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THE REACTIONS OF ISOTHIAZOLIUM SALTS WITH NITROGEN NUCLEOPHILIC REAGENTS

MOHAMED E. HASSAN*, M.A. MAGRABY and MAGDA A.AZIZ

Chemistry Department, Aswan University, Aswan, Egypt

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Abstract - Isothiazolium salts were allowed to react with a number of nitrogen nucleophiles including ammonia, hydrazine phenylhydrazine, hydroxylamine, and benzylamine. The products obtained suggest that the position of initial nucleophilic attack is at the sulphur atom of the heterocyclic cation.

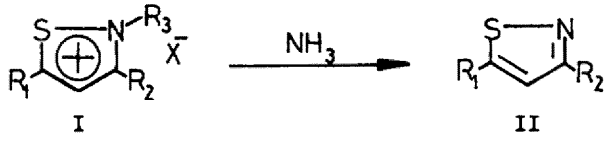
The nucleophilic attack on isothiazolium salts has been the subject of controversy for some time. The earlier works interpreted these reactions as taking place via an initial attack at carbon atom 3 of the heterocyclic cation [1-3]. We have demonstrated later, that the reaction with sulphur as well as carbon nucleophiles, does in fact take place on the ring sulphur [4-6]. Sykes and Ullah [7] reported similar results with sulphur nucleophiles. On the other hand, they proposed carbons 3 and 5 as the preferential sites of attack of nitrogen nucleophilic reagents. Contrary to both inductive and coulombic considerations, some products seems to result from attack at carbon 5 as the favourite reaction site, some have been obtained from attack at the most hindered carbon atom.

In this work we wish to report some of our results on the nucleophilic reactions of isothiazolium salts with several nitrogen nucleophiles which would provide evidence on the initial site of nucleophilic attack

Treatment of isothiazolium salts I with ethanolic ammonia yielded the corresponding substituted isothiazoles II as previously reported [3,7]. However the isothiazoles obtained from unsymmetrically substituted cations were of mechanistic value. The reaction with 2,3-diphenyl or with 2-methyl-3-phenylisothiazolium salts I_b and I_a gave 3-phenyl-isothiazole II_a as the sole identified heterocyclic product. Similarly, 2-methyl-3-phenyl-5-methylthioisothiazolium salt I_c afforded 3-phenyl-5-methylthioisothiazole II_b. On the other hand, 2-methyl-3-methylthio-5-phenylisothiazolium salt I_d afforded 3-methylamino-5-phenylisothiazole II_c.

Formation of isothiazoles from these reactions may be rationalized by nucleophilic attack on either carbon 3 or the ring sulphur atom, except the last case where formation of II_c could only be explained by initial attack on the sulphur atom. In all cases recyclization to isothiazole is accompanied by loss of amine. In the case of I_d, however methanethiolate anion, a better leaving group, is lost instead with the formation of isothiazole II_c (Scheme 1). Nucleophilic attack on carbon would certainly be favored at 3-position by inductive and coulombic considerations [8]. Moreover had nucleophilic attack of ammonia taken place on C-5,

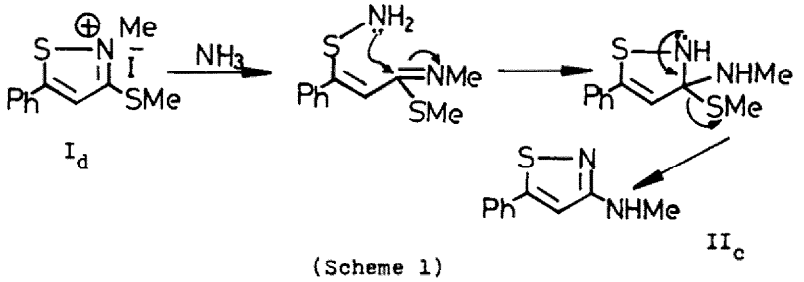
substituted pyrazoles would have been expected.



I II

a: R_1=H, R_2=Ph, R_3=Me, X=ClO
b: R_1=H, R_2=R_3=Ph, X=ClO_4
c: R_1=SMe, R_2=Ph, R_3=Me, X=ClO_4
d: R_1=Ph, R_2=SMe, R_3=Me, X=I

a: R_1=H, R_2=Ph
b: R_1=SMe, R_2=Ph
c: R_1=Ph, R_2=NHMe

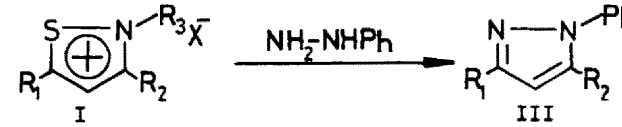


I_d II_c

(Scheme 1)

Phenylhydrazine reacted with unsymmetrical isothiazolium salts I to give pyrazoles III. 2-Methyl-5-phenylisothiazolium salt I_e afforded a mixture of 1,3-diphenylpyrazole III_a and 1,5-diphenylpyrazole III_b, with relative ratio (4:1). The reaction with 2-methyl-3-phenylisothiazolium salt I_a gave only one pyrazole, the 1,5-diphenylpyrazole III_b. Similarly I_c afforded the 1,5-diphenyl-3-methylthiopyrazole III_c. 1,3-Diphenyl-5-methylaminopyrazole III_d was the only pyrazole obtained from the reaction of isothiazolium salt I_d.

The major product in the reaction of I_e seems to result from preferential attack on the ring sulphur atom (path a in scheme 2). On the obther hand the minor product could has been resulted from attack on the subsidiary reaction site, the sterically unhindered carbon 3 (path b). Formation of the pyrazole mixture from compound I_e could not be explained by two competing reactions on C_3 and C_5, since in this case the major product would have been derived from the initial attack on the sterically hindered carbon atom.



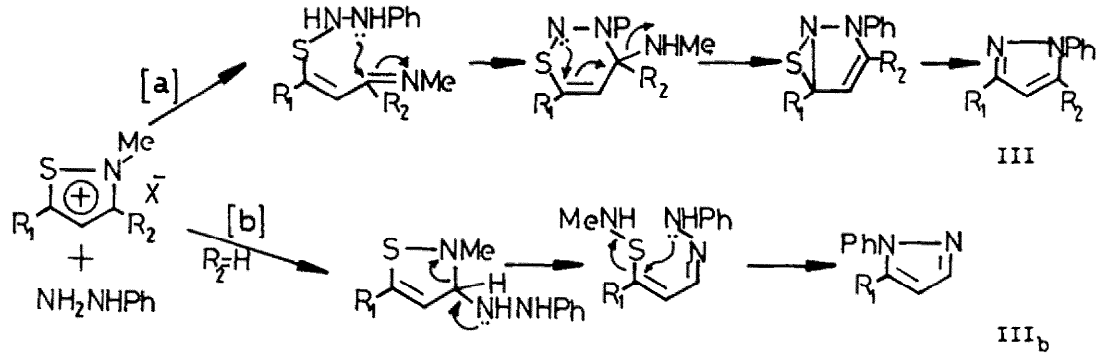
I III

a: R_1=H, R_2=Ph, R_3=Me, X=ClO_4
c: R_1=SMe, R_2=Ph, R_3=Me, X=ClO_4
d: R_1=Ph, R_2=SMe, R_3=Me, X=I
e: R_1=Ph, R_2=H, R_3=Me, X=ClO_4

a: R_1=Ph, R_2=H
b: R_1=H, R_2=Ph
c: R_1=SMe, R_2=Ph
d: R_1=Ph, R_2=NHMe

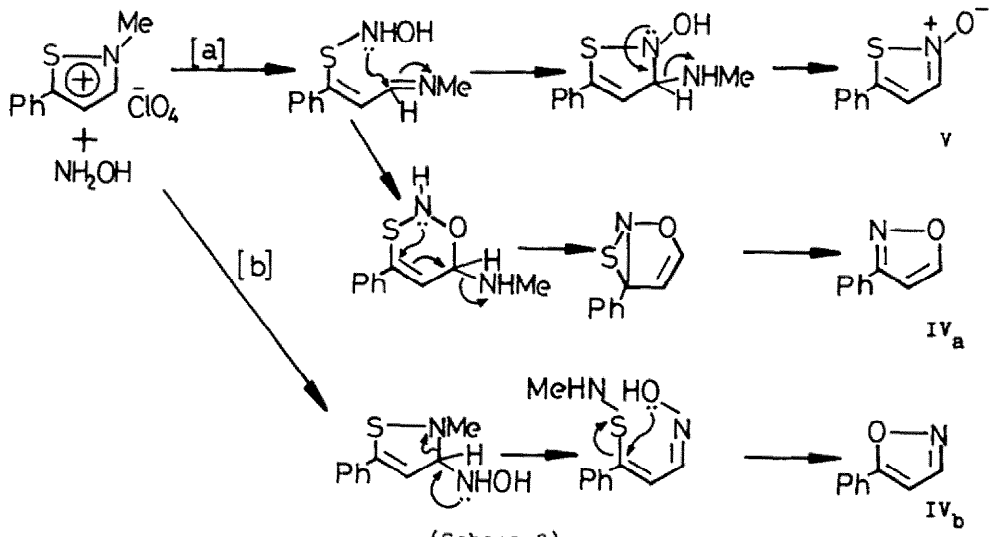
It is difficult to explain the formation of III_d on the basis of initial nucleophilic attack at C-3 or C-5, but simple in terms of initial attack on the ring sulphur atom (path a). Similarly, formation of III_b and III_c seems to result

from preferential attack on the ring sulphur atom.



(Scheme 2)

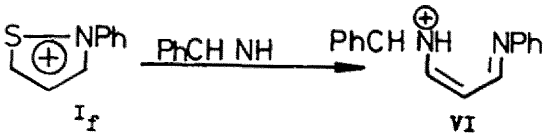
The reaction of I_e with hydroxylamine afforded a 4:1 mixture of 3-and 5-phenylisoxazoles (IV_a and IV_b respectively), as well as isothiazole N-oxide V. On the other hand the reaction with I_a gave 5-phenylisoxazole IV_b and the isothiazole N-oxide V.



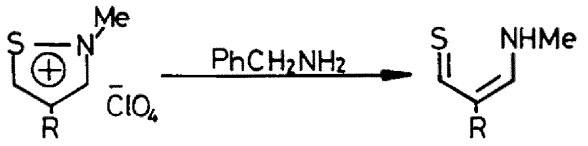
(Scheme 3)

The N-oxide as well as the major isoxazole component seems to result from initial attack on the ring sulphur atom. The minor component most probably resulted from attack at the subsidiary reaction site C_3. Formation of the isoxazole mixture could not be explained by two competing reactions at carbon 3 and 5.

The reaction of benzylamine with 3,5-unsubstituted isothiazolium salt I_f, is reported to afford an acyclic dianil salt VI[7].



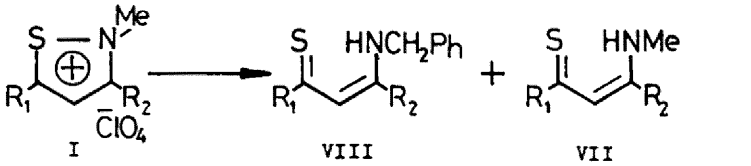
Accordingly, 4-phenylisothiazolium salt I_g and 4-tolylisothiazolium salt I_h were treated with benzylamine under similar conditions to yield an acyclic thione of structure VII.



I_{g}. R=Ph
h. R=p.tol

VII_a. R=Ph
b. R=p.tol

Isothiazolium salts with substituents on carbon 3 or 5 or both afforded a mixture of acyclic thiones when treated with 1 equiv. of benzylamine. In each case a mixture of two thiones was obtained; a methylaminothione of structure VII, as well as a benzylaminothione of structure VIII. Only the benzylaminothione VIII was obtained when threefold excess of benzylamine was used. However, the thione VIII does not appear to be derived from VII since prolonged treatment of the latter with benzylamine failed to afford VIII.



I

I a: R_1=H, R_2=Ph
e: R_1=Ph, R_2=H
c: R_1=SMe, R_2=Ph

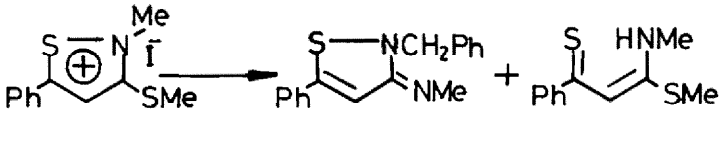
VIII

a: R_1=H, R_2=Ph
b: R_1=Ph, R_2=H
c: R_1=SMe, R_2=Ph

VII

c: R_1=H, R_2=Ph
d: R_1=Ph, R_2=H
e: R_1=SMe, R_2=Ph.

In the reaction with 2-methyl-3-methylthio-5-phenyl iodide I_d, the 3-methylamino-3-methylthio-1-phenylpropene-1-thione VII_f was obtained. However, the other product was not a benzylaminothione, but was the 2-benzyl-3-methylimino-5-phenylisothiazoline IX.

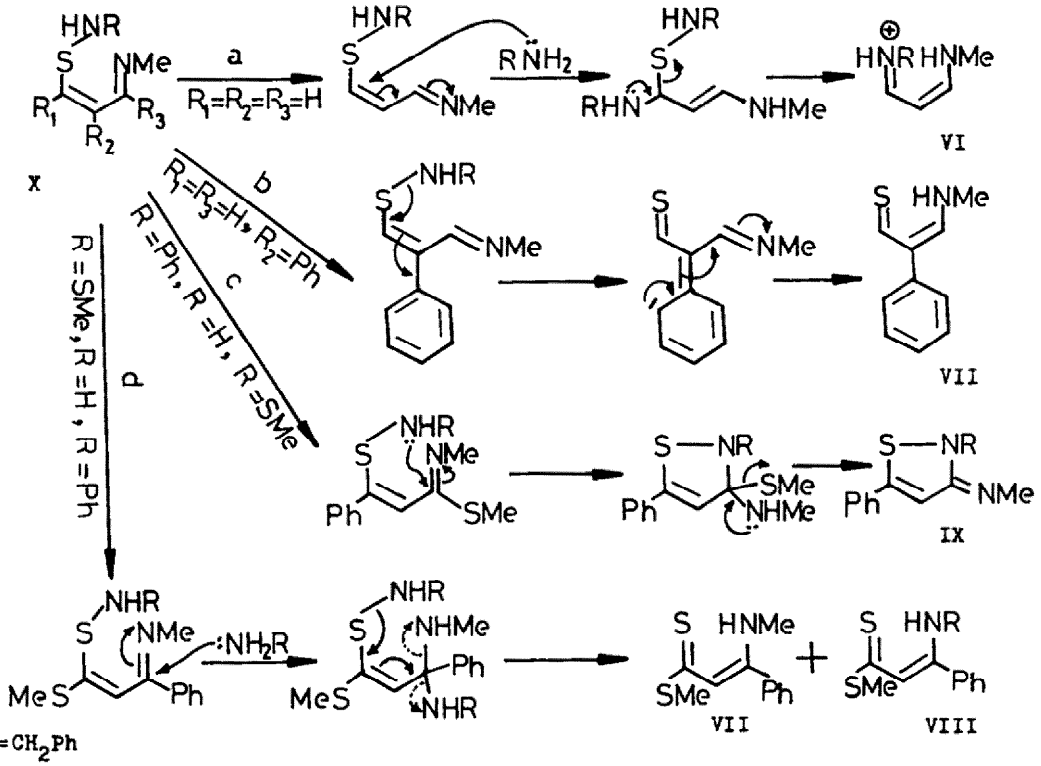


I_d IX VII_f

The retention of the N-substituent in the acyclic dianil VI, demonstrats that the initial attack of benzylamine does not take place on carbon 3. In the same time retention of the thio group in the acyclic products VII and VIII indicates that carbon 5 is not the site of initial attack even when it is unsubstituted. It is most probably that the three acyclic products VI, VII, and VIII arise from a common intermediate X formed from an initial attack on the ring sulphur.

In the absence of phenyl substituents, intermediate X may undergo further attack by another molecule of benzylamine on the ene-imine function to give the dianil VI. On the other hand a phenyl or tolyl groub at R_2 in X facilitates the loss of the benzylamine group and formation of the thione VII, by its stabilizing conjugative effect with the forming thio group. The presence of methylthio group at C-3 render the imine function in the intermediate X, more susceptible to

intramolecular nucleophilic attack by the benzylamino group leading to the formation of the isothiazoline derivative IX. Finally, a phenyl substituent at R_1 or R_3 (or both) of the intermediate X facilitates the reaction of the imine function with another molecule of benzylamine to afford the acyclic thione VIII, as well as VII (Scheme 4).



(Scheme 4)

EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were measured with a Unicam S.P 2006, and U.V. spectra with a Perkin-Elmer 554 recording spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian 56/60 A. Unless indicated C, H, N analysis were ± 0.4 % of the calculated values, and were performed by Cairo University Micor-analytical Center.

REACTIONS OF ISOTHIAZOLIUM SALTS WITH AMMONIA:

(A) 2-Methyl-3-phenylisothiazolium perchlorate I_a:

Dry ammonia was bubbled for 30 minutes through a stirred solution of I_a(275mg, 1 mmol) dissolved in 10 ml of ethanol saturated with dry ammonia. The solvent was removed under reduced pressure, and T.l.C. of the residue (silica; toluene-chloroform) afforded one major band (72%), which was identical (NMR, IR) with authentic 3-phenylisothiazole [2].

(B) 2,3-Diphenylisothiazolium perchlorate I_b:

Similar treatment of I_b (169 mg, 0.5 mmol) afforded 3-phenylisothiazole[2](64 %).

(C) Methyl-3-phenyl -5-methylthioisothiazolium perchlorate I_c:

Treatment of I_c (500 mg, 1.56 mmol) with ammonia under the above conditions afforded 5-methylthio-3-phenylisothiazole, which was alkylated by heating with dimethyl sulphate (1 ml) at 100° for 1 h . The mixture then was treated with ether and the precipitate dissolved in acetic acid and treated with 70 % perchloric acid (0.5 ml) to afford I_c[4] 5(67% yield).

(D) 2-Methyl-3-methylthio-5-phenylisothiazolium iodide I_d:

Treatment of I_d (500 mg, 1.56 mmol) with ammonia under the same conditions afforded 3-methylamino-5-phenylisothiazole II_c, which was recrystallised from benzene-pet. ether as pale yellow prisms m.p. 88-90°C.(53% yield) λ max 265, NMR H^1 δ 3.00 (3H doublet, J=1.0 Hz, the N-Me); 4.81 (1H broad, the NH proton), 6.70 (1H singlet, the isothiazole C_4 proton), 7.3-7.7 (5H bands, the aromatic protons). Analysis for $C_{10}H_{10}N_2S$ Calc: C, 63.15; H, 5.26; N, 14.74; S, 16.84. Found C, 63.70; H, 4.93; N, 14.37; S, 17.27.

REACTIONS OF ISOTHIAZOLIUM SALTS WITH PHENYLHYDRAZINE :

(A) 2-Methyl-3-phenylisothiazolium perchlorate I_a:

Phenylhydrazine (108 mg, 1 mmol) in 15 ml ethanol was added dropwise to a stirred solution of Ia (275 mg, 1 mmol) in 15 ml ethanol. After 24 h the solvent was removed under vacuum, and the residue extracted with chloroform. T.L.C.(silica; toluene-chloroform 10 %) afforded 1,5-diphenylpyrazole[9] (110 mg, 48%).

(B) 2-Methyl-5-phenylisothiazolium perchlorate I_e:

Similar treatment of Ie afforded 1,5-diphenylpyrazole[9] (25 mg, 11.4 %) and 1,3-diphenylpyrazole[9] (95 mg, 43 %).

(C) 2-Methyl-3-phenyl-5-methylthioisothiazolium perchlorate I_c:

Similar treatment of I_c (321 mg, 1mmol) afforded 1,5-diphenyl-3-methylthio-pyrazole III_c, (125 mg, 47%) m.p. 153 °C. Analysis for $C_{16}H_{14}N_2S$ Calc. C,72.18; H, 5.26; N, 10.52; S, 12.03. Found C, 72.61; H, 5.82; N, 10.19; S, 11.49.

(D) 2-Methyl-3-methylthio-5-phenylisothiazolium iodid I_d:

Under the same conditions, I_d(321 mg, 1 mmol) afforded 1,3-diphenyl-5-methyl-aminopyrazole III_d (92 mg, 37%) m.p. 160°C. Analysis for $C_{16}H_{15}N_3$ Calc. C,77.11; H, 6.02; N, 16.87. Found C, 76.85; H, 6.47; N, 17.12.

REACTIONS OF ISOTHIAZOLIUM SALTS WITH HYDROXYLAMINE:

(A) 2-Methyl-3-phenylisothiazolium perchlorate I_a:

An ethanolic solution of hydroxylamine prepared from hydroxylamine hydrochloride (0.695 gm 10 mmol) and ethanolic sodium ethoxide (10 mmol) in 50 ml ethanol, was added dropwise to a stirred solution of I_a(275 mg, 1 mmol) in ethanol (20 ml). The mixture was refluxed for ½ h and then stirred for an additional 2 h at room temp. Dilution with ether, removal of the inorganic material by filtration, and subsequent evaporation of the solvent yielded a yellow oil. T.L.C. (Silica, toluene-chloroform 5%) afforded 5-phenylisoxazole[9] (15 mg, 10%) and 3-phenylisothiazole N-oxide (54 mg, 30%)[7].

(B) 2-Methyl-5-phenylisothiazolium perchlorate I_e:

Similar treatment of Ie afforded 3-phenylisoxazole (21 mg, 14.5 %), 5-phenyl-isoxazole (5 mg, 3.5 %) and 5-phenylisothiazole N-oxide (64 mg, 36 %).

REACTIONS OF ISOTHIAZOLIUM SALTS WITH BENZYLAMINE:

(A) 2-Methyl-4-phenylisothiazolium perchlorate I_g:

Benzylamine (214 mg, 2.0 mmol) was added to an ethanolic solution (50 ml) of I_g (500 mg, 1.8 mmol) and the mixture was refluxed for 4 h. Removal of the solvent and T.L.C. (silica,toluene-chloroform 10 %) afforded one major band of 3-methylamino-2-phenylpropene-1-thione VII_a. Oxidation of VII_a by treatment with ethanolic iodine solution afforded I_g(51 % yield).

(B) 2-Methyl-4-p.tolylisothiazolium perchlorate I_h:

Similar treatment of I_h (500 mg, 1.73 mmol) afforded 3-methylamino-2-p.tolyl-propene-1-thione VII_b, which upon similar oxidation afforded I_h (55% yield).

(C) 2-Methyl-3-phenylizothiazolium perchlorate I_a:

Treatment of I_a under similar conditions afforded a mixture of 3-benzylamino-3-phenylpropene-1-thione $VIII_a$ (26% yield)[7], and 3-methylamino-3-phenylpropene-1-thione VII_c (18%). Both were oxidized to the corresponding isothiazolium salts.

Repeating the reaction with a threefold excess of benzylamine gave 3-benzylamino-3-phenylpropene-1-thione $VIII_a$ (39% yield). Treatment of VII_c with a twofold excess of benzylamine and reflux for 8 h yielded only unchanged material.

(D) 2-Methyl-5-phenylisothiazolium perchlorate I_e:

Similar treatment of I_e (500 mg, 1.8 mmol) afforded $VIII_b$ (23% yield) and VII_d (20% yield). Both were oxidized to the corresponding isothiazolium salts.

(E) 2-Methyl-3-phenyl-5-methylthioisothiazolium perchlorate I_c:

Similarly I_c (321 mg, 1 mmol) afforded $VIII_c$ (24% yield), and VII_e(17% yield). Both afforded the corresponding isothiazolium salt when subjected to iodine oxidation as above.

(F) 2-Methyl-3-methylthio-5-phenylisothiazolium perchlorate I_d:

The reaction, performed as above, gave VII_f (12% yield) and 2-benzyl-3-methyl-

imino-5-phenylisothiazoline IX, m.p. 110°C (20% yield) ^{1}H-NMR (CD_3Cl) δ 3.6 (3H,s., N-methyl), 5.78 (2H,s., $PhCH_2$), 7.1-7.48 (5H bands, aromatic protons), 7.61 (5H, s., aromatic protons). Analysis for $C_{17}H_{16}N_2S$ calc. C,72.86; H,5.71; N, 10.00 . Found C, 72.51; H, 5.94; N, 9.73.

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