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COMMUNICATION

Benzoylureas as removable *cis* amide inducers: synthesis of cyclic amides *via* ring closing metathesis (RCM)†

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Rapid and high yielding synthesis of medium ring lactams was made possible through the use of a benzoylurea auxiliary that serves to stabilize a *cisoid* amide conformation, facilitating cyclization. The auxiliary is released after activation under the mild conditions required to deprotect a primary amine, such as acidolysis of a Boc group in the examples given here. This methodology is a promising tool for the synthesis of medium ring lactams, macrocyclic natural products and peptides.

In the design of peptidomimetics, introducing covalent conformational constraints through the formation of macrocycles such as lactams and cyclopeptides is a proven strategy to reduce unfavorable entropy loss upon binding and thus improve binding affinity.[1] However, the synthesis of cyclic structures is often difficult due to a large energy cost in arranging the linear precursor into a transition state prefigurating the cyclic final product.[2] Ring formations involving a secondary amide group are particularly difficult if cyclization requires the thermodynamically disfavoured *cis*-conformation to be adopted,[3] which is typically the case for rings that are 11-membered or smaller.[4] Even for the preparation of larger rings, such as hexapeptide 16-mers where all *trans* peptide bonds may be tolerated, transient stabilization of a *cisoid* peptide bond in the precursors may be required for efficient cyclization to occur.[5] The most popular approach to stabilizing a *cisoid* conformation is the *N*-alkylation of secondary amides.[6,7] This strategy includes the use of proline or pseudoprolines[5,8] in cyclopeptides and has also been successfully applied to the preparation of cyclic sulfonamides.[9] Notably, pseudoprolines are restricted to necessarily regenerate either serine[8] or threonine[7,10] and cyclisation involving *N*-benzyl tertiary amides can be fickle.[7]

During our investigations into the use of benzoylureas as α-helical mimetics of the BH3-only proteins,[11] we targeted cyclic analogs such as **2** (Scheme 1) as a means to constrain τ1 in these scaffolds in order to induce the bioactive conformation. Efforts to conformationally constrain the benzoylurea scaffold focused on the synthesis of lactams of the type **3** as precursors of the constrained targets **2** (Scheme 1).

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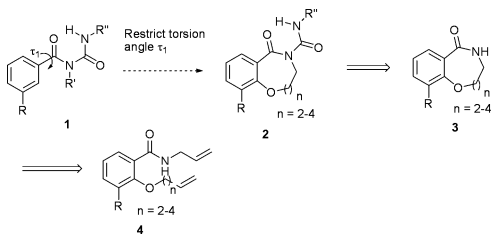
† Electronic supplementary information (ESI) available: Experimental procedures; copies of ^{1}H and ^{13}C NMR spectra; references. See DOI: 10.1039/c0ob00723d

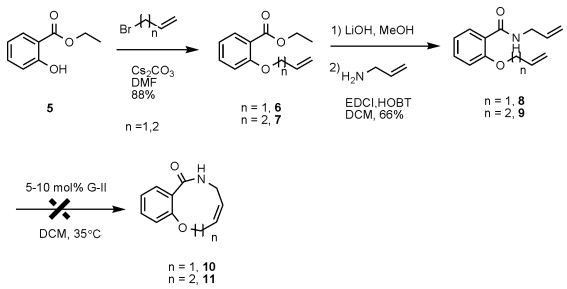
Table 1 Conditions for attempted RCM of the substrate **9**

Entry	GII (%)	Solvent	Temp/°C	Time/h	% Yield
1	10	DCM	40	12	0
2	20	DCM	40	12	0
3	10	Toluene	100	12	0
4	20	Toluene	100	12	0



Scheme 1 Retrosynthesis of constrained mimetics **2**.

Grubbs Ring Closing Metathesis (RCM) is recognised as an effective synthetic approach to forming cyclic moieties,[12] particularly in the field of natural products[13] and peptidomimetics.[9,14] We envisaged that this chemistry would be particularly suitable for the synthesis of our target macrolactams, employing dienes such as **4** as substrates (Scheme 1). An exemplary synthesis for metathesis substrates **8** and **9** is shown in Scheme 2, and occurs *via* alkylation of ethyl salicylate **5** to give allyl ether **6** and **7**, followed by saponification of the ester group and amidation with allylamine.



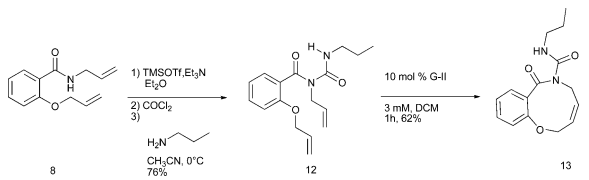
Scheme 2 Diene synthesis and attempted RCM.

Unfortunately, RCM with substrates **8** and **9** failed to form the target lactams (Scheme 2). Variation in conditions as shown in Table 1 failed to affect the RCM. We suspected that the failure to effect ring closure was a result of the nature of the substrate,

particularly the secondary amide's preference towards the *trans* conformation.

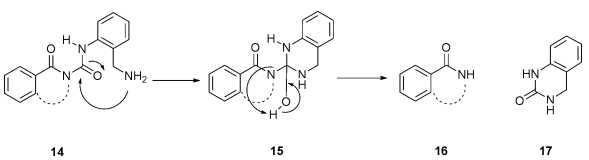
We have shown[11] that benzoylureas can adopt a 'closed' conformation maintained by a strong intramolecular hydrogen bond as shown for **1** in Scheme 1, which effectively renders the benzamide bond *cisoid*-like in character.

We postulated that this conformation could facilitate macrocyclization. A simple model system was employed to test this hypothesis. As shown in Scheme 3, benzoylurea **12** was prepared by reacting the silylated amide group of **8** with a carbonyl donor (phosgene). The resulting carbamoyl chloride was then on-reacted with propylamine. Gratifyingly, when the benzoylurea **12** was subjected to RCM with 5 mol% Grubbs II in refluxing DCM, the target lactam **13** was smoothly generated in 1 h and in 62% yield.

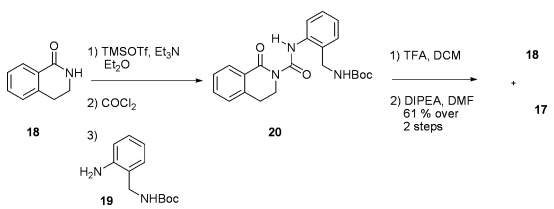


Scheme 3 Model RCM induced by a benzoylurea group.

Encouraged by this result, we envisaged that a suitably functionalised macrocyclic acylurea such as **14** in Scheme 4 could self-cleave *via* an intramolecular nucleophilic attack, to release a lactam **16** and the auxiliary by-product **17**. This strategy was again evaluated on a model system, employing reaction of the carbamoyl chloride of the commercially available lactam **18** with Boc-protected 2-aminobenzylamine **19**, to give **20** as shown in Scheme 5. Following deprotection of the amine in **20** with TFA, neutralisation with DIPEA and warming to 60 °C in DMF the desired self-cleavage was indeed observed to give lactam **18** and by-product **17**.[15]



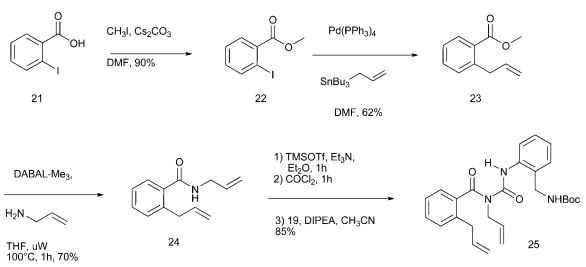
Scheme 4 Removal of auxiliary *via* intramolecular nucleophilic attack with release of target lactams **16**.



Scheme 5 Synthesis of model benzoylurea auxiliary **20** and self-cleavage to release the expected lactams.

With a cleavable auxiliary in hand, the ability to synthesise and isolate lactams of various sizes was explored. In particular, we focused on the 8–10 membered rings, as cyclisation was not achievable using the precursor secondary amides.

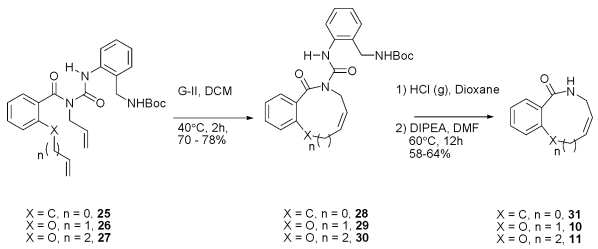
In the case of the smaller 8-membered ring, we opted for a carbon linked alkene formed using a Stille coupling between



Scheme 6 Synthesis of macrocycle precursor **25**, fitted with the benzoylurea auxiliary.

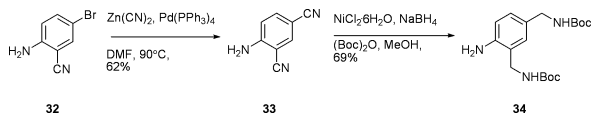
the aryl iodide **22** and allyltributyltin, yielding **23** (Scheme 6). The ester was then converted directly to the amide **24** using DABAL-Me_3, an air stable, solid derivative of trimethyl aluminium.[16]

With the necessary precursors in hand, the effect of the 'closed' conformation was evident by the rapid and high yielding RCM (Scheme 7).



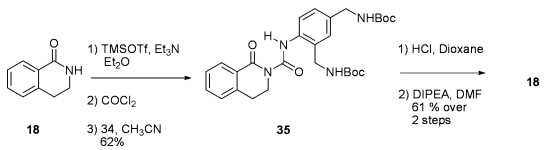
Scheme 7 Acylurea-induced RCM and release of auxiliary.

Removal of the auxiliary facilitated the release and subsequent isolation of the desired lactams. In order to further extend the general utility of this self-cleavage reaction, we next investigated the possibility of using, in the acylurea synthesis, an appropriately functionalised aniline that could give rise to a by-product more readily removed than **17**. In particular, we envisaged that a second methylenamine unit on the auxiliary (compound **34**, Scheme 8) would allow efficient removal of the deprotection by-product using an acidic work-up. Additionally, the use of similar protecting groups on both primary amines would facilitate the deprotection/removal step. Shown in Scheme 8 are the results of our efforts. The functionalised auxiliary, *tert*-butyl-(4-amino-1,3-phenylene)bis(methylene)dicarbamate **34** was prepared in 2 steps from 2-amino-5-bromobenzonitrile **32**. After aryl cyanation of **33**, a one-pot reduction/Boc-protection reaction afforded the desired compound **34**.



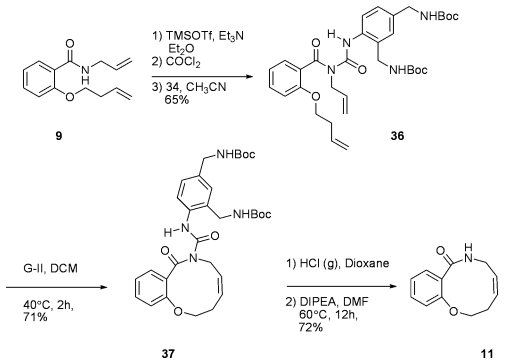
Scheme 8 Preparation of functionalized auxiliary.

The functionalised aniline **34** was then used to prepare the model benzoylurea **35**, which was then subjected to the deprotection conditions (Scheme 9). Pleasingly, with this auxiliary, the amide **18** was regenerated cleanly following simple aqueous work up without the need for column chromatography. With this improved auxiliary in hand, we then demonstrated the effectiveness of our



Scheme 9 Employing the functionalized auxiliary to isolate the amide **18**.

approach for the synthesis of a lactam *via* RCM. As shown in Scheme 10, the functionalised auxiliary **34** was able to effect the cyclisation as well as auxiliary **19**, and enable a much more facile isolation of the desired macrocycle **11**.



Scheme 10 Employing the functionalized aniline to facilitate isolation of the lactam.

In summary, we have described a new auxiliary that facilitates the formation of macrocyclic lactams *via* stabilization of a *cisoid* amide bond, promoting rapid and high yielding ring closure *via* RCM.

To the best of our knowledge, this is the first time that an acylurea has been regarded as a masked *cisoid* secondary amide. This conformation is maintained by the strong intramolecular hydrogen bond characteristic of the closed form of the acylurea.[11b] There are several attractive features of our approach. Firstly, the masked amide is rigidly maintained in the *cis* conformation.[17] This is in contrast with *N*-alkylated tertiary amides where the *cis* form is only relatively stabilized but not necessarily thermodynamically preferred over the *trans* form. As such, it is not uncommon for cyclization reaction times involving *N*-alkyl tertiary amides to be measured in the order of days rather than hours.[6] Secondly, the use of amine deprotection to initiate self-cleavage allows for great versatility in the choice of protecting groups beyond the use of Boc. In principle Fmoc protecting groups could allow for initiation of self-cleavage under basic conditions.

We believe there is much scope for this auxiliary methodology to become a valuable tool for the synthesis of macrocyclic lactams, peptidomimetics, cyclic peptides and natural products *via* RCM.

Acknowledgements

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