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Author(s)	Tanaka, Kazuhiko
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The Cyanide-Ion Cleavage of Organic Disulfides

Kazuhiko TANAKA*

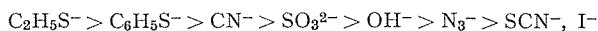
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I. INTRODUCTION

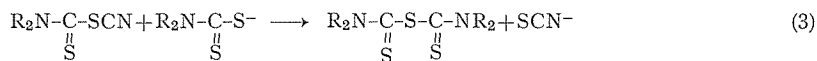
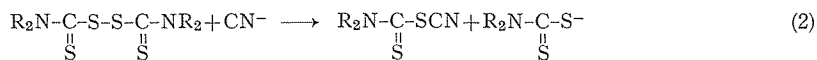
The scission of the sulfur-sulfur bond takes place when an attacking nucleophile, Y^- , has a greater affinity for sulfur than the displaced group, $R'S^-$ (Eq. 1). This affinity for sulfur



is called "S-nucleophilicity" or "thiophilicity".¹⁾ The reactions of nitro-substituted aromatic disulfides with various S-nucleophiles were reported by Parker and Kharasch.²⁾ The results indicate that the more stable (less basic) thiolate anion is displaced; the order of thiophilicity is found to be as follows:



The cyanide ion is regarded as a typical thioanion, which has a great affinity for sulfur to form a thioanion (the thiocyanate ion).³⁾ The first example of desulfurization of disulfides with cyanide ion was reported by Braun and Stechele in 1903.⁴⁾ They found that bis(dialkylthiocarbamoyl) disulfides and bis(alkylarylthiocarbamoyl) disulfides react with potassium cyanide to give the corresponding monosulfides. In 1930, Cambron concluded that these reactions take place in two steps as follows:⁵⁾



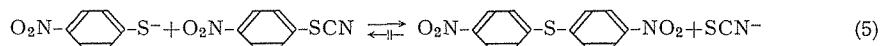
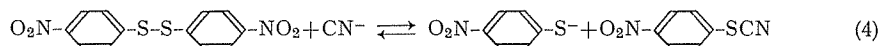
The analogous desulfurization of symmetrical disulfides has been reported for dioxanthyl disulfide,⁶⁾ bis(2-benzothiazolyl) disulfide,⁷⁾ dithiodiglycolic acid,⁸⁾ and diallyl disulfide,⁹⁾ however, diphenyl disulfide,⁶⁾ bis(*p*-tolyl) disulfide,⁸⁾ and dibenzyl disulfide⁸⁾ do not react with cyanide ion. The unsymmetrical disulfides with electron-withdrawing substituents on the aromatic nucleus were reported to be cleaved by cyanide ion at room temperature in ethanol.²⁾

In this short review, detailed discussions will be made on the reactions of symmetrical disulfides with cyanide ion in various solvents.¹⁰⁻¹²⁾

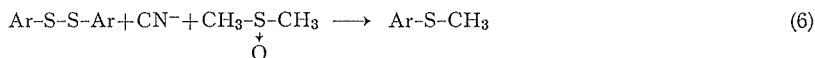
* 田中和彦: Department of Chemistry, Faculty of Science, Kyoto University, Sakyo-ku, Kyoto.

II. REACTION OF DISULFIDES WITH CYANIDE ION IN DIPOLAR APROTIC SOLVENTS

Since the nucleophilicity of cyanide ion is enhanced $\sim 10^5$ times in dipolar aprotic solvents,¹³⁾ it is expected that dialkyl disulfides and diaryl disulfides can react with cyanide ion in dipolar aprotic solvents. Thus, dibenzyl disulfide afforded dibenzyl monosulfide on treatment with cyanide ion in dimethyl sulfoxide. The results are summarized in Table 1. Bis(*p*-nitrophenyl) and bis(*o*-nitrophenyl) disulfides were easily cleaved by cyanide ion and gave the corresponding monosulfides in 60% and 76% yields respectively; while bis(*m*-nitrophenyl), diphenyl, and bis(*p*-tolyl) disulfides were not desulfurized to monosulfides on treatment with cyanide ion in dimethyl sulfoxide. Bis(*p*-nitrophenyl) sulfide did not react with thiocyanate ion in dimethyl sulfoxide at 80°C for 50 hr, and was recovered unchanged. Hence, the reverse reaction in Eq. (5) should be neglected.



As cited above, diaryl disulfides which have electron-donating substituents were not desulfurized at 65°C, however, they afforded aryl methyl sulfide on treatment with cyanide ion in dimethyl sulfoxide at 180°C.



Phenyl thiocyanate and thiophenol, which were formed by the cleavage of diphenyl disulfide with cyanide ion, also reacted with dimethyl sulfoxide in the presence of cyanide ion to afford aryl methyl sulfides in 63% and 65% yields respectively. Reaction conditions

Table 1. Desulfurization of Disulfides with Cyanide Ion.

$$\text{R}-\text{S}-\text{S}-\text{R} + \text{CN}^- \longrightarrow \text{R}-\text{S}-\text{R} + \text{SCN}^-$$

Disulfide	Cyanide	Solvent	Reaction		Monosulfide Yield (%)
			temp. (°C)	time (hr)	
(<i>n</i> -C ₃ H ₇ S-)₂	NaCN	DMSO	80	15	(<i>n</i> -C ₃ H ₇ -)₂S 61
[-(CH ₂)₄-] [S-S]	NaCN	DMF	80	2	[-(CH ₂)₄-] [S] 43
(C ₆ H ₅ CH ₂ S-)₂	NaCN	DMSO	r.t.	72	(C ₆ H ₅ CH ₂ -)₂S 58
(C ₆ H ₅ CH ₂ S-)₂	NaCN	DMF	60	14	(C ₆ H ₅ CH ₂ -)₂S 36
(<i>p</i> -CH ₃ C ₆ H ₄ S-)₂	NaCN	DMSO	65	6	(<i>p</i> -CH ₃ C ₆ H ₄ S-)₂ (73) ^{a)}
(<i>o</i> -NO ₂ C ₆ H ₄ S-)₂	NaCN	DMSO	60	3	(<i>o</i> -NO ₂ C ₆ H ₄ -)₂S 76
(<i>m</i> -NO ₂ C ₆ H ₄ S-)₂	NaCN	DMSO	60	3	(<i>m</i> -NO ₂ C ₆ H ₄ S-)₂ (36) ^{a)}
(<i>p</i> -NO ₂ C ₆ H ₄ S-)₂	NaCN	DMSO	60	3	(<i>p</i> -NO ₂ C ₆ H ₄ -)₂S 60
(2-NO ₂ -4-ClC ₆ H ₃ S-)₂	NaCN	DMSO	80	9	(2-NO ₂ -4-ClC ₆ H ₃ -)₂S 36

a) Recovered disulfide.

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Table 2. Formation of Alkyl Aryl Sulfide in the Reaction of Disulfide with Cyanide Ion.

$$\text{R-S-S-R} + \text{DMSO} \xrightarrow{\text{CN}^-} \text{R-S-CH}_3$$

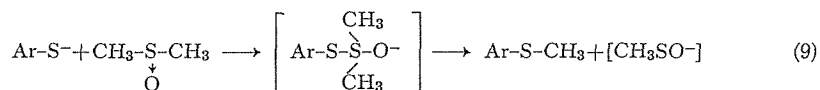
Disulfide	Cyanide	Reaction		Yield of sulfide (%)
		temp. (°C)	time (hr)	
(C ₆ H ₅ S-) ₂	NaCN (1 equiv.)	reflux	6	C ₆ H ₅ SCH ₃ (52)
(C ₆ H ₅ S-) ₂	NaCN (2 equiv.)	reflux	6	C ₆ H ₅ SCH ₃ (66)
(<i>p</i> -CH ₃ C ₆ H ₄ S-) ₂	NaCN (1 equiv.)	reflux	6	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (63)

Table 3. Methylation of Thiophenols and Thiocyanates with DMSO in the Presence of Cyanide Ion.

Starting material	Cyanide	Reaction		Product Yield (%)
		temp. (°C)	time (hr)	
C ₆ H ₅ SH	NaCN (1 equiv.)	reflux	24	C ₆ H ₅ SCH ₃ (65)
<i>o</i> -CH ₃ C ₆ H ₄ SH	NaCN (1 equiv.)	reflux	19	<i>o</i> -CH ₃ C ₆ H ₄ SCH ₃ (73)
<i>m</i> -CH ₃ C ₆ H ₄ SH	NaCN (1 equiv.)	reflux	14	<i>m</i> -CH ₃ C ₆ H ₄ SCH ₃ (73)
<i>p</i> -CH ₃ C ₆ H ₄ SH	none	reflux	6	(<i>p</i> -CH ₃ C ₆ H ₄ S-) ₂ (86)
<i>p</i> -CH ₃ C ₆ H ₄ SH	NaCN (1 equiv.)	reflux	8	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (86)
<i>p</i> -CH ₃ C ₆ H ₄ SH	NaCN (1 equiv.)	reflux	24	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (92)
<i>p</i> -CH ₃ C ₆ H ₄ SH	NaCN (0.2 equiv.)	reflux	24	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (70)
<i>p</i> -CH ₃ C ₆ H ₄ SH	NaOH (1 equiv.)	reflux	7	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (74)
<i>p</i> -CH ₃ C ₆ H ₄ SNa	none	reflux	6	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (80)
<i>p</i> -CH ₃ C ₆ H ₄ SH	NaCN (1 equiv.)	170	6	<i>p</i> -CH ₃ C ₆ H ₄ SC ₂ H ₅ (46) ^{a)}
C ₆ H ₅ SCN	NaCN (1 equiv.)	reflux	6	C ₆ H ₅ SCH ₃ (63)
<i>p</i> -CH ₃ C ₆ H ₄ SCN	NaCN (1 equiv.)	reflux	6	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (58)

a) Diethyl sulfoxide was used instead of DMSO.

and yield of products are summarized in Table 2 and 3. The mechanistic pathway would be as follows:



Although the detailed mechanism of this novel reaction is not yet clear, the *S*-methylation of thiols with dimethyl sulfoxide is a useful method for preparing aryl methyl sulfides.

III. REACTION OF DIARYL DISULFIDES WITH CYANIDE ION IN ALCOHOLS

Whitby and Greenberg reported that diaryl disulfides do not react with cyanide ion

Table 4. Formation of Alkyl Aryl Sulfide in the Reaction of Disulfide with Cyanide Ion in Alcohol.

$$\text{Ar-S-S-Ar} + \text{ROH} \xrightarrow{\text{CN}^-} \text{Ar-S-R} + \text{HCN} + \text{OCN}^-$$

Disulfide	Cyanide	Alcohol	Reaction ^{a)} time (hr)	Yield of Sulfide (%)
(C ₆ H ₅ S-) ₂	NaCN (2.7 equiv.)	CH ₃ OH	3	C ₆ H ₅ SCH ₃ (66)
(<i>p</i> -CH ₃ C ₆ H ₄ S-) ₂	NaCN (2.7 equiv.)	CH ₃ OH	3	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₃ (67)
(<i>p</i> -ClC ₆ H ₄ S-) ₂	NaCN (2.7 equiv.)	CH ₃ OH	3	<i>p</i> -ClC ₆ H ₄ SCH ₃ (60)
(<i>o</i> -NO ₂ C ₆ H ₄ S-) ₂	NaCN (2.7 equiv.)	CH ₃ OH	3	<i>o</i> -NO ₂ C ₆ H ₄ SCH ₃ (81)
(<i>m</i> -NO ₂ C ₆ H ₄ S-) ₂	NaCN (2.7 equiv.)	CH ₃ OH	3	<i>m</i> -NO ₂ C ₆ H ₄ SCH ₃ (81)
(<i>p</i> -NO ₂ C ₆ H ₄ S-) ₂	NaCN (2.7 equiv.)	CH ₃ OH	3	<i>p</i> -NO ₂ C ₆ H ₄ SCH ₃ (79)
(3-NO ₂ -4-ClC ₆ H ₃ S-) ₂	NaCN (1.2 equiv.)	CH ₃ OH	5	3-NO ₂ -4-ClC ₆ H ₃ SCH ₃ (55)
(2-Cl-5-NO ₂ C ₆ H ₃ S-) ₂	KCN (2.5 equiv.)	CH ₃ OH	4	2-Cl-5-NO ₂ C ₆ H ₃ SCH ₃ (78)
(2-Cl-5-NO ₂ C ₆ H ₃ S-) ₂	NaCN (1.7 equiv.)	C ₂ H ₅ OH	4	2-Cl-5-NO ₂ C ₆ H ₃ SC ₂ H ₅ (48)
(2-Br-5-NO ₂ C ₆ H ₃ S-) ₂	NaCN (1.4 equiv.)	CH ₃ OH	2	2-Br-5-NO ₂ C ₆ H ₃ SCH ₃ (55)

a) Refluxing in alcohol.

in alcohol.⁶⁾ We have found that symmetrical diaryl disulfides react with alcohols to give alkyl aryl sulfides in high yields in the presence of cyanide ion. The results of this novel reaction are summarized in Table 4.

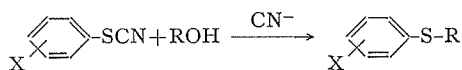
It is expected that alkyl aryl sulfides would be derived from aryl thiocyanates. Thus, aryl thiocyanates were found to react with alcohols in the presence of cyanide ion to give alkyl aryl sulfides. The reaction conditions and the yields of alkyl aryl sulfides are listed in Table 5. In order to examine the general application of this novel reaction, we attempted to prepare benzyl and *n*-butyl aryl sulfides by the same procedure. However, sodium cyanide and potassium cyanide were only slightly soluble in these alcohols. This was overcome by using dimethyl sulfoxide as a solvent or by using tetraethylammonium cyanide as a cyanide in acetonitrile. Thus, benzyl *p*-tolyl sulfide was obtained in a 68% yield in the reaction of *p*-tolyl thiocyanate with benzyl alcohol in the presence of sodium cyanide in dimethyl sulfoxide, and *n*-butyl *p*-tolyl sulfide was obtained in a 59% yield by using tetraethylammonium cyanide in a mixture of *n*-butyl alcohol and acetonitrile.

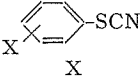
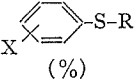
When *p*-tolyl thiocyanate was treated with cyanide ion in methanol at 0°C, *O*-methyl *S*-*p*-tolyl thioiminocarbonate was obtained. *O*-Alkyl *S*-aryl thioiminocarbonates, which were synthesized independently, were treated with base in alcohol. In all the cases studied, alkyl aryl sulfides were isolated in fairly good yields. The results are summarized in Table 6 and 7.

The reaction of *O*-methyl *S*-*p*-tolyl thioiminocarbonate with cyanide ion in ethanol afforded methyl *p*-tolyl sulfide exclusively, while the reaction of *O*-ethyl *S*-*p*-tolyl thioiminocarbonate with cyanide ion in methanol gave a mixture of ethyl *p*-tolyl sulfide (64%) and methyl *p*-tolyl sulfide (7%). These results show that the alkyl moieties of sulfides were derived from that of thioiminocarbonates, not from the alcohol used as a solvent. The mixture of *O*-methyl *S*-*p*-tolyl thioiminocarbonate and *O*-ethyl *S*-*p*-chlorophenyl thioimino-

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Table 5. Formation of Alkyl Aryl Sulfides in the Reaction of Aryl Thiocyanates with Alcohols in the Presence of Cyanide Ion.



Aryl thiocyanate 	Alcohol ^{a)} ROH R	Cyanide	Reaction		Product ^{b)}  (%)
			temp. (°C)	time (hr)	
<i>p</i> -Me ₂ N	Me	NaCN	60	3	50
<i>o</i> -Me	Me	NaCN	50	3	59
<i>m</i> -Me	Me	NaCN	50	3	50
<i>p</i> -Me	Me	NaCN	50	3	55
<i>p</i> -Me	Me	NaCN (2 eq. excess)	50	3	58
<i>p</i> -Me	Me	NaCN	0, 50 ^{c)}	0.5, 3 ^{c)}	66
<i>p</i> -Me	<i>n</i> -Bu	Et ₄ NCN (in CH ₃ CN) ^{d)}	r.t.	21	59
<i>p</i> -Me	<i>n</i> -Bu	NaCN (in DMSO) ^{d)}	r.t.	22	60
<i>p</i> -Me	Me	NaCN	50	24	78
<i>p</i> -Me	Bz ^{e)}	NaCN (in DMSO) ^{d)}	50	20	68
H	Me	NaCN	r.t.	3	51
<i>o</i> -Cl	Et	NaCN	r.t.	5	47
<i>o</i> -Cl	<i>n</i> -Pr	NaCN	50	4	29
<i>o</i> -Cl	<i>n</i> -Pr	NaCN (in DMSO) ^{d)}	50	5	50
<i>o</i> -Cl	<i>i</i> -Pr	NaCN (in DMSO) ^{d)}	50	5	34
<i>m</i> -Cl	Me	NaCN	r.t.	3	61
<i>p</i> -Cl	Me	NaCN	50	1	59
<i>p</i> -Br	Me	NaCN	r.t.	5	59
<i>p</i> -SCN	Me	NaCN (2 eq. excess)	50	4	37
<i>o</i> -NO ₂	Me	NaCN	45	1	70
<i>o</i> -NO ₂	Et	NaCN	50	2	36
<i>m</i> -NO ₂	Me	NaCN	r.t.	0.5	66
<i>m</i> -NO ₂	Et	NaCN	r.t.	1	50
<i>p</i> -NO ₂	Me	NaCN	50	2	70
2-Cl-5-NO ₂	Me	KCN	reflux	4	48
2-NO ₂ -4-Cl	Et	NaCN	50	4	27

a) Alcohol was used as solvent

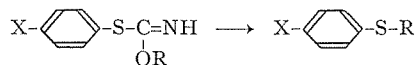
b) Isolated yield

c) 0.5 hr at 0°C, then 3 hr at 50°C

d) Mixture of alcohol and DMSO or CH₃CN

e) Benzyl

carbonate was treated with cyanide ion in ethanol, all four sulfides, *i.e.*, methyl *p*-tolyl sulfide, ethyl *p*-tolyl sulfide, methyl *p*-chlorophenyl sulfide, and ethyl *p*-chlorophenyl sulfide were obtained. As previously discussed, *O*-methyl *S*-*p*-tolyl thioiminocarbonate underwent no ester exchange with ethanol used as the solvent, and the following is considered to be a quite reasonable mechanism.

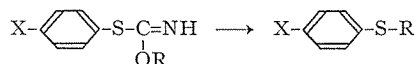
Table 6. Formation of Alkyl Aryl Sulfides in the Reaction of *O*-Alkyl *S*-Aryl Thioiminocarbonates with Bases.

Thioiminocarbonate		Solvent	Base	Reaction		Yield of Sulfide (%)
X	R			temp. (°C)	time (hr)	
Me	Me	MeOH	NaCN	50	3	<i>p</i> -MeC ₆ H ₄ SMe 55
Me	Me	DMSO	NaCN	r.t.	5	<i>p</i> -MeC ₆ H ₄ SMe 81
Me	Et	EtOH	IR-45 ^{a)}	60	12	<i>p</i> -MeC ₆ H ₄ SEt 53
Me	Et	EtOH	b	reflux	7.5	c

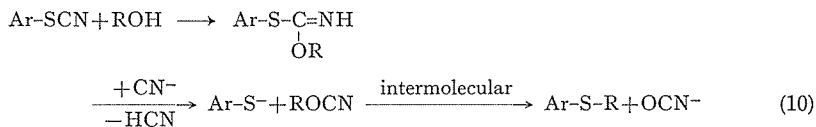
a) Weak basic ion-exchange resin Amberlite IR-45 (OH-form).

b) Without base.

c) 87% of starting material was recovered unchanged.

Table 7. Formation of Alkyl Aryl Sulfides in the Reaction of *O*-Alkyl *S*-Aryl Thioiminocarbonates with Cyanide Ion.

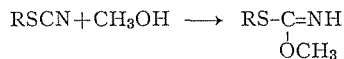
Thioiminocarbonate		Solvent	Cyanide	Reaction		Product Yield (%)
X	R			temp. (°C)	time (hr)	
Me	Me	EtOH	NaCN	50	3	<i>p</i> -MeC ₆ H ₄ SMe (67%)
Me	Et	MeOH	NaCN	50	3	<i>p</i> -MeC ₆ H ₄ SMe (7%) <i>p</i> -MeC ₆ H ₄ SEt (64%)



Direct evidence for the existence of aryl mercaptide ion was obtained by the reaction of *O*-methyl *S*-*p*-tolyl thioiminocarbonate with cyanide ion in the presence of 2,4-dinitrochlorobenzene, which is known to be a good mercaptide ion scavenger. Thus, when *O*-methyl *S*-*p*-tolyl thioiminocarbonate was treated with cyanide ion in the presence of 2,4-dinitrochlorobenzene in methanol, 2,4-dinitrophenyl *p*-tolyl sulfide was isolated in a 24% yield. Furthermore, it was found that thiocyanates reacted with alcohol in the presence of a catalytic amount of cyanide ion to give thioiminocarbonates. Of the various catalysts examined, it was found that sodium azide and sodium methoxide were effective, while triethylamine, sodium thiocyanate, potassium iodide, triphenylphosphine, sodium acetate, and mercuric cyanide were ineffective in the formation of thioiminocarbonates.

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Table 8. Preparation of Thioiminocarbonates.

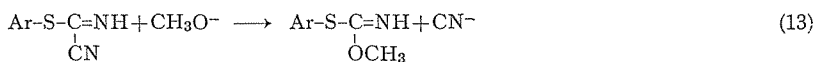
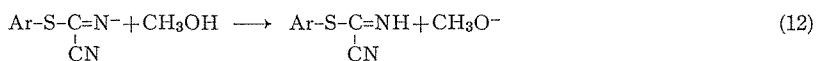


R-SCN R	Catalyst	R-SCN: Catalyst (mol ratio)	Reaction		Yield of thioiminocarbonate (%)
			temp. (°C)	time (hr)	
C ₆ H ₅ -	NaCN	7 : 1	0	6	72
C ₆ H ₅ -	NaOCH ₃	9 : 1	0	6	77
C ₆ H ₅ -	NaN ₃	7 : 1	0	7	73
<i>p</i> -CH ₃ OC ₆ H ₄ -	NaCN	8 : 1	0	17	84
<i>p</i> -CH ₃ C ₆ H ₄ -	NaN ₃	5 : 1	0	1	70
<i>p</i> -CH ₃ C ₆ H ₄ -	NaOCH ₃	5 : 1	0	1	64
<i>p</i> -CH ₃ C ₆ H ₄ -	NaCN	5 : 1	0	1	70
<i>p</i> -CH ₃ C ₆ H ₄ -	NaCN	8 : 1	0	8.5	74
<i>m</i> -CH ₃ C ₆ H ₄ -	NaCN	11 : 1	0	17	84
<i>p</i> -ClC ₆ H ₄ -	NaCN	7 : 1	0	6	74
C ₂ H ₅ -	NaCN	8 : 1	0	24	60

Thioiminocarbonate formation was enhanced by the presence of electron-withdrawing groups on the aryl thiocyanates:



The reaction scheme of the addition of methanol to thiocyanates in the presence of cyanide-ion catalyst may be postulated to be as follows:



IV. SUMMARY AND CONCLUSION

1. Dialkyl disulfides and *ortho*- and *para*-nitro-substituted diaryl disulfides give the corresponding monosulfides in the reaction with cyanide ion in dipolar aprotic solvents.
2. Diaryl disulfides with electron-donating substituents react with dimethyl sulfoxide to afford aryl methyl sulfides.
3. Diaryl disulfides react with cyanide ion in alcohol to give alkyl aryl sulfides.
4. Thiocyanates react with alcohol in the presence of a catalytic amount of cyanide ion to afford thioiminocarbonates.

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