Periodica Polytechnica
Chemical Engineering

Preparation of Pyridine *N*-oxide Derivatives in Microreactor

58(2), pp. 195-205, 2014
DOI:10.3311/PPch.7451

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RESEARCH ARTICLE

RECEIVED 1 APRIL 2014; ACCEPTED AFTER REVISION 12 JUNE 2014

Abstract

N-oxidations of different nitrogen-containing heterocyclic molecules are often applied for synthetic transformations in chemistry. The industrial implementation of classical batch oxidation processes are limited due to safety concerns derived from metal ion catalyzed decompositions. These restrictions and other safety concern issues can be minimized or even avoided by applying glass made microreactor setups for this transformation. The N-oxidation of different pyridine derivative, quinoline and isoquinoline is studied using two popular oxidizing reagents. The further transformation of pyridine derivatives is studied through the Polonovski rearrangement in microreactor.

Keywords

microreactor technology · N-oxide · oxidation · Polonovski rearrangement · safety concern reaction

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Introduction

Microflow technology

In the recent years the importance of microreactors are continuously growing in R&D and industrial applications as well. This popularity originates from the unique properties of this technology such as: very precise temperature control, outstanding mixing and heat exchange due to the high surface to volume ratio. With an extremely low active reactor volume, 'safety concern' chemicals and chemical processes can be handled in safe manner under inert conditions. Based on evidence gained from several examples, the scale-up of microreactors is also expected to be less problematic compared to batch processes, due to the reduced amount of critical scale-up parameters. [1]

In this paper, we describe our recent results on the *N*-oxidation of different pyridine derivatives, quinoline and isoquinoline with *m*-CPBA in DCM or aqueous H_2O_2 in acetic acid using microreactor technology.

N-oxide derivatives

The *N*-oxide type molecules can be found in several active pharmaceutical ingredients (such as: Chlordiazepoxide as sedative, [2] Tirapazamine as anticancer, [3] Phenazopyridine, [4] Flupirtine, [5] Propirame [6] as analgestic, Phenyramidol muscle relaxant [7]) (Figure 1), in addition *N*-oxides are typical metabolic intermediates in the human organism, so the synthetic preparation of those *N*-oxides from tertiary amines has a high importance in drug development [8].

Since the aromatic substitution reactions of pyridine leads to *meta*-substituted derivatives even under harsh conditions, the *N*-oxide derivative has significance in synthetic transformations. In the substitution reaction of pyridine *N*-oxides the preferred products are *ortho*- and *para*-substituted derivatives, additionally the *N*-oxide can be easily reduced by PCl_3, [9, 10] PPh_3, [11] Raney Ni/H_2 or Pd/C, [12] Fe/AcOH, [13] Zn/aq NH_4Cl, [14] $NaBH_4/AlCl_3$, [15] NH_4COOH-Pd/C, [16] $TiCl_3$, [17] AlI_3. [18]

Another very important application of the *N*-oxide intermediate is the preparation of 2-hydroxypyridine derivatives,

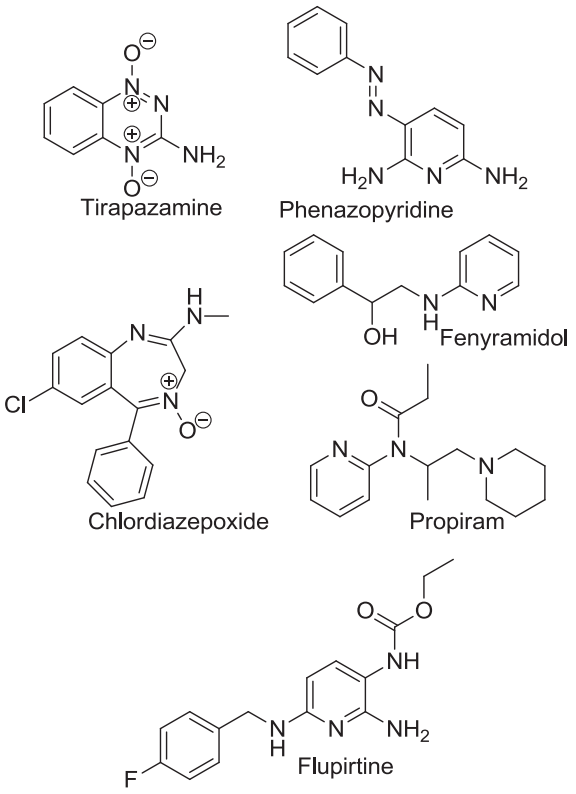

Fig. 1. Biologically active 2-substituated pyridine and N-oxide derivatives

which can be synthesized with Polonovski rearrangement in the presence of TFAA or with Ac_2O at high temperature. [19, 20] The 2-hydroxypyridines can be further functionalized into different 2-substituted pyridine derivatives. [21-26]

N-oxidants

Different *N*-oxidants are well known in the literature for heteroatom oxidation. In our studies, the reactions were carried out with *m*-CPBA in DCM or with aqueous H_2O_2 in acetic acid, so these compounds were described in detail regarding their safety aspect.

The *m*-chloroperoxybenzoic acid (*m*-CPBA) is an expensive reagent ($62/kg calculate to 1 ton pyridine). The material related safety concerns and issues are well-known in pharmaceutical pilot scale applications. [27, 28] The *m*-CPBA (commercial grade is 70-77%) is a shock sensitive and explosive compound but it can be stabilized by 3-chlorobenzoic acid. [29] Because of ~30% 3-chlorobenzoic acid the atom economy is low, so the application of the compound is not preferred environmentally.

The other important oxidant is H_2O_2. The heterocyclic compounds do not react with a unique H_2O_2 therefore the utilization of an acid is necessary, with which peracids are prepared *in situ.* The percarboxylic acids are very popular and easy to handle reactants, including the well-known and mostly applied peracetic acid. Hydrogen peroxide is an inexpensive (~$0.5/kg calculate to 1 ton pyridine) and easy to use reagent, but as a powerful oxidant, there are some limiting safety aspects for the

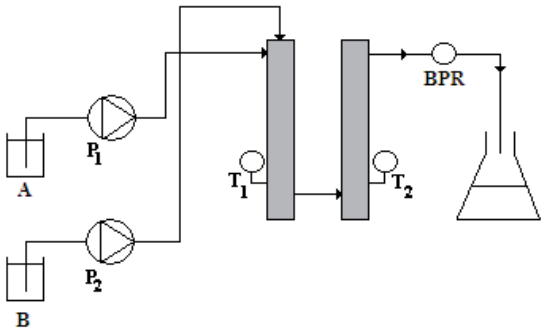

Fig. 2. Corning LF reactor with two plates (A) Nitrogen-containing compound in solvent. (B) Oxidant. BPR: back pressure regulator

large scale applications. Peroxide decomposes to oxygen and water while a large amount of heat is liberated which can lead to an increased rate of decomposition. The decomposition of H_2O_2 is continuous and goes on slow rate, but the decomposition rate accelerates with increasing temperature. This rate increases about 2.2 times per 10°C temperature increase over the range 20 and 100°C. [30] The oxidizable materials (metals and their ions) catalyze exothermic decomposition of H_2O_2 and the effectiveness of decomposition decreases in the following order of metals: osmium, palladium, platinum, iridium, gold, silver, manganese, cobalt, copper, lead. [31] The addition of H_2O_2 is incompatible with acetic anhydride, acetone, alcohols, carboxylic acids, nitrogen-containing bases, organic compounds, since they catalyze its decomposition and it can cause explosion. [32] Pilot and industrial scale processes and the safe utilization of hydrogen peroxide are also well known. [27] *N*-oxidation with hydrogen peroxide in acetic acid is an eco-friendly process, generating water in the reaction. The used microreactor is made of borosilicate glass and it does not contain any metal, so H_2O_2 does not decompose under the applied conditions.

In addition, other popular reagents for *N*-oxidations are: perphtalic acids (magnesium- monoperphtalate (MMPP)), [33] performic acid, [34] pertrifuoricacetic acid, [35, 36] peroxymonosulfuric acid, [37] bromate, metal oxidants such as chromic acid and permanganate, [38] perphosphoric acid, [39] permaleinic acid [40, 41, 42] and urea-hydrogen peroxide (UHP). [43]

Results and Discussion

The applicability of a continuous *N*-oxidation is investigated using pyridine with *m*-CPBA in DCM (Figure 2). The conversions are determined by HPLC. For the continuous process a Corning LF type microreactor is used with two reactor plates (2x0.45ml volume) and a two line dosing with Encynova Novasync pump is applied (P1: pump 1 and P2: pump 2). The nitrogen-containing compounds in solvent are dosed through one of them, and the other line is used for the oxidant. The reaction mixture is quenched with 10% water solution of sodium pyrosulfite. The effect of different reaction parameters under continuous conditions are investigated and summarized in

Tab. 1. Results of pyridine with *m*-CPBA reactions in microreactor (2 bars)

	temperature (°C)	residence time (min)	HPLC (relative area %)	
			2a	1a
1	50	0.25	89	11
2	50	0.5	94	6
3	50	1	95	5
4	50	2	98	2
5	50	3	100	0
6	100	0.25	94	6
7	100	0.5	94	6
8	100	1	94	6

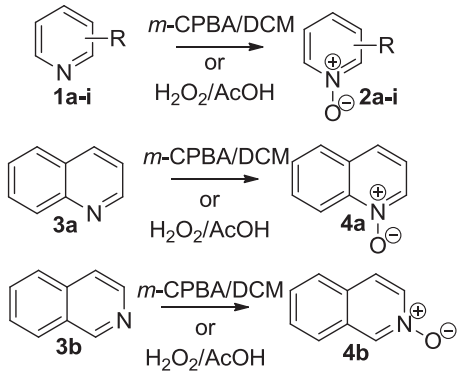

Fig. 3. Reactions of pyridine derivatives, quinoline and isoquinoline with *m*-CPBA in DCM or with 27% water solution of H_2O_2 in acetic acid

Table 1. The residence time and temperature are changed and the best result is achieved at 3 min residence time and 50 C, so all the other derivatives of pyridine are studied under this optimized condition (Figure 3). Under batch conditions the reaction is carried out at room temperature and 3 min reaction time. The results of batch and continuous mode operation are compared but significant differences cannot be noticed in this case. This result can be explained by the rapid reaction therefore the advantage of using a microreactor in this case is not significant (Table 2).

Tab. 3. Fast screening of pyridine with 27% water solution of H_2O_2 in acetic acid and microreactor (2 bars), 1.1 equivalent (eq) H_2O_2

	temperature (°C)	residence time (min)	HPLC (relative area %)	
			2a	1a
1	50	1	0	100
2	50	5	0	100
3	50	10	0	100
4	100	10	12	88
5	150	10	34	66

Tab. 4. Temperature dependency of pyridine with 27% water solution of H_2O_2 in acetic acid in microreactor (2 bars) 5 eq H_2O_2, 30 min residence time

	temperature (°C)	HPLC (relative area %)	
		2a	1a
1	100	49	51
2	110	33	67
3	120	12	88
4	130	9	91
5	140	13	87
6	150	33	67

Since the original aim of this research work is to develop an appropriate and environmentally friendly synthetic method for *N*-oxidation, next the effect of parameters on the *N*-oxidation of pyridine is studied with hydrogen peroxide in acetic acid as well (Table 3).

When the temperature is increased up to 150°C, 34% *N*-oxide is observed at increased residence time. The reaction is also studied between 100 and 150°C at increased residence time (30 min) and 5 eq H_2O_2 (Table 4). The best conversion is can be reached at 130°C, which is 91.5%.

Tab. 2. The comparison of results of pyridine derivatives, quinoline and isoquinoline with *m*-CPBA

	Heterocycles				
	Pyridine derivatives	HPLC (realtive area %, batch) RT		HPLC (realtive area %, μreaktor) 50 °C, 2 bar	
1	pyridine	96 (**12a**)	4 (**11a**)	100 (**12a**)	0 (**11a**)
2	2-methyl	95 (**12b**)	5 (**11b**)	95 (**12b**)	5 (**11b**)
3	2-ethyl	97 (**12c**)	3 (**11c**)	99,5 (**12c**)	0,5 (**11c**)
4	2-benzyl	92 (**12d**)	8 (**11d**)	92,5 (**12d**)	7,5 (**11d**)
5	3-methyl	96 (**12e**)	4 (**11e**)	97 (**12e**)	3 (**11e**)
6	2-bromo	90 (**12f**)	10 (**11f**)	92 (**12f**)	8 (**11f**)
7	3-bromo	80,5 (**12g**)	19,5 (**11g**)	84 (**12g**)	16 (**11g**)
8	2-cyano	54 (**12h**)	46 (**11h**)	56 (**12h**)	44 (**11h**)
9	4-cyano	47 (**12i**)	53 (**11i**)	60 (**12i**)	40 (**11i**)
10	quinoline	87 (**25a**)	13 (**24a**)	90 (**25a**)	10 (**24a**)
11	isoquinoline	85 (**25b**)	15 (**24b**)	92 (**25b**)	8 (**24b**)

Tab. 5. Residence time dependency of pyridine with 27% water solution of H_2O_2 in acetic acid (2 bars) 5 eq H_2O_2, at 130°C

	residence time (min)	HPLC (relative area %)	
		2a	1a
1	18	15	85
2	24	12	88
3	30	8.5	91.5
4	36	16.5	83.5

Tab. 6. Residence time dependency of pyridine with 27% water solution of H_2O_2 in acetic acid in microreactor (2 bars) 30 min residence time at 130°C

	H_2O_2 excess	HPLC (relative area %)	
		2a	1a
1	18	15	85
2	24	12	88
3	30	8.5	91.5
4	36	16.5	83.5

Tab. 7. The comparison of results of pyridine derivatives, quinoline and isoquinoline with 27% water solution of H_2O_2 in acetic acid

	Heterocycles				
	Pyridine derivatives	HPLC (realtive area %, batch) 70 °C		HPLC (relative area %, μreaktor) 130°C, 2 bar	
1	pyridine	34 (**12a**)	66 (**11a**)	100 (**12a**)	0 (**11a**)
2	2-methyl	16 (**12b**)	84 (**11b**)	62 (**12b**)	38 (**11b**)
3	2-ethyl	15 (**12c**)	85 (**11c**)	78 (**12c**)	22 (**11c**)
4	2-benzyl	19 (**12d**)	81 (**11d**)	66 (**12d**)	34 (**11d**)
5	3-methyl	28 (**12e**)	72 (**11e**)	80 (**12e**)	20 (**11e**)
6	2-bromo	2 (**12f**)	98 (**11f**)	15 (**12f**)	85 (**11f**)
7	3-bromo	9 (**12g**)	91 (**11g**)	65 (**12g**)	35 (**11g**)
8	2-cyano	41 (**12h**)	59 (**11h**)	79 (**12h**)	21 (**11h**)
9	4-cyano	30 (**12i**)	70 (**11i**)	92 (**12i**)	8 (**11i**)
10	quinoline	37 (**25a**)	64 (**24a**)	74 (**25a**)	26 (**24a**)
11	isoquinoline	26 (**25b**)	74 (**24b**)	64 (**25b**)	36 (**24b**)

In the later experiments the temperature is fixed at 130°C. From the effect of residence time it can be seen that the conversion decreases if the residence time is higher than 30 min, which can be due to the decomposition of the product (Table 5).

In the following experiments beside the fixed residence time and temperature, the effect of hydrogen peroxide excess is studied (Table 6). Complete conversion is reached at 7 eq of H_2O_2.

The optimized parameters (130°C, 7 eq H_2O_2, 30 min residence time; Table 5) are applied to study the *N*-oxidation of other *N*-heterocyclic compounds. Since the peracetic acid may explode at 110°C, [31] our batch reactions were carried out at 70°C based on the results of Ochiai E. [9] In the reaction of pyridine 34% conversion is reached in batch, contrary to the complete conversion in microreactor. The other nitrogen-containing compounds are studied without optimization of the parameters, since our aim is to study and compare the different derivatives. The 2- and 3-substituted compounds give *N*-oxide products at low conversion in batch operation if H_2O_2 is present. Especially the 2-bromopyridine give poor conversion in batch (2%), but in microreactor (15%), which can be further increased with reaction optimization. The quinoline and isoquinoline give similar results to those of the pyridine derivatives. In each cases, the results are significantly better in the microreactor than under batch conditions (Table 7).

Polonovski rearrangement

Pyridine *N*-oxide derivatives of Polonovski reaction are generally reacted with Ac_2O for 2-8 hours at 130-160°C, so 2-hydroxy or 2-acetate acid esters are produced. [20] Besides TFAA, other anhydrides can be used. [44, 45] The 2-hydroxy pyridine is produced from pyridine *N*-oxide at 130°C in batch and 33% conversion is can be achieved. This reaction is carried out in microreactor at 170°C and 43% conversion is can be reached. The conversions are determined by ^{1}H NMR. The reaction is not optimized and only pyridine is studied as substance. Our aim is to investigate the Polonovski rearrangement under microreactor conditions, so a two steps reaction in microreactor is assumed from pyridine derivatives to 2-hydroxy pyridine derivatives. Since our Encynova Novasync pump is limited up to two line dosing, therefore the two steps are implemented separately. In the case of an existing additional pump the two steps reaction could be performed in the microreactor (Figure 5).

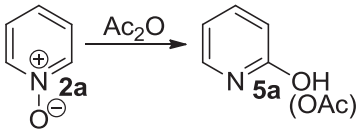

Fig. 4. Polonovski reaction of pyridine *N*-oxide with Ac_2O

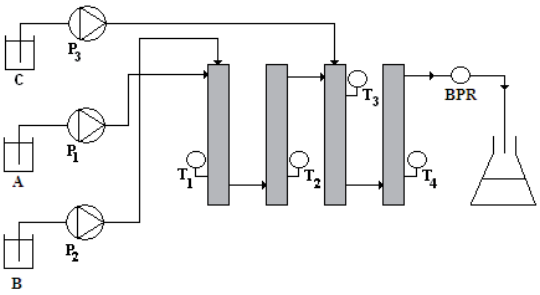

Fig. 5. *N*-oxidation and Polonovski rearrangement reactions in Corning LF reactor with four plates (A) Nitrogen-containing compound in solvent. (B) Oxidant. (C) Ac_2O. BPR: back pressure regulator

Conclusion

We present herein a beneficial continuous *N*-oxidation process executed in a microreactor which is compared to the classical batch process. Applying the expensive *m*-CPBA reagent no significant differences are noticed between the continuous and the batch processes, except the increased process safety. The developed environmentally friendly synthetic method with aqueous H_2O_2 in acetic acid shows a significant improvement in a continuous mode compared to the classical batch process. Applicability of microreactor technology is also demonstrated on the Polonovski rearrangement. The further extension of the developed processes is in progress.

Experimental Section

All chemicals are purchased from Sigma-Aldrich except the 27% water solution of H_2O_2 which is bought from Alfa Aesar. The pyridine is purchased from Reanal.

Reverse phase HPLC analyses are performed on an Agilent 1100 equipment using a Waters Symmetry C18 column 150x4.6mm, 5 µm using 10 mmol KH_2PO_4/H_3PO_4 buffer and acetonitrile (ACN) as eluent, the column temperature of 30°C, the flow rate of 1.0 mL/min. The standard gradient is used 10 to 90% ACN over 5 min, followed by 90% ACN over 1 min and then 90 to 10% ACN over 0.1 min and 10% ACN for 3.9 min.

Reacttions in batch:

Pyridine *N*-oxide 65 µl **1a** (63.28 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (255 nm, RT: **1a**: 1.2, **2a**: 1.7). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2a** are identical to the ones described in the literature. [46]

2-Methylpyridine *N*-oxide 81 µl **1b** (74.50 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (258 nm, RT: **1b**: 1.3, **2b**: 1.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2b** are identical to the ones described in the literature. [47]

2-Ethylpyridine *N*-oxide 94 µl **1c** (85.72 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (258 nm, RT: **1c**: 1.4, **2c**: 3.4). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2c** are identical to the ones described in the literature. [48]

2-Benzylpyridine *N*-oxide 131 µl **1d** (135.38 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (262 nm, RT: **1d**: 3.6, **2d**: 4.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2d** are identical to the ones described in the literature. [49]

3-Methylpyridine *N*-oxide 79 µl **1e** (74.50 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (258 nm, RT: **1e**: 1.3, **2e**: 1.9). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2e** are identical to the ones described in the literature. [49]

2-Bromopyridine *N*-oxide 76 µl **1f** (126.40 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (262 nm, RT: **1f**: 5.3, **2f**: 2.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2f** are identical to the ones described in the literature. [48]

3-Bromopyridine *N*-oxide 77 µl **1g** (126.40 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (265 nm, RT: **1g**: 4.3, **2g**: 3.0). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2g** are identical to the ones described in the literature. [50]

2-Cyanopyridine *N*-oxide 72 µl **1h** (83.29 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and

197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (222 nm, RT: **1h**: 4.3, **2h**: 5.0). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2h** are identical to the ones described in the literature. [51]

4-Cyanopyridine *N*-oxide 84.98 mg **1i** (0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (220 nm, RT: **1i**: 4.0, **2i**: 1.9). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2i** are identical to the ones described in the literature. [48]

Quinoline *N*-oxide 97 µl **3a** (103.33 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (230 nm, RT: **3a**: 1.8, **4a**: 3.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **4a** are identical to the ones described in the literature. [48]

Isoquinoline *N*-oxide 97 µl **3b** (103.33 mg, 0.8 mmol) is stirred in 0.5 ml dichloromethane at room temperature and 197.22 mg (0.88 mmol, 77%) *m*-CPBA is added. The reaction is stirred at 3 min and checked by HPLC (215 nm, RT: **3b**: 1.8, **4b**: 3.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **4b** are identical to the ones described in the literature. [48]

Pyridine *N*-oxide 65 µl **1a** (63.28 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (255 nm, RT: **1a**: 1.2, **2a**: 1.7). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2a** are identical to the ones described in the literature. [46]

2-Methylpyridine *N*-oxide 81 µl **1b** (74.50 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (258 nm, RT: **1b**: 1.3, **2b**: 1.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2b** are identical to the ones described in the literature. [47]

2-Ethylpyridine *N*-oxide 94 µl **1c** (85.72 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (258 nm, RT: **1c**: 1.4, **2c**: 3.4). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2c** are identical to the ones described in the literature. [47]

2-Benzylpyridine *N*-oxide 131 µl **1d** (135.38 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (262 nm, RT: **1d**: 3.6, **2d**: 4.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2d** are identical to the ones described in the literature. [48]

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2-Bromopyridine *N*-oxide 76 µl **1f** (126.40 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (262 nm, RT: **1f**: 5.3, **2f**: 2.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2f** are identical to the ones described in the literature. [48]

3-Bromopyridine *N*-oxide 77 µl **1g** (126.40 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (265 nm, RT: **1g**: 4.3, **2g**: 3.0). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2g** are identical to the ones described in the literature. [50]

2-Cyanopyridine *N*-oxide 72 µl **1h** (83.29 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (222 nm, RT: **1h**: 4.3, **2h**: 5.0). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for

analysis. All other analytical data of **2h** are identical to the ones described in the literature. [51]

4-Cyanopyridine *N*-oxide 84.98 mg **1i** (0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (220 nm, RT: **1i**: 4.0, **2i**: 1.9). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **2i** are identical to the ones described in the literature. [48]

Quinoline *N*-oxide 97 µl **3a** (103.33 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (230 nm, RT: **3a**: 1.8, **4a**: 3.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **4a** are identical to the ones described in the literature. [48]

Isoquinoline *N*-oxide 97 µl **3b** (103.33 mg, 0.8 mmol) is stirred in 0.5 ml acetic acid at 70°C and 641 µl (705.6 mg, 5.6 mmol) 27% water solution of H_2O_2 is added. The reaction is stirred at 30 min and checked by HPLC (215 nm, RT: **3b**: 1.8, **4b**: 3.8). The reaction mixture is added to 10% water solution of sodium pyrosulfite and washed with water (2x1 ml). Two phases are separated and organic phase is evaporated for analysis. All other analytical data of **4b** are identical to the ones described in the literature. [48]

2-Hydroxypyridine 0.0125g **2a** (0.13 mmol) is stirred in 0.5 ml acetic anhydride at 130°C. The reaction is stirred at 30 min and 1 ml water is added. The reaction mixture is evaporated for analysis with heptane, which is checked by 1H NMR. All other analytical data of **5a** are identical to the ones described in the literature. [52]

Reactions in the microreactor:

The reactions are studied in Corning LF reactor: The microreactor is fitted with a glass micro reactor (reactor volume = 0.45 mL). Channel height: 3.34-3.66 mm, the smallest point in the microreactor: 0.4 mm in width. Reactant solutions are introduced into the reactor through two lines of Encynova Novasync pump (Car-May LLC., USA) capable of delivering three solutions at flow rates between 1 µL/min and 120 mL/min. The system is maintained at max. 13 bar of back pressure in order to prevent the reactants and solvent system from boiling when temperatures above the atmospheric boiling point are employed. The solution of pyridine derivative (**1a-1i, 3a, 3b**) is pumped into the reactor from inlet A, the 27% water solution of H_2O_2 or *m*-CPBA in DCM is introduced from inlet B. After the system volume has passed through the reactor three times the reaction reached a steady state. The sample is then collected and analyzed offline by HPLC.

Tab. 8. Flow rates with *m*-CPBA in Corning LF

pyridine derivatives		temperature (°C)	residence time (min)	flow rate (µL/min)	
	R=			pyridine	m-CPBA
1a	H	50	0.25	1200	2400
1a	H	50	0.50	600	1200
1a	H	50	1.00	300	600
1a	H	50	2.00	150	300
1a	H	50	3.00	100	200
1a	H	100	0.25	1200	2400
1a	H	100	0.50	600	1200
1a	H	100	1.00	300	600
1b	2-Me	50	3.00	71	229
1c	2-Et	50	3.00	100	200
1d	2-Bz	50	3.00	103	197
1e	3-Me	50	3.00	100	200
1f	2-Br	50	3.00	70	230
1g	3-Br	50	3.00	70	230
1h	2-CN	50	3.00	70	230
1i	4-CN	50	3.00	100	200
3a	H	50	3.00	83	217
3b	H	50	3.00	83	217

Tab. 9. Flow rates with H_2O_2 in Corning LF

pyridine derivatives		temperature (°C)	H_2O_2 excess	residence time (min)	flow rate (µL/min)	
	R =				pyridine	m-CPBA
1a	H	50	1.1	1	600	300
1a	H	50	1.1	5	120	60
1a	H	50	1.1	10	60	30
1a	H	100	1.1	10	60	30
1a	H	150	1.1	10	60	30
1a	H	100	5	30	17	13
1a	H	110	5	30	17	13
1a	H	120	5	30	17	13
1a	H	130	5	30	17	13
1a	H	140	5	30	17	13
1a	H	150	5	30	17	13
1a	H	130	5	18	28	22
1a	H	130	5	24	21	16
1a	H	130	5	36	14	11
1a	H	130	4	30	17	13
1a	H	130	6	30	16	14
1a	H	130	7	30	15	15
1b	2-Me	130	7	30	16	15
1c	2-Et	130	7	30	17	13
1d	2-Bz	130	7	30	17	13
1e	3-Me	130	7	30	15	15
1f	2-Br	130	7	30	15	15
1g	3-Br	130	7	30	14	16
1h	2-CN	130	7	30	15	15
1i	4-CN	130	7	30	15	15
3a	H	130	7	30	15	15
3b	H	130	7	30	15	15

Tab. 10. Preparation of reaction mixtures in Corning LF

pyridine derivatives	residence time (min)	P_1 pump		P_2 pump	
		1a-i; 3a-b (mL)	DCM (mL)	77% *m*-CPBA (g)	DCM (mL)
pyridine **(1a)**	30	1	21	1.5	20
	60	1	21	1.5	20
	120	1	21	1.5	20
	180	1	21	1.5	20
	15	1	21	1.5	20
2-methypiridine (1b)	180	1	16.60	1.5	20
2-etilpiridin (1c)	180	1	14.00	1.5	20
2-benzylpyridine (1d)	180	1	9.80	1.5	20
3-methylpyridine (1e)	180	1	17.00	1.5	20
2-bromopyridine (1f)	180	1	17.55	1.5	20
3-bromopyridine (1g)	180	1	17.35	1.5	20
2-cyanopyridine (1h)	180	1	17.15	1.5	20
4-cyanopyridine (1i)	180	1[a]	15.65	1.5	20
quinoline (3a)	180	1	13.65	1.5	20
isoquinoline (3b)	180	1	13.60	1.5	20

[a] 4-cyanopyridine (**1i**) 1 g is dissolved in DCM

Tab. 11. Preparation of reaction mixture in Corning LF

pyridine derivatives	H_2O_2 excess (eq.)	residence time (min)	P_1 pump		P_2 pump	
			1a-i; 3a-b (mL)	AcOH (mL)	27% H_2O_2 (mL)	H_2O (mL)
pyridine **(1a)**	1.1	1	2	15	10	17.50
	1.1	5	2	15	10	17.50
	1.1	10	2	15	10	17.50
	1.1	10	2	15	10	17.50
	1.1	10	2	15	10	17.50
	5	30	1	8.30	20	0
	5	30	1	8.30	20	0
	5	30	1	8.30	20	0
	5	30	1	8.30	20	0
	5	30	1	8.30	20	0
	5	30	1	8.30	20	0
	5	18	1	8.00	20	0
	5	24	1	8.30	20	0
	5	36	1	8.00	20	0
	4	30	1	6.40	20	0
	6	30	1	8.70	20	0
	7	30	1	8.90	20	0
2-methypiridine (1b)	7	30	1	6.95	20	0
2-etilpiridin (1c)	7	30	1	7.90	20	0
2-benzylpyridine (1d)	7	30	1	5.40	20	0
3-methylpyridine (1e)	7	30	1	7.15	20	0
2-bromopyridine (1f)	7	30	1	7.25	20	0
3-bromopyridine (1g)	7	30	1	6.30	20	0
2-cyanopyridine (1h)	7	30	1	7.25	20	0
4-cyanopyridine (1i)	7	30	1[a]	6.55	20	0
quinoline (3a)	7	30	1	5.65	20	0
isoquinoline (3b)	7	30	1	5.60	20	0

[a] 4-cyanopyridine (**1i**) 1 g is dissolved in AcOH

Acknowledgement

This paper is dedicated to the memory of István Hermecz (1944–2011).

Special acknowledgements go to: Edit Alattyáni, Péter Hudáky, Attila Németh. The author expresses his gratitude to Sanofi for contributing to his PhD scholarship, and is grateful to Pro Progressio and to József Varga Foundations for their financial support.

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