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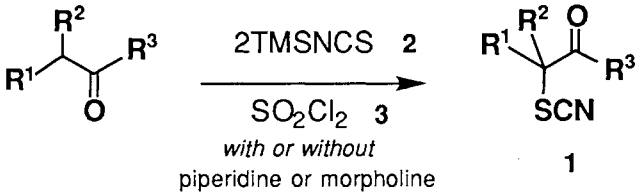
Direct and Electrophilic Preparation of α-Thiocyanatoketones and Aldehydes Using Thiocyanatotrimethylsilane and Sulfuryl Chloride

Yoo TANABE,* Takuya MAKITA, and Kei MORI
School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya, Hyogo 662

The thiocyanato (-SCN) group was directly and regioselectively introduced into the α-position of ketones, aldehydes, and aldols in an electrophilic manner by the combined use of thiocyanatotrimethylsilane and sulfuryl chloride with or without cyclic *sec*-amine catalysts under mild reaction conditions.

Thiocyanates (RSCN) play an important role in versatile areas of organosulfur chemistry.[1] The thiocyanation, classically called rhodanation, is generally conducted *via* a nucleophilic reaction using the thiocyanato ion ($^-$SCN). Among the thiocyanates, α-thiocyanatoketones or aldehydes **1** are recognized as a favorite precursor of several types of thiazoles,[2] some of which have recently draw attention as herbicides or other important biological active compounds.[3] These α-thiocyanatoketones (aldehydes) **1** have been conventionally prepared from ketones *via* an indirect way that includes nucleophilic displacement of α-haloketones or nucleophilic epoxy ring opening using $^-$SCN[4] followed by oxidation. These methods, however, sometimes required severe reaction conditions resulting in low yields due to the inherent poor nucleophilicity of $^-$SCN.

On the other hand, thiocyanogen (NCSSCN, **4**) and thiocyanogen chloride (ClSCN, **5**) are known as electophilic reagents for the thiocyanation, but the reaction is limited to cases using alkenes, alkynes, and reactive aromatics as the substrate.[5] Previously, we described the regioselective α-methoxycarbonylsulfenylation of carbonyl compounds *via* methoxycarbonylsulfenyl cationic species which served as a way to synthesize useful synthons for *S,N*-containing heterocycles.[6] We report here a direct method for the preparation of α-thiocyanatoketones **1**, aldols **7**, and aldehydes **9** using available thiocyanatotrimethylsilane (TMSNCS, **2**)[7] and sulfuryl chloride (**3**) with or without a piperidine (or morpholine) catalyst in an electrophilic (i.e., umpolung) manner. One of the characteristic features worth noting is the first, direct and unequivocal preparation of α-thiocyanatoaldols **7** and of relatively unstable α-thiocyanatoaldehydes **9**.



The reported procedure of thiocyanogen (KSCN and Br_2) with acetophenone in CH_2Cl_2 for one hour was first examined, but the yield was only 10%. The displacement of KSCN with TMSNCS (**2**) was found to raise the yield to 72%. Although propiophenone underwent only bromination in 90% yield using the TMSNCS (**2**)/Br_2 combination, the TMSNCS (**2**)/SO_2Cl_2 (**3**) system was found to give the desired α-

thiocyanatopropiophenone in 90% yield. This successful result employing SO_2Cl_2 (**3**) could be explained as follows: formation of a stable Si-Cl bond compared to the Si-Br bond promoted the smooth generation of NCSSCN (**4**) or ClSCN (**5**) acting as the cationic species of ^+SCN. The results of using other ketones are listed in Table 1. Acetonitrile and CH_2Cl_2 were better solvents for this reaction than benzene, THF, and DMF. These reactions of unsymmetrical ketones and β-oxo esters proceeded preferentially at the more substituted α-site, whose facts would suggest thermodynamic enols of those ketones react *in situ* with ^+SCN.[6]

Although the reaction of benzylacetone (4-phenyl-2-butanone) and aldehydes **8** gave complex mixtures, the use of an additive such as piperidine or morpholine effectively facilitated the desired reaction, wherein these substrates would be activated to the corresponding enamines for the electrophilic reaction. The effect of these *sec*-amine catalysts was not so significant for the reaction using other ketones.

A representative procedure is as follows (Entry 12): To a stirred solution of thiocyanatotrimethylsilane (**2**; 788 mg, 6.0 mmol) in CH_3CN (5 ml) was added SO_2Cl_2 (**3**, 337 mg, 2.5 mmol) at -5 °C-0 °C and then the mixture was kept at room temperature for 0.5 h. 4-Phenyl-2-butanone (371 mg, 2.5 mmol) in CH_3CN (5 ml) and morpholine (218 mg, 2.5 mmol) were successively added to the mixture at 0 °C-5 °C and the mixture was allowed to warm and then maintained at room temp. for 5 h with stirring. Water was added and the usual work up followed by SiO_2-column chromatographic purification (hexane/ethyl acetate=10:1) gave 5:1 mixtures (400 mg) of 4-phenyl-3-thiocyanato-2-butanone and 4-phenyl-1-thiocyanato-2-butanone in a 78% total yield.

The following reaction mechanism is proposed. One may suppose that the reaction proceeds *via* the initial formation of the α-chloroketone followed by displacement with ^-SCN. The reaction of phenacyl chloride with TMSNCS (**2**)/SO_2Cl_2 (**3**) gave α-thiocyanato-α-chloroacetophenone as the main product in 28% yield and the starting phenacyl chloride was almost recovered with a trace amount of phenacyl thiocyanate. This result negates the possibility of a nucleophilic reaction. The reactions of TMSNCS (**2**) with SO_2Cl_2 (**3**) are supposed to proceed *via* the following two equations.

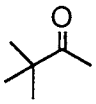
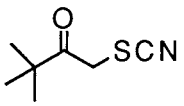
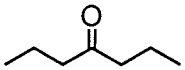
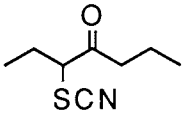
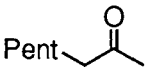
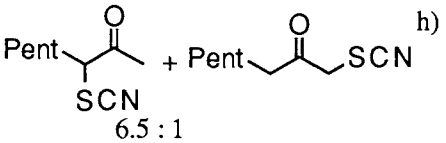
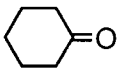
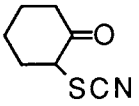
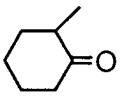
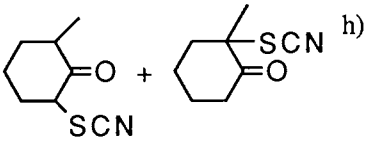
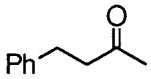
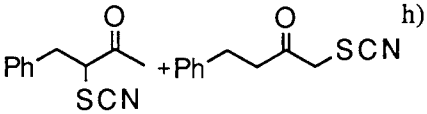
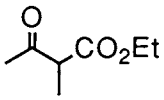
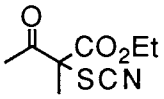
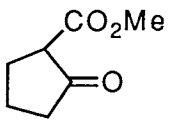
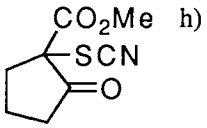
$$\underset{\mathbf{2}}{2TMSNCS} + \underset{\mathbf{3}}{SO_2Cl_2} \longrightarrow \underset{\mathbf{4}}{NCSSCN} + 2TMSCl + SO_2$$

$$\underset{\mathbf{2}}{TMSNCS} + \underset{\mathbf{3}}{SO_2Cl_2} \longrightarrow \underset{\mathbf{5}}{ClSCN} + TMSCl + SO_2$$

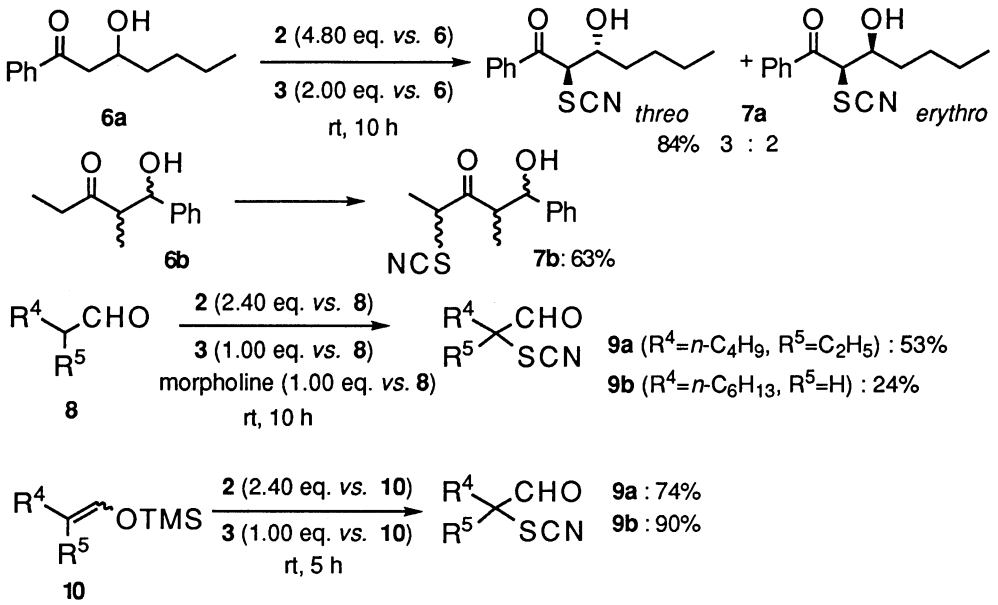
To determine whether the active species is NCSSCN (**4**) or ClSCN (**5**), the conversion of **2** with **3** at two different ratios (**2**:**3** = 2:1 and 1:1) was monitored by both ^1H and ^{13}C NMR measurements in CD_3CN at rt.[8] ^1H NMR showed both reactions finished within 15 min. with complete consumption of TMSNCS (**2**; δ 0.30 ppm) and the sole production of TMSCl (δ 0.42 ppm). Two observable peaks appeared on ^{13}C NMR in both reactions: TMSCl (δ 3.10 ppm) and one -SCN species (δ 111.70 ppm). If the active species was ClSCN (**5**), TMSNCS (**2**) would have substantially remained in the former experiment. These results indicate the active species would be NCSSCN (**4**) rather than ClSCN (**5**).

α-Thiocyanatoaldols **7**[9] could also be obtained from aldols **6**, wherein the methylene positions of **6** were regioselectively thiocyanated. α-Thiocyanatoaldehydes **9**[10] could be also prepared from aldehydes **8** by the present method. Additionally, the reaction using the silylenol ethers **10** of **8** gave these aldehydes **9** in better yields. These facts also suggest these reactions proceeded in an electrophilic manner under mild conditions. Those α-thiocyanatocarbonyl compounds would serve not only as synthons for new sulfur-containing compounds but also as precursors for masked mercapto group compounds.

Table 1. α-Thiocyanations of Ketones Using TMSNCS (**2**) and SO_2Cl_2 (**3**)[a]

Entry	Ketone	Reagent[b]	Catalyst	Product	Yield/%
1	Acetophenone	A	none	Phenacyl thiocyanate[c]	20
2	Acetophenone	B	none	Phenacyl thiocyanate	72
3	Propiophenone	C	none	α-thiocyanatopropiophenone[d]	90
4	Isobutyrophenone	C	none	α-thiocyanatoisobutyrophenone[e]	32
5		C	none	 f)	75
6		C	none	 g)	80
7		C	none	 h) 6.5 : 1	77
8		C	none	 i)	75
9		C	none	 h) 1 : 8.5	64
10		C	none	 h)	trace
11			piperidine		72
12			morpholine	5.0 : 1	78
				5.0 : 1	
13		C	morpholine	 h)	69
14		C	none	 h)	67

a) These reactions were carried out at room temperature for 5 h. Solvents used were CH_2Cl_2 (Entries 1-4) and CH_3CN (Entries 5-14). Molar ratios were Ketones:TMSNCS:SO_2Cl_2:(Catalyst)=1.00:2.40:1.00:(1.00). Isomers ratios were determined by ^1H NMR (400 MHz) measurements. b) A: KSCN/Br_2, B: TMSNCS (**2**)/Br_2, C: TMSNCS (**2**)/SO_2Cl_2 (**3**). c) Ref. 11 d) Ref. 12. e) Ref. 11. f) Ref. 13. g) Ref. 14. h) These are new compounds whose ^1H NMR and IR spectra supported the structures. i) Ref. 15.



To our knowledge this is the first example of a direct and general method for introducing the thiocyanato group into the α-position of these carbonyl compounds. The use of the TMSNCS/SO_2Cl_2 system is, therefore, considered to be a new method for the generation of thiocyanogen (NCSSCN).

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7) Commercially available from Aldrich Chemical Co., Ltd.
8) Both reactions were homogeneous. On the contrary, those in $CDCl_3$ produced insoluble products.
9) The *threo* isomer of **7a**: selected data of ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, d, J = 9.0Hz, C<u>H</u>-SCN) and ^{13}C NMR ($CDCl_3$) δ 110.47 (-S<u>C</u>N), 195.16 (<u>C</u>=O). The *erythro* isomer of **7a**: selected data of ^{1}H NMR δ 4.82 (1H, d, J = 4.0Hz, C<u>H</u>-SCN) and ^{13}C NMR δ 111.59 (-S<u>C</u>N), 195.37 (<u>C</u>=O).
10) Selected data of **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s ; -C<u>H</u>O) and ^{13}C NMR (400 MHz, $CDCl_3$) δ 109.32 (-S<u>C</u>N), 195.03 (<u>C</u>=O). Those of **9b**: ^{1}H NMR δ 3.70 [1H, dt, J = 7.0 Hz, 2.0 Hz; -C<u>H</u>(CHO)(SCN)], 9.60 (1H, d, J = 2.0Hz; -C<u>H</u>O) and ^{13}C NMR δ 109.21 (-S<u>C</u>N), 192.98 (<u>C</u>=O).
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