

MASTER

Optimization of key steps towards rufinamide and aripiprazole

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Optimization of key steps towards Rufinamide and Aripiprazole

Abstract

Micro reactor technology has been applied on the continuous multi-step flow synthesis of rufinamide. Herein, the second reaction step consists of the synthesis of benzyl azide from benzyl chloride and sodium azide. The small volume of the microreactor is beneficial for the use of sodium azide because of its explosive and toxic nature. An optimization of the synthesis of benzyl azide has been performed by varying the reactor temperature and residence time and it has been shown that 97 % yield of benzyl azide can be obtained at 150 °C within 2.5 minutes residence time. In addition, the formation of approximately 2 % benzyl alcohol has been observed.

Furthermore, the synthesis of 2,3-dichlorophenylpiperazine by reaction of 2,3-dichloroaniline and bis(2-chloroethyl)amine has been investigated. When a conventional batch procedure is used for this purpose a yield of approximately 60 % is been obtained in 8 hours reaction time at 150 °C. In a PFA micro flow reactor the maximum yield that has been achieved is 30.6 % at 170 °C at 1 hour residence time. To increase the reactor temperature research has been done on a flow reactor built of stainless steel. When the same reactants system is used as in PFA tubing, corrosion has been observed. To prevent this corrosion, methods involving the bases sodium hydroxide and triethylamine have been applied. However, both methods have also led to corrosion after some time.

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1 Introduction

1.1 Novel Process Windows

Novel Process Windows (NPW) is a concept focusing on the identification of chemical processes and its conditions both utilizing the apparatus' maximum performance and the chemical potential of the reaction.¹ Many industrial operations, like careful mixing of very reactive chemicals, are intrinsically for industrial apparatuses rather than for the engineering of chemical reactions. Such type of limitations can be overcome by the use of flow-chemistry reactors on micro- and milli-scale. Via this way NPW is able to achieve tremendous process intensification. Hereto, chemical reactors and processes should be re-designed focusing on enabling chemistry instead of employing conventional reactors. Although conventional reactors are still better for a lot of industrial applications, much research is done on micro reactors since it can lead to major innovations. This approach can lead to improvements by orders of magnitude of space-time yields and the productivity of the reactor. In addition, it often leads to harsh process conditions far from the conventional standard.

The synergy of the microdimensions and the harsh process conditions has resulted in improvements on various levels of the intensification of a reaction system, namely transport, chemical and process design intensification.² NPW is constituted by the latter two. Numerous research groups have succeeded in demonstrating accurate residence time and heat transfer control, efficient mixing and 'right' handling of chemicals in microchannels.³⁻⁸

NPW provides different methods of applying unconventional process conditions in order to improve existing processes.⁸ These methods can be assigned to six major topics:

- Routes at much elevated temperature
- Routes at much elevated pressure
- Routes at increased concentration or even solvent-free
- Routes in the explosive or thermal runaway regime
- Process integration or simplification
- New chemical transformations

Frequently, innovative technologies and concepts are included in these unconventional processes, such as microwave heating and direct-one step syntheses.

1.2 Transition from batch to flow processes

Continuously operating flow reactors possess several advantages over traditional batch reactor technology. Particularly, micro flow reactors have a large surface-to-volume ratio providing enhanced heat and mass transfer which opens ways to perform highly reactive, exothermic and hazardous reactions. Besides, the machine assisted approach helps creating a more sustainable working environment in laboratories,⁹ facilitates 24/7 working regimes and provides enhanced reaction optimization and even reaction discovery.¹⁰

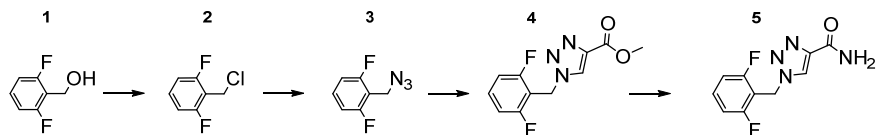
Flow processes provide relatively easy scale-up with little or no extra process development stages by either changing the reactor volume and flow rate or by running multiple flow reactors in parallel.¹¹ Another major difference between batch and flow processes is the way of conducting multistep reactions.¹¹ By putting multiple flow reactors in series a multistep process can be designed and reagents can be introduced into the flow system anywhere at precisely the time required for the reaction.

Typically, multi-step reactions lead to complex molecules and are, therefore, often involved in the synthesis of the majority of the pharmaceuticals. Examples of drugs which are interesting from this point of view for continuous flow synthesis are Rufinamide and Aripiprazole.

1.3 Synthesis of Rufinamide

An important application of a one-flow multistep reaction route is the synthesis of Rufinamide since it is one of the best-selling five-membered heterocyclic pharmaceuticals. It contains a 1,2,3-triazole moiety and it is commonly produced by a [3 + 2] cycloaddition of 2,6-difluorobenzyl azide with 2-chloroacrylnitrile.¹² The global reaction scheme of interest in the current research for the production of Rufinamide is shown in Scheme 1.^{13,14}

Scheme 1: Global reaction scheme for the production of Rufinamide



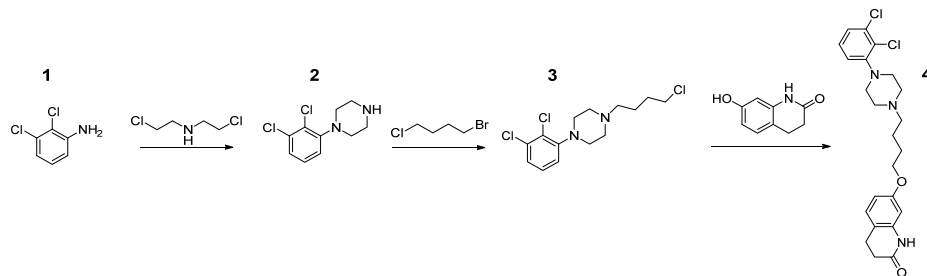
This multistep synthesis starts from difluoro-substituted benzyl alcohol [1] which is converted to benzyl chloride [2]. Forthcoming research on this reaction by our group will focus on using hydrogen chloride gas as reactant to provide an optimal green process with water as only by-product. Benzyl chloride will, subsequently, be converted to benzyl azide [3]; this reaction has been investigated in the current report. The formation of the rufinamide precursor [4] has already been investigated by Hessel *et al*¹³ showing 83 % yield at 210 °C within 10 minutes residence time in microflow. As a final step the precursor ester can be converted to the desired rufinamide [5] by reaction with ammonia.¹⁵

1.4 Piperazine-based pharmaceuticals

1.4.1 Synthesis of Aripiprazole

Aripiprazole is an important neuroleptic drug which is used in the treatment of schizophrenia and related psychoses.¹⁶ It is better known under its brand name 'Abilify' and it was the number one medicine by non-discounted spending in 2013.¹⁷ A multi-step production route for aripiprazole, which will be the focus of our group, is given in Scheme 2 and is closely related to the process published by Ramakrishnan *et al.*¹⁸

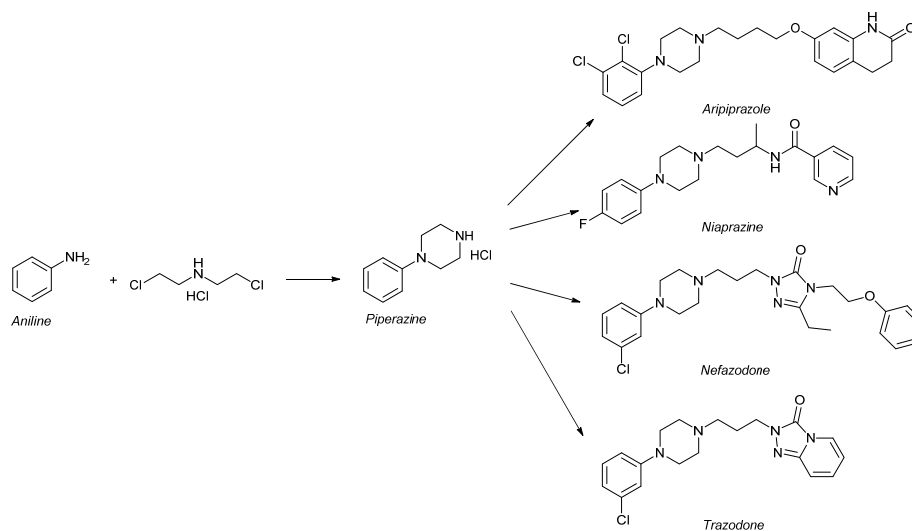
Scheme 2: Multi-step production route of aripiprazole



The first step in this multi-step synthesis is the ring-closing reaction between 2-chlorosubstituted aniline [1] and a bisalkylating agent towards the piperazine [2], which, thereafter, reacts to [3]. Via reaction with the carbostyryl derivative the desired product aripiprazole [4] can be obtained.

Piperazines derived from anilines can not only be converted to aripiprazole, also niaprazine, nefazodone and trazodone belong to the large class of phenylpiperazines. Niaprazine is a sedative-hypnotic drug while nefazodone and trazodone are anti-depressants. The structures of these drugs are given in Scheme 3.

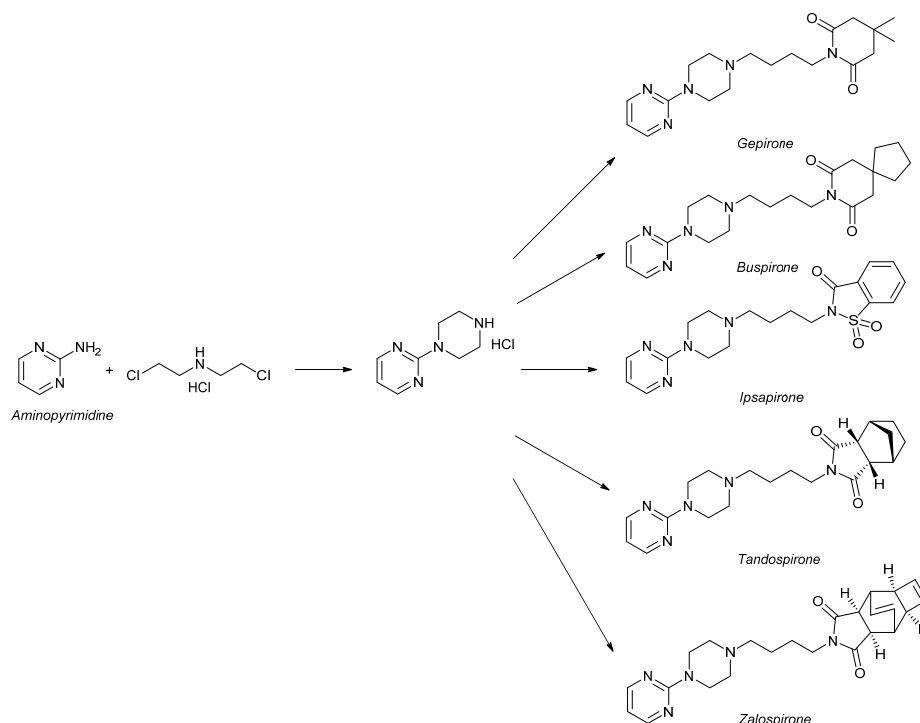
Scheme 3: Reaction routes to phenylpiperazine-derived pharmaceuticals



1.4.2 Other piperazine-derived pharmaceuticals

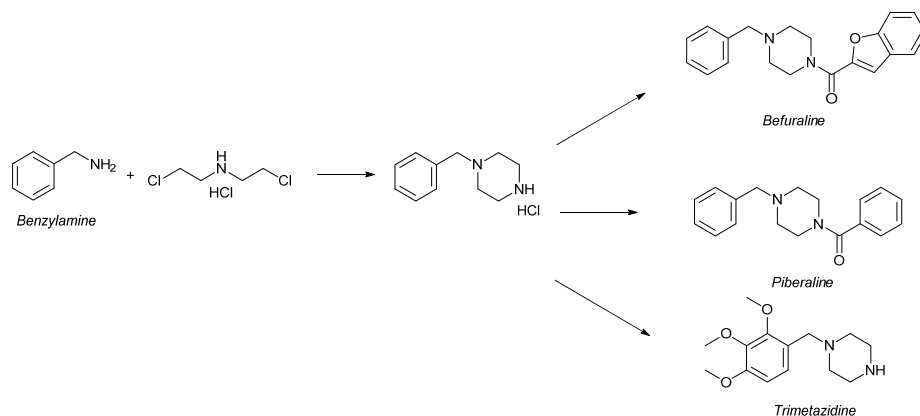
Comparable to the synthesis of phenylpiperazine from aniline, also other amines can be employed to the ring-closing reaction with a bisalkylating agent. When 2-aminopyrimidine is used as starting compound different kinds of pharmaceuticals can be synthesized of which a few are shown in Scheme 4. These pharmaceuticals are important due to their antidepressant and anxiolytic effects.

Scheme 4: Reaction routes to pyrimidinylpiperazine-derived pharmaceuticals

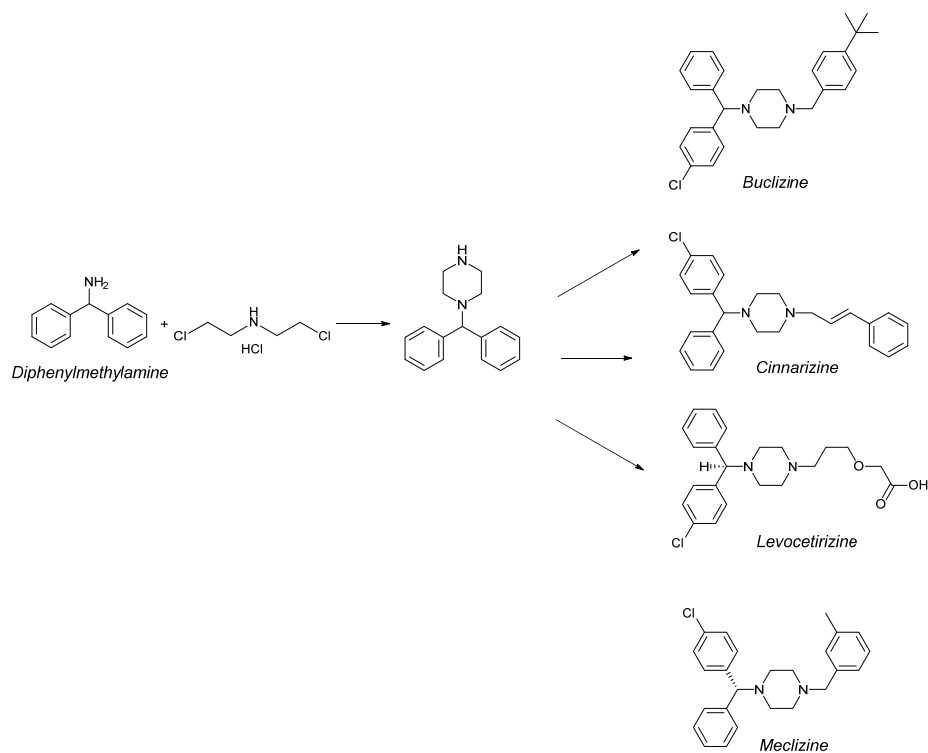


In addition, benzylamine and diphenylamine can be used to synthesize piperazines and examples of resulting pharmaceuticals are given in respectively Scheme 5 and Scheme 6. Befuraline and Piberaline have stimulant and antidepressant effects and trimetazidine is used as drug for angina pectoris. The drugs shown in Scheme 6 are all known as antihistamines.

Scheme 5: Reaction routes to benzylpiperazine-derived pharmaceuticals



Scheme 6: Reaction routes to diphenylmethylpiperazine-derived pharmaceuticals



1.5 Objective

This project will be focused on the rufinamide process as well as the synthesis of phenylpiperazine. First, the microflow synthesis of benzyl azide from benzyl chloride will be investigated and an optimization of the yield will be performed with respect to temperature and residence time. Thereafter, the synthesis of 1,2-dichlorophenylpiperazine via a ring-closure reaction of bis(2-chloroethyl)amine and 2,3-dichloroaniline will be investigated. Hereto, the reaction rate will be determined in a common batch procedure followed by testing the feasibility of the reaction in a capillary microflow reactor.

2 State-of-the-art

2.1 Synthesis of alkyl azides

2.1.1 Historical background

Organic azides form a group of compounds which acts as a valuable and energy-rich intermediate in organic synthesis.¹⁹ The first organic azide, phenyl azide, has been synthesized by Peter Grieb in 1864²⁰ and a few years later Curtius discovered the rearrangement of acyl azides to the corresponding isocyanates using hydrogen azide, known as the Curtius rearrangement.²¹ Most azide compounds are well known due to their toxicity and explosive nature: little input of external energy can cause decomposition of the azide with the release of nitrogen gas. Since the current research is on the synthesis of benzyl azide and the synthesis of aromatic and aliphatic azides vary considerably,¹⁹ the state-of-the-art will be focused on the alkyl azide synthesis.

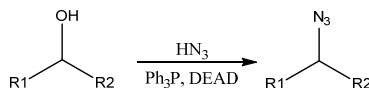
2.1.2 Batch approach

Extensive research has been done on the synthesis of alkyl azides. Here, some different synthetic strategies will be summarized.

The most classical way of synthesizing alkyl azides is by a nucleophilic, S_N2 type, substitution. For this purpose sodium azide is most commonly used as the azide source.¹⁹ Other potential azide sources are tetra-alkylammonium azides, polymer-bound azides²² and the highly explosive silver azide.²¹ As leaving groups halides, carboxylates and sulfonates as well as mesylates, nosylates and triflates are often used.¹⁹

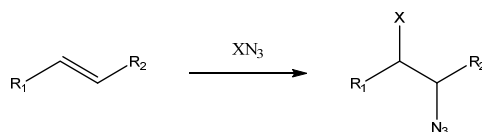
Another way to synthesize alkyl azides is a derivation of the Mitsunobu reaction in which organic azides can be made from alcohols.²³ The general form of this reaction is shown in Scheme 7. Primary as well as secondary alcohols can be converted to the corresponding azide by reaction with hydrogen azide, triphenylphosphine and diethyl azodicarboxylate (DEAD).

Scheme 7: Synthesis of alkyl azides by using the Mitsunobu reaction



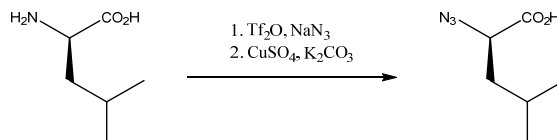
The 1,2-addition of halogen azides to non-activated olefins has been described by Hassner and Levy²⁴ and has opened ways to a broad range of vinyl azides. The general structure for this reaction is given in Scheme 8. Besides halogen azides also other azide sources, e.g. sodium azide, are employed for the addition to olefins.¹⁹

Scheme 8: Addition of halogen azides to olefins



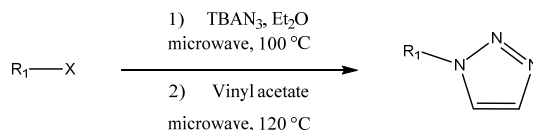
A very different way to synthesize alkyl azides is by making use of diazo transfer.¹⁹ Herewith, primary aliphatic amines can be converted into the corresponding azides. In Scheme 9 a typical reaction system is shown.²⁵ In the first reaction step triflyl azide is being formed by reaction between sodium azide and trifluoromethanesulfonic anhydride (Tf₂O). The alkyl azide is being formed in the second reaction step in the presence of a copper catalyst with an 84 % yield.

Scheme 9: Synthesis of alkyl azides via diazo transfer



More recently, Hansen and Jensen have investigated the uncatalyzed microwave-assisted preparation of alkyl azide as part of the synthesis of unsubstituted *N*-linked 1,2,3-triazoles. This multistep synthesis is given in Scheme 10. It has been found that a single-step yield of benzyl azide of 84% could be obtained within 10 minutes reaction time.²⁶

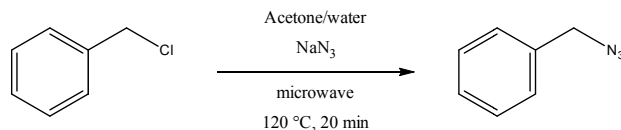
Scheme 10: Two-step, one-pot, microwave-assisted azidation-cycloaddition of alkyl halides



Kappe *et al*²⁷ have done research on copper(I)-catalyzed azide-alkyne cycloadditions in continuous flow conditions. The preparation on benzyl azide has been performed in an acetone/water mixture in a batch reactor without catalyst, as

shown in Scheme 11, and it has been shown that a yield of benzyl azide of 96 % can be obtained with 20 minutes reaction time and a temperature of 120 °C.

Scheme 11: Synthesis of benzyl azide under microwave conditions



Wei *et al*²⁸ have investigated ionic liquid “brushes” as a highly efficient and reusable catalyst for water-based nucleophilic substitutions. The molecular environment of this catalyst and its role in a general nucleophilic substitution is shown in Figure 1. The conversion of benzyl chloride towards benzyl azide has been used as prototypical reaction and it has been shown that 95 % yield can be obtained at 80 °C. The reaction time, however, is equal to 5 hours.

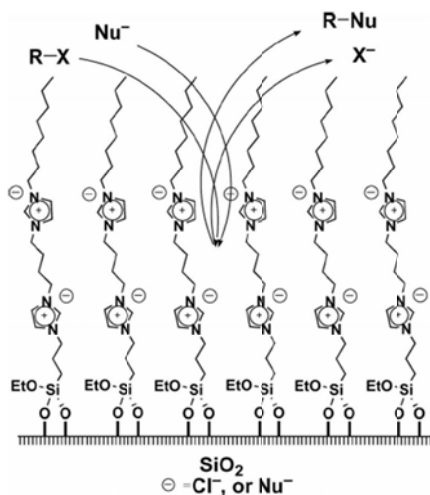


Figure 1: Chart of the brush catalyst and its role in a nucleophilic substitution²⁸

Highly branched polyacrylamide, shown in Figure 2, has been investigated as a novel multi-site polymeric phase transfer catalyst by Mahdavi and Amirsadeghi²⁹ and has been applied to the production of benzyl azide as well. At a temperature of 70 °C a 100 % yield has been obtained within 30 minutes reaction time.

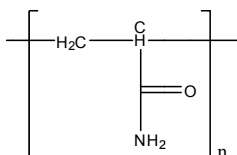


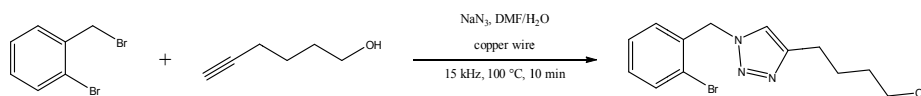
Figure 2: Chemical structure of polyacrylamide

2.1.3 Micro flow approach

Micro flow technology has the advantage of good mass and heat transfer and it enables the use of small volumes. In the synthesis of alkyl azides these small volumes are particularly important when sodium azide is used, since sodium azide is both explosive and toxic.

The yield of benzyl azide from reaction of benzyl chloride with sodium azide has not been reported yet. Kirschning *et al.*³⁰ have investigated continuous copper-catalyzed Huisgen cycloaddition with inductive heating as shown in Scheme 12. Hereto, 2-bromobenzyl bromide has undergone the cycloaddition in which the reaction with sodium azide is the first step. An overall yield of 90 % has been obtained; however, the exact yield of the alkyl azide synthesis is unknown. Furthermore, bromide is a better leaving group than chloride, which makes a comparison of different leaving groups inaccurate. However, in the current research chloride has been used as leaving group since it is greener and cheaper compared to bromide.

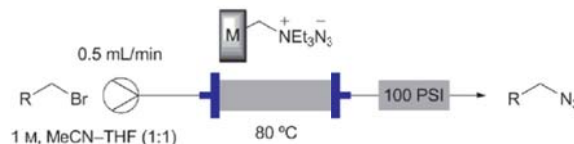
Scheme 12: Inductively heated copper flow Huisgen cycloaddition



The Huisgen cycloaddition has further been utilized by Lei *et al.*³¹ using benzyl bromide in a micro flow reactor. It has been shown that an overall yield of 95 % can be obtained in 3 minutes residence time and 65 °C, indicating that the yield of the alkyl azide production with bromide as leaving group is at least above 95 %.

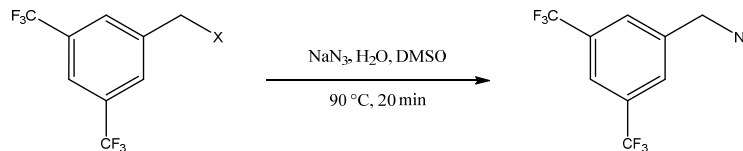
Smith *et al.*³² have reported the synthesis of several organic azides in continuous flow using an azide ion exchange monolith reactor. This reactor system is given in Scheme 13. The reaction of 1-bromo-3-phenylpropane has shown a yield towards the corresponding alkyl azide of 99 % with a residence time of 25 minutes and a temperature of 80 °C. This promising method has, however, not been applied to alkyl chlorides.

Scheme 13: Flow synthesis of alkyl azides in ion exchange monolith reactor³²



The only continuous flow synthesis of alkyl azides from alkyl chlorides has been reported by Kopach *et al.*³³ In their research on the development of batch and microflow azide processes 3,5-bis-(trifluoromethyl)benzyl chloride has been converted towards its corresponding azide using sodium azide as shown in Scheme 14. Without using any catalyst a yield of azide has been obtained of 94 % with 20 minutes residence time and a temperature of 90 °C.

Scheme 14: Substituted benzyl azide synthesis in a capillary micro reactor



2.1.4 Overview

In Table 1, an overview is given of the reaction conditions and yields of the syntheses of alkyl azides from alkyl chlorides and sodium azide.

Table 1: Schematic overview of various syntheses of alkyl azides from alkyl chlorides and sodium azide including reaction conditions and yield

Entry	Reactor	(Residence) time (min)	T (°C)	C (mol L ⁻¹)	Cat.	Yield (%)	Ref
1	Batch	300	80	2.5	Yes	95.4	28
2	Batch	30	70	1	Yes	10	29
3	Batch	20	120	0.5	No	96	27
4	Flow	20	90	0.5	No	94	33
5	Batch	10	100	0.9	No	84	26

2.2 Synthesis of piperazine-derived molecules

2.2.1 Synthesis of piperazine

Different methods are available for the synthesis of piperazine, of which the structure is given in Figure 3.

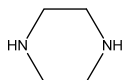
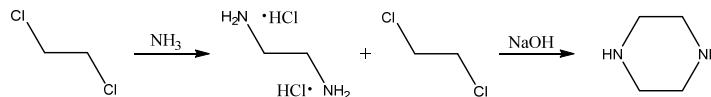


Figure 3: Chemical structure of piperazine

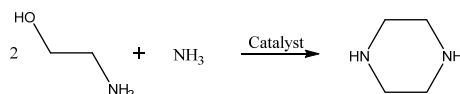
In industry the conventional way of synthesizing piperazine is by reaction of ethylene dichloride and an excess of ammonia under high pressure and moderate temperature.³⁴ The resultant ethyleneamine hydrochloride solution is neutralized with caustic soda to form piperazine. The reaction pathway is shown in Scheme 15.

Scheme 15: Synthesis of piperazine from ethylene dichloride and ammonia



Another way of synthesizing piperazine is by the reductive amination process as shown in Scheme 16.³⁴ Herein, monoethanolamine and ammonia react over a catalyst to produce piperazine and other ethyleneamines.

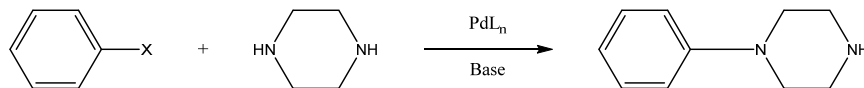
Scheme 16: Synthesis of piperazine from monoethanolamine and ammonia



2.2.2 Palladium-catalyzed amination towards piperazine containing compounds

The benchmark of the synthesis of arylpiperazines, or more general the formation of carbon-nitrogen bonds, is called the Buchwald-Hartwig amination. This synthesis is named after Stephen L. Buchwald and John F. Hartwig who have independently done research on the amination starting with a first publication in 1994. The general reaction procedure for the production of benzyl piperazine is given in Scheme 17.

Scheme 17: Buchwald-Hartwig amination for the production phenyl piperazine



Guram and Buchwald published yields in the range of 55 to 88 % at around 105 °C and 4 hours using bromide as leaving group for a large library of either aromatic and aliphatic amines.³⁵ Hereafter, Buchwald *et al* investigated the use of basic conditions, iodine as leaving group and phosphine ligands, which improved the reaction performance and expanded the range of potential substrates for the amination procedure.³⁶⁻³⁸ In their initial research on the amination reaction, Hartwig *et al* investigated the use of tin amides as reagents.^{39,40} Yields of dimethylaniline in the order of 75 to 85 % were achieved at temperatures between 90 and 110 °C. To avoid the use of toxic tin amides, Louie and Hartwig⁴¹ have investigated the use of basic conditions combined with the palladium catalyst. Using an arylbromide and piperidine yields are obtained of 76 to 94 % at 100 °C and in 2 hours.

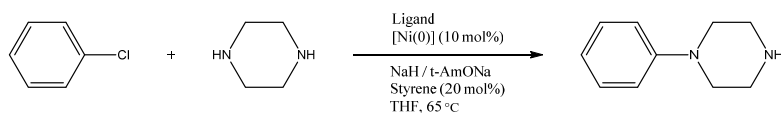
Encouraged by the synthetic success of Buchwald and Hartwig, Zhao *et al* have investigated the palladium-catalyzed synthesis of arylpiperazines.⁴² For a large library of substrates yields have been obtained varying from 13 to 63 % at a temperature of 100 °C and a reaction time of 2 to 5 hours. Ward and Farina⁴³ have applied the amination method on resin-bound aromatic bromides. When methoxyanilines and different kind of phosphine ligands are used yields have been obtained of 100 %. This solid phase synthesis of aryl amines has further been utilized by Willoughby and Chapman⁴⁴ who investigated this reaction system for a variety of aniline derivatives and cyclic and acyclic secondary amines. At temperatures of 70 to 80 °C yield have been obtained from 75 to above 95 %. So far, the Buchwald-Hartwig amination of piperazine compounds have been performed using a large excess of piperazine in order to suppress the competitive bis-arylation of piperazines. Gala *et al*⁴⁵ have investigated the use of a Pd⁰-catalyst at 80 to 90 °C without using a large excess of piperazine and they have found that reaction times in the order of days are necessary to obtain yields from 10 to 80 %. Finally, Beller *et al*⁴⁶ have investigated the influence of different ligands using just

benzylpiperazine as reactant and they have obtained a maximum yield of 96 % in 20 hours and 110 °C.

2.2.3 Alternative metal-catalyzed amination

In the absence of a large excess of piperazine the palladium-catalyzed amination of piperazines requires long reaction times in order to obtain high yields. Fort *et al*⁴⁷ investigated the potential of an in situ generated colloidal nickel catalyst using a large library of aryl chlorides. The reaction procedure is given in Scheme 18.

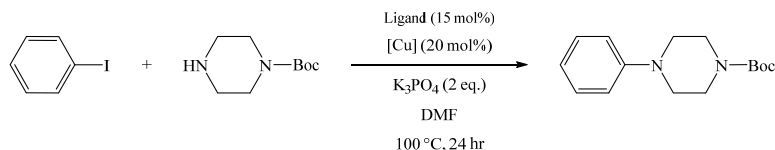
Scheme 18: Nickel-catalyzed amination of phenylpiperazine



When a little excess of piperazine is used, yields have been obtained of 23 to 84 % in 8 to 12 hours at 65 °C. This yield strongly depends on the substituents on the aryl chloride. The bis-arylation product has also been observed in yields of 1 to 28 % and by using a larger excess of piperazine it has been shown that the selectivity towards the mono-arylpiperazine can be increased significantly. Furthermore, the scope of the procedure of using a little excess of piperazine has been extended to a number of substituted piperazines showing yields of 26 to 70 % in 9 to 13 hours.

Recently, research has been done of the cross-coupling of piperazine-based secondary amines using a copper catalyst.⁴⁸ The detailed reaction procedure for the synthesis of phenylpiperazine, including the protecting group, is given in Scheme 19. For a large number of aryl iodides yields have been obtained of 36 to 72 % in 24 hours.

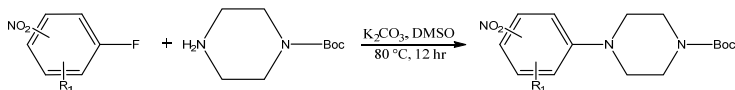
Scheme 19: Copper-catalyzed synthesis of phenylpiperazine including protecting group



2.2.4 Base-catalyzed synthesis of piperazine derivatives

The metal-free synthesis of arylpiperazines has been investigated by Neville and Zhu⁴⁹ focusing on the presence of a strong electron withdrawing group on the *ortho* or *para* position. The reaction including its best conditions are given in Scheme 20.

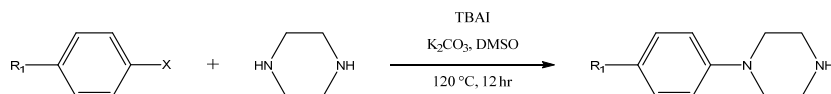
Scheme 20: Base-catalyzed synthesis of phenylpiperazine derivatives including protecting group



Basic conditions are used to facilitate the alkylation by scavenging the generated hydrogen halide. By using a large excess of N-Boc piperazine a consistent yield of at least 95 % can be achieved including the deprotection step for a number of benzyl fluorides.

In order to avoid the use of harsh reaction conditions or a protecting group, Gala *et al*⁵⁰ have done research on the selective mono-arylation of piperazine under mild laboratory conditions using a reaction system as given in Scheme 21.

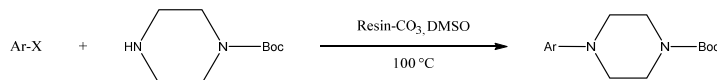
Scheme 21: Synthesis of phenylpiperazines by basic conditions and a phase transfer catalyst



By using tetra-N-butylammonium iodide (TBAI) as phase transfer catalyst, yields have been obtained up to 98 %. Furthermore, it has been shown that the reactivity of the aromatic halide strongly depends on the electron density of the aromatic ring: a low electron density is favorable. The reaction system can further be simplified by dropping the use of the phase transfer catalyst, which decreases the yield with 10 to 15 %.

Dunston *et al*⁵¹ employed a basic ion exchange resin in order to convert structured varying aryl halides with low electron density to the corresponding arylpiperazine. The reaction system is given in Scheme 22.

Scheme 22: Synthesis of arylpiperazines in the presence polymer-supported carbonate

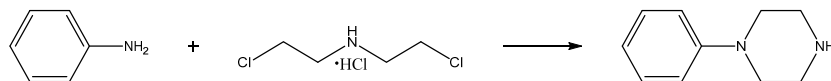


This system has led to yields of 20 to 91 % in more than 90 % purity. The exact reaction time for this nucleophilic aromatic displacement has not been specified. However, it was found that the reaction time could significantly be reduced by using a microwave-assisted approach. Hereby, a temperature of 140 °C is sufficient to obtain yields in the same order of magnitude within 30 minutes.

2.2.5 Ring-closing synthesis of piperazine derivatives

A classical way for the synthesis of piperazine derivatives has originated in the thirties of the last century. In 1934 Pollard and MacDowell⁵² have reported the synthesis of N-monophenylpiperazine by heating together aniline and diethanolamine hydrochloride. After a reaction time of six to eight hours and a temperature of 220 to 240 °C a yield has been obtained higher than 50 %. In addition, the formation of a by-product, bis(2-phenylaminoethyl)amine, has been observed by reaction of diethanolamine with two equivalents of aniline. In Scheme 23 the reaction system has been given which is employed most often for the synthesis of benzylpiperazine via reaction of a secondary amine with two leaving groups.

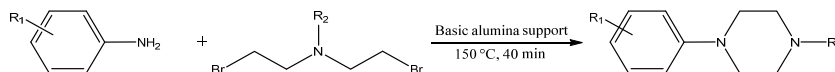
Scheme 23: General synthesis of phenylpiperazine via reaction of aniline and bis(2-chloroethyl)amine hydrochloride



This reaction strategy has been investigated at lower temperatures and sodium carbonate catalyzed by Kiritsy and Yung.⁵³ Around 78 °C yields have been obtained up to 87%, strongly depending on the substituted aniline, in the order of 48 hours reaction time.

Welch *et al*⁵⁴ have significantly reduced the reaction time by using the reaction route as described in Scheme 24.

Scheme 24: Basic alumina supported synthesis of arylpiperazines



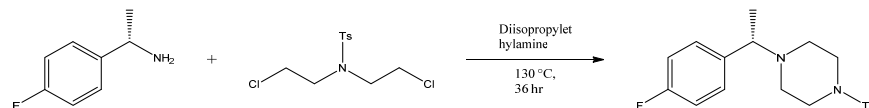
It is believed that the active alumina is able to activate the aniline and, moreover, to scavenge the hydrogen bromide liberated after the first bromo replacement. Herewith, yields have been obtained of 70 to 80 % and it has been concluded that the presence of an electron withdrawing group on the aromatic ring did not affect the yield.

An efficient synthesis of 1-arylpiperazines has been reported by Jaisinghani and Khadilkar⁵⁵ by using microwave irradiation. Herein, the reaction times are reduced tremendously: yields of 47 to 73 % are obtained within 1 to 3 minutes for a number of substituted anilines. These short reaction times could be of immense importance when short-living radioisotopes are used for production of potent neurological radiopharmaceuticals.

Liu and Robichaud⁵⁶ have done research on the synthesis of N-aryl piperazines for a large library of anilines. Although many reported N-aryl piperazine syntheses have made use of basic conditions in order to scavenge the generated hydrogen halide, here these conditions have been avoided since it is believed that basic conditions are partially responsible for the low yields earlier reported. A possible explanation for this is the competitive side reaction between N-aryl piperazine and bis(2-haloethyl)amine. At 150 °C yields have been obtained of 60 to 90 % in 6 to 12 hours. The optimal solvent for giving consistently good to excellent results appeared to be diethylene glycol monomethyl ether.

The use of a protecting group on the bisalkylating agent has further been investigated by Thiel *et al*⁵⁷ whose reaction system is given in Scheme 25.

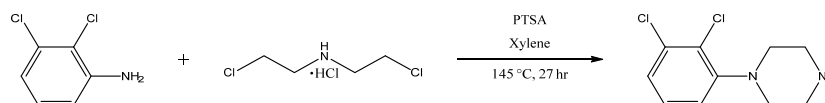
Scheme 25: Production of piperazine derivative by using toluenesulfonamide as protecting group



Herein, diisopropylethylamine has been used as organic base where the formation of the side reaction between N-aryl piperazine and the bisalkylating agent has been prevented by using the toluenesulfonamide protecting group. A yield has been obtained of 96 %.

Pai *et al*⁵⁸ have done research on the synthesis of substituted benzylpiperazine by employing xylene as apolar solvent and p-toluenesulfonic acid as catalyst, as shown in Scheme 26.

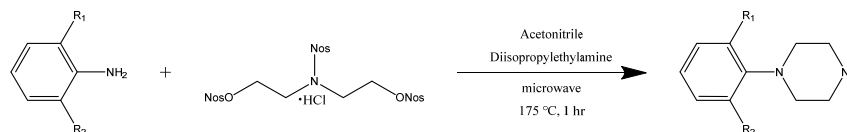
Scheme 26: Synthesis of 2,3-dichlorophenylpiperazine via ring-closing bisalkylating agent and acid catalysis



Hereby, it is believed that the strong acid is able to increase the ability of chlorine to act as leaving group and, thus, to facilitate the nucleophilic substitution. By using this method a yield has been obtained of 82 %.

The research on the synthesis of substituted benzylpiperazines has, so far, mainly been focused on unhindered substituents. Therefore, Gao and Canney⁵⁹ have focused their research on creating efficient routes for the synthesis of N-arylpiperazines with bulky aromatic substituents. Their synthetic approach is given in Scheme 27.

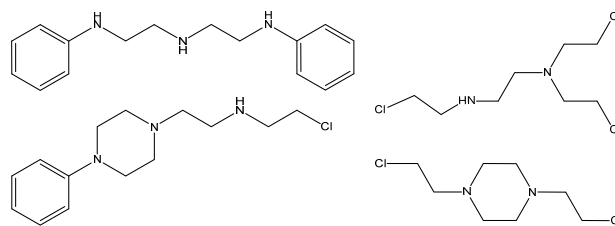
Scheme 27: Synthesis of arylpiperazines with bulky aromatic substituents



Since basic conditions are used, a nosyl protecting group is present to prevent side reactions and, furthermore, this structure has been used as leaving group in ether-form. With this reaction system yields have been obtained of 60 to 86 %.

In the ring-closure synthesis of phenylpiperazine a few by-products can, eventually, be formed. As mentioned before two molecules of aniline can attack the same molecule of bis(2-chloroethyl)amine. Furthermore, especially when using basic conditions, the amine function of bis(2-chloroethyl)amine can become more active, which can potentially lead to several by-products. These potential by-product are shown in Scheme 28.

Scheme 28: Potential by-product in the ring-closure synthesis of phenylpiperazine



In order to shorten the reaction time it is interesting to investigate the synthesis of phenylpiperazine at higher temperatures. However, when a green solvent such as ethanol is used for this purpose, the pressure of the reactor has to be increased. For this reason a micro flow reactor becomes of interest since high reactor pressures can easily be achieved by a back pressure regulator and, because of the small reactor radius, efficient heating of the reactor is guaranteed. A potential problem in a micro flow system is the use of high concentrations. Since the reactor solution has to be pumped into the reactor by an HPLC-pump the reactants should be dissolved without heating the solvent. This can be a limiting factor for the reaction system. When lower concentrations have to be used, the reaction rate can be decreased.

3 Experimental setup

3.1 Synthesis of benzyl azide

An experimental setup has been built in order to investigate the conversion of benzyl chloride and sodium azide towards benzyl azide. The setup is graphically depicted in Figure 4.

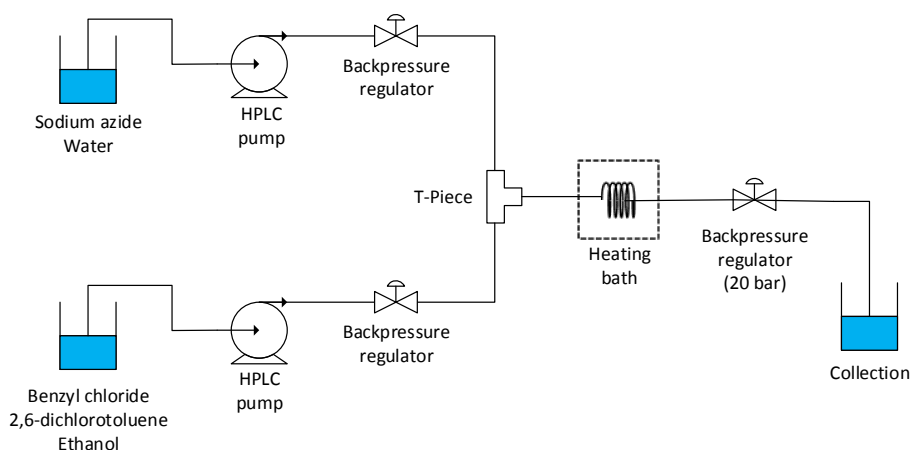


Figure 4: P&ID of the assembled setup, consisting of 2 HPLC pumps, T-piece, heating oil bath and 3 BPR's

The volume of the transparent PFA tubing reactor is 1.74 ml with an inner diameter of 750 μm and a length of 4 m. The HPLC pumps (Knauer Smartline Pump 1050, Ti 10 ml pump head) are able to deliver flow rates in between 0.001 and 9.999 ml/min up to a maximum pressure of 400 bar. The heating is provided by a LAUDA Proline P 8 heating oil bath with a maximum temperature of 300 $^{\circ}\text{C}$ and the reactor pressure achieved by the cartridge back pressure regulator (idex-hs) is around 20 bar.

An aqueous solution is prepared in which sodium azide is dissolved in water and an organic solution is prepared in which benzyl chloride and an internal standard, 2,6-dichlorotoluene, are dissolved in ethanol to make the solution being processable by the pump. The flows are combined before the heating bath with a Tefzel T-piece.

3.2 Synthesis of 2,3-dichlorophenylpiperazine

The synthesis of 2,3-dichlorophenylpiperazine has been investigated in microflow. A typical setup for this purpose has been given in Figure 5.

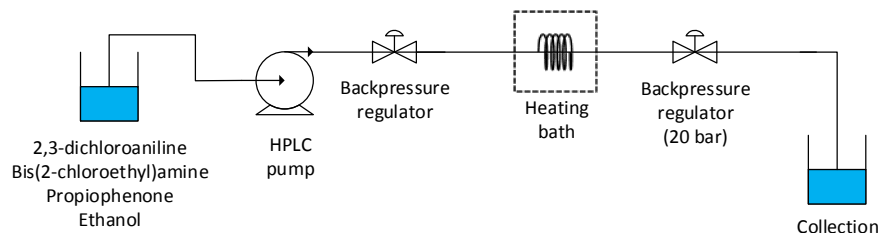


Figure 5: P&ID of the assembled setup, consisting of an HPLC pump, 2 BPR's and an heating oil bath

In the research on this microflow synthesis both stainless steel and PFA have been used as reactor material. The volume of the PFA tubing reactor is 1.3 ml with an inner diameter of 500 μm and a length of 6.7 m. The HPLC pump (Knauer Smartline Pump 1050, Ti 10 ml pump head) is able to deliver flow rates in between 0.001 and 9.999 ml/min up to a maximum pressure of 400 bar. A LAUDA Proline P 8 heating oil bath is used to heat up the reactor up to a maximum of 300 $^{\circ}\text{C}$ and the pressure is regulated by a cartridge back pressure regulator (idex-hs) of 20 bar.

The research on the stainless steel reactor has been done in a similar setup as shown in Figure 5 using SS316 as reactor material provided by Vici. The volume of the reactor is 1.73 ml with an inner diameter of 500 μm and a length of 8.8 m. The pressure is regulated by a 60 bar back pressure regulator and an additional HPLC pump is used to quench the reactor outlet stream with ethanol.

4 Results and discussion

4.1 Synthesis of benzyl azide

To investigate the performance of the capillary microreactor on the production of benzyl azide from benzyl chloride and sodium azide, experiments have been performed while varying the reactor temperature and residence time of the reactants. In order to make the organic solution being processable by the pump the benzyl chloride is diluted with ethanol in a ratio of 1 : 2.6. The inlet concentrations of both benzyl chloride and sodium azide have been kept constant in every experiment and equal to 2.3 mol L^{-1} . The volumetric flow rates are equal for both solutions as well and depend on the residence time of the involved experiment.

Experiments have been performed with residence times of respectively 2.5, 5 and 10 minutes and each residence time is investigated for a temperature range of 60 to 150 °C. The yield of benzyl azide for each experiment is graphically depicted in Figure 6. It has been shown that 97 % yield of benzyl azide has been obtained within 2.5 minutes residence time. Hereto, a temperature of approximately 150 °C is necessary. Increasing the residence time up to 10 minutes allows decreasing the reactor temperature to 120 °C while keeping 97 % yield.

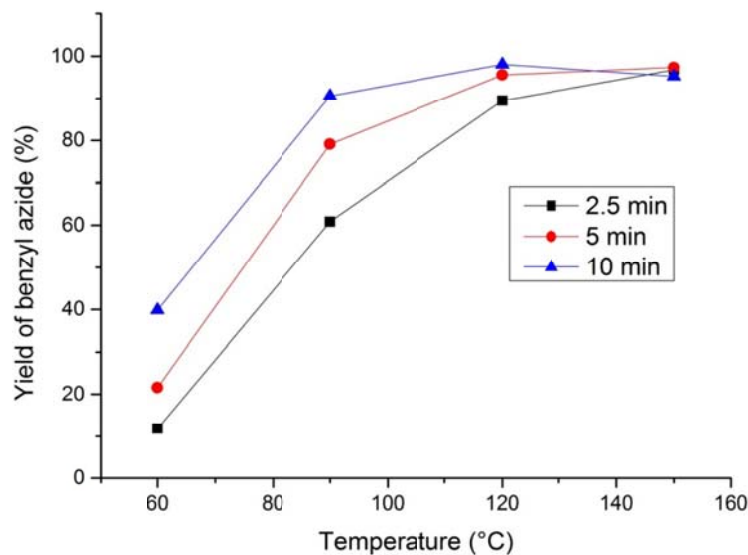


Figure 6: Yield of benzyl azide as function of temperature for 2.5, 5 and 10 minutes residence time

Since in the reactor both benzyl chloride and water are present, the hydrolysis of benzyl chloride can take place. It has been verified that at higher temperature and residence time benzyl alcohol is formed. This explains the small decrease in yield of benzyl azide at 10 minutes residence time above 120 °C as observed in Figure 6. At 120 °C benzyl chloride has been completely converted within 10 minutes residence time; approximately 2 % has been converted in benzyl alcohol.

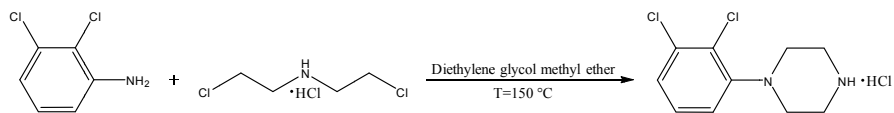
With the obtained results the research on the synthesis of benzyl azide in the multistep synthesis of rufinamide has been completed. Since the setup for the first step in this multistep synthesis, the chlorination of alcohols using hydrogen chloride gas, is still under development and the following steps have already been investigated by our group, the focus of this project has been shifted towards the synthesis of piperazine derivatives.

4.2 Synthesis of 2,3-dichlorophenylpiperazine

4.2.1 Reaction in batch

In order to investigate the reaction rate of the synthesis of 2,3-dichlorophenylpiperazine the procedure of Liu and Robichaud⁵⁶ has been applied on 2,3-dichloroaniline and bis(2-chloroethyl)amine, as shown in Scheme 29.

Scheme 29: Synthesis of 2,3-dichlorophenylpiperazine via a ring-closure reaction between 2,3-dichloroaniline and bis(2-chloroethyl)amine



Hereto, both reactants have been dissolved in diethylene glycol monomethyl ether in stoichiometric amounts at 4 mol L^{-1} . Since the reaction consists of two consecutive second order nucleophilic substitutions these high concentrations are in principle favorable for the reaction rate. The intermediate that has been formed in between is shown in Figure 7.

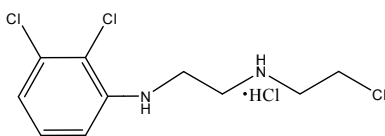


Figure 7: Intermediate formed in the ring-closure synthesis of 2,3-dichlorophenylpiperazine

The reaction has been done at 150 °C and propiophenone has been used as internal standard for the yield determination. The yield of 2,3-dichlorophenylpiperazine as function of time is depicted in Figure 8.

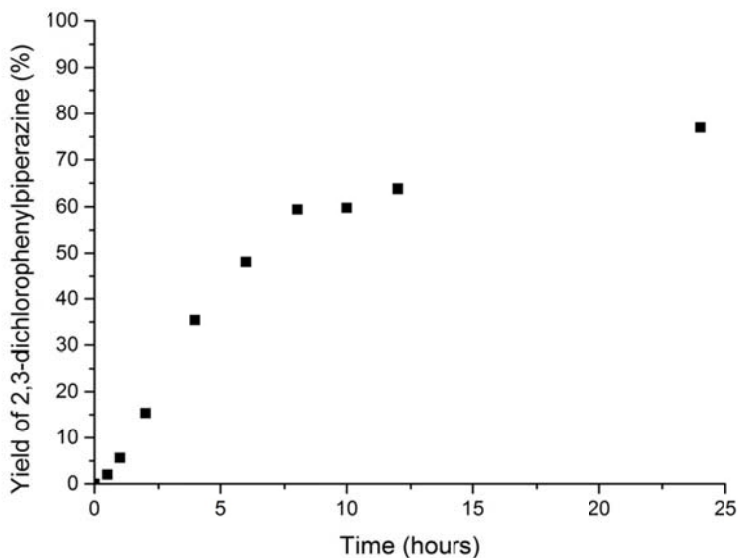


Figure 8: Yield of 2,3-dichlorophenylpiperazine as function of time

It has been shown that the yield of 2,3-dichlorophenylpiperazine after 8 hours reaction time equals approximately 60 %. Hereafter, the yield is slowly increasing further up to approximately 77 % after 24 hours. Liu and Robichaud have

investigated different kind of anilines; however, they have not tested the current substrate. They have found yields in 6 to 12 hours of 60 to 95 %. Direct comparison of these results with the current yield is inaccurate, since the exact reaction time per experiment is unknown.

To boost the reactivity of the reactants it would be favorable to increase the temperature. In a microflow setup higher temperatures can be achieved by applying pressure on the system. Furthermore, a microflow system would open the way to use a much greener solvent, e.g. ethanol, since its boiling point can be significantly increased by the pressure. However, since the concentrations in the batch experiment are very high, this can be a problem in the flow setup due to clogging.

4.2.2 Reaction in flow

As a first attempt to produce 1,2-dichlorophenylpiperazine in microflow a stainless steel microreactor has been used. A stainless steel reactor has been chosen since this type of material is excellent for high pressure and temperature investigations. A higher temperature could, potentially, accelerate the reaction since it increases the reaction rate constant via the Arrhenius equation. For this purpose bis(2-chloroethyl)amine and 2,3-dichloroaniline are dissolved in ethanol and fed through a reactor of 7.86 ml at a temperature of 210 °C at a pressure of 60 bars. The residence time was equal to 60 minutes, meaning a flow rate of 0.131 ml/min. When this reaction system is operated for a few hours it has been observed that the reactor was leaking. The probable cause for this event is the presence of a hydrogen chloride molecule on the bisalkylating agent. At high temperatures it is likely that these acidic conditions are enabling corrosion at the metallic surface which can, after some time, lead to leaking. This is supported by the diagram, shown in Figure 9, in which the rate of corrosion in stainless steel 316 is given as function of temperature and hydrochloric acid concentration.⁶⁰ Obviously, this system differs from the current reaction system since in the diagram aqueous hydrochloric acid has been used. However, the diagram shows that above 50 °C the rate of corrosion is more than 1 mm year⁻¹. In the experiment the concentration of bis(2-chloroethyl)amine hydrogen chloride was equal to 0.75 mol L⁻¹. When the formation of additional hydrogen chloride as by-product is being ignored and the concentration hydrogen chloride is assumed to be equal to 0.75 mol L⁻¹, the weight percentage hydrogen chloride is approximately 3.5 %. Combined with the high reactor temperature of 210 °C, leakage due to corrosion is probable. It is unlikely that the corrosion has been caused just by ethanol and the high temperature, since research on corrosion of the same type of stainless steel at various conditions showed that there was no corrosion at 200 °C with pure ethanol.⁶¹

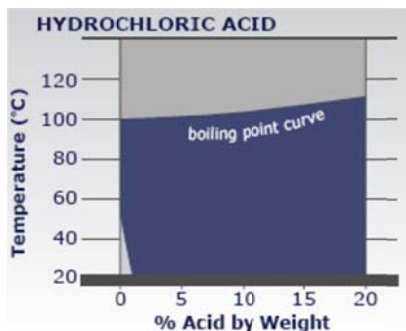


Figure 9: Corrosion resistance for SS316 as function of weight % hydrochloric acid⁶⁰

In order to prevent corrosion the bis(2-chloroethyl)amine has been treated with a base. For this purpose caustic soda has been used. As solvent for this reaction 2-methyltetrahydrofuran has been used because this solvent is immiscible with water and, therefore, enables extraction. When the reaction has been done with a concentration of bis(2-chloroethyl)amine of 1.0 mol L^{-1} clogging has been observed within a few minutes at a residence time of 5 minutes. Decreasing the concentration to 0.5 mol L^{-1} has delayed the clogging to 10 minutes residence time and when the concentration of bis(2-chloroethyl)amine has been decreased to 0.2 mol L^{-1} the clogging occurred at a residence time of 30 minutes.

Moreover, it has also been observed that, when the stainless steel tubing is exposed to the neutralized reaction mixture, still leakages are being formed after some time. That means that other options to prevent corrosion have to be investigated. Since the clogging is always, after some time, accompanied with leakages due to corrosion it is believed that the clogging has been caused by the corrosion. When the reactor is being unclogged a viscous slurry leaves the reactor at the outlet. Possibly, this slurry consists of reactants combined with heating oil entering the reactor due to the leakage upon cooling.

To investigate the micro flow synthesis of 2,3-dichlorophenylpiperazine without clogging and leakages PFA tubing has been investigated as reactor material. PFA has excellent chemical resistance which means that corrosion is unlikely. With respect to stainless steel PFA tubing has the disadvantage that it is less strong which limits the pressure and temperature that can be applied on the reactor. The pressure in the reactor is limited to 20 bars while the temperature cannot be higher than $180 \text{ }^\circ\text{C}$. The lowest concentration that has been investigated in the stainless steel reactor equals 0.2 mol L^{-1} and, therefore, this concentration has been used as initial concentration in the PFA tubing reactor. This concentration can, after successful operation, be increased step by step to see the influence of the concentration. Since corrosion is not an issue the extraction to neutralize the bis(2-chloroethyl)amine has been left out. The pressure in the reactor has been regulated by a back pressure regulator of 20 bars and the temperature has been set to $170 \text{ }^\circ\text{C}$. When a residence time of 1 hour is used the yield of 2,3-dichlorophenylpiperazine equaled 6.4 %. Compared with its yield at 1 hour reaction time in the batch experiment, the yield in the flow experiment is approximately the same.

Another possible solution to prevent corrosion in a stainless steel tubing reactor is mixing the reactants mixture with an organic base instead of extracting bis(2-chloroethyl)amine with a base prior to mixing. In order to investigate the influence

of such an organic base on the reactor performance, a test experiment has been performed in PFA tubing. Triethylamine has been selected as a base since it is relatively inexpensive and it has been mixed with 2,3-dichloroaniline, bis(2-chloroethyl)amine and an internal standard. The conditions have been kept constant, meaning that the reactor temperature is 170 °C and the residence time is one hour. With this reaction system it has been shown that the yield of 2,3-dichlorophenylpiperazine is equal to 4.2 %. Since this yield is approximately equal to two-thirds of the yield obtained without using triethylamine it has been shown that the organic base has a negative influence on the reactor performance.

So far, the best results in microflow has been obtained in PFA tubing at 170 °C, 1 hour residence time and 0.2 mol L⁻¹ of bis(2-chloroethyl)amine in 1.5 equivalents excess. To intensify this process it has been investigated how the reactor performs at higher concentrations in identical conditions. The yield as function of the bis(2-chloroethyl)amine concentration is depicted in Figure 10. When the bis(2-chloroethyl)amine has a concentration of 0.5 mol L⁻¹ the yield of 2,3-dichlorophenylpiperazine has been increased up to 15.4 %. Increasing the concentration even further to 1.0 mol L⁻¹ has resulted in a yield of 26.5 %. This significant improvement of the yield has been caused by the increase of the concentrations, since the reaction is a second order nucleophilic substitution.

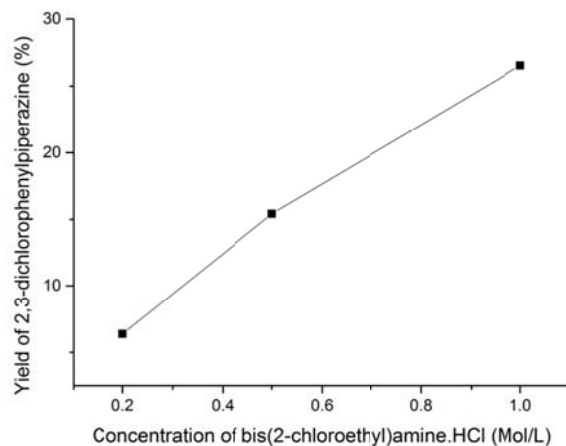


Figure 10: Yield of 2,3-dichlorophenylpiperazine as function of concentration of bis(2-chloroethyl)amine.HCl at 170 °C and 1 hour residence time

Hereafter, the concentration of 2,3-dichloroaniline has been kept constant at 0.67 mol L⁻¹ as in the experiment at 1 mol L⁻¹ of bis(2-chloroethyl)amine. The concentration of the bisalkylating agent has been increased to investigate the influence of different stoichiometric ratios. When 2 equivalents of bis(2-chloroethyl)amine are used the yield of 2,3-dichlorophenylpiperazine has been increased to 30.6 %.

Although the PFA tubing has been tested at its limitations regarding temperature and pressure, the achieved yields are still not satisfactory. Therefore, stainless steel tubing is becoming of interest since this has a larger potential for research at high temperature and pressure. However, it has already been shown

that with the common reaction system corrosion occurs after some time. Furthermore, extraction of bis-2-chloroethylamine with sodium hydroxide did not have the desired effect. PFA tubing has been used to test the influence of the organic base triethylamine on the reactor performance and it has been shown that it had a negative influence on the yield. However, when triethylamine would enable the use of stainless steel, the improvement in temperature could eventually compensate the loss in reactivity due to the base or even improve the performance. Stoichiometric amounts of reactants have been used and the concentration was 0.8 mol L^{-1} . The excess of triethylamine was equal to 1.5 equivalents and the reactor flow has been quenched with 0.8 ml/min of ethanol at the reactor outlet. At $180 \text{ }^\circ\text{C}$ and 30 minutes residence time it has been shown that the yield of 2,3-dichlorophenylpiperazine was equal to 7.0 %. When the temperature was increased to $200 \text{ }^\circ\text{C}$ the reactor started to clog.

5 Conclusions and recommendations

5.1 Conclusions

5.1.1 Synthesis of benzyl azide

A capillary microreactor has been used in order to investigate the continuous flow synthesis of benzyl azide by reaction of benzyl chloride and sodium azide. Benzyl chloride has been diluted with 2.6 volume equivalents of ethanol to make it being processable by the pump. When the concentrations of both sodium azide in water and benzyl chloride were equal to 2.3 mol L^{-1} and equal flow rates were used to obtain stoichiometric amounts, the yield of benzyl azide has been investigated as function of temperature and residence time. It has been shown that 97 % yield of benzyl azide can be obtained within 2.5 minutes residence time at $150 \text{ }^\circ\text{C}$ with no excess of azide. Furthermore, it has been shown that at higher temperatures the hydrolysis of benzyl chloride to benzyl alcohol becomes more significant. The formation of this by-product was shown to have a yield of 3 % at $150 \text{ }^\circ\text{C}$ and 2.5 minutes residence time.

5.1.2 Synthesis of 2,3-dichlorophenylpiperazine

The synthesis of 2,3-dichlorophenylpiperazine has been investigated in batch using a general applied synthetic strategy. Hereto, 2,3-dichloroaniline and bis(2-chloroethyl)amine reacted at $150 \text{ }^\circ\text{C}$ in diethylene glycol monomethyl ether. After 8 hours a yield has been obtained of approximately 60 %. In a PFA capillary microreactor ethanol has been tested as solvent and a maximum yield has been obtained of 30.6 % using 2 equivalents of bis(2-chloroethyl)amine. It has been shown that this yield strongly depends on the concentration of reactants. When the same reactants system is used in a stainless steel micro reactor corrosion of the reactor has been observed. Extraction of bis(2-chloroethyl)amine hydrogen chloride adduct with sodium hydroxide was performed prior to its use in a stainless steel micro reactor to remove hydrogen chloride and prevent corrosion, however this did not prevent the corrosion. Furthermore, 1.5 equivalents of triethylamine were added to the reacting mixture to remove hydrogen chloride from the reacting medium. When performed in PFA tubing at $170 \text{ }^\circ\text{C}$ and 60 minutes residence time, the reaction resulted in 4.2 % yield, a decrease of approximately 34 % compared to the experiment without the use of a base. In stainless steel tubing at $180 \text{ }^\circ\text{C}$, 30 minutes residence time and 0.8 mol L^{-1} the yield was 7 %. With increase in temperature up to $200 \text{ }^\circ\text{C}$ clogging was observed.

5.2 Recommendations

Since the experiments in a micro flow reactor did not have the desired results other options have to be investigated. Herein, the focus should be on reactors that can be exposed to high temperatures and pressure combined with excellent corrosion resistance. A reactor which meets these requirements is the ESK micro flow reactor out of EKasic Silicon Carbide. It is claimed that this reactor has a temperature resistance up to 1500 °C and that it has an excellent chemical resistance against aggressive media. When corrosion in this reactor does not take place after exposure to bis(2-chloroethylamine), addition of a base is unnecessary. Since it has been shown that triethylamine has a negative influence on the reactor performance, this reactor would, then, be very high-potential.

Another potential micro flow reactor material is called Hastelloy alloy C-276. This alloy, consisting mainly of nickel, chromium and molybdenum, is claimed to be the most versatile corrosion resistant alloy available. In Figure 11 the corrosion rate as function of temperature and concentration hydrochloric acid is given. It is shown that at 3.5 weight % hydrochloric acid and 100 °C, the rate of corrosion is approximately 1.3 mm year⁻¹. Since the temperature of interest is much higher and the nature of the hydrogen chloride is different, no conclusions can be drawn regarding Hastelloy-276 as reactor material for the synthesis of 2,3-dichlorophenylpiperazine. However, the material shows more potential than stainless steel.

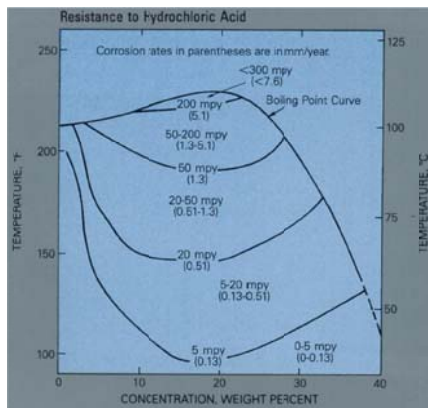


Figure 11: Corrosion resistance for Hastelloy C-276 as function of weight % hydrochloric acid

Once a suitable flow reactor has been found the reaction between 2,3-dichloroaniline and bis(2-chloroethyl)amine can be optimized regarding concentrations, temperature and residence time. These optimal conditions can, thereafter, be applied on the other amines. In the introduction it has been noticed that benzyl amine, diphenylamine and aminopyrimidine are interesting substrates due to their applications in the pharmaceutical industry.

6 Supplementary Information

For analytical purposes GC-FID and HPLC have been used for respectively the experiments with sodium azide and piperazines. A quantitative analysis of the GC-FID data has been performed using 2,6-dichlorotoluene as internal standard and for the HPLC propiophenone has been used for the same purpose. Chemicals have been purchased in their highest purity available from Sigma-Aldrich.

6.1 Analytical methods

6.1.1 GC method for determination yield of benzyl azide

Column: cp-sil 5 cb
Length: 30 m
Inner diameter: 0.25 mm
Film thickness: 1 μm
Injection volume: 0.2 μl
Split ratio: 1/10
Injection temperature: 250 $^{\circ}\text{C}$
Detector temperature: 280 $^{\circ}\text{C}$
Air flow: 300 ml min^{-1}
Hydrogen flow: 30 ml min^{-1}
Make up flow: 25 ml min^{-1}
Initial temperature: 50 $^{\circ}\text{C}$ (2 min)
Rate a: 10 $^{\circ}\text{C/min}$ (up to 150 $^{\circ}\text{C}$)
Rate b: 15 $^{\circ}\text{C/min}$ (up to 230 $^{\circ}\text{C}$)
End temperature: 230 $^{\circ}\text{C}$ (2 min)

6.1.2 HPLC method for determination yield of 2,3-dichlorophenylpiperazine

Deliverer: Shimadzu
Pump type: LC-20AD xr
Column: GraceSmart RP 18 5u
Length: 150 mm
Internal diameter: 4.6 mm
Detector: Photodiode array (PDA), SPD-M20A
Wavelength: 230 nm
Injection volume: 1 μl
Temperature oven: 35 $^{\circ}\text{C}$
Eluent: 0.1 vol% formic acid in water (75 %), acetonitrile (25 %)

Flow rate: 1 ml/min
Running time: 25 min

6.2 Synthetic procedures

6.2.1 Flow synthesis of benzyl azide

Sodium azide (1.50 g, 23 mmol) was dissolved in 10 ml water to obtain a solution of 2.3 mol L⁻¹. Benzyl chloride (2.91 g, 23 mmol) and 2,6-dichlorotoluene (0.741 g, 4.6 mmol) were dissolved in 10 ml ethanol. HPLC pumps (Knauer Smartline pump 1050, Ti 10 ml pump head) are used to pump both solutions. The flow rates of both pumps were equal and depending on the residence time desired. The volume of the PFA capillary micro reactor was 1.74 ml and a LAUDA Proline P 8 heating oil bath was used to heat the reactor to the desired temperature. The pressure was 20 bar and it was regulated by a back pressure regulator. Samples were collected at the outlet of the reactor and analyzed by GC. Three reactor volumes were allowed to pass as waste before taking a sample of two reactor volumes.

6.2.2 Batch synthesis of 2,3-dichlorophenylpiperazine

Procedure is reproduced from Liu and Robichaud, *Tetrahedron Letters* 46 (2005) 7921-7922

2,3-dichloroaniline (0.486 g, 3 mmol), bis(2-chloroethyl)amine hydrochloride (0.535 g, 3 mmol) and propiophenone (0.081 g, 0.6 mmol) were dissolved in diethylene glycol monomethyl ether (0.75 ml). The mixture was heated to 150 °C for 6 hours and the yield of 2,3-dichlorophenylpiperazine was monitored via HPLC.

6.2.3 Flow synthesis of 2,3-dichlorophenylpiperazine in stainless steel tubing after base extraction

Bis(2-chloroethyl)amine (6.25 g, 35 mmol) was mixed with 70 ml 2-methyltetrahydrofuran in a beaker and, subsequently, 70 ml of 0.5 mol L⁻¹ sodium hydroxide in water was added. After mixing and extraction the organic layer was mixed with 2,3-dichloroaniline (3.78 g, 23 mmol) and propiophenone (0.626 g, 4.7 mmol). An HPLC pump (Knauer Smartline pump 1050, Ti 10 ml pump head) is used to pump the solution through a 4.56 ml stainless steel reactor and the flow rate depends on the residence time of interest. The reactor was heated to 210 °C by a LAUDA Proline P 8 heating oil bath and the pressure in the reactor was fixed at 60 bar by a back pressure regulator. Three reactor volumes were allowed to pass as waste before taking three samples which were analyzed by HPLC. When clogging was observed by a rapidly increasing pressure the flow was stopped and switched to tetrahydrofuran. If necessary the clogging was tried to be removed by sonication.

6.2.4 Flow synthesis of 2,3-dichlorophenylpiperazine in PFA tubing

Bis(2-chloroethyl)amine (3.57 g, 20 mmol), 2,3-dichloroaniline (2.16 g, 13.3 mmol), propiophenone (0.358 g, 2.67 mmol) were dissolved in ethanol (20 ml). An HPLC pump (Knauer Smartline pump 1050, Ti 10 ml pump head) is used to pump the solution and the flow rate depends on the residence time desired. The volume of the PFA capillary micro reactor was 1.3 ml and a LAUDA Proline P 8 heating oil bath was used to heat the reactor to the desired temperature. The pressure was 20

bar and it was regulated by a back pressure regulator. Samples were collected at the outlet of the reactor and analyzed by HPLC. Three reactor volumes were allowed to pass as waste before taking three samples per experiment. This procedure can be adjusted to other concentrations of interest. Furthermore, triethylamine can be added to the same solution.

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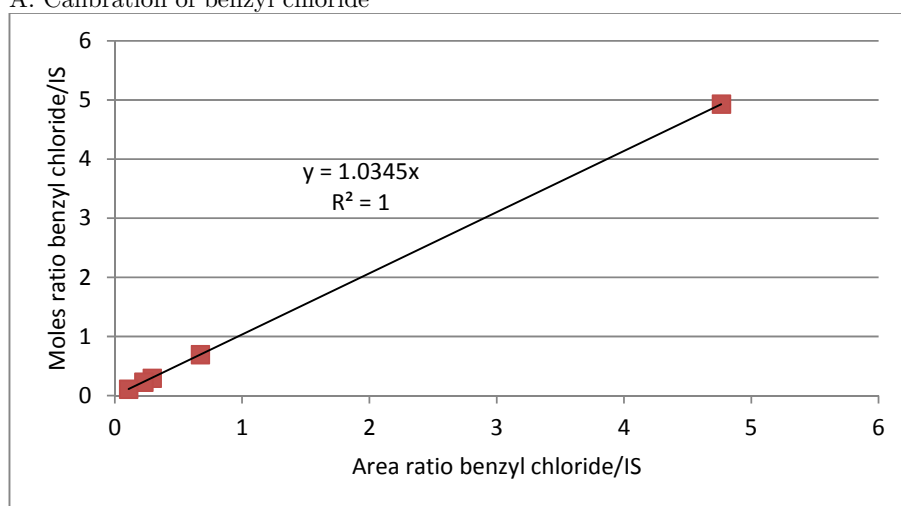
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8 Appendices

A: Calibration of benzyl chloride



B: Calibration of 1,2-dichlorophenylpiperazine

