A Mild and Simple Method for the Preparation of Isocyanates from Aliphatic Amines Using Trichloromethyl Chloroformate. Synthesis of an Isocyanate Containing an Activated Disulfide

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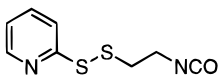
Recently we developed a cross-linking methodology for probing the tertiary structure of RNA and used it to assess the catalytic competence of two different three-dimensional models of the hammerhead ribozyme.[1] During our continued effort toward unravelling tertiary interactions within complex nucleic acid structures, we were interested in the preparation of isocyanate **1** for the site-specific incorporation of an activated thiol into oligonucleotides. We decided to prepare **1** from the corresponding amine, which was readily available in one step from commercially available materials.[2] Preliminary attempts to synthesize **1** using a variety of methods[3−5] were not successful, primarily resulting in complex mixtures of products. It was concluded that the pyridyl disulfide functionality was incompatible with the reaction conditions and a milder method for the preparation of **1** was sought.



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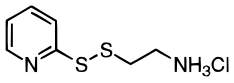

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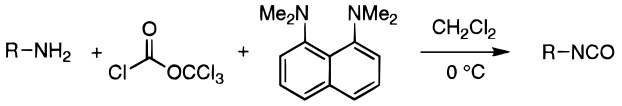
Trichloromethyl chloroformate (diphosgene) has been used for the preparation of aromatic isocyanates from the corresponding amine hydrochlorides.[6] However, this method could not be extended to aliphatic amines, as illustrated by their lack of success in converting 1,6-diaminohexane hydrochloride to its corresponding diisocyanate.[6] We have now established that the reaction of aliphatic amines with diphosgene at 0 °C, in the presence of the non-nucleophilic base 1,8-bis(dimethylamino)-naphthalene, affords isocyanates in good to excellent yields (Scheme 1). Furthermore, the products can be obtained in greater than 95% purity by mere extractive workup of the reaction mixtures, making further purification unnecessary. This is in contrast to most other reported procedures for the preparation of isocyanates which rely on distillation for the purification of products.[7−9] Thus, this procedure enables the preparation of heat-sensitive and/or nonvolatile isocyanates. Additionally, this technique would be useful in the synthesis of isocyanates in small quantities and for generating combinatorial isocyanate libraries. By using this method, 1,6-diisocyanatohexane, benzyl isocyanate, and (*R*)-(+)-methylbenzyl isocyanate were prepared from their corresponding amines in 73%, 78%, and 81% yields, respectively.

Scheme 1. Synthesis of Isocyanates from Aliphatic Amines



For the synthesis of **1**, compound **2** was prepared[2] and partitioned between aqueous NaOH and CH_2Cl_2 to yield the free amine, which partially degraded upon subsequent concentration of the organic phase. Therefore, a solution of the free amine, after extraction, was used directly in the reaction with diphosgene to yield **1**. However, due to the sensitivity of the pyridyl disulfide functionality in **1** toward diphosgene, the general procedure used for the preparation of the aforementioned isocyanates was slightly modified: the amine was reacted with only 0.4 equiv of diphosgene, as opposed to 0.6, and the excess amine present after the reaction was extracted from the solution with 1 N HCl, to prevent the formation of a substituted urea. This modified procedure afforded **1** in 39% yield (based on **2**) which was stable for several days in $CDCl_3$ at 25 °C.

In conclusion, we present a simple procedure for the conversion of aliphatic amines to the corresponding isocyanates. The mildness of the reaction was demonstrated by the successful synthesis of **1** whose application to structural studies of nucleic acids will be reported in due course.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 360.13 and 90.55 MHz, respectively. Chemical shifts are reported in ppm, relative to tetramethylsilane at δ 0.0 ppm. Coupling constants (*J*) are reported in hertz. Reactions were carried out in dry dichloromethane (Merck) with exclusion of moisture. Other chemicals were purchased from Aldrich. The isocyanates, with the exception of **1**, were characterized by comparison to commercially available material (Aldrich) using ^{1}H and ^{13}C NMR spectroscopy.

General Procedure. *Warning: Trichloromethyl chloroformate (diphosgene) and aliphatic isocyanates are toxic and thus should be handled wearing protective clothing in a well-ventilated area.* The procedure is illustrated by the preparation of (*R*)-(+)-methylbenzyl isocyanate. A solution of (*R*)-(+)-methylbenzylamine (0.470 g; 3.88 mmol) and 1,8-bis(dimethylamino)-naphthalene (1.66 g; 7.75 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of trichloromethyl chloroformate (0.460 g; 2.33 mmol) in CH_2Cl_2 (10 mL) at 0 °C over a period of 5 min. The ice bath was then removed and the solution stirred for a further 10 min before evaporation of the volatiles *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 1 N HCl (10 mL), and the organic phase was separated and washed successively with 1 N HCl (3 × 10 mL) and 1 N NaOH (10 mL). After the organic phase was dried (Na_2SO_4), the solvent was removed *in vacuo* to yield (*R*)-(+)-methylbenzyl isocyanate as a pale yellow oil (0.460 g; 81%), whose optical purity was not determined. For the synthesis of 1,6-diisocyanatohexane, the amount of both diphosgene and 1,8-bis(dimethylamino)naphthalene was doubled.

2-Isocyanatoethyl 2-Pyridyl Disulfide (1). *S*-(2-Pyridyldithio)cysteamine hydrochloride (**2**)[2] (0.173 g; 0.775 mmol) was partitioned between CH_2Cl_2 (2 mL) and 1 N NaOH (2 mL), and the organic phase was separated and dried (Na_2SO_4). 1,8-Bis-

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(dimethylamino)naphthalene (0.333 g; 1.55 mmol) was dissolved in the solution containing the amine and the resulting solution added dropwise to a stirred solution of trichloromethyl chloroformate (0.061 g; 0.31 mmol) in CH_2Cl_2 (2 mL) at 0 °C over a period of 1 min. After the solution was stirred for 2 min, 1 N HCl (5 mL) and CH_2Cl_2 (10 mL) was added, the mixture was shaken, and the organic phase was separated and washed successively with 1 N HCl (4 × 5 mL) and 1 N NaOH (1 × 5 mL). After the organic phase was dried (Na_2SO_4), the solvent was removed *in vacuo* to yield **1** as a pale yellow oil (0.064 g; 39% based on **2**) which was ca. 95% pure as determined by ^{1}H NMR analysis. ^{1}H NMR: δ 2.99 (2H, t, J = 6.2, SCH_2), 3.61 (2H, t, J = 6.2, CH_2N), 7.13 (1H, m, ArH), 7.66 (2H, m, ArH), 8.50 (1H, m, ArH). ^{13}C NMR: δ 40.1, 41.6, 120.4, 121.2, 123.7 (broad, NCO), 137.1, 149.8, 159.1. IR: ν 2264 cm^{-1} (NCO). HRMS: 212.0072 (calcd 212.0078 for $C_8H_8N_2OS_2$).

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