SYNTHESIS AND STABILITY OF 2-OXOISOTHIOCYANATES

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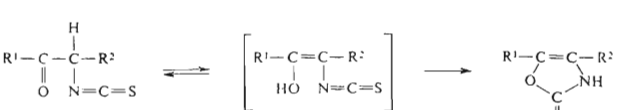
Enolizable 2-oxoisothiocyanates *Ia*—*If* were prepared from hydrochlorides of amino ketones, containing a hydrogen atom in the α-position, by reaction with thiophosgene in the presence of $CaCO_3$. At room temperature the enol form of these compounds undergoes slow cyclization to give the isomeric 4-oxazoline-2-thiones *IIb*—*IIf*. In the presence of bases this isomerization proceeds rapidly even at room temperature. 2-Isothiocyanatocyclopentanone (*Ia*) does not cyclize to the corresponding oxazolinethione either on heating or action of bases. The rate of the thermally initiated isomerization of the 2-oxoisothiocyanates *Ib*—*If* was determined by IR spectroscopy.

In contrast with many papers on 1- and 3-oxoisothiocyanates, no reports on synthesis of 2-oxoisothiocyanates occured until 1976 when Jochims prepared compounds of the type $R^1COC(R^2)(R^3)NCS$ by dehydrosulfuration of dithiocarbamic acids with N,N'-dicyclohexylcarbodiimide. This reaction afforded 2-oxoisothiocyanates only if the substituents R^2 and R^3 were not hydrogen atoms, otherwise only the isomeric 4-oxazoline-2-thiones were isolated which arised by rapid intramolecular cyclization of the enol form of the primarily formed 2-oxoisothiocyanate.



Ia, $R^1, R^2 = (CH_2)_3$
Ib, $R^1, R^2 = (CH_2)_4$
Ic, $R^1, R^2 = (CH_2)_5$
Id, $R^1 = CH_3$, $R^2 = H$
Ie, $R^1 = C_6H_5$, $R^2 = H$
If, R^1 = 2-furyl, $R^2 = H$

IIb, $R^1, R^2 = (CH_2)_4$
IIc, $R^1, R^2 = (CH_2)_5$
IId, $R^1 = CH_3$, $R^2 = H$
IIe, $R^1 = C_6H_5$, $R^2 = H$
IIf, R^1 = 2-furyl, $R^2 = H$

SCHEME 1

In the present investigation we prepared the enolizable 2-oxoisothiocyanates *Ia–If* (Scheme 1, Table I) from hydrochlorides of α-amino ketones by a heterogeneous reaction with thiophosgene. It appeared that the reaction course was decisively influenced by the base employed. Calcium carbonate gave best yields of isothiocyanates *Ia–If*, the isomeric 4-oxazoline-2-thiones *IIb–IIf* (Scheme 1) arising only in traces (found by thin-layer chromatography). On the other hand, an exclusive formation of the oxazolines was observed with stronger bases such as $NaHCO_3$, Na_2CO_3 or $(C_2H_5)_3N$. Chloroform was found to be the solvent of choice. The reaction yields depended on the order and manner of addition of the components, on temperature and time (see Experimental). Slow addition of aqueous hydrochloride solutions or prolonged reaction time lowered the yield, increasing simultaneously the amount of the oxazoline and polymeric products. Cooling had no effect on the formation of side-products.

The obtained 2-oxoisothiocyanates are relatively stable at room temperature: in benzene solutions they cyclize to the corresponding 4-oxazoline-2-thiones in several weeks (Scheme 1). In boiling toluene the cyclization is complete in 10 hours.

TABLE I
Analytical data for 2-oxoisothiocyanates

Compound	B.p., °C (yield, %)	Reaction time, min	Formula (mol. wt.)	Calculated/ /Found	
				% N	% S
Ia	75–78[a] (81·5)	60	C_6H_7NOS (141·1)	9·94 9·71	22·65 22·49
Ib	85–87[a] (80·0)	45	C_7H_9NOS (155·1)	9·03 9·19	20·63 20·39
Ic	103[a] (57·7)	50	$C_8H_{11}NOS$ (169·1)	8·27 8·11	18·92 18·71
Id	63–65[b] (32)	20	C_4H_5NOS (115·1)	12·17 12·30	28·83 27·71
Ie	[c] (71·7)	30	C_9H_7NOS (177·1)	7·91 8·09	18·06 17·91
If	[c] (38·7)	30	$C_7H_5NO_2S$ (167·1)	8·38 8·26	19·16 19·04

[a] At 8 Pa; [b] at 233 Pa; [c] solid compound, on heating to its m.p. it isomerizes to the corresponding 4-oxazoline-2-thione.

The 4-oxazoline-2-thiones *IIb*–*IIf* are stable compounds, described already in the literature.

The characteristic feature of the isothiocyanates *Ib*–*If* is their high sensitivity towards bases which catalyze their cyclization to the corresponding oxazolinethiones. Thus, addition of a catalytic amount of triethylamine to a benzene solution of the isothiocyanate brings about a practically instantaneous isomerization to the oxazoline. This behavior could explain the unsuccessful attempts to prepare enolizable 2-oxoisothiocyanates from dithiocarbamic acids[1] because the employed N,N'-dicyclohexylcarbodiimide acts as a base. 2-Isothiocyanatocyclopentanone (*Ia*) occupies an exclusive position among the synthesized isothiocyanates because it does not undergo the intramolecular cyclization to oxazolinethione, either on heating or by treatment with bases. This behaviour is probably connected with the sterically unfavourable formation of an endocyclic double bond in the cyclopentane ring[2].

Kinetics of the thermally initiated cyclization of isothiocyanates *Ib*–*If* to oxazolinethiones *IIb*–*IIf* was followed by IR spectroscopy. The highest rate constant k was found for *Ie* (Table II); in this compound the intermediary enol form is stabilized by conjugation with the benzene ring. On the other hand, due to a weaker conjugation

TABLE II

Rate constants for isomerization of 2-oxoisothiocyanates *Ib*–*If* in boiling toluene (110°C)

Isomerization	*Ib* → *IIb*	*Ic* → *IIc*	*Id* → *IId*	*Ie* → *IIe*	*If* → *IIf*
k . 10^{-4} s^{-1}	2·88	1·60	0·44	6·46	1·15

TABLE III

IR and ^{1}H NMR spectral data for compounds *Ia*–*If*

Compound	ν(C=O), cm^{-1}	ν(N–C=S), cm^{-1}	CH_2 δ, ppm	H-2 δ, ppm
Ia	1 773	2 061	—	4·15
Ib	1 745	2 051	—	4·25
Ic	1 737	2 054	—	4·13
Id	1 751	2 066	4·40	—
Ie	1 715	2 064	4·93	—
If	1 713	2 053	4·81	—

of furan ring with the enol double bond, the k value for compound *If* is lower than that for *Ie*. The rate constant values for isomerization of the isothiocyanates *Ib*–*Id* can be interpreted using data on the steric situation in molecules of aliphatic and alicyclic ketones. Thus, the high k value for *Ib* is in accord with the high concentration of the enol form in cyclohexanone and its 2-substituted derivatives[3]. On the other hand, the much lower (by an order of magnitude) k value for *Id* confirms that aliphatic ketones are generally less enolized that their alicyclic analogues[4].

The IR spectra of the prepared isothiocyanates (Table III) exhibit a complex ν(N=C=S) absorption band at 2 050–2 065 cm^{-1}. The shift of the ν(C=O) band of 2-oxoisothiocyanates towards shorter wavelengths relative to the unsubstituted ketones can be ascribed to the electron acceptor effect of the N=C=S group. The ^{1}H NMR spectra of isothiocyanates *Ia*–*Ic* (Table III) contain a characteristic multiplet of the $H_{(2)}$ proton (X proton of an ABX system). The spectra of compounds *Id*–*If* exhibit the CH_2 singlet at a considerably low field strength.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. The IR spectra of the prepared isothiocyanates and their isomerization rates were measured in toluene on a UNICAM SP-100 spectrophotometer. ^{1}H NMR spectra were obtained with a Tesla BS-487 C (80 MHz) instrument in deuteriochloroform with tetramethylsilane as internal standard. The following starting amino ketones were prepared according to the literature: 1-amino-2-propanone[7], 2-aminocyclopentanone[8], 2-aminocycloheptanone[8], 2-aminocyclohexanone[9], α-aminoacetophenone[10] and 2-aminoacetylfuran[6].

Preparation of 2-Oxoisothiocyanates *Ia*–*If*

A solution of the corresponding α-amino ketone hydrochloride (40 mmol) in water (100 ml) was added in one portion to a stirred mixture of thiophosgene (3·5 ml; 44 mmol), chloroform (100 ml) and $CaCO_3$ (10 g) and the stirring was continued at room temperature for 20–60 min. The unreacted $CaCO_3$ was filtered off, the chloroform layer of the filtrate was separated and the aqueous one was extracted with chloroform (50 ml). The combined organic layers were dried over magnesium sulfate and taken down. Compounds *Ia*–*Id* were distilled under diminished pressure to give oily products, solidifying in refrigerator (except *Id*). In the case of *Ie* and *If*, the residue after removal of chloroform was mixed with benzene (10 ml), treated with charcoal, filtered and the filtrate was mixed with light petroleum (10 ml) and kept in a refrigerator. The crystalline product was collected and washed with light petroleum.

Isomerization of Isothiocyanates *Ib*–*If* to 4-Oxazoline-2-thiones *IIb*–*IIf*

a) A solution of the isothiocyanate (0·01 mol) in toluene (15 ml) was refluxed for 10 h, cooled and the crystals were collected and crystallized from toluene.

b) Triethylamine (3 drops) was added to a stirred solution of the isothiocyanate (0·01 mol) in benzene (20 ml). After 5 min the solvent was evaporated under diminished pressure and the residue was crystallized from toluene; *IIb* m.p. 154–155°C, ref.[5]; *IIc* m.p. 158–159°C, *IId* m.p. 111 to 112°C, *IIe* m.p. 221–222°C, ref.[1]; *IIf* m.p. 205–206°C, ref. [6] (*IIc* and *IId* is not described in the literatur).

Kinetic Measurements of Thermally Initiated Isomerization of Isothiocyanates *Ib—If*

The dependence of the 2-oxoisothiocyanate concentration on time was followed as the decrease in the IR carbonyl absorption. A solution of the isothiocyanate in toluene (initial concentration 0·3 mol l^{-1}) was refluxed, the withdrawn samples were cooled and their IR spectrum in the region 1 600—1 800 cm^{-1} was taken. For each isothiocyanate 7 samples were taken which exhibited 80—20% of the original carbonyl absorption. The isomerization rate constants were calculated using the first order kinetic equation.

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