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PAPER

Preparation of fluoxetine by multiple flow processing steps

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Microflow technology is established as a modern and fashionable tool in synthetic organic chemistry, bringing great improvement and potential, on account of a series of advantages over flask methods. The study presented here focuses on the application of flow chemistry process in performing an efficient multiple step syntheses of (±)-fluoxetine as an alternative to conventional synthetic methods, and one of the few examples of total synthesis accomplished by flow technique.

Introduction

The preparation of many drugs and natural products remains a challenge of organic chemistry in spite of the advances in synthetic methodologies. For instance, generating a scalable synthetic pathway often demands laborious and time-consuming optimization studies. As a consequence, new techniques are continuously introduced as tools for the chemist to meet the need for rapid and flexible synthetic pathways on various scales.[1] One of the newest and most innovative techniques that have increasingly attracted attention over the recent years is microflow technology, on account of a series of advantages over traditional flask method, of its flexibility and its amenability to integration between chemistry and other scientific disciplines.[2] Shorter diffusion distances and higher surface-to-volume ratios compared to flask, in fact, significantly improve heat transfer and reduce mixing times, hence hot spots are eliminated and side-reactions are reduced considerably. Amongst other benefits, reagent introduction techniques create a reacting mixture of constant composition thus avoiding the accumulation of unreacted reagents; reduced systems size is advantageous with respect both to safety and economy, as small amounts of valuable catalysts or reagents are required in optimization; reaction conditions can be screened sequentially; finally, computer-controlled automation has the potential to afford highly controlled systems with a great degree of autonomy.[3] Not surprisingly, microflow technology has become one of the most revolutionary and fashionable branches of chemistry bringing enormous improvement and potential in synthetic organic chemistry. Additionally, microflow provides a very efficient and innovative approach to the total synthesis of molecules of particular interest. The above-mentioned advantages of flow over flask, in fact, become very useful especially when carrying out syntheses with multiple steps. Thanks to the intrinsic nature of the flow, multiple step syntheses using flow system can be accomplished not only by carrying out the synthetic steps individually followed by purification, just as in flask, but also as a consecutive synthetic process linked into one continuous sequence with in-line purification between steps. This can be achieved by assembling one multi-component flow system where additional inlets are inserted for in-line sequential introduction of reagents exactly where needed, with a great degree of efficiency.[4] A large portion of literature works on flow chemistry in recent years has focused on a number of single-step organic reactions, emphasizing the benefits that flow can bring to those specific reactions.[5] On the other hand, fewer works have been published on more complex syntheses of molecules of interest, requiring more than one step, using flow technology, probably on account of the greater challenge they represents. For instance, Cheng-Lee and co-workers accomplished the synthesis of a radio-labelled imaging probe 2-[^{18}F]-Fluorodioxyglucose in flow, involving a [^{18}F]-fluoride substitution on the mannose triflate precursor to afford 2-[^{18}F]-FDG in 38% radiochemical yield, with a purity of 98%.[6] In another noteworthy example, Ley and co-workers described the first enantioselective total synthesis of 2-aryl-2,3-dihydro-3-benzofurancarboxyamide neolignan (grossamide) in excellent purity under flow conditions.[7] The uniqueness of Ley's method is the integration of pre-packed columns of solid-supported reagents into the flow system with a double purpose, either as immobilised reactants or as scavengers for in-line purification in between steps. In this case the synthesis of grossamide involved the use of a polymer-supported coupling reagent in the first step followed by in-line scavenging of any residual amine precursor before the biotransformation of the intermediate into the final product using silica-supported enzyme peroxidase. Using the same methodology, the authors also accomplished the seven-step synthesis of natural alkaloid (±)-oxomaritidine including hydrogenation, oxidation and azide formation with an overall yield of 40% under continuous flow conditions, by use of a series of packed columns of immobilise reagents, catalysts, and scavengers, combined with the use of a glass microreactor.[8] The study presented here aimed to investigate the application of flow technique as an alternative to flask in performing the synthesis of (±)-fluoxetine 5, as one of the few examples of reactions requiring more than one step to be

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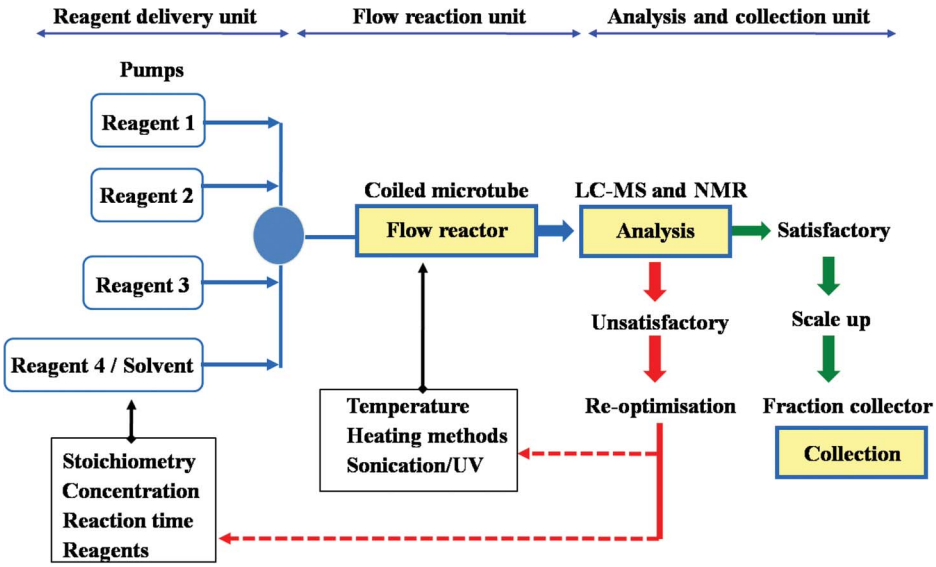


Fig. 1 The general method set-up of flow process used for the synthesis of (±)- fluoxetine.

accomplished by flow technique. Fluoxetine hydrochloride (3-(p-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine·HCl) is known under the trade name Prozac (trade mark Eli Lilly Co.).[9] In this work we adapted a synthetic route reported in literature taking the challenge of providing an alternative route to conventional flask methods.[10]

Results and discussion

The typical setup of our flow system used in the synthesis of (±)-fluoxetine **5** consisted of three main units as illustrated in Fig. 1; in the reagents delivery unit, each reagent is transported from the bulk reservoir into the flow reaction unit using New Era syringe pumps (NE-1000 model) or HPLC Knauer Smartline pumps (K-100 model). As the reagents are pumped into the flow reaction unit, all separate reagent streams merge and mix at the meeting junction forming one stream of reaction mixture flowing continuously through the flow reactor. Computer-controlled pumps using in-house built software Flow System Controller (FSC) allowed easy and rapid modification of reaction conditions, including residence time, concentration and stoichiometry. A good sealing connection between the flow reactor and the pumps was accomplished by using multi-, cross-, or T-connectors from Upchurch Scientific.[11] Fluorinated polymer tubings were frequently used in the flow reactor setup, with 1.58 mm outside diameter (o.d) and 0.50–1.00 mm internal diameter (i.d). Polymers such as polytetrafluoroethylene (PTFE) or perfluoroalkoxyethylene (PFA) are economical and flexible, therefore easily adaptable to modifications, and have a good visibility with a good degree of chemical and physical resistance. In a typical setup, the flow reactor was coiled around a glass or metal core unit, in order to fit easily and neatly into a heating or cooling bath as well as a sonication or microwave cavity. Once the flow stream reaches the end of the flow reactor, monitoring of the reaction progress takes place by analysing small samples taken from the emerging flow, using LC-MS or NMR. Analytical samples were collected only after the flow had reached the steady state, *i.e.* allowing the passing of a volume equal to at least 1.5 times the flow reactor volume. The eluting product can be easily collected using an automated fraction collector (Foxy Junior), coupled with a UV-triggered liquid handler. In the case of unsatisfactory outcome, a re-optimisation study can take place (Fig. 1) using the software to modify reaction parameters for both reagent delivery unit and the flow reaction unit. This allows sequential screening of reaction conditions. Between each screening cycle, a solvent wash of the system was carried out to ensure segregation between different sets of conditions in order to avoid contamination. In addition to the in-house built system, a commercially available Vapourtec R Series flow system was also used to conduct the synthesis of (±)-fluoxetine **5** (Fig. 2).[12] The Vapourtec R Series flow system consists of an R2+ delivery unit using two HPLC pumps and an R4 flow reactor unit integrated with an automated fraction collector. Following the reagent

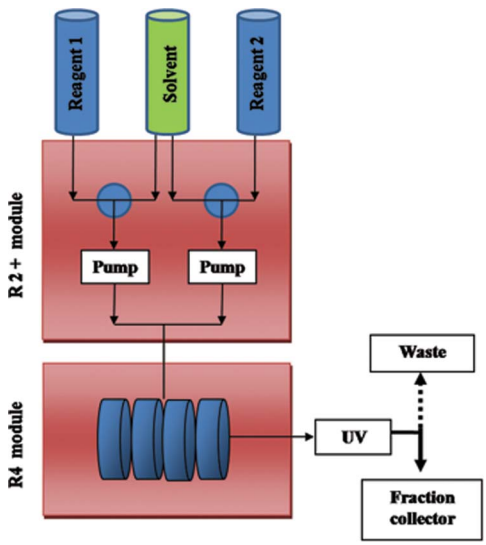


Fig. 2 The Vapourtec R series flow system set-up.

delivery (R2+), the merging and mixing of the streams occurs in a T-connector, with the resulting mixture flowing continuously into the reactor unit (R4). The R4 reactor holds up to four coiled tubing reactors arranged into four independently heated zones ranging from ambient temperature to 150 °C, using a built-in hot air jet system to enable fast transition between different temperatures with rapid response up to 80 °C per minute and precise temperature control. In addition, the system is fitted with a back-pressure regulator (100 psi) at the end of the flow reactor allowing superheating of the reaction mixture. As with the in-house built system setup (Fig. 1), the monitoring of the reaction takes place after the flow reaches the steady state. Once the optimal conditions are found, product collection is carried out using an automated fraction collector accompanied with a software-triggered liquid handler. The whole process is integrated with Flow Commander Software, allowing sequential screening by rapid modification of reaction parameters. Also in this system, automated solvent washing cycles between reactions are included. In addition, Vapourtec R Series systems can be adjusted to fit synthetic requirements, allowing us to carry out successful flow reaction trials using a system with two additional pumps (Fig. 3).

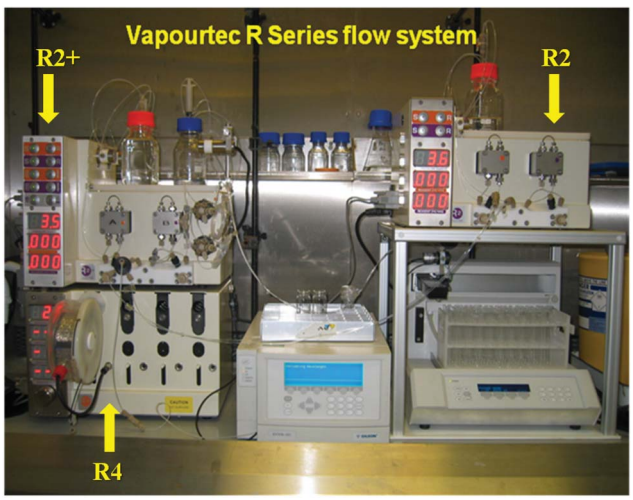
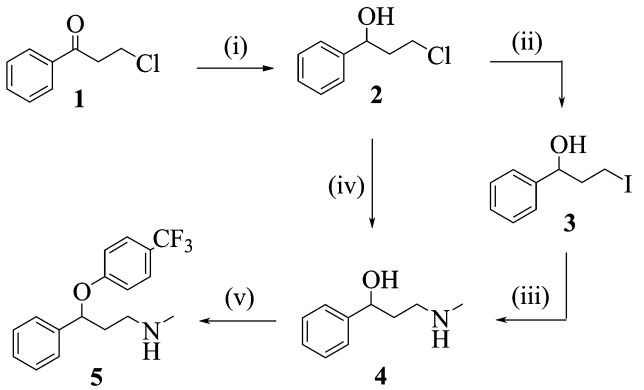


Fig. 3 The modified setup of Vapourtec R series flow system including an extra set of two pumps (R2) on the RHS in addition to the base set of two pumps (R2+) on the LHS.

The synthesis of (±)-fluoxetine **5** in flow was carried out using the sequence shown in Scheme 1. In the first step, 3-chloro-1-phenyl-propan-1-one **1** was reduced under flow conditions to the corresponding secondary alcohol, 3-chloro-1-phenyl-propan-1-ol **2**, using a stoichiometric amount of a hydride donor (Scheme 1, step i). In search for the optimal reduction conditions a range of reducing agents were tried. Attempts to accomplish the reduction of **1** using sodium borohydride were unsuccessful, due to difficulties encountered in solubilising sodium borohydride for introduction into the flow reactor.[13,14] The use of a commercially available homogeneous solution of sodium borohydride in triethylene glycol dimethyl ether, on the other hand, enabled an easy introduction of the reducing agent into the flow reactor. However, after several reduction trials, the ketone precursor remained unreacted under a variety of conditions. Alternatively, the use of commercially available BH_3·THF solution proved successful both in terms of



Scheme 1 Synthesis of (±)-fluoxetine in flow: (i) BH_3·THF, r.t., 5 min (77%); (ii) NaI, toluene: water, 100 °C, 20 min (43%); (iii); $MeNH_2$ (aq), tetrahydrofuran (THF), 80 °C, 10 min (89%); (iv) $MeNH_2$ (aq), acetonitrile (MeCN), 140 °C, 10 min (95%); (v) DIAD, PBu_3, *p*-hydroxybenzotrifluoride, DCM: dimethylacetamide, 70 °C, 5 min (86%).

easy delivery into the flow reactor and also in the reduction of the ketone precursor. The major drawback with the use of BH_3·THF reagent was its thermal instability, leading to evolution of gas with consequent pressure build-up within the flow system. Unfortunately, from a technical point of view, the use of Knauer HPLC continuous pumps proved undesirable in this case, as their intrinsic mechanism tended to create friction leading to further evolution of gas within the system. In order to overcome this difficulty, we opted for the use of syringe pumps to deliver the reaction components whilst cooling the glass syringe to reduce any thermal instability. Cooling of the syringe was accomplished by keeping it in contact with a plastic bag filled with ice and salt, which was replaced when required. In a general reduction procedure, using the diagram shown in Fig. 4, a solution of the ketone **1** in THF was introduced from inlet A, whilst simultaneously introducing a solution of the BH_3·THF from inlet B. Once the two streams of reactants were combined, starting the reaction, the flow proceeded through the flow reactor, before being quenched just prior to collection and analysis.

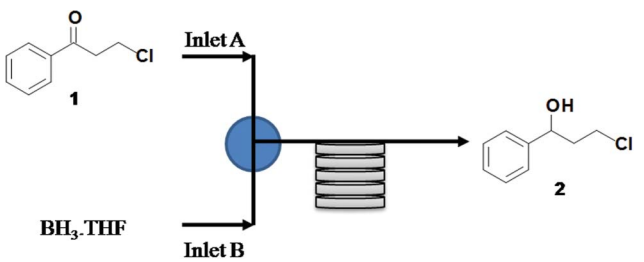


Fig. 4 Flow system set-up for the reduction of **1**.

Optimisation of the reduction at room temperature was carried out by varying three main parameters; residence time, reagent stoichiometry, and reaction mixture concentration with respect to ketone **1**. While maintaining the reducing agent stoichiometric ratio and the reaction concentration fixed (2 equiv. and 0.25 M respectively), the residence time was varied by carrying the reaction for fixed intervals of 2, 5 and 10 min, showing significant increase of the reaction progress with time, although without a complete reduction. In an attempt to maintain short resident times while

trying to improve the reaction progress, the number of molar equivalents of the reducing agent was increased to 3.5, successfully leading to a complete reduction to the corresponding alcohol **2** within 10 min. Subsequently, we found that complete reduction was achieved in only 5 min just by increasing the reaction concentration from 0.25 M to 0.40 M when using 2 equivalents of BH_3·THF. On scale-up, we used this optimal set of conditions (5 min, 2 equivalents BH_3·THF and 0.4 M at room temperature) in a larger reactor volume to increase the reaction productivity. A direct scale-up was attempted using 9.1 mL of reactor volume and, after ensuring the reaction completion by LC-MS, the system was run further to obtain the desired alcohol **2**. The emerging reaction flow was continuously quenched using water followed by manual liquid extraction of the crude product. The alcohol product was then directed to the second step of the synthesis after purification by flash chromatography to obtain alcohol **2** in 77% yield with a productivity of 34 mmol product per hour. At later stage, we also attempted a further modification of the flow process by lowering the reaction temperature to minimize the evolution of gas inside the flow reactor, and found that the reduction goes to completion between 5 °C and r.t. without the need to alter the other reaction parameters. Below 5 °C the reaction performance starts to decrease while heating above ambient, on the other hand, gave no additional benefits. Overall, the above-described difficulties encountered with carrying the reduction in flow (such as avoiding flow instability due to clogging, bubble formation or thermal instability) are a demonstration that reproducing literature flask methodologies in flow condition is not always a straightforward task. On the other hand, once the method has been established, the ease of optimisation and scale-up by software-controlled process is one of the clear advantages in flow synthesis. The feasibility of obtaining an enantiomerically pure isomer of the secondary alcohol **2** using flow technique was next investigated. One way to achieve this is *via* selective acylation of one enantiomer from the obtained racemic mixture of 3-chloro-1-phenyl-propan-1-ol **2**, with the aid of a biocatalyst. Performing enantioselective bioprocesses in a conventional flask is a well established technique,[15] and carrying out these reactions under flow conditions is becoming increasingly popular especially by use of immobilized enzymes packed in a flow column, on account of the higher surface-to-volume ratio compared to conventional flask.[16] In particular, enzymatic resolution of secondary alcohols under flow conditions using immobilized biocatalysts is already established; in one recent publication by Csajági and co-workers[17] the author compared flow and flask for the enzymatic resolution of various secondary alcohols using immobilized lipases. Although high enantiomeric selectivities were attained using both techniques, higher productivities were achieved in the flow reaction. Using these conditions, we attempted preliminary enantioselective acylation of the racemic alcohol **2** using vinyl acetate. A few selected immobilized biocatalysts were screened, including Lipozyme™ *Mucor Miehei*, Amano lipase, and Lipase-porcine pancreas, by pumping a flow of the racemic alcohol solution in a 2 : 1 : 1 mixture of hexane, THF and vinyl acetate respectively, through a pre-packed column containing the immobilized enzyme. In these preliminary studies however, no acylation was observed with any of the selected enzymes. Subsequently, we investigated a direct route to enantioselective reduction of ketone **1** *via* enantioselective borane reduction using the Corey–Bakshi–Shibata (CBS) conditions, catalyzed by chiral oxazaborolidine catalyst **6** in the presence of a suitable reducing agent.[10,18] The flow method used the same setup as in the racemic flow reduction, except for the extra inlet now added for the introduction of the oxazaborolidine catalyst (Fig. 5). The CBS reduction was carried out using borane-*N*,*N*-diethylaniline complex (DEANB) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine **6** as catalyst, both introduced into the flow reactor simultaneously along with a solution of ketone **1** in dichloromethane (DCM). Unlike the BH_3·THF complex, DEANB is thermally stable and is available at higher concentrations. However, when we tried to use DEANB instead of BH_3·THF in the racemic reduction of **1** we found that, in the absence of the catalyst **6**, DEANB is a worse reducing agent. Enantioselective reduction of **1** was optimized with respect to residence time, reaction concentration, temperature, catalyst loading, and stoichiometry of borane. Most literature methods for the CBS reduction in flask strongly emphasize that the rate of the ketone addition to the catalyst should be considered as one of the key factors in reaction optimization.[16a,b] The reduction carried in flow benefits from the controlled addition and continuous mixing of reagents. Preliminary tests carried on the CBS reduction demonstrated that the concentration of ketone **1** played a key role in improving the outcome of the reaction. Accordingly, the CBS reduction was first carried out using a range of concentrations between 0.24 M to 0.40 M, whilst increasing the residence time in intervals up to 10 min and varying both the loading of catalyst **6** (up to 30 mol %) and the stoichiometry of the borane reductant (up to 3 equivalents). Unfortunately within these range of parameters no reduction was observed (Table 1,

Table 1 Summary of optimisation results of the enantioselective CBS reduction of ketone **1** under flow conditions

Entry	Time (min)	Cat. **6** (mol%)	DEANB (equiv.)	[**1**] in reaction (mol L^{-1})	T/°C	Yield (%)	ee (%)
1	5	15	2.0	0.4	23	0	—
2	5	30	3.0	0.24	23	0	—
3	5	30	3.0	0.7	23	98	72
4	5	30	3.0	0.7	−7	0	—
5[a]	10	30	3.0	0.7	−7	88	92
6[b]	10	30	3.0	0.7	−7	70	84

[a] Total flow system volume of 0.17 mL. [b] Total flow system volume of 19.8 mL.

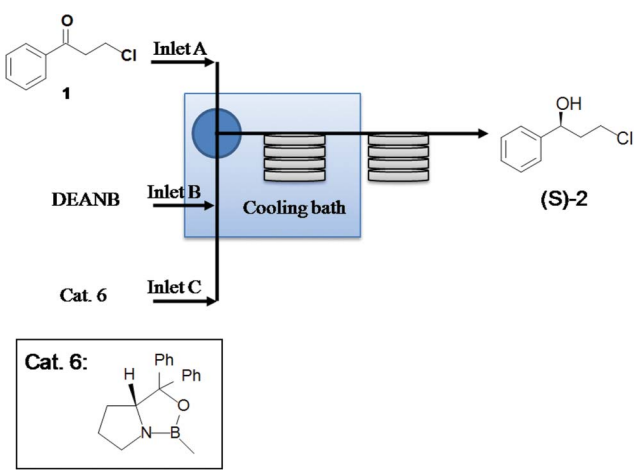


Fig. 5 Flow system set-up for the enantioselective CBS reduction of **1**.

entry 1 and 2). However, repeating the CBS reduction by increasing the concentration to 0.70 M, led to a significant improvement in the reduction outcome reproducibly. A complete reduction was achieved within 5 min using 3 equivalents of the borane reductant and 30 mol % of catalyst **6** at ambient temperature to afford (*S*)-3-chloro-1-phenyl-1-propanol (*S*)-**2**, in 98% yield and enantiomeric excess of 72% (Table 1, entry 3). As a general remark, the use of higher stoichiometry to increase throughput has little or no downstream effect since purification is carried out at the end of each step. The reaction work-up in the case of the enantiomerically pure alcohol (*S*)-**2**, was carried out by a similar procedure as described above for the racemic product, by quenching of the flow using methanol followed by liquid–liquid extraction and finally purification of the product *via* HPLC.

To optimize further the enantioselectivity of the catalytic system, we studied the effect of lowering the reaction temperature. Lowering the temperature to −7 °C was not effective with residence times up to 5 min (Table 1, entry 4). However, as the residence time was increased to 10 min, a complete reduction was achieved at −7 °C, (Table 1, entry 5) to yield the (*S*)-**2** in 88% yield with a much improved enantiomeric excess of 92%. It is important to point out that the most efficient setup was obtained by cooling down only the first half of the flow reactor, as shown in Fig. 5, leaving the second half of the flow reactor length, up to the collection point, to warm up to room temperature. To increase the production of the CBS reduction even further we increased the system volume up to 19.8 mL to obtain 83.2 mmol per hour of the alcohol (*S*)-**2** in 70% yield and 84% ee (Table 1, entry 6). The scale-up lowered both yield and enantiomeric excess to some extent. We are not entirely sure of the reason for that, but perhaps pumps working at considerably larger flow rates with such ambitiously larger scale-up volumes, can cause fluctuations in various reaction parameters, leading to an overall less controlled process.

For the following step, in an attempt to convert the chloro-alcohol **2** to 3-methylamino-1-phenyl-propan-1-ol **4** in flow, we first carried out a halogen exchange with sodium iodide followed by an amination of the resulting 3-iodo-1-phenyl-propan-1-ol **3**. Under flask conditions the conversion of a chloro-derivative into an amino-derivative *via* direct amination is often a difficult process to achieve.[19] Due to initial difficulties found in the iodination of **2** in flow (*vide infra*) the optimisation of the amination step (Scheme 1, step iii) was carried out using iodo-alcohol **3** synthesised in a flask (91% yield).[20] The amination was then carried out in flow using THF with 40% aqueous methylamine ($MeNH_2$). Literature methods (flask) require a minimum of 50 equivalents of $MeNH_2$ to achieve complete amination.[16c] A number of variables were tested in the course of our optimization in an attempt to lower the excess of amine needed, with no success. We found that using 50 equivalents of $MeNH_2$ we obtained a complete amination of **3** at a temperature of 80 °C and, with a total concentration of 0.16 M within 10 min of resident time. The effect of reaction concentration (with respect to **3**) on the amination exhibited an interesting behaviour. Varying the total reaction concentration, while maintaining the stoichiometric ratio of $MeNH_2$ constant, showed that a complete amination was achievable at 0.16 M and that with any higher or lower concentration the amount of the unreacted **3** would start to increase. The iodination of chloro-alcohol **2** in flow proved rather challenging. Since the reaction is typically run in an organic medium, usually acetone, the precipitation of by-product NaCl pushes the equilibrium forward. However, salt precipitation in flow causes clogging of the channel. On the other hand, the use of a solvent system where all reaction components -including NaCl- are soluble would lower the rate of the halogen exchange.[21] Hence, by switching to an organic-aqueous biphasic solvent system we aimed to overcome the clogging as the presence of an additional aqueous phase can quickly dissolve the salt by-product as soon as it forms, thus maintaining the equilibrium in favour of the product (by subtraction of the by-product from the equilibrium *via* extraction instead of precipitation). Based on this, the biphasic reaction was performed by pumping simultaneously into the flow reactor a solution of the chloro-alcohol **2** in an organic solvent (toluene) and an aqueous solution of sodium iodide, generating a segmented flow pattern in which each phase forms a serial train of liquid packets flowing across the channel whilst remaining separated from the other phase (Fig. 6). The resulting large interface area, typical of these systems, provides an improved mixing compared to conventional biphasic mixing in flask, highlighting one of the main advantages of flow reactions.[22]

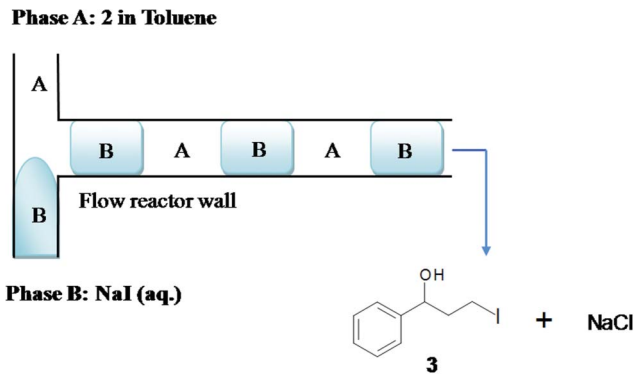


Fig. 6 Halogen exchange of chloro-alcohol **2** under segmented flow conditions.

We screened a number of biphasic reaction conditions and as a result a general improvement on the iodination outcome was observed, with much less solid precipitation compared to the single organic phase flow system using acetone. The toluene-aqueous system was found to be optimum. Other solvents such as DCM and ethyl acetate were found not to be suitable. The least solid precipitation was observed in the toluene-aqueous system using 9 equivalents of NaI and 0.6 M chloride **2** at 100 °C. Under these conditions, however, the best conversion we were able to achieve was 43% within 20 min residence time. Isolation and purification of **3** obtained under flow conditions was achieved first by separating the emerging biphasic toluene-water solution by manual extraction, followed by standard work-up of the toluene phase containing the crude product and finally purification by flash chromatography. Furthermore, attempts to increase the reaction concentration were unsuccessful because of the challenge given by the presence of the insoluble by-product. In the course of our screening we observed that on the one hand higher concentrations led to more solid precipitation, while on the other hand higher dilution led to low conversions. Overall our observations confirmed how solid precipitation represents

one of the major challenges for flow chemistry. Therefore the use of flow systems might not be ideal with reactions where the formation of an insoluble by-product is essential to drive the reaction forward since yields can be lowered considerably. As an alternative, we successfully performed direct amination of **2** to obtain **4** using aqueous $MeNH_2$ under superheated conditions using the Vapourtec R Series flow system. Apart from the high temperature required for this experiment (140 °C), the optimal conditions for this reaction were similar to those used for the amination of iodo-alcohol **3**. Complete amination was achieved in MeCN with 10 min residence time (Scheme 1, step iv), giving a productivity of 9.5 mmol per hour of **4** when a 10 mL flow reactor used. The amino-alcohol **4** was then easily isolated in 95% yield by the "catch-and-release" method using silica-bound cation exchanger propylsulfonic acid (SCX-2).[23,24]

In the final step we attempted the conversion of amino-alcohol **4** into the target product (±)-fluoxetine **5** under flow conditions. The majority of literature methods for the synthesis of **5** involve an arylation *via* nucleophilic aromatic substitution (S_NAr) with sodium hydride (NaH) to generate the alkoxide, which acts as nucleophile towards the substrate *p*-chlorobenzotrifluoride.[16c,17,25] However, the use of NaH in flow created constant problems of clogging due to its low solubility even when a solubility enhancer such as 15-crown-5ether was used. Additionally, not even the use of alternative bases such as sodium bis(trimethylsilyl)amide (NaHMDS) or Phosphazene-BEMP promoted the S_NAr and the amino-alcohol **4** remained unreacted. However the arylation of **4** was successfully carried out in flow using the Mitsunobu reaction conditions instead (Scheme 1, step v). The amino-alcohol **4** is converted to the phenyl ether derivative **5** through a nucleophilic substitution of the hydroxyl moiety with *p*-hydroxybenzotrifluoride **7**.[26] Standard Mitsunobu reagents, tributylphosphine (PBu_3) combined with diethyl-diisopropyl-azo-dicarboxylate (DIAD), were used to generate the phosphonium betaine intermediate **8** *in situ* as shown in Fig. 7. During the optimization in flow, we realized that the addition order of the reagents plays an important role on the reaction outcome. We observed that there was only one successful order of addition to perform the reaction. DIAD and PBu_3 first were combined in flow to form the betaine intermediate **8**, then, *p*-hydroxybenzotrifluoride **7** and amino-alcohol **4** were introduced in sequence through separate inlets as shown in Fig. 7.

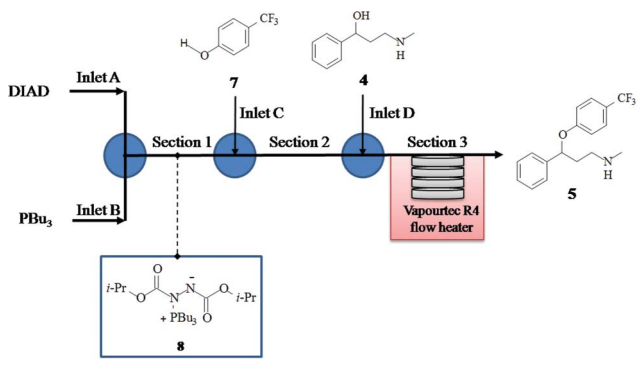


Fig. 7 Flow system set-up for the preparation of (±)-fluoxetine **5**.

Optimization of the reaction was performed using the Vapourtec R Series system by looking at the effect of stoichiometry, temperature, and residence time. Since we needed to introduce each reagent individually, we used the modified Vapourtec R Series system with four pumps controlled by the modified Flow Commander™ software, as shown in Fig. 3. The performance of the Mitsunobu reaction in flow was initially very poor when carried out at room temperature using 1 equivalent of each reagent at a reaction concentration of 0.2 M with respect to **4** and a residence time between 5 and 20 min. A moderate improvement of the reaction progress was achieved by increasing the molar ratio of PBu_3 and DIAD, however significant improvement was observed when the temperature was increased. The conversion of **4** was achieved within 5 min at 70 °C, using 3 equivalents of PBu_3 and DIAD along with 1 equivalent of the nucleophile **7**, at a reaction concentration of 0.2 M using a 2 mL volume of flow reactor. The collected crude mixture was treated with hexane to remove excess tributylphosphine oxide, before purification by chromatography to obtain the product in 86% yield, giving a productivity of 4.8 mmol product per hour.

Conclusions

Due to the increasing interest chemists are showing in using flow synthesis, our aim was to carry out a study to verify its feasibility. To better demonstrate this we decided to use flow for multiple steps of a total synthesis of a relevant medicinal compound. We delivered a multiple step approach to the synthesis of (±)-fluoxetine in flow, thus developing an efficient and scalable synthetic route as an alternative to conventional flask methods. In particular, we easily carried out the direct amination of the chloro-alcohol precursor, quite difficult to achieve in a flask, thus cutting down the number of steps in the total synthesis. The intrinsic nature of flow combined with the aid of automation and software control, facilitated fast sequential optimisation of reaction conditions for each step using both in-house and commercial flow systems, and hence enabled us to rapidly identify which parameters were key to enhancing productivity. Such accomplishment is often the result of a fine balance between the parameters at play. For instance, as the reaction concentration is increased to maximise the yield, channel clogging can become an issue. Similarly, the use of high temperature can create system instability (gas evolution, decomposition), longer resident times required for scale-up purposes might end up affecting throughput efficiency and increasing the system volume can lead to large fluctuations of parameters. We showed how essential it is to achieve the right balance between reaction parameters in order to make the most of the many great advantages offered by flow technique. The method hereby presented has the potential to develop into a continuous flow multistep synthesis by introduction of suitable in-line purification. Overall, the multiple step synthesis of fluoxetine using flow technique is presented in this study as a valid alternative to flask synthesis.

Experimental

Unless otherwise indicated, all chemicals used were of reagent grade and starting materials were purchased from commercial sources and used without further purification. ^{1}H-NMR spectra were recorded on Bruker DPX-300, DPX-400 or DRX-500 spectrometers and the chemical shifts were reported in ppm with the solvent resonance as the internal standard ($CHCl_3$ δ_H: 7.26 ppm).

^{1}H-NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (J) in Hz. LC-MS analysis was performed on an Agilent HP 1100 chromatograph (Phenomenex Gemini column: C18, 3 μm, 2 mm × 50 mm) equipped with a diode array detector for UV signals, a single quadrupole mass spectrometer and an electrospray source on the mass spectrometer. The Elution was carried out at 1 mL min^{-1} over 2.5 min using a gradient of MeCN : water (5–100% MeCN in water), both containing 0.1% formic acid. Flash purification performed on SiliCycle Silia*Sep*™ 40–63 μm 60 Å cartridges using an automated flash chromatography coupled with a UV detector at 254 nm. HPLC purification performed using Phenomenex Gemini column (C18, 5 μm, 30 mm × 100 mm), configured with column dilution. Elution was carried out at 60 mL min^{-1} over 9 min using a reversed-phase gradient of MeCN : water (10–100% MeCN in water), both containing 0.1% trifluoroacetic acid. Thin layer chromatography (TLC) was performed on glass backed plates pre-coated with silica (Merck DC-platten Kieselgel 60 F254), which were developed using standard visualizing agents: Ultraviolet light or potassium permanganate. Optical rotation values were recorded on a Perkin-Elmer 341 automatic polarimeter at 589 nm (Na/Hal) with a path length of 1 dm and concentrations (c) quoted in g/100 mL.

General procedures

Preparation of racemic 3-chloro-1-phenyl-1-propanol (2)[27] in flask. To a solution of the ketone **1** (15 g; 89 mmol) in THF (210 mL) and water (15 mL), $NaBH_4$ was added (4 g; 107 mmol). The mixture was left to stir for 12 h at room temperature. After completion, the crude mixture was treated with water (150 mL), extracted with ethyl acetate (150 mL × 2), dried over magnesium sulfate and filtered followed by solvent evaporation. The crude product was purified by flash chromatography using 40% diethyl ether in hexane to afford the racemic alcohol **2** (12.9 g, 85% yield) as yellow oil.

Preparation of racemic 3-chloro-1-phenyl-1-propanol (2) in flow. The following solutions were prepared: (i) 2 M solution of the ketone **1** (4.7 g; 28 mmol) in THF; and (ii) 1 M solution of BH_3·THF (56 mL; 56 mmol). Each solution was individually loaded into a gas-tight glass syringe connected to the flow system (9.1 mL, 1 mm i.d) through a designated inlet as illustrated in Fig. 4. Using the syringe pump, both solutions were then delivered simultaneously into the flow system, at the desired residence time of 5 min (solution (i) flow rate at 1 equiv. = 364 μL min^{-1} and solution (ii) flow rate at 2 equiv. = 1457 μL min^{-1}). After continuously quenching the emerging flow of the crude mixture using water, the crude was extracted with ethyl acetate (50 mL × 3), washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography using 35% diethyl ether in hexane to afford the racemic alcohol **2** (3.66 g, 77% yield) as yellow oil.

Preparation of (*S*)-3-chloro-1-phenyl-1-propanol (2) in flow. The following solutions were prepared: (i) 1.5 M solution of the ketone **1** (0.51 g; 3 mmol) in DCM; (ii) 1 M solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine **6** (0.9 mL; 0.9 mmol) in toluene; (iii) 5.6 M neat solution of borane-*N*,*N*-diethylaniline complex (DEANB) (1.6 mL; 9 mmol). Each solution was then individually loaded into a gas-tight glass syringe connected to the flow system (0.17 mL, 0.5 mm i.d) through a designated inlet as illustrated in Fig. 5. First half of the flow reactor was cooled down to −7 °C, leaving the second half of the flow reactor length up to the collection point to warm up to room temperature (Fig. 5). Using syringe pumps, all solutions were then delivered simultaneously into the flow system for the desired residence time of 10 min (solution (i) flow rate at 1 equiv. = 7.8 μL min^{-1}, solution (ii) flow rate at 0.3 equiv. = 3.5 μL min^{-1}; and solution (iii) flow rate at 3 equiv. = 6.3 μL min^{-1}). After continuously quenching the emerging flow of the crude mixture using MeOH, the crude was concentrated under vacuum followed by dilution with diethyl ether, washed with 1 N aqueous HCl (10 mL), water (10 mL), then brine, dried over magnesium sulfate, filtered and concentrated to dryness. The crude product was purified by HPLC to afford the (*S*)-alcohol (*S*)-**2** (0.45 g, 88% yield) as a white solid. $[\alpha]_D^{20}$ −23, (c = 1, $CHCl_3$) for 92% ee.[28] Retention time = 1.13 min, M + Na m/z = 193.70. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.4–7.3 (5H, m), 4.9 (1H, dd, J = 4.9, 8.3 Hz), 3.8–3.7 (1H, m), 3.6–3.3 (1H, m), 2.3–2.2 (1H, m), 2.1–2.0 (1H, m), 1.9 (1H, s).

Preparation of racemic 3-iodo-1-phenyl-propan-1-ol (3)[10] in flask. To a solution of chloro-alcohol **2** (3.2 g; 18.7 mmol) in acetone (250 mL), NaI was added (5.5 g; 36 mmol). The mixture was left to stir for 16 h under reflux. The resulting mixture was filtered then concentrated under vacuum followed by dilution with diethyl ether, washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness to afford iodo-alcohol **3** (4.5 g, 91% yield). No further purification was required as analysis indicated that the obtained iodo-alcohol **3** was clean enough to carry through the next step. Retention time = 1.19 min, M + Na m/z = 285.00. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.4–7.2 (5H, m), 4.7 (1H, dd, J = 4.8, 8.0 Hz), 3.3–3.2 (1H, m), 3.2–3.1 (1H, m), 2.3 (1H, s), 2.3–2.1 (2H, m).

Preparation of racemic 3-iodo-1-phenyl-propan-1-ol (3) in flow under biphasic conditions. The following solutions were prepared: (i) 0.6 M solution of chloro-alcohol **2** (0.5 g; 2.9 mmol) in toluene; and (ii) 5.3 M aqueous solution of NaI (4 g; 27 mmol). Each solution was individually loaded into a glass flask connected through a designated inlet to a flow system (0.40 mL, 0.5 mm i.d) fitted with back pressure regulator (100 psi). Using the Knauer HPLC pump, both solutions were then delivered simultaneously into the flow system, heated at 100 °C, to create a continuous segmented flow (Fig. 6) at residence time of 20 min (solution (i) flow rate at 1 equiv. = 10 μL min^{-1} and solution (ii) flow rate at 9 equiv. = 10 μL min^{-1}). Once the emerging segmented phases of toluene-water flow collected from the output, the toluene phase, containing the crude mixture, was separated. The toluene phase was then concentrated under vacuum followed by dilution with diethyl ether, washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography using 10% diethyl ether in hexane to afford the racemic iodo-alcohol **3** (0.33 g, 43% yield) as light brown solid.

Preparation of racemic 3-methylamino-1-phenyl-propan-1-ol (4)[10] in flow. The following solutions were prepared: (i) 0.6 M solution of the halo-alcohol **2** (16 mmol) in MeCN or **3** (16 mmol)

in THF; and (ii) 11.6 M aqueous solution of $MeNH_2$ (69 mL; 800 mmol). Each solution was loaded individually into the Vapourtec R Series flow system using the two pumps R2+ system. The solutions were first pumped in, then merged into a T-connector and finally directed into the R4 flow reactor (10 mL, 1 mm i.d.) heated at 80 °C (when iodo-alcohol **3** used) or 140 °C (when chloro-alcohol **2** used), flowing at a residence time of 10 min (solution (i) flow rate at 1 equiv. = 279 μL min^{-1}; and solution (ii) flow rate at 50 equiv. = 721 μL min^{-1}). The collected crude mixture was then concentrated under vacuum, to remove the excess $MeNH_2$, then purified using the catch-and-release purification technique.[22] The crude was poured over a flash SCX-2 column and washed with MeOH (150 mL) followed by 7 M solution of ammonia in MeOH (150 mL) to release the desired secondary amine product. The obtained material was concentrated under vacuum to afford the amino-alcohol **4** (2.53 g; 95% yield (from **2**)) and (2.4 g; 89% yield (from **3**)) as colourless oil. Retention time = 1.42 min, M + H m/z = 166.20 (High pH). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.4–7.2 (5H, m), 4.9 (1H, dd, J = 3.0, 8.3 Hz), 4.3 (2H, s), 2.9–2.7 (2H, m), 2.4 (3H, s), 1.9 –1.7 (2H, m).

Preparation of (±)-fluoxetine (5)[10] in flow. The following solutions were prepared: (i) 1.1 M solution of the amino-alcohol **4** (1 g; 5.9 mmol) in DCM; (ii) 1 M solution of *p*-hydroxybenzotrifluoride **7** (1.1 g; 6.68 mmol) in a mixture of DCM : dimethylacetamide (4 : 1) ; (iii) 1.6 M solution of PBu_3 (4.5 mL; 18 mmol) in DCM; (iv) 3 M solution of DIAD (3.6 mL; 18 mmol) in DCM. Each solution was loaded individually into the Vapourtec R Series flow system in the required addition order (Fig. 7) using the four-pump modification of the Vapourtec R Series system. The solutions were mixed using a T-connector then directed into the R4 flow reactor (2 mL, 1 mm i.d) heated at 70 °C, flowing at a residence time of 5 min (solution (i) flow rate at 1 equiv. = 76 μL min^{-1}, solution (ii) flow rate at 1.1 equiv. = 84 μL min^{-1}; and solution (iii) flow rate at 3 equiv. = 157 μL min^{-1}, (iv) flow rate at 3 equiv. = 84 μL min^{-1}). The collected crude mixture was then concentrated under vacuum followed by dilution with diethyl ether and slow addition of hexane (30 mL) while stirring until the cloud point was reached. The precipitated tributylphosphine oxide was then removed by filtration then the filtrate was concentrated and purified by chromatography using 10% DCM in MeOH to afford the (±)-fluoxetine **5** (1.6 g; 86%) as a pale yellow oil. Retention time = 0.98 min, M + H m/z = 310.20. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.4 (2H, d, J = 8.3 Hz), 7.3 –7.2 (5H, m), 6.9 (2H, d, J = 8.3 Hz), 5.3 (1H, dd, J = 4.8, 7.8 Hz), 2.7 (2H, t, J = 6.8 Hz), 2.4 (3H, s), 2.2–2.1 (1H, m), 2.0–1.9 (1H, m).

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