Multi-Step Flow Chemistry

Flow-Assisted Synthesis: A Key Fragment of SR 142948A
Matthew O. Kitching,[a] Olivia E. Dixon,[a] Marcus Baumann,[a] and Ian R. Baxendale*[a]

Abstract: We report a series of multi-step flow operations to deliver an advanced hydrazine intermediate used in the assembly of the neurotensin modulator SR 142948A. Several new reactor configurations have enabled chemical transformations that would be otherwise difficult or dangerous to perform at scale. Overall the flow approach has allowed the preparation of kilogram quantities of the required hydrazine through a short and efficient route.

Introduction

Neurotensin (NT, 1) is an endogenously expressed tridecapeptide first isolated from bovine hypothalamus in 1973.[1] NT has many roles in regulating numerous biological processes including temperature control,[2] pain sensation,[3] modulation of appetite,[4] and pituitary hormone secretion.[5] As a modulator of the body’s dopaminergic systems, disruption of NT binding has also been proposed as a possible route to intervention in diseases such as schizophrenia and Parkinson’s.[6] Furthermore, upregulation of NT receptor (NTR) expression has been reported to occur in various cancers: lung,[7] breast,[8] pancreas,[9] pituitary[10] and prostate, therefore investigation of its physiological mechanisms is an important area of study.[11] Unfortunately, as a potential therapeutic and investigative tool NT itself has several drawbacks. As a oligopeptide, NT has inherent poor stability in vivo and is degraded by several common endopeptidases and metalloproteases.[12] Its size also prevents easy passage across the blood–brain barrier, which results in poor bioavailability and requires injection of NT directly into the CNS.[13] Finally, NT is only capable of NTR agonism. Consequently synthetically viable, easily modified small molecule probes capable of tailored interaction with the NTR (agonist/antagonist) represent powerful investigatory tools in medicinal chemistry (Figure 1).

As part of our synthetic efforts to prepare a toolbox of NT molecular probes, we have already explored the preparation of the NT modulator meclinertant (2) by using a flow-chemistry approach.[14] In an extension of this work, we herein disclose efforts towards a synthetically more challenging derivative SR 142948A (3).[15] We envisaged a convergent synthesis to allow assembly of this new derivative 3 from three fragments (4–6, Figure 2), two of which were common to the previous meclinertant synthesis (4 and 5) and had already been prepared at scale.[16] The general retrosynthetic disconnection of 3 is presented in Figure 2, which would ideally be accessed in a multi-step synthesis from the commercial

![Figure 1. Structures of neurotensin (1), meclinertant (2), and SR 142948A (3).](image1)

![Figure 2. Synthetic fragments of SR 142948A (3) and proposed retrosynthesis of hydrazine 6.](image2)
cial and readily available starting material 2-isopropyl aniline (10).

Results and Discussion

Our strategic approach was to perform an acylation on commercially available isopropyl aniline (10), necessary to regulate the subsequent bromination step and furnish selectively intermediate 8. This would then enable either a cyanation or carboxylation followed by hydrolysis to access the desired carboxylic acid 7. Diazotization and direct reduction would then yield the corresponding hydrazine product 6. Although encompassing conceptionally straightforward chemistry, many of these transformations have intrinsic risks associated, especially when conducted at scale such as exotherms (acylation step), or issues due to hazardous (diazotization) or toxic (carboxylation, cyanation) reagents/intermediates. It was anticipated that through the adoption of flow processing techniques, these risks could be managed, minimized or completely avoided.

The initial acyl protection of aniline (10 → 9) was associated with a large exotherm when dichloroethane solutions of acetic anhydride (1.73 M; 3 mL/min; 1.1 equiv.) and aniline 10 (1.57 M; 3 mL/min) were combined (Scheme 1). Indeed, at equivalent concentrations the reaction required active cooling to prevent runaway in batch but instead could be easily performed in a microfluidic mixing chip as a flow process, which ensured good thermal transfer to the surrounding environment. In this way, the solution could be continuously processed while maintaining a temperature <55 °C. Beneficially, it was discovered that the following bromination step (9 → 8) required heating to achieve complete conversion. By creating a sandwich assembly from two additional mixing chips (inputs for the N-bromo-succinimide) in direct thermal contact with the first acylation reactor, the excess heat produced in the acylation could be used in a productive fashion to prewarm the reaction media for the second step (Figure 3).

The reaction stream from the first acylation step was therefore split and directly combined with input streams containing NBS in dichloroethane (DCE, 0.94 M; 3 mL/min in two parallel channels; 1.2 equiv.) (Scheme 1). The two flow streams were reunited and then passed through further residence time coils (4 × 52 mL) maintained at 70 °C to ensure complete bromination. The reaction mixture was quenched and an in-line work-up was performed (through two parallel streams) by mixing with a stream of basic sodium sulfite and separated by using a mixer-settler membrane unit. The device was constructed around a Biotage universal separator[18] which allowed the bifurcation of the organic product containing phase and the aqueous waste (Figure 4).[14a,19] Run as a continuous process, this allowed the isolation of the amide product 8 by direct evaporation of the DCE. In total, over 120 L of organic solution was processed in a continuous operation over the course of 167 h (ca. seven days), thus generating an isolated mass of 11.52 kg of product equating to 96 % yield. Furthermore, we were able to establish a refilling schedule for the input stock solutions (2.5–5 L batches) based upon their consumption flow rates that enabled the efficient recycling of recovered DCE from the final evaporation stage. Consequently the process only required the use of 26.7 L of DCE amounting to a significant reduction in the amount of organic solvent used.

With kilogram quantities of the bromide 8 in hand, further derivatization to the corresponding nitrile 11 was undertaken by employing a palladium-catalyzed approach (Scheme 2).[20] These experiments were evaluated by using an automated microwave setup. Initial investigation of reaction conditions showed the importance of including a reductant in the reaction.

Scheme 1. Flow-reactor schematic for the synthesis of brominated amide 8.
mixture (Table 1; entries 1–4). In the absence of poly(methylhydrosiloxane) (PMHS),\textsuperscript{21} no conversion was observed with either supported or solution-phase catalysts. Screens of common supported forms of palladium (Table 1; entries 5, 6, 8, and 9) showed lower conversion and extended reaction times compared to the use of solution-phase palladium(II) acetate. A solvent screen determined that a mixture of DMF/H$_2$O (95:5) gave optimal results.

To process material on a semi-preparative scale, the automated microwave reactor was utilized as a sequential batch process reacting 39 mmol of substrate and allowing 6.8 g of nitrile 11 to be isolated in 86 % yield. Although this approach was convenient for small laboratory-scale preparation to generate sufficient material for further scoping studies, the observed low solubility of the reagents (only becoming soluble as the reaction progressed) led us to conclude that this would be a difficult reaction to translate to continuous flow and therefore alternative approaches were sought.

The possibility of performing a carbonylation reaction continuously was next investigated. Again, the initial investigation and optimization work was conducted using an automated microwave setup. The use of microwave vials allowed easy introduction of CO gas and pressurization of the reaction mixture up to 5 bar. Both ethanol and methanol could be successfully
Table 1. Optimization of microwave cyanation conditions.

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<td>DMF/H₂O</td>
<td>3</td>
<td>74</td>
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</table>

[a] Standard loading 2.2 mol-%.  
[b] Loading 4.4 mol-% based upon Pd loading.  
[c] Solvent ratio 95:5.

used in the transformation; however, ethanol showed the highest conversion while minimizing the amount of protodehalogenation (as determined by 1H NMR analysis of the crude reactions).

By using the microwave automation a sequential run of ten reactions allowed the processing of the bromide 8 on a 59 mmol scale to generate 12 g of material in 81 % isolated yield (Scheme 3). Additionally, it was observed that the yield for each run was consistent (indicating catalyst/substrate stability over time), and the reaction mixtures remained essentially homogeneous throughout the processing (some indication of Pd black formation was noted). This immediately allowed us to consider translation of the conditions to a flow based system.

The configuration of the flow reactor used is depicted in Scheme 4. The system consisted of a mixing chip fed by an ethanolic solution of the substrate, catalyst and base to be blended with a low-pressure input (3 bar, 2.5 mL/min) of CO-regulated through a flow meter. A plug flow regime was generated and used directly as the feed for a HPLC pump. The pump was used to upregulate the pressure to 10 bar, which makes the reaction mixture homogeneous and delivers sufficient CO for efficient carbonylation in the subsequent coil-reactor stage (Polar Bear Plus ca. 37 min; 120 °C). It was noted that during the reaction, colloidal palladium particles formed in the coil reactor (additives like tetraalkyl ammonium salts, DMF and alternative metal chelating ligands were investigated but failed to have any effect on the process). This gave no issues with reactor blocking through aggregation with the particulates being efficiently progressed through the reactor even over prolonged reaction periods. However, clogging of the in-line back-pressure regulator (BPR), required to maintain the system pressure, rapidly occurred. In addition, significant and uncontrolled degassing was also an issue at the exit of the reactor; this was made more problematic due to the particulates in the system, which were explosively jettisoned from the flow stream leading to etching of the collecting vessel and creating containment problems.

To overcome both of these issues, we constructed a simple membrane partitioned sedimentation tank, which also acted as a controlled gas exhaust. The unit was constructed from a stainless-steel pressure chamber with an embedded thermocouple and pressure dial. An adjustable pressure release valve was fitted into the cap to enable controlled discharge of the CO gas. In our first assembly, the input feed delivered the solution and particulates from the reactor into the sedimentation chamber and the exit line was fitted with a polytetrafluoroethylene (PTFE) solvent filter (see the Supporting Information). This output line was connected as a feed to an HPLC pump, which progressed the filtered product solution through the scavenging column. Although this approach worked well over
short processing times, we noticed that build-up of the particulate material around the in-line PTFE solvent filter started to impair the pumping efficiency of the exit HPLC pump by restricting its input flow. This was easily observed by noting the decline in the flow rate of the exit solution, indeed, HPLC systems are well known for having very little tolerance on the pressure drop of the input line. We found that by alternatively using an extraction thimble filter[28] fitted at the inlet of the sedimentation chamber and utilizing the pressure drop from the reactor more effective, filtration of the particulate matter could be achieved. In this way, the pressure feed of the solvent for the exiting HPLC remained constant. The reactor could be run for up to 8 h before particulate build-up required a scheduled shutdown and exchange or cleaning of the thimble filter. Finally, the solution pumped from the sedimentation tank was directed through a column of QP-TU (a thiourea functionalized resin) to remove residual metal contaminants before batch collection and solvent evaporation. The crude product was directly triturated with a mixture of water/ethanol (20:1) and filtered. The tan-coloured solid was air-dried to yield the desired ester product in excellent purity as assessed by 1H NMR and LC-MS. During a typical 8 h run, 120 g of starting material could be processed in 87 % isolated yield equating to a productivity of 12.7 g/h (58.5 mmol/h).

Although delivering high-quality material, this approach did not fulfill our target throughput requirements for a continuous process and was uneconomic due to the high loading and associated cost of the palladium and dppf ligand. We therefore sought other approaches; a strategy which offered simplicity and directness seemed to be a Sonogashira coupling followed by an oxidative cleavage of the acetylene to furnish a carboxylic acid moiety (Scheme 5).

We initially performed a scope evaluation on the Sonogashira reaction by using a series of automated microwave reactions systematically assessing catalysts (palladium and copper sources), bases, solvents, concentration/stoichiometry, temperature and reaction times. All reactions were rapidly assessed as % conversion by using calibrated LC-MS analysis (a summary of the findings appear in the Supporting Information). From this study, a set of optimum conditions (90 % isolated after column chromatography) were defined that seemed to also favour translation of the reaction to a flow processing regime (Scheme 6). We were also able to demonstrate that in the presence of a basic solution of RuO2 and the co-oxidant NaIO4 (or oxone), oxidative cleavage of the alkyne occurred (3.5 h) to give 94 % isolated yield of the corresponding carboxylic acid product 13.[29]

Based upon these findings we embarked upon the translation of the Sonogashira step to flow.[30] First however, an additional incubation study (48 h) was performed where the different reaction components were tested for their stability, compatibility and prolonged solubility in different combinations (see
the Supporting Information). This was conducted to ensure that stable stock solutions of the components could be prepared to enable prolonged processing without constant manual intervention. From this investigation, a simple two-channel flow setup was conceived; channel A, delivered a flow stream comprising of the aryl bromide 8 (2.5 M), the TMG base and the CuBr in MeOH (Scheme 7); channel B, a methanolic solution of the propargylic alcohol (3 M), palladium catalyst and associated PPh₃ ligand. The two streams (1:1 flow rate of 1 mL/min) were united at a simple T-piece mixer before progressing into a heated coil reactor (two conjoined 52 mL Polar Bear plus systems) maintained at 100 °C (microwave optimized temperature) with a 250 psi BPR used to maintain the system pressure. The exiting solution indicated a steady-state conversion of 93 %, which could be driven to complete conversion by simply raising the reactor temperature to 105 °C. This gave a theoretical throughput of 0.15 m/h or 38.9 g/h. The product could be readily isolated by evaporation of the solvent and pouring the resulting crude oil obtained into a stirred solution of 3 M HCl (0 °C). The product precipitated over the course of approximately 1 h and could be filtered and dried at 40 °C under vacuum to give an overall isolated yield of 93 % (5 h run). To demonstrate the robustness of the system, a continuous run over five days was performed to collect the reactor output into individual batches, which equated to daily production, which were then manually worked up. Overall a yield of 90 % with a deviation of +3.7 % was obtained, which equated to a total of 4.2 kg of isolated material.

It was our initial intention to attempt direct oxidation of the acetylene product 16 without work-up and isolation. However, we found that attempts to directly use solutions of the reactor output under the previously attempted oxidation conditions (RuO₂/NaIO₄) inevitably gave an alternative major dibrominated adduct 17 (Scheme 8). Presumably, this product formed through preferential oxidation of bromide (carried TMG·HBr salt), which generates in situ bromine, which adds to the alkyne leading to 17 through hydrolysis.[31] This was partially confirmed by demonstrating that when basic (K₂CO₃) solutions of acetylene 16 in 1:1 solutions of MeOH/H₂O were treated with bromine the identified product 17 rapidly formed. As all related oxidation processes would potentially generate the same difficulties, we investigated adding an additional purification stage.
To achieve the reaction stream clean-up we elected to employ a dual-stage scavenging process (Scheme 9) to first utilize a cartridge of Ambersep 900 OH resin (Columns A–E), to neutralise the TMG·HBr salt, followed by a second cartridge of a sulfonic acid resin (QP-SA, Columns F–J), which sequestered the free TMG base. Although a mixed bed of the two resins was also effective, we found it much more efficient to stage the scavenging sequence as this helped in constructing a simple automated column-exchange process, which enabled interchange of the two types of scavenging columns as they became depleted. Introduction of replacement columns and ensuring the washing/regeneration of depleted units was conducted by a simple multi-port valve system as described previously. For this process we set the unit to trigger based upon a timing event to correspond to the sequestering threshold of the various packed columns as calculated from the flow rate and theoretical concentration of the TMG input. This generated a flow stage as depicted in Scheme 9.

Although this in-line work-up was effective, we were still unable to achieve an efficient oxidative cleavage of the alkyne (< 42 % conversion) without first effecting a solvent swap to the original acetonitrile/water/CHCl₃ mixture. As we desired to produce a telescoped sequence by linking the oxidation to the Sonogashira step, we decided to explore more amenable strategies.

There are only limited studies in the literature regarding the ozonolysis of alkynes. In addition, there is no clear view as to which substrates yield anhydride or carboxylic acid products valuable for our study and which substrates result in benzil derivatives, which would be of less use. We however thought it would be of speculative interest to evaluate the transformation with regard to our particular substrate 16. We aimed to make use of the fact that the ozonolysis reaction could be performed in an alcoholic solvent to, in theory, aid the breakdown of the ozonide intermediates and fragment the intermediate anhydrides if produced. Ultimately, we wished to perform the ozonolysis directly on the methanolic reactor output used in the preparation of 16 (Scheme 7). Several flow reactors have been reported for ozonolysis reactions, however, we elected to use a simple wavy annular flow ozonolysis design, which we had previously employed successfully at scale (Scheme 10). This used a simple T-assembly to inject a flow of substrate 16 from a capillary input into a fast flowing gas flow of the O₃ reactant.

From the initial ozonolysis runs we were pleased to identify the oxidative fragmentation products 13, 14, 7 and 21 and small amounts of 2-hydroxy-2-methylpropanoic acid 19 as well as the corresponding methyl ester adduct 20. Table 2 summarizes some of the further informative optimization results. As can be seen, temperature controls the distribution of aryl products through direct and secondary hydrolysis, however, it has a nominal influence on conversion. Concentration and residence time were found to be the main parameters determining starting-material consumption. The addition of additives such as acids...
(e.g. HCl, PTSA) or bases (pyridine, DMAP, K₂CO₃) neither enhance conversion nor reaction rates and had only small effects on product proportions.

Table 2. Subset optimization of flow ozonolysis reaction conditions.

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<th>Ent.</th>
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<th>Substrate flow rate[b]</th>
<th>Temp °C</th>
<th>Conv. %</th>
<th>Ratio[f]</th>
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<tr>
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[a] O₂ flow rate was controlled by using a Brukhurst flow meter. [b] 0.5 m in MeOH. [c] 0.7 m in MeOH. [d] 0.9 m in MeOH. [e] 1 m in MeOH. [f] As determined by UV-LC rounded to nearest %. Nd = not determined.

For the final flow process we elected to use a concentration of 1 m and flow rates of 2 and 0.85 mL/min for the oxygen and substrate streams, respectively; at ambient temperature this gave quantitative conversion. This additionally produced a good match for the concentration of the exiting stream from the Sonogashira step. Although the oxidation of alkynes to anhydrides avoids the production of classical intermediates such as ozonides and peroxides, upon analysis the processed solution still contained low levels of peroxy species (≈ 10 mg/L).[37] To aid decomposition of these residual peroxy species a short packed column of MnO₂ was added in-line, which reduced the amount of peroxy components below detectable levels. Overall, a processing capacity of 51 mmol/h was achieved which would equate to approximately 12 g/h of product. Figure 5 shows a representative ¹H NMR spectrum of the crude reaction mixture directly following evaporation of the output stream. The final
The product could be isolated by solvent evaporation and allowed the crude product to crystallize upon standing in a 65 % yield after filtration and washing with cold hexane. The corresponding carboxylic acid could be obtained quantitatively by heating the same crude material dissolved in 3 M HCl at 125 °C for 30 min by passage through a tubular flow coil reactor. As these acidic conditions met our need for the subsequent sequence, we anticipated using this solution directly in the next operation.

To access hydrazine would require a further two-step sequence of diazotization and reduction. Here we were able to rely on some previously devised flow chemistry involving reaction of a diazonium salt generated in situ with ascorbic acid to affect the reduction [Scheme 11]. As an alternative and backup approach we also evaluated a more classical reduction involving a mixture of SnCl2 and HCl, which was shown to work well in batch.

To extend this sequence (Scheme 11 – reactor part 2), we incorporated a further pump to deliver an aqueous stream of the ascorbic acid reductant and passed the flow stream into a coil reactor (52 mL, Polar Bear Plus [28] – 23 min residence time). A suspension rapidly formed but could be easily propagated through the reactor without causing blockage. The reactor output was dispensed directly onto a sintered filter. After 60 min of operation, the filter cake was washed with water to give 3.48 g, 84 % isolated yield of the hydrazine salt after drying.

The success of the aqueous conditions for the diazotization in this latter transformation and the environmental benefits of the ascorbic acid reduction prompted us to attempt to assimilate the two processes to furnish an improved protocol. We also wished to try and telescope the previous acid-mediated hydrolysis of the protected aniline into this new assembly. We therefore devised the modified setup as depicted in Scheme 13.
Scheme 12. Flow diazotization and Sn-mediated reduction starting from acid aniline 7.

under the previously determined acidic conditions (Scheme 13). The processed flow stream then passed through a cooling zone before next being mixed with an aqueous solution of NaNO₂ and entering a short residence-time flow coil (FEP 5 mL) maintained at 0 °C. This flow stream, containing the intermediate diazonium, was immediately combined with the reducing ascorbic acid solution, and the resulting hydrazine ester adduct, which formed in situ was digested as it passed through a heated flow coil furnishing the oxamic acid 23. To facilitate a partial workup, a quench solution of NaOH was first injected into the flow to generate a basic solution followed by an input of EtOAc to form a biphasic flow. The organic- and product-containing aqueous streams were at this stage phase separated by using the previously described in-line extractor (Figure 4). This resulted in isolation of a basic solution of the oxamic acid product that could be subsequently isolated by careful acidification and extraction (of particular note was that the more aqueous soluble acid 19 was not found as a contaminant in the product[42]).

As a proof of concept, we were also able to demonstrate that this final acidification and extraction could also be achieved as a flow sequence, again by utilizing the in-line separator. However, in practice it was found more efficient to simply batch the product solution and acidify this in bulk prior to extraction.

Pleasingly, we achieved a reliable isolated yield of compound 23 in 80 % both for short reactor runs (1–3 h) and over prolonged usage (full-day runs of 8–10 h). This enabled a reasonable productivity of 34 mmol/h that delivered over 8.9 g/h for the integrated four-step transformation.

Finally, in the context of this project, we exemplified that the target hydrazine adduct 23 could be successfully utilized in the desired reaction with fragment 4 under thermal conditions to synthesize pyrazole 25 (Scheme 14). This was achieved by heating a solution of compounds 4 and 23 in 1,4-dioxane in the presence of 10 mol-% p-TSA at 120 °C for 2.5 h. The reaction gave an 86 % isolated yield of 25 after work-up and purification by column chromatography.

Scheme 13. Telescoped synthesis of hydrazine adduct 23.

Scheme 14. Preparation of pyrazole 25 by batch microwave synthesis.
Conclusions

In this work we have developed a set of multi-step flow sequences starting from readily available aniline 10 to an advanced hydrazine derivative 23. The route generated has a number of staging points that were natural breaks in the processing allowing the batching of intermediates, in each case as bench stable solids (Figure 6). As part of our flow-processing strategy we have made use of some established flow transformations (e.g., diazotization and reduction) as well as developed new chemistries (e.g., selective ozonolysis of an alkyne). This has generated several improvements with regards to solvent usage (synthesis of 8 and telescoping 16 → 14), energy utilization (synthesis of 8) and the number of required reaction steps. Ultimately we have been able to create a set of linked flow operations, which deliver high quality material with good productivity (Figure 6).

By employing this chemistry, we have successfully generated 4.27 kg of the final hydrazine derivative 23 for use in the synthesis of SR 142948A (3) and other important derivatives.

![Figure 6](image-url)

**Figure 6.** Key intermediates and outputs for the flow synthesis towards compound 23: a synthetic equivalent of target hydrazide 6.

Experimental Section

For protocols and reactor descriptors see the Supporting Information.

1H NMR spectra were recorded with a Bruker Avance DPX-400, DRX-600, Avance 400 NQF Cryo, or Avance 500 Cryo spectrometer with the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm, [D₆]DMSO = 2.50 ppm). 1H resonances are reported to the nearest 0.01 ppm. 13C NMR Spectra were recorded with the same spectrometers with the central resonance of the solvent peak as the internal reference (CDCl₃ = 77.16 ppm, [D₆]DMSO = 2.50 ppm). 1H resonances are reported to the nearest 0.01 ppm.

For protocols and reactor descriptors see the Supporting Information.
1H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 12.83 (s, 1 H), 9.47 (s, 1 H), 7.87 (d, $J$ = 2.1 Hz, 1 H), 7.73 (dd, $J$ = 8.3, 2.1 Hz, 1 H), 7.54 (d, $J$ = 8.3 Hz, 1 H), 3.35 (sept, $J$ = 6.8 Hz, 1 H), 2.10 (s, 3 H), 1.17 (d, $J$ = 6.8 Hz, 6 H) ppm.

$^{13}$C NMR (101 MHz, [D$_6$]DMSO): $\delta$ = 169.34 (C), 167.59 (C), 142.12 (C), 139.74 (C), 128.01 (C), 127.39 (CH), 127.15 (CH), 126.11 (CH), 27.19 (CH$_3$), 23.82 (CH), 23.46 (CH$_2$) ppm. IR: $\tilde{\nu}$ = 2925.9 (m), 2968.9 (m), 2555.6 (br. w), 1668.6 (s), 1645.0 (s), 1670.8 (m), 1581.2 (m), 1520.8 (s) cm$^{-1}$. HRMS: Calcld for [C$_2$H$_4$N$_2$O$_3$]$^+$ = 222.1130, found 222.1127, $\Delta$ = 0.3 ppm.

**Methyl 4-Acetamido-3-isopropylbenzoate (21):** White solid; Mp: 128.9–130.2 °C; LC-MS: Rt 1.93, [MH$^+$]$^+$ = 236.8, [2MH$^+$]$^+$ = 471.4. 1H NMR (400 MHz, CDCl$_3$): [MH$^+$] = 9.50 (s, 1 H), 7.89 (d, $J$ = 2.1 Hz, 1 H), 7.76 (dd, $J$ = 8.4, 2.1 Hz, 1 H), 7.60 (d, $J$ = 8.4 Hz, 1 H), 3.84 (s, 3 H), 3.27 (sept, $J$ = 6.8 Hz, 1 H), 2.11 (s, 3 H), 1.17 (d, $J$ = 6.8 Hz, 6 H) ppm. $^{13}$C NMR (101 MHz, [D$_6$]DMSO): $\delta$ = 169.34 (C), 166.47 (C), 142.12 (C), 140.14 (C), 127.27 (CH), 126.79 (C), 126.97 (CH), 126.09 (CH), 52.42 (CH$_3$), 27.13 (CH$_3$), 23.83 (CH), 23.40 (CH$_2$) ppm. IR: $\tilde{\nu}$ = 1520.8 (s) cm$^{-1}$. HRMS: Calcld for [C$_{12}$H$_{16}$NO$_3$]$^+$ = 226.1287, found 226.1296, $\Delta$ = 3.8 ppm.

**N-[4-(3-Hydroxy-3-methylbutyl-1-yl)-2-isopropylanilino]acetamide (16):** Off-white solid; Mp: 136.2–137.4 °C; LC-MS: Rt 1.89, [MH$^+$] = 261.0. Indication of rotameric structure: $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.78–7.75 (m, 1 H), 7.55–7.40 (m, 1 H), 7.29 (s, 1 H), 7.13 (t, $J$ = 6.0 Hz, 1 H), 2.99 (h, $J$ = 6.8 Hz, 1 H), 2.20–2.05 (br. s, 3 H), 1.65–1.50 (m, 6 H), 1.17 (d, $J$ = 6.8 Hz, 7 H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 169.29 (C), 149.02 (C), 134.11 (C), 129.56 (C), 129.10 (CH), 125.04 (CH), 120.32 (C), 93.54 (C), 82.00 (C), 65.49 (C), 31.50 (CH$_3$), 27.22 (CH$_2$), 23.99 (CH$_3$), 22.94 (CH$_2$) ppm. HRM: Calcld for [C$_{16}$H$_{23}$N$_2$O$_3$]$^+$ = 308.1792, found 308.1794, $\Delta$ = 0.2 ppm. $^{1}$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 2.07 (s, 3 H), 1.47 (s, 6 H), 1.14 (d, $J$ = 6.8 Hz, 6 H) ppm. $^{13}$C NMR (101 MHz, [D$_6$]DMSO): $\delta$ = 169.20 (C), 143.07 (C), 135.34 (C), 129.06 (CH$_2$), 128.90 (CH), 126.94 (CH), 120.24 (C), 95.87 (C), 80.92 (C), 64.08 (C), 32.11 (CH$_3$), 27.22 (CH$_3$), 26.38 (CH$_2$), 23.43 (CH$_3$) ppm. IR: $\tilde{\nu}$ = 3233.2 (br. m), 2971.9 (m), 1658.5 (s), 1577.9 (w), 1520.8 (s) cm$^{-1}$. HRMS: Calcld for [C$_{16}$H$_{25}$N$_2$O$_3$]$^+$ = 260.1651, found 260.1648, $\Delta$ = -1.2 ppm.
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Keywords: Continuous flow · Flow chemistry · Ozonolysis · Cross-coupling · Multi-step synthesis · Synthetic methods

[12] A small amount (1.2–3 %) of the fully deprotected acetylene 18 was also detected after prolonged stirring.
[13] A small amount of 1–3 % of the fully deprotected acetylene 18 was also detected after prolonged stirring.
[14] It appeared from a basic evaluation of the limited substrate scope that aliphatic substituted acetylenes gave the corresponding anhydrides or acids (in the presence of water) whereas diaryl acetylenes i.e. from diphenylacetylene produced the corresponding benzoic acid. However this was contradicted in several papers based upon the same substrate.
[17] Quantum® peroxides test sticks available from Sigma Aldrich cat. no. Z101680. Range 0, 0.5, 2, 5, 10, 25 mg/L.
We believe based upon analysis of samples that a significant proportion of the 2-hydroxyisobutyric acid decomposes to CO and acetone under the acidic conditions used in the preparation of 22 simplifying work up. This type of reaction is known in the literature but normally requires an activator:
a) R. A. Singh, A. Kumar, Oxidation Commun. 2013, 36, 965–972;
b) G. E. M. Moussa, M. E. Shaban, F. A. Fouli, A. N. Hegazi, J. Chem. Soc. Pak. 1987, 9, 239–244. It does however resemble the acid promoted oxidation of malic acid to coumaric acid see:


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