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The Heck reaction applied to the synthesis of Chlorambucil

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Abstract

The Heck reaction plays an important role in organic synthesis because of the versatility of aryl halides and olefins that can be employed. Therefore, a synthetic route to chlorambucil through the Heck reaction was proposed. However, the oxidative addition of the proposed halide to the palladium catalyst was not sucessful. An alternative Heck-Matsuda approach showed better results for the synthesis of a carboxylic acid derivative of chlorambucil.

Key words:

chlorambucil, Heck reaction, redox relay.

Introduction

The Heck reaction was described by Richard Heck at the late 1980s to produce C-C bonds using palladium catalysts. He was awarded the 2010 Nobel Prize in Chemistry with Negishi and Suzuki for their work in cross-coupling reactions.

The main idea of this project was to apply the Heck reaction to the synthesis of chlorambucil (a molecule used at lymphoma treatment) and optimize the catalytic parameters. A retrosynthetic analysis is shown in Figure 1.

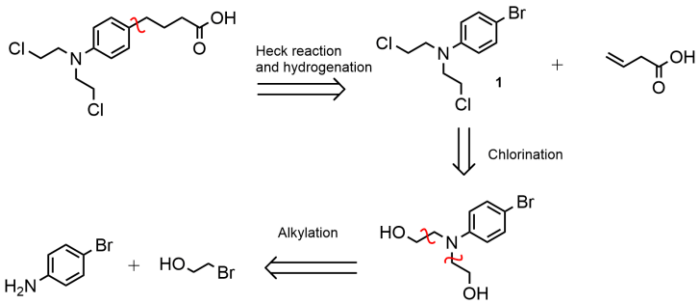

Figure 1. Retrosynthesis of chlorambucil using the Heck reaction.

Results and Discussion

The aryl halide **1** was successfully synthetized (40% yield) and characterized: ^{1}H NMR (500MHz, $CDCl_3$) δ 7.24 (d, J=9Hz, 2H), 6.53 (d, J=9Hz, 2H), 3.63 (t, J=6,5Hz, 4H), 3.54 (t, J=6,5Hz, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 40.1, 53.6, 110.2, 114.1, 144.8, 147.1.

The viability of the oxidative addition of **1** to palladium, followed by migration to the coordinated olefin, was tested using $Pd(PPh_3)_4$ as a catalyst and styrene as the olefin (a standard Heck reaction). The presence of bromine in TOF-MS analysis (Figure 2) of the reaction solution suggested that lateral reactions were favored over oxidative addition.

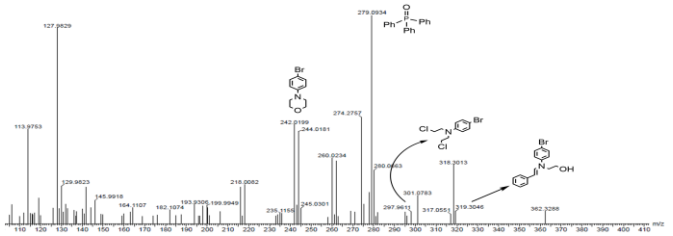

Figure 2. TOF-MS for the Heck reaction of styrene with **1** and $Pd(PPh_3)_4$.

An alternative synthetic route was proposed, using a Heck-Matsuda[1,2] as the first step (Figure 3).

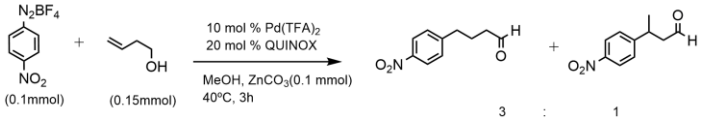

Figure 3. Heck-Matsuda step.

The resulting mixture was then oxidized using the Pinnick oxidation, which is selective for the oxidation of aldehydes with good yields.[3]

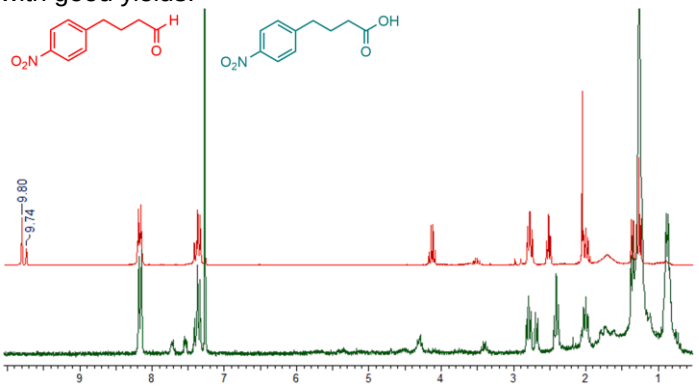

Figure 4. ^{1}H NMR spectra of the mixture of aldehydes and carboxylic acids following the Pinnick oxidation.

Further steps include the reduction of the nitro group of the carboxylic acid followed by alkylation, using the same route employed in the synthesis of **1**, and then, optimize the catalytic step parameters.

Conclusions

The Heck reaction initially proposed was not effective, probably because of the oxidative addition step. The Heck-Matsuda methodology showed good results in the synthesis of an aldehyde derivative of chlorambucil, which will be used in the synthetic route.

Acknowledgements

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