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Application of Flow Chemistry to the Selective Reduction of Esters to Aldehydes

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The reduction of esters to aldehydes is an important transformation in organic chemistry and several reducing agents have been described. However, the use of this reaction in medicinal and natural product chemistry is limited due to the instability of the intermediates and the high reactivity of the reaction products. In the current article, the general and selective reduction of esters with diisobutyl-*tert*-butoxyaluminum hydride in flow is reported. This reagent allows esters to be reduced in the presence of different functional groups, including those considered to be of similar or higher reactivity.

Introduction

The partial and chemoselective one-step reduction of esters to aldehydes is an important transformation in organic chemistry and several reducing agents have been described to perform this reaction.[1] Among them, diisobutylaluminum hydride (DIBAL-H) has become the most popular reagent for this transformation, although its use requires very low temperatures and provides moderate yields due to the instability of the intermediates formed.[2] Other reducing agents have also been reported: lithium tri-*tert*-butoxyaluminum hydride (LTBA),[3] bis(4-methyl-1-piperazinyl)aluminum hydride,[4] lithium tris(diethylamino)aluminum hydride [$LiAlH(NEt_2)_3$],[5] sodium diethylpiperidinohydroaluminate (SDPA),[6] and lithium diisobutylpiperidinohydroaluminate (LDBPA).[7] However, these reagents cannot achieve the reduction of both aromatic and aliphatic esters. More recently, lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA) was reported as a more effective and general reducing agent.[8] Due to the lack of a general procedure, this transformation is usually carried out in total syntheses in a two-step sequence: complete reduction to the alcohol followed by reoxidation to the aldehyde.[2c]

In recent years, flow chemistry and microreactors have appeared as novel technologies that, among other advantages, allow much better control of reactions where unstable intermediates are involved, as these species are produced and reacted in line. Microreactors have a high surface-to-volume ratio in microchannels and this permits very efficient heat transfer and, as a consequence, good control of the reaction temperature, thus 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. Optimization of reaction conditions is performed by control of residence time and scalability of this kind of reaction is simply a matter of pumping, mixing, and quenching the reagents continuously through the microreactor. This approach permits rapid experimentation and scale-up, thus shortening the time from research to development and production. From an environmental point of view, production of hazardous waste is also reduced.[9]

Results and Discussion

In order to overcome the limitations in the reduction of esters to aldehydes, we envisaged the application of flow chemistry to this transformation. We used the commercially available cooling module of the R2+R4 Vapourtec reactor. One of the lines was fed with the ester and the other with the reducing agent. Both streams were conditioned in the module at the reaction temperature and mixed in a T-mixer. The mixture was then matured in a coil. The output of the coil was poured into a quenching solution. Alternatively, the output could be directed to a column containing the scavenger and then collected (Figure 1). No difference in the outcome of the reaction was observed between on-line and off-line workup.

To the best of our knowledge, only two examples involving the use of DIBAL-H in this context have been described. In both cases, an aliphatic ester was reduced in good yields to its corresponding aldehyde.[2c,10] Following these initial reports we explored the use of DIBAL-H to

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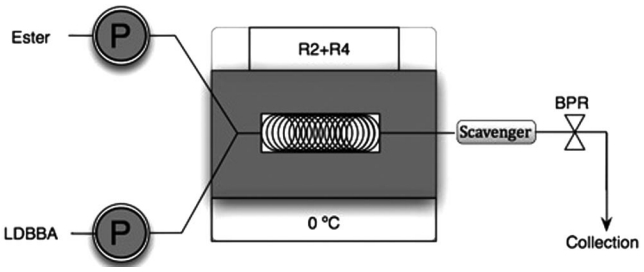
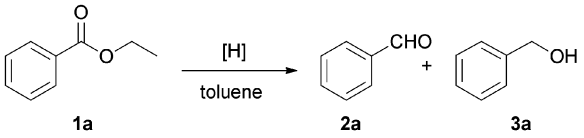


Figure 1. Experimental set up of the flow system.

reduce ethyl benzoate (**1a**) to benzaldehyde (**2a**), but the conditions explored proved unsuccessful (Table 1, Entries 1–4). These results are consistent with the previously reported reduction of methyl 4-bromobenzoate to its corresponding alcohol in flow with DIBAL-H.[10]

Table 1. Reaction optimization using ethyl benzoate.



1a **2a** **3a**

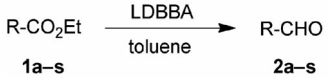
Entry	[H]	Equiv.	*T* / °C	*t* / min	Conversion / %[a]		
					1a	**2a**	**3a**
1	DIBAL-H	1	–70	2.5	53	0	39
2	DIBAL-H	1	–40	0.5	50	0	42
3	DIBAL-H	1	–20	0.5	50	0	43
4	DIBAL-H	1	0	2.5	53	0	39
5	LDBBA	1.3	0	20	1	75	16
6	LDBBA	1.3	–20	20	3	72	14
7	LDBBA	1.3	25	20	3	61	27
8	LDBBA	1.1	0	20	7	79	14
9	LDBBA	1.1	0	10	10	77	13
10	LDBBA	1.1	0	5	56	32	8
11	LDBBA[b]	1.2	0	180	–	74	–

[a] Conversion by GC–MS. [b] Batch reaction as described in ref.[8]

According to these results, the selective reduction of aryl esters is difficult with this reducing agent and, for this reason, we considered other reducing agents. As described in the Introduction, LDBBA appears to be the most general and effective alternative to DIBAL-H. Both reagents can be handled similarly, having the caution of injecting them under an inert atmosphere. The first conditions tried in flow were based on the batch procedure described previously[8] (Table 1, Entry 11). The results were similar (Table 1, Entry 5) but the reaction was complete in 20 min instead of 3 h. The reaction was optimized by modulating the temperature, time, and equivalents of reducing agent to reduce the amount of alcohol **3a** and to increase the amount of aldehyde **2a** (Table 1, Entries 6–10). Decreasing the temperature did not improve the selectivity over **3a** (Table 1, Entry 6). When the temperature was increased to 25 °C, more over-reduction product was observed (Table 1, Entry 7). Decreasing the equivalents of reducing agent provided the expected aldehyde in similar yields, although more unreacted starting material was found in an overall cleaner reaction mixture (Table 1, Entry 8). On increasing the flow rate, while using the same number of equivalents, the optimal conditions were obtained for retention times between 10 and 20 min (Table 1, Entry 9 vs. Entries 8 and 10).

The conditions reported in Table 1, Entry 9 were selected to explore the scope of the reaction and they proved to be very successful for a wide range of compounds (Table 2). In this way, different functional groups were compatible with this reagent, regardless of their electron-donating or electron-withdrawing properties and their position in the aryl ring (see **1a**–**h**). It is worth noting the selective reduction of the ester group can occur in the presence of a cyano group (see **1e**). Reduction of nitriles has been described with lithium diisobutylisopropoxyaluminum hydride (LDBIPA), a reducing agent similar to LDBBA.[11] This example was scaled up 20-fold with almost identical yield, thus demonstrating the value of flow technology.

Table 2. Scope of the reaction.



1a–s **2a–s**

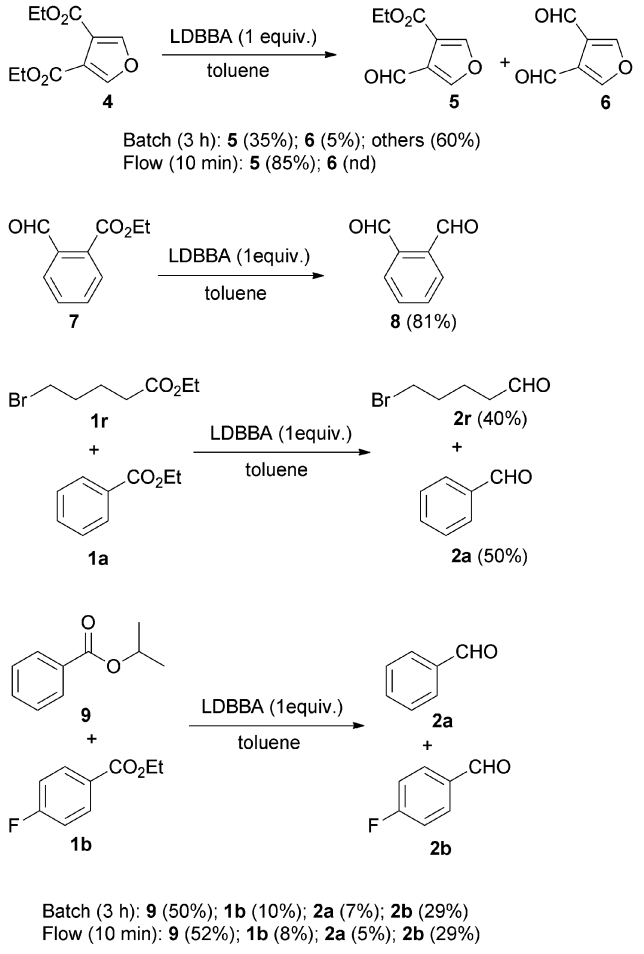
Compd.	R	Yield / %	Compd.	R	Yield / %
1a	C_6H_5	79	**1j**	3-pyridyl	97
1b	*p*-FC_6H_4	80	**1k**	2-pyridyl	94
1c	*p*-ClC_6H_4	83	**1l**	4-pyrazolyl	97
1d	2-Cl-4-FC_6H_4	85	**1m**	2-Br-5-thienyl	89[b]
1e	*m*-CNC_6H_4	97	**1n**	5-oxazolyl	80
1e	*m*-CNC_6H_4	96[a]	**1o**	benzyl	87
1f	*p*-$MeOC_6H_4$	85	**1p**	*n*-propyl	90
1g	*o*-$MeOC_6H_4$	82	**1q**	cinnamyl	79
1h	*p*-MeC_6H_4	90	**1r**	4-Br-butyl	80
1i	4-pyridyl	76	**1s**	N-Boc-4-piperidinyl	84

[a] Reaction performed on 18 mmol scale. [b] LDBBA (1.3 equiv.).

Heteroaromatic esters were also reduced effectively. Pyridyl analogues **1i**–**k** provided the corresponding aldehydes in good to excellent yields. Pyrazolyl **1l** and thienyl **1m** were also reduced, although the latter required a larger excess of the reducing agent. Aliphatic esters, such as benzyl and alkyl esters (i.e., **1o**–**s**) were also examined. These were converted into their corresponding aldehydes under the conditions used for aromatic esters. It is remarkable that other reducible groups, such as conjugated double bonds (i.e., **1q**) or alkyl halides (i.e., **1r**), were not transformed, proving the high selectivity of this reducing agent. As a final example, Boc-protected piperidine **1s** was selected to check that these reaction conditions are compatible with this widely used protecting group.

Encouraged by the results obtained, four experiments were designed to explore further the selectivity of the reaction: Selective reduction of one ester group in a diester compound, selective reduction of esters in the presence of an

aldehyde, selective reduction between alkyl and aryl esters, and selective reduction between primary and secondary esters (Scheme 1).



Scheme 1. Selectivity of LDBBA reductions.

The first example, selective reduction of one ester group in diester **4**, was achieved easily in flow under the standard conditions. By contrast, the reaction was not complete in batch after 3 h of reaction, and dialdehyde **6** was identified. It is worth noting that in batch conditions, in a comparable reaction time to that used for flow conditions (10 min), diester **4** remained unaltered in solution. This is a good example of an outcome that can only be achieved by flow. As long as diester **4** is reduced to compound **5** this latter compound does not come into contact with more LDBBA to be reduced to dialdehyde **6**, as is the case in batch mode.

The second example, the selective reduction of an ester in the presence of an aldehyde, was tested with compound **7**. Unexpectedly, the ester was reduced selectively to aldehyde **8**. To the best of our knowledge this is a unique example of ester reduction in the presence of a more reactive group such as an aldehyde.

Unfortunately, it was not possible to obtain selectivity between alkyl or aryl esters. When both **1r** and **1a** were present in solution, they were reduced almost to the same extent. Finally, the selective reduction between primary and secondary esters was tested with compounds **9** and **1b**. According to the original article, both esters were reduced under the same conditions.[8] Under flow conditions, the ethyl ester was reduced selectively in the presence of the isopropyl one, with a **2b**/**2a** ratio of 5:1. Similar results were achieved in batch after 3 h of reaction but there was almost no conversion after 10 min, thus demonstrating the efficiency of the flow approach.

Conclusions

In summary, the reduction of esters to aldehydes with LDBBA in flow has proven to be a valuable alternative to batch procedures. Aromatic, aliphatic, heteroaromatic, and heteroaliphatic aldehydes were obtained in good to excellent yields under flow conditions. It is important to highlight the selective reduction of an ester group in the presence of an aldehyde, the selective reduction of a single ester group, which cannot be achieved under traditional batch conditions, and the selective reduction of a primary ester in the presence of a secondary ester. All of these results offer new possibilities for the preparation of more complex molecules in medicinal and natural product chemistry.

Experimental Section

General Procedure for the LDBBA Reduction in Flow: The manifold system (pumps, valves, PFA tubing, and reactor coil) of a Vapourtec R2+R4 unit was dried with isopropyl alcohol (2 mL/min, 15 min) and anhydrous THF (0.5 mL/min, 20 min). A solution of the ester (0.909 mmol, 1 equiv.) in THF was loaded into a sample loop (2 mL) on a Vapourtec R2+R4. A solution of LDBBA[8] (1 mmol, 1.1 equiv.) in THF/hexane was loaded into a second sample loop (2 mL). The two sample loops were switched in-line into streams of THF, each flowing at 0.250 mL/min, and mixed in the cold reactor at 0 °C. The mixture was then matured in the cold reactor by using the 5 mL coil. The output of the coil was then poured directly into a 1 M HCl solution. The reaction mixture was extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to dryness.

Workup On-Line: The output of the coil was directed into a 10 mm diameter Omnifit column filled with $Na_2SO_4 \cdot 10H_2O$ (2 g, 6.20 mmol) and $MgSO_4$ (1 g, 8.3 mmol). The solution collected was evaporated to dryness.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of compounds, and GC–MS of selective LDBBA reductions.

Acknowledgments

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