Post-Synthetic Modifications of Amide-Enaminone-Based [2]Rotaxanes for the Stereocontrolled Synthesis of Functionalized β-Lactams

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Abstract: Novel amido-enaminone threads serve as efficient templates for the assembly of hydrogen-bonded [2]rotaxanes, enabling versatile post-synthetic modifications. Benzyl groups on the amido moiety allow for diastereoselective intramolecular cyclizations, yielding interlocked β-lactams. The enaminone motif makes possible the stopper exchange while preserving the mechanical bond. Combining cyclization with one-pot stopper exchange and dethreading enables the stereoselective synthesis of highly functionalized non-interlocked lactams featuring a second heterocycle at their side chain via reactions with hydrazines or hydroxylamine.

Introduction

Over the past decades, numerous research groups have focused on the synthesis and applications of mechanically interlocked molecules (MIMs),[1-2] revealing significant advancements in artificial molecular machinery.[3-8] One of the main challenges in MIM's assembly is their obtention of high yields. In this line, highly efficient syntheses have been achieved by following diverse templating methodologies.[9-15] In addition, various strategies for post-synthetic modification of interlocked structures have been developed in order to generate more sophisticated entangled architectures.[16-17] In rotaxanes, the modification of the functionalities at the thread within the macrocycle cavity is particularly challenging due to its steric protection by the ring, causing their stabilization,[18-24] but, at the same time, the orthogonal arrangement of components can create a confined space that allows a precise control of diverse chemical processes.[25-26] There are scarce examples where the mechanical bond actively influences the reactivity at the thread, with the preorganization of entwined components being crucial for controlling a selected process. Goldup and co-workers achieved the synthesis of acrylamide-based rotaxanes via an active template Cu-mediated alkyne-azide cycloaddition-rearrangement, a transformation that only occurs in the presence of a macrocycle.[27] In the absence of the mechanical bond, the expected triazole derivatives were obtained. In this line, the mechanical interlocking of glutaconamides enables their chemoselective oxidation to β,γ-unsaturated α-ketoamides, where the presence of the macrocycle dampened the formation of other species, markedly differing from the behaviour of the non-interlocked substrates.[28]

Related to the topic presented herein, we have reported that interlocked *N*-benzylfumaramides can smoothly undergo a base-promoted intramolecular cyclization reaction, diastereoselectively yielding the corresponding interlocked β-lactams. The mechanical bond actively plays a crucial role on this process outcome, activating and stereocontrolling the reaction (Figure 1a).[29-30] In addition, bis(enaminone)-based rotaxanes experience a double stopper-exchange process by nucleophilic attack (Figure 1b),[31] where depending on the bulkiness of the nucleophile, e. g. bulky primary amines, the mechanical bond can be maintained.[32-39] Thus, in this work, we investigate the dual post-synthetic modifications of hydrogen-bonded rotaxanes **1**, built from tailored amide-enaminone threads that showed excellent templating ability when a five-component clipping protocol is followed (Figure 1c). We planned to study the versatility of the dual post-synthetic modification of the interlocked systems **1**. Initially, a base-promoted cyclization by intramolecular attack of the benzyl groups attached to the amide function would occur, forming the expected β-lactams. Afterwards, the enaminone at the other extreme of the thread would experience a stopper-exchange protocol by using low steric-demanding hydrazines or hydroxylamine as nucleophiles (and subsequent dethreading) resulting in the formation of novel, highly functionalized β-lactamic derivatives **2** with an additional heterocycle on their structure.

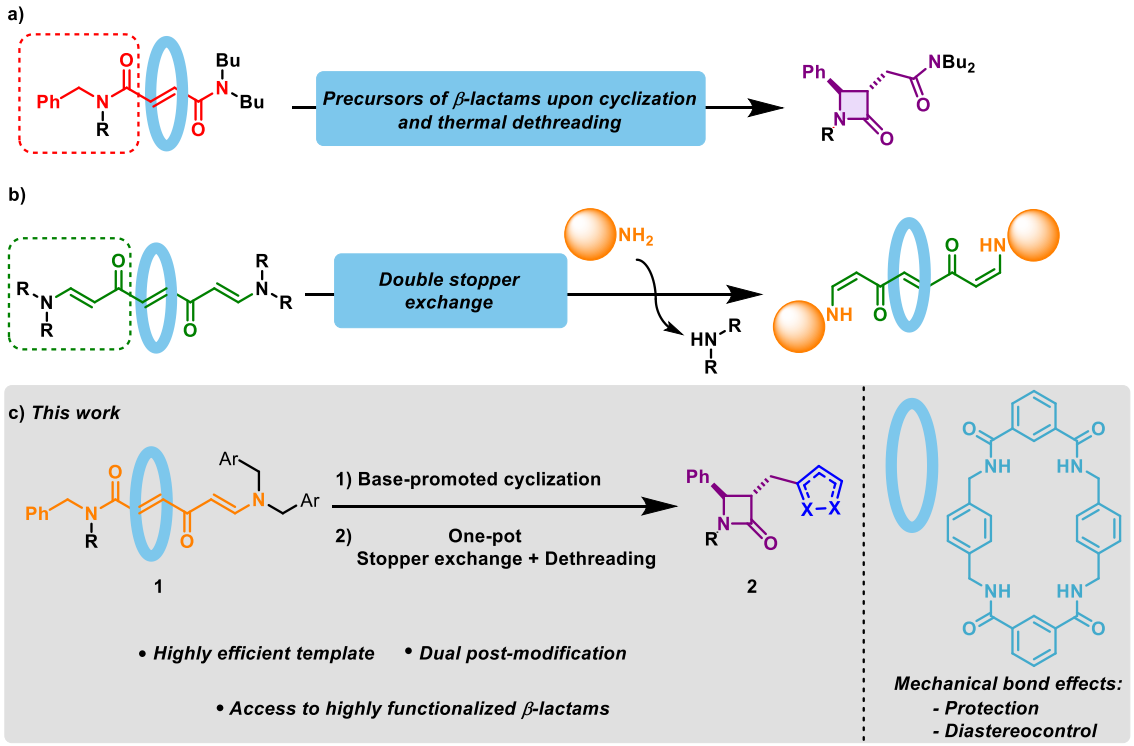
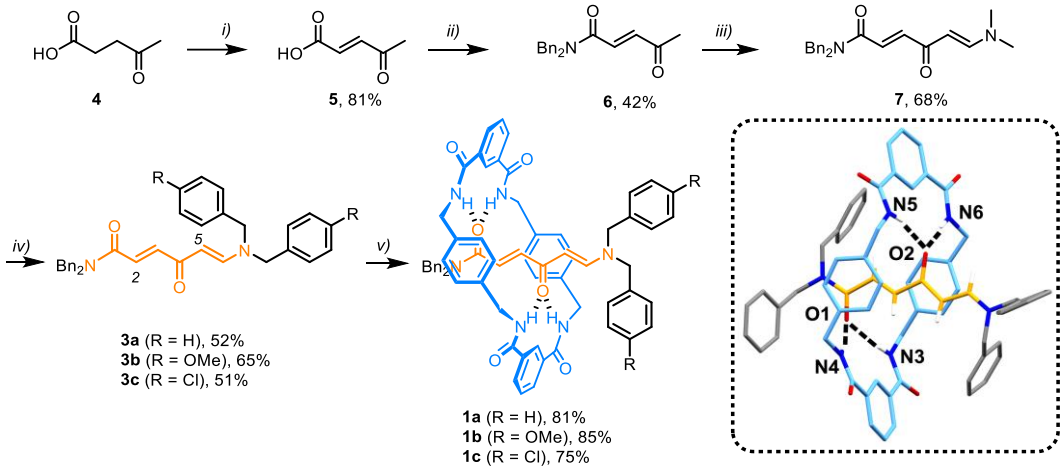


Figure 1. a) Interlocked *N*-benzylfumaramides as precursors for the selective obtention of *trans*-β-lactams;[29] b) Interlocked conjugated bis(enaminones) able to perform a double stopper-exchange reaction while maintaining the mechanical bond;[31] c) Hydrogen-bonded rotaxanes 1 with mixed amido-enaminones threads, for the obtention of functionalized β-lactams 2 upon cyclization followed by a stopper-exchange process and subsequent dethreading (*this work*).

Results and Discussion

A series of threads **3** were synthesized by following a four-step synthetic process (Scheme 1). (*E*)-4-oxopent-2-enoic acid (**5**) was obtained by treating the commercially available levulinic acid (**4**)

with bromine, followed by an elimination reaction using sodium acetate in acidic media.[40] Acid **5** smoothly reacted with dibenzylamine in the presence of DCC, yielding amide **6**, which was further treated with DMF·DMA, giving compound **7**, common precursor for threads **3**. The dimethylamino group of **7** underwent a nucleophilic substitution with different dibenzylamines in refluxing ethanol,[41-42] isolating threads **3a-c** in moderate yields. Finally, the clipping reaction of the threads **3a-c** with *p*-xylylenediamine and isophthaloyl chloride in the presence of Et_3N afforded rotaxanes **1a-c** with high yields (75-85%), demonstrating the high efficiency of this novel template, which, as expected, lies between that of tetrabenzylfumaramide (36%)[29] and those of the conjugated bis-enaminone systems (90%).[31] In solution, the most stable (2*E*,5*E*) isomers of threads **3** and rotaxanes **1** are the only observed species (see numbering in Scheme 1). At the solid state (suitable crystals of compound **1a** were grown by slow diffusion of pentane in a solution of $CHCl_3$), the thread in rotaxane **1a** also maintains the approximately planar and highly stable (2*E*,5*E*) conformation (see inset in Scheme 1, and Supporting Information, Tables S1-2 and Figure S87).[43] Moreover, the thread establishes four intercomponent bifurcated hydrogen bonds with the macrocycle, that adopts a highly symmetrical chair-like conformation, commonly considered as a good indication of the high templating ability of the system.

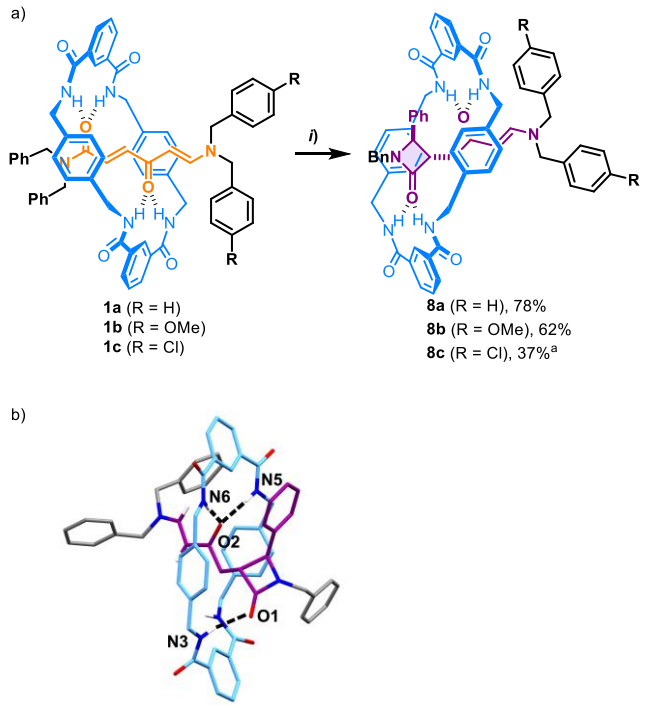


Scheme 1. Synthesis of conjugated amido-enaminone-based threads 3 and their corresponding hydrogen-bonded rotaxanes **1**. Inset: X-ray structure of rotaxane **1a**. *Reaction conditions: i*) a) Bromine, acetone/water, 0 ºC to 25 ºC, 5 h; b) sodium acetate, AcOH, 100 ºC, 45 min; *ii*) dibenzylamine, DCC, HOBt, DMAP, DCM, 25 ºC, 24 h; *iii*) DMF·DMA, toluene, 110 ºC, 12h; *iv*) $(ArCH_2)NH_2$, ethanol, 80 ºC, 12 h; *v*) *p*-xylylenediamine, isophthaloyl dichloride, Et_3N, $CHCl_3$, 25 ºC, 4 h. Intramolecular hydrogen-bond lengths [Å] (and angles [º]): N3–H03...O1 2.46 (174º); N4–H04...O1 2.18 (164º); N5–H05...O2 2.45 (161º); N6–H06...O2 2.18 (171º). For clarity, selected hydrogens atoms and solvent molecules ($CHCl_3$) have been deleted.

Next, we checked the suitability of the synthesized threads **3** and their rotaxanes **1** on the base-promoted cyclization of interlocked *N*-benzylfumaramides.[29] Thread **3a** showed to be highly unstable in the presence of CsOH in DMF, yielding a complex mixture of products, not observing the formation of the desired non-interlocked lactam (see Supporting Information, Figure S68). In stark contrast, the reaction of rotaxane **1a** under the same conditions triggered the formation of the expected interlocked β-lactam **8a** as the main product, isolated in 78% yield in a totally diastereoselective manner (only the *trans* isomer is observed) (Scheme 2a). Thus, the mechanical

bond actively participates on this process in a dual mode: i) protecting the formed β-lactam inside the macrocycle cavity, and also, ii) perfectly controlling the diastereoselectivity of the cyclization. Similarly, the reaction of rotaxane **1b-c** yielded the interlocked lactams **8b-c** in moderate yields. The analysis of the structure of compound **8a** by X-ray diffraction technique, using single crystals grown by slow diffusion of pentane in a solution of $CHCl_3$, confirmed the *trans* disposition of the lactam core (Scheme 2b, and Supporting Information, Tables S3-4 and Figures S88-89).[44] In this case, the new lactam thread maintains the *E* conformation of the enaminone double bond, with an important deformation of the macrocyclic component, establishing three intercomponent hydrogen bonds with the thread.

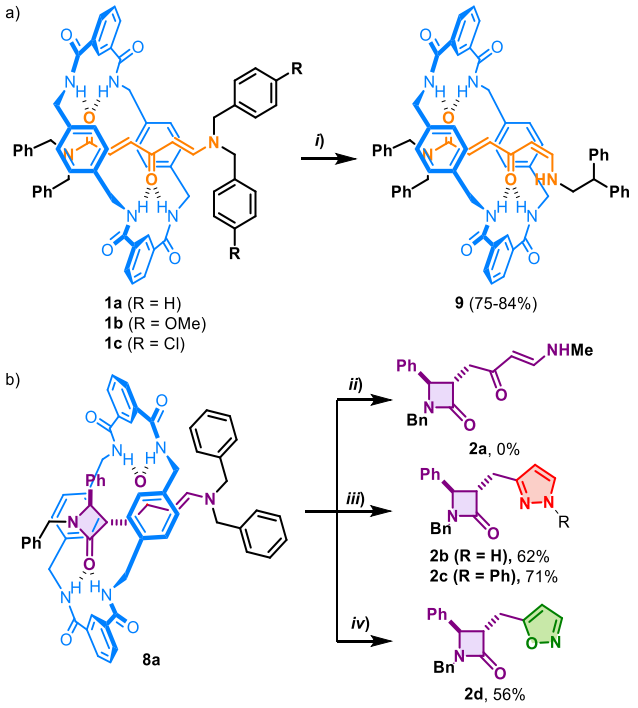
The substituents at the *para* position of benzyl groups in fumaramide-based rotaxanes significantly impact the cyclization kinetics, accelerating it with electron-withdrawing groups.[29] In addition, the variations on polyamide macrocycle also modulates this process.[30] We also checked herein the cyclization kinetics of rotaxanes **1a-c**, differing in the benzyl group substituents at their enaminone motif, far away from the reaction centers, by monitoring the conversions of their cyclizations over time (see Supporting Information, Figures S48-51). As we presumed in these cases, the substituent's influence was negligible, yielding similar rate constants when modelled as first-order reactions.



Scheme 2. a) Synthesis of interlocked lactams **8**; b) X-ray structure of interlocked lactam **8a**. *Reaction conditions: i*) rotaxane **1** (0.05 mmol), CsOH (2 equiv), DMF (2 mL), 25 ºC, 4 h. [a] 4 mL of DMF were required to completely dissolve the starting material **1c**. Intramolecular hydrogen-bond lengths [Å] (and angles [°]): N3−H03...O1 2.02 (151.2º); N5−H05...O2 2.17 (178.5º); N6−H06...O2 2.22 (174.9º). For clarity, selected hydrogens atoms have been deleted.

For the synthesis of non-interlocked lactam derivatives starting from fumaramide-based rotaxanes, a simple strategy has been commonly followed in order to remove the mechanical bond. In all cases, the presence of lineal flexible and low steric-demanding alkyl groups (i. e. *n*-butyl or *n*-propyl groups) as stoppers[45-46] was required, allowing the dethreading[47-50] of the interlocked lactams, yielding the free ones. This is the reason why next assayed a stopper-exchange reaction, by displacing the dibenzylamine group from compounds **8** with a small amine. Unfortunately, the reaction between rotaxane **8a** and $MeNH_2$ gave no results, recovering the starting material (Scheme 3b). By comparing with our previous experiments (Figure 1b),[31] it seems that the loss of the extended π conjugation of the system **8a** once the lactam core is formed (one double bond is lost compared with **1a**) highly decreases the electrophilic character of the enaminone double bond towards a nucleophilic attack from an external amine. Indeed, to our knowledge no examples have been previously reported on amine substitutions in enaminones bearing an enolizable alkyl group. In stark contrast, the pristine rotaxanes **1a-c** gave excellent results on the stopper exchange process with a bulky primary amine such as 2,2-diphenylethylamine, obtaining rotaxane **9** (in a *E,Z* conformation of the double bonds) in high yields, and without observing the formation of the corresponding free thread resulted from the breaking of the mechanical bond (Scheme 3a). A careful study of this transformation showed that the different substituents at the benzyl group in the enaminone motif slightly influence its kinetics (see Supporting Information, Figure S41). Electron-withdrawing chlorine atoms (rotaxane **1c**) accelerate the stopper exchange, while methoxy groups (rotaxane **1b**) slow it down, setting the reactivity of rotaxane **1a** in between.

To overcome the lack of reactivity with small primary amines shown by rotaxanes **8**, we focused on the reaction with other nucleophiles able to perform the desired tandem stopper exchange plus dethreading processes. Fortunately, hydrazine derivatives[51-52] and hydroxylamine[53] were found to be suitable substrates for this goal (Scheme 3b). The reaction of rotaxane **8a** with hydrazine hydrate in the presence of acetic acid at room temperature smoothly yielded compound **2b**, which owns two heterocyclic cores: a *trans*-β-lactam and a pyrazole, with a complementary volume that allowed an easy dethreading of the macrocycle. Similarly, the reaction with phenylhydrazine, under reflux of toluene and catalytic amounts of *p*-toluensulfonic acid, exclusively gave the substituted pyrazole-derived lactam **2c**. Finally, by using hydroxylamine as the nucleophile, compound **2d** was isolated, functionalized with a second oxazole core. Thus, this protocol allows us to access novel highly functionalized valuable β-lactams in a highly selective manner with a perfect diastereoselectivity controlled by the mechanical bond, which also serves as a protecting shield against its decomposition.



Scheme 3. a) Stopper-exchange reaction of rotaxanes **1** with 2,2-diphenylethylamine; b) Synthesis of the non-interlocked lactams **2** through a tandem stopper-exchange plus dethreading protocol. *Reaction conditions: i)* 2,2-diphenylethylamine (2.2 equiv), TCE, 100 °C, 12 h; *ii*) $MeNH_2$, TCE, 100 °C, 12 h; *iii*) NH_2NH_2, AcOH, 25 ºC, 2 h or NH_2NHPh, PTSA, toluene, 110 ºC, 4 h; *iv*) $NH_2OH{\cdot}HCl$, AcOH, 25 ºC, 2 h.

Conclusion

In summary, we have demonstrated the high efficiency of novel amido-enaminone threads as templates for assembling hydrogen-bonded rotaxanes, excellent substrates for two consecutive post-synthetic modifications: a diastereoselective base-promoted intramolecular cyclization, resulting in interlocked *trans*-β-lactams, followed by a one-pot stopper-exchange and dethreading process via nucleophilic attack. The mechanical bond within these structures provides significant advantages, including the protection of the threads during the cyclization and the control of the diastereoselectivity. Utilizing small-size nucleophilic reagents, such as hydrazine or hydroxylamine derivatives, a stopper-exchange process was achieved, followed by the release of the thread to yield highly functionalized non-interlocked lactams with an additional attached heterocycle.

Supporting Information

Supplemental experimental procedures, Figures S1–S89, Tables S1–S4, X-ray refinement data and supplemental references.

The authors have cited additional references within the Supporting Information.[54, 58]

Acknowledgements

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Keywords: mechanical bond • new template • hydrogen bond • rotaxane • keyword 5

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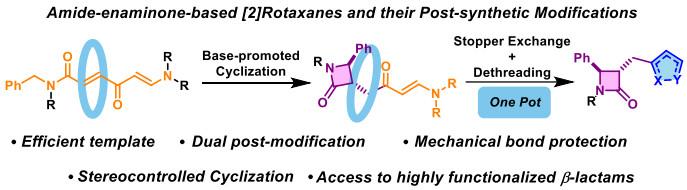
Entry for the Table of Contents



Novel amido-enaminone threads efficiently template the formation of hydrogen-bonded [2]rotaxanes and enable diverse post-synthetic modifications. Benzyl groups promote diastereoselective cyclizations to interlocked lactams while the enaminone motif allows stopper exchange while preserving the mechanical bond. One-pot cyclization plus dethreading yield stereoselective, functionalized lactams with side-chain heterocycles.