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# Application of flow chemistry to the reduction of nitriles to aldehydes

reaction applying continuous flow technology.

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### ARTICLE INFO

## ABSTRACT

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Microreactor

Partial and chemoselective one step reduction of nitriles to aldehydes is an important transformation in organic chemistry. Several reducing agents have been described to perform this reaction.<sup>1</sup> From all of them DIBAL-H has become the reagent of choice for this transformation since it was first reported in the late 50's.<sup>2</sup> Despite this fact, important limitations of DIBAL-H reductions exist and are related to the instability of the intermediates formed.<sup>2c</sup> Other reducing agents, such as a dissolving metal (Al or Fe) covered with a promoter metal (Ni) by cementation, has also been applied.<sup>3</sup> In this case, the variables of cementation have been found to greatly influence the particle size and morphology of the bimetallic system and the yield of aldehyde formation. More recently, two new agents, lithium diisobutyl-t-butoxyaluminium hydride (LDBBA) and lithium diisobutyl-iso-propoxyaluminium hydride (LDBIPA), have shown to be highly effective in the reduction of nitriles to aldehydes.<sup>4</sup> However, aliphatic nitriles are totally resistant to both reducing agents and the method has been proved in a 0.5 mmol scale. These drawbacks require developing a general and reproducible reduction method, especially when needed for scale up to several grams.

In recent years flow chemistry and microreactors have appeared as a novel technology that, among other advantages, allows a much better control of reactions where unstable intermediates are involved, as they can be produced and reacted in line.<sup>5</sup> Microreactors have a high surface-to volume ratio in microchannels that permit a very efficient heat transfer and, as a consequence, a good control of

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the reaction temperature, avoiding the problems associated with highly exothermic reactions. Mass transfer is also enhanced and the use of dangerous or air and moisture-sensitive compounds is improved due to the lower reaction volume. From an environmental viewpoint production of hazardous waste is also reduced.

Reduction of nitriles to aldehydes with diisobutylaluminium hydride (DIBAL-H) is an important transfor-

mation in organic chemistry. But the use of this reaction is limited for the lack of reproducibility due to

the instability of the intermediates formed. In the current article we disclose the improvement of the

Optimization of reaction conditions is performed by the control of residence time and scalability of this kind of reactions is just a matter of pumping, mixing and quenching continuously the reagents through the microreactor. This permits a rapid experimentation and scale up thus shortening the time from research to development and production.

In order to overcome the limitations of the reduction of nitriles to aldehydes with DIBAL-H, we envisaged the application of flow chemistry to this reaction. No literature precedent exists to our knowledge, although DIBAL-H has been already used for the reduc-



Presure control

Presure control

pump 1

Reactant 1

Reactant 2

Scheme 1. Schematic of the flow reactor.







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Control unit

Temperature

control

Micro-

Product

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Figure 1. Experimental set up of the flow system.

# Table 1Reaction optimization using benzonitrile

CN DIBAL-H Toluene + NH <sub>2</sub>								
1	la		2a		3a			
Entry	Batch/Flow	<i>T</i> (°C)	Eq. DIBAL-H	τ (s)	Con	Conversion <sup>a</sup> (%)		
					1a	2a	3a	
1	Batch	-40	1	300	50	50	0	
2	Flow	-40	1	60	36	64	0	
3	Flow	-40	1.5	60	23	72	5	
4	Flow	0	1	30	40	60	0	
5	Flow	0	1.2	30	25	75	0	
6	Flow	0	1.5	20	1	99	0	

<sup>a</sup> Yield by GCMS.

## Table 2

Scope of the reaction

tion of ester to aldehydes in flow.<sup>2c,2d</sup> In order to achieve this goal, the Sigma–Aldrich Starter Kit<sup>™</sup> microreactor connected to a syringe pump was used as the flow reactor (Scheme 1, Fig. 1). At the end of the line the reaction mixture was poured dropwise into the appropriate quenching solution.

Using this simple set up reaction conditions were optimized for the reduction of benzonitrile **1a** to benzaldehyde **2a** (Table 1). The best conditions were found at 0 °C, 1.5 equiv of reducing agent and a residence time of 20 sec. At -40 °C reaction was not completed with 1 equiv of DIBAL-H and 1 min retention time, even though conversion in batch under the same conditions for 5 min was even lower, proving the value of the flow approach.<sup>6</sup>

These optimized reaction conditions were used successfully for other aromatic nitriles **1b**, **1c** and **1d** (Table 2). But the conditions were modified according to the substrate to be reduced. Strong electron-withdrawing groups, such as nitro group **1e**, required longer residence times and additional amount of reducing agent. Pyridyl analogues **1f**, **1g** and **1h** were reduced, similarly, at room temperature. The same conditions were used for thienyl analogue **1l**. Other aromatic heterocycles, such as pyrrole **1m**, required 42 min for complete conversion. Benzyl nitriles, such as **1i**, required less equivalents of DIBAL-H and shorter reaction time at room temperature. Aliphatic nitriles, exemplified by **1j**, were reduced at -20 °C and 14 min reaction time. It is worth highlighting that cinnamaldehyde **1k** can be obtained from the corresponding nitrile in high selectivity and yield.

Finally, aliphatic nitrile **1n** was selected because aldehyde **2n** is an interesting scaffold for medicinal chemistry programmes (Table 3).<sup>7</sup> Reduction of this nitrile has been previously described using lithium aluminium hydride in good to excellent yields. However, the use of lithium aluminium hydride is very hazardous and a very slow addition is needed in order to avoid overreduction.<sup>2b</sup> In flow, by the use of DIBAL-H, this compound can be obtained in excellent yield at 50 °C. Moreover, this example was scaled up to 15 mmol scale successfully resulting in a better yield. The reason for this increased yield is the longer steady state. Using this system productivities of 3 g h<sup>-1</sup> were achieved for this scaffold.

In summary reduction of nitriles to aldehydes with Dibal-H has been successfully transferred to flow systems, proving to be a valu-

		R-CN	DIBAL-H	R-CHO +	R <sup>NH</sup> 2			
		1a-m	Toluene	2a-m	3a-m			
Compound	R	T (°C)	Eq. DIBAL-H	τ (s)		Conversion <sup>a</sup> (%)		Yield <sup>b</sup> (%)
					1	2	3	
1a	C <sub>6</sub> H <sub>5</sub>	0	1.5	20	1	99	0	70
1b	o-Me-C <sub>6</sub> H <sub>4</sub>	0	1.5	20	5	95	0	75
1c	m-MeO-C <sub>6</sub> H <sub>4</sub>	0	1.5	20	5	95	0	88
1d	$p-F-C_6H_4$	0	1.5	20	2	98	0	85
1e	p-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	0	2	800	7	89	2	79
1f	4-Pyridyl	rt	2	800	7	92	1	53
1g	3-Pyridyl	rt	2	800	5	91	4	52
1h	2-Pyridyl	rt	2	800	9	90	1	56
1i	Benzyl	rt	1.5	60	8	90	2	75
1j	n-Propyl	-20	1.5	800	9	87	4	64
1k	Cinnamyl	rt	2	50	8	85	7	77
11	2-Thienyl	rt	2	800	9	85	6	60
1m	2-Pyrrolyl	rt	2	2500	5	95	0	59

<sup>a</sup> Conversion by GCMS.

<sup>b</sup> Isolated yield. **General Procedure**: Solutions of nitrile dissolved in Toluene (5 mL) and DIBAL (1 M) in Toluene were pumped at the appropriate flow rate and mixed in a 0.85 mL Microreactor Explorer Kit chip reactor. For longer residence times extra 20 ml tubing was added at the end of the reactor. The solution at the microreactor outlet was poured into a 1% Sodium Tartrate solution at 0 °C. The crude solution was extracted with EtOAc. The extracts were dried over MgSO<sub>4</sub>, filtered and evaporated to yield the desired product. All products obtained and discussed in this work have been previously reported and characterized.

## Table 3

Scale up of nitrilie **1n**<sup>a</sup>



Entry	Scale (mmol)	Conversion <sup>b</sup> (%)			Yield <sup>c</sup> (%)
		1n	2n	3n	
1	3	16	84	0	80
2	15	7	93	0	91

<sup>a</sup> Reaction conditions: 1.5 equiv of DIBAL-H, T = 50 °C,  $\tau$  = 800 s.

b Conversion by GCMS.

<sup>c</sup> Isolated yield.

able alternative to batch procedures, especially when scaling up. All the examples reported are obtained in good to excellent yields and selectivities using a simple and economical set up. They were selected as representatives for aryl, benzyl, alkyl and heterocyclic aldehydes, providing good starting points for the future analogues to be reduced.

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