Synthesis of new squaramide backbone peptidomimetics catalysts

Sandrina I. R. M. Silva, Lucas Pozzi, Bianca T. Matsuo, Arlene G. Corrêa, Marcio W. Paixão

University Federal of São Carlos UFSCar, SP – Brazil.

**sandrina.silva@ufscar.br*

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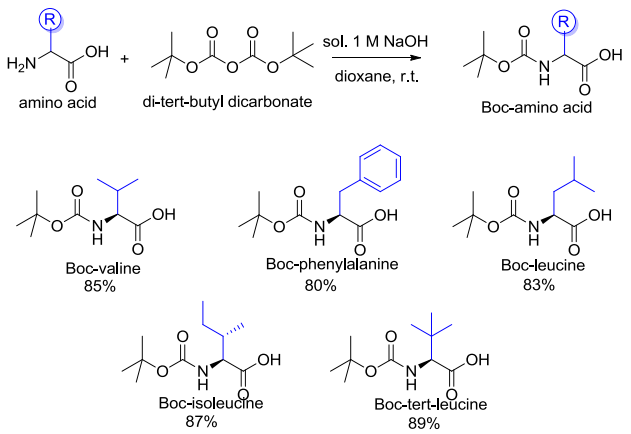
INTRODUCTION

Organocatalysis, i.e., the use of organic molecules for the construction of new chemical bonds in the absence of metals, is a ramification of asymmetric catalysis which has been rapidly developed in the last decade.[1] In order to have high enantioselectivity levels, the choose of the chiral catalyst should be planned very carefully. In the search for new organocatalyst for asymmetric addition, combinatorial chemistry has been applied and has shown to be very efficient. Due to high efficiency and versatility of amino acids and peptides as organocatalyst, the search for new synthetic methodologies to achieve them is of high importance. In particular, the study of Ugi multicomponent reaction is very interesting due to atom economy and high variety of chiral blocks which can be easily achieved through the use of this reaction.[2] Herein, we report the synthesis of new peptoid catalysts using Ugi 4-CR and their insertion on squaramide template, in order to be used as hydrogen bond activators in 1,6-Michael additions.

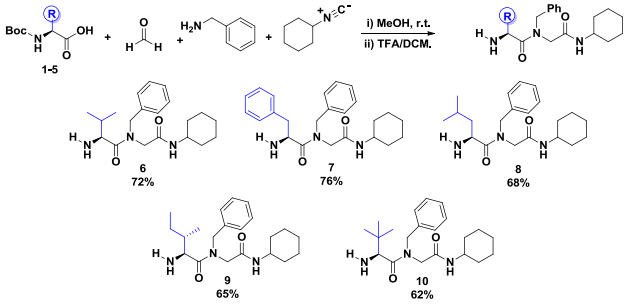
RESULTS AND DISCUSSION

Our study has started with the choice of five amino acids (valine, phenylalanine, leucine, iso-leucine and tert-leucine) and respective *N*-protection using di-tert-butyl dicarbonate under basic conditions. As shown in scheme 1, we have recovered the respective *N*-Boc protected amino-acids in excellent yields (80-89%).



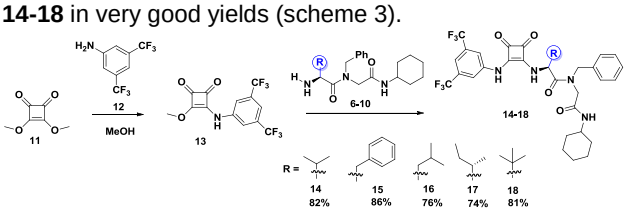
Scheme 1. N-protection of amino-acids.

In the presence of *p*-formaldehyde, benzylamine, and cyclohexyl isonitrile, *N*-Boc protected derivatives **1**-**5** were then engaged in Ugi multicomponent reaction, and respective desired products were obtained in good yields. Amine deprotection in the presence of TFA, lead to peptidomimetics **6**-**10**, which were isolated in fair two steps overall yield (scheme 2).



Scheme 2. Synthesis of peptidomimetic structures **6-10**.

In order to access new conformationally controlled structures to use as hydrogen bond activators in several reactions, we have modulated the dimethyl squarate template **11**. Firstly, the reaction with difluoromethyl aniline **12** and then with 1 equivalent of our peptidomimetic structures 6-10 allowed the isolation of the new catalysts **14-18** in very good yields (scheme 3).



Scheme 2. Synthesis of squaramide based catalysts **14-18.**

CONCLUSION

From this studay, we can conclude that Ugi reaction proved to be a very efficient tool for the preparation of different peptidomimetic structures. Also, the preparation of squaramide based catalysts proved to be very efficient.

Studies of the new structures **14-18** as efficient catalysts in 1,6-Michael addition reactions are now ongoing in our laboratory.

ACKNOWLEDGEMENTS

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