
Claudio Battilocchio,[a] Benjamin J. Deadman,[a] Nikzad Nikbin,[a] Matthew O. Kitching,[a] Ian R. Baxendale,[b] and Steven V. Ley*[a]

Abstract: Here we report the direct comparison of a conventional batch mode synthesis of Meclinertant (SR48692, 1), a neurotensin receptor-1 antagonist, with its machine-assisted flow chemistry alternative. By using these enabling tools, combined with solid-supported reagents and scavengers, many process advantages were observed. Care, however, must be taken not to convert these techniques into expensive solutions to problems that do not exist.

Introduction

The discovery and development of new pharmaceutical substances is a major scientific priority for society. It involves multiple stages and can be an expensive process requiring the combined workings of scientists from many disciplines, spanning medicinal chemists to clinicians. Chemical synthesis is one of the most challenging aspects of this discovery process and manifests itself in nearly every stage of development. In the early phases of hit-to-lead and lead optimisation a quick and versatile synthetic route is needed for preparing a large number of compounds. Nevertheless, later on, molecules have to be made on larger scale for toxicology where there is the challenge of designing a scalable, reliable and robust process for clinical studies and eventual commercialisation.[5]

Over the years, chemists have improved tremendously many of the methods used in organic synthesis. For example, the development of transition-metal mediated transformations and asymmetric catalysis have expanded the range of molecules that can now be accessed. By way of contrast, the technology and many of the tools used to perform synthetic operations have remained more or less constant. Although batch-mode working is the most common manner of conducting reactions and subsequent downstream manipulations, there are many advantages in augmenting this with modern enabling technologies. Indeed, all components of a chemical process, such as reagent delivery, mixing, heating, analytical monitoring, quenching, work-up and finally purification can affect the overall success of the reaction and consequently all could benefit from improvement.

Recently, machine-assisted protocols have been influencing the way that molecules are being prepared.[2] In particular our group and others are addressing some of the recurring challenges that face organic synthesis by providing simpler and more efficient processing tools. In order to achieve this, we have been evaluating the utility of flow-based chemical synthesis. Under a dynamic flow regime mixing and heat transfer can be controlled more accurately[3] and the use of solid-phase reagents and catalysts can facilitate the purification as an in-line integrated process.[4] The importance of monitoring devices for learning and understanding these processes cannot be underestimated. Advanced systems are now available for detailed studies of each component of a reaction pathway.[5] Additionally the use of flow technologies has helped minimise tedious downstream processes (work-up, extraction and purification)[4] while gas-liquid flow reactors have changed the way we handle gases in the research environment.[7] Machines can assist in almost every aspect of the synthesis process and can even help in the integration of chemical synthesis and biological screening, which aids the discovery process.[6] Our group has special interest in using and developing these new methods to streamline the routes to new medicinal agents.[8] However, when developing new tools care must be taken to avoid creating technology for the sake of technology. To quote George M. Whitesides:[10]

“...the devices that have been developed have been elegantly imagined, immensely stimulating in their requirements for new methods of fabrication, and remarkable in their demonstrations of microtechnology and fluid physics, but they have not solved problems that are otherwise insoluble.”

[a] Dr. C. Battilocchio, B. J. Deadman, Dr. N. Nikbin, Dr. M. O. Kitching, Prof. S. V. Ley
Innovative Technology Centre, Department of Chemistry
University of Cambridge, Lensfield Road
Cambridge, CB2 1EW (UK)
Fax: (+44)1223-336442
E-mail: svl1000@cam.ac.uk

[b] Prof. I. R. Baxendale
Department of Chemistry, Durham University
South Road, Durham, DH1 3LE (UK)

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Neurotensin (NT) is a neuropeptide which can be found in the nervous system and peripheral tissues. NT displays a wide range of biological effects and is considered a promising target for drug discovery.\cite{11} It has important roles in the pathogenesis of Parkinson’s disease.\cite{12} Additionally, NT has been shown to be effective in inhibiting pro-proliferative and pro-survival signalling in colon, pancreatic and prostate cancer cells.\cite{13} Recently, NT and its analogues have been investigated as potential radiosensitisers in prostate cancer cells.\cite{14}

SR48692, Meclinertant (1), developed by Sanofi–Aventis, is a selective neurotensin probe (Figure 1). This non-peptide antagonist binds to the neurotensin receptor-1 (NTR-1; \(K_i = 2.6(\pm 0.2)\) nm) and inhibits the downstream effects associated with this receptor stimulation, such as EGFR and Src activation.\cite{15} To date however, only one poorly documented synthesis of SR48692 has been reported.\cite{16}

\begin{center}
\textbf{Figure 1. Chemical structure of Meclinertant (1) and amino acid 2.}
\end{center}

Our work began, therefore, with the development of a new procedure for the preparation of the amino acid (2), which was recently reported.\cite{17} Here, we make a direct comparison of the reported synthesis of SR48692 (Meclinertant) and evaluate the advantages of machine-assisted procedures over the conventional batch processes. In particular, we report on how flow chemistry can assist in overcoming difficulties encountered in batch mode and also demonstrate that these new concepts can be telescoped together to provide even higher levels of efficiency throughout the synthesis of SR48692 (1).

**Results and Discussion**

For the flow preparation of SR48692, it was decided to adopt an approach similar to that reported by Sanofi–Aventis.\cite{18} It is important to emphasise here that this work was not undertaken as validation of the synthetic route but as the application of new tools to solving problems that chemists face in everyday chemical synthesis. The ultimate goal was therefore to evaluate how enabling technologies could be applied systematically to improve each step of this existing route.

The first general issue to address was the availability of appropriate starting materials. While it is true in general that starting from advanced commercially available compounds can accelerate a project, the cost, number of steps and the robustness of the selected chemistry at scale are also key criteria when taking a more holistic view. More importantly, having a reliable and cheap synthetic route to the starting material, can allow diversification and preparation of libraries of compounds when analogues are needed for evaluation. Flow chemistry is well suited to scaling processes to deliver quantities of building blocks, this is particularly effective when multiple reaction steps can be telescoped together into a single flow process.\cite{16,17,18}

In terms of overall plan, we envisaged that ketone 3, which is commercially available, could best be obtained from cheap starting materials using machine-assisted procedures (Scheme 1). The route commences with an O-acylation of cyclohexa-1,3-diene (4), which is subsequently converted to the triketone 6 via rearrangement. Iodine in MeOH effects oxidation to aromatise the triketone intermediate 6 to the monomethoxyacetophenone (7). A final methylation step using dimethyl carbonate and 1,2-dimethylimidazole furnishes the desired dimethoxyacetophenone (3). Not only was this route more cost effective than purchasing acetophenone 3 but it could also give the opportunity to diversify the phenolic substitution pattern for later analogue preparation.

The acetophenone derivative 3 is further elaborated in the total process by condensation with diethyl oxalate and combined with hydrazine to yield the pyrazole precursor 10. Uniting compound 10 with the commercially available hydrazine 9 followed by hydrolysis of the pendant ester of 10 gave compound 11. This material was directly coupled with the protected amino acid 12 to form SR48692 (Meclinertant, 1) after deprotection (Scheme 2). Here we evaluate and discuss whether new technologies can have a positive impact on each of the steps of this synthesis of SR48692 when compared to the conventional batch route.

**Stage I: cyclohexadiene acylation and development of a monolithic reactor**

The route commenced with the O-acylation of diketone 4. While the batch reaction can be performed on milligram-scale without difficulties, scaling up the

\begin{center}
\textbf{Scheme 1. Synthesis of acetophenone 3. Reagents and conditions: a) acetyl chloride, DIPEA, toluene; b) DMAP (M1), toluene; c) iodine, methanol; d) DMI, DMC, methanol.}
\end{center}
procedure past 50 mmol gives rise to a rapid increase of the reaction temperature, which is difficult to control and results in by-product formation. This required careful cooling along with the slow addition of the acetyl chloride to avoid reaction runaway and the formation of multiple side-products. Flow chemistry can therefore offer an immediate advantage. Simply introducing the diketone and the base solution from one pump, with the acetyl chloride solution delivered from a second pump at 0.25 mL min⁻¹, into a 10 mL reactor maintained at 40°C controlled the exothermic process and resulted in complete consumption of 4 to give the O-acylated product 5 in high purity. This enabled us to prepare the product routinely on a 130 mmol scale after a simple aqueous acid wash (Scheme 3). The handling of exothermic reactions when conducting larger scale chemistry is a well-documented advantage of flow chemistry and proved to be beneficial in the chemistry used here.

The rearrangement of O-acylated diketone 5 to the triketone 6 is reported employing AlCl₃. This Lewis acid is toxic and corrosive and the inevitable acid work-up is problematic when processing large amounts of material, especially due to the significant quantities of aluminum salts produced. Alternatively dimethylaminopyridine (DMAP) catalysed rearrangements of O-acyl to C-acyl derivatives have also been described in the literature. However, most of these procedures require a prolonged reaction time of at least 12 h. Indeed, in our hands the batch reaction on 1 mmol scale using 20 mol% of soluble DMAP delivered full conversion, overnight, at ambient temperature. Interestingly, however, increasing the temperature to 120°C led to completion reaction within 4 h on a 2 mmol scale.

We therefore speculated that a heterogeneous, supported DMAP catalyst could significantly improve this process. DMAP has well-known toxicity concerns so use of a poly-
mer-supported DMAP version would simultaneously address safety and recycling issues. Secondly, heating a large flask at 120°C in batch mode can consume large amounts of energy. More importantly, less ideal heat transfer in batch can lead to low conversions and by-product formation.

Initially therefore we investigated the use of commercially available polymer-supported DMAP under the batch conditions. As suspected, we discovered that increasing the amount of starting material prolonged the reaction times: starting from 100 mmol of O-acyl 5 derivative, complete consumption of the starting material was only possible after 5 days at 120°C (using 3 mol% of PS-DMAP). This was likely due to the low accessibility of the functional sites within the polymer beads. We therefore saw this as an opportunity to use another enabling method to increase the substrate to catalyst interactions under a flowing regime.

Our group has been involved for several years in the development of monolithic flow reactors for a number of synthesis applications. The use of monolithic reactors has been proven to expedite flow processes and overcome many synthetic problems, such as waste disposal and by-product formation.[21] A polymeric monolith is a single continuous piece of porous material prepared by precipitation polymerisation of monomers and a cross-linker within glass cartridges, in the presence of a porogenic mixture (Figure 2).[20] Monolithic reactors are akin to macroporous resins and have a permanent porous structure that, unlike gel-type beads, are independent of the nature of the solvent. They can be made on existing flow chemistry equipment in a range of shapes and sizes.[22] Their porosity can be fine-tuned to allow optimum flow of solvents and reagents at reasonable pressures. As they are highly cross-linked, monolithic polymers do not exhibit swelling and shrinking with different solvents, and most importantly they operate through convection flow mode instead of diffusion, allowing molecules to interact with the functional sites more efficiently.[23] Another obvious advantage of monoliths compared to beads is the lack of solvent channelling, which can severely affect the efficiency of packed bed reactors when used in flow. Considering these potential gains, the generation of a monolithic reactor containing a DMAP catalyst was considered to be beneficial to our program. Preparation of the necessary monomer (15) was easily achieved through a simple one-pot reaction (Scheme 4). Using a mixture of divinylbenzene (15% w/w), styrene (15% w/w) and monomer (15; 10% w/w) in the presence of dodecanol (60% w/w) as porogen and aza-bis(cyclohexanecarbonitrile) (ACHC, 2 mol% excluding the porogen), a monolith with very good porosity and physical robustness was obtained which filled the glass reactor as a white amorphous polymeric structure (Figure 3). After flushing the polymer (to elute the porogen), the monolithic reactor was ready to use. The O-acylated substrate (5) was then passed through the heated reactor. Under optimised flow conditions, two grams (17.8 mmol) of the precursor (5) were processed through the monolithic reactor M1 heated at 100°C, delivering the solution of triketone 6 at a flow rate of 50 μL min⁻¹ with a residence time of 20 min and in high purity (Scheme 5).

Monolithic reactors are akin to macroporous resins and have a permanent porous structure that, unlike gel-type beads, are independent of the nature of the solvent. They can be made on existing flow chemistry equipment in a range of shapes and sizes.[22] Their porosity can be fine-tuned to allow optimum flow of solvents and reagents at reasonable pressures. As they are highly cross-linked, monolithic polymers do not exhibit swelling and shrinking with different solvents, and most importantly they operate through convection flow mode instead of diffusion, allowing molecules to interact with the functional sites more efficiently.[23] Another obvious advantage of monoliths compared to beads is the lack of solvent channelling, which can severely affect the efficiency of packed bed reactors when used in flow. Considering these potential gains, the generation of a monolithic reactor containing a DMAP catalyst was considered to be beneficial to our program. Preparation of the necessary monomer (15) was easily achieved through
vection within the monolith, reduces the required reaction
time to only 20 min.

To further examine the effect of the monolithic structure,
we packed commercially available polymer-supported
DMAP in a column of the same size and performed reac-
tions at different temperatures and flow rates. In all cases
the conversion was low (less than 30%) at temperatures
below 80 °C, even when applying very low flow rates. In-
creasing the temperature led to blockages of the system due
to the excessive swelling of the polystyrene support. At-
ttempts to reduce the density of the column packing by
adding sand were unsuccessful. Overall the commercial
product in our hands was far inferior to the monolithic ma-
terial for this reaction.

A further known advantage of flow processing compared
to batch is the ease by which sequential reactions can be
coupled together to generate multistep sequences.[24] Having
found that the use of toluene as solvent is of particular im-
portance for the rearrangement using the DMAP monolith,
we were pleased to find that the O-acylation reaction could
also be run in toluene. Therefore, the reactor output stream
from the acylation step was filtered in-line to eliminate any
solid particulates and directed into the glass column contain-
ing the DMAP monolith (M1). Collection and concentration
of the final solution gave the triketone 6 as a telescoped
product, in 94% yield on a 90 mmol scale (Scheme 6).

**Stage 2: iodine oxidation:** Iodine in MeOH has been suc-
cessfully employed for the transformation of a number of
different 2-acyl-1,3-cyclohexadiones, giving access to aceto-
phenones in good yields.[25] This reaction was successfully re-
produced in our laboratory on 1 mmol scale in batch mode.
However, again upon scaling the reaction, a wide range of
by-products, such as deacetylated anisole derivatives and io-
dinated products, were also formed. Here as before, flow
chemistry presented an opportunity to circumvent these
problems. The presence of these by-products on large scale
can be attributed to the accumulation of hydroiodic acid. In
flow, however, such an elevated concentration of hydroiodic
acid in contact with the product or starting materials for an
extended period is minimised.

After screening various conditions, the final flow set-up
used a stream of 6 in MeOH, which was combined with a
MeOH solution of iodine, both delivered at a flow rate of
0.20 mL min⁻¹. The united stream was reacted thereafter in
a tubular coil reactor (14 mL) at 80 °C; the resulting solution
was directed to a glass column packed with a mixture of cal-
cium carbonate and sand to scavenge the hydroiodic acid
formed. The sand in the column acted as a diluent, and re-
duced rapid increases in pressure due to an associated re-
lease of CO₂. The exiting flow stream from the calcium car-
bonate column was subsequently directed to another device
packed with thiosulfate functional beads intermixed with
Celite® to capture the excess iodine (Figure 4).[26]

![Figure 4. Thiosulfate beads mixed with Celite® for the removal of excess iodine.](image)

The final output stream was collected and concentrated in
vacuo to obtain the monomethoxyacetophenone 7 in 68 %
yield and better than 99 % purity (Scheme 7). This lower-
than-ideal yield was thought to be a result of the interaction
of the phenolic product (7) with the calcium carbonate, and
hence material was retained on the column. Unfortunately,
alternative strategies to remove the hydroiodic acid formed
during the reaction proved more detrimental, leading to a
further drop in yield. Nevertheless, the flow set-up still pre-
sented a genuine improvement compared to the batch pro-
cess: the pure product was obtained with minimum down-

stream manipulations and no chromatography was required (unlike in the batch process).

**Stage 3: methylation and reaction telescoping**: Conventional methylation procedures usually rely on highly reactive and toxic reagents, such as methyl iodide. One way to avoid the high toxicity in vivo is to use less reactive reagents and to perform the required methylation at high temperatures. For example, the recently reported methylaing mixture of di-methylcarbonate (DMC) and 1,2-dimethylimidazole (DMI) is far less toxic to humans. DMC is considered a green solvent and DMI is a poor nucleophile at ambient temperature.

A batch reaction for methylating the resorcinol-based starting material 7 using DMI/DMC was carried out at 120°C in a high boiling solvent (DMF). Although this worked efficiently it obviously creates problems, not the least of which is the difficulty of removing it at a later stage. Again, a flow-derived process should be of immense help in circumventing this issue. In a flow reactor we conveniently switched the solvent to MeOH and easily achieved a temperature of 150°C by using a 250 psi back-pressure regulator. In laboratory scale synthesis, it is often argued that the same superheated conditions can be achieved using sealed reactors.

However, it should be noted that a pressurised flow reactor is essentially a monophasic closed system whereas a batch reactor possesses a headspace. In practice this means it is difficult to achieve 150°C with MeOH and easily achieved a temperature of 150°C by using a 250 psi back-pressure regulator. In laboratory scale synthesis, it is often argued that the same superheated conditions can be achieved using sealed reactors.

When transferring this set-up to flow, a solution of acetophenone 7 in MeOH (flow rate 0.7 mL min⁻¹) and a solution of DMI in DMC (flow rate 0.7 mL min⁻¹) were combined in a T-piece and then directed to a perfluoroalkoxy polymer (PFA) tubular flow coil (14 mL) heated at 150°C to obtain the methylated product (3) in quantitative yield (95% isolated yield) after concentration and a trivial extraction procedure. Since DMC is unstable to strong acid and DMI can be retained by very strong acid media, an immobilised acid scavenger (QP-SA) was incorporated to complete an in-line workup (Scheme 8). We were encouraged that MeOH proved to be effective in this reaction as this provided an opportunity for telescoping this and the previous aromatisation step. Following the procedure outlined earlier, the material (a solution of compound 6 in MeOH) from the aromatisation step was then directed into a second reactor where it was combined with the solution of DMC and DMI. Eventually, we were able to achieve a 63% yield of ketone 3 over the last two steps, employing an overall flow rate of 0.80 mL min⁻¹ for the final methylation step (Scheme 9).

**Stage 4: the Claisen condensation**: The Claisen condensation reaction between acetophenone 3 and diethyl oxalyl ester is a straightforward process in batch. Simply stirring the two reagents in the presence of sodium ethoxide at room temperature for 3 h led to an isolated yield of around 60% of the 1,3-dicarbonyl product (8). Screening a number of conditions under microwave irradiation indicated that the reaction could be driven to completion after just 30 min at 80°C, using EtOH as the solvent. Superheating the reaction therefore in a flow reactor might provide a faster alternative to batch. However, the reaction set-up for the flow process

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**Scheme 7. Iodine-mediated aromatisation of 7.**

**Scheme 8. Methylation in flow using DMC/DMI.**
proved initially troublesome due to blockages caused by precipitation of the product. It was noticed that with higher concentrations of sodium ethoxide solution this problem was amplified and at lower concentration the reaction failed to proceed to completion. It was therefore concluded that, from a process point of view, no immediate advantage could be gained by transferring this step to flow. Nevertheless, we saw this as an opportunity to evaluate an alternative back-pressure regulator designed within our group for handling of reaction slurries in flow (Figure 5).

This device consists of a stainless-steel tank, which is pressurised with a house nitrogen line to maintain up to 5 bar back-pressure in the flow system. It has been designed specifically to deal with the problem of solid accumulation in conventional spring-based back-pressure regulators and proved to be effective in handling thick slurries of 8 in flow (Figure 6). A detailed exploded diagram version of this device and explanation of the working mechanism are presented in the Supporting Information.

In order to transfer this key step to flow, a solution of acetoephone 3 and diethyl oxalyl ester in ethanol (flow rate 1.20 mL min⁻¹) was combined in a T-piece with a 1 M solution of sodium ethoxide in ethanol (flow rate 1.20 mL min⁻¹) and heated to 115 °C in a 52 mL PFA coil (1/8” o.d.). This wider i.d. was essential to avoid blockage within the PFA reactor. The output from the reactor was attached to the pressure chamber, which was under 5 bar pressure, allowing the reaction to be run continuously without any precipitation or blockage problems (Scheme 10).

**Stages 5 and 6: pyrazole core synthesis and hydrolysis:** The reaction between the commercially available hydrazine 9 and the 1,3-dicarbonyl product (8) from the previous synthe-

![Figure 5. In-house designed back-pressure regulator for handling chemical slurries.](image-url)
sis step was evaluated using microwave irradiation in batch. DMF proved to be the most effective solvent. The reaction went to completion under microwave conditions when heated to 140°C for 2 h in the presence of sulfuric acid. Scaling the reaction up under batch conditions also proved successful, albeit with a drop in yield from 87 to 70%. However, as stated above, there are problems associated with performing reactions in DMF at high temperatures in batch mode, especially considering the eventual scale-up process in a system with headspace. Again, here we considered the advantages that flow could provide over batch in terms of safety, reliability and robustness of the process. Under flow conditions, a mixture of hydrazine 9 and 1,3-dicarbonyl 8 in DMF were delivered to a T-piece to meet a solution of concentrated sulfuric acid in DMF. The mixture was then heated in a 52 mL PFA coil (1/8” o.d.) at 140°C. Collection, extraction and concentration of the output afforded the pyrazole ester 10 in a very good yield (89%) and purity on a 3.58 mmol scale, without requiring the chromatography needed in the batch-mode process (Scheme 11). While in this example, at the scale that the reaction was performed (3.58 mmol), both batch and flow would be equally effective, when the work-up and purification steps are considered, the flow platform again proved to be advantageous.

We recently reported on a camera-controlled liquid–liquid extraction system to aid work-up following a flow synthesis. An alternative solution to the problem of continuous liquid–liquid extraction is to use a universal membrane extraction device (Figure 7). This allowed for a simple integration of the unit into the flow set-up to facilitate continuous work-up.

The final flow experimental set-up was arranged in a way whereby the product stream of the reactor was further Figure 6. Uniqsis Flowsyn connected to our in-house “pressure chamber”.

Figure 7. Biotage® universal phase separator; kit form: a) as supplied, and b) assembled.

Scheme 11. Knorr pyrazole condensation to obtain 10.
merged, first with an aqueous stream of sodium carbonate and then at another T-piece with a stream of dichloromethane. The resulting biphasic output was dispensed into a semipermeable membrane, where the hydrophilic membrane allowed passage of the organic phase whilst retaining the aqueous washings, effecting a simple and direct liquid-liquid extraction (Scheme 12).

This proved to be a very efficient method of working-up this reaction sequence with minimal user intervention. Attempts to telescope the extracted solution of ester 10 directly into a hydrolytic cleavage step were unsuccessful, possibly because of incompatibility of residual DMF with the hydrolysis conditions. The batch protocol proved to be a simple and efficient way to achieve hydrolysis. Indeed, refluxing a solution of pyrazole ester in THF/H₂O resulted in a 90% yield of the acid after just concentration and precipitation with HCl (3m aqueous solution). Although trivial, we envisaged this step could be run in flow where the efficient micro-mixing and heat transfer could provide a faster reaction and a safer system, especially when scaling up the process.

Indeed, the flow protocol allowed the reaction to reach completion after just 14 min, while the batch mode required much longer reaction times (1.5 h). We then established a flow procedure for the hydrolysis of the pyrazole ester by reacting it as a THF solution with 3m aqueous KOH united via a T-piece (flow rate 0.50 mL min⁻¹ for each pump). The mixture was progressed into a 14 mL PFA coil reactor maintained at 140°C. The output stream was collected and the THF was removed, in vacuo. Addition of 3m aqueous HCl solution gave a precipitate of acid 11 at pH 3 which could be isolated by filtration in the normal way (Scheme 13).

Stage 7: synthesis of the protected amino acid and amide coupling: Our initial attempts to achieve the coupling between the carboxylic acid 11 and the amino acid 2 partner closely followed the route established by Sanofi–Aventis.[16] The pyrazole acid was activated as its acid chloride before introducing the adamantane amino acid 2 into a third stream. The first problem encountered when trying to translate this process into flow was the extremely poor solubility of amino acid 2. Attempts to solubilise the amino acid in dichloromethane with an equivalent of DIPEA were unsuccessful. The amino acid could be solubilised in neat pyridine or DIPEA but using these solutions in flow resulted in poor conversions (45–47% as determined by LC-MS). Ultimately it was necessary to protect the amino acid as its tert-butyl ester to increase its solubility. The protection of the amino acid was performed in batch. We found this process to be low yielding (55% yield) but it provided sufficient quantities of the protected amino acid for us to proceed with the synthesis of SR48692 (Scheme 14). The insoluble nature of the adamantane amino acid starting material meant that transferring the protection process to flow was not practical.

The final amide bond formation in batch is a well-studied transformation. To find the desired conditions various activating agents were investigated in a microwave reactor. The activated carbonyl which formed was quenched after the 30 min by addition of excess ethanol to allow simple analysis by LC-MS. Thionyl chloride, Ghosez reagent (1-chloro-
N,N,2-trimethyl-1-propenylamine), propylphosphonic anhydride (T3P) and 1,1'-carbonyldiimidazole (CDI) were all tested and found to be poor activators of the acid (0 to 36% conversion by LC-MS). More success was found using phosphogene generated by the addition of catalytic pyridine to a dichloromethane solution of triphosgene (92% conversion by LC-MS after just 10 min at ambient temperature). The high toxicity and volatility of phosphogene makes its direct use in chemical synthesis a potential challenge. It is generally preferable to generate phosphogene in situ from other less hazardous reagents, such as triphosgene.[31]

The batch reaction was difficult to optimise. Triphosgene was activated with 2,6-lutidine to provide a controlled release of phosphogene and then treated with the acid 11; samples of the reaction mixture were followed by LC-MS and NMR analyses after quenching with ethanol. The protected amino acid 12 was added to obtain compound 13. Despite our attempts to optimise these batch conditions, we were aware that the main drawback of this process was hazards associated with generation and handling of phosphogene gas.

Recently Fuse et al. demonstrated that a safe and reliable process for this type of coupling could be made by containing the phosphogene generated during reaction in a sealed fluidic system.[32] Inspired by this new protocol, a flow stream of triphosgene (0.037 M) in dichloromethane was combined with a second flow stream of DIPEA (0.01 M) in dichloromethane at a T-piece mixer (flow rate 0.2 mL min⁻¹ per channel). The mixed solution was then passed through a 0.5 mL stainless steel heat exchanger at 100 °C to initiate nucleophilic decomposition of the triphosgene into phosphogene. The solution then passed through a 2.5 mL stainless steel coil reactor to complete the formation of the acid chloride. A FlowIR™ inline infrared spectrometer[5b,c] was used to monitor the formation of phosphogene without exposing the operator to this hazardous gas during analysis (Scheme 15).

A solution of pyrazole carboxylic acid 11 and DIPEA in dichloromethane was injected into the DIPEA/dichloromethane flow stream to react with the in situ generated phosphogene yielding the corresponding acid chloride. Monitoring the reaction by infrared spectroscopy (observing a disappearance of the phosphogene C–Cl stretch at 803 cm⁻¹, Figure 8) allowed an injection of a matching solution of the protected amino acid 12 to be timed to meet the plug of acid chloride as it travelled through the flow reactor. The combined reaction flow was directed into a 14 mL reactor coil, heated at 100 °C, undergoing amide coupling to afford 13. The reactor output was collected into a flask containing

![Scheme 15. In-line monitoring in the synthesis of protected SR4692 (13).](image)
saturated ammonium chloride to quench the reaction. Simple extraction with EtOAc and filtration through a pad of silica gel provided the tert-buty ester 13 in 85% yield. Although the flow system provided a contained environment for the phosgene, care must be taken to ensure the reactor safety before performing these reactions.

Stage 8: deprotection and synthesis of Meclinertant (SR48692, 1): Stirring a dichloromethane solution of the crude product 13 with Quadrapure sulfonic acid (QP-SA) removed the tert-buty protecting group, overnight, to generate 1. This batch reaction, aided by an immobilised reagent, proved to be versatile. Since this was the last step in the synthesis, it was not performed on a large scale. However, if this was an objective a column packed with commercial QP-SA could be used to transform readily the reaction to flow mode.

Conclusion

The initial aim of this work was to impartially investigate whether enabling methods could accelerate a multistep synthesis project of high complexity. Although a batch process had been defined previously, we have clearly demonstrated that new technologies can help chemists overcome many synthesis issues. Flow chemistry has mastered exothermic events and controlled superheating of solvents efficiently as well as streamlining the synthesis by allowing reaction telescoping. It has also helped circumvent problems arising due to back mixing and accumulation of by-products. Furthermore, utilising polymer-supported reagents has simplified the downstream processing of reaction streams and has significantly enhanced the safety of reactions. In-line monitoring aided the tracking of hazardous intermediates. In one instance in-line extraction and phase separation improved downstream processing. In summary, we believe these new technologies, if used correctly can be powerful tools but care must be taken not to convert them to expensive solutions that do not exist.

Experimental Section

General experimental section: 1H NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with the residual solvent peak as the internal reference (CDCl 3 = 7.26 ppm, D2J/DMSO = 2.50 ppm). 13C resonances are reported to the nearest 0.01 ppm. 13C NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference (CDCl 3 = 77.16 ppm, D2J/DMSO = 39.52 ppm). All 13C resonances are reported to the nearest 0.1 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. The multiplicity of 1H signals are indicated as: s — singlet, d — doublet, t — triplet, m — multiplet, br — broad, or combinations of thereof. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Unless stated otherwise, reagents were obtained from commercial sources and were used without purification. Laboratory reagent grade EtOAc, petroleum ether 40–60, and dichloromethane were obtained from Fisher Scientific and distilled before use. Unless stated otherwise, heating was conducted using standard laboratory apparatus. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. Melting points were performed on either a Stanford Research Systems MPA100 (OptiMelt) automated melting point system and are uncorrected. High resolution mass spectrometry (HRMS) was performed with a Waters Micromass LCT Premier 19F spectrometer using time of flight with positive ESI, or conducted by Mr. Paul Skelton (Department of Chemistry, University of Cambridge) on a Bruker BioApex 47e FTICR spectrometer using positive ESI or EI at 70 eV to within a tolerance of 5 ppm of the theoretically calculated value. LC-MS analysis was performed on an Agilent HP 1100 series chromatography (Mercury Luna 3u C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESI ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of acetonitrile and water containing 0.1% formic acid. Retention time (t(R)) is given in min to the nearest 0.1 min and the m/z value is reported to the nearest mass unit (m.u.). X-ray crystal structures were determined by Dr. John Davies (Department of Chemistry, University of Cambridge). CIF numbers are reported as part of compound characterisation. Elemental analyses within a tolerance of ±0.3% of the theoretical values were determined by Mr. Alan Dickerson and Mrs. Patricia Irele in the microanalytical laboratories at the Department of Chemistry, University of Cambridge. Unless otherwise specified all the flow reactions were performed in a Uniqsis Flowsyn flow platform.[50]

3-Acetoxyl 2-cyclohexen-1-one (5): Batch reaction: To a solution of 1,3-cyclohexandione (4; 2.0 g, 17.8 mmol) and DIPEA (4 mL; 23 mmol) in anhydrous toluene (30 mL), acetyl chloride (1.4 mL; 19.6 mmol) was added dropwise over 2 min. The reaction was stirred for 2 h at RT before the salts formed were filtered off. The organic fraction was extracted with EtOAc and washed with aqueous HCl (1N). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated to afford the product as a yellow oil (yield 2.45 g, 15.89 mmol, 89%). 1H NMR (400 MHz, CDCl 3, 25°C): δ = 5.75 (s, 1H), 2.42 (t, 2H, J = 6.9 Hz), 2.30 (t, 2H, J = 6.9 Hz). 2.21 (s, 3H), 1.94 ppm (m, 2H, J = 6.9 Hz); 13C NMR (100 MHz, CDCl 3, 25°C): δ = 139.55 (C), 126.52 (C), 124.22 (C), 117.34 (CH), 36.61 (CH), 28.22 (CH), 21.16 (CH), 21.14 ppm (CH); FT-IR (neat): 2954, 1768, 1660, 1640, 1363, 1182, 1115, 1007, 979, 878 cm−1; LC-MS: t(R) = 1.21 min, m/z: [M+H]+ = 154.48; HRMS (ESI): m/z calculated for C6H11O2: 155.1110; found 155.1111.

2-Acetyl 1,3-cyclohexandione (6): Batch reaction: To a solution of 5 was added PS-DMAP (0.5 g, 3 mmol) and the mixture was microwave irradiated for 3 h. The reaction mixture was then filtered to remove the PS-DMAP and the solution washed with aqueous HCl (2N) and saturated brine. The organic fraction was obtained as a red oil (yield 2.30 g, 14.9 mmol, 84%). 1H NMR (400 MHz, CDCl 3, 25°C): δ = 15.75 (s, 1H), 2.65 (t, 2H, J = 6.9 Hz), 2.61 (s, 3H), 2.48 (t, 2H, J = 6.9 Hz). 13C NMR (100 MHz, CDCl 3, 25°C): δ = 30.05 (C), 198.69 (C), 195.38 (C), 113.18 (CH), 35.35 (CH), 33.21 (CH), 18.98 ppm (CH); FT-IR (neat): 2953, 1660, 1550, 1410, 1315, 1188, 1007, 919, 841 cm−1; LC-MS: t(R) = 2.62 min, m/z: [M+H]+ = 155.35; HRMS (ESI): m/z calculated for C9H10O2: 155.0708; found 155.0705.

2-Hydroxy-6-methoxy-acetophenone (7): Batch reaction: Iodine (2 equiv, 6.8 g, 26.9 mmol) was added to a solution of 6 (2 g, 13 mmol) in MeOH (30 mL) and the reaction mixture was heated under microwave irradiation for 9 h. The mixture was then passed through calcium carbonate and a polymer supported sulfite resin mixed with Celite. The organic fraction was obtained as a yellow needles (yield 1.75 g, 10.5 mmol, 80%). 1H NMR (400 MHz, CDCl 3, 25°C): δ = 13.23 (s, 1H), 7.32 (t, 1H, J = 5.2 Hz), 6.55 (d, 1H, J = 5.2 Hz), 6.34 (d, 1H, J = 8.9 Hz), 3.90 (s, 3H), 2.67 ppm (s, 3H); 13C NMR (100 MHz, CDCl 3, 25°C): δ = 205.17 (C), 164.65 (C), 161.55 (C), 136.09 (CH), 111.32 (CH), 101.15 (CH), 55.86 (CH), 33.66 ppm (CH); FT-IR (neat): 2944, 1628, 1608, 1483,1367, 1325, 1211, 1180, 1035, 979, 841 cm−1; LC-MS: t(R) = 5.75 min, m/z: [M+H]+ = 213.25; HRMS (ESI): m/z calculated for C9H10O3: 213.0700; found 213.0700.
Ethyl 1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1H-pyrrole-3-carboxylate (10): Batch reaction: A solution of ethyl 4-(2,6-dimethoxy)-2,4-dioxobutanate (8; 0.14 g, 0.50 mmol) and 1-(7-chloroquinolin-4-yl)hydrazine (9; 0.12 g, 0.65 mmol, 1.3 equiv) in dimethylformamide (3 mL) was microwave irradiated at 145 °C for 3 h. Sulfonic acid (5 g). The resultant solution was delivered (flow rate 0.50 mL min⁻¹, pump B) into a PFA reactor at 140 °C after combining at a T-piece (28 min residence time). A 100 psi back pressure regulator was placed after the reactor. The exit stream was collected and concentration of the solution gave the title compound (5). A C H T U N G T R E N N U N G

<table>
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<tr>
<th>Chemical Name</th>
<th>Formula</th>
<th>Molecular Weight</th>
<th>% Yield</th>
<th>% Calcd</th>
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<td>Ethyl 1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1H-pyrrole-3-carboxylate</td>
<td>C₂₆H₂₅ClN₂O₂</td>
<td>438.1221</td>
<td>63.09% (62.80%)</td>
<td>H 4.60% (4.62%)</td>
<td>N 9.60% (9.53%)</td>
</tr>
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</table>
A Machine-Assisted Flow Synthesis of SR48692

**FULL PAPER**

| (C), 143.3 (C), 138.9 (C), 134.7 (C), 131.8 (CH), 128.0 (CH), 127.7 (CH), 125.9 (CH), 122.1 (C), 118.1 (CH), 117.7 (CH), 106.5 (C), 104.0 (CH), 55.3 ppm (CH); FT-IR (neat): 1687, 1575, 1479, 1453, 1434 cm⁻¹; LC-MS: m/z = 435.4 min, m/z [M]+ = 410.25; HRMS (ESI): m/z c-calcd for C₂₅H₂₄N₃O₃Cl = 509.1602; found 509.1600; m/z [M]+ = 410.2554; HRMS (ESI): m/z c-calcd for C₂₅H₂₄N₃O₃Cl = 509.1602; found 509.1600.  

tert-Butyl 2-aminoadamantane-2-carboxylate (12): Batch reaction: HClO₄ (0.09 mL, 70% aqueous solution) was added dropwise to a sealed solution of (2) (0.150 g, 0.65 mmol) in tert-butyl acetate (5.4 mL) cooled to 0°C. The reaction was stirred at RT for 6 h and then quenched slowly at 0°C with NaOH solution (1N) until the pH reached 9–10. The mixture was extracted with EtOAc (4–5 mL) and washed with brine. After being dried with sodium sulfate, the solution was filtered and concentrated to give the product as an off-white solid (yield 0.090 g, 0.36 mmol, 55%). M.p. 101–103°C; ³¹P NMR (400 MHz, CDCl₃, 25°C); δ = 3.32 (s, 2H), 2.40 (2H, J = 12.1 Hz), 1.91 (s, 2H), 1.72 (m, 2H), 1.67 (m, 4H), 1.60 (m, 2H), 1.40–1.42 ppm (m, 11H); ¹³C NMR (125 MHz, CDCl₃, 25°C); δ = 176.1 (C), 78.8 (C), 61.0 (C), 37.3 (CH), 34.6 (CH₃), 33.5 (CH), 31.4 (CH), 27.5 (CH), 26.7 (CH), 26.3 ppm (CH₂); ¹³C NMR (100 MHz, CDCl₃, 25°C); δ = 176.1 (C), 80.1 (C), 62.0 (C), 37.9 (CH), 35.3 (CH), 32.1 (CH), 28.1 (CH), 27.3 (CH), 27.0 ppm (CH); FT-IR (neat): 2901, 2851, 1710, 1606, 1101, 1077, 1031, 1006, 957, 882, 865, 823, 779, 725, 682 cm⁻¹; LC-MS: m/z = 328.1 (M⁺), 283.3 (M⁺-CH₃), 248.26; HRMS (ESI): m/z c-calcd for C₂₅H₂₄N₃O₃Cl = 509.1602; found 509.1600; microanalysis calculated for C₁₂H₁₆N₃O₄Cl: C 61.54 (61.30%), H 3.94% (4.00%), N 5.55% (5.74%).

**Acknowledgements**

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