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FEASIBILITY STUDY OF ORGANIC CHEMICAL SYNTHESIS IN CONTINUOUS FLOW REACTORS

Outline of the Ph.D. thesis

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1. Introduction and aim of my work

In the past decades, applications of eco-friendly technologies are required in the fine chemical and pharmaceutical industry, which are safer and produce fewer by-products and higher yield can be achieved than with the usage of the earlier technologies. Preparation of 1 kg drug results 25-100 kg waste.[1] In the chemical industry the amount of waste and the reduction of the environmental impact are very important. In addition, nowadays the faster and more cost-effective production of molecules has become increasingly important due to the growing costs.
In my PhD work I mostly dealt with the feasibility study of dangerous reaction types in microreactors in the framework of cooperation between Budapest University of Technology and Economics Department of Chemical and Environmental Process Engineering and Sanofi (Chinoin Ltd.) Pharmaceutical company.
In my thesis I dealt with reactions, which Sanofi R&D Chemical Development considered as dangerous. The usage of microreactors corresponds to the previously mentioned requirements and the application of continuous flow technologies afford a fast optimization possibility of the reaction parameters. The use of exothermic reactions and dangerous reactants are safer and better controllable in microreactors, than in batch, because there is only a small amount of material is in the reactor simultaneously.

Taking into consideration the former results of our research group in my thesis I deal with another eco-friendly technology, with the application of ionic liquids (ILs). The ILs have a lot of advantages compared to the molecular solvents. I wanted to study an eco-friendly, selective technology, which is applicable for changing the formerly used molecular solvents.

In my thesis my aim was to study reaction types considered dangerous by Sanofi R&D Chemical Development from a safety point of view. These are not safe as the plant is in a residential area, so the production on industrial scale is very risky.
Due to the several advantages of application of micro-reactors we can reduce safety risk, thereby batch technologies may be replaced by continuous technologies. My aim was to study reaction types developed by Sanofi Chemical Development and in order to examine the reactions better I extended the reactions to the same compound types.

2. Literature background

Nowadays the application of microreactor technology becomes conspicuous due to several advantages not only at an academical level but also in the fine chemical and pharmaceutical industry.

The microreactors (or by another name: continuous flow reactors) have a lot of advantages compared to batch. The scale of continuous flow reactors is less than 1 mm, which is characterized by laminar flow. In batch the mixing takes significantly more time, so in batch micro mixing can occur, which can lead to inhomogenization. As a consequence of the bad heat transfer, local overheat can happen. As opposed to this, micro-reactors have small size ranges, curvy capillaries and the repeated touch of the material with the wall leads to secondary flow. The secondary flow creates high flow rate, which causes rapid and efficient μs mixing.[2]

Due to the unfavourable mixing in batch not only concentration gradient develops, but also the temperature distribution becomes inhomogeneous, so production and selectivity may decrease. In case of microreactors there is a precise temperature maintenance, so in some cases kinetic and

[1] Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chem.* **2004**, *6*, 43.
[2] Jiménez-Gonzalez, C.; Poechlauer, P.; Broxterman, Q. B.; Yang, B. S.; am Ende, D.; Baird, J.; Bertsch, C.; Hannah, R., E.; Dell'Orco, P.; Noorman, H.; Yee, S.; Raintjens, R.; Wells, A.; Massonneau, V.; Manley, J. *Org. Process Res. Dev.*, **2011**, *15*, 900.

thermodynamic product can arise depending on the residence time. The continuous flow reactors can be used within a wide temperature range (-89 - + 350 °C), it is depending on the material of the reactor and varies with manufacturer.

In a microreactor higher pressure than the atmospheric one is easily achievable depending on the material of the microreactor, so it is possible to work at a higher temperature than the boiling point of the solvent. Cooling and heating of reactions are very important, as microreactors have 3-4 times bigger order of surface/volume ratio,[3] than batch, so exothermic reactions are easy to handle in continuous flow reactors. Scaling up of micro-reactors can easily be carried out by making the chips parallel. The flow is achieved by hydrodynamic or electrokinetic technique.[4]

A big advantage of the continuous flow reactors is that the reaction parameters can be changed easily and fast, because the different parameters (T, p, c, q) are studied quickly and the examination can be programmed by a computer (Design of Experiment).[5] A main aspect of microreactors is that during the reaction no blockages can happen, so the homogenity of the reaction is important.

3. Results

During my PhD thesis my aim was to study reaction types considered dangerous by Sanofi R&D Chemical Development from a safety point of view. These are not safe as the plant is in a residential area, so the production on industrial scale is very risky. Application of microreactors at the following reaction types reduce the safety risk because of the previously mentioned advantages. Firstly I examined the reaction types at Sanofi Chemical Development and in order to have a better understanding about the reactions, I extended the reaction to the studied compounds. Firstly, the aim was to examine of the homogeneity in batch and after that I changed to the usage of microreactors. During my PhD thesis I used mainly two types of reactors: Labtrix® S1 reactor (10µL), which is mainly meant for the production of analytical samples, and the Corning LF reactor (0,45 mL/chip), which is applicable for the production of gram scale products. In a few cases I used the Corning AF (8 mL/ chip) and the X-Cube Flash reactors (16 mL). In the last part of my thesis I examined the amidoxim production regarding the earlier results of the Chemical Development Researching group, taking into consideration another eco-friendly technology: the ionic liquid. I tried to achieve (with the usage of ionic liquid) a selective technology which means less danger for the environment. With the usage of this technology the molecular solvents could be changed.

The information regarding chemical reactions, each reaction type are at the beginning of each part separately, to make them understandable.

3.1 Mitsunobu reaction

3.1.1 Literature background

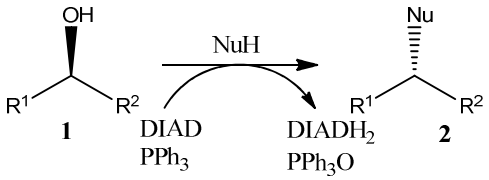
The Mitsunobu reaction plays an important role in the pharmaceutical industry, as it could be the key step at the production of a molecule. During the reaction C-O, C-N, C-S, C-C bonds can be created with a dialkyl azodicarboxylate (mostly diisopropyl azodicarboxylate (DIAD), or diethyl azodicarboxylate (DEAD)) trialkyl-, or triarylphosphine, (mostly triphenylphosphine (TPP)) with redox system.

Azodicarboxylates are explosive materials. During my thesis I used diisopropyl azodicarboxilate

[3] Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K. G. *Org. Process Res. Dev.* **2001**, *5*, 652.
[4] McDonald, J. C.; Duffy, D. C.; Anderson, J. R.; Chiu, D. T.; Wu, H. K.; Schueller, O. J. A.; Whitesides, G. M. *Electrophoresis* **2000**, *21*, 27.
[5] Kockmann, N.; Gottsponer, M.; Zimmermann, B.; Roberge, D. M. *Chem. Eur. J.* **2008**, *14*, 7470.

(DIAD) which is a less explosive compound. [6]

During the reaction from TPP arose triphenylphosphine oxide (TPPO), from azodicarboxylate arose (AD) hydrazinedicarboxylate (ADH_2) (**Scheme 1**).



Scheme 1: Mitsunobu reaction

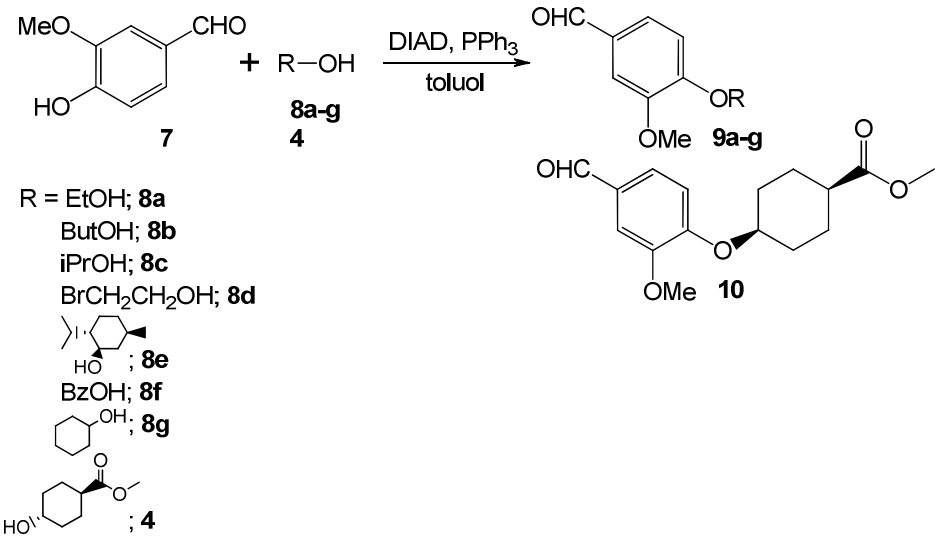
The expected products can be reached by the reaction of mostly primary or secundary alcohols and nucleophile (Nu) reagents contain a relative acid group (-OH, -SH, -NH, -CH). The pKa value of those groups should be less than 15, but rather less than 11. The reaction is carried out between 0-25 °C, but it is usually carried out at a lower temperature -10 - -20 °C with long reaction time (1-72h) in toluene, DMF, ACN, diethylether, THF DKM or in 1,4 dioxane solvent under inert circumstances. In reagents containing acid proton. The reaction is always carried out with inversion in case of chiral secundary alcohols. The nucleophile the literature two patents can be found, based on those the Mitsunobu reaction was carried out at a higher (50-60°C) temperature.[7, 8]

3.1.2 Results

At Sanofi Chemical Development the Mitsunobu reaction seemed to be the critical step from a safety point of view at the creation of a potential drug. After the optimization of the reaction in batch I examined the parameter dependency of the reaction, and I scaled up the reaction from 10 µL to 4,5 mL. During my work I carried out the production of a ca. 300g resynthesis batch (76,5%) for toxicology studies in microreactor, which was the first process in the history of Chinoin. Making this reaction in a conventional reactor this was 84% during a significant shorter period. Conducting the reaction in a continuous flow reactor would be better from a safety point of view because of the high exothermicity.

I extended the Mitsunobu reactions to different alific and aromatic alcohol derivatives. I carried out these reactions in Labtrix® S1 microreactor and in a vial similar to the reaction parameters of the earlier molecules and I also worked with the TPP-DIAD redox system. I chose as basic molecule: vanillin and I added the chosen alcohol derivatives (**Scheme 2**).

[6] Urben, P. G.; Bretherick, L. *Bretherick's handbook of reactive chemical hazards.* 6th Edition, Oxford: Butterworth-Heinemann. **1999**.
[7] Glaxo patent, WO2010/023170, **2010**.
[8] Glaxo patent, WO2010/018231, **2010**.



Scheme 2: Mitsunobu reaction of alcohol derivatives with vanillin

I summarized the results of the reactions with alcohol derivatives in **Table 1**. It is clearly noticeable that I received similar results in batch and in the microreactor. With alcohol **8a-8d** I received perfect conversion, while in the case of L-menthol (**8e**) assumingly due to a steric barrier I reached medium conversion (**9e**, 56 and 59%). Almost full conversion was reached at benzilic and **4** trans-**4** hydroxycyclohexanecarbonicacid methylesther reaction, while the expected **9g** product arose in case of **8g** cyclohexanol in microreactor 70,5% and in batch in 76%.

Sor	Alkohol-származék	Batch (%) 50 °C, 30 min	µreaktor (%) 50 °C, 60s
1	**8a**	97	100[a]
2	**8b**	97	96
3	**8c**	94	97
4	**8d**	97	94
5	**8e**	56	59
6	**8f**	98	93,5
7	**8g**	76	70,5[b]
8	**4**	92	88[c]

[a]30s; [b]120s, 100 °C; [c]120s

Table 1: Mitsunobu reaction with vanillin (1,1 eq. TPP-DIAD; 1,1 eq. 8a-8g, 4)

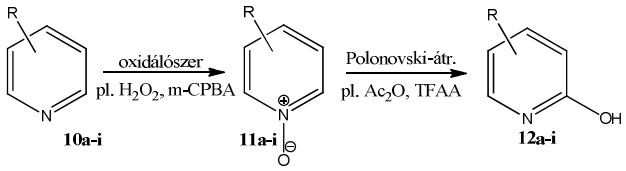
3.2 Production of N-oxid

3.2.1 Literature background

The production of *N*-oxide is a frequent reaction in the chemical industry. Many drugs contain *N*-oxide type moleculepart, or they contain further arranged heterocyclic compound from *N*-oxide with Polonovski rearrangement. The production of molecules containing *N*-oxide is important as drugs contain tertiary amine metabolise to *N*-oxide in the human organism. So their synthesis during medicine-development to methabolstudies is necessary in all medicines containing tertiary amine.[9] The aromatic substitution reactions of pyridine could carry out under harsh circumstances. During this reaction *meta* substituted products arose, while during *N*-oxide reactions mainly the *ortho* substituted products are preferred but *para* isomers can be yielded, too. After this the oxide can be easily reduced with the usage of PCl_3, [10, 11] PPh_3, [12] Raney Ni/H_2 or Pd/C,[13] Fe/AcOH, [14]

[9] Bickel, M. H. *Xenobiotica* **1971**, *1*, 313.
[10] Ochiai, E. *J. Org. Chem.*, **1953**, *18*, 534.

Zn/watery NH_4Cl,[15] $NaBH_4/AlCl_3$,[16] NH_4COOH-Pd/C ,[17] $TiCl_3$,[18] AlI_3 [19]. So it is possible to receive the pyridine *ortho* and *para* substituted derivatives. A further meaning of the *N*-oxide compounds is that they can react next to Polonovski rearrangement to 2-hydroxypyridine derivatives with trifluoroaceticacid anhydride (TFAA), or with aceticacid anhydride (Ac_2O) at a high temperature. [20, 21] (**Scheme 3**)



Scheme 3: Preparation of aromatic *N*-oxide, and the 2-hydroxy-pyridinederivative formation with Polonovski rearrangemnet

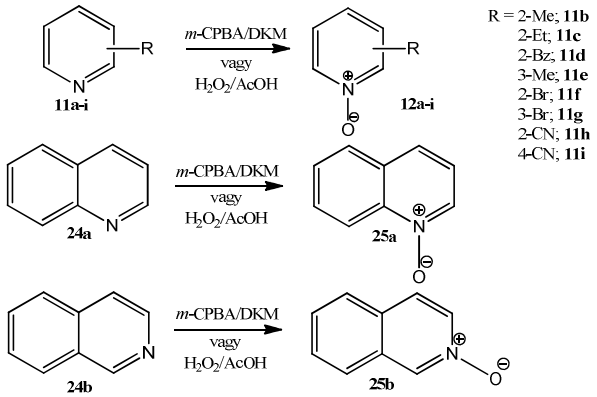
In my thesis I used two oxidants: *m*-chloro-perbenzoicacid (m-CPBA) and the 27% water solution of H_2O_2. The *N*-heterocyclical compounds don't react clearly with the hydrogen peroxide. They create *in situ* peracid if we add acid. The peracid is already a reactive compound which is easy to handle. Metals: for example osmium, palladium, platinum, iridium, gold, silver, manganese, cobalt, copper, plummet and their salts catalyse the exotherm decomposition.[22] The microreactor contains metal, so its usage can make the handling of peroxide reactions easy.

3.2.2 Results

Because of the high price of a potential drug, the company's own manufacturing occured at Sanofi Chemical Development. A critical step for it is the *N*-oxidation, which is not preferred because of safety concerns. I examined the reaction in two ways (normal and inverse reaction route) with *m*-CPBA and H_2O_2/aceticacid oxidants. In case of the *m*-CPBA both in batch (**17** 80, and **20** 85%) and in microreactor (**17** 82, and **20** 85%) I reached similar conversion with both reaction routes, because the reaction rate is fast, so except the safety there is no other benefits of the microreactor. I examined the reactions with H_2O_2/acetic acid oxidants, but in this case based on the HPLC-MS the methylesther hydrolyzed to acid (**22** and **23**), the product could not be demonstrated in the mixture, consequently I haven't studied this reaction route any more.

The reactions were extended to different pyridine derivatives, quinoline and isoquinoline (**Scheme 4**).

[11] Howard, E. Jr.; Olszewski, W. F. *J. Am. Chem. Soc.* **1959**, *81*, 1483.
[12] Sanz, R.; Escribano, J.; Fernández, Y.; Aguado, R.; Pedrosa, M. R.; Arnáiz, F. J. Synlett **2005**, *9*, 1389.
[13] Katritzky, A. R.; Monro, A. M. *J. Chem. Soc.* **1958**, 1263.
[14] Essery, J. M.; Schofield, K. *J. Chem. Soc.* **1960**, 4953.
[15] Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, 891.
[16] Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 2582.
[17] Balicki, R. *Synthesis* **1989**, 645.
[18] McCall, J. M.; Tenbrink, R. E. *Synthesis* **1975**, 335.
[19] Konwar, D.; Boruah, R. C.; Sandhu, J. S. *Synthesis* **1990**, 337.
[20] Cavé, C.; Kan-Fan, C.; Potier, P.; Le Men, J. *Tetrahedron*, **1967**, *23*, 4681.
[21] Nagano, H; Nawata, Y.; Hamana, M. *Chem. Pharm. Bull*. **1987**, *135*, 4068.
[22] Urben, P. G.; Bretherick, L. *Bretherick's handbook of reactive chemical hazards.* 6th Edition, Oxford: Butterworth-Heinemann. **1999**.



Scheme 4: *N*-oxidation of pyridine derivatives, quinoline and isoquinoline

The optimization of the reaction was carried out with **11a** pyridine in Corning LF reactor with both oxidants. I examined the further derivatives at the optimal reaction circumstances. The optimal excesses were:

in case of *m*-CBPA 50°C, 3 minutes residence time, 1,1 eq. oxidant

– in case of hydrogen peroxide 130°C, 30 minutes residence time, 7 eq. oxidant.

Similarly to **20** potential drugs, the result of the fast reaction rate is that the microreactor doesn't have big advantages (which appear in conversion as well) compared to the conventional reactor, but it is a safer process compared to batch.

The peraceticacid can explode at 110°C, [23] so working with peroxide in batch was carried out at a lower temperature. *Ochiai E. and colleagues* conducted *N*-oxidization at 70°C, so I also produced different *N*-oxide derivatives at this temperature. [24] I reached 2-41% conversion in batch, and 15-100% conversion in microreactor at this temperature.

The *N*-oxide Polonovski rearrangement of pyridine **12a** was carried out with the addition of Ac_2O in microreactor: at 170°C, 43% conversion, in vial: at 130°C, 33% conversion during 30 minutes with ^1H NMR.

I haven't optimalized the reaction, I just wanted to find out if the Polonovski rearrangement is possible in microreactor. As the pump has only 2 streams, I did the two steps one after the other

3.3 Hydroboration

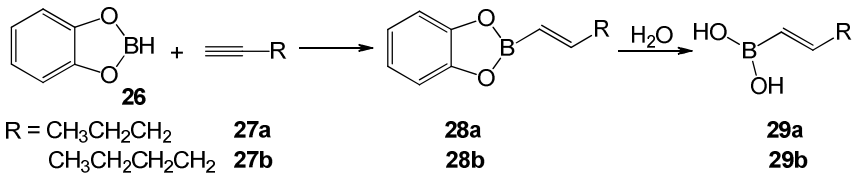
3.3.1 Literature background

Hydroboration is a slow reaction, mainly in the presence of solvents, so for the preparation of alkenyl boronicacid derivatives harsh circumstances should be used.[25] In general the solvent free medium and higher temperature are in favour of the reaction.[26] The production of certain derivatives at high temperature is not possible on atmospheric pressure because of the boiling point of the acetylene derivatives. Therefore in some cases the hydroboration is accelerated by chatalysers.[27]

[23] Urben, P. G.; Bretherick, L. *Bretherick's handbook of reactive chemical hazards.* 6th Edition, Oxford: Butterworth-Heinemann. **1999**.
[24] Ochiai, E. *J. Org. Chem.*, **1953**, *18*, 534.
[25] Ramachandran, P. V.; Chandra, J. S. *e-Eros Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, **2005.**
[26] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.*, **1975**, *97*, 5249.
[27] Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K., *Synth. Commun.* **1995**, *25*, 1957.

3.3.2 Results

During my work I examined the feasibility of hydroboration reactions in microreactor. I reacted catecholborane with alkyne (**27**), so I received alkenyl catecholborane **28**. Hydrolizing **29** this alkenilboronic acid derivatives can be received, which could be the start up material for Suzuki coupling (**Scheme 5**)



Scheme 5: Alkenylboronic acid production

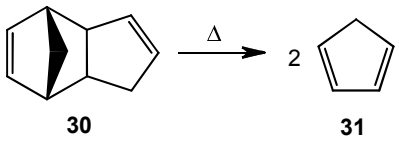
I successfully produced pentenyl- (**28a**) and hexenylcatecholborane (**28b**) in microreactor with full conversion during 1 minute, with 1,2 eq. alkyne excess at 60°C on 2,7 bar pressure. The content of the mixture was determined with the help of ^{13}C NMR.

Catecholborane (**26**) decomposes in the presence of a little water, there is a regular failure at the piston pumps and the inertization is difficult. Due to this problem in order to implement the reaction in the future, piston pumps should be changed to pressureproof syringe pumps. I had no chance at Sanofi Chemical Development to do this, so I couldn't conduct any further examination of the reactions.

3.4 Preparation of cyclopentadiene from dicyclopentadiene

3.4.1 Literature background

The basic material of the Corey prostaglandin-creation is the cyclopentadiene (CPD, **31**), which is created from dicyclopentadiene (DCPD, **30**) with monomerization **(Scheme 6)**. At monomerization DCPD is dropped into 195 °C oil, and the main fraction is condensated for cooling at -20°C. The main fraction contains 97% of the product and it is worth reacting further immediately, as it polymerizes quickly. A not good quality CPD cannot be monomerized again, as with heat it dimerizates, which can lead to explosion as a consequence of sudden boiling.[28]



Scheme 6: Monomerization from DCPD (**30**) to CPD (**31**)

3.4.2 Results

Together with Sanofi PG Development I wanted to work out a technology for the monomerization of compound 30 where I could more economically and easily create the expected molecule than in the previous process.

Forming CPD in Labtrix® S1 reactor at 200°C was only possible with weak (22%) conversion, so for increasing the temperature (300°C) I used the Thalesnano X-Cube Flash reactor.

[28] PG Üzletág - *BP-1 Üzemkísérleti előirat*

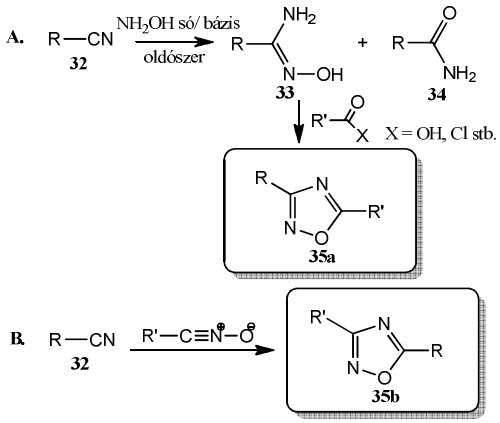
At 300 °C, with a 10-minute residence time, at 100 bar pressure, I created **31** from 5 % solution of DCPD based on GC with 93 % conversion. As the reaction mixture was too diluted, I wanted to concentrate the mixture to 25%, but in this case the CDP (assumingly due to the material of the reactor, which was metal) polymerized and the reactor was blocked. I couldn't conduct further experiments, but it was certain, that the increase of temperature has a good effect on the conversion, but the material of the reactor is critical. So furthermore at such high temperature the presence of metal should be avoided. Assumingly the reaction could be feasible in a metal free reactor at 300-350°C.

3.5 Preparation of amidoxime in microreactor

3.5.1 Literature background

The amidoxime molecules are important elements and intermediers of several heterocyclical compounds [29], among them many drugs can be found: 1,2,4-oxadiazole [30, 31, 32, 33] and types of amide.[34,35,36] In this case the amidoxime is turned into the expected amidine with transfer hydrogenation.

Several production methods of 1,2,4-oxadiazoles (**35**) are known in the literature, [37, 38, 39, 40, 41, 42, 43] but mostly hydroxylamine (which is *in situ* liberated from its salt with the help of base) is additioned with the proper nitrile derivative in protic solvent (**Scheme 7**), which is followed by a carbonic acid derivative ring closure step. [44]



Scheme 7: General production of 1,2,4-oxadiazole (**35**) compound types

During the reaction by-products can arise in huge amounts, up to 40%. The decomposition of

[29] Plapinger, R.; Owens, O. *J. Org. Chem*., **1956**, *21*, 1186.
[30] Nicolaides, D. N.; Varella, E. A.; Patai, S., *The Chemistry of Acid Derivatives*; Interscience: New York, **1992**, *2*, 875.
[31] Clapp, L. B.; Katritzky, A. R.; Boulton, A. J. *Advances in Heterocyclic Chemistry*; Academic Press Inc.: New York, **1976**; *20*, 65.
[32] Clapp, L. B.; Potts, K. T. *Comprehensive Heterocyclic Chemistry*;
Pergamon Press: Oxford, **1984**; *6*, 365.
[33] Jochims, J. C.; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, **1996**; *4*, 179.
[34] Stephens, C. E.; Tanious, E.; Kim, S.; Wilson, D. W.; Schell, W. A.; Perfect, J. R.; Frazblau, S. G.; Boykin, D. W. *J. Med. Chem*. **2001**, *44*, 1741.
[35] Collins, J. L.; Shearer, B. G.; Oplinger, J. A.; Lee, S.; Garvey, E. P.; Salter, B. G.; Oplinger, J. A.; Lee, S.; Garvey, E. P.; Salter, M.; Dufry.; Burnette, T. C. *J. Med. Chem.* **1998**, *41*, 285.
[36] Nakamura, H.; Sasaki, Y.; Uno, M.; Yoshikawa, T.; Ansano, T.; Ban, H. S.; Fukazawa, S.; Uehara, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5127.
[37] LaMattina, J. L.; Mularski, C. J. *J. Org. Chem.* **1984**, *49*, 4800.
[38] Liang, G. B.; Qian, X. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2101.
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[40] Tyrkov, A. G. *Khim. Khimich. Tekhnol.* **2000**, *43*, 73.
[41] Young, J. R.; DeVita, R. J. *Tetrahedron Lett.* **1998**, *39*, 3931.
[42] Neidlein, R.; Sheng, L. *Synth. Commun.* **1995**, *25*, 2379.
[43] Neidlein, R.; Sheng, L. J. *Heterocycl. Chem.* **1996**, *33*, 1943.
[44] Eloy, F.; Lenaers, R. *Chem.Rev*. **1962**, *62*, 155.

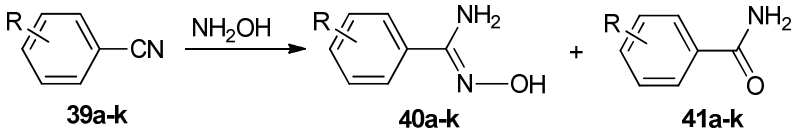
the by-product means a problem. Whereas in many cases the creator of a compound is not aware of the formation of the by-products.

Hydroxylamine (HA) is widely used in fine chemistry and in the pharmaceutical industry. It is a toxic and dangerous reagent.

The initial temperature of HA T_{onset} is 136 ± 5 °C, which depends on the concentration and the quality of the catalytic metalion. So in acidproof steal between 10 and 50% HA content 63 ± 3°C, while above 50% it decreases with the increase of the concentration. Iron, copper, nickel, chromium, titanium and manganese reduce the value of $T_{onset.}$ [45, 46]. In an industrial process there might be metalions in the system, particularly ironion. Considering this, metal free circumstances are not possible among industrial condition.

3.5.2 Results

At the creation of the last intermedier of a potential drug which is under development not only the safety risk, but also the bigger amount of the generated by-product should be taken into account. Because this reaction is the last intermedier of a synthesis, its cleanness has a key importance (**Scheme 8**). At scaling up another problem was that the reaction was not robustness, the by-product was generated in variable amounts.



Scheme 8: Generation of amidoxime derivatives

I conducted the quick parameterscreening of the reaction in Labtrix® S1 microreactor (10 µL) [dilution (14x – 22x), HA excess (1 eq – 7 eq), temperature (100 – 150 °C)]. After that I examined it the scaling up of the reaction in Corning LF reactor (4,5 mL). I wanted to achieve further, industrial size scaling up (72 mL) in Corning AF reactor, but I couldn't conduct it as only a two stream pump was availabe. So I examined the possibility of liquid inlet through one stream. First I mixed the reaction mixture and with the help of HLPC I examined the mixture.

I did the experiments again in Labtrix® S1 microreactor, and then scaling up in Corning LF reactor, and from here in the industrial sized Corning AF reactor.

At all 3 reactors in both cases (one- two pumpstream) I experienced the same effects, so the medium sized reactor (Corning LF) could be excluded form the scaling up.

After the parameter optimization I did a one hour sampling with Corning AF reactor in optimal conditions (145 °C, 7 eq. HA and 14-fold dilution) and during this period of time I received a 127 g NMP solution, and I reached full conversion with 5% amid by-product. After the process I received 8,79 g product, its by-product was 5,5%.

A parameter screening was conducted with benzonitrile in Labtrix® S1 microreactor [temperature (75 – 125 °C), HA excess (1-7 eq.) and residence time (1-9 min)]. I could reach full conversion in two cases (125°C, 4 eq. HA, 5 min; and 100°C, 7 eq. HA, 5 min). I conducted the experiments in optimal circumstances with electrondonating (**39h-k**, 4-Me, 2-Me, 4-MeO, 2-MeO), electronwithdrawing (**39b-g**, 4-F, 4-Cl, 2-Cl, 2,4-Cl, 4-Cl 2-F, 2-Cl 4-F) and with heterocyclical (**42a**, 4-Py, **42b**, 2-Py) nitrile derivatives in Labtrix® S1 microreactor, so I could easily compare the effect of the substituents.

It is remarkable that the compound (**39b-g**) containing electronwithdrawing substituents react with different speed with HA, depending on the position of the substituens. The *para*-halogenated compunds (**39c, 39d**) are highly reactive, but the *ortho*-substituens slowed down the reaction,

[45] Iwata, Y.; Koseki, H. *Process Saf. Prog.* **2002**, *21*, 136.
[46] Iwata, Y.; Koseki, H. *J. Hazard. Mater.* **2003**, *104*, 39.

presumably because of the steric barrier. With the 2-F, 4-Cl compounds (**39f**) full conversion can be reached. Probably because the fluoro is a smaller molecule. Compared to the **39e** 2,4-dichloro compound, the speed of the reaction was also high when the molecule contained fluoro in position 4 and chloro in position 2 (**39g**). The reason for this is probably the bigger electron negativity of the fluoro and the positive charge of carbon in position 1.
As expected in *para* position the compounds containing an electrondonating group **(39h, 39j)** they reacted worse compared to the reaction of compounds containing electronwithdrawing group in similar situation. Compounds containing methyl- and methoxygroup in *ortho* position had similar results to compounds containing chloro in position 2. (**39d, 39e, 39g**). From these experiments it is clear that in *ortho* position the steric barrier has a bigger effect on the reaction, than the electronwithdrawing effect.

There is no steric barrier in case of the two piridine compounds (**42a, 42b**), so I received the expected **43a, 43b** products very quickly, with full conversion.

At those reactions where I haven't reached full conversion, I could reach it by increasing the residence time to 20 minutes.

I did the scaling up of the reactions in Corning LF reactor (0,45 mL) based on the conditions which were optimal in Labtrix® S1 microreactor. I reached full conversion in all cases, so further optimization was not necessary.

At the second scaling up, what I did at **39a**, **39b** and **39i**, my aim was to increase the productivity, so I made the chips (4 pieces) parallel. The productivity (because of the further scaling up) increased 4-fold with the parallelism.

3.6 Amidoximeproduction in ionic liquid

3.6.1 Literature background

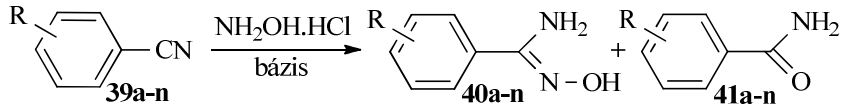
After the examination of the amidoximeproduction in microreactor I wanted to continue the earlier work of the research group and so I examined the reaction in ionic liquid too.[47] With the usage of the ionic liquid I wanted to accomplish a selective technology which means less danger for the environment. With the help of this technology the earlier used molecular solvents could be replaced.

The ionic liquids consist of an organic cation and one belonging organic or inorganic anion. [48] These could be mentioned as green solvents, as they have a lot of features compared to the molecular solvents, which make their usage beneficial. Their melting point is below 100°C, but they have a big viscosity. Among their several benefits it is worth to mention that their vapourtension is negligible, they are not flammable, the temperature range of liquid phase can reach more than 400 K, their density is bigger than water's, it is between ca. 1-1,6 g/cm^3 . The density decreases with the increase of the alkylchain-length. Many ionic liquids are sensitive to humidity, for example halogenide, or the chloroaluminate anion containing ionic liquid.

3.6.2 Results

At the usage of ionic liquids I examined the heterogene route which is used in the industry. In this case HA.HCI is added to the nitrilecompound base solution, so *in situ* it is liberated from its salts. (**Scheme 9**)

[47] Baán Zoltán *Ionos folyadékok alkalmazásának vizsgálata katalitikus transzfer hidrogénezésekben*, PhD értekezés, **2008**
[48] Marsh, K. N.; Boxall, J. A.; Lichtenthaler, R. *Fluid Phase Equilibria* **2004**, *219*, 93.



Scheme 9: Creation of aromatic nitrilcompounds with HA.HCl

I produced first at 80°C, with 2 eq. HA.HCI with 1 and 2 eq. Et_3N or Na_2CO_3 in different solvents the **40a** benzamidoxime in lockable 4 mL sample glass. I examined the molecular solvents [*N* -methylpirrolidone (NMP), 2-methyltetrahydrofurane (Me-THF), propyl alcohol, ethyl alcohol] and the effect of the quality and quantity of the bases on amidoxime and on benzamide generation. Based on the results the reaction speed was similar in bipolar aprotic NMP with Et_3N, as in polar solvents, for example in propanol (ε = 20,33) or in ethanol (ε = 24,55). Comparing the two aprotic solvents: Me-THF (ε = 6,97) and NMP (ε = 32,2), presumably due to the increased permittivity the conversion increased in NMP (16%) compared to Me-THF (1%).
With the combination of protic solvents (EtOH, n-PrOH, H_2O) and the organic base (Et_3N), a higher conversion can be reached (88-95%), than with Na_2CO_3 (23–82%). Due to the increased solubility similar results can be experienced in water (ε = 80.1) with the addition of inorganic base (82%) as with Et_3N (88–95%) in alcohol. The amount of the base is a critical parameter in the reactions. The increase of the base will worsen the selectivity of the reaction from the amidoxime point of view, while the conversion decreases.
I studied the reactions at a lower temperature, 50°C, but in this case I just used 1 eq. base.

Conducting the experiments in hexafluoroisopropyl alcohol (HFIP) and in trifluoroethanol (TFE) solvents, which are capable of making two extremely strong hydrogene bonds, the conversion decreased (33 and 60%) compared to IPA (44%) and to EtOH (76%). But the amount of amid by-product hasn't changed (1-2%). This effect is assumingly due to the strong hydrogen bond between the OH group and the HA nitrogen of the solvent.

As a matter of course I conducted the reactions with the two groups of the ionic liquids. In the first group belong the anions of strong acids (pKa < 2), which are weak bases, so is for example trifluoromethanesulfonate (TFMSI), Cl^-, $AlCl_4^-$, BF_4^-, PF_6^-, $alkylSO_4^-$, OTs^-, trifluoroacetate (TFA). In the second group belong those anions, which are strong bases, for example: carboxilate (OAc^-, OBz^-, lactate). In this case a real chemical equilibrium exists between the cation-anion pair and the neutral counterpart. I examined many different cations which were involved as the positively charged counterpart of the IL, such as imidazolium, phosphonium and ammonium. I reached low conversion with the IL belonging to the first group, except the one containing TFA ion (40%). However changing the parameters, with these ILs the reaction has not happened.

With the usage of ionic liquids belonging to the second group I received the expected product chemoselectively (90-100%), independently from the quality and quantity of the base. So in case of [BMIM][OAc], I also conducted the reaction without the addition of base, and I received similar results, as with the base. This can be explained by the behaviour of anion as a strong base as it liberates HA from its salt.

For further experiments I chose from the molecular solvents ethanol and from the ionic liquids [BMIM][OAc].

At the reaction of *ortho* halogenated (2-Cl; **39d**) and nitro (2-NO_2; **39m**) compounds due to the steric barrier the desired product resulted in a smaller amount than expected (20% and 51%). This observation is confirmed by the reaction of 2- and 4-piridinecarbonitrile (**42b; 42a**). In these reactions I received the expected product with 100% conversion, selectively. In case of initial materials which contain electrondonating groups, the reaction speed of the products slowed down. The electrondonating *ortho* substituents show always a lower conversion (9%, **39k**; 10%, **39i**), than the appropriate *para* substituents (45%, **39j**; 46%, **39h**), which confirms again the steric effect of the *ortho* substituted. The low, 16% conversion of the steric barriered 2,6-dimethylbenzonitrile (**39n**) proves the *ortho* shielding. In case of 2-MeO and 2-Me derivative I examined long reaction

time. I measured in EtOH during 20 hours 40% and 33%, in IL during 10 hours 59% and 86%. However the reacion slowes down in ionic liquid, the results show that the amidoxime derivative is formed more quickly and selectively.

Consequently it can be concluded that with the usage of [BMIM][OAc] both the amount (38-100%) of the expected product, and the selectivity increased (0-3% by-product) in all cases of the substituents compared to EtOH.

3.6.3 Mechanism-examination

The theoretical calculations were created with the Gaussian (G09) program on a server [49] at the University of Szeged with DTF method [B3LYP/6-31G(d,p)][50].

During the examination of the mechanism I examined the reaction in solvent free medium, in EtOH and in ionic liquid. I took the earlier hypothesis [51, 52] into consideration.

I wanted to prove the origin of the benzamide of nitrogen with isotopic examination, so I used $^{15}NH_2OH.HCl$ (^{15}HA.HCl) labelled with isotope. During the reaction the ^{15}N could be found only in benzamidoxime (**37a***, $M+H^+$ = 137,1 Da). The benzamide contained only ^{14}N ($M+H^+$ = 121,1 Da).

Conducting the reverse experiment I did the basic reaction with ^{15}N isotope labelled benzonitrile. In this case another version of isotope labelled benzamidoxime (**40a****) and the isotope labellede benzamide (**41a***, $M+H^+$ = 122,1 Da) was generated. From these two experiments it can be concluded that the nitrogen of the benzamide doesn't build from HA, but the original benzonitrile contains it.

With the help of a few experiments I examined if during the reaction from benzamidoxime benzamide can arise. I reacted benzonitrile with strong base (NaH), the oxygen deprotonated, so, as expected, only benzamide arose.

Due to the two methylgroup of the *N*,*N*-dimethylhydroxylamine hydrochloride (DMHA.HCl) can solely attack the benzonitrile with the oxygen side, so the formation of benzamidoxime can be excluded. Having conducted the reaction for 2 hours **41a** benzamide arose in 9%, while I identified in 91% the original **39a** benzonitrile with the help of HLPC.

With the previously mentioned studies I wanted to exclude all possible processes which are responsible for amid formation. Furthermore I investigated the origin of amid nitrogen.

After the examination of benzonitrile and its derivatives I extended the reaction to the optimized condition, earlier in microreactor examined (at Sanofi Chemical Development) molecule **36**, so I conducted the reaction in solvents which were already examined at benzonitrile and in [BMIM][OAc] and in [BMIM][Cl] ionic liquid. I haven't examined water as solvent, as neither the original material nor the product can be dissolved in it. i reached the best conversion in NMP which has already been used during development, but at this point amid **38** by-product was generated in large quantities. In the [BMIM][OAc] without base similarly to the experiences with benzonitrile, I received selectively **37** amidoxime, but in [BMIM][Cl] the reaction was not successful.

I would like to point out that during the reaction the recyclability of the ionic liquid was not studied, as it was not my aim, but there are a few examples in literature in this topic.[53, 54, 55]

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4. Thesis

The main aim of my PhD work was to examine the feasibility and manufacturing of those reactions in microreactors which were already worked out in the pharmaceutical industry. So the safety construction of the reactions and their conversion can be improved, and the benefits of microreactors were adaptable, as for example: quick optimization, reaction safety, the possibility of working above the boiling point of the solvent.

During my work I achieved the following scientific results:

1. I created the intermediery of a potential drug with Mitsunobu reaction in size *of resynthesis batch* under safe conditions which is suitable for toxicology examinations. I created different Mitsunobu products in microreactor with similar conversion to batch reaction, but with shorter residence time and more safely.

2. I worked out a cheaper and safer process in the microreactor for the N-oxidation of pyridine derivatives with 27% hydrogen peroxid, in aceticacid. At each derivative I received better results in microreactor than in batch. From a reactionsafety point of view it is worth to mention that working with H_2O_2 in industrial size at a pharmaceutical company which is in the middle of a residential area is very risky in batch, but in microreactor it is easy to carry out.

3. Instead of the currently used difficult technology, I created during hydroboration reaction pentenyl (intermedier of a potential drug) under quick, safe and soft conditions and I also created hexenylboronic acid. These reactions took more hours in batch. This technology would be suitable for reactions with volatile acetylene derivatives.

4. I created the initial material of prostaglandinmanufacturing (cyclopentadyene) under diluted conditions (5%) in monomerization reaction in microreactor. The reaction is extremely dangerous, so there is no option for creating this material with the batch method. I suggested to make the reaction more concentrated (50-75%) at a higher temperature, under metal free circumstances, in continuous flow reactor.

5. I carried out the 7200-fold scaling up of a potential drug in microreactor under safe conditions and I reduced the amount of the amide by-product to a constant level, while at the scaling up in batch the amid by-product was generated in a big amount (not robust). For the reaction hydroxylamine was used in a huge amount, which is an explosive compound, so its usage in the industry is very dangerous. I extended the reaction to other nitrile derivatives as well. Due to this I did the amidoxime creation in microreactor quickly and safely feasible.

6. I implemented amidoximeproduction with microreactor technology and also under heterogenous circumstances, in carboxylate anioinic ionic liquid, chemoselectively, without the addition of base. The reaction was extended to different nitrile derivatives, and to the synthesis of the intermedier of a potential drug. The reactions were carried out quickly and more selectively in carboxylate anion-containing ionic liquid, than in molecular solvents.

7. I made a suggestion for the mechanism of amidoximeproduction reaction, for the formation of the amid by-product. I demonstrated these experiments with quantum chemical calculations.

5. Possibilities for application

My results and the sample reactions verified the several benefits of microreactors. With the help of microreactors the safety risk can be reduced, so it would be possible to replace the technologies in vial and conduct technologies which were not possible until now or were too risky in the industry. Considering the results of the examined reaction types could be easily and safely feasible.
Examinations in ionic liquid could be important for the industry at the creation of 1,2,4-oxadiazole drugs, because their creation under homogeneous circumstances is dangerous because of the features of hydroxylamine. The heterogeneous reaction is not robust. I could create the amidoxime derivative during a short period, selectively, without the addition of base, so it would be possible to extend it in the pharmaceutical industry for further derivatives.

6. Publications

Publications in the topic of my thesis

[1] Vörös, A.; Baán, Z.; Hermecz, I.; Mizsey, P.; Finta Z.: Mikroreaktorok alkalmazása szerves kémiai reakciókban, *Magyar Kémiai Folyóirat* **2011**, *117*, 22.

[2] Vörös, A.; Baán, Z.; Mizsey, P.; Finta Z.: Formation of Aromatic Amidoximes with Hydroxylamine using Microreactor Technology, *Org. Proc. Res. Dev.* **2012**, *16*, 1717. [IF: 2,739]

[3] Vörös, A.; Baán, Z.; Timári, G.; Hermecz, I.; Mizsey, P.; Finta Z.: Highly Efficient and Selective Addition of Hydroxylamine to Nitriles in Ionic Liquids, *Curr. Org. Synth.* **2014** (in press) [IF: 2,038 (2012.)]

[4] Vörös, A.; Mucsi, Z.; Baán, Z.; Timári, G.; Hermecz, I.; Mizsey, P.; Finta Z.: Selective Amidoxime Synthesis from Nitriles and Hydroxylamine in Ionic Liquids An experimental and Theoretical Study of Reaction Mechanism, *Org. Biomol. Chem.* **2014** (submitted for publication) [IF: 3,568 (2012)]

[5] Vörös, A.; Timári, G.; Baán, Z.; Mizsey, P.; Finta Z.: Preparation of Pyridine *N*-oxide Derivatives in Microreactor, *Periodica Polytechnica* **2014** (accepted) [IF: 0,269 (2013.)]

Presentations in the topic of my thesis

1. XXXIII. Kémiai Előadói Napok **2010.**, HUNGARY, *Szeged*
   Vörös A., Baán Z., Hermecz I., Mizsey P., Finta Z.; *Mikroreaktorok alkalmazása egy gyógyszerintermedier előállításában*

2. Heterociklusos kémiai munkabizottság ülése **2011.**, HUNGARY, *Balatonszemes*
   Vörös A., Molnár K., Baán Z., Hermecz I., Mizsey P., Finta Z.: *A mikroreaktor technológia helye napjaink vegyiparában*

3. Scalable Flow Chemistry Mini Symposium **2011.**, *GERMANY, Frankfurt am Main*
   A. Vörös, K. Molnár, Z. Baán, I. Hermecz, P. Mizsey, Z. Finta: *Compability of microreactors from different suppliers*

4. Oláh György Doktori Iskola konferenciája **2013.**, HUNGARY, *Budapest*
   Vörös A., Baán Z., Timári G., Alattyáni E., Mizsey P., Finta Z.: *Aromás amidoxim származékok előállítása mikroreaktorban és ionos folyadékban*

5. Műszaki Kémiai Napok **2013.**, HUNGARY, *Veszprém*
   Vörös A., Baán Z., Timári G., Mizsey P., Finta Z.: *Aromás amidoxim származékok előállítása mikroreaktorban*

6. Heterociklusos kémiai munkabizottság ülése **2013.**, HUNGARY, *Balatonszemes*
Vörös A., Baán Z., Timári G., Mizsey P., Finta Z.: *Pyridin N-oxidok gyors és biztonságos előllítása és továbbalakítasa mikroreaktorban*

Posters in the topic of my thesis

1. Sanofi-aventis/ Chinoin PhD nap **2010.**, HUNGARY, Budapest
   A. Vörös, Z. Baán, I. Hermecz, P. Mizsey, Z. Finta: *Application of continuous flow microreactors in chemical develepment*

2. Oláh György Doktori Iskola konferenciája **2011.**, HUNGARY, *Budapest*
   Vörös A., Baán Z., Hermecz I., Mizsey P., Finta Z.: *Folyamatos áramlású mikroreaktorok alkalmazása a kémiai fejlesztésben*

3. XIVth Conference on Heterocycles in Bio-organic Chemistry **2011.,** *Czech Republic, Brno*
   A. Vörös, K. Molnár, Z. Baán, I. Hermecz, P. Mizsey, Z. Finta: *Formation of aromatic amidoximes with hydroxylamine and scale up in microreactor*

4. Microwave and Flow Chemistry Conference **2012.**, *SPAIN, Lanzarote*
   A. Vörös, Z. Baán, G. Timári, P. Mizsey, Z. Finta: *Fast and safe ether production in microreactor*