

The Game of Synthesis: A Domino Heck-Condensation Reaction for Obtaining Highly Substituted Quinolines from Morita-Baylis-Hillman Adducts

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Abstract

The synthesis of highly substituted quinolines was accomplished through a Heck reaction of substituted 2-iodoanilines with Morita-Baylis-Hillman (MBH) adducts employing Nájera *N*-oxime derived palladacycle as catalyst. The reaction is completely regioselective and gives the products with good to excellent yields (up to 89%) with low catalyst loading (0.5 mol%) and TONs of up to 89.

Keywords: Morita-Baylis-Hillman, Quinolines, Mizoroki-Heck

Introduction

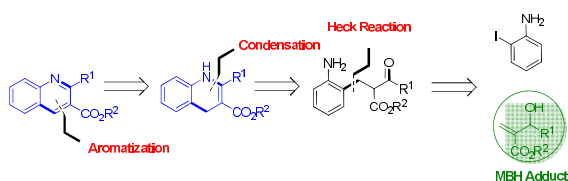
The quinoline ring has been encountered widely among natural products and figures among some commercial drugs.¹

Due to the large interest in this class of molecules for the treatment of various diseases, mainly neglected ones, new methods to synthesize quinolines with diverse substitution patterns have been developed.²

We herein describe the synthesis of 2,3-substituted quinolines, employing a Nájera *N*-oxime-derived palladacycle³ as the catalyst, in a domino Heck-condensation reaction of Morita-Baylis-Hillman adducts with substituted 2-iodoanilines.

Results and Discussion

We started our research based on the fact that, when MBH adducts are used in a Heck reaction catalyzed by Nájera *N*-Oxime derived palladacycle, only 1,3-dicarbonyl compounds are obtained. So we have decided to use 2-substituted iodoaryls, namely 2-iodoanilines, to perform a Heck reaction, expecting that the aniline would condense with the newly formed carbonyl in a condensation reaction that would generate a 2,3-substituted dihydroquinoline, which would then be oxidized to the desired quinolines (Scheme 1).⁴



Scheme 1. Strategy for the Synthesis of Quinolines from MBH Adducts.

To our delight, in the first reaction we performed, we observed that after the domino Heck-Condensation reaction, the aromatization step occurred spontaneously. This might be explained due to the fact that palladium (II) is produced in the Heck reaction catalytic cycle, and this species can act as the oxidizing agent.⁵

After optimization of the reaction conditions, we synthesized seventeen different quinolines to explore the versatility of the method, employing different MBH adducts as well as different 2-iodoanilines.⁶

Conclusions

In summary, we have developed a completely chemo- and regioselective method for the synthesis of 2,3-substituted quinolines in a single step starting from MBH adducts.

The anticancer and antimalarial potential of the quinolines synthesized are being evaluated, as well as the catalytic cycle for the reaction.

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