Synthesis of Hydroxyalkyl Isothiocyanates

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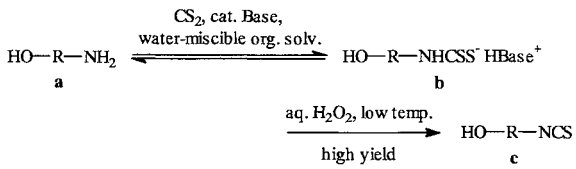
Abstract: Hydroxyalkyl isothiocyanates are prepared in high yields by treating aqueous hydrogen peroxide with a mixture of the corresponding hydroxy primary amine, carbon disulfide, and a catalytic amount of triethylamine, in a water-miscible organic solvent at 0~10 °C.

Naturally occurring and synthetic isothiocyanates are widespread compounds with biological activity. Some alkyl isothiocyanates with a hydroxy substituent are also known to exist in nature,[1,2,3] and thus these isothiocyanates can have interesting biological properties. For example, Drobnica et al.[4] and Carter et al.[5] have reported that the presence of the hydroxy group on phenyl isothiocyanate is important for antimicrobial activity. In our preliminary work, we tried to obtain hydroxyalkyl isothiocyanates by applying the usual methods using thiophosgene[6,7] or chloroethylformate[8] in the reaction, but hydroxyalkyl isothiocyanates could not be obtained in high yields. On the other hand, the use of aqueous hydrogen peroxide as the dehydrosulfurization reagent in the synthesis of alkyl isothiocyanates has also been reported by Johar *et al.*[9] and Schwarze *et al.*[10] However, in our attempt to synthesize hydroxyalkyl isothiocyanates, their methods did not afford those isothiocyanates (see Table 1, entries 20 and 21).

In the course of studies on the synthesis of isothiocyanate compounds, we have found that hydroxyalkyl isothiocyanates **c** can be easily prepared in one pot from hydroxy primary amines **a** and carbon disulfide via hydroxyalkyl dithiocarbamates **b,** using aqueous hydrogen peroxide as the dehydrosulfurization reagent (scheme). The reaction was performed in a water-miscible organic solvent at a controlled low temperature for dehydrosulfurization.



Scheme

In order to find out the best condition for the synthesis of hydroxyalkyl isothiocyanates, reactions under various conditions were closely examined, using 2-(2-hydroxyethoxy)ethylamine as a model compound.[11] The results are summarized in Table 1. In reactions (entries 1~6) with some amines as catalysts, the use of triethylamine gave the best result (entry 1). It should be noted that only a catalytic amount (0.1 equiv.) of base was used in all the experiments due to the fact that too much base present in the reaction mixture decreased the yields via inter- and (or) intra- molecular condensation. On the other hand, when no base was used, the conversion was only 47% (entry 7). The dehydrosulfurization temperature affected the conversions. As the dehydrosulfurization temperature increased from 0~10 °C to 43~45 °C, the corresponding conversion was approximately halved (entries 1, 8, 9, and 10). This tendency seems to result from the instability of the formed hydroxyalkyl isothiocyanates. The solvents, especially water-immiscible solvents, significantly affected the conversions. When a water-immiscible solvent was used, the corresponding conversion was markedly reduced (entries 16, 17, and 19). Finally, when water was used as the reaction medium, the obtained conversion was only 7% (entry 18). Since the solubility of carbon disulfide in water is extremely low, the dithiocarbamation process is far from complete, especially when the base is insufficient in amount. As a result, the interaction between the formed product and the unreacted primary amine becomes significant. In this work, we also tried to make hydroxyalkyl isothiocyanates by applying the methods of Johar *et al.*[9] and Schwarze *et al.*[10], and confirmed that no desired products were produced (entries 20 and 21). This is not surprising since their reaction conditions, especially the high dehydrosulfurization temperatures, are not favorable as we discussed earlier.

Table 1. Conditions for Synthesis of 2-(2-Hydroxyethoxy)ethyl Isothiocyanate.[a]

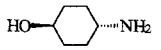
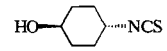
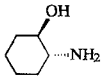
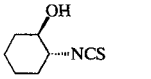
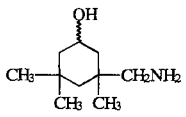
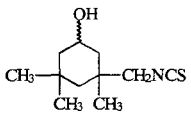
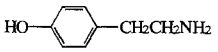
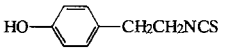
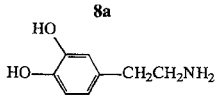
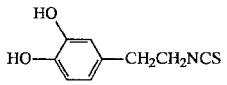
Entry	Solv.	Base	Temp[b] °C	Conversion[c] %
1	THF	NEt_3	0-10	100
2	THF	NPr_3	0-10	88
3	THF	NBu_3	0-10	67
4	THF	Pyridine	0-10	92
5	THF	$(C_2H_5)_4NOH$	0-10	80
6	THF	$(C_2H_5)_2NH$	0-10	94
7	THF	NB[f]	0-10	47
8	THF	NEt_3	26-30	91
9	THF	NEt_3	33-37	68
10	THF	NEt_3	43-45	55
11	1,4-dioxane	NEt_3	0-10	95
12	acetone	NEt_3	0-10	92
13	acetonitrile	NEt_3	0-10	91
14	2-propanol	NEt_3	0-10	90
15	methanol	NEt_3	0-10	83
16	chloroform	NEt_3	0-10	50
17	benzene	NEt_3	0-10	17
18	water	NEt_3	0-10	7
19	n-hexane	NEt_3	0-10	2
20[d]	NS[g]	$(C_2H_5)_2NH$	20-80	0
21[e]	water	NaOH	87-100	0

[a] Present condition (amine/CS_2/base/H_2O_2=1 : 5 : 0.1 : 2.8). [b] Temperature controlled during addition of hydrogen peroxide. [c] Conversion of the amine to the isothiocyanate was determined by HPLC. [d] Condition in Ref. 9 (amine/CS_2/base/H_2O_2=1 : 1.7 : 1.1 : 1, without controlling dehydrosulfurization temp.). [e] Condition in Ref. 10 (amine/CS_2/base/H_2O_2=1 : 1.1 : 1 : 2.8, pH=5~8). [f] NB: no base. [g] NS: no solvent.

We also prepared a series of hydroxyalkyl isothiocyanates, including some new compounds **3c~7c**, **9c**,[12] from the corresponding hydroxy primary amines under the condition (entry 1) at which quantitative conversion of 2-(2-hydroxyethoxy)ethyl isothiocyanate was achieved (Table 2). The yields of products **1c~7c** were obtained at 86~95%. In general, alkyl isothiocyanates, which have the hydroxy group on the β-carbon of the isothiocyanato group, spontaneously cyclize to oxazolidinethiones derivatives.[7,13,14] However, compound **6c** did not cyclize because of steric hindrance of "*trans*" form. 4-Hydroxy- and 3,4-dihydroxy-β-phenylethyl isothiocyanates, derivatives of 2-phenylethyl isothiocyanate that is known to have a strong antifungal activity,[15] were prepared at 93 % and 96 % yields, respectively (**8c**, **9c**).

In this work, we presented a simple and efficient method for the preparation of hydroxyalkyl isothiocyanates, which is characterized by the use of aqueous hydrogen peroxide in a mixture of the corresponding hydroxy primary amines, carbon disulfide, a catalytic amount of triethylamine, and a water-miscible organic solvent at 0~10 °C.

Table 2. Preparation of Hydroxyalkyl Isothiocyanates

Hydroxyalkyl amine	Product[a,b]	Yield[c] (%)
$HO\text{-}(CH_2)_4\text{-}NH_2$ **1a**	$HO\text{-}(CH_2)_4\text{-}NCS$ **1c**	95
$HO\text{-}(CH_2)_5\text{-}NH_2$ **2a**	$HO\text{-}(CH_2)_5\text{-}NCS$ **2c**	95
$HO\text{-}CH_2C(CH_3)_2CH_2\text{-}NH_2$ **3a**	$HO\text{-}CH_2C(CH_3)_2CH_2\text{-}NCS$ **3c**	87
$HO\text{-}CH_2CH_2OCH_2CH_2\text{-}NH_2$ **4a**	$HO\text{-}CH_2CH_2OCH_2CH_2\text{-}NCS$ **4c**	92
 **5a**	 **5c**	86
 **6a**	 **6c**	94
 **7a**[d]	 **7c**[d]	93
 **8a**	 **8c**	93
 **9a**	 **9c**	96

[a] Satisfactory elemental and spectral analyses for **1c~9c** obtained. [b] The products **1c~4c** and **5c~9c** were obtained as oils and solids, respectively. [c] Yields of isolated purified products. [d] mixture of *cis* and *trans*.

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(11) Typical experimental procedure: Carbon disulfide (22.5 ml, 380 mmol) was added to a THF (75 ml) solution containing 2-(2-hydroxyethoxy)ethylamine (8.0 g, 75 mmol), a catalytic amount of triethylamine (0.77g, 7.5 mmol), and the mixture was stirred for 30 minutes at 30-35 °C. After cooling to 0~5°C in an ice-bath, to this solution was added dropwise at controlled temperature 0~10 °C 30% hydrogen peroxide aq. (21.5 ml, 0.21 mol) slowly. As soon as the hydrogen peroxide was added, the solution was acidified with concentrated hydrochloric acid, concentrated, and filtered to remove free sulfur. The filtrate was extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$, concentrated in vacuo to afford a yellow oily residue. Purification was performed by silica-gel column chromatography (ethyl acetate/chloroform 25 : 75) to give a light yellow oil, yield 10.1 g (92%).

(12) **3c**: IR (neat) 2190, 2100 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.43 (s, 2H), 3.41 (s, 2H), 2.1 (s, 1H), 0.95 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 131, 68.4, 52.3, 37.8, 22.0. EIMS (m/z): 145 (M^+). **4c**: IR (neat) 2200, 2120 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.82-3.59 (m, 8H), 2.05 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 133, 72.5, 69.2, 61.7, 45.4. EIMS (m/z): 147 (M^+). **5c**: IR (KBr) 2180, 2100 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.90-3.57 (m, 2H), 2.25-1.81 (m, 5H), 1.69-1.24 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 131, 67.6, 54.6, 31.5, 29.3. EIMS (m/z): 157 (M^+). **6c**: IR (KBr) 2200, 2100 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79-3.35 (m, 2H), 2.83 (s, 1H), 2.22-1.25 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 133, 63.0, 32.8, 31.9, 23.8, 23.5. EIMS (m/z): 157 (M^+). **7c**: IR (KBr) 2190, 2100 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.84 (m,1H), 3.52, 3.48, 3.26 (s, s, s, 2H), 2.01 (s, 1H), 1.82-0.99 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 131, 65.4, 65.0, 59.0, 53.5, 48.4, 48.2, 46.8, 46.5, 44.3, 43.9, 37.8, 37.7, 34.8, 32.3, 32.1, 30.1, 28.1, 27.6, 24.0. EIMS (m/z): 213 (M^+). **9c**: IR (KBr) 2200, 2110 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.78-6.52 (m, 3H), 4.86 (s, 2H), 3.66 (t, 6.8Hz, 2H), 2.80 (t, 6.8Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 146.3, 145.2, 131, 130.4, 121.3, 117.0, 116.5, 47.6, 36.8. EIMS (m/z): 195 (M^+).

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