THIOCYANATES IN HETEROCYCLIC SYNTHESIS THROUGH NITRILIUM SALTS'

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Abstract—In connexion with a new synthetic approach to heterocyclic systems via nitrilium salts, the reaction of organic thiocyanates, in place of the nitriles (with the exception of benzyl and *p*-nitrophenyl thiocyanates) yields heterocyclic compounds carrying a thioalkoxy group in the position next to the nitrogen atom in the ring.

The new method of preparing 3,4-dihydroisoquinoline derivatives,² has been applied to the preparation of dihydropapaverine and related compounds,³ and several isoquinoline-5,8-quinones.⁴ If the β -haloethylbenzene derivative as the halogenated component is substituted in these reactions, by 2-(β -chloroethyl)thiophene or 3-(β bromoethyl)indole, derivatives of 6,7-dihydro-thieno(3,2-c)pyridine⁵ and β -carboline,⁶ respectively are produced in low yields.

By taking advantage of the reactivity of the nitrilium salt toward electron-rich functional groups such as the amino and carbonyl, new preparative methods for 3,4and 1,4-dihydroquinazolines,⁷ oxazoles,⁸ and 4*H*-1,3-oxazines⁹ have been developed. The general application of this method with different halogenated components,¹⁰ as well as its application to the synthesis of compounds related to certain quinazolinealkaloids¹¹ has been investigated.

In every case, the nitrilium salt results from the interaction between a nitrile-tin tetrachloride complex and a halogenated component bearing a functional group in a position suitable for cyclization.

The possibility of substituting the nitriles in this reaction by other cyano compounds, such as organic cyanates, thiocyanates, selenocyanates and mercuricyanates and substituted cyanamides has been considered and in this paper the results obtained with alkyl and aryl thiocyanates are reported.

¹ This paper should be considered as Part VIII of our series on Nitrilium Salts. For Part VII see Ref 10.

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Reimschneider¹² has noted that some alcohols and olefins react with thiocyanates to give thiocarbamates (II). Though Ritter^{13,14} postulates that this reaction takes place

$$(Me)_{3}C-OH+R-SCN \longrightarrow [(Me)_{3}C-N \equiv C-S-R]$$

$$I$$

$$I$$

$$H_{2}O$$

$$(Me)_{3}C-NH \cdot OC-S-R$$

$$II$$

via an imidoyl hydrogen sulphate, Meyers¹⁵ has recently reported that a nitrilium salt (I) may be an intermediate.

More recently the use of methyl thiocyanate in the synthesis of quinazoline derivatives via a nitrilium salt has been developed¹⁶ and Schmidt,¹⁷ using the synthetic scheme developed by our group,⁹ obtained 2-thiomethoxy-4,6-diphenyl-4*H*-1,3-oxazinium stannichloride, starting from β -chloro- β -phenylpropiophenone and the methyl thiocyanate-tin tetrachloride complex.

The possibility of using organic thiocyanates in the previously-developed synthesis of heterocyclic rings, together with the possible effect of radicals attached to the thiocyanate group has prompted this investigation.

1. 1-Thioalkoxy-3,4-dihydroisoquinolines

Experiments carried out with n-propyl thiocyanate and β -chloroethylbenzene proceeded in the usual way², yielding a basic product which gave a picrate, m.p. 117°. The analysis was compatible with the expected structure, and the IR spectrum shows the three typical bands¹⁸ of the 3,4-dihydroisoquinoline structure (V) which could be formed according to the following scheme:



Methyl, ethyl, phenyl, *p*-chlorophenyl, *p*-ethoxyphenyl, and *p*-nitrophenyl thiocyanates behaved similarly. Table 1 presents the physical constants and analytical data of the 3,4-dihydroisoquinolines prepared.

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Obtained					Analysis	
V, R =	Yield	Physical constants		С	H H	N
Ме	50	B.p. 98–100°/0·7 mm. n_D^{15} 1·6190	Reqd. Found	67·78 67·65	6·25 6·22	7·90 8·17
(Picrate)		M.p. 136° (from EtOH)	Reqd. Found	47∙28 47∙54	3·47 3·47	13·79 13·73
Et	60	B.p. 89–90°/0·5 mm. n ¹⁵ 1·5984	Reqd. Found	69∙06 68∙83	6·85 6·85	7·32 7·32
(Picrate)		M.p. 130° (from EtOH)	Reqd. Found	48∙56 48∙67	3·83 3·94	13·33 13·09
<i>n</i> -Pr	80	B.p. $120^{\circ}/1 \text{ mm}$ $n_{\rm D}^{22} 1.5900$	Reqd. Found	70∙20 70∙42	7·36 7·54	6·82 7·00
(Picrate)		M.p. 117° (from EtOH)	Reqd. Found	49∙90 49∙50	4·17 4·01	12·90 13·09
Ph	40	M.p. 79-80° (from EtOH)	Reqd. Found	75·28 75·37	5∙47 5∙67	5∙85 6∙03
(Picrate)		M.p. 178° desc. (from ethanol)	Reqd. Found	53·84 53·94	3·44 3·74	11-96 11-68
<i>p</i> -Cl.C ₆ H ₄	60	M.p. 83° (from EtOH)	Reqd. Found	65·82 65·58	4·42 4·23	5-12 5-39
(Picrate)		M.p. 167° (from methyl ethyl ketone)	Reqd. Found	50∙15 50∙48	2·80 2·96	11·14 11·01
<i>p</i> -EtO.C ₆ H₄	60	M.p. 119° (from EtOH)	Reqd. Found	72∙04 72∙20	6·04 6·10	4∙81 4∙84
(Picrate)		M.p. 168° (from EtOH)	Reqd. Found	53∙90 53∙68	3∙93 4•17	10-93 10-64
$p-NO_2 \cdot C_6H_4$ (Picrate)		M.p. 142° (from EtOH)	Reqd. Found	49·16 49·46	2·95 3·07	13·65 13·47

Table 1. 3,4-Dihydroisoquinoline derivatives obtained from β -chloroethylbenzen and organic thiocyanates

The product from *p*-nitrophenyl thiocyanate formed a picrate, m.p. 142°, the analysis of which corresponded to the expected structure V ($R = p-NO_2.C_6H_4$). But, during crystallization of the base from ethanol, a product, m.p. 179.5°, incapable of giving a picrate was formed. Its IR spectrum does not show the typical bands of the 3,4-dihydroisoquinoline ring, given by the crude product, but is consistent with a *p*-disubstituted aromatic compound. After analysis the compound, $C_{12}H_8N_2O_4S_2$, was identified as *p*-nitrophenyl disulphide, by comparison with an authentic sample prepared according to Willgerodt.¹⁹ The 3,4-dihydroisoquinoline V ($R = p-NO_2.C_6H_4$ could hydrolyse to produce *p*-nitrothiophenol which on spontaneous oxidation would yield the disulphide. This interpretation is supported by the fact that *p*-nitrothiophenol is oxidized in air to the disulphide.²⁰

Benzyl thiocyanate does not condense with β -chloroethylbenzene, to give 1-thiobenzyloxy-3,4-dihydroisoquinoline. Probably the special character of the benzyl group induces hydrolysis during isolation of the product, giving 1-oxo-1,2,3,4-tetrahydroisoquinoline. Nevertheless, all attempts to identify the products or improve the results by the use of other electrophilic metal halides, or different experimental conditions failed.

Experiments with 1-(2,5-dimethoxyphenyl)2-chloroethane (VI) as halogenated



component yielded 5,8-dimethoxy-3,4-dihydroisoquinolines (VII). The physical properties are reported in Table 2.

2. 2-Thioalkoxyoxazoles

Desyl chloride (VIII) with alkyl and aryl thiocyanates, readily forms nitrilium salts (IX), which spontaneously cyclize to 2-thioalkoxy- and 2-thioaryloxy-4,5-diphenyl-oxazoles (X). Table 3 presents physical and analytical data of the products prepared.



The structures were confirmed by analysis and by comparison of the IR spectra with those of analogous known compounds without sulphur.⁸

Benzyl thiocyanate is again an exception and does not condense with desyl chloride, even under drastic conditions. Further, *p*-nitrophenyl thiocyanate does not yield the expected oxazole derivative under the experimental conditions used; neither is *p*-nitrophenyl disulphide obtained, but the starting materials were recovered almost completely.

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²⁰ A. W. Hofmann, Ber. Dtsch. Chem. Ges. 18, 2755 (1885).

Obtained					Analysis	
VII, R =	Yield	Physical constants		С	н	N
Ме	40	B.p. 143-4°/0·6 mm. m.p. 57-8°	Reqd. Found	60∙75 60∙94	6·32 6·55	5∙90 6∙04
(Picrate)		M.p. 155° (from EtOH)	Reqd. Found	46·35 46·55	4∙08 4∙19	12·01 11·98
Et	60	B.p. 140°/0·4 mm.				
(Picrate)		M.p. 160° (from EtOH)	Reqd. Found	47∙50 47∙71	4·16 4·36	11∙66 11∙80
<i>n</i> -Pr	60	B.p. 170–1°/1 mm. m.p. 38°	Reqd. Found	63·39 63·62	7∙17 7∙40	5·28 5·28
(Picrate)		M.p. 141° (from EtOH)	Reqd. Found	48∙58 48•86	4∙45 4∙18	11·35 11·10

 TABLE 2.
 5,8-Dimethoxy-3,4-dihydroisoquinolines
 obtained
 from
 1-(2,5-dimethoxyphenyl)-2-chloroethane

 PHENYL)-2-chloroethane
 and organic thiocyanates

TABLE 3. 4,5-DIPHENYLOXAZOLES OBTAINED FROM DESYL CHLORIDE AND ORGANIC THIOCYANATES

Obtained				Analysis		
X, R =	Yield	Physical constants		C	н	N
Me	40	B.p. 168–170°/0·5 mm. m.p. 70–72°	Reqd. Found	71·91 71·66	4∙86 4•56	5·24 5·51
Et	85	M.p. 88-89° (from EtOH)	Reqd. Found	72·59 72·80	5·33 5·40	4∙98 5∙09
Pr	80	M.p. 71-73° (from MeOH)	Reqd. Found	73∙22 73∙07	5∙76 5∙47	4·74 4·94
Ph	40	M.p. 96–98° (from EtOH)	Reqd. Found	76∙ 59 76∙66	4∙55 4∙37	4·25 4·02

Obtained					Analysis	
product XIII, R =	Yield Physical constants			С	н	N
Me	60	B.p. 49–50°/1·5 mm n ²³ _D 1·4980	Reqd. Found	56·14 55·96	7·60 7·66	8·19 8·36
Et	70	B.p. 54–56°/1 mm. n_D^{20} 1•4950	Reqd. Found	58·30 58·09	8·10 7·94	7·56 7·51
Pr	50	B.p. 60–61°/1 mm. <i>n</i> ¹⁵ _D 1∙4924	Reqd. Found	60∙04 60∙06	8∙54 8∙59	7∙03 6∙97
ph.CH ₂	5	B.p. 85–87°/0·2 mm. n_{D}^{18} 1·5305	Reqd. Found	67·70 67·96	6∙88 6∙60	5-68 5-80
Ph	10	B.p. 72°/0·2 mm. n_D^{18} 1·5608	Reqd. Found	66·95 67·10	6∙43 6∙23	6·86 6·81
p-Cl.C ₆ H₄	60	B.p. 92–93°/0·1 mm. $n_{\rm D}^{18}$ 1·5621	Reqd. Found	58·31 58·29	5·23 5·40	5·23 5·32

TABLE 4. 4,4,6-TRIMETHYL-4H-1,3-OXAZINES OBTAINED FROM 4-CHLORO-4-METHYL-PENTAN-2-ONE AND ORGANIC THIOCYANATES

TABLE 5. 6-METHYL-4,4-PENTAMETHYLEN-4H-1,3-OXAZINES OBTAINED FROM 1-CHLORO-1-ACETONYL CYCLOHEXANE AND ORGANIC THIOCYANATES

Obtained		<u>,</u> <u>.</u> <u>.</u>			Analysis	
product $XV, R =$	Yield Physical constants			C	Н	N
Me	75	B.p. 82–83°/0·2 mm. n_D^{15} 1·5265	Reqd. Found	62·80 62·65	8·06 8·10	6·62 6·48
Et	60	B.p. 115-116°/0·8 mm. n_D^{20} 1·5286	Reqd. Found	64∙00 64∙10	8∙44 8∙46	6·22 6·25
<i>n</i> -Pr	50	B.p. 89–91°/0·1 mm. $n_{\rm D}^{18}$ 1·5152	Reqd. Found	65·27 65·21	8∙78 8∙75	5∙85 5∙88
Ph	20	B.p. 78–79°/0·1 mm. $n_{\rm D}^{21}$ 1·5488	Reqd. Found	70·33 70·21	6·95 6·89	5·12 5·15
p-Cl.C ₆ H ₄	10	B.p. 91-92°/0·3 mm. $n_{\rm D}^{20}$ 1·5571	Regd. Found	62·44 62·40	5∙84 5∙63	4·55 4·29

3. 2-Thioalkoxy-4H-1,3-oxazines

4-Chloro-4-methylpentan-2-one and the methyl thiocyanate-tin tetrachloride complex according to the method described in the experimental, yielded a liquid product b.p. $49-50^{\circ}/1.5 \text{ mm}$, n_D^{23} 1.4980, in 60% yield. Its analysis and IR spectra supported the structure 4,4,6-trimethyl-2-thiomethoxy-4*H*-1,3-oxazine (XIII; R = Me).



Other thiocyanates including benzyl thiocyanate (Table 4) behave similarly, but *p*-nitrophenyl thiocyanate yields *p*-nitrophenyl disulphide.

We have also studied 1-chloro-1-acetonylcyclohexane (XIV) reacts with thiocyanates, yielding the expected derivatives of 6-methyl-4-4-pentametilene-2-thioalkoxy-4H-1,3-oxazines (XV) (Table 5). As before, the yields with alkyl are much



better than with aryl thiocyanates. Benzyl thiocyanate does not react with XIV; and *p*-nitrophenyl thiocyanate, yields *p*-nitrophenyl disulphide.

EXPERIMENTAL

All temps are uncorrected. IR spectra: Perkin-Elmer infracord spectrophotometer model 137 E. Desyl chloride,²¹ cyclohexenylacetone,²² and n-propyl,²³ benzyl,²⁴ phenyl,²⁵ p-chlorophenyl,²⁶ p-ethoxyphenyl²⁷ and p-nitrophenyl thiocyanates²⁸ were prepared by the usual methods and distilled before use.

General methods of reaction

Reagents were used in stoichiometric proportions, and in quantities of 0.03 to 0.1 mole.

(a) 3,4-Dihydroisoquinolines. The reaction was performed in a flask fitted with reflux condenser and CaCl₂ tube. The electrophilic halide was added through the condenser to a mixture of β -chloroethylbenzene [or 1-(2,5-mimethoxyphenyl)2-chloroethane⁴] and thiocyanate and heated 3 hr at 145–150°.

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- ²² O. Wallach, Liebig's Ann. 394, 376 (1912).
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- ²⁷ J. W. Bienske, Rec. Trav. Chim. 50, 165 (1931).
- ²⁸ H. A. Muller, Z. f. Farbenindustrie 5, 357, 1/10 (1906); (C.Z. II, 1588 (1906).

After cooling, it was made basic with 20% NaOH aq and extracted with ether. The ethereal soln was washed with 20% HCl. After neutralization with NaOH it was extracted with ether until the extracts did not give a positive Mayer reaction. The combined extracts are dried (Na₂SO₄) and after evapn of the ether, the base was purified by vacuum distillation or crystallization.

The reaction if carried out in a solvent, such as nitrobenzene, o-dichlorobenzene, carbon disulphide, or an excess of the halogenated component gave similar results.

Physical constants, elementary analysis and yields are given in Tables 1 and 2.

(b) Oxazoles. In a two-necked flask provided with a dropping funnel and condenser, protected from moisture, a mixture of desyl chloride and thiocyanate was warmed gently until liquid. Tin tetrachloride was added dropwise with occasional stirring and the mixture then left for several hr at room temp. If after 4 hr the mixture was green instead of amber in colour, it was heated on a water bath for $\frac{1}{2}$ hr. Finally, the product was dissolved in AcOEt and poured into NaHCO₃ aq. The aqueous phase was extracted several times with AcOEt and the combined extracts dried over Na₂SO₄. Elementary analysis, yields and physical constants are given in Table 3.

(c) 4*H*-1,3-oxazines. Due to their instability, both 4-chloro-4-methylpentan-2-one and 1-chloro-1acetonylcyclohexane were prepared just before using as follows: In a flask fitted with a gas-inlet tube and CaCl₂ tube 0·1 mole of mesityl oxide (or Δ^1 -cyclohexenylacetone), at a temp below 3° was sat with dry HCl gas.

Simultaneously, the thiocyanate-tin tetrachloride complex was prepared as follows: In a threenecked flask fitted with a mechanical stirrer, dropping funnel, reflux condenser and CaCl₂ tube, 0.1mole of the desired thiocyanate was dissolved or suspended in about 100 ml dry CS₂. To the cooled soln 0.1 mole SnCl₄ was added dropwise with stirring.

When the complex had formed, the previously prepared halogenated component was added with external cooling. After about 15 min, the CS_2 was removed by distillation, and the mixture heated at $90-100^{\circ}$ for 3 hr.

After cooling, small volumes of ether and NaHCO₃ aq were added successively, until the semisolid mass was completely broken up and the base dissolved in the ether phase. This was separated and the aqueous layer extracted several times with ether. The combined extracts were washed with water and dried over Na₂SO₄. Finally the solvent was removed *in vacuo*.

The physical constants, analysis and yields are given in Tables 4 and 5.

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