SYNTHESIS AND REACTIONS OF *cis*-3-(2-FURYL)PROPENOYL ISOCYANATE

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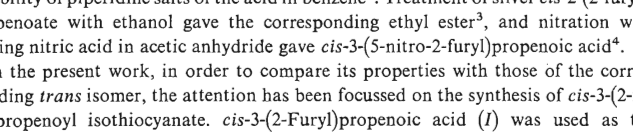
cis-3-(2-Furyl)propenoyl isothiocyanate has been synthesized and its properties have been compared with those of the *trans*-isomer. Treatment of the foregoing isothiocyanates with benzylamine, piperidine or diazomethane yielded the corresponding thiourea and thiadiazole derivatives having unchanged configuration. Oxidation of the thiourea derivatives with bromine, or reaction of the isomeric isothiocyanates with NaSH and diphenylamine is independent of the configuration of the starting substances: the same thiazoline or perhydro and dihydrothiazine derivatives are formed. It has been concluded, based on ^{1}H and ^{13}C-NMR data that, relative to the C=C bond, the furan ring in *cis*- and *trans*-3-(2-furyl)propenoyl derivative exists in *s-cis* and *s-trans* conformation, respectively.

In the literature there are several works that describe synthesis of *cis*-3-(2-furyl)propenoic acid and its derivatives. Decarboxylation of furfurylidenemalonic acid in acetic anhydride gave a 1 : 1 mixture of *cis*- and *trans*-3-(2-furyl)propenoic acid[1]. Pure *cis* acid was obtained by separation of the mixture, taking advantage of different solubility of piperidine salts of the acid in benzene[2]. Treatment of silver *cis*-2-(2-furyl)-propenoate with ethanol gave the corresponding ethyl ester[3], and nitration with fuming nitric acid in acetic anhydride gave *cis*-3-(5-nitro-2-furyl)propenoic acid[4].

In the present work, in order to compare its properties with those of the corresponding *trans* isomer, the attention has been focussed on the synthesis of *cis*-3-(2-furyl)propenoyl isothiocyanate. *cis*-3-(2-Furyl)propenoic acid (*I*) was used as the starting material. Treatment of *I* in benzene with PCl_3 at ambient temperature gave *cis*-3-(2-furyl)propenoyl chloride (*II*). Hydrogen chloride was removed with

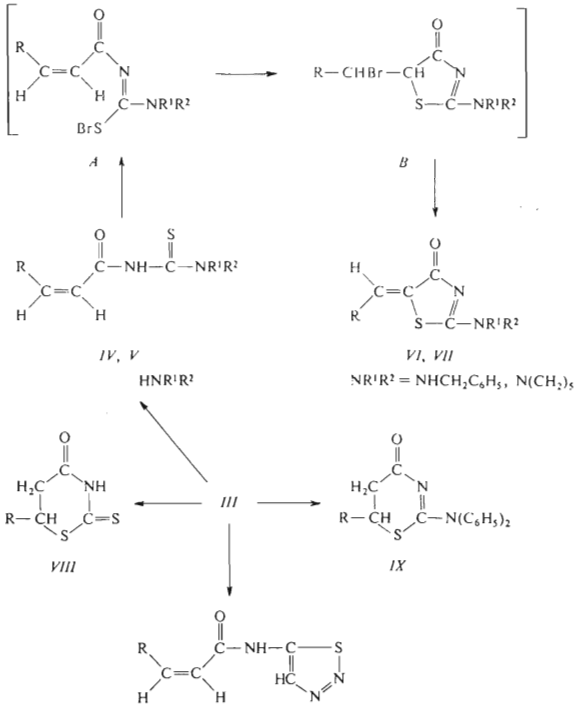


I *II* *III*

SCHEME 1

Ag_2O in the presence of a molecular sieve, and subsequent treatment of the *cis*-chloride *II* in benzene at 55–60°C with $Pb(SCN)_2$ yielded *cis*-3-(2-furyl)propenoyl isothiocyanate (*III*), (Scheme 1).

When the reaction of *II* with $Pb(SCN)_2$ was performed without removal of HCl, a mixture of *cis*- and *trans*-3-(2-furyl)propenoyl isothiocyanate was obtained. On contact with water, chloride *II* and isothiocyanate *III* hydrolyze within a few minutes into the corresponding acid *I*; the *trans*-isomers are less moisture-sensitive, their hydrolysis takes several hours. Since compounds *II* and *III* isomerize quantitatively



SCHEME 2

at the boiling temperature, it was necessary to work with crude products that were sufficiently pure for the next reactions. The reaction of the *cis*-isothiocyanate *III* with benzylamine and piperidine afforded the thiourea derivatives *IV* and *V*, respectively, having *cis*-configuration at the C=C bond; the substances isomerize on standing into *trans*-isomers. Oxidation with bromine in $CHCl_3$ of isomeric *trans*-thiourea derivatives, obtained from *trans*-3-(2-furyl)propenoyl isothiocyanate, gives exclusively *Z*-isomers of 2-substituted 5-furfurylidenethiazoline-4-ones[5]. It seemed interesting to explore whether the same reaction carried out with *cis*-thiourea derivatives *IV* and *V* would afford the corresponding *E*-isomers. Unwanted isomerization of the formed *E*-isomers by means of HBr liberated during the reaction was excluded by an addition of triethylamine or Ag_2O as acid-scavengers. Nevertheless, *Z*-isomers of 2-substituted 5-furfurylidenethiazoline-4-ones *VI* and *VII* (Scheme 2) were obtained as sole products.

Based on the aforementioned data it can be assumed that the elimination of HBr from the intermediate B occurs *via* carbonium ion to yield the more stable product, *i.e.* the *Z*-isomer.

In the reaction with NaSH or with diphenylamine gives *cis*-isothiocyanate *III*, perhydro- and dihydro-1,3-thiazine derivatives *VIII* and *IX* (Scheme 2), identical with products of analogous reactions of *trans*-3-(2-furyl)propenoyl isothiocyanate[6,7].

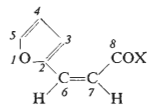
1,3-Dipolar cycloaddition of diazomethane with *cis*- and *trans*-3-(2-furyl)propenoyl isothiocyanate has also been studied. We were interested in the possibility of the formation of various cycloadducts resulting from the interaction of the reagent with either the NCS group or with the ethylennic double bond. The reaction has been carried out in solvents of different polarity (cyclohexane, ether, chloroform, tetrahydrofuran, dioxane) at temperatures ranging from +10 to −80°C using 1−10 fold molar excess of diazomethane. Under these conditions the addition occurred only at the C=S bond of the NCS group yielding 5-substituted 1,2,3-thiazoles *X* and *XI* having unchanged *cis*- or *trans*-configuration at the C=C bond. This can be explained, similarly to the case of 2-substituted 3-phenylpropenoyl isothiocyanates[8], by the faster reaction of diazomethane with the NCS group than with the C=C arrangement. The formed thiadiazole is a very insoluble substance, it separates from the reaction mixture, this being another factor that prevents further reaction of the C=C bond with diazomethane. The best yield of the thiadiazole was obtained when three-fold excess of diazomethane in ether at 0°C was used.

The structures of the synthesized substances were deduced on the basis of elemental analyses and IR, ^1H, and ^{13}C-NMR spectral data. Compounds *VI*–*IX* are identical with products of analogous reactions of *trans*-3-(2-furyl)propenoyl isothiocyanate and their structure is discussed elsewhere[5–7].

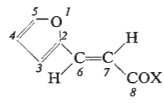
The IR spectra of *cis*-3-(2-furyl)propenoic acid (*I*) and its derivatives *II*–*V* and *X* show absorption bands of deformation stretchings of *cis*-ethylenic C—H bonds γ(CH=CH) at 837–858 cm^{-1}. The *trans*-isomers show the corresponding bands

TABLE I

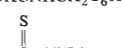
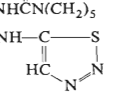
^{1}H-NMR Spectra of *cis*- and *trans*-3-(2-Furyl)propanoyl Derivatives (measured in $CDCl_3$)



cis, s-cis



trans, s-trans

Compound	X	δ_{ppm}[a] *cis*/*trans*					
		H_3	H_4	H_5	H_6	H_7	δ other
I	OH	7·68	6·52	7·49	6·91	5·75	—
		6·67	6·44	7·49	7·39	6·23	—
II	Cl	7·76	6·55	7·58	6·85	6·02	—
		6·84	6·53	7·57	7·55	6·51	—
III	NCS	7·92	6·55	7·55	6·95	5·74	—
		6·76	6·52	7·54	7·49	6·32	—
IV		7·47	6·45	7·33	6·81	5·66	4·88[b]
		6·55	6·43	7·35	7·53	6·73	4·91
V		7·54	6·45	7·45	6·71	5·79	3·46, 4·02[c]
		6·55	6·47	7·47	7·43	6·43	3·58, 4·08
VI[d]		7·83	6·60	7·70	6·86	6·02	8·61[e]
		6·80	6·58	7·65	7·60	6·65	8·65

[a] Coupling constants: $J_{H_6,H_7} = 13$ Hz (*cis*), $J_{H_6,H_7} = 16$ Hz (*trans*), $J_{H_3,H_4} = 4$ Hz, $J_{H_4,H_5} = 2$ Hz (for *cis* and *trans*). [b] d, CH_2, $J = 5$ Hz. [c] m, CH_2. [d] measured in 1 : 3 $CDCl_3$–DMSO-d_6. [e] s, =CH—.

TABLE II

^{13}C-NMR Spectra of *cis*- and *trans*-3(2-Furyl)propenoic Acids (measured in $CDCl_3$)

Configuration	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(5)}$	$C_{(7)}$	$C_{(8)}$
cis	150·5	118·3	112·9	144·5	132·7	113·0	171·4
trans	150·6	115·7	112·4	145·9	133·0	114·9	172·4

at 964–976 cm^{-1}. The absorption bands of the deformation stretchings of the C—H bonds of the furan ring appear in the spectra of both *cis*- and *trans*-isomers within a narrow range at 885–890 cm^{-1}.

Important information about the geometrical isomery and conformation of the studied substances were obtained from ^{1}H-NMR spectra (Table I). The spectra of *cis*-isomers show two doublets for *cis*-ethylenic protons (J_{H_6,H_7} = 13 Hz); the J_{H_6,H_7} value for the *trans* isomers is 16 Hz. As expected, as a result of weaker shielding effect, an upfield shift of signals is observed in the spectra of *cis*-isomers. In the case of furan protons a pronounced difference between chemical shifts of H_3 in *cis*- and *trans*-isomers is observed ($\Delta\delta = (\delta_{H_3}^{cis} - \delta_{H_3}^{trans}) = 0{\cdot}82 - 1{\cdot}16$ ppm). Since chemical shifts of H_4 and H_5 are not affected by the configuration at the double bond (Table I) it can be assumed that the downfield shift of H_3 signal in the spectra of *cis*-isomers is caused by an anisotropic effect of the COX group, indicating that conformational factors play an important role here as well. Analogous differences in chemical shifts of H_3 signal and long-range interactions across five bonds were used to determine the predominating *s-cis* or *s-trans* conformation of the 5-membered heterocycles and of the C=C bond[9–17]. In the case of long-range interactions a stronger interaction is shown by protons linked by five linkages in a *W* arrangements. In *s-cis* and *s-trans* conformers this condition is fulfilled by H_4 and H_6, and H_5 and H_6, respectively. It was proved in this way that in *trans*-3-(2-furyl)propenoic acid predominates the *s-trans* conformation ($^5J_{H_4,H_6} < 0{\cdot}1$ Hz; $^5J_{H_5H_6}$ = = 0·46 Hz) (ref.[9]), which is in an agreement with the results of X-ray analysis[18]. In this work long-range coupling constants have been measured for the *cis*-acid (*I*). The found coupling constants ($^5J_{H_4,H_5} = 0{\cdot}7$ Hz, $^5J_{H_5,H_6} < 0{\cdot}2$ Hz), together with the aforementioned differences observed for chemical shifts of H_3, suggest that in *cis*-isomers *s-cis* conformation predominates whereas *s-trans* isomers exist predominantly in *s-trans* conformation (Table I). These conclusions prove also ^{13}C-NMR spectra of isomeric 3-(2-furyl)propenoic acids (Table II). As in ^{1}H:NMR spectra the signal for $C_{(3)}$ of the *cis*-isomer is shifted downfield ($\Delta\delta = 2{\cdot}6$ ppm), as a result of the anisotropic effect of the carbonyl group.

EXPERIMENTAL

trans-3-(2-Furyl)propenoyl chloride[19], *trans*-3-(2-furyl)propenoyl isothiocyanate[20,21], N-benzyl-N'-[*trans*-3-(2-furyl)propenoyl]thiourea[22] and 1[N-(*trans*-3-(2-furyl)propenoyl)thio-carbamoyl]piperidine[5] have been described. *cis*-3-(2-Furyl)propenoic acid (*I*) was prepared according to Liebermann[1,2]. IR Data ($CHCl_3$): ν(C=O) 1696 cm^{-1}, ν(C=C) 1621 cm^{-1}, ν (skeletal furan) 1022 cm^{-1}, γ(CH=CH) 841 cm^{-1}.

cis-3-(2-Furyl)propenoyl Chloride (*II*)

A solution of (*I*) (0·5 g, 3·5 mmol) and PCl_3 (0·2 g, 5 mmol) in benzene (20 ml) was left in the dark for 17 h. The solution was decanted, to remove H_3PO_4, and solvents together with the excess

of PCl_3 were evaporated at reduced pressure. The residue was dissolved in benzene (20 ml), and Ag_2O (1 g, 4 mmol) and Nalcit-4 (1 g) was added. The mixture was stirred for 1 h, filtered and concentrated at reduced pressure to give 0·45 (79%) of a crude product. IR Data ($CHCl_3$): ν(C=O) 1 751 cm^{-1}, ν(C=C) 1 600 cm^{-1}, ν (skeletal furan) 1 008 cm^{-1}, γ(CH=CH) 851 cm^{-1}.

cis-3-(2-Furyl)propenoyl Isothiocyanate (*III*)

A mixture of *II* (0·45 g, 2·9 mmol) and $Pb(SCN)_2$ (0·6 g, 1·8 mmol) in benzene (20 ml) was stirred at 55—60°C for 2 g. After filtration, the solution was concentrated at reduced pressure to give a crude product (0·4 g, 80%). IR Data ($CHCl_3$): ν_{as}(NCS) 1 986 cm^{-1}, ν(C=O) 1 695 cm^{-1}, ν(C=C) 1 606 cm^{-1}, ν (skeletal furan) 1 028 cm^{-1}, γ(CH=CH) 860 cm^{-1}.

N-Substituted N'-[*cis*-3-(2-furyl)propenoyl]thiourea Derivatives (*IV*, *V*)

A solution of an amine (2 mmol) in cyclohexane (5 ml) was added dropwise and with stirring into a solution of *III* (0·4 g, 2 mmol) in cyclohexane (15 ml). The precipitate was filtered off, washed with cyclohexane (20 ml), dried, and crystallized from a suitable solvent.

N-*Benzyl*-N'-(*cis*-3-[2-*furyl*]*propenoyl*)*thiourea* (IV): yield, 61%, m.p. 109—111°C (from methanol–water). For $C_{15}H_{14}N_2O_2S$ (284·6) calculated: 61·91% C; 4·92% H; 9·78 N; found: 62·12% C; 4·85% H; 9·81% N. IR Data ($CHCl_3$): $\nu(NH)_{free}$ 3248 cm^{-1}, $\nu(NH)_{assoc}$ 3175 cm^{-1}, ν(C=O) 1681 cm^{-1}, ν(C=C) 1617 cm^{-1}, ν(NHCS) 1510 cm^{-1}, ν (skeletal furan) 1022 cm^{-1}, γ(CH=CH) 837 cm^{-1}.

1-(N-cis-3-(2*Furyl*)*propenoyl*)*thiocarbamoyl*)*piperidine* (V): yield, 67%, m.p. 156—158°C (from acetone–water). For $C_{13}H_{16}N_2O_2S$ (264·4) calculated: 59·06% C; 6·01% H; 10·59% N; found: 59·22% C; 6·18% H; 10·38% N. IR Data ($CHCl_3$): $\nu(NH)_{free}$ 3392 cm^{-1}, $\nu(NH)_{assoc}$ 3150 cm^{-1}, $\nu_{as}(CH_2)$ 2946 cm^{-1}, $\nu_s(CH_2)$ 2861 cm^{-1}, ν(C=O) 1692 cm^{-1}, ν(C=C) 1629 cm^{-1} cm^{-1}, ν(NHCS) 1534 cm^{-1}, ν(skeletal furan) 1017 cm^{-1}, γ(CH=CH) 847 cm^{-1}.

2-Substituted 5-Furfurylidenethiazoline-4-ones (*VI*, *VII*)

Bromine (2·5 ml) was added dropwise to a mixture of thiourea *IV* or *V*, 2·5 mmol) and triethylamine or Ag_2O (15 mmol) in chloroform (15 ml), and the mixture was stirred for 20 min. The filtrate was treated with charcoal (thrice) and the product was precipitated by an addition of light petroleum (four volumes). The precipitate was filtered off, dried and recrystallized from an ethanol–water mixture. Yield, 75—80%. Compounds *VI* and *VII* showed the same properties as did analogous products obtained from the *trans*-isomers[5].

6-(2-*Furyl*)*perhydro*-1,3-*thiazine*-2-*thione*-4-*one* (VIII) *and* 2-*diphenylamino*-6-(2-*furyl*)*dihydro*--1,3-*thiazine*-4-*one* (IX) were obtained from *cis*-3-(2-furyl)propenoyl isothiocyanate and NaSH or diphenylamine, as described for the same reaction of *trans*-3-(2-furyl)propenoyl isothiocyanate[6,7].

5-Substituted-1,2,3-thiadiazoles (*X*, *XI*)

Ethereal diazomethane (9 mmol) was added at 0°C dropwise during 5 min to a solution of *trans*- or *cis*-3-(2-furyl)propenoyl isothiocyanate (3 mmol) in ether (20 ml). Stirring at 0°C was continued for 50 min and then at room temperature for 45 min. The precipitate was collected, washed with ether (20 ml) and recrystallized from an ethanol–water mixture.

5-(cis-3-[2-*Furyl*]*propenoylamino*)-1,2,3-*thiadiazole* (X): yield, 57%, m.p. 270—271°C. For $C_9H_7N_3O_2S$ (221·2) calculated: 48·86% C; 3·18% H; 18·99% N; found: 48·72% C; 3·05% H; 18·70% N. IR Data (KBr): ν(C=O) 1 703 cm^{-1}, ν(C=C) 1 604 cm^{-1}, ν (skeletal thiadiazole) 1 560 cm^{-1}, ν (skeletal furan) 1 036 cm^{-1}, γ(CH=CH) 848 cm^{-1}.

5-(trans-3-[2-*Furyl*]*propenoylamino*)-1,2,3-*thiazole* (XI): yield 74%, m.p. 274—275°C. For $C_9H_7N_3O_2S$ (221·2) calculated: 48·86% C; 3·18% H; 18·99% N; found: 48·91% C; 2·98% H; 19·10% N. IR Data (KBr): ν(C=O) 1 675 cm^{-1}, ν(C=C) 1 628 cm^{-1}, ν (skeletal thiadiazole) 1 552 cm^{-1}, ν (skeletal furan) 1 028 cm^{-1}, γ(CH=CH) 976 cm^{-1}.

Spectral Measurements

The IR spectra (800—3 500 cm^{-1}) were obtained with an IR-75 (Zeiss, Jena) spectrometer calibrated against a polystyrene foil. ^{1}H-NMR (80 MHz) and ^{13}C-NMR (25·04 MHz) spectra were obtained with Tesla BS 487 B and Jeol FX 100 spectrometers, respectively, with tetramethylsilane as the internal standard. Carbon-signal assignments were made by selective proton-decoupling technique.

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