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Telescoped diazo transfer and rhodium-catalysed S–H insertion in continuous flow

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ABSTRACT

Rhodium-catalysed S–H insertion of α-diazo-γ-butyrolactams has been successfully telescoped using continuous processing with *in situ* generated triflyl azide in flow and deacylative diazo transfer, incorporating real-time reaction monitoring of the final process outflow by IR spectroscopy. Significantly, the α-diazo-γ-butyrolactam reaction stream was sufficiently pure to progress to the rhodium-catalysed S–H insertion step without detrimental impact on the rhodium catalyst or the reaction efficiency.

Introduction

α-Diazocarbonyl compounds display remarkable synthetic versatility in organic chemistry, [1] leading to powerful transformations under mild conditions, which are not easily achieved through other methodologies, for example cyclopropanations, [2,3] X–H insertion reactions [4] and cycloadditions. [5] However, translating the synthetic potential of α-diazocarbonyl compounds at scale, has to date been limited by inherent safety concerns associated with their use and, in particular, with their precursors, such as sulfonyl azides and diazo alkanes [6,7].

Flow chemistry platforms are key enabling technologies for the use of hazardous compounds in synthesis. Continuous flow methodologies readily facilitate in-line reaction monitoring, automation, and the efficient transfer of heat and mass, due to the high surface-area-to-volume ratios that are intrinsic to most continuous tubular or pipe-type reactors; these are features which all afford enhanced process control, relative to batch chemistry [8–14]. Furthermore, a significant safety advantage of continuous platforms is the ability to generate *in situ* hazardous materials in small quantities for direct use, without handling or isolation [15].

Recent advances have prompted efforts to develop safer, continuous flow processes for preparation of α-diazocarbonyl compounds, including *via* diazo transfer. Although most of the reports of the diazo transfer process in flow have employed sulfonyl azides directly as reagents, [9,16–18] more recently, this has been extended to include the *in situ* preparation of the diazo transfer reagents [8,19–25].

Previous work within the Maguire–Collins group has demonstrated that *in situ* generation of mesyl, [24] tosyl [23] and triflyl azide [25] can be used to effect efficient diazo transfer to a range of substrates in continuous flow, obviating the need to isolate, handle or store the sulfonyl azides at any point. The use of *in situ* generated triflyl azide **2** was found to enable preparation of α-diazolactam **3** in good yield *via* a deacylative diazo transfer approach (Scheme 1) [25]. A deacylative diazo transfer strategy has been previously employed under traditional batch conditions by Krasavin and co-workers [26], to generate a series of α-diazolactams, including **3** and **4**, as substrates for synthesis of aryl(alkyl) thiolactam scaffolds *via* S–H insertion [27]. These scaffolds are present in several molecules of pharmaceutical interest, including Eli Lilly's 11β-HSD1 inhibitor for the treatment of hyperglycemia-associated diseases [28] and Bristol–Myers–Squibb's melanin hormone receptor-1 antagonist for the treatment of diabetes [29].

The biological activity of the α-thiolactam motif (see, for example, structures in Scheme 3) together with the established potential for use of diazo chemistry and rhodium catalysis in its synthesis

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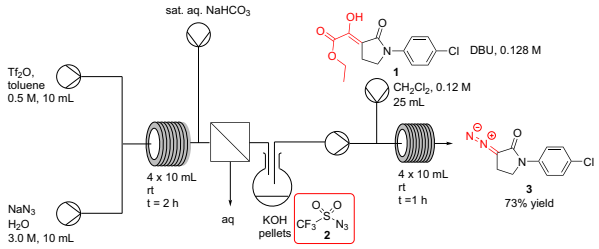


Scheme 1. Telescoped *in situ* generation of triflyl azide **2** and diazo transfer to form α-diazolactam **3**.

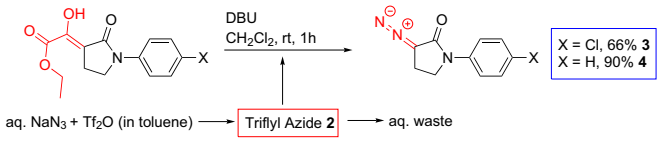
attracted our interest in the compounds as candidates for the development of a continuous, telescoped flow process combining the *in situ* generation of triflyl azide **2** as diazo transfer reagent [25], diazo transfer and rhodium-catalysed S–H insertion. To date, there have been few reports in the literature of continuous processes involving X–H insertions of diazo compounds; many of these reports have focused on a semi-continuous approach with generation of the diazo compound in flow followed by N–H [30], O–H [30] or S–H [31] insertion in batch. Rhodium-catalysed S–H insertion described by Wirth [32] and photo-induced S–H insertions demonstrated by Qiu and Guo [33], are among the rare examples where S–H insertion in continuous flow has been reported. The key challenge in telescoping the synthesis of a α-diazolactam *via* diazo transfer with rhodium-catalysed S–H insertion is ensuring the reaction stream of the α-diazolactam is sufficiently clean to progress to the S–H insertion step without detrimentally affecting the activity or selectivity of the rhodium catalyst.

While Krasavin [26,27] has demonstrated the synthesis of α-thiolactams by rhodium-mediated S–H insertion reactions in traditional batch processes, herein, a fully telescoped process for triflyl azide generation, diazo transfer and S–H insertion in continuous flow is described for the first time.

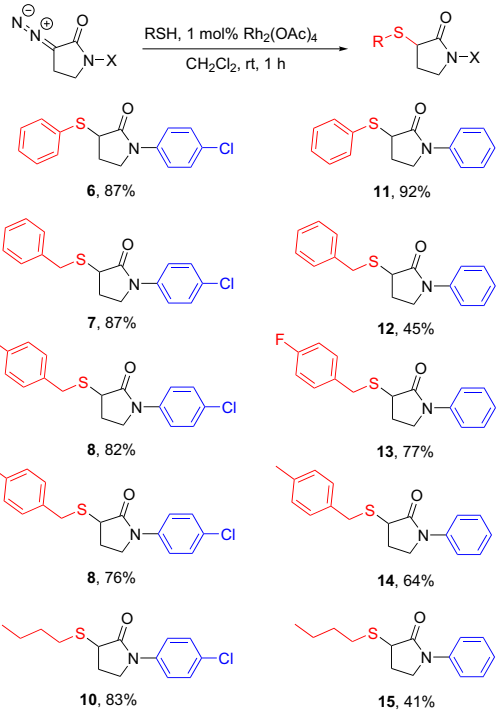
While the α-thiolactams could potentially be accessed by alternative synthetic methodologies, such as reaction of an enolate with a disulfide [34], or reaction of a thiolate with a α-halolactam [35], one clear advantage of this methodology is the use of neutral reaction conditions for the final introduction of the sulfide moiety, which broadens the potential scope of application.

Results and discussion

At the outset of this work, synthesis of the α-thiolactams **6**–**15** was undertaken using a batch approach. Diazo compounds **3** and **4** were synthesised following the conditions outlined in Scheme 2, with triflyl azide **2** being freshly generated [36] as a solution in toluene prior to use, while it had been previously reported in other solvents [36–42]. As a particularly labile sulfonyl azide, triflyl azide **2** was never isolated or handled as a pure compound [6,40]. Generating the triflyl azide **2** in toluene, avoids any risk associated with using sodium azide with dichloromethane [25]. Furthermore, use of toluene as a solvent ensures compatibility with the downstream rhodium catalyst in the telescoped process. The deacylative diazo transfer using triflyl azide **2** proceeds with comparable efficiencies to Krasavin's report using NBSA in traditional batch conditions



Scheme 2. Generation of α-diazolactams **3** and **4** under batch conditions.

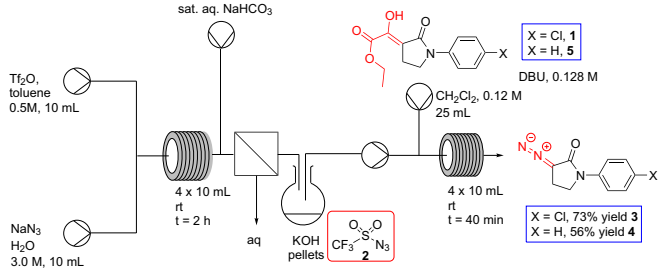


Scheme 3. Rhodium-catalysed S–H insertion reaction to form a library of α-thiobutyrolactams.

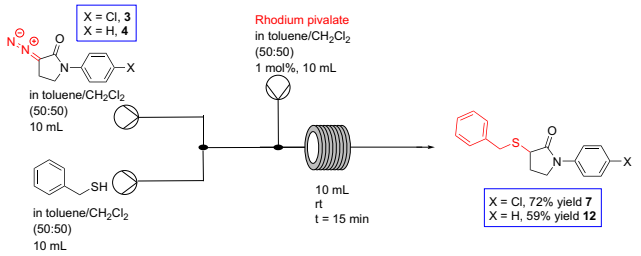
[26]. α- Diazolactams **3** and **4** were synthesized in 66% and 90% yield after column chromatography, respectively; IR spectroscopy was used to confirm the absence of residual hazardous triflyl azide **2** prior to concentration of the crude product solution.

α-Diazolactams **3** and **4** were subsequently subjected to rhodium acetate-mediated S–H insertion in dichloromethane at room temperature, to afford the novel α-thiolactams **6**–**10** and **13**–**15** in moderate yields (Scheme 3), in addition to the previously reported **11** and **12**, utilising reaction conditions described by Krasavin for this step [27].

Following successful synthesis of α-diazolactams **3** and **4** and α-thiolactams **6**–**15** in batch, focus next turned to transferring these processes to a continuous flow platform. Recent work in our group has demonstrated a continuous method for the *in situ* generation of triflyl azide **2** followed by diazo transfer to activated lactam **1** to give the desired α-diazolactam **3** in a 73% yield following column chromatography [25]. During this study, this protocol was applied for the first time to the activated lactam **5** to give the desired α-diazolactam **4** in a 56% yield (Scheme 4). Addition of DBU enhanced the solubility of the lactam precursors **1** and **5** in dichloromethane and care was taken to ensure that all the material was progressed into the reactor coils, by visual inspection.



Scheme 4. Telescoped *in situ* generation of triflyl azide **2** and diazo transfer to form α-diazolactams **3** and **4**.



Scheme 5. S–H insertion of **3** and **4** with benzyl mercaptan using rhodium pivalate in continuous flow to form α-thiolactams **7** and **12**.

While the use of rhodium acetate as the catalyst for the S–H insertion in flow was challenging for solubility reasons, rhodium pivalate was readily soluble in a toluene:dichloromethane (50:50) mixture and when employed in a continuous flow process, afforded α-thiolactams **7** and **12** in 72% and 59% yields, respectively (Scheme 5). These promising results highlight the versatility of the rhodium-catalysed S–H insertion reaction and indicated its potential for incorporation in a fully telescoped process. Preliminary investigations have indicated that the S–H insertion can be affected with an immobilised rhodium carboxylate catalyst, full details of which will be reported in due course.

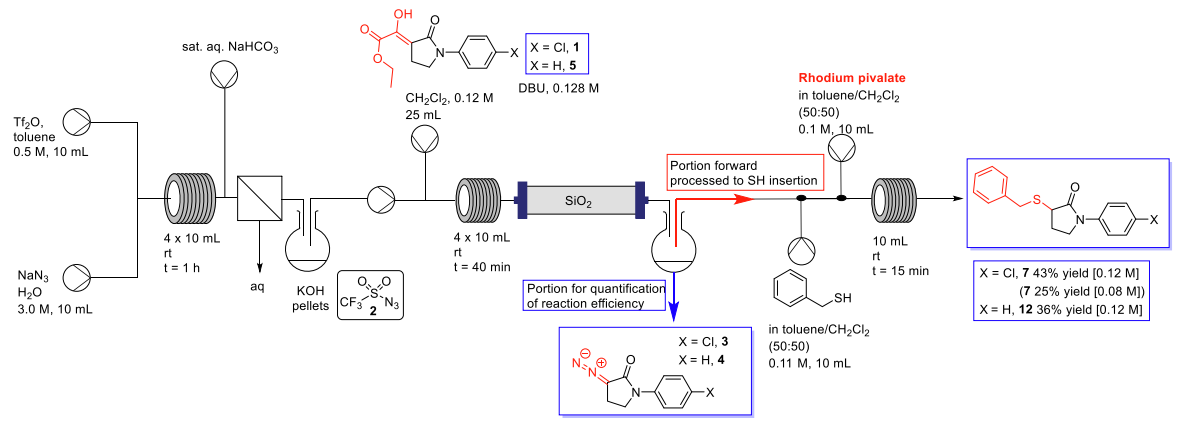
Having established the viability of continuous flow processes for both the diazo transfer and S–H insertion steps separately, telescoping these steps was next explored. A fully telescoped sequence was envisaged leading to the α-thiolactams **7** and **12**, combining the *in situ* generation of triflyl azide **2**, diazo transfer to activated lactams **1** and **5** and S–H insertion reactions of α-diazolactams **3** and **4** with benzyl mercaptan using rhodium pivalate (Scheme 6).

The key challenge to achieving this is accessing the solution of the α-diazolactam sufficiently clean to progress to the rhodium-catalysed S–H insertion step; equimolar amounts of DBU and the sulfonamide by-product, in part as a salt, are present in the reaction stream following the diazo transfer and, in addition to other by-products, have the potential to impact negatively on the rhodium-catalysed S–H insertion reaction. To address this issue, a short column of silica gel was placed in-line after the diazo transfer step and prior to the addition of the rhodium catalyst for the S–H insertion reaction. The outflow from the diazo transfer was passed through a glass-column (6.6 mm × 150 mm) packed with silica gel and collected in a round-bottomed flask. The process was typically carried out on a 3 mmol scale of the activated lactam precursor **1** or **5**, and following the passage through silica gel, a portion of the solution was progressed to the rhodium-catalysed S–H insertion step, while the remainder of the solution was concentrated and employed to quantify the efficiency of the diazo transfer step. This method allowed estimation of the efficiency of each of the individual steps, in addition to the overall yield recovered over the two steps. For the portion of the α-diazolactam solution following the silica gel column, which was purified and quantified, the efficiency of formation and recovery of the α-diazolactams was identified as 78% for diazolactam **3** and 47% for diazolactam **4**, confirming very little impact on the yield by in-line passage through silica gel, relative to Scheme 4.

The α-thiolactams **7** and **12** were isolated in overall yields (two steps) of 43% and 36%, respectively, from the telescoped sequence. Significantly, we have shown that both α-diazolactams **3** and **4** can be passed through silica gel and forward processed without impacting significantly on the efficiency of the S–H insertion reaction or detectably poisoning the rhodium catalyst. In particular, for the S–H insertion step, the calculated yields of 55% and 76%, for **7** and **12**, respectively, were of a similar order of magnitude to the yields reported in Scheme 5 starting from pure α-diazolactams **3** and **4** (72% and 59%), demonstrating the robustness of this flow procedure. Critically, it is evident that while introduction of a silica gel column was effective in providing a clean solution of the α-diazolactam, it had no detrimental impact on the yields of either step or of the telescoped process.

When a more dilute solution of activated lactam **1** was used (0.08 M vs 0.12 M), the overall efficiency of the telescoped process decreased to 25% yield. Interestingly, a decrease in the efficiency of the diazo transfer step was seen, which was partly offset by increased efficiency in the rhodium-catalysed S–H insertion step at the lower concentration. Thus, a 27% yield of α-diazolactam **3** was achieved (based on the yield following chromatography of the portion of the α-diazolactam solution retained); and following rhodium-catalysed S–H insertion, the α-thiolactam **7** was isolated in an overall yield of 25% for the telescoped process, corresponding to a 92% yield for the S–H insertion step. While the efficiency of the diazo transfer decreases with reduced concentrations of the lactam substrate **1** and triflyl azide **2**, the efficiency of the rhodium-catalysed S–H insertion step is enhanced at lower concentration resulting in 25% overall yield.

Use of α-diazocarbonyl compounds in continuous flow processes offer a distinct advantage in terms of monitoring through the use of in-line IR spectroscopy due to the strong and characteristic bands at 2000–2210 cm^{-1}, where few other absorptions are seen. An IR probe was integrated into the telescoped process and was employed at two points in the sequence, for real-time analysis of the diazo **3** product stream prior to, and following, the S–H insertion reaction. When in-line with the substrate diazo stream



Scheme 6. Telescoped diazo transfer and rhodium-catalysed S–H insertion using continuous flow.

after the in-line silica gel column, IR reaction monitoring showed efficient formation of the α-diazolactam **3** (diazo stretch 2089 cm^{-1}). Similarly, when IR reaction monitoring was conducted in-line with the outflow of the S–H insertion step, complete consumption of the diazo starting material was evident by the disappearance of the diazo stretch at 2089 cm^{-1}. The ability to monitor the presence of triflyl azide **2** and the α-diazolactam **3** in real time offers clear safety advantages if this process was to be operated at larger scale.

By harnessing the benefits of flow technology, the rhodium-catalysed S–H insertion yielding α-thiolactams **7** and **12** has been successfully telescoped in good conversions and yields, with the generation of the α-diazolactam precursors **3** and **4** using in-line generation of triflyl azide **2** in a safe manner, without isolation or handling. To the best of our knowledge, this is the first example of a fully telescoped process that incorporates generation of the sulfonyl azide, diazo transfer and S–H insertion steps in continuous flow; critical to success was passing the solutions of diazolactams **3** and **4** through an in-line silica gel column to ensure they were sufficiently clean to progress to the rhodium-catalysed step. Notably, the efficiency of the rhodium-catalysed S–H insertion was essentially unaffected by telescoping, despite the risk of catalyst poisoning by side products. Furthermore, from a synthetic perspective, this telescoped sequence can be completed in hours, avoiding the effort invested in work-up and isolation steps in a traditional batch approach. Critically, the telescoped flow process offers the potential for a larger scale reaction than might be safely conducted in batch.

Conclusion

A telescoped synthesis of α-thio-γ-butyrolactams **7** and **12** has been developed involving diazo transfer with *in situ* generated triflyl azide **2** in continuous flow, followed directly by rhodium-catalysed S–H insertion of the resulting α-diazo-γ-butyrolactams. The steps were undertaken without the need for handling or isolation of either the sulfonyl azide or the diazo substrates, and afford α-thio-γ-butyrolactams **7** and **12** in 43% and 36% yields over two steps, respectively. Use of real-time reaction monitoring by IR spectroscopy was shown to verify both formation and consumption of the diazo substrate, and offers distinct safety advantages.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153438.

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