Implementation of in-line analysis using two different types of flow reactors: a way to minimize waste and time

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Introduction

This minor research was part of the Light-up Project, trying to provide an optimal setup using two different flow reactors (Labtrix and Kiloflow) to analyse the Hantzsch synthesis in-line with IR, H-NMR and UV-VIS. The research was conducted by Zuyd hogeschool and partners*.

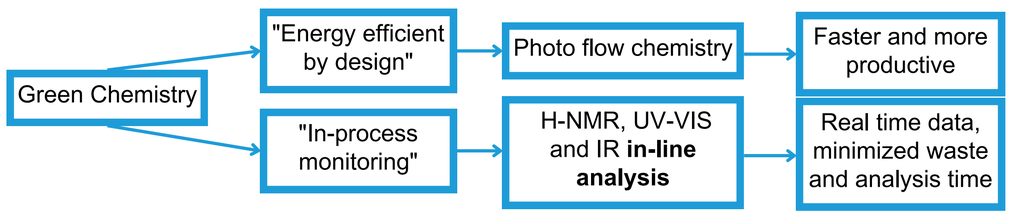

Figure 1. Context and justification of the research

The Hantzsch Synthesis is an important reaction for the pharmaceutical industry, since it allows the synthesis of commercial drugs in less steps when compared to other alternatives.

Materials and methods

The general method consists of preparing the reagents solutions at the desired concentration and pumping them separately with the specific pump through the used reactor (Labtrix or Kiloflow). The three used set-ups are shown in figures 3 to 5.

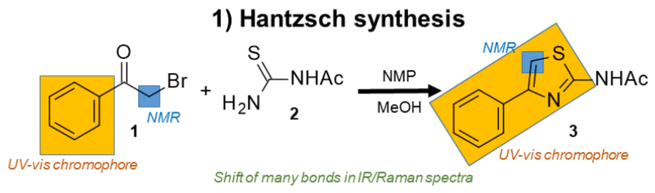

*Figure 2. Hantzsch Reaction scheme. **1**: 2-bromoacetophenone; **2**: N-acetylthiourea; **3**: 2-acetamido-4-phenylthiazole*

Figure 3. Labtrix set-up with in-line UV-VIS

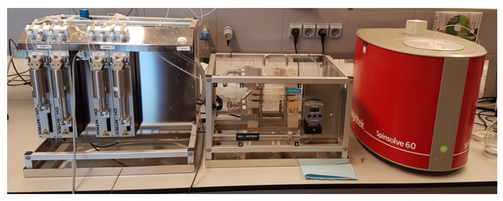

Figure 4. Kiloflow set-up with in-line H-NMR

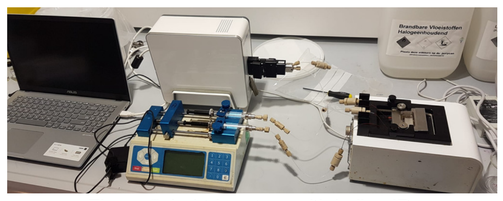

Figure 5. Labtrix set-up with in-line IR

Results

A full IR spectra overlay of reagents, product and solvents show separate peaks, indicating that is possible to follow the reaction using this technique when using the correct solvent.

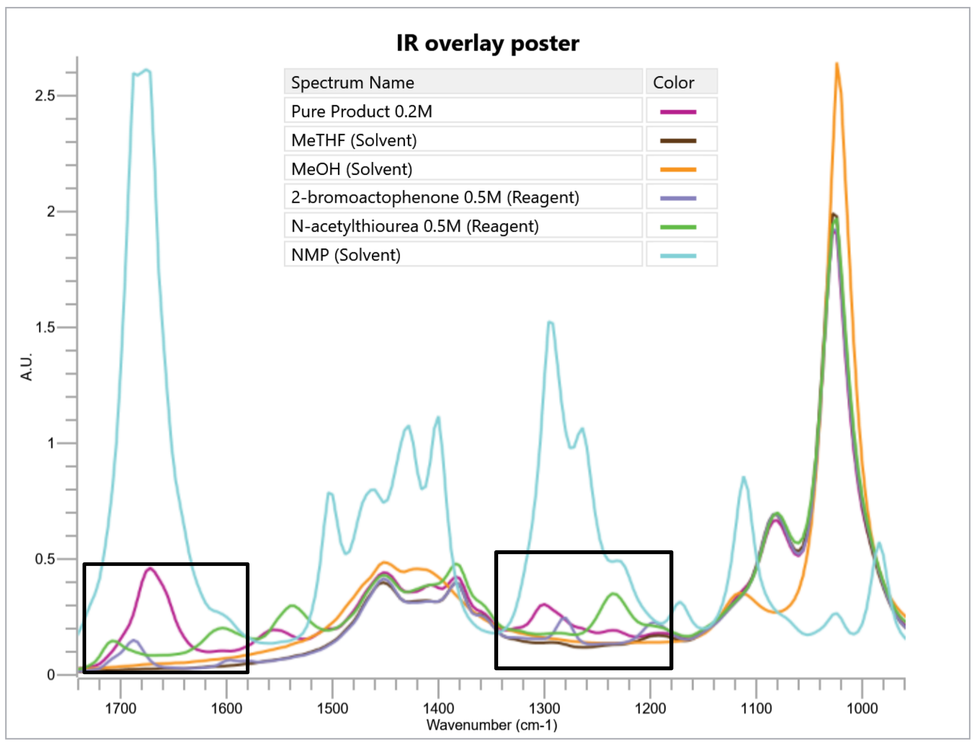

Figure 6. Spectra overlay with reagents, solvents and product

Results

A test was conducted to see the effects of different flow rates on the H-NMR. The comparison shows that some peaks can be measured at low flow rates but not at higher ones.

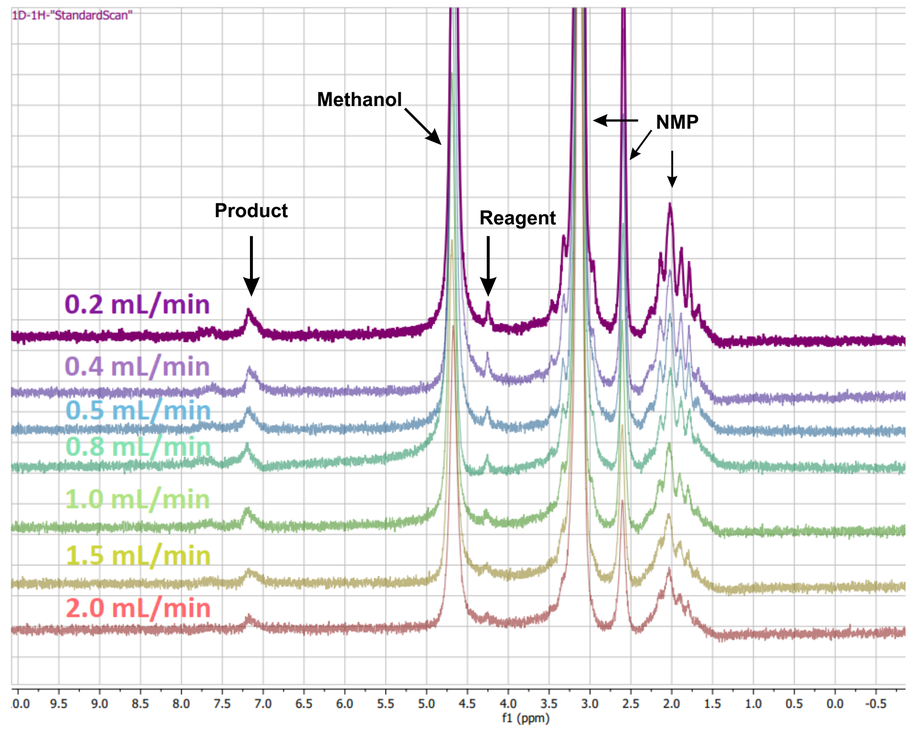

Figure 7. In-line H-NMR measurements of a reaction at 0.5 M at different flow rates

By changing the settings from the H-NMR software, i.e., acquisition time, number of scans and repetition time, a readable flow measurement can be done without needing to stop the reaction or to take samples.

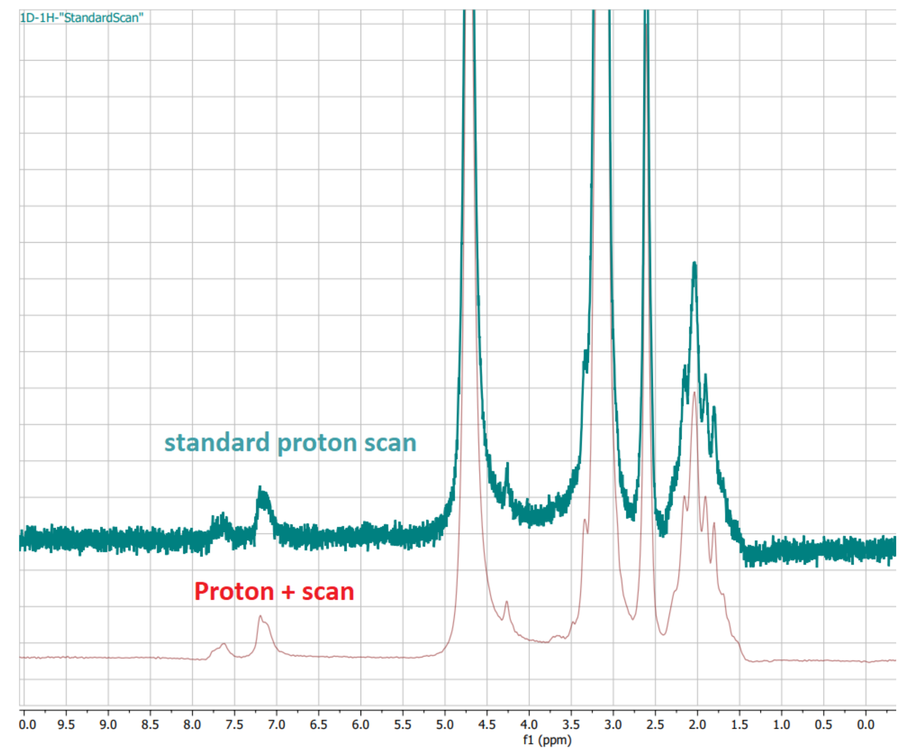

Figure 8. Comparison between an H-NMR measurement done with the standard proton scan and one done with the proton + scan. Both measurements were done with reagents at 0.5M and 0.5 ml/min

Conclusion

- It is feasible to analyse the Hantzsch synthesis in-line with UV-VIS, IR and H-NMR, which shows promising possibilities for efficient and cost-effective monitoring

Challenges:

- Readable concentration
- Influence of flow rate
- Solvents with overlapped signals
- Formation of the intermediate product instead of the product

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