# Organic & Biomolecular Chemistry



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**Cite this:** Org. Biomol. Chem., 2024, **22**, 2985

# Expanding the scope of the successive ring expansion strategy for macrocycle and medium-sized ring synthesis: unreactive and reactive lactams<sup>+</sup>

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Received 22nd February 2024, Accepted 20th March 2024 DOI: 10.1039/d4ob00285g rsc.li/obc New methods are described that expand the scope of the Successive Ring Expansion (SuRE) with respect to synthetically challenging lactams. A protocol has been developed for use with 'unreactive' lactams, enabling SuRE reactions to be performed on subsrates that fail under previously established conditions. Ring expansion is also demonstarted on 'reactive' lactams derived from iminosugars for the first time. The new SuRE methods were used to prepare a diverse array of medium-sized and macrocyclic lactams and lactones, which were evaluted in an anti-bacterial assay against *E. coli* BW25113WT.

## Introduction

Macrocycles (12 + membered rings) and medium-sized rings (8–11-membered) are important ring systems in medicinal chemistry, with many drugs based on these large-ring frameworks on the market.<sup>1</sup> New methods to synthesise large rings are therefore of value, especially those that can be performed on scale and avoid the problems typically associated with end-to-end macrocyclisation reactions,<sup>2,3</sup> most notably competing intermolecular coupling. Ring expansion reactions<sup>4,5</sup> are important in this regard, as they allow macrocycles and medium-sized rings to be prepared without the need to perform a discrete end-to-end macrocyclisation step; in well-designed cases, large ring products can be obtained without resorting to high-dilution conditions, *via* rearrangements that operate solely *via* 'normal-sized ring' (5–7-membered) cyclisation reactions.<sup>4e</sup>

A major focus of our group in recent years has been the development of side-chain insertion type ring expansion reactions,<sup>4a</sup> for the synthesis of medium-sized and macrocyclic lactams,<sup>6</sup> lactones,<sup>7</sup> thiolactones,<sup>8</sup> sulfonamides<sup>9</sup> and phosphonate esters.<sup>10</sup> Within this programme, the development of 'Successive Ring Expansion' (SuRE) methods has been a major driver. The general SuRE strategy is summarised in Scheme 1a, which depicts a method for the ring expansion of lactams 1, *via N*-acylation ( $1 \rightarrow 3$ , X can be NR, O or S), protecting group cleavage ( $3 \rightarrow 4$ ) and ring expansion ( $4 \rightarrow 5$ ).<sup>11</sup> A key design principle in SuRE is that the ring expanded product (in this case 5) can itself be expanded again *via* another iteration of the same sequence; thus, the reaction of 5 with acid chloride **2b** in the same way can enable successive ring expansion to form lactam **6**.

A range of lactam derivatives have been demonstrated to undergo SuRE ring expansions of the type summarised in Scheme 1a. Nonetheless, the requirement to *N*-acylate a lactam – a comparatively weak nitrogen nucleophile – can be challenging. Our published *N*-acylation conditions involve heating the lactam and acyl chloride with pyridine and DMAP in refluxing DCM. In some cases, *N*-acylation using this method fails; for example, lactams **7–9** (prepared using published SuRE reactions)<sup>6</sup> all failed to undergo *N*-acylation with Fmoc- $\beta$ -Ala-Cl under the standard conditions.

The discovery of alternative conditions that enable *N*-acylation of unreactive lactam starting materials therefore would represent an important extension to the SuRE method. The successful development of such conditions for use with

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**Scheme 1** Expanding the scope of the Successive Ring Expansion strategy for macrocycle and medium-sized ring synthesis. <sup>a</sup> X = NR, O or S; PG = Fmoc, CBz, Bn or Fm; n = 1-2, m = various ring sizes.

'unreactive' lactams is reported herein, with the application of the new conditions in the synthesis of a range of macrocyclic lactam and lactone products described in Results and Discussion Section i. We were also keen to extend the scope of the SuRE method to more functionalised, 'reactive' lactams. This work – which focuses on the ring expansion of iminosugar derivatives of the type **10** – is described in Results and discussion section ii. Both series permitted the biological evaluation of a selection of ring expanded products for their potential to be used as anti-bacterial agents (Results and discussion section iii).

### **Results and discussion**

# (i) Unreactive lactams: alternative conditions for the *N*-acylation of poorly reactive lactams

The search for new lactam *N*-acylation conditions started by exploring the reaction of 12-membered ring lactam **9** with propionyl chloride **12**. Lactam **9** was already shown not to react with Fmoc- $\beta$ -Ala-Cl under the standard conditions (0% conversion),<sup>6</sup> and similarly, none of the acylated product **13** was isolated when the same conditions were tested using propionyl chloride **12** (Scheme 2 Table, entry 1). Extensive optimisation



Scheme 2 Optimisation of N-acylation using propionyl chloride 12.

of this N-acylation reaction was therefore undertaken. Variation of the reaction solvent, temperature, time, the base/ nucleophilic catalyst and the addition of Lewis acidic additives was explored. Full details of these optimisation experiments can be found in the ESI (see ESI, Tables S1-4<sup>†</sup>) with selected results summarised in Scheme 2. This optimisation culminating in the discovery of the optimised conditions described in entry 8 of the Scheme 2 Table. These N-acylation conditions are radically different to those used in the established SuRE methodology; the temperature (80 °C) is higher, the solvent (benzene) and the base (N-methyl morpholine; NMM) have both been changed and catalytic CuO was also found to improve the reaction. We are unable to fully rationalise why all of these changes combine to make such a difference to the reaction conversion. However, in general we think that enabling the N-acylation rate to be increased without also promoting degradation of the sensitive acyl chloride moiety is important. The best conditions are presumably those that achieve the most favourable balance between these competing pathways. It is possible that ketene formation from the acid chloride may play some part in effecting the change in reactivity.<sup>12</sup> However, the observation that optically active products were obtained in all cases in which enantiopure Fmoc-Pro-Cl was used (see later) suggests that if ketene-formation does play a role, it is not the sole reaction pathway.<sup>13</sup> Pleasingly, lactams 7 and 8 – another two lactams that react poorly under the standard N-acylation conditions - reacted well using the same method, to afford imides 14 and 15 each in good yield.

Attention then turned to testing the new *N*-acylation conditions using three representative acid chloride types that typically work well in SuRE reactions (**16–18**, a  $\beta$ -amino,  $\alpha$ -amino and  $\beta$ -phenolic acid chloride) and six lactams (**7–9**, **29**, **36**, **43**) that are known to react poorly using the standard conditions (Scheme 3). These six lactams were themselves prepared using

published SuRE reactions,<sup>6</sup> with the fragment inserted in the first SuRE reaction indicated in red. This series of reactions was therefore focused on the more challenging second SuRE reaction, with the linear fragment inserted indicated in blue.

First, lactam 7 was reacted with Fmoc-Pro-Cl **16** and *N*-acylation proceeded smoothly, with imide **19** being isolated



Scheme 3 Expanded scope of SuRE reactions for poorly reactive lactams. Conditions: (i) Lactam (1 equiv.), acid chloride (3 equiv.), NMM (6 equiv.), CuO (0.1 equiv.), benzene (0.2 M), 80 °C, 18 h; (ii) Imide (1 equiv.), DBU (10 equiv.), DCM (0.1 M), RT, 18 h; (iii) Imide (1 equiv.), hydrogen (balloon), Pd/ C (100 mg mmol<sup>-1</sup> of imide), ethyl acetate (0.1 M), RT, 16.

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in 60% yield. Subsequent reaction with DBU then promoted Fmoc cleavage and ring expansion to afford 14-membered ring bis-proline adduct 20. Notably, product 20 was found to have a non-zero optical rotation, confirming that racemisation of the proline stereogenic centre did not take place under the reaction conditions (although this does not necessarily rule out partial epimerisation).<sup>13</sup> Similarly, 12-membered lactam 8 was acylated successfully with Fmoc-Pro-Cl 16, and the same lactam was also acylated with Fmoc protected β-alanine derived acid chloride 17 and benzyl protected phenolic acid chloride 18, to afford imides 21, 23 and 25 respectively. Each imide then went on to undergo protecting group cleavage and ring expansion, upon reaction with DBU (for Fmoc derivatives 21 and 23) or hydrogenolysis (for OBn derivative 25), to form ring expanded products 22, 24 and 26 in good overall yields. Four more lactams (9, 29, 36, 43) were treated in the same way with some/all of acid chlorides 16-18, to form a range of macrocyclic lactam and lactone products (28, 31, 33, 35, 38, 40, 42 and 45). The expected ring expansion products were obtained in all cases tested, with the exception of lactone 47; in this case, the N-acylation proceeded as expected to form imide 46, but failed at the hydrogenolysis step.

Thus, the new *N*-acylation conditions were shown to work well across a range of lactams that perform poorly using the published method. It is important to note that the published conditions still work well for many lactam substrates and certainly should not be discounted.<sup>6</sup> Nonetheless, in cases in which *N*-acylation is found to be sluggish, the new conditions represent a very useful alternative.

#### (ii) Reactive lactams: ring expansion of iminosugar lactams

Having established new SuRE conditions compatible with poorly reactive lactams, attention then turned to demonstrating that SuRE reactions can also be performed on more reactive, and more functionalised lactams. This was done using sugar-derived lactam starting materials. The high degree of oxygenation and steric crowding in lactams like **48** was expected to provide a significant synthetic challenge to our established SuRE protocols. Of further interest, nitrogen-containing sugars and carbohydrate mimetics are well known for their useful biological properties, for example as potent inhibitors of glycosidases and glycosyltransferases.<sup>14,15a</sup>

We started by examining glucose-derived lactam **48** (Scheme 4a).<sup>15</sup> In this case, the lactam was sufficiently reactive to undergo *N*-acylation with acid chloride **17** using our standard, published SuRE conditions, with pyridine and DMAP in refluxing DCM. The resulting imide **49** was then treated with DBU in DCM at RT, which duly promoted Fmoc cleavage and ring expansion as expected, to afford 10-membered bislactam **50** in 67% yield. Cleavage of the benzyl ether protecting groups was also achieved, by hydrogenolysis under acidic conditions, without cleaving the N–Bn bond, to afford 10-membered ring cyclic tetrol **51**.

The same protocol was also used for the ring expansion of lactam 48 with alternative  $\beta$ -amino acid chlorides 52 and 53, resulting in the formation of ring expanded bislactams 56 and



Scheme 4 Ring expansion of sugar-derived lactams.

57 (Scheme 4b). Debenzylation of lactam 57 was also achieved, using the same hydrogenolysis method as before. Alternative sugar-derived lactam starting materials  $54^{16}$  and  $55^{17}$  are also compatible with the SuRE protocol, affording bislactams 59 and 60, respectively.

The challenge of working with these highly functionalised substrates was highlighted during the attempted ring expansion of lactam **48** using OBn-containing acid chloride **61** (Scheme 4c). In this case, *N*-acylation went relatively smoothly, with imide **62** isolated in 50% yield. Next, the hope then was that hydrogenolysis would promote concomitant debenzylation of all five protected alcohols and enable ring expansion in situ to form lactone 63. However, while cleavage of the five benzyl groups was successful, an alternative acyl transfer reactions took place instead, with migration of the  $\beta$ -hydroxy acid fragment on the primary alcohol (*i.e.* 64  $\rightarrow$  65) taking place. Given the known difficulty of 'normal-to-medium' sized ring expansion,<sup>4e</sup> it is likely that this alternative rearrangement is simply a lower energy, more kinetically favourable pathway. The structure of the product 65 was confirmed by X-ray crystallography.<sup>18</sup>

Thus, the efficacy of SuRE reactions on functionalised sugar-derived lactams has been confirmed. A small series of 10-membered ring bislactams have been assembled, *via* the overall insertion of a  $\beta$ -amino acid fragment into a 6-membered ring iminosugar. This is potentially important, given the known efficacy of related iminosugar derivatives to inhibit glycosidases and glycosyltransferases, as noted above.<sup>14,15*a*</sup> Furthermore, analogy can be made between these products and biologically important macrocycles; for example, related compounds are known to have human renin inhibitor activity,<sup>19</sup> can be used for the immunomodulation of  $\alpha$ -galactosylceramides related to KRN 7000<sup>20</sup> and could potentially be used as building blocks for the synthesis novel classes of biomaterials.<sup>21</sup>

#### (iii) Biological evaluation

Due to the large current interest in the evaluation of macrocycles as novel anti-bacterial agents,<sup>22</sup> we screened 17 of the reported medium-sized rings and macrocycles in a minimum inhibitory concentration (MIC) growth assay against *E. coli* BW25113WT. Unfortunately, no appreciable growth inhibition was observed for any of the compounds screened in this assay, at a range of concentrations up to 1 mM. More information on the compounds screened, the assay protocol and the results are included in section 5 of the ESI.<sup>†</sup>

### Conclusions

In summary, the scope of the SuRE method has been expanded through the development of a new protocol for the N-acylation of 'unreactive' lactams. This new approach enabled SuRE reactions to be performed on substrates that failed to react using previously published SuRE methods. Furthermore, the ring expansion of iminosugar derived lactams has been demonstrated for the first time, showing that the methodology is compatible with these oxygen-rich, highly functionalised 'reactive' lactams. Through both series, a range of novel medium-sized ring and macrocyclic products was synthesised, and a selection of these products was evaluated in an E. coli BW25113WT inhibition growth assay. Unfortunately, none of the compounds tested showed significant anti-bacterial activity against this target. Nonetheless, the value of SuRE method to prepare diverse libraries of medium-sized rings and macrocycles for bioassay has been demonstrated. The synthesis of larger compound libraries for biological evaluation, and

testing against a wider range of targets, will be a major focus of our future work.

# Author contributions

The project was conceived by WPU and PC. Initial method development and all of the ring expansion chemistry was done by ZY. Synthesis of iminosugar starting materials was done by MA and DH. Bioassays were performed by ORH and JN, with guidance from MAF and CDS. X-ray crystallography was done by ACW. The manuscript was written through contributions from all authors, led by WPU. The project was directed and managed by WPU.

# Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The authors would like to thank the China Scholarship Council for funding the PhD studentship of Z. Y.

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