Multi-Component Reactions of Methyleneaziridines using Organozincates

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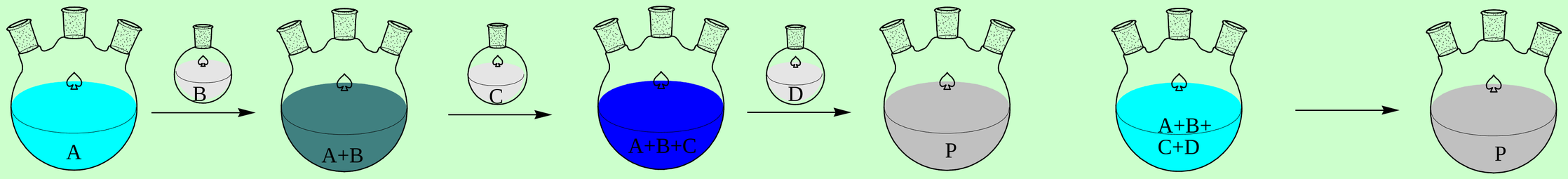
What are Multi-Component Reactions?

The “classic” approach to organic synthesis consists of a series of stepwise reactions, each modification followed by a purification step.



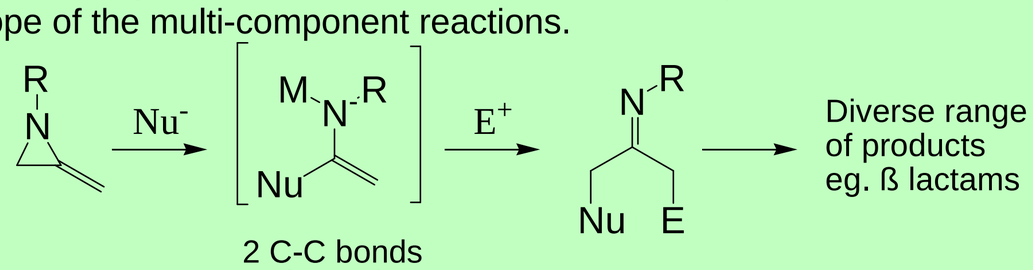
"Classic" Stepwise approach

Multi-Component approach

Multi-Component Reactions (MCRs) are a more direct and efficient approach to chemical synthesis. All the reaction components are combined together in one step saving time and reducing waste by-products.

MCRs at Warwick

At Warwick the MCRs currently studied involve the use of methyleneaziridine with Grignard reagents as the nucleophile, this has limitations upon the chemistry that can be undertaken.
It was thought that the use of a different nucleophile could increase the scope of the multi-component reactions.



2 C-C bonds formed

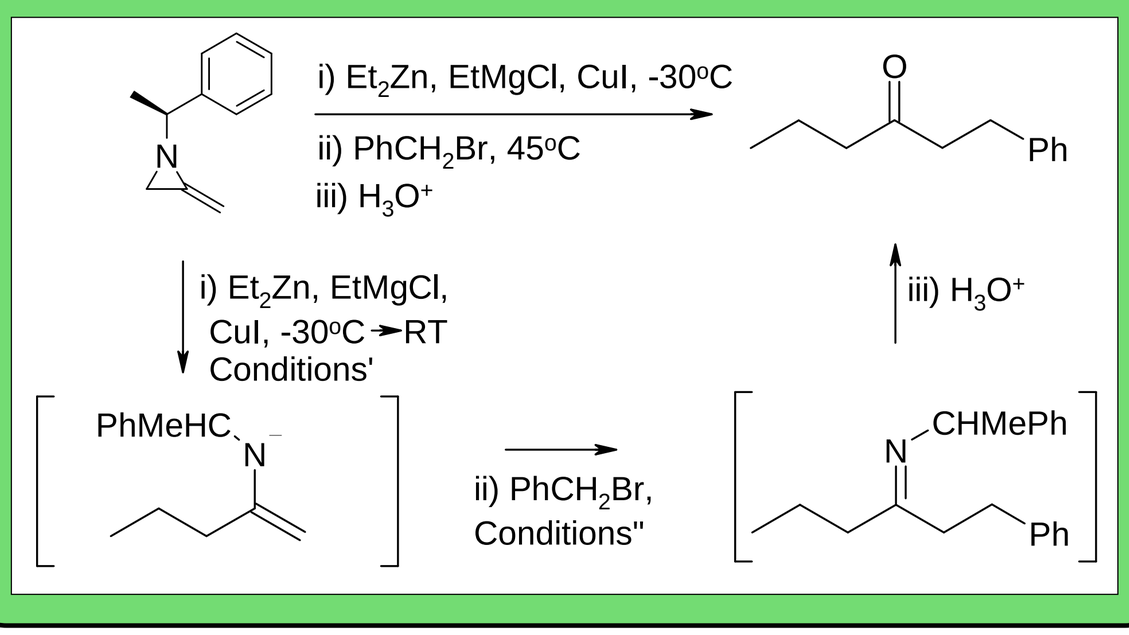
Organozincates

It has been shown that organozincates are very useful nucleophiles, it is thought the difference in the nucleophilicity between the organozincates and the Grignard reagent may affect the selectivity.
Organozinc compounds are reacted with a Grignard reagent to form the organozincate, the intermediates formed are more nucleophilic, which are then added to the methyleneaziridine.

The MCR

After the formation of sufficient methyleneaziridine, it was possible to attempt some multi-component reactions. These reactions take place in one-pot.
Copper Iodide is used as catalyst in the reaction. In this multi-component reaction there were 3 steps:-

- Formation of the metalloenamine, upon addition of the nucleophilic organozincate to the methyleneaziridine.
- Formation of ketimine after addition of electrophile.
- Formation of ketone after acidic work-up.



“Super-Strained” Methyleneaziridines

Methyleneaziridines are strained heterocycles that are extremely versatile intermediates in organic synthesis.
Their synthetic utility lies in the propensity of these systems to undergo ring opening reactions with a wide range of nucleophiles, with the relief of ring strain providing a powerful thermodynamic driving force for chemical reactions.
Methyleneaziridines have an exocyclic double bond. This additional feature makes them “super-strained” by comparison to other aziridines.

Project Aims

The aim of the project was to see if new types of MCRs could be realised. Specifically if organozincate nucleophiles could be used with methyleneaziridines.

Results

A series of experiments were planned to test if the reaction proceeds, this process enabled the alterations of conditions to improve the reaction conditions.

Et_2Zn	EtMgCl	CuI	Conditions’	$PhCH_2Br$	Conditions”	Isolated Yield (%)
-	1	20 mol %	O/N	1.5	6 hrs, 45°C	54
1.1	1	20 mol %	O/N	1.5	6 hrs, 45°C	5-10
1.1	-	20 mol %	O/N	1.5	6 hrs, 45°C	Decomposition
1.1	1	-	O/N	1.5	6 hrs, 45°C	Decomposition
1.1	1	50 mol %	O/N	1.5	6 hrs, 45°C	-
1.1	1	20 mol %	36 hrs	1.5	6 hrs, 45°C	-
1.1	1	20 mol %	6 hrs	1.5	6 hrs, 45°C	-
1.1	1	20 mol %	O/N	1.5	O/N, 55°C	18
1.1	1	20 mol %	O/N	1.5	O/N , 65°C	25

Table 1

Column chromatography was used to separate the product from unwanted side products. In some cases product was seen but not isolated, as a result the value isn’t quoted.

Conclusions

The results show that organozincate nucleophiles can be used in MCRs, albeit in low yields.
Use of elevated temperatures for prolonged times after the addition of the electrophile leads to an improvement in isolated yield. This suggests that the alkylation step is slower when the metalloenamine is zinc based.
In the 10 weeks in which I was involved in the URSS, I felt this scheme gave me an excellent chance to experience academic research, including a project where I was able to develop many research skills, which I enjoyed greatly.

Acknowledgements

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References

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