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Continuous flow as an enabling technology: a fast and versatile entry to functionalized glyoxal derivatives†

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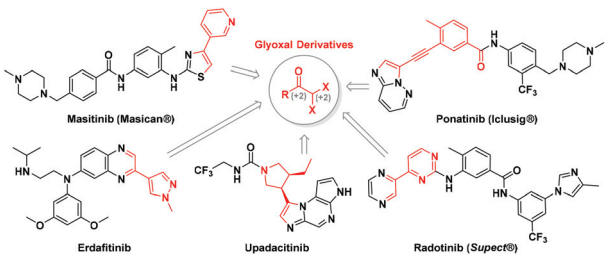
We herein report two complementary strategies employing organolithium chemistry for the synthesis of glyoxal derivatives. Micromixer technology allows for the generation of unstable organometallic intermediates and their instantaneous in-line quenching with esters as electrophiles. Selective mono-addition was observed *via* putative stabilized tetrahedral intermediates. Advantages offered by flow chemistry technologies facilitate direct and efficient access to masked 1,2-dicarbonyl compounds while mitigating undesired by-product formation. These two approaches enable the production of advanced and valuable synthetic building blocks for heterocyclic chemistry with throughputs of grams per minute.

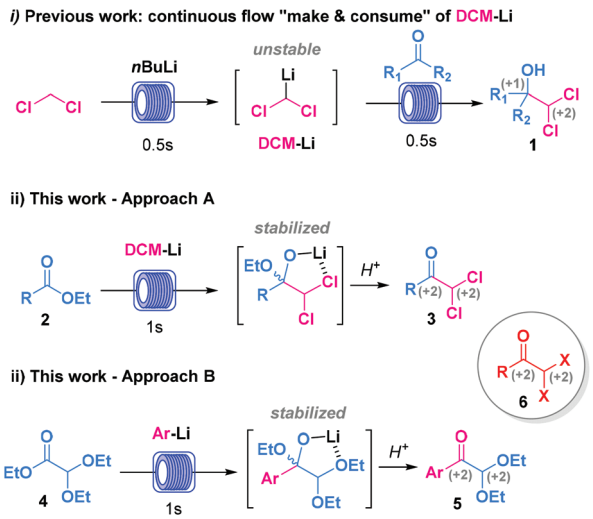
Functionalized glyoxal derivatives are important precursors for the synthesis of a plethora of heteroaromatic compounds such as pyrazines, quinazolines, 1,2,4-triazines, oxazoles, thiazoles, imidazoles and derivatives thereof.[1,2] These 5- and 6-membered heterocycles are commonly encountered pharmacophores[3–5] and therefore are of high importance in the pharmaceutical small-molecules landscape as exemplified in the recurrence of these motifs in recently discovered kinase inhibitors (Scheme 1).[6]

Previously, we reported on the formation of dichloromethyl lithium (**DCM-Li**) in continuous flow mode and its electrophilic quench onto aldehydes to afford α,α′-bis-chloro carbinols (**1**) as outlined in Scheme 2.[46]

Inspired by this developmental work we envisaged to expanded on this concept and targeted the synthesis of glyoxal derivatives (**3** and **5**) in a single step approach. The challenge with the described chemistry is to identify a high yielding and atom-efficient entry to dicarbonyls (**3** and **5**) while mitigating the formation of the undesired tertiary alcohol by-product, amongst others.[7–10] The selective mono-addition of an organometallic species to a carboxylic acid derivative is a well-established method for the synthesis of ketone derivatives.[11] However, pre-functionalization (*e.g.* as amides[12]) is required to



Scheme 1 Highlight of the possible use of glyoxal derivatives in the synthesis of a selection of kinase inhibitors.[6]



Scheme 2 Flow methods to access glyoxal derivatives.

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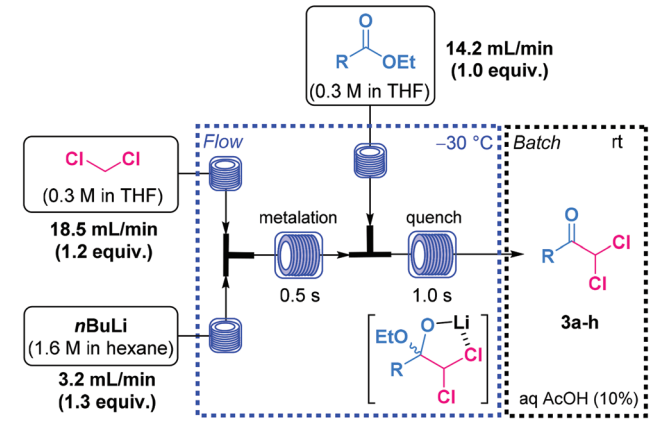
perform chemoselective transformations to ketones.[12–20] Despite their broad chemical availability, esters are rarely used as electrophiles to access ketones, reasons being the greater instability of the transient tetrahedral intermediate leading to unavoidable, consecutive over-addition products.[21,22] Some pioneering studies made use of stabilization of the corresponding tetrahedral intermediates *via* chelation[23–25] or inductive effects[25–29] under cryogenic conditions to enable selective ketone formation from esters. We therefore postulated that the quenching of selected flow generated organolitium species (DCM-Li and Ar-Li) with esters could allow the access of both α,α′-bis-chloro ketones (**3**) and the keto-acetals (**5**) from chelate stabilized intermediates (Scheme 2). Finally, both synthetic approaches A and B pose fundamental issues when conducted in traditional batch mode; firstly due to the involvement of unstable organolithium moieties and secondly because of the inherent formation of the tertiary alcohol as a dominant by-product by consecutive over-addition. Inspired by the advantages of continuous flow methodologies[30–37] and to complement existing methodologies for the synthesis of ketones in continuous flow,[38–42] we envisioned to develop a *flash chemistry* (chemical synthesis on a timescale of <1 second) platform that would facilitate the outlined strategy.

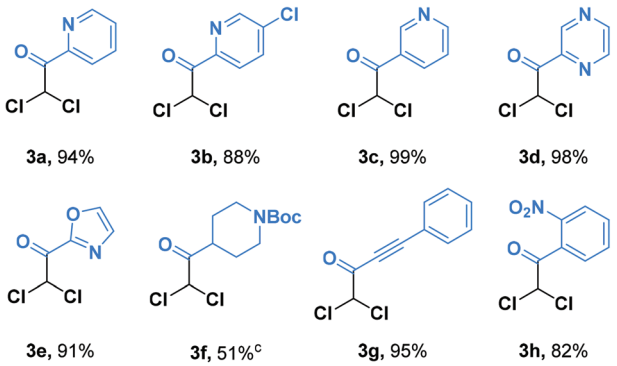
We started our investigation with the reaction of dichloromethyl lithium (DCM-Li) and compound **2a** following Approach A to form **3a** (Table 1).

Based on our previous work in the field of organometallic reactions, we reverted to our established continuous flow setup which is a reliable working horse in our process development labs.[43] The automated flow platform dedicated to organolithium chemistry consists of simple PTFE T-pieces (ID = 0.5 mm) as mixing elements and PFA tubing (ID = 0.8 mm) as tubular reactors. Minimum total flow rates of ~20 mL min^{-1} per mixing element are essential to ensure highly efficient mixing and short mixing times (≤500 ms).[43] Pleasingly, we observed excellent results without the necessity to adjust or optimize any process parameter compared to our previously reported protocol and α,α′-bis-chloroketone **3a** was obtained in excellent yield and purity. With a particular focus on medicinally relevant heterocyclic examples, our methodology was successfully applied to pyridines (**3a** to **3c**), pyrazine (**3d**), oxazole (**3e**) and a *N*-Boc-protected piperidine (**3f**). Also, an alkynyl ester and *ortho*-nitro benzoyl reacted smoothly affording α,α′-bis-chloroketones **3g** and **3h**. It should be noted that most α,α′-bis-chloro ketones were synthesized in high purity following a simple extractive work-up without the need for column chromatography or crystallization.

The limited number of commercially available functionalized esters encouraged us to seek for more available substrates. In an effort to extend the scope of this chemistry we next turned our attention to Approach B (Scheme 2). Aryl- and heteroaryl bromides are readily available and pose a rich and valuable source of starting materials for our investigation. A series of commercially available aryl bromides were engaged in the mono-addition to ethyl diethoxy acetate **4** using our optimized *flash chemistry* protocol (Table 2).

Table 1 Approach A: access to α,α′-bis-chloroketones[a,b]





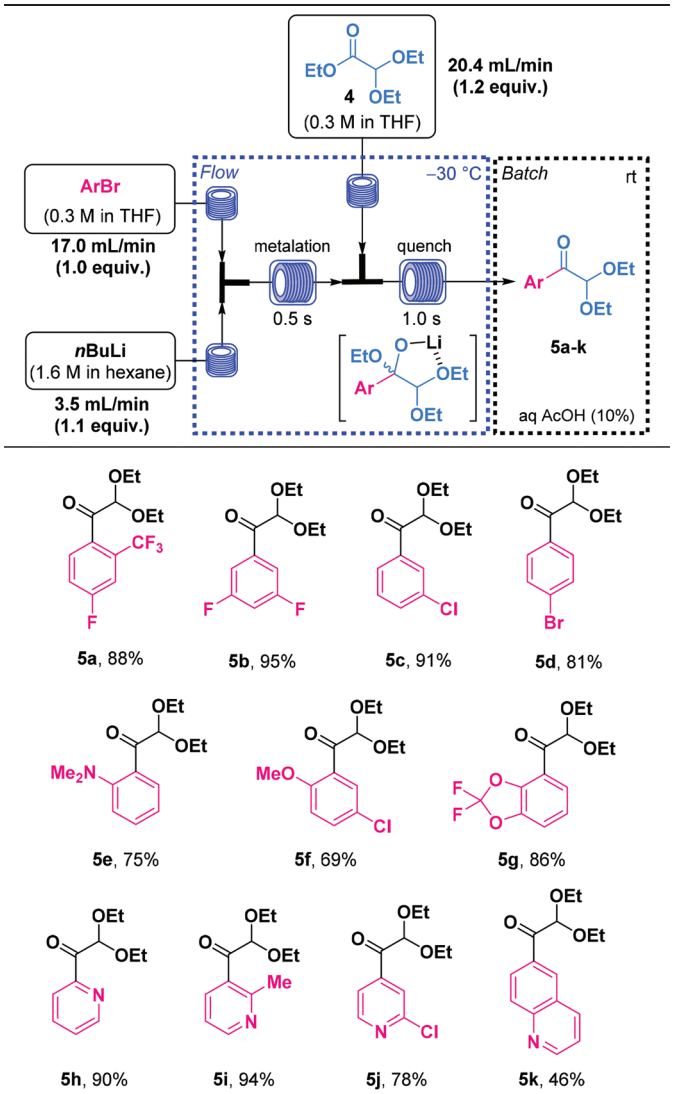
[a] Reactions were performed on 8.5 mmol scale (2.0 min run, 255 mmol h^{-1} throughput). [b] Isolated yield without column chromatography. [c] Obtained after column chromatography of the crude mixture.

For the Br/Li exchange reaction we reverted to our previously established continuous flow protocol.[43,44] Fluorine-containing aromatics were well tolerated in this reaction and provided scaffolds **5a** and **5b** in excellent yields (88 and 95% respectively).

The precise control of flow rates and stoichiometry of *n*BuLi relative to aryl bromide allows for a selective single Br/Li exchange of a dibrominated aromatic compound (**5d**). Electron-rich aromatic systems could also be successfully engaged in selective mono-additions with **4** resulting in a range of benzo keto acetals **5e–g**. Finally, we were pleased to observe that all positions around the pyridine core were well tolerated giving rise to highly functionalized heterocycles (**5h–j**). 5-Bromoquinoline could also be engaged, albeit less selectively in our method, further demonstrating the possibility to extend the range of compatible heterocyclic compounds. The structural motif of aryl keto acetals (**5**) is barely reported in the literature and the two outlined approaches now open doors to new ways to install biaryl heterocycles by classical condensation reactions.

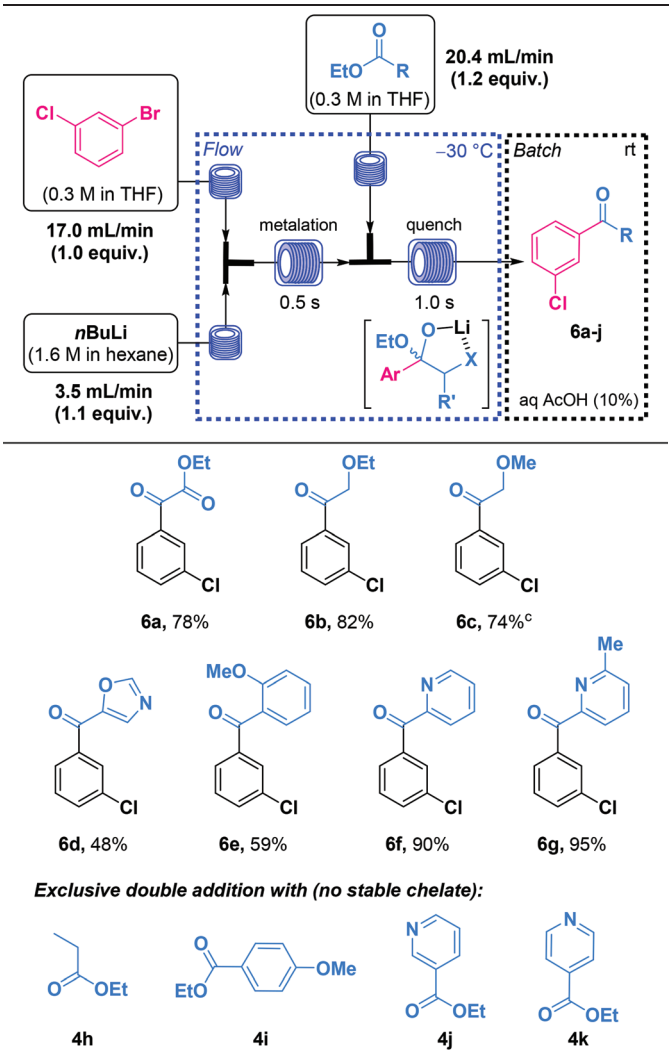
In an effort to confirm the origin of selectivity in this mono-addition to esters, we reacted 3-bromochlorobenzene with a selection of ester derivatives (Table 3). The ester screening revealed the importance of the presence of heteroatoms on

Table 2 Approach B: access to ketoacetals[a,b]



[a] Reactions were performed on 10.2 mmol scale (2.0 min run, 306 mmol h^{-1} throughput). [b] Isolated yield after column chromatography is given.

Table 3 Approach B: extension and limits of electrophile scope[a,b]



[a] Reactions were performed on 1.7 mmol scale (20 s, 306 mmol h^{-1} throughput). [b] Isolated yield after column chromatography is given. [c] From the corresponding methyl ester.

the ester moiety for coordination and stabilization of reaction intermediates. Indeed, alkyl esters bearing α-heteroatom were successfully transformed into their respective ketones **6a–c** in 74 to 82% yield. While in the absence of a heteroatom (and therefore no coordination), using esters **4h** to **4k** exclusively formed the corresponding tertiary alcohols (over-addition products). These observations are in line with the hypothesis that a lithium chelate stabilization of the tetrahedral adduct is necessary in order to observe selective ketone formation. These observations were backed with literature precedence with similar systems.[25] Based on this rational, we identified ethyl 5-oxazole carboxylate (see **6d**) and 2-anisole carboxylate (see **6e**) to be suitable reaction partners while the 4-anisole substrate (**4i**) was transformed into its corresponding tertiary alcohol. Finally, 2-pyridyl carboxylates were also identified as excellent scaffolds in this transformation, giving rise to unsymmetrical diaryl ketones **6f** and **6g**,[45] while 3- and 4-positions of pyridine (**4j** and **4k**) both exclusively resulted in over-addition.

These observations emphasize the complementarity of the two approaches and allow to design the synthesis of a desired glyoxal derivative accordingly. We believe that in approach B a 5-membered chelate stabilization of the tetravalent adduct was responsible for the high selectivity.[23–25] The tetrahedral adduct from Approach A could also benefit from a similar stabilization effect in addition from an inductive stabilization originating from the dichloromethyl moiety.[25–29]

Conclusions

In conclusion, we expanded on an established and reliable continuous flow protocol to synthesize aryl glyoxal building

blocks, which serve as valuable intermediates for the formation of medicinally relevant heterocyclic motifs. Two complementary routes are presented leading to a wide range of α,α′-bis-chloro ketones (**3**) and aryl keto acetals (**5**) with high throughputs. We added two synthetically valuable transformations to the "*flow toolbox*" using the identical flow reactor setup as previously reported for lithiation/borylation[43] or/sulfination[44] and *Matteson* chemistry.[46] This strongly emphasizes the usefulness and scope of this flow platform and showcases the synthetic utility of organolithium chemistry. The reported flow setup is equally suitable for the delivery of small quantities for medicinal chemistry purposes or for larger quantities for early development phases. The straightforward concept boosts the synthetic utility of organolithium chemistry, reduces development times and appeals attractive to the scientific community.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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