University of Szeged

Doctoral School of Pharmaceutical Sciences

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Continuous-flow methodologies for deuteration of haloarenes, *N*-acetyaltion and amide formation reactions

Summary of PhD thesis

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1. Introduction and aims

Since The Industrial Revolution, chemical manufacturing is still using the traditional batch chemistry methodology, the general principle of which has been around for hundreds of years and remained virtually unchanged in that time. Chemical batch processes are reactions carried out in single vessels. In case of multistep syntheses, batch reactions usually require significant manual labour, as the reaction products from each step must be processed separately (start–stop batch processing). Chemical production has traditionally been the process of the production of fine chemicals, pesticides and medical drugs. At the start of the 21st century, technical and economic innovations led to a paradigm shift. The traditional chemical process model has undergone a tremendous change in a particular direction: continuous process. The driving force behind this effort of paradigm shift is minimizing waste, improving sustainability, and safety standards, finding economic and selective ways to earn greater yields and profit.

The field of flow chemistry has garnered considerable attention over the past two decades, scientists around the world report a huge number of publications accessing continuous-flow (CF) chemistry techniques. The most significant adoption of flow technology is in pharmaceutical industry. The new technology has the ability to facilitate the discovery of new medicines, high-speed development and optimization of scale-up of potential drug candidates.

CF processing can permit special reaction conditions, such as highly pressurized and superheating reactions. Furthermore, it permits better safe use of unstable and/or toxic reagents, allowing atom-efficient reagents to be better exploited, it can help exploration of atom-economical reactions. The CF chemistry is a versatile tool of not just the laboratory users, but it can be used in any possible area of synthetic chemistry.

Our aim was to apply continuous-flow in existing reactions to improve efficiency, to make them more green, more selective and as safe as possible. Highlighting the reactions where we had applied the flow chemistry technology, we investigated the following areas in CF: (*i*) catalytic deuterodehalogenation of haloarenes in H-Cube® device, (*ii*) N-acetylation of amines with acetonitrile as solvent and acetyl group source, (*iii*) direct amide formation mediated by carbon disulfide.

2. Method

Reagents and materials were commercially available and used as received. The synthesized compounds were separated and purified by column chromatography on silica gel. The compounds were characterized by NMR spectroscopy. Deuterateration reactions were carried out in H-Cube device. Acetylation and amide formation reactions were carried out in a "home-made" flow reactors consisting of an HPLC pump, a stainless steel HPLC column as the active reactor zone, a stainless steel preheating coil and a back-pressure regulator. The parts of the system were connected with stainless steel and PEEK capillary tubing. The stainless steel, the preheating coil and HPLC column were placed in a gas chromatograph oven.

3. Results and discussion

3.1. Deuteration of haloarenes in H-Cube® CF device

CF deuterodehalogenation reaction of haloarenes was developed in H-Cube® device. For the initial optimization study, the deuterodehalogenation reaction of 4-bromoacetanilide was chosen as a test reaction. It was found that the harsh reaction conditions (100 °C and 100 bar), a novel spherical supported palladium catalyst (10% Pd/PBSAC) and propylene carbonate solvent were necessary to achieve complete conversion with 96% deuterium incorporation value (Scheme 1).

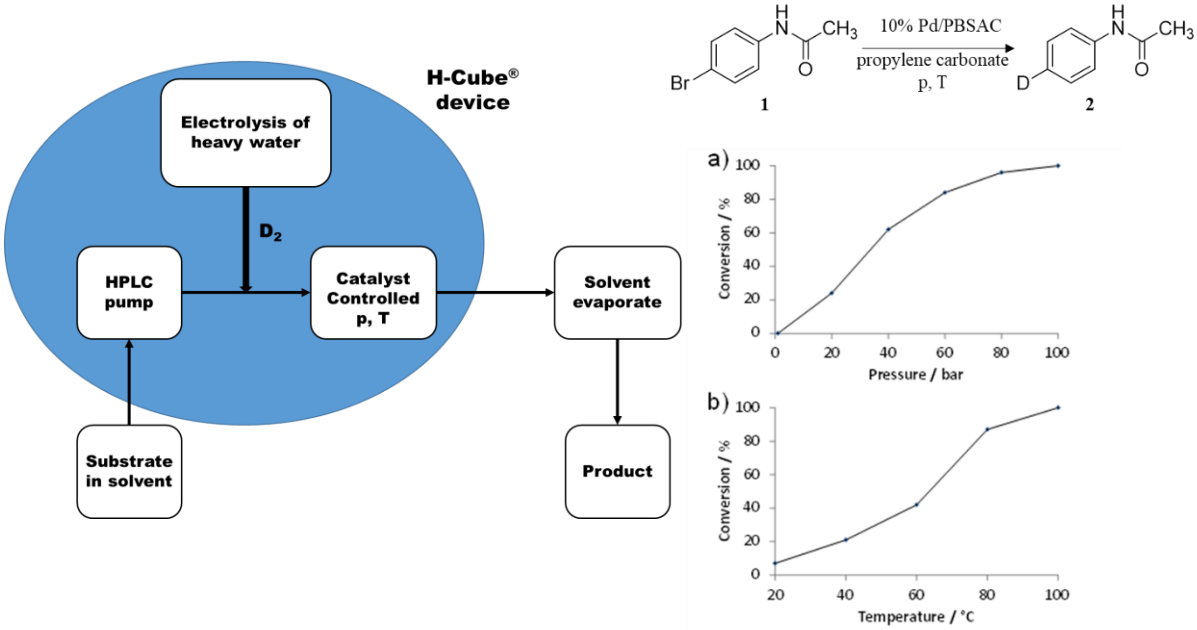
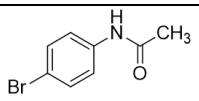
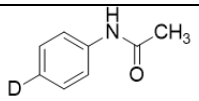
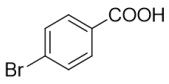
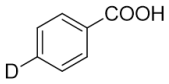
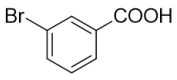
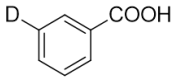
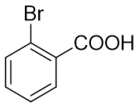
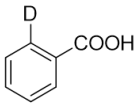
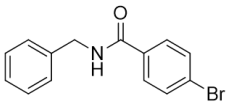
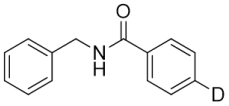
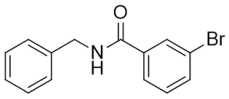
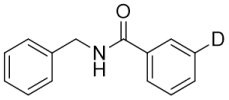
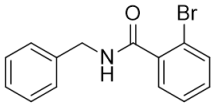
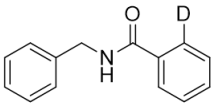


Figure 1. *Schematic illustration of the H-Cube reactor and the diagram of optimization reaction of the 4-bromoacetanilide (**1**).*

With the optimized reaction conditions in hand, we investigated the scope and limitations of the reaction. The reaction was tested first with various bromine-substituted aromatic

compounds. As shown in Table 1, for these regioisomers complete conversions were observed with >95% deuterium incorporation values. A further set of test compounds, aromatic amides **9**, **11** and **13**, were investigated possessing a bromo substituent. We achieved excellent conversion and deuterium incorporation value in all cases. Debenzylation reaction by reductive cleavage over palladium metal catalysts with molecular hydrogen was a general method in organic chemistry, however, no debenzylation was observed for the deuteration amide compounds.

Table 1. *Results of the deuteration reaction of several bromine-substituted compounds.*

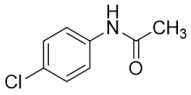
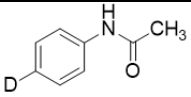
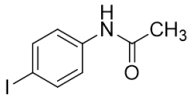
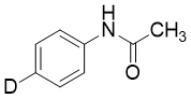
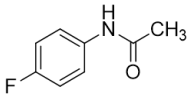
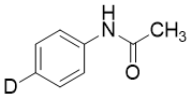
Entry	Substrate	Product	Deuterium incorporation value (%)	Yield (%)
1	 **1**	 **2**	96	96
2	 **3**	 **4**	96	97
3	 **5**	 **6**	95	95
4	 **7**	 **8**	98[a]	94
5	 **9**	 **10**	97	98
6	 **11**	 **12**	96	94
7	 **13**	 **14**	98[a]	95

[a] Achieved by pre-treating the starting molecule with deuterated methanol.

The other halogen substitutes compounds were also tested by the optimized reaction. In case of *para* chlorine-substituted acetanilide, total conversion was observed with a high deuterium incorporation value. Importantly, the *para* iodine-substituted acetanilide poisoned palladium PBSAC catalyst. The fluorine-substituted acetanilide remained intact and no conversion was

observed. Thus, selective flow deuteration can be performed in the presence of a fluorine substituent.

Table 2. *Results of the optimized deuteration reaction with substrates possessing chlorine, iodine and fluorine acetanilide analogs.*

Entry	Substrate	Product	Deuterium incorporation value (%)	Yield (%)
1	 **15**	 **2**	96	96
2	 **16**	 **2**	n.d.	30
3	 **17**	 **2**	n.d.	0

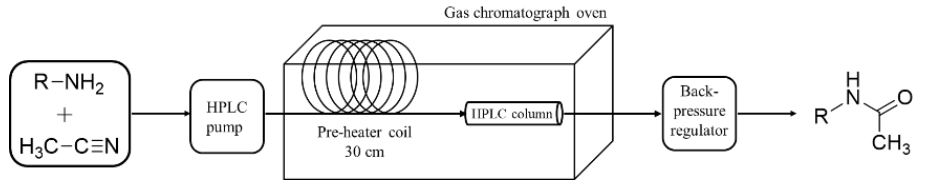
We focused the context of green chemistry criteria, where catalyst reusability is an important issue. Therefore, the robustness of our deuteration was also tested. The spherical supported palladium catalyst (10%/PBSAC) showed moderate reusability.

3.2. *N*-acetylation of amines in a "home-made" CF reactor with acetonitrile

An efficient CF methodology was developed for the synthesis of *N*-acetylated amine compounds. The reactions were carried out in a home-made CF reactor which consists of an HPLC pump that transport the starting material dissolved in acetonitrile as a solvent and an acetylation agent. The reaction mixture is feed into a fillable HPLC column that is filled with a solid Al_2O_3 catalyst. Additionally, there is a GC oven and an in-line back pressure regulator in the system to regulate the temperature and pressure. As model reaction for the optimization study, N-acetylation of aniline was chosen. We found that the optimized reaction conditions were 200 °C, 50 bar, 0.1 mL min^{-1} in flow rate and 27 min residence time and the most useful solid Lewis catalyst for the CF acetylation synthesis was the Al_2O_3 catalyst.

The scope of the method was extended to the synthesis of several acetamide compounds (Table 2.). The reactions were carried out in a single run and the products were analyzed by ^{1}H and ^{13}C NMR spectroscopy. Column chromatography purification of the product was only needed for compound **23**, for the others, only a simple evaporation of acetonitrile was needed.

Table 3. *Results of the N-acetylation reaction of several amine compounds.*



19 >99%

21 93%

23 51%

25 >99%

27 >99%

29 >99%

31 0

33 0

35 0

37 >99%

39 >99%

41 >99%

43 >99%

45 >99%

Conditions: 200 °C, 50 bar, 0.1 mL min^{-1}, 27 min residence time
Isolated yields indicated under each compound.

The 4-aminophenol was acetylated with excellent yield and the drug substance paracetamol **21** with quantitative yield after recrystallization. Lower yield was achieved for 4-methoxyaniline, and the acetylated product **23** was isolated after column chromatography with

a 51% yield. For the halogen substituted aniline derivatives excellent yields (**25**, **27** and **29**) were observed. For the nitroaniline derivatives, no conversion was observed and only the starting materials were isolated. The highly electron-withdrawing nature of the nitro group which reduces the nucleophilicity of the amino group might explaine the absence of product formation. Aliphatic primary and secondary amines were also tested. The primary benzylic amine was converted to the corresponding acetamide **41** with excellent yield. When secondary amines, piperidine and morpholine were examined, the acetylated derivatives (**37**, **39**) were isolated with quantitative yields. The stereoselective property of this reaction was also tested with acetylation reaction carried out for the two enantiomers of 1-phenylethanamine. For both enantiomers the acetylated derivative was achieved with quantitative yield and the complete retention of the enatiomerical purity. The isolated products (**43**, **45**) were investigated by optical rotation and was found to be identical to literature data, so that the chance of heat-induced racemization was not observed.

The catalyst reusability is an important property in sustainable chemical reactions, this property was also tested. It was found that the activity of the catalyst did not decrease significantly until 10 cycles and one cycle was carried out with 20 mg of benzylamine. The excellent results of catalyst reusability study opened the way to scale up to the reaction, which was tested with the same reaction, the process could be scale up 2 g of benzylamine without decrease of the significant product conversion. The *N*-benzylacetamide product **41** was isolated with 94% yield after recrystallization. The reaction was completed within 28 hours, this is considerably faster than what has been reported with already known technology.

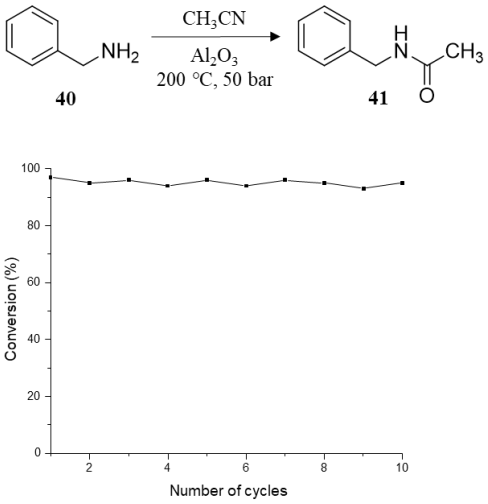


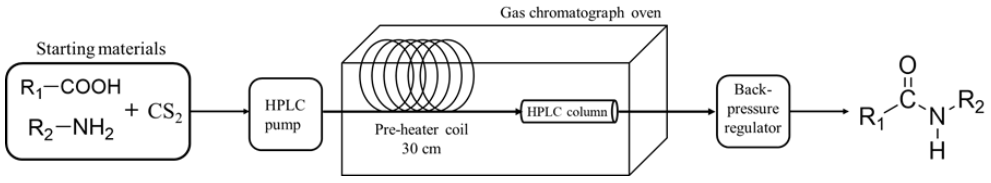
Figure 2. *Robustness of acetylation of the benzylamine (**40**), the same reaction was repeated 10 times on the same Al_2O_3 catalyst*

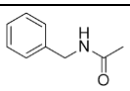
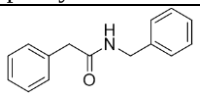
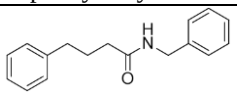
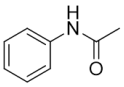
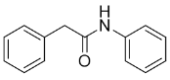
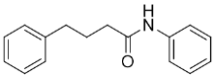
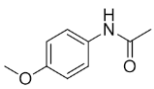
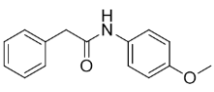
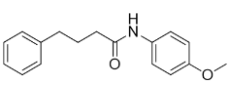
3.3. Direct amide formation in a "home-made" CF reactor mediated by carbon disulfide

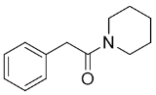
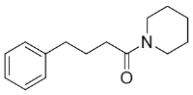
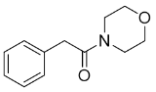
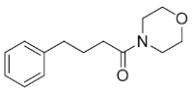
Direct amide synthesis from cheap and easily available carboxylic acids and amines was developed in the same home-made CF reactor that was used in acetylation reactions. As model reaction was selected utilizing benzylamine and 4-phenylbutyric acid as substrates dissolved in acetonitrile to provide a 100 mM solution. Several Lewis acids, solvents and additives were tested in different conditions (temperature, pressure, flow rate and concentration). We found that the optimized reaction conditions were 200 °C, 50 bar, 0.1 mL min^{-1} flow rate and 27 min residence time and we used Al_2O_3 catalyst, 4-dimethylaminopyridine (DMAP) in catalytic amount and 1 equiv. carbon disulfide as coupling agent.

With the optimized conditions, the reaction was extended to the preparation of 15 diverse amides (Table 3.). Reactions were carried out with three different carboxylic acids and five amines, including primary and secondary aliphatic and primary aromatic amines. In general, full conversions and excellent yields were achieved, without the need of any intensive purification step.

Table 4. *Substrate scope of amide formation with isolated yield data*



Substrates	acetic acid	phenylacetic acid	4-phenylbutyric acid
benzylamine	 **41** 98%	 **49** 96%	 **47** 98%
aniline	 **19** 98%	 **50** 95%	 **51** 96%
p-anisidine	 **23** 97%	 **52** 95%	 **53** 94%

piperidine	 **37** 98%	 **54** 97%	 **55** 96%
morpholine	 **39** 97%	 **56** 98%	 **57** 97%

Each reaction was 1 equiv. carboxylic acid (100 mM), 1 equiv. amine (100 mM), Lewis acid: Al_2O_3, Reagent: 1 equiv. CS_2, Adduct: 20 mol% DMAP and conditions: 200 ºC, 50 bar, 0.1 mL min-1 and 27 min residence time. Isolated yields indicated under each compound.

The utilized alumina catalyst showed excellent reusability. Additionally, the reaction was successfully scaled up to 2-gram quantity performed in ca. 13 hours. These facts prove this methodology could become broadly applicable for direct amide synthesis utilizing the industrially reliable continuous technology.

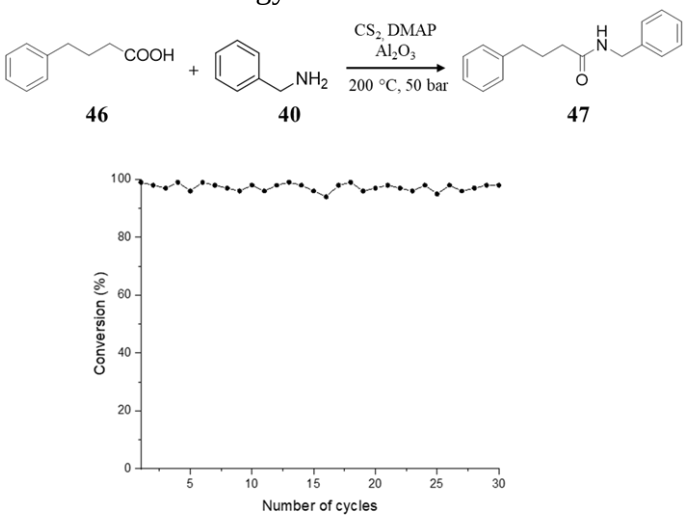


Figure 3. *Robustness of the amide formation reaction was investigated in the reaction of model substrates. The same reaction was repeated 30 times on the same catalyst.*

List of publications and lectures

Papers related to thesis

I. **György Orsy**, Ferenc Fülöp, István M. Mándity:
Continuous-flow catalytic deuterodehalogenation carried out in propylene carbonate
Green Chem., 2019, **21**, 956-961. IF.: 9.480

II. **György Orsy**, Ferenc Fülöp, István M. Mándity:
N-Acetylation of Amines in Continuous-Flow with Acetonitrile-No Need for Hazardous and Toxic Carboxylic Acid Derivatives
Molecules, 2020, **25**, 1985. IF.:3.267

III. **György Orsy**, Ferenc Fülöp, István M. Mándity:
Direct amide formation in a continuous-flow system mediated by carbon disulfide
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