A flow-based synthesis of Imatinib: the API of Gleevec†

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A concise, flow-based synthesis of Imatinib, a compound used for the treatment of chronic myeloid leukaemia, is described whereby all steps are conducted in tubular flow coils or cartridges packed with reagents or scavengers to effect clean product formation. An in-line solvent switching procedure was developed enabling the procedure to be performed with limited manual handling of intermediates.

Currently batch-mode methods for the synthesis of active pharmaceutical ingredients (APIs) involve many labour intensive and time consuming processes.[1] These multi-step operations necessitate individual reaction control, optimisation, work-up and purification techniques which are only achievable with a highly skilled workforce in dedicated and expensive facilities. We have recently been developing flow-based continuous processing tools[2] to enable a machine-assisted approach to chemical production as an alternative strategy that can lead to many readily recognised benefits.

Microreactors and related devices are now commercially available and can be adapted to accommodate a wide range of chemical reactions including multi-step sequences leading to functional molecules.[3] As a particularly challenging test to this developing technology, we report here a new and short flow-based synthesis of Imatinib (**1**). This compound imposes significant solubility restrictions and intermediate handling difficulties currently perceived not to be ideal for flow chemistry platforms. Indeed, by overcoming these hurdles we hope to demonstrate the wider value of this approach to molecular assembly programmes.

Gleevec (Imatinib mesylate) is a tyrosine kinase inhibitor, developed by Novartis AG, and is used for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours.[4] Although the original process route to Gleevec[5] was composed of several steps that afforded insoluble intermediates to assist in individual compound purification, other alternative routes have also been developed claiming improvements over the previous route.[6,7] A batch-mode solid-supported synthesis of **1** has also been achieved.[8]

Our flow strategy to **1** (Fig. 1) comprised a number of straightforward disconnections similar to those followed in the batch-mode syntheses,[5–8] although employed in a different order. The first step (Scheme 1) involved the formation of the amide core *via* the reaction between acid chloride **2** and aniline **3**. A solution of the acid chloride **2** (1.5 equiv., 0.3 M,
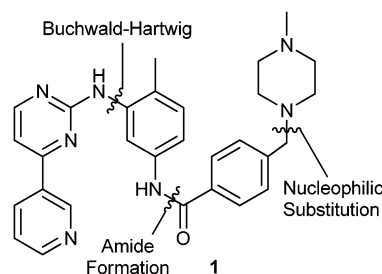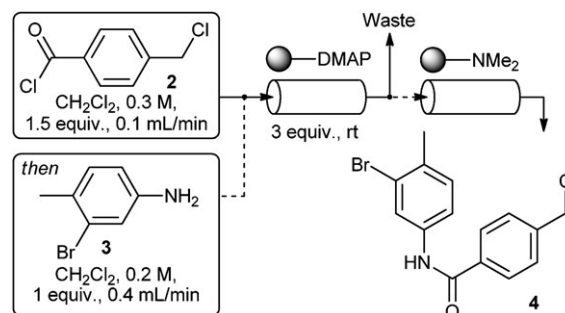

**Fig. 1** Planned disconnections for Imatinib (**1**).

Scheme 1 Step 1: formation of amide **4**.

CH_2Cl_2, 0.1 mL min^{-1} flow rate) was preloaded onto polystyrene-supported DMAP (3 equiv.) contained in a glass column trapping the acid chloride in an activated form on the resin.[9] After washing the column with further CH_2Cl_2, a solution of aniline **3** (1 equiv., 0.2 M, CH_2Cl_2, 0.4 mL min^{-1}) was pumped through the column, thereby reacting and releasing amide **4**. We envisaged using an excess of the DMAP resin relative to **2** to scavenge any corresponding carboxylic acid formed from hydrolysis.[10] Unfortunately, this was not the case and a further column of polymer-supported dimethylamine (QP-DMA) was added in-line to effectively scavenge the acid component from the reaction mixture. Compound **4** could be directly isolated following solvent evaporation in 78% yield and excellent purity (> 95%).

The next step in the synthesis (Scheme 2) was the S_N2 displacement of the chloride in **4** with *N*-methylpiperazine (**5**). Preliminary batch experiments indicated the solubility of the product **6** was very poor in CH_2Cl_2, hence a 1 : 1 CH_2Cl_2/DMF mixture was used as the solvent for the flow steps with the hope of telescoping the steps at a later stage. Therefore an 1 : 2 mixture of **4** and **5** in CH_2Cl_2/DMF (1 : 1; 0.015 M based on **4**) was pumped at 0.1 mL min^{-1} through a column of $CaCO_3$ held at 80 °C to bring about the transformation. Alternatively polymer-supported TBD was also successfully used in place of $CaCO_3$, but its cost and the longer resulting retention time prohibited its use at scale. The presence of

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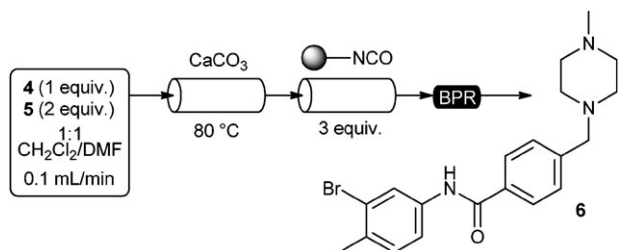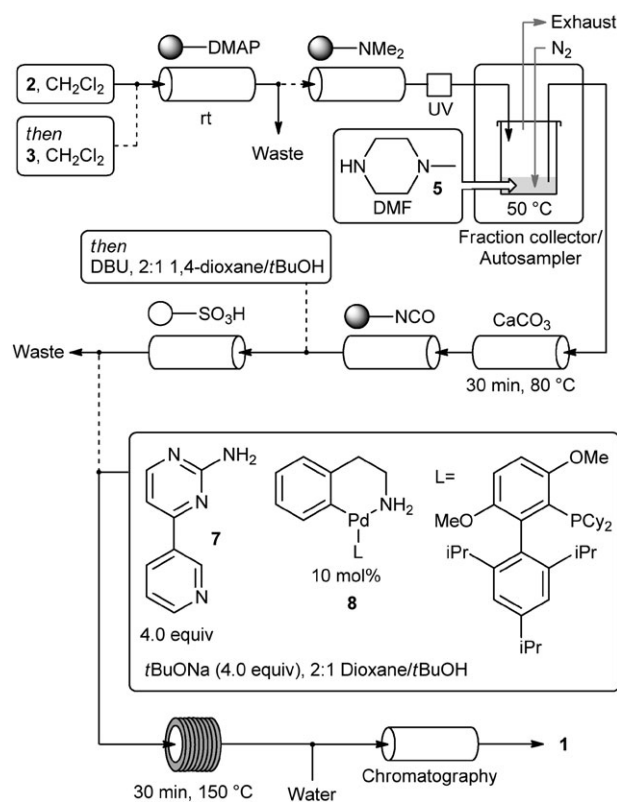
Scheme 2 Step 2: flow formation of **6**.

CH_2Cl_2 in the mixture did not preclude the use of relatively high reaction temperatures which could be utilised by the addition of a 100 psi back-pressure regulator (BPR) inserted at the end of the reactor configuration. The output stream was then passed through a cartridge containing polystyrene-supported isocyanate (3 equiv.) to scavenge any unreacted **5** from the mixture resulting in a 70% conversion to **6**. In our final procedure we envisaged a 'catch and release' purification[11] of **6** at this stage, but first investigated combining the first two steps into one flow sequence.

However, linking the first two steps to produce a synthesis of **6** requiring no manual handling of intermediates was not trivial. Incorporating a UV spectrometer in-line to monitor the output of step 1 showed that significant dispersion of the product was taking place as the material flowed through the supported reagent columns. Our initial plan was to combine a secondary stream of **5** directly to that of **4**. However, since the concentration of product emerging from the reactor was changing with time, control of the stoichiometry of the two coupling flows was therefore not possible and a large excess of **5** would be required. In many cases this solution would be acceptable, but in our case the excess of **5** would then need to be scavenged using a relatively expensive isocyanate resin.

To avoid using more of piperazine **5** than was necessary, an automated fraction collector was attached to the UV spectro-meter and set to collect the output of the reaction with a defined UV absorption threshold. The output was divided into 3 fractions (4 mL each) enabling the first, highly concentrated portion of the output peak to be collected, although this equated to 75% (59% overall) based on isolated product of the total sample. The collected sample was aliquoted directly into a vial already containing a solution of **5** (0.06 M, 2 equiv., DMF) thus producing a homogenous mixture (0.015 M based on **4**) of known relative stoichiometry ready to be re-injected into the next step. Therefore, when step 1 was complete and **4** collected, the fraction collector served as an autosampler, aspirating the homogeneous mixture of **4** and **5** and dispensing it into a sample loop ready for injection into the next step, forming **6** as previously described. The flow stream of the newly formed intermediate **6** was then directed into a column containing silica-supported sulfonic acid to perform a catch and release purification with any unreacted **4** simply passing through to waste. A brief washing sequence (MeOH, 0.4 mL min^{-1}) was used to elute the residual DMF prior to release of the product by passage of NH_3 in MeOH (2.0 M, 0.1 mL min^{-1}) to give the product in 53% isolated yield and excellent purity (>95%) with no additional purification being required.

Further experiments indicated that the reaction proceeded with >95% conversion when a 0.03 M solution of **4** in DMF was injected into the reactor. Increasing the relative ratio of DMF to CH_2Cl_2 in order to achieve higher conversions was attempted by increasing the volume of DMF in the vial that the output was directed into, but the reduced overall concentration did not result in increased conversion. To overcome this problem a solvent switch was required. This could have been achieved simply by manually evaporating the CH_2Cl_2 *in vacuo*, however an in-line solution to the problem was desired to avoid manual handling of intermediate **4**. The fraction collector was set to collect the first fraction of the output of **4** from the first step into a heated (50 °C) vial sealed with a rubber septum and containing the solution of **5** (0.06 M, 2 equiv., DMF). Nitrogen gas (0.5 bar) was bubbled into the solution through a polymer tube to evaporate the CH_2Cl_2 as it was collected to perform the solvent exchange. A second piece of tubing was used to direct solvent vapour from the vial head space to an exhaust. After a further 30 min, the resultant DMF solution of **4** and **5** (0.03 M based on **4**) was aspirated by the autosampler, injected into step 2 followed by a column of silica-supported sulfonic acid and the product released with NH_3 in MeOH as previously described to give a significantly improved yield of **6** (80%) also in excellent (>95%) purity.

The final step to generate **1** employed a Buchwald–Hartwig coupling between **6** and **7** (Scheme 3). This has previously been achieved in batch mode in 72% yield using $Pd_2(dba)_3 \cdot CHCl_3$, NaO*t*Bu and *rac*-BINAP in xylenes.[7] Unfortunately, this procedure could not be used in flow since traditional non-polar solvents for the Buchwald–Hartwig coupling, for example toluene and xylenes, did not fully solubilise the starting

Scheme 3 Flow formation of **1**.

materials. Further precedent for the coupling of **7** was found in the synthesis of Nilotinib, a related tyrosine kinase inhibitor also developed by Novartis.[12] In this case Pd$_2$(dba)$_3$, Cs$_2$CO$_3$ and XantPhos in a co-solvent system of 1,4-dioxane and tBuOH were used to give Nilotinib in 89% yield.[13] In our case, we found a 2 : 1 mixture of 1,4-dioxane/tBuOH ideal for dissolving all the substrates and could additionally be heated to the high temperatures required for the reaction. When these conditions were transferred to flow, significant formation of Pd black and NaBr precipitates caused reactor blocking by accumulation at the BPR. The problem was easily overcome by changing to the BrettPhos Pd precatalyst[14] **8** as this did not show significant decomposition to Pd black at the temperatures used. Since the precipitation of NaBr could not be avoided, the addition of a water stream at the end of the reactor facilitated dissolution of the NaBr prior to the BPR and thus eliminated the problem.

Assimilating this final step into the flow sequence involved releasing the immobilised bromide **6** into a flow stream containing the Buchwald–Hartwig components. Thus by eluting with a solution of DBU (76 mM, 2 equiv., 2 : 1 1,4-dioxane : tBuOH) the substrate **6** could be released for further reaction. Ideally we envisaged a series of scavenging columns placed at the end of the coupling sequence to clean-up the reaction stream and furnish pure material without the need for further purification. Analysis indicated that the output stream contained a number of components: product **1**, unreacted **6** and **7**, and protodehalogenated **6**. Unfortunately, we were unable to easily chemically differentiate between these species and resorted to a chromatographic purification strategy as a practical solution to the problem. However, this was not problematic since the output of the reactor could be concentrated *in vacuo* directly onto a silica samplet cartridge, and eluted automatically using a Biotage SP1 purification system to give the final product in 69% yield (32% overall) with better than 95% purity.

In conclusion, we have demonstrated a flow-based synthesis of Imatinib (**1**) using a procedure requiring limited manual handling of reagents or intermediates. In addition the use of the in-line solvent switching technique permits reaction solvents to be changed as part of the continuous process. This represents a significant improvement over existing protocols that require manual intervention. The synthetic route as outlined also has the potential to be used for analogue synthesis and clearly demonstrates the role of flow chemistry techniques in the assembly of challenging and poorly soluble molecules.

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