Furan derivatives. XXXV. Preparation of substituted 5-phenyl-2-furfuryl bromides, isothiocyanates, and thiocyanates

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By the effect of phosphorus tribromide on 5-(X-phenyl)-2-furfuryl alcohols 5-(X-phenyl)-2-furfuryl bromides were prepared. From these substances 5-(X-phenyl)-2-furfuryl thiocyanates were obtained by using ammonium thiocyanate. (X = 4-NO_2, 3-NO_2, 2-NO_2, 4-Cl, 3-Cl, 2-Cl, 4-Br, H, and 4-CH_3.) Moreover, there is presented a synthesis of some isothiocyanates of 5-(X-phenyl)-2-furfuryl type based on the direct action of thiophosgene on the corresponding amines or on the heating of corresponding 5-(X-phenyl)-2-furfuryl bromides with potassium thiocyanate in dimethylformamide.

The study of the synthesis of furfuryl thiocyanates [1—3] and their rearrangements to corresponding isothiocyanates [4, 5] has been stimulated by a high biological activity of these substances [6, 7]. In the series of 5-phenyl-2-furfuryl derivatives some 5-phenyl-2-furfuryl alcohols [8] and 5-phenyl-2-furylacetic acids [9, 10] have hitherto been described.

In this paper the synthesis of substituted 5-phenyl-2-furfuryl thiocyanates and isothiocyanates as well as of corresponding starting 5-phenyl-2-furfuryl bromides is studied with the purpose to investigate their biological activity.

Experimental

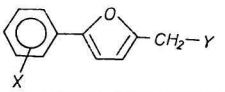
Spectral measurements

The infrared absorption spectra were measured with a double-beam UR 10 (Zeiss, Jena) prism spectrophotometer in the region from 1900 to 2200 cm^{-1}. The measurements were carried out with 0.01 M solutions in spectroscopically pure chloroform. The width of cell was 0.4 mm. The calibration of instrument was performed with a polystyrene foil the width of which was 25 μm. The reading accuracy of the wave numbers was ± 1 cm^{-1}.

The yields, physical constants, and results of elemental analysis for the compounds synthesized are given in Table 1.

5-(X-Phenyl)-2-furfuryl bromides

Phosphorus tribromide (2.35 g; 0.0085 mole) in ether (20 ml) was added dropwise under constant stirring into a cooled (0°C) solution of corresponding 5-phenyl-2-furfuryl

Table 1. List of the synthesized 5-(X-phenyl)-2-furfuryl bromides, isothiocyanates, and thiocyanates 

No.	X	Formula	*M*	Calculated/found					Yield	M.p. [°C]
				% C	% H	% N	% S	% Hal.	[%]	(Kofler)
I	4-NO_2	$C_{11}H_8BrNO_3$	282.09			4.96		28.32	92	113
						5.16		28.06		
II	3-NO_2	$C_{11}H_8BrNO_3$	282.09			4.96		28.32	91	118
						5.12		28.10		
III	2-NO_2	$C_{11}H_8BrNO_3$	282.09			4.96		28.32	92	74–75
						5.06		28.01		
IV	4-NO_2	$C_{12}H_8N_2O_3S$	260.26	55.37	3.09	10.76	12.32		36	119–121
				55.47	3.20	10.70	12.28			
V	4-Cl	$C_{12}H_8ClNOS$	249.70	57.71	3.23	5.61	12.84		32	64–66
				57.81	3.48	5.59	12.54			
VI	4-Br	$C_{12}H_8BrNOS$	294.16	48.99	2.94	4.76	10.90		68	93–94
				49.10	2.78	4.88	10.67			
VII	H	$C_{12}H_9NOS$	215.26	66.95	4.27	6.50	14.89		67	36–38
				66.88	4.18	6.36	14.65			
VIII	4-NO_2	$C_{12}H_8N_2O_3S$	260.26	55.37	3.09	10.76	12.32		93	135–136
				55.28	3.16	10.85	12.16			
IX	3-NO_2	$C_{12}H_8N_2O_3S$	260.26	55.37	3.09	10.76	12.32		92	105–106
				55.52	3.26	10.89	12.26			
X	2-NO_2	$C_{12}H_8N_2O_3S$	260.26	55.37	3.09	10.76	12.32		89	44–45
				55.47	3.02	10.86	12.20			
XI	4-Cl	$C_{12}H_8ClNOS$	249.70	57.71	3.23	5.61	12.84		84	68–70
				57.76	3.32	5.71	12.74			
XII	3-Cl	$C_{12}H_8ClNOS$	249.70	57.71	3.23	5.61	12.84		80	56–58
				57.68	3.20	5.63	12.90			
XIII	2-Cl	$C_{12}H_8ClNOS$	249.70	57.71	3.23	5.61	12.84		81	52–54
				57.66	3.24	5.70	12.88			
XIV	4-Br	$C_{12}H_8BrNOS$	294.16	48.99	2.74	4.76	10.90		88	82–84
				48.86	2.82	4.70	10.88			
XV	H	$C_{12}H_9NOS$	215.26	66.95	4.21	6.50	14.89		72	70–73
				66.82	4.32	6.62	14.93			
XVI	4-CH_3	$C_{13}H_{11}NOS$	229.28	68.09	4.83	6.10	13.98		70	52–54
				68.20	4.92	6.16	13.86			

Y in compounds *I*–*III* = Br; *IV*–*VII* = NCS; *VIII*–*XVI* = SCN.
Compound *IV* was crystallized from the mixture benzene–hexane (1 1); *VI* from hexane; *V* and *VII* from petrolether.

alcohol (0.02 mole) in absolute ether (100 ml). Then the reaction mixture was stirred for another 90 minutes at room temperature. The etheric solution was decanted and the resinous residues were washed with ether. The collected etheric solutions were shaked with a cold 50% sodium hydroxide solution and desiccated over solid potassium hydroxide. Ether was evaporated under reduced pressure at room temperature.

5-(X-Phenyl)-2-furfuryl isothiocyanates

Method A

The corresponding 5-(X-phenyl)-2-furfuryl bromide (0.02 mole) was dissolved in absolute ethanol (20 ml) to which hexamethylenetetraamine (2.82 g; 0.02 mole) in absolute ethanol (80 ml) was added. The mixture was heated under reflux for 60 minutes. An intense flow of dry HCl was introduced to the complex salt formed. After the spontaneous heating hydrogen chloride was introduced for another hour. The hot reaction mixture was filtered, condensed to the volume of about 20 ml, and then 5-(X-phenyl)--2-furfurylammonium chloride was allowed to crystallize.

The aqueous solution (100—200 ml) of corresponding substituted 5-phenyl-2-furfurylammonium chloride (0.02 mole) was dropped under vigorous stirring and cooling with ice-cold water into a mixture of thiophosgene (0.02 mole), chloroform (80 ml), and $CaCO_3$ (2.2 g; 0.022 mole). The reaction mixture was stirred for another 4 hours at room temperature. After the reaction finished, the chloroform layer was separated and desiccated with anhydrous calcium chloride. The chloroform solution was filtered and allowed to flow through a column of Al_2O_3 (*ca.* 10 g of Al_2O_3 per 1 g of product). Then it was eluted with benzene. After the evaporation of solvents the corresponding isothiocyanate was obtained in 30—40% yield. This substance was purified by crystallization.

Method B

The appropriate 5-phenyl-2-furfuryl bromide (0.01 mole) was dissolved in dimethylformamide (25 ml) into which potassium thiocyanate (0.98 g; 0.01 mole) was added. The mixture was kept at boiling point for 7—10 minutes and after cooling it was poured into water. The crude product was purified by crystallization from a suitable solvent.

The compounds *IV* and *V* were prepared according to the method *A* while the method *B* was used for the preparation of the compounds *IV*, *VI*, and *VII*.

5-(X-Phenyl)-2-furfuryl thiocyanates

The corresponding 5-(X-phenyl)-2-furfuryl bromide (0.01 mole) was dissolved in the needed amount of absolute acetone (15—30 ml) and subsequently ammonium thiocyanate (0.84 g; 0.01 mole) in anhydrous acetone (15 ml) was gradually added under vigorous stirring and cooling (approximately 0°C). After this operation the reaction mixture was mixed for another hour at room temperature. The precipitated inorganic portion was filtered off. Water (200 ml) was added to the filtrate. The precipitate was sucked and dried thoroughly on filter. Provided the product was liquid, the benzene extraction was carried out. The crude product dissolved in benzene was purified chromatographically on a column with Al_2O_3 (10 g Al_2O_3/1 g thiocyanate). The benzene eluates were condensed at laboratory temperature to the volume of about 20 ml. To the solution thus obtained *n*-hexane (20 ml) was introduced and the product was allowed to crystallize. Thus the pure product was obtained in about 40% yield. Another portion of product was obtained after distillation of the solvents.

Results and discussion

The synthesized bromides of 5-phenyl-2-furfuryl type are relatively unstable compounds [9, 10] which may, however, be preserved in etheric solution over solid KOH at 0°C without substantial changes. Relatively more stable are 2-, 3-, and 4-nitrophenyl derivatives which were also identified (Table 1). Other 5-(X-phenyl)-2-furfuryl bromides were used without preliminary identification for the preparation of corresponding thiocyanates. The low stability of the halogenides of furfuryl type was described by *Scott* and *Johnson* [11] who stated that 5-methyl-2-chloromethylfuran could be preserved only in etheric solution. Nevertheless, provided a substituent with deactivation effect is present in position 5 the relevant furfuryl halogenides are more stable [12—18]. The comparison between the stabilities of 5-nitro-furfuryl bromide and nitrosubstituted 5-phenyl-2-furfuryl bromide enables us to conclude that the stabilizing effect of the nitro group bonded to benzene ring of 5-phenyl-2-furfuryl bromide is smaller than that of the nitro group bonded to furan ring in position 5. This fact is evidently in connexion with the character of nitrophenyl residue as well as with the mutual angular orientation of the planes of benzene and furan rings.

During the preparation of substituted 5-(X-phenyl)-2-furfuryl thiocyanates (*VIII*—*XVI*; Table 1) a rearrangement under formation of corresponding isothiocyanates was observed as well. Provided the reaction took place at the boiling point of solvent, a mixture of both isomers was obtained. The presence of individual isomers was proved by infrared spectroscopy. It was found that the broad absorption band of isothiocyanate group with the maximum at 2060 cm^{-1} appeared besides the characteristic sharp band at about 2160 cm^{-1}.

Therefore the method developed for the synthesis of pure thiocyanates is based on the fact that the reaction of the appropriate 5-(X-phenyl)-2-furfuryl bromide with KSCN takes place at low temperatures (approximately 0°C). Because of a high reactivity of individual 5-phenyl-2-furfuryl bromides, the reaction finished as early as after 60 minutes. If the reaction time is prolonged, the reaction product contains some traces of isothiocyanate, too, especially in the case of the derivatives where X is a substituent with electron-donor character. As it was expected, the nitrosubstituted 5-phenyl-2-furfuryl thiocyanates showed the smallest tendency to rearrangement. Some of the synthesized isothiocyanates (*IV*, *V*) were also prepared by the thiophosgene method which affords unambiguously isothiocyanate according to literature [19]. The corresponding amine was obtained by the method of *Delepine* [20, 21] and used without further purification for the preparation of isothiocyanates. Isothiocyanates were prepared by the thiophosgene method as well as by the method *B* [22]. Both methods gave identical products in good yields. The kinetic investigation of the rearrangement of thiocyanates to isothiocyanates of the 5-phenyl-2-furfuryl type will be the subject of our further study.

In the infrared spectra of the synthesized isothiocyanates (*IV*—*VII*) a maximum of the broad absorption band belonging to the asymmetric vibrations of NCS bonds [23—25] appears at 2060—2061 cm^{-1}. The substituted 5-(X-phenyl)-2-furfuryl thiocyanates (*VIII*—*XVI*) have an intense absorption band at 2162—2160 cm^{-1} which characterizes the wave numbers of SCN bonds [25]. The substituent X bonded to benzene ring has no marked influence on the position of absorption maximum of SCN and NCS bonds.

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