PAPER

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Synthesis of medium-ring lactams and macrocyclic peptide mimetics *via* conjugate addition/ring expansion cascade reactions†‡

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A novel conjugate addition/ring expansion (CARE) cascade reaction sequence is reported that enables medium-sized ring and macrocyclic bis-lactams to be prepared from primary amines and cyclic imides. The reactions are simple to perform, generally high yielding, and very broad in scope, especially with respect to the primary amine component. CARE reactions can also be performed iteratively, enabling β-peptoid-based macrocyclic peptide mimetics to be 'grown' *via* well controlled, sequential 4-atom ring expansion reactions, with the incorporation of varied functionalised amines during each iteration.

Introduction

Cascade reaction sequences are widely used in synthetic chemistry to streamline the preparation of complex molecules.[1,2] Performing multiple reaction steps in a single operation brings obvious benefits in terms of the overall brevity of synthetic routes and can obviate the need to directly handle reactive and/or toxic intermediates. This strategy can also lead to the development of synthetic cascades greater than the sum of their parts, whereby the overall cascade reaction proceeds more efficiently than the analogous stepwise process.[3] Ring expansion reactions are also important in synthetic chemistry,[4,5] especially for the synthesis of biologically relevant medium-sized rings and macrocycles,[6] compounds that can be difficult to make using classical end-to-end cyclisation methods.[7] This manuscript is focused on combining these two individually powerful approaches for the synthesis of macrocyclic peptide mimetics, using a novel Conjugate Addition/Ring Expansion (CARE) cascade reaction sequence.

Previous work from our laboratory has established a robust method for the 3- and 4-atom ring expansion of lactams **1** upon reaction with acyl chlorides derived from Fmoc-protected amino acids (*e.g.* **2a**); following *N*-acylation of the lactam to form imide **3**, reaction with base promotes Fmoc-cleavage (**3** → **3a**) and spontaneous ring expansion (**3a** → **4**, Scheme 1a).[8] The

reactions typically proceed in good yield over two steps, and the lactams products **4** can themselves be expanded further by repeating the same two-step sequence (*e.g.* **4** → **5**), thus enabling Successive Ring Expansion (SuRE).[8,9] However, there are limitations associated with the use of acid chlorides of the type **2a**, most notably that a 3- or 4-step synthesis is typically needed to make them (**6** or **7** → **2a**, Scheme 1b), and that carbamate-mediated acid chloride deactivation/degradation (**8** → **9**, Scheme 1b box) can negatively affect the reactions in cases where lactam acylation is sluggish.[10]

Avoiding the use of protecting groups was therefore a key factor when designing the new method in this manuscript. We postulated that *N*-acylation of a lactam **1** using a simple acryloyl chloride derivative **10** would generate imide **11**, and that this Michael acceptor could engage in a conjugate addition (**11** → **12**) ring expansion (**12** → **13** → **14**, Scheme 1c) cascade reaction sequence upon treatment with primary amine nucleophiles.[11] The successful realisation of this approach is described herein. The method is extremely broad in scope, with 54 novel CARE reactions reported in this manuscript, demonstrated across a diverse array of functionalised lactams and amines. The reactions are easy to perform, they are insensitive to air and moisture, and work in a wide range of solvents, including water. CARE reactions can also be performed iteratively, to enable the synthesis of macrocyclic peptide mimetics, based on β-peptoid linkages,[12] by performing sequential *N*-acylation and CARE reactions.
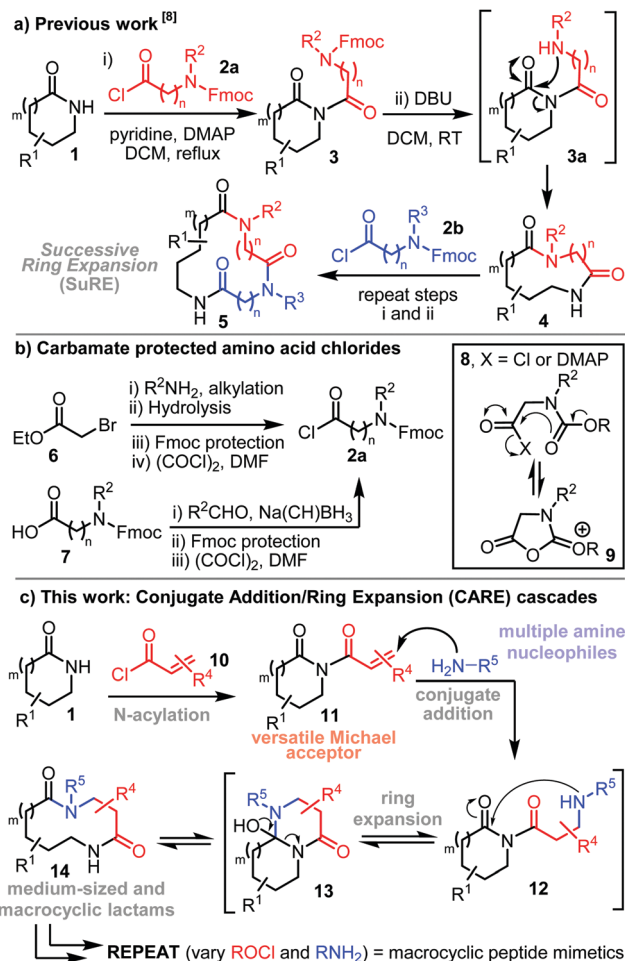
Results and discussion

Reaction optimisation (Table 1) was performed using 6-membered ring imide **11a**, itself prepared *via* the *N*-acylation

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‡ Electronic supplementary information (ESI) available. CCDC 2122955 and 2122961. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cb00245g

Scheme 1 Lactam ring expansion reactions.

Table 1 CARE optimisation and solvent compatibility

Entry	Solvent	Conc.	Base	14a/%[a]
1	DCM[b]	0.1 M	DBU (10 equiv.)	33
2	DCM[b]	0.5 M	DBU (10 equiv.)	32
3	DCM	0.5 M	—	42
4	Toluene	0.5 M	—	48
5	THF	0.5 M	—	52
6	Et$_2$O	0.5 M	—	41
7	hexane	0.5 M	—	38
8	DME	0.5 M	—	48
9	MeCN	0.5 M	—	51
10	DMSO	0.5 M	—	77
11	DMF	0.5 M	—	77
12	DMA	0.5 M	—	78
13	NMP	0.5 M	—	80
14	MeOH	0.5 M	—	82 (86)[c]
15	EtOH	0.5 M	—	80
16	i-PrOH	0.5 M	—	71
17	t-BuOH	0.5 M	—	73
18	TFE	0.5 M	—	52
19	HFIP	0.5 M	—	58
20	H$_2$O	0.5 M	—	69

[a] Imide **11a** (1 equiv.) and amine **15** (1.1 equiv.) were stirred in the stated solvent at RT for 4 h unless stated, performed on a 0.5 mmol scale. 3,5-Bis(trifluoromethyl)bromobenzene (1 equiv.) was then added before an aliquot of the reaction mixture (ca. 0.2 mL) was taken, diluted with CDCl$_3$ and analyzed directly by ^{19}F NMR. Conversion to **14a** was determined by the ratio of the ^{19}F NMR resonance of **14a** to that of the 3,5-bis(trifluoromethyl)bromobenzene internal standard. [b] 18 h reaction time. [c] isolated yield in parentheses, performed on a 5.0 mmol scale.

of δ-valerolactam with acryloyl chloride.[13] *p*-Fluorobenzylamine **15** was chosen as a model primary amine as its fluorine group provided a convenient handle for reaction monitoring using ^{19}F NMR. Initially, imide **11a** (1 equiv.) and amine **15** (1.1 equiv.) were stirred in DCM (0.1 M) at RT with an excess of DBU (10 equiv.). These conditions were chosen to start as they were used to promote the ring expansion step in our published SuRE chemistry,[8] and pleasingly, resulted in modest conversion (33%) into 10-membered lactam **14a** (entry 1). Next, the reaction concentration was increased (0.1 M → 0.5 M, entry 2) as increasing the concentration has been shown to promote amine conjugate addition in related systems;[14] this change did not improve conversion, but it had no significant negative impact either so was retained for further optimisation. We then questioned whether the base was necessary, and indeed, performing the same reaction without DBU led to improved conversion (entry 3).

A range of alternative solvents were then explored (entries 4–20); in total, 18 were tested and remarkably, all resulted in some conversion into 10-membered lactam **14a**, including solvents compatible with biological systems, most notably water (entry 20). Overall, polar solvents tend to perform better, with alcohol solvents particularly effective (entries 14–17). Importantly, the conversion as

measured using ^{19}F NMR translates into a comparable synthetic yield, with **14a** isolated in 86% following column chromatography, tested on a 5.0 mmol scale reaction using methanol as the solvent (entry 14). Methanol was therefore selected to take forward to the substrate scoping phase of the project, but the versatility of the reaction in terms of solvent is also notable and is important in scenarios where methanol is less effective (see later for examples).

The scope with respect to lactam ring size was examined first, with 4–8-membered ring imides **11a–e** prepared from the corresponding lactams and acryloyl chloride. All were reacted with *p*-fluorobenzylamine **15** and in all cases the desired ring-expanded products were formed (**14a–e**, Scheme 2A). The standard protocol (methanol, 0.5 M, 4 h) was used in all examples, except for the expansion of 4-membered imide **11b** into 8-membered **14b**. In this case, a complex mixture of products was formed when the reaction was done in methanol, with the only tractable products arising from unwanted ring opening of the β-lactam, both by the amine **15** and methanol (see ESI† for details). However, by performing the reaction in DCM instead of methanol and increasing the reaction time, the desired ring expanded product **14b** could be isolated in 68% yield. This result highlights the value of the wide solvent compatibility of CARE in finding contingencies for substrates that have chemical functionality not compatible with the

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Scheme 2 Scope of Conjugate Addition/Ring Expansion (CARE). [a] Unless stated the following procedure was used: Imide (1 equiv.) and amine (1.1 equiv.) were stirred in methanol (0.5 M) for 4 h at RT, concentrated and purified directly by column chromatography; [b] reaction stirred for 3 days; [c] DCM (0.5 M) used in place of methanol; [d] reaction stirred for 5 h; [e] DMF (0.5 M) used in place of methanol; [f] reaction stirred for 2 h; [g] contaminated with morpholin-3-one.

standard methanol conditions. The assigned structures of products **14a** and **14b** were both confirmed *via* X-ray crystallography (Fig. 1).[15]

Functionalised lactam starting materials (**16a–f**) were also examined, with the expected ring expanded products **17a–f** all formed in good yields; this series includes sulfide-, carbamate- and
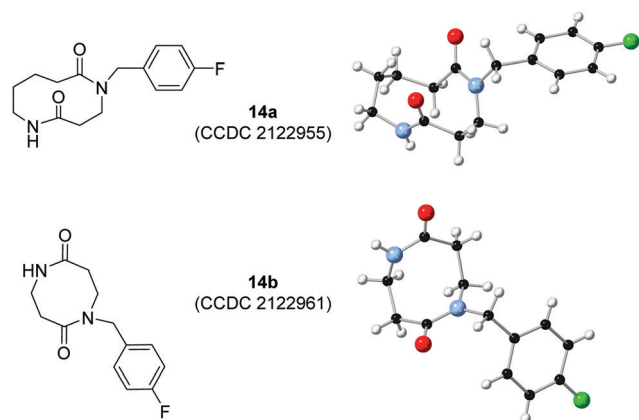
Fig. 1 X-Ray crystal structures of **14a** and **14b**. CCDC 2122955 and 2122961.

alkene-containing lactams, as well as bicyclic and steroidal lactams (Scheme 2B). Substitution on the Michael acceptor is also tolerated both at the α- and β-position (**19a–c**, Scheme 2C), although a notable exception is cinnamoyl-derivative **18d** (R = Ph at the β-position) which failed to react, presumably due to its lower electrophilicity as a Michael acceptor.

The ability to freely vary the primary amine coupling partner is arguably the most powerful feature of the CARE method (Scheme 2D). Aliphatic primary amines typically work well, provided they are not too bulky; the steric influence on the reaction yields is clear when comparing relatively unhindered cyclopropylamine (**20c**, 90%), moderately bulky iso-propylamine (**20d**, 50%) and bulky *tert*-butylamine (**20e**, 0%). Unsurprisingly, electronics also influence the CARE reactions, presumably by modulated the amine's nucleophilicity; for example, when comparing aniline derivatives, the electron-rich *p*-OMe substituted product **20f** was formed in 83% using the standard protocol, but there was a drop in yield when moving to aniline itself (**20g**, 48%) and an electron-poor *p*-NO$_2$ derivative (**20h**, 21%), even when using longer reaction times.

The excellent functional group compatibility of CARE is exemplified by the range of functionalised amines used to make products (**20i–zb**); all were formed in good to excellent yields from amines containing a wide array of functional groups, including esters, halides, carbamates, terminal alkynes, sulfides, amides, acetals, furans, various aza-heterocycles, hydroxylamine derivatives and others. Notably, the primary amine motif can also out-compete other unprotected nucleophiles like phenols, alcohols and anilines (**20zc–f**), while the diamine-tethered bis-lactam **20zg** was also made from *p*-xylylene diamine.

Thus, the CARE method has been demonstrated to work well across a wide range of substrates, with most reactions tested working well. However, as well as highlighting the successful cases, it is instructive to consider the relatively rare cases in which the reaction does not proceed in the typical way (Scheme 2E). The biggest challenge relates to chemoselectivity, specifically that the imide starting materials typically contain three electrophilic centres. One of these is the β-position of the Michael acceptor (*i.e.* the required site for conjugate addition), and based on our previous
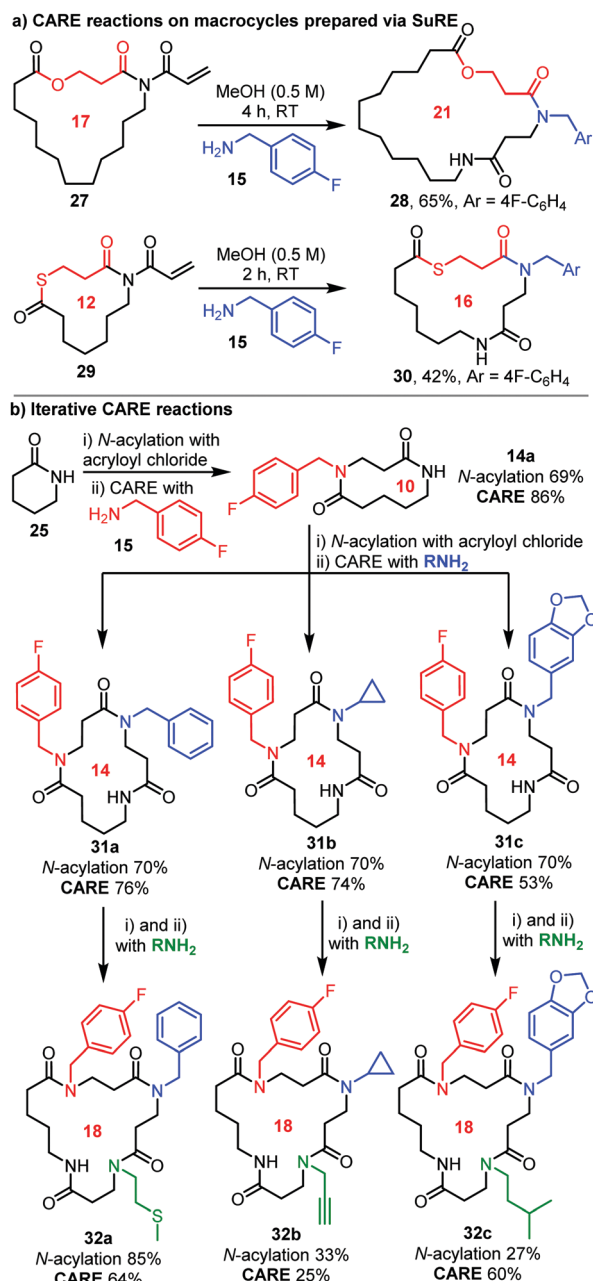
ring expansion work, which includes detailed DFT studies,[8c] we are confident that once conjugate addition has taken place the ring expansion step should be facile. However, both carbonyl groups of the imide are also electrophilic and can react competitively with the primary amine and/or nucleophilic solvent molecules. For example, when imide **21** was reacted under the standard conditions, none of the expected ring expanded product **22** was formed; instead linear products **23** and **24** were isolated, arising from nucleophilic ring opening through attack at the internal imide carbonyl (highlighted with a star) by methanol or *p*-fluorobenzylamine respectively (Scheme 2E, eqn (1)). Presumably, the cyclic ether oxygen increases the electrophilicity of the adjacent carbonyl and changes the typical kinetic preference for conjugate addition. This is a similar observation to that described earlier, during the CARE of the β-lactam-based imide **11b** into 8-membered **14b** (Scheme 2A).

Competing nucleophilic attack at the external imide carbonyl has also been observed in cases where the conjugate addition step is sluggish; for example, when imide **11a** was reacted with relatively bulky i-propylamine under the standard conditions, de-acylated lactam **25** was formed in the reaction, presumably as a result of nucleophilic attack by methanol and/or the amine at the highlighted carbonyl, alongside ring-opened side product **26** and the desired ring expanded product **20d** (Scheme 2E, eqn (2)). In situations like this, where the methanol solvent promotes side reactions, alternative solvents can be considered, and in this case a solvent switch to DMF resulted in a modest increase in yield of the ring expanded product **20d** (50%, Scheme 2D).

The requisite imides used for all the CARE reactions in this manuscript were prepared using basic reaction conditions, using one of the three related *N*-acylation methods summarised in Scheme 2F, with full details for all imide preparations included in the ESI.‡

The products in Scheme 2 are all lactams that can potentially be used in CARE reactions themselves. Therefore, the possibility of using CARE in iterative ring expansion processes was explored. First, lactone- and thiolactone-containing macrocyclic imides **27** and **29** were tested, with the precursor lactams prepared using our published SuRE method (with the section inserted *via* the first ring expansion highlighted in red).[8b,d] Pleasingly, both imides were converted into the ring-expanded products **28** and **30** respectively using amine **15** and the standard conditions (Scheme 3a). It is also possible to perform CARE reactions iteratively (Scheme 3b). For example, starting from δ-valerolactam **25**, *N*-acylation with acryloyl chloride followed by CARE with *p*-fluorobenzylamine **15** delivered 10-membered bis-lactam **14a**. Then, another *N*-acylation/CARE sequence was performed starting from **14a** using three different amines (shown in blue) to afford 14-membered products **31a–c** in good yields. Each of compounds **31a–c** were then expanded a third time in the same way (amine shown in green) to furnish 18-membered β-peptoid-based tetra-peptide mimetics **32a–c**. This ability to use CARE to install different functionalised building blocks in sequence was a major driving force when developing the reaction. Sequence specific cyclic peptides have numerous important biochemical applications, for example arginine-glycine-aspartic acid (RGD) peptides, that have found wide utility in cell

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Scheme 3 Iterative CARE reactions.

based on β-peptoid linkages. The imide precursors that undergo the CARE cascade can react with a wide array of functionalised amines without the need for protecting groups. The products can be thought of as macrocyclic peptide/peptoid mimetics, a compound class with significant potential for use in medicinal and biological chemistry applications.[17] The iterative nature of the CARE reactions will be of value when optimising the properties of the macrocyclic products (*e.g.* in structure activity relationship studies), and its operational simplicity and wide scope should ensure that the CARE method is well-used, both by specialist synthetic chemists, and by researchers working in more applied fields.

The demonstrated wide solvent compatibility of CARE should also have important implications. For example, CARE reactions have been successfully applied in solvents like DMSO and water, that are commonly used to handle biologically relevant molecules like peptides or proteins. This, coupled with the demonstrated high selectivity for reaction on primary amines in the presence of a wide array of other functional groups, provides encouragement that CARE reactions based on the selective functionalisation amines in complex macromolecules (*e.g.* lysine residues in peptides/proteins) could emerge over time.

Author contributions

The project was conceived by WPU and KYP. Initial method development and optimisation was done by KYP. Reaction scope and further method development was done by KYP and ZY. The manuscript was written through contributions from all authors. X-ray crystallography data acquisition, processing and analysis was done by ACW. The project was directed and managed by WPU.

Conflicts of interest

There are no conflicts to declare.

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culture models and as targeted therapeutic agents.[16] Of course, the CARE method can only be used to promote 4-atom ring expansion, and hence cannot be used to target cyclic peptides based on proteinogenic amino acids. Nonetheless, what is does offer is a versatile route to sequence specific β-peptoid-based macrocycles, that could become similarly useful in future biochemical studies.

Conclusions

In summary, a practical and versatile iterative conjugate addition/ring expansion sequence is described for the synthesis of medium-sized/macrocyclic lactams and peptide mimetics

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