Ireland-Claisen Rearrangements in a Continuous Flow Process

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Abstract

The Ireland-Claisen Rearrangement is a well-known and powerful tool in organic synthesis. It enables the formation of γ,δ-unsaturated acids from their corresponding allylic esters by [3,3] sigmatropic rearrangement. Typically the allylic ester is subjected to a strong base to form the enolate ester, which can then readily rearrange to produce the desired acid.Even though this rearrangement was an improvement from previous Claisen reactions (harsh conditions, low yields), it still employed long reaction times and reagents that required special handling, such as alkyl lithiums and air-sensitive catalysts. To overcome these obstacles, we have utilized continuous flow microreactors to aid in lowering reaction times and minimize handling of reagents. Flow chemistry is an emerging technology that has shown a wide-range of benefits in organic chemistry, such as efficient mixing and heat transfer, increased reaction kinetics, as well as the ability to develop automated variants. Initial results have shown reduced reaction times for the standard rearrangement conditions. Optimizations as well as enantioselective Ireland-Claisen rearrangements in a continuous flow microreactor process will be presented.

Introduction

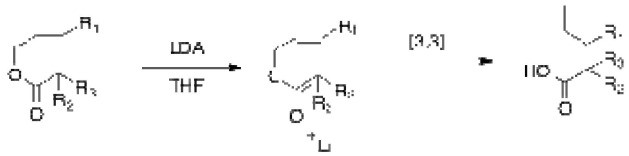


Figure 1. General scheme of the Ireland-Claisen rearrangement

The Ireland-Claisen rearrangement was first reported in 1972 by the late Dr. Robert Ireland.[1] By this time there were a number of other variations of the popular Claisen rearrangement already employed in organic synthesis, such as the vinyl ether[2]and the Johnson orthoester[3], yet the Ireland modification brought the major advantage of easy preparation and subsequent rearrangement of allyl vinyl ethers as their lithium enolates.Initially, unwanted aldol condensation side products were observed due to the unprotected nucleophilic oxygen, yet this was remedied with the addition of trimethylsilyl chloride (TMSCl) to act as a protecting group on the oxygen. This was able to increase the observed yields and make the Ireland-Claisen a stronger tool in organic synthesis.[1]

Other pitfalls of this reaction have been observed though. Time is one of these issues encountered with the Ireland-Claisen rearrangement. Reactions often need anywhere from 10-24 hours[4][5][6], yet it has been demonstrated that flow technology can be used to dramatically reduce lengthy reaction times.[7]Solvents can also play a large effect on the yield and enantioselectivity observed in products. The addition of different metal-chelating solvents along with THF can influence both of these factors. THF alone can produce a *Z*:*E* ratio of 6:94, while THF/45% DMPU can give 93:7, with both giving a 90% yield.[8] Aside from solvent ratios, chiral boron reagents can also be used to promote enantioselectivity. The e.e. of these reactions range anywhere from 90-97%, yet these boron reagents are unpleasant to work with.[9]

We hope to merge the flexibility and wide range of flow technology with the robustness of the Ireland-Claisen rearrangement to develop a process that can serve to provide a simple, rapid, and safe way to utilize this reaction in organic synthesis.

Flow Instrumentation

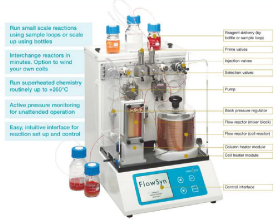


Figure 2. FlowSyn System by Uniqsis

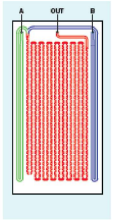


Figure 3. Chip used with FlowSyn, cesigned for two reagents

Figure 4. Detail of staggered oriented ridges used for micromixing within the flow apparatus

Why Go with the Flow??

- Superb heat transfer
- Efficient mixing
- Reaction automation
- *In situ* purification
- Increased reaction kinetics
- Integrated analytical instrumentation
- Green chemistry
- Safely handle dangerous reagents
- Scale up potential

Reaction Scheme & Mechanism

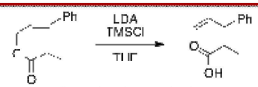


Figure 5. Scheme of synthesis used in FlowSyn system

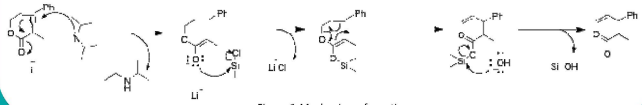
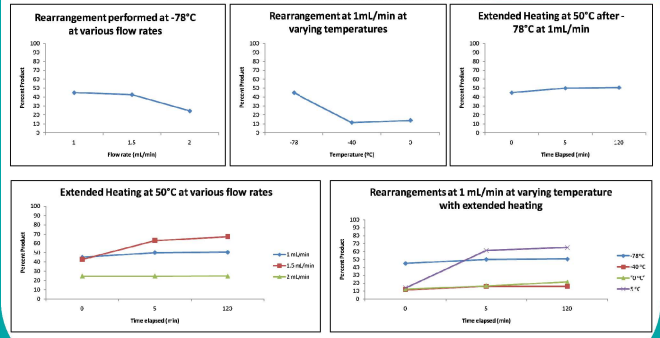
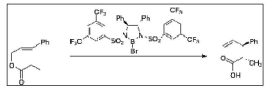


Figure 6. Mechanism of reaction

Results



Conclusion



- Continuous flow microreactor technology enabled a reduction in reaction time, while producing a yield of nearly 70%. Further optimization is under way to increase the reaction yield of this proof-of-principle rearrangement. Once optimized, scope will then be evaluated.
- Flow chemistry has allowed for decreased handling of reactive reagents, such as LDA, and this can be further exploited in varying type of reactions.
- Future plans include exploring the synthesis of new products, as well as the use of chiral boron reagents for enantioselective synthesis of chiral compounds.

Acknowledgments

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