The Reaction of Alkyl Halides with Mercuric Thiocyanate

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(Received July 18, 1974)

The reaction of secondary and tertiary alkyl halides with mercuric thiocyanate in less-polar solvents (*e.g.*, *n*-hexane, di-*n*-butyl ether, and 1,2-dichloroethane) was found to afford predominantly *N*-alkylation products, alkyl isothiocyanates, in contrast to the reaction with potassium salt in DMF. Especially, from *t*-butyl bromide, α-phenethyl bromide and benzhydryl chloride, the corresponding pure isothiocyanates were obtained in good yields. A most probable reaction mechanism is suggested, based on the relative rate data, the stereochemical result of the reaction with optically active α-phenethyl bromide, and the well-known catalytic effect of silver or mercury salt in S_N1 reaction.

The ambident nature of SCN^- has been known for a long time, as illustrated in the following scheme.

$$RX + KSCN \longrightarrow RSCN + KX$$

$$RCOX + KSCN \longrightarrow RCONCS + KX$$

The HASB principle has recently been applied to explain such a mode of attack; that is, alkyl halides react at the soft S atom of SCN^-, while the harder acyl halides react at the harder N atom.[1] In the thiocyanation of certain alkyl halides having a considerable S_N1 reactivity, however, the content of isothiocyanates in the products has been found to reach 35%.[2] This observation is also compatible with the above concept, because the increasing order of hardness of alkyl groups is primary<secondary<tertiary.[1] On the other hand, it has been shown that a change in the reacting site of the nucleophiles is caused by the variation of the counterions in the alkylation of various ambident nucleophiles, such as NO_2^-,[3] CN^-,[4] the anions of 1,3-dicarbonyl compounds,[5] and the anion of formamide.[4] These facts suggest that under appropriate conditions the predominant formation of alkyl isothiocyanates from the corresponding halides might be achieved. In view of the fact that sulfur atom is very powerful nucleophile, it seemed of interest for us to examine whether a preferable attack on the N atom of SCN^- may occur.

Results and Discussion

First of all, we examined the reaction of isopropyl iodide with various metal thiocyanates to know the effect of metal cations on the isomer distribution. The reaction was conducted in less-polar solvent such as *n*-hexane, because the fact is known that in the preparation of alkyl thiocyanates a considerable improvement in yields was achieved by use of polar aprotic solvents.[6] All metal salts used are hardly soluble in *n*-hexane, and the reaction is a heterogeneous process. The results are shown in Table 1. As can be seen from Table 1, $Hg(SCN)_2$ showed the best result for the *N*-alkylation of SCN^-, while other metal salts were less or not satisfactory. Although a predominant attack on the more electronegative (hard) site of the anions has been observed in the alkylation of NO_2^- and CN^- by using silver salts,[4] the attack on the soft S atom was preferred in the alkylation of SCN^- at least in *n*-hexane as solvent by using AgSCN and $Pb(SCN)_2$ as well as KSCN.

TABLE 1. REACTION OF VARIOUS METAL THIOCYANATES WITH ISOPROPYL IODIDE[a]

$M(SCN)_n$	React. temp. (°C)	React. time (hr)	Products: Yield[b] (%)	Isomer ratio[c]: *i*-PrNCS	*i*-PrSCN
$Hg(SCN)_2$	64—65	6	69	75	25
HgSCN	62—65	7	64	55	45
$Cu(NCS)_2$	63—65	7	12	63	37
CuNCS	61—64	5	0	—	—
$Ni(NCS)_2$	64—65	8	0	—	—
AgSCN	63—65	8	35	20	80
$Pb(SCN)_2$	67—69	10	1	9	91
KSCN	60—65	10	0	—	—
KSCN[d]	65—68	7	4	3	97

a) *i*-PrI and $M(SCN)_n$, each of 38 mmol. *n*-Hexane (30 ml) as solvent. b) Isolated yield. c) Determined by glc. d) 2,5,8,15,18,21-Hexaoxatricyclo[20,4,0,0[9,14]]hexacosane[19] (crown ether) (38 mmol) was added to increase the solubility of KSCN.

Next, the effect of alkyl groups upon the isomer ratio in the products was studied in the reactions of several primary, secondary, and tertiary alkyl or aralkyl bro-

TABLE 2. REACTION OF RBr WITH $Hg(SCN)_2$[a]

R in RBr	React. temp. (°C)	React. time (hr)	Products: Yield[b] (%)	Isomer ratio[c]: RNCS	RSCN
n-Bu	80—90	50	23	21	79
$PhCH_2$	70—75	1	74	36	64
i-Pr	70—75	8	44[d]	85	15
c-C_6H_{11}	75—80	11	16	73	27
PhCH(Me)	75—80	0.66	87	99	1[d]
PhCH(Me)	0—1	1	70	99	1[d]
t-Bu	70—72	0.66	68	96	4
Ph_2CH[e]	30—34	2.5	90	100	0[d]

a) RBr and $Hg(SCN)_2$, each of 38 mmol. $(n\text{-Bu})_2O$ (30 ml) as solvent. b) Isolated yield. c) Determined by glc. d) Determined by titration method. e) Chloride.

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mides with $Hg(SCN)_2$ in di-*n*-butyl ether. The reaction mixtures were heterogeneous in all cases. The results are presented in Table 2. As shown in Table 2, isothiocyanates became the predominant isomer when secondary and tertiary bromides were submitted to the reaction, and particularly in cases of the bromides which were capable of forming stable carbonium ions the selectivity was excellent. In addition, a formation of a small amount of the elimination product was observed in the reaction with some bromides. These observations appeared to agree with those expected for S_N1 process.

Since the thermal isomerization of alkyl thiocyanates into isothiocyanates (where alkyl groups are tertiary or aralkyl ones), especially with ease in the presence of $ZnCl_2$, has been known,[7] some controlled experiments on the isomerization were undertaken. For example, when a mixture of *t*-butyl thiocyanate and isothiocyanate (42.6: 57.4) was heated at 70—72 °C for 0.66 hr in di-*n*-butyl ether in the presence of $Hg(SCN)_2$ or $HgBr_2$, the isomer ratio in the resulting mixture was almost unchanged (42.4: 57.6 and 40.9: 59.1, respectively). For a mixture of α-phenethyl thiocyanate and isothiocyanate, a change in the isomer ratio was very little (from 97: 3 to 95.6: 4.4) after heating in di-*n*-butyl ether in the presence of $Hg(SCN)_2$ at 70 °C for 0.75 hr. Similarly, no isomerization was observed in cases of isopropyl and cyclohexyl thiocyanates. Hence, it can be said that the isomer ratios shown in Table 2 are kinetically controlled.

On the other hand, no details on the isomer distribution in the reaction of alkyl halides with alkali metal thiocyanates in polar aprotic solvents have been reported, where the reaction is believed to proceed by S_N2 process. Therefore, we have examined it in DMF solvent using alkyl bromide as alkylating agent. The data are shown in Table 3. Primary and secondary

TABLE 3. REACTION OF RBr WITH KSCN[a]

R in RBr	React. temp. (°C)	React. time (hr)	Products: Yield[b] (%)	Isomer ratio[c]: RNCS	RSCN
n-Bu	75—80	8	87	1	99
n-Bu	70—75	0.66	89	1	99
$PhCH_2$	75—80	3	95	2	98
i-Pr	75—80	6	81	2	98
c-C_6H_{11}	85—90	6	78	4	96
PhCH(Me)	75—80	0.66	76	3	97[d]
PhCH(Me)	75—80	5	86	52	48[d]
t-Bu	70—75	0.66	37	52	48
Ph_2CH[e]	70—75	0.66	86	100[d]	0[f]
Ph_2CH[e]	30—32	0.66	8[g]	0	100[g]

a) RBr 38 mmol, KSCN 57 mmol. DMF (30 ml) as solvent. b) Isolated yield. c) Determined by glc. d) Determined by titration method. e) Chloride. f) It has been reported that the reaction of benzhydryl bromide with KSCN in boiling benzene or alcohol gives only thermodynamically controlled diphenylmethyl isothiocyanate.[20] g) Determined by NMR. $Ph_2C\underline{H}NCS$ δ 5.83, $Ph_2C\underline{H}SCN$ δ 5.63 (in CCl_4).

TABLE 4. REACTION OF *i*-PrX WITH $Hg(SCN)_2$ IN VARIOUS SOLVENTS[a]

X in *i*-PrX	Solvent (30 ml)	React. temp. (°C)	React. time (hr)	Products: Yield[b] (%)	Isomer ratio[c]: *i*-PrNCS	*i*-PrSCN
Br	$(n\text{-Bu})_2O$	70—75	8	44[d]	85	15
I	$(n\text{-Bu})_2O$	70—75	4	72[d]	83	17
Br	*n*-hexane	60—65	22	29	85	15
I	*n*-hexane	60—65	6	69	75	25
Br	$ClCH_2$-CH_2Cl	70—75	18	41	83	17
I	$ClCH_2$-CH_2Cl	65—70	4	66	80	20
Br	CH_3CN	65—70	3.5	5	71	29
I	CH_3CN	60—65	3	16	63	37
I	DMF	75—80	5	11	61	39

a) *i*-PrX and $Hg(SCN)_2$, each of 38 mmol. The reaction was homogeneous only in DMF. b) Isolated yield. c) Determined by glc. d) Determined by titration method.

bromides reacted more readily than tertiary one, as expected, and the obtained alkyl thiocyanates were generally contaminated with few percent of isomeric isothiocyanates, except for some cases. In contrast to the results in di-*n*-butyl ether, the isomerization of α-phenethyl and *t*-butyl thiocyanates to the corresponding isothiocyanates occurred readily in DMF.

The impressive solvent effect on the course of ambident anion alkylations has been mentioned very often.[5] Therefore, the reactions of isopropyl bromide or iodide with $Hg(SCN)_2$ were conducted in various solvents and the effect of solvents on the isomer ratio was studied. The results, which are recorded in Table 4, show that the requirement for the predominant isothiocyanate formation is the use of less-polar solvents such as di-*n*-butyl ether, *n*-hexane, and 1,2-dichloroethane. The isomer ratios were almost constant at least in these solvents. Further, isopropyl iodide reacted more rapidly than the bromide as expected, but the observed isomer ratios for the products obtained from both halides were almost identical. This would be natural if an S_N1 mechanism is operative for this reaction. Of particular interest are the facts that a preference for *N*-alkylation was held even in polar aprotic solvents and that the total yield of two isomers and the product selectivity in a homogeneous system (reaction in DMF) were quite similar to those in a heterogeneous one (reaction in acetonitrile). In addition, the yield of isopropyl thiocyanate formed by the reaction with $Hg(SCN)_2$ in DMF was surprisingly poor (compare the data in Tables 3 and 4), indicating that no considerable amounts of free SCN^- are formed even in a homogeneous system. Significant decreases in the yields of the isomeric mixture for the reaction in DMF and acetonitrile may be ascribed to the strong solvation of the dissolved $Hg(SCN)_2$ species by these solvents, because a strong interaction between metal salts or metal cations with such solvent molecules has been well-known.

In order to obtain further information on the mecha-

nism of the reaction, the studies on the relative reaction rates in alkyl bromides and also on the stereochemistry of the reaction were undertaken. First, by competitive reactions with any two alkyl bromides, the following data were obtained. The observed reactivity

n-BuBr:i-PrBr:t-BuBr = 1:10:10^4 (at 65°C, in n-hexane)

$PhCH_2Br$:PhCH(Me)Br = 1:7 (at 0—1°C, in n-hexane)

order, tertiary≫secondary>primary, appears to confirm that the reaction is essentially pictured as an S_N1 type substitution.[8] Moreover, such an order did not change when the partial rates for each product were compared. Hence, a possibility is considered that both isomeric products are produced *via* a common alkyl cation formed by the attack of $Hg(SCN)_2$ on the halogen atom. That the formation of such a mercury–halogen bond furnishes an important part of the driving force for the ionization is clear from the failure of sulfonates such as isopropyl tosylate to react with $Hg(SCN)_2$ (at 80 °C, for 23 hr, in di-n-butyl ether), because sulfonates are known to be generally more reactive than the corresponding bromides toward nucleophiles.[9a] It should be also noted that silver or mercury-salt catalysis of S_N1-like substitution of alkyl halide is quite well-known.[9b]

Second, after treatment of (R)-α-phenethyl bromide (optical purity, 62.3%) with $Hg(SCN)_2$ suspended in n-hexane (at 0 °C for 1 hr), the isothiocyanate in a mixture of isomeric products (77% yield) was converted into the thiourea derivative by the addition of benzylamine. The isolated N-benzyl-N'-α-phenethylthiourea after recrystallization from ethanol was almost optically inactive (see Experimental). The same result was obtained by using (S)-α-phenethyl bromide (optical purity, 38.7%). Here, there is no possibility that the optically active isothiocyanate was initially formed and then racemized, because no appreciable racemization of (S)-α-phenethyl isothiocyanate was observed under reaction conditions (at 0—1 °C, for 1 hr, in n-hexane, in the presence of $Hg(SCN)_2$). Further there may be some possibility that in the experiment described above the starting α-phenethyl bromide is racemized catalytically by mercury salt before isothiocyanation. When (R)-α-phenethyl bromide was treated with $HgBr_2$ in n-hexane (at 0—1 °C, for 1 hr), however, the recovered bromide still retained 22% of optical purity (78% racemization). These results indicate that isothiocyanation proceeds with almost complete racemization. The result that the extent of racemization by $HgBr_2$ agrees well with the total yields of the racemized isomeric mixture of SCN compounds suggest that both reactions proceed through the common ionization step which is rate-determining.

There are some data on the relative reactivity of the S- to the N-end of SCN^- towards carbonium ions. Fava *et al.*[10] found the value $k_S/k_N=5$ toward 4,4'-dimethylbenzhydryl cation in acetonitrile, by estimating the partition of radioactivity. In the solvolysis of 4,4'-dimethylbenzhydryl halides in 65% aqueous acetone containing SCN^-, the same value was obtained.[10] Taft and Cannell[2] obtained the values ranging from 2 to 9, from the product ratio in the reaction of certain carbonium ion precursors. In contrast to these data, much lower values were observed in the reaction of secondary and tertiary alkyl halides with $Hg(SCN)_2$ as described above, regardless of the solvent polarity. For example, the k_S/k_N values calculated from the isomer ratios were 0.41 and 0.18 for isopropyl cation in acetonitrile and di-n-butyl ether, respectively, and less than 0.01 for α-phenethyl cation in di-n-butyl ether. Such a high selectivity for N-alkylation may be correlated with the structure of $Hg(SCN)_2$, which is confirmed to be S-bonded.[11] Since the existence of considerable amounts of free SCN^- in the reaction system is unexpectable as described above, the anion should be present mostly in the form of $XHg(SCN)_2^-$ which is the counter ion at the carbonium ion formation. If this complex ion serves as a source of SCN^-, the reaction with cationic species would occur mainly at the terminal N atom which is the sterically favorable and more electronegative site.

A presumed mechanism for the reaction with secondary and tertiary halides can be summarized in the following scheme.

$$RX + Hg(SCN)_2 \xrightarrow{\text{slow}} R^+ + XHg(SCN)_2^-$$
$$R^+ + XHg(SCN)_2^- \longrightarrow RNCS(\text{major}) + RSCN + HgX(SCN)$$

Finally we must add a short comment on the reaction of primary halides with $Hg(SCN)_2$ in less polar solvents, although no decisive data are available at present. On accounts of considerable instability of primary cations, a push-pull process which involves the push by SCN^-, probably formed in a small amount by the ionization of the dissolved $Hg(SCN)_2$, and the pull by $Hg(SCN)_2$ may be operative in this case together with the mechanism described above. In a similar reaction of alkyl halides with silver nitrate, the contribution of a push-pull mechanism has been already established.[3]

Experimental

All the organic substances, including the solvents, were used after distillation. Commercial metal thiocyanates and $HgBr_2$ (best grade) were used without further purification.

The isomer ratios of alkyl thiocyanates and isothiocyanates were mostly determined by gas chromatography (glc), and in some cases where glc analyses were unapplicable they were determined by titration method or NMR analysis. The glc analyses were carried out with a Shimadzu 5APTF apparatus using Apz-L (1 m) and PEG-6000 (3 m) columns (carrier gas, N_2). The titration method is based on the addition of butylamine to alkyl isothiocyanates.[12] The NMR spectra were obtained on a Varian A-60 spectrometer (solvent, CCl_4; internal standard, TMS). Optical rotations were measured on a JASCO DIP-180 automatic polarimeter.

Reaction of Alkyl Halides with Mercuric Thiocyanate. Several examples of the reaction of isopropyl halides with $Hg(SCN)_2$ are given below.

a) *In* n-*Hexane*: To a stirred suspension of $Hg(SCN)_2$ (12.0 g, 38 mmol) in n-hexane (30 ml) isopropyl iodide (6.5 g, 38 mmol) was added slowly at 64—65 °C, and the mixture was kept for 6 hr under stirring. The reaction mixture was cooled and filtered to remove the precipitate of inorganic salts. The solvent in the filtrate was removed, and the

resulting residue was distilled, affording a mixture of isopropyl thiocyanate and isothiocyanate (2.6 g, 69% yield), bp 57—58 °C/45 mmHg. The isomer ratio of S/N by glc was 25/75.

b) *In Di-n-butyl Ether*: In a similar way, isopropyl bromide (9.7 g, 79 mmol) was allowed to react with a suspension of $Hg(SCN)_2$ (24.0 g, 76 mmol) in di-*n*-butyl ether (60 ml) under stirring at 70—75 °C for 8 hr. Since the boiling point of the solvent is close to that of the products in this case, the filtrate was analyzed by glc without the evaporation of the solvent. The observed isomer ratio was 15/85. The amount of isopropyl isothiocyanate in the filtrate was determined by the titration method. Based on this, the total yield was calculated (3.5 g, 44%).

c) *In DMF*: Isopropyl iodide (6.5 g, 38 mmol) was similarly treated with a homogeneous solution of $Hg(SCN)_2$ (12.0 g, 38 mmol) in DMF (30 ml) under stirring at 75—80 °C for 5 hr. The reaction mixture was then cooled, filtered, and poured into a large amount of ether (*ca.* 200 ml), and washed by water (2×100 ml). The ether layer was dried by $MgSO_4$ and evaporated to give an oily residue. Distillation afforded a mixture of the expected thiocyanate and isothiocyanate (0.42 g, 11%), bp 61—64 °C/45 mmHg. By glc, the isomer ratio was found to be 39/61.

Competitive Reactions. To a stirred suspension of $Hg(SCN)_2$ (24.0 g, 76 mmol) in *n*-hexane (60 ml) a mixture of isopropyl bromide (8.5 g, 69.1 mmol) and *t*-butyl bromide (1.05 g, 7.6 mmol) was added slowly at 65 °C. After stirring for 1 hr at that temperature, the mixture was worked up as before. A distillate boiling at 60—62 °C/50 mmHg was collected (0.45 g) and analyzed by glc. The combined yield of isopropyl thiocyanate and isothiocyanate was 0.052% (0.036 mmol) and that *t*-butyl compounds was 50% (3.8 mmol). Then the relative rate for these two bromides was 1:960. In a similar way, the competitive reaction of *n*-butyl and isopropyl bromides (each of 38 mmol) (at 65 °C for 7 hr) afforded the corresponding isomeric mixtures in yields of 1.2 mmol and 12.4 mmol, respectively, indicating a 1:10 relative rate. Similarly, the relative rate of benzyl and α-phenethyl bromides was found to be 1:7 at 0—1 °C. In this case, analysis was carried out by NMR method. The following signals were taken up for analysis: δ values for α-H of benzyl thiocyanate and isothiocyanate was 4.03 and 4.59, and those for α-CH_3 of α-phenethyl thiocyanate and isothiocyanate were 1.78, 1.90(d) and 1.60, 1.70(d).

Stereochemical Data. a) *Reaction of (R)-α-Phenethyl Bromide with $Hg(SCN)_2$ in n-Hexane.* (*R*)-α-Phenethyl bromide, α_D^{20} +105.88° (neat) (optical purity, 62.3%[13]) was prepared from the corresponding optically active alcohol by the procedure of Gerrard.[14] This bromide (3.5 g, 18.9 mmol) was treated with $Hg(SCN)_2$ (9.0 g, 28.4 mmol) in *n*-hexane (30 ml) at 0—1 °C for 1 hr under stirring, and the reaction mixture was worked up as usual. A distillate boiling at 111—112 °C/6.5 mmHg was collected (2.38 g, 77%). This product (1.1 g, 6.74 mmol) was converted into *N*-benzyl-*N'*-α-phenethylthiourea (1.7 g, 94%) by the addition of benzylamine (1.4 g, 13.4 mmol) in ether. Recrystallization from ethanol afforded the pure thiourea, mp 100—101 °C (lit,[11] 100 °C), $[\alpha]_D^{20}$ −0.066 (*c* 5.9, 96% EtOH) (optical purity, 0.26%).[15] Additional crystals obtained from the mother liquor did not show any optical rotation.

Quite similar treatment using (*S*)-α-phenethyl bromide, α_D^{20} −65.74° (neat) (optical purity, 38.7%), gave *N*-benzyl-*N'*-α-phenethylthiourea of $[\alpha]_D^{20}$ −0.020 (*c* 5.9, 96% EtOH), and additional crystals obtained from the mother liquor did not show any optical activity.

b) *Racemization of (R)-α-Phenethyl Bromide with $HgBr_2$ in n-Hexane.* When a solution of the above bromide (1.01 g, 5.47 mmol) in *n*-hexane (10 ml) was treated with $HgBr_2$ (3.0 g, 8.32 mmol) at 0—1 °C for 1 hr, a decrease in the optical rotation from $[\alpha]_D^{20}$ +63.24° to 13.60° (*c* 10.12, *n*-hexane) was observed, which corresponds to 78% of racemization.

c) *Attempted Racemization of (S)-α-Phenethyl Isothiocyanate with $Hg(SCN)_2$ in n-Hexane.* (*S*)-α-Phenethyl isothiocyanate, α_D^{20} +28.76° (neat) was prepared from the corresponding optically active amine by the method of Teventev.[16] This isothiocyanate (7.5 g, 46 mmol) was treated with $Hg(SCN)_2$ (30 g, 95 mmol) in *n*-hexane (100 ml) at 0—1 °C for 1 hr, and it was recovered by distillation after usual work-up procedure. It showed α_D^{20} +28.74° (neat), indicating no loss of the optical activity.

Authentic Samples for Glc Analyses. Alkyl thiocyanates were prepared by the reaction of alkyl bromides with KSCN in DMF,[6] though they were generally contaminated with a small amount of the isomers. Alkyl isothiocyanates were synthesized from the corresponding amines (*via* thiocarbamates) by the method of Martin.[17] Benzhydryl isothiocyanate was isolated from the reaction product by distillation, bp 160—165 °C/4 mmHg, mp 59 °C (from EtOH, lit,[18] 58 °C).

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