

Selective Grignard Addition to Dialkyl Oxalates: A Flow Chemistry Approach

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INTRODUCTION

During the production of an intermediate of a major product of Bayer CropScience Schweiz AG in Muttenz, Switzerland, a side compound is formed that lowers yield and removal requires intensive workup. In the reaction the Grignard reagent **2** reacts with dialkyl oxalate **1** to an α -keto ester **3** (Fig. 1). Currently a semi-batch operation mode is used (Fig. 2).

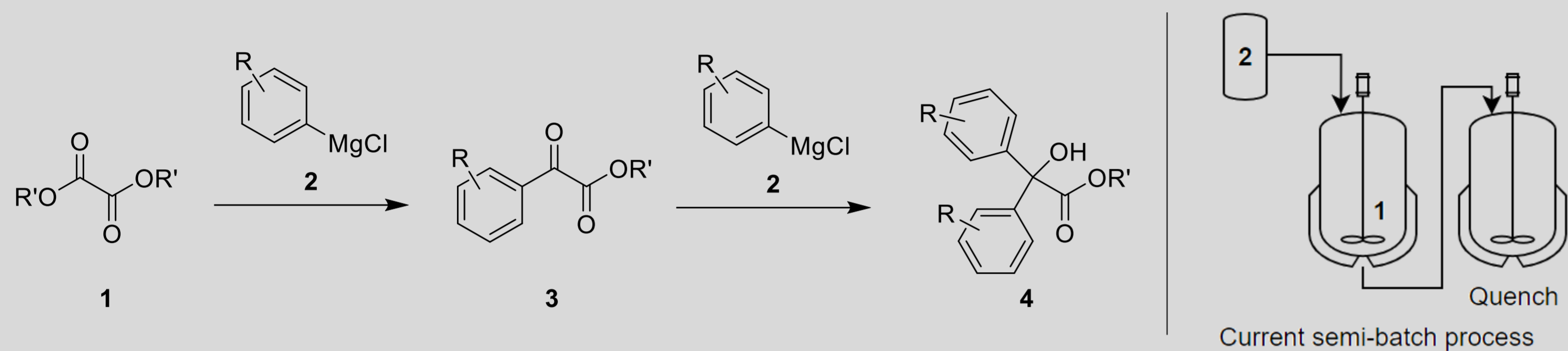


Fig. 1 and 2: Simplified synthesis of desired compound **3** and formation of undesired side compound **4** and current batch process

A second addition (overreaction) of the Grignard reagent **2** to compound **3** can occur and the undesired side compound **4** is formed. The following potentials have been identified:

- Increasing the yield would enhance the overall efficiency of the process.
- Reduction of bis-alcohol (**4**) would be desirable for both, economic and environmental impact.
- An optimized and simplified process would lead to more flexibility in the production plant of Bayer CropScience Schweiz AG in Muttenz.

CONCEPT

The combination of reaction kinetics and different mixing mechanisms will determine if either flow or batch conditions are beneficial. The relationship between mass transfer and the reaction time is described with the Damköhler number (Da) an additional dimensionless number (Fig. 3).

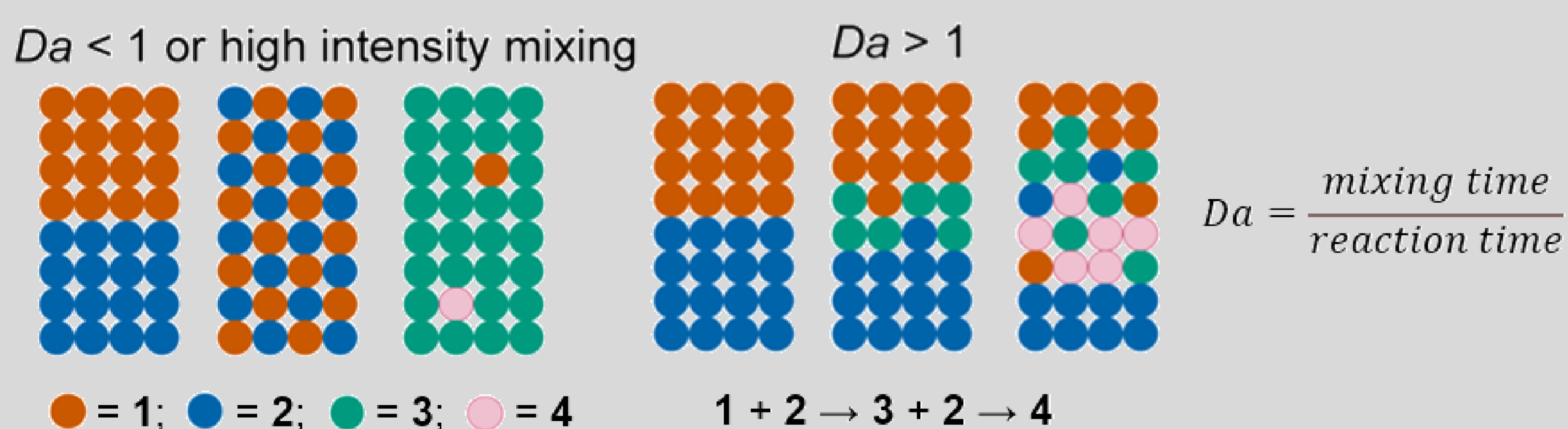


Fig. 3: Damköhler number and mixing effects. Adapted from "The Hitchhiker's Guide to Flow Chemistry" [1].

If the reaction time is very short, reactions are usually mixing dependent ($Da > 1$). Increased mixing can be achieved with high flow rates and a narrow diameter of the mixing element.

Usually in flow chemistry the surface to volume ratio is much larger in comparison to batch and therefore a more efficient heat transfer is achieved. In addition, flow chemistry can avoid process safety risks and often a more selective reaction profile is observed. In literature good selectivity for additions of aryl lithium reagents to dialkyl oxalates (similar to **1**) was shown. Low temperature and efficient mixing did increase the selectivity and the yield [2].

RESULTS

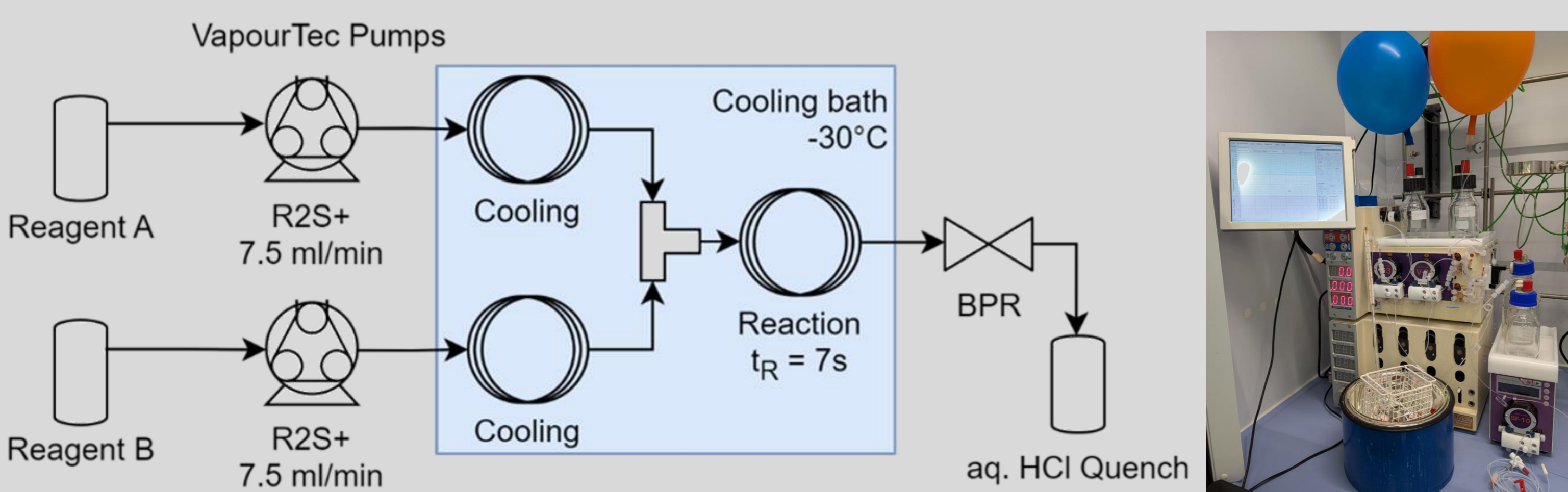


Fig. 4: Diagram and picture of lab flow setup.

VapourTec's R2S+ peristaltic pumps have been used (Fig. 4) in this work. The reagents are cooled in PTFE loops before they are mixed in a T-piece. The reaction mass is quenched into a cooled batch vessel. A back pressure regulator (BPR) that ensures constant pressure was also used.

Tab. 1: Results of lab flow experiments.

Experiment	Flow rate [ml/min]	Temperature [°C]	Residence time [s]	Side compound yield loss [%]
A	8	-30	14	3.5
B (best)	15	-30	7	1.5
C	15	-20	7	2.2
Current process	-	-	-	10

The yield loss due to side compound **4** formation, was reduced from 10% to 1.5% (Tab. 1). In addition, the yield was significantly increased compared to the current semi-batch process. It was found that the reaction is very fast completed in under 2 seconds.

CONCEPTUAL DESIGN

To calculate a production scale plant, isoperibol batch experiments were conducted in a test tube to obtain more insights into the reaction. The reaction temperature was monitored while the temperature of the cooling bath was kept constant. It is suggested that the test tube experiment is a good representation of the production scale flow reactor. The fast reaction is very difficult to cool especially in the necessary scale of the flow reactor.

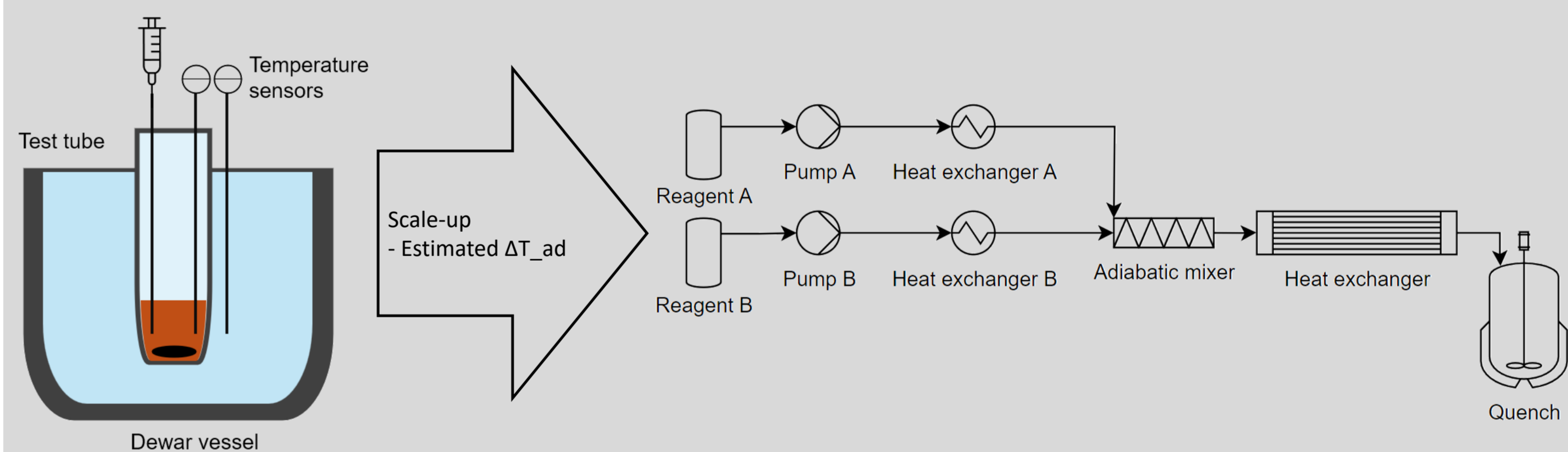


Fig. 5: Isoperibol batch experiment used for conceptual design of production scale flow plant.

Consequently, it was suggested to use an adiabatic mixer followed by a heat exchanger for the continuous production. The adiabatic temperature rise was estimated based on the isoperibol experiments (Fig. 5).

CONCLUSION

In summary, a protocol was developed using continuous flow conditions for the addition of Grignard reagents to dialkyl oxalates. Based on the conceptual design a cost analysis can be made, providing a foundation for defining the next steps. It was found that the flow reactor could be easily implemented into the current plant. Beside the increased yield, and decreased formation of side compound **4**, the new process would free up reactors that can be used for other products.

REFERENCES

- [1] Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117* (18), 11796–11893.
- [2] Nagaki, A.; Ichinari, D.; Yoshida, J. Reactions of Organolithiums with Dialkyl Oxalates. A Flow Microreactor Approach to Synthesis of Functionalized α -Keto Esters. *Chem. Commun.* **2013**, *49* (31), 3242.