Control of sequential cyclization-coupling reactions of acetylenic β-dicarbonyl compounds

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Abstract

In this dissertation, I have described the results of three research projects focusing on tandem cyclization/coupling reactions of acetylenated β-dicarbonyl compounds with aryl (pseudo)halides under palladium-catalysis. In the first project, I focused on the synthesis of 2,3,5-substituted furans and 2-benzylidene-dihydrofurans as products of 5-*exo*-*dig* oxocyclization/coupling of internal α-propargylic β-dicarbonyl compounds. The 2-benzylidene-dihydrofurans served as direct precursors to the obtained furans, which I could synthesize under mild reaction conditions. This is particularly significant due to lack of literature reports on the successful synthesis of these compounds within a tandem catalytic cycle involving oxidative addition, cyclization, and reductive elimination. Both methods featured broad scope and excellent functional group tolerance including broad range of electronically varied aryl and heteroaryl bromides. Mechanistic and kinetic studies, as well as DFT calculations concluded the research on this project. During the course of these studies, I observed that 2-benzylidene-dihydrofurans exhibited high reactivity, which I decided to utilize for further functionalizations. The second project involved the development of an unprecedented one-pot functionalization of the in situ formed 2-benzylidene-dihydrofurans to produce 2-alkenyl-furans. The reaction, proceeding via oxidative-dehydrogenation with DDQ as the oxidant, was tested with various β-dicarbonyl compounds and aryl bromides, yielding expected products in high yields. Mechanistic and kinetic studies played a significant role in the project, supporting a reaction's mechanism initiated by hydride abstraction from the 2-benzylidene-dihydrofuran ring followed by deprotonation. Alternative reaction paths, including radical or addition-elimination, were excluded based on mechanistic and DFT studies. During the work on this project, I also investigated other methods of functionalization of 2-benzylidene-dihydrofurans through one-pot transformations. The third project involved designing a method for tandem *5-endo-dig* carbocyclization of terminal α-homopropargylic β-dicarbonyl compounds. The results available in the literature described only tandem *6-exo-dig* oxocyclization of the aforementioned compounds. Use of lithium hydroxide was found to be crucial, most likely due formation of enolate with lithium cation chelating a dicarbonyl system, thereby blocking the oxocyclization pathway. The developed method was tested with various β-dicarbonyl compounds and aryl bromides. I also proposed a complementary reaction procedure using aryl and vinyl triflates, allowing the synthesis of non-trivial, biologically significant derivatives. Mechanistic issues and selectivity of the cyclization were addressed through DFT calculations.