SYNTHESIS OF HETEROCYCLES USING PRODUCTS OF THE ADDITION OF POLYHALOALKANES TO UNSATURATED SYSTEMS.

5.* SYNTHESIS OF SUBSTITUTED THIAZOLES

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First syntheses are reported for 2-aminothiazoles, 2-chlorothiazoles, and 2-thiazolones with a 2,2,-trichloroethyl group at $C_{(5)}$ using the products of the homolytic addition of CCl_4 and trichloroacetonitrile to methyl vinyl ketone. Further transformation of this substituent may be carried out for the preparation of compounds with possible biological activity.

We have already shown that the product of the addition of CCl_4 to methyl vinyl ketone, namely, 3,5,5,5-tetrachloro-2-pentanone (I), may be transformed by the pathway known for the reactions of α-ketones to C-nucleophiles to give substituted furans, which are key compounds in the synthesis of furo[2,3-*d*]pyrimidines [1]. These compounds, which have a 2,2,2-trichloroethyl substituent, may be seen as precursors of the corresponding hetarylacetic acids and 2,2-dichlorovinyl derivatives, which hold interest in the synthesis of biologically active compounds. In a previous communication [2], we demonstrated the possibility of also using chloroketone I to prepare thiazole derivatives. In the present work, we synthesized thiazole derivatives using chloroketone I as well as 5-oxo-2,2,4-trichlorocapronitrile (II) and 3-thiocyano-5,5,5-trichloro-2-pentanone (III).

Chloroketone I was obtained according to Sasson and Rempel [3] by the homolytic addition of CCl_4 to methyl vinyl ketone in the presence of $RuCl_2(Ph_3P)_3$.

Chlorocyanoketone II is the product of the homolytic addition of trichloroacetonitrile to methyl vinyl ketone in the presence of CuCl and PPh_3. This compound was prepared according to a reported procedure [4] but using acetonitrile instead of propionitrile as the solvent. Thiocyanoketone III was prepared from chloroketone I by the action of potassium thiocyanate in acetonitrile at reflux. In this case, ethanol, which is often used as the solvent in the preparation of thiocyanates [5], proved unsuitable. Heavy tar formation was noted in the reaction of chlorocyanoketone II with potassium thiocyanate and the expected thiocyanoketone could not be isolated. Products I-III were characterized by PMR spectroscopy (Table 1). A detailed examination of the structure and stereochemistry of these compounds was not part of our problem, but we should note the high sensitivity of the chemical shifts and coupling constants to the replacement of the chlorine atoms in I by cyano and thiocyanate groups.

Water, methanol, ethanol, or their mixture are usually employed as the solvent in the preparation of 2-aminothiazoles from α-halocarbonyl compounds and thiourea [6, 7]. However, the reaction of chloroketone I with thiourea does not proceed in these solvents and the starting reagents are recovered unchanged. The replacement of protic solvents by aprotic solvents permits us to carry out the reaction of the chloroketone with thiourea. Thus, the corresponding N-formyl-2-aminothiazole (IV) was obtained when the reaction was carried out in DMF. The formation of N-formyl derivatives of 2-aminothiazoles when

* For communication 4, see [1].

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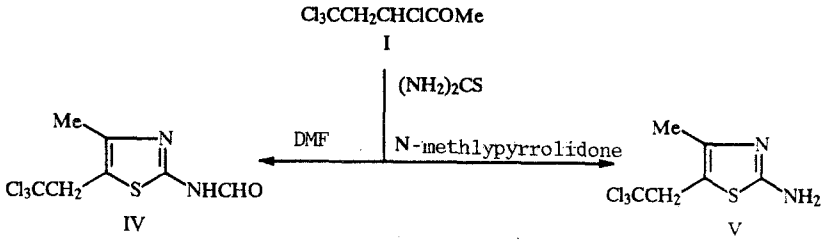
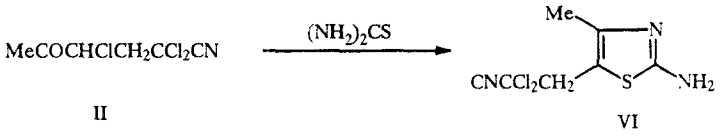
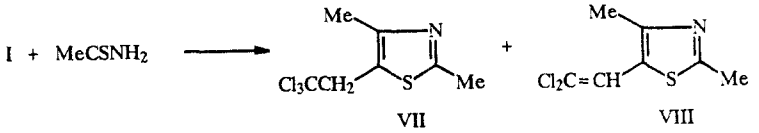
DMF is used as the solvent has been noted, for example, by Catsoulakos and Kallias [8]. 2-Amino-4-methyl-5-(2,2,2-trichloroethyl)thiazole (V) was obtained in good yield when the reaction was carried out in anhydrous N-methylpyrrolidone. We should note that the formation of N-formylaminothiazole IV is not observed upon the prolonged heating of aminothiazole V in DMF at reflux.



The reaction of chlorocyanoketone II with thiourea in N-methylpyrrolidone gives the corresponding aminothiazole (VI) in good yield.



Heating chloroketone I with thioacetamide in N-methylpyrrolidone leads to a mixture of 2,4-dimethyl-5-(2,2,2-trichloroethyl)thiazole (VII) and 2,4-dimethyl-5-(2,2-dichlorovinyl)thiazole (VIII). The optimal temperature for this reaction is 82-86°C and significant tar formation occurs above this temperature. We were unable to separate this mixture either by distillation or column chromatography. The product ratio (VII:VIII = 70:30) was found by GC/MS and PMR spectroscopy.



Various thiazole derivatives were synthesized under mild conditions in good yield from thiocyanatoketone III according to Chernyak [5]. Thus, heating this ketone with aniline in benzene at reflux in the presence of aniline hydrochloride gave a quantitative yield of the corresponding phenylaminothiazole (IX). The action of aqueous hydrochloric acid on ketone III in a mixture of dioxane and acetone leads to 2-thiazolone (X) in good yield. The structure of X was established by the broad NH signal in the PMR spectrum at δ 10.38 ppm and $\nu_{C=O}$ band at 1665 cm^{-1} in the IR spectrum. Treatment of thiocyanatoketone III by gaseous HCl in anhydrous ether leads to the formation of 2-chlorothiazole (XI) with a trace of thiazolone X.

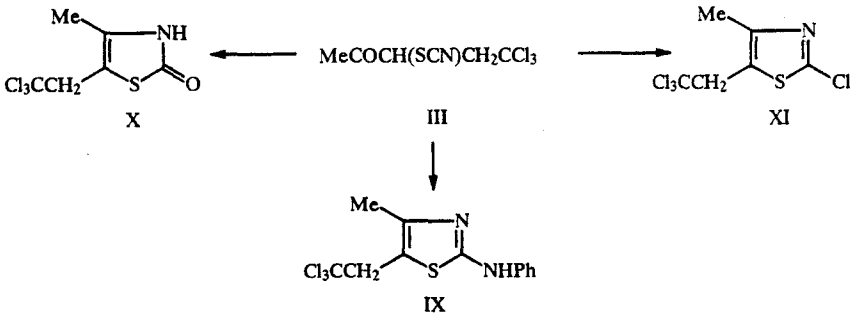


TABLE 1. PMR Spectra of Substituted Aliphatic Ketones I-III $CH_3COCHY-CH_2-CCl_2Z$

Compound	Chemical shifts, δ, ppm				Coupling constants, J, Hz		
	CH_3, s	CH_2 H_a dd	H_m dd	CH dd H_x	$^2J_{am}$	$^3J_{ax}$	$^3J_{mx}$
I (Y = Z = Cl)	2,40	3,08	3,84	4,56	16,0	4,5	6,3
II (Y = Cl, Z = CN)	2,41	2,93	3,47	4,54	16,0	7,0	4,5
III (Y = SCN, Z = Cl)	2,51	3,18	3,96	4,03	14,5	2,8	7,0

TABLE 2. Characteristics of Thiazole Derivatives IV-XI

Compound	Chemical formula	mp, °C	M^+ (^{35}Cl)	Chemical shifts, δ, ppm			Yield, %
				4-CH_3	CH_2	other signals	
IV	$C_7H_7Cl_3N_2OS$	170...173	272	2,44	4,06	8,68 s (CH) 12,68 br.s (NH)	45
V	$C_6H_7Cl_3N_2S$	164...165	244	2,27	3,92	5,03 br.s (NH_2)	82
VI	$C_7H_7Cl_2N_3S$	158...158,5	235	2,26	3,75	5,21 br.s (NH_2)	68
VII	—	—	243	2,40	4,00	2,64 s (H^2)	
VIII	—	—	207	2,38	—	2,63 s (H^2), 6,92 s (CH)	
IX	$C_{12}H_{11}Cl_3N_2S$	145...146	320	2,32	3,96	7,06...7,42 m (Ph)	99
X	$C_6H_6Cl_3NOS$	186,5...187,5	245	2,18	3,78	10,38 br.s (NH)	91
XI	$C_6H_5Cl_4NS$	67...68	263	2,41	4,02	—	64

EXPERIMENTAL

The PMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz in $CDCl_3$. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer with direct sample inlet into the ion source. The ionizing voltage was 100 μA and the emission current was 70 eV. The GC/MS spectra were obtained on a Finnigan MAT instrument. The ionizing voltage was 70 eV and the emission current was 100 μA.

The reaction course was followed by thin-layer chromatography on Silufol UV-254 plates with chloroform or 1:4 to 1:1 ethyl acetate—hexane as the eluent.

The yield and characteristics of thiazoles IV-XI are given in Table 2.

The elemental analysis data for C, H, Cl, N, and S for the III-XI, which are reported for the first time, are in accord with the calculated values.

A sample of 3,5,5,5-tetrachloro-2-pentanone I was obtained according to Sasson [3].

5-Oxo-2,2,4-trichlorocapronitrile (II). A mixture of 50 g (0.35 mole) trichloroacetonitrile, 35.7 g (0.51 mole) methyl vinyl ketone, 90 ml acetonitrile, 0.9 g triphenylphosphine, and 0.9 g CuCl was heated at reflux for 12 h and cooled. The solution was evaporated on a water bath at 20 mm Hg. Then, 100 ml hexane and 10 g silica gel were added to the residue. The mixture was stirred and filtered. The silica gel was washed with a small amount of chloroform. The combined filtrate was evaporated and distillation of the residue in vacuum gave nitrile II, bp 72-76°C (0.24-0.44 mm Hg), n_D^{20} 1.4825. These indices are in accord with those given in the literature [4]. The yield of II was 41.4 g (55.8%).

3-Thiocyano-5,5,5-trichloro-2-pentanone (III). A solution of 22.4 g (0.1 mole) ketone I in 17 ml acetonitrile was added dropwise with stirring to a solution of 10.3 g (0.11 mole) potassium thiocyanate in 120 ml anhydrous acetonitrile maintained at reflux. The mixture darkened and a precipitate appeared after 15-20 min. The mixture was heated at reflux for 15 h and cooled. The solvent was removed in vacuum. Crystallization of the residue gave III, $C_6H_6Cl_3NOS$, mp 70.5-72.0°C. The yield of III was 21.4 g (86.8%).

4-Methyl-5-(2,2,2-trichloroethyl)-2-(formylamino)thiazole (IV). A solution of 4.4 g (0.196 mole) chloroketone I in 4 ml DMF was added with stirring over 10 min to a solution of 1.52 g (0.02 mole) thiourea in 20 ml DMF heated at 82-86°C. The reaction mixture was maintained at this temperature for 20 h, cooled, poured into 70 ml water, and brought to pH 7. Product IV was filtered off, washed with a small amount of water, and dried in a vacuum desiccator.

2-Amino-4-methyl-5-(2,2,2-trichloroethyl)thiazole (VI) was obtained by analogy to V from cyanoketone II.

2,4-Dimethyl-5-(2,2,2-trichloroethyl)thiazole (VII) and 2,4-Dimethyl-5-(2,2-dichlorovinyl)thiazole (VIII). The reaction of 6.58 g (0.029 mole) ketone I with 2.26 g (0.03 mole) thioacetamide was carried out by analogy to the synthesis described for thiazoles V and VI but extraction with three 30-ml chloroform portions was used to separate the product mixture. The combined extract was washed with water and dried. The solvent was removed and distillation of the residue gave 3.01 g of the indicated mixture (44% yield), which distilled at 100-104°C (2 mm Hg). PMR spectroscopy indicated that the VII/VIII ratio in this mixture was 70:30.

4-Methyl-2-phenylamino-5-(2,2,2-trichloroethyl)thiazole (IX). A mixture of 2.46 g (0.01 mole) thiocyanatoketone III, 1.86 g (0.02 mole) aniline, and 0.2 g (1.54 mmole) aniline hydrochloride in 30 ml dry benzene was heated at reflux for 9 h. The mixture was cooled and filtered. The residue on the filtrate was washed with benzene. The combined filtrate was evaporated in vacuum. Crystallization of the residue from ethanol gave product IX. An additional amount of product was isolated from the mother liquor.

4-Methyl-5-(2,2,2-trichloroethyl)-2-thiazolone (X). A solution of 2.47 g (0.01 mole) thiocyanatoketone III in a mixture of 35 ml 1,4-dioxane, 28 ml acetone, and 14 ml concentrated hydrochloric acid was heated at reflux for 2 h. The reaction mixture was cooled, poured into 150 ml water, and filtered to give thiazolone X, which was dried in a vacuum desiccator.

4-Methyl-2-chloro-5-(2,2,2-trichloroethyl)thiazole (XI). A stream of dry hydrogen chloride was passed through a solution of 6.16 g (0.025 mole) thiocyanatoketone III in 40 ml dry ether with ice cooling and stirring for 2.5 h. The mixture was maintained for 10 h at 20°C and evaporated to remove excess HCl. The residue was dissolved in chloroform, washed with aqueous sodium carbonate and then water, and dried over $MgSO_4$. The solvent was removed in vacuum and the solid residue was extracted with hot hexane. The hexane extract was evaporated and crystallization of the residue from pentane gave product XI. The yield of hexane-insoluble thiazolone X was 0.67 g (10.9%).

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