CASE STUDY: Nucleophilic substitution of the nitro group in aromatic compound in flow conditions

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ABSTRACT

This project was carried out thanks to a collaboration between academia (University of Milan, DISFARM) and industry (Olon S.p.A.-Segrate). A process was developed to optimize a **nucleophilic substitution of nitro group in aromatic compound with the use of a base** (**Scheme 1.**)

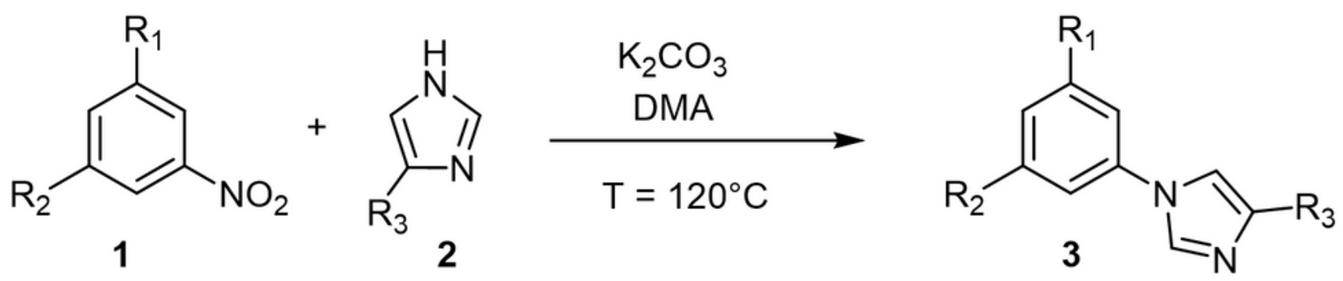
Different issues regarding the yield and the impurity profile have been found using batch conditions.

Different flow procedures have been considered in lab scale (work carried out at the University of Milan);

The good conversion results obtained allowed the **scale-up** of the reaction in an **industrial pilot plant**.

BATCH CONDITIONS

The batch procedure involves dropwise addition of **the solution containing the two reagents into a suspension of potassium hydrogencarbonate in DMA preheated to 120 °C.** The temperature of the reaction was set to 120 °C and it is considered finished after about 2h. (Evaluation of normalized area % of starting material with respect to the product).



Scheme 1. Nucleophilic substitution reaction.

FLOW CHEMISTRY

WHY?

- **Low yields** in batch
- Formation of reaction **by-products**
- **Thermal instability** of aromatic compound, product and of DMA in presence of K_2CO_3.
- Dropwise addition process of several hours.

PILOT PLANT FLOW CONDITIONS

The final setting of the flow reaction has been reported in the following **Scheme 2.** A solution of nitro compound and imidazole in DMA was prepared in a reactor. This solution was pumped in a **10 L column packed with ground quartz (3-6 mm) and potassium hydrogencarbonate** in different percentages.

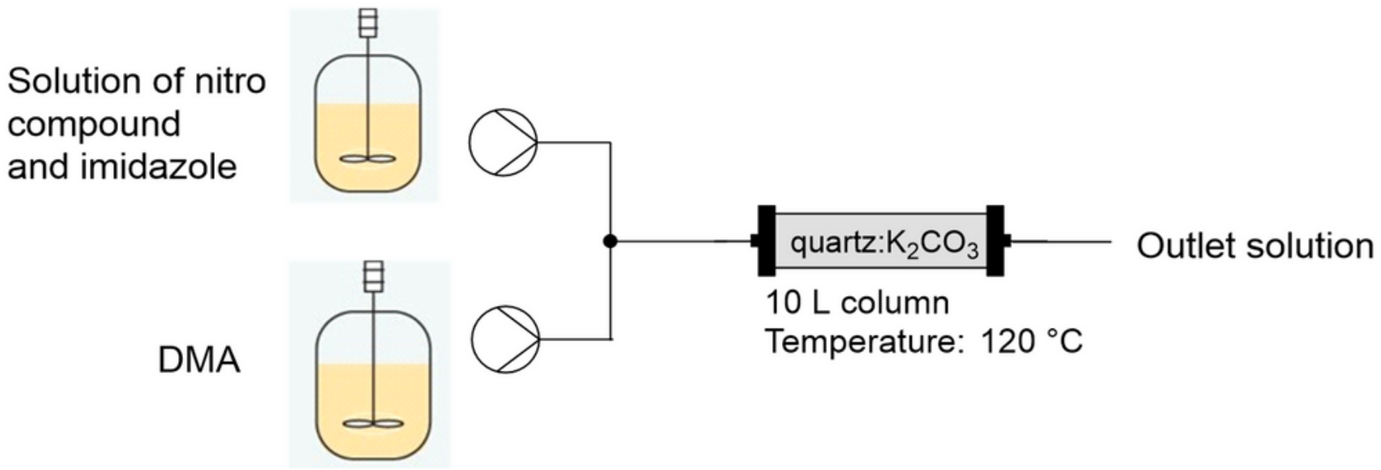
- **Jacketed INOX reactor**
- Internal volume: 10 L; **dead volume 4.2 L**
- Tapped density K_2CO_3 =1.19 g/ml, crystal density K_2CO_3 = 2.43 g/ml
- **Ground quartz:** added to **avoid pressure increases** due to **a cake formation**.
- Temperature: **120 °C** (two temperature probes)
- Flow stream: pre-heated dimethylacetamide.

RESULTS & CONCLUSION

- Different experiments were carried out and **different residence time** were evaluated.

BATCH	K_2CO_3: ground quartz	Flow rate (mL/min)	Rt (min)	Conversion (%)*
01	76:24	380	11	95.4
02	76:24	210	20	95.2
03	70:30	210	20	90.5
04	37:63	300	12	91.2

**Conversion calculation: average of the conversion of the fraction collected.*



Scheme 2. Setting of the flow reaction.

- **Conversions** obtained on a **pilot scale correspond** to those obtained on a **lab-scale** → the scalability of reaction was simpler than that carried out in batch.
- **Productivity**: 1.9 kg of product/h*
- The **molar yield** in flow is **higher** than in batch (1.26 vs. 1)** and the isolated product is **within specification**.

data obtained from assay of reaction 02. **Molar yield of the reactions 01-02 with **K_2CO_3: inert material 76:24*

References: Vladislav M Vlasov 2003 *Russ. Chem. Rev.* **72** 681; Buck, Peter Dipl Ing. “Reactions of Aromatic Nitro Compounds with Bases.” *Angewandte Chemie* 8 (1969): 120-131.