R	Yield %	B.p. (°C/0·1 kPa) IR (cm^{-1}) ν(C=N)	Formula (M_r)[a,b]	Calculated/Found % C	% H	% N
IIIa	72	110—113	C_9H_9NOS	60·33	5·02	7·82
H		1 630	(179·1)	60·13	3·98	7·62
IIIb	74	127—130	$C_{10}H_{11}NOS$	62·17	5·69	7·24
2-CH_3		1 631	(193·2)	61·99	5·65	7·20
IIIc	67	120—123	$C_{10}H_{11}NOS$	62·17	5·69	7·24
3-CH_3		1 634	(193·2)	62·13	5·54	7·25
IIId	72	122—125	$C_{10}H_{11}NOS$	62·17	5·69	7·24
4-CH_3		1 629	(193·2)	62·40	5·66	7·24
IIIe	57	126—128	C_9H_8ClNOS	50·60	3·74	6·55
2-Cl		1 635	(213·6)	51·05	3·38	6·35
IIIf	68	129—131	C_9H_8ClNOS	50·60	3·74	6·55
3-Cl		1 632	(213·6)	50·85	3·48	6·34
IIIg	87	137—139	C_9H_8ClNOS	50·60	3·74	6·55
4-Cl		1 630	(213·6)	50·35	3·81	6·50
IIIh	61	147—150	$C_{10}H_{11}NO_2S$	57·42	5·25	6·69
4-CH_3O		1 633	(209·1)	57·13	5·28	6·75
IIIi	81	140—143	C_9H_8BrNOS	41·88	3·10	5·42
4-Br		1 632	(258·0)	41·49	3·15	5·45

[a] The ^1H NMR spectra of thiazolines display characteristic signals of CH_2 protons at δ 3·45—3·50 (t) and 4·00—4·05 ppm (t), and at 6·77—7·49 ppm (m, protons at an aromatic ring); [b] measured in chloroform.



SCHEME 2

TABLE II

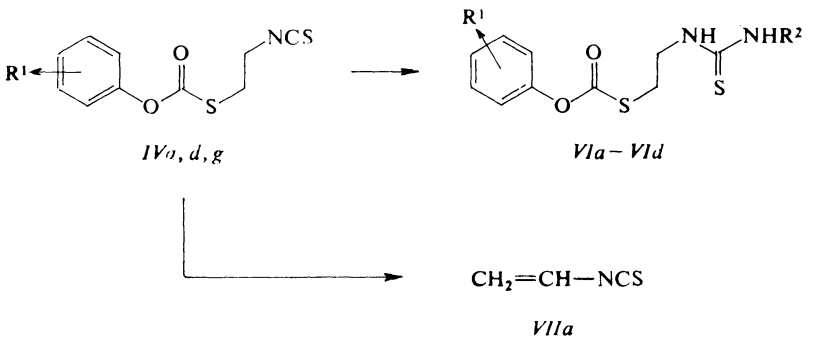
2-(S-Aryloxycarbonylthio)ethyl isothiocyanates *IVa*—*IVi*

Product R	Formula[a] (M_r)	Yield, % b.p., °C/0·3 Pa	Calculated/Found				νCO[b] νNCS
			% C	% H	% N	% S	
IVa[c]	$C_{10}H_9NO_2S_2$	82	50·19	3·76	5·85	26·74	1 722
H	(239·3)	138—140	50·04	3·78	5·80	26·80	2 075
IVb	$C_{11}H_{11}NO_2S_2$	81	52·15	4·38	5·53	25·31	1 725
2-CH_3	(253·3)	137—140	52·20	4·39	5·55	25·30	2 070
IVc	$C_{11}H_{11}NO_2S_2$	76	52·15	4·38	5·53	25·31	1 720
3-CH_3	(253·3)	145—148	52·18	4·40	5·49	25·29	2 081
IVd	$C_{11}H_{11}NO_2S_2$	79	52·15	4·38	5·53	25·31	1 723
4-CH_3	(253·3)	143—145	52·10	4·35	5·55	25·33	2 078
IVe	$C_{10}H_8ClNO_2S_2$	66	43·87	2·92	5·11	23·38	1 727
2-Cl	(273·8)	155—156	43·59	2·68	5·22	23·07	2 078
IVf	$C_{10}H_8ClNO_2S_2$	78	43·87	2·92	5·11	23·38	1 728
3-Cl	(273·8)	165—167	53·62	2·83	5·10	23·41	2 080
IVg[d]	$C_{10}H_8ClNO_2S_2$	86	43·87	2·92	5·11	23·38	1 726
4-Cl	(273·8)	—	43·56	2·91	4·69	23·13	2 079
IVh	$C_{11}H_{11}NO_3S_2$	80	49·05	4·08	5·19	23·76	1 727
4-CH_3O	(269·3)	152—155	48·95	4·07	4·99	23·54	2 080
IVi[d]	$C_{10}H_8BrNO_2S_2$	85	37·74	2·51	4·39	20·11	1 726
4-Br	(318·2)	—	37·68	2·50	4·37	20·21	2 078

[a] The ^1H NMR spectra of isothiocyanates display characteristic signals of CH_2 protons at δ 3·12 to 3·17 (t), and 3·76—3·78 ppm (t), as well as at δ6·98—7·42 ppm (m, C—H_{arom}); [b] values in cm^{-1}, measured in chloroform; [c] mass spectrum, m/z (assignment, % of intensity): 239 (M^+, 23), 211 ($M-CO^+$, 51), 146 ($M-C_6H_5CO_2^+$, 100), 86 ($M-C_6H_5CO_2S^+$, 96), ^{13}C NMR spectrum (C^2HCl_3), δ, ppm: 29·5 $C_{(1)}$, 42·8 ($C_{(2)}$), 120·6 $C_{(3)}$, 127·7 $C_{(4)}$, 128·1 $C_{(5)}$, 129·9 $C_{(6)}$, 147·5 $C_{(7)}$, 166·9 $C_{(8)}$, *cf.* Scheme 1; [d] m.p. *IVg* 39—41°C, *IVi* 27—30°C.

Compounds *IVa–IVi* afforded with amines (ammonia, *p*-toluidine, *p*-anisidine) exclusively thioureas *VIa–VId* (Table III, Scheme 3), although they possess two electrophilic centres (CO, NCS). Compound *IVa* gave vinyl isothiocyanate (*VIIa*) upon heating in dichlorobenzene in a low yield.

The synthesized isothiocyanates exhibited high antimicrobial activity mainly towards yeasts (*Candida albicans*, *Sacharomyces cerevisiae*; MIC $1 . 10^{-5}$ to $1 . . 10^{-3}$ mol l^{-1}) and molds (*Aspergillus niger*, *Penicillium cyclopium*, *Rhizopus oryzae*; MIC $1 . 10^{-4}$ to $1 . 10^{-3}$ mol l^{-1}).



SCHEME 3

TABLE III

N-Aryl-N′-2-(S-phenoxycarbonylthioethyl)thioureas *VIa–VId*

Product	R^1 R^2	Formula (M_r)	M.p., °C yield, %	CO[a] NH	Calculated/Found		
					% C	% H	% N
VIa	4-CH_3	$C_{11}H_{14}N_2O_2S_2$	122–123	1 700	48·87	5·22	10·36
	H	(270·3)	87	3 500, 3 350	48·89	5·25	10·35
VIb	H	$C_{17}H_{18}N_2O_2S_2$	112–113	1 720	58·93	5·24	8·09
	4-$CH_3C_6H_4$	(346·4)	95	3 405	58·90	5·20	8·10
VIc	4-CH_3	$C_{18}H_{20}N_2O_3S_2$	148–149	1 719	57·42	5·35	7·44
	4-$CH_3OC_6H_4$	(376·5)	90	3 402	57·44	5·38	7·46
VId	4-Cl	$C_{17}H_{17}N_2ClO_2S_2$	140–141	1 722	53·60	4·50	7·35
	4-$CH_3C_6H_4$		76	3 405	53·63	4·51	7·37

Values cm^{-1}, measured in chloroform.

EXPERIMENTAL

Spectral Measurements

The IR spectra were measured with a Specord 75 IR (Zeiss, Jena) spectrophotometer, the ^1H and ^{13}C NMR spectra of deuteriochloroform solutions containing tetramethylsilane were recorded with a Tesla BS 407 A (80 MHz) and Tesla BS 567 (15·15 MHz) apparatuses, respectively. The multiplicity of signals was ascribed by the ^1H-off-resonance technique. The mass spectrum was run with an LKE 9000 instrument by a direct evaporation into the ion source at 70 eV ionization energy.

2-Phenoxythiazolines *IIIa*—*IIIi*

2-Bromoethyl isothiocyanate *II* (50 mmol) was added to a solution of the phenolate *Ia*—*Ii* (50 mmol) in benzene (70 ml). The mixture was refluxed for 3 h, cooled and the insoluble salts were filtered off. Benzene was evaporated under reduced pressure and the residue was vacuum-distilled.

2-(S-Aryloxycarbonylthio)ethyl Isothiocyanates *IVa*—*IVi*

A solution of thiophosgene (5·75 g, 50 mmol) in dichloromethane (70 ml) was added to a suspension of $CaCO_3$ (10g) in water (100 ml) at 0—5°C. A solution of the respective thiazoline (50 ml) in dichloromethane (40 ml) was added during 20 min into the stirred suspension at this temperature, and the stirring was continued for 1 h at 0—5°C, and at room temperature for additional 3 h. The organic layer was separated, dried with $MgSO_4$ and distilled off. The residue was purified either by a distillation under diminished pressure, or by chromatography on a silica gel column using chloroform as an eluent.

N-Aryl-N′-2-(S-phenoxycarbonylthioethyl)thioureas *VIb*—*VId*

p-Toluidine, or *p*-anisidine (10 mmol) in ether (20 ml) was added to a solution of *IVa, d, g* (10 mmol) in ether (20 ml). The mixture was stirred for 5 h, ether was distilled off under reduced pressure, and the residue was purified by thin-layer chromatography on silica gel LSL_{254} to which 7% of plastrum was added (glass plates 25 × 20 cm, coating 3 mm, eluent chloroform). R_F Values of the respective compounds are: *VIb* 0·72, *VIc* 0·35, *VId* 0·31 (chloroform).

N-2-(S-Phenoxycarbonylthioethyl)thiourea (*VIa*)

A slow stream of gaseous ammonia was introduced into an ethereal solution of isothiocyanate *IVd* (2·53 g, 10 mmol). The solvent was evaporated after 2 h and the residue, crystallized from chloroform–light petroleum, had m.p. 139—141°C. The analytical sample having m.p. 140 to 141 °C was obtained by thin-layer chromatography on silica gel similarly as with *VIb*—*VId*. Its R_F was found to be 0·2.

Thermal Decomposition of *IVa*

A solution of *IVa* (5 g, 25 mmol) in 1,2-dichlorobenzene (50 ml) was refluxed under nitrogen for 2 h, cooled, washed with dilute sodium carbonate solution and water, dried and fractionally distilled. Yield 0·25 g (12%) of *VII*, b.p. 51—62°C/15 kPa or 46°C/13 kPa.

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REFERENCES

1. Hull R.: J. Chem. Soc. C *1968*, 1977.
2. Boyle F. T., Hull R.: J. Chem. Soc., Perkin I *1974*, 1541.
3. Hull R.: Syn. Commun. *9*, 477 (1977).
4. Hull R., Seden T. P.: Syn. Commun. *10*, 489 (1980).
5. Drobnica L., Kristian P., Augustín J.: *The Chemistry of Cyanates and their Thio Derivatives* (S. Patai, Ed.), p. 1007. Wiley-Interscience, New York 1977.
6. Heakler R. E., Balko T. W.: Syn. Commun. *5*, 143 (1975).
7. Woodgate P. D., Lee H. H., Ruthledge P. S., Cambie R. C.: Heterocycles *7*, 109 (1977).
8. Martvoň A., Uher M., Stankovský Š.: This Journal *42*, 745 (1977).
9. Jones G. D., Zimmerman R. L.: U.S. 2 757 190; Chem. Abstr. *50*, 15 129 (1956).

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