Synthesis of new scaffolds: bisoxazolidines, thiazolidinyloxazolidines and spirothiazolidines.

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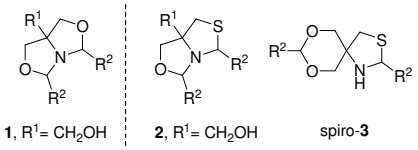
INTRODUCTION

The discovery of new reactions and scaffolds suitable to Dynamic Combinatorial Chemistry (DCC) requires the use of different synthetic tools. Ring-chain tautomerism can be applied to DCC as it involves a reversible movement of a proton accompanied by a change from an open structure to a ring.[1]

The oxygen-containing heterocycles **1**, reported in the literature many years ago, have attractive biological properties which could be shared or further enhanced by the sulfur analogues.[2]

Scheme 1. Bicycle **1,** sulfur analogue **2** and its tautomer **3**

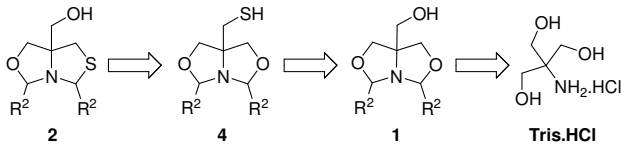


The present work describes our findings in the synthesis of thiazolidinyloxazolidine **2**, the sulfur analogue of bicycle **1**, as a potential DCC scaffold (Scheme 1).

RESULTS AND DISCUSSION

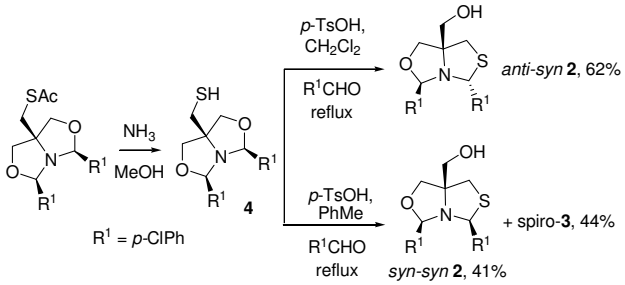
We explored many alternatives for the synthesis of the analogue bicycle **2**, using Tris·HCl reagent as starting material. The key step was the replacement of a hydroxyl group with a thiol in the fused bicycle (Scheme 2).

Scheme 2. Retrosynthetic analysis



We synthesized the thiol-bisoxazolidine **4** in two steps starting from bicycle **1**, product of the condensation of Tris and R^1CHO in acidic media.[3] A substitution of the free hydroxyl group of **1** using thioacetic acid as nucleophile (Mitsunobu conditions) gave the AcS-bicycle in good yield (65-80%). Then a smooth hydrolysis with NH_3/MeOH led to the free thiol **4**. Previously, our group described the ability of related fused bicycles to exchange carbonyl units at the oxazolidine site.[4] We decided to explore such an interconversion in this new system, using different conditions (solvent, temperature and R^1CHO) for the re-equilibration in acidic media (Results shown in scheme 4).

Scheme 4. Synthesis of thiazolidinyloxazolidine **2**



The structural isomer spirothiazolidine **3** was isolated as a new product of the ring-chain-ring tautomerism. Thiazolidines are known to be more stable than oxazolidines, this could explain why spirocycle **3** is formed but the corresponding spirocycle oxygen analogue is still unknown.

CONCLUSION

We were able to synthesize the fused thiobicycles **2** and the unexpected spiro tautomer **3** for the first time. Two methodologies were developed for the selective preparation of both diastereomers, the *syn-syn*-**2** in PhMe as well as the *anti-syn*-**2**, in CH_2Cl_2.

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