Sociedade Brasileira de Química (SBQ)

Vinylogous Aldol Reaction of Tetronamides with Aromatic Aldehydes: Controlling Diastereoselectivity *via* Retro-aldol/Aldol Equilibration

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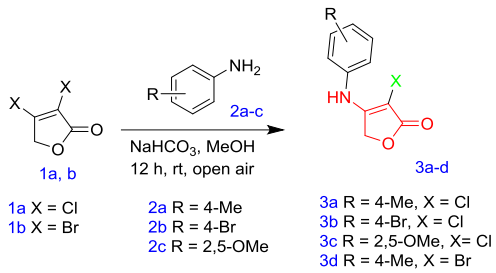
Introduction

4-Amino-2(5H)-furanones, commonly referred to as tetronamides, are precursors of structurally diverse natural or non-natural products with interesting biological activities.[1]

In this work, we are investigating the scope of a direct vinylogous aldol reaction[2] of 3-halotetronamides **(3a-d)** with aromatic aldehydes as a direct, stereoselective means of generating libraries of the aldol adducts.

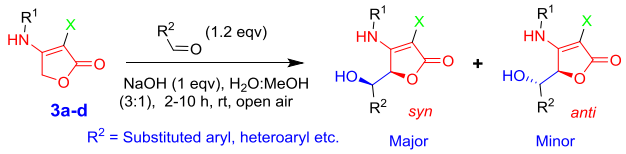
Results and discussion

We prepared the desired starting compounds (**3a-d**) by employing the addition-elimination reaction starting from commercially available lactones[3] **1a** and **1b** (**Scheme 1**).



Scheme 1. Preparation of tetronamides from common lactones

For the aldol reaction several bases and reaction conditions were investigated and the best results were afforded by the use of MeOH and H_2O as solvent and NaOH as base **(Scheme 2)**.



Scheme 2. Vinylogous aldol reaction of tetrinamides in optimized reaction conditions

The reaction often proceeded with high diastereoselectivity and high conversion (**Fig. 1**). The thermodynamic control of the diastereoselective aldol reaction in the present case is most likely due to an increase in reaction times.

Evidence for the aldol/retro-aldol equilibrium was secured by a competition experiment involving the addition of benzaldehyde to aldol isomer mixture **6ab** under our standard conditions (**Scheme 3**).

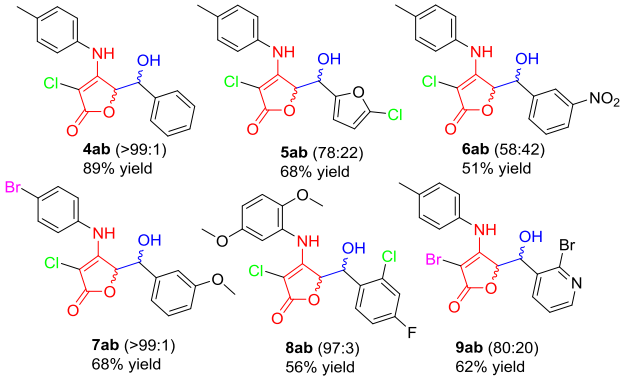
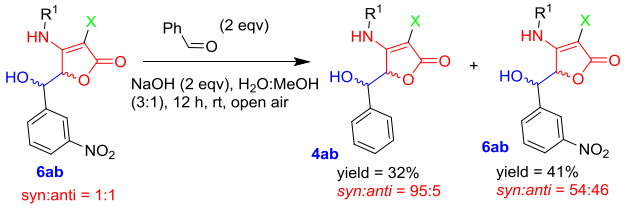


Figure 1. Selectivity and substrate scope of the vinylogous aldol reaction of tetronamides (dr = *syn:anti*)

The structures and stereochemistry of the products were determined by spectroscopic analyses (IR, MS, NMR) and single crystal X-ray crystallography.



Scheme 3. Evidence of the retro-aldol/ aldol equilibration

Conclusions

In conclusion, we have developed a vinylogous aldol reaction of tetronamides with aromatic aldehydes enabling simple, stereoselective access to aldol products in high yields. This methodology could be further modified and applied to the synthesis of new substances endowed with potential pharmacological activity.

Acknowledgements

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