A Two-Step Continuous-Flow Procedure towards Ribociclib

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Received: 29 April 2016; accepted: 08 June 2016

This work describes the manufacturing of ribociclib following the concept of an end-to-end continuous-flow process. The active pharmaceutical ingredient (API) is produced in a two-step telescoped flow process with integrated in-line liquid–liquid extraction and semibatch crystallization.

Keywords: continuous-flow chemistry, end-to-end manufacture, in-line purification

1. Introduction

The pharmaceutical industry undertakes constant efforts to improve process efficiency and to reduce development and manufacturing costs of new pharmaceuticals. In this context, manufacturing of active pharmaceutical ingredients (APIs) applying continuous-flow technologies receives significant attention due to the potential of cost reductions, improved reproducibility and process robustness, enhanced process safety, and shortened lead time to patient [1]. Considering certain factors, such as inventory, cost of quality, manufacturing footprint, and cycle time as well as operational costs and economic benefits, can be expected for certain cases when transforming a traditional batch process into continuous flow or semibatch mode. To maximize the benefit of a continuous-flow process, it is of paramount importance to link upstream and subsequent downstream operations, such as liquid–liquid extraction, distillation, adsorption, and crystallization to purify and isolate the target compound [2].

Our downscale continuous-flow platform for laboratory process development consists of precooling loops for all reagent streams, tubular reactors, continuous syringe pumps (Syrdos2 [3]), pressure sensors for each reagent stream, and a Coriolis mass-flow controller [4]. The platform is software controlled (HiTecZang [3]), enabling for on-line monitoring of temperatures, flow rates, mass-flow, and system pressures, as well as safety shutdown actions based on operator predefined parameters, thereby mitigating the risk of safety relevant incidents.

Herein, we present a two-step telescoped flow process with integrated in-line purification operation and semibatch crystallization towards ribociclib (Figure 1). The synthetic pyrrolopyrimidine moiety **1** is an orally bioavailable, potent, and selective small molecule inhibitor of CDK4/CDK6 for the potential treatment of breast cancers and pediatric solid tumors [5].

2. Results and Discussion

Following the concept of end-to-end manufacture of APIs, we investigated the feasibility of a continuous-flow process towards ribociclib (**1**) starting from the advanced precursors **2** and **3**. Initially, the synthesis of intermediate **4** relied on a palladium-catalyzed Buchwald–Hartwig amination reaction between chloropyrimidine **2** and aminopyridine **3** using the conditions depicted in Scheme 1 [6].

Depletion of residual palladium impurities down to low ppm levels following standard treatment with resins, activated charcoal, and L-cysteine revealed a major challenge to the project and triggered the investigation of an alternative, transition-metal free synthesis of compound **4**.

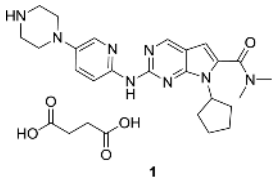

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Figure 1. Ribociclib (**1**)

As the pyrimidine moiety of chloropyrimidine **2** seemed to be sufficiently electron-poor for a nucleophilic aromatic substitution reaction, we envisioned the possibility to form the desired new C–N bond by a nucleophilic attack of aminopyridine **3** towards the heteroaryl chloride **2**.

In a set of screening experiments, a mixture of **2** and **3** was treated with different acids and bases, and the conversion was determined by high-performance liquid chromatography (HPLC) (Table 1). Neither acidic (conc. HCl, AcOH) (entries a and b) [7] nor classical base-promoted conditions [8] led to conversion to the desired intermediate **4**. Thus, bases such as KO*t*Bu, Hunigs base, or DBU either failed to promote the desired reaction or resulted in decomposition of **2** (entries c–e). However, by using more basic non-nucleophilic lithium hexamethyldisilazide (LiHMDS), we were able to obtain 50% conversion to the target compound (entry f). Having identified a promising base, we further improved the transformation by optimizing the base equivalents. Eventually, it was possible to synthesize **4** in 93% by HPLC using 2.2 equivalents of LiHMDS in tetrahydrofuran (THF) at room temperature (entry g). The required excess of base is plausible as the generated secondary amine (**4**) consumes one equivalent of base.

With the new synthesis for compound **4** in place, we next assessed the transformation of **4** to **5**. After a quick optimization, **4** could be converted quantitatively to **5*HCl** using aqueous HCl (3.0 M). Consecutive treatment with aqueous K_2CO_3 (4.8 M) converted **5*HCl** quantitatively to the free base **5** (Scheme 2).

After having optimized both steps in batch mode, we transferred the chemistry into continuous-flow mode using our in-house flow platform. Thus, a mixture of **2** (0.68 M) and **3** (0.70 M) in THF was prepared (stream 1) and mixed with a solution of LiHMDS (1.5 M) in THF (stream 2) using a simple T-piece (perfluoroalkoxy alkanes [PFA], internal diameter [ID] = 0.78 mm) followed by a first tubular reactor (R1) filled with static mixture elements [9] (PFA, outside diameter [OD] = 7 mm, ID = 5 mm) as depicted in Scheme 3. To elaborate the optimal flow conditions for the nucleophilic aromatic substitution, different reaction times and temperatures have been assessed, showing that best conversion to **4** was obtained using a residence time of 3.2 min at 60 °C (bath temperature). Under optimized conditions, stream 1 containing **2** and **3** (0.68 M, 1.0 equiv. and 0.70 M, 1.03 equiv. in THF) with a flow rate of 3.1 mL/min was mixed in a T-piece (PFA, ID = 0.78 mm) with stream 2 containing LiHMDS (1.50 M in THF) with a flow

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DOI: 10.1556/1846.2016.00017

First published online: 11 July 2016

Scheme 1. Original synthesis of **4** via Pd-catalyzed cross-coupling reaction

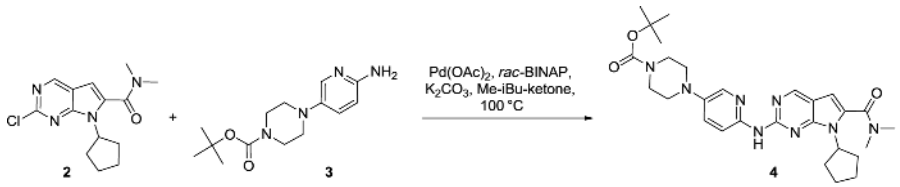
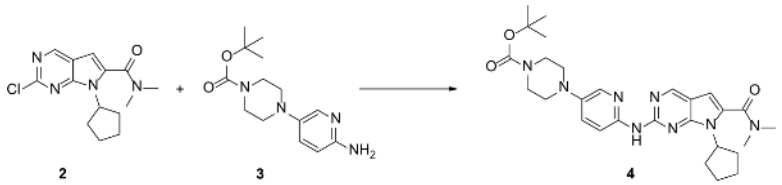


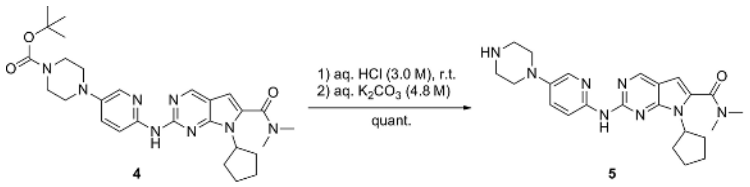
Table 1. Optimization of the reaction conditions for the metal-free synthesis of **4**



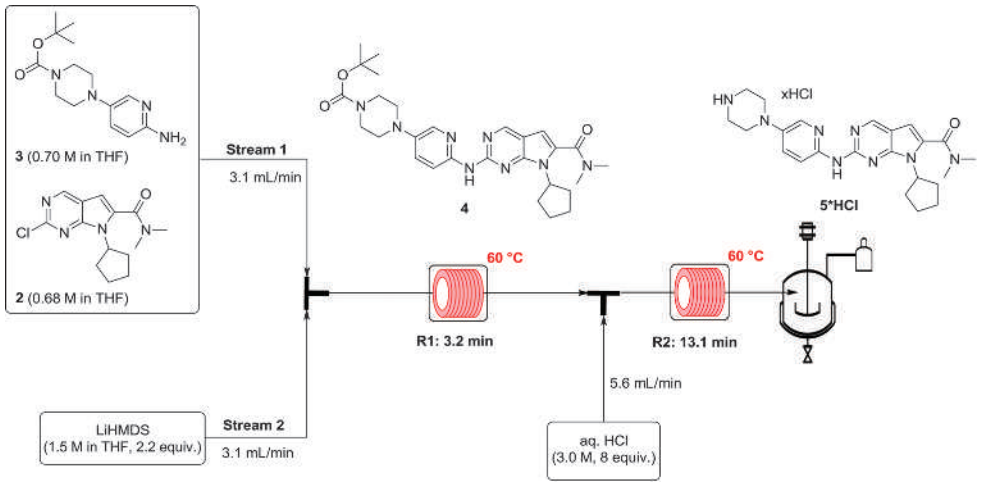
Entry	Additives	Equiv.	Solvent	Conditions	Conversion to **4**[a]
a	HCl (37%)	2.00	NMP	MW150 °C, 10 min	No conversion
b	AcOH	Excess	–	MW150 °C, 10 min	No conversion
c	Hunigs base	2.00	NMP	MW150 °C, 10 min	No conversion
d	*t*BuOK	2.00	*t*BuOH	MW100 °C, 2 min	Decomposition
e	DBU	2.00	*t*BuOH	MW150 °C, 2 min	No conversion
f	LiHMDS	1.05	THF	r.t., 40 min	50%
g	LiHMDS	2.20	THF	r.t., 40 min	94%

[a] Conversion was determined by HPLC (uncorrected) at 210 nm.

Scheme 2. Deprotection of **4** towards the free base **5**



Scheme 3. Continuous-flow setup for the synthesis of **5*HCl**



rate of 3.1 mL/min. The mixture then entered a first reactor (R1, PFA tubing, OD = 7 mm, ID = 5 mm, filled with static mixer elements, vol. = 20 mL) with a residence time of 3.2 min at 60 °C (bath temperature). For the deprotection step, aqueous HCl (3.0 M) with a flow rate of 5.6 mL/min was added using a second T-piece (PFA, ID = 0.78 mm). The reaction mixture was then directed to a second tubular reactor (R2, PFA tubing, OD = 7 mm, ID = 5 mm, filled with static mixer elements, vol. = 154 mL) giving a residence time of 13.1 min at 60 °C (bath temperature), yielding crude **5*HCl** in a purity of 91% by HPLC.

To establish the end-to-end concept towards the synthesis of ribociclib, we further developed an in-line purification device for **5*HCl**, as highly pure material is required for the final crystallization of the succinate salt **1**. Due to the generation of CO_2 and isobutene off-gas during the acid-mediated deprotection step which could lead to safety issues as well as homogeneity problems, the envisioned in-line liquid–liquid extraction system had to resolve these issues. Therefore, we designed the continuous-flow workup unit depicted in Figure 2.

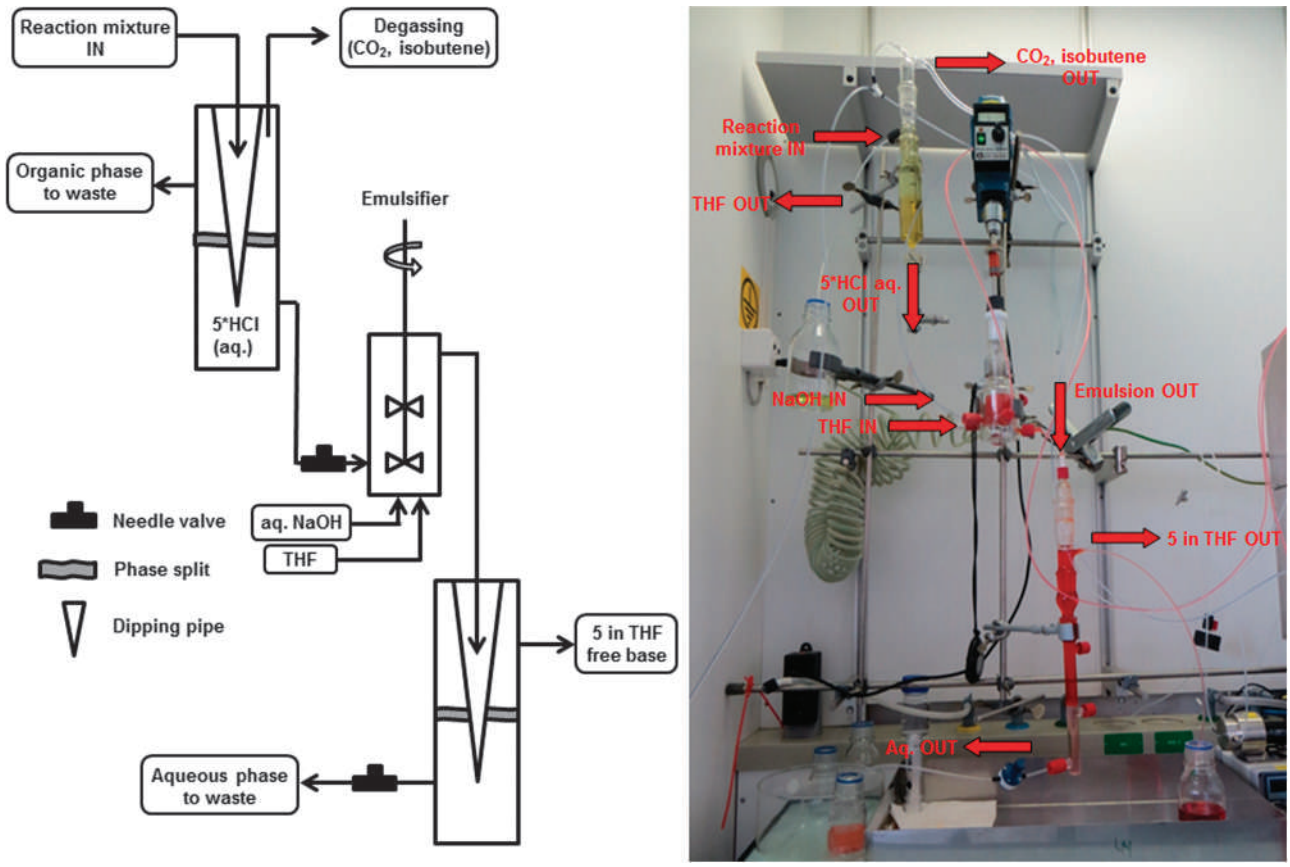


Figure 2. In-line purification system used for the purification of crude **5*HCl**

The crude **5*HCl** reaction stream (THF, water) enters the homemade workup unit at the top through a dipping tube, allowing the two phases to rapidly split. The high salt load in the aqueous layer facilitates the phase separation. The organic phase containing silanes originating from LiHMDS and excess of aminopyridine **3** is removed to waste by an overflow exit. Evolving CO_2 and isobutene off-gas from the deprotection are removed by an exhaust stream. A needle valve positioned at the exit of the first settler unit allows for the initial adjustment of the level of the phase split. The acidic aqueous phase containing **5*HCl** exits the settler unit via the bottom valve and is directed to an emulsifier device. Under vigorous mixing using an overhead stirrer, the acidic reaction mixture is diluted with a THF stream and an aqueous NaOH stream adjusting the reaction mass to pH = 13. Under basic conditions, the desired product **5** is extracted to the organic phase. The emulsion is then transferred to a second settler unit through a dipping tube, allowing the aqueous and organic layers to separate. An additional needle valve positioned at the exit of the second settler unit allows for the initial adjustment of the level of the phase split. While the aqueous phase is directed to waste removing the inorganic salts, the organic layer containing the purified free base **5** overflows and is continuously collected for further processing.

Integrating the extraction device into the developed continuous-flow process (Scheme 4) allowed us to demonstrate the system's technical and chemical feasibility by a 90-min run. During this experiment, **5** was synthesized and purified in a fully continuous manner, delivering the desired product with a throughput of 0.85 g/min (based on internal standard) and steady purity (95%). The free base **5** is converted to the final API **1** following a solvent switch from THF (bp: 66 °C; low-boiler) to *iso*-propanol (bp: 82 °C; high-boiler) and consecutive crystallization using succinic acid according to an established protocol [5b].

In conclusion, we described a two-step continuous-flow process towards ribociclib (**1**). In course of the process development, we established a Pd-free coupling towards intermediate **4**, eliminating the necessity of laborious Pd depletion. Furthermore, we designed a powerful liquid–liquid extraction device for in-line purification, ensuring the required purity of the free base **5** for the consecutive crystallization of the API (**1**). The feasibility of the overall flow setup (Scheme 4) was demonstrated during a 90-minute run which delivered the desired product **5** in high yield (92.5%) and purity (95%) with a throughput of 51.0 g/h. This continuous-flow process is considered to be competitive with operating in batch mode in respect of yield and impurity profile of the free base **5**. Linking the upstream operations in flow mode with downstream operations in traditional and existing batch equipment rates this concept is economically attractive.

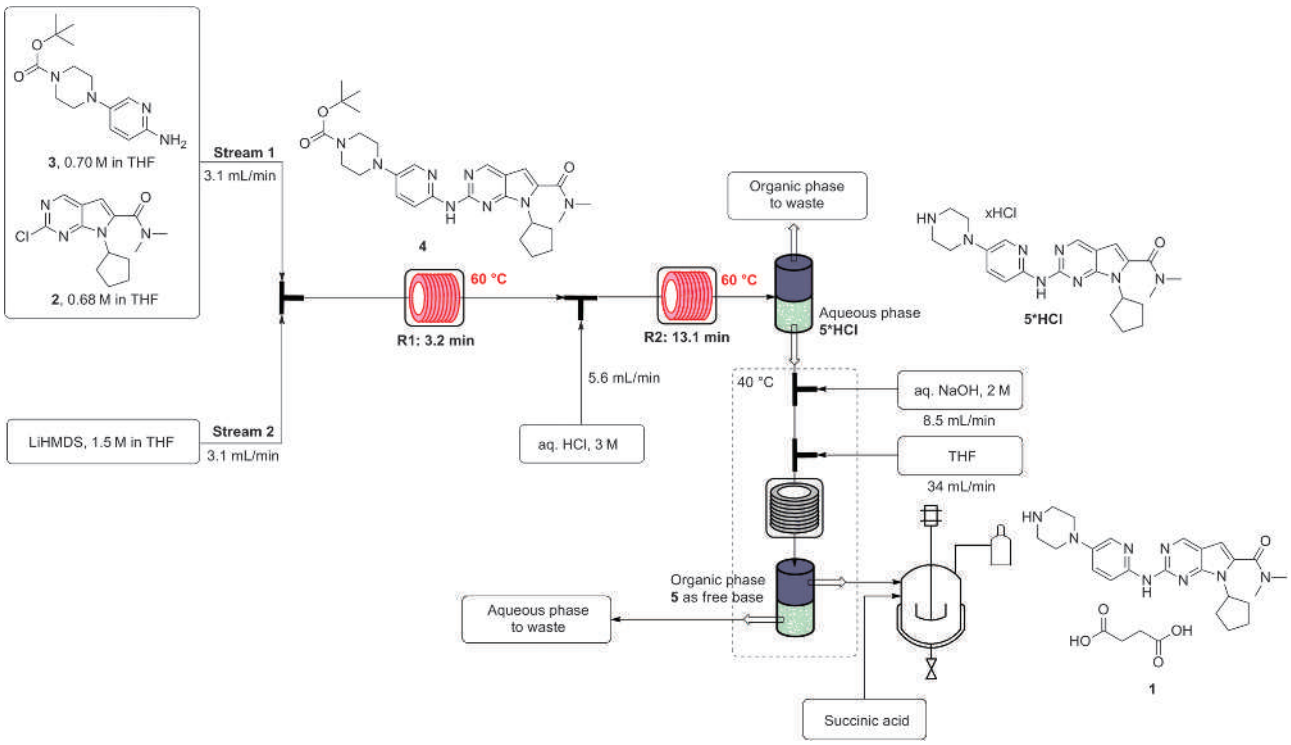
3. Experimental Section

For an experiment over 90 min under steady state following the setup depicted in Scheme 4, the following feedstock solutions A–D are prepared. The quantities of feedstock solution required to reach steady-state operation are not included in the calculation and need to be added accordingly.

Feedstock A: 51.4 g, 175.5 mmol, 1.0 equiv. (**2**); 50.3 g, 180.8 mmol, 1.03 equiv. (**3**); add THF (175 mL) to reach a total volume of 258 mL; Feedstock B: LiHMDS is used as commercially available solution in THF (279 mL, 351 mmol, 2.2 equiv., 1.5 M); Feedstock C: HCl is used as an aqueous solution (504 mL, 1404 mmol, 8.0 equiv., 3.0 M); and Feedstock D: NaOH is used as an aqueous solution (765 mL, 1530 mmol, 8.7 equiv., 2.0 M).

A mixture of 2-chloro-7-cyclopentyl-*N*,*N*-dimethyl-7Hpyrrolo[2,3-d]pyrimidine-6-carboxamide (**2**) (0.68 M) and *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (**3**) (0.7 M, 1.03 equiv.) in anhydrous THF (3.1 mL/min; Feedstock

Scheme 4. End-to-end continuous-flow setup for the synthesis of ribociclib (**1**)



A) was mixed with a stream of lithium bis(trimethylsilyl)amide (1.5 M, 2.2 equiv.) in anhydrous THF (3.1 mL/min; Feedstock B) using a T-piece (PFA, ID = 0.78 mm). The resulting stream entered a first reactor (R1, PFA tubing OD = 7 mm, ID = 5 mm, filled with static mixer, V = 20 mL) for 3.2 min of residence time at 60 ± 3 °C (bath temperature). Afterwards, aqueous hydrochloric acid (3.0 M, 8.0 equiv., 5.6 mL/min; Feedstock C) was added at 60 ± 3 °C (bath temperature) using a second T-piece (PFA, ID = 0.78 mm). The resulting stream was directed to a second reactor (R2, PFA tube, OD = 7 mm, ID = 5 mm, filled with static mixer, vol. = 154 mL) for 13.1 min of residence time at 60 ± 3 °C (bath temperature). After the reactor, the stream containing crude **5*HCl** was directly purified using the in-line purification system shown in Figure 2. After continuous purification and pH adjustment using aqueous NaOH (2.0 M, 8.5 mL/min; Feedstock D) followed by extraction using THF (34 mL/min), the desired product 7-cyclopentyl-*N*,*N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d] pyrimidine-6-carboxamide **5** was obtained in 92.5% yield and 95% purity with a throughput of 51.0 g/h (=117 mmol/h).

3.1. Synthesis of the Final API 1. THF was removed in vacuo, and *iso*-propanol was added (0.06 M, 1.00 equiv.). The solution was heated to 80 °C, and succinic acid dissolved in *iso*-propanol (0.30 M, 1.05 equiv.) was added over 1 h. After 80% of the succinic acid was added, seeds of the final API were added to the mixture. The mixture was stirred for 1 h at 80 °C and then cooled down to 20 °C over another hour. The suspension was stirred for another 30 min and then filtered. The filter cake was washed with *iso*-propanol to give the pure API **1** [5b].

Supporting Information

Electronic Supplementary Material (ESM) with full characterization (^{1}H and ^{13}C NMR data and spectra, UV, and HRMS) for all new compounds can be found in the online version at doi: 10.1556/1846.2016.00017.

Acknowledgment. We thank Eva Neumann, Ulrich Onken, Baoqing Gong, Daniel Nährig, Gilles Gerber, Hans Bläuer, and Berthold Schenkel for chemical and engineering support. For analytical support, we thank Stephane Schmitt, Ernst Küsters, Angelique Schneider, Markus Blatter, and Thiamo Boussemghoune.

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9. Length 65 mm, diam. 4.8 mm, PTFE glass fiber reinforced; for details, see: http://www.esska.de.