Multicomponent Synthesis of Bifunctional Thiourea Organocatalysts for the Enantioselective Aldol Reaction

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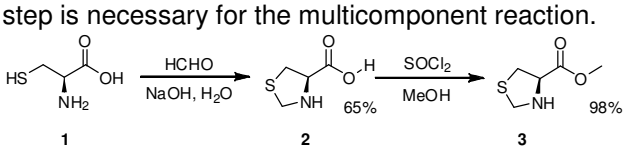
INTRODUCTION

During the past decade the field of organic chemistry has witnessed a tremendous rise in the number of synthetic applications of organocatalysis. In this scenario, *L*-proline has proved to be an important and versatile organocatalyst for applications in different types of reactions.[1] The amino acid derivative, thiazolidine, has equivalent efficiency, versatility and cost when compared to the natural amino acid *L*-proline according to the literature.[2] Thioureas, as bifunctional organocatalyst, brings a functional chelating hydrogen bond in the thiourea portion and an asymmetric induction is achieved by a highly ordered transition state. Organocatalysis using thioureas catalysts may replace earlier methods used for the asymmetric synthesis of aldol products, in which metal catalysts were used, resulting in a greener production of the same molecules.[2,3] In this work we present our initial results on the synthesis of new bifunctional organocatalysts **6**, based on thiazolidine, for the enantioselective aldol reaction.

RESULTS AND DISCUSSION

Multicomponent reactions involve atom economy and steps reduction, which aggregate even more ecological value to the methods of synthesis. In this way we developed a strategy for a one pot synthesis of the organocatalysts. Initially, the natural aminoacid *L*-cysteine **1** was cyclized with paraformaldehyde leading to thiazolidine **2.** The ester thizolididine **3** was obtained under classical conditions. It is worth to mention that no protection step is necessary for the multicomponent reaction.



Scheme 1. Synthesis of thiazolidine **3**

The multicomponent reaction between hydrazine **4**, methyl thiazolidine ester **3** and phenyl isothiocyanate **5** using methanol as solvent gives a thiourea organocatalyst **6** in 41 % yield after 3h with a facile work-up, as an advantage.

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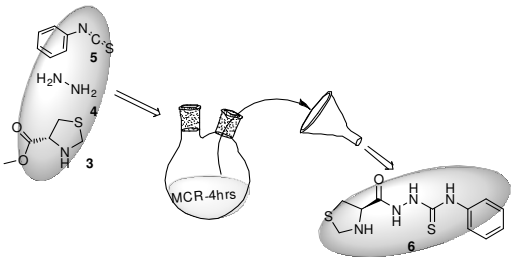
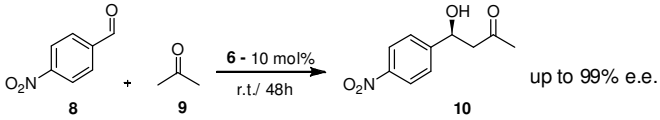


Figure 1. Multicomponent reaction for thiourea catalyst

Having obtained the thiourea organocatalyst, we turned our attention to investigate the efficiency of this catalyst on the asymmetric aldol reaction using a system with acetone **9**, p-nitro benzaldehyde **8** and 10 mol% catalyst load. The aldol products **10** were obtained with enantiomeric excesses up to 99% after 48 hours.



Scheme 2. Asymmetric Aldol reaction

These results encouraged us to continue our investigations, focusing on the organocatalyst modular construction which should permit the fine tuning of the enantioselectivity. Variation on aldol reaction scopes are also ongoing.

CONCLUSION

The suggested multicomponent synthesis of bifunctional thiourea **6** produced an efficient catalyst which could be successful applied on the aldol reaction furnishing the desired product with 99% *ee*.

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