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A Rapid Total Synthesis of Ciprofloxacin Hydrochloride in Continuous Flow

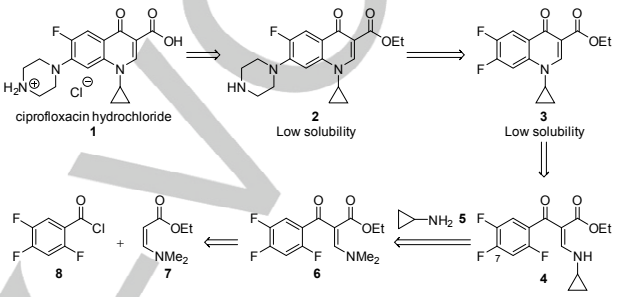
Hongkun Lin,[a] Chunhui Dai,[b] Timothy F. Jamison*[b] and Klavs F. Jensen*[a]

Abstract: Within a total residence time of 9 min, the sodium salt of ciprofloxacin was prepared from simple building blocks via a linear sequence of six chemical reactions in five flow reactors. Sequential offline acidifications and filtrations afforded ciprofloxacin and ciprofloxacin hydrochloride. The overall yield of the eight-step sequence was 60 %. No separation of intermediates was required throughout the synthesis when a single acylation reaction was applied to remove the main byproduct, dimethylamine.

Continuous flow synthesis has emerged as an efficient technique in synthetic chemistry. The rapid mixing as well as enhanced heat and mass transfer in flow reactors allow better control of reaction selectivity.[1] An elegant example is the selective reduction of esters to aldehydes.[2] Extremely rapid lithiation reactions also showcase the unprecedented control of reactions in microreactors.[3] In addition, flow reaction technology enables much safer operation under conditions of high temperature and high pressure.[1d,4]

Several elegant examples of multistep synthesis have been performed in flow reactors,[5] but efficient telescoping of reactions still remains a challenge owing to needs for solvent switches,[5c,5f-h,6a] mismatch of flow rates,[5c,5f-h] and necessity of workup[5a,5g-h]. Herein, we report a total synthesis of ciprofloxacin in **continuous** flow, in which six reactions are telescoped in five reactors sequentially without any separation or isolation of intermediates. To the best of our knowledge, this is the longest linear sequence of reactions telescoped in flow to date, without holding the reaction stream.[7]

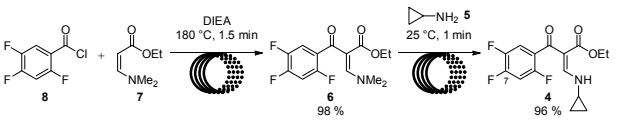
Ciprofloxacin is on the World Health Organization List of Essential Medicines.[8] It belongs to the family of fluoro-quinolone antibiotics and is used to treat a number of types of bacterial infections. Bayer AG developed and patented a seven-step synthesis in the 1980s, with an overall yield of 49 % and > 24 h of reaction time.[9] Later, a similar sequence of reactions were performed on resin supported analog of **6** (Scheme 1), slightly increasing the overall yield to 57 % but with > 100 h reaction time.[10]



Scheme 1. Retrosynthesis of ciprofloxacin hydrochloride.

Taking advantage of flow chemistry, we are aiming to increase the synthetic efficiency of ciprofloxacin. Our synthetic plan is shown in Scheme 1. Acylation of commercially available acyl chloride **8** with vinylogous carbamate **7** would afford **6**. Ciprofloxacin hydrochloride **1** would be generated after displacement with cyclopropylamine **5**, two regioselective S_NAr reactions, hydrolysis of ester and acidification.

We started with screening solvents and bases for the acylation of vinylogous carbamate **7** with **8**. Although **6** was obtained in good yields with a handful of bases and solvents in batch, in the context of continuous flow synthesis, the requirement to avoid generation of any precipitates needed to be satisfied. Three combinations of solvent/base were identified, acetonitrile/*N*,*N*-diisopropylethylamine (DIEA), chloroform/DIEA and chloroform/triethylamine (See supporting information for details of screening).[11] Considering that the U.S. Food and Drug Administration (FDA) imposes a concentration limit of 60 ppm of chloroform and 410 ppm of acetonitrile,[12] we selected the combination of acetonitrile/DIEA. At 180 °C and 175 psi, 98 % of **6** was generated with a residence time of 1.5 min. Addition of cyclopropylamine to the crude stream of **6** furnished exchange product **4** in 96 % isolated yield (Scheme 2).



Scheme 2. Preparation of **4** in flow reactors. 1.0 equiv. of **7**, 1.2 equiv. of **8**, 1.15 equiv. of DIEA, 1.25 equiv. of **5**. See supporting information for details.

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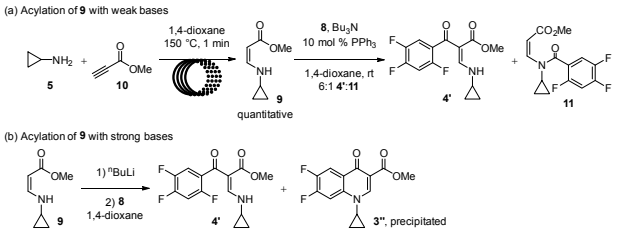
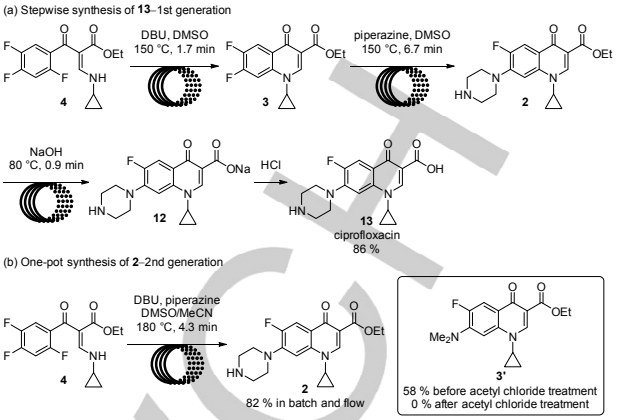
Meanwhile, we also investigated various batch reaction conditions for the direct acylation of **9**, which was prepared by addition of **5** to **10** quantitatively either in batch or in flow.[13] When **9** was treated with weak bases, we obtained a mixture of *C*-acylation (**4'**) and *N*-acylation (**11**) products. Under our best conditions, the ratio of **4'**:**11** was 6:1.[14] Moreover, the reaction was much slower than acylation of **7**, reflecting significant difference in the nucleophilicity of both substrates (Scheme 3a). In contrast, when **9** was deprotonated with strong base ^{n}BuLi, followed by acylation with **8**, cyclization product **3''** immediately precipitated along with a small amount of **4'** (Scheme 3b). We did not optimize this set of conditions in flow, considering both the intolerance of flow reactors with rapid precipitation of **3''** and the higher cost of **10** than **7**.[15]



Scheme 3. Alternative unoptimized methods for preparation of **4'**. Conditions for preparation of **9** in a continuous flow reactor: 1.0 equiv. of **5** (2.0 M in 1,4-dioxane, 222.0 µL/min), 1.0 equiv. of **10** (2.0 M in 1,4-dioxane, 222.0 µL/min), 150 °C, 1 min, 200 psi back pressure.

We continued our flow synthesis with the acylation-exchange method. In agreement with Schwalbe's report,[11] competitive substitution by $HNMe_2$ to form **3'** (Scheme 4),[16] lowered the yield of desired cyclization product **3** to 24 %. Different from Schwalbe and coworkers who removed $HNMe_2$ by evaporation, which would otherwise result in discontinuous operation, we employed a rapid acylation reaction for the removal of $HNMe_2$ to ensure continuous operation. Simply by mixing the crude reaction mixture of **4** after exchange with acetyl chloride and DIEA at ambient temperature for a residence time of 1 min, $HNMe_2$ was completely converted to *N*,*N*-dimethylacetamide (DMA), which did not interfere cyclization under the reaction conditions (Schemes 4 and 5).

Now the stage is set for cyclization. It is noteworthy that the solubility of **2** and **3** is low in a variety of polar aprotic solvents suitable for S_NAr reactions at ambient temperature (*e.g.* solubility of **3** < 0.016 M in DMSO), possibly due to π-π stacking interactions, therefore either higher temperature or high dilution is required for continuous flow synthesis to prevent clogging of reactors. As we observed that it took 1-2 min for the crystals of **2**/**3** to nucleate when cooling from a hot solution, we insulated related connections to prevent clogging. Initially we tried stepwise cyclization and S_NAr reaction and found a residence time of 1.7 min was sufficient for the rapid intramolecular cyclization. Mixing the stream of **3** with a stream of piperazine afforded **2** after a reaction of 6.7 min. Hydrolysis and acidification afforded ciprofloxacin **13** in 86 % yield. Inspired by the formation of side product **3'**, we envisioned that one-pot cyclization and piperazine substitution may be feasible. Indeed, when pure **4** was subjected



Scheme 4. Stepwise and one-pot synthesis of **2** in flow. Reaction conditions: (a) 1.0 equiv. of **4** (0.15 M in DMSO, 2.8 mL/min), 2.0 equiv. of DBU (neat, 118.0 µL/min), 150 °C, 1.7 min; 3.0 equiv. of piperazine (0.8 M in DMSO, 1.58 mL/min), 150 °C, 6.7 min; 4.0 equiv. of NaOH (2 M in H_2O, 0.84 mL/min); Adjusting pH to 7 with HCl offline; 86 % isolated yield. (b) 82 % isolated yield. See supporting information for details.

to DBU and piperazine, **2** was obtained with 82 % yield in batch. After some optimization (Table 1), almost identical batch yield was observed when crude **4** after acetyl chloride treatment was used. The one-pot reaction was monitored by ^{1}H NMR. **4** was first deprotonated to form one anionic species followed by cyclization and piperazine substitution sequentially. We were then able to telescope the five reactions to afford **2** in 82 % overall yield in flow under optimized conditions (Schemes 4b and 5).

Table 1. Optimization of one-pot cyclization–S_NAr reaction of crude **4** in batch.[a]

Entry	DBU (equiv.)	Piperazine (equiv.)	Yield of **3** (%)[b]	Yield of **2** (%)[b]
1	1.5	1.2	49	16
2	3	1.2	28	59
3	1.5	2.5	53	11
4	3.0	2.5	17	67
5	3.0	3.0	-	81

[a] Reactions were run at 180 °C in sealed vessels for 5 min. [b] ^{1}H NMR yields. 1,3,5-Trimethoxybenzene was used as standard.

Mixing the stream of **2** with a stream of 1.0 M aqueous NaOH for a residence time of 0.9 min afforded the sodium carboxylate **12**. Adjusting the pH of the solution to 7 with aqueous HCl offline enabled precipitation of crude ciprofloxacin **13** in 75 % yield. It was then dissolved in a minimal volume of aqueous HCl to form hydrochloride salt of ciprofloxacin **1**, which was crystallized by additon of acetone (Scheme 5).

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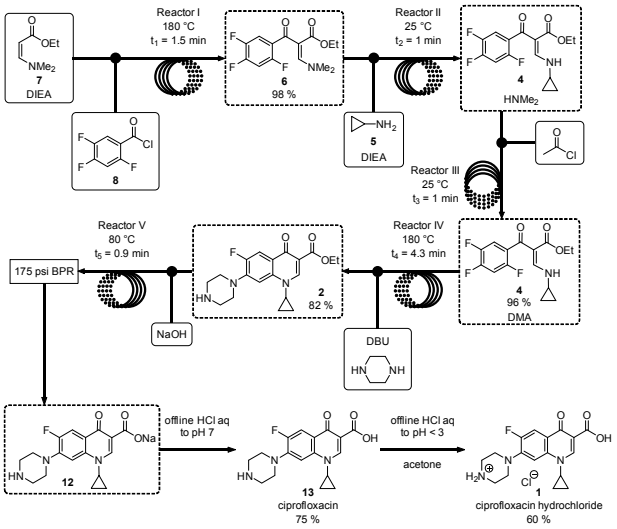

Scheme 5. Flow scheme of continuous total synthesis of ciprofloxacin. 1.0 equiv. of **7**, 1.2 equiv. of **8**,[17] 1.15 equiv. of DIEA, 1.25 equiv. of **5**, 1.15 equiv. of DIEA, 1.2 equiv. of acetyl chloride, 3.5 equiv. of DBU, 3.5 equiv. of piperazine, 6.0 equiv. of NaOH. See supporting information for details. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

In summary, we have developed a rapid total synthesis of ciprofloxacin in continuous flow. The total residence time is 9 minutes, compared to over 24 hours in patented synthesis[9,14] and polymer supported synthesis[10]. The 60 % overall yield is comparable to batch[14] and semi-batch syntheses[11]. To the best of our knowledge, it is the longest linear sequence of reactions telescoped in continuous flow to date without interrupting the flow by any workup requirements. Through meticulous selection of reaction conditions, only one inline workup step is required for the six-step sequence of reactions, in complement to modular flow synthesis.[5c,18] The key to continuous operation is (1) inline acylation of byproduct dimethylamine and (2) keeping the crude solution of **2** warm before entering Reactor V to avoid solid formation, due to its low solubility. Isolation of pure ciprofloxacin involves simple pH adjustment, filtration and washing. This synthesis enables significant reduction of reaction time and waste production.

Acknowledgements

We are grateful to Professor Kai Wang of Tsinghua University, Dr. Jisong Zhang, Dr. Guohua Liang, Dr. Nopphon Weeranoppanant for technical support and helpful discussions. We thank Dr. Marcus O'Mahony and Dr. Naomi Briggs for solubility data of ciprofloxacin **13** and ciprofloxacin hydrochloride salt **1**. We also thank Dr. Bruce Adams in the Department of Chemistry Instrumentation Facility (DCIF) at MIT for NMR assistance. This work was supported by Defense Advanced Research Projects Agency (DARPA) (N666001-11-C-4005).

Keywords: aromatic substitution • ciprofloxacin • continuous flow • multicomponent reactions • multistep synthesis

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[15] For comparison, **10** and **7** are provided by Alfa Aesar at $5.85/gram and $2.20/gram, respectively.

[16] Based on basicity, $HNMe_2$, a byproduct in the exchange reaction, is presumably protonated by DIEA•HCl present in the mixture. $HNMe_2$ is released via neutralization of $HNMe_2$•HCl by DBU under cyclization conditions.

[17] Although the yield of **6** was unchanged with excess of **7**, it is critical to use excess of **8** to ensure complete conversion of **7**, otherwise unreacted **7** would exchange with piperazine to form **3'** in Reactor IV.

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Layout 1:

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Rapid assembly of five building blocks to make ciprofloxacin was achieved in nine minutes in flow. A total of six reactions took place in five reactors to afford ciprofloxacin sodium salt. Simple offline pH adjustment, filtration and crystallization afforded ciprofloxacin hydrochloride crystal.

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