A three step continuous flow synthesis of the biaryl unit of the HIV protease inhibitor Atazanavir

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The development of multistep continuous flow reactions for the synthesis of important intermediates for the pharmaceutical industry is still a significant challenge. In the present contribution the biaryl-hydrazone unit of Atazanavir, an important HIV protease inhibitor, was prepared in a three-step continuous flow sequence in 74% overall yield. The synthesis involved Pd-catalyzed Suzuki–Miyaura cross-coupling, followed by hydrazone formation and a subsequent hydrogenation step, and additionally incorporates a liquid–liquid extraction step.

Introduction

Continuous flow technology has attracted the attention of the organic chemistry community in the last decade, both as an enabling tool to enhance organic synthesis and as a manufacturing method. In 2007, the ACS Green Chemistry Institute (GCI) ranked continuous flow processing as a high priority research area for pharmaceutical and fine chemical manufacturing. Since that time, significant progress has been made in establishing continuous flow methods for the production of important target compounds or valuable synthetic building blocks. Several reviews discuss in detail the benefits of applying continuous flow methods in organic synthesis, including better mixing, efficient mass and heat transfer and the ability to readily scale-up a given flow process by applying numbering-up or scaling-out principles. A particularly challenging area in flow chemistry is to perform multi-step reaction sequences where each synthetic step – if possible – should be directly linked to the following step without isolation or purification of the corresponding intermediates. The continuous flow synthesis of active pharmaceutical ingredients (APIs), which typically involves a significant number of synthetic steps, is therefore a rather complex operation.

In this context we believe that a continuous flow synthesis of the protease inhibitor Atazanavir (1) is of significant interest. Atazanavir, approved by the U.S. Food and Drug Administration (FDA) in 2003, is an antiretroviral drug that is used to treat infection with human immunodeficiency virus (HIV). It is estimated that nearly 7.7 million people in Africa need treatment for HIV and do not have access to appropriate medication. Notably, Brazil is a pioneer in providing free medication to HIV patients and in 2007 the Brazilian government spent 850 million USD treating 200,000 HIV patients. Atazanavir is one of the most prescribed protease inhibitors in Brazil (and worldwide) and thus a sufficient and cost effective supply of Atazanavir is of prime importance.

The general retrosynthetic analysis of the Atazanavir (1) molecule is shown in Fig. 1 and reveals an assembly of three different building blocks.

Results and discussion

The synthetic route developed by Bristol–Meyers–Squibb (BMS) for the N-Boc hydrazine biaryl intermediate 3 is depicted in Fig. 1 General retrosynthetic analysis for Atazanavir (1).
The synthetic steps consist of a Suzuki–Miyaura coupling of 4-formyl-phenylboronic acid (5) and 2-bromo pyridine (6), leading to the formation of biaryl moiety 7, which is then reacted with Boc-hydrazine (tert-butyl carbazate) to furnish hydrazone 8. After transfer hydrogenation, the target intermediate 3 can be obtained in 53% overall yield.

We envisaged that the biphasic conditions proposed for the Suzuki–Miyaura cross coupling reaction (Scheme 1) could be a good starting point for our investigations since the desired biaryl product 7 could potentially be separated from the reaction mixture by simple phase separation, without involving complicated purification steps. The Suzuki–Miyaura cross-coupling employing 0.2 mol% Pd(PPh₃)₄ was therefore performed under sealed vessel microwave heating using essentially the BMS conditions described in Scheme 1. By applying 150 °C for 20 min, the conversion to product was higher than 99% as indicated in Table 1 (entry 1). Despite showing high conversion, this procedure was not considered economical owing to the large excess (1.9 equiv.) of boronic acid 5 used. In our hands, attempts to reduce the amount of boronic acid were unsuccessful, leading to reduced conversion and/or selectivity.

In a recent publication, Buchwald and co-workers have reported a very efficient biphasic continuous flow carbon–nitrogen coupling protocol where the addition of tribasic potassium phosphate and tetrabutylammonium bromide (TBAB) to the aqueous phase enhanced the conversion to the biaryl product. Evaluating these coupling conditions for the Suzuki–Miyaura batch coupling reaction described herein provided 94% conversion to the desired biaryl product 7 using only 1 equiv. of the boronic acid and 0.3 mol% of the Pd catalyst (Table 1, entry 2). Cross-coupling without the addition of TBAB also resulted in good conversion and high selectivity to the desired biaryl product 7, demonstrating that no phase-transfer catalyst (PTC) is required under the high-temperature microwave conditions (Table 1, entry 3). Increasing the boronic acid concentration to 1.2 equiv. and reducing the amount of base slightly increased the product conversion (Table 1, entries 4 and 5). The desired biaryl derivative 7 was isolated in 91% yield from the latter experiment.

The microwave batch conditions were then translated to a continuous flow protocol utilizing an ASIA microreactor employing a two-feed (or a three-feed in the case of hydrazone formation) set-up with preheated 4 mL stainless steel coils (additional 325 μL preheating zone volume and 2175 μL cooling zone volume) with an inner diameter of 0.02 inch (~0.5 mm). After some experimentation and minor modifications to reagent stoichiometry, a 95% conversion at 150 °C and 20 min residence time was achieved (Scheme 2). It is important to note that using a fixed bed reactor filled with 60–125 μm stainless steel beads of identical geometry as described by Buchwald did not improve the conversion or selectivity in this reaction compared to the coil reactor (data not shown). The conversion could also not be improved by increasing reaction temperature or residence time.

We subsequently evaluated the hydrazone formation 7 → 8 (Scheme 1) under microwave conditions, using the crude reaction mixture containing biaryl 7 obtained after a simple phase

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Scheme 1 Synthetic route developed by Bristol–Meyers–Squibb (BMS) for the N-Boc hydrazine biaryl intermediate 3. Reagents and conditions: (a) 1.9 equiv. 5, 0.2 mol% Pd[PPh₃]₄, aqueous 3 M Na₂CO₃, toluene–ethanol (4 : 3), reflux 20 h, 80% yield. (b) N-Boc hydrazine (1 equiv.), toluene–2-propanol (4 : 3), reflux 2 h and then 22 °C for 16 h, 85% yield. (c) 1 mol% Pd/C (10%), HCO₂Na (0.8 equiv.), ethanol–water (5.5 : 1), 57 °C for 1.5 h, 78% yield (overall yield 53%).

Table 1 Optimization of Suzuki–Miyaura reaction under microwave conditions

| Entry | Boronic acid (equiv.) | Pd[PPh₃]₄ (mol%) | Base/additive | Solvent | Conversion (%) |
|-------|----------------------|-----------------|--------------|---------|---------------|
| 1     | 1.9                  | 0.2             | Na₂CO₃ (3.3 M) | Toluene–EtOH (4 : 3) | 99.2 | 0.8 |
| 2     | 1.0                  | 0.3             | K₂PO₄ (3.3 M) TBAB (10 mol%) | Toluene–EtOH (4 : 3) | 94.2 | 2.5 |
| 3     | 1.0                  | 0.3             | K₂PO₄ (3.3 M) | Toluene–EtOH (4 : 3) | 96.5 | 2.3 |
| 4     | 1.2                  | 0.3             | K₂PO₄ (3.3 M) | Toluene–EtOH (4 : 3) | 96.7 | 2.1 |
| 5     | 1.2                  | 0.3             | K₂PO₄ (1.6 M) | Toluene–EtOH (4 : 3) | 97.2 | 2.5 |

Reagents and conditions: organic phase: 2-bromo-pyridine 6 (0.23 mmol, 1 equiv.), 4-formyl-phenylboronic acid 5, and Pd[PPh₃]₄ as a catalyst in 2.3 mL of organic solvent. Aqueous phase: a solution of the base in the indicated concentration (350 μL). Microwave heating was performed at 150 °C for 20 min. HPLC peak area integration at 254 nm.
acid as described in the BMS procedure, but in our hands it
described above. The hydrazone formation was initially tested
wave-assisted biphasic Suzuki–Miyaura reaction. Gratifyingly, under these conditions
precipitate, 0.5 equiv. of trimethylsilyltriflate (TMSOTf) was

Table 2 Optimization of hydrazone formation under microwave conditions

| Entry | Acid | Conditions | Conversion (%) |
|-------|------|------------|----------------|
| 1     | HCl  | 50 °C/5 min | 98             |
| 2     | AcOH | 50 °C/5 min | 78             |
| 3     | CF$_3$SO$_3$H (0.5 eq.) | 50 °C/5 min | 97             |
| 4     | TMSOTf (0.5 eq.) | 50 °C/5 min | 98             |
| 5     | No acid | 120 °C/25 min | 10             |

Reagents and conditions: crude organic phase from the Suzuki–Miyaura reaction (HCl, 0.5 M, theoretical concentration of 0.1 M, see Table 1, entry 3), tert-butyl carbazate (0.23 mmol, 1 equiv.) and 5 equiv. acid concentration unless otherwise stated. Conversion to product, HPLC peak area integration at 254 nm.
provides a biphasic toluene–ethanol mixture, containing biaryl intermediate which is injected through a third pump to a second coil. Simultaneously, solutions of TMSOTf and tert-butyl-carbazate in toluene–ethanol (4 : 3) are pumped into the coil using two separate pumps. Hydrazone (8) formation takes place in this second coil at 50 °C and a residence time of 8 min. The outgoing stream is then pumped through a continuous flow liquid/liquid extractor (FLLEX) together with an aqueous potassium carbonate solution to eliminate the acid from the previous step. After the extraction, crude hydrazone 8 is pumped through a flow hydrogenation unit applying a 10% Pd/C cartridge to provide the final biaryl product 3 in 74% overall yield after chromatographic purification.

Conclusion

In conclusion, in the present contribution we have developed a multistep synthesis of biaryl N-Boc-hydrazine 3 under continuous-flow conditions. The overall yield in this continuous process is 74%, which compares very favorably to the 53% overall batch yield originally described in the literature. In addition to the increased overall yield and the environmental and safety advantages inherent to the continuous process, our method does not require any off-line purification of intermediates and uses only phase extraction which can be readily automated. The fully continuous flow synthesis of the key intermediate 2 in the Atazanavir synthesis is currently under evaluation in our laboratories.

Experimental section

General

1H-NMR spectra were recorded using a Bruker 300 MHz instrument. Chemical shifts (d) are expressed in ppm downfield from TMS as an internal standard. The letters s, bs, d, t, q, and m are used to indicate singlet, broad singlet, doublet,
products and intermediates was done by comparison with the literature spectrum data.

**Microwave experiments**

Microwave irradiation experiments were carried out using a Monowave 300 single-mode microwave reactor from Anton Paar GmbH (Graz, Austria). The experiments were performed in a 10 mL Pyrex microwave process vial equipped with a magnetic stirring bar at a rate of 600 rpm. Reaction times refer to hold times at the temperatures indicated and not to total irradiation times. The reaction conversions were evaluated by HPLC analysis at 254 nm.

**General procedure for Suzuki–Miyaura cross-coupling under microwave conditions** (Table 1)

In a microwave process vial were placed: the organic reaction mixture containing 0.23 mmol (36.3 mg) of 2-bromo-pyridine, 0.28 mmol (42.0 mg) of 4-formyl-phenylboronic acid (1.2 equiv.) and 0.2 or 0.3 mol% of Pd(PPh₃)₄ in 2.3 mL of a mixture of toluene and ethanol (4:3); and the aqueous base, 1.6 M K₃PO₄ (350 µL). The vials were sealed with PEEK snap caps and standard polytetrafluoroethylene (PTFE)-coated silicon septa and the samples were irradiated for 20 minutes (fixed hold time) at 150 °C (∼9 bar). After the reaction time elapsed, the mixtures were cooled to 55 °C using compressed air.

**Purification:** the biphasic reaction mixture was separated and the organic layer was evaporated and subjected to silica gel column chromatography using a mixture of petroleum ether, ethyl acetate and triethylamine as an eluent (1:2:0.03). Yield of 8 under optimized conditions: 38.5 mg of 8 (91%).

**4-Pyridin-2-yl-benzaldehyde** (7). ¹H-NMR (300 MHz, CDCl₃, TMS): 7.32 (1H, m, pyridyl ring), 7.81 (2H, m, pyridyl ring), 8.00 (2H, d, J(H,H) = 8.4 Hz, para-substituted ring), 8.19 (2H, d, J(H,H) = 8.4 Hz, meta-substituted ring), 8.75 (1H, s, carbonyl hydrogen).

**General procedure for the synthesis of hydrazone 8 under microwave conditions** (Table 2)

The biphasic mixture resulting from the Suzuki–Miyaura reaction (see above) was separated and to the organic solution (theoretical concentration of 0.1 M of Suzuki–Miyaura product 7) was added tert-butyl carbazate (0.23 mmol, 30.4 mg, 1 equiv.) and TMSOTf (0.12 mmol, 26.7 mg, 0.5 equiv.) in a microwave vial. The vials were sealed with PEEK snap caps and standard polytetrafluoroethylene (PTFE)-coated silicon septa and the samples were heated for 5 min (fixed hold time) at 50 °C. After the reaction time elapsed, the mixtures were cooled to 45 °C using compressed air.

**Purification:** the reaction mixture was neutralized with triethylamine and the solvent was evaporated. The crude residue was subjected to silica gel column chromatography using a mixture of petroleum ether, ethyl acetate and triethylamine as an eluent (1:2:0.03). Yield of 8 under optimized conditions: 61.5 mg (90%).
**General procedure for Suzuki–Miyaura coupling in flow**

**Scheme 2**

Ten milliliters of the organic mixture containing 2-bromo-pyridine (4 : 3) were loaded into the 10 mL PTFE loop module. By pumping the organic solvent toluene–ethanol 4 : 3 (flow rate for feed A: 200 µL min\(^{-1}\) and feed B: 200 µL min\(^{-1}\) into the loops, the crude Suzuki–Miyaura product and the TMSOTf solution were driven into the micro-reactor, while feed C (0.24 M carbazole in toluene–ethanol 4 : 3, flow rate 100 µL min\(^{-1}\)) was directly pumped into the 3rd feed of the 4 mL stainless steel coil reactor. The 4 mL stainless steel coil reactor was heated to 50 °C on the coil heater adapter. The reaction mixture was pumped through the coil-reactor (overall flow rate of 500 µL min\(^{-1}\)) and it left the micro-reactor after 13 min (8 min of residence time) of reaction time by passing through a backpressure regulator (7 bar). A total volume of 20 mL of the homogeneous hydrazone reaction mixture has been collected and immediately extracted continuously using the Asia FLEX-module (Syrris Ltd), which relies on a porous hydrophobic PTFE membrane based separation technology that selectively wets the organic phase. During our continuous flow extraction optimization we observed the formation of some kind of blockage in the 100 µL extraction tubing and in the separator (blocking the membrane and chip channels); thus we decided to use a guard column ahead of the extraction unit (Fig. 2). The crude hydrazone mixture (feed A: 100 µL min\(^{-1}\)) was mixed with the extraction media (aqueous solution of 0.5 M K₂CO₃, feed B: 100 µL min\(^{-1}\)) in a T-mixer and processed through a guard column (filled with celite; void volume ~1200 µL), the standard 100 µL tubing and the pressurized (main pressure = 3 bar and cross membrane pressure 250 mbar) FLEX-separator unit (containing the extraction base chip, the PTFE membrane and the corresponding top chip). After collection of ~24 mL (20 mL reaction volume + 4 mL flush volume) the liquid–liquid flow extraction was completed and the obtained reaction mixture was used for the following hydrogenation step in the H-Cube Pro.

**General procedure for the hydrogenation of hydrazone 8 in flow**

The optimization experiments were performed using a stock solution of pure hydrazone (0.1 M) in toluene–ethanol (4 : 3). The H-Cube Pro instrument was equipped with a fresh catalyst cartridge (10% Pd/C, 70 × 4 mm i.d.) and a flow rate of 1 mL min\(^{-1}\), H₂ pressure (atmospheric pressure), and cartridge temperatures (10–40 °C) were set on the input panel of the instrument. A constant flow of pure solvent was pumped through the instrument until the system had stabilized at the chosen set points. At that moment the inlet filter frit of the H-Cube Pro was switched from the solvent reservoir into the pressurized (main pressure = 3 bar and cross membrane pressure 250 mbar) FLEX-separator unit (containing the extraction base chip, the PTFE membrane and the corresponding top chip). After collection of ~24 mL (20 mL reaction volume + 4 mL flush volume) the liquid–liquid flow extraction was completed and the obtained reaction mixture was used for the following hydrogenation step in the H-Cube Pro.
the flow extraction (∼24 mL) was entirely pumped into the H-Cube Pro. The outlet collection started from the zero time of injection and lasted until 5 min after the inlet solution had finished.

**Purification:** The reaction mixture obtained from H-Cube Pro was evaporated and purified by silica gel column chromatography using a mixture of petroleum ether, ethyl acetate and triethylamine (5 : 5 : 0.1) as an eluent. This procedure afforded the pure hydrazine in 74% (124 mg, 0.415 mmol) overall yield (for the three steps and the liquid–liquid extraction under continuous flow conditions after the 2nd step). The yield was calculated considering full conversion in the 1st step (of the 2-bromo-pyridine substrate into the 4-(pyridin-2-yl)-benzaldehyde product) and the volume of the collected fraction (steady state fraction: 5 mL of a 0.1 M reaction mixture; 0.5 mmol). All further calculations on the overall yield have been defined by this sampling; thus the overall yield refers to a theoretical yield of 0.5 mmol of final product 3 (N-1(tert-butyloxycarbonyl)-N-2-[4-(pyridine-2-yl)benzylidene]-hydrazine).

N-1(tert-Butyloxycarbonyl)-N-2-[4-(pyridine-2-yl)benzylidene]-hydrazine. 1H-NMR (300 MHz, CDCl3, TMS): 1.45 (9H, s, CH3), 4.03 (2H, s, CH2), 6.49 (1H, s, NH), 7.18 (1H, m, pyridyl ring), 7.43 (2H, d, 3J[HKH] = 8.1 Hz, para-substituted ring), 7.69 (2H, m, pyridyl ring), 7.93 (2H, d, 3J[HKH] = 8.1 Hz, para-substituted ring), 8.65 (1H, m, pyridyl ring).

**Acknowledgements**

We wish to thank CNPq, CAPES, FAPERJ and FINEP for financial support. COK acknowledges the Science without Borders program for a special visiting researcher fellowship. This research was also supported by the Christian Doppler research society.

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