Flow Synthesis

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Heating under High-Frequency Inductive Conditions: Application to the Continuous Synthesis of the Neurolepticum Olanzapine (Zyprexa)**

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The use of micro- or mesofluidic reactors has become a key enabling technology[1] in academia and industry.[2] The rapid heating of reactants inside the flow device is an important issue when syntheses are conducted in mesofluidic reactors at high flow rates. Ideally, heating should be combined with high pressure to achieve sufficiently high reaction rates.[3] Conventional heating relies on convective heat transfer which is often too slow to serve the purposes of flow chemistry. Alternative techniques are: a) heating with microwave irradiation, which can be utilized when reactor materials are microwave transparent[4] and b) the direct electric heating of tubular reactors.[5]

Recently, we applied inductive heating (IH) to mesofluidic reactors by using ferromagnetic materials like steel beads, copper metal, and superparamagnetic nanostructured particles in fixed beds.[6,7] Magnetic and conductive materials normally heat up in an oscillating magnetic field due to Joule's heating and hysteresis; however, superparamagnetic particles heat up due to Brown and Néel relaxation.[6] Depending on the external inductor, an oscillating field with medium (15–25 KHz) or high frequency (780–850 KHz) can be generated (Figure 1). We found that this technique allows for very rapid heating of a large number of diverse reactions under flow conditions, thereby avoiding hazardous radiation.[7] Commonly, a stronger magnetic field (H) and higher frequency (f) increase the amount of induced heat for most materials. The frequency also correlates with the skin depth, which is the distance at which most of the induced energy is absorbed within the material. Because of this phenomenon, medium frequencies are preferentially employed when larger objects are heated, whereas high frequencies are ideally suited for smaller objects and superparamagnetic nanomaterials.[8,9]

Herein we disclose the first applications of high-frequency (hf) inductors to organic synthesis. We further demonstrate that this new heating technique can be utilized in a complex application. The continuous multistep flow synthesis of the atypical neurolepticum olanzapine (Zyprexa)[10] could only be accomplished with an advanced heating method. In this study we employed a custom-made high-frequency inductor (Figure 1a)[11] which can accommodate a cartridge-type flow reactor made of glass, PEEK (polyether ether ketone), ceramic, and a coil reactor made of Hastelloy C-steel.

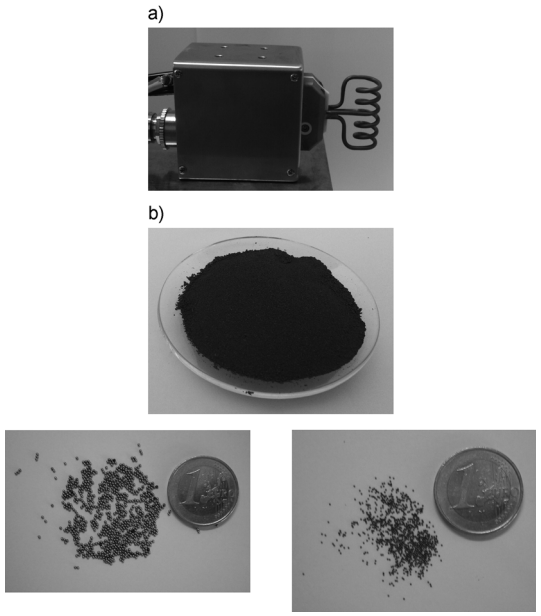

Figure 1. a) HF inductor with inductor coil; b) MAGSILICA 300[12] (top), steel beads 0.4 mm (bottom, left), steel beads 0.8 mm[13] (bottom, right).

To compare the two types of inductors (mf, hf) we first placed several magnetic and/or conducting materials of the same volume in microwave vials and then positioned them in medium-frequency (15–25 kHz) and a high-frequency (300 and 780–800 kHz, respectively) oscillating fields. For comparison, all experiments were run at maximum power and the temperature on the surface was measured with an IR pyrometer (see the Supporting Information (SI)).

In the case of MAGSILICA 300,[12] high-frequency induction provided temperatures close to 300 °C in less than 1 min, while the medium-frequency inductor was inefficient in heating these nanostructured particles. Steel beads with a diameter of 0.4 mm demonstrated more extreme behavior: only hf induction provided temperatures around 400 °C. In

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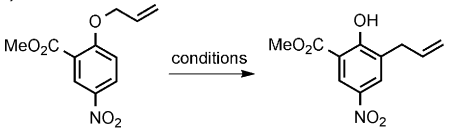
addition, we investigated the use of a Hastelloy C-steel coil reactor (inner diameter = 0.75 mm; length = 70 cm; V = 0.3 mL); toluene was pumped through the coil reactor at a flow rate of 4 mL min^{-1} at a power input of 10%. In the pressurized system temperatures up to 360 °C could be achieved at this high flow rate. It must be noted that it is not possible to determine the temperature precisely yet, because the temperature of the reactor surface is measured, not that of the heating material. These simple experiments showed us that extremely rapid heating to high temperatures can be achieved when magnetic/conductive materials are used in combination with hf induction. Such high and rapid heating is ideally suited to flow chemistry applications where residence time is short. The reaction vessel was heated by embedding the whole reactor in the homogeneous electromagnetic field of either a U-shaped [IH (mf)] or a coil-shaped [IH (hf)] electromagnetic inductor. This guarantees homogeneous heating of the whole vessel. After a short warmup period the temperature of the vessel is only influenced by the cold solvent that enters the reactor which results in a small temperature drop of 5–10 °C at the reactor inlet. We went on to demonstrate the utility of this heating method in the difficult Claisen rearrangement of allyl aryl ether **1** under batch conditions (Table 1). We had shown that this test reaction can be conducted at around 200 °C, but under conventional conditions we never achieved full conversion.[6b]

When a capped vial was heated in an oil bath, the rearranged product **2** was isolated in only 17% yield after 2 h, while microwave heating and inductive heating under similar conditions provided **2** in yields of 38% and 39%, respectively. It is noteworthy that under high-frequency conditions almost complete conversion was achieved at 205 °C in a much shorter time, while at 225 °C a substantial degree of decomposition was observed. High-frequency inductive heating seems to resultsin a much hotter surface, which leads to higher reaction rates in close proximity to the nanostructured particles. We extended our studies to flow experiments using a ceramic reactor filled with MAGSILICA (Scheme 1). At a flow rate of 0.5 mL min^{-1} and a temperature of 240 °C complete conversion was achieved along with a high yield of isolated product (91%). This example clearly shows the advantages of high rapid heating in organic synthesis. Reactions that are difficult to achieve under standard convection heating may now be possible.

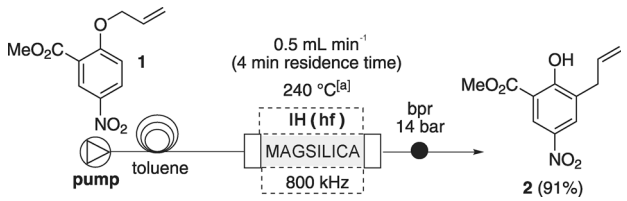
Table 1: Comparison between conventional heating (external oil bath), microwave irradiation, and medium- and high-frequency inductive heating (IH) under batch conditions.



1 **2**

Heating mode	Conditions[a]	Yield [%][b]
oil bath	200 °C, toluene, 120 min	17
microwave heating[c]	Si/C, 200 °C, toluene, 120 min	38
IH (mf)	25 kHz, 200 °C, MAGSILICA, toluene, 120 min	39
IH (hf)	800 kHz, 205 °C,[d] MAGSILICA, toluene, 20 min	89
IH (hf)	800 kHz, 225 °C,[d] MAGSILICA, toluene, 20 min	decomp.

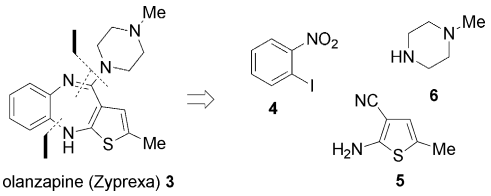
[a] The experiments were conducted at 200 °C in a closed vial, well above the boiling point of toluene. [b] Yield of isolated product. [c] Microwave heating was conducted in the presence of SiC as toluene does not absorb microwave irradiation efficiently; temperature measurement: experiments with microwave and oil bath heating: temperature sensor; IH experiments: IR pyrometer. [d] Adjusted by inductor power.



Scheme 1. Claisen rearrangement of allyl aryl ether **1** under flow conditions by IH (hf) with MAGSILICA. [a] Temperature determined on the reactor surface using an IR pyrometer. bpr = back pressure regulator.

We then went on to increase the complexity of the application by demonstrating that it can be used in a multistep flow sequence. We chose olanzapine (**3**), one of the best-selling drugs worldwide. It exerts antagonistic activity towards the dopamine receptor type 4 (D4 receptor) and the serotonine receptor type 2 (5HT2 receptor).[10,14]

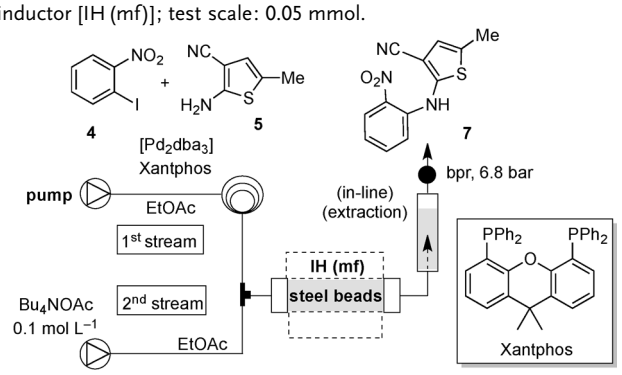
Our synthesis is related to a previously published sequence.[15] However, while the patent describes a nucleophilic aromatic substitution between 2-fluoronitrobenzene and aminothiazole **5**, which proceeds in only modest yield, we employed the Buchwald–Hartwig amination[16] of aryl iodide **4** and aminothiazole **5** as the initial step (Scheme 2). We tested many reaction conditions and found that the Xantphos ligand in combination with tetra-*n*-butylammonium acetate promoted amination of aryl iodide **4** in excellent yield (> 90%) in THF and in ethyl acetate (Table 2). Ethyl acetate was the solvent of choice because of its full compatibility in the subsequent steps.



Scheme 2. Olanzapine (**3**) and building blocks **4**–**6**.

A 1:1 mixture of iodobenzene **4** and aminothiazole **5** was pumped into a reactor that was filled with steel beads and encased in an inductor. Mixing the starting materials with the base Bu_4NAc right at the start resulted in the formation of **7** in

Table 2: Optimization of the Buchwald–Hartwig reaction under flow conditions; reactor filled with steel beads (0.8 mm) and placed in an inductor [IH (mf)]; test scale: 0.05 mmol.



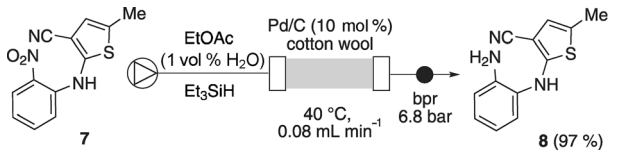
T [°C][a]	Flow rate [mL min^{-1}]	Base addition[b]	In-line extraction[c]	Yield [%][d]
50	0.06	1st stream	–	73
50	0.08	2nd stream	–	81
50	0.06	2nd stream	–	91
50	0.06	2nd stream	+	90

[a] Temperature measured on surface with IR pyrometer. [b] Mode of base addition; the term 2nd stream refers to a solution of base that is added to the 1st stream composed of reactants and catalyst. [c] Vertically placed reactor (5 mL), equipped with cotton wool on bottom and filled with distilled water. [d] Yield of isolated product.

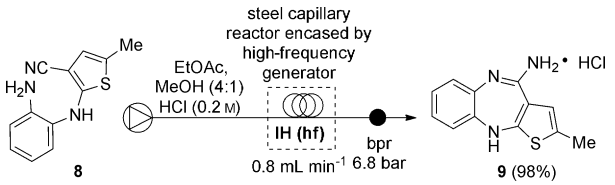
comparably low yield (73%). When the base was added to the first stream directly before the reactor inlet, undesired reactions in the storage flask were prevented. The coupling product **7** was isolated in 91% yield, comparable to the yield under batch conditions (60°C, 2 h, 89%; RT, 18 h, 92%). Higher flow rates or lower temperatures resulted in reduced yields, while higher temperatures led to decomposition. We found that the base had to be removed from the crude product to achieve good yields in the next step. An in-line extractor, consisting of a vertically oriented cylinder, equipped with a frit or cotton wool at the bottom and filled with distilled water, turned out to be a practical solution.

For the subsequent reduction of the nitro group we chose the metal-free reducing agent triethylsilane and a Pd-doped fixed-bed reactor.[17] Gratifyingly, the reduction proceeded smoothly in ethyl acetate under flow conditions (97%; batch 94%) using Pd/C (Scheme 3). Here, heating was achieved externally by encasing the reactor in a metal block. Remarkably, the catalyst could be used for more than 250 h without loss of activity (corresponds to a loading of less than 0.3 mol%).

The development of a flow protocol for the acid-promoted cyclization of aniline **8** and formation of thieno[1,5]-benzodiazepine **9** demonstrated the advantages of hf over mf inductive heating (Scheme 4). High-frequency induction



Scheme 3. Reduction of nitroarene **7** under flow conditions. Test scale: 0.058 mmol, Pd/C 30 mg (10 mol%), reactor volume 3 mL.

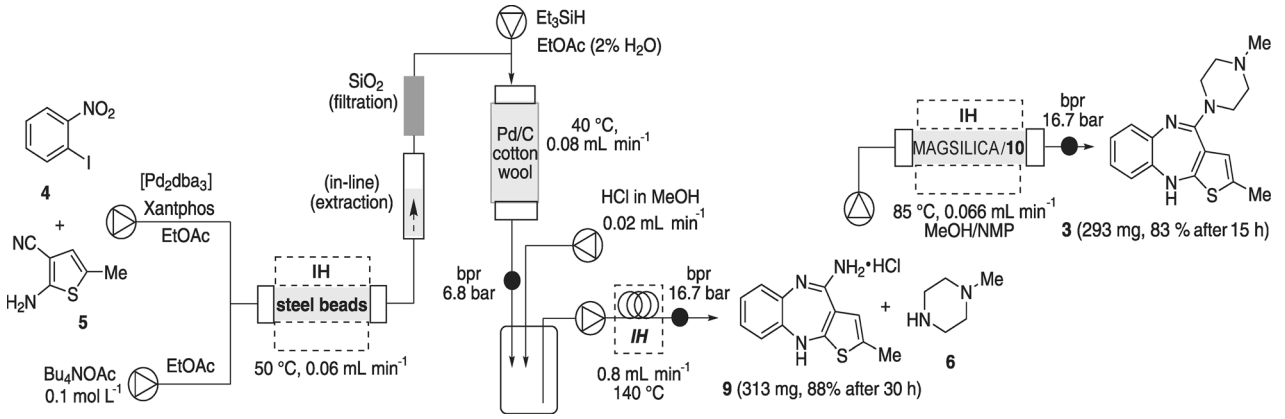


Scheme 4. Acid-promoted cyclization of aniline **8** under flow conditions using a coil reactor in inductive high-frequency field (test scale: 0.05 mmol); temperature measured on surface by IR pyrometer: 80°C, solution temperature measured after the reactor with K-element: 140°C.

leads to rapid heating to higher temperatures inside the tubular reactor so that exposure of the reaction mixture to high temperatures can be better controlled by reactor length and flow rate alone. We found that mf conditions always provided an impure product, while hf inductive heating of **8** dissolved in a 0.2 M HCl solution in EtOAc/MeOH (4:1) at 80°C quantitatively provided benzodiazepine **9**. Lower flow rates led to decomposition; higher flow rates did not give full conversion. Also, the HCl concentration (< 0.4 M) was crucial, otherwise substantial decomposition and polymerization occurred. In pure ethyl acetate no conversion to benzodiazepine **9** was observed, while the reaction in pure methanol gave low yields. Solvent mixtures consisting of ethyl acetate and dichloromethane also gave good overall yields of crystalline benzodiazepine **9** at 80°C, but the reaction time had to be extended by a factor of 3.

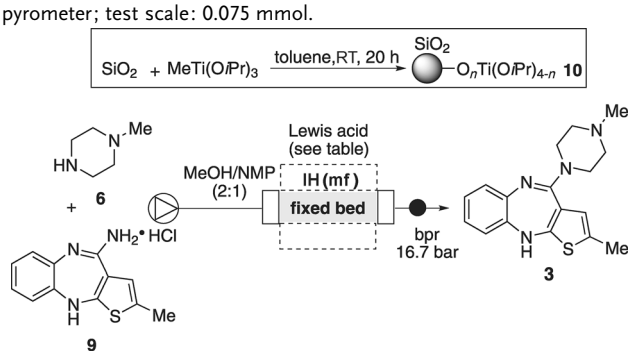
Next, we investigated the preparation of olanzapine (**3**) from benzodiazepine **9** and piperazine **6** under thermal conditions (≥ 150°C). Both batch and flow conditions led to substantial decomposition. When lower temperatures (110–140°C) were employed, yields for **3** were below 35%. Lewis acids dramatically improved the yields (Table 3). We prepared a new silica-supported titanium catalyst (**10**; see the Supporting Information) which provided **3** in over 90% yield at 120°C. Under batch and flow conditions the best results were obtained with $BF_3{\cdot}Et_2O$ (Table 3, entries 1 and 2). However, the silica-based titanium Lewis acid **10** can be applied as a fixed-bed material. In this case MAGSILICA was the material of choice, because when it was mixed with the Lewis acid **10**, rapid and "homogeneous" catalyst heating was achieved which furnished a cleaner product (Table 3, entry 4). Conventional heating of the same reactor with a steel block gave lower yields and more byproducts (Table 3, entry 3). Remarkably, olanzapine (**3**) could still be isolated in 87% yield after the reaction had been repeated seven times (each 0.075 mmol scale). ICP-MS analysis revealed that Ti leaching is negligible with only 0.0135% loss after a period of 6 h in methanol at 120°C (see the Supporting Information). Under the typical reaction conditions, titanium leaching of $\delta = 0.136$ ppm during the first 6 h and $\delta = 0.261$ ppm for the following 20 h in solution were observed, resulting in $\delta = 19.9$ ppm titanium in the final product. Thus most of the titanium (> 99%) remains immobilized, which guarantees the durability of the catalyst for long-term application as well as low contamination of the drug.

With the results from the individual reactions in hand, we commenced with the continuous three-step synthesis of



Scheme 5. Continuous synthesis of olanzapine (**3**): **4** and **5** each 0.027 M; Et_3SiH in EtOAc [2 vol% H_2O] 0.6 M; HCl in MeOH 0.6 M; benzodiazepine **9** 0.019 M; MeOH/NMP (3:1); temperature measured on surface with IR pyrometer for inductively heated reactors; temperature measured by K-Element for steel-block reactors and for reaction mixtures leaving reactors after hf induction.

Table 3: Lewis acid promoted introduction of the piperazine moiety under flow conditions; temperature measured on surface by IR pyrometer; test scale: 0.075 mmol.



Entry	Mode	Lewis acid	*T* [°C]	Time or flow rate	Yield [%][a]
1	batch	BF_3OEt_2	120	18 h	91
2	flow[b]	BF_3OEt_2	75[c]	0.06 mL min^{-1}	92
3	flow	**10**	120[d]	0.066 mL min^{-1}	80
4	flow[e]	**10**	85[c]	0.066 mL min^{-1}	87[f]

[a] Yield of isolated product. [b] Steel beads. [c] Surface temperature generally lower than internal temperature. [d] MAGSILICA conventionally heated by external steel block. [e] MAGSILICA. [f] Yield of isolated product after 7th run; packed bed.

thieno[1,5]-benzodiazepine **9** starting from aryl iodide **4** and thiophene **5** (Scheme 4). Besides the in-line extraction, the process was further improved by including a cartridge filled with silica after the in-line extractor in order to remove traces of Pd.[18] Furthermore, the reaction mixture that left the second reactor after reduction of the nitro group was collected in a glass vessel where remaining hydrogen gas was liberated allowing for more constant flow rates. At this point a stream of HCl in MeOH (0.6 M) was added and the solution was injected into the tubular reactor. It was possible to conduct the three steps continuously for 30 h without chromatographic purification to obtain 313 mg (88% yield) of thieno[1,5]-benzodiazepine **9**. It is noteworthy that the overall reactor volume is about 8 mL for all three steps and no solvent switch is necessary. The formation of olanzapine (**3**) was achieved with an additional reactor (3 mL volume) providing 293 mg in 83% yield. In this test study we chose relatively dilute conditions compared to what industrial processes ideally require. Still, the productivity is high, in terms of time and overall reaction volume. The patent describes a productivity of 1.88 mmol $L_R^{-1} h^{-1}$ (L_R = reaction volume in liters) in a discontinuous batch system. The method reported here, not optimized with respect to productivity, already has a productivity of 3.97 mmol $L_R^{-1} h^{-1}$ (Scheme 5).

In conclusion, we have disclosed the first applications of high-frequency inductive heating [IH(hf)] in synthetic organic chemistry. High reaction temperatures can be generated rapidly in pressure-resistant flow devices in a simple setup. This heating technology was implemented in a multistep continuous process for the preparation of the neuroleptic olanzapine.[19] It was possible to substantially reduce the required time and amount of materials. This showcase synthesis demonstrates the power of inductive heating in combination with different reactor designs and heating materials.

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Keywords: Buchwald–Hartwig reaction · flow chemistry · inductive heating · medicinal chemistry · microreactors

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