Synthesis of β-lactams from multicomponent reactions of methyleneaziridines.

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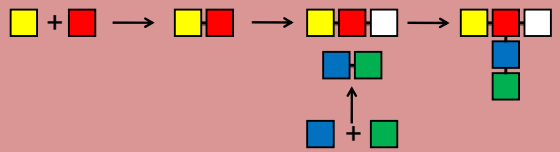
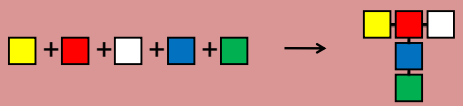
Multicomponent Reactions

Traditionally, total synthesis of a chemical compound consists of a series of stepwise reactions, each performing one modification to the molecule followed by a purification procedure.



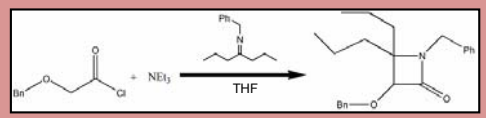
In a multicomponent reaction, all reagents are added sequentially to the same reaction mixture. Obtaining a final product with no isolation or purification of any intermediates is clearly a highly desirable method for organic synthesis.



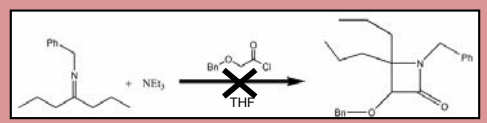
Analogous Imine Experiments

The solvent used for the multicomponent reaction was the first problem to overcome. Forming the imine from the aziridine takes place in tetrahydrofuran[1], while the Staudinger reaction is shown to work in dichloromethane.[2]

Using an analogous imine and benzyloxyacetyl chloride, the cycloaddition was shown to work in tetrahydrofuran providing that the imine was added to premixed acid chloride and base.

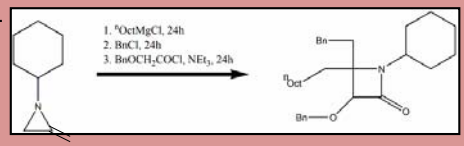


Addition of acid chloride to a mixture of base and imine gave the incorrect product, so the ketene clearly needs to be preformed before exposure to the imine when performing this reaction in tetrahydrofuran.



Analogous Multicomponent Reactions

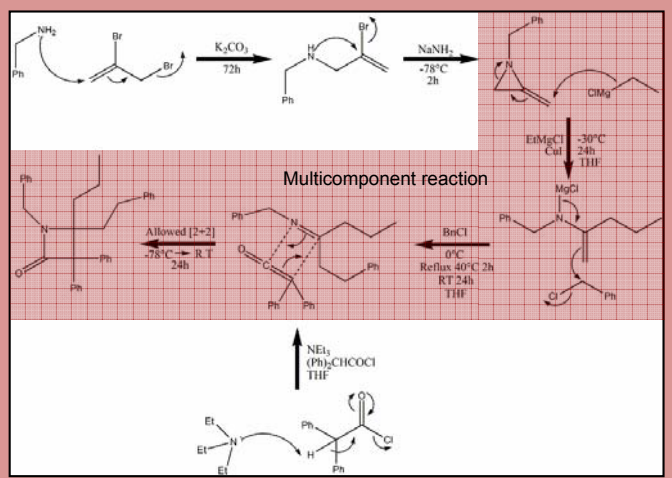
An analogous multicomponent reaction using cyclohexyl methyleneaziridine, ^{n}Octyl magnesium chloride and benzyl chloride showed evidence of lactam formation in NMR, ESMS and IR. A further analogous multicomponent reaction failed when the mixture stopped stirring over a weekend and produced several by-products. No lactam was shown by ESMS.



At this point, it was decided that focus should switch to making benzyl methylene aziridine and the target synthesis.

Unfortunately, the aziridination took several weeks to produce a useful yield of clean benzyl methyleneaziridine. By which time it was impossible to complete a multicomponent reaction with it as each reaction takes 3 days to perform and only 2 days of lab time remained.

Target Synthesis



Aziridination

The acyclic precursor used was particularly difficult to cyclise and proved to be the most problematic step of the synthesis. This molecule was chosen due to the ease with which the benzyl group could be removed from the nitrogen after formation of the lactam. The experiments performed are summarised below. All reactions are performed at -78°C.[3]

Substrate (mmol)	Ammonia$_{(l)}$ (ml)	Sodium$_{(s)}$ (molar equivalents)	Reaction time (h)	Result
4.4	50	2.3	1	Aziridine + Starting Materials
4.4	50	5	2	Aziridine (11.8%)
13.2	150	5	2	Side Products
2.2 Distilled	50	5	1.5	Aziridine + Side Products
6.6 Distilled	100	5	2	Aziridine + Side Products
4.4 Distilled	100	5	2.5	Aziridine (33%)

It was essential that the crude was mostly clean of side products and starting materials or it was impossible to purify as the aziridine decomposes on silica and the contaminants distilled out with the aziridine.

Conclusions

Although the target synthesis was never attempted due to the time constraints of the project, the analogous experiments show promise for this reaction.

Diphenylacetyl chloride was proposed for this synthesis in order to eliminate a stereocentre on the lactam ring, so that the molecule would not exist as a pair of diastereoisomers and as such, a single product could be isolated, making this an elegant method for β-lactam formation.

The difficulty in cyclising the acyclic precursor proved to be the only problematic reaction, but each cyclisation reaction took a full day to perform and a further one to analyse and possibly purify the product which all added up to be a significant amount of time.

The next step as regards the future of this synthesis is further investigation to optimise the cyclisation and experimentation with the parameters of the multicomponent reaction to form the lactam cleanly.

References

1. Hayes J, Shipman M, Twin H. *J. Org. Chem.* **2002,** *67,* 935-942.
2. Palomo C. et al. *J. Org. Chem*. **1997**, *62*, 2070-2079.
3. Shiers J. *PhD Thesis*. **2005.** University of Warwick.

Acknowledgements

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