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Development of a Process to Prepare 2-Cyanopyrimidine on Commercial Scale

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Abstract. 2-Chloropyrimidine is converted to 2-cyanopyrimidine under very mild conditions in nearly quantitative yield using 1,4-diazabicyclo[2.2.2]octane as catalyst. The development of the process for commercial batch production of 2-cyanopyrimidine regarding processing of the materials in technical equipment, process safety, conservation, economic raw material use and work load is described.

1. Introduction

Within the pharma division of *F. Hoffmann-La Roche*, chemical process development is responsible for developing chemical processes for new molecular entities which are used to produce *Roche*'s clinical drug substance requirements. These chemical processes have to meet stringent requirements to ensure that commercial costs are acceptable and enviromental burdens are minimised. A team of scientists work on this demanding task which consists of an analytical development, a synthesis developing group and a group performing the first scale-up in the pilot plant/mini plant.

The following article highlights features of our work exemplified by the first step of the bosentan (**5**) synthesis (*Scheme 1*), *i.e.* the preparation of 2-cyanopyrimidine (**2**). (Bosentan is developed for the indication of congestive heard failure.)

The construction of the second pyrimidine ring bearing all substituents of the 2,2'-bipyrimidine system follows a classical approach. From **2**, the amidine hydrochloride is prepared which is subsequently reacted with the guaiacolyl dimethyl malonate to form **3.** Conversion of **3** to **4** is achieved by treatment with $POCl_3$. Thus, the system is activated enough to introduce the sulfonamide side chain and the ethylene-glycol moiety sequentially.

For one side chain of the convergent synthesis of **5** we had to develop a batch process to prepare **2** in multipurpose equipment.

2. 2-Cyanopyrimidine – A View of the Chemistry

The nucleophilic displacement at electron-deficient heteroaromatic halides is one of the most important procedures to prepare the corresponding carbonitriles [1][2]. This applies particularly to the synthesis of **2,** because 2-chloropyrimidine (**1**) is available in large quantities. There are in principle two procedures which can be used starting with **1**:

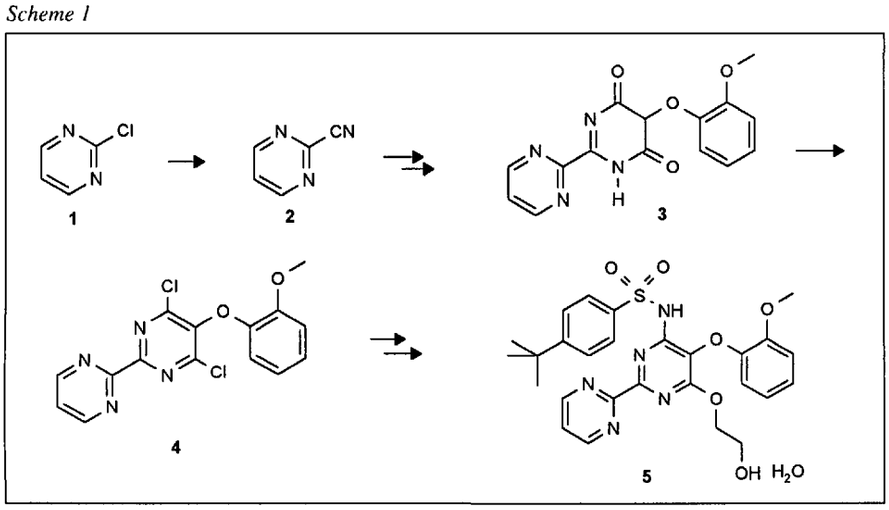
1. Substitution of chloride with an alkali cyanide (use of a tetraalkylammonium cyanide [3] is to expensive) in a polar aprotic solvent. If this procedure is performed with excess NaCN in DMF, at 80–90°, it yields a mixture with a considerable amount of tarry side products. Therefore, a costly and trouble-prone workup procedure follows and the yield of **2** is only 66–70% [4]. The formation of small quantities of 2-(dimethylamino)pyrimidine (identified by GC-MS) reveals that the decomposition of DMF is caused by nucleophilic attack of CN^- [5]. This is an important observation which raises naturally a number of safety concerns.
2. The displacement *via* trimethylpyridin-2-ylammonium chloride (**6**) (*Scheme 2*) avoids the above-mentioned difficulties, because $N(CH_3)_3$ is a better leaving group than chloride, and **2** is obtained in high yield. However, a two-step procedure is required [6].
   The reaction time to obtain **6** is long but a significant reduction is not possible, because at elevated temperature, demethylation of **6** by $N(CH_3)_3$ leads to the unwanted 2-(dimethylamino)pyrimidine [6].

The transformation of **6** to **2** in a two-phase system requires stoichiometric amounts of $N(C_2H_5)_4Cl$. This compound is rather expensive and after workup it stays in the water phase causing an additional problem since $N(C_2H_5)_4Cl$ cannot be degraded by microbiological waste treatment. Therefore, it must be removed from the waste water stream.

Other conditions are reported like using KCN in *N,N*-dimethylacetamide at 80–90° to effectuate the displacement of $N(CH_3)_3$, but the yield of **2** is only 42% [7].

At the end of this two-step procedure, $N(CH_3)_3$ is produced. Hence, it should be possible to combine these steps into one step using $N(CH_3)_3$ in catalytic amounts [8]. Indeed, this experiment works as ex-

Scheme 1



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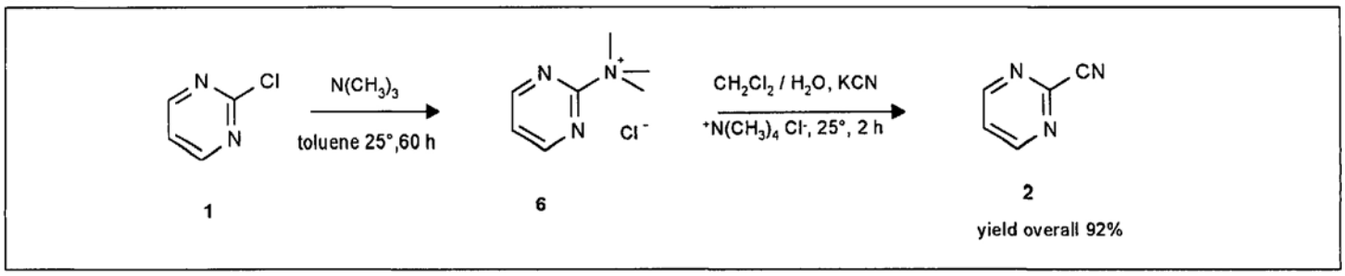
Scheme 2



pected. With DMF as solvent at 25° after 66 h we obtained a yield of 95% by HPLC (*Entry 1* in the *Table*). The strong smell of $N(CH_3)_3$ because of its volatility makes handling on production scale difficult.

For a commercial process it is thus important to look for more convenient N- or P-nucleophiles used as catalysts. The following *Table* sums up our results of a quick screening to primarily find a better catalyst than trimethylamine, in addition, we have tested the reaction in DMF and DMSO (technical grade) and tried to reduce the excess of NaCN.

The results of the *Table* show DABCO [9] and quinuclidine are superior catalysts if reaction time and yields are compared with the other compounds. An excess of NaCN is not necessary and DMSO is the solvent of choice. We used DMSO and DMF in technical grade and the observed differences in reaction time (*Entries 5–7*) can be attributed to the different solubilities of NaCN in DMSO (1.8% *w/w*, 25°) *vs.* DMF (0.11% *w/w*, 25°). Very low conversions are noted with NMM and $N(C_2H_5)_3$ (*Entries 2–4*). Therefore, we prepared the corresponding trialkylpyrimidin-2-ylammonium chlorides [7][11]. With DABCO or quinuclidine **7** and **8** are easily obtained when mixing the amines with **1** in toluene. Immediatly after combining the educts in toluene at 25° cyrstallization of **7** or **8** starts. This is not the case with NMM or $N(C_2H_5)_3$. After 20 h at 25° the toluene solution remains clear and **1** seems to be unchanged (TLC analysis). When the reaction temperature is increased (40°), conversion of **1** is observed but not only to the ammonium salt. It seems that subsequent dealkylation of the intermediate trialkylpyrimidin-2-ylammonium chlorides (*Scheme 3*) plays a major role using these tertiary amines [6][10].

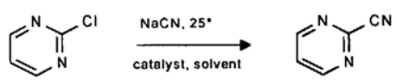
Therefore, NMM or $N(C_2H_5)_3$ are not suitable as catalysts because at 25° the reactivity in respect to **1** is to low, and at increased reaction temperatures, dealkylation of the intermediate ammonium salt results in the loss of catalyst activity.

The P-nucleophiles (*Entries 9* and *10*) show inferior results in both cases. With tris(dimethylamino)phosphane only a part of **1** yields **2** and triphenylphosphane results in a low conversion. These observations have not been further investigated.

We checked another variant of the DABCO-promoted cyanation of **1**, as well. In a two-phase H_2O/CH_2Cl_2 system, we obtained **2** in 78% yield (isolated), however, more than 10% of **1** is hydrolysed to 2-hydroxypyrimidine.

We conclude that the experiment of *Entry 7* serves as a basis developing a commercial process (DABCO is cheaper than quinuclidine). Two possiblities were investigated in depth differing mainly in the method of workup.

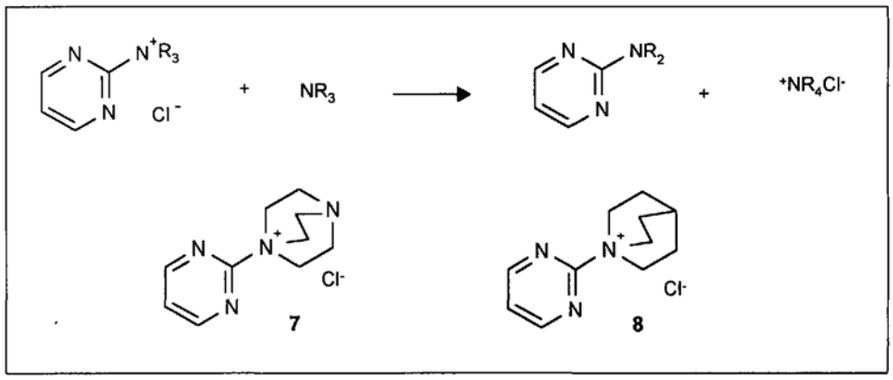
Table



Entry	Catalyst 0.1 equiv.[a])	Amount NaCN (equiv.)[a])	Solvent	Reaction time [h]	**2** [%][d])	**1** [%][d])
1	$N(CH_3)_3$	2	DMF	66	95	<1
2	NMM[b])	2	DMF	48	15	81
3	$N(C_2H_5)_3$	2	DMF	22	16	74
4	$N(C_2H_5)_3$	1.05	DMSO	70	60	23
5	DABCO[c])	2	DMF	6	86	2
6	DABCO	2	DMSO	1.5	87	1
7	DABCO	1.05	DMSO	2.5	91	<1
8	quinuclidine	2	DMF	5	89	<1
9	$P(N(CH_3)_2)_3$	1.05	DMSO	72	27	34
10	$P(C_6H_5)_3$	2.0	DMF	48	13	79

[a]) Stoichiometry ref. to **1**; [b]) *N*-methylmorpholine; [c]) 1,4-diazabicyclo[2.2.2]octane; [d]) yield of **2** and unconverted **1** determined by HPLC.

Scheme 3



Variant 1: Separation of **2** from DMSO and inorganic by-products applying an extractive workup.

Variant 2: Compound **2** is not isolated. Workup operations are kept to the smallest possible number, and we intend to proceed through three chemical transformations starting with **1** and ending up with **3**. This consideration drives the design of the DABCO-catalysed cyanation.

These two processes are discussed side by side under the headings of *Sect. 3* to include process safety aspects.

3. Development of the Processes

3.1. *Mixing the Raw Materials, Reaction Parameters*

A simple mixing of the raw materials (all solids are placed into the reactor and the solvent is added) is not acceptable in our case for two reasons:

1. Due to the high reaction enthalpy and heat flow rates (see *Sect. 3.3*) the reaction can't be controlled on a larger scale because of insufficient cooling capacity.
2. When DMSO is added to NaCN, we observed on bench-scale experiments that a very hard crust is formed perturbing the course of the reaction (incomplete conversion, increased reaction time, reduced yields).

Therefore, in our first variant (the extractive workup) we dissolved NaCN and DABCO in a small volume of H_2O and DMSO and fed to a solution of **1** in DMSO keeping the reaction mixture below 30°. The H_2O content relative to the amount of DMSO is 22% and causes no hydrolysis of **1** during the reaction.

For the second variant (no isolation of **2**) the volume of DMSO is kept as low as possible.The amount of DMSO used has a direct influence on the isolated yield of **3** (**3** is precipitated from a basic H_2O/DMSO mixture by acidification with acetic acid). The presence of H_2O is not acceptable due to the fact the next chemical transformation of **2** to 2-amidinopyrimidine hydrochloride does not proceed. Thus, addition of solid **1** to NaCN and DABCO in DMSO is the preferred variant.

A careful study was necessary to evaluate the influence of the following parameters on the yield of the reaction and usability of crude **2** (in DMSO) for the next chemical steps: how many portions of **1**, the time intervals between the addition of each portion, the starting temperature and temperature range for the reaction.

From a process saftey point of view, continous addition of the solid **1** or dividing the amount of **1** in 4 to 6 portions was desirable (see *Sect. 3.3*). However, a series of bench-scale experiments showed, that 3 equal portions of **1** is best added in time intervals of 15–30 min each, beginning with a temperature of 30° and a temperature range during the reaction of 25–35°. Typical reaction times observed are 3–5 h to meet the intermediate specifications (ratio of **1** to **2** < 3%, applying HPLC analysis).

3.2. *Workup Procedures*

The extractive workup is rather costly because the distribution coefficient of **2** between DMSO/H_2O and technical useful solvents (*tert*-butyl methyl ether (TBME), toluene, different acetic acid esters) is low (*ca.* 3.5). With TBME five extraction steps are necessary to reduce the level of **2** in the DMSO/H_2O phase below 3–4%. After extraction of **2** into TBME, it is not necessary to crystallize the material in order to effectuate the next chemical transformation (in the experimental part we describe the crystallization of **2** from TBME/hexane, as well). The next operation is a solvent exchange to MeOH.

For the second variant, we decided to remove the formed NaCl with the residual NaCN (4–5%), although in principle this is not necessary. However, removal of the remaining NaCN reduces the generation of HCN to very low levels (max. 60 ppm) in the subsequent operations (the analytical development group found a elegant headspace GC method to determine traces of HCN). Another benefit deals with the workup of **3**, *i.e.* requiring a smaller H_2O drown to obtain a clean separation of **3** from the inorganic by-products.

During the reaction NaCl is obtained as a fine solid which makes liquid-solid separation difficult. Therefore, different techniques are tested in the pilot plant. It turns out that centrifugation is the most convenient method. Filtration through a bag filter is very time consuming and therefore not acceptable.

3.3. *Process Data for Thermal Scale-Up and Safety Evaluation*

The optimization defined by chemical process development demands portionwise addition of solid **1** at a reaction temperature of 25–35°. Under these conditions, a first calorimetric measurement [12] was obtained to get the basic information necessary to ensure thermally safe operating in the temperature range. Thus, we measured the reaction enthalpy of the desired reaction in order to obtain the maximum temperature that could be reached in the reaction mixture under adiabatic conditions. This represents the worst-case scenario of total cooling failure during the process.

The addition of the first portion of 50% of solid **1** results in an adiabatic temperature rise of 65°, based on the measured specific heat of the reaction mixture of 1.80 kJ/kg·K, a molar concentration of 1.97 mol/kg reaction mass, and the reaction enthalpy $\Delta_r H = -136$ kJ/mol **1** (exothermic), reduced by the enthalpy of dissolution $\Delta_{sol} H = +18$ kJ/mol **1** (endothermic), to give a net enthalpy in the process of $\Delta H = -118$ kJ/mol.

Theoretical calculations show that the enthalpic driving force of the reaction is due to the high difference in the enthalpies of formation of −323.7 kJ/mol between NaCl and NaCN [17]. This exothermic value overcompensates the estimated endothermic difference of +230 kJ/mol between the enthalpies of formation of **1** and **2** [18][19]. The difference between theoretical and experimental reaction enthalpy may be assigned to uncertainties in the heat-of-formation estimation methods and mainly to the differences in the enthalpies of solution of reagents and products.

With these experimental results it was evident, that the safe upper-limit operating temperature of 60° [13] would be exceeded. Starting with a reaction temperature of 30°, it could result in a final reaction temperature of 95°, possibly initiating an uncontrollable thermal decomposition leading to a dangerous runaway reaction.

The obvious precaution, namely the reduction of the reaction temperature, could not be used, since the reaction becomes too slow below 25°, and consequently the product quality is inferior, which is also the case if the maximum temperature of 35° is exceeded. Given this narrow temperature range, it was evident that the addition of **1** should be done continuously or at least in small portions. Further studies in chemical development group showed that the reaction did not go to completion by applying other addition modes, even in 4 equal portions of 25%. The sequential addition of three equal portions was found to yield the desired result.

Under these conditions, further isothermal calorimetric measurements were performed at different temperatures in the desired temperature range. A typical diagram, representing functions of time, specific heat flow and integrated heat evolution, results in the final reaction enthalpy, which is shown in *Fig. 1*. Depending on the reaction parameters, especially the re-

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action temperature, at certain stages of the addition an endothermic process was observed, which is thought to result from a phase transition or adduct formation of the intermediate salt, which manifests itself visually as a significant change in the viscosity of the solution. The endothermic heat flow is compensated for later in the reaction, so that the total enthalpy of the process is not changed.

After each addition of **1**, the steady state was reached after overshooting the control loop and the heat-flow curve could be described by an exponential decay function of the first order

$$dn/dt = -k_1 \cdot n$$

Introducing a temperature dependence of the *Arrhenius* type

$$k_1 = A \cdot \exp(-E_a/R \cdot T)$$

and using the correlation of heat flow with reaction enthalpy

$$\Delta_r q = -dn/dt \cdot \Delta_r H$$

the following general expression for heat-flow modeling could be established:

$$\Delta_r q = n \cdot \Delta_r H \cdot A \cdot \exp(-E_a/R \cdot T)$$

In this expression, $\Delta_r q$ is the heat flow due to the chemical reaction in J/s, n the mole number of **1**, $\Delta_r H$ the reaction enthalpy (–136 kJ/mol), A the preexponential factor ($1.23 \cdot 10^{+6}$ s^{-1}), E_a the activation energy (53.2 kJ/mol), R the universal gas constant (8.314 kJ/K·mol) and T the absolute temperature of the reaction in K. This model does not represent a correct molecular model of the reaction mechanism, but is rather a *pseudo*-first-order description of the apparent heat flow. At the end of the reaction, heat-flow measurement is not significant enough to detect a continuous change from the *pseudo*-first-order to a second-order process. But the important aspect, for safety and engineering purposes, is in the high heat-flow region at the beginning of addition. This phenomena is well substantiated by the model.

FT-IR measurements [16] were performed simultaneously with the heat-flow measurements. They confirmed the quantitative correlation of the decrease of the specific IR bands of **1** (see *Fig. 2*) with the decrease of the heat-flow signal (see *Fig. 1*). Both curves are a measure of the change of the actual concentration of **1**.

The established model for heat-flow calculations allowed for the quantitative recalculation of the isothermal heat-flow

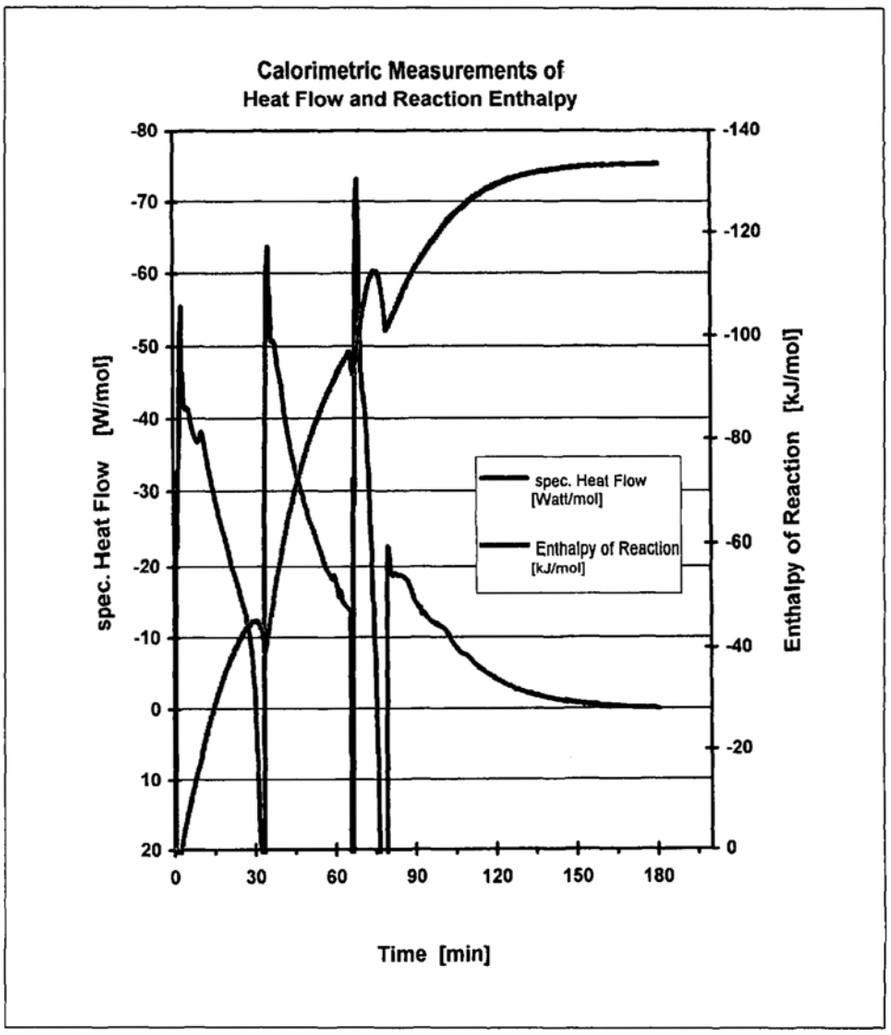

Fig. 1. *Calorimetric measurements of heat flow and reaction enthalpy*

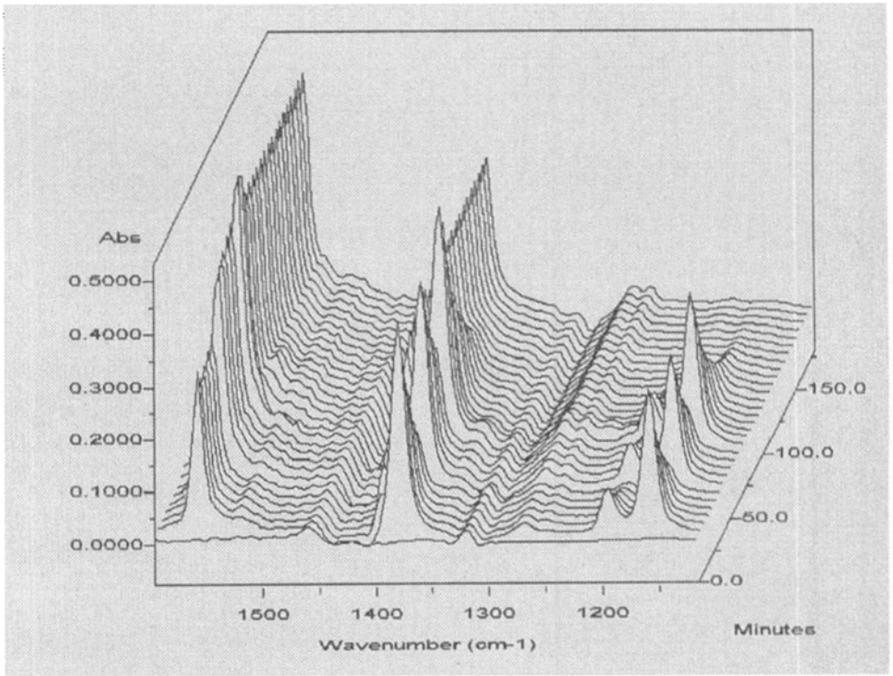

Fig. 2. *FT-IR Diagrams in function of time, showing the disappearance of characteristic bands at 1162 cm^{-1} and 1382 cm^{-1} of* **1**, *added in 3 equal portions in a time interval of 30 min*

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diagrams of the bench-scale experiments at different temperature levels. This was the validity check for the formula to be applied in simulation calculations for the thermal scale-up.

Mass balance, heat balance, some few physical property and apparatus-related data, and the established model were applied in spread sheet calculations. First, the course of the temperature and the concentration profile in the mini-plant production could be confirmed within the rather broad experimental limits of the equipment used at this stage of development [14].

The next step in the thermal scale up seemed to be critical in regard to the equipment available at that time. Estimations of the heat flow at supply production scale and comparison of the heat-removal possibilities in the designated apparatus, based on the cooling curve measurements, showed that this specific apparatus was not suitable for this process. The reaction time and the narrow temperature range needed for the specified product quality could not be realized. Consequently, the apparatus with the best possible heat removal had to be chosen within the time frame of the development work. Simulation calculations for this production plant showed that the heat flow of the reaction was far below the heat-removal limits, hence insuring that the reaction could be completed within the time limits necessary to complete reaction and the required quality of the product, within a narrow temperature range, without endangering the thermal controllability of the process. These simulation calculations have to be confirmed by comparison of the temperature profile as a function of time [15] to the profile calculated from the model (see *Fig. 3*). The agreement between calculated and experimental values is quite good, some deviations after the third addition are due to the fact that the reaction proceeds only to *ca.* 90% completion, whereas the calculation assumes reaction completion.

This kind of development work clearly shows the usefulness of modeling for safety and engineering purposes. Simulation calculations assist in learning about the behaviour of the process during technical and thermal scale up. The applicability of the thermal scale-up calculations was verified for each scale-up step from bench scale to mini plant, to pilot plant and finally to production.

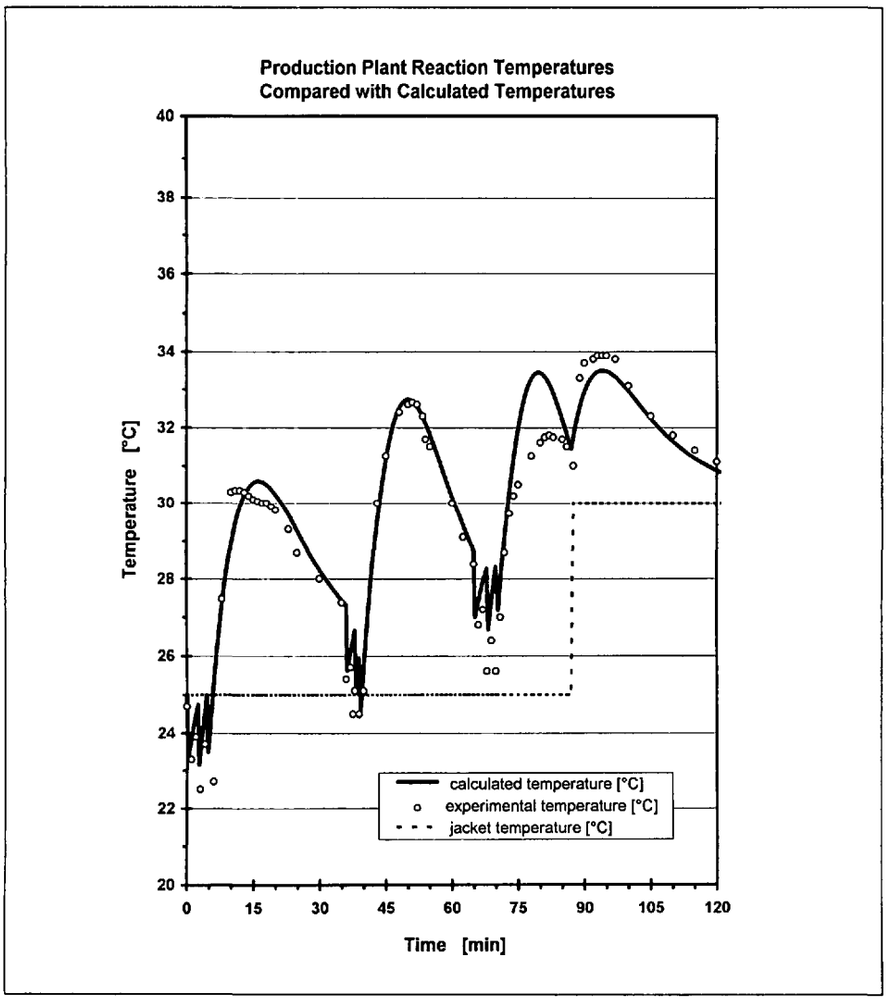

Fig. 3. *Production-plant reaction temperatures compared with calculated temperatures*

3.4. *Waste Streams*

Variant 1 produces a waste water stream containing the residual NaCN and a TBME destillate. The exhaust from the reactor is passed through a scrubber using hypochloride solution to ensure destruction of HCN.

Using *Variant 2* NaCl is contaminated with NaCN as the only generated waste. To dispose of this material, it is dissolved into H_2O and treated with hypochloride solution or hydrogen peroxide to destroy the cyanide.

Generally before an aqueous waste stream is discharged to the waste water plant, its biodegradeability is checked. When the specifications are not met, further treatment is required.

For liquid organic waste streams, solvent recovery is an option or thermal incineration, depending on quantities and the ease of separability of the solvent mixtures. If the pure solvent is removed in a simple destillation (concentration of an extraction layer), it is often possible to use it directly in the next production batch.

3.5. *Conclusion*

Analysing the described operations of the DABCO-catalysed cyanation of **1**, it is obvious that *Variant 2* is the most convenient process in regard to the equipment needed, consumption of raw materials, generation of waste streams, process safety and workload. The subsequent chemical transformations could take place without isolation of **2** and the 2-amidinopyrimidine hydrochloride. Overall yields obtained (**3** based on **1**) are 74–78%. Therefore, *Variant 2* is used for the commercial production.

4. Experimental

4.1. *Preparation of* **2** *(Variant 1)*

Apparatus: A 1500-ml-glas vessel is equiped with a stirrer, a thermometer dipping into the reaction mixture and a dropping funnel. The glass vessel is immersed in a cryostat (*LAUDA RK20*). Further requirements are two 2-l-separatory funnels for the extractions, a rotary evaporator and a vacuum filter.

Reaction: Put 26.25 g (525 mmol) of NaCN and 5.63 g (50 mmol) of DABCO into the glass vessel. Add 60 ml of H_2O and dilute with 30 ml of DMSO (adjust the temp. of the cryostat to 20°). Prepare a soln. of 57.56 g (500 mmol) of **1** in 500 ml of DMSO and place it into the dropping funnel. Add over a period of *ca.* 15 min the soln.

of **1** to the stirred reactor content and keep the temp. below 30°. After completion of addition, rinse the dropping funnel with 60 ml of DMSO and add it to the reaction mixture. After 2 h reaction time, adjust the temp. of the cryostat to 30° and extend the reaction for further 2 h. Withdraw a sample of the reaction mixture and analyse it by HPLC (method is described below). When the ratio of **1** to **2** is < 3% start with workup, otherwise the reaction time is extended for 1 h.

Workup Procedure: Adjust the cryostat to 10°. When the inside temp. is 15°, add slowly (using the dropping funnel) 180 ml of H_2O (max. temp. inside 25°). After dilution with H_2O, adjust the cryostat to 20°, add 250 ml of TBME and stir the mixture *ca.* 10 min. Stop the stirrer, transfer the reactor content into a 2-l-separatory funnel and allow to separate the org. and aq. layer. Separate the lower aq. layer and extract it four times with 200 ml of TBME each (total 800 ml). Combine the org. layers and wash them twice with 80 ml of H_2O (total of 160 ml). Dilute the combined aq. layers (from washing) with 5 ml of brine and extract twice with 50 ml of TBME (total 100 ml). Concentrate the combined org. extracts with an r.v. to *ca.* 100 ml under reduced pressure (bath temp. 30°). Determine the content of **2** by HPLC in the org. and aq. layers (typical result, 96% yield, consisting of 93% in the org. layer and 3% in the aq. layer).

Place the TBME soln. into a glass vessel and dilute with 150 ml of TBME. Add with stirring 350 ml of hexane (technical grade) and seed. Stir the mixture for 8–12 h at 8–10°. Adjust the bath temp. to –20° and stirr for 1 h. Filter the suspension using a vacuum filter and rinse the filter cake twice with 15 ml of precooled (–20°) hexane each (total 30 ml). Dry the crystals in a vacuum drier at 25° (10 mbar for *ca.* 18 h). Reduce the volume of the combined washes and mother liquors to *ca.* 100 ml and take a second crop.

Result of a Representative Run: First crop 38.4 g (content > 99%), yield 73.1%, second crop 6.8 g (content > 99%), yield 12.9 %, total yield 86%. Determination of **2** in the mother liquor corresponds to 7.2%; m.p. 40° ([7]: 41–42°); Anal calc. for $C_5H_3N_3$ (105.1): C 57.14, H 2.88, N 39.98; found: C 56.90, H 2.82, N 39.41.

4.2. *Preparation of* 2 *in DMSO/Propan-2-ol Solution (Variant 2)*

Apparatus: A 500-ml-glas vessel equiped with a stirrer, thermometer dipping into the solution, a powder funnel and a vacuum filter. The glas vessel is immersed into a cyrostat (*LAUDA RK 20*).

Reaction: Place 2.8 g (25 mmol) of DABCO and 75 ml of DMSO into the glas vessel. Adjust the temp. of the cryostat to 30°. With efficient stirring add 12.6 g (250 mmol) of NaCN commercially available. Stir the suspension for 5–10 min and add 9.67 g (83.3 mmol) of **1**. Add the next two portions of **1** (9.67 g each) in time intervals of 15 min each. After addition of the last portion of **1**, stir the mixture for 10 min and adjust the cryostat to 35°. Take a sample for HPLC analysis after 4 h reaction time. When the ratio of **1** to **2** is < 3 % adjust the temp. of the cryostat to 20° (otherwise reaction time is prolonged for 1 h).

Workup procedure: Dilute with 30 ml of propan-2-ol, stir 10–20 min, filter the suspension through a vacuum filter and rinse the filter cake twice with 10 ml of propan-2-ol (total 20 ml). Weigh the DMSO/propan-2-ol soln. and determine the content of **2** by HPLC.

Result of a Representative Run: yield 93%.

Compound **2** in DMSO/propan-2-ol soln. is directly used to prepare 2-amidinopyrimidine hydrochloride.

4.3. *HPLC Method to Determine* 1, 2

Equipment: *Hewlett-Packard* 1050 liquid chromatograph. *Column*: *LiChrospher 60 RP-Select B* (5 µm), 250 x 4 mm (*Merck*); place the column into an oven and adjust the temp. to 40°. *Eluent*: Prepare a mixture of 10 mM KH_2PO_4, 3 mM octyl sodium sulfate, 70%(*v/v*) H_2O and 30% (*v/v*) MeOH. Adjust the pH to 2.45–2.55 with orthophosphoric acid 85%. *Flow rate*: 1.0 ml/min. *Detection wavelength*: 210 nm.

4.4. *Determination of Cyanide by Head-Space Gas Chromatography*

Equipment: *Perkin-Elmer* Autosystem GC coupled with a *Perkin-Elmer HS40* head-space sampler by the mean of a fused silica transfer line. *Column*: *OV1701* 5% cyanopropyl-/7% phenyl-/88% methylsilicon, 1.0 µm df, 50 m x 0.32 mm (*Macherey-Nagel*). Carrier gas: He, linear velocity 40 cm/s (35°, constant pressure). *Oven temp.*: 40° hold for 3 min, then up to 230° with a heating rate of 30°/min. *Detection*: FID at 300°. *Headspace sampler conditions*: Valve, transfer line and injector temp. 110°, transfer line back pressure and vial pressurization 20 PSI; plate temp. 80°, sample equilibration time 7 min, pressurization time 0.5 min, injection time 0.08 min. Acidify the samples by addition of orthophosphoric acid.

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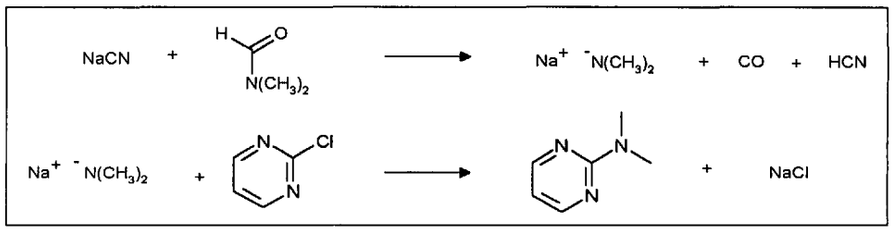
Scheme 4



[1] Access to pyrimidinecarbonitriles: an overview is given in 'The Chemistry of Heterocyclic Compounds' Ed. E.C.Taylor, Vol. 52, 'The Pyrimidines', John Wiley & Sons, New York, 1994, p. 708.

[2] More general: G.P. Ellis, T.M. Romney-Alexander, 'Cyanation of Aromatic Halides', *Chem. Rev.* **1987**, *87*, 779.

[3] K. Hermann, G. Simchen, *Liebigs Ann. Chem.* **1981**, 333.

[4] This is a result from our kilolaboratory campaign and corresponds to the observations reported in the literature (*e.g.* [3]).

[5] R.C. Paul, B.R. Sreenathan, *Indian J. Chem.* **1966**, *4*, 382 (see *Scheme 4*). To control these exothermic side reactions, safety lab recomments a limit for the reaction temperature of 70°, if a such process is used on commercial scale.

[6] Our drug discovery group followed a procedure developed by *Klötzer* who introduced the use of $N(CH_3)_3$ to improve these nucleophilic displacements: W. Klötzer, *Monatsh. Chem.* **1956**, *87*, 131, 526, 536.

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[8] P. Herdewijn, A. Van Aerschot, W. Pfleiderer, *Synthesis* **1989**, 91. This paper reports the transformation of a 2-amino-6-chloropurine derivative to its 2-amino-6-cyanopurine at r.t. in CH_3CN with $N(C_2H_5)_4CN$ promoted by a catal. amount of $N(CH_3)_3$.

[9] J.A. Linn, E.W. McLean, J.L. Kelly describe a successfull application of DABCO in similar displacement reactions '1,4-Diazabicyclo[2.2.2]octane-catalysed Hydrolysis and Alcoholysis Reactions of 2-Amino-9-benzyl-6-chloro-9*H*-purine', *J. Chem. Soc., Chem. Commun.* **1994**, 913.

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[12] Reaction calorimeter RC1, *Mettler-Toledo*, equipped with *SV01* pharma reactor and *ReactIR™1000* (*Applied Systems* FT-IR System, with diamond or ZnS probe); measurements and technical assistance: Mr. *W. Deichtmann* and Ms. *P. Margraff*.

[13] *K. Hofer, R. Panter*, internal communication: results of thermal stability testing in the safety Lab *Roche*, Basel.

[14] *A. Hell*, internal communication: protocol and data registration of mini-plant production.

[15] *G. Schoettel*, internal communication: data registration of supply production.

[16] *P. Hidber*, introducing the FT-IR measuring technique is acknowledged.

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