An Integrated Flow and Batch-Based Approach for the Synthesis of O-Methyl Siphonazole

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Abstract: The bisoxazole containing natural product O-methyl siphonazole was assembled using a suite of microreactors via a flow-based approach in concert with traditional batch methods. The use of a toolbox of solid-supported scavengers and reagents to aid purification afforded the natural product in a total of nine steps.

Key words: oxazoles, Claisen condensation, flow chemistry, microreactors, solid-supported reagents

As part of our ongoing interest in oxazole-containing natural products,1 we have devised a synthetic route to the bisoxazole alkaloid O-methyl siphonazole (2), which was discovered by König and co-workers in 2006, along with the C-21-demethylated parent compound siphonazole (1, Scheme 1).2 While Moody3 and Ciufolini4 reported the first syntheses of the siphonazoles in 2008 and 2009, a detailed biological profile of these metabolites of Herpetosiphon sp. has not been thoroughly established. Thus, a modular synthesis of the natural products 1 and 2, flexible enough for the production of unnatural analogues, is of interest.

In this article we disclose our results on the preparation of O-methyl siphonazole (2) based on an integrated approach combining conventional batch and new flow chemistry methods. The application of flow techniques in organic synthesis as described by numerous laboratories5 has transformed flow chemistry from an academic interest to a valuable enabling technology that overcomes several of the bottlenecks traditionally faced by synthetic chemists.6 As such the generation and immediate use of hazardous, toxic, or unstable intermediates7 has been reported as well as the possibility to more reliably perform reaction scale-up.8 Furthermore, flow reactors can be transformed into automated platforms by the addition of liquid handling and fraction collector modules expanding the working capabilities of the units and allowing for 24/7 working regimes.9 Finally, individual reactions can be telescoped into one continuous flow sequence, thus avoiding the iterative isolation, purification, and reprocessing of intermediates.10 With these potential advantages in mind, we have orchestrated an improved total synthesis of O-methyl siphonazole by making use of flow techniques in order to expedite certain steps in the synthesis. Our first synthetic target was the oxazole carboxylic acid 10 which we intended to access from commercially available dimethoxycinnamic acid (6, Scheme 2).

In order to process this material quickly we decided to employ the Vapourtec R2+/R4 flow system11 where two small HPLC pumps deliver streams of starting materials which are subsequently mixed at either a T-piece or within a microchip. The resulting stream can then be introduced into a tubular convection flow coil (CFC) which is

Scheme 1 Siphonazole (1) and its building blocks 3–5

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heated or cooled to a desired temperature. The reaction stream is then subjected to in-line purification using solid-supported quenching and scavenger resins prior to the product being collected or relayed directly into the next step of the synthesis sequence. Using this flow configuration we established conditions for converting dimethoxy-cinnamic acid (6) into oxazoline derivative 9 as shown in Scheme 2. The carboxylic acid was activated with CDI and coupled with threonine tert-butyl ester hydrochloride (7) in situ before adding a third stream containing diethylaminosulfur trifluoride (DAST) 12 to accomplish the cyclodehydration of the intermediate amide. A set of heterogeneous scavengers such as a sulfonic acid (QP-SA, to remove Et3N, imidazole and residual threonine tert-butyl ester), a tertiary amine (QP-DMA, to remove residual acid), and plugs of CaCO3 and SiO2 (to quench and trap DAST and HF) were used in glass columns affording oxazoline 9 in greater than 95% purity. In a second step this oxazoline was then oxidized to the corresponding oxazole using BrCCl3 and DBU where again all steps were performed by convenient batch methods (Scheme 3).

In order to progress the synthesis, acid chloride 3 was coupled by a Claisen condensation with the oxazole esters 4a–c (Scheme 4). It was observed that the diesters 4b and 4c were prone to self-condensation upon treatment with NaHMDS, therefore the base (2.3 equiv) was added, via a syringe pump to the mixture of acid chloride 3 (1.3 equiv) and oxazole esters 4a–c in THF (1.0 equiv each) at −78

Scheme 2 Flow synthesis of oxazole carboxylic acid 10
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Scheme 3  Preparation of oxazoles 4b and 4c. Reagents and conditions: (a) methyl malonate monoamide, Rh₂(OAc)₄ (2 mol%), CH₂Cl₂, reflux, syringe pump addition, 84% for 13, 56% for 14; (b) I₂, Ph₃P, Et₃N, CH₂Cl₂, r.t., 55%; (c) I₂, Ph₃P, i-Pr₂NEt, PhMe, 80 °C, 71%.

Scheme 4  Claisen condensation of acid chloride 3 with oxazoles 4a–c. Reagents and conditions: (a) NaHMDS (2.3 equiv) added at –78 °C, via a syringe pump, to 3 (1.3 equiv) and 4a–c (1.0 equiv) in THF.

Scheme 5  Claisen reaction of oxazole 3 and 4a induced by PS-BEMP as polymer-supported base in the presence of LiBr.

This procedure cleanly generated the desired adducts 15a–c, which were employed without purification in the subsequent decarboxylation step.

The use of a polymer-supported base for the Claisen condensation of acid chloride 3 with oxazole esters 4a–c was also examined. As illustrated in Scheme 5, stock solutions of 3 and 4a in MeCN were mixed in a microreactor, followed by elution through a cartridge containing PS-BEMP. Unfortunately this procedure did not deliver the expected coupled material. Ultimately, it was found that both the product and excess starting material 4a were retained as the corresponding enolates by the immobilized base. This was potentially very problematic because applying any standard release protocol involving displacement of the product from the column by treatment with an acidic solution would also liberate the excess starting material and acid via hydrolysis of the acyl chloride 3. As a result additional processing through subsequent in-line scavenging or column chromatography of the crude product would be required. However, pleasingly it was discovered that when LiBr was added to the stock solution of ester 4a, the desired product 15a could then be obtained cleanly in 85% yield after aqueous quenching. It is proposed that the addition of the LiBr leads to the formation of the strongly chelated and highly soluble lithium enolate 16. This therefore enables flow processing of the reaction with the advantage that the major potential contaminants of excess 4a and hydrolyzed carboxylic acid of 3 are more strongly bound on the polymeric support and so removed from the product stream of enolate 16.

Next the decarboxylation of Claisen adducts 15a–c was studied in detail (Table 1). Adduct 15a cleanly underwent decarboxylation in the presence of excess NaCl (20 equiv) in wet DMSO, to produce bisoxazole nitrile 17a in 73% overall yield (two steps from 4a). When the corresponding bismethylester 15b was reacted under identical condi-
tions, surprisingly, no easily identified products could be obtained, and recovery of the starting material after chromatographic separation was poor. However, decarboxylation of 15b in the absence of NaCl did allow for the isolation of product 17b albeit in very low yield (7%). The salt-free decarboxylation of adduct 15c, bearing a phenyl ester group at C-2 (instead of the methyl ester) on the other hand produced bisoxazole ester 17c in a correspondingly higher 40% overall yield from 4c.

These results suggest that in the case of substrate isolation of product with a methyl ester in the 2-position, both the BAL2 and BAC2 cleavage mechanisms operate with almost the same efficiency. This is supported by the observation that although both pathways might be possible in the presence of chloride ions, presumably only the latter mechanism is possible when water is the sole nucleophile. However, the disappointingly low yield of bisoxazole 17b (7%) from the salt-free reaction indicates that the C-2 methyl ester is highly reactive towards hydrolysis at elevated temperatures, and so it was not possible to tune the reactivity by switching the external nucleophile from chloride to water. Furthermore, it would appear that the free C-2 carboxylate generated from 15b is highly unstable and prone to thermal decarboxylation, followed by a further decomposition of the resulting C-2 carbanion precluding this as a viable synthetic route. Compared to substrate 15b, the alternative diester substrate 15c demonstrated improved stability, as the BAL2 mechanism cannot operate at the site of the C-2 phenyl ester. Thus, it was possible to isolate the decarboxylation product 17c in 40% yield. This was lower than the 73% yield of the C-2 cyano compound 17a, due to partial hydrolysis of the phenyl ester of 15c via the BAC2 mechanism.

Table 1 Decarboxylation of Keto Esters 15a-c to Bisoxazole Ketones 15a-c

<table>
<thead>
<tr>
<th>R</th>
<th>Conditions</th>
<th>Yield from 4a-c (%)</th>
</tr>
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<tbody>
<tr>
<td>CN</td>
<td>NaCl, DMSO, H2O, MW, 160 °C, 1 h</td>
<td>17a 73</td>
</tr>
<tr>
<td>CO2Me</td>
<td>NaCl, DMSO, H2O, MW, 160 °C, 1 h</td>
<td>17b 0</td>
</tr>
<tr>
<td>CO2Me</td>
<td>DMSO, H2O, MW, 150 °C, 1 h</td>
<td>17b 7</td>
</tr>
<tr>
<td>CO2Ph</td>
<td>DMSO, H2O, MW, 150 °C, 1 h</td>
<td>17c 40</td>
</tr>
</tbody>
</table>

Nevertheless, the bisoxazole nitrile 17a was not a suitable precursor to the natural product 2 as the cyano group at C-2 resisted all attempts at hydrolysis to the carboxylic acid. Even strongly acidic or basic conditions only led to the corresponding carboxamide in low yields, accompanied by significant demethylation of the C-20 methoxy group. Pleasingly, however, bisoxazole phenyl ester 17c readily hydrolyzed when treated with barium hydroxide generating the corresponding acid, which was obtained in 1:1 mixture with phenol. Purification and isolation of the acid was possible, however, it was found that the crude material could be coupled with pentadienyl amine 522 directly even in the presence of the phenol (Scheme 6). When the acid was activated with TBTU23 (1.5 equiv), and amine 5 (2.2 equiv) was added to the mixture after 15 minutes incubation, no product derived from phenol addition was observed, with O-methyl siphonazole (2)24 being formed exclusively, and enabling isolation in 47% combined yield over the two steps.

Scheme 6 Conversion of bisoxazole ester 17c into O-methyl siphonazole 2. Reagents and conditions: (a) BaOH2·8H2O, THF–H2O, r.t.; (b) TBTU (1.5 equiv), 5 (2.2 equiv), DMF, r.t., 47% (2 steps).

The outcome of our efforts presented in this article shows that the synthesis of the natural product O-methyl siphonazole (2) from oxazole units 3 and 4c, and amine 5 was accomplished via a short sequence including a Claisen condensation and Krapcho decarboxylation as key steps. Furthermore, the use of flow techniques in concert with immobilized reagents and scavengers greatly improved the overall efficiency of the synthesis by circumventing unnecessary isolation and purification steps. In summary, this work exemplifies the benefit of an integrated approach combining traditional batch procedures with appropriate enabling techniques such as flow chemistry. This strategy afforded O-methyl siphonazole in nine steps.

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References and Notes


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(11) Vapourtec® R+R4 system was used; website: www.vapourtec.co.uk.


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3'-H), 6.31 (td, $J = 10.3, 17.0$ Hz, 1 H, 4'-H), 6.75 (d, $J = 16.4$, 1 H, 10-H), 6.88 (d, $J = 8.2$ Hz, 1 H, 16-H), 7.00 (t, $J = 5.8$ Hz, 1 H, NH), 7.07 (d, $J = 1.6$ Hz, 1 H, 13-H), 7.09 (dd, $J = 1.6, 8.2$ Hz, 1 H, 11-H) ppm. $^{13}$C NMR (150 MHz): $\delta = 11.7, 12.4$ (2 q, C-18, C-19), 39.4 (t, C-5), 40.3 (t, C-1'), 55.9, 56.0 (2 q, C-20, C-21), 108.9 (d, C-13), 110.8 (d, C-10), 111.2 (d, C-16), 117.4 (t, C-5'), 121.5 (d, C-17), 128.1 (s, C-12), 129.45, 129.49 (2 d, C-2', C-3'), 132.8 (s, C-2), 134.5 (s, C-7), 136.1 (d, C-4'), 137.3 (d, C-11), 149.3, 150.6 (2 s, C-14, C-15), 153.8 (s, C-3), 155.3 (s, C-8), 155.6 (s, C-4), 159.1 (s, C-9), 161.7 (s, C-1), 189.4 (s, C-6) ppm.