Scale-Up and Safety Evaluation of a Sandmeyer Reaction

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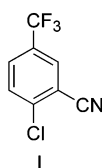
Abstract:

A scale-up of a new process for the production of 2-chloro-5-trifluoromethyl-benzonitrile by a Sandmeyer reaction of 2-Chloro-5-trifluoromethylaniline with copper cyanide/sodium cyanide is described. To ensure a safe implementation, a safety evaluation of the process was carried out, which is described in the following. The new process gives a better working environment and better productivity due to shorter reaction time.
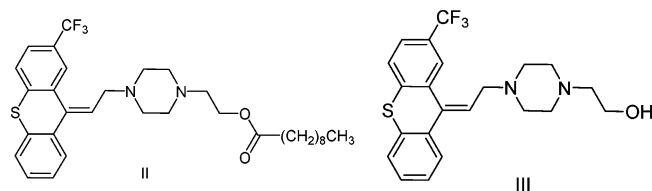
Introduction

During the last two decades, Chemical Production at Lundbeck have produced 2-chloro-5-trifluoromethyl-benzonitrile (**I**) (Scheme 1). The product is a key intermediate

Scheme 1

in the production of the anti-psychotic drugs Fluanxol and Fluanxol Depot (**III** and **II**) (Scheme 2).
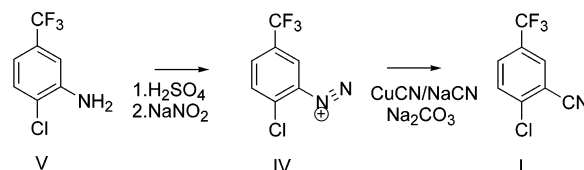
Scheme 2

Recently it was decided to reevaluate the process to develop a procedure suitable for scale-up and moreover to improve the personal safety for the operators performing the reactions.

In connection with the scale-up, a process safety evaluation was performed.

2-Chloro-5-trifluoromethyl-benzonitrile is produced by a Sandmeyer reaction of 2-chloro-5-trifluoromethylaniline (**V**) with sodium nitrite in aqueous sulfuric acid. The formed diazonium salt (**IV**) is then reacted with a mixture of copper-(I) cyanide and sodium cyanide in the presence of sodium carbonate to afford the desired product (Scheme 3).

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Scheme 3. **Formation of 2-chloro-5-trifluoromethyl-benzonitrile**

In the current procedure, developed in the early 1970s, four batches of the diazonium salt solution were produced by mixing **V** (2.0 kg) with ice (4 L) and concentrated sulfuric acid (1.3 L) in an open container (28 L). After stirring for 30 min, sodium nitrite (0.8 kg) dissolved in water was added to the container, which was cooled to −2 to +2 °C by addition of ice. The procedure was performed in a large-scale hood.

The four batches were filtered on a steel nutsche filter, and the combined filtrates were added to sodium carbonate (12 kg), copper cyanide (3.8 kg), and sodium cyanide (3.2 kg) suspended in water (30 L) in a 250-L reactor.

After stirring for 2 h, the heptane was added to the mixture, and the phases were separated. A small volume of interphase emulsion was filtered on a steel nutsche filter and the recovered aqueous phase returned to the heptane phase.

This procedure was repeated five times (giving a total of 10 diazonium batches), and the combined heptane phases were washed with hot water.

After evaporation to dryness the product (**I**) was distilled under reduced pressure.

It took about 5 days to produce one batch to give a yield of 25 kg/week.

Process Scale-Up

A number of issues had to be addressed to scale-up the original process. The main focus was on optimization of the unit operations to ensure a safe overall process.

One of the main scale-up problems with the original process was the filtration of the potentially explosive diazonium salt. The filtration was performed due to problems with an interphase emulsion, but we found that addition of toluene could break the emulsion down. We found that the best procedure was to add toluene prior to the addition of sodium nitrite to practically eliminate the foam formation and thereby avoid its reaching the overhead condenser. Other issues were problems with the formation of NO_x gases and hot spots during the mixing of the sodium nitrite solution with **V**. This problem was solved by addition of the nitrite solution through a dip pipe.

After the diazotation process, the phases were allowed to separate, the toluene phase was discharged, and the water phase (containing the diazonium ions) was further processed.

Table 1. Some general stability features regarding aromatic diazonium ions

destabilising effects of aromatic diazonium ions	stabilising effects on aromatic diazonium ions
(a) oxidizing substituents on the aromatic moiety[5]	(d) sulphate and chloride anions are reported as having stabilizing effects on the diazonium ion[1]
(b) solid aromatic diazonium ions are destabilized by oxidizing anions[5]	(e) the explosive character is diminished by higher molecular weight and large and complex anions (with no oxidizing properties)[5]
(c) electron-withdrawing substituents and potential leaving groups favor elimination leading to a highly reactive benzyne intermediate and possible isomerisation by addition[6]	(f) enhanced stability against nucleophilic attack (i.e. phenol formation in aqueous solution) and electrophilic substitution by electron-withdrawing substituents on the aromatic moiety[5]

This easily enabled scaling-up the diazotation step by a factor of 20, allowing further scale-up if required.

The overall reaction concentration in connection with the diazotation was reduced from 1:13 to 1:6 by using external cooling instead of ice as used in the original procedure.

The aqueous phase was then transferred to a slurry of sodium carbonate, copper cyanide, and sodium cyanide at 80 °C, and after reacting for an additional 2 h the product was extracted with heptane. The subsequent heptane and water phases were separated, and the water phase was removed. A small intermediate heptane/water emulsion was filtered on a steel nutsche filter and the recovered aqueous phase added back to the heptane phase.

The heptane phase was evaporated to dryness and the residue distilled under reduced pressure to give the product.

A further advance of the new revised procedure is that it is now possible to perform the process in conventional production vessels. This is a major improvement in relation to the working environment for the operators performing the process due to the fact that the procedure is now is conducted in closed vessels and not in open containers.

Safety Investigations

Published warnings of the use of diazonium ions are stated on the basis of experience from previous accidents. The incident reports found[1−3] are based on the conclusions that a sensitive diazonium salt precipitates in valves or in a reactor and is hence detonated by friction during cleaning/disposal of the equipment. In a single case a decomposition of dissolved diazonium ion is reported.[4]

The diazonium ion is known to exhibit unstable characteristics that can cause some salts to be explosive. The reactivity of each individual diazonium compound should be investigated to determine their explosive potential.

The main reason for the instability of the diazonium compound lies in the properties of molecular nitrogen, which is an extremely good leaving group. The reactivity of the diazonium compounds is therefore very high, which in many cases leads to impurities forming side reactions during synthesis/handling. More problematic, however, is the propensity for diazonium compounds to undergo rapid decomposition with low activation energy leading to thermal

runaway. Some general features that influence the stability of aromatic diazonium ions are listed in Table 1:

Comparing to the actual case in which 2-chloro-5-trifluoromethyl-benzenediazonium ion (**IV**) is used, we see that the negative counterion is well chosen since the sulphate group is relatively large and non-oxidizing (cf. d and e in Table 1). With both chlorine and the trifluoromethyl group present, there is a possibility of elimination of hydrogen chloride leading to a highly reactive benzyne intermediate followed by a possible addition and isomerization[7] (cf. c in Table 1). This reaction happens in basic environment and is therefore not expected to happen to any greater extent as the diazonium ion is dissolved in aqueous sulfuric acid. By addition to the Sandmeyer solution, which is basic (pH ≈ 11), the benzyne formation can occur, but as it then competes with the Sandmeyer reaction, it is not expected to happen in large proportions.

The lack of electron-donating substituents and the presence of trifluoromethyl group diminishes the affinity towards nucleophilic attack, i.e., the hydrolysis in aqueous solutions yielding phenols and molecular nitrogen (cf. f). This should limit formation of side products.

The above structural analysis of **IV** indicates that the compound is probably not too unstable for scale-up and changed handling. A structural analysis is of course not made to replace physical testing of the materials but merely to achieve some knowledge of what to expect in the physical testing. To ensure that this process was also safe for scale-up, in reality a thorough experimental testing of the synthesis and the relevant compounds was needed.

Thermal Screenings

Equipment: Mettler-Toledo DSC 821e using standard aluminum crucibles (40 μL) and high-pressure gold-plated crucibles (50 μL). Setaram C80 II calorimeter using a high-pressure Hastelloy C276 vessel with pressure transducer.

Results

More than 20 thermal screenings of the diazonium ion were conducted at varying concentrations and ramp rates. Both open and sealed crucibles were used during the DSC

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(2) Urben, P. G. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth Heinemann: Oxford, 1999; Vol. 2, pp 96−97.
(3) Anon.; *Sichere Chemiearbeit* **1993**, *45*, 8.
(4) 6th International Symposium, *Loss Prevention and Safety Promotion in the Process Industries*, Oslo, Norway, June 19−22, 1989; Vol. 2, pp 37.l1−37.l5.
(5) Schank, K., Patai, S., Eds. In *The Chemistry of Diazonium and Diazo Groups;* Part 2: Preparation of Diazonium Groups; Wiley and Sons: New York, 1978; pp 646−647.
(6) Wulfman, D. S., Patai S., Eds. In *The Chemistry of Diazonium and Diazo Groups*; Part 2: Synthetic Applications of Diazonium Ions; Wiley and Sons: New York, 1978; pp 251.
(7) Carey, F. A.; Sundberg R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Part B, p 599.

Table 2. Values of thermal screenings by DSC[a]

sample	heating rate (K/min)	onset (°C)	peak (°C)	energy (J/g)
>10 samples of a 5−9% diazonium ion soln	5−10	>64	>72	<119
		ca. 110	ca. 120	<334
		ca. 170	ca. 175	<357
DSC of ca. 9% diazonium ion soln: oxidized in air 24 h	5	55.1	66.1	105
		159.1	163.3	195
		225.5	234.3	45

[a] First entry reveals the minimum onset and peak values and maximum energy release values measured in more than 10 samples. Every sample was run in both standard aluminum crucibles with pierced lid and sealed high-pressure gold-plated crucibles. Second entry shows the data from the experiment showing the lowest onset. This experiment was run in a standard aluminum crucible with pierced lid.

Table 3. Values of thermal screenings by Setaram C80[a]

sample	ramp and heating rate	onset (°C)	peak (°C)	onset, gas evolution (°C)	energy (J/g)
9% diazonium ion soln	30−100 °C 0.03 °C/min	>63.4	>79.3	>63	<179
5% diazonium ion soln: isothermal study	50 °C 22 h	N.D.	N.D.	N.D.	N.D.
5% diazonium ion soln: isothermal study	45 °C 22 h	N.D.	N.D.	N.D.	N.D.

[a] First entry reveals the minimum onset and peak values and maximum energy release values measured in five experiments. An Antoine plot was made from the pressure data obtained during the experiments to find the onset of gas evolution.

experiments to establish whether a dramatic lowering of the onset was found in either case. No general trend was found, however, apart from the fact that the decomposition of the diazonium ion was very unpredictable in the sense that only in a minority of the DSC-runs was the first onset reported to be below 80 °C.

As seen in Table 2, the decomposition of the diazonium ion is liable to form three distinct peaks in solution. Attempts to crystallize the diazonium salt have thus far been unsuccessful, and all runs have therefore been performed on the reaction mixture with a diazonium ion concentration of 5−9%. Overall the lowest onset is seen at 55.1 °C in a sample that was oxidized in air for 24 h. Attempts to reproduce such low onset by oxidizing other samples were not possible. The overall energy emitted was in the range of ~350−800 J/g.

Since DSC analysis is known to give results with a relative high uncertainty regarding the decomposition onset due to the small sample size and high heating rates, it was important to carry out screening experiments in a larger sample size. This was done in a Setaram C80II equipped with a high-pressure vessel. As seen in Table 3, however, a drop in the decomposition onset was not observed in comparison to the DSC-data—despite the larger sample size (approximately 1 g) and a very low heating rate. During the isothermal study at 50 °C referred to in Table 3, the sample had clearly undergone some degree of decomposition according to the visual inspection after the test (charring of sample), but no thermal effects were measured. At 45 °C, the solution remained yellow as characteristic of the ion.

Concluding the thermal screenings, no thermal effects were monitored by the decomposition happening during the isothermal tests performed at 50 °C in the Setaram C80 (decomposition visually detected on sample after run). The lowest onset measured in C80- and DSC-screenings of samples representative to the process conditions was 63 °C. Applying the usual safety margin of 50 °C to the onset of large-scale thermal screenings in the absence of adiabatic test results, the temperature limit for this process reaches 13 °C. However, on the basis of the 20-year process experience with this reaction and handling of the diazonium solution, it has been decided to set the temperature limit of the diazonium ion solution at 15 °C, which is found reasonable.
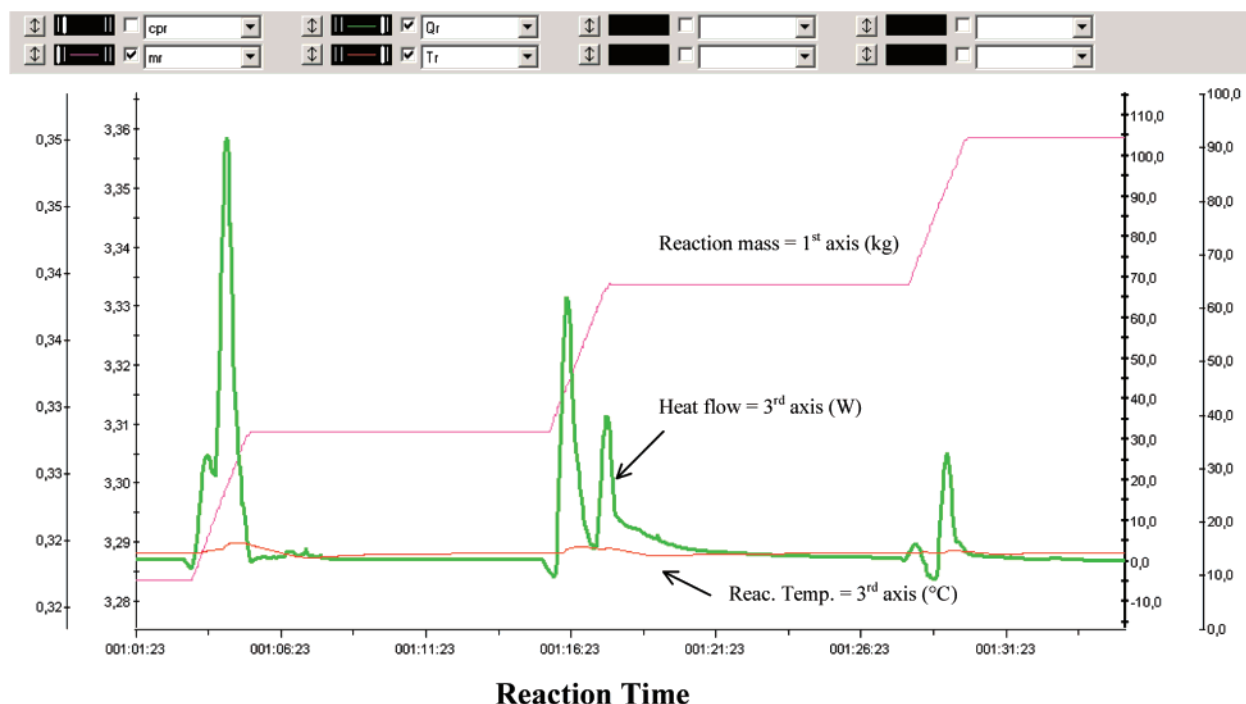
Reaction Calorimetry

To ensure that a scale-up would not result in an uncontrolled temperature rise during the synthesis, which would make it impossible to keep the temperature below the limits, a series of reaction calorimetric tests was performed in a Mettler-Toledo RC-1 system. This was made by performing six independent experiments with three measurements of the diazonium ion synthesis and three measurements of the Sandmeyer reaction. In each of the experiments, measurements on the diazonium salt formation and subsequent Sandmeyer reaction were made using the following procedures.

Equipment. Mettler-Toledo RC-1 reaction calorimeter equipped with a 1-L conical shaped reactor (SV01) with a metal/PTFE cover (MT01) and a custom-made (Fauske), glass-lined paddle stirrer.

Diazotation. After forming the sulphate salt of **V**, the resulting slurry was cooled to 2 °C. To this solution a 44.4% sodium nitrite solution held at ca. 10 °C was added. The resulting solution was divided into three equally sized portions and then added to either heptane (first two portions) or toluene (last portion) and then charged to the SV01-vessel prepared for the following Sandmeyer reaction.

The Sandmeyer Reaction. The Sandmeyer solution (NaCN, CuCN, and sodium carbonate dissolved in water) was heated to 65 or 80 °C (portions 1 and 2 and portion 3,

Figure 1. Reaction calorimetric profile of one of the diazonium ion formations performed in the RC-1. 3rd axis refers to both the heat flow effect and the temperature of the reaction mixture.

Table 4. Results of reaction calorimetric investigations

reaction	heat capacity of reaction mass (J/kg·K)	maximum heat flow (W/L)	heat released (kJ/mol)	ΔT_{AD} (K)
diazonium ion formation (three expts)	3.12−3.39	315 (short-lived)	44−66 (of **V**)	7−9
Sandmeyer reaction (three expts)	3.62−3.99	135	200−280 (of diazonium ion)	9−16

respectively), and to this mixture the diazonium solution was added slowly. After the addition of the diazonium solution, heptane/toluene (portions 1 and 2 and portion 3, respectively) was added, and the mixture in solutions 1 and 2 was then left stirring at 65/80 °C for 2 h. During the course of the experiments, the proposed process changed, and this is the reason for the changes in the procedure.[8]

Results and Discussion of Reaction Calorimetric Data[9]

As seen in Figure 1, the addition of sodium nitrite solution was divided into three portions of equal size to get the best possible idea of any possible accumulation of reactants. Irregularities in the heat flow are due to the fact that only a

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(8) No solvent was added in experiment 3: crude **I** was tapped from the bottom valve after stirring at 65 °C for 2 h.

(9) Reaction Calorimetric Theory: The energy balance of the investigations is made on the basis of the following eq 1:

$$Q_r = Q_{flow} + Q_{accum} + Q_{dose} \qquad (1)$$

where: Q_r = heat of reaction expressed in watts (J/s). Q_{flow} = the heat flow through the jacket of the vessel which equals $U_oA(T_r - T_a)$. T_r is the reaction temperature, T_a is the average jacket temperature, and U_o is the overall heat transfer coefficient, and A is the heat transfer area of the virtual volume of the reaction mass. Q_{accum} = the combined heat flow accumulation of the reaction mass and the inserts. This equals $(m_rCp_r + m_iCp_i)\ dT_r/dt$ where mCp is referring to the mass and heat capacity of the reaction mass (m_rCp_r) and of the inserts (m_iCp_i).

small quantity is dosed (33 g in total), making the mixing less continuous; additionally, a short pump failure is seen during the second addition where the heat flow drops markedly. Despite the irregularities, it is seen in Figure 1 that no accumulation happens to any large extent. Table 4 shows the values measured in both the diazonium ion formation and the Sandmeyer reaction, and it is seen that the diazonium ion formation in general emits a fairly low amount of energy in all three experiments. The adiabatic temperature rise in the three solutions is calculated to be 7−9 K based on the relation (eq 2):

$$\Delta T_{adiabatic} = \Delta H/m\text{Cp} \qquad (2)$$

The peak emission is relatively high with an emission of about 315 W/L. The emission by peak rate is short-lived, though, and the total energy emitted is therefore low.
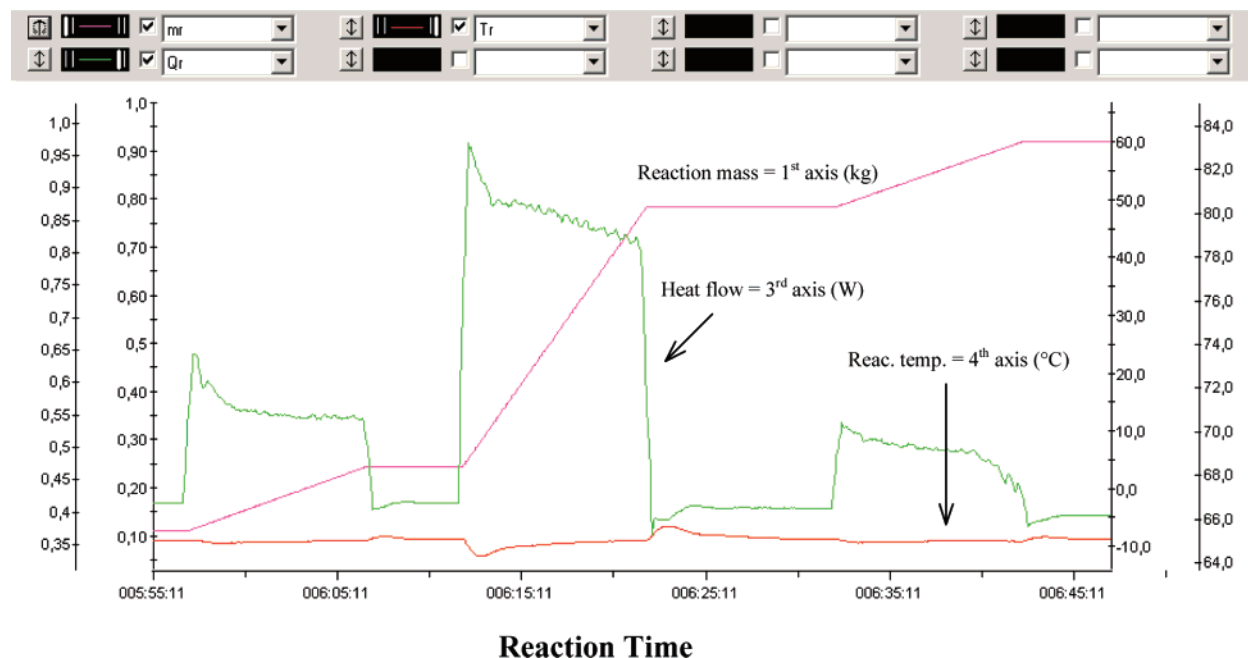
The calorimetric profile of the Sandmeyer reaction is shown in Figure 2. The addition of the diazonium ion solution to the Sandmeyer mixture was divided into three portions of unequal size, and evidently there is no accumulation seen in either of the dosings. By a relatively high dosing rate, the emission of heat is averaged to about 100 W/L with a peak emission of about 135 W/L. Corrections are made to

Reaction Time

Figure 2. Reaction calorimetric profile of one of the Sandmeyer reactions measured in the RC-1.

compensate for the cooling effect coming from the addition of a cold liquid to a warm, but the overall heat flow results in a decrease in the reaction temperature during addition. The combined energy emitted during the Sandmeyer reaction is moderately high (200−280 kJ/mol diazonium ion), but due to the dilution and the high heat capacity of the solution the $\Delta T_{\text{adiabatic}}$ is only 9−16 °C (Table 4).

Provided that precautions are taken against the low onset of the decomposition of the diazonium ion, the data presented does not reveal any serious threat seen from a process safety viewpoint.

Given the unpredictable nature of the diazonium functionality, conservative standards have been set as a frame of the large-scale production of **I**. In this context it should be emphasized that the process temperature must be kept at ca. 2 °C, and that the temperature of any bulk diazonium ion solution never exceeds 15 °C.

Process Implementation

To implement the modified process, we had to take into consideration the potential danger in handling the diazonium salt solution. Due to the hazardous nature of diazonium compounds, the process equipment should be designed and constructed in such a manner that the risk of depositing small amounts of diazonium compound—which may later dry up and thereby become a safety hazard—is reduced to a minimum.

After the formation of the diazonium salt, the solution is transferred to a second reactor containing the slurry of cyanides. To avoid any mechanical stress to the diazonium salt and the risk of having diazonium salt deposits in the pump chambers, the transfer of the diazonium salt solution is performed using vacuum.

All the valves in contact with the diazonium salt solution are diaphragm valves, which—due to their design—eliminate/reduce the risk of depositing diazonium salt in the death lock

of the valve. Also, the number of valves is minimized to further reduce this problem.

After each batch, the valves are inspected to ensure that solids are not deposited in the death lock of the valves.

Conclusions

A scalable Sandmeyer process has been developed. The process is conducted in closed but not pressurized vessels to ensure a better working environment for the operators performing the reaction.

The process has been safety evaluated and proven safe for scale-up.

Due to a much shorter batch time (0.75 days) this new improved procedure is capable of producing 70−90 kg/week.

This procedure is scalable, and we plan to scale up this procedure further by a factor of 10 to about 800 kg/week

Experimental Section

General. All reagents and solvents were obtained from commercial suppliers and used without further purification.

The GC analysis data is reported in area %, not adjusted to weight %.

2-Chloro-5-trifluoromethyl-benzonitrile (1). Water (80 L) and concentrated sulfuric acid (29 kg, 245 mol) are added to a 250-L apparatus. The solution is cooled to <14 °C and 2-chloro-5-trifluoromethylaniline (24 kg, 123 mol) is added, keeping the temperature below 15 °C. After stirring for approximately 30 min, toluene (50 L) is added. After cooling the mixture to 3 °C, a solution of sodium nitrite (9.6 kg, 139 mol) in water (20 L) is added, keeping the temperature below 3 °C.

The reaction mixture is stirred for 45 min, the phases are separated, and the toluene phase is discharged.

The water phase is added to a hot (80 °C) slurry of sodium carbonate (36 kg, 340 mol), copper(I) cyanide (11.3 kg, 402 mol), and sodium cyanide (9.6 kg, 196 mol) in water (87 L)

in a 800-L apparatus. The temperature during the addition is almost constant.

After stirring for 2 h (at 65 °C), heptane (175 L) is added, and the phases are separated. A small volume of interphase emulsion is filtered on a steel nutsche filter, and the recovered aqueous phase is returned to the heptane phase.

The heptane phase is evaporated to dryness and the residue (**I**) is distilled under reduced pressure. Yield: 12.5 kg (50%); bp 94−98 °C (1.3−2.6 Pa). Purity 94.4% by GC (HP Innowax, capillary GC column, 30 m/0.32 mm), nitrogen gas operating at a flow rate of 2 mL/min; inlet temperature 250 °C; column temperature ramped from 100 to 160 °C during 15 min, maintained for 12 min. Retention times: 2-Chloro-5-trifluoromethylaniline 16.1 min, 2-chloro-5-trifluoromethyl-benzonitrile 9.6 min.