Nucleophilic Attack on Some Isothiazolium Salts

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A variety of isothiazolium salts has been prepared and allowed to react with sodium benzoylacetate. 2-Benzoylthiophenes are obtained, suggesting that the position of initial nucleophilic attack is at the sulfur atom of the heterocyclic cation. Reaction with hydrogen sulfide gave acyclic reduction products, or 1,2-dithiole derivatives, depending on the type of substituent on nitrogen in the isothiazolium salts.

Une série de sels d'isothiazolium a été préparée et mise en réaction avec le benzoylacétate de sodium. Des benzoyl-2 thiophènes ont été obtenus laissant penser que l'attaque nucléophile initiale se faisait sur l'atome de soufre du cation hétérocyclique. La réaction avec l'hydrogène sulfuré conduit aux produits de réduction acyclique ou aux dérivés dithiole-1,2, en fonction du type de substituant sur l'azote dans les sels d'isothiazolium. [Traduit par le journal]

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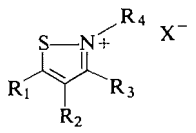
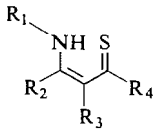
While studies of nucleophilic attack on isothiazoles (1) and isothiazolones (2–5) indicate that the attack takes place at the ring sulfur atom, the situation with isothiazolium salts is by no means as clear. Various reactions of isothiazolium salts **1** with nucleophiles have been interpreted as occurring at carbon atom 3 (1, 6, 7), but in these reactions the products obtained could also have been formed by initial attack at sulfur. The reaction of certain 5-methylthioisothiazolium salts with hydrosulfide (8) has been suggested to occur at ring sulfur and recently (9) attack at carbon atom 3 by nitrogen nucleophiles, and at sulfur by hydrogen sulfide, has been demonstrated. In this work we wish to report some of our studies on the isothiazolium system which provide evidence on the position of nucleophilic attack.



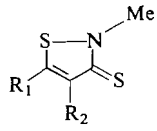
1

	R_1	R_2	R_3	R_4	X
a	H	H	H	Me	ClO_4
b	Ph	H	H	Me	ClO_4
c	Ph	H	H	Ph	ClO_4
d	Ph	Ph	H	Me	ClO_4
e	Ph	H	Ph	Ph	ClO_4
f	Ph	H	SMe	Me	I
g	SMe	Ph	H	Ph	ClO_4
h	SMe	H	Ph	Me	ClO_4
i	H	Ph	H	Ph	ClO_4
j	Ph	Ph	H	Ph	ClO_4
k	H	Ph	H	Me	ClO_4



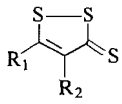
2

	R_1	R_2	R_3	R_4
a	Ph	H	H	Ph
b	Ph	Ph	H	Ph
c	Ph	H	Ph	SMe
d	Me	Ph	H	SMe
e	Ph	H	Ph	Ph
f	Me	Ph	H	NHMe
g	Me	SMe	H	Ph



3

a R_1 = Ph, R_2 = H
b R_1 = R_2 = Ph



4

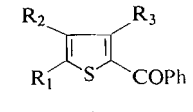
a R_1 = H, R_2 = Ph
b R_1 = Ph, R_2 = H

A variety of isothiazolium salts **1**(*a–k*) was used in the investigation. Most of these except **1***h* had been made before. Compound **1***a* had been isolated as its iodide (10), but we found it simpler to alkylate isothiazole by dimethyl sulfate and isolate the salt as its perchlorate. **1***g* was prepared by alkylation of 2,4-diphenylisothiazoline-3-thione, the reverse of a reaction previously described (8). Compound **1***h*, which was new, was prepared by iodine oxidation of methyl 3-methylaminodithiocinnamate (**2***d*) similarly to known methods (8, 11). The dithioester was prepared by treatment of 3-methylthio-5-phenyl-1,2-

dithiolium iodide with methylamine according to known methods (12). It is reported to be accompanied by 2-methyl-5-phenylisothiazoline-3-thione (**3***a*) and by 5-phenyl-1,2-dithiole-3-thione (**4***b*). In our investigation we found that the former compound was accompanied by greater or lesser amounts of *N*-methyl 3-methylaminothiocinnanamide (**2***f*), depending on the quantity of methylamine used, and in fact when a large excess of methylamine was used, the isothiazolinethione was not found and the amide was obtained instead. Treatment of the thione with methylamine gave no reaction, suggesting that the thione is not a precursor of the thioamide, and that the latter arises instead via some mechanistic change in the reaction of the dithiolium salt with the amine.

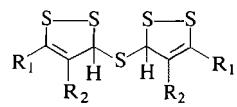
The isothiazoline-3-thione from the above reaction was smoothly converted by hydrogen peroxide in acetic acid into the 2-methyl-5-phenylisothiazolium cation, isolated as its perchlorate (**1***b*). Likewise, 2-methyl-4,5-diphenylisothiazoline-3-thione (**3***b*), prepared by reaction of 3-methylthio-4,5-diphenyl-1,2-dithiolium iodide with methylamine, was converted to 2-methyl-4,5-diphenylisothiazolium perchlorate (**1***d*). These oxidations by hydrogen peroxide in acetic acid are related to reactions of isothiazoline-5-thiones (8), and dithiolethiones (13, 14). Since *N*-alkylisothiazolium salts can be dealkylated to isothiazoles (15), the reaction represents another synthesis of these from dithiolium salts. These salts were identical to ones prepared (8) by methylation of isothiazoles, and by another method, the treatment of 1,2-dithiolium salts with methylamine to form β-methylaminopropenethiones **2** (16), which oxidized by iodine to form the *N*-methylisothiazolium salts **1***b* and *d*, isolated as the perchlorates. Yields by this method were rather poor, comparable to one such reaction previously studied (11), but it does at least represent a quick synthesis of *N*-alkylisothiazolium salts from the readily accessible (13, 14) 1,2-dithiolium salts.

Treatment of the isothiazolium salts **1** with sodium benzoylacetate yielded 2-benzoylthiophenes **5** in all cases. The formation of these can be explained by nucleophilic attack of a phenacyl ion (actual or potential) on ring sulfur, to give ring opening, followed by attack of the activated methylene group on the imine function to give recyclization to the thiophenes. The results from the 3- or 5-alkylthioisothiazolium salts **1***f*, *g*, and *h* are especially striking. By analogy with other related heterocyclic systems (16), had nucleophilic attack occurred at carbon, 3- or 5-acylmethleneisothiazoles would have been expected. For all cases except **1***f* cyclization occurs by loss of amine, but in that case, methanethiolate anion, a better leaving group, is lost instead, with formation of a 3-amino-2-benzoylthiophene (**5***e*). This reaction also afforded the acyclic reduction product **2***g*, which could have arisen by reaction of eliminated methanethiolate ion with another molecule of starting isothiazolium salt, either by reduction, or by nucleophilic attack. Similar results have been obtained for the attack of benzenethiol (**9**) or benzenethiolate anion (below) on isothiazolium salts. Likewise, the attack of hydrosulfide ion on two alkylthioisothiazolium salts in ethanol (8) may be rationalized as occurring by a similar route.



5

	R_1	R_2	R_3
a	H	H	H
b	Ph	H	H
c	Ph	Ph	H
d	Ph	H	Ph
e	Ph	H	NHMe
f	SMe	Ph	H
g	SMe	H	Ph
h	H	Ph	H



6

a $R_1 = R_2 = Ph$
b $R_1 = H, R_2 = Ph$

Sykes and Ullah (9) found that attack of hydrogen sulfide on the isothiazolium system in aqueous solution gave bis-1,2-dithiol-3-yl sulfides **6** instead of reduction products. Accordingly, we treated a number of the isothiazolium salts with hydrosulfide ion in ethanol, or hydrogen sulfide in water, and examined the products. Little difference if any was found in the reaction products derived from either method, and the course of the reaction appears to depend mainly on whether the original isothiazolium salt is *N*-aryl or *N*-alkyl substituted. The former give mainly reduction products, β-aminopropenethiones or derivatives **2**, while the latter give reduction, bis-1,2-dithiol-3-yl sulfides **6**, or 1,2-dithiole-3-thione **4** products.

The differences in the products obtained probably arise from changes in the mechanism shown in Scheme 1.

The intermediate disulfide imine A could either

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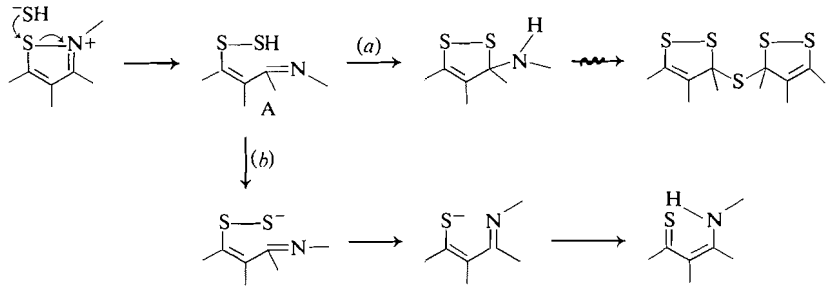
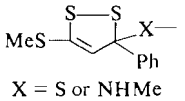


SCHEME 1

add to the imine group (path a), to give an aminodithiole, with eventual formation of a bis-dithiolyl sulfide, or extrude sulfur (path b) to give a β-aminothione derivative. For aliphatic imines A the former would be the preferred route, but where the imine is stabilized by conjugation with an aromatic ring, the latter would be preferred, leading to an acyclic reduction product. Path a is analogous to a step in the formation of 1,2-dithiolium salts from 1,3-diketones with hydrogen disulfide in acidic media (14), while path b is analogous to steps in the known reactions of 1,2-dithiolium salts with bases, particularly with primary aromatic amines (17). In path a, the conversion of the aminodithiole to the sulfide could be accomplished by nucleophilic exchange between the aminodithiole and hydrogen sulfide, as has been suggested (17) for reactions of 1,3-dithioles. Intermediate formation of a 1,2-dithiolium cation (9) may be involved.

With one compound, 2-methyl-5-methylthio-3-phenylisothiazolium perchlorate (**1***h*) the acyclic reduction product **2***d* was obtained. The other product isolated was not a bis-dithiolyl sulfide, but was 5-phenyl-1,2-dithiole-3-thione (**4***b*). While the exact mechanism leading to this is unknown, it is not unreasonable that it could be derived from a compound of the type



X = S or NHMe

formed by cyclization of the intermediate disulfide suggested in Scheme 1. The reactions leading to the formation of **2***d* and **5***b* from isothiazolium salt **1***h* and of **2***g* and **4***b* from **1***f* likely follow a similar scheme.

The isolation of only the thione **4***a* from reaction of the isothiazolium salt **1***k*, instead of a sulfide **6***b*, presents some difficulty. However, the thione does appear to be derived from the sulfide since prolonged treatment of the latter with hydrogen sulfide or sodium hydrosulfide gave thione. The necessary oxidation could be accomplished by unreacted isothiazolium salt, intermediate dithiolium cation as suggested above, or by sulfur arising from decomposition of either of these.

Treatment of two isothiazolium salts **1***e* and **1***b* with sodium benzenethiolate in ethanol gave reduction products **2***b* and **2***d* respectively, and diphenyldisulfide. These results are comparable to other such studies made (9).

Experimental

The i.r. spectra were obtained on a Perkin–Elmer model 337 spectrophotometer in liquid paraffin mulls. The n.m.r. spectra were obtained on a Varian Model 56/60A spectrometer and, unless otherwise stated, in deuterochloroform at 40°, using tetramethylsilane as an internal standard. Mass spectra were obtained on a Finnegan 1015 quadrupole mass spectrometer. T.l.c. was performed using "Camag" silica gel D.S.F.5, and column chromatography on alumina 506-C-1, Brockman activity 1, both supplied by Mondray Ltd. Development of both, unless otherwise stated, was by benzene. Melting points were obtained on a Fisher–Johns melting point apparatus.

*Preparation of 2-Methylisothiazolium Perchlorate (**1***a*)*

Isothiazole (0.85 g, 0.01 mol) and dimethyl sulfate (1 ml) were heated at 100° for 1 h. The mixture was treated with ether and the precipitated oil dissolved in acetic acid, and treated with 70% perchloric acid (0.5 ml). Colorless needles, m.p. 145°, were obtained (61%). A sample of the perchlorate treated with aqueous sodium iodide gave the iodide identical (mixed m.p. and i.r.) with an authentic sample (10).

Reaction of 3-Methylthio-5-phenyl-1,2-dithiolium Iodide with Methylamine

This reaction was performed as described (12) except that the equivalent quantity of 40% ethanolic methylamine solution was used. Work-up gave 5-phenyl-1,2-dithiole-3-thione, methyl β-methylaminodithiocinnamate, and 2-methyl-5-phenylisothiazoline-3-thione as described. When the reaction was performed with a fourfold excess of the

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TABLE 1. Reactions of isothiazolium salts with sodium benzoylacetate

Isothiazolium salt **1**	Source	Product **5**	Yield %	M.p. °C	Analysis							
					Calculated (%)				Found (%)			
					C	H	N	S	C	H	N	S
a	*	*a*	71	57†								
b	*	*b*	68	132‡								
c	§	*b*	63	132								
d	*	*c*	68	150–152	81.13	4.71	—	9.41	81.17	4.84	—	9.51
e	§	*d*	42	101‖								
f	¶	*e*	38	108–109	73.51	5.12	4.76	10.95	73.45	5.25	4.67	10.91
g	*	*f*	77	89–91	69.75	4.52	—	20.65	70.07	4.62	—	20.88
h	*	*g*	74	82–83	69.75	4.52	—	20.65	70.04	4.69	—	20.85
i	**	*h*	40	96	77.35	4.54	—	12.12	77.07	4.69	—	12.24

*This work.
†Literature (19) 57°.
‡Literature (20) 132°.
§Reference 11.
‖Reference 21 m.p. 101°.
¶Reference 12.
**Reference 8.

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amine solution, and the mixture worked up as above, chromatography on 5% deactivated alumina gave initially 5-phenyl-1,2-dithiole-3-thione and methyl β-methylaminodithiocinnamate. Extraction of a broad strongly adsorbed band with acetone gave a yellow oil which crystallized on scratching. Recrystallization from ethanol gave pale-yellow prisms, m.p. 96–98° (35%).

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.21; H, 6.83; N, 13.59; S, 15.55. Found: C, 63.92; H, 6.89; N, 13.52; S, 15.64.

N.m.r. τ 7.28 (3H doublet, $J = 3.2$ Hz, the amidic methyl), 7.00 (3H doublet, $J = 3.2$ Hz, the amine methyl), 5.02 (1H singlet, vinylic proton), 3.40 (1H band, the amidic NH), 2.68 (5H multiplet, the aromatic protons), −1.20 (1H band, the amine NH, hydrogen bonded to C=S).

The mass spectrum: M^+ 206, calcd. 206, 173 (M—SH)

*Preparation of 2-Methyl-5-methylthio-3-phenylisothiazolium Perchlorate (**1h**)*

Methyl β-methylaminodithiocinnamate (446 mg, 2 mmol) in ethanol (5 ml) was treated with saturated iodine solution until there was a slight permanent cloudiness. 70% perchloric acid (1 ml) was added, and dilution with ether produced yellow crystals. The product was recrystallized from acetic acid containing perchloric acid as yellow needles, m.p. 184–186 (83%).

Anal. Calcd. for $C_{11}H_{12}NS_2ClO_4$: C, 41.05; H, 3.73; N, 4.35; S, 20.55; Cl, 11.05. Found: C, 41.07; H, 3.86; N, 4.23; S, 20.08; Cl, 10.92.

N.m.r. (dimethylsulfoxide-d_6) τ 7.21 (3H singlet, the S—CH_3 group), 5.99 (3H singlet, the N—CH_3 group), 2.51–2.15 (5H bands, the aromatic protons).

Treatment of 2-Methyl-5-phenylisothiazoline-3-thione with Methylamine

The thione (50 mg) and 40% methylamine solution in ethanol (1 ml) were refluxed together 1 h. The starting material was recovered on work-up.

*Reaction of 3-Methylthio-4,5-diphenyl-1,2-dithiolium Iodide with Methylamine, 2-Methyl-4,5-diphenylisothiazoline-3-thione (**3b**)*

The salt (4.28 g, 0.01 mol) in tetrahydrofuran (70 ml) was treated with 60% methylamine solution in ethanol (6 ml) at room temperature and stirred until homogeneous. The solution was evaporated, and the residue chromatographed in benzene on 5% deactivated alumina. Two bands were obtained. A red band gave 4,5-diphenyl-1,2-dithiole-3-thione (31%), and a strongly adsorbed yellow band was extracted with acetone. Evaporation gave a yellow solid which was recrystallized from ethanol as pale-yellow needles, m.p. 133° (28%).

Anal. Calcd. for $C_{16}H_{13}NS_2$: C, 67.85; H, 4.59; N, 4.94; S, 22.62. Found: C, 67.82; H, 4.45; N, 5.01; S, 22.81.

N.m.r. τ 6.21 (3H singlet, the methyl protons), 2.53–2.87 (10H bands, the aromatic protons).

The mass spectrum: calcd. M^+ 283. Found, 283.

*Preparation of 2-Methyl-5-phenylisothiazolium Perchlorate (**1b**)*

(a) From 2-Methyl-5-phenylisothiazoline-3-thione

Powdered thione (103.5 mg, 0.5 mmol) in acetic acid (4 ml) was treated with 30% hydrogen peroxide (0.15 ml). The solid dissolved almost immediately and the solution became dark yellow. After 1 h, the solution was treated with ether, and the precipitated oil treated with 70% perchloric acid (0.1 ml). The oil solidified and was recrystallized from acetic acid as pale-yellow plates, m.p. 144–145° (80%). Identical mixed m.p. and i.r. with an authentic specimen (11).

(b) From 3-Phenyl-1,2-dithiolium Perchlorate

The perchlorate (1.035 g, 5 mmol) in ethanol (10 ml) was treated with 40% ethanolic methylamine solution (2 ml) and warmed gently with stirring until homogeneous. The red solution was treated with saturated ethanolic iodine solution (2 ml), and 70% perchloric acid (1 ml) added. Dilution with ether and scratching gave a brown precipitate which was recrystallized from acetic acid containing perchloric acid as yellow plates, identical (mixed m.p. and i.r.) with the above (20%).

*Preparation of 2-Methyl-4,5-diphenylisothiazolium Perchlorate (**1d**)*

(a) From 2-Methyl-4,5-diphenylisothiazoline-3-thione

This reaction was performed as for the previous synthesis. Pale-yellow needles, m.p. 99°, were obtained (75%). Identical (mixed m.p. and i.r.) with an authentic specimen (8).

(b) From 3,4-Diphenyl-1,2-dithiolium Perchlorate

This reaction was carried out as described for the previous compound, except that recrystallization was effected from acetone containing perchloric acid. Pale-yellow needles of the salt were obtained (25%), identical (mixed m.p. and i.r.) to an authentic specimen.

*Preparation of 5-Methylthio-2,4-diphenylisothiazolium Perchlorate (**1g**)*

2,4-Diphenylisothiazoline-5-thione (8) (0.566 g, 2 mmol) in *n*-butyl acetate (10 ml) was treated with methyl iodide (2 ml) and allowed to stand. An oily precipitate which was deposited initially crystallized on further standing. The mixture was diluted with ether, filtered, and the salt converted to the perchlorate in acetic acid containing perchloric acid. Recrystallization from acetic acid gave pale-yellow prisms, m.p. 158°, identical (mixed m.p. and i.r.) with an authentic specimen (8).

Reaction of Isothiazolium Salts with Sodium Benzoylacetate: General Method

The isothiazolium salts (~1 mmol) were added to a suspension in ethanol of sodium benzoylacetate (~1.5 mmol) (prepared by addition of benzoylacetic acid (18) to a molar solution of sodium ethoxide in ethanol). The mixture was stirred and gently warmed until homogeneous. The mixture was diluted with water and the ether extract dried. Evaporation gave either crystalline material directly or oils which were purified by t.l.c. prior to crystallization. Products were recrystallized from ethanol or ethanol–benzene, 1:1, mixture. Reactions and products are summarized in Table 1.

Treatment of salt **1*f*** with sodium benzoylacetate gave an oily product which on examination by t.l.c. gave the thiophene **5*e***. The first band on elution gave 30 mg of an orange oil, whose n.m.r. had a broad band at −4.5 τ, typical of β-aminoenethiones (9, 22). This was not analyzed, but an iodine oxidation in the presence of perchloric acid gave back salt **1*f***, confirming its structure as **2*g***.

TABLE 2. Reactions of isothiazolium salts with sodium hydrosulfide (method a) or hydrogen sulfide (method b)

Isothiazolium salt **1**	Source	Method	Products in order of elution (yields %)
c	*	a	**2***a*(52)
c	*	b	**2***a*(56)
d	*	b	**6***a*(40)†
e	*	b	**2***b*(45)
f	*	a	**2***g*(32)‡, **4***b*(28)
g	*	b	**2***c*(45), **4***a*(49)
h	*	b	**2***d*(43), **4***b*(45)
j	§	b	**2***e*(20)
k	‖	b	**4***a*(21)

*See Table 1.
†This could not be isolated sufficiently pure for analysis, and was converted by treatment with perchloric acid into 3,4-diphenyl-1,2-dithiolium perchlorate (11), similarly to known methods (17).
‡Identified by conversion (I_2, $HClO_4$) to 1*f*.
§Reference 11.
‖Reference 8.

Reactions of Isothiazolium Salts with Hydrogen Sulfide or Sodium Hydrogen Sulfide

(a) The isothiazolium salts (~1 mmol) in ethanol (10 ml) were treated with equivalent quantities of ethanolic molar sodium hydrosulfide solution, and stirred until homogeneous. The solutions were diluted with water and ether-extracted.

(b) The salts (~1 mmol) in water suspension were treated with hydrogen sulfide and boiled 10 min. The mixtures were cooled and ether-extracted.

The ether extracts from *a* or *b* were dried, evaporated, and examined by t.l.c. The results are summarized in Table 2. There was little to choose between the two methods, and yields and products by each were comparable when performed on identical compounds.

Reaction of 2,3,5-Triphenylisothiazolium Perchlorate (1e) with Sodium Benzenethiolate

The isothiazolium salt (613.5 mg, 1 mmol) in ethanol (20 ml) was treated with the equivalent quantity of sodium benzenethiolate in ethanol (1 ml), and stirred until homogeneous. The dark-red solution was diluted with water and extracted with ether. Chromatography afforded 1-anilino-1,3-diphenylprop-1-ene-3-thione (81%) identical (mixed m.p. and i.r.) with an authentic sample (17). Diphenyl disulfide (89 mg) was also isolated from the reaction mixture.

Reaction of 2-Methyl-5-methylthio-3-phenylisothiazolium Perchlorate (1h) with Sodium Benzenethiolate

The reaction, performed as above, gave methyl β-methylaminodithiocinnamate (59%), identical with an authentic specimen (12).

Reaction of Bis-4-phenyl-1,2-dithiol-3-yl Sulfide with Hydrogen Sulfide

The sulfide (0.2 g) (23) in water (10 ml) was boiled and a stream of hydrogen sulfide passed through. After 10 min the mixture was cooled and ether-extracted. The extract on examination by t.l.c. gave unreacted material, and 4-phenyl-1,2-dithiole-3-thione **4***a* (30%). Boiling of the sulfide with sodium hydrogen sulfide gave similar results.

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