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VIP

Establishing a Flow Process to Coumarin-8-Carbaldehydes as Important Synthetic Scaffolds

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Abstract: Despite their usefulness as fluorophores and synthetic precursors, efficient and reliable routes to coumarin-8-carbaldehydes are lacking. We describe here a high-yielding continuous flow synthesis that requires no manual intermediate purification or work-up, giving access to multigram quantities of the aldehyde product.

Keywords: coumarins · flow chemistry · heterocycles · microreactors · solid-supported reagents

Introduction

Coumarins are a general structural class of aromatic heterocycle defined by the naturally occurring parent compound (Figure 1), which was first isolated in 1822 from Tonka beans (Dipteryx odorata).[1] Molecules possessing the 2*H*-chromen-2-one core display a diverse range of interesting properties—many are highly coloured, absorbing strongly in the ultraviolet region and exhibiting potent fluorescence and luminescence.[2] In addition, they possess a wide range of biological activities and have long been considered attractive drug scaffolds being used in the treatment of viral infections,[3] neurodegenerative diseases,[4] oedema,[5] inflammation, and as hepatoprotective agents and antioxidants.[6] Indeed, several coumarins derivatives[7] (Figure 1) have already found pharmaceutical application as vitamin K antagonists (Warfarin), anticoagulants (Phenprocoumon), antibiotics (Novobiocin) and antispasmodics (Hymecromone). Furthermore, their utilisation in the fight against cancer is another prominent area, with both natural and synthetic coumarins showing promising activity in in vivo rat models and importantly against malignant human cell lines.[8] Apart from their medicinal applications, coumarins have also found use as sunscreen ingredients,[9] microbiological markers,[10] textile and laser dyes,[11] fluorescent labels[12] and, more recently, as solar cell sensitisers. As a consequence of their general functionality many synthetic methods for their preparation have been reported.[13]

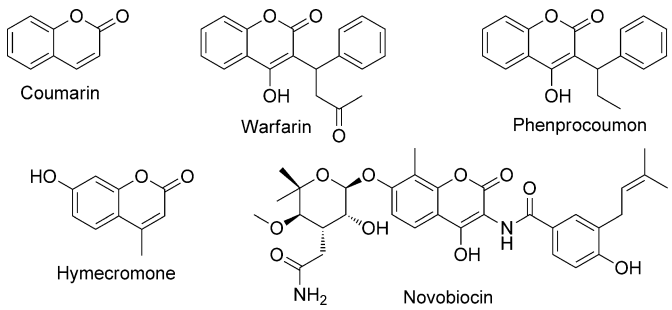

Figure 1. Coumarin and coumarin derivatives of pharmaceutical importance.

However, one particular functional pattern that despite its simple chemical architecture has proven challenging to access reliably is the 7-hydroxycoumarin-8-carbaldehyde (e.g., **5a**, Scheme 1).[14] This is an important structure motif with the juxtaposed formyl and phenoxy groups imparting enhanced fluorescent characteristics and enabling easy assembly of Schiff base Salen ligands which have found many applications in diagnostic and detection systems.[15] Historically, installation of the formyl unit is achieved through functionalization of the corresponding 7-hydroxycoumarin using a Gattermann–Koch,[16] Reimer–Tiemann,[17] Vilsmeier–Haack[18] or Duff[14] reaction. Unfortunately, these methods all suffer from poor conversion and often require extensive work-up leading to further loss of yield and resulting in an overall inefficient process (Table 1). Requiring access to large quantities of **5a** as a biological probe[23] we decided to evaluate alternative synthesis protocols.

We have found that the application of flow processing technologies[24] offers several advantages for the synthesis of

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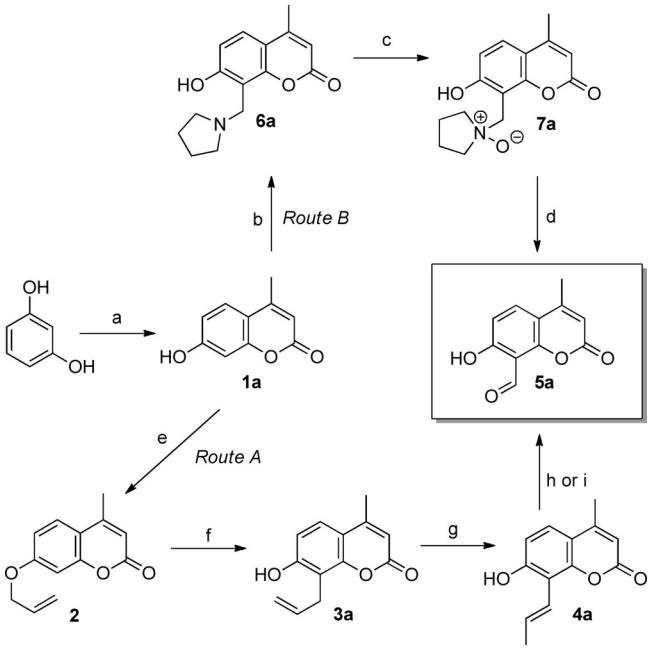
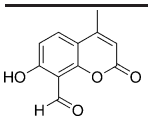
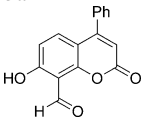
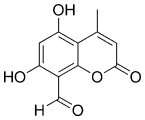
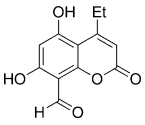


Scheme 1. Proposed routes to 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (**5a**).

Table 1. Data of comparative yields for the synthesis of 7-hydroxy-coumarin structures.

Product	Reaction	Yield [%]	Ref.
 **5a**	Duff reaction[a]	22	[19]
5a	Duff reaction[a]	20	[14d]
5a	Duff reaction[a]	15	[20]
5a	Duff reaction[a]	15	[21]
5a	Duff reaction[a]	22	[14b]
	Duff reaction[a]	60	[22]
	Vilsmeier reaction[b]	54	[18a]
	Vilsmeier reaction[b]	84	[18b]

Reaction conditions: [a] 1) hexamethylene tetramine, glacial acetic acid, 60–80 °C, 2) HCl. [b] *N*-methylformanilide, $POCl_3$, dichloroethane, 70–75 °C.

complex natural products and their derivatives.[25] Of particular value is the possibility of carrying out two or more sequential reactions with no or minimal intermediate workup and purification between transformations. Indeed, the continuous processing and downstream clean-up of reaction streams can be readily facilitated by the incorporation of fixed bed supported reagent cartridges and in-line scavenging columns.[26] Such an approach appeared to us to be ideal for achieving a fast, reliable and readily scalable route to various coumarin carbaldehydes.

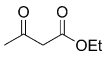
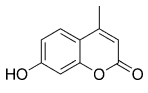
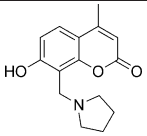
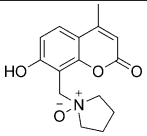
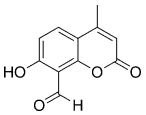
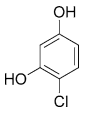
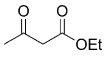
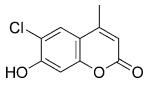
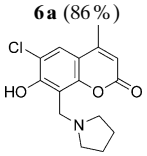
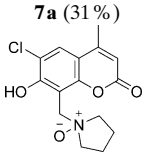
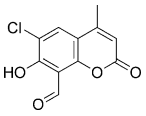
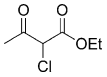
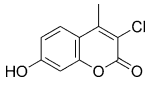
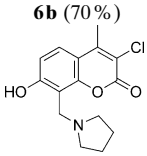
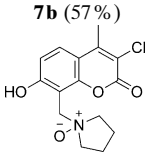
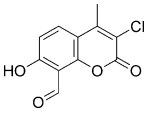
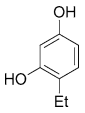
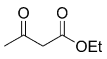
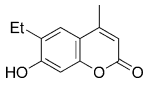
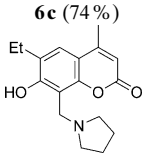
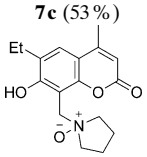
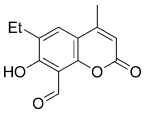
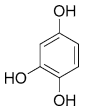
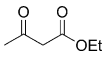
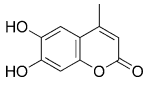
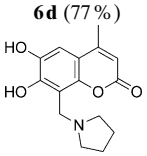
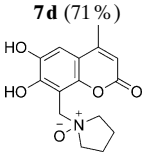
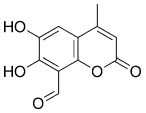
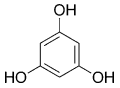
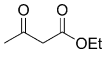
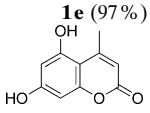
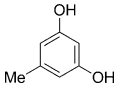
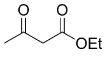
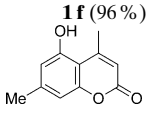
Results and Discussion

Having considered several potential routes we selected two complementary strategies (Scheme 1) which we believed would deliver high yields of the desired products and gain significant efficiencies by adoption of flow processing technologies. However, in order to first facilitate a direct comparison of the routes against the pre-existing literature methods both proposed sequences were evaluated using standard batch conditions.

The basic route development and reaction optimisation was thus conducted on the basic target structure **5a**. The first step of both synthetic pathways is common and involves the formation of the coumarin core. This was achieved using a Pechmann condensation reaction.[27] A protocol using trifluoroacetic acid (TFA) as a catalyst was identified being both high-yielding and a generic method of preparation from simple readily available starting materials; resorcinols and acetoacetate derivatives. From this reaction numerous coumarin derivatives were prepared in good yields and excellent regioselectivity (Table 2) when heated at 100 °C for 1 h under microwave irradiation. Using this protocol, only one coumarin derivative failed to form with the anticipated regiocontrol. Thus attempts to prepare the corresponding 2*H*-chromen-2-one from orcinol and ethyl acetoacetate (Table 2, entry 7) gave compound **1g**[28] instead of the expected 7-hydroxy-4,5-dimethyl-2*H*-chromen-2-one; the structure of **1g** was unambiguously confirmed by X-ray crystallography (see the Supporting Information). This is an interesting result as under many alternative reaction conditions 7-hydroxy-4,5-dimethyl-2*H*-chromen-2-one is the only product isolated often in exceptionally high yield.[29] Indeed, following a similar protocol[30] but using H_2SO_4 as the acid catalyst we also isolated the 7-hydroxy coumarin derivative **1g**.

Following the Pechmann cyclisation the two pathways diverge (Scheme 1). In *Route A* the installation of the formyl group is provided for through alkene **4a** acting as a latent carbonyl group revealed by ozonolysis. The proceeding alkenylation of the aryl ring occurs by a standard allylation of the phenol (**1a**→**2**) followed by a Claisen rearrangement and metal catalysed isomerisation to yield the necessary conjugated alkene **4a**. Alternatively *Route B* involved an aminoalkylation of the coumarin followed by *N*-oxidation and a regioselective Polonovski reaction leading to an intermediate benzylic iminium species. Direct iminium hydrolysis would then furnish the corresponding aldehyde **5a**. Each transformation of both sequences was high yielding and furnishes adequately clean material for further processing without the need for extensive purification.

Table 2. Synthesized coumarin-carbaldehydes and their synthetic intermediates.

Entry	Starting material	Starting material	Pechmann reaction product	Mannich reaction product	*N*-Oxidation reaction product	Polonovski reaction product
1			 **1a** (quantitative yield)	 **6a** (86%)	 **7a** (31%)	 **5a** (44%)
2			 **1b** (92%)	 **6b** (70%)	 **7b** (57%)	 **5b** (41%)
3			 **1c** (quantitative yield)	 **6c** (74%)	 **7c** (53%)	 **5c** (52%)
4			 **1d** (quantitative yield)	 **6d** (77%)	 **7d** (71%)	 **5d** (79%)
5			 **1e** (97%)	 **6e** (99%)	 **7e** (36%)	 **5e** (67%)
6			 **1f** (96%)	No reaction		
7			 **1g** (72%)	No reaction		

***Route A* batch conditions**: The allylation step proceeded smoothly in essentially quantitative yield using K_2CO_3 in acetone under mild conditions (60°C, 1 h), aqueous extraction to remove inorganic salts was the only work-up necessary. The subsequent [3,3]-sigmatropic rearrangement was found to require elevated temperatures (200°C) and generated a mixture of two isomers (**3a**/**3b** 9:2) albeit these could be readily separated by column chromatography (note that the two isomers can also be carried through the subsequent steps without separation and the minor isomer easily removed by crystallisation at the stage of the aldehyde formation **5a**). Isomerisation of alkene **3a** to yield the vinyl system **4a** was promoted using Felkin's iridium catalyst [(1,5-cyclooctadiene)-*bis*(methyldiphenylphosphine)iridium(I) hexafluorophosphate].[31] This gave complete conversion in 24 h using 5 mol% of the catalyst in THF with only the *trans* configured alkene being detected by ^{1}H NMR analysis of the crude product. As a simple purification step the reaction mixture was filtered through a short plug of silica and then the resulting THF solution directly subjected to the ozonolysis conditions. Treatment with ozone gave a rapid and clean conversion to the corresponding aldehyde **5a** in 20 min as determined by TLC analysis. The intermediate ozonide was subsequently cleaved by treatment with a polymer-supported triphenylphosphine equivalent (PS-PPh_2, 3 equiv) giving the desired product in 91% isolated yield after filtration and solvent removal. Although this procedure worked very efficiently we also decided to investigate an alternative method. It has been widely reported that vinyl systems, as present in compound **4a**, can be oxidatively fragmented using a combination of osmium tetraoxide and periodate. To facilitate expedient work-up we selected to use a microencapsulated osmium source (OsEnCat[32]). In a THF/water mixture using 4 mol% of the OsEnCat and a molar excess of $NaIO_4$ at ambient temperature the substrate **4a** was efficiently converted to the corresponding aldehyde **5a** over a period of 4 h. Following work-up and purification an isolated yield of 78% of **5a** was obtained. We

were particularly pleased by these results as both of these cleavage methods offered potential for scaling and transferral to flow.

***Route B* batch conditions**: Having successfully demonstrated the feasibility of the first proposed sequence we next evaluated the second pathway - *Route B*.

The aminoalkylation was achieved via a Mannich reaction, characterised by excellent regioselectivity and high yields under relatively mild conditions.[33] The scope of this reaction was further investigated using several additional coumarin derivatives; furnishing amines **6b–e** (Table 2), which were also prepared in good yields using microwave heating (100 °C for 1 h). Next, the *N*-oxidation was conducted using *m*-CPBA. The reaction was found to proceed rapidly at 0 °C and proved universally applicable to all the amines previously prepared. In addition the reaction was also easily scaled to >20 mmol and was amenable to facile purification by solid-phase scavenging using QP-DMA resin (*N*,*N*-dimethylbenzylamine polystyrene). A crystal structure for *N*-oxide (**7c**) was obtained, showing the expected planar geometry of the coumarin rings and the puckered pyrrolidine (Figure 2).

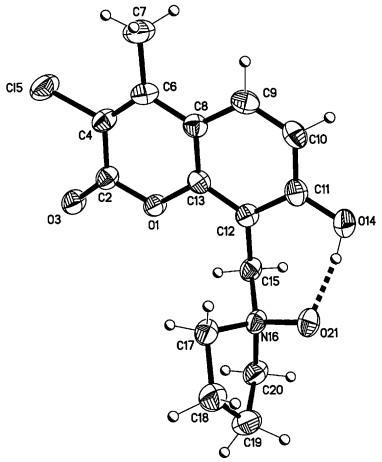


Figure 2. X-ray structure of *N*-oxide **7c** showing an intramolecular hydrogen bond.

The final stage in the sequence was the Polonovski reaction[34] leading to the benzylic iminium cation, which was immediately hydrolysed using dilute aqueous hydrochloric acid (1 M). The Polonovski reaction required very careful control to achieve the desired regioselectivity. It was found that the formation of the benzylic iminium was favoured by the use of trifluoroacetic anhydride (TFAA, Potier–Polonovski conditions[35]) and the absence of heating as opposed to the more classical conditions using acetic anhydride at elevated temperatures.

Unfortunately, the final two steps of the sequence (*N*-oxidation and Polonovski reaction) proceeded in only modest overall conversion, 31 and 44 % respectively. However, we were still able to successfully apply the route to the synthesis of several different 7-hydroxy-carbaldehydes (Table 1) demonstrating the route's general applicability. Regrettably though the low isolated yields and highly capricious nature of these later two reactions even with only minor changes in the rates of reagent addition, purity of the intermediate or length of reaction incubation was a significant issue in batch. However, we considered this sequence to be ideally suited to automated flow processing where fine tuning of reactant mixing, thermal regulation and reaction residence time can be easily achieved.[36] Our main goal was therefore to develop a simple, reliable and directly scalable continuous flow method for the synthesis of 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde (**5a**). Our ideal vision was the assembly of an integrated "one-stream" synthesis of the target molecule where reagents would be added sequentially to the downstream flow path progressing the synthesis without recourse to offline work-up or intermediate isolation.

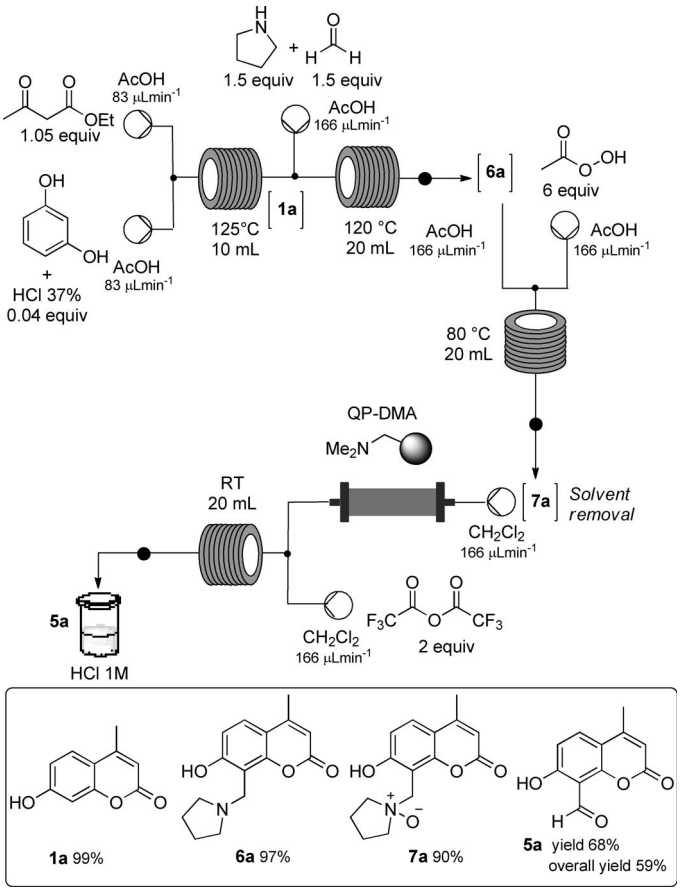
Flow based approach to *Route B*: Starting with the general sequence as outlined in *Route B* (Scheme 1) the individual reaction steps were transferred to flow separately and then combined into a single integrated synthetic pathway.

Route B in flow: The Pechmann condensation was readily converted occurring in quantitative yield by flowing an acetic acid solution of resorcinol and ethyl acetoacetate through a CFC (Continuous Flow Coil) reactor maintained at 125 °C (1 h residence time). We surveyed a range of co-catalysts for the condensation but quickly found that 4 mol % of HCl (37 %) was extremely efficient. In light of this result, we studied the potential for performing all the subsequent reactions in AcOH thereby avoiding any solvent switching operations.

The Mannich reaction could also be successfully performed in AcOH under flow conditions. The desired product was obtained in 97 % yield in 1 h at a temperature of 120 °C using paraformaldehyde and pyrrolidine (1.5 equiv). In the batch mode we performed the *N*-oxidation reaction using *m*-CPBA but, since this reaction required the use of CH_2Cl_2 as solvent, we decided to test the reaction in AcOH using H_2O_2 as the oxidant. Pleasingly, good conversion to the *N*-oxide product **7a** (90 % yield) was achieved when flowing the amine and the H_2O_2 through a preheated CFC coil held at 100 °C with a residence time of 1 h although a large excess of peroxide (11 equiv) was necessary. Considering the likely identity of H_2O_2 in AcOH is invariably that of peracetic acid we attempted to carry out the same reaction directly using a solution of peracetic acid. We were able to achieve a halving in the number of equivalents of oxidant required (6 equiv of peracetic acid, 1 h) and a modest reduction in the reaction temperature to 80 °C. It was also encouraging to discover that the *N*-oxidation of both purified amine **6a** and a crude solution obtained directly from the Mannich reaction gave excellent and comparable conversion to **7a**, enabling the possibility of telescoping the pathway.

Next, we appraised the potential for conducting the Polonovski reaction in AcOH as the solvent, however we observed no product formation under a wide range of reaction conditions. Even when using pure isolated *N*-oxide **7a** we were unable to promote the desired elimination in the presence of AcOH quantitatively recovering the starting material. Alternatively a good conversion of the crude *N*-oxide **7a** to the desired aldehyde **5a** could be achieved after AcOH solvent exchange. The flow sequence could be reinitiated by re-dissolving the crude product in CH_2Cl_2 and passing the solution through a column containing QP-DMA in order to sequester any peroxides and residual acid. The output stream was then mixed with a second stream of TFAA also in CH_2Cl_2. The optimal conditions for this reaction were found to be 2 equivalents of the TFAA at ambient temperature, and a residence time of 1 h. The reactor output was then collected into a flask containing an appropriate volume of dilute aqueous HCl (1 M) solution to hydrolyse the intermediate and induce precipitation of the final product. The solid product was readily filtered affording coumarin-8-carbaldehyde **5a** as a pale yellow powder (68% isolated yield). On the basis of these results, we combined the steps as shown in Scheme 2 to create an abridged flow system.

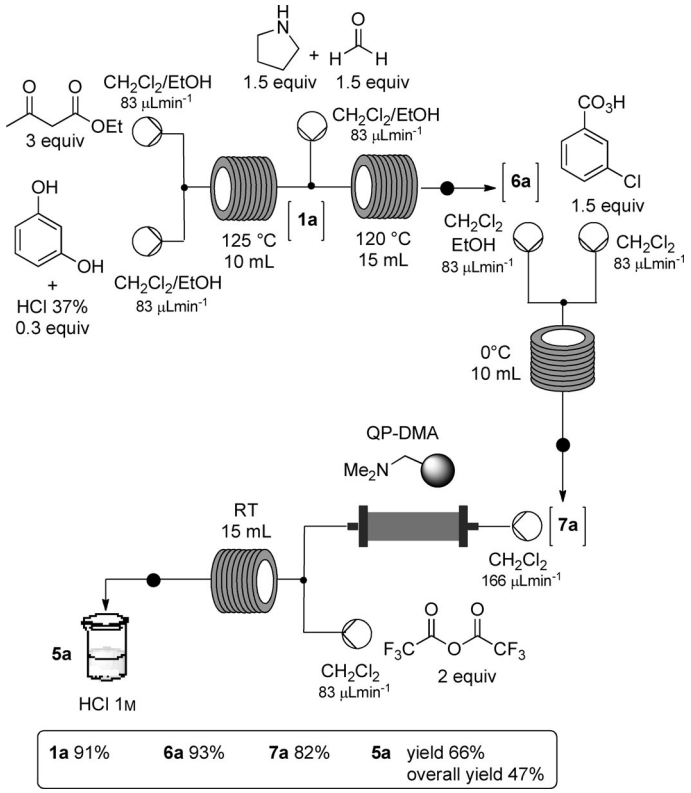
Integrated flow sequence - *Route B*: For the unified flow process the output of the Pechmann condensation (**1a**) was directly coupled with a further input channel containing the premixed Mannich components (Scheme 2). The stream of the amine adduct (**6a**) from these two linked steps was integrated with the *N*-oxidation reaction performed as previously described using peracetic acid at 80 °C. The resulting *N*-oxide (**7a**) was collected as a batch and the AcOH solvent was removed under reduced pressure. The *N*-oxide was then re-dissolved in CH_2Cl_2 to process it through the final elimination step. Again, removal of acidic impurities including peracetic acid was readily achieved using a column of QP-DMA. The elimination step was best conducted with a two-fold excess of TFAA which gave quantitative conversion to the iminium species. Hydrolysis with aqueous HCl in batch gave the desired aldehyde **5a** which precipitated and permitted isolation by simple filtration.



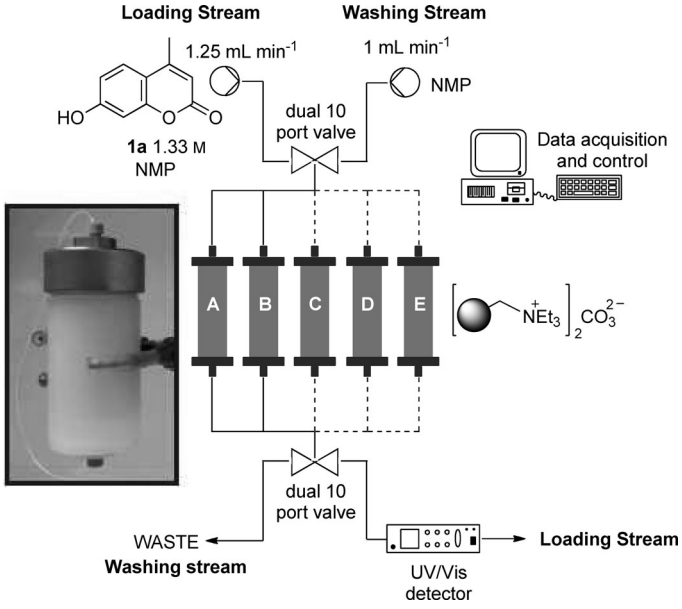
Scheme 2. Flow synthesis of **4a** using AcOH as main solvent.

By conducting the reaction in this linked fashion a much improved and reproducible overall yield of 59% was realized. Furthermore the only intermediate handling operation required of the user is a simple solvent-switch procedure from AcOH to CH_2Cl_2. However, our originally stated desire was to achieve a fully telescoped flow synthesis avoiding any user handling operations. We therefore elected to investigate the potential of performing all the reaction steps in an alternative solvent system.

The Polonovski elimination had proven the most solvent sensitive step but had been shown to work very efficiently in CH_2Cl_2. However, we knew from earlier trials that the Pechmann condensation required a protic solvent. Consequently we screened a series of binary solvent mixtures based upon CH_2Cl_2 and an alcohol. We eventually arrived at a 2:1 blend of CH_2Cl_2/EtOH. Using identical time and temperature parameters as previous, a 91% conversion was achieved for the Pechmann reaction albeit this necessitated an increase in the number of equivalents of ethyl acetoacetate from 1.05 to 3 and the addition of a larger quantity of the HCl 37% (0.3 equiv) catalyst (Scheme 3). The need for an excess of ethyl acetoacetate was ascribed to the rapid hydrolysis and subsequent decarboxylation of the β-dicarbonyl which occurred under these modified solvent conditions. Fortunately the liberated acetone had no noticeable effect on the subsequent reactions (no incorporation into the Mannich reaction was observed). The following Mannich reaction was conducted using the previously optimized conditions delivering a similar result (93% conversion). The *N*-oxidation reaction also progressed well in 82% in the presence of *m*-CPBA as the oxidant at 0 °C and with a 1 h residence time (CFC reactor submerged in an ice-bath). The reaction stream containing the newly generated *N*-oxide was then passed through a scavenging column containing QP-DMA before being combined with a stream of TFAA in CH_2Cl_2 which facilitated the Polonovski reaction yielding the desired aldehyde **5a** in 47% overall yield (>95% purity by LC-MS and NMR spectroscopic analysis). The entire multistep sequence was therefore performed without the need for purification, work-up or solvent switching (excluding a simple filtration), thereby providing access to this valuable product in one flow sequence.



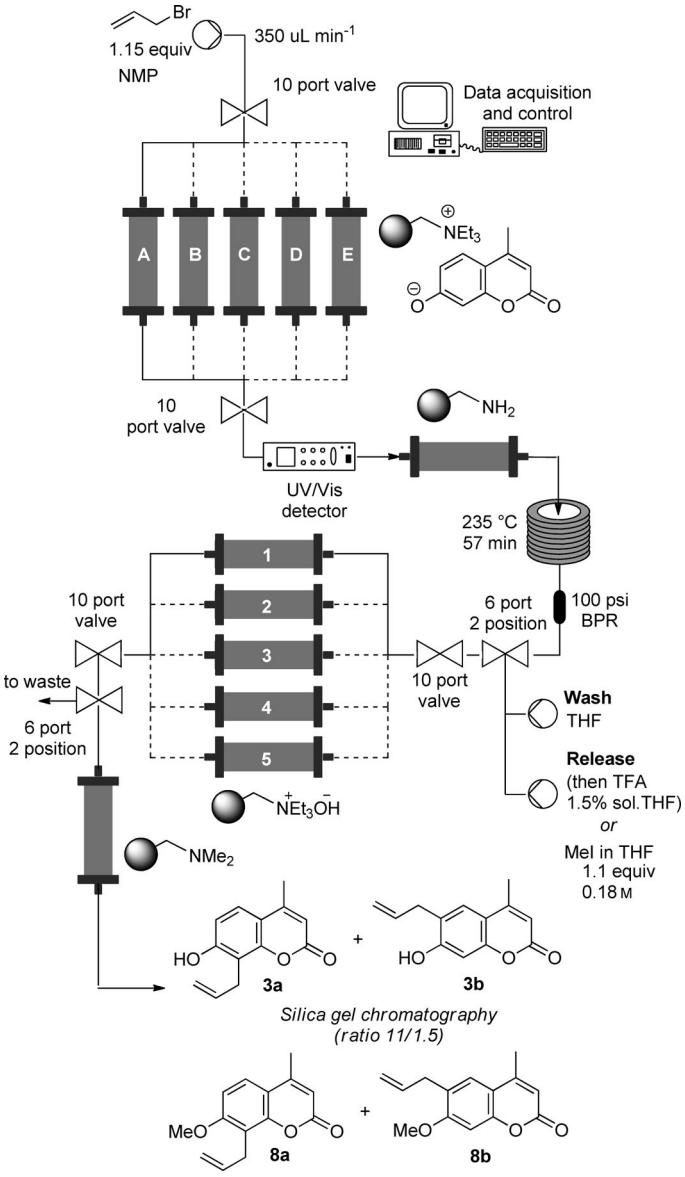
Scheme 3. Telescoped flow synthesis of **4a** using CH_2Cl_2 as main solvent.



Scheme 4. Automated loading procedure for Supleco cartridges. Only 5 of the 10 columns used are shown for clarity.

Integrated flow sequence - *Route A*: We next turned our attention to the conversion of the original Claisen batch conditions (*Route A*, Scheme 1) into a flow based procedure. We elected to enlist the pre-made 7-hydroxycoumarin **1a** (2.1 mol) as our starting point as isolation of this material was readily achieved at scale from our previous acetic acid flow procedure by direct induced precipitation by dilution of the output stream with water. The subsequent sequence was extremely tolerant of moisture meaning only a filtration of the solid product was required before progressing the substrate. This was felt to be a more pragmatic approach rather that requiring the removal of the acetic acid solvent before the base catalysed allylation. The first step of the sequence was therefore the allylation of the phenolic group with allyl bromide which occurred in NMP (*N*-methyl-2-pyrrolidone) in the presence of an immobilised carbonate base (Biotage MP-Carbonate, Part No. 800314, 3.2 mmol g^{-1}). To conduct this reaction a bulk solution of the 7-hydroxycoumarin **1a** in NMP was loaded into a series of Supleco cartridges (40 mm i.d. 75 mm depth, 62 g resin; insert Scheme 4) containing the carbonate resin. A relatively high concentration and flow rate could be used for this rapid and efficient ion exchange process. To aid loading two dual automated 10 position valves (VICI 20271) were used to exchange between individual columns as the resin became saturated by the substrate (see supplementary information for the valve configuration). Breakthrough was monitored for by an in-line UV/Vis detector (Gilson 156 @254 nm) using a threshold based voltage trip switch which triggered upon detection of a threshold level of the eluting coumarin **1a**. A second HPLC pump (NMP solvent delivery) enabled sequential column washing of the newly loaded column thereby eluting any nonbound starting material **1a** which could be recycled (Scheme 4). The entire loading procedure could be run using Gilson Unipoint control software.[24g,m,25k]

A modified set-up was then used for the subsequent *O*-allylation reaction and Claisen rearrangement process (Scheme 5). The primary input feed was switched to a solution of allyl bromide in NMP (0.93 M). A single 10 port valve assembly was used to direct the flow stream through the first phenoxide loaded column. Upon *O*-allylation the coumarin material **2** was released and passed through a scavenging step (QP-BZA) to sequester any unreacted allyl bromide. Real-time monitoring of the reaction stream using a UV/Vis device enabled automatic succession to a new phenoxide cartridge (columns A–E) when the signal intensity received by the detector fell below a pre-prescribed absorption threshold (also triggering exchange of the latter scavenger column. Labelled 1–5 in Scheme 5). This allowed an automatic and essentially seamless transition between the different reactor cartridges. The reaction flow stream containing **5** was next relayed into a stainless steel CFC (20 mL) which was heated at 235 °C promoting the Claisen sigmatropic rearrangement. Interestingly, an improved ratio between the two possible products was obtained compared to the batch conditions (22:3 compared to 9:2). At this stage the Claisen products **3a/b** were captured onto a second ion exchange resin, supported tetraalkylammonium hydroxide (Ambersep 900 hydroxide form, 1.86 mmol g^{-1} packed into Biotage chromatography columns, 108 g per column). This approach simplified the isolation of the coumarin products **3a/b** from the high boiling point NMP solvent as well as en-



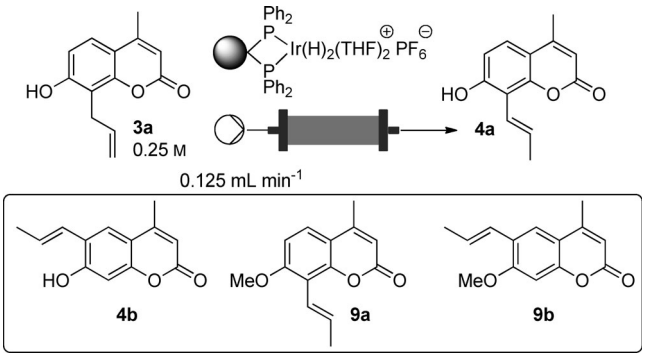
Scheme 5. Claisen flow synthesis of **3a/b** or analogues **8a/b**. In each case only 5 of the 10 columns used are shown for clarity.

abling their separation from any residual non-rearranged intermediate **2** (2.5–4%). Following washing of the column with THF the release from the resin could be affected eluting with a 1.5% (v/v) solution of TFA in THF. Further passage of this solution through two consecutive columns containing QP-DMA (3.8 mmol g^{-1}, Biotage chromatography column, 160 g) could be used to remove excess TFA or the material could be isolated directly by solvent evaporation. Alternatively, we also demonstrated that a second alkylation step (formation of **8a/b**) could be performed as part of the release step (using MeI in THF solution instead of TFA) adding additional diversity to the sequence. Using this approach we were able to process 2.1 mol of material corresponding to over 344.7 g of isolated intermediate **3a/b** in 76% overall yield.

As explained for the Batch *Route A*, it was possible to separate the isomers **3a/3b** by chromatography column (ratio **3a/3b** 11:1.5). However, due to the large scale flow route, it was more convenient carrying the two isomers through the subsequent steps without separation then easily remove the minor isomer by crystallisation at the end of the process.

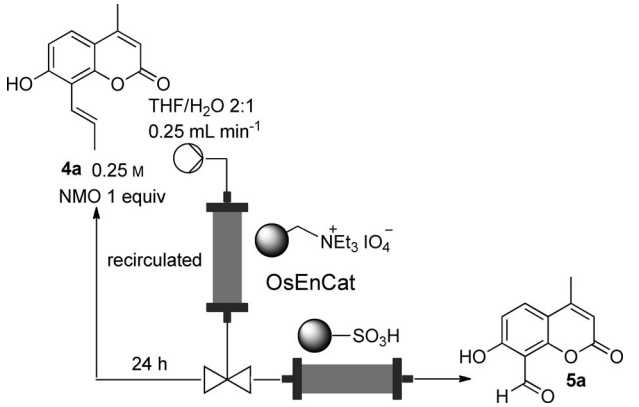
Taking a portion of the neutralised **3a/3b** flow stream (from Scheme 5), after treatment with QP-DMA, we investigated the isomerisation of the double bonds and the subsequent oxidative cleavage steps.

We had previously shown in another project[37] that an immobilised version of Felkin's iridium catalyst (Scheme 6)



Scheme 6. Isomerisation of **3a/b** and **8a/b** using an immobilized iridium catalyst.

could be prepared and it could function as an effective double bond isomerisation catalyst which we felt would also work well in flow. Indeed, this was found to be the case. By flowing a solution of **3a/b** or **8a/b** through a column containing the solid supported catalyst (5 mm i.d. × 100 mm) held at 60 °C the corresponding conjugated alkenes **4a/b** and **9a/b** could be generated quantitatively (Scheme 7). A flow rate of 125 μL min^{-1} was found to effect complete conversion in a calculated residence time of about 47 min.

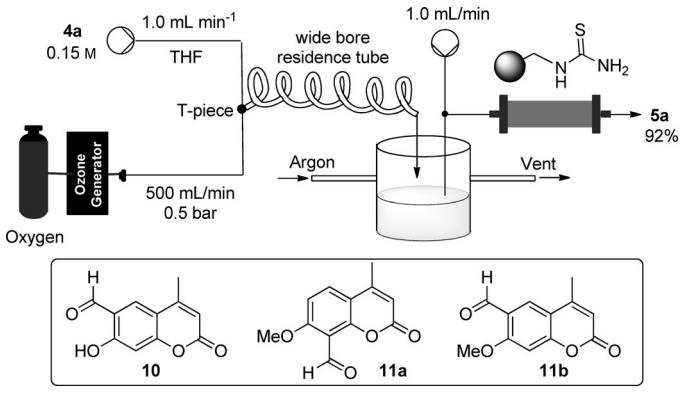


Scheme 7. Oxidative cleavage of the vinyl substrates **4a/b** using OsEnCat catalyst.

For the oxidative cleavage of the double bond we first evaluated a flow protocol based on the OsEnCat and $NaIO_4$ procedure previously used in batch. A mixed bed of the OsEnCat and a polymer-supported periodate variant was prepared and the solution of the isomerised substrate flowed through the cartridge in a recycling set-up (Scheme 7).[38] Unfortunately, it was discovered that the use of only periodate was ineffective at turning over the osmium catalyst giving only low conversion to the desired aldehyde (18% conversion). However, the addition of a stoichiometric amount of *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant permitted the reaction to progress to completion. The resulting amine from the reduced NMO could be effectively scavenged using a column of QP-SA (a sulfonic acid resin). This enabled the target compound to be isolated in 89% yield following solvent evaporation.

However, one major difficulty associated with this procedure was that direct scale-up of the sequence was found not to be possible. The recycling requirement necessary due to the prolonged reaction time of the oxidation created significant complications due to non-linear expansion of the processing times. For this reason we decided that although effective for small scale operation this method would not be ideal for processing larger quantities of material. We therefore decided to test the potential scalability of the alternative ozonolysis in flow.

Having some previous experience performing ozonolysis reactions in flow[39] we quickly established a simple set-up to perform the transformation using QP-TU as a solid ozonide quenching agent.[40] The flow setup (Scheme 8) used



Scheme 8. Oxidative cleavage of the vinyl substrates **4a/b** and **9a/b** via ozonolysis.

a Knauer K100 HPLC pump to deliver a stream of the substrate **4a/b** (0.25 M, 4 mL min^{-1}) into a continuous gas flow (O_2/O_3, 500 mL min^{-1}) through a T-piece. The united flow stream was then directed into a PFA tubular reactor coil (6.5 mL, 2.5 mm i.d.) giving a residence time of approximately 75 s. The reactor output which constituted a droplet spray was collected into a nitrogen blanketed purge vessel where the excess ozone was eliminated by passing a constant flow of nitrogen through the chamber. The expunged solution was continuously pumped from the chamber as it condensed through a packed bed cartridge containing an excess of the polymer-supported thiourea inducing reductive cleavage of the ozonide. This gave the corresponding aldehydes **5a/10** in quantitative conversion and 92% isolated yield (95% for **11a/11b** from **9a/9b**). Using the crude reaction solution containing a mixture **4a/b**, the desired aldehyde was isolated pure via recrystallisation from EtOAc in 73% yield. Using this method we were able to process 37 g of **5a** in 4.5 h.

In total this four step sequence involving allylation, Claisen rearrangement, isomerisation and ozonolysis could be used to deliver the desired product **5a** in 51% overall yield after crystallisation. The limiting step of the route was the iridium catalysed isomerisation although this could conceivably be performed using parallel reactor cartridges thereby increasing the throughput.

Conclusion

We have developed two complementary flow syntheses for the delivery of 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde **5a** via key *N*-oxide or Claisen derived intermediates. In the first synthetic route we established a four step telescoped sequence to the target molecule which avoided the need for purification excluding a single filtration. The protocol could also be readily applied to the synthesis of various analogues and was shown to be easily scaled. An alternative Claisen based sequence proved very efficient allowing a four step process to the desired molecule from previously prepared 7-hydroxycoumarin (**1a**). The route was highly automated using in-line monitoring to control reagent delivery and enable 'catch-and-release' purification yielding the product in high yield and purity. This work clearly represents a further demonstration of the advantages of flow processing in the assembly of synthetically challenging molecules.

Acknowledgements

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