Organic Process Research & Development

Article

pubs.acs.org/OPRD

Formation of Aromatic Amidoximes with Hydroxylamine using Microreactor Technology

Attila Vörös,*[†,‡] Zoltán Baán,[†] Péter Mizsey,[‡] and Zoltán Finta[†]

[†]Sanofi R&D, Hungary, 1045 Budapest, Tó u. 1-5

[‡]Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Hungary, 1111 Budapest, Budafoki út 8

ABSTRACT: In this contribution, the application of microreactor technology for amidoxime formation is demonstrated, with different aromatic nitriles reacted with a 50% solution of hydroxylamine (HA) under homogeneous conditions to reach full conversion. All reactions were executed in the presence of an excess of HA at an elevated temperature near to T_{onset} of HA, but in safe mode. Upscaling was performed with success by the adaptation of an increased volume microreactor and by numbering-up.

INTRODUCTION

Microflow Technology. In the past decade, microreactor technology has gained in importance in the field of pharmaceutical and fine chemical products due to its attractive properties compared to those of batch technology. Generally, this technology has highly efficient mixing properties combined with superior heat exchange ability, which renders this technology attractive. Its high surface to volume ratio allows for running highly exothermic and hazardous reactions in a safe manner. Microreactors are preferred to macro-, meso-, or microstructured systems for performing reactions with the risk of runaway. Additionally, microreactors also facilitate safe handling of highly toxic and dangerous materials under inert conditions.

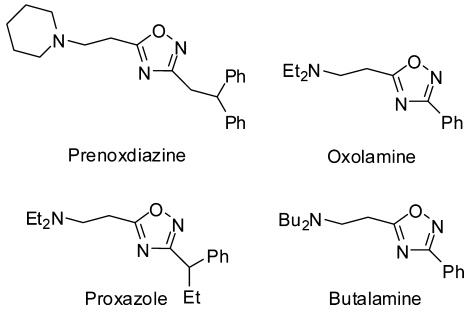
Refined conditions after optimization at 10 μL scale can, as a rule, be used for the production of larger quantities of material very easily, providing multigrams or multikilograms, or even on an industrial scale in a very smooth way. Two options of upscaling are generally used: either by applying an increased volume of reactor space combined with flow rate enhancement or by multiplying the number of the same type and volume reactors.[1,2] Both options lead to fast transfer of the process to an industrial setting when compared to the conventional scale up of batch processes.

As the upscaling of highly exothermic reactions using hazardous and toxic reagents remains of high concern for chemical manufacturing from the point of safety, productivity, and cost, the possibilities offered by microreactor technology are also of interest for pharma chemists. This is becoming increasingly evident as more and more key opinion leaders publish their results achieved in microreactors and disclose their experiences about possible applications.

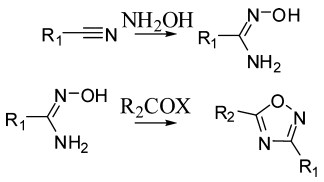
In this contribution, we describe our results on aromatic amidoxime formation reactions achieved in commercially available microflow reactors and our observations concerning upscaling possibilities.

Amidoximes. In pharmaceutical chemistry, amidoximes provide one of the shortest ways to reach certain heterocycles, such as oxadiazoles, which are well-known as bioactive scaffolds.[3−6] As a pharmacophoric scaffold, oxadiazole is a well-studied core structural unit of various muscarinic agonists,[7] benzodiazepine receptor partial agonists,[8] dopamine transporters,[9] antirhinovirals,[10] a growth hormone secretagogue,[11] and 5-HT agonists,[12] as well as an urea bioisostere in β_3-adrenergic receptor agonists.[13] Among oxadiazoles, 1,2,4-oxadiazole derivatives have gained more importance in medicinal chemistry, suffice it to mention prenoxdiazole, oxolamine, proxazole, or butalamine (Scheme 1). Several methods have been reported in the literature for the synthesis of 1,2,4-oxadiazoles,[14−20] with one of the most common methods being the addition of hydroxylamine to a nitrile, followed by a ring closure with a carboxylic acid derivative (Scheme 2).

Scheme 1. Biologically active oxadiazoles



Scheme 2. General preparation method for 1,2,4-oxadiazoles



Received: May 4, 2012
Published: October 25, 2012

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717−1726

Hydroxylamine. Hydroxylamine (HA) is a widely used reagent in the research of semiconductors, apart from its use in the chemical and pharmaceutical industries. HA is classified as a corrosive substance (Class 8) by the United Nations (UN) recommendations on the transport of dangerous goods (12th ed.). HA itself is a crystalline material with a highly explosive property. Its water solution above a concentration of 70% is also very explosive.[21,22]

HA is also considered to be toxic and from the point of view of process safety a problematic reagent that is mainly available in a stable salt form or, recently in water solution, as bulk material containing stabilizing agents. Water solutions of HA are very advantageous from a chemical engineering point of view, but they need very cautious handling and storage due to their thermal instability and catalytic decomposition potential, which are well described in the literature.[23] Heating onset temperature (T_{onset}) and the heat of decomposition are dependent on the concentration of the solution and can be catalyzed by metal ions. The T_{onset} in DTA gold cell is around 136 ± 5 °C,[23] which is almost constant irrespective of concentration. However, this value is much lower in stainless steel cells (T_{onset} = 63 ± 3 °C), which decreases as a function of increasing concentration of HA between 10 and 50%.[23] Nevertheless, dependence was found in all cases to be a function of metal ions, such as iron, copper, nickel, chromium, titanium, and manganese ions, available in the system.[24] All of these ions decrease T_{onset} dramatically below 100 °C with titanium ions, for example, reducing the T_{onset} of HA to room temperature.[23]

The heat of the decomposition of 100% pure HA is 4.3−4.6 kJ/g, the data of which is comparable to the value of TNT (5.1 kJ/g).[23,25,26] Highly concentrated solutions (>70%) or HA itself has a detonation ability, too.[23] To avoid a runaway reaction during a process, less than a 50 °C increase of adiabatic reaction heat has to be ensured during the reaction by definition. When applying organic solvents, approximately 20 times dilution is necessary for the reaction with HA 50%, which is found to be very unfavorable from the point of view of productivity.

During the chemical process, the most frequently encountered trace metal ions are the different ions of iron. Since many reactors in the industry are made of metal (such as stainless steel or Hastelloy) or at least contain metal parts as a potential source of iron or rust, no metal-free conditions can be ensured.

On the basis of the above-mentioned properties of HA and its water solution, thermal behavior of HA in 50% solution has been extensively examined in the presence on iron ions, such as rust.[24]

In order to avoid storage and handling of thermally instable HA, salt formation is used most frequently. Chloride salt and sulfate, even more so, bear sufficient stability for long-term storage.[27] However, amidoxime formation reactions work with liberated HA; thus for a good yield, liberation from the salt needs to be effected before the reaction or *in situ*. During salt liberation, T_{onset} can be decreased by the presence and concentration of KOH or KCl. T_{onset} of HA 50% solution (6 mL) in the presence of 2 mL of 8 N KOH is 46 ± 2 °C.[28] HA solutions treated by acids are more likely to increase decomposition heat than alkaline solutions.[28] On the basis of the decomposition equations, which are different in the presence of acidic or alkaline solutions, considerable gas evolution can be observed during the reaction, which increases the pressure in the reactor (Scheme 3).[29]

Scheme 3. Typical decomposition of hydroxylamine

$$3\ NH_2OH \longrightarrow 3\ H_2O + NH_3 + N_2$$

To avoid heterogeneous conditions and strong heat accumulation during the reaction (*in situ* HA liberation), the application of HA in water solution (up to 50%) is increasingly common. In this case, metal-free conditions during storage and handling are highly recommended, too.[24]

For successful reactions with HA, elevated temperatures are required in most of the cases, which are around or above the decomposition temperature of HA measured in the presence of metal impurities. For the full conversion of reactants, an excess of HA is to be used, which is generally 1−4 equivalents.[30,31] This, at a large scale, makes the situation more problematic in batch mode.

The final reaction mixture usually contains a considerable amount of HA, which needs further attention during processing or storage before effecting any further treatment. After the separation of the final product, the waste should be treated with special care. Acidifying is one of the possible solutions before incineration. All solutions that can decrease the risk of the application of HA are welcome in the industry, on the basis of the facts mentioned above.

RESULTS AND DISCUSSION

The following section outlines the adaptation to continuous flow technology of aromatic amidoxime formation using HA. At first, all model reactions were performed in batch mode under homogeneous condition using HA in water solution, which was followed by adaptation to microflow technology. All reactions were performed in 50% concentrated HA water solution in order to obtain homogeneous conditions during the reaction. Selecting the optimal reaction solvent was an essential step to avoid thermally unsafe HA crystal formation during the reaction and to avoid the plugging of the microflow system.

At first, we analyzed amidoxime formation via the reaction of benzonitrile (**1a**) and HA in batch mode. In this case, isopropyl alcohol proved to be an appropriate solvent, which ensured homogeneity during the full process. In batch mode, we examined the effects of reaction temperature, excess of HA, and reaction time on conversion. The analysis of the results showed that reaction temperature and excess of HA proved to be influencing factors of conversion (Figure 1.).

Thus, reaction time needed for full conversion is highly influenced by the temperature and the stoichiometry of HA. The limit of reaction temperature to be considered in this case is T_{onset} temperature of HA (136 ± 5 °C) and the boiling point of isopropanol (82 °C).[23] Increasing the proportion of HA is also a limiting factor with a view to safety considerations and waste handling. Since these factors have a strong effect on the reaction, it has been expected that full conversion is achievable through adaptation of the reaction using microflow technology.

For fast screening in microflow conditions, the Labtrix S1 reactor by Chemtrix BV (NL) was selected. This is a commercially available microflow reactor, which allows screening and reaction optimization on the microliter scale in a very economical way.[32]

Factors selected for screening were the same as in batch mode, but we defined values closer to the critical region (this raises safety concerns). Maximum reaction temperature was set slightly below T_{onset} 136 ± 5 °C of HA, and we also applied a greater excess of HA as a maximum value.[23] As the reactive

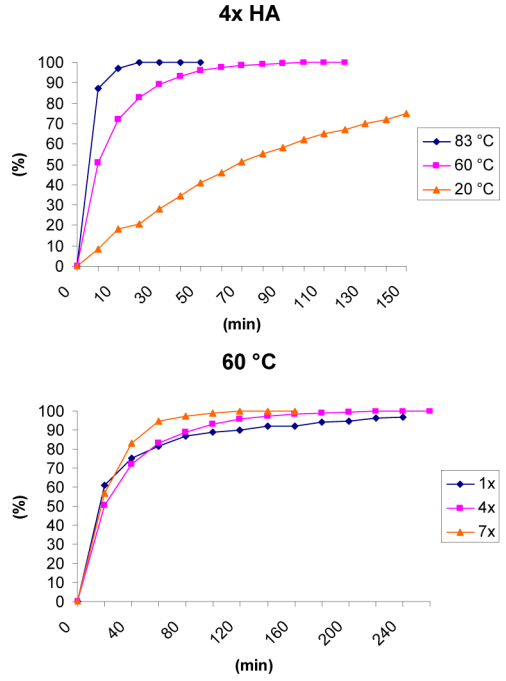


Figure 1. Reaction of benzonitrile (**1a**) in batch.

mass (volume) we worked with could only be at the microliter scale in a microreactor, which was supported by very effective heat exchange, no risk of runaway was predicted in the flow system. Furthermore, the use of glass and polymeric wetted parts meant that no metal contamination could be foreseen; thus, no risk of T_{onset} decrease was predicted.

For precise screening, we employed the Design of Experiment (DOE) approach (Central Composite Design) using factors of reaction temperature (75−125 °C), HA stoichiometry (1−7 equiv), and residence time (1−9 min) (Table 1).

Table 1. DOE plan and results of benzamidoxime formation (1a) in Labtrix S1

			HPLC (relative area %)	
temperature (°C)	HA exess (equiv)	residence time (min)	amidoxime	nitrile
75	1	1	14	86
125	1	1	32	68
100	1	5	60	40
75	1	9	48	52
125	1	9	78	22
100	4	1	56	44
100	4	5	97	3
75	4	5	74	26
100	4	5	88	12
125	4	5	100	0
100	4	5	91	9
100	4	9	98	2
75	7	1	37	63
125	7	1	89	11
100	7	5	100	0
75	7	9	96	4
125	7	9	100	0

The coefficient and contour plots of the results showed that all factors had a positive effect on the conversion within the residence time range we selected (Figures 2 and 3.).

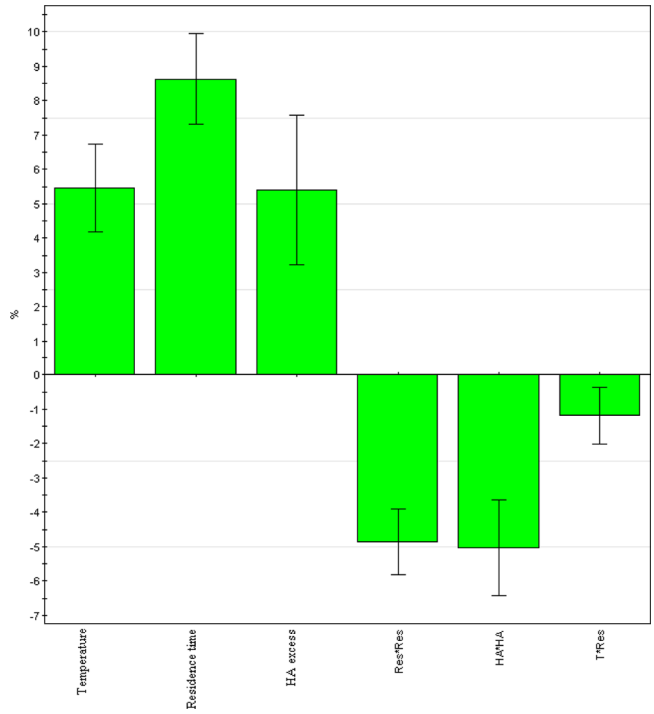


Figure 2. Coefficient plot of benzamidoxime formation.

The results clearly indicate that more than one factor setting is possible to achieve full conversion.

The two extreme values are as follows:

(1) A highly elevated temperature (125 °C) with moderate excess (4 equiv) of HA can be chosen if the compound has no temperature sensitivity.

(2) A reduced temperature (100 °C) with greater excess (7 equiv) of HA can be chosen if there is certain temperature sensitivity.

Alternatively, we can also use other combinations along the value chain between the extreme values, as required.

To extend the validity of our model, benzonitrile derivatives with groups containing different electron-donating properties were selected for testing, which was followed by some heteroaromatic derivatives as illustrated in Scheme 4 and Table 2.

In order to achieve homogeneous conditions in batch mode, the first step in all cases was the selection of the solvent, which was followed by continuous mode processes. During microflow experiments, we used the two extreme values for testing, based on the reaction conditions previously determined for benzonitrile (**1a**) (Table 2).

The comparison of the conversion data shows that benzonitrile derivatives with electron-withdrawing substituents did not react at unanimous reaction rates. Fast reactions were observed in the case of para-halogeno substituted benzonitriles, irrespective of the type of halogen involved. For ortho derivatives and for dihalo derivatives, a 5-min reaction time was not sufficient for full conversion (except R = F), a phenomenon which suggests a steric substituent effect.

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717−1726

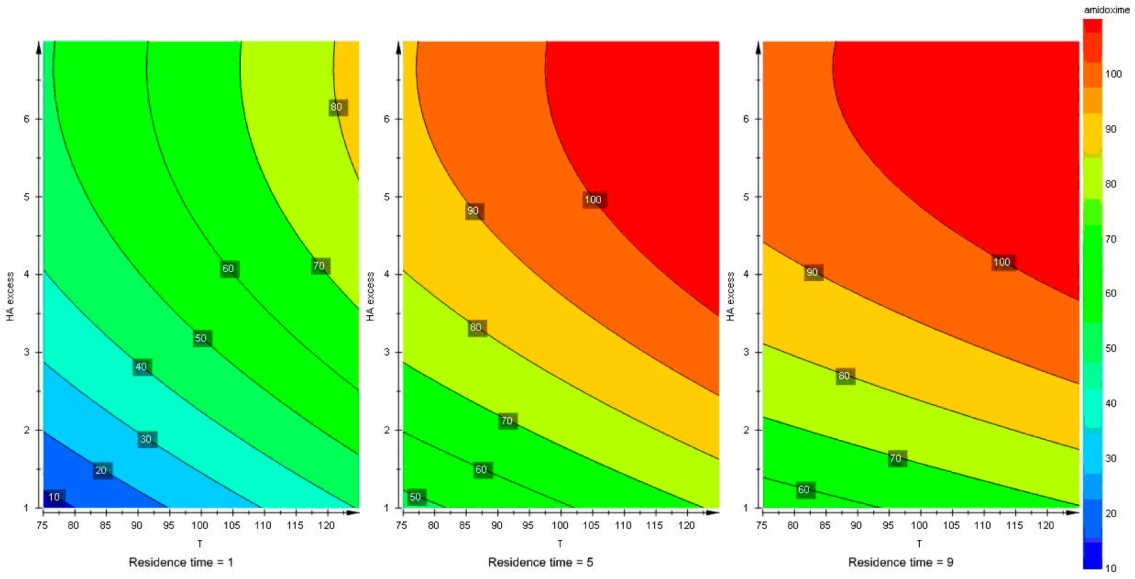
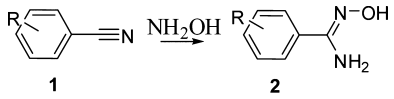


Figure 3. Contour plot of benzamidoxime formation.

Scheme 4. Reaction of nitrile derivatives with hydroxylamine



Electron-donating groups also had a negative effect on conversion time under the same conditions. These observations are in line with reactions performed in batch mode.

In the case of pyridine derivatives (Scheme 5, Table 3), reactions were very fast; probably less than 5 min is enough for full conversion.

In order to complete conversion, the best approach was to extend residence time under the same condition as before. Further elevation of temperature (above 125 °C, T_{onset} = 136 ± 5 °C), or further excess of HA can very easily cause safety concerns.

The application of 20 min as residence time instead of 5 min drives all reactions to full conversion without any byproduct formation (Table 4). In certain examples (Tables 2, 4, 5, 7), we prepared products by quenching the final reaction mixture. In all cases, yields were in line with the HPLC results of the reaction mixtures. This result is appropriate for analyzing upscaling possibilities in a microflow system, which constitutes the next step of our study.

Scheme 5. Reaction of pyridine derivatives with hydroxylamine

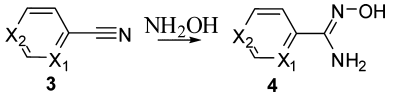


Table 3. Results of pyridine derivatives (5 min residence time, 20 bar)

pyridine derivatives				HPLC (relative area %) 100 °C, 7×		HPLC (relative area %) 125 °C, 4×	
	X_1 =	X_2 =	solvent	amidoxime	nitrile	amidoxime	nitrile
3a	H	N	MeOH	100	0	100	0
3b	N	H	MeOH	100	0	100	0

Scalability. We examined the upscaling possibilities of the reactions, applying the rapid scalability theory of microflow technologies. For this reason, a Corning system was selected, which is also a commercially available flow system with larger

Table 2. Results using nitrile derivatives[a]

benzonitrile derivatives			HPLC (relative area %) 100 °C, 7×		HPLC (relative area %) 125 °C, 4×		yield (%)
	R =	solvent	amidoxime	nitrile	amidoxime	nitrile	amidoxime
1a	H	IPA	100	0	100	0	90
1b	4-F	IPA	100	0	100	0	91
1c	4-Cl	EtOH	100	0	100	0	–
1d	2-Cl	IPA	31	69	28	72	–
1e	2,4-Cl	IPA	31	69	36	64	–
1f	4-Cl-2-F	MeOH	100	0	100	0	–
1g	2-Cl-4-F	MeOH	67	33	66	34	–
1h	4-Me	EtOH	85	15	59	41	–
1i	2-Me	BuOH	31	69	23	77	–
1j	4-MeO	IPA	73	27	52	48	–
1k	2-MeO	IPA	48	52	46	54	–

[a]5 min residence time, 20 bar.

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717−1726

Table 4. Results of nitrile derivatives[a]

nitrile derivatives			HPLC (relative area %) 100 °C, 7×, 20 min		yield (%)
	R =	solvent	amidoxime	nitrile	amidoxime
1d	2-Cl	IPA	100	0	–
1e	2,4-Cl	IPA	100	0	–
1g	2-Cl-4-F	MeOH	100	0	–
1h	4-Me	EtOH	100	0	90
1i	2-Me	BuOH	100	0	89
1j	4-MeO	IPA	100	0	–
1k	2-MeO	IPA	100	0	–

[a]20 min residence time, 20 bar.

volumes than Labtrix (but below the microflow region), and allows parallelization as an additional option.

The Corning Low Flow microreactor features reaction plates made of glass, which was important for constantly providing metal contamination-free conditions. A further advantage of this Corning system is the upscaling possibility of the system to industrial level with no change in the critical parameters of scalability such as geometrical similarity of reaction plates.

The Labtrix S1 microflow system used for screening had a 10 μL volume reaction microreactor, equipped with a T mixing and Peltier-based temperature control system (Figure 4.

For comparison, the Corning Low Flow system was set with reactor plates at 0.45 mL scale/plate (see Figure 5). This system can be used with, at a maximum, nine plates at a time and is equipped with T mixing with a jacketed heat exchange.

From the point of view of upscaling, 45-fold scale-up was performed by the definition of reactor plate, and one Corning plate was used. Since Labtrix S1 and the Corning plates have different configurations, no geometrical dependence was established during the adaptation of the process to the Corning system. In similar cases, mixing and dispersion abilities influenced the reaction, so we predicted further optimization would be required.

All the reactions of the previously examined aromatic nitrile derivatives were also performed in the Corning system under the same conditions as the ones optimal for the Labtrix system (Tables 5 and 6).

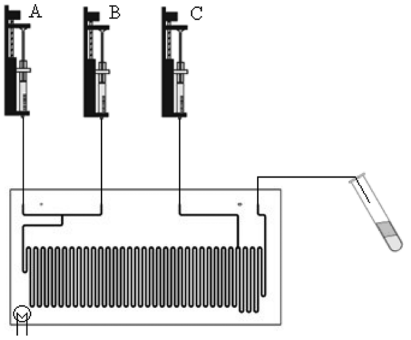


Figure 4. Labtrix S1 microreactor (10 μL)[30] A: nitrile compound in solvent, B: HA, C: quenching by solvent.

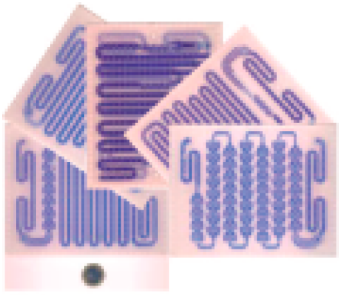


Figure 5. Corning reactorplates.[33,34]

The same results were obtained as previously, so no further optimization was necessary to reach full conversion. The results' independence from the applied microflow systems suggests that the amidoxime formation reaction can easily be adapted in different microflow systems. Furthermore, the geometrical differences do not seem to be a critical parameter of scalability in the case of the flow rates we used.

The second upscaling approach was the numbering up of the plates in order to increase productivity. By setting up four Corning plates (0.45 mL/plate) in parallel, productivity could be increased by 4 times (Figure 6).

The conditions were the same as previously, without any further refinement (Table 7).

Table 5. Results in Corning LF reactor I[a]

benzonitrile derivatives						HPLC (relative area %)		yield (%)
	R =	solvent	temperature (°C)	HA excess (equiv)	residence time (min)	amidoxime	nitrile	amidoxime
1a	H	IPA	100	7	5	100	0	–
1a	H	IPA	125	4	5	100	0	–
1b	4-F	IPA	100	7	5	100	0	–
1b	4-F	IPA	125	4	5	100	0	–
1c	4-Cl	EtOH	100	7	5	100	0	–
1c	4-Cl	EtOH	125	4	5	100	0	–
1d	2-Cl	IPA	100	7	20	100	0	–
1e	2,4-Cl	IPA	100	7	20	100	0	–
1f	4-Cl-2-F	MeOH	100	7	5	100	0	–
1f	4-Cl-2-F	MeOH	125	4	5	100	0	–
1g	2-Cl-4-F	MeOH	100	7	20	100	0	–
1h	4-Me	EtOH	100	7	20	100	0	93
1i	2-Me	BuOH	100	7	20	100	0	97
1j	4-MeO	IPA	100	7	20	100	0	–
1k	2-MeO	IPA	100	7	20	100	0	–

[a]0.45 mL reactor volume, 2.5–3 bar.

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717–1726

Table 6. Results in Corning LF reactor II[a]

pyridine derivatives							HPLC (relative area %)	
	X_1 =	X_2 =	solvent	temperature (°C)	HA exess (equiv)	residence time (min)	amidoxime	nitrile
1l	H	N	MeOH	100	7	5	100	0
1l	H	N	MeOH	125	4	5	100	0
1m	N	H	MeOH	100	7	5	100	0
1m	N	H	MeOH	125	4	5	100	0

[a]0.45 mL reactor volume, 2.5−3 bar.

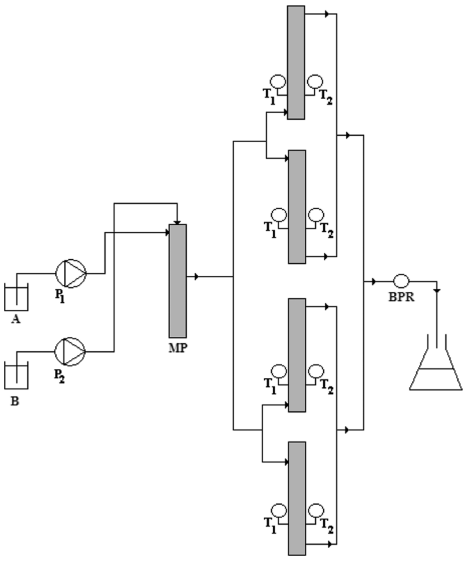


Figure 6. Corning LF reactor with four plates.[31] (A) Nitrile compound in solvent. (B) HA, MP: mixing plate. BPR: back pressure regulator.

The selected three model reactions gave the same conversions as the conversion previously observed in the case of one plate. In all the cases, final reaction mixtures were quenched with icy HCl solution after the reaction mixtures had been collected. The precipitated product was easily separated from the residues. The mother liquor was contaminated by the remaining part of the HA.HCl salt, which was found safe enough for further handling, such as incineration.

CONCLUSION

Amidoxime formation with HA can be safely performed in commercially available microflow reactors. This technique has numerous advantages compared to batch reactions, including safe reaction management, full conversion with a short reaction time and effective increase in productivity without an upscaling effect. Results from selected models showed a wide range of application possibilities for aromatic nitriles, with no limitation for sterically hindered or electron rich aromatic nitriles. The method is also useful for reactions under homogeneous conditions using commercially available HA water solution. Metal-free conditions were easily ensured in order to avoid runaway decomposition of reaction mixtures at reaction temperature.

DESCRIPTION OF THE EXPERIMENTS

All chemicals were purchased from Sigma-Aldrich except for 4-chloro-2-fluorobenzonitrile, which was bought from Acros Organics. 4-Chlorobenzonitrile and 2,4-dichlorobenzonitrile were purchased from Merck, and the 50% water solution of hydroxylamine was purchased from BASF.

All the reactions were tracked using appropriate HPLC methods on Merck Hitachi Elite Lachrom equipment, column temperature was 30 °C in each of the four methods in Table 8. ^{1}H and ^{13}C NMR spectra were obtained at room temperature as solutions in DMSO using tetramethylsilane as an internal standard. The spectra were recorded using a Bruker Avance 200 MHz spectrometer.

The HRMS spectra were recorded on a Micromass Q-TOF Premier spectrometer.

FT IR spectra were recorded on the solid state as KBr dispersion using PerkinElmer Spectrum 100 FT-IR spectrophotometer.

Benzamidoxime 2a. 6.00 mL of **1a** (6.00 g, 58 mmol) was heated in 60 mL of isopropyl alcohol to boiling, and 25.2 mL (7 equiv) of 50% water solution of HA was added dropwise. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.1, 215 nm, RT: **1a**: 3.5, **2a**: 1.2). The reaction mixture was added to iced water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. Analytical data of **2a** was identical to that described in the literature.[35]

4-Fluoro-benzamidoxime 2b. 0.50 g of **1b** (4.13 mmol) in 5 mL isopropyl alcohol was heated to boiling and 1.00 mL (0.55 g, 16.52 mmol) of 50% water solution of HA was added dropwise. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.1, 230 nm, RT: **1b**: 1.1, **2b**: 0.6). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. Analytical data of **2b** was identical to that reported in the literature.[35]

Table 7. Results of the parallel Corning LF reactor (4 × 0.45 mL, 2.5−3 bar)

benzonitrile compound						HPLC (relative area %)		yield (%)
	R =	solvent	temperature (°C)	HA excess (equiv)	residence time (min)	amidoxime	nitrile	amidoxime
1a	H	IPA	100	7	5	100	0	97
1a	H	IPA	125	4	5	100	0	–
1b	4-F	IPA	100	7	5	100	0	96
1b	4-F	IPA	125	4	5	100	0	–
1i	2-Me	BuOH	100	7	20	100	0	96

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717−1726

Table 8. HPLC methods

method no.	column	parameters	buffer	eluent	flow rate (ml/min)	gradient
1	Chromolit Performance RP-18e	4.6 × 100 mm, 2 μm	25 mmol NaH_2PO_4/ Na_2HPO_4	MeOH	3	10% MeOH, 1 min 10 → 20% MeOH, 1 min 20% MeOH, 3 min 20 → 10% MeOH, 1 min 10% MeOH, 3 min
2	Chromolit Performance RP-18e	4.6 × 100 mm, 2 μm	10 mmol KH_2PO_4/ H_3PO_4 (+5% MeCN)	MeOH	3	30 → 70% MeOH, 10 min 70 → 30% MeOH, 0.5 min 30% MeOH, 1.5 min
3	Chromolit Performance RP-18e	4.6 × 100 mm, 2 μm	10 mmol KH_2PO_4/ H_3PO_4 (+5% MeCN)	MeCN	3	30 → 70% MeCN, 10 min 70 → 30% MeCN, 0.5 min 30% MeCN, 1.5 min
4	Xbridge C18	2.1 × 100 mm, 3.5 μm	10 mmol KH_2PO_4/ H_3PO_4 (+5% MeCN)	MeCN	0.4	10% MeCN, 1 min 10 → 70% MeCN, 9 min 70 → 10% MeCN, 1 min 10% MeCN, 2 min

4-Chloro-benzamidoxime 2c. 0.50 g of **1c** (3.64 mmol) was heated in 8 mL of ethyl alcohol to boiling, and 0.89 mL (0.96 g, 14.56 mmol)of water solution of HA was added dropwise. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 205 nm, RT: **1c**: 1.6, **2c**: 0.7). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All analytical data of **2c** was identical to that described in the literature.[36]

2-Chloro-benzamidoxime 2d. 0.50 g of **1d** (3.64 mmol) was heated in 8 mL of ethyl alcohol to boiling, and 0.89 mL (0.96 g, 14.56 mmol) of water solution of HA was added dropwise. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 205 nm, RT: **1d**: 1.8, **2d**: 0.6). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2d** are identical to the ones described in the literature.[37]

2,4-Dichloro-benzamidoxime 2e. 1.00 g of **1e** (5.81 mmol) was heated in 30 mL of isopropyl alcohol to boiling, and 1.42 mL (1.54 g, 23.24 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 230 nm, RT: **1e**: 2.4, **2e**: 0.7). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2e** are identical to the ones described in the literature.[38]

4-Chloro-2-fluoro-benzamidoxime 2f. 0.50 g of **1f** (3.21 mmol) was heated in 8 mL of methyl alcohol to boiling, and 0.79 mL (0.85 g, 12.84 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 205 nm, RT: **1f**: 1.8, **2f**: 0.8). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. ^{1}H NMR (DMSO-d_6) δ: 9.71 (s, 1H), 7.49 (m, 2H), 7.30 (m, 1H), 5.85 (s, 2H). ^{13}C NMR (DMSO-d_6) δ: 116.9 (d, J = 26.5 Hz, CH(3)), 121.4 (d, J = 13.3 Hz, C(1)), 124.8 (d, J = 3.0 Hz, CH(6)), 131.5 (d, J = 4.1 Hz, CH(5)), 134.5 (d, J = 10.3 Hz, C−Cl(4)), 147.9 (s, C(C-amidoxime)), 160.1 (d, J = 253.6 Hz, C−F(2)). IR (KBr, cm^{-1}): 3492, 3371, 1673, 1596, 1570, 1496, 1413, 1213, 1073, 951, 904, 859, 832, 719. HRMS (ESI): Calcd for $C_7H_6N_2OClF$ (M^+ + H) 189.0231, Found 189.0223. HPLC−MS: (m/z) (MH^+) = 189.

2-Chloro-4-fluoro-benzamidoxime 2g. 0.50 g of **1g** (3.21 mmol) was heated in 8 mL of methyl alcohol to boiling, and 0.79 mL (0.85 g, 12.84 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 205 nm, RT: **1g**: 1.7, **2g**: 0.7). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. ^{1}H NMR (DMSO-d_6) δ: 9.48 (s, 1H), 7.44 (m, 2H), 7.23 (m, 1H), 5.83 (s, 2H). ^{13}C NMR (DMSO-d_6) δ: 114.4 (d, J = 21.4 Hz, CH(5)), 117.1 (d, J = 25.1 Hz, CH(3)), 130.7 (d, J = 3.3 Hz, C(1)), 133.0 (d, J = 9.2 Hz, CH(6)), 133.7 (d, J = 11.1 Hz, C−Cl(2)), 150.2 (s, C(C-amidoxime)), 162.2 (d, J = 248.8 Hz, C−F(4)). IR (KBr, cm^{-1}): 3489, 3365, 3061, 2821, 1662, 1588, 1511, 1404, 1373, 1270, 1220, 1045, 958, 946, 907, 826, 680. HRMS (ESI): Calcd for $C_7H_6N_2OClF$ (M^+ + H) 189.0231, Found 189.0231. HPLC−MS: (m/z) (MH^+) = 189.

4-Methylbenzamidoxime 2h. 0.76 g of **1h** (6.52 mmol) was heated in 15 mL of ethyl alcohol to boiling, and 1.60 mL (1.72 g, 26.08 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 230 nm, RT: **1h**: 0.6, **2h**: 1.1). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2e** are identical to the ones described in the literature.[39]

2-Methylbenzamidoxime 2i. 0.327 mL of **1i** (0.50 g, 4.27 mmol) was heated in 15 mL of butyl alcohol to boiling, and 1.05 mL (1.13 g, 17.08 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.3, 205 nm, RT: **1i**: 1.2, **2i**: 0.6) The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2e** are identical to the ones described in the literature.[40]

4-Methoxybenzamidoxime 2j. 1.00 g of **1j** (7.51 mmol) was heated in 10 mL of isopropyl alcohol to boiling, and 1.84 mL (1.98 g, 30.04 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.4, 205 nm, RT: **1j**: 10.2, **2j**: 1.2). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2e** are identical to the ones described in the literature.[35]

2-Methoxybenzamidoxime 2k. 0.915 mL of **1k** (1.00 g, 7.51 mmol) was heated in 10 mL of isopropyl alcohol to boiling, and 1.84 mL (1.98 g, 30.04 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.4, 205 nm, RT: **1k**: 8.8, **2k**: 1.0). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. ^{1}H NMR (DMSO-d_6) δ: 9.37 (s, 1H), 7.35 (m, 2H), 6.98(m, 2H), 5.58 (s, 2H). ^{13}C NMR (DMSO-d_6) δ: 55.6 (s, CH_3(methoxy)), 112.1 (s, CH(3)),

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717−1726

Table 9. Flow rates in Labtrix S1

benzonitrile derivatives						flow rate (μL/min)		
	R =	temperature (°C)	HA excess (equiv)	residence time (min)	solvent	nitrile	HA	quench
1a	H	75	1	1	IPA	9.49	0.51	20
1a	H	125	1	1	IPA	9.49	0.51	20
1a	H	100	1	5	IPA	1.90	0.10	10
1a	H	75	1	9	IPA	1.05	0.06	6
1a	H	125	1	9	IPA	1.05	0.06	6
1a	H	100	4	1	IPA	8.22	1.78	20
1a	H	100	4	5	IPA	1.64	0.36	10
1a	H	75	4	5	IPA	1.64	0.36	10
1a	H	125	4	5	IPA	1.64	0.36	10
1a	H	100	4	9	IPA	0.91	0.2	6
1a	H	75	7	1	IPA	7.25	2.75	20
1a	H	125	7	1	IPA	7.25	2.75	20
1a	H	100	7	5	IPA	1.45	0.55	10
1a	H	75	7	9	IPA	0.81	0.31	6
1a	H	125	7	9	IPA	0.81	0.31	6
1b	4-F	125	4	5	IPA	1.69	0.31	10
1b	4-F	100	7	5	IPA	1.51	0.49	10
1c	4-Cl	125	4	5	EtOH	1.81	0.19	10
1c	4-Cl	100	7	5	EtOH	1.69	0.31	10
1d	2-Cl	125	4	5	IPA	1.81	0.19	10
1d	2-Cl	100	7	5	IPA	1.69	0.31	10
1d	2-Cl	100	7	20	IPA	0.42	0.08	3
1e	2,4-Cl	125	4	5	IPA	1.91	0.09	10
1e	2,4-Cl	100	7	5	IPA	1.85	0.15	10
1e	2,4-Cl	100	7	20	IPA	0.46	0.04	3
1f	4-Cl-2-F	125	4	5	MeOH	1.83	0.17	10
1f	4-Cl-2-F	100	7	5	MeOH	1.72	0.28	10
1g	2-Cl-4-F	125	4	5	MeOH	1.83	0.17	10
1g	2-Cl-4-F	100	7	5	MeOH	1.72	0.28	10
1g	2-Cl-4-F	100	7	20	MeOH	0.43	0.07	3
1h	4-Me	125	4	5	EtOH	1.70	0.30	10
1h	4-Me	100	7	5	EtOH	1.82	0.18	10
1h	4-Me	100	7	20	EtOH	0.45	0.05	3
1i	2-Me	125	4	5	BuOH	1.79	0.21	10
1i	2-Me	100	7	5	BuOH	1.87	0.13	10
1i	2-Me	100	7	20	BuOH	0.45	0.03	3
1j	4-MeO	125	4	5	IPA	1.71	0.29	10
1j	4-MeO	100	7	5	IPA	1.55	0.46	10
1j	4-MeO	100	7	20	IPA	0.38	0.11	3
1k	2-MeO	125	4	5	IPA	1.71	0.29	10
1k	2-MeO	100	7	5	IPA	1.55	0.46	10
1k	2-MeO	100	7	20	IPA	0.38	0.11	3
3a	4-Py	125	4	5	MeOH	1.80	0.20	10
3a	4-Py	100	7	5	MeOH	1.67	0.33	10
3b	2-Py	125	4	5	MeOH	1.83	0.17	10
3b	2-Py	100	7	5	MeOH	1.73	0.27	10

120.5 (s, CH(5)), 122.9 (s, CH(2)), 129.9 (s, CH(4)), 130.5 (s, CH(6)), 151.2 (s, C(1)), 157.4 (s, C(C-amidoxime)). IR (KBr, cm^{-1}): 3470, 3358, 2939, 1675, 1596, 1500, 1463, 1437, 1385, 1282, 1246, 1017, 930, 835, 781, 758. HRMS (ESI): Calcd for $C_7H_6N_2O_2$ (M^+ + H) 167.0785, Found 167.0782. HPLC-MS: (m/z) (MH^+) = 167.

4-Pyridine-benzamidoxime 4a. 0.50 g **3a** (4.71 mmol) was heated in 10 mL of methyl alcohol to boiling, and 1.15 mL (1.24 g, 18.84 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.2, 230 nm, RT: **3a**: 1.0, **4a**: 0.7). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2e** are identical to the ones described in the literature.[40]

2-Pyridine-benzamidoxime 4b. 0.40 g **3b** (3.84 mmol) was heated in 9 mL of methyl alcohol to boiling and 0.94 mL (1.01 g, 15.36 mmol) of water solution of HA was added drop by drop. The reaction was stirred under reflux to full conversion and checked by HPLC (method No.2, 210 nm, RT: **3b**: 0.9, **4b**: 0.6). The reaction mixture was added to icy water, the product was filtered off, washed with water (2 × 5 mL), and dried for analysis. All other analytical data of **2e** are identical to the ones described in the literature.[40]

dx.doi.org/10.1021/op300113w | Org. Process Res. Dev. 2012, 16, 1717−1726

Table 10. Flow rates in Corning LF

nitrile derivatives							
	R =	temperature (°C)	HA excess (equiv)	residence time (min)	solvent	nitrile (μL/min)	HA (μL/min)
1a	H	100	7	5	IPA	65	25
1a	H	125	4	5	IPA	74	16
1b	4-F	100	7	5	IPA	68	22
1b	4-F	125	4	5	IPA	76	14
1c	4-Cl	125	4	5	EtOH	81	9
1c	4-Cl	100	7	5	EtOH	76	14
1d	2-Cl	100	7	20	IPA	19	4
1e	2,4-Cl	100	7	20	IPA	21	2
1f	4-Cl-2-F	125	4	5	MeOH	82	8
1f	4-Cl-2-F	100	7	5	MeOH	77	13
1g	2-Cl-4-F	100	7	20	MeOH	19	3
1h	4-Me	100	7	20	EtOH	20	2
1i	2-Me	100	7	20	BuOH	20	1
1j	4-MeO	100	7	20	IPA	17	5
1k	2-MeO	100	7	20	IPA	17	5
3a	4-Py	125	4	5	MeOH	81	9
3a	4-Py	100	7	5	MeOH	75	15
3b	2-Py	125	4	5	MeOH	82	8
3b	2-Py	100	7	5	MeOH	78	12

Table 11. Flow rates in Corning LF parallel

Nitrile derivatives							
	R =	temperature (°C)	HA excess (equiv)	residence time (min)	solvent	nitrile (μL/min)	HA (μL/min)
1a	H	100	7	5	IPA	261	99
1a	H	125	4	5	IPA	296	64
1b	4-F	100	7	5	IPA	272	88
1b	4-F	125	4	5	IPA	304	56
1i	2-Me	100	7	20	BuOH	80	10

Reactions in the Microreactor. Labtrix S1 (Chemtrix BV, NL): Flow system was fitted with a glass microreactor (3023, reactor volume =10 μL + 1.5 μL quench volume). Channel width: 300 μm, channel depth: 60 μm and effective channel length: 60.8 cm. Reactant solutions were introduced into the reactor through three 1 mL gastight syringes (SGE, UK) capable of delivering three solutions at flow rates between 0.1 and 25 μL/min. The system was maintained at 20 bar of back pressure by means of a preset ultralow dead-volume back-pressure regulator (Upchurch Scientific, USA) in order to prevent the reactants and solvent system from boiling when temperatures above the atmospheric boiling point were employed. The system was controlled through the Labtrix S1 software, which enables the control of reactant flow rate (total flow rate ≤80 μL/min, reactant residence time (7.5 s to 50 min (for a 10 μL reactor)), reactor temperature (−15 to 195 °C), equilibration time, and sample collection into one of 29 2-mL sample vials. The software also archives system parameters such as the set and actual temperatures, system pressure, reactor type, and the programmed flow rates along with the sample collection time and vessel, all of which can be reviewed both during and after the experiment.[41] Each respective solution of benzonitrile derivative (**1a**−**1k**, **3a** and **3b**) was pumped into the reactor from inlet A, the 50% water solution of HA was introduced from inlet B, and the solvent was introduced as a diluent from inlet C. After the system volume had passed through the reactor three times, the reaction reached a steady state, and a sample was then collected and analyzed offline by HPLC (Table 9).

Corning LF reactor: The system was fitted with a glass microreactor (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 were 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 was maintained at maximum 13 bar of back pressure in order to prevent the reactants and solvent system from boiling when temperatures above the atmospheric boiling point were employed. The solution of nitrile derivatives (**1a**−**1k**, **3a** and **3b**) was pumped into the reactor from inlet A, and the 50% water solution of HA was introduced from inlet B. After the system volume had passed through the reactor three times, the reaction reached a steady state. A sample was then collected and analyzed offline by HPLC (see Tables 10 and 11).

The DOE plan, contour plot, and coefficient plot were made with MODDE 9.0 software.

AUTHOR INFORMATION

Corresponding Author

*E-mails: attila.voros@sanofi.com, vorosattila85@gmail.com. Telephone: +36-1-505-17-56.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to the memory of István Hermecz (1944−2011). Special acknowledgement goes to: László Drahos, Lászlóné Grosz, Árpád Illár, Ilona Koleszár, Zsolt Regényi, Gábor Vlád, Charlotte Wiles and Chemtrix BV for making the use of Labtrix S1 equipment. The author expresses his gratitude to Sanofi for contributing to his Ph.D. scholarship and is grateful to Pro Progressio and to József Varga Foundations for their financial support.

■ REFERENCES

(1) Wiles, C.; Watts, P. *Chim. Oggi* **2010**, *28*, 3−5.
(2) Nieuwland, P. J.; Segers, R.; Koch, K.; van Hest, J. C. M; Rutjes, F. P. J. T. *Org. Process Res. Dev.* **2011**, *15*, 783−787.
(3) Nicolaides, D. N.; Varella, E. A.; Patai, S., *The Chemistry of Acid Derivatives*; Interscience: New York, 1992, *2*, 875−966.
(4) Clapp, L.B.; Katritzky, A.R.; Boulton, A.J. *Advances in Heterocyclic Chemistry*; Academic Press Inc.: New York, 1976; Vol. *20*, pp 65−116.
(5) Clapp, L. B.; Potts, K. T. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. *6*, pp 365−392.
(6) Jochims, J. C.; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1996; Vol. *4*, pp 179−228.
(7) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726−2735.
(8) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282−2291.
(9) Carroll, F. I.; Gray, J. L.; Abrahm, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1993**, *36*, 2886−2890.
(10) Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421−2436.
(11) Ankersen, M.; Peschke, B.; Hansen, B. S.; Hansen, T. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1293−1298.
(12) Chen, C.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738−3741.
(13) Mathvink, R. J.; Barritta, A. M.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1869−1874.
(14) LaMattina, J. L.; Mularski, C. J. *J. Org. Chem.* **1984**, *49*, 4800−4805.
(15) Liang, G. B.; Qian, X. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2101−2104.
(16) Liang, G. B.; Feng, D. D. *Tetrahedron Lett.* **1996**, *37*, 6627−6630.
(17) Tyrkov, A. G. *Khim. Khimich. Tekhnol.* **2000**, *43*, 73−77.
(18) Young, J. R.; DeVita, R. J. *Tetrahedron Lett.* **1998**, *39*, 3931−3934.
(19) Neidlein, R.; Sheng, L. *Synth. Commun.* **1995**, *25*, 2379−2394.
(20) Neidlein, R.; Sheng, L. J. *Heterocycl. Chem.* **1996**, *33*, 1943−1949.
(21) *The Explosion at Concept Sciences: Hazards of Hydroxylamine* U.S. Chemical Safety and Hazard Investigation Board2002, 1999-13-C-PA.
(22) *Report of Investigation Explosive Fire of Hydroxylamine at a Chemical Plant in Gunma Prefecture*, Hazardous Materials Safety Techniques AssociationMarch 2001 (in Japanese).
(23) Iwata, Y.; Koseki, H. *Process Saf. Prog.* **2002**, *21*, 136−141.
(24) Iwata, Y.; Koseki, H. *J. Hazard. Mater.* **2003**, *104*, 39−49.
(25) Bretherick, L. *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann: Woburn, MA, 1995.
(26) Iwata, Y.; Koseki, H.; Hosoya, F. *J. Loss Prev. Process Ind.* **2003**, *16*, 41−53.
(27) Cisneros, L. O.; Rogers, W. J.; Mannan, S. M. *Thermochim. Acta* **2004**, *414*, 177−183.
(28) Wei, C.; Saraf, S. R.; Rogers, W. J.; Mannan, S. M. *Thermochim. Acta* **2004**, *421*, 1−9.
(29) Stephenson, L.; Warbutron, W. K.; Wilson, M. J. *J. Chem. Soc. C.* **1969**, 861−864.
(30) Godovikova, T. I.; Vorontsova, S. K.; Konyushkin, L. D.; Firgang, S. I.; Rakitin, O. A. *Russ. Chem. Bull. Int. Ed.* **2008**, *57*, 2440−2442.
(31) Lee, Wai Mun; Novel nitrile and amidoxime compounds and methods preparation. WO/2009/058277, 2009.
(32) http://www.chemtrix.com.
(33) http://www.corning.com.
(34) Barthe, P.; Guermeur, C.; Lobet, O.; Moreno, M.; Woehl, P.; Roberge, D. M.; Bieler, N.; Zimmermann, B. *Chem. Eng. Chem. Eng. Technol.* **2008**, *31*, 1146−1154.
(35) Yang, X.; Li, H.; Zhang, Y.; Li, C.; Liu, B.; Liang, W.; Zhao, G.; Liu, G.; Song, D.; Wang, R.; Jing, Y. *J. Med. Chem.* **2010**, *53*, 1015−1022.
(36) Holsworth, D.; Waaler, J.; Machon, O.; Krauss, S.; Golding, L. Azole derivatives as WTN pathway inhibitors. WO/2010/139966, 2010
(37) Cottrell, D. M.; Capers, J.; Salem, M. M.; Deluca-Fradley, K.; Croft, S. L.; Werbovetz, K. A. *Bioorg. Med. Chem.* **2004**, *12*, 2815−2824.
(38) Cai, S. X.; Zhang, H.-Z.; Drewe, J. A.; Reddy, P. S.; Kasibhatla, S.; Kuemmerle, J. D.; Ollis, K. P. Preparation of 3,5-diaryl-1,2,4-oxadiazoles and analogs as activators of caspases and inducers of apoptosis. U.S. Pat. Appl. 2003/45546, 2003
(39) Hirono, S.; Shiozawa, S.; Chaki, H.; Kotsubo, H.; Tanaka, T.; Aikawa, Y. Preparation of benzophenone derivatives as AP-1 inhibitors for treatment of arthritis. EP1445249, 2004
(40) Lessel, J. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 383−390.
(41) Wiles, C.; Watts, P. *Beilstein J. Org. Chem.* **2011**, *7*, 1360−1371.