AN APPROACH TO THE SYNTHESIS OF SUBSTITUTED CYCLOPENTENONES WITH POTENTIAL ANTI-INFLAMMATORY ACTIVITY FROM MORITA-BAYLIS-HILLMAN ADDUCT

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INTRODUCTION

The cyclopentenone prostanoids are derived prostaglandin D₂, the latter being a byproduct of the metabolism of arachidonic acid in inflammation. The cyclopentenone core play several biological activities, namely: anti-inflammatory, anticancer and antiviral. Due to the biological importance of this structural motif, we began a research project aimed at synthesizing some potentially anti-inflammatory cyclopentenone derivatives using a Morita-Baylis-Hillman adduct as substrate. So, we described herein a new approach for the construction of substituted cyclopentenone derivatives. These cyclopentenones present in their structures some requirements to deliver anti-inflammatory activity.

RESULTS AND DISCUSSION

Our approach for the synthesis of our target cyclopentenones is based on a rhodium-catalyzed 1,4-addition between a Morita-Baylis-Hillman adduct and a suitable substituted boronate, using a protocol described by Gênet et al (Scheme 1).

This reaction affords α-substituted cinnamate derivatives, in moderate to good yield and high E-selectivity. These derivatives were readily transformed into allylic bromides in two steps. The C2 homologation we need to prepare our 5-membered ring was made using a classical approach. So, the allylic bromides prepared above were used as alkylating agent in a reaction with ethyl malonate, in the presence of NaH. After decarboxylation and hydrolysis the resulting γ-unsaturated acid was used in an intramolecular Friedel-Crafts alkylation to afford the required substituted cyclopentenones in 8 steps and 31% (R = F), 14% (R = SO₂CH₃) and 10% (R = SO₂NH₂) overall yield (Scheme 1).

CONCLUSION

This approach has allowed the synthesis of cyclopentenone derivatives 14-16 in 8 steps. At present the anti-inflammatory activity of these cyclopentenones is under evaluation in experimental models of allergic inflammation and non-allergic by observing the effectiveness of this molecule on the hallmarks of inflammation, namely edema, cell migration, excessive mucus production, and bronchial hyperreactivity chemical mediators.

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REFERENCES