Continuous Flow Hot Paper

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A Three-Minute Synthesis and Purification of Ibuprofen: Pushing the Limits of Continuous-Flow Processing**

*David R. Snead and Timothy F. Jamison**

Abstract: *In a total residence time of three minutes, ibuprofen was assembled from its elementary building blocks with an average yield of above 90% for each step. A scale-up of this five-stage process (3 bond-forming steps, one work-up, and one in-line liquid–liquid separation) provided ibuprofen at a rate of 8.09 g h^{-1} (equivalent to 70.8 kg y^{-1}) using a system with an overall footprint of half the size of a standard laboratory fume hood. Aside from the high throughput, several other aspects of this synthesis expand the capabilities of continuous-flow processing, including a Friedel–Crafts acylation run under neat conditions and promoted by $AlCl_3$, an exothermic in-line quench of high concentrations of precipitation-prone $AlCl_3$, liquid–liquid separations run at or above 200 psi to provide solvent-free product, and the use of highly aggressive oxidants, such as iodine monochloride. The use of simple, inexpensive, and readily available reagents thus affords a practical synthesis of this important generic pharmaceutical.*

Continuous-flow organic synthesis is of growing importance in research, development, and manufacturing.[1] Particular emphasis has been placed on continuous pharmaceutical processing,[2] and a recent program in our laboratory is dedicated to the on-demand production of active pharmaceutical ingredients (APIs) through the use of continuous-flow methods.[3] For example, we have developed or are developing such syntheses of several APIs included in the World Health Organization's (WHO) list of essential medicines,[4] which includes ibuprofen (**1**). Inspired by McQuade's landmark continuous synthesis,[5] we sought to develop a scalable continuous synthesis of this generic pharmaceutical. Compared to McQuade's procedure, our main aims were to avoid the use of triflic acid (TfOH, 5 equiv), effect a more economical oxidative rearrangement (to replace $PhI(OAc)_2$), and conduct the synthesis in a more concentrated fashion and shorter time to increase throughput and minimize cost and waste.

[*] Dr. D. R. Snead, Prof. Dr. T. F. Jamison
Department of Chemistry
Massachusetts Institute of Technology
77 Massachusetts Ave., Cambridge, MA 02139 (USA)
E-mail: tfj@mit.edu

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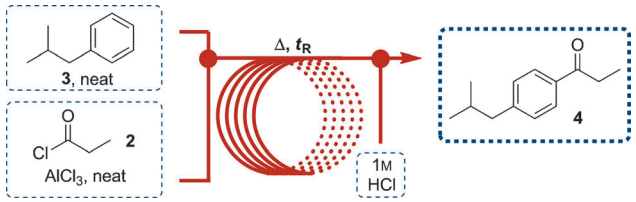
We herein report a highly efficient continuous synthesis of ibuprofen that pushes the limits of existing continuous-flow technologies. Three chemical transformations were performed in a total of three minutes (1 min/step), each with a yield in excess of 90%. Inexpensive and readily available reagents were employed (e.g., $AlCl_3$, ICl), and the use of solvent was minimized (no additional solvent for the Friedel–Crafts acylation or the oxidative 1,2-aryl shift). Aggressive reagents, such as a solution of $AlCl_3$ in propionyl chloride (**2**) and neat ICl, were delivered without incident or reactor fouling for several hours, and in-line pressurized liquid–liquid extractions safely neutralized and removed problematic reagents and byproducts. The risks associated with highly exothermic reactions and quenches (Friedel–Crafts acylation conducted under neat conditions and at elevated temperature and oxidative 1,2-aryl shift) were mitigated through a fundamental advantage of continuous flow over batch synthesis; only a small amount of material relative to the output of the system is utilized at any given time. Overall, this synthesis illustrates many of the features and opportunities offered by continuous synthesis.

The Friedel–Crafts acylation of isobutylbenzene (**3**) with propionyl chloride (**2**) to produce aryl ketone **4** was first examined. Whereas a soluble Brønsted acid promoter that is less harsh than TfOH would have been desirable for the activation of propionyl chloride, none of those examined (acetic acid, sulfuric acid, methanesulfonic acid, and hydrochloric acid) gave appreciable quantities of **4** (see the Supporting Information for details).

We thus turned our attention to Lewis acid promoters, in particular the commonly employed $AlCl_3$.[6] Readily available and inexpensive, this classic reagent created several other problems. Typical Friedel–Crafts conditions (for example, $AlCl_3$, acid chloride, and arene in dichloromethane) often give heterogeneous mixtures and are generally not appropriate for continuous-flow synthesis or, at the very least, prone to reactor clogging. Possible solutions included the addition of benzophenone or the use of acetone as the solvent to solvate $AlCl_3$ throughout the course of the reaction. However, these modifications also attenuate the Lewis acidity of the promoter, and accordingly, the rate of product formation (**4**) was sluggish at best.

In a similar vein, we thus explored the possibility of using propionyl chloride (**2**) itself as the means of delivering $AlCl_3$ and thus as the "solvent" (Table 1); approximately 1:1 mixtures of these two reagents were stable for at least three days. With a slight excess of **2** and $AlCl_3$, the reaction afforded aryl ketone **4** in high yield (entry 1). Residence times and reactor temperature could be decreased significantly (entries 2–5) before the reaction yield began to suffer

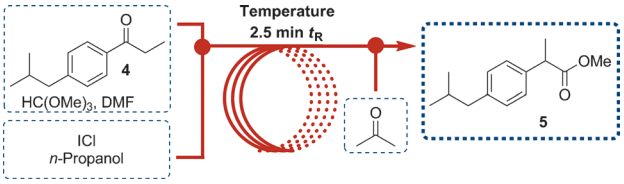
Table 1: Solvent-free and continuous Friedel–Crafts acylation.[a]



Entry	T [°C]	t_R [min]	4[a] [%]	3[b] [%]
1	90	10	96	–
2	90	1.25	92	–
3	70	1.25	99	–
4	50	1.25	97	–
5	30	5	87	–
6	30	2.5	72	24

[a] See the Supporting Information for the reaction conditions. **3** (1.00 equiv, 6.36 M) was combined with **2** (1.17 equiv, 6.5 M) and $AlCl_3$ (1.11 equiv, 6.19 M) in a 600 μL PFA reactor at 250 psi. [b] Yield determined by ^{1}H NMR spectroscopy with an external standard.

Table 2: Oxidative 1,2-aryl migration effected by ICl.[a]



Entry	T [°C]	ICl [equiv]	TMOF [equiv]	Yield[b] [%]
1	90	1	8	17
2	90	2	8	53
3	90	3	8	86
4	90	3	2	15
5	90	3	4	71
6	70	3	8	90
7	50	3	8	88
8	30	3	8	87

[a] See the Supporting Information for the reaction conditions. **4** (1.00 equiv, 0.915 M), TMOF, and DMF (0.25 equiv, 0.23 M) were combined with the indicated amounts of ICl and *n*-propanol in a 120 μL PFA reactor at 250 psi. [b] Yield determined by ^{1}H NMR spectroscopy with an external standard.

(entry 6). Heating of this highly exothermic reaction demonstrates operational advantages and capabilities of continuous-flow synthesis over the analogous batch processes.

The aluminum reagent was not compatible with subsequent reactions, however, causing immediate reactor clogging. An in-line quench of the Lewis acid provided a solution (Table 1). Whereas aluminum oxides flocculate in neutral or basic aqueous media, they are soluble below pH 4.5.

Using HCl (1M) for quenching the Friedel–Crafts acylation smoothly afforded an easily handled mixture of two immiscible liquids (product **4** (neat) and Al byproducts in water), further demonstrating the benefit of continuous flow. Uncontrolled exothermic processes and the release of large quantities of HCl vapors were thus avoided. Use of an in-line liquid–liquid separator after this quench afforded the desired product **4** as a neat liquid in 90% yield.

Based on the method of Yamauchi, I_2, ICl, and ICl_3 were explored as promoters of the 1,2-aryl migration leading to methyl ester **5**.[7] All of these reagents are relatively inexpensive and readily obtained sources of I^I or I^{III}; however, both I_2 and ICl_3 required significant quantities of solvent for dissolution, and stock solutions of I_2 appeared to lose efficacy rapidly. On the other hand, ICl is a low-melting, polymorphic solid (α-ICl, m.p. 13.9 °C; β-ICl, m.p. 27.2 °C), and as shown in Table 2, only very small amounts of solvent were required to use this deliquescent solid in the continuous-flow system ($[ICl]_0$ ca. 15 M).

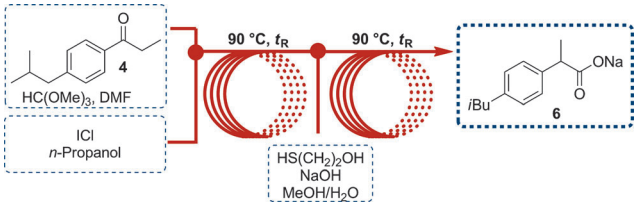
Whereas the Yamauchi conditions in batch afforded the product at room temperature over 24 hours, ICl in continuous flow provides the desired methyl ester very rapidly (t_R = 2.5 min, 90 °C). The stoichiometry of both ICl and trimethyl orthoformate (TMOF) affected the reaction outcome (entries 1–5). The presence of α-haloketones and their dimethyl ketal derivatives as well as recovered starting material accounted for the mass balance in low-yielding reactions. The reactor temperature could be decreased significantly while still maintaining high conversion (entries 6–8).

In order for the reaction to proceed successfully, *N*,*N*-dimethylformamide (DMF) was added to the TMOF feedstock to dissolve any I_2 formed in situ, which would otherwise clog the reactor. Acetone quenched any remaining ICl, which was necessary to avoid rapid oxidation and ultimately destruction of the gold spring inside the back-pressure regulator.

Unfortunately, employment of the acetone quench was not compatible with the subsequent hydrolysis of **5**. The iodo- and chloroacetone formed in the ICl reaction suppressed the mass transfer of **5** into the basic aqueous solution, thus preventing hydrolysis. Alternatively, 2-mercaptoethanol could be used as a water-soluble ICl quenching agent (Table 3). Aqueous solutions with a high methanol content (similar to those of McQuade) did not support the large amounts of sodium halide salts present, and the reactors subsequently clogged (entries 1–3). However, in the absence of methanol, no conversion was noted (entry 4); methanol appears to be needed for phase transfer of the substrate into the aqueous layer. The use of a mixture of methanol and water (1:3) solvated all salts and proved to be a suitable medium for promoting hydrolysis (entries 6 and 7).

With the optimized synthesis in hand, we next developed a continuous multistep large-scale production of ibuprofen sodium carboxylate (**6**) that would be robust for multiple hours (Figure 1). As different pumps are required to handle continuous delivery on this scale, they were exchanged (from standard syringe pumps to Syrris Asia or Knauer HPLC pumps), and a number of problems were manifest from the outset of our studies. These included a need for membrane separation at elevated pressure, the inability of pumps to withstand aggressive reagents (ICl), the instability of reagents (ICl), and clogging as a result of inconsistent reagent delivery ($AlCl_3$). A larger tube diameter in the hydrolysis reaction led to inefficient mixing of the organic and aqueous layers and thus lower substrate conversion. The bigger tubing also

Table 3: Simultaneous quench of excess oxidant and saponification of ester **5**.[a]



Entry	NaOH [M]	MeOH/H_2O	t_R [min]	Yield[b] [%]
1	5	4:1	3	0 (clog)
2	5	2:1	3	0 (clog)
3	5	1:1	3	0 (clog)
4	3	0:1	3	0
5	3	1:3	3	12
6	7	1:3	3	92
7	7	1:3	1	89

[a] See the Supporting Information for the reaction conditions. **4** (1.00 equiv, 0.915 M), TMOF (8.00 equiv, 7.44 M), and DMF (0.25 equiv, 0.23 M) were combined with ICl (3.00 equiv, 15 M) and *n*-propanol (0.71 equiv, 3.5 M) in a 120 μL PFA reactor. This reaction stream was combined with the indicated amounts of 2-mercaptoethanol, NaOH, MeOH, and H_2O in a 200 μL reactor at 250 psi. [b] Yield determined by ^{1}H NMR spectroscopy with an external standard.

seemed to cause over-pressurization of the system as sediments sporadically settled, built to a critical mass, and then flushed through the reactor in concentrated portions.

The use of a single pumping system (i.e., exclusively syringe pumps or exclusively HPLC pumps) was not feasible. For example, Syrris syringe pumps could not be used for the quench with HCl (1N) because the transient delays in the delivery of fluid that occur when the internal pump valves change direction would create small slugs of unquenched, concentrated $AlCl_3$, invariably leading to clogging. HPLC pumps could not be deployed for certain operations because they are not chemically compatible with the aggressive $AlCl_3$ and ICl reagents.

Nevertheless, a combination of pumps provided a robust system. For instance, the Syrris Asia pump handled the mixture of **2** and $AlCl_3$, and an HPLC pump provided smooth, consistent delivery of the quenching solution. In this way, the Friedel–Crafts reaction was scaled up in a 1 mL reactor to production rates of 0.540 g of **4** per minute.

Separation of aryl ketone **4** from aluminum-containing aqueous fractions was key, as solid formation resulted from presence of the Lewis acid in the company of subsequent reagents. To effect the isolation of **4**, a pressurized, in-line liquid–liquid separation system was developed. In situ formation of HCl and vaporization of water in the exothermic quench could lead to high volumes of gases and inconsistent flow rates thus disrupting membrane separation. However, operation under elevated pressure mitigated these concerns and allowed for the smooth isolation of the aqueous and organic phases. A very fine degree of control over the pressure was achieved by using back-pressure regulators designed by Zaiput, a requisite condition for successful separation. Separations are highly important in multistep syntheses. The removal of undesired compounds aids purification and decreases the chances of clogging in subsequent transformations. As such, this strategy will likely find further use in the future.

Iodine monochloride also caused problems under longer continuous operation; however, these difficulties led to the development of an even more attractive solution. First, ICl in *n*-propanol tends to disproportionate over time, forming the less soluble I_2, which clogs syringes and is of lower reactivity in the oxidative rearrangement. Second, the aggressive oxidant could not be pumped by the Asia syringe pump; ICl corroded the pump valves, leading to excessive leaking and failure of the system. The latter problem was solved through redesign of the pump valve by Syrris.[8] The problem of disproportionation was solved by eliminating the use of *n*-propanol to liquefy the oxidant (Figure 2).

As ICl melts at low temperatures, it could be pumped neat, that is, without the use of an alcohol solvent that would

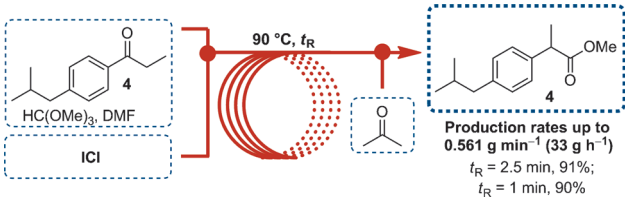


Figure 2. Oxidative 1,2-aryl shift effected by neat ICl. Reaction conditions: **4** (1.00 equiv, 0.915 M), TMOF (8.00 equiv, 7.44 M), and DMF (0.25 equiv, 0.23 M) were combined with ICl (3.00 equiv, 19 M) in a 120 μL PFA reactor held at 250 psi.

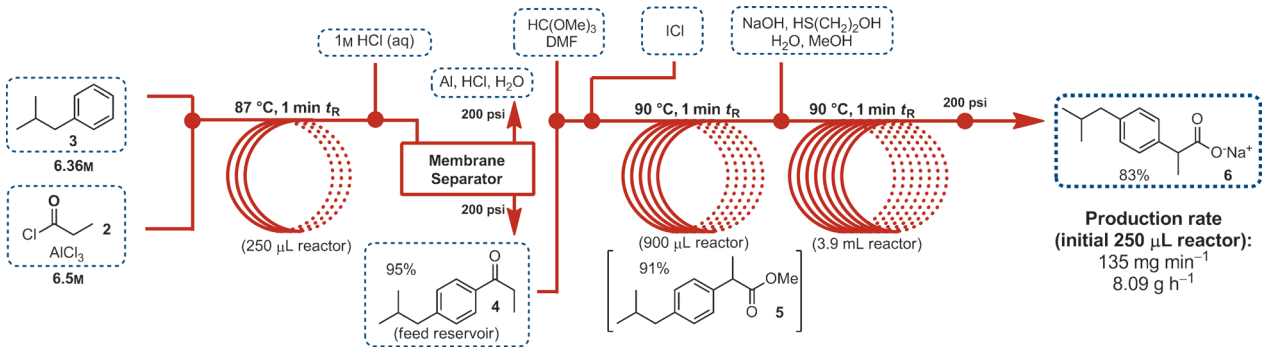


Figure 1. Scale-up of the three-minute ibuprofen synthesis. See the Experimental Section for details.

promote conversion into I_2 and thus promote clogging. Depending on the source and lot number, ICl is supplied commercially as a liquid, solid, or as a mixture of both, the proportion being dependent upon the ratio of the α and β polymorphs. If the reagent is a solid, it can be pumped either by gently warming at 35 °C prior to use or by addition of I_2 (5–10 mol %), which melts the solid ICl. With ICl pumped neat, 91 % yield was obtained with $t_R = 2.5$ min. The residence time was further shortened to one minute with little effect on yield, and rates of production of over 500 mg of **5** per minute were achieved.

The reagent solution for the ICl quench and ester hydrolysis directly joined the reaction mixture feed. With a t_R of only one minute, carboxylate **6** was formed in high yield, thus completing the ibuprofen synthesis. The use of tubing with a narrow inner diameter (0.03 inches) was critical to the success of the reaction. When tubing with a larger inner diameter was selected, the reaction failed to reach complete conversion owing to inefficient mixing of the aqueous/organic biphasic system. More alarming was the accompanying steady rise in pressure (up to 380 psi). The system would eventually fail, releasing the contents of the reactors. The pressure rise was attributed to small amounts of sediment that slowly accumulated and deposited at the bottom of the reactor coils. These settled solids seemed to flush through the system in concentrated segments. After the system had been operated for several resident times, these solids accumulated to a level that restricted liquid flow. The increase in pressure would periodically dislodge solids, driving them through the reactor to the narrower inlet of a downstream pressure regulator.

When reactors were constructed from narrower tubing (inner diameter: 0.03 inches), the sediment was observed neither in the reactor nor in the effluent. As a result, a pressure rise was not observed, and the system could be run for up to two hours without incident. Possibly explanations include that better mixing dissolved the salts or that better conversion minimized precipitation. The addition of a second in-line separation step after the hydrolysis afforded pure ibuprofen (> 98 %, analyzed by ^{1}H NMR spectroscopy). Hexane was used to remove organic impurities, and hydrochloric acid precipitated ibuprofen from the aqueous stream.

The synthesis demonstrates the capability of continuous-flow procedures to handle extreme conditions in the production of pharmaceutical compounds and to generate large quantities of APIs from small-footprint reactors. Three synthetic operations were conducted sequentially, and each reaction was complete within one minute. An overall yield of 83 % was achieved for the three-minute synthesis of ibuprofen. Simple, inexpensive, and readily available reagents were employed, replacing triflic acid with aluminum chloride and (diacetoxy)iodobenzene with iodine monochloride. The exothermic Friedel–Crafts reaction was conducted not only at elevated temperature, but also without external solvent. Starting material **2** and product **4** successfully kept the inorganic salt $AlCl_3$ in solution, and the small quantities of reactants at a given time mitigated the risk of uncontrolled exothermic processes. Highly corrosive iodine monochloride was pumped neat for several hours without pump failure, enabling very rapid methyl ester formation in the oxidative 1,2-aryl rearrangement. Current efforts are directed towards extending the use of continuous-flow methods to even more challenging multistep syntheses.

Experimental Section

Scale-up of the synthesis of sodium 2-(4-isobutylphenyl)propanoate (**6**): A combination of Syrris Asia syringe pumps and Knauer HPLC pumps were used, and reactors were made from coils of perfluoroalkoxyalkane (PFA) tubing (inner diameter: 0.03 inches) immersed in heated oil baths (Friedel–Crafts reaction: 250 μL; oxidative aryl shift: 900 μL; hydrolysis: 3.9 mL). Reagent streams were combined using Tefzel T-mixers with inner diameters of 0.02 inches (IDEX). Fine pressure control was required to achieve separation of the aqueous and organic phases at elevated pressures. Pressure regulators by Zaiput were used to achieve this fine control along with the liquid–liquid separator previously described,[3a] and the system pressure was adjusted to 200 psi. The outlets of the separator were connected to the pressure regulator.

Isobutyl benzene was transported with an HPLC pump (114 μL min^{-1}) while a Syrris Asia pump was used for the mixture of propionyl chloride (16.7 mL, 191 mmol) and $AlCl_3$ (24.2 g, 182 mmol; 136 μL min^{-1}). The reaction was heated just below the point at which HCl would escape from solution, 87 °C. After the reaction, 1 M HCl was added with an HPLC pump (500 μL min^{-1}). The quenched solution flowed through a mixing loop (1.5 mL) and then into the liquid–liquid separator.

Neat aryl ketone **5** was collected in a scintillation vial acting as a substrate reservoir for the oxidative aryl shift. A Knauer HPLC pump enabled the flow of **5** (144 μL min^{-1}), which joined the stream of TMOF (97.8 mL, 894 mmol) and DMF (2.17 mL, 28.1 mmol), also transported by an HPLC pump (630 μL min^{-1}). Iodine monochloride was added subsequently with an Asia syringe pump (109 μL min^{-1}). The reactor was heated at 90 °C ($t_R = 1$ min).

After the oxidative aryl shift, the hydrolysis mixture (500 mL), which consisted of 2-mercaptoethanol (18.0 mL, 265 mmol) and NaOH (140 g, 3.5 mol), was dissolved in a 3:1 mixture of water and methanol and added to the flow of the reaction mixture at a rate of 3 mL min^{-1} with aid of an HPLC pump. The reaction was performed at 90 °C ($t_R = 1$ min). After the amount corresponding to 15 resident volumes had passed, a sample was collected for analysis. The sample was collected for a period of one minute, and the base was immediately neutralized with 1 M HCl to pH 3 to prevent further hydrolysis of the remaining methyl ester **5**. Ibuprofen was extracted three times with hexanes, and the combined organic fractions were dried with $MgSO_4$. Mesitylene was added as an external standard, and a ^{1}H NMR spectrum was acquired in $CDCl_3$ to analyze the reaction. The proton NMR shifts matched those reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$ (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 3.81 (q, $J = 7.2$ Hz, 1H), 2.56 (d, $J = 7.2$ Hz, 2H), 2.04–1.89 (m, 1H), 1.61 (d, $J = 7.2$ Hz, 3H), 1.02 ppm (d, $J = 6.6$ Hz, 6H).

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