Synthesis Design

DOI: 10.1002/anie.200903055

The Continuous-Flow Synthesis of Ibuprofen**

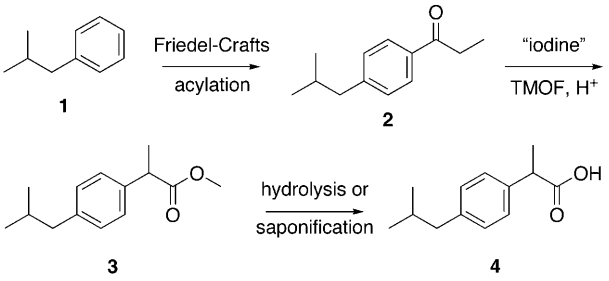
*Andrew R. Bogdan, Sarah L. Poe, Daniel C. Kubis, Steven J. Broadwater, and D. Tyler McQuade**

Organic synthesis is a powerful enterprise that continues to develop more selective and efficient chemical methods and synthetic routes. To synthesize complex molecules, whether in academic laboratories or industrial manufacturing, reactions are often performed iteratively in batch reactors. Although these stepwise methods are effective, they are also very wasteful. The pharmaceutical industry, for example, produces 25–100 kg of waste for every kilogram of a complex molecule synthesized.[1] Though chemists are constantly striving to devise more efficient syntheses, recent reminders of a resource-limited world underscore the need for more sustainable methods and technologies to synthesize molecules of importance.[2] The application of new technologies, such as microreactors, to organic synthesis can be used to achieve this goal.[3–13]

Microreactors are a developing technology used to perform safer, more efficient, and more selective chemical transformations in microchannels or narrow-bore tubing.[3–19] The many advantages associated with conducting reactions in flow are attributed to large surface-area-to-volume ratios[5] that allow precise reaction control through rapid heat transfer and mixing.[20–23] The syntheses can be scaled up by running a single reactor for extended periods of time[24] or by the addition of more identical flow reactors in parallel, a process known as numbering up.[25–27]

Although most applications of microreactors in organic synthesis have focused on single-step reactions,[3–19] recent examples have demonstrated multistep reaction sequences in flow.[20,28–32] Our group has a long-standing interest in the development of new methodologies that enable the rapid and efficient synthesis of important small molecules.[33–36] Specifically, we have aimed to run multistep reaction sequences in one pot (i.e. in batch reactors)[35,36] or in series (i.e. in microreactors).[33,34] We report herein a three-step, continuous-flow synthesis of ibuprofen, a high-volume, nonsteroidal anti-inflammatory drug (NSAID), using a simplified microreactor that eliminates the need for purification and isolation steps.

To achieve this continuous-flow synthesis, a careful retrosynthetic analysis of ibuprofen was performed, considering the synthesis of ibuprofen as an entity, as opposed to a series of independent reactions steps. Reactions therefore had to be designed such that byproducts and excess reagents from one reaction were compatible with downstream reactions. In this way, reactions could be performed in sequence without any breaks in the synthesis. The general three-step synthesis of ibuprofen we investigated is outlined in Scheme 1.[37]



Scheme 1. Proposed synthetic route to ibuprofen. "iodine" = I_2 or PhI(OAc)$_2$, TMOF = trimethylorthoformate.

We surveyed multiple catalysts for the Friedel–Crafts acylation. Of these, $AlCl_3$ provided the highest yield, but byproducts from this reaction proved to be incompatible with downstream steps. Mixing isobutylbenzene (IBB, **1**) and propionic acid with triflic acid (TfOH) proved to also be an effective method to synthesize **2** (Figure 1).[38–40] This TfOH/propionic acid system was not only effective with the first step but was also compatible with the second step.

To run acylation experiments under continuous-flow conditions, a solution of IBB and propionic acid was mixed with a stream of TfOH at a tee junction,[41] resulting in plug flow (see the Supporting Information). When the reactor was heated to 50 °C with a five-minute residence time, only a 15 %

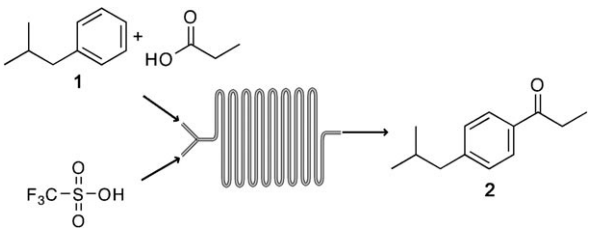


Figure 1. Setup of the Friedel–Crafts acylation in a flow reactor.

[*] D. T. McQuade
Department of Chemistry and Biochemistry
Florida State University, Chemical Sciences Laboratory
Tallahasee, FL 32306 (USA)
Fax: (+1) 850-644-8281
E-mail: mcquade@chem.fsu.edu

A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater
Department of Chemistry and Chemical Biology
Cornell University, Baker Laboratory, Ithaca, NY 14853 (USA)

[**] D.T.M. acknowledges NSF SGER, ARO (grant no. W911NF-06-1-0315), NSF (CHE-0809261), and Florida State University for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903055.

conversion was obtained (Table 1, entry 1). Increasing the reaction temperature produced better results, with 150 °C giving the highest conversion and yield (Table 1, entry 3).[42]

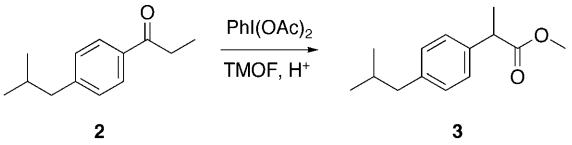
Table 1: The optimization of the Friedel–Crafts acylation under continuous-flow conditions.[a]

Entry	Flow rate [μL min^{-1}]	Residence time [min]	T [°C]	Conv. [%][b]
1	87.5	5	50	15
2	87.5	5	100	52
3	87.5	5	150	91 (70)[c]

[a] Standard reactions conditions: 1.0 equiv IBB, 1.0 equiv propionic acid, and 5.0 equiv TfOH. [b] Conversion determined using GC with dodecane as an internal standard. [c] Number in parentheses corresponds to yield of product isolated after column chromatography.

In a continuous-flow synthesis requiring no intermediate purification steps, byproducts and excess reagents from prior steps must be compatible with downstream reactions. Therefore, it was essential that the excess reagents (TfOH and unreacted IBB) used in the Friedel–Crafts acylation were compatible with the second step of our reaction sequence, the 1,2-aryl migration. Literature precedence indicates the addition of acid to a mixture of aryl ketones, trimethyl orthoformate (TMOF), and PhI(OAc)$_2$ affords 2-arylpropanoates in high yield (Scheme 2).[37,43,44]

Using propiophenone as a test substrate, we discovered that TfOH is compatible with the 1,2-aryl migration (Scheme 2), affording high yields of methyl ester **5** with a 2-min residence time (Figure 2). These conditions were used in the second step of our multistep reaction sequence to convert **2** to methyl ester **3**. For a detailed description of the optimization, see the Supporting Information.



Scheme 2. The PhI(OAc)$_2$-mediated 1,2-aryl migration of 4-isobutylpropiophenone.

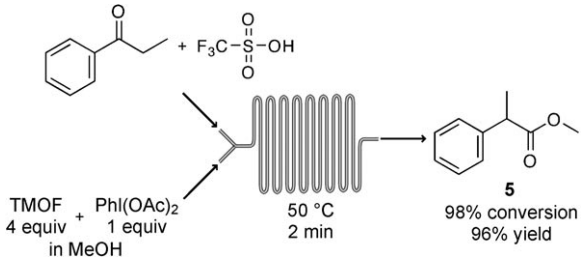


Figure 2. Optimized reaction conditions for the PhI(OAc)$_2$-mediated 1,2-aryl migration in a flow reactor.

With the first two reactions separately optimized, we assembled the system so that the product stream from the Friedel–Crafts acylation was immediately relayed into the 1,2-aryl migration using the conditions outlined above (Figure 3). This system requires no additional acid because the TfOH from the Friedel–Crafts acylation also facilitates the 1,2-aryl migration. To achieve efficient mixing of the outlet stream from the first step with the PhI(OAc)$_2$/TMOF reagent stream for the second step, a tee junction was modified such that the inner diameter was 0.75 mm and packed with glass beads (250–300 μm). This mixer was cooled to 0 °C and proved to mix the two streams effectively,[45] resulting in a 70% yield for the two steps after column chromatography, with quantitative conversion of **2** to methyl ester **3**.

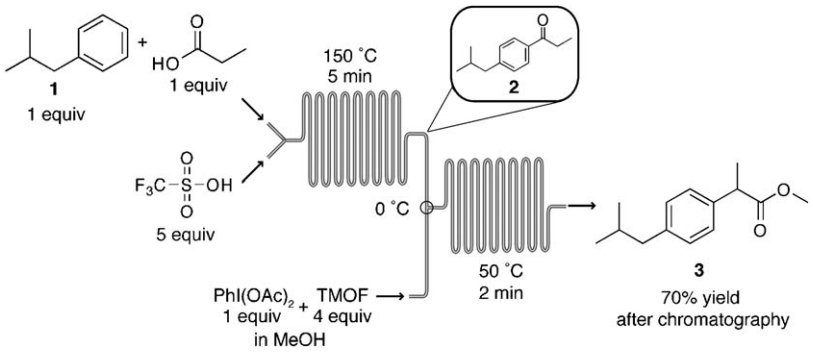


Figure 3. The two-step reaction sequence to methyl ester **3**.

The final step in the continuous-flow synthesis of ibuprofen was achieved by saponifying methyl ester **3** with KOH (Figure 4). The outlet stream from the second step was combined with a stream of 5 M KOH and heated to 65 °C for three minutes. The excellent heat transfer of the microreactor allows the acidic stream to be mixed with the basic stream without danger from the exotherm. Sampling the outlet stream showed only the presence of residual IBB, iodobenzene,[46] and trace amounts of methyl ester **3**. After an acidic workup, ibuprofen (**4**) was obtained in 68% crude yield and 51% yield (99% purity by GC and NMR analysis) after recrystallization.[47]

In summary, we have developed a continuous-flow synthesis of ibuprofen using an efficient three-step process that requires no purification of intermediates. Using less than 500 cm of tubing and five syringe pumps, the flow synthesis reported herein generates approximately 9 mg min^{-1} crude ibuprofen. Addition of parallel reactors or lengthening the channels coupled with alternative pumping mechanisms would permit a continuous, high-throughput synthesis of ibuprofen. Potential scale-up of this method would also benefit from the precise temperature control (from 150 °C to 50 °C in sequential steps) and the excellent control of exotherms (caused by transitioning from pH 1 to 14). Performing this series of reactions on large scale in batch would be unfavorable because of the energy requirements to safely control these temperatures. We seek to apply this

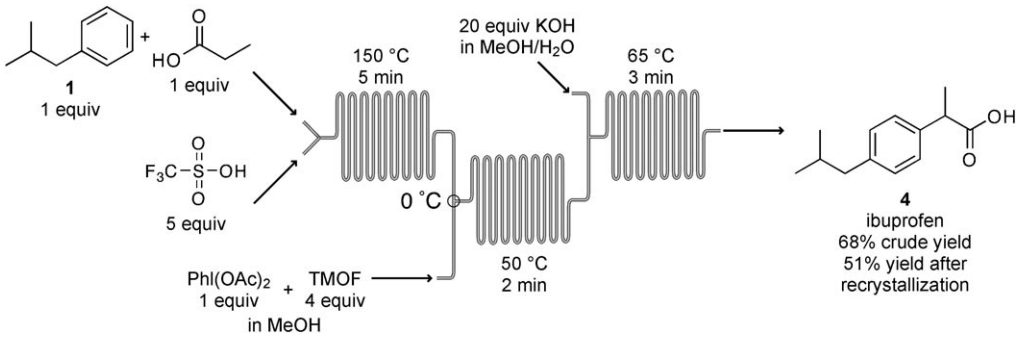


Figure 4. The three-step, continuous-flow synthesis of ibuprofen.

methodology to other 2-arylpropionic acid derivatives, such as naproxen, and to develop recyclable, supported catalysts for the Friedel–Crafts acylation and 1,2-aryl migration.

Experimental Section

General description of the continuous-flow synthesis of ibuprofen: In one syringe was placed a solution of IBB (4.3 M) and propionic acid (4.3 M), and in another syringe was placed neat TfOH (11.3 M). The IBB/propionic acid syringe was set to 15.1 μL min^{-1} (64.9 μmol min^{-1}), and the TfOH syringe was set to 28.7 μL min^{-1} (324.6 μmol min^{-1}). The reaction stream was allowed to pass through a 50 cm segment of perfluoroalkoxy (PFA) tubing submerged into an oil bath set to 150 °C.

To the outlet of the first reactor was attached an ethylene tetrafluoroethylene (ETFE) tee. A solution of $PhI(OAc)_2$ (0.5 M) and TMOF (2.0 M) in MeOH was placed in a syringe and set to 131.5 μL min^{-1} (65.8 μmol $PhI(OAc)_2$ min^{-1} and 259.6 μmol TMOF min^{-1}) and connected to the tee. The tee was submerged in an ice bath, and the outlet of the tee was connected to an 80 cm segment of PFA tubing and submerged into an oil bath set to 50 °C.

To the outlet of the second reactor was attached an ETFE tee using a flangeless nut. A solution of KOH (5.0 M) in MeOH/H_2O (4:1 v/v) was placed in a syringe and set to 260.0 μL min^{-1} (1300.0 μmol min^{-1}). The outlet of the tee was connected to a 300 cm segment of PFA tubing submerged into a water bath set to 65 °C.

The reaction was collected in a 100 mL round-bottom flask. Once the collection was complete, deionized (DI) H_2O (25 mL) was added to the round-bottom flask, and the methanol was evaporated using rotary evaporation. The aqueous phase was washed with Et_2O (3 × 30 mL), acidified with concentrated HCl, and extracted with Et_2O (3 × 30 mL). The organic extracts were repeatedly washed with DI H_2O (5 × 20 mL) until the pH of the aqueous phase was neutral. The organic extracts were subsequently washed with brine (1 × 20 mL), dried over Na_2SO_4, filtered, concentrated, and dried to yield a light orange solid (68 % crude yield, average of three trials, ≈96 % purity by GC and GC–MS analysis). The solid was dissolved in Et_2O and treated with activated carbon. The activated carbon was removed by filtration through a plug of anhydrous $MgSO_4$. The Et_2O was removed to yield an off-white solid, which was recrystallized from heptane. A seed crystal was added to initiate crystallization. The filtrate was removed and the crystals were dried under vacuum to afford ibuprofen as an off-white solid (51 % yield, average of three trials, 99 % purity by GC and GC–MS analysis). Additional charcoal treatments could be performed to remove residual color after recrystallization without impacting yield: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$ (d, 2H), 7.13 (d, 2H), 3.71 (m, 4H), 2.48 (d, 2H), 1.86 (m, 1H), 1.52 (d, 3H), 0.93 ppm (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.4$, 140.7, 137.9, 129.5, 127.3, 52.1, 45.21, 45.18, 30.3, 22.6, 18.8 ppm. MS m/z 220 [M^+].

Received: June 6, 2009
Published online: October 6, 2009

Keywords: continuous processing · flow chemistry · microreactors · reactor design · synthetic methods

[1] R. A. Sheldon, *J. Chem. Technol. Biotechnol.* **1997**, *68*, 381.
[2] P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686.
[3] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300.
[4] V. Hessel, P. Löb, H. Löwe, *Curr. Org. Chem.* **2005**, *9*, 765.
[5] V. Hessel, H. Löwe, *Chem. Eng. Technol.* **2005**, *28*, 267.
[6] P. Hodge, *Curr. Opin. Chem. Biol.* **2003**, *7*, 362.
[7] G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708.
[8] A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem.* **2001**, *113*, 670; *Angew. Chem. Int. Ed.* **2001**, *40*, 650.
[9] H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Löwe, *Org. Process Res. Dev.* **2004**, *8*, 422.
[10] *Microreactors in Organic Synthesis and Catalysis* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2008**.
[11] P. Watts, C. Wiles, *Org. Biomol. Chem.* **2007**, *5*, 727.
[12] T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151.
[13] B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733.
[14] M. T. Reetz, W. Wiesenhofer, G. Francio, W. Leitner, *Adv. Synth. Catal.* **2003**, *345*, 1221.
[15] C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* **2003**, *59*, 10173.
[16] P. W. Miller, N. J. Long, A. J. Mello, R. Vilar, J. Passchier, A. Gee, *Chem. Commun.* **2006**, 546.
[17] G. Shore, S. Morin, M. G. Organ, *Angew. Chem.* **2006**, *118*, 2827; *Angew. Chem. Int. Ed.* **2006**, *45*, 2761.
[18] F. Bonfils, I. Cazaux, P. Hodge, C. Caze, *Org. Biomol. Chem.* **2006**, *4*, 493.
[19] I. R. Baxendale, C. H. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407.
[20] J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450, and references therein.
[21] A. Nagaki, N. Takabayashi, Y. Tomida, J. Yoshida, *Org. Lett.* **2008**, *10*, 3937.
[22] A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem.* **2008**, *120*, 7951; *Angew. Chem. Int. Ed.* **2008**, *47*, 7833.
[23] J. M. J. van der Linden, P. W. Hilberink, C. M. P. Kronenburg, G. J. Kemperman, *Org. Process Res. Dev.* **2008**, *12*, 911.
[24] A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849.

[25] W. Ehrfeld, V. Hessel, H. Lowe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, **2000**.
[26] C. H. Hornung, M. R. Mackley, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 399.
[27] D. R. J. Acke, C. V. Stevens, *Org. Process Res. Dev.* **2006**, *10*, 417.
[28] H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 5806; *Angew. Chem. Int. Ed.* **2007**, *46*, 5704.
[29] I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566.
[30] I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017.
[31] I. R. Baxendale, C. H. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Synlett* **2006**, 42.
[32] D. Grant, R. Dahl, N. D. P. Cosford, *J. Org. Chem.* **2008**, *73*, 7219.
[33] A. R. Bogdan, B. P. Mason, K. T. Sylvester, D. T. McQuade, *Angew. Chem.* **2007**, *119*, 1728; *Angew. Chem. Int. Ed.* **2007**, *46*, 1698.
[34] A. R. Bogdan, D. T. McQuade, *Beilstein J. Org. Chem.* **2009**, *5*, 17.
[35] S. L. Poe, M. Kobašlija, D. T. McQuade, *J. Am. Chem. Soc.* **2006**, *128*, 15586.
[36] S. L. Poe, M. Kobašlija, D. T. McQuade, *J. Am. Chem. Soc.* **2007**, *129*, 9216.
[37] Y. Tamura, T. Yakura, Y. Shirouchi, J. Haruta, *Chem. Pharm. Bull.* **1985**, *3*, 1097.
[38] R. M. G. Roberts, A. R. Sadri, *Tetrahedron* **1983**, *39*, 137.
[39] F. Effenberger, G. Epple, *Angew. Chem.* **1972**, *84*, 295; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 300.
[40] It is proposed that the reaction of triflic acid with propionic acid leads to the generation of a protonated mixed anhydride, a very active acylating agent.
[41] In our flow reactor, the use of PFA tubing and unions was critical to withstand the caustic nature of TfOH. For a detailed description of the materials used, see the Supporting Information.
[42] Similar yields were obtained when the Friedel–Crafts acylation was performed in batch at 150 °C.
[43] O. V. Singh, O. Prakash, C. P. Garg, R. P. Kapoor, *Ind. J. Org. Chem.* **1989**, *28B*, 814.
[44] O. Prakash, S. Goyal, R. M. Moriarty, J. S. Khosrowshahi, *Ind. J. Org. Chem.* **1990**, *289B*, 304.
[45] It was found to be necessary to cool the tee junction owing to significant off-gassing that occurred when it was held at room temperature. This off-gassing did not occur during the optimization and therefore this tee junction did not need to be cooled.
[46] Iodobenzene is the byproduct of the 1,2-aryl migration. It can be converted back to $PhI(OAc)_2$ by treatment with peracetic acid.
[47] The low yield from the recrystallization of ibuprofen is most likely a consequence of the small scale. The recrystallizations of larger batches of ibuprofen gave higher yields.

