Isothiazoles X. 3-Alkoxyisothiazole Derivatives

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Halogenation of a number of 3-alkoxyisothiazoles, occurring exclusively in the 4-position, followed by cyanation led to various carboxylic acid, carboxamide and amine derivatives. Subsequent dealkylation provided 4-substituted-4-isothiazolin-3-ones.

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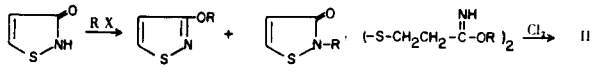
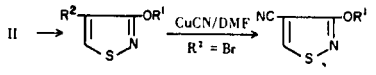
As part of a continuing study on the chemistry of isothiazoles, we prepared a representative series of 3-alkoxyisothiazoles and subjected these to various transformations. Alkylation of 4-isothiazolin-3-one (I), as reported by Crow (1,2), led to a mixture of *O* and *N* products, with the 3-alkoxyisothiazoles (II) predominating. The lower boiling 3-alkoxy derivatives were readily distilled from the crude reaction mixture. Alternatively, 3-alkoxyisothiazoles (II) were also prepared by the previously disclosed (3) chlorination-cyclization of dialkyl dithiodipropionimidates (IV).



I II III IV

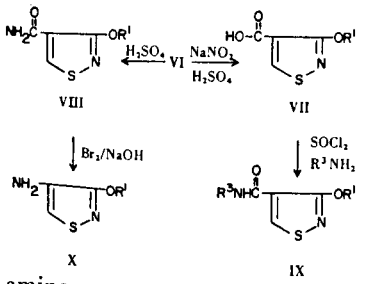
Bromination, iodination and nitration of II gave exclusively 4-substituted derivatives V, confirming other observations (4,5) that the 4-position of the isothiazole ring is very susceptible to attack by electrophilic reagents. 3-Alkoxy-4-cyanoisothiazoles (VI) were prepared from the corresponding 4-bromo derivatives utilizing a cuprous cyanide/DMF cyanation procedure.



V VI

$R^2 = NO_2$, Br, I

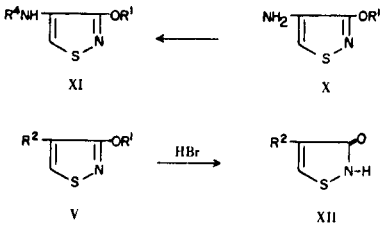
Depending on the reaction conditions employed, acid hydrolysis of the 4-cyano derivatives VI provided either the 4-carboxy derivatives VII or the carbamoyl derivatives VIII. 4-Carboxylic acids VII on treatment with thionyl chloride gave acid chlorides, which were readily converted to *N*-substituted carbamoyl derivatives IX. 3-Alkoxy-4-aminoisothiazoles (X) were prepared from 4-carbamoyl derivatives by a standard Hofmann degradation procedure.



VIII VII

X IX

The 4-amino group of X was also incorporated into arylsulfonamide, aryl and alkylcarboxamides as well as urea and carbamate derivatives XI. Dealkylation of 3-alkoxyisothiazoles (V) afforded 4-substituted-4-isothiazolin-3-ones (XII).



XI X

V XII

The crude products were purified by recrystallization, distillation or by column chromatography. Elemental analysis, ir and nmr spectral data are consistent with the assigned structures. Table I summarizes the pertinent data on 3-alkoxyisothiazole derivatives; no effort was made to optimize yields.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Ir spectra were taken as mineral oil mulls on a Perkin-Elmer Infracord, Model 137. 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.

3-Methoxyisothiazole.

To a suspension of 61.8 g. (0.2 mole) of freshly prepared dimethyl dithiodipropionimidate hydrochloride in 650 ml. of ethyl acetate at 16° was added over a 1-hour period 44.7 g. (0.63 mole) of chlorine. The temperature rose to 25° within 10 minutes and was maintained at 25° for the remainder of the chlorine addition. The mixture was stirred for an additional hour and was filtered. The hydrochloride product was dissolved in 100 ml. of water and the solution neutralized (sodium bicarbonate). The mixture was extracted with ether (3 x 50 ml.). The extract was dried (magnesium sulfate) and distilled to give 26.8 g. (58%) of product, b.p. 147-150°/760 mm.

3-Propoxyisothiazole.

To a solution of 101 g. (1 mole) of 4-isothiazolin-3-one in 1000 ml. of methanol was added dropwise 238 g. (1.1 mole) of a 25% methanolic sodium methoxide solution maintaining the temperature below 30°. The mixture was then heated at reflux while 135 g. (1.1 mole) of 1-bromopropane was added dropwise. Heating at reflux was continued for 20 hours. The mixture was cooled, filtered, concentrated and redissolved in a mixture of ether and water. The layers were separated and the ether solution was dried (magnesium sulfate) and decolorized (Nuchar). The solution was filtered and evaporated under reduced pressure. The residual oil was distilled providing 37.6 g. (26%) of product, b.p. 30-37°/0.3

Table I

Structure	R^1	R^2, R^3, R^4	Yield %	M.p./B.p. mm°C	Empirical Formula	Elemental Analysis Found C	H	N	S	Calculated C	H	N	S
II	R^1 - CH_3 (a)		58	147-150/760	C_4H_5NOS	41.77	4.35	11.95	27.90	41.74	4.35	12.17	27.83
II	R^1 -C_3H_7n		26	30-37/0.3	C_6H_9NOS	50.35	6.29	9.79	22.38	50.42	6.49	9.92	22.44
II	R^1 -$C_6H_{13}n$		42	61-64/0.4	$C_9H_{15}NOS$	58.38	8.11	7.57	17.29	58.59	7.98	7.51	17.18
V	R^1 -CH_3	R^2 -Br	72	70-76/5.0	C_4H_4BrNOS	24.74	2.06	7.22	16.50	24.82	2.18	7.20	16.21
V	R^1 -CH_3	R^2 -I	41	61-63	C_4H_4INOS	19.92	1.66	5.81	13.28	19.43	1.50	5.51	13.32
V	R^1 -CH_3	R^2 -NO_2	13	122-123	$C_4H_4N_2O_3S$	30.00	2.50	17.50	20.00	30.13	2.60	17.49	19.95
V	R^1 -C_3H_7n	R^2 -Br	99	45-50/0.05	C_6H_8BrNOS	32.14	3.60	6.31	14.41	33.13	3.79	6.08	14.14
V	R^1 -$C_6H_{13}n$	R^2 -Br	51	130-133/5.0	$C_9H_{14}BrNOS$	40.91	5.30	5.30	12.12	41.26	5.47	5.21	12.01
VI	R^1 -CH_3		45	51-53	$C_5H_4N_2OS$	42.86	2.86	20.00	22.86	42.40	2.98	19.98	22.44
VI	R^1 -C_3H_7n		72	70/0.025	$C_7H_8N_2OS$	50.00	4.76	15.67	19.05	50.51	5.50	15.53	18.99
VI	R^1 -$C_6H_{13}n$		20	40-42	$C_{10}H_{14}N_2OS$	57.14	6.67	13.33	15.24	56.83	6.51	13.18	15.13
VII	R^1 -CH_3		67	182-185	$C_5H_5NO_3S$	37.74	3.14	8.80	20.13	38.13	3.13	8.74	20.02
VII	R^1 -C_3H_7n		83	90-93	$C_7H_9NO_3S$	44.92	4.81	7.49	17.11	44.61	4.70	7.58	17.27
VIII	R^1 -CH_3		66	165-168	$C_5H_6N_2O_2S$	37.97	3.80	17.72	20.25	38.16	3.78	17.60	20.24
VIII	R^1 -C_3H_7n		43	100-101	$C_7H_{10}N_2O_2S$	45.17	5.49	14.82	17.20	45.16	5.38	15.05	17.37
IX	R^1 -C_3H_7n	R^3 -$C_6H_3Cl_2$ (3,4)	71	116-118	$C_{13}H_{12}Cl_2NO_2S$	47.13	3.62	8.46	9.57	47.05	3.56	8.28	10.01
X	R^1 -C_3H_7n		55	149-150	$C_6H_{10}N_2OS$·HCl	37.02	5.66	14.40	16.40	37.28	5.71	14.19	16.71
XI	R^1 -C_3H_7n	R^4 -$SO_2C_6H_4NH_2$ (4)	97	138-140	$C_{12}H_{15}N_3O_3S$	46.01	4.79	13.42	20.45	45.76	4.76	13.22	20.45
XI	R^1 -C_3H_7n	R^4 -$COC_6H_3Cl_2$ (3,4)	58	57-60	$C_{13}H_{12}Cl_2NO_2S$	47.13	3.62	8.46	9.67	47.14	3.61	8.29	9.69
XI	R^1 -C_3H_7n	R^4 -$CONHCH_3$	55	123-128	$C_8H_{13}N_3O_2S$	44.65	6.05	19.53	14.88	44.38	6.23	19.51	14.42
XI	R^1 -C_3H_7n	R^4 -$COCH_2Cl$	95	64-65	$C_8H_{11}ClN_2O_2S$	40.94	4.69	11.94	13.64	41.12	4.80	12.08	13.88
XI	R^1 -C_3H_7n	R^4 -$CO_2CH(CH_3)_2$	27	139-140/0.9	$C_{10}H_{16}N_2O_3S$	49.18	6.55	11.47	13.12	48.91	6.59	11.62	13.17
XII		R^2 -H (b)	87	73-74	C_3H_3NOS	35.40	3.08	13.70	31.80	35.64	2.97	13.86	31.68
XII		R^2 -CO_2H (c)	48	202-204	$C_4H_3NO_3S$	33.27	2.05	9.55	21.77	33.10	2.07	9.66	22.07
XII		R^2 -NO_2 (b)	64	169-170	$C_3H_2N_2O_3S$	25.32	1.52	18.81	21.67	24.66	1.37	19.18	21.92

(a) Prepared from dimethyl dithiodipropionimidate. (b) From structure V where $R^1 = CH_3$. (c) From structure V when $R^1 = CH_3$ and $R^2 = CN$.

mm, n_D^{22} 1.4998.

4-Bromo-3-methoxyisothiazole.

To a solution of 9.2 g. (0.08 mole) of 3-methoxyisothiazole in 20 ml. of glacial acetic acid was added at room temperature a solution of 12.8 g. (0.08 mole) of bromine in 20 ml. of acetic acid. The mixture was stirred for 3 hours and allowed to stand overnight. The mixture was poured into 400 ml. of ice and allowed to stand for a few hours. Solid separated which was dissolved in ether. The layers were separated and the aqueous layer neutralized (sodium bicarbonate). The neutralized solution was further extracted with ether and the ether solutions were combined and dried (magnesium sulfate). The ether was evaporated and the residual oil was distilled to give 11.2 g. (72%) of product, b.p. 70-75°/5 mm.

4-Iodo-3-methoxyisothiazole.

To a solution of 1.15 g. (0.01 mole) of 3-methoxyisothiazole in 5 ml. of glacial acetic acid was added dropwise over a 10-minute period 1.80 g. (0.011 mole) of iodine monochloride. The temperature rose slightly. The mixture was allowed to stand for 3 days and poured into ice water. An oil separated which on standing solidified to give 1.0 g. (41%) of product, m.p. 61-63° (hexane).

4-Nitro-3-methoxyisothiazole.

To 1.0 g. (0.0087 mole) of 3-methoxyisothiazole in 7 ml. of concentrated sulfuric acid at 10° was added dropwise 1 ml. of fuming nitric acid. The temperature rose to 25°. After stirring for 4 hours, the mixture was cooled to 10° and poured onto crushed ice. Filtration and subsequent recrystallization from ethanol provided 0.18 g. (13%) of 4-nitro-3-methoxyisothiazole, m.p. 118-122° (ethanol).

4-Cyano-3-methoxyisothiazole.

To a solution of 2.88 g. (0.0148 mole) of 4-bromo-3-methoxyisothiazole in 8 ml. of *N,N*-dimethylformamide was added 5.4 g. (0.06 mole) of cuprous cyanide. The mixture was stirred and heated at reflux for 1 hour. After cooling to room temperature, the mixture was stirred vigorously with a warm solution of 4 g. (0.082 mole) of sodium cyanide in 12 ml. of water and extracted with ether. The extracts were washed with 20 ml. of 10% aqueous sodium cyanide and 20 ml. of cold water. The ether solution was dried (magnesium sulfate), decolorized (Norit A) and evaporated to give 0.94 g. (45%) of product, m.p. 51-53°.

4-Carboxy-3-propoxyisothiazole.

To a solution of 5.6 g. (0.03 mole) of 4-carbamoyl-3-propoxyisothiazole in 15 ml. of concentrated sulfuric acid at 5° was added dropwise a solution of 6.9 g. (0.1 mole) of sodium nitrite in 10 ml. of water. The temperature was maintained below 5° by external cooling. The mixture was allowed to warm to room temperature and diluted with 200 ml. of cold water. The mixture was shaken with ether (100 ml.) and the layers separated. The extraction was repeated. The ether extracts were extracted with 100 ml. of 2*N* sodium hydroxide. The basic extract was acidified by dropwise addition of concentrated hydrochloric acid unitl precipitation was complete. The solid was collected and dried providing 4.67 g. (83%) of product, m.p. 92-93°.

4-Carbamoyl-3-propoxyisothiazole.

To 22 ml. of 80% sulfuric acid at 80° was added 1.7 g. (0.01 mole) of 4-cyano-3-propoxyisothiazole. The mixture was stirred and allowed to cool to room temperature. After pouring onto 100 ml. of crushed ice, crystalline solid separated. The solid was collected and dried to give 0.8 g. (43%) of product, m.p. 100-101° (hexane).

4-[*N*-(3,4-Dichlorophenyl)carbamoyl]-3-propoxyisothiazole.

A paste consisting of 9.3 g. (0.05 mole) of 4-carboxy-3-propoxyisothiazole and 24.0 g. (0.2 mole) of thionyl chloride was stirred for 16 hours. The resulting clear solution was concentrated to remove excess thionyl chloride. The residual oil was diluted with 20 ml. of benzene and added dropwise to a solution of 12.2 g. (0.075 mole) of 3,4-dichloroaniline in 40 ml. of benzene, keeping the temperature below 10°. When the addition was complete the mixture was allowed to warm to room temperature and filtered. The filtrate was evaporated and the solid residue was triturated with ligroine providing 8.4 g. (71%) of product, m.p. 116-118°.

4-Amino-3-propoxyisothiazole Hydrochloride.

To a cooled solution of 3 g. (0.075 mole) of sodium hydroxide in 32 ml. of water was added 3.8 g. (0.024 mole) of bromine. To this solution at 0° was added 2.9 g. (0.0156 mole) of 4-carbamoyl-3-propoxyisothiazole. The resulting yellow suspension was allowed to warm and by 15° all solid dissolved. The solution was heated slowly to 75° and the temperature maintained for 45 minutes. After cooling to room temperature, 7 g. of sodium chloride was added and the solution extracted with 3 x 50 ml. of ether. The extracts were dried (magnesium sulfate), decolorized (Darco G-60) and concentrated. The residue was redissolved in ether and saturated with dry hydrogen chloride. A cream-color solid separated which was collected and dried giving 1.68 g. (55%) of product, m.p. 149-150°.

4-(4-Aminophenylsulfonylamino)-3-propoxyisothiazole.

To 200 ml. of pyridine maintained below 100° was added 12 g. (0.062 mole) of 4-amino-3-propoxyisothiazole hydrochloride and 33 g. (0.14 mole) of *p*-acetamidobenzenesulfonyl chloride. The mixture was warmed at 65° for 1.5 hours, and poured onto 900 ml. of crushed ice. The ice was allowed to melt and the solid which had separated was collected. The solid, 4-(4-acetamidophenylsulfonylamino)-3-propoxyisothiazole, in quantitative yield was dried *in vacuo*, m.p. 204-207°.

To 25 ml. of 2*N* sodium hydroxide was added 3.9 g. (0.011 mole) of the acetamido derivative. On agitation a gel resulted which was stirred and heated at reflux for 1.5 hours. The mixture was decolorized (Nuchar), filtered and the filtrate allowed to cool. The filtrate was acidified to *p*H 6 precipitating 3.22 g. (97%) of product, m.p. 138-140°.

4-Methylureido-3-propoxyisothiazole.

To a stirred suspension of 9.72 g. (0.05 mole) of 4-amino-3-propoxyisothiazole hydrochloride in 150 ml. of benzene was added 5.55 g. (0.055 mole) of triethylamine. The suspension was filtered and the filtrate transferred to another reactor. A solution of 2.85 g. (0.05 mole) of methylisocyanate in 10 ml. of benzene was added and the mixture allowed to stand 20 hours. The solution was then evaporated to provide 7.79 g. (72%) of crude product. An analytical sample was obtained by recrystallization from ethanol-water, m.p. 123-128°.

4-(α-Chloroacetamido)-3-propoxyisothiazole.

To a solution of 1.6 g. (0.04 mole) of sodium hydroxide in 15 ml. of water was added 7.78 g. (0.04 mole) of 4-amino-3-propoxyisothiazole hydrochloride. The mixture was extracted with ether and the extract dried (magnesium sulfate). To the dried ether solution was added dropwise a solution of 2.26 g. (0.02 mole) of chloroacetyl chloride in 25 ml. of ether. The mixture was filtered removing 3.30 g. of 4-amino-3-propoxyisothiazole hydrochloride. The filtrate was evaporated. The residue solidified on cooling.

Recrystallization from ethanol-water gave 4.44 g. (95%) of product, m.p. 64-65°.

4-Carboxy-4-isothiazolin-3-one.

To 195 ml. of 80% sulfuric acid at 100° was added 12.5 g. (0.089 mole) of 4-cyano-3-methoxyisothiazole. The mixture was cooled to 10° and a solution of 18 g. (0.26 mole) of sodium nitrite in 35 ml. of water was added. The mixture was heated at 60° for several minutes and poured into 450 ml. of ice water. 4-Carboxy-3-methoxyisothiazole separated as a white solid. The solid was collected and stirred with 200 ml. of 48% hydrobromic acid for 45 minutes while bringing the mixture to boiling. Heating was maintained for another hour. On cooling a cream-colored solid separated. The crystallization from water provided 6.14 g. (48%) of product as white crystalline solid, m.p. 202-204°.

4-Nitro-4-isothiazolin-3-one.

A mixture of 2 g. (0.0125 mole) of 3-methoxy-4-nitroisothiazole and 100 ml. of 48% hydrobromic acid was stirred at room temperature for 72 hours. The mixture was extracted with ether. The extract was dried (magnesium sulfate) and evaporated giving 1.17 g. (64%) of crude product. Recrystallization from benzene gave an analytical sample, m.p. 169-170°.

REFERENCES AND NOTES

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