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Studies on Isothiazoles. IV.[1] A New Synthetic Route to 4-Cyanoisothiazoles

Takayuki NAITO, Susumu NAKAGAWA, Jun OKUMURA, Kiyoshi TAKAHASHI, Kenji MASUKO and Yukio NARITA

Bristol-Banyu Research Institute Ltd., Meguro-ku, Tokyo

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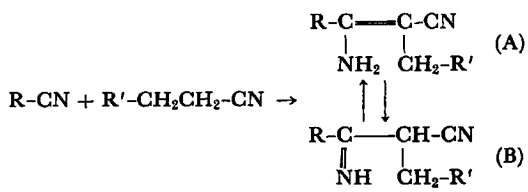
4-Cyanoisothiazoles have been prepared by a novel procedure which comprises the reacreaction of β-cyano enamines with thionyl chloride or sulfur monochloride. The reaction proceeds favorably in nonpolar solvents or in the absence of solvent. However, the cyclization did not occur in dimethylformamide and instead an amidine derivative was isolated. The preparations of the corresponding isothiazole-4-carboxylic acids are also described briefly.

Direct preparation of 4-cyanoisothiazoles from open-chain compounds has been carried out by reaction of methacrylonitrile with sulfur dioxide and ammonia in the presence of activated alumina,[2] by oxidative ring closure of α-cyano-β-iminothioamides[3,4] and by cyclization of dicyanoethylene thiolates with sulfur,[5,6] chlorine[7] or chloramide.[8] However, 4-cyanoisothiazoles having alkyl or aryl group(s) at position(s) 3 and/or 5 have not been prepared by any of the above procedures, but by the substitution reaction of 4-bromoisothiazoles with cuprous cyanide.[9-12] The present paper reports a direct formation of 3- and/or 5-alkyl- or aryl-substituted 4-cyanoisothiazoles by heating β-cyano enamines with thionyl chloride or sulfur monochloride.

The starting enamines were prepared by Thorpe condensation[13,14] of the corresponding nitriles in the presence of (a) metallic sodium, (b) sodium amide or (c) sodium hydride as shown in Table 1. The IR spectra of the enamines showed three bands in a range of 3100—3600 cm^{-1} due to N-H stretching vibrations. This suggests that these compounds are present as an equilibrium mixture of two tautomers, β-cyano enamine (A) and β-imino nitrile (B). In this paper the compounds of this family are represented and named by formula (A).



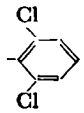
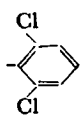
The preliminary experiments were carried out in dimethylformamide (DMF) with thionyl chloride and 1-amino-2-cyano-1-phenyl-1-butene (Ia) under similar conditions to the preparation of 4-hydroxyisothiazoles.[1] An exothermic reaction occurred, but no desired product was afforded. The only product isolated was a compound III, which has cyano (ν 2230 cm^{-1}), -C=N- (ν 1635 cm^{-1}), dimethylamino (3H singlet at 2.84*1 and 3H singlet at 3.03), ethyl (3H triplet at 1.15 and 2H quartet at 2.54; J=7.7 cps), =C-H (1H singlet at 7.12) and phenyl groups (5H multiplet centered at 7.37).

The reaction proceeded in the desired direction to give 4-cyano-5-methyl-3-phenylisothiazole (IIa)[12] when Ia was treated with thionyl chloride or sulfur monochloride in benzene, toluene, tetrahydrofuran, ligroin or solvent naptha, or without any solvent as shown in Table 2. Similarly, 1-amino-2-cyano-1-(2,6-dichlorophenyl)-1-butene (Ib) and 4-amino-3-cyano-3-heptene (Ic) gave 4-

1) Part III: T. Naito, S. Nakagawa, J. Okumura, K. Takahashi and K. Kasai, This Bulletin, **41**, 959 (1968).
2) F. Hübenett and H. Hofmann, *Angew. Chem.*, **75**, 420 (1963).
3) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **96**, 526 (1963).
4) J. Goerdeler and U. Keuser, *ibid.*, **97**, 3106 (1964).
5) W. R. Hatchard, *J. Org. Chem.*, **29**, 665 (1964).
6) E. Soderback, *Acta Chem. Scand.*, **17**, 362 (1963).
7) W. R. Hatchard, *J. Org. Chem.*, **29**, 660 (1964).
8) K. Hartke and L. Peshkar, *Angew. Chem.*, **79**, 56 (1967).
9) D. Buttimore, D. H. Jones, R. Slack and K. R. H. Wooldridge, *J. Chem. Soc.*, **1963**, 2032.
10) M. P. L. Caton, D. H. Jones, R. Slack and K. R. H. Wooldrigde, *ibid.*, **1964**, 446.
11) M. S. Grant, D. L. Pain and R. Slack, *ibid.*, **1965**, 3842.
12) T. Naito, S. Nakagawa and K. Takahashi, *Chem. Pharm. Bull.*, **16**, 148 (1968).
13) H. Baron, F. G. P. Pemery and J. F. Thorpe, *J. Chem. Soc.*, **85**, 1726 (1904).
14) G. A. Reynolds, W. J. Humphlett, F. W. Swamer and C. R. Hauser, *J. Org. Chem.*, **16**, 165 (1951).

*1 All NMR spectra were run in 10% solution of either carbon tetrachloride or deuteriochloroform with a Varian A-60 spectrometer, for which the authors are indebted to Assistant Professor M. Goto and Dr. Urushibara of Gakushuin University. Chemical shifts are represented in ppm from an internal reference, TMS.

TABLE 1. β-CYANO ENAMINES $R-C(NH_2)=C(CH_2-R')-CN$

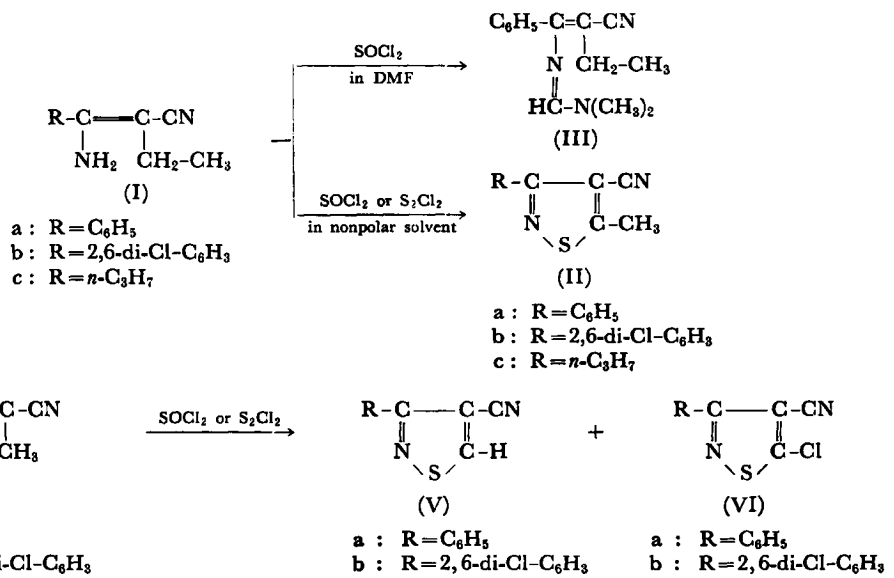
No.	R	R′	Method	Yield %	Bp °C/mmHg [Mp* °C]	λ_{max}^{EtOH} mμ (ε)	ν_{NH} cm^{-1}	Molecular formula		Anal, % C	H	N
Ia	C_6H_5	CH_3	a b c	46 50 11	130/1	222 (21700) 287 (15200)	3190 3320 3480	$C_{11}H_{12}N_2$	Calcd Found	76.71 76.32	7.02 6.40	16.27 16.04
Ib		CH_3	a b	25 9.4	[127—129]	218 (sh) (14900) 266 (16300)	3240 3360 3500	$C_{11}H_{10}Cl_2N_2$	Calcd Found	54.79 55.11	4.18 4.37	11.62 11.69
Ic	n-C_3H_7	CH_3	a	29	140—142/7.5—9**		3280 3440 3540					
IVa	C_6H_5	H	a b	39 34	[102—103]	221.5 (12900) 233 (sh) (9700) 287 (8300)	3260 3380 3500	$C_{10}H_{10}N_2$	Calcd Found	75.92 75.75	6.37 6.40	17.71 17.32
IVb		H	a b	28 22	[95—98]	218 (sh) (11200) 262 (12400)	3240 3380 3520	$C_{10}H_8Cl_2N_2$	Calcd Found	52.88 53.01	3.53 3.37	12.34 12.01

* Recrystallized from ligroin-benzene.

** H. Adkins and G. M. Whitman, *J. Am. Chem. Soc.*, **64**, 150 (1942); bp 137—142°C/7 mmHg.

TABLE 2. PREPARATION OF 4-CYANOISOTHIAZOLES

Starting enamine	Cyclization reagent	Solvent	Reaction time hr	Product Compd. No.	Product Yield, %
Ia	$SOCl_2$	benzene	3	IIa	15
Ia	$SOCl_2$	benzene	4	IIa	23
Ia	$SOCl_2$	toluene	4	IIa	31
Ia	$SOCl_2$	toluene	16	IIa	46
Ia	$SOCl_2$	tetrahydrofuran	4	IIa	8.5
Ia	$SOCl_2$	ligroin	4	IIa	18
Ia	$SOCl_2$	naphtha	18	IIa	41
Ia	$SOCl_2$	none	4	IIa	17
Ia	S_2Cl_2	toluene	16	IIa	12
Ia	S_2Cl_2	none	16	IIa	32
Ib	$SOCl_2$	toluene	48	IIb	55
Ib	S_2Cl_2	toluene	45	IIb	29
Ic	$SOCl_2$	benzene	20	IIc	7.5
IVa	$SOCl_2$	toluene	5	Va VIa	31 3.5
IVa	S_2Cl_2	toluene	5	Va VIa	42 trace
IVb	$SOCl_2$	toluene	10	Vb	40
IVb	S_2Cl_2	toluene	48	Vb	47

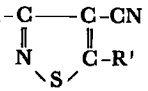


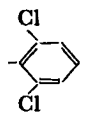
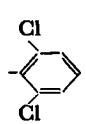
cyano-3-(2, 6-dichlorophenyl)-5-methylisothiazole (IIb) and 4-cyano-5-methyl-3-*n*-propylisothiazole (IIc), respectively.

The reaction of 1-amino-2-cyano-1-phenyl-1-propene (IVa) with thionyl chloride gave two kinds of cyanoisothiazoles, which were separated by an alumina column chromatography. The main product was the expected 4-cyano-3-phenylisothiazole (Va)[12] ($\nu_{C\equiv N}$ 2240 cm^{-1}; 5-H proton 9.30 ppm). The minor component was 5-chloro-4-cyano-3-phenylisothiazole (VIa) ($\nu_{C\equiv N}$ 2240 cm^{-1}; M^+ peak[*2] at *m/e* 220 with the isotpe peak at *m/e* 222), which lacks the C-5 proton singlet in the NMR spectrum. Sulfur monochloride was allowed to react with IVa under similar conditions and Va was isolated, while VIa was detected by gas chromatography. In the reaction of 1-amino-2-cyano-1-(2,6-dichlorophenyl)-1-propene (IVb) with thionyl chloride or sulfur monochloride, 4-cyano-3-(2,6-dichlorophenyl)isothiazole (Vb) was isolated, but the 5-chloro derivative (VIb) was not detected.

[*2] Mass spectrum was run with a Hitachi RMU-6 spectrometer by a heating inlet system (chamber voltage, 80 V; reservoir temp., 110°C; electron multiplier voltage, 2000 V), for which the authors are indebted to Professor S. Hishida of Nihon University.

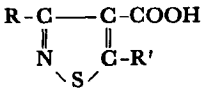
TABLE 3. 4-CYANOISOTHIAZOLES

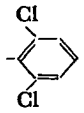
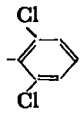


No.	R	R′	Mp °C	λ_{max}^{EtOH} mμ (ε)	$\nu_{C\equiv N}$ cm^{-1}	δ ppm	Molecular formula		Anal, % C	H	N	Cl
IIa	C_6H_5	CH_3	78*	264 (11300)	2280	2.73 (3H, s) 7.40—7.60 (3H, m) 7.97—8.17 (2H, m)						
IIb		CH_3	124—125	257 (9000)	2260	2.80 (3H, s) 7.37 (3H, m)	$C_{11}H_6Cl_2N_2S$	Calcd Found	49.08 48.87	2.25 2.51	10.41 10.70	26.35 26.62
IIc	n-C_3H_7	CH_3	bp 73—76 (4.5—5.5 mmHg)	257.5 (6000) 262 (sh) (5600)	2260	0.99 (3H, t) 1.80 (2H, sex) 2.72 (3H, s) 2.87 (2H, t)						
Va	C_6H_5	H	54—55**	256.5 (11800) 273 (10500)	2260	7.45—7.65 (3H, m) 8.00—8.25 (2H, m) 9.30 (1H, s)						
VIa	C_6H_5	Cl	75—76	241.5 (20000)	2220	7.42—7.78 (3H, m) 7.96—8.26 (2H, m)	$C_{10}H_5ClN_2S$	Calcd Found	54.42 54.47	2.49 2.49	12.70 12.77	16.07 16.35
Vb		H	151—152	258.5 (9000)	2240	7.56 (3H, m) 9.50 (1H, s)	$C_{10}H_4Cl_2N_2S$	Calcd Found	47.17 47.39	1.58 1.30	10.98 10.87	27.80 27.71

* Ref. 12, mp 79—80°C ** Ref. 12, mp 54—55°C

TABLE 4. ISOTHIAZOLE-4-CARBOXYLIC ACIDS



R	R'	Method	Yield %	Mp °C	λ_{max}^{EtOH} mμ (ε)	$\nu_{C=O}$ cm^{-1}	Molecular formula		Anal, % C	H	N	Cl
C_6H_5	CH_3	a	80	153—154*	264 (10000)	1670						
	CH_3	b	81	213—213.5	255.5 (8400)	1670	$C_{11}H_7Cl_2NO_2S$	Calcd Found	45.85 46.27	2.45 2.19	4.86 4.94	24.61 24.54
n-C_3H_7	CH_3	a	14	83—84.5	257 (14000) 228 (sh) (7500)	1690	$C_8H_{11}NO_2S$	Calcd Found	51.87 51.63	5.99 5.72	7.56 7.26	
C_6H_5	H	a	78	165—166**	259 (10300)	1730						
	H	b	82	182—183	255 (7100)	1690	$C_{10}H_5Cl_2NO_2S$	Calcd Found	43.81 43.66	1.84 1.80	5.11 4.85	25.87 26.44

* Ref. 12, mp 153—154°C.
** Ref. 12, mp 165—166°C.

4-Cyanoisothiazoles prepared in the present study were readily converted into the corresponding isothiazole-4-carboxylic acids either (a) by heating with sulfuric acid followed by treatment with aqueous sodium nitrite, or (b) by hydrolysis with potassium hydroxide in aqueous ethylene glycol (Table 4).

Experimental

β-Cyano Enamines (Table 1). Representative examples of the preparation of β-cyano enamines, Ia—c and IVa, b, are given below.

a) A mixture of 105 g (1.0 mol) of benzonitrile and 70 g (1.0 mol) of *n*-butyronitrile in 500 m*l* of ether was added slowly to a dispersion of 23 g (1.0 atom) of metallic sodium in toluene under stirring over a period of about 2.5 hr at 20—30°C. The color of the mixture gradually turned to red. The reaction mixture was stirred for 6 hr at room temperature and allowed to stand overnight. Excess sodium was decomposed by adding water slowly under stirring. The ether layer was separated, washed with three 200-m*l* portions of saturated aqueous solution of sodium chloride and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue distilled under diminished pressure to give 79 g (46%) of Ia.

b) To 200 m*l* of liquid ammonia containing about 0.1 g of ferric nitrate was added portionwise 4.8 g (0.21 atom) of sodium at −40 to −50°C. To the blue solution of sodium amide was added dropwise a solution of 20.6 g (0.2 mol) of benzonitrile and 13.8 g (0.2 mol) of butyronitrile in 100 m*l* of ether. After the addition was completed, liquid ammonia was replaced with 200 m*l* of dry ether and the solution was refluxed for three hours. To the reaction mixture was cautiously added 200 m*l* of water and the ether layer which separated was washed with four 200-m*l* portions of water, dried over anhydrous sodium sulfate and the solvent evaporated. The residue was distilled to give 17.1 g (50%) of Ia.

c) A 50% dispersion of sodium hydride in mineral oil (4.8 g, 0.1 mol) was mixed with 100 m*l* of dry benzene and to the stirred mixture was added a solution of 10.3 g (0.1 mol) of benzonitrile and 6.9 g (0.1 mol) of butyronitrile in 100 m*l* of dry benzene at 40—50°C. After the addition was completed, the mixture was stirred for 4 hr at 70°C, then cooled to room temperature and 200 m*l* of water was cautiously added dropwise. The benzene layer was distilled under reduced pressure and a fraction boiling at 100—160°C/1.5 mmHg was collected and redistilled to give 1.8 g (11%) of Ia.

2-Cyano-1-(*N*,*N*-dimethylforamidino)-1-phenyl-1-butene (III). To a stirred solution of 1.7 g (0.01 mol) of Ia in 15 m*l* of DMF was added dropwise 3.6 g (0.03 mol) of thionyl chloride. An exothermic reaction occurred and the temperature of the solution rose to about 50°C. After the exothermic reaction had ceased, stirring was continued for 4 hr. The reaction mixture was poured into ice-water, made alkaline by dil. sodium hydroxide solution and extracted with ether. The extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue distilled under reduced pressure to give 1.1 g (48%) of III boiling at 163°C/1.0 mmHg, which solidified at room temperature. Recrystallization from ligroin gave colorless prisms melting at 50—52°C. λ_{max}^{EtOH} 309 mμ (ε 28000).

Found: C, 74.20; H, 7.95; N, 18.25%. Calcd for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49%.

4-Cyanoisothiazoles (Tables 2 and 3). To a solution of β-cyano enamine in an appropriate solvent shown in Table 2 was added 3—5 mol of thionyl chloride or sulfur monochloride in one portion. The mixture was refluxed for a certain period of time as shown in Table 2, then allowed to stand overnight at room temperature, poured into crushed ice and extracted twice with 50 m*l* of ether. The combined ethereal extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue crystallized from ligroin (IIb and Vb) or distilled under reduced pressure (IIc).

The residue obtained by the reaction with Ia dissolved in ligroin. The solution was subjected to an alumina column chromatography and developed with ligroin followed with ligroin-benzene (1 : 1), the eluate being divided into 100—200 m*l* portions. Each of the fractions was evaporated into dryness. The residues were subjected to gas chromatography and the fractions which appeared to be rich in IIa were combined and crystallized from ligroin to give a pure sample of IIa.

The residue obtained by the reaction with IVa was dissolved in ligroin, chromatographed on an alumina column and eluted with ligroin. The eluate was collected in 50-m*l* portions, each fraction being analyzed by gas chromatography. The second and third fractions of the eluate were combined and evaporated to dryness to give a crystalline residue. Recrystallization from petroleum ether gave colorless needles of 5-chloro-4-cyano-3-phenylisothiazole (VIa). Evaporation of fractions No. 4—No. 10 and subsequent recrystallization from ligroin gave 4-cyano-3-phenylisothiazole (Va).

The results are shown in Table 2 and the properties and analyses of the products in Table 3.

Isothiazole-4-carboxylic Acids (Table 4). Hydrolysis of 4-cyanoisothiazoles was carried out by either one of the procedures illustrated in representative examples given below.

a) 5-Methyl-3-n-propylisothiazole-4-carboxylic Acid. A mixture of 0.52 g (0.00314 mol) of IIc and 15 m*l* of concentrated sulfuric acid was heated at 70—75°C for 6 hr and allowed to stand overnight at room temperature. The reaction mixture was cooled below 10°C and a solution of 0.27 g of sodium nitrite in 1 m*l* of water was cautiously added dropwise. The mixture was stirred for 20 min at 5—9°C, for 30 min at room temperature and finally for 30 min at 40°C. The reaction mixture was poured onto 40 g of crushed ice, insoluble material removed and the filtrate extracted with ether. The ethereal extracts were dried with anhydrous sodium sulfate, the solvent being evaporated. The residue was dissolved in aqueous sodium bicarbonate, washed with ether, treated with a small amount of active carbon and acidified with dilute hydrochloric acid to give 5-methyl-3-*n*-propylisothiazole-4-carboxylic acid which was recrystallized from benzene-ligroin (1 : 2).

b) 3-(2,6-Dichlorophenyl)-5-methylisothiazole-4-carboxylic Acid. A mixture of 2.3 g (0.0085 mol) of II, 1 g (0.018 mol) of potassium hydroxide, 1.8 m*l* of water and 9 m*l* of ethylene glycol was refluxed for 48.5 hr

and the reaction mixture was poured into 50 ml of water. A small amount of insoluble material was filtered off and the filtrate was acidified with dilute hydrochloric acid to separate 2.15 g of the crude acid. Recrystallization from ligroin-ethyl acetate gave 3-(2,6-dichlorophenyl)-5-methylisothiazole-4-carboxylic acid.

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