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Catalyst-Free, Efficient, and Facile Conversion of Epoxides to β-Hydroxy Thiocyanates Under Neutral Conditions

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Abstract: Epoxides are efficiently and easily converted to their corresponding β-hydroxy thiocyanates by NH_4SCN in refluxing acetonitrile in a regio- and chemoselective manner under neutral conditions without using a catalyst, in spite of the use of many different catalysts reported in the literature for this purpose.

Keywords: Catalyst-free, epoxide, β-hydroxy thiocyanate

Epoxides are important intermediates in organic synthesis.[1] Their facile regio- and stereoselective ring-opening reactions with a wide variety of nucleophiles provide a powerful strategy in organic chemistry.[1–6] However, in most of the epoxide ring-opening reactions under acidic conditions, the formation of a mixture of regio-isomers and polymerization is observed. On the other hand, thiocyanates have gained considerable importance in various areas of organosulfur chemistry.[7] For example, the thiocyanato group occurs as an important functionality in certain anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables.[8,9] In this connection, β-hydroxy thiocyanates are also important intermediates in agricultural and pharmaceutical chemistry. These compounds represent an interesting subclass and have multiple modes of reactivity. Thus, the development of simple

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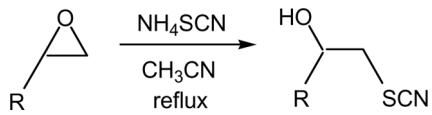
and efficient methods for the preparation of β-hydroxy thiocyanates, especially from epoxides, is desirable.

Several methods have been reported for the preparation of β-hydroxy thiocyanates using different reagents or catalysts. In one method, thiocyanohydrins are prepared by the opening of a cyclic sulfate with NH_4SCN to form the corresponding β-sulfate, which is hydrolyzed to the thiocyanohydrin. A second method involves the addition of thiocyanic acid (generated in situ at low temperature) to the epoxide.[10] It has been reported for these syntheses that the presence of some DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) or hydroquinone (benzene-1,4-diol) is required to stabilize the produced β-hydroxy thiocyanate and to inhibit its conversion to thiirane.[11] Also, reagents such as $Ti(O^iPr)_4$,[12] triphenylphosphine–thiocyanogen (TPPT),[13] $TiCl_3$,[14] and $Pd(PPh_3)_4$[15] have been introduced for the conversion of specific oxiranes to β-hydroxy thiocyanates using the SCN^- anion. In addition, the conversion of epoxides to β-hydroxy thiocyanates has been carried out using ammonium thiocyanate in the presence of thioxanthenone-fused azacrown ethers,[16] metalloporphyrins,[17] $SbCl_3$,[18] and selectfluor.[19]

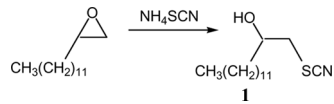
Recently, Bellomo and Gonzalez have reported the ring opening of a specific vinyl epoxide with ammonium or potassium thiocyanate from its allylic position, affording to its corresponding thiocyanohydrin in the absence of a catalyst and at room temperature.[20] Herein, in continuation of our work on the ring opening of epoxides by halide anions producing β-halohydrins,[21] we now report that also the conversion of simple other epoxides to their corresponding β-hydroxy thiocyanates does not require to a catalyst and is easily and efficiently carried out using merely ammonium thiocyanate in refluxing acetonitrile under neutral conditions in a regio- and chemoselective manner (Scheme 1).

First, we took 1,2-epoxytetradecane as an example and optimized the reaction conditions for its catalyst-free conversion to 2-hydroxytetradecyl thiocyanate **1** using NH_4SCN. The results are shown in Table 1. As shown in this table, this conversion was unsuccessful under solvent-free conditions at room temperature even via grinding of reactants using 2.4 equivalents of NH_4SCN (Table 1, entries 1 and 2). In the same conditions, the yield of this reaction was not much improved by increasing



Scheme 1. Catalyst-free conversion of epoxides to β-hydroxy thiocyanates using NH_4SCN in refluxing acetonitrile under neutral conditions.

Table 1. Catalyst-free conversion of 1,2-epoxytetradecane to 2-hydroxytetradecyl thiocyanate **1** using NH_4SCN in different conditions



1

Entry	Solvent	Molar ratio[a]	Temperature (°C)	Time (h)	Yield (%)
1	—	1:1.2	rt	28	0
2	—	1:2.4	rt	2	30[b]
3	—	1:1.2	80	2	40[c,d]
4	—	1:2.4	80	2	50[c,d]
5	CH_2Cl_2	1:2.4	rt	25	10
6	CH_2Cl_2	1:2.4	Reflux	25	30
7	CH_3CN	1:2.4	rt	25	70
8	CH_3CN	1:1.2	Reflux	19	60
9	CH_3CN	1:2	Reflux	16	80
10	CH_3CN	1:2.4	Reflux	1.5	91

[a]Molar ratio is related to epoxide: NH_4SCN.
[b]The reactants were ground in a glass test tube.
[c]The reaction was not clean, and a mixture of undesired other products was formed in this case.
[d]This reaction was performed in an oil bath.

reaction temperature (Table 1, entries 3 and 4). Also, this reaction was unsuccessful in CH_2Cl_2 as solvent. In this case, the desired product was obtained in merely 10–30% yield after 25 h at room temperature or under reflux conditions (Table 1, entries 5 and 6). Using CH_3CN as solvent instead of CH_2Cl_2 caused the improvement of the reaction so that **1** was produced in good yield at room temperature after 25 h (Table 1, entry 7). This reaction afforded better results in CH_3CN under reflux conditions, and finally the best result was obtained in this reaction condition with 2.4 equivalents of NH_4SCN so that 2-hydroxytetradecyl thiocyanate **1** was produced in 91% yield after only 1.5 h (Table 1, entry 10).

We therefore used this catalyst-free method (Table 1, entry 10) for the conversion of other epoxides to their corresponding β-hydroxy thiocyanates. The results are shown in Table 2. As shown in this table, epoxides are efficiently converted to β-hydroxy thiocyanates by NH_4SCN in refluxing acetonitrile without using a catalyst under neutral conditions. Except for the case of styrene oxide, which produced two regio-isomers in a regioselective manner in contrast to the literature[16,17,19] (Table 2, entry 3), the reaction of other unsymmetrical epoxides occurred with high

regioselectivity, and the thiocyanate anion attacked at the less-hindered side of the epoxide ring because of the combination of steric and electronic factors.

Under these reaction conditions, the ethereal bonds, ester groups, phenyl ring, carbon–halogen bonds, and carbon–carbon double bonds as functional groups that are present in the epoxide molecules remained intact.

In conclusion, the present investigation has demonstrated that the use of NH_4SCN in refluxing acetonitrile without a catalyst offers an easy and efficient method for the conversion of wide varieties of epoxides to their corresponding β-hydroxy thiocyanates under neutral conditions. This method can be efficiently used for the preparation of β-hydroxy thiocyanates even in the presence of some other functional groups with excellent chemoselectivity. Excellent yields, easy workup, reduced pollution, and excellent regioselectivity are considered as other advantages of this new method.

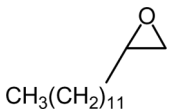
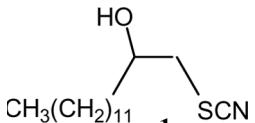
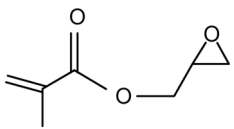
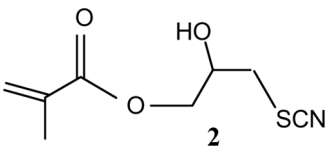
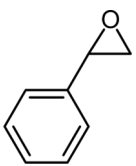
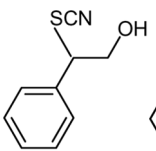
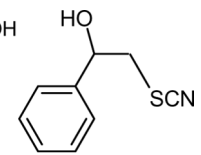
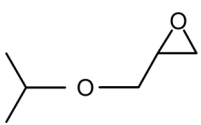
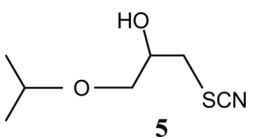
EXPERIMENTAL

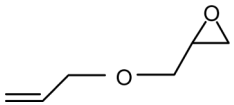
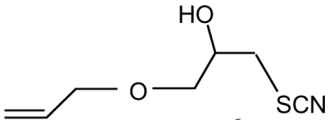
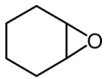
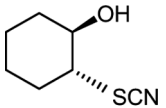
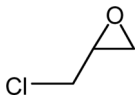
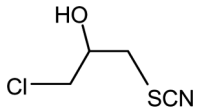
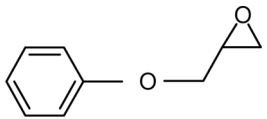
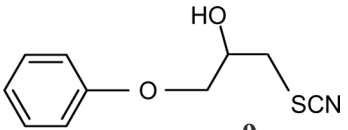
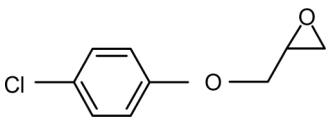
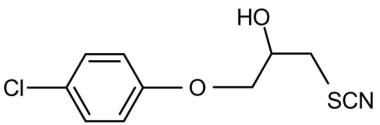
Solvents, reagents, and chemicals were obtained from Merck (Germany) and Fluka (Switzerland) chemical companies. Products are known compounds[14,16,17,22] and were characterized by comparison of their physical or spectral data with those prepared according to literature procedures. Fourier transform–infrared (FT-IR) spectra were recorded on a Perkin-Elmer RXI spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker Avance DRX-500 spectrometer. Thin-layer chromatography (TLC) was carried out on silica-gel 254 analytical sheets obtained from Fluka.

Typical Procedure for the Catalyst-Free Conversion of 1-Chloro-2,3-epoxypropane to 3-Chloro-2-hydroxypropyl Thiocyanate (8)

1-Chloro-2,3-epoxypropane (0.078 ml, 1 mmol) was added to a flask containing NH_4SCN (0.18 g, 2.4 mmol) in refluxing acetonitrile (10 ml). The reflux was continued for 2.5 h until TLC showed the completion of the reaction. After evaporation of solvent, the crude mixture was subjected to short column chromatography on silica gel 60 (0.063–0.200 mm) using petroleum benzine–ethyl acetate (60:1) to give 3-chloro-2-hydroxypropyl thiocyanate **8**, 0.136 g, 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.86 (s, br, 1H), 3.09–3.13 (dd, 1H, $J = 14$, 7 Hz), 3.20–3.24 (dd, 1H, $J = 14$, 5 Hz), 3.68–3.75 (m, 2H), 4.18–4.22 (m, 1H)

Table 2. Catalyst-free conversion of epoxides to β-hydroxy thiocyanates using NH_4SCN (2.4 eq) in refluxing acetonitrile under neutral conditions

Entry	Epoxide	β-Hydroxy Thiocyanate	Time (h)	Yield (%)[a]
1		 **1**	1.5	91
2		 **2**	2.5	95[b]
3		 **3**  **4**	1.25	56 (24)[c,d]
4		 **5**	2	97

5		 **6**	6	96
6		 **7**	2	95
7		 **8**	2.5	90
8		 **9**	1.5	98
9		 **10**	3	97

[a]Isolated yields.

[b]The IR spectra of this product showed two main peaks at 3464 (br) and 2157 (s) cm^{-1} due to OH and SCN groups respectively, and similar to other products of this table.

[c]Yield is based on NMR analysis.

[d]The yield in parentheses is related to 2-hydroxy-2-phenylethyl thiocyanate **4**.

ppm; ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 37.66, 47.59, 70.29, 112.35 ppm; FT-IR (neat): 3435 (br), 2918 (s), 2850 (m), 2157 (s), 1072 (s), 771 (s), 694 (w), 567 (w) cm^{-1}.

Data

2-Hydroxy-3-isopropyloxypropyl Thiocyanate **(5)**

Yield 97%; oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20–1.21 (d, 6H, $J = 6.1$ Hz), 2.83 (br, 1H), 3.10–3.14 (dd, 1H, $J = 13.28$, 7.11 Hz), 3.19–3.22 (dd, 1H, $J = 13.28$, 4.87 Hz), 3.52–3.55 (dd, 1H, $J = 9.5$, 5.3 Hz), 3.58–3.61 (dd, 1H, $J = 9.5$, 4.1 Hz), 3.64–3.69 (m, 1H), 4.08 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 22.34, 37.73, 69.82, 72.98, 73.03, 112.97 ppm; FT-IR (neat): 3446 (br), 2973 (s), 2918 (s), 2872 (s), 2156 (s), 1128 (s), 1092 (s), 925 (w), 822 (w) cm^{-1}.

2-Hydroxytetradecyl Thiocyanate **(1)**

Yield 91%; oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85–0.88 (t, 3H, $J = 7$ Hz), 1.24–1.47 (m, 20H), 1.54–1.58 (m, 2H), 2.29 (br, 1H), 2.89–2.93 (dd, 1H, $J = 13.2$, 8.1 Hz), 3.14–3.17 (dd, 1H, $J = 13.2$, 3.4 Hz), 3.91 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 14.57, 23.12, 25.93, 29.78, 29.84, 29.92, 29.97, 30.06, 30.07, 30.09, 32.35, 36.37, 41.56, 70.72, 113.05 ppm; FT-IR (neat): 3435 (br), 2924 (s), 2853 (s), 2156 (m), 1466 (m), 721 (w) cm^{-1}; mass spectra m/e: 271 (M, 1.5%), 253 (M–H_2O, 1%), 194 (M–H_2O–HSCN, 20%).

2-Hydroxy-1-phenylethyl Thiocyanate **(3)**

Yield 56%; oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.08–4.16 (m, 2H), 4.48–4.51 (t, 1H, $J = 6.8$ Hz), 7.36–7.41 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 55.47, 65.12, 112.00, 128.39, 129.67, 129.75, 136.08 ppm.

3-Allyloxy-2-hydroxypropyl Thiocyanate **(6)**

Yield 96%; oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.07–3.12 (dd, 1H, $J = 13.29$, 7.38 Hz), 3.19–3.23 (dd, 1H, $J = 13.35$, 4.53 Hz), 3.33 (br, 1H), 3.53–3.59 (m, 2H), 4.04-4.05 (d, 2H, $J = 5.7$ Hz), 4.08–4.12 (m, 1H), 5.22–5.25 (d, 1H, $J = 10.37$ Hz), 5.28–5.31 (d, 1H, $J = 17.25$ Hz), 5.86–5.94 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 37.74,

69.48, 71.98, 72.84, 113.19, 118.37, 134.35 ppm; FT-IR (neat): 3448 (br), 3082 (w), 3014 (w), 2918 (s), 2851 (s), 2156 (s), 1647 (w), 1420 (m), 1110 (s), 933 (m), 771 (m) cm^{-1}.

trans-2-Hydroxycyclohexyl Thiocyanate **(7)**

Yield 95%; oil; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.30–1.40 (m, 3H), 1.66–1.74 (m, 1H), 1.81–1.82 (m, 2H), 2.15–2.19 (m, 1H), 2.27–2.29 (m, 1H), 2.93–2.99 (m, 1H), 3.11 (br, 1H), 3.54–3.59 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 24.47, 26.30, 33.27, 35.60, 55.61, 73.08, 111.74 ppm; FT-IR (neat): 3420 (br), 2928 (s), 2857 (s), 2152 (m), 1449 (m), 1069 (m), 958 (m), 770 (w), 719 (w) cm^{-1}.

2-Hydroxy-3-phenoxypropyl Thiocyanate **(9)**

Yield 98%; oil; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.62 (br, 1H), 3.16–3.20 (dd, 1H, $J = 13.8$, 7.0 Hz), 3.27–3.31 (dd, 1H, $J = 13.8$, 4.6 Hz), 4.05–4.10 (m, 2H), 4.31–4.35 (m, 1H), 6.91–7.34 (m, 5H) ppm; FT-IR (neat): 3445 (br), 3062 (w), 3040 (w), 2918 (s), 2849 (m), 2156 (s), 1598 (s), 1588 (s), 1495 (s), 1243 (s), 1045 (m), 755 (s), 691 (m) cm^{-1}.

3-(4-Chlorophenoxy)-2-hydroxypropyl Thiocyanate **(10)**

Yield 97%; oil; FT-IR (neat): 3446 (br), 3103 (w), 3073 (w), 2926 (m), 2877 (w), 2156 (m), 1596 (m), 1582 (w), 1492 (s), 1243 (s), 1040 (m), 824 (m), 669 (w), 508 (w) cm^{-1}.

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