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# The Development of a General Strategy for the Synthesis of Tyramine-Based Natural Products by Using Continuous Flow Techniques

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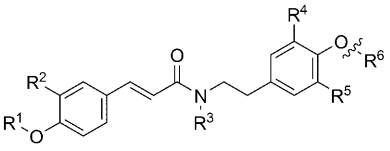
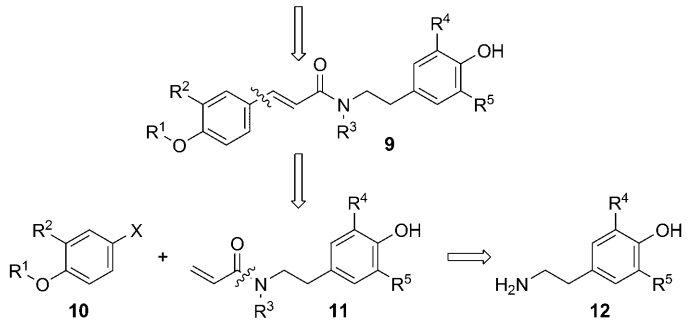
The movement of synthetic chemistry from a traditional batch format (e.g., round-bottom flask or kettle reactor) to a flowed platform offers many advantages.[1] In smaller reaction channels, the chemical transformation itself can benefit from improved mass and thermal transfer leading to enhanced kinetics and cleaner product mixtures with fewer by-products. The latter benefits are significantly affected by the introduction of both a space and time element to the reaction process. For example, starting materials and/or catalysts can be kept separate and only brought together at the point of reaction and every resultant minute plug of reaction mixture thus formed is continuously moved away from infusing reactants eliminating many side reactions. Operationally, the movement of synthesis to a flowed platform allows for real-time reaction monitoring coupled with instantaneous changes of reaction parameters that vastly truncates reaction process optimization. Finally, once optimal conditions are achieved, larger quantities of product can be obtained by simply flowing using those parameters for the necessary time (or in parallel reaction tubes) to accrue the desired amount of product, a concept termed 'scale-out'.

We have been developing microwave-assisted, continuous-flow organic synthesis (MACOS) and applying it in single-step reactions including those promoted by thin-metal films that line the reaction tube.[2] Most recently we have investigated by using the scale-out strategy with MACOS to produce multigram quantities of benzo-fused sultams.[3] Here we are furthering the development of this platform to multi-step transformations for the production of tyramine-based natural products entirely by flow[4] (see Scheme 1 for target structures).[5–8] We are attracted to the members of this family of natural products for their inherent biological activity,[9–13] but additionally they can themselves serve as templates for the diversity-oriented synthesis of analogues. Indeed, family members contain alkylating sites, a Michael acceptor for addition reactions, and in some cases halides for substitution reactions (e.g., cross-coupling). As such, it would be beneficial to demonstrate the capability to prepare them potentially on at least a gram scale using a scale-out synthetic approach. The retrosynthetic route that we developed to approach all of the members of this natural product family by flow revolves around a Heck/alkylation sequence (Scheme 1). Unsaturated amides **11** were prepared readily by simple acylation of either tyramine itself (**12**, $R^4 = R^5 =$ H) or the appropriate derivative with acryloyl chloride.[14]



**1**, $R^1$ = H , $R^2$ = H, $R^3$ = H, $R^4$ = H, $R^5$ = H, $R^6$ = H (N-*trans*-coumaroyl tyramine)
**2**, $R^1$ = H , $R^2$ = H, $R^3$ = $CH_3$, $R^4$ = H, $R^5$ = H, $R^6$ = $CH_3$ (Ailanthamide)
**3**, $R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = H, $R^4$ = H, $R^5$ = H, $R^6$ = H (N-*trans*-feruloyl tyramine)
**4**, $R^1$ = $CH_3$, $R^2$ = $OCH_3$, $R^3$ = $CH_3$, $R^4$ = H, $R^5$ = H, $R^6$ = H
**5**, $R^1$ = $CH_3$, $R^2$ = $OCH_3$, $R^3$ = $CH_3$, $R^4$ = H, $R^5$ = H, $R^6$ = $CH_3$ (Beecheyamide)
**6**, $R^1$ = $CH_3$, $R^2$ = Br, $R^3$ = H, $R^4$ = H, $R^5$ = H, $R^6$ = H
**7**, $R^1$ = $CH_3$, $R^2$ = Br, $R^3$ = H, $R^4$ = H, $R^5$ = H, $R^6$ = $CH_2CH_2CH_2NH_2$
**8**, $R^1$ = $CH_3$, $R^2$ = Br, $R^3$ = H, $R^4$ = Br, $R^5$ = Br, $R^6$ = $CH_2CH_2CH_2NH_2$ (Aplysamine 6)



Scheme 1. Synthetic approach to the tyramine-based family of natural products and analogues.

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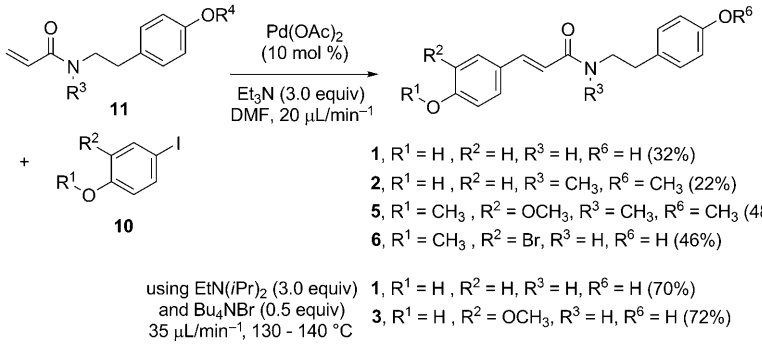
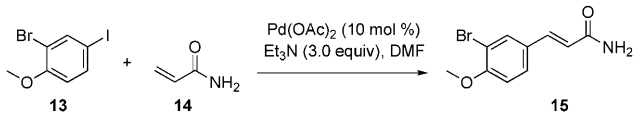
Heck reactions are generally run at relatively high temperatures (> 100 °C) for several hours. However, for the flow sequence to be effective, the reaction has to reach a high level of completion during the time in which it is receiving microwave irradiation while it is traversing the reaction capillary; this is in the order of minutes. To explore how the Heck reaction could be made to perform under flow conditions,[15] we first examined a simplified set of starting materials (Table 1). As a control, we performed the reaction first under batch conditions in an oil bath (Table 1, entry 1) and found that 18 h were required to achieve full conversion. Knowing that the flowing reaction only resides for a few minutes in the microwave irradiation zone, we irradiated it with enough power to create temperatures well in excess of 100 °C (Table 1, entries 2–7). With optimization of concentration, flow rate, and temperature, excellent levels of conversion were attained using MACOS. Using the conditions outlined in Table 1, entry 5, compounds **1**, **2**, **5**, and **6** were prepared from their corresponding Heck precursors (**10** and **11**, where compound **11** was used directly from the acylation procedure) in 32, 22, 48, and 46% yield, respectively (Scheme 2).[16]




Scheme 2. Heck reaction between fragments **10** and **11**.[16]

Table 1. Optimization of the Heck reaction.




| Entry | **14** [equiv] | Conc. of **13**[a] [M] | Time or flow rate[b] | Temp. [°C][c] | Conversion [%][d] |
|---|---|---|---|---|---|
| 1 | 1.5 | 0.6 | 18 h | 90 | 100 |
| 2 | 1.8 | 0.6 | 20 | 100 | 76 |
| 3 | 1.8 | 0.6 | 20 | 135 | 85 |
| 4 | 1.8 | 0.6 | 15 | 125 | 94 |
| 5 | 1.5 | 0.6 | 20 | 140 | 92 |
| 6 | 1.8 | 0.9 | 20 | 110 | 65 |
| 7 | 1.8 | 1.5 | 20 | 140 | complex mixture |

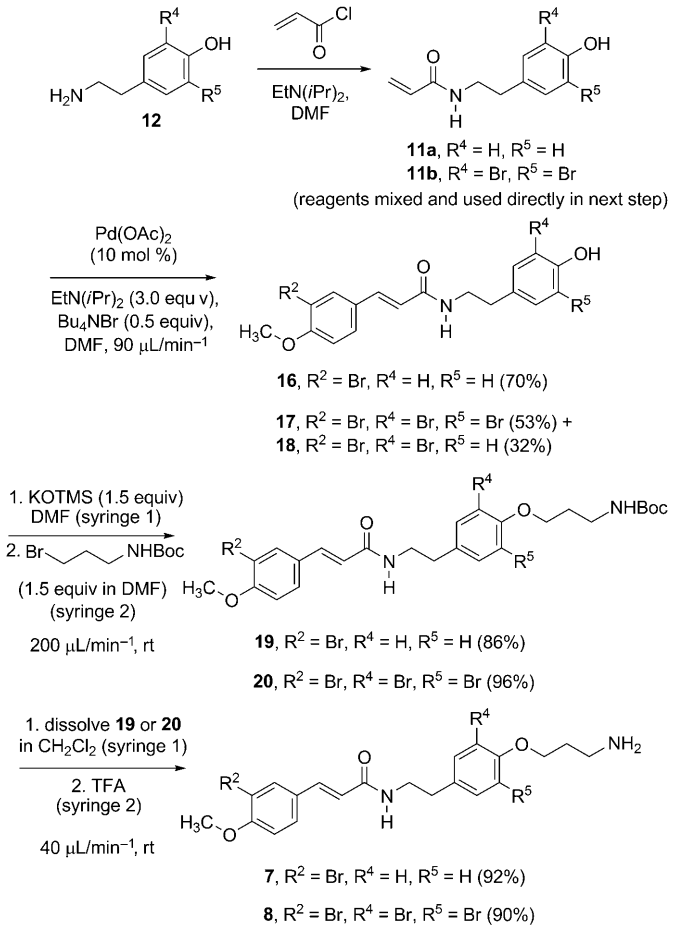
[a] Concentration is based on **14**. [b] The experiment in entry 1 is a batch reaction performed in an oil bath for 18 h, all other entries are flowed reactions and the rate listed is in $\mu L\,min^{-1}$. [c] The temperature listed in entry 1 is of the oil bath. All other temperatures are the temperature recorded off the surface of the reaction capillary by the internal IR sensor of the Biotage Initiator Synthesizer. [d] Percent conversion is determined by taking an aliquot from the eluent stream from the capillary (crude material) and calculating the ratio of the peaks of the starting materials and product in the proton NMR spectrum.

From the above applied results, some shortcomings of the Heck conditions were realized. Most importantly, yield dropped off sharply, which was found to be primarily the result of the target products undergoing a second Heck reaction.[17] With some investigation, it was found that the excess tryamine from the acylation reaction (used crude in the next step) was present as the HCl salt and was being deprotonated by the triethylamine that was originally used for the subsequent Heck reaction. The resultant tyramine free base (in excess) then underwent a Michael reaction with compound **11**, the initially formed desired product, thus removing it from the reaction mixture; the aryl iodide, now in excess due to the depletion of **11**, underwent a second undesired Heck coupling. This problem was overcome by the use of equimolar quantities of tryamine and acryloyl chloride and only a slight excess of Hunig's base in the Heck reaction, which now led to good yields of analogues **1** and **3** (see bottom of Scheme 2). The addition of tetrabutylammonium bromide and Hunig's base, which has a soluble conjugate acid, were key to this yield improvement and instrumental to producing larger quantities (vide infra).

With the first two steps worked out, we extended the flow process to include a subsequent alkylation step to approach **7** and aplysamine 6 (**8**) (Scheme 3).[18] Acylation proceeded cleanly and the crude material was used directly, as usual, in the Heck reaction. Coupling of mono bromide **11a** proceeded uneventfully and in excellent recovery. However, unexpectedly, the dibromide (**11b**) underwent reduction of one of the bromides. To probe the origin of this undesired reaction, we first repeated it with identical reactions conditions only in batch, and the same result was attained. Thus, the side reaction is not a consequence of flow. Clearly, the propensity for reduction diminishes when one of the bromides is removed as we never observed reduction in the case of **11a**. Perhaps the hydroxyl group in **17** makes the ring electron-rich enough to avoid oxidative addition of a single bromide under these reaction conditions, but the presence of the second bromide tips the balance and activates the ring. The next question is the hydride source for this reduction. We suspected the phenol and to test this we protected it as a methyl ether; this halted reduction confirming the phenol as the source of the problem.

Carrying on with the preparation of the final tyramine analogues, we set out to alkylate the phenol position. The reaction was thought to work best with a soluble base that had a




Scheme 3. Full protocol to prepare brominated tyramine derivatives **7** and **8**.[16]

soluble conjugate acid that could facilitate kinetic deprotonation of the phenol. With only minor optimization, potassium trimethylsilanoxide was loaded into one syringe along with **16** or **17**, while the alkyl bromide was loaded into a second syringe. Substitution proceeded cleanly providing the corresponding alkylated products **19** and **20**. It was determined that deprotection with TFA could not be carried out in DMF. Thus, the solvent had to be swapped out to $CH_2Cl_2$ meaning that the two steps could not be flowed directly from one to the next. Nevertheless, deprotection also proceeded nicely at room temperature providing desired products **7** and **8** with excellent recovery (Scheme 3).

As mentioned, we were developing a process to make the compounds in this natural product series with an eye on the potential to produce larger quantities of final product. To this end, compounds **1** and **2** were prepared on a 1.02- and 1.64-gram scale using the corresponding two-step sequence described in Scheme 2. Compounds **7** and **8** (aplysamine 6) were prepared by using the four-step protocol detailed in Scheme 3 in final quantities of 1.5 and 0.63 grams, respectively.

In summary, we have developed a general synthetic method for the preparation of a number of tyramine-derived natural products and analogues that is based on a combination of room-temperature alkylation and deprotection processes with microwave-heated Heck coupling. The protocol has been demonstrated to be suitable for scale-out, meaning that we can prepare, in principle, any quantity of these compounds we require without the need for process reoptimization. Applications of multistep, flow synthesis of natural products of progressing complexity are underway in our laboratory.

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**Keywords:** flow chemistry · Heck reaction · microwave chemistry · tyramine

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