REACTIONS OF α-SUBSTITUTED CINNAMOYL ISOTHIOCYANATES WITH SODIUM HYDROSULPHIDE AND DIAZOMETHANE

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Received September 24th, 1976

Addition-cyclisation reaction of α-substituted cinnamoyl isothiocyanates with sodium hydrosulphide and [3 + 2] cycloaddition reaction of these compounds with diazomethane have been studied. The reaction with sodium hydrosulphide leads to 6-substituted 4-oxo-2-thioxoperhydro--1,3-thiazines or 5-benzylidene-1-oxo-2-thioxo-1,3-thiazolidine, depending upon the type of substituents. With α-chloro- and α-cyanocinnamoyl isothiocyanate, and with *E*-isomer of α-bromocinnamoyl isothiocyanate, the reaction proceeds with decomposition to form corresponding methyl cinnamates. α-Substituted cinnamoyl isothiocyanates react with diazomethane to give 5-substituted 1,2,3-thiadiazoles. Configuration around the C=C bond of these compounds has been determined by ^{1}H-NMR spectroscopy using the method of additive shielding increments.

As we found in the previous study, α,β-unsaturated acyl isothiocyanates react with alkali metal hydrosulphides to produce 6-substituted 4-oxo-2-thioxoperhydro--1,3-thiazines[1]. In order to examine substituent effects upon the course of this addition-cyclisation reaction, in the present work we have studied the above reaction with α-substituted cinnamoyl isothiocyanates. In the reaction of these compounds with diazomethane we have been interested in the possibility of formation of various cycloadducts, both on the NCS group, and on the C=C bond.

α-Substituted cinnamoyl isothiocyanates were prepared by reaction of thionyl chloride with the corresponding cinnamic acid, followed by treatment of formed cinnamoyl chlorides with lead(II) or silver(I) thiocyanate in an organic solvent[2]. α-Methylcinnamic acid (*Z* : *E* isomer ratio = 1 : 1), (*Z*)-α-phenylcinnamic acid, and (*E*)-α-cyanocinnamic acid was prepared by Perkin or Knoevenagel reaction[3,4]. *Z*-isomers of α-bromo- and α-chlorocinnamic acids were synthesised by the method reported by Park and Wright[5] which is based upon displacement of the HgCl group in α-chloromercuricinnamic acid with halogen. (*E*)-α-bromocinnamic acid was obtained by elimination of HBr from α,β-dibromo-β-phenylpropionic acid[6] (Table I). Prepared isothiocyanates were unstable compounds, except for α-cyanocinnamoyl isothiocyanate. Because of their instability they could be identified only by IR spectra. of crude products (characteristic bands ν(NCS) and ν(C=O)). We expected that α-substituted cinnamoyl isothiocyanates would behave in the reaction with sodium

hydrosulphide similarly as cinnamoyl isothiocyanates. However, we have found that the course of the above reaction depends upon the type of substituent, as shown in Scheme 1.

With substituents having inexpressive electronic effects (CH_3, C_6H_5), the reaction proceeds similarly as with the parent compound (Scheme 1*A*). Another course of the reaction has been observed with bromine as the substituent that belongs to easily leaving groups. In this case the transiently formed dithiocarbamate attacks the α-carbon of cinnamoyl isothiocyanate to form the five-membered ring of 5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidine (Scheme 1*B*). In order to confirm the structure of the product, we have prepared this substance from rhodanine by condensation with benzaldehyde[7]. Identical elemental analyses, spectral data as well as physical constants of both products confirmed the formation of the five-membered ring. The reaction of α-cyano-, α-chloro- and (*E*)-α-bromocinnamoyl isothiocyanate with sodium hydrosulphide proceeds with decomposition to give the corresponding methyl cinnamates (Scheme 1*C*). These were isolated from the reaction mixture and identified by IR and ^{1}H-NMR spectroscopy and by comparing their physicochemical constants with reported data[8–10]. The formation of these esters can be explained by the electron acceptor effect of the α-substituents which labilize transiently formed

TABLE I

Determination of the Configuration of α-Substituted Cinnamic Acids $C_6H_5CH{=}CX{-}COOH$ by the Method of Additive Shielding Increments

X	$\delta(CH)_{exp.}$	$\delta(CH)_{calcld.}$		Configuration	M.p., °C (solvent)
		Z	*E*		
CH_3	7·70	6·73	7·76	E	97–98 (cyclohexane)
C_6H_5	7·80	7·70	7·54	Z	175–177 (ethanol–water)
CN	8·20	8·09	8·16	E	178–179 (ethanol–water)
Cl	7·90	7·74	7·52	Z	137–138 (ethanol–water)
Br	8·22	8·16	7·40	Z	130 (ethanol–water)
Br	7·47	8·16	7·40	E	120–121 (benzene–light petroleum)

dithiocarbamates. This labilization leads to the decomposition of these intermediates in the reaction mixture. Difference in the behaviour of the *Z*- and *E*-isomers of α-bromocinnamoyl isothiocyanate arises from the different steric arrangement of substituents in the vicinity of the α-carbon of the C=C bond.

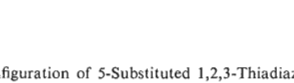
In the study of the reaction of α-substituted cinnamoyl isothiocyanates with diazomethane we have made experiments with varying rations of the reactants. In all cases except the cyano derivative (which did not react with diazomethane) only one product, 5-substituted 1,2,3-thiadiazole, has been isolated from the reaction mixture (Scheme 2).

In the above cycloaddition reactions the C=C double bond is not attacked. This could be due to the competition reaction of diazomethane with the NCS bond being much faster than the reaction with the C=C bond. The thiadiazole formed by this reaction precipitates from the reaction mixture which prevents diazomethane from reacting with the ethylenic group. Isolated yields of the products decrease with increasing electron acceptor ability of the substituent (Scheme 2). The configuration on the C=C bond of prepared thiadiazoles (Table II) has been determined by the method of additive shielding increments according to Matter and coworkers[11]. This method is based on comparison of the experimental and calculated values of the chemical shifts of the olefinic proton $\delta(C{=}CH)$ according to the relation:

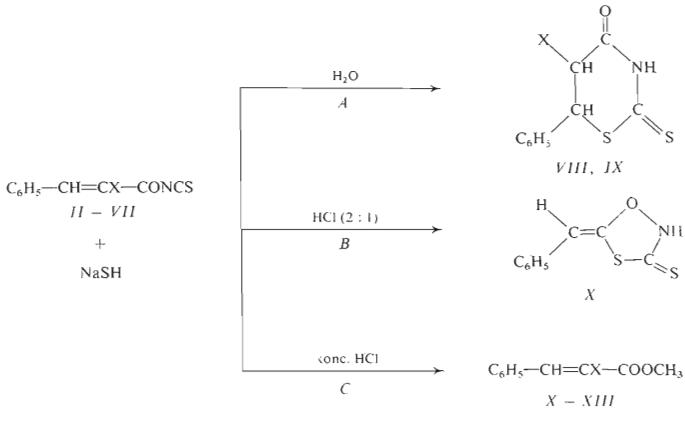
$$\delta(C{=}CH) = 5{\cdot}25 + Z_{gem} + Z_{cis} + Z_{trans},$$

TABLE II

Determination of the Configuration of 5-Substituted 1,2,3-Thiadiazoles by the Method of Additive Shielding Increments

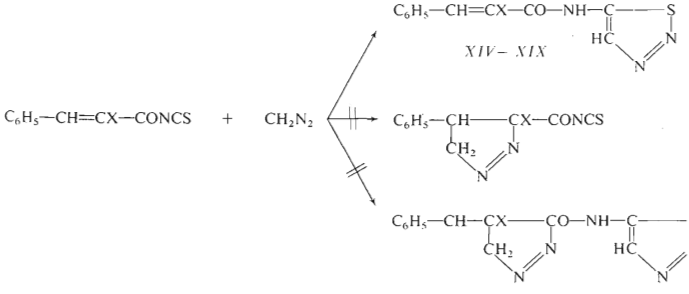


No	Experimental δ_A	Calculated		Configuration
		$\delta_A Z$	$\delta_A E$	
XIV	7·69	7·08	7·61	*E*
XV	7·50	6·87	7·33	*E*
XVI	7·90	7·86	7·54	*Z*
XVII	7·95	7·74	7·27	*Z*
XVIII	8·23	8·16	7·54	*Z*
XIX	7·42	8·16	7·54	*E*



A: X = CH_3, C_6H_5 *B*: X = Br (*Z*-isomere) *C*: X = CN, Cl, Br, (*E*-isomere)

SCHEME 1



X	CH_3	C_6H_5	H	Cl	Br	CN
Yield, %	67	58	34	30	8	0

SCHEME 2

where 5·25 is the basic value derived from the chemical shift in ethylene and Z_{gem}, Z_{cis}, and Z_{trans} are the so-called additive shielding increments of substituents on the double bond.

From the results presented in Table I one can assume that the configuration of the starting α-substituted cinnamoyl isothiocyanates is the same as the configuration of the corresponding thiadiazoles, since the ethylenic double bond does not participate in the above cycloaddition reaction. The configuration of isothiocyanates could not be determined by this method since the value of the increments for —CONCS is not yet known. The configuration of α-cyanocinnamoyl isothiocyanate has been determined based on the known configuration of α-cyanocinnamic acid which does not undergo changes during the synthesis. In the case of α-methylcinnamoyl chloride, which is a mixture of the *Z*- and *E*-isomers in the 1 : 1 ratio, distillation of the crude products leads to quantitative transformation of the *Z*- into *E*-isomer. The configuration of the product of the reaction of α-methylcinnamoyl isothiocyanate with diazomethane corresponds to *E*-isomer, which proves that the corresponding isothiocyanate has configuration which is identical with that of α-methylcinnamoyl chloride.

EXPERIMENTAL

Cinnamoyl isothiocyanate (*I*) was described in our previous work[2]. (*E*)-α-Methylcinnamoyl isothiocyanate (*II*), 93% yield; IR spectrum ($CHCl_3$): ν(C=C) 1 628 cm^{-1}, ν(C=O) 1 685 cm^{-1}, ν(NCS) 1 980 cm^{-1}. (*Z*)-α-Phenylcinnamoyl isothiocyanate (*III*), 60% yield; IR spectrum ($CHCl_3$): ν(C=C) 1 622 cm^{-1}, ν(C=O) 1 716 cm^{-1}, ν(NCS) 1 980 cm^{-1}. (*Z*)-α-Chlorocinnamoyl isothiocyanate (*IV*), 72% yield; IR spectrum ($CHCl_3$): ν(C=C) 1 609 cm^{-1}, ν(C=O) 1 700 cm^{-1}, ν(NCS) 1 975 cm^{-1}. (*Z*)-α-Bromocinnamoyl isothiocyanate (*V*), 80% yield; IR spectrum ($CHCl_3$): ν(C=C) 1 592 cm^{-1}, ν(C=O) 1 708 cm^{-1}, ν(NCS) 1 970 cm^{-1}. (*E*)-α-Bromocinnamoyl isothiocyanate (*VI*), 60% yield; IR spectrum ($CHCl_3$): ν(C=C) 1 603 cm^{-1}, ν(C=O) 1 700 cm^{-1}, ν(NCS) 1 966 cm^{-1}. (*E*)-α-Cyanocinnamoyl isothiocyanate (*VII*), 36% yield, m.p. 84—85°C (cyclohexane). For $C_{11}H_6N_2OS$ (214·3) calculated: 61·67% C, 2·82% H, 13·08% N; found: 61·35% C, 2·96% H, 13·24% N. IR spectrum ($CHCl_3$): ν(C=C) 1 594 cm^{-1}, ν(C=O) 1 700 cm^{-1}, ν(NCS) 1 955 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ scale): 8·20 (singlet, —CH—), 7·67 (multiplet, C_6H_5). Derivatives *II* and *VII* were prepared by treatment of the corresponding cinnamoyl chlorides with $Pb(SNC)_2$ and derivatives *III*—*VI* by treatment with AgSCN. All isothiocyanates except the derivative *VII* were obtained only as crude viscous oils.

Reactions of α-Substituted Cinnamoyl Isothiocyanates with Sodium Hydrosulphide (Scheme 1)

A) Isothiocyanates *II*, *III* (0·007 mol) were added to 30 ml of methanolic solution of sodium hydrosulphide (0·014 mol) in small portions with stirring. After addition of water, the precipitate formed was filtered off, washed with water and recrystallized from an appropriate solvent. By this procedure the following substances have been obtained: 6-Phenyl-5-methyl-4-oxo-2-thioxoperhydro-1,3-thiazine (*VIII*), 67% yield, m.p. 171—172°C (CCl_4). For $C_{11}H_{11}NOS_2$ (237·4) calculated: 55·67% C, 4·68% H, 5·90% N; found: 55·60% C, 4·81% H, 5·73% N, IR spectrum

($CHCl_3$): ν(NH) 3348 cm^{-1}, ν(C=O) 1720 cm^{-1}, ν(NHCS) 1429 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$, δ scale): 9·57 (singlet, NH), 4·53 (doublet, —CH—), 3·25 (octet, —CH), 2·46 (multiplet, C_6H_5), 1·20 (doublet, CH_3). 5,6-Diphenyl-4-oxo-2-thioxoperhydro-1,3-thiazine (*IX*), 63% yield, m.p. 217—218°C (benzene–tetrachloromethane 1 : 1). For $C_{16}H_{13}NOS_2$ (299·4) calculated: 64·12% C, 4·37% H, 4·67% N; found: 64·33% C, 4·59% H, 4·56% N. IR spectrum ($CHCl_3$): ν(NH) 3347 cm^{-1}, ν(C=O) 1718 cm^{-1}, ν(NHCS) 1440 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$–hexadeuteriodimethyl sulphoxide 5 : 2) 7·07 (multiplet, C_6H_5), 5·08 and 4·43 (dublets, CH).

B) The same procedure as in the previous case has been used except that the precipitate was obtained by treatment of the reaction mixture with dilute hydrochloric acid (2 : 1). Using this procedure, the *Z*-isomer of α-bromocinnamoyl isothiocyanate (*V*) gave 5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidine (*X*) in 61% yield; m.p. 205—206°C (benzene–tetrachloromethane 1 : 1). For $C_{10}H_7NOS_2$ (221·3) calculated: 54·27% C, 3·19% H, 6·28% N; found: 54·38% C, 3·08% H, 6·45% N. IR spectrum ($CHCl_3$): ν(NH) 3396 cm^{-1}, ν(C=O) 1730 cm^{-1}, ν(C=C) 1608 cm^{-1}, ν(NHCS) 1413 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$-hexadeuteriodimethyl sulphoxide 6 : 1): 7·50 (singlet, —CH—), 7·38 (multiplet, C_6H_5).

C) To the reaction mixture containing the corresponding isothiocyanate and sodium hydrosulphide, concentrated hydrochloric acid is added and the resulting oil is extracted with chloroform. The chloroform layer is evaporated and the crude product is purified by vacuum distillation. By this procedure isothiocyanates *IV*, *VI* and *VII* afforded corresponding methyl cinnamates. Methyl α-chlorocinnamate (*XI*), 52% yield, b.p. 93°C/4 Torr. IR spectrum ($CHCl_3$): ν(C=O) 1735 cm^{-1}, ν(C=C) 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7·94 (singlet, —CH—), 7·28 (multiplet. C_6H_5), 3·56 (singlet. CH_3). Methyl α-bromocinnamate (*XII*), 57% yield, b.p. 88°C/4 Torr, IR spectrum ($CHCl_3$): ν(C=O) 1732 cm^{-1}, ν(C=C) 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7·82 (singlet, —CH—), 7·15 (multiplet, C_6H_5), 3·42 (singlet, CH_3). Methyl α-cyanocinnamate(*XIII*), 64% yield, b.p. 106°C/4 Torr. IR spectrum ($CHCl_3$): ν(C≡N) 2210 cm^{-1}, ν(C=O) 1743 cm^{-1}, ν(C=C) 1624 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 8·35 (singlet, —CH—), 7·46 (multiplet, C_6H_5), 3·87 (singlet, CH_3).

5-Substituted 1,2,3-Thiadiazoles *XIV*—*XIX*

An ethereal solution of diazomethane (0·02 mol) is added dropwise at —10°C during 20 min into isothiocyanates *I*—*IV* and *VII* (0·01) dissolved in ether. Stirring is continued for 30 min with cooling and then for 45 min at room temperature. The product is isolated by filtration with suction, washed with ether, dried and recrystallized from the appropriate solvent. In the case of isothiocyanates *V* and *VI* the temperature was —80°C. The following compounds have been prepared by this way: 5-Cinnamoylamino-1,2,3-thiadiazole (*XIV*), 34% yield, m.p. 245—246·5°C (ethanol–water 2 : 3). For $C_{11}H_9N_3OS$ (231·9) calculated: 57·13% C, 3·92% H, 18·17% N; found: 57·25% C, 3·77% H, 18·05% N. IR spectrum (KBr): ν(C=O) 1677 cm^{-1}, ν(C=C) 1631 cm^{-1}. ^{1}H-NMR ($CDCl_3$–hexadeuteriodimethyl sulphoxide): 12·03 (singlet, NH), 8·55 (singlet, CH), 7·74 and 6·69 (doublets, —CH=CH—, J_{AB} = 16 Hz), 7·38 (multiplet, C_6H_5). 5-(α-Methylcinnamoylamino)-1,2,3-thiadiazole (*XV*), 65% yield, m.p. 199—200°C (ethanol–water 2 : 3). For $C_{12}H_{11}N_3OS$ (245·3) calculated: 58·75% C, 4·45% H, 17·09% N; found: 58·68% C, 4·74% H, 17·07% N. IR spectrum (KBr): ν(C=O) 1665 cm^{-1}, ν(C=C) 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$–hexadeuteriodimethyl sulphoxide): 11·95 (singlet, NH), 8·72 (singlet, —CH—), 7·55 (multiplet, C_6H_5), 7·34 (quadruplet, —CH—), 2·28 (doublet, CH_3). 5-(α-Phenylcinnamoylamino)-1,2,3-thiadiazole (*XVI*), 50% yield, m.p. 219—220°C (ethanol–water 3 : 1). For $C_{17}H_{13}N_3OS$ (307·4) calculated: 66·42% C, 4·26% H, 13·67% N; found: 66·60% C, 4·14% H, 13·49% N. IR spectrum ($CHCl_3$): ν(C=O) 1675 cm^{-1}, ν(C=C) 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$–hexadeuteriodimethyl

sulphoxide): 11·15 (singlet, NH), 8·71 (singlet, —CH—), 7·95 (singlet, —CH). 5-(α-Chlorocinnamoylamino)-1,2,3-thiadiazole (*XVII*), 27% yield, m.p. 258—259°C (ethanol–water 2 : 1). For $C_{11}H_8ClN_3OS$ (267·7) calculated: 50·10% C, 3·01% H, 15·69% N; found: 50·26% C, 3·28% H, 15·64% N. IR spectrum (KBr): ν(C=O) 1659 cm^{-1}, ν(C=C) 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$–hexadeuteriodimethyl sulphoxide): 8·93 (singlet, —CH—), 8·28 (singlet, —CH—), 7·68 (multiplet, C_6H_5). 5-((*Z*)-α-Bromocinnamoylamino)-1,2,3-thiadiazole (*XVIII*), 8% yield, m.p. 229 to 231°C (ethanol–water 2 : 1). For $C_{11}H_8BrN_3OS$ (312·2) calculated: 42·96% C, 3·55% H, 13·45% N; found: 42·75% C, 3·31% H, 13·42% N. IR spectrum (KBr): ν(C=O) 1651 cm^{-1}, ν(C=C) 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$–hexadeuteriodimethyl sulphoxide): 8·93 (singlet, —CH—), 8·28 (singlet, —CH—), 7·68 (multiplet, C_6H_5). 5-((*E*)-α-Bromocinnamoylamino)-1,2,3-thiadiazole (*XIX*), 7% yield m.p. 212—214°C. For $C_{11}H_8BrN_3OS$ (312·2) calculated: 42·96% C, 3·55% H, 13·45% N; found: 42·64% C, 3·72% H, 13·27% N. IR spectrum (KBr): ν(C=O) 1653 cm^{-1}, ν(C=C) 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$–hexadeuteriodimethyl sulphoxide): 12·50 (singlet, NH), 8·90, 7·37 (singlets, —CH—), 7·35 (multiplet, C_6H_5).

Spectral Measurements

Infrared absorption spectra, in the 800—3500 cm^{-1} region, of synthesized compounds were recorded with a double-beam Zeiss UR-20 spectrophotometer in chloroform and KBr pellets. The instrument was calibrated with a polystyrene foil. NMR spectra were measured on a Tesla BS 487 instrument working at 80 MHz, using deuterated chloroform and dimethylsulphoxide. Hexamethyldisiloxane has been used as internal reference.

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Translated by J. Hetflejš.