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Facile and chemo-selective synthesis of tertiary alkyl isothiocyanates from alcohols

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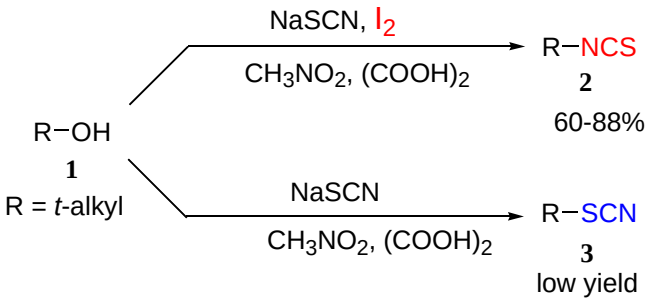
Graphical Abstract



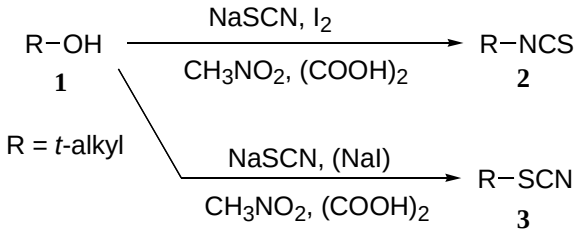
Abstract

When *tert*-alcohols were treated with $(COOH)_2$ and NaSCN in the presence of iodine, *tert*-alkyl isothiocyanates were obtained in good yield, whereas the corresponding thiocyanates were obtained in low yield in the absence of iodine.

1. Introduction

Isothiocyanates are useful intermediates in organic synthesis,[1] and they are also interesting in their biological activities.[2] However, effective synthesis of isothiocyanates is not easy. One possible synthesis of isothiocyanate is a nucleophilic substitution between an alkyl halide and SCN^-. However, because of the ambident character of SCN^-, the reaction often gives not isothiocyanate but thiocyanate as a major product.[3] In the case of *tert*-alkyl halide, undesired elimination of HX occurs as a main reaction, whereas the method using toxic $Hg(SCN)_2$ as a nucleophile gives *tert*-butyl isothiocyanate in 68% yield.[4] In order to avoid the problems described above, substrates other than alkyl halide are often used. For example, amines,[5] phosphoroamidates,[6] amides,[7] dithiocarbamates,[8] and isocyanates[9] are used as a substrate to synthesize isothiocyanate. However, the synthesis of *tert*-alkyl isothiocyanates can be accomplished in very limited instances, or the yields of isothiocyanates are poor.[7] And even in these methods, the synthesis of the precursors of the *tert*-alkyl isothiocyanates comes to be a new problem. Recently, new syntheses of tertiary alkyl isothiocyanates from alcohols by reaction with Ph_3P–DDQ–*n*-Bu_4NSCN[10] or Ph_3P–DEAD–NH_4SCN[11] were reported. However, so far as the examples shown in these reports go, only benzylic tertiary alcohols gave isothiocyanates in good selectivity. Otherwise thiocyanates were obtained.

Recently, we found that some alcohols react with NaSCN in the presence of oxalic acid to give thiocyanates and/or isothiocyanates, and the selectivities of the reactions depend on the structure of the alcohols.[12] For example, benzylic tertiary alcohols gave isothiocyanates, and non-benzylic tertiary alcohols and benzylic secondary alcohols gave thiocyanate chemo-selectively. However, when iodine was added, the chemoselectivity of the reaction changed dramatically. In this paper, we report the details of the iodine-mediated chemoselective synthesis of tertiary alkyl isothiocyanate (**2**) from tertiary alcohols (**1**) and NaSCN.



Scheme 1

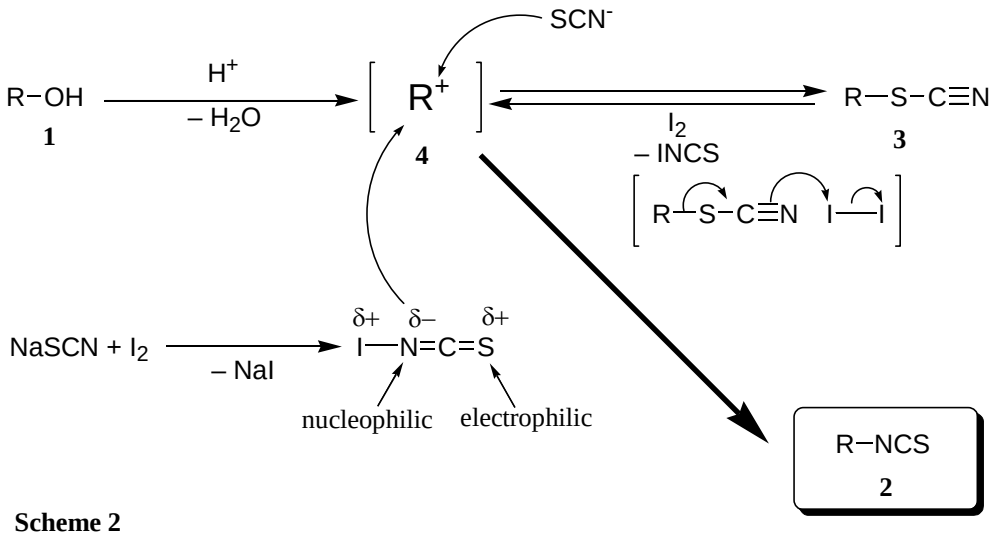
2. Results and Discussion

The oxalic acid-mediated reaction between non-benzylic tertiary alcohols (**1**) in nitromethane proceeded slowly at 60°C, and thiocyanate (**3**) was obtained as a main product in low yield. Addition of NaI accelerated the reaction and improved the yield of **3**. When I_2 was added to the reaction, isothiocyanate (**2**) was obtained as a major product (Scheme 1). The results are summarized in Table 1.

When 3-ethylheptan-3-ol (**1a**) was treated with NaSCN and oxalic acid at 60°C, the reaction proceeded slowly to give a thiocyanate **3a** in 17% yield (Entry 1). However, when NaI was added, the reaction proceeded smoothly, and the yield of **3a** was improved to some extent, and a small amount of isothiocyanate **2a** was obtained at the same time (Entry 3). However, a prolonged reaction gave **2a** as a major product (Entry 4). These results suggest that thiocyanate **3a** isomerized to isothiocyanate **2a** during the course of the prolonged reaction. Interestingly, when 0.5 equivalent of I_2 was added, the yield of **2a** was improved dramatically, and **3a** was not obtained. Supposedly, I_2, which is generated by the air oxidation of I^-, caused the isomerization from **3a** to **2a**. In most cases shown in Table 1, the reaction in the presence of iodine proceeded at 60°C to give isothiocyanate **2** in good yield. Trichloroacetic acid is as effective as oxalic acid for this transformation. However, oxalic acid can be removed more easily than trichloroacetic acid by simple aqueous work-up, and we use oxalic acid for this reaction. Relatively weak carboxylic acids, such as acetic acid, are not effective.

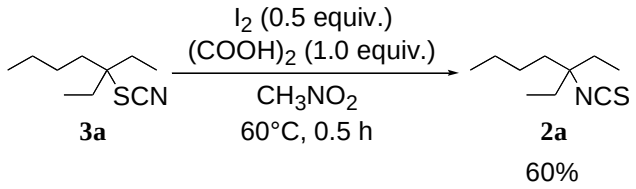
The mechanism of this reaction can be explained as follows (Scheme 2). Oxalic acid promotes the formation of tertiary alkyl cation **4**. The tertiary alkyl cation **4** reacts with SCN^- in the absence of I_2 to give thiocyanate **2**. However, in the presence of I_2, NaSCN reacts with I_2 to give NaI and iodine thiocyanate (INCS). According to Nelson,[13] the iodine atom of INCS has a cationic character, and is attached to the *N*-end of NCS,

whereas chlorine or bromine atoms of ClSCN or BrSCN have an anionic character[14] and attached to the *S*-end of SCN. The iodine atom and sulfur atom of INCS are cationic, whereas the nitrogen atom is anionic. The tertiary alkyl cation reacts at the anionic nitrogen atom of INCS to give isothiocyanate **2** selectively. Some of **1** may react with SCN^-, even in the presence of I_2 to give thiocyanate **3**. Supposedly, it isomerizes to isothiocyanate **2** under these conditions.



Scheme 2

In order to confirm the isomerization described above, we treated thiocyanate **3a** with I_2 in the presence of oxalic acid. When **3a** was treated with I_2 (0.5 equiv.) and oxalic acid (1.0 equiv.) in nitromethane at 60°C, the isomerization proceeded smoothly to give **2a** in 60% yield (Scheme 3).



Scheme 3

The mechanism of the isomerization of **3** to **2** is explained as follows. An electrophilic attack of I_2 causes the R–S bond cleavage of R–SCN (**3**) to give R^+ (**4**), INCS (**5**), and I^-. The reaction between **4** and **5** produced the final product **2**.

The acceleration of the reaction rate by the addition of NaI is explained as follows. Because of the high nucleophilicity of I^-, NaI causes a rapid formation of R–I (**6**) in the presence of oxalic acid. Tertiary alkyl iodide **6** is more reactive than **1** and reacts with SCN^- to give **3**.

It must be noted that benzylic tertiary alcohols give isothiocyanate selectively even in the absence of I_2[12] and these results can be explained by the HSAB principle.

3. Conclusion

Addition of iodine can effectively improve the yield and selectivity of the oxalic acid-mediated reaction of tertiary alcohols with NaSCN. This method is useful for preparing tertiary alkyl isothiocyanates.

4. Experimental

4.1 General

Oxalic acid, nitromethane, NaSCN, and iodine were used as purchased from commercial suppliers without further purification. IR spectra were recorded on SHIMADZU IR-408 and HORIBA FT-710 spectrometers. NMR spectra were recorded on a JEOL JNM-AL300 spectrometer. HRMS spectra were recorded on a JEOL JMS-SX102 spectrometer.

4.2. Procedures and Analytical Data

4.2.1. 3-Ethyl-3-isothiocyanatoheptane (**2a**) (Table 1, Entry 5). The procedures are described as follows as typical procedures. To a nitromethane (2 mL) solution of 3-ethylheptan-3-ol (**1a**) (0.29 g, 2.0 mmol) was added I_2 (0.13 g, 1.0 mmol) and a powdered mixture of NaSCN (0.20 g, 2.4 mmol) and oxalic acid (0.18 g, 2.0 mmol). The mixture was stirred at 60°C for 8 h. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 3% $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel to obtain **2a** as a colorless oil (0.28 g, 1.52 mmol) in a 76% yield. IR (–NCS): 2070 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 0.91–0.96 (9H, m), 1.29–1.37 (4H, m), 1.56–1.69 (6H, m); ^{13}C NMR ($CDCl_3$): δ (ppm) 8.0, 13.8, 22.7, 25.6, 30.7, 37.0, 67.8, 129.6; HRMS (EI) calcd for $C_{10}H_{19}NS$ (M^+): 185.1238, found:

185.1232.

4.2.2. 3-Ethyl-3-thiocyanatoheptane (**3a**). IR (–NCS): 2120 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.91-1.01 (9H, m), 1.32-1.37 (4H, m), 1.64-1.78 (6H, m); ^{13}C NMR ($CDCl_3$): δ (ppm) 8.3, 13.9, 22.8, 25.9, 30.0, 36.1, 64.8, 111.8; HRMS (EI) calcd for C_9H_{19} ($[M\text{-}SCN]^+$): 127.1487, found: 127.1492.

4.2.3. 3-Ethyl-3-isothiocyanatooctatane (**2b**). IR (–NCS): 2070 cm^{-1}; ^{1}H NMR ($CDCl_3$): d (ppm) 0.88-0.96 (9H, m), 1.25-1.36 (6H, m), 1.55-1.68 (6H, m); ^{13}C NMR ($CDCl_3$): d (ppm) 8.1, 13.9, 22.4, 23.2, 30.7, 31.8, 37.3, 67.9, 129.6; HRMS (EI) calcd for $C_{11}H_{21}NS$ (M^+): 199.1395, found: 199.1391.

4.2.4. 3-Ethyl-3-isothiocyanatononane (2c). IR (–NCS): 2060 cm^{-1}; ^{1}H NMR ($CDCl_3$): d (ppm) 0.90-0.96 (9H, m), 1.26-1.30 (8H, m), 1.56-1.68 (6H, m); ^{13}C NMR ($CDCl_3$): d (ppm) 8.1, 13.9, 22.5, 23.5, 29.3, 30.7, 31.6, 37.4, 67.9, 129.8; HRMS (EI) calcd for $C_{12}H_{23}NS$ (M^+): 213.1551, $C_{11}H_{23}$ ($[M\text{-}NCS]^+$):155.1800, $C_{10}H_{18}NS$ ($[M\text{-}C_2H_5]^+$): 184.1160, found: 213.1578, 155.1798, 184.1162.

4.2.5. 2-Isothiocyanato-2-methyloctane (2d). IR (–NCS): 2050 cm^{-1}; ^{1}H NMR ($CDCl_3$): d (ppm) 0.87-0.92 (3H, m), 1.29-1.35 (6H, m), 1.36-1.44 (8H, m), 1.56-1.61 (2H, m); ^{13}C NMR ($CDCl_3$): d (ppm) 14.0, 22.5, 24.3, 28.8, 29.1, 31.6, 43.1, 61.2, 129.7; HRMS (EI) calcd for C_9H_{19} ($[M\text{-}NCS]^+$): 127.1487, C_4H_6NS ($[M\text{-}C_6H_{13}]^+$): 100.0221, found: 127.1488, 100.0225.

4.2.6. 5-Butyl-5-isothiocyanatononane (2e). IR (–NCS): 2070 cm^{-1}; ^{1}H NMR ($CDCl_3$): d (ppm) 0.93 (9H, t, *J* = 6.6 Hz), 1.29-1.34 (12H, m), 1.56-1.61 (6H, m); ^{13}C NMR ($CDCl_3$): d (ppm) 13.8, 22.7, 25.7, 38.1, 67.0, 129.6; HRMS (EI) calcd for $C_{13}H_{27}$ ($[M\text{-}NCS]^+$): 183.2092, found: 183.2113.

4.2.7. 6-Isothiocyanato-6-pentylundecane (2f). IR (–NCS): 2090 cm^{-1}; ^{1}H NMR ($CDCl_3$): d (ppm) 0.88-0.92 (9H, m), 1.31 (18H, m), 1.57-1.58 (6H, m); ^{13}C NMR ($CDCl_3$): 14.0, 22.5, 23.5, 31.8, 38.4, 67.3, 129.4; HRMS (EI) calcd for $C_{16}H_{33}$ ($[M\text{-}NCS]^+$): 225.2582, C_4H_6NS ($[M\text{-}C_5H_{11}]^+$): 212.1473, found: 225.2548, 212.1449.

4.2.8. 6-Pentyl-6-thiocyanatoundecane (3f). IR (–NCS): 2145 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.85-0.87 (9H, m), 1.28-1.40 (18H, m), 1.62-1.64 (6H, m); ^{13}C NMR ($CDCl_3$): 13.9, 22.4, 23.5, 31.8, 37.6, 64.1, 111.9; HRMS (EI) calcd for $C_{16}H_{33}$ ($[M\text{-}HSCN]^+$): 224.2504, found: 224.2501.

4.2.9. 1-Hexyl-1-isothiocyanatocyclohexane (2g). IR (–NCS): 2050 cm^{-1}; ^{1}H NMR ($CDCl_3$): d (ppm) 0.87-0.91 (3H, m), 1.14-1.46 (10H, m), 1.52-1.72 (8H, m), 1.87-1.91

(2H, m) ; ^{13}C NMR ($CDCl_3$): 13.9, 22.1, 22.4, 23.2, 25.2, 29.2, 31.6, 37.2, 42.4, 64.6, 129.8; HRMS (EI) calcd for $C_{12}H_{23}$ ([M-NCS]$^+$): 167.1800, $C_7H_{10}NS$ ([M-C_6H_{13}]$^+$): 140.0534, found: 167.1799, 140.0559

5. Supporting information

^{1}H and ^{13}C NMR spectra of **2a-2g**, **3a**, and **3f** are available as supporting information.

References and Notes

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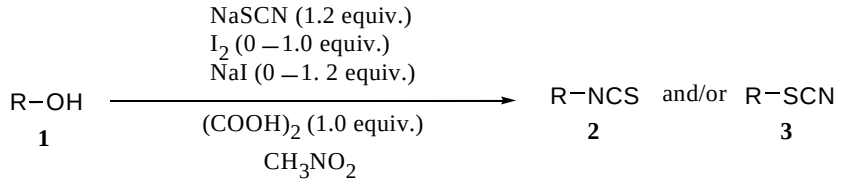
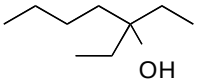
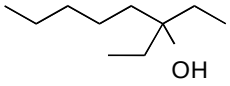
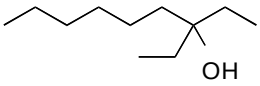
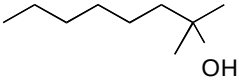
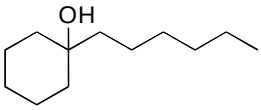
Table 1. Synthesis of isothiocyanates and thiocyanates from alcohols



Entry	Alcohol (**1**)		Additive(equiv.)	Conditions	Isolated yield **2**/ %	Isolated yield **3**/ %
1		**1a**	none	60 °C, 13 h	–	**3a** 17
2			NaI (0.5)	60 °C, 5 h	–	**3a** 32
3			NaI (1.2)	60 °C, 2 h	**2a** 7	**3a** 46
4			NaI (1.2)	60 °C, 10 h	**2a** 50	–
5			I_2 (0.5)	60 °C, 8 h	**2a** 76	–
6		**1b**	I_2 (0.5)	60 °C, 2 h	**2b** 77	–
7		**1c**	I_2 (1.0)	60 °C, 3 h	**2c** 88	–
8		**1d**	I_2 (1.0)	60 °C, 5 h	**2d** 81	–
9	$(n\text{-}C_4H_9)_3C–OH$	**1e**	I_2 (1.0)	60 °C, 20 h	**2e** 87	–
10	$(n\text{-}C_5H_{11})_3C–OH$	**1f**	none	60 °C, 3 h	–	**3f** 20
11			NaI (1.2)	60 °C, 2 h	–	**3f** 40
12			I_2 (1.0)	60 °C, 4 h	**2f** 76	–
13		**1g**	I_2 (1.0)	60 °C, 4 h	**2g** 60	–