Coumarins from Free *ortho*-Hydroxy Cinnamates by Heck-Matsuda Arylations and their Application in the Total Synthesis of (*R*)-Tolterodine

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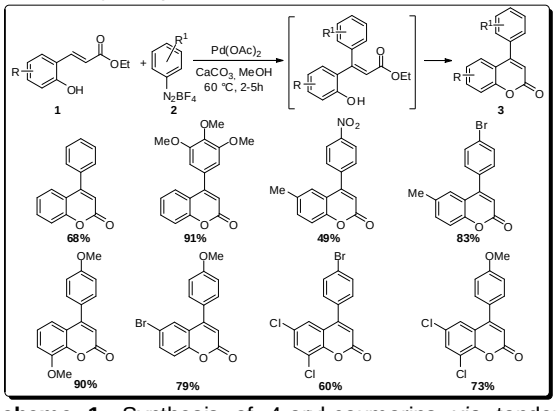
INTRODUCTION

Arylation methods are among the most important reaction types in organic synthesis.[1] In recent years, our group and others have been exploring the palladium-catalyzed coupling of arenediazonium salts to olefins (Heck-Matsuda reaction) as a convenient method to obtain arylated and diarylated compounds of biological and medicinal interest.[2] In this context, coumarins might be considered representative diarylated species of great interest due to their biological properties.[3]

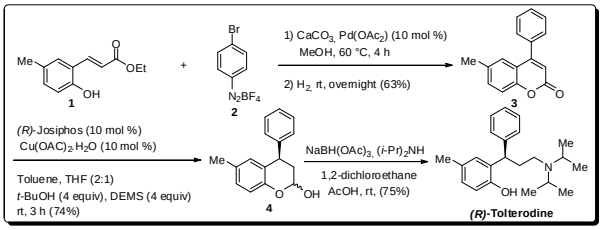
RESULTS AND DISCUSSION

In this work, we describe a method for the synthesis of 4-aryl-coumarins **3** from free *o*-hydroxy-cinnamate ester derivatives **1** and the arenediazonium salts **2** *via* a tandem Heck-Matsuda cyclisation procedure under mild conditions. Many aryldiazonium salts possessing electron-neutral, electron-donating (ED), and electron withdrawing groups (EWG) were well-tolerated under the reaction conditions (Scheme 1).[4] The prevalence of the Heck coupling over the well-known diazonium coupling, leading to azo dyes, is striking since the diazonium coupling is a very facile base-catalyzed process.



Scheme 1. Synthesis of 4-aryl-coumarins *via* tandem Heck-Matsuda arylation/cyclisation.

After this, the generality of this new Heck-Matsuda protocol was demonstrated by a concise and enantioselective total synthesis of *(R)*-tolterodine, an antimuscarinic drug used in the treatment of urinary incontinence[5] (Scheme 2).



Scheme 2. Synthesis of (*R*)-tolterodine.

CONCLUSION

In summary, we have described an efficient, mild, and operationally simple method for the synthesis of 4-aryl-coumarins from free *o*-hydroxy-cinnamate ester derivatives *via* a tandem Heck arylation/cyclisation employing arenediazonium salts under palladium catalysis and aerobic conditions. Furthermore, the 6-methyl-4-phenyl-coumarin obtained in the current protocol was used as an intermediate for a concise (4 steps) asymmetric total synthesis of (*R*)-tolterodine in 30% overall yield and 98% *ee*.

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