

## Oxalic Acid-catalyzed Reaction of Alcohols with NaSCN: The Effects of Additives NaI and I<sub>2</sub>

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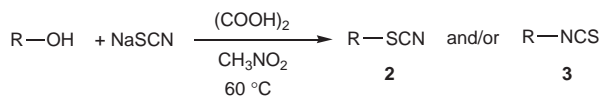
Oxalic acid-mediated conversion of alcohols to thiocyanate and/or isothiocyanate is described. Aliphatic tertiary alcohols give isothiocyanate by the reaction with NaSCN in the presence of I<sub>2</sub>, whereas they give thiocyanate without it.

Nucleophilic substitution is one of the most fundamental reactions in organic chemistry. A hydroxy group is a poor leaving group under basic conditions, and replacing a hydroxy group was usually accomplished after conversion into a good leaving group, such as tosyl, mesyl, or halogens. Although the C–O bond cleavage of alcohol occurs under acidic conditions, most nucleophiles are unreactive under acidic conditions. Recently, we discovered that oxalic acid catalyst in nitromethane solvent can assist C–O bond cleavage and cause nucleophilic substitution between some alcohols and some nucleophiles. In this paper, we report an oxalic acid-catalyzed direct conversion of some alcohols to thiocyanate and/or isothiocyanate by reaction with sodium thiocyanate.

Nucleophilic substitution of thiocyanate anion SCN<sup>−</sup> with alkyl halide is one of the most widely used methods of thiocyanate and/or isothiocyanate synthesis.<sup>1</sup> According to previous studies, the chemoselectivity of the reaction is a crucial problem that is often difficult to control. For example, a counter cation of SCN<sup>−</sup> affects chemoselectivity. A heavy-metal thiocyanate, such as Hg(SCN)<sub>2</sub>, gives isothiocyanate by reaction with 2-iodopropane, whereas KSCN and Cu(SCN)<sub>2</sub> give thiocyanate.<sup>2</sup> The structure of alkyl halide is also important. The amount of isothiocyanate increases in the order of primary < secondary ≪ tertiary alkylhalides.<sup>3</sup> The PPh<sub>3</sub>-DDQ mediated reaction of alcohols with *n*-Bu<sub>4</sub>NSCN shows a similar tendency.<sup>4</sup> These results are usually explained by hard and soft acids and bases (HSAB) principle.<sup>5</sup>

































The replacement of alcohols with NaSCN can be accomplished as follows (Scheme 1). When alcohols **1** were treated with oxalic acid and NaSCN in nitromethane at 60 °C, the replacement of a hydroxy group proceeded to give thiocyanate **2** and/or isothiocyanate **3**.<sup>6</sup> Results are summarized in Table 1. Secondary benzylic alcohols **1a–1d** and non-benzylic tertiary alcohols **1e** and **1f** give thiocyanate **2a–2f**, respectively.

These results are also explained by the HSAB principle. The substrates **1a–1f**, which give thiocyanate **2**, are relatively soft among those listed in Table 1, and they reacted with SCN<sup>−</sup> at the soft end (*S*-end). Similarly, the relatively hard substrates



Scheme 1.

Table 1. Reaction between alcohols and NaSCN

Substrate	Reaction time/h	Thiocyanate Yield/% <sup>a</sup>	Isothiocyanate Yield/% <sup>a</sup>
	8	 <b>2a</b>	45
	8	 <b>2b</b>	53
	9	 <b>2c</b>	48
	5	 <b>2d</b>	55
	13	 <b>2e</b>	17
	3	 <b>2f</b>	20
	4	 <b>2g</b>	10
	2	 <b>3g</b>	82
	5	 <b>3h</b>	78
	6	 <b>3i</b>	52
	6	 <b>3j</b>	81
	4	 <b>3k</b>	77
	3	 <b>3l</b>	69
	3	 <b>3m</b>	46
	3	 <b>3n</b>	75
	3	 <b>3o</b>	87





<sup>a</sup>Isolated yield.

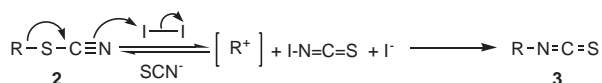
**1h–1o** reacted at the hard end (*N*-end) of SCN<sup>−</sup>. Diphenylmethanol **1g** seems to be a “borderline” substrate and gave both thiocyanate **2g** and isothiocyanate **3g** under these conditions.

Since some substrates gave **2** and/or **3** in poor yield, we used additives to improve the yield. Results are summarized in Table 2. In the cases of **1a**, **1e**, and **1f**, the addition of NaI accelerated the reaction rate, and improved the yield of **2a**, **2e**, and **2f**, respectively. However, in the case of **1c**, the yield of **2c** decreased, and a considerable amount of 1-phenyl-1-hexene was obtained. These differences can be explained as follows. Due to the strong nucleophilicity of I<sup>−</sup>, the hydroxy group of **1a** and **1c** was replaced by iodine, and the unstability of 1-iodo-1-phenylhexane eliminated HI to give a considerable amount of 1-phenyl-1-hexene preceding substitution with SCN<sup>−</sup>. 1-Iodo-1-phenylethane is more stable than 1-iodo-1-phenylhexane, and so the elimination of HI is not a serious drawback.

The addition of NaI influences the chemoselectivity of the

**Table 2.** Reaction between alcohols and NaSCN in the presence of NaI and/or I<sub>2</sub>

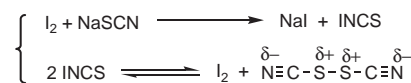
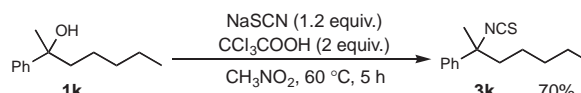
Substrate	Additive (equiv.)		React. time/h	R-SCN Yield/% <sup>a</sup>	R-NCS Yield/% <sup>a</sup>
	NaI	I <sub>2</sub>			
 <b>1a</b>	0	0	8	<b>2a</b> 45	<b>3a</b> 0
	1.2	0	4	66	0
	1.2	0.5	2	62	0
	0	0.5	2	0	81
 <b>1c</b>	0	0	9	<b>2c</b> 48	<b>3c</b> 0
	1.2	0	2	35	0
	0	0.5	2	60	15
	0	1	15	42	31
 <b>1e</b>	0	0	13	<b>2e</b> 17	<b>3e</b> 0
	1.2	0	2	46	7
	1.2	0	10	0	50
	1.2	0.5	2	0	61
	1.2	0.2	2	9	41
	0	0.5	8	0	77
(n-C <sub>9</sub> H <sub>19</sub> ) <sub>3</sub> C-OH <b>1f</b>	0	0	3	<b>2f</b> 20	<b>3f</b> 0
	1.2	0	3	40	0
	1.2	0.5	2	0	44
 <b>1g</b>	0	0	4	<b>2g</b> 10	<b>3g</b> 82
	1.2	0	4	0	88

<sup>a</sup>Isolated yield.**Scheme 2.**

reaction to some extent. Prolonged reaction time of the substitution of **1e** in the presence of NaI causes isomerization of **2e** to **3e**. Isothiocyanate **3e** was obtained in 50% yield after a 10-h reaction, whereas thiocyanate **2e** was obtained as major product after a 2-h reaction. When a 0.5 equiv. of I<sub>2</sub> and 1.2 equiv. of NaI were added, the formation of **3e** was accelerated to give **3e** in 61% yield within 2 h. These results suggest that I<sub>2</sub>, which may be generated by air oxidation of NaI, accelerated isomerization.

Further study on the additives has shown that the existence of NaI is not crucial to obtain isothiocyanate. When I<sub>2</sub> was used as a sole additive, **1a** and **1e** gave isothiocyanates **3a** and **3e** in good yield. Although **1c** gave thiocyanate **2c** as a major product in the presence of a 0.5 equiv. of I<sub>2</sub> after a 2-h reaction, longer reaction time and an increase in the amount of I<sub>2</sub> can cause the isomerization of **2c** to **3c**, and the yield of **3c** increased to some extent.

The role of I<sub>2</sub> in this reaction is explained as follows. An electrophilic attack of I<sub>2</sub> to the nitrogen atom of thiocyanate **2** causes C-S bond cleavage to give carbocation R<sup>+</sup> and I-N=C=S (Scheme 2). According to Nelson,<sup>7</sup> the iodine atom of iodine thiocyanate has cationic character and is attached to the N-end of SCN, whereas chlorine or bromine atoms of ClSCN or BrSCN have anionic character<sup>8</sup> and are attached to the S-end of SCN. Apparently, the nitrogen atom of **2** is less hindered than the sulfur atom, and the electrophilic attack of I<sub>2</sub> to the nitrogen

**Scheme 3.****Scheme 4.**

atom is expected to proceed easily.

The addition of I<sub>2</sub> is expected to cause the formation of an equilibrium mixture of INCS and thiocyanogen ((SCN)<sub>2</sub>) by reaction with NaSCN (Scheme 3). Due to the polarization of (SCN)<sub>2</sub> shown in Scheme 3, carbocation R<sup>+</sup> is expected to react at the nucleophilic (anionic) N-end to give isothiocyanate **3**, whereas such nucleophiles as an alkene react at the electrophilic (cationic) S-end to give a thiocyanate.<sup>6</sup>

Not only oxalic acid but also relatively strong carboxylic acids are effective as catalysts. For example, trichloroacetic acid is as effective as oxalic acid, and 2-phenyl-2-heptanol **1k** reacted with NaSCN under similar conditions to give isothiocyanate **3k** in 70% yield (Scheme 4).

Further study on the chemoselective synthesis of isothiocyanates is in progress.

The general procedure is as follows. To a nitromethane (5 mL) solution of **1** (2.0 mmol), powdered oxalic acid (2.0 mmol) and NaSCN (2.4 mmol) were added. The mixture was stirred for several hours at 60 °C. The mixture was poured into water and extracted with ethyl acetate. After a usual workup, the crude mixture was purified by column chromatography on silica gel.

## References and Notes

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- Characteristic spectral data are as follows. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 111.6–112.1 (R-SCN), 131.3–131.9 (R-NCS, R = benzyl), 129.4–129.8 (R-NCS, R = non-benzylic alkyl); IR (neat): 2140–2160 cm<sup>-1</sup> (sharp, R-SCN), 2040–2060 cm<sup>-1</sup> (broad, R-NCS).
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