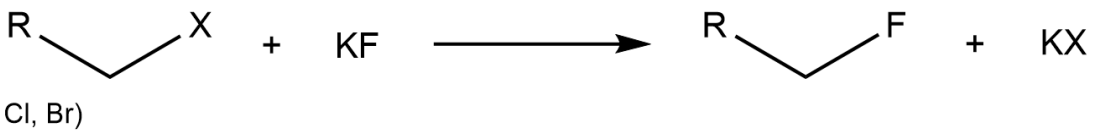
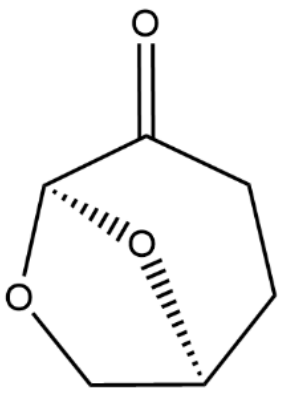
Sustainable Fluorination in a Green Solvent

Introduction & Aim

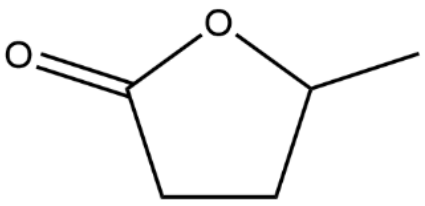
Fluorination reactions are prominent in pharmaceuticals with at least 20% of commercial drugs containing a fluorine atom (Inoue, Sumii & Shibata, 2020) but they are conducted using large quantities of typically toxic solvents. The project aim is to conduct fluorination reactions using the environmentally friendly solvents shown below. Conversion was analysed and calculated using Nuclear Magnetic Resonance Spectroscopy (NMR).



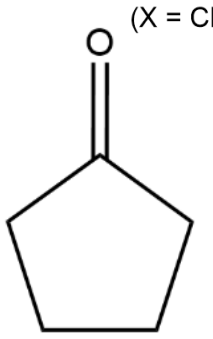
Solvents:



Cyrene



GVL



Cyclopentanone

Methodology

- Reactant (2 mmol), KF (4 mmol) and solvent (5 ml) were left to heat in a round bottom flask overnight (approx. 20 hours) whilst stirring with an air condenser attached
- The temperatures used were 100, 150, 180 and 200 °C
- The solution was cooled and separated via liquid-liquid extraction
- The organic layer was dried, and solvent was removed using a rotary evaporator
- The solution was analysed using NMR
- When using GVL at 150 °C, the solutions were purified using column chromatography
- Following this, another NMR spectra was obtained

Results & Discussion

Results table showing crude yields:

	Cyrene	Cyclopentanone
100 °C 2C5NP	Minimal	N/A
100 °C 2BMN	None	N/A
150 °C 2C5NP	N/A	None
150 °C 2BMN	N/A	None
150 °C 2BAP	N/A	76% + impurities
180 °C 2C5NP	N/A	N/A
180 °C 2BMN	N/A	N/A
180 °C 2BAP	N/A	N/A
200 °C 2C5NP	N/A	N/A

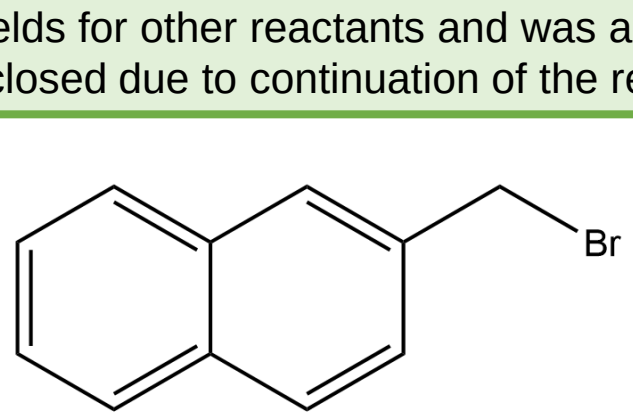
Cyrene:

- As the temperature increased, the solution thickened and solidified
- The solution was unusable for any experiments above 100°C

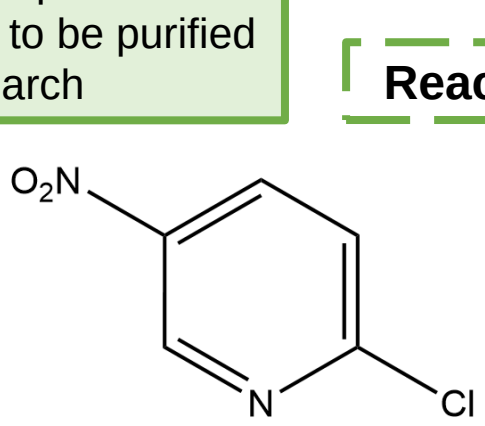
GVL:

- No conversion of 2-chloro-5-nitropyridine at any of the temperatures
- Showed the best yields for other reactants and was able to be purified
- Data cannot be disclosed due to continuation of the research

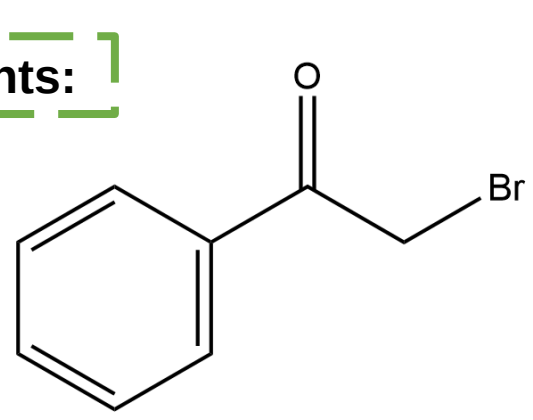
Reactants:



2-(bromomethyl)naphthalene



2-chloro-5-nitropyridine



2-bromoacetophenone

Conclusion

GVL showed the most potential as a green alternative due to its satisfactory yields and the ease of purification of the reaction mixture compared to the other solvents. As a result, it will be researched further by Dr Graham Pattison.

Reference: Inoue, M., Sumii, Y. & Shibata, N. 2020, "Contribution of Organofluorine Compounds to Pharmaceuticals", ACS Omega, vol. 5, no. 19, pp. 10633–10640.

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