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A Continuous Flow Process Using a Sequence of Microreactors with In-line IR Analysis for the Preparation of *N*,*N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide as a Potent and Highly Selective δ-Opioid Receptor Agonist

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Abstract: This article describes the design, optimisation and development of a continuous flow synthesis of *N*,*N*-diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)-benzamide, a potent δ-opioid receptor agonist developed by AstraZeneca. The process employs a sequence of flow-based microreactors, with integrated purification employing solid-supported reagents and in-line IR analytical protocols using a newly developed ReactIR flow cell. With this monitoring device, initiation of the fourth input flow stream can be precisely controlled during the synthesis.

Keywords: flow chemistry · IR spectroscopy · microreactors · solid-phase synthesis

Introduction

The development of flow chemistry has considerably expanded the armoury of chemical processing tools available to the modern day organic chemists.[1] The impact and significance of this technology is reflected by the exponential increase and by the diverse nature of the synthetic transformations facilitated by these methods.[2] By comparison to the conventional batch-mode synthesis, flow chemistry offers much improved efficiency through telescoped reaction processes.[3] Moreover, by incorporating solid-supported scavengers for the removal of by-products,[4] pure products can be obtained with no need for standard purification procedures such as aqueous workup, distillation and column chromatography.[5] Consequently, less solvent is necessary and reduced amounts of waste materials are generated, making the procedure more sustainable.[6] Furthermore, any toxic and potentially hazardous reaction intermediates can be generated and used in situ within the confines of the device, allowing much safer handling of chemicals.[7]

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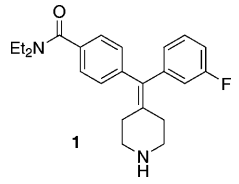
To further demonstrate the advantages of continuous flow chemistry to produce drug molecules and their derivatives,[8] we chose to synthesise the olefinic piperidine compound **1** (see below), a novel, exceptionally selective and potent δ-opioid receptor agonist developed by AstraZeneca.[9] Like all members of the opioid receptor family, agonists for δ-opioid receptors have been shown to exhibit analgesic effects.[10]However, as was later established, a selective δ-opioid receptor agonist can achieve the desired pain relief without the side effects associated with other members of the family (e.g., respiratory depression, dependence liability, and dysphoria).[11] This discovery has provided the momentum for developing selective nonpeptide δ-opioid receptor agonist.

In 2003, Wei and co-workers published a five-step synthesis of the target molecule **1**, with an overall yield of 6%.[9] Our aim was to improve upon this yield and the efficiency of the synthesis using flow-based methodologies. We also wished to determine new methods to overcome some of the current difficulties encountered in flow chemistry, namely, the precise control and introduction of additional flow streams to non-steady state fluid flows. In many operations the dispersion of a reaction plug through diffusion precludes the precise estimation of reactants and product eluting through the system in a multi-step sequence. Consequently, the addition of auxiliary reac-



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tants delivered by a third or fourth reaction stream is difficult to control and regulate. In this research a newly developed ReactIR flow cell was used as a convenient in-line analytical tool for expediting continuous processing. Indeed, recent work within our group has already demonstrated the power of this IR monitoring device, and its potential for solving key issues associated with multi-step reaction sequences where knowledge of reagent concentration at all stages is of paramount importance.[12]

In this new work, we describe the development of a four-step continuous flow sequence to **1** using the commercially available Vapourtec R2+/R4 reactor and Mettler-Toledo ReactIR 45 m system (Figure 1).[13]

Figure 1. Vapourtec R2+/R4 microreactor and Mettler–Toledo ReactIR 45 m.

Results and Discussion

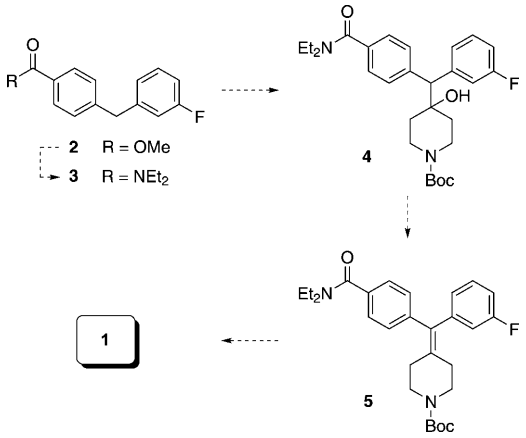
The general synthesis scheme to diarylpiperadine **1** is shown in Scheme 1, whereby the initial step requires the development of an amide bond-forming process (**2**→**3**).

First, we attempted to use conditions that were applied in the reported batch synthesis to generate the diethyl amide using *i*PrMgCl at −40 °C (Scheme 2, Table 1).[14] However, this method caused precipitation of magnesium salts and resulted in blocking of the instruments tubing and valves. By switching to a solution of *i*PrMgCl·LiCl with diethylamine, the precipitation issue was avoided. Solutions of the cooled *i*PrMgCl·LiCl (1.16 M, 1.5 equiv, −40 °C) and a mixture of diethylamine (1.55 M, 2.0 equiv) and ester **2** (0.77 M, 1.0 equiv) in THF were loaded into two identical PEEK sample loops (2 mL internal volume, 0.16 mm i.d.).The two sample loops were simultaneously injected into the main flow stream through a T-piece connector at a flow rate of 0.125 mL min^{-1} per channel. The combined stream was then directed through a convection flow coil (CFC, 10 mL volume, 1 mm i.d. polyfluoro acetate, PFA tubing) submerged in a mixture of MeCN and dry ice, which was maintained at −40 °C giving a residence time of 40 min. The exiting flow stream from the CFC reactor was then directed into a glass column (10 mm × 10 cm)[15]which was packed with a 1:1 mixture of Quadrapure-benzylamine (QP-BZA, 5 equiv) and Quadrapure-sulfonic acid (QP-SA, 5 equiv)[16] to work up the product stream and scavenge the residual amine starting material and base. A second glass column loaded with silica gel (600 mg) was then employed to trap the magnesium salts generated during the process. Despite initially poor results (Table 1), we eventually found the best conditions were to conduct the reaction at ambient temperature (25 °C), which gave the desired product **3** in essentially quantitative yield (Scheme 2, Table 1).

Table 1. Condition screening for the flow synthesis of the amide **3** from the ester **2**.

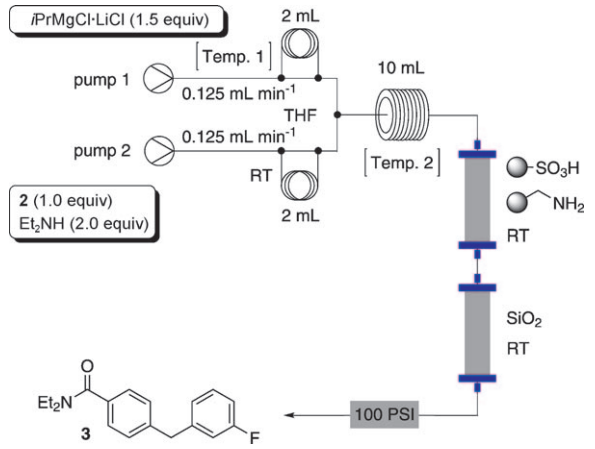
Grignard reagent	Temp. 1 [°C]	Temp. 2 [°C]	Yield **3** [%]
*i*PrMgCl	−40	−40	0[a]
*i*PrMgCl·LiCl	−40	−40	0
*i*PrMgCl·LiCl	−40	0	0
*i*PrMgCl·LiCl	0	0	40
*i*PrMgCl·LiCl	25	0	60
*i*PrMgCl·LiCl	25	25	99
*i*PrMgCl	25	25	0[a]

[a] Yields could not be obtained for these reactions due to blockage of the instrument tubing/valves during the reaction.



Scheme 1. General scheme showing the intermediate structures for the synthesis of **1**.

Moreover, when the amide coupling reaction was conducted at room temperature, the reaction mixture became bright red in colour (Figure 2), which was not observed at 0 °C. It was suspected that this could be due to the additional deprotonation of the diarylmethyl proton. To confirm the colour change was not related to simple the amide coupling reaction itself, a control reaction was performed with methyl benzoate under identical condition. In this case, no significant colour change was observed during the process. Therefore, we concluded the amide coupling reaction and deprotonation of the ester **2** occurred simultaneously at room temperature, such that we could then further couple with 1-Boc-4-piperidone (**6**), to directly form the key intermediate **4** in a single operation.



Scheme 2. Amide coupling reaction in flow.

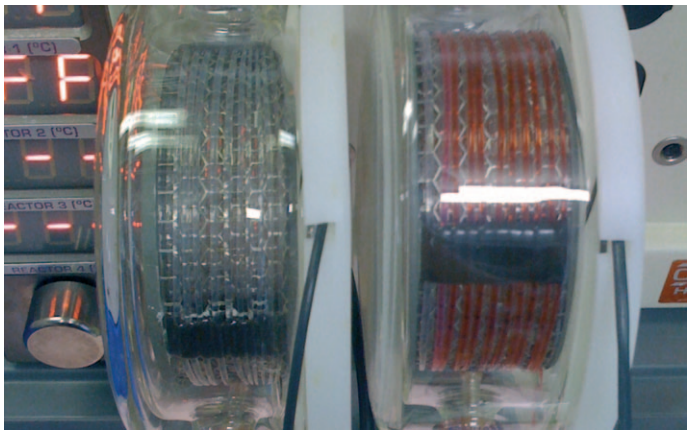
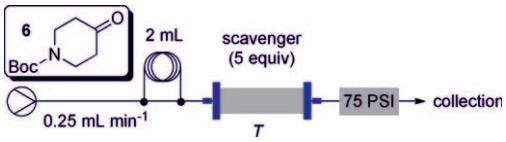


Figure 2. Bright red colour observed during the amide coupling reaction at 25 °C.

Accordingly we optimised the two-step continuous flow sequence to form the key intermediate **4**. Knowing that we would have to use the 1-Boc-4-piperidone (**6**) in excess; we began by scrutinising suitable scavengers for removal of this excess reagent (Scheme 3, Table 2). While QP-BZA was ineffective in this process, polystyrene sulfonyl hydrazide resin (MP-TsNHNH$_2$, 5 equiv)[17] performed well essentially removing all the piperidone **6** upon heating at 60 °C.The reagent could then be used in a cartridge format to progress the synthesis of the key intermediate **4**.

We used the new conditions for the amide coupling reaction but increased the mole equivalents of diethylamine (from 2.0 to 2.5) and *i*PrMgCl·LiCl (from 1.5 to 2.0) for complete deprotonation of the intermediate amide **3**. The 1-



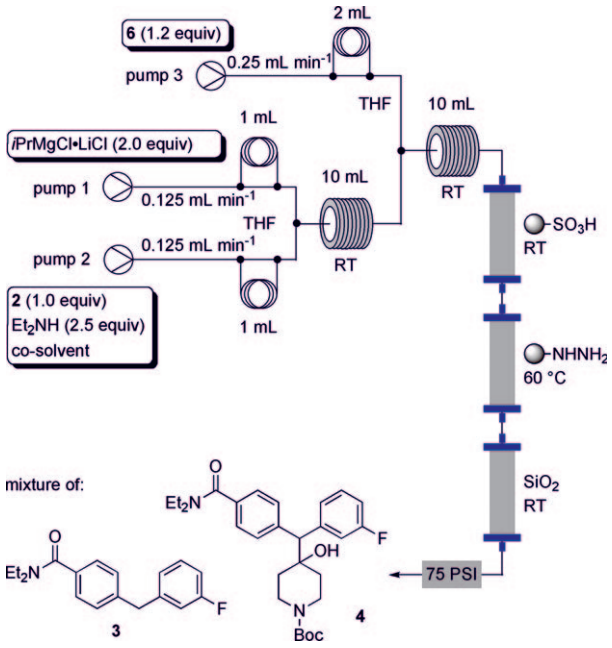
Scheme 3. Scavenger screening for 1-Boc-4-piperidone (**6**).

Table 2. Scavenger screening for 1-Boc-4-piperidone(**6**).

Scavenger	*T* [°C]	Recovered **6** [%]
QP-BZA	25	99
QP-BZA	60	99
MP-TsNHNH$_2$	25	40
MP-TsNHNH$_2$	60	0

All reactions were performed using a solution of **6** (2 mmol, 1 equiv) in THF (2 mL) and 5 equivalents of scavengers.

Boc-4-piperidone (**6**) was introduced later using a third pump at 0.25 mL min^{-1} (Scheme 4). Since the initial stream of the reaction was brightly coloured, the timing for the subsequent addition could be accurately controlled to meet and combine with the ketone **6**. The resultant flow stream was then passed through a CFC (10 mL) maintained at ambient temperature, followed by in-line treatment comprising of three consecutive columns; 1) QP-SA (3 equiv), 2) MP-TsNHNH$_2$ (5 equiv) and finally 3) silica gel (600 mg). Unfortunately, a yield of only 10 % of the desired product **4** was realised using this process, suggesting that the dual deprotonation had proceeded poorly. To enhance the deprotonation, a series of co-solvents were screened (Scheme 4, Table 3), where 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) gave the best results, yielding 50 % of the desired product **4** after purification by column chromatography.



Scheme 4. Continuous flow synthesis of the key intermediate **4**.

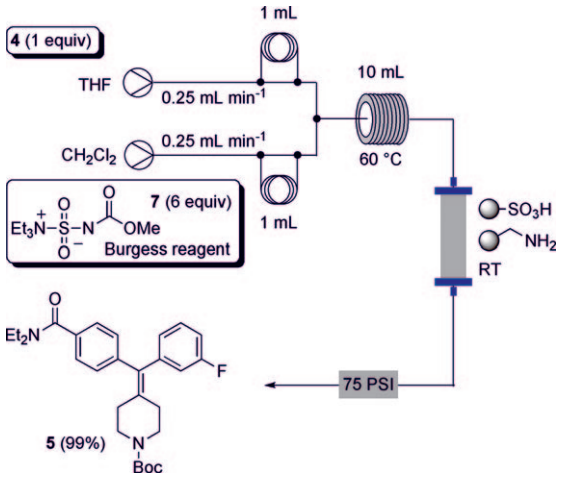
The next step of the process, the dehydration of intermediate **4** was accomplished using the Burgess reagent (**7**). The procedure required solutions of the Burgess reagent (3.0 M, 6.0 equiv) in CH_2Cl_2 and alcohol **4** (0.5 M, 1.0 equiv) in THF to be loaded into two separate PEEK sample loops

Table 3. Condition screening for the continuous flow synthesis of the key intermediate **4**.

Co-solvent	Yield **3** [%]	Yield **4** [%]
THF	85	10
HMPA	50	48
dimethoxymethane	0	0[a]
DMF	99	0
DMPU	45	50

[a] The yield could not be obtained for this reaction due to precipitation occurring during the reaction.

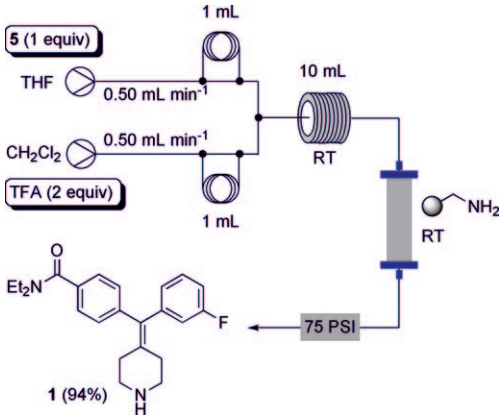
(1 mL internal volume). A solvent flow rate of 0.25 mL min^{-1} was used to introduce the two compounds and combine their pathways at a standard T-piece mixer (Scheme 5). The reaction stream was then passed through a CFC (10 mL volume), which was heated at 60 °C, followed by a column loaded with a mixture of QP-SA (3 equiv) and QP-BZA (5 equiv) to sequester the excess Burgess reagent and associated by-products. The resultant solution was then concentrated in vacuo to give the desired product alkene **5** in near quantitative yield (99 %).



Scheme 5. Dehydration reaction in flow.

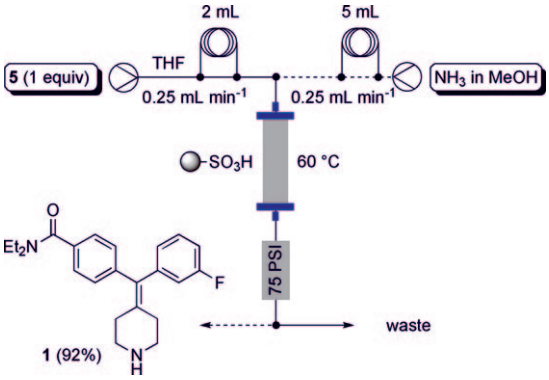
The final stage Boc deprotection was well precedented,[9] hence our initial effort involved conducting the reaction following the reported batch conditions. Two solutions, one comprising of trifluoroacetic acid (TFA) in CH_2Cl_2 (1.0 M, 2.0 equiv) and the second containing the Boc-protected amide **5** in THF (0.5 M, 1.0 equiv) were loaded into PEEK sample loops (1 mL internal volume). These solutions were then introduced at 0.50 mL min^{-1} per channel to the main stream via a T-piece connector (Scheme 6). The reaction stream was progressed through a CFC (10 mL volume), which was held at 25 °C, and then purified by passage through a column of QP-BZA (10 equiv) allowing isolation of the target molecule **1** in an acceptable 94 % yield.

Previous work within the group, however, suggested the Boc deprotection could be performed using a heterogeneous acid catalysts, such as QP-SA, at elevated temperatures. As



Scheme 6. Homogeneous Boc deprotection in flow.

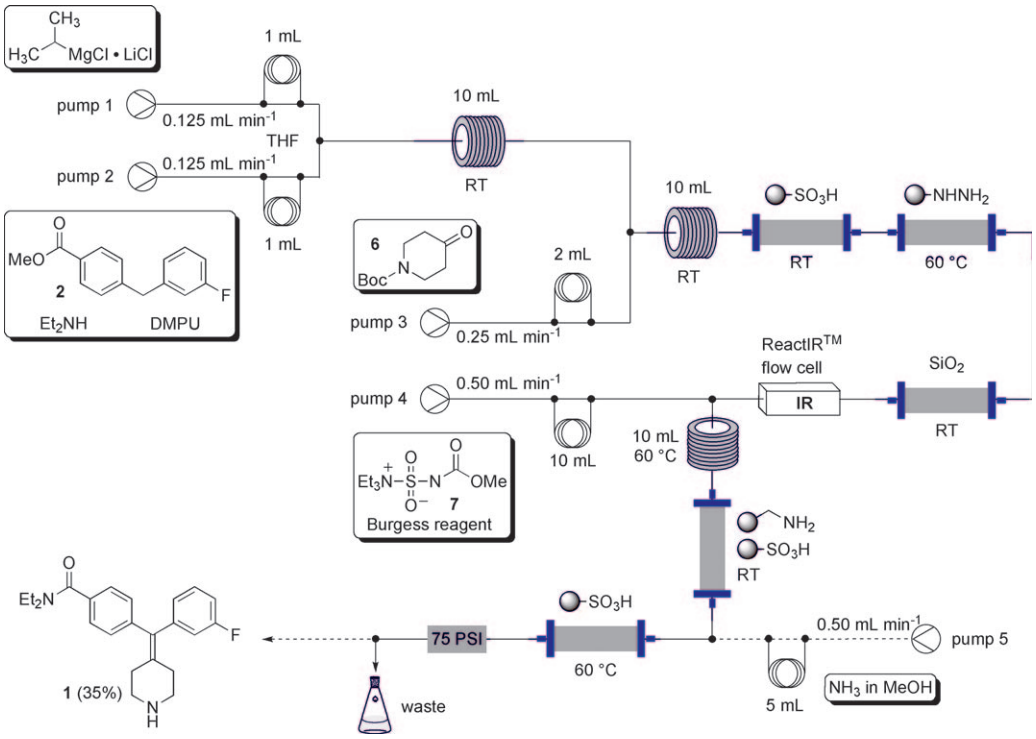
shown in Scheme 7, a solution of protected material **5** (0.5 M, 1.0 equiv) in THF was therefore passed through a heated column (60 °C) of QP-SA (5.0 equiv), enabling the deprotected amine **1** to be concurrently protonated and retained within the acidic column. The column was allowed to cool to room temperature, and the product could then be later released by eluting the column with a solution of ammonia in MeOH (2.0 M, 5 equiv).This "catch and release" procedure proved very reliable for delivering high pure product requiring only concentration in vacuo to yield the desired product **1** (92 %).



Scheme 7. Heterogeneous Boc deprotection in flow.

Both methods gave the desired product in comparable yield. However, for the continuous flow synthesis, we decided in favour of the heterogeneous route. This was mainly due to the fact that with one less chemical being introduced in the reaction sequence, the setup and control of the overall system would be much simpler.

Having completed the flow synthesis of the target molecule in three phases, we aspired to develop the reaction into a single flow sequence. The first problem we encountered involved synchronising the introduction of a fourth reaction stream (the Burgess Reagent). This issue was overcome by using the ReactIR 45 m flow cell (Figure 1, Scheme 8). To



Scheme 8. Continuous flow synthesis of the target molecule **1**.

establish the in-line monitoring system, we first recorded the IR spectrum of all the solvents and reagents involved in these reactions.[18] Next, the intermediate **4** was scanned and a characteristic stretching frequency between 1690 and 1700 cm^{-1} identified (Figure 3). Therefore, by recording the intensity of IR absorption at this spectral region over the time of the reaction, we were able to directly synchronise the introduction of the fourth input stream containing the Burgess reagent (Figure 4). Moreover, we were able to determine the extent of dispersion of compound **4** during our initial experiment, and hence calculate the exact concentration and volume (0.5 mL min^{-1} × 20 min = 10 mL) of Burgess reagent needed to perform the reaction.

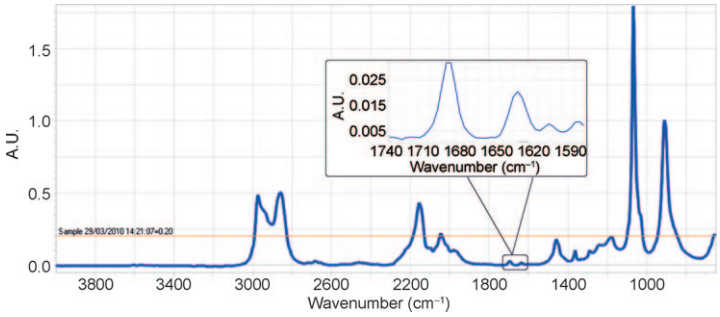


Figure 3. Recorded IR spectrum of the key intermediate **4**.

With all these results in hand, we were finally able to complete the continuous flow synthesis of the target molecule as an integrated process (Scheme 8). As previously described solutions of *i*PrMgCl·LiCl (1.16 M, 2.0 equiv) and a mixture of DMPU, diethylamine (1.45 M, 2.5 equiv) and the ester **2** (0.58 M, 1.0 equiv) in THF were combined at a T-piece connector. The resultant mixture was flowed through a CFC reactor (10 mL, 25 °C) before being merging with a third stream of the 1-Boc-4-piperidone (**6**, 0.33 M, 1.2 equiv) via a second T-piece mixer. The reaction stream was then directed through a second CFC (10 mL, 25 °C), followed by three columns containing in order of QP-SA (3 equiv), MP-$TsNHNH_2$ (5 equiv) and silica gel (600 mg). The exiting stream then entered the ReactIR flow cell, and as soon as the indicative fingerprint signal was detected (i.e., IR stretching frequency 1690–1700 cm^{-1}, Figure 4), the fourth

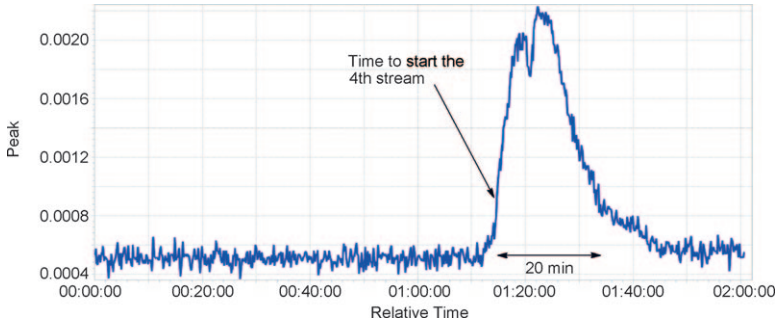


Figure 4. Intensity of IR absorption for the amide stretching frequency for key intermediate **4**over the time of the continuous flow synthesis.

and final input stream was started, allowing the Burgess reagent (0.34 M, 6 equiv) to join the main reaction stream. The reaction mixture was pumped through a third CFC (10 mL, 60 °C) before entering a column loaded with a mixture of QP-SA (3 equiv) and QP-BZA (5 equiv). Finally, a heated column of QP-SA (5 equiv) was used to deprotect and catch the target molecule. Any unreacted amide **3** from the first two steps was simply pumped to waste, while all the key intermediate **4** had already been cleanly converted to the desired product **1**. Elution of the acidic column using a solution of NH_3 in MeOH (2.0 M, 6 equiv) completed the synthesis in a continuous fashion, and gave the product **1** in 35% overall yield and in high purity over the four steps.

Conclusion

In summary, we have developed a four-step flow synthesis of a potent δ-opioid receptor agonist. In this work, we have used a combination of pumping devices together with cartridges packed with appropriate reagents or scavengers to effect clean delivery of the product. Importantly, we have also reported the use of in-line ReactIR monitoring to synchronise pumping of a late input stream to coordinate reactive components. We believe this flow chemistry sequence further demonstrates the power of these methods for multistep, multi-component coupling processes leading to functional molecules with potential commercial and healthcare benefits.

Experimental Section

General: Infrared spectra were recorded using a Perkin–Elmer One FT-IR spectrometer fitted with an ATR sampling accessory as either liquid films or dilute solutions in spectroscopic grade chloroform or dichloromethane. The intensity of the signals is designated by the following abbreviations: s, strong; m, medium; w, weak; br, broad; sh, sharp.^{1}H NMR spectra were recorded on Bruker DPX-500 (500 MHz) instrument and ^{19}F NMR spectra were recorded on a Bruker DPX-400 (400 MHz) instrument as dilute solutions in deuterated chloroform unless otherwise stated. ^{13}C NMR spectra were recorded at 125 MHz on Bruker DPX-500 instrument with $CDCl_3$ as the solvent. The chemical shifts are reported relative to residual chloroform as an internal standard, and all coupling constants, *J*, are reported in Hertz (Hz).LC-MS analysis was performed on an Agilent HP 1100 series chromatograph (Mercury Luna 3 m C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionization source in ESI mode. Mass spectra were obtained on a Kratos-QTQF spectrometer using electrospray ionisation (+ESI) or LCT Premier spectrometer by Waters using Micromass MS software by electrospray ionisation (+ESI) at the Department of Chemistry, Cambridge.

Procedure for the continuous flow synthesis of compound 1: A solution of *i*PrMgCl·LiCl in THF (1.16 M, 1.16 mmol, 1 mL, 2.0 equiv) and a mixture of diethylamine (0.15 mL, 1.45 mmol, 2.5 equiv), DMPU (0.4 mL) and the ester **2** (142 mg, 0.58 mmol, 1.0 equiv) in dry THF (0.4 mL) were loaded into two 1 mL sample loops (sample loop 1 and 2). At the meantime, solutions of **6** (139 mg, 0.70 mmol, 1.2 equiv) in dry THF (1.9 mL) and the Burgess reagent (**7**) (1.66 g, 6.96 mmol, 6.0 equiv) in dry CH_2Cl_2 (10 mL) were loaded into sample loop 3 (2 mL) and 4 (10 mL) respectively. To initiate, sample loops 1 and 2 were simultaneously injected into the main flow stream via a T-piece connector at a flow rate of 0.125 mL min^{-1} per channel. The combined stream was brightly coloured (red) and was then directed through a CFC (10 mL) attached via a glass jacket to the R4 unit, which was maintained at ambient temperature, giving a residence time of 40 min. Towards the end of this sequence, sample loop 3 was switched in-line with a switching valve to introduce **6** into the main flow stream via a T-piece connector at a flow rate of 0.25 mL min^{-1}. The resultant stream was then passed through a second CFC (10 mL) maintained at room temperature, followed by in-line treatment comprising of three consecutive columns; 1) QP-SA (580 mg, 1.74 mmol, 3 equiv), 2) MP-TsNHNH$_2$ (1.0 g, 2.9 mmol, 5 equiv) and finally 3) silica gel (600 mg).The exiting stream then entered the ReactIR flow cell, and as soon as the indicative fingerprint signal was detected (i.e., IR stretching frequency 1690–1700 cm^{-1}, Figure 4), the 4th sample loop was switched in-line, allowing the Burgess reagent to join the main reaction stream. The reaction mixture was pumped through a third CFC (10 mL, 60 °C) before entering a column loaded with a mixture of QP-SA (580 mg, 1.74 mmol, 3 equiv) and QP-BZA (530 mg, 2.9 mmol, 5 equiv). In the end, a heated column of QP-SA (1 g, 2.9 mmol, 5 equiv, 60 °C) was used to deprotect and catch the target molecule. The acidic column was then allowed to cool to ambient temperature, and elution of which using a solution of NH_3 in MeOH (3.5 mL, 7 mmol, 6 equiv) completed the synthesis in a continuous fashion, and gave the desired product **1** as a yellow oil (74 mg, 35%).R_f = 0.03 (EtOAc/hexane 2:1); LC t_R = 2.728 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.0 Hz, 2H; Ar-H), 7.24 (td, *J* = 7.8 Hz, 6.1 Hz, 1H; Ar-H), 7.11 (d, *J* = 8.0 Hz, 2H; Ar-H), 6.88–6.91 (m, 2H; Ar-H), 6.80 (dt, *J* = 9.7 Hz, 1.8 Hz, 1H; Ar-H), 3.52 (br s, 2H; N-CH_2), 3.27 (br s, 2H; N-CH_2), 2.90 (qn, *J* = 5.8 Hz, 4H; piperidine N-CH_2), 2.31 (t, *J* = 5.7 Hz, 4H; piperidine CH_2), 2.07 (br s, 1H; NH), 1.23 (br s, 3H; CH_3), 1.11 ppm (br s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1 (s; C=O, benzamide), 162.6 (d, *J*(C,F) = 244.6 Hz; Ar-F), 144.2 (d, *J*(C,F) = 7.3 Hz; Ar), 142.7 (s; Ar), 137.5 (s; C=C), 135.4 (s; Ar), 134.2 (s; piperidine C=C), 129.7 (s; Ar), 129.5 (d, *J*(C,F) = 8.5 Hz; Ar), 126.3 (s; Ar), 125.6 (d, *J*(C,F) = 2.8 Hz; Ar), 116.7 (d, *J*(C,F) = 20.8 Hz; Ar), 113.4 (d, *J*(C, F) = 20.9 Hz; Ar), 48.3 (s; piperidine N-CH_2), 43.3 (s; N-CH_2), 39.2 (s; N-CH_2), 33.2 (s; piperidine CH_2), 14.2 (s; CH_3), 12.8 ppm (s; CH_3); ^{19}F NMR (400 MHz, $CDCl_3$): δ = −113.77 ppm (Ar-F); IR (film): ν_{max} = 3302 (br w, NH), 3245, 2968, 2934 (m, CH), 1623 (s, C=O, amide), 1609, 1580, 1473, 1459, 1429, 1382, 1365, 1312, 1288, 1263, 1220, 1138, 1096, 1013, 969, 943, 879, 855, 805, 787, 763 cm^{-1}; ESI MS: *m*/*z*: 367.20 [*M*+H]$^+$; HRMS (+ESI): *m*/*z*: calcd for $C_{23}H_{27}N_2OF$: 367.2186, found: 367.2186 [*M*+H]$^+$.

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[1] a) L. F. Raveglia, G. A. M. Giardina, *Future Med. Chem.* **2009**, *1*, 1019–1023; b) C. Wiles, P. Watts, *Future Med. Chem.* **2009**, *1*, 1593–1612; c) U. Kunz, T. Turek, *Beilstein J. Org. Chem.* **2009**, *5*, 70; d) I. R. Baxendale, J. J. Hayward, S. V. Ley, *Comb. Chem. High Throughput Screening* **2007**, *10*, 802–836; e) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; f) I. R. Baxendale, M. R. Pitts, *Chem. Today* **2006**, *24*, 41–45.

[2] For selected examples, see: a) A. Palmieri, S. V. Ley, K. Hammond, A. Polyzos, I. R. Baxendale, *Tetrahedron Lett.* **2009**, *50*, 3287–3289; b) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077–4081; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4021; c) A. Palmieri, S. V. Ley, A. Polyzos, M. Ladlow, I. R. Baxendale, *Beilstein J. Org. Chem.* **2009**, *5*, 23; d) J. Sedelmeier, S. V. Ley, I. R. Baxendale, *Green Chem.* **2009**, *11*, 683–685; e) T. P. Petersen, A. Ritzén, T. Ulven, *Org. Lett.* **2009**, *11*, 5134–5137; f) J. Rolland, X. C. Cambeirol, C. Rodríguez-Escrich, M. A. Pericàs, *Beilstein J. Org. Chem.* **2009**, *5*, 56; g) L. Tamborini, P. Conti, A. Pinto, D. C.

Micheli, *Tetrahedron: Asymmetry* **2009**, *20*, 508–511; h) M. Grafton, A. C. Mansfield, M. J. Fray, *Tetrahedron Lett.* **2010**, *51*, 1026–1029; i) J. Sedelmeier, S. V. Ley, H. Lange, I. R. Baxendale, *Eur. J. Org. Chem.* **2009**, 4412–4420; j) B. Wahab, G. Ellames, S. Passey, P. Watts, *Tetrahedron* **2010**, *66*, 3861–3865; k) L. R. Odell, J. Lindh, T. Gustafsson, M. Larhed, *Eur. J. Org. Chem.* **2010**, 2270–2274.

[3] a) F. Benito-López, R. J. M. Egberink, D. N. Reinhoudt, W. Verboom, *Tetrahedron* **2008**, *64*, 10023–10040; b) I. R. Baxendale, S. V. Ley, C. D. Smith, L. Tamborini, A.-F. Voica, *J. Comb. Chem.* **2008**, *10*, 851–857; c) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733–740; d) V. T. N. Glasnov, C. O. Kappe, *Macromol. Rapid Commun.* **2007**, *28*, 395–410; e) C. D. Smith, I. R. Baxendale, G. K. Tranmer, M. Baumann, S. C. Smith, R. A. Lewthwaite, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 1562–1568; f) C. J. Smith, F. J. Iglesias-Sigüenza, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 2758–2761; g) C. M. Griffiths-Jones, M. D. Hopkin, D. S. Jönssen, S. V. Ley, D. J. Tapolczay, E. Vickerstaffe, M. Ladlow, *J. Comb. Chem.* **2007**, *9*, 422–430; h) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972–5990; i) M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith, G. K. Tranmer, *Org. Lett.* **2006**, *8*, 5231–5234; j) S. Saaby, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 3365–3368; k) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410–451; *Angew. Chem. Int. Ed.* **2004**, *43*, 406–446; l) P. Hodge, *Curr. Opin. Chem. Biol.* **2003**, *7*, 362–373; m) A. M. Hafez, A. E. Taggi, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 10853–10859; n) A. Tomin, G. Hornyanszkya, K. Kupai, Z. Dorko, L. Urge, F. Darvas, L. Poppe, *Proc. Biochem.* **2010**, *45*, 859–865.

[4] a) P. H. Seeberger, *Nat. Chem.* **2009**, *1*, 258–260; b) S. V. Ley, I. R. Baxendale, *Nat. Rev. Drug Discovery* **2002**, *1*, 573–586; c) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195; d) P. Hodge, *Ind. Eng. Chem. Res.* **2005**, *44*, 8542–8553; e) G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708–5723; f) I. R. Baxendale, S. V. Ley, *Curr. Org. Chem.* **2005**, *9*, 1521–1534; g) A. Kirschning, G. Jas, in *Topics in Current Chemistry, Vol. 242: Immobilized Catalysts* (Ed.: A. Kirschning), Springer Berlin/Heidelberg, **2004**, pp. 209–240.

[5] a) A. Solinas, M. Taddei, *Synthesis* **2007**, 2409–2453; b) R. I. Storer, T. Takemoto, P. S. Jackson, D. S. Brown, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2004**, *10*, 2529–2547; c) A. Kirschning, H, Monenschein, R, Wittenberg, *Angew. Chem.* **2001**, *113*, 670–701; *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679; d) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, and G. K. Tranmer, *Synlett* **2006**, 427–430; e) I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566–2568; f) A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning, K. Greia, *J. Am. Chem. Soc.* **2006**, *128*, 13261–13267; g) G. Dräger, C. Kiss, U. Kunz, A. Kirschning, *Org. Biomol. Chem.* **2007**, *5*, 3657–3664.

[6] a) A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849–854; b) J. Pelleter, F. Renaud, *Org. Process Res. Dev.* **2009**, *13*, 698–705; c) R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald, B. H. Warrington, *Org. Process Res. Dev.* **2007**, *11*, 704–710; d) I. R. Baxendale, J. J. Hayward, S. V. Ley, G. K. Tranmer, *ChemMedChem* **2007**, *2*, 768–788; e) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407–4416; f) A. A. Kulkarni, V. S. Kalyani, R. A. Joshi, R. R. Joshi, *Org. Process Res. Dev.* **2009**, *13*, 999–1002; g) S. Hübner, U. Bentrup, U. Budde, K. Lovis, T. Dietrich, A. Freitag, L. Küpper, K. Jähnisch, *Org. Process Res. Dev.* **2009**, *13*, 952–960; h) J.-I. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450–7459.

[7] a) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1587–1593; b) J. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, Wiley, Chichester, **2008**; c) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith, J. P. Tierney, *Org. Biomol. Chem.* **2008**, *6*, 1577–1586; d) T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J. Yoshida, *Angew. Chem.* **2005**, *117*, 2465–2468; *Angew. Chem. Int. Ed.* **2005**, *44*, 2413–2416; e) J. J. M. van der Linden, P. W. Hilberink, C. M. P. Kronenburg, G. J. Kemperman, *Org. Process Res. Dev.* **2008**, *12*, 911–920; f) C. D. Smith, I. R. Baxendale, S. Lanners, J. J. Hayward, S. C. Smith, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 1559–1561; g) C. H. Hornung, M. R. Mackley, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 399–405; h) N. Nikbin, M. Ladlow, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 458–462; i) V. Hessel, H. Löwe, A. Müller, G. Kolb, *Chemical Micro Proccess Engineering: Processing and Plants*, Wiley-VCH, Weinheim, **2005**; j) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions*, Wiley-VCH, Weinheim, **2004**.

[8] a) Z. Qian, I. R. Baxendale, S. V. Ley, *Synlett* **2010**, *4*, 505–508; b) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450–2452; c) F. Venturoni, N. Nikbin, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 1798–1806; d) P. Styring, A. I. R. Parracho, *Beilstein J. Org. Chem.* **2009**, *5*, 29; e) T. D. Gross, S. Chou, D. Bonneville, R. S. Gross, Peng Wang, O. Campopiano, M. A. Ouellette, S. E. Zook, J. P. Reddy, W. J. Moree, F. Jovic, S. Chopade, *Org. Process Res. Dev.* **2008**, *12*, 929–939; f) E. Riva, S. Gagliardi, M. Martinelli, D. Passarella, D. Vigo, A. Rencurosi, *Tetrahedron* **2010**, *66*, 3242–3247; g) M. C. Bagley, V. Fusillo, R. L. Jenkins, C. M. Lubinu, C. Mason, *Org. Biomol. Chem.* **2010**, *8*, 22452251; h) K. Geyer, J. D. Codee, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434–8442.

[9] Z. Y. Wei, W. Brown, B. Takasaki, N. Plobeck, D. Delorme, F. Zhou, H. Yang, P. Jones, L. Gawell, H. Gagnon, R. Schmidt, S. Y. Yue, C. Walpole, K. Payza, S. St-Onge, M. Labarre, C. Godbout, A. Jakob, J. Butterworth, A. Kamassah, P. E. Morin, D. Projean, J. Ducharme, E. Roberts, *J. Med. Chem.* **2000**, *43*, 3895–3905.

[10] M. Millan, *Pain* **1986**, *27*, 303–347.

[11] a) F. Porreca, H. I. Mosberg, V. J. Hruby, T. F. Burks, *Life Sci.* **1983**, *33*, 457–460; b) J. J. Galligan, H. I. Mosberg, R. Hurst, V. J. Hruby, T. F. Burks, *J. Pharmacol. Exp. Ther.* **1984**, *229*, 641–648; c) R. J. Sheldon, P. J. Riviere, M. E. Malarchik, H. I. Mosberg, T. F. Burks, *J. Pharmacol. Exp. Ther.* **1990**, *253*, 144–151; d) R. S. Rapaka, F. Porreca, *Pharm. Res.* **1991**, *8*, 1–8; e) P. Y. Cheng, D. Wu, J. Decena, Y. Soong, S. McCabe, H. H. Szeto, *Eur. J. Pharmacol.* **1993**, *230*, 85–88.

[12] a) C. F. Carter, I. R. Baxendale, M. O′Brien, J. B. J. Pavey, S. V. Ley, *Org. Biomol. Chem.* **2009**, *7*, 4594–4597; b) C. F. Carter, H. Lange, S. V. Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode, N. L. Gaunt, *Org. Process Res. Dev.* **2010**, *14*, 393–404.

[13] a) Vapourtec R2+/R4 units are available from Vapourtec Ltd, website: http://www.vapourtec.co.uk; b) The ReactIR 45 m and the reaction analysis software iC IR 4.0 are available from Mettler-Toledo AutoChem, 7075 Samuel Morse Drive, Columbia, Maryland, U.S.A. Webinars are available detailing the use of these two previously launched parts of the analytical tool; website: http://www.mt.com.

[14] K. Chiba, H. Du, Y. Eguchi, M. Fujita, M. Goto, F. Gusovsky, J. Harmange, A. Inoue, M. Kawada, T. Kawai, Y. Kawakami, A. Kimura, M. Kotake, Y. Kuboi, T. Matsushima, Y. Mizui, K. Muramoto, H. Sakurai, Y. Shen, H. Shirota, M. Spyvee, I. Tanaka, J. Wang, R. Wood, S. Yamamoto, N. Yoneda, U.S. Pat. Appl. Publ., **2004**, 299, WO 2004/0224936.

[15] Omnifit glass chromatography columns with an adjustable height end piece. Website: http://www.omnifit.com.

[16] Quadrapure benzylamine (QP-BZA) and Quadrapure sulfonic acid (QP-SA) are high-loading scavengers commercially available from Reaxa. Website: http://www.reaxa.com.

[17] Polystyrene sulfonyl hydrazide resin is commercially available from Aldrich. Website: http://www.sigmaaldrich.com.

[18] IR spectra of all solvents and other important intermediate compound can be found in the Supporting Information.

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