Isothiazoles VIII: Isothiazolidin-3-one Derivatives

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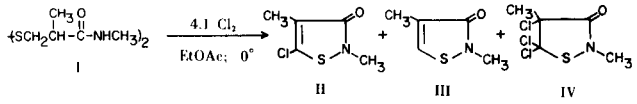
Useful procedures for preparing novel 4-methyl-4,5,5-trichloroisothiazolidin-3-ones and 4,4,5,5-tetrachloroisothiazolidin-3-ones are reported.

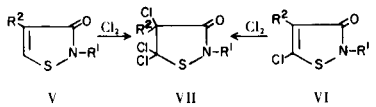
J. Heterocyclic Chem., 13, 1321 (1976).

In previous papers we described the chlorine induced cyclization of 3,3′-dithiodipropionamides and 3,3′-dithiodiisobutyramides to provide a comprehensive series of 4-isothiazolin-3-one derivatives (1,2). Utilizing the incremental amide addition procedure (2), developed to favor preparation of 5-chloro-4-isothiazolin-3-one derivatives, cyclization of *N,N′*-dimethyl-3,3′-dithiodiisobutyramide (I) gave the expected 5-chloro-2,4-dimethyl-4-isothiazolin-3-one (II), small amounts of 2,4-dimethyl-4-isothiazolin-3-one (III) and the hitherto unknown 2,4-dimethyl-4,5,5-trichloroisothiazolidin-3-one (IV). Other dithiodiisobutyramides were found to give similar results. We also wish to report the easy preparation of representative isothiazolidin-3-ones by chlorination of various 4-isothiazolin-3-one derivatives.



I II III IV

Direct chlorination of either 2-substituted-4-isothiazolin-3-one (V) or 5-chloro-2-substituted-4-isothiazolin-3-ones (VI) provided the desired isothiazolidin-3-ones (VII). If 4-isothiazolin-3-ones or 5-chloro-4-isothiazolin-3-ones were the starting materials, 4,5-dichloro derivatives were often identified as minor side products. Various sulfoxides were also by-products but these products could be easily minimized by employing thoroughly dry solvents.



V VII VI

The isothiazolidin-3-one derivatives were not sufficiently basic to afford solid hydrochlorides under the strongly acid reaction conditions. The crude products were readily purified by distillation, recrystallization or column chromatography. Elemental analyses, ir and nmr spectral data were consistent with structures VII. The preparations of a large variety of these derivatives by these methods are summarized in Table I; little effort was made to optimize the reported yields.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus; all melting and boiling points are uncorrected. IR spectra were taken in mineral oil mulls on an Infracord Spectrophotometer, Model 137. The elemental analyses were performed by the analytical department of the Research Division of the Rohm and Haas Company.

The following experiments illustrate the general reaction procedures employed.

2,4-Dimethyl-4,5,5-trichloroisothiazolidin-3-one.

To 100 ml. of ethyl acetate, stirred and maintained at -5 to 0°, was added during one hour, 29.1 g. (0.41 mole) of chlorine, continuously, and 26.4 (0.1 mole) of *N,N′*-dimethyl-3,3′-dithiodiisobutyramide in 40 equal portions at 1.5 minute intervals. After completion of additions, the pale yellow suspension was filtered. Additional solid which separated from the filtrate was also collected. Both portions were identified as 2,4-dimethyl-4-isothiazolin-3-one, hydrochloride, 22 g. (66%). The yellow filtrate was neutralized by washing with sodium carbonate and water, dried over anhydrous magnesium sulfate and evaporated, leaving a yellow orange residual oil. The oil was distilled; b.p. 59-61°/0.15 mm. Further purification *via* column chromatography (100% methylene chloride: silica) provided 4.4 g. (9%) of pure product; m.p. 46-48°.

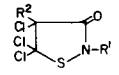
2-Methyl-4,4,5,5-tetrachloroisothiazolidin-3-one.

Method A.

To a suspension of 37.2 g. (0.2 mole) of 5-chloro-2-methyl-4-isothiazolin-3-one hydrochloride in 200 ml. of 1:1 (v:v) ethyl acetate-dimethylformamide was slowly added 28.4 g. (0.4 mole) of chlorine. The reaction temperature was maintained below 35° during the chlorine addition. The clear solution was cooled to 0°

Table I

Isothiazolidin-3-one Derivatives



R^1	R^2	b.p./m.p. °C	Yield % (Method)	Empirical Formula	Elemental Analysis Calcd. C	H	N	S	Found C	H	N	S
CH_3	CH_3	46-48 (a)	68 (A)	$C_6H_5Cl_3NOS$	25.59	2.56	5.97	13.65	25.78	2.49	5.47	13.53
CH_3	Cl	79-81 (b)	17 (B)	$C_4H_3Cl_4NOS$	18.82	1.18	5.49	12.55	19.01	1.00	5.34	12.61
C_2H_5	Cl	55-56 (c)	14 (A)	$C_5H_5Cl_4NOS$	22.31	1.86	5.20	11.90	22.81	2.01	5.23	11.70
C_4H_9-*n*	CH_3	88-98 (0.2)	84 (B)	$C_8H_{12}Cl_3NOS$	34.72	4.34	5.06	11.57	35.08	4.39	5.14	11.35
C_4H_9-*n*	Cl	102-107 (0.2)	27 (A)	$C_7H_9Cl_4NOS$	28.28	3.03	4.71	10.77	28.28	3.16	4.74	10.79
C_4H_9-*iso*	Cl	96-100 (0.3)	76 (A)	$C_7H_9Cl_4NOS$	28.28	3.03	4.71	10.77	28.55	3.11	4.75	10.72
C_6H_{13}-*n*	Cl	128-140 (0.3)	24 (A)	$C_9H_{13}Cl_4NOS$	33.23	4.00	4.31	9.58	33.48	3.76	4.10	9.59
C_6H_{11}-*cyclo*	Cl	69-71 (c)	18 (A)	$C_9H_{11}Cl_4NOS$	33.44	3.41	4.33	9.91	33.57	3.47	4.25	9.75
C_8H_{17}*n*	Cl	138-142 (0.15)	90 (A)	$C_{11}H_{17}Cl_4NOS$	37.41	4.85	3.96	9.08	37.24	4.64	3.78	9.13
C_6H_5	Cl	92-95 (d)	4 (A)	$C_9H_5Cl_4NOS$	34.07	1.58	4.42	10.09	34.31	1.51	4.17	9.91
$CH_2C_6H_5$	CH_3	138-142 (0.3)	51 (B)	$C_{11}H_{10}Cl_3NOS$	42.55	3.22	4.51	10.31	43.02	3.11	4.46	10.07
$CH_2C_6H_5$	Cl	142-143 (0.35)	22 (A)	$C_{10}H_7Cl_4NOS$	36.25	2.11	4.23	9.67	36.30	3.23	4.22	9.59
$CH_2C_6H_4Cl$ (4)	Cl	177-178 (0.4)	27 (A)	$C_{10}H_6Cl_5NOS$	32.86	1.66	3.83	8.77	32.62	1.56	3.77	8.79
$CH_2C_6H_4CH_3$ (4)	Cl	oil	28 (A)	$C_{11}H_9Cl_4NOS$	38.28	2.63	4.06	9.29	38.16	2.73	3.98	9.24
$CH_2C_6H_4CN$ (4)	Cl	90-92 (c)	16 (A)	$C_{11}H_6Cl_4NOS$	37.10	1.70	7.87	9.00	37.32	1.69	8.02	8.98
$CH_2C_6H_3Cl_2$ (3,4)	CH_3	oil	62 (C)	$C_{11}H_8Cl_5NOS$	34.81	2.13	3.69	8.45	34.66	2.11	3.73	8.43
$CH_2C_6H_3Cl_2$ (3,4)	Cl	87-89 (e)	68 (A)	$C_{10}H_5Cl_6NOS$	30.03	1.26	3.50	8.02	29.88	1.22	3.40	7.89
$C_2H_4C_6H_5$	Cl	49-51 (d)	23 (A)	$C_{11}H_9Cl_4NOS$	38.26	2.61	4.06	9.28	38.48	2.70	3.91	9.55

(a) Recrystallized from heptane. (b) Recrystallized from benzene. (c) Recrystallized from methanol. (d) Recrystallized from hexane. (e) Method of preparation: A - chlorination of 4-methyl-4-isothiazolin-3-one or 4-isothiazolin-3-one; B - chlorination of 5-chloro-4-methyl-4-isothiazolin-3-one or 5-chloro-4-isothiazolin-3-one; C - chlorination of dithiodiisobutyramide.

causing separation of 14.3 g. of 4,5-dichloro-2-methyl-4-isothiazolin-3-one. Concentration of the filtrate provided 19.7 g. of crude product. The latter was purified *via* column chromatography (100% benzene-silica) to give 8.5 g. (17%) of the desired product, m.p. 79-81°; ir: 5.85 (C=O) μ.

Method B.

To a suspension of 30.3 g. (0.2 mole) of 2-methyl-4-isothiazolin-3-one hydrochloride in 200 ml. of ethyl acetate was added 71 g. (1.0 mole) of chlorine over a period of one hour. The reaction mixture was allowed to warm to 55°. The clear solution was degassed with nitrogen and concentrated to provide a mushy solid. Crystallization of the mushy solid from methanol gave 16.8 g. of 4,5-dichloro-2-methyl-4-isothiazolin-3-one. Concentration of the filtrate yielded 23.4 g. of crude product. Further purification *via* column chromatography (100% toluene-silica) gave 8.8 g. (18%) of product, m.p. 77-80°.

2-*n*-Butyl-4,4,5,5-tetrachloroisothiazolidin-3-one.

To a solution of 15.7 g. (0.1 mole) of 2-*n*-butyl-4-isothiazolin-3-one in 100 ml. of ethyl acetate was added 21.3 g. (0.3 mole) of chlorine over a period of 30 minutes. The reaction mixture was allowed to warm to 62°. The solution was then cooled to room temperature and concentrated to give 26.6 g. of crude product. Further purification *via* column chromatography (100% toluene-silica) and distillation provided 8.1 g. (27%) of pure product, b.p. 102-107°/0.4 mm; ir: 5.84 (C=O) μ.

2-*n*-Butyl-4-methyl-4,5,5-trichloroisothiazolidin-3-one.

To a solution of 10.0 g. (0.0487 mole) of 2-*n*-butyl-5-chloro-4-methyl-4-isothiazolin-3-one in 100 ml. of ethyl acetate was added 3.55 g. (0.05 mole) of chlorine over a period of 30 minutes. Concentration of the reaction mixture gave a yellow oil which was distilled to give 11.33 g. (84%) of product, b.p. 88-89°/0.2 mm; ir: 5.86 (C=O) μ.

2-Benzyl-4,4,5,5-tetrachloroisothiazolidin-3-one.

To a solution of 18.9 g. (0.1 mole) of 2-benzyl-4-isothiazolin-3-one in 100 ml. of ethyl acetate was added 21.3 g. (0.3 mole) of chlorine over a period of 30 minutes. The reaction mixture was allowed to warm to 68°. The solution was cooled to room temperature and concentrated to give an orange oil. Purification of this oil *via* column chromatography (100% toluene-silica) and subsequent distillation yielded 7.2 g. (22%) of pure product, b.p. 142-143°/0.35 mm; ir: 5.84 (C=O) μ.

2-(3,4-Dichlorobenzyl)-4,4,5,5-tetrachloroisothiazolidin-3-one.

To a slurry of 47.9 g. (0.18 mole) of 2-(3,4-dichlorobenzyl)-4-isothiazolin-3-one in 100 ml. of 1:1 (v:v) ethyl acetate-dimethylformamide was added approximately 40 g. (0.56 mole) of chlorine over a period of one hour. The temperature rose to 70°. The mixture was degassed with nitrogen, concentrated and diluted with water. The white precipitate was filtered and dried to give 44.9 g. (68%) of product, m.p. 91-94° (methanol); ir: 5.80-5.85 (C=O) μ.

REFERENCES AND NOTES

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(2) G. A. Miller, E. D. Weiler and M. Hausman, *ibid.*, 8, 582 (1971).