The Thallium(I) Salt-catalyzed Formation of Isothiocyanates from Isocyanides and Disulfides

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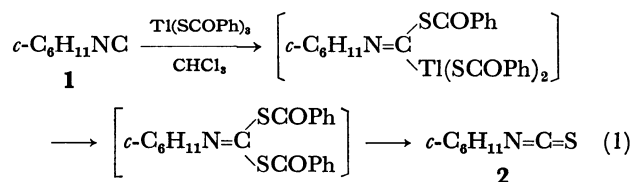
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The reactions of various isocyanides with diacyl disulfides or tetraethylthiuram disulfide occur smoothly in the presence of thallium(I) acetate and thiocarboxylates in various organic solvents to give the corresponding isothiocyanates in good yields. Lead(II) acetate has an activity almost identical with that of thallium(I), while cadmium(II) and silver(I) acetates and copper(I) oxide show a slightly lower activity than the above thallium and lead salts. An ionic scheme involving a complex formation between the metal salt and one S atom of the disulfide, followed by a nucleophilic attack of isocyanide on the adjacent S atom, is proposed for this reaction. It is revealed that the reaction of isocyanide with one equivalent of thallium(III) thiobenzoate in refluxing chloroform similarly affords a good yield of the isothiocyanate through the above mechanism after the decomposition of the thallium(III) salt to thallium(I) thiobenzoate and dibenzoyl disulfide, rather than through a pathway involving thiothallation (α-addition).

Several reactions involving the oxymetallation of isocyanides (α-addition) with Hg(II), Tl(III), or Pb(IV) salts have recently been reported.[1] While examining the reaction of isocyanides with similar metal salts containing a S atom, we have found that dibenzoyl disulfide, which can be derived from Tl(III) thiobenzoate, reacts smoothly with isocyanides in the presence of a catalytic amount of Tl(I) salt to afford the corresponding isothiocyanates. We wish now to report the results of the Tl(I)- or some other metal salt-catalyzed formation of isothiocyanates from various disulfides and isocyanides, and to discuss its reaction mechanism. It should be noted here that similar metal salt-promoted reactions of disulfide have been known[2] in the cases of amine and methanesulfinate ion using Ag(I) salt.

Results and Discussion

Reaction of Cyclohexyl Isocyanide (1) with Metal Thiocarboxylates (Table 1). By analogy with the oxidation of isocyanides with Hg(II), Tl(III), or Pb(IV) acetate giving isocyanates,[1c] isothiocyanate formation can be expected to proceed by means of the reaction of isocyanides with these salts of thiocarboxylic acids. When 1 was treated with Tl(III) thiobenzoate in chloroform under reflux, cyclohexyl isothiocyanate (2) was obtained in a good yield, whereas none of it was formed by the reaction with Hg(II) thioacetate. If the product is

TABLE 1. THE REACTION OF 1 WITH METAL THIOCARBOXYLATES IN CHCl$_3$[a]

Metal Salt	2(%)[b]	Recovered 1(%)[b]
Tl(SCOPh)$_3$	66	28
Hg(SCOMe)$_2$	0	86
TlSCOPh	0	100
TlSCOMe	28	63
Pb(SCOPh)$_2$	trace	100
S[c]	3	75
S[c]+TlOAc	8	81

a) 1 (1 mmol), Metal Salt (1 mmol), and CHCl$_3$ (10 ml) were used; at reflux for 3 h. b) By GLC. c) 10 mmol.

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formed through the thiometallation of 1 (Scheme 1), it should also be obtained by the use of Hg(II) thiocarboxylate, since it is generally known that oxymercuration occurs more rapidly than oxythallation.[3]

$$c\text{-}C_6H_{11}NC \xrightarrow[\text{CHCl}_3]{\text{Tl(SCOPh)}_3} \left[c\text{-}C_6H_{11}N=C\begin{array}{l} \diagup SCOPh \\ \diagdown Tl(SCOPh)_2 \end{array} \right]$$
$$\mathbf{1}$$

$$\longrightarrow \left[c\text{-}C_6H_{11}N=C\begin{array}{l} \diagup SCOPh \\ \diagdown SCOPh \end{array} \right] \longrightarrow c\text{-}C_6H_{11}N=C=S \quad (1)$$
$$\mathbf{2}$$

Furthermore, although the reaction with Tl(I) or Pb(II) thiobenzoate did not give 2, that with Tl(I) thioacetate did afford it.[4] The formation of 2 with the Tl salt of a lower oxidation state can not also be explained by this scheme. Therefore, such a mechanism does not seem to be operative for the isothiocyanate formation. The possibility of the participation of elemental sulfur, which might be formed from the Tl salts in some way or other,[5] can nearly be excluded also, because separate experiments revealed that only a small amount of 2 was formed from 1 and solid sulfur in either the presence or absence of Tl(I) acetate under similar reaction conditions. The most likely route is the nucleophilic attack of 1 upon dibenzoyl or diacetyl disulfide, which can be formed by the thermal decomposition of the corresponding Tl(III)[4a] or Tl(I) thiocarboxylate (Schemes 2 and 3), since similar S–S bond scissions in alkyl, aryl, and acyl disulfides by various O-, S-, N-, P-, As-, and C-nucleophiles have been reported.[2,6,7] In fact, when 1 was treated with dibenzoyl disulfide in the presence of Tl(I) thiobenzoate, 2 was obtained in a good yield. On the other hand, the yield of 2 was quite low without the addition of the Tl(I) salt, suggesting that the electrophilic assistance of Tl(I) salt may be involved, as in the case of other Ag(I)-catalyzed reactions:[2]

$$\text{Tl(SCOPh)}_3 \longrightarrow (\text{PhCOS})_2 + \text{PhCOSTl} \quad (2)$$

$$2\text{TlSCOMe} \longrightarrow (\text{MeCOS})_2 + 2\text{Tl} \quad (3)$$

Reaction of Isocyanides with Various Disulfides in the Presence of Tl(I) Salts (Table 2). Since the Tl(I)-assisted interaction between 1 and dibenzoyl disulfide was proved, the scope and limitations of this reaction were examined by using various kinds of disulfides,

TABLE 2. THE REACTION OF ISOCYANIDES WITH DISULFIDES IN THE PRESENCE OF Tl(I) SALTS

RNC (1 mmol) R	R'SSR' (1 mmol) R'	Tl(I)Z (1 mmol) Z	Solvent (10 ml)	Temp (°C)	Time (h)	Product (%)[a] RNCS	Product (%)[a] RNC recovered
c-C_6H_{11}	PhCO	—	$CHCl_3$	61	3	9	86
c-C_6H_{11}	PhCO	OCOMe	$CHCl_3$	61	3	96	0
c-C_6H_{11}	PhCO	OCOMe	$CHCl_3$	30	3	44	56
c-C_6H_{11}	PhCO	OCOMe	$CHCl_3$	61	0.5	82	13
c-C_6H_{11}	PhCO	OCOMe	$CHCl_3$[b]	61	0.5	85	trace
c-C_6H_{11}	PhCO	OCOMe	$CHCl_3$[c]	61	0.5	76	15
c-C_6H_{11}	PhCO	OCOMe[d]	$CHCl_3$	61	3	85	14
c-C_6H_{11}	PhCO	OCOMe	Toluene	85	3	94	trace
c-C_6H_{11}	PhCO	OCOMe	C_6H_{10}[e]	83	3	74	0
c-C_6H_{11}	PhCO	OCOMe	EtOH	78	3	83	0
c-C_6H_{11}	PhCO	OCOMe	Dioxane	84	3	81	trace
c-C_6H_{11}	PhCO	SPh	$CHCl_3$	61	3	41	59
c-C_6H_{11}	PhCO	SCOPh	$CHCl_3$	61	3	77	21
Ph	PhCO	OCOMe	$CHCl_3$	61	3	100	0
t-Bu	PhCO	OCOMe	$CHCl_3$	61	3	100	0
n-Bu	PhCO	OCOMe	$CHCl_3$	61	3	100	0
$EtO(CH_2)_4$	PhCO	OCOMe	$CHCl_3$	61	3	100	0
c-C_6H_{11}	Et_2NCS	OCOMe	$CHCl_3$	61	3	66	18
c-C_6H_{11}	MeCO	SCOMe	$CHCl_3$	61	3	48	6
c-C_6H_{11}	$PhCH_2$	OCOMe	$CHCl_3$	61	3	1	82
c-C_6H_{11}	Ph	OCOMe	$CHCl_3$	61	3	2	98
c-C_6H_{11}	n-Bu	OCOMe	$CHCl_3$	61	3	0	100

a) By GLC. b) p-Benzoquinone (0.5 mmol) was added. c) t-Butylcatechol (0.5 mmol) was added. d) TlOAc (0.1 mmol) was used. e) Cyclohexene.

isocyanides, Tl(I) salts, and solvents (Scheme 4). The following points are evident from the table: (i) Dibenzo-

$$RNC + R'SSR' \xrightarrow[\text{Solvent}]{\text{Tl(I)Z}} RNCS \quad (4)$$
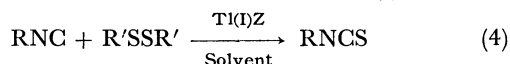
R = c-C_6H_{11}(**1**), Ph, n-Bu, t-Bu, $EtO(CH_2)_4$
R' = PhCO, MeCO, Et_2NCS, Ph, $PhCH_2$

yl, diacetyl, and tetraethylthiuram disulfides give good yields of isothiocyanates, while dialkyl and diaryl disulfides scarcely react at all. (ii) Tl(I) acetate is the most effective salt among the salts examined, and a catalytic amount of it is enough for the reaction. (iii) The reaction is applicable to both aliphatic and aromatic isocyanides. (iv) The yield of isothiocyanate does not vary significantly when the solvents are changed. (v) The reaction seems to proceed through an ionic pathway, since many radical scavengers exert no effect on the reaction.

Reaction of **1** *with Dibenzoyl Disulfide in the Presence of Various Kinds of Metal Salts (Table 3).* The catalytic effects of several metal salts other than Tl(I) were examined in the reaction of **1** with dibenzoyl disulfide under reflux for 3 h in chloroform. As can be seen from the table, the salts of soft metal ions (soft acid) are generally effective ($Tl^+ \geqslant Pb^{2+} > Cd^{2+} \geqslant Ag^+ \geqslant Cu^+ \geqslant Hg^+$) in the preparation of **2**, while those of hard ones are not at all effective. From the HSAB principle,[8] it can be deduced that the interaction of soft metal ions with either of the two S atoms of the disulfide (soft base) plays an important role in this reaction. Though considerable differences in catalytic activity between two salts of Cu(I) or Fe(II) (depending on the anion

TABLE 3. THE REACTION OF **1** WITH DIBENZOYL DISULFIDE IN THE PRESENCE OF VARIOUS METAL SALTS IN $CHCl_3$[a]

Metal Salt	**2** (%)[b]	Recovered **1** (%)[b]
$Pb(OAc)_2 \cdot 3H_2O$	89	11
$Pb(OAc)_2 \cdot 3H_2O$[c]	61	25
$Cd(OAc)_2 \cdot 2H_2O$	75	6
$Cd(OAc)_2 \cdot 2H_2O$[c]	51	46
HgOAc	39	2
AgOAc	65	23
Cu_2O	66	29
CuCl	30	56
$Cu(OAc)_2 \cdot H_2O$	28	72
$Zn(OAc)_2 \cdot 2H_2O$	14	64
$FeSO_4 \cdot 7H_2O$	4	71
$Fe[CH_3CH(OH)CO_2]_2$	26	32
$Co(OAc)_2 \cdot 4H_2O$	30	26[d]
$Ni(OAc)_2 \cdot 4H_2O$	32	16[d]
$Cr(OAc)_3 \cdot H_2O$	2	87
$Mn(OAc)_2 \cdot 4H_2O$	5	59
KSCOMe	3	95

a) **1** (1 mmol), Metal Salt (1 mmol), and $CHCl_3$ (10 ml) were used; at reflux for 3 h. b) By GLC. c) 0.1 mmol. d) In these cases, some polymerized compounds were also formed.

component) were observed, it appears to be difficult to offer a reasonable explanation.

Reaction Scheme. In order to clarify the reaction scheme, the following experiments were carried out in the presence of Tl(I) acetate as a catalyst. First, the

TABLE 4. THE REACTION OF 1 WITH p-SUBSTITUTED
DIBENZOYL DISULFIDES IN THE PRESENCE OF
TlOAc IN $CHCl_3$[a]

R'SSR' (1 mmol)	Time (h)	2 (%)[b]	Recovered 1 (%)[b]
R'=p-NO$_2$C$_6$H$_4$CO	0.25	87	13
C$_6$H$_5$CO	0.25	59	41
p-MeOC$_6$H$_4$CO	0.25	40	60
R'=p-NO$_2$C$_6$H$_4$CO	0.5	97	3
C$_6$H$_5$CO	0.5	82	13
p-MeOC$_6$H$_4$CO	0.5	63	37
R'=p-NO$_2$C$_6$H$_4$CO	3	100	0
C$_6$H$_5$CO	3	96	0
p-MeOC$_6$H$_4$CO	3	100	0

a) 1 (1 mmol), TlOAc (1 mmol), and CHCl$_3$ (10 ml)
were used; at reflux. b) By GLC.

competitive reaction between 1 and phenyl isocyanide
with dibenzoyl disulfide (1 mmol of each reactant) in
chloroform at reflux for 3 h afforded 2 (60%) and
phenyl isothiocyanate (40%), the unreacted 1 and
phenyl isocyanide amounting to 19% and 38% respec-
tively. Second, the yields of 2 in the reaction of 1 with
representative 4,4'-disubstituted dibenzoyl disulfides
were compared with that with a non-substituted one
(Table 4). As a result, it was revealed that the reaction
rate decreases in the following order: p-NO$_2$>H>p-
MeO. Both results can be explained by assuming that
a nucleophilic attack of isocyanide on one S atom of
disulfide is an important step in this reaction.

By summarizing all the data described above, we
propose Scheme 5 as a reaction scheme. The reaction
may involve the initial complex formation between soft
metal salt and one S atom of disulfide and the sub-
sequent nucleophilic attack of isocyanide on the adjacent
S atom. The latter step would be rate-determining.
The removal of the benzoyl cation from the transient
imidoyl cation affords isothiocyanate. The last step,
namely, the combination of the benzoyl cation with the
anion, was explained by the presence of PhCOSPh and
PhCOOAc as products of the reactions using TlSPh and
TlOAc respectively:

$$PhC-S-S-CPh \underset{}{\overset{MZ_x}{\rightleftharpoons}} PhC-S-S-CPh \overset{RNC}{\longrightarrow}$$

$$\left[R-N=\overset{+}{C}-S-CPh\right] + PhC\bar{S}MZ_x$$

$$PhC\bar{S}MZ_x \rightleftharpoons Z^- + PhCSMZ_{x-1}$$

and/or $MZ_x + PhCS^-$

$$\left[R-N=\overset{+}{C}-S-CPh\right] \longrightarrow$$

$$RNCS + \left[Ph\overset{+}{C}\right] \begin{array}{c} \overset{PhCOS^-}{\nearrow} PhCSCPh \\ \underset{Z^-}{\searrow} PhCZ \end{array} \quad (5)$$

There may be another route involving the attack of
the isocyanide-metal salt complex on disulfide, since
isocyanides are known to form complexes with various
metal salts.[9] It is obvious, however, that the nucleo-
philic reactivity of isocyanide decreases with complexa-
tion,[10] and so such a pathway would be less probable.
It was observed in a separate experiment that, when the
cyclohexyl isocyanide–CuCl complex prepared separate-
ly[9] was treated with dibenzoyl disulfide, 2 (21%) and
free 1 (79%) were obtained under reflux for 3 h in
chloroform. The result is comparable to that of the
reaction catalyzed by CuCl; this suggests that no
significant participation of the isocyanide-metal complex
is present.

Experimental

Materials. Most of the isocyanides (RNC: R=c-C$_6$H$_{11}$,
n-Bu, t-Bu, Ph) were prepared by the dehydration of N-sub-
stituted formamides with POCl$_3$,[11] while 4-ethoxybutyl isocy-
anide[R=EtO(CH$_2$)$_4$] was prepared by the reaction of the
corresponding bromide with AgCN at 75—80 °C for 24 h;
bp 89—94 °C/30 mmHg. The cyclohexyl, butyl, t-butyl, and
4-ethoxybutyl isothiocyanates (prepared previously in our
laboratory[12]) and commercial phenyl isothiocyanate were
used as authentic samples for GLC analyses. Some disulfides
(R'SSR': R'=MeCO,[4a] PhCO,[4a] Ph,[4a] PhCH$_2$,[4a] p-MeO-,
and p-NO$_2$C$_6$H$_4$CO[13]) were prepared by the oxidation of the
corresponding thiols or thiocarboxylic acids, while those of
R'=n-Bu and Et$_2$NCS were commercial products. Metal
salts such as Tl(SCOPh)$_3$,[4a] TlSCOPh,[4a] TlSCOMe,[4a] Tl-
SPh,[4a] and Pb(SCOPh)$_2$[4b] were prepared by the respective
reported methods. The Hg(SCOMe)$_2$[mp 140 °C (d)] was
prepared by the reaction of yellow HgO with thioacetic acid
in chloroform at 5—10 °C for 1 h and then recrystallized
from chloroform. The radical scavengers and other metal
salts were commercial products and were used without further
purification. The organic solvents were purified by distilla-
tion before use.

Reaction of 1 with Tl(SCOPh)$_3$. To a stirred suspension
of Tl(SCOPh)$_3$(0.62 g, 1 mmol) in chloroform(8 ml) we added
1 (0.11 g, 1 mmol) in chloroform(2 ml) at 55 °C; the resulting
mixture was stirred for 3 h under reflux. After being cooled,
the solid was filtered off and the filtrate was washed with
water, dried over Na$_2$SO$_4$, and analyzed by GLC, using
iodobenzene as the internal standard. Analysis revealed the
presence of 0.66 mmol(66% yield; based on Tl salt) of 2 and
0.28 mmol of unreacted 1.

From the reaction using 1 (20 mmol), Tl(SCOPh)$_3$ (10
mmol), and chloform(20 ml), 2 was isolated by distillation
(1.20 g; bp 72 °C/7 mmHg, $\nu_{N=C=S}$ 2120 cm^{-1}); it was iden-
tical with an authentic sample in GLC, NMR, and IR. In
addition, 2.4 g of benzoic acid was isolated by the column
chromatography of the residue after distillation (Wakogel
C-100; diethyl ether as the eluent). No (PhCO)$_2$S or PhCOSH
was obtained by this procedure. These substances may be
hydrolyzed to benzoic acid by these treatment.

Reaction of 1 with Dibenzoyl Disulfide in the Presence of TlOAc.
To a stirred suspension of TlOAc (0.263 g, 1 mmol) in
chloroform (5 ml) we added slowly a mixture of 1 (0.109 g,
1 mmol) and dibenzoyl disulfide (0.274 g, 1 mmol) in chloro-

form (5 ml) at room temperature, after which the resulting mixture was stirred for 3 h under reflux. After being cooled, the solid was filtered off and the filtrate was washed with water and dried over Na_2SO_4. Its GLC analysis reveled the presence of 0.96 mmol (96% yield; based on Tl salt) of **2**. The presence of PhCOOAc was confirmed by the IR of the residue after the evaporation of the solvent from the filtrate.

Competitive Reaction between 1 and Phenyl Isocyanide. A mixture of **1** (0.109 g, 1 mmol), phenyl isocyanide (0.103 g, 1 mmol), and dibenzoyl disulfide (0.274 g, 1 mmol) was stirred for 3 h under reflux in the presence of TlOAc (0.263 g, 1 mmol) in chloroform (10 ml). After treatment as described above, the GLC analysis of the filtrate revealed the presence of 0.60 mmol of **2** (60%), 0.40 mmol of phenyl isothiocyanate (40%), **1** (0.19 mmol, 19%), and phenyl isocyanide (0.38 mmol, 38%).

Reaction of 1 with Dibenzoyl Disulfide in the Presence of TlSPh. A mixture of **1** (1.09 g, 10 mmol), dibenzoyl disulfide (2.74 g, 10 mmol), and TlSPh (3.13 g, 10 mmol) in chloroform (10 ml) was stirred for 3 h under reflux and then treated as above. The GLC analysis of the filtrate revealed the presence of **2** (4.26 mmol, 43%), **1** (5.60 mmol, 56%), diphenyl disulfide (3.84 mmol, 38%), and PhCOSPh (2.37 mmol, 24%). The last two compounds were separated by column chromatography (Wakogel C-100; benzene–ethyl acetate as the eluent), the retention time of GLC, the melting point, and IR spectrum being found identical with those of an authentic sample for each compound.

Reaction of Cyclohexyl Isocyanide-Copper(I) Chloride Complex with Dibenzoyl Disulfide. To a chloroform (10 ml, freed from ethanol) solution of the 1–CuCl complex[9] (0.208 g, 1 mmol) we added dibenzoyl disulfide (0.274 g, 1 mmol) at room temperature, and the resulting mixture was stirred for 3 h under reflux. After being cooled, the precipitated solid was filtered off. The GLC analysis of the filtrate revealed the presence of 0.21 mmol of **2** (21% yield; based on the complex) and 0.79 mmol of **1** (79%).

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