This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Continuous Flow Chemistry: A Discovery Tool for New Chemical Reactivity Patterns

Jan Hartwig, Jan B. Metternich, Nikzad Nikbin, Andreas Kirschning, and Steven V. Ley

Continuous flow chemistry as a process intensification tool is well known. However, its ability to enable chemists to perform reactions which are not possible in batch is less well studied or understood. Here we present an example, where a new reactivity pattern and extended reaction scope has been achieved by transferring a reaction from batch mode to flow. This new reactivity can be explained by suppressing back mixing and precise control of temperature in a flow reactor set up.

Dedicated to Professor Richard J.K. Taylor on the occasion of his 65th birthday with respect and warmest best wishes.

Introduction

The last decade has witnessed a substantial increase in the number of publications which use continuous flow reactors to perform synthesis. The positive impact of continuous flow chemistry on chemical processes is well studied and has been covered by many review articles. The main benefits which are frequently cited are the improved heat and mass transfer, greater reaction control, the ease of heating solvents above their boiling point, higher safety when dealing with reactive and hazardous intermediates and relative simplicity of their automation and telescoping of multistep reactions. Together these lead to overall process intensification. However, the application and general utility of flow reactors would significantly increase if new reactions or novel reactivity patterns were discovered especially those that are not possible in normal batch mode operation. To date this has not been the primary focus of flow chemistry researchers although there is evidence that this is possible through manipulation of the dynamics of flow systems such that the scope of particular reactions can be changed. For example, lithium nucleophiles generated from methyl pyridines can be made to add to ethyl esters selectively to obtain the single addition product in flow whereas the double addition is expected in batch mode operation unless Weinreb amides or similar are used as substrates. We therefore have decided to systematically investigate reactions in flow looking for new reactivity patterns simply not possible in batch.

Indeed opportunity arose when we began a study of homologation reactions involving addition of lithiated dibromomethane to esters. Kowalski et al. had already investigated the preparation of different bromomethyl ketones (G) via this reaction (scheme 1). The authors considered different pathways and reported a wide reaction scope based on esters containing primary alkyl, alkynyl, alkenyl or aromatic substituents. The only limitation for accessing monobromo ketones in their work was that more hindered R substituents were apparently not tolerated.

However, unlike the original report by Kowalski we targeted α-dibromoketones D as the desired product outcome to be used in one of our medicinal chemistry programmes. These are useful intermediates that can be used for the preparation of pyrazines.
Organic & Biomolecular Chemistry

Chemistry Manuscript

2 Table 1 Formation of α-dibromoketone from esters with aromatic or sp²-hybridized carbon-substituents as R.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield Batch</th>
<th>Yield Flow</th>
<th>Entry</th>
<th>Product</th>
<th>Yield Batch</th>
<th>Yield Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>80%</td>
<td>95%</td>
<td>5</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>70%</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>-</td>
<td>72%</td>
<td>6</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td><img src="structure5.png" alt="Structure" /></td>
<td>58%</td>
<td>62%</td>
<td>7</td>
<td><img src="structure6.png" alt="Structure" /></td>
<td>-</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td><img src="structure7.png" alt="Structure" /></td>
<td>66%</td>
<td>38%</td>
<td>8</td>
<td><img src="structure8.png" alt="Structure" /></td>
<td>-</td>
<td>50%</td>
</tr>
</tbody>
</table>

Table 1

1.05 mmol scale, c(LDA) = c(CH₂Br₂) = 0.5 M, c(ester) = 0.5 M, total residence time for flow was nearly 12 minutes while batch reaction time was 15 minutes. LDA and CH₂Br₂ were used in excess (2.2 eq.). Both reaction modes were performed at -90°C.

15, triazines, 16 imidazoles 15 or alkynol ethers. In the present project they were needed as intermediates in the formation of α-keto esters via oxidative esterification. The dibromoketone D can be obtained by direct protonation of the highly reactive dibromo enolate anion C, which even at -90 °C can undergo side reactions. The exact control of the reaction conditions is therefore crucial especially with more elaborate substrates. Indeed the reaction was severely limited in batch when we attempted to isolate the dibromo ketones D. It was therefore decided to conduct the reaction on a flow chemistry platform to examine whether control of the reaction conditions could be improved. More importantly we intended to see if new reactivity patterns could be obtained under the flow regime (see below).

Results and Discussion

The clean preparation of lithiated dibromomethane in these reactions was therefore one of the crucial steps in the overall process. Following mixing of dibromomethane with LDA we found it takes several minutes to completely consume the base at -90 °C. Therefore short mixing times cause a decrease in the amount of lithiated dibromomethane and consequently reduce the conversion during the initial phase of the reaction. Lithiated dibromomethane on the other hand has a short half-life and substantial decomposition can occur even at -90 °C for larger scale batch reactions. This is an inherent problem in batch mode where extended reaction times are incompatible with unstable intermediates or products. In this case, as described by Yoshida et al. 16 mixing is the limiting factor for the lithiation to occur hence the continuous flow process provides a robust and reliable alternative where the intermediate reacts upon
formation due to superior mixing and better defined residence times.

The reaction setup is depicted in scheme 2 whereby the solutions of LDA and dibromomethane were introduced via sample loops, mixed in a T-piece and entered the first reactor at -90 °C to form the deprotonated dibromomethane species. Upon exiting the reactor this mixes with a pre-cooled solution of an ester in THF. Since the first step produces the deprotonated dibromomethane species it requires stabilisation at -90 °C. We are also aware of the third stream problem in flow reaction systems\(^\text{19}\) where dispersion within the first reactor can lead to less than accurate stoichiometries when introducing a third reagent. However, as the ester is used substoichiometrically, no exact matching of the third stream was necessary and small manual adjustment of pumps was enough to facilitate the desired reaction. The product was obtained by collection into a round bottom flask charged with ethanol and a small amount of concentrated sulfuric acid. The full details of the flow set up can be found in the supplementary information.

As seen in table 1, in most cases the isolated yield increases in going from batch to flow although an exception was observed (entry 4). A variety of heterocycles, such as pyridines, thiophenes or isoxazoles, are all tolerated, as is the ortho-nitrobenzene substrate which was reported to fail in the original work by Kowalski et al. The increase of the yield in flow can be explained by better mixing and control of the temperature under flow conditions. In case of entry 4, presumably the lithiated dibromomethane intermediate undergoes lithium-halogen exchange and forms some α-monobromoketone by-products which of course affects the selectivity of the reaction.

Satisfied with the general improvement in flow, we next turned our attention to developing new reactivity patterns not possible in batch mode. When studying compounds with acidic protons in α position adjacent to the ester, it became apparent that this was not possible in batch and complete recovery of the starting material was always observed. This was not unexpected on the basis that the reaction prefers to follow pathway (b) as opposed to (a) in scheme 3 for kinetic reasons.

Thus, in intermediate B in Scheme 1 when the side chain bears no α hydrogen atoms, a second equivalent of base removes the proton from the only available site leading to dibromoenolate C. Subsequent quenching of this dibromoenolate results in the α-dibromo ketone being formed as the product. However, if α-proton is present (Scheme 3) the scenario is quite different and the second equivalent of base removes the most accessible proton, hence producing the kinetic intermediate J. Protonating this intermediate results in the recovery of the starting material. Next, we reasoned that by accelerating mixing and suppressing back mixing we could stop the second equivalent of base reacting with the intermediate H, prolonging existence of this species long enough to be quenched subsequently by acid. Protonating this tetrahedral intermediate in both cases of presence (H) or absence (B) of an α-proton essentially leads to the desired dibromoketone. In addition we anticipated that precise temperature control in flow mode would help preserve intermediates deemed too unstable to survive under the batch conditions. These could arise during addition to fumarates as substrates or those containing sensitive functional groups such as nitrile or alkynes (vide infra). The hypothesis suggests that the fate of an intermediate would change on transferring to continuous flow mode and therefore create a new reactivity pattern that could be exploited with a range of substrates simply not possible in batch.

This new reactivity was first observed in the reaction of methyl 2-phenylbutanoate 1 as substrate. The product 1,1-dibromo-3-phenylpentan-2-one 2 was isolated in only 10% yield after several attempts in batch. However, in flow-mode 49% yield could be achieved with 42% recovered starting material under similar conditions and pleasingly up to 95% yield if the amount of lithiated dibromomethane was increased to 4.4 equivalents (table 2).

![Scheme 3 Possible pathways for the deprotonation after addition of lithiated dibromomethane to esters with acidic α-protons.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mode</th>
<th>Eq. LiCHBr₂</th>
<th>Yield (%)</th>
<th>Rsm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1⁺</td>
<td>Batch</td>
<td>2.2</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2⁺</td>
<td>Flow</td>
<td>2.2</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>3⁻</td>
<td>Flow</td>
<td>4.4</td>
<td>95</td>
<td>0</td>
</tr>
</tbody>
</table>

* 1.05 mmol scale, c(LDA)= c(CH₂Br₂)= 0.81 M, c(ester)= 0.58 M, c(ester)= 0.29 M. Both reaction modes were performed at -90°C. Total residence time for flow reaction was nearly 12 minutes while batch reaction time was 15 minutes.

With the knowledge of this changed and unexpected reactivity in flow more complex substrates were investigated in order to briefly explore the limits of this new reactivity (table 3).
Remarkably, we noticed compounds that are considered to be poor substrates in batch, were successful in flow albeit in modest yields. The flow arrangement tolerated a degree of chemoselectivity in the presence of various functional groups. For example the desired product could be isolated in the presence of triple bonds (entry 1) or nitriles (entry 3) in 53% and 22% yields respectively. Under batch reaction conditions no product or a yield of only up to of 10% was observed. Maleic methyl ester (entry 4) surprisingly showed only single addition to the ester function and no Michael addition during the reaction in flow. Only a 17% yield of the product was isolated due to its inherent instability. Benzyl protected phenylalanine ethyl ester (entry 2) afforded 54% yield while only starting material could be isolated during the batch reaction. The product of the reaction in entry 5 formed in 25% yield was unstable owing to the epoxide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield Batch</th>
<th>Yield Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure" /></td>
<td>10%</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure" /></td>
<td>0%</td>
<td>54%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure" /></td>
<td>0%</td>
<td>22%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure" /></td>
<td>0%</td>
<td>25%*</td>
</tr>
</tbody>
</table>

1.05 mmol scale, c(LDA)= c(CH$_3$Br$_2$)= 0.81 M, c(ester)= 0.58, total residence time for flow was nearly 12 minutes while batch reaction time was 15 minutes. LDA and CH$_3$Br$_2$ were used in excess (2.2 eq.). Both reaction modes were performed at -90°C. *Calculated based upon NMR data

Conclusions

We have demonstrated that the efficiency of certain batch reactions can be improved considerably by conducting them in the flow regime. More importantly, it was also shown that new reactivity and extended reaction scope can be observed in flow for processes that are simply not viable in traditional batch mode operations. The general reactivity of esters with lithiated dibromomethane could be improved compared to previous studies, including the preparation of various α-dibromoketones which could not be obtained in batch experiments. The dibromoketone products are useful building blocks for ongoing medicinal chemistry programmes. Many of these reactions can also be performed on larger scales and are faster and more efficient compared to the corresponding batch mode operation. Based on the observations made in this work we suggest that reactions which are affected seriously by back-mixing should be investigated in flow mode to extend both the scope of reactions and to discover new reactivity patterns.

Acknowledgements

We would like to thank the EPSRC grant EP/F069685/1 (NN) and the Fonds der Chemischen Industrie (JH) for financial support.

Notes and references


14 Patent WO 03/093272 A1, Merck & Co., Inc (published 13.11.2003);

