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A Commercially Viable Synthesis of Cyanotrimethylsilane

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Abstract:

The important synthetic reagent cyanotrimethylsilane is readily formed by the direct trimethylsilylation of 3 equiv of hydrogen cyanide with 1 equiv each of trimethylchlorosilane and hexamethyldisilazane in a solvent-free reaction. This results in the formation of cyanotrimethylsilane in 98% yield. The product, which comes out of the reactor in 97.5% purity, does not require distillation. The process has been scaled to a level of 1780 lb in a single batch.

Introduction

The potential of cyanotrimethylsilane as a synthetic reagent began to blossom after the report of Evans and coworkers[1] on the facile addition of this reagent to ketones and aldehydes, including many that would not react with hydrogen cyanide, to form the corresponding trimethylsilyl-protected cyanohydrins. This reagent has also been shown to react with acyl chlorides to form acyl nitriles, with metal chlorides to provide metal cyanides, and with various multiple bonds as well as being an excellent source of cyanide in nucleophilic cyanations.[2]

The synthesis of cyanotrimethylsilane has been accomplished by a number of routes. The best among these have employed the reaction of a metal cyanide salt with trimethylchlorosilane. The most economical of these have centered on the cyanides of lithium, sodium, or potassium as the cyanide source. These approaches have resulted in yields ranging from about 50 to 90% with the best among them being the more expensive and "in-situ" generated lithium cyanide or requiring a strong polar solvent such as *N*-methylpyrrolidinone or the presence of a phase transfer catalyst.[2] An additional disadvantage of these existing processes is the difficulty of conducting the syntheses at a commercially viable level. Furthermore, these processes suffer from the generation of solid waste which is normally high in cyanide content and therefore difficult and expensive to handle.

It was clear to us that the commercial future of cyanotrimethylsilane would be dependent on the development of a rapid, clean, high-yield synthesis that would readily lend itself to the production of multiton quantities. On the basis of these requirements, the investigation of the direct trimethylsilylation of hydrogen cyanide to cyanotrimethylsilane was undertaken.

Results

It is well-known that hexamethyldisilazane can be used to silylate a wide variety of active protic groups including alcohols, carboxylic acids, amines, and the like. This silylation is often carried out in the presence of trimethylchlorosilane as a catalyst, with the result being a cleaner, higher yield and shorter reaction time.[3] This is especially true when the material to be silylated is a weak acid such as HCN. DuPont chemists had looked into the direct silylation of HCN as a route to cyanotrimethylsilane, but were able to obtain only a 37.6% yield of the desired product along with ammonium cyanide as the byproduct.[4]

An investigation of the reaction of hexamethyldisilazane with HCN in the presence of a catalytic amount of trimethylchlorosilane did provide the desired cyanotrimethylsilane in better yield than that employing only hexamethyldisilazane, but only in a rather slow reaction and with incomplete conversion. Further consideration, however, indicated that the use of 1 equiv each of trimethylchlorosilane and hexamethyldisilazane with 3 equiv of HCN would provide 3 equiv of cyanotrimethylsilane along with 1 equiv of ammonium chloride. The initial attempts at this approach were to run the reaction in hexane or diethylbenzene as solvent. These reactions provided the desired product in a rather slow but nearly quantitative manner. Separation of the product from the large amounts of solvent in these reactions proved to be a step that would add cost to the process and resulted in yield loss. Moreover, the product has a melting point of 11 °C, making it difficult to distill and condense, especially in large-scale industrial equipment. Therefore, what was deemed most desirable was to be able to run the reaction, filter the ammonium chloride salt, and isolate the product of high purity without distillation. This proved to be the case.[5] Thus, the addition of liquid HCN to a mixture of hexamethyldisilazane and trimethylchlorosilane

$$3\mathrm{HCN} + \mathrm{Me_3SiNHSiMe_3} + \mathrm{Me_3SiCl} \xrightarrow{5-20\ ^\circ\mathrm{C}} 3\mathrm{Me_3SiCN} + \mathrm{NH_4Cl}$$

in the absence of solvent and at a temperature below 20 °C resulted in the immediate formation of ammonium chloride and the clean formation of cyanotrimethylsilane. Filtration of the resulting mixture provided product of 97.5% purity containing small amounts of trimethylchlorosilane and hexamethyldisiloxane. Washing of the salts with hexane was required in the laboratory runs in order to bring the yield to

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the high 90% range. This was not necessary in a pilot run where pressure could be applied to the filter cake to force out the product. If the reaction is run or filtered at temperatures above about 25 °C, a reversal to trimethylchlorosilane, HCN, and ammonia takes place. Warming of the filtered product will produce a small amount of trimethylchlorosilane upon standing due to small amounts of dissolved ammonium chloride reacting with the product.

The cyanotrimethylsilane as generated above was shown to react with ethyl chloroformate to give ethyl cyanoformate, and with benzaldehyde and cyclohexanone to provide the corresponding trimethylsilylated cyanohydrins in a manner equal to that of the distilled material. The process has been scaled to the level of 1780 lb of cyanotrimethylsilane in a single batch.

Experimental Section

A dry 1-L reaction flask equipped with reflux condenser, addition funnel, magnetic stirrer, and nitrogen inlet was charged with 180 g (1.66 mol) of trimethylchlorosilane and 269 g (1.66 mol) of hexamethyldisilazane. The reaction mixture was cooled to 5 °C with an ice bath, and 135 g (5.00 mol) of hydrogen cyanide (HCN) **(CAUTION!)**[6] was added dropwise from the addition funnel over a 30-min period. During the addition of the HCN the temperature of the reaction mixture increased to 15 °C. After the addition was complete, the reaction mixture was stirred for an additional 20 min at 20 °C. The ammonium chloride was filtered under a nitrogen atmosphere. This provided 250 g of product of 97.5% purity. Washing of the ammonium chloride salts with hexane followed by distillation of the hexane produced an additional 198 g of product. The total combined yield was 448 g (98.2% of theory) of 97.5% purity.

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(6) Extreme caution must be used when handling hydrogen cyanide.

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