Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional N,N-Dimethylamides and Tetramethylurea in Toluene

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Abstract: The continuous flow reaction of various aryl or heteroaryl bromides in toluene in the presence of THF (1.0 equiv) with sec-BuLi (1.1 equiv) provided at 25 °C within 40 sec the corresponding aryllithiums which were acylated with various functionalized N,N-dimethylamides including easily enolizable amides at −20 °C within 27 sec, producing highly functionalized ketones in 48–90% yield (36 examples). This method was well suited for the preparation of α-chiral ketones such as naproxene and ibuprofen derived ketones with 99% ee. A one-pot stepwise bis-addition of two different lithium organometallics to 1,1,3,3-tetramethylurea (TMU) provided unsymmetrical ketones in 69–79% yield (9 examples).

The acylation of organometallics with carbonyl derivatives represents an excellent preparation of ketones which are of high interest in medicinal, agrochemical and material chemistry. Although acid chlorides were often used as acylation reagents, alternative carboxyl derivatives such as 2-thiopyridyl esters, Weinreb amides, 2-pyridylamides, N-aclypyrroles or N,N-dimethylamides have been used successfully in combination with appropriate organometallics or transition metal catalysts.

The performance of organometallic reactions in continuous flow has recently given a novel dimension to a range of these synthetic methods. The accurate control of residence times, temperatures and concentrations greatly improved many reactions involving organometallic intermediates. Thus, Nagakiki and Yoshida have recently reported the synthesis of functionalized ketones from acid chlorides and lithium reagents by extremely fast micro-mixing. Although functionalized ketones were prepared, this method required the use of water sensitive acid chlorides as well as extremely fast mixing not accessible on commercial flow apparatus. The use of ecologically and industrially friendly halide free acylation reagents would be highly desirable. Hattan and Jamison have described double additions to carbon dioxide for the preparation of various ketones (Scheme 1a). Kappe has used mixed anhydrides for a continuous flow synthesis of α-haloketones. The continuous flow mode has also allowed a convenient use of esters as acylating agents.

Herein, we report the use of readily available and convenient N,N-dimethylamides of type 1 as convenient and supported information for this article is available on the WWW under https://doi.org/10.1002/chem.202102805
effective reagents for the acylation of various (hetero)aryl lithiums of type \(2^{[17]}\) in toluene using a continuous flow set-up leading to various functionalized ketones of type \(3\) including halogenomethyl ketones and \(\alpha\)-chiral ketones (Scheme 1b).

We have shown that TMU (1,1,3,3-tetramethylurea, 4) allows an efficient and selective synthesis of new unsymmetrical ketones of type \(5\) via in situ generated arylated \(N,N\)-dimethylamides 6 and batch-prepared \(R^2\)-Li species of type \(7\) (Scheme 1b).

Thus, in preliminary experiments, we have optimized the preparation of aryllithiums of type \(2\). In order to achieve a fast exchange with a stable aryllithium intermediate of type \(2\), we have explored the metal-exchange and electrophilic quench of 1-bromo-4-methylthiobenzene (8a)\(^{[17]}\) in both THF and toluene at ambient temperatures. Therefore, we treated 8a with sec-BuLi (1.1 equiv) in THF or toluene. We found that the Br/Li-exchange was fast in THF leading to the aryllithium \(2\) \(^{[18,19,20]}\), which afforded the better lithium species 2a in better yields, but the Br/Li-exchange reaction was too sluggish and required up to 2 h reaction time for completion (Table 1, entries 1–5). In balance, we found that simply adding 1.0 equiv. of THF to the toluene solution of 8a led to a fast Br/Li-exchange within 1 min at 25 °C and produced, after quenching with 9, the alcohol 10 in 95% calibrated GC-yield (Table 1, entry 6).

In contrast, using n-BuLi led to a slower Br/Li exchange of 8a incompatible with the stability of the generated metal species. Longer storage time of 2a at 25 °C (10–30 min) afforded lower yields of 10 showing the instability of 2a over time (Table 1, entries 7 and 8). In counterpoint, performing this reaction at this temperature in flow led to a quantitative formation of 10, showing that a flow set-up using toluene in the presence of 1.0 equiv. of THF was most advantageous (entry 9). The low stability of aryllithiums at ambient temperatures justified this “on-demand” preparation in continuous flow and enabled potential scale-ups. In preliminary reactions, we observed that proton-quenching via amide enolization in THF led to proto-desbrominated products (thioanisole). The present solvent system (toluene containing 1.0 equiv. of THF) also reduced this enolization side-reactions on amides bearing acidic protons\(^{[21,22]}\).

By optimizing the concentration of 8a and sec-BuLi, the residence times for the Br/Li-exchange as well as the acylation temperature, a high GC-yield of the ketone 3aa \(^{[23]}\) was achieved. Thus, performing the acylation reaction in continuous flow at either 25°C or 0°C led only to 50–67% of the ketone 3aa (Table 2, entries 1 and 2). However, lowering the reaction temperature to –20°C or –40°C gave satisfactory yields (82–84%; entries 3 and 4).

With these conditions in hand, using the aryl bromide 8a (0.25 M in toluene containing 1.0 equiv. of THF) with a flow rate of 5.0 mL/min and sec-BuLi (1.1 equiv, 1.35 M in n-hexane) with a flow rate of 1.1 mL/min, we have quantitatively generated the corresponding aryllithium 2a at 25°C (t\(^{*}\) = 40 sec). After precooling the lithium species for 10 sec, the acylation step was performed at −20°C (t\(^{*}\) = 27 sec) affording, via the formation of the tetrahedral intermediate 11 and subsequent quenching with sat. aq. NH\(_4\)Cl, the desired ketone 3aa in 82% isolated yield. A scale-up of this reaction in continuous flow was easily

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**Table 1. Optimization of the aryllithium generation in batch and flow.**

| entry | set-up | solvent | time [min] | Conversion of 8a [GC-%] | Formation of 10 [GC-%] |
|-------|--------|---------|-----------|-------------------------|-----------------------|
| 1     | batch  | THF     | 1         | 90                      | 24                    |
| 2     | batch  | THF     | 30        | 93                      | 27                    |
| 3     | batch  | toluene | 1         | 18                      | 8                     |
| 4     | batch  | toluene | 30        | 75                      | 49                    |
| 5     | batch  | toluene | 120       | 94                      | 57                    |
| 6     | batch  | toluene\(^{[18]}\) | 1       | 96                      | 95                    |
| 7     | batch  | toluene\(^{[18]}\) | 10      | 98                      | 85                    |
| 8     | batch  | toluene\(^{[18]}\) | 30      | >99                     | 60                    |
| 9     | flow   | toluene\(^{[18]}\) | 1       | >99                     | 99                    |

[a] 1.0 equiv. of THF was added which corresponded to a ca. 50:1 toluene:THF mixture.

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**Table 2. Optimization of the acylation temperature continuous flow.**

| entry | T [°C] | 2a conversion of 8a [GC-%] | product formation 3aa [GC-%] |
|-------|--------|---------------------------|-----------------------------|
| 1     | 25     | >99                       | 50                          |
| 2     | 0      | >99                       | 67                          |
| 3     | –20    | >99                       | 82                          |
| 4     | –40    | >99                       | 84                          |
achieved by simply prolonging the collecting time (from 0.5 min to 6.5 min) and led to a comparable yield (78%, Scheme 2).

Various aryllithiums (2b-e) bearing MeO, Br or Cl as substituents were quantitatively prepared by Br/Li-exchange from the corresponding aryl bromides and their acylation with 1a afforded the expected ketones 3ab-ae in 75–85% isolated yield. Also, heterocyclic lithium species were generated in this way and the acylation with 1a produced the heterocyclic ketones 3af and 3ag in 82–89% yield. A related functionalized amide such as 2,2-diethoxy-N,N-dimethylacetamide (1b) behaved in the same way providing, after the reaction with fluorosubstituted aryllithiums, the ketones 3bh–bj in 74–78% yield. Also, various α-monofluoro-, difluoro- or monochloro-substituted amides 1c, 1d and 1e gave the expected ketones despite the presence of readily enolizable protons at the α-position to the amide group. The use of the non-polar solvent toluene significantly reduced such enolization side-reactions as mentioned above.[21] Thus, the α-halogenated ketones 3cg–cj, 3da–dl and 3ef were obtained in 48–78% yield. N,N-Dimethylamides such as 1f, 1g and 1h, bearing remote oxygen- or nitrogen-containing functional groups, provided aromatic and heterocyclic ketones 3ff–fn, 3gk and 3ho in 63–81% isolated yield. As a limitation, we have found that N,N-dimethyl-phenylacetamide (1i) gave in this procedure only average yields of the desired aryl benzyl ketones 3ia and 3ik due to competitive enolization and consequent proto-debromination of the starting material (ca. 25% of enolization was noticed in the present solvent system, whereas over 70% enolization was found in pure THF).[1,1,1]-bicyclopentane carboxamide 1j was also a suitable substrate and the reaction with various lithiums of type 2 furnished the bicyclopent-1-yl ketones 3jp and 3jr in 59–70% isolated yield.[22] Finally, the dialkyl ketone 3hs was prepared by directly using n-BuLi as organolithium species via a 2-pump system (Scheme 2).

Next, we turned our attention to the preparation of highly functionalized benzenophene derivatives and heterocyclic ketones (Scheme 3). Thus, the cyano group in N,N-dimethyl-4-cyanobenzamide (6a)[17] was well tolerated leading to the cyano-substituted benzenophenes 12ae–an in 61–79% isolated yield. Remarkably, by using N,N-dimethyl-4-iodosobenzamide (6b), no competitive I/Li-exchange was observed and the desired iodo-substituted benzenophones 12bj and 12br were obtained in 63–79% yield. Also, commercially available N,N-diethylaminocinnamide (6c) provided the heterocyclic ketone 12cr in 58% yield after the usual sequence in continuous flow.

The preparation of racemizable α-chiral ketones was readily achieved with this new acylation procedure (Scheme 4). This is demonstrated in the case of naproxen and ibuprofen derived α-chiral ketones. Those analogues of non-steroidal anti-inflammatory drugs (NSAIDs) were of interest in the pursuit of antivirals[24] and to tackle gastrointestinal side-effects such as ulceration.[25] Thus, the readily available chiral N,N-dimethylamide of naproxen 13a (99% ee) was treated under standard continuous flow conditions with various functionalized aryllithiums of type 2 leading to the desired chiral ketones 14ac–an in 65–88% yield.

Scheme 2. A continuous flow acylation of various amides 1 with in situ generated lithium organometallics 2 leading to polyfunctional ketones 3. [a] The indicated yields refer to yields of isolated products.
with complete retention of chirality (99% ee).\(^\text{[24]}\) Also, the chiral \(N,N\)-dimethylamide of ibuprofen \(13\ b\) (99% ee) was acylated with (hetero)aryllithiums to give the chiral ketones \(14\ bh\)-bs in 75–89% isolated yield (98-99% ee).

Finally, we have extended this acylation in continuous flow to a semi-batch telescoped procedure for the preparation of unsymmetrical ketones of type 5 using TMU (4) as a C1-building block (Scheme 5).\(^\text{[5,27]}\) Thus, the treatment of a mixture of \(ArBr\) (8) and TMU (4) in toluene with sec-BuLi at \(-20^\circ\text{C}\) for 50 sec in continuous flow provided the tetrahedral intermediate 15 which was poured into a toluene solution of various organolithiums \(R-Li\) (7, \(R = \text{Bu, (Het)Ar or Bn}\)). These organolithiums were conveniently prepared via direct metalation, using sec-BuLi and TMEDA (1.0 equiv) in toluene at \(-20^\circ\text{C}\) (10-30 min) in batch. Presumably, due to a high stability of the intermediate 15, the second addition was quite slow and took up to 12 h at 25°C. After aqueous workup, the corresponding ketones \(5a\)–\(5f\) were obtained in 69–79% yield. Remarkably, no additional equivalent of THF was needed to ensure a fast Br/Li-exchange, showing that TMU played a similar activator role as THF for the fast formation of the lithium species.\(^\text{[28]}\)

In summary, we have reported a new convenient acylation of organolithiums 2 with various enolizable and functionalized \(N,N\)-dimethylamides 1 in continuous flow at \(-20^\circ\text{C}\). The required aryllithiums (2) were also prepared in continuous flow at 25°C using a Br/Li-exchange mediated by sec-BuLi with toluene as solvent in the presence of 1.0 equiv. of THF. This acylation was scalable without further optimization and was found to be suitable for the preparation for a broad range of polyfunctional ketones, including \(\alpha\)-chiral ketones of type 14 with excellent enantioselectivities. Furthermore, this method was extended to a semi-batch telescoped preparation of unsymmetrical ketones using TMU (4) as C1-building block. Compared to previous acylation procedures, readily prepared and stable \(N,N\)-dimethylamides\(^\text{[16]}\) of moderate toxicity, tolerating many functionalities, were used. The solvent toluene in the presence of 2 vol% THF minimized enolization side reactions and allowed ambient reaction temperatures. Further applications are underway.

**Acknowledgements**

B. Heinz thanks the Novartis Pharma AG for the fellowship. We thank Albermarle (Hoechst, Germany) and BASF for the generous gift of chemicals and Vapourtec for technical support. Open Access funding enabled and organized by Projekt DEAL.

**Conflict of Interest**

The authors declare no conflict of interest.

**Keywords:** amide · acylation · continuous flow · lithium · toluene

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[16] Various N,N-dimethylamides were readily prepared in large scale by treating the corresponding methyl or ethyl esters with commercially available MeNH·HCl and NaOMe in methanol. See Supporting Information for a detailed procedure; pages 18–19; b) We concentrated our efforts on the atom economical dimethylamides, but control experiments showed that N,N-dimethylamides or N-morpholinooamides were also suitable substrates for these acylations while ethyl esters gave a significant amount of double addition, see Supporting Information (page 17).

[17] For a list of (hetero)aryl bromides of type 8, (hetero)aryliithiums of type 2 and amides of type 1 and 6, see Supporting Information (pages 4–5).