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

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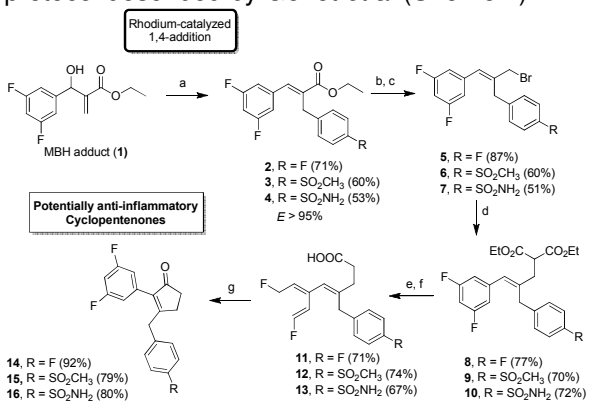
INTRODUCTION

The cyclopentenone prostanoids are derived prostaglandin D_2, 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[1] is based on a rhodium-catalyzed 1,4-addition[2] between a Morita-Baylis-Hillman adduct[3] and a suitable substituted boronate[4], using a protocol described by Gênet *et al* (Sheme 1).



Reagents and conditions: a) $[Rh(cod)Cl]_2$ 1-2 mol%; toluene/methanol ; reflux 3-8h; b) DIBAL-H; CH_2Cl_2; -78°C; 1h; c) CBr_4; PPh_3; $CH2Cl_2$; 0°C - r.t.; 2h; d) Ethyl malonate, NaH; THF; 0°C; e) NaCl; H_2O; DMSO; reflux 18h; f) Ethanol; NaOH 2N; reflux 3h; g) i. DMF; CH_2Cl_2; $(COCl)_2$; 0°C - r.t.; 1h; ii. $AlCl_3$; HCl 1N; 0°C - r.t.; 2h;

Scheme 1. Preparation of target cyclopentenones from Morita-Baylis-Hillman adducts

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 = SO_2CH_3) and 10% (R = SO_2NH_2) 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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