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A safe production method for acetone cyanohydrin

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ABSTRACT

An easily amenable method is presented to produce acetone cyanohydrin on mole scale (output 39 g/h), using a continuous flow system to overcome the high risks associated with the large-scale use of hydrogen cyanide.

1. Introduction

Acetone cyanohydrin is a widely used source of hydrogen cyanide. Its liquid state allows safe and convenient handling and in contrast to cyanide salts, no acid is needed to liberate the hydrogen cyanide. Given these advantages, acetone cyanohydrin has frequently been used in recent literature as a source of nucleophilic cyanide.[1] Some examples are Strecker syntheses,[2] Appel and Mitsunobu type reactions,[3] Michael additions to unsaturated compounds[4] and the rearrangement of 3-oxo alkenyl esters to acyl diketones.[5] Furthermore, acetone cyanohydrin is an important industrial intermediate in the synthesis of methacrylamide and methacrylates.

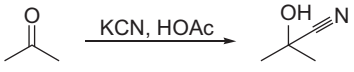
However, despite the importance of this simple molecule, many suppliers have stopped the distribution of acetone cyanohydrin to research laboratories. This presents a major issue for many researchers. Although the synthesis of acetone cyanohydrin is well described in the literature, it mostly involves the generation of one or more equivalents of hydrogen cyanide in the reaction vessel.[6] This poses high risks: in case of spillage or accidental leakage, large amounts of hydrogen cyanide will be liberated into the working environment.

To overcome these problems, closed continuous flow systems in which only minute amounts of hydrogen cyanide are generated, have been reported.[7] These reports however, are mostly situated in patent literature and as such these systems are not readily available to the organic chemist. In this Letter we present a safe synthesis of acetone cyanohydrins (Scheme 1), using a commercially available microreactor system on a scale easily amenable to the standard organic chemical lab.

Microreactor technology is a relatively young field: the first microreactor system was described in a German patent dated 1986. Microreactors offer a myriad of advantages over classical batch processes: miniaturization obviously leads to the use of smaller quantities of materials, providing economical and environmental benefits and easier control of the reactions' safety; flow conditions ensure good mixing of the reagents and strictly respected stoichiometry. Another important convenience of the technology is the increased surface to-volume ratio and the heat-exchange efficiency, which allows better thermal control of the reactions and makes microreactors suitable for exothermic reactions, sometimes even eliminating the need for external cooling and thus decreasing the overall process energy demands. Additionally, thanks to the enhanced temperature distribution, it is also possible to reduce the reaction time under carefully controlled conditions by increasing the temperature while avoiding the formation of side products. The main asset of microreactor technology adding an industrially important significance is its scalability, often mentioned as 'scale-out' instead of 'scale-up'.[8]

2. Results and discussion

In this study, the CYTOS College System, a microreactor manufactured by CPC—Cellular Process Chemistry Systems GmbH, was



Scheme 1. Acetone cyanohydrin synthesis.

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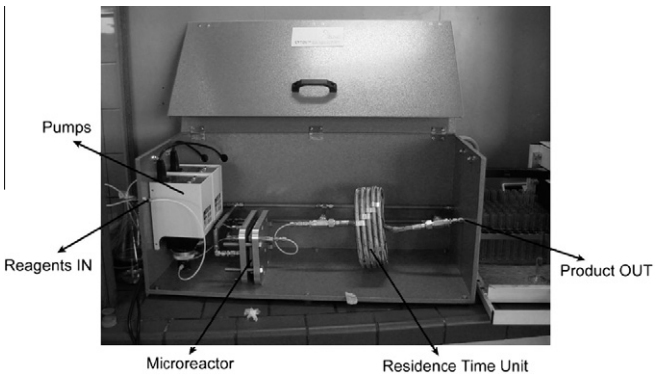

Figure 1. The Cytos College System microreactor.

used (Fig. 1). This device consists of a stacked plate microreactor with an internal volume of 2 ml and a residence time unit (RTU), that is, an insulated tube with an internal volume of 45 ml to increase the reaction time. The microreactor itself has a mixing zone and a reaction zone. Pumping of the reagents through the system is pressure driven.

Inside the microreactor, hydrogen cyanide is generated from two solutions containing potassium cyanide and acetic acid, respectively. Due to limitations on the flow rate through the microreactor system, high concentrations of these reagents are needed to provide an acceptable output. Furthermore, no precipitation of the reagents may occur during the reaction in order to avoid clogging of the microchannels. Combining these two facts, water (and to a lesser extent methanol) is the only viable solvent for potassium cyanide. Acetone is used as the solvent for acetic acid, providing an excess of the electrophile.

With this solvent system, several runs were performed, as depicted in Table 1. The microreactor was allowed to reach steady state conditions by running the reaction for a period representing twice the retention time. Subsequently, a sample of 40 ml was collected and extracted with diethylether, delivering pure acetone cyanohydrin with the indicated yield. For safety reasons, the collection flask is placed under a gentle flow of nitrogen gas, flushing any liberated excess of hydrogen cyanide through two consecutive traps containing a 1 M KOH solution and a 1 M $Na_2S_2O_3$ solution. A first attempt using a 300 ml/h flow for both the acetone and cyanide solution gave quite satisfactory results. A yield of 64% was obtained, delivering a product output of 62.6 g/h.

Lowering the flow rates to 180 ml/h (entry 2) and 90 ml/h (entry 3) to increase the retention time, improved this yield to 71% and 76%, respectively. However, this gain in yield does not justify the considerable drop in output from 62.6 g/h to 41.7 g/h and 22.3 g/h, respectively. Increasing the reaction temperature (entry 4) caused a slight drop of the yield. The condensation of acetone and hydrogen cyanide gas is disfavored at higher temperatures due to an amplification of entropic effects. Lowering the temperature (entry 5) causes an even greater drop in yield. This is accounted for by the lower reaction speed.

When adding 5 mol % LiCl to the aqueous solution as a Lewis acid to activate the acetone, and thereby increasing the reaction rate, a significant drop in yield is observed (entries 7 and 8). This can be attributed to aldol condensation of acetone, which was shown to occur by isolation of the resulting polymeric material.[9] It should be noted that, when using LiCl, the yields drop upon increasing the reaction times. Both acetone cyanohydrin formation and aldol condensation are reversible processes, and as reaction time increases, the thermodynamically more favored aldol condensation takes the upper hand.

The same problem with aldol condensation was encountered when increasing the flow rate of the acetone/acetic acid solution to provide a larger excess of acetone (entry 6). This causes an excess of acetic acid, leading to aldol condensation.

It is however possible to increase the excess of acetone present without altering the equivalents of acetic acid. In runs 9 and 10 the concentration of acetic acid was reduced by a factor two and the flow rate of the acetone/acetic acid solution was doubled. During these runs there is no excess of acetic acid while the acetone over cyanide ratio is increased to 6.3. These conditions do indeed largely improve the product formation. Entry 9 presents a yield of 99% and an output of 39 g/h, a scale which one would hesitate to attempt in a batch. Although this output is somewhat lower than that for entries 1 and 2, only a small amount (1%) of HCN is lost during this reaction, as opposed to 36% and 29% for entries 1 and 2. Therefore, this entry represents a satisfactory method to produce acetone cyanohydrin in a straightforward way.

3. Conclusion

A safe protocol for the mole scale production of acetone cyanohydrin was developed. The synthesis takes advantage of the assets of microreactor technology avoiding the formation of large amounts of hydrogen cyanide. Acetone cyanohydrin is formed quantitatively from potassium cyanide and acetone with an output of 39 g/h.

4. Experimental section

The CYTOS College System, a microreactor manufactured by CPC—Cellular Process Chemistry Systems GmbH. was allowed to reach 30 °C, using the Unistat Tango thermostat. Inlet A was equipped with a 3.8 M (0.25 g/ml) aqueous solution of KCN. Inlet B was equipped with a 1.9 M (0.114 g/ml) solution of acetic acid in acetone. Flowrates were set at 120 ml/h for inlet A and 240 ml/h for inlet B (delivering 456 mmol/h of both acetic acid

Table 1
Optimisation of conditions for acetone cyanohydrin synthesis

Entry	t (°C)	Q_A (ml/h)	Q_B (ml/h)	C_{KCN} (M)	$C_{acetone}$ (M)	C_{HOAc} (M)	Equiv acetone/KCN	Equiv HOAc/KCN	Mol % LiCl	Y (%)	Output (g/h)
1	30	300	300	3.8	10.8	3.8	2.8	1	0	64	62.6
2	30	180	180	3.8	10.8	3.8	2.8	1	0	71	41.7
3	30	90	90	3.8	10.8	3.8	2.8	1	0	76	22.3
4	45	300	300	3.8	10.8	3.8	2.8	1	0	60	58.7
5	5	180	180	3.8	10.8	3.8	2.8	1	0	3	1.8
6	30	150	300	3.8	10.8	3.8	5.6	2	0	3	1.5
7	30	180	180	3.8	10.8	3.8	2.8	1	5	49	28.8
8	30	90	90	3.8	10.8	3.8	2.8	1	5	20	5.9
9	**30**	**120**	**240**	**3.8**	**12.1**	**1.9**	**6.3**	**1**	**0**	**99**	**39.1**
10	30	60	120	3.8	12.1	1.9	6.3	1	0	92	18.0

t: temperature; Q: flowrate (A: KCN/H_2O, B: HOAc/acetone); C: concentration; Y: yield.

and KCN). The reaction was run for 16 min (2.04 τ) after which product collection was started for 6 min 40 s (40 ml). This (aqueous) sample was extracted with diethyl ether and dried using $MgSO_4$. After filtration, the volatiles were removed in vacuo at 30 °C, delivering 98+% pure (by GC-FID analysis) acetone cyanohydrin in 99% yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.004.

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9. The presence of polymers originating from the selfcondensation of acetone was shown by the evaporation of the crude reaction mixture (before extraction). The obtained solids were washed with water to remove LiCl and KOAc salts. Infrared analysis of the residual, non-water soluble solid showed the presence of highly conjugated double bonds (1564 cm^{-1}) and methyl ketone groups (1398 cm^{-1}).