Diels-Alder/Ene Reactions as an Approach to Anti-Cancer Drugs

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1. Introduction and Aims

The overall aim of this project was to investigate Diels-Alder/ene reactions of 2-vinyl indoles with the target of synthesising analogues of the **kinase** inhibitor, granulatimide[1](kinases are enzymes that play a major role in the phosphorylation of proteins). Such compounds may be candidates as anti-cancer drugs.

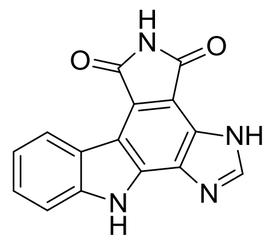


Figure 1: Granulatimide

Granulatimide has been shown to inhibit the Chk1 kinase, an enzyme playing a pivotal role in the G2 **cell cycle checkpoint**. Cell cycle checkpoints are mechanisms activated after damage to DNA to regulate cell division. Many cancerous cells have a defective G2 checkpoint and so they continue to divide when they should not[2]. Hence inhibition of Chk1 can halt the growth of tumours because the cells cannot progress to the next stage in cell division, leading to cell death.

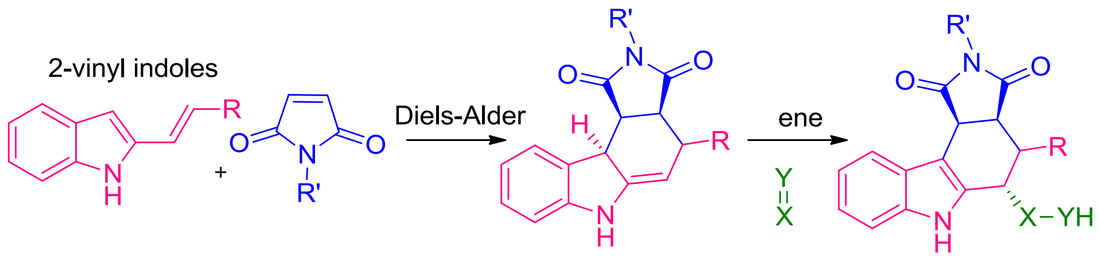


Figure 2: General reaction scheme proposed for the synthesis of granulatimide analogues

However, in order to carry out the Diels-Alder/ene reactions, a quick way of making 2-vinyl indoles had to be found.

2. Chemistry Background

Functional Groups

Functional groups are a collection of atoms within a molecule that determine its chemical reactivity. Generally a particular functional group will undergo similar reactions regardless of what the molecule is.

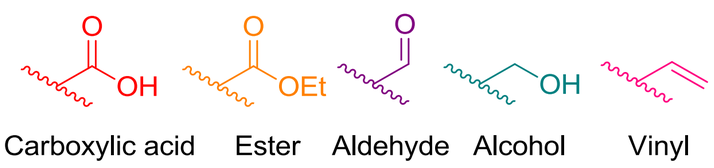


Figure 3: Examples of functional groups

2-vinyl indoles are so named because they have a vinyl functional group at the 2 position of the indole ring.

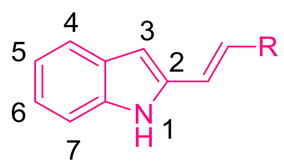


Figure 4: Structure and numbering system of 2-vinyl indoles

Product Analysis

Nuclear Magnetic Resonance (**NMR**) spectroscopy was used to determine the structure of the compounds made throughout the project. When a magnetic field is applied, certain atoms within a molecule **resonate** at different frequencies depending on their chemical environment. This allows us to work out what features are present in the compound.

Product Purification

Column chromatography was used to purify products. The mixtures were passed through silica gel. The products formed different strength interactions to the silica gel compared to the impurities and so they passed through it at **different times**, allowing the two to be separated.

3. Reactions

Hydrogenation of Potassium Salt

This was an attempt to make indole-2-ethyl ester with the intention of converting it to 2-vinyl indole.

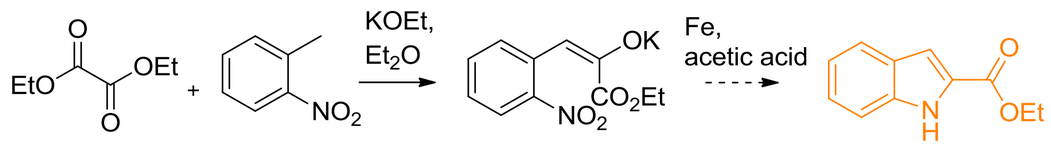


Figure 5: Reaction scheme for the synthesis and hydrogenation of the potassium salt

We used a different method to that reported in the original 1960s paper to avoid using hydrogen gas which is extremely flammable.

Work on Indole-2-carboxylic acid

We then started work on indole-2-carboxylic acid which was readily available. Figure 6 shows the route we took.

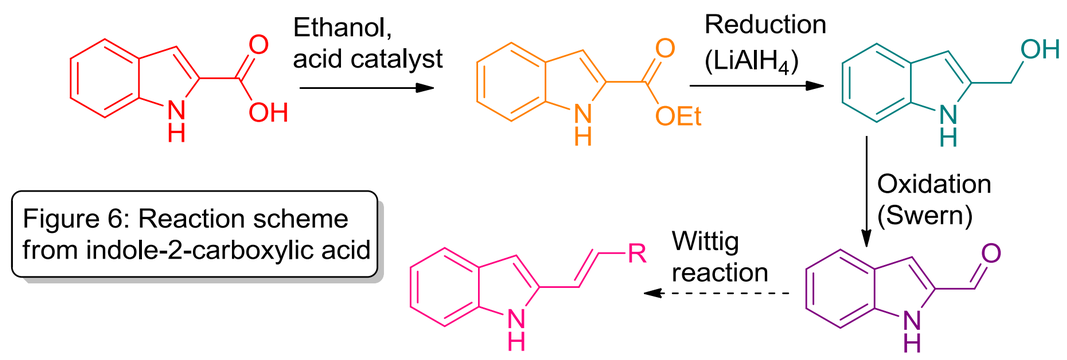


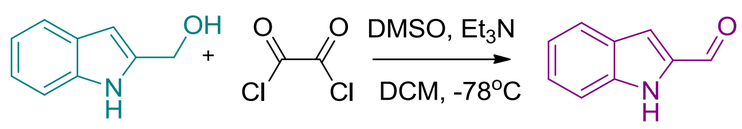
Figure 6: Reaction scheme from indole-2-carboxylic acid

Green Chemistry

Oxidation reactions to achieve aldehydes are notoriously tricky. Originally we decided to try the **Swern** oxidation because the product is easy to purify and it is less hazardous than using chromium based reagents.

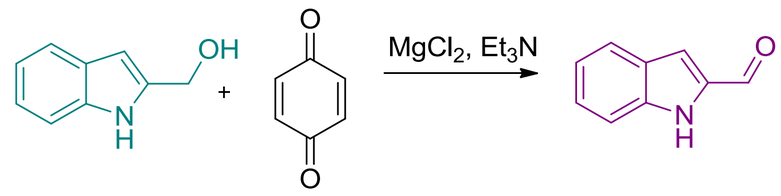
From the reaction scheme it is obvious that this is not the most environmentally friendly reaction as it requires the maintenance of a low temperature. Also DMS is generated which is a toxic gas that smells horrible.

Figure 7: Reaction scheme for the Swern oxidation



We therefore decided to try a novel **Oppenauer** oxidation which uses cheap, non-toxic materials and does not require such energy consuming conditions.

Figure 8: Reaction scheme for the Oppenauer oxidation



It also uses a non-toxic metal catalyst which is not damaging to the environment. This is advantageous compared to other common oxidation reactions that use toxic chromium metal.

4. Findings and Future Work

The **hydrogenation of the potassium salt** did produce indole-2-ethyl ester. However, a side product was also produced that was too chemically similar to the desired product for them to be easily separated via chromatography. Therefore this work was discontinued.

Work on indole-2-carboxylic acid produced the most promising results. The conversion of the acid to the ester was very successful with high product yields. The reduction of the ester achieved the alcohol in a high yield also.

The **Swern** reaction did produce aldehyde but more purification of the product would be required.

The novel **Oppenauer** reaction produced some aldehyde. More experiments were tested using different solvents to try and improve the reaction to make it synthetically useful as the original reaction took several days and led to an impure product. Some improvement was seen. In the future, more work could be carried out to perfect the Oppenauer oxidation and to test other oxidation methods to achieve the aldehyde. Subsequently the Wittig reaction could be carried out to make 2-vinyl indoles, followed by Diels-Alder/ene reactions to make the granulatimide analogues.

5. Acknowledgements

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References

1. Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, l.; Roberge, M.; Moreira da Rocha, R.; Andersen R. J.; *J. Org. Chem.*, **1998**, 63 (26), 9850
2. Deslandes, S.; Chassaing, S.; Delfourne, E.; *Mar. Drugs.,* **2009**, 7, 754