An Improved Procedure for the Preparation of Isothiocyanates from Primary Amines by Using Hydrogen Peroxide as the Dehydrosulfurization Reagent

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The use of hydrogen peroxide as a dehydrosulfurization reagent in the preparation of alkyl isothiocyanate was first reported by Johar *et al.*[1] in 1970. In their experiments, isothiocyanate was made in one step by reacting hydrogen peroxide with a mixture of primary amine and carbon disulfide in the presence of a secondary aliphatic amine. No heating was required and the total reaction time was less than 10 min. Although it was a simple, rapid, and economical process, the yield was only moderate for aliphatic isothiocyanates and very low for aromatic isothiocyanates. It was also pointed out that this method failed to prepare diisothiocyanates.

It was claimed in 1972 in a German patent[2] that alkyl isothiocyanates could be made in 70−95% yield by reacting hydrogen peroxide with the corresponding primary amines and carbon disulfide in an aqueous solution. Instead of secondary aliphatic amine, NaOH was used as the base. The reaction temperature and the pH of the solution were controlled at 80−120 °C and 5−9, respectively.

These two works, to the best of our knowledge, are the only ones involving hydrogen peroxide in the synthesis of isothiocyanates from primary amines. In our attempts to synthesize hydroxyalkyl isothiocyanates from the corresponding amino alcohols, we found that the methods mentioned above did not result in any desired products.[3] Further, we were unable to reproduce the experiments described in the German patent.[4]

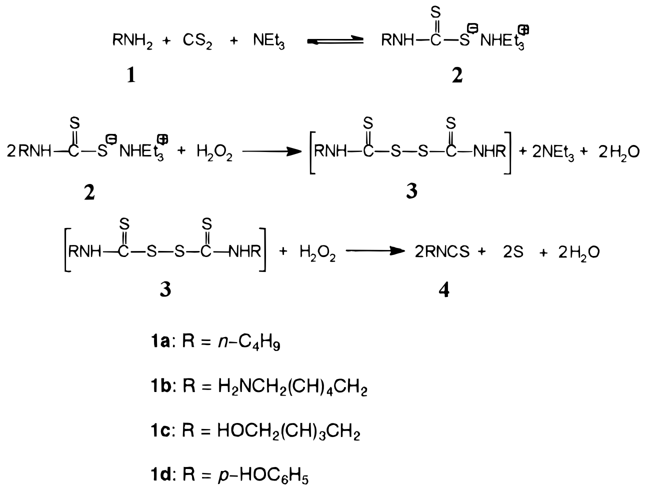
In this paper we will report a modified method that has been proven to be very efficient for the preparation of not only alkyl isothiocyanates, but diisothiocyanates, hydroxyl isothiocyanates, and some aromatic isothiocyanates as well (Table 1). This method consists of the reaction of hydrogen peroxide with a mixture of primary amine, carbon disulfide, and base in an organic solvent that is essentially miscible with water. Excess carbon disulfide is generally required. Various bases, including NaOH, ammonia, triethylamine (TEA), etc., can be used. In preparing hydroxyl isothiocyanates, only a catalytic amount of base should be used in order to minimize the inter- and/or intramolecular condensation. The reaction temperature is generally kept below 15 °C but can be slightly higher in some cases. In any case, reaction temperatures exceeding 50 °C should be avoided.

The isothiocyanation is proposed to pass through thiuram disulfide as shown in the following equations:

Table 1. Preparation of Various Isothiocyanates

starting material	reactant (mmol) amine	CS_2	base	H_2O_2	temp[a] (°C)	product	isolated yield (%)
1a	100	500	100[b]	300	30−40	**4a**	93
1b	57	340	110[b]	340	20−30	**4b**[d]	92
1c	75	360	7.5[c]	210	0−10	**4c**	95
1d	100	100	100[c]	100	0−10	**4d**	84

[a] Dehydrosulfurization temperature. [b] NaOH was used, and the solvent contained 10% of water. [c] Triethylamine was used. [d] R = $SCNCH_2(CH)_4CH_2$.



Thiuram disulfide, despite its very low concentration, is confirmed to exist in the reaction mixture through monitoring the whole reaction process with HPLC. In an independent experiment, hydrogen peroxide is added to a thiuram disulfide solution, and the yield of isothiocyanate is found to be about 90%, which strongly supported our above proposal.

A similar mechanism was mentioned by Giesselmann *et al.* in their review[5] that isothiocyanation passed through thiuram disulfide. It was described, however, that thiuram disulfide decomposed to the corresponding isothiocyanate and H_2S that was subsequently oxidized by hydrogen peroxide to either Na_2SO_4 or $Na_2S_2O_3$ depending on the oxidant amount. Although we also observed that thiuram disulfide slowly decomposed to isothiocyanate when standing at room temperature, it was evident that H_2S did not exist in the system since no black PbS solid was generated when thiuram disulfide was mixed with $Pb(NO_3)_2$ in an aqueous solution. As a result we want to point out here that their proposal seems very unlikely.

Experimental Section

General Procedure for the Preparation of Isothiocyanates 4a−d. To a stirred solution of amine **1** (∼0.1 mol) and base (0.1−2 equiv) in a THF solution (100 mL) was added carbon disulfide (1−5 equiv) with ice cooling. Agitation was continued for 0.5 h followed by dropwise addition of hydrogen peroxide (30%, 1−6 equiv) with the reaction temperature being controlled at 0−40 °C. The reaction mixture was neutralized with hydrochloric acid, evaporated under reduced pressure, and extracted with ethyl acetate. Removing the ester by evaporation under reduced pressure resulted in a yellowish oily residue. Purification was carried out by distillation in vacuo or liquid chromatography on a silica gel column, except as mentioned otherwise.

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[2] Schwarze, W.; Weigert, W. DE 2,105,473, 1971.

[3] Tajima, H.; Li, G. Japanese Patent Application 96-9985, 1996.

[4] Li, G.; Tajima, H.; Ohtani, T. Japanese Patent Application 96-9975, 1996.

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***n*-Butyl isothiocyanate[6] (4a):** obtained as a colorless oil after distillation in vacuo, 93% yield: IR (neat) 2175−2105 cm^{-1}(ν_{NCS}); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (t, 3 H, *J* = 7.4 Hz), 1.39−1.52 (m, 2 H), 1.64−1.74 (m, 2 H), 3.54 (t, 2 H, *J* = 6.5 Hz); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 13.3, 19.8, 31.9, 44.8, 129.9.

1,6-Hexamethylene diisothiocyanate[7] (4b): obtained as a colorless oil after liquid chromatography, using benzene/hexane (1/1) mixed solvent as the eluant, 92% yield: IR (neat) 2190−2100 cm^{-1}(ν_{NCS}); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44−1.52 (m, 4 H), 1.68−1.79 (m, 4 H), 3.56 (t, 4 H, *J* = 6.6 Hz); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 25.8, 29.7, 45.0, 129.8.

5-Isothiocyanato-1-pentanol[3] (4c): obtained as a colorless oil after liquid chromatography, using ethyl acetate/chloroform (5/4) mixed solvent as the eluant, 95% yield: IR (neat) 2190−2100 cm^{-1}(ν_{NCS}); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.43−1.90 (m, 6 H), 2.23 (s, 1 H), 3.55 (t, 2 H, *J* = 6.3 Hz), 3.65 (t, 2 H, *J* = 5.9 Hz); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 22.9, 29.7, 31.7, 45.0, 62.3, 129.3.

***p*-Hydroxyphenyl Isothiocyanate[8] (4d).** The crude product was dissolved in methanol, filtered, and concentrated under reduced pressure. The remaining substance was finally dissolved in dichloromethane, washed with water, dried over anhydrous $MgSO_4$, and recovered by removing the solvent under reduced pressure as a colorless oil:[9] 84% yield; IR (neat) 2174−2120 cm^{-1}(ν_{NCS}); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.1 (br s, 1 H), 6.78−6.82 (m, 2 H), 7.04−7.09 (m, 2 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 116.3, 123.5, 127.1, 133.5, 154.3.

Synthesis of *N*,*N*-Di-*n*-butylthiuram Disulfide (3a).[10] Solid iodine (0.1 mol) was added with stirring to a mixture of **1a** (0.2 mol) and carbon disulfide (0.1 mol) in a methanol solution (10 mL) under ice cooling. The white solid was washed with cold methanol/water (8/2) mixed solvent several times and vacuum dried under ice cooling, yielding 12.4 g (84%) **3a**: mp 53−54 °C dec; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, 6 H, *J* = 7.3 Hz), 1.30−1.44 (m, 4 H), 1.61−1.72 (m, 4 H), 3.70−3.77 (m, 4 H), 8.21 (br s, 2 H); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 13.6, 20.0, 30.1, 46.5, 185.7; EIMS *m*/*z* 296 (M$^+$).

Reaction of *N*,*N*′-Di-*n*-butylthiuram Disulfide (3a) with Hydrogen Peroxide. Hydrogen peroxide (30%, ∼1.5 mL) was added dropwise to a stirred THF solution (40 mL) containing **3a** (2.0 g) and NaOH (0.02 g) under ice cooling. The yield of **4a** determined with HPLC was 1.40 g (90%).

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[9] Only one spot was observed on the TLC plate visualized with iodine vapor.

[10] Rosen, A. A. *J. Am. Chem. Soc.* **1952**, *74*, 2994.