Sustainable Fluorination in a Green Solvent

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Abstract

The following project was funded by the University of Lincoln's UROS programme, allowing undergraduate students to work alongside academics to gain experience as co-researchers on a live project. Chemical solvents are a key contributor to environmental pollution but are also essential on a large scale in many industries. Fluorination reactions are hugely significant in the pharmaceutical industry and require the use of polar aprotic solvents. These are non-renewable and some of the most toxic solvents available, such as Nmethyl-2-pyrrolidone (NMP), dimethylformamide (DMF) and dimethyl sulfoxide (DMSO). As a result, this projects aim was to conduct fluorination reactions using non-toxic alternatives such as dihydrolevoglucosenone (Cyrene), cyclopentanone and y-valerolactone (GVL). NMR spectroscopy was used to determine the extent of conversion and to analyse the purity of the compound at various stages. This was performed using varying conditions to identify the best conditions for significant conversion, which can then be refined in future research. As the temperature was increased, Cyrene thickened and eventually solidified, making it unusable at most of the trialled temperatures. Cyclopentanone only showed conversion in one of the three attempted reactions with a high yield and multiple impurities. It was concluded that GVL showed the best results as an alternative and will therefore be pursued further by Dr Graham Pattison and his research group.

Keywords: Fluorination, Sustainability, Green Solvents, Alternatives, NMR Spectroscopy.

Introduction

This project was conducted through the Undergraduate Research Opportunities Scheme (UROS), which provides students at the University of Lincoln the opportunity to gain experience working on research projects with academic staff. The area for this project was green chemistry with the aim of reducing the environmental impact of chemical synthesis without compromising the effectiveness. Fluorination reactions will be the focal point of this project, due to their widespread use within the pharmaceutical industry. It is known that at least 20% of commercial pharmaceuticals contain a fluorine atom (Inoue, Sumii & Shibata, 2020), and creating these products requires large quantities of typically toxic solvents. The project aim is to conduct successful fluorination reactions using environmentally friendly solvents and identify the conditions for the highest crude yield.





The chosen green solvents are dihydrolevoglucosenone (Cyrene), cyclopentanone and γ -valerolactone (GVL) as they are all polar aprotic, making them similar to the typical solvents for this type of reaction. As a chemistry student with an enthusiasm towards organic chemistry, this research has a direct link to my professional aspirations. Taking part in this project has enhanced both my laboratory competency and my knowledge which I hope to apply in the future within a workplace.



Project Background

The pharmaceutical industry has the highest waste generation and amount of organic solvents used per mass of product produced for any commercial sector (Slater, Savelski, 2007). Polar aprotic solvents are usually the best solvents for fluoride-assisted reactions (Clark, 1980) and many such as NMP, DMF, DMAc and more are known to be highly toxic. These are difficult to produce renewably due to the scarcity of natural molecules that are polar and lacking hydroxyl groups (Komarova, Dick & Luterbacher, 2021). As a result, typical waste from drug manufacture contains a significant quantity of solvents that are non-renewable and environmentally damaging.

Cyrene is formed from a two-step synthesis using biomass, most commonly cellulose, which is converted into levoglucosenone (LGO) using pyrolysis and can then be hydrogenated into Cyrene (Camp, 2018). Similarly, GVL can be synthesised from nonedible vegetable matter, also called lignocellulosic biomass which includes cellulose, hemicellulose and lignin (Liguori, Moreno-Marrodan & Barbaro, 2015). Furthermore, cyclopentanone can be obtained by hydrogenation of furfural and 5-hydroxymethyl furfural which are derived from biomass (Hronec, Fulajtarová, 2012). These green solvents have substantially lower toxicity and reduced environmental effects, which could be hugely beneficial to the environment if they can be utilised

industrially. This is relevant to my studies because it allows me to further practice the techniques that I have learnt in my undergraduate laboratory sessions and apply them to a different area of chemistry.

Literature Review

A variety of fluorination reactions with a likeness to this research have been investigated previously. For the methodology, potassium fluoride was used as the fluorinating agent at temperatures between 80-200 °C, and some of the reactions required either DMSO or DMF as the solvent (Hall, 1997). Additional research further emphasised that fluorination reactions "generally require forcing conditions (>130 °C for >12 h)", as well as an electron withdrawing substituent on the substrate for stabilisation (See et al., 2020). This research also utilised a multitude of toxic solvents such as DMSO, sulfolane, THF, DMF and MeCN to conduct their work, which further highlights the need for safer alternatives. The reaction conditions used in these papers have many similarities, which contributed to the formation of the methodology for this project.

Previous research has also already explored using Cyrene as a green alternative. For example, (Zhang et al., 2016) used Cyrene to replace DMF for MOF synthesis, however they still used DMF as a wash solvent. The results show a 35% yield when using Cyrene which is identical to DMF, indicating that Cyrene has been an appropriate substitute in some cases. GVL has also been trialled previously as a renewable alternative for the Hiyama reaction (Ismalaj et al., 2014). Using GVL, yields of 74-94% were obtained for several biaryls and it was concluded to be an 'efficient medium' for this reaction. In addition, GVL has been used in phosphatidylserine synthesis with yields up to 95%, a fast initial reaction rate and minimal side product formation (Duan, Hu, 2012). Cyclopentanone has been researched before as a probe for IGC analysis of poly (2,2,2-trifluoroethyl methacrylate) amongst other solvents (Papadopoulou, Panayiotou, 2014). The results showed that cyclopentanone was a 'moderate' solvent in the examined temperature range of 120-150 °C, which is similar to the desired reaction conditions for this project.

Methodology





Br





2-bromoacetophenone

2-chloro-5-nitropyridine Figure 3: Structures of reactants for fluorination

The reactants above were fluorinated using cyclopentanone, Cyrene and GVL as the solvents at various temperatures from 100-200 °C. The reactant (2 mmol), KF (4 mmol) and solvent (5 ml) were each measured into a round bottom flask. An air condenser was attached to each round bottom flask and the reaction mixtures were left to heat overnight for approximately 20 hours whilst stirring. After this, the reaction mixtures were allowed to cool to room temperature and poured into a separating funnel for a liquid-liquid extraction with water and ethyl acetate. The subsequent organic layer was collected and dried using magnesium sulphate, and volatiles were removed in vacuo. After this process, a ¹H-NMR spectrum was obtained for each solution and used to determine whether any conversion had occurred. This was done by identifying the chemical structure of the product using the NMR spectrum and deciding whether the bromine and chlorine were still present.

When using GVL at 150 °C, a further attempt was made to isolate the fluorinated compound. After the NMR was conducted, thin layer chromatography (TLC) was performed using each solution to determine the number of compounds within them. TLC shows the number of components present by spotting the solution onto a silicacoated plate and partially immersing the plate in a solvent. Each compound moves up the plate at a different speed based on its chemical structure, resulting in a distinct spot for each. The 2-(bromomethyl)naphthalene solution showed the presence of 3 compounds and was mounted onto the auto column. The obtained fractions from the auto column that contained the same compound were combined in a round bottom flask and reduced under a vacuum, weighed to calculate the yield and identified using NMR. The 2-bromoacetophenone solution showed 2 compounds, so was mounted onto a manual column. The solutions from the manual column were tested using TLC to identify which contained the desired product. Those containing the product were combined in a round bottom flask and reduced under a vacuum to remove the remaining solvent. The product of this was weighed and made into an NMR sample which was used for both ¹H and ¹⁹F NMR spectroscopy. Using these two spectra, it can be confirmed whether the conversion and purification have been successful. This is because the desired C-F bond can be observed using ¹⁹F-NMR and this is further confirmed by the absence of a CH-Br bond in the ¹H-NMR spectrum. Also, ¹H-NMR can be used to identify any impurities in the mixture due to the presence of unexpected or unexplainable peaks.

Results

Cyrene was found to be an unsuitable solvent for all the fluorinations as it was unable to withstand the reaction temperatures. At 100 °C, the ¹H and ¹⁹F NMR spectra showed very minimal conversion of 2-chloro-5-nitropyridine and zero conversion of 2-(bromomethyl)naphthalene. As the reaction temperature was increased, the Cyrene became thicker and increasingly difficult to remove from the reaction mixture. At 200 °C, the Cyrene solidified and the reaction mixtures were unable to be analysed. As a result, these round bottom flasks were cleaned using a base bath and the reaction mixture was discarded. This outcome has also been found previously, especially when inorganic bases were present in the reaction mixture (Wilson et al., 2016). This

study determined that certain reaction conditions can lead to the formation of two different aldol products, as well as gelation or complete solidification of the reaction. Therefore, Cyrene is suggested to display sensitivity to different bases and temperatures, making it incompatible with the chosen reaction conditions.



Figure 4: Structures of aldol products from Cyrene (Wilson et al., 2016, p. 2007).

Cyclopentanone was investigated at 150 °C for all three substrates but only showed conversion of 2-bromoacetophenone. The ¹H NMR gave an approximate yield of 76%, however the reaction mixture still contained multiple unidentified impurities after the liquid-liquid extraction. This indicates that the true yield is much lower than what was calculated, and not being able to identify the impurities means that an appropriate method could not be determined to remove them. As a result, the desired product was unable to be isolated and the fluorination was not re-attempted.

The results acquired using GVL showed the highest potential and will be pursued further by Dr Graham Pattison in the future, therefore they currently cannot be disclosed. Conversion of 2-chloro-5-nitropyridine was unsuccessful at all temperatures, however 2-bromoacetophenone and 2-(bromomethyl)naphthalene did show promising yields from their crude and purified reaction mixtures. There is a general trend shown in the crude yields of the compounds, which will be utilised in future work to form a more refined methodology.

UROS Experience

A clear benefit of my UROS project was how much being part of the research increased my confidence and experience within the laboratory. Due to the nature of my project, I had to conduct ¹⁹F NMR and learn how to interpret the spectra, which I had no prior knowledge of. As well as this, to obtain my pure compound I had to use column chromatography both manually and using the automatic machine. This was a method that I knew of but had never performed myself, so the project has broadened by competency within the laboratory for using different techniques. I was responsible for data collection for this research project within the allotted timeframe, therefore I had to manage my time efficiently. This all had a positive impact on my time management skills within the laboratory, as well as my problem-solving skills for when things went wrong and had to be swiftly resolved to maintain my schedule.

Working with both academics and a PhD student during my project really helped me to learn from their expert knowledge and advice on my project area and built professional relationships. Their assistance has been key for my understanding of how to plan, conduct and interpret a research project, which will benefit me for future work. I am entering my third year of university and will have to lead a project in a similar manner for my dissertation, so UROS has allowed me to become familiar with this process in advance.

Additionally, my undergraduate course requires laboratory reports to aid understanding of the practical sessions. These are written in a similar format to this journal paper, enabling me to further develop my academic writing skills, which I can apply to my work both within and after university. My project emphasis on green chemistry has sparked my interest in this sector. I have studied and been fascinated by sustainability previously from a geographical point of view but have never applied this to chemistry. Having the opportunity to explore this interest from a chemistry perspective has shown me the extensive possibilities that exist within this research area. As a result, it has inspired me for potential career options that are available in the future and has given me greatly beneficial academic and laboratory experience.

Conclusion

From this project we can conclude that green solvents do have the potential to replace the toxic, non-renewable solvents currently being utilized within the pharmaceutical industry. For Cyrene to be a viable alternative, the methodology needs to consider the sensitivity of the reaction mixture to prevent solidification. Cyclopentanone did show positive results for 2-bromoacetophenone, which may be improved with further analysis to identify and reduce impurities. Research using GVL will hopefully be continued due to its promising results and eventually lead to a positive application. As well as this, there is previous literature for all three solvents that emphasizes their potential as they have been effective for a variety of processes already. This highlights that despite cyclopentanone and Cyrene not showing immediate success for fluorination, they have shown promise for other chemical reactions. Overall, this preliminary work has provided an adequate foundation for research into sustainable fluorination that can be developed in the future.

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