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Fused Bis-lactams to Spirolactams: A New Member of the Family of Ring-Contraction Reaction

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Abstract: A new ring contraction of fused bis-lactams into spirolactams is presented here. In the presence of a triflate catalyst in various solvents under microwave irradiation, this rearrangement allows a clean conversion of some fused bicycles into spirocycles with good yields. The interest of this work thus lies in the use of activated 2,5-diketopiperazines as starting materials and demonstrates the wide range of applications of ring contraction reactions.

Keywords: Spirolactams, ring-contraction, heterocycles.

1. INTRODUCTION

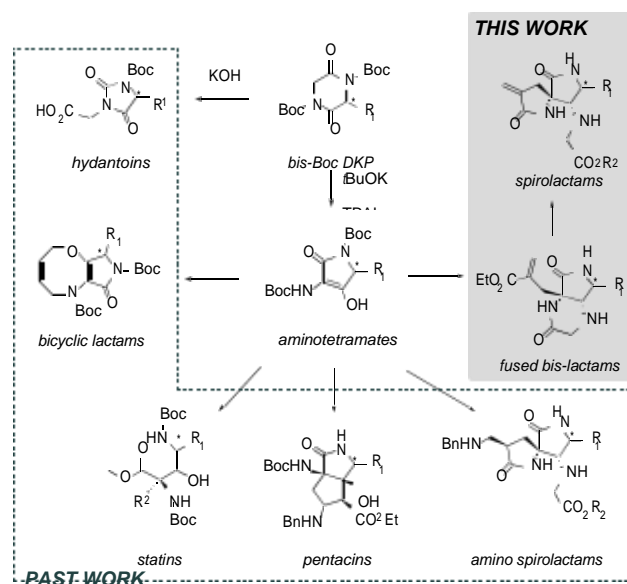
For medicinal chemists, ring transformations or homologous variations in a cyclic series belong to essential rules of investigation on the structure-activity relationship. Being then a crucial tool for bioorganic chemists, ring-contraction reactions allow the facile modification of cyclic compounds, leading to structural analogues which could otherwise be difficult to access. Among these is the well-known Favorskii rearrangement which converts α -halocyclohexanones to cyclopentane derivatives under basic conditions [1]. Famous for over a century, this rearrangement can be classified as a carbocyclic ring-contraction [2-4], a class of reactions that has been overall intensely studied.

Analogously, heterocyclic ring-contraction reactions allow a pertinent access to a wide array of common scaffolds such as pyrroles [5, 6], iminosugars [7] oxetanes [8, 9] or thiiranes [10] being often a key step in the total synthesis of natural products [11]. In this context, our group has been focused on highlighting bis-Boc diketopiperazines (DKPs) as key reagents for the development of original ring-contraction reactions (Fig. 1). The specific reactivity induced by the presence of the two Boc groups in these bicyclic peptidic

structures was previously illustrated by two rearrangements occurring in basic media. In the presence of potassium hydroxide, bis-Boc DKPs are thus converted to hydantoins [12], while a stronger and less nucleophilic base, such as potassium *tert*-butoxide, promoted the selective production

of aminotetramates [13]. This Transannular Rearrangement of Activated Lactams (TRAL) offers convenient access to a useful reactive scaffold, which has been used to synthesize statins, pentacins, bicyclic lactams, and amino spirolactams [14, 15].

In this way, we described here our interest to the stereoselective conversion of aminotetramates to bis-lactams able to rearrange into spirolactams.



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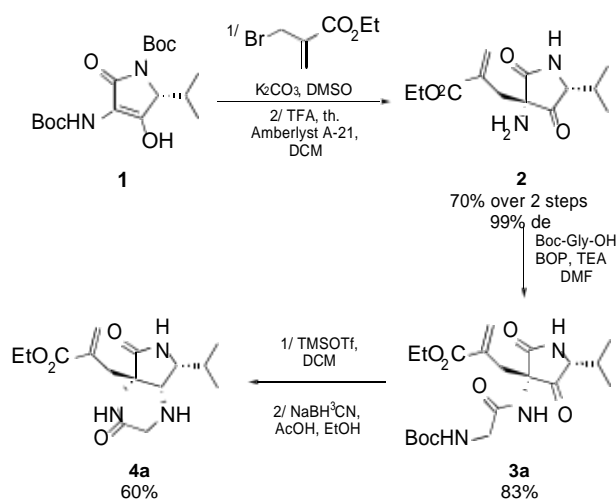
Fig. (1). Overview of ring-contraction reactions employing bis-Boc DKPs and their derivatives.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Fused bis-lactams

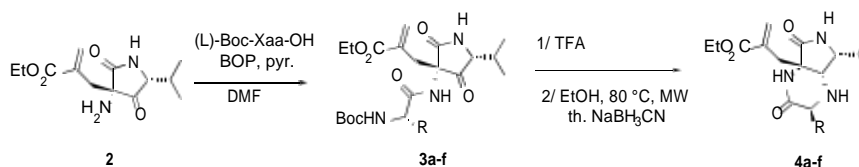
Starting from aminotetramate **1**, a diastereoselective tandem *O*-alkylation/Claisen rearrangement sequence led to pyrrolidine-dione **2** after a quantitative TFA deprotection of the Boc groups (Scheme 1). Coupling of the resulting primary amine with Boc-glycine delivered Boc-amino-ester **3a** which was subsequently deprotected before undergoing intramolecular reductive amination. This reduction occurred with a complete diastereoselectivity, probably due to the steric hindrance of the *i*Pr group and the lactam ring at both α and α' positions, dictating the approach of the reducing agent to the Re face of the newly formed imine (not shown).³

This sequence to access bicyclic lactams **4a** proceeded with a good overall yield of 35% over 6 steps and, more importantly, with complete diastereoselectivity, leading to the creation of two novel stereogenic centers whose configurations were confirmed by X-ray crystallography [16].



Scheme (1). Synthesis of fused bis-lactams ring systems.

Table 1. Scope of the fused bis-lactams ring systems synthesis.



Xaa	3	Yield (%) ^a	4	Yield (%) ^a	t (h)
Gly	3a	82	4a	60	1.5
Asp(OBn)	3b	70	4b	37	1.5
Phe	3c	64	4c	63	1.5
Ser(Bn)	3d	60	4d	60	2
Lys(Z)	3e	74	4e	53	1.5
Dap(Z)	3f	60	4f	51	2.5

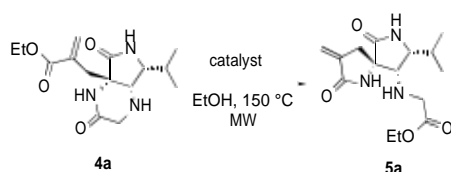
^aYield of isolated product.

Driven by these results, we next turned our attention to the synthesis of more complex bis-lactams by using chiral (L)-Boc-aminoacids instead of Boc-glycine (Table 1). However, the coupling of pyrrolidine-dione **2** with Boc-lysine resulted in a 1:1 mixture of diastereomers, presumably because of racemisation of the amino acid under the reaction conditions (BOP, NEt₃). This was circumvented by replacing triethylamine with pyridine, resulting in the formation of diastereopure bicyclic precursors **3b-f** in decent yields. Then, the optimization of the preparation of bis-lactams, involving a stepwise imine formation/diastereoselective reduction, delivered the corresponding bis-lactams **4b-f** with acceptable yields and lower reaction times.

2.1. Ring-contraction of Fused bis-lactams

With this small library of six bis-lactams **4a-f** in hand, we turned our attention to their oligomerisation, hypothesizing that such oligomers could potentially display interesting foldamer properties, given the rigidity of their backbones. However, despite many attempts, the coupling between the secondary amine and the corresponding α,β -unsaturated acid proved unsuccessful, presumably because of the steric hindrance around the amine. However, we were delighted to see that an original rearrangement occurred when bis-lactam **4a** was heated under microwave irradiation in the presence of an acid in absolute ethanol, leading to spiro lactam **5a** (Table 2). To the best of our knowledge, such a rearrangement has not yet been reported, offering an interesting access to complex skeletons.

Among the different conditions screened to improve the yield of the ring contraction reaction of bicycle **4a**, we noticed an influence of the strength of the Brønsted acids (Table 2, entries 1-4). While using acetic acid resulted in a moderate conversion, better conversion was observed with triflic acid. Switching to Lewis acids gave better yields in general, especially when employing zinc, manganese, magnesium or iron(II) triflates, while lanthanide triflates led to the decomposition of the starting material (Table 2, entries 5-7).

Table 2. Screening of conditions for the fused bis-lactam to spiro lactam ring-contraction reaction.

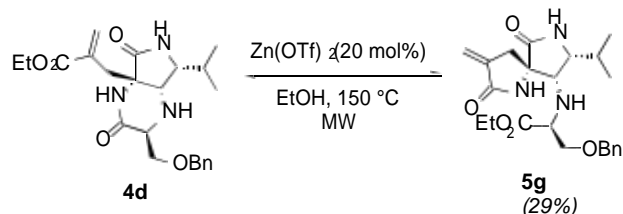
Entry	Catalyst ^a	Yield (%) ^b
1	AcOH	5
2	TFA	7
3	H ₂ SO ₄	21
4	TfOH	45
5	Yb(OTf) ₃	Decomposition
6	Sm(OTf) ₃	Decomposition
7	Er(OTf) ₃	Decomposition
8	Mn(OTf) ₂	55
9	Fe(OTf) ₂	55
10	Mg(OTf) ₂	55
11	Zn(OTf) ₂	55
12	Li(OTf)	30
13	Na(OTf)	5
14	K(OTf)	5
15	Zn(NTf ₂) ₂	55
16	ZnO	10
17	ZnCl ₂	6
18	Zn(OTf) ₂ ^c	42

^aCatalyst loading 20 mol%, ^bYield of isolated product, ^cCatalyst loading 10 mol%.

Interestingly, while triflic acid and lithium triflate gave acceptable conversions, both sodium and potassium triflates failed to catalyze the rearrangement (Table 2, entries 4, 12-14). However, variations of the counteranion did not have a marked effect on certain metals' catalytic activities (see SI), which might demonstrate the coexistence of two catalytic cycles: one involving triflic acid and a second one involving the triflate salts. Moreover, the reaction proved to be reversible, as subjecting pure **5a** to the reaction conditions led to the partial formation of **4a** in similar ratios as before (determined by HPLC). As it was found to be the optimal loading, 20 mol % of zinc triflate was then used for studying the scope of the reaction. Water and other alcohol solvents – methanol, allyl alcohol, isopropanol and *tert*-butanol – were then screened (Table 3). Similar yields were obtained when ethanol, methanol or allyl alcohol was employed, with the spiro lactams **5a-c** being isolated as their corresponding esters (Table 3, entries 1-3). It is worth mentioning that these reactions are extremely clean, resulting only in a mixture of spiro lactam

and transesterified starting material. The use of water as solvent delivered 49% of carboxylic acid **5d** along with 50 % of recovered starting material, with only traces of hydrolysed bis-lactam **6d** (Table 3, entry 4). The steric bulk of the nucleophile revealed to be a crucial factor: employing *tert*-butanol resulted in no apparent conversion, whereas the use of isopropanol allowed the isolation of 65% of spiro lactam **5f** (Table 3, entries 5-6).

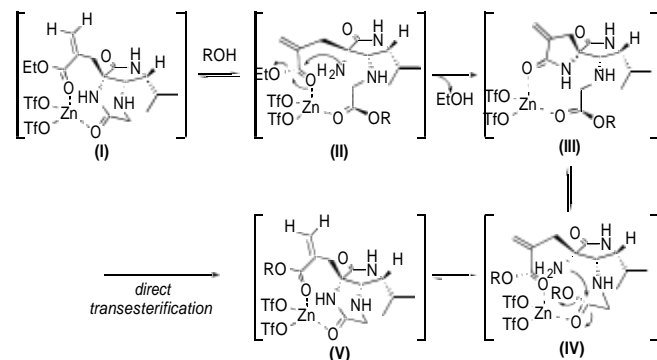
With these conditions in hand, we then focused our attention on the more challenging substituted bis-lactams **4b-f**. However, the presence of an extra substituent on the 6-membered lactam seemed to prevent any rearrangement from occurring under our developed conditions, highlighting a fine balance in sterics between the substrates and the alcohol nucleophiles. Even in ethanol, amino-bearing bis-lactams **4e-f** proved unreactive, but bis-lactams **4b-d** were converted to their corresponding spiro lactams, although a yield could only be calculated for spiro lactam **4d**.



Scheme (2). Application of the new fused to spiro rearrangement to more complex substrate.

2.1. Suggested Mechanism

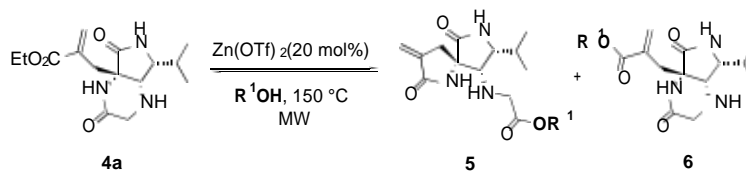
A plausible mechanism for this new rearrangement is depicted in Scheme 3.



Scheme (3). Proposed mechanism for the bis-lactam to spiro rearrangement.

We postulate that activation of the two carbonyl groups by the zinc(II) species could result in ring-opening of the 6-membered lactam by the nucleophilic alcohol to give the intermediate (II). A 5-*exo-trig* cyclisation would then lead to spiro lactam (III), which could be in equilibrium with transesterified derivative (V). When isopropanol is employed (R = *i*Pr), the hindrance caused by the two isopropyl esters in

Table 3. Solvent scope of the new fused bis-lactam to spiro lactam ring-contraction reaction.



Entry	R ¹	5	Yield of 5 (%) ^a	6	Yield of 6 (%) ^a	Remaining 4a
1	-Et	5a	55	-	-	45
2	-Me	5b	55	6b	45	0
3	-Allyl	5c	55	6c	45	0
4	-H	5d	49	6d	<5	50
5	- <i>t</i> -Bu	5e	0	6e	0	100
6	- <i>i</i> Pr	5f	65	6f	0	35

^aYield of isolated product.

the intermediate (IV) could prevent the 6-*exo-trig* cyclisation from occurring, thus favoring the formation of spiro lactam (III) instead of transesterified bis-lactam (V). However, direct transesterification of bis-lactam (I) to (V) cannot be ruled out either, even though this mechanism might only occur when non-hindered alcohols are used (Table 3, entry 6 vs 2).

CONCLUSION

In conclusion, a synthesis of novel fused bis-lactam skeletons was developed. Some of those could be converted to spiro lactams in the presence of zinc(II) triflate in a protic and nucleophilic solvent. This ring-contraction reaction represents an unusual and interesting reactivity, affording complex, and otherwise hard-to-access heterocyclic compounds.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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