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Facile Synthesis of Spirocyclic Lactams via [3+2] and [3+3] Aza-Annulation Reactions

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Spirocyclic pyrrolidones and piperidones were synthesized starting from readily available α-ketolactones and α-ketolactams employing [3+2]- and [3+3]-aza-annulation reactions. Annulation reactions proceeded with good yields and further reduction of the exocyclic C=C double bond of the enamide moiety proceeded with excellent diastereoselectivity. Overall, one C–C and two C–N bonds, as well as three new stereocenters were created in a diastereoselective manner resulting in a fast upbuild of molecular complexity.

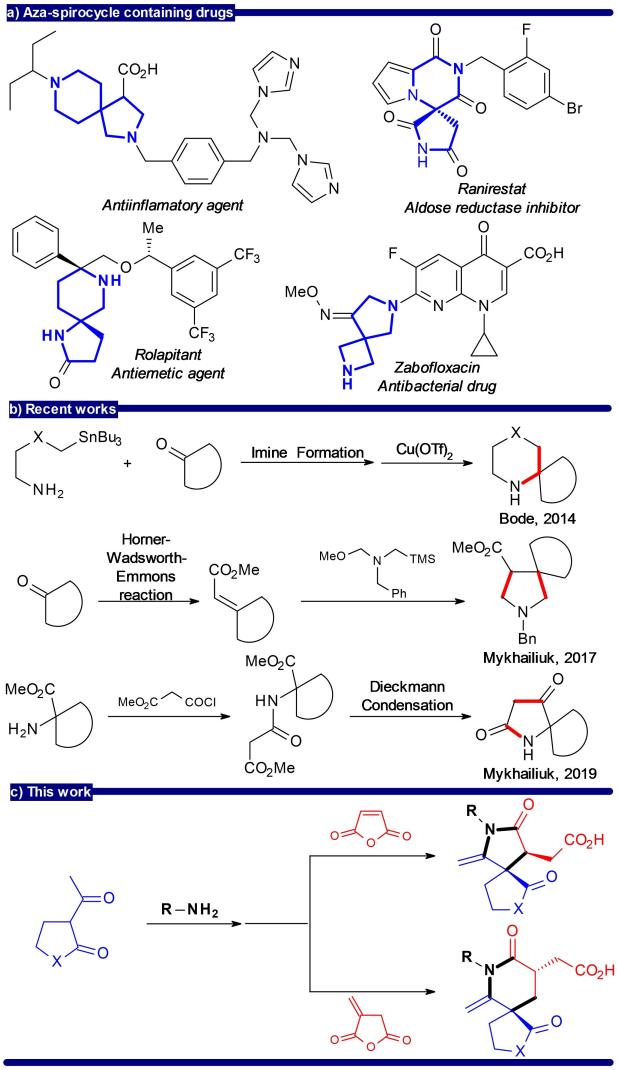
Introduction

Spirocyclic N-heterocycles are privileged building blocks in drug discovery because of their 3D character[1,2] (escaping from aromatic flatland), conformational restriction, improved physicochemical properties, compared to their monocyclic analogs, and improved metabolic resistance (Scheme 1a).[3–8]

Common methodologies for assembling spirocyclic scaffolds are mainly relaying on intramolecular S_N2 alkylation[9–19] and N-acylation,[11,20,21] ring closing metathesis[20,22–24] of the appropriate precursors. Additionally, metal-catalyzed[25–28] and hypervalent iodine mediated[29] dearmoatization reactions, Prins reaction[30–32] and cycloaddition reactions[23,33–35] should be mentioned.

Recently several appealing approaches have been reported for *de-novo* assembly of the aza-spirocycles. Bode suggested a spirocyclization strategy relying on SnAP cyclization reaction.[36,37] Despite its chemical elegance it suffers from the waste intensiveness and high toxicity of the used precursors, reagents, and produced waste (tributyltin compounds). Mykhailiuk from Enamine Ltd. proposed a spirocyclization method based on [3+2]-cycloaddition reaction between electron-deficient alkenes and in situ generated highly reactive azomethine ylide.[38,39] However, the lack of stereocontrol during the key cycloaddition step is the main weakness of this strategy. Recently Mykhailiuk reported a unified spirolactam synthesis from α-aminoesters, relying on Dieckmann condensation (Scheme 1b).[40] Gaunt reported a visible-light-mediated synthesis of aza-sprirocycles using photocatalytic single electron transfer (SET) reduction of iminium intermediate-radical cyclization sequence.[41] Bode employed catalytic hydrogen atom transfer reduction of electron-rich olefins with a generation of C-centered radicals in the presence of imines for the intramolecular radical cyclization with the formation of spirocyclic morpholines.[42] Recently Krasavin group reported several spirocyclization procedures based on α-diazolactam chemistry.[43,44]

To the best of our knowledge, [3+2] and [3+3]-aza-annulation reactions between enamines and maleic and



Scheme 1. Aza-spirocyclic motifs in drugs and recent works in the synthesis of N-spirocyclic building blocks. Herein we would like to disclose a divergent synthesis of 5,5- and 5,6-spirocyclic lactams based on the aza-annulation reaction (Scheme 1c).

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itaconic anhydrides,[45–48] were not employed for the construction of spirocycles up to date, whereas such reactions would be advantageous from the standpoints of stereochemical control and prospects of post-synthetic modifications of the newly formed building blocks.

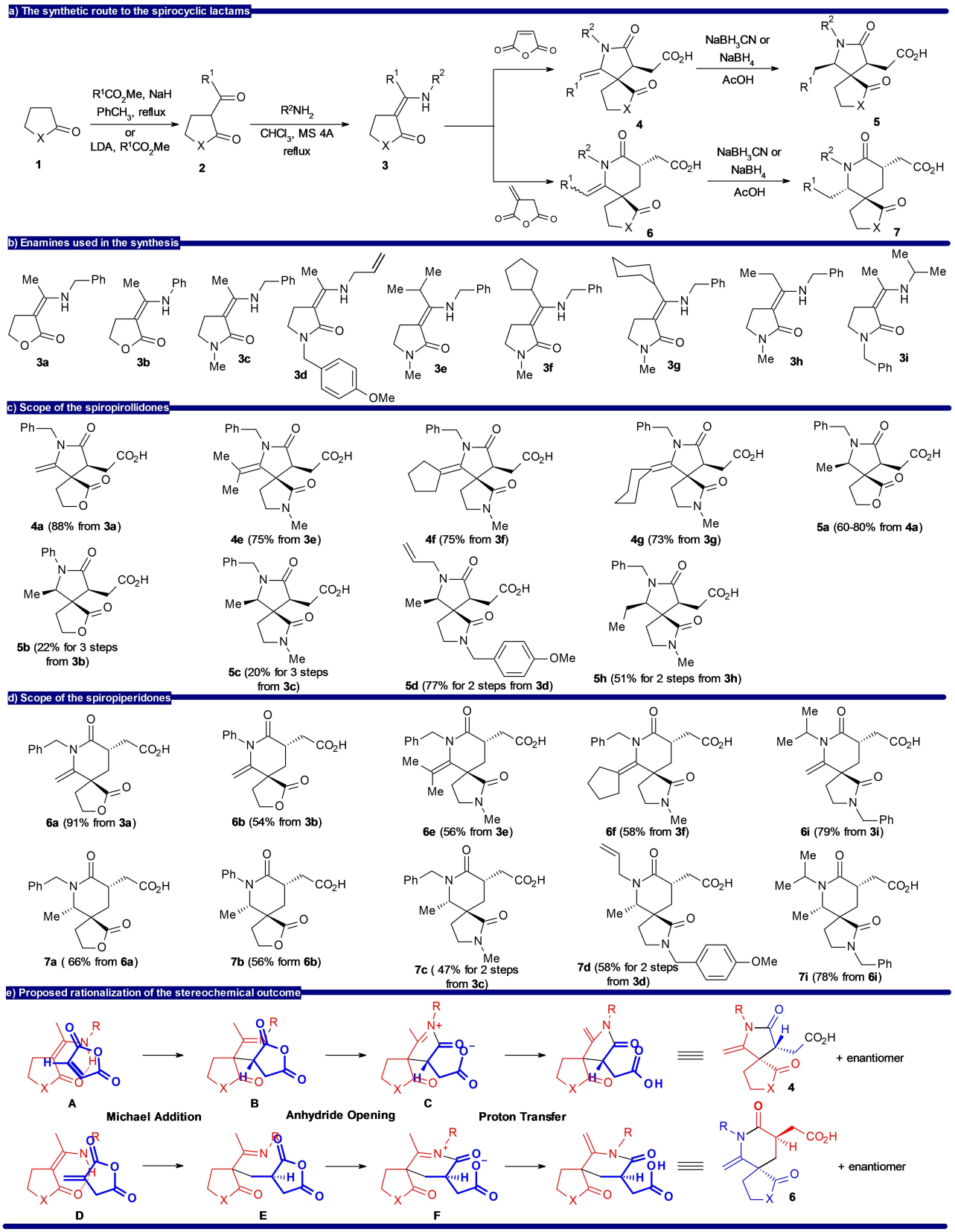
Results and Discussion

In our synthetic studies, we relied on readily available starting materials. Thus, α-ketolactams (**2c–i**, see supporting information) were prepared by Dieckmann-type condensation of lactams (1) with appropriate esters in refluxing toluene, using NaH as the base[49] (Scheme 2a). Despite moderate yields (26–44%) of such reactions, their practical applicability is justified by the availability of starting materials and the practicability of purification of the α-ketolactams via their Na-salts, thus avoiding column chromatography. Alternatively, the desired ketolactams can be prepared by deprotonation of lactams with LDA at low temperatures and quenching the Li-enolates with appropriate esters,[50] however in the latter case the yields were comparable with the NaH method (see supporting information for the details). Condensation between α-ketolactams as well as α-acetylbutyrolactone with primary amines proceeded readily in refluxing chloroform while using 4 Å molecular sieves as the dehydrating agent (**3a**, **c**, **d**, **h**, **i**). However, in the case of bulky ketones (**3e–g**) and less nucleophilic amines (**3b**) full conversion was achieved after one week of reaction time (Scheme 2a, Scheme 2b).

As an entry into spirocyclic lactams, we chose the interaction of enamines **3a–i** with maleic anhydride (Scheme 2a, Scheme 2c). To our delight, the cyclization between maleic anhydride and enamine **3a** proceeded with excellent selectivity and afforded spirolactam **4a** with 88% yield as a single diastereomer. To underline the practical utility of the reaction, we performed a scale-up experiment, which afforded 13.04 g (87%) of **4a** straightforwardly, without the need for chromatographic purification. Not surprisingly, the exocyclic enamide double bond in the resulting molecule **4a** turned to be unstable under acidic conditions, such as chromatography on silica gel with an acidic eluent ($CHCl_3$/MeOH/AcOH) and Fisher esterification (MeOH, H_2SO_4). Reduction of enamide **4a** with both $NaBH_3CN$ and $NaBH_4$ in acetic acid proceeded diastereoselectively providing reduced spirocycle **5a** with good yields (60–80%). The scale-up reduction with $NaBH_4$ in acetic acid provided 8.53 g (80%) of **5a**. Whereas in most cases the annulation products could be obtained directly in a decently pure form via precipitation or trituration with appropriate solvents, in several cases additional purification was required. Because of the sensitivity of the exocyclic enamide moiety to the acidic chromatography conditions (silica gel, eluent with 5% acetic acid) a short workaround was required in order to obtain analytically pure compounds. Thus, esterification of carboxylate function with CH_3I/K_2CO_3 followed by chromatographic purification of the ester, reduction with $NaBH_3CN$, and hydrolysis of the methyl ester was performed for **5b** and **5c** (see supporting information). As an alternative procedure, the reaction mixture from **3d** and maleic anhydride was reduced directly in a one-pot procedure to provide spirocycle **5d**, which was purified using column chromatography without any complications. Interaction of bulky enamines **3e–g** with maleic anhydride proceeded smoothly and afforded desired spirolactams **4e–g** with good yields (73–75%) as single diastereomers. Interestingly, the substitution of terminal hydrogens of the exocyclic enamide C=C double bond with alkyl groups resulted in complete suppression of its reactivity in the reduction with borohydride reagents under acidic conditions. Cyclization of enamine **3h** with maleic anhydride resulted in a mixture of E/Z isomers (95:5) of the monosubstituted exocyclic double bond, as expected. Reduction of the obtained mixture of isomers under standard conditions was somehow sluggish and prolonged reaction times were required to achieve full conversion and afford spirolactam **5h** as a single diastereomer. Finally, the interaction of enamine **3i**, bearing bulky isopropylamine moiety, with maleic anhydride resulted in a complicated reaction mixture.

Next, we investigated [3 + 3] aza-annulation reaction enamines **3a–i** with itaconic anhydride which would result in a formation of spirocyclic piperidones (Scheme 2d). Thus, in the case of enamines **3a–b** cyclization proceeded with excellent selectivity, affording the desired spiropiperidones **6a–b** as single diastereomers. The reduction of the enamide double bond with borohydride reagents, such as $NaBH_4$ and $NaBH_3CN$ in acetic acid proceeded with good yields (54–56%) and excellent selectivity. In the case of interaction of **3d** with itaconic anhydride, the non-chromatographic isolation of the cyclization product was not viable and the desired spirocycle **7d** was purified by standard column chromatography after the one-pot aza-annulation/reduction sequence. The cyclization of itaconic anhydride with bulky enamines **3e–f** proceeded smoothly and afforded spiropiperidones **6e–f** with good yields (56–58%) as single diastereomers. However, in contrast to [3 + 2]-annulation, aza-annulation with enamine **3g** failed and its interaction with itaconic anhydride resulted in a complex mixture. Analogously to **4e–g**, enamides **6e–f** turned to be stable in the acidic media and they remained untouched under reductive conditions ($NaBH_3CN$ or $NaBH_4$/AcOH). Not surprisingly, enamine **3h** afforded a mixture of E/Z isomers, upon treatment with itaconic anhydride and the attempted reduction of the reaction mixture with $NaBH_4$ in AcOH was sluggish and never went to completion. Finally, while the cyclization of bulky enamine **3i** with maleic anhydride failed, its interaction with itaconic anhydride resulted in spirocycle **6i** with 79% yield as a single diastereomer. The increased bulkiness of the N-substituent in **6i** did not have any noticeable effect in the reduction of the enamide moiety and the product **7i** was obtained in 78% yield as a single diastereomer.

The rationalization of the observed diastereoselectivity of cyclization reactions is shown in Scheme 2e.[46] First, the conjugate addition of maleic and itaconic anhydrides results in intermediates **B** and **E**, respectively, where the imine moiety is located in close proximity to the anhydride group. Next, anhydride opening (intermediates **C** and **F**) and proton transfer steps would provide the final spirocycles **4** and **6** with the given



Scheme 2. Synthesis of the spirocyclic lactams, scope of the method, and rationalization of the observed diastereoselectivity.

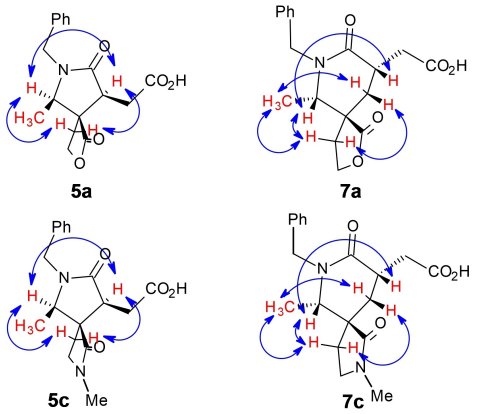


Figure 1. Key NOE correlations in **5a**. **5c**,**7a**, and **7c**.

diastereoselectivity. The attack on the enamide C=C double bond by borohydride reagents proceeded from the opposite side of the transannular $-CH_2CO_2H$ substituent. It is worthy to mention that esterification of the carboxylic acid did not affect the stereochemical outcome of the reduction for both spiropyrrolidones and spiropiperidones. Key NOE interactions for some of the final spirocycles are shown in Figure 1.

Conclusions

In conclusion, we have developed a divergent synthetic method to access 5,5- and 5,6-spirocyclic aza-heterocycles starting from simple, inexpensive, and readily available precursors. The key cyclization step is Michael addition, intramolecular acylation sequence between enamine, derived from α-ketolactone or lactam and maleic and itaconic anhydrides. Aza-annulation reaction as well as further reduction of the enamide C=C double bond with borohydride reagents proceeded with excellent diastereoselectivty and provided rapid buildup of molecular complexity. Due to the presence of carboxylic acid functionality in the obtained spirocyclic building blocks, they can be used for the synthesis of libraries of compounds via amide formation reaction.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Annulation · Diastereoselectivity · Lactams · Nitrogen heterocycles · Spiro compounds

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