Continuous flow processing from microreactors to mesoscale: the Bohlmann–Rahtz cyclodehydration reaction†‡

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The cyclodehydration of a number of Bohlmann–Rahtz aminodienones exemplifies the use of continuous flow processing to transfer operations from commercial microreactors and microwave batch reactors to mesoscale production using different technology platforms, including a microwave flow reactor.

Introduction

The last decade has seen new focus on the need to harness enabling technology in order to facilitate and simplify processes in organic synthesis. Built upon recent advances in automation, that were principally driven by the needs of combinatorial chemistry, the realization that technological advances could open up new molecular space, streamline process efficiency and integrate synthetic operations with other necessary processes such as purification, analysis and biological evaluation has driven us to re-examine the age-old traditions of synthetic experimental design. Combining different enabling technologies, such as solid-supported reagents, continuous flow reactors, microwave-accelerated reactions, fluorous synthesis, new reaction media and novel catalysts, has the potential to revolutionize the way that chemists plan and carry out their activities.[1] The justification for this orchestration originates from the enticing promise of new and formidable capability, but of course will give rise to unfamiliar challenges and that is why it has become hugely popular amongst academia and industry alike in very recent times.

The combination of microwave heating[2] and continuous flow reactor design[3] has long been realized as an ideal marriage of technologies.[4] Strauss first demonstrated the feasibility of this system in 1994[5] and since then a number of groups have offered their own solutions to scale up issues of microwave-assisted reactions,[6] with the limited penetration depth of microwave irradiation into absorbing media and the physical limitations on the dimensions of a standing wave cavity, by combining continuous flow processing with microwave heating.[7] Continuous flow processing offers the facility for ready automation, improved reproducibility, enhanced safety and considerable process reliability, whereas microwave heating promises improved kinetics and even selective coupling, thus providing opportunities for the rapid processing of material. The scale out of processes using microreactor technology offers additional complementary benefits, such as controlled temperature gradients, improved mixing and a safe environment for the processing of toxic and/or hazardous materials.[8] These multiple emerging technologies have been combined by Organ and co-workers, who showed that microwave irradiation can facilitate metathesis reactions and cross-coupling processes in a Pd-coated capillary placed within the cavity of a single mode microwave reactor.[9] Similarly, Haswell and co-workers utilized a thin layer of gold on the outer surface as a selective heating element under microwave irradiation for a solid-supported catalyst in a Suzuki coupling using a continuous flow capillary reactor.[10] However, there is a clear need for microwave reactors to have the capability to provide products routinely on a multikilogramme scale. Towards this goal, Ley and co-workers have demonstrated that it is possible to quickly process gramme quantities of products from a microwave-assisted Suzuki–Miyaura coupling using an encapsulated palladium catalyst.[11] Leadbeater and co-workers have reported the continuous flow preparation of biodiesel using microwave heating at a staggering processing rate of up to 7.2 L min^{-1}.[12] Other novel combinations of microwave and flow technology have been reported, including the scale-up of microwave-assisted cationic ring-opening polymerization reactions,[13] the use of PEEK [poly(ether ether ketone)] reactors containing immobilized Pd^0 catalysts accommodated within Raschig rings,[14] and the hydrodechlorination of chlorobenzene using an active catalyst bed in a quartz U-tube reactor,[15] amongst others.[4]

Our own studies have described apparatus for carrying out microwave-assisted reactions under continuous flow processing in a single-mode reactor.[16] The principal design of our flow reactor featured the use of proprietary equipment, the need to make optimum use of the standing-wave cavity and the facility to monitor the temperature of the flow cell directly using the instrument's in-built IR sensor. In a number of synthetic operations, including Fischer indole synthesis and Bohlmann–Rahtz cyclodehydration, this equipment was found to out-perform a Teflon coil reactor heated using the same single-mode instrument. Kappe has shown that a similar reactor design can facilitate the Dimroth rearrangement of 1,3-thiazines to dihydropyrimidines using a 10 mL vessel under continuous flow processing.[17] A particularly attractive feature of this apparatus is the potential for synthetic operations to be rapidly transferred from discovery scale to process development. It has long been established that continuous flow processing

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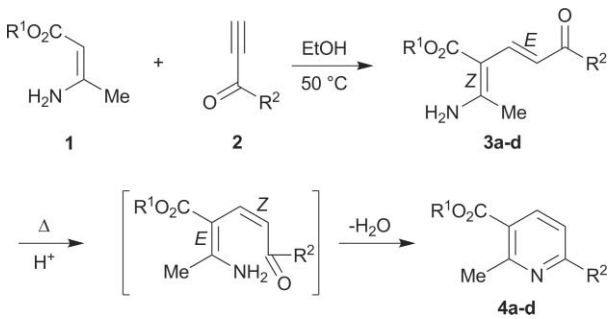
could facilitate this transition,[3,18] allowing the ready transfer from micro- to mesoscale production without the need for extensive re-optimization of procedures. Kappe and co-workers have shown that for Claisen rearrangements and Mizoroki–Heck reactions, conditions optimized under high temperature batch conditions in a microwave reactor could be translated successfully to a flow regime using a microtubular stainless steel conductive heating flow reactor.[19] This manuscript investigates the validity of an alternative hypothesis: that reactions optimized using a conductive heating microreactor platform or in microwave-assisted chemistry can then be transferred to production, for example using microwave dielectric heating, all under a continuous flow regime. For this study we chose a familiar model reaction, the Bohlmann–Rahtz cyclodehydration of aminodienones to pyridines,[20] to test if the transfer of parameters on scale up proceeds readily from apparatus to apparatus[21] for a relatively simple synthetic procedure that we have already established can be facilitated under microwave irradiation.[22]

Bohlmann and Rahtz first reported the synthesis of trisubstituted pyridines from ethyl β-aminocrotonate **1** and ethynyl ketones back in 1957.[20a] Since that date numerous applications have appeared in the literature,[20b,22] in particular in recent years. The reaction is completely regioselective and proceeds with initial Michael addition to the ethynyl ketone **2** by enamine **1** *C*-alkylation to give an aminodiene intermediate **3** that is isolated and purified in high yield (Scheme 1).[20a] The aminodienone intermediate **3** is kinetically stable with respect to the heteroannelation product, pyridine **4**, due to the enone *E*-geometry but on heating to temperatures of 120–170 °C, *E*/*Z*-isomerization precedes spontaneous cyclodehydration to give the 2,3,6-trisubstituted pyridine **4** in excellent overall yield and with total regiocontrol.[20] This process is reliant upon the temperature but may also be facilitated using a Brønsted or Lewis acid catalyst in order to accelerate *E*/*Z*-isomerization.[23] Thus, it was envisaged that high temperatures in combination with the use of a Brønsted acid catalyst would minimize residence times and so deliver high processing rates.



Scheme 1 Bohlmann–Rahtz pyridine synthesis.

Results and discussion

Feasibility study in a single-mode microwave batch reactor

Four aminodienones **3a–d** were generated by Michael addition of ethyl β-aminocrotonate **1** and the respective ethynyl ketone **2a–d**, prepared from the corresponding propargylic alcohol according to our previously established methods.[23,24] Prior to optimization studies under continuous flow processing, a series of cyclodehydration experiments were carried out on aminodienone **3a** (R^1 = Et, R^2 = Ph) in batch mode using microwave dielectric heating (Table 1) in order to establish the optimum solvent and confirm reaction homogeneity under the reaction conditions. Preliminary experiments of this nature carried out before transfer to continuous flow processing were found to be very useful in identifying potential problems, such as the precipitation of products, and are strongly recommended. Previous studies have shown that Bohlmann–Rahtz cyclodehydration proceeds at elevated temperatures in DMSO,[22a] alcoholic solvents[25] and toluene–acetic acid,[23] and so these solvents were reviewed in the microwave batch experiments. Of these, the Brønsted acid catalyzed procedure (entry 3) was established as the most promising for optimization under a flow regime, giving pyridine **4a** in quantitative isolated yield upon 20 min irradiation at a temperature of only 50 °C. Increasing the temperature to 70 °C (entry 4) or 100 °C (entry 5) did not compromise the efficiency of the process and in the latter case reduced the reaction time to only 2 min (hold time); thus was considered suitable for transfer to a microreactor for further investigation.

Table 1 Microwave-assisted cyclodehydration of aminodienone **3a** (R^1 = Et, R^2 = Ph) in batch experiments to find an appropriate reaction solvent

Entry	Solvent	Temp/°C[a]	Time/min[b]	Yield (%)[c]
1	EtOH	130	40	—[d]
2	DMSO	170	20	98
3	PhMe–AcOH (5 : 1)	50	20	>98
4	PhMe–AcOH (5 : 1)	70	10	>98
5	PhMe–AcOH (5 : 1)	100	2	>98

[a] A constant temperature was maintained by the moderation of the initial microwave power (150 W). [b] Time that reaction is held at the given temperature (hold time), not total irradiation time. [c] Isolated yield of pyridine **4a**. [d] A mixture of **3a** and **4a** was obtained.

Reaction optimization: continuous processing under conductive heating using a microreactor

The cyclodehydration of aminodienones **3a–d** was carried out in a Syrris AFRICA® microreactor fitted with a pressurization module, single reagent feed and injection module, conductive heating chip reactor and product collection module. In order to provide a valid comparison with the microwave batch experiments, a 0.1 M stock solution of each aminodienone **3a–d** in toluene–acetic acid in turn was processed through the chip reactor at a temperature of 100 °C, varying the flow rate and thus the residence time (Table 2). However, the cyclodehydration of aminodienone **3c** at this concentration resulted in the precipitation of pyridine **4c**, thus blocking the line, and so for this substrate the experiments were performed at a concentration of 0.05 M (entry 4). In each experiment, the outflow was sampled using GCMS and the analysis was further complemented by ^{1}H NMR spectroscopic studies following aqueous extraction, once sufficient outflow was collected. For all four substrates **3a–d**, a residence time of 1 or 2 min (entry 1) gave incomplete conversion to the corresponding pyridine **4a–d**, whereas residence times of 4 min resulted in complete (>98%) conversions (entries 2–5). This discrepancy in residence time between the conductive heating microreactor platform and microwave batch experiment, could just be attributed to small differences in the heating profiles of these systems, in particular

Table 2 Cyclodehydration of aminodienones **3a–d** in a microreactor[a]

Entry	3	R^1	R^2	Residence time/min	Conversion (%)[b]
1	**a–d**			2	—[c]
2	**a**	Et	Ph	4	>98
3	**b**	Et	*p*-C_6H_4Cl	4	>98
4[d]	**c**	Et	Me	4	>98
5	**d**	*t*-Bu	Me	4	>98

[a] Reactions were carried out on a 0.1 M solution of the corresponding aminodienone **3a–d** in PhMe–AcOH (5 : 1) using a Syrris AFRICA® microreactor at 100 °C for the indicated residence time. [b] Conversion from aminodienone **3** to the corresponding pyridine **4** was established by GCMS and ^{1}H NMR spectroscopy after aqueous work-up. [c] A mixture of **3** and **4** was obtained in each case. [d] A 0.05 M solution of **3c** was used.

Table 3 Microwave-assisted cyclodehydration of aminodienones **3a–c** in a multimode batch reactor[a]

Entry	3	R^1	R^2	mmol[b]	Yield (%)[c]
1[d]	**a**	Et	Ph	1.9	96
2[e]	**a**	Et	Ph	7.7	65
3[d]	**b**	Et	*p*-C_6H_4Cl	1.7	78
4[d]	**c**	Et	Me	0.9	87
5[d]	**c**	Et	Me	3.8	93

[a] Reactions were carried out under microwave irradiation in a pressure rated Teflon vessel (60 or 100 mL) at 100 °C for 2 min (hold time) in PhMe–AcOH (5 : 1) using a multimodal MILESTONE BatchSynth™ instrument, operating at an initial power of 150 W (which was modulated to maintain a constant reaction temperature). [b] Refers to aminodienone **3**. [c] Isolated yield of pyridine **4** after aqueous work-up. [d] 60 mL vessel. [e] 100 mL vessel.

considering the heating and cooling ramp times but were noted as a point of caution.

Scale-up in a multimode microwave batch reactor

Scale-up of the cyclodehydration reaction was first investigated in a sealed vessel under microwave-assisted conditions using a multimode batch reactor.[26,27] Starting with aminodienone **1a**, a 0.1 M solution in toluene–acetic acid was irradiated for 2 min (hold time) at 100 °C using two different vessel sizes (60 and 100 mL) and volumes (Table 3) in order to explore any differences in heating efficiencies on increasing scale. On a relatively small scale (1.9 mmol of **3a** in 19 mL solvent in a 60 mL vessel), the multimode instrument was found to perform well giving efficient conversion to the corresponding pyridine **4a** (96% yield, entry 1). However, on a larger scale (7.7 mmol of **3a** in 75 mL solvent in a 100 mL vessel) a significant reduction in the yield of product was observed (65% yield, entry 2). When similar conditions were investigated in the 60 mL vessel for two further substrates **3b**,**c** the yield of pyrdine **4b**,**c** was found to vary (entries 3–5). These variations were attributed to a combination of temperature and reactivity differences. In the comparison of reactions run in different vessels (entries 1 and 2), problems with the penetration depth of microwave irradiation was thought to have led to irregularities of heating, although differences in ramp heating times could not be discounted. It was clear that a more reliable and robust method was required for the scale-up of this microwave-assisted reaction.

Table 4 Continuous processing of pyridines **4a–c** in a stop-flow single-mode microwave reactor[a]

Entry	3	R^1	R^2	mmol[b]	Hold time/min[c]	Processing time/min[d]	Yield (%)[e]
1	**a**	Et	Ph	2.0	2	21	81
2	**b**	Et	*p*-C_6H_4Cl	0.9	2	20	94
3	**c**	Et	Me	2.0	2	15	83

[a] Reactions were carried out under microwave irradiation at 100 °C for 2 min (hold time) in PhMe–AcOH (5 : 1) using a CEM Voyager® platform on the Discover® single-mode microwave synthesizer, operating at an initial power of 150 W (which was modulated to maintain a constant reaction temperature). [b] Refers to aminodienone **3**. [c] Time the vessel was held at a temperature of 100 °C under microwave irradiation. [d] Time to process product through the reactor, including pump-in, temperature ramp-up, irradiation, cooling, pump-out and the wash-out of the reactor to the receiver. [e] Isolated yield of pyridine **4** after aqueous work-up.

Scale-up: continuous processing under microwave heating using a stop-flow single-mode reactor

One solution to challenges in carrying out microwave-assisted reactions on a preparative scale is offered by the use of a single-mode microwave reactor operating under stop-flow conditions, such as with the CEM Voyager® platform. This apparatus has the advantage that it enables continuous batch production without any need to manually manipulate vessels[26] and has been shown to be an efficient and convenient system for the scale-up of Buchwald–Hartwig aminations in a CEM Discover® microwave synthesizer[26] and the scaling out of pharmaceutically relevant transformations.[28] Carrying out the Bohlmann–Rahtz cyclodehydration on this platform enabled pyridines **4a–c** to be processed in good yield (Table 4). All reactions were carried out at 0.1 M apart from aminodienone **3b** (entry 2) which was processed at 0.05 M concentration in order to prevent any problems with product precipitation blocking the line.[27c] Under these conditions, the apparatus was found to be reliable for all of the substrates, with isolated yields varying between 81 and 94%. Stop-flow operation facilitated the ready transfer of parameters directly from batch-mode to continuous processing for this microwave-assisted transformation and so offers a highly effective method for scaling-out production,[27,28] although overall the processing rates were modest.

Scale-up: continuous processing under microwave heating using a 10 mL glass flow reactor

In order to investigate if improved processing rates could be obtained by continuous flow processing, 0.1 M solutions of aminodienones **3a–d** in toluene–acetic acid were irradiated at 100 °C for 2 min (residence time) under continuous flow processing, using our 10 mL flow cell apparatus,[16] and the results compared to microwave batch experiments using the same single-mode cavity. The flow cell was filled with sand, to help prevent back-mixing, and stabilized at 100 °C with eluent at a flow rate of 1.5 mL min^{-1} using an initial microwave power of 200 W. Each substrate was then passed through the flow cell in turn and discharged with further portions of eluent into an aqueous base quench. In all cases, the process was found to give an excellent yield of the corresponding pyridine **4a–d** (Table 5), with some experiments showing improved performance (entries 2–4) over

Table 5 Comparison of continuous processing of pyridines **4a–d** in a single-mode microwave glass microwave reactor and the corresponding microwave batch reaction in a sealed tube[a]

Entry	3	R^1	R^2	Batch yield (%)[b]	Flow cell yield (%)[c]
1	**a**	Et	Ph	>98	>98
2	**b**	Et	*p*-C_6H_4Cl	98	>98
3	**c**	Et	Me	80	96
4	**d**	*t*-Bu	Me	82	98

[a] The reaction of each aminodienone **3a–d** (0.3 mmol) was carried out under microwave irradiation at 100 °C for 2 min in PhMe–AcOH (5 : 1) using a CEM Discover® single-mode microwave synthesizer, operating at the given initial power (150 or 200 W) which was modulated to maintain a constant reaction temperature. [b] Isolated yield of pyridine **4** after irradiation at 100 °C (150 W initial power) in a sealed tube for 2 min (hold time), cooling in a stream of compressed air and aqueous work up. [c] Isolated yield of pyridine **4** after irradiation (200 W initial power), with a residence time of 2 min, in the glass flow cell and aqueous work-up.

the comparable microwave batch reaction. Considering that the batch experiments were subjected to microwave irradiation for a longer period of time, with ramp heating being followed by a hold time of 2 min, the improved performance of the microwave flow reactor could be attributed to small but significant differences in reaction temperature between batch and flow experiments. The flow cell might be at a higher internal reaction temperature when registering the same measurement on the outer glass wall using the IR sensor. Despite these small differences, it was evident that parameters for batch microwave reactions could be transferred readily to continuous flow processing using this flow cell and, thus, this represents a robust and efficient means to scale up microwave reactions, with prospects for improved performance over batch methods.

Scale-up: continuous processing using a stainless steel conductive heating flow reactor

The use of conductive heating continuous flow reactor platforms offers a viable alternative for the scale-up of microwave-assisted transformations carried out in batch mode.[19] To explore these opportunities, 0.1 M solutions of aminodienones **3a**,**b** were processed using the UNIQSIS FlowSyn™ conductive heating platform (Table 6) at 100 °C through a 5 mL stainless steel coil for 2 min (residence time), in order to establish if this would give efficient conversion to the corresponding pyridines **4a**,**b**, for comparison with the microwave-assisted methods. Although the processing rate for this apparatus was reasonably high, the isolated yield of pyridines **4a** and **4b** was compromised (62 and 52%, respectively) due to incomplete conversion. It was felt the reduction in efficiency was due to differences in how the temperature was measured between the conductive heating coil and microwave-heated reactors. On analysis, parameters for the stainless steel flow reactor had transferred successfully from the corresponding microreactor, which was also less efficient at 2 min residence time.

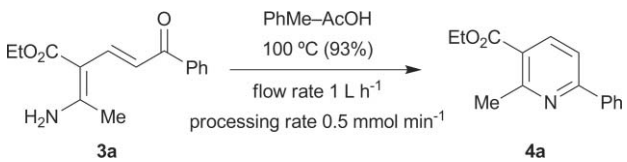
Table 6 Continuous processing of pyridines **4a**,**b** in a stainless steel conductive heating flow reactor[a]

Entry	3	R^1	R^2	Residence time/min[b]	Processing rate/mmol min^{-1}[c]	Yield (%)[d]
1	**a**	Et	Ph	2	0.25	62
2	**b**	Et	*p*-C_6H_4Cl	2	0.25	52

[a] Reactions were carried out using a 0.1 M solution of **3** in PhMe–AcOH (5 : 1) in a stainless steel heating coil (5 mL) with a UNIQSIS FlowSyn™ operating at a flow rate of 2.5 mL min^{-1}. [b] Time of residence in the heated stainless steel reactor coil. [c] Rate of processing aminodienone **3** through the reactor, during continuous operation. [d] Isolated yield of pyridine **4** after aqueous work-up.

Mesoscale continuous processing under microwave heating

Finally, given the success of the microwave flow reactions in providing efficient conversion to the corresponding pyridines, efforts were made to improve the processing rate and transfer the established parameters to mesoscale production under continuous flow processing. For this purpose, a multimode Milestone BatchSynth™ microwave synthesizer was operated under continuous flow processing using the FlowSynth™ platform. A solution (0.05 M) of aminodienone **3a** in toluene–acetic acid (5 : 1), diluted so as to avoid any problems of product precipitation, was passed through the microwave cavity at a flow rate of 1 L h^{-1} and heated to 100 °C under microwave irradiation using an initial power of 150 W (Scheme 2). At this flow rate, the residence time would be substantially longer (~12.5 min) but it was thought this would account for field and temperature inhomogeneities and would still deliver improved production rates. After aqueous work up, pyridine **4a** was isolated in 93% yield. Even with the increased dilution and longer residence time, this represented a substrate processing rate of 0.5 mmol min^{-1}, which was significantly higher than with any other platform.



Scheme 2 Mesoscale production of pyridine **4a** using a continuous flow microwave reactor.

Experimental

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Unless otherwise stated, reactions were performed under an atmosphere of dry nitrogen. Microwave irradiation experiments were performed under an atmosphere of air using a self-tunable CEM Discover® focused monomodal microwave synthesizer, operating in batch, stop-flow Voyager® or continuous flow mode, MILESTONE BatchSynth™ microwave synthesizer or on the MILESTONE FlowSynth™ platform at the given temperature, measured using the instrument's in-built temperature measuring device, by varying the irradiation power (initial power given in parentheses). Conductive heating flow reactions were performed using a Syrris AFRICA® microreactor or the UNIQSIS FlowSyn™ using the instrument's in-built temperature measurement. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck

Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm). *In vacuo* refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

Fully characterized compounds were chromatographically homogeneous. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infra-red spectra were recorded in the range 4000–600 cm^{-1} on a Perkin–Elmer 1600 series FTIR spectrometer using KBr disks or as a nujol mull for solid samples and thin films between NaCl plates for liquid samples and are reported in cm^{-1}. NMR spectra were recorded using a Bruker DPX 400 instrument or 500 Avance instrument operating at 400 MHz for ^1H spectra and 100 or 125 MHz for ^{13}C spectra; *J* values were recorded in Hz and multiplicities were expressed by the usual conventions. Low resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument using atmospheric pressure chemical ionization (APcI) unless otherwise stated. High resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, UK using the ionization methods specified.

General procedure for the synthesis of aminodienones by Michael addition of enamine 1 and ethynyl ketone 2[23,24]

A solution of enamine **1** (5.8 mmol) and ethynyl ketone **2** (7.5 mmol) in EtOH (80 mL) was stirred at 50 °C for 1–7 h, cooled and evaporated *in vacuo* to give the crude aminodienone **3**.

(2*Z*,4*E*)-2-Amino-3-ethoxycarbonyl-6-phenylhexadien-6-one (3a). Obtained as a yellow solid, mp 159–161 °C (light petroleum–EtOAc) (lit.[29] mp 164 °C) (Found: MH^+, 260.1279. $C_{15}H_{18}NO_3$ [*MH*] requires 260.1281); R_f 0.38 (EtOAc–light petroleum, 4 : 1); IR (nujol)/cm^{-1} ν_{max} 3339, 1625, 1584, 1537, 1499, 1379, 1350, 1322, 1287, 1223, 1207, 1178, 1111, 1058, 1036, 1022, 982, 848, 707, 628; ^1H NMR (400 MHz; $CDCl_3$) δ 9.71 (1H, br s, NH*H*), 7.95 (2H, m, *o*-Ph*H*), 7.88 (1H, d, *J* 15.1, 4–H), 7.45 (3H, *m*,*p*-Ph*H*), 7.42 (1H, d, *J* 15.1, 5–H), 5.73 (1H, br s, N*H*H), 4.22 (2H, q, *J* 7.1, OCH_2CH_3), 2.31 (3H, s, CH_3), 1.37 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 191.0 (C), 169.8 (C), 166.7 (C), 141.0 (CH), 139.7 (C), 131.8 (CH), 128.3 (CH), 128.1 (CH), 115.8 (CH), 95.5 (C), 60.0 (CH_2), 22.6 (CH_3), 14.5 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 260 (MH^+, 100%), 243 (26), 214 (18).

(2*Z*,4*E*)-2-Amino-3-ethoxycarbonyl-6-(4-chlorophenyl)-hexadien-6-one (3b). Obtained as a yellow solid, mp 164–165 °C (light petroleum–EtOAc) (Found: MH^+, 294.0892. $C_{15}H_{17}{}^{35}ClNO_3$ [*MH*] requires 294.0891); R_f 0.51 (EtOAc–light petroleum, 4 : 1); IR (nujol)/cm^{-1} ν_{max} 3348, 1655, 1628, 1596, 1570, 1542, 1488, 1353, 1321, 1289, 1224, 1175, 1122, 1089, 1058, 1040, 1011, 976, 855, 823, 745, 717, 646, 588, 537, 501; ^1H NMR (400 MHz; $CDCl_3$) δ 9.68 (1H, br s, NH*H*), 7.86 (1H, d, *J* 15.0, 4–H), 7.86 (2H, app d, *J* 8.4, 2′,6′-Ph*H*), 7.35 (2H, app d, *J* 8.4, 3′,5′-Ph*H*), 7.31 (1H, d, *J* 15.0, 5–H), 5.81 (1H, br s, N*H*H), 4.23 (2H, q, *J* 7.1, OCH_2CH_3), 2.27 (3H, s, CH_3), 1.35 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 189.6 (C), 169.7 (C), 167.0 (C), 141.6 (CH), 138.1 (C), 138.0 (C), 129.5 (CH), 128.6 (CH), 115.1 (CH), 95.6 (C), 60.1 (CH_2), 22.6 (CH_3), 14.5 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 296 (MH^+, 32%), 294 (MH^+, 100), 277 (17), 260 (18).

(2*Z*,4*E*)-2-Amino-3-ethoxycarbonylheptadien-6-one (3c). Obtained as a pale yellow solid, mp 135–137 °C (light petroleum–EtOAc) (lit.[23] mp 135 °C) (Found: MH^+, 198.1127. $C_{10}H_{16}NO_3$ [*MH*] requires 198.1125); R_f 0.29 (EtOAc–light petroleum, 4 : 1); IR (nujol)/cm^{-1} ν_{max} 3332, 1648, 1554, 1489, 1443, 1352, 1310, 1277, 1200, 1183, 1111, 1023; ^1H NMR (400 MHz; $CDCl_3$) δ 9.62 (1H, br s, NH*H*), 7.52 (1H, d, *J* 15.4, 4–H), 6.49 (1H, d, *J* 15.4, 5–H), 5.53 (1H, br s, N*H*H), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 2.22 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.27 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.4 (C), 169.3 (C), 165.9 (C), 139.2 (CH), 121.1 (CH), 94.5 (C), 60.1 (CH_2), 28.2 (CH_3), 22.8 (CH_3), 14.2 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 198 (MH^+, 100%), 180 (57).

(2*Z*,4*E*)-2-Amino-3-*tert*-butoxycarbonylheptadien-6-one (3d). Obtained as a pale yellow solid, mp 142–144 °C (light petroleum–EtOAc) (Found: MH^+, 226.1441. $C_{12}H_{20}NO_3$ [*MH*] requires 226.1438); R_f 0.26 (light petroleum–EtOAc, 1 : 1); IR (nujol)/cm^{-1} ν_{max} 3344, 1654, 1543, 1488, 1442, 1360, 1321, 1289, 1221, 1161, 1103, 1031; ^1H NMR (400 MHz; $CDCl_3$) δ 9.65 (1H, br s, NH*H*), 7.47 (1H, d, *J* 15.3, 4–H), 6.41 (1H, d, *J* 15.3, 5–H), 5.41 (1H, br s, N*H*H), 2.19 (3H, s, CH_3), 2.20 (3H, s, CH_3), 1.46 (9H, s, CMe_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.2 (C), 169.6 (C), 165.3 (C), 139.5 (CH), 121.3 (CH), 96.0 (C), 81.1 (C), 28.3 (CH_3), 28.2 (CH_3), 22.4 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 226 (MH^+, 98%), 209 (56), 170 (83), 153 (100).

General procedure for the microwave-assisted cyclodehydration of aminodienone 3 in a sealed tube

A solution of aminodienone **3** (0.31 mmol) in toluene–glacial acetic acid (5 : 1; 3 mL) was irradiated for 2 min (hold time) at 100 °C in a CEM Discover® microwave synthesizer at an initial power of 150 W. The solution was allowed to cool and partitioned between saturated aqueous $NaHCO_3$ (25 mL) and EtOAc (25 mL). The aqueous layer was further extracted with EtOAc (2 × 15 mL) and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the corresponding pyridine **4**.

General procedure for the cyclodehydration of aminodienone 3 in a microreactor

A solution of aminodienone **3** (0.1 M) in toluene–glacial acetic acid (5 : 1) was passed through a microfluidic reaction chip, heated at 100 °C, for 4 min using a Syrris AFRICA® microreactor assembled with a pressurization module, reagent feed module, reagent injection module, chip reactor module and product collection module. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, extracted with EtOAc (3 × 30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the corresponding pyridine **4**.

General procedure for the cyclodehydration of aminodienone 3 in a multimode microwave batch reactor

A solution of aminodienone **3** (0.1 M) in toluene–glacial acetic acid (5 : 1) was irradiated at 100 °C for 2 min (hold time) in a pressure rated Teflon vessel (60 or 100 mL) using a multimodal MILESTONE BatchSynth™ microwave synthesizer at an initial

power of 150 W. After cooling, the reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the corresponding pyridine **4**.

General procedure for the microwave-assisted cyclodehydration of aminodienone 3 in a stop-flow reactor

A solution of aminodienone **3** (0.05 or 0.1 M) in toluene–glacial acetic acid (5 : 1) was irradiated at 100 °C in a borosilicate glass vessel (80 mL) using a CEM Discover® microwave synthesizer operating in stop-flow Voyager® mode at an initial power of 150 W. After cooling, the reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the corresponding pyridine **4**.

General procedure for the microwave-assisted cyclodehydration of aminodienone 3 in a glass tube reactor

A glass tube flow cell (10 mL) filled with sand (~12 g) was primed with toluene–glacial acetic acid (5 : 1) at a flow rate of 1.5 mL min^{-1}, irradiated at an initial power of 200 W and stabilized at 100 °C. A flask was charged with a solution of aminodienone **3** (0.31 mmol) in toluene–glacial acetic acid (5 : 1, 3 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, extracted with EtOAc (3 × 30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the corresponding pyridine **4**.

General procedure for the cyclodehydration of aminodienone 3 in a stainless steel conductive heating flow reactor

A solution of aminodienone **3** (0.1 M) in toluene–glacial acetic acid (5 : 1) was passed through a stainless steel coil reactor (5 mL) of a UNIQSIS FlowSyn™ at 100 °C and a flow rate of 2.5 mL min^{-1}. The outflow from the collection valve was quenched in a stirred solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the corresponding pyridine **4**.

Mesoscale production of pyridine 4a using a continuous flow microwave reactor

A solution (0.05 M) of aminodienone **3a** (7.90 g, 30.5 mmol) in toluene–glacial acetic acid (5 : 1) (650 mL) was irradiated at 100 °C using a MILESTONE BatchSynth™ microwave synthesizer at an initial power of 150 W operating under continuous flow processing on the FlowSynth™ platform at a flow rate of 1 L h^{-1}. The outflow was cooled using the system's water-cooling jacket and quenched immediately in a stirred solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give pyridine **4a** (6.95 g, 94%) as a yellow solid, mp 41–43 °C (MeOH) (lit.[20a] mp 44 °C) (found: MH^+, 242.1179; $C_{15}H_{16}NO_2$ [*MH*] requires 242.1181); R_f 0.45 (light petroleum–ethyl acetate, 4 : 1); IR (KBr) ν_{max} 2995, 2905, 2346, 1715, 1581, 1476, 1270, 1091, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* 8.2), 7.98 (2H, m), 7.55 (1H, d, *J* 8.2), 7.44–7.35 (3H), 4.32 (2H, q, *J* 7.1), 2.84 (3H, s), 1.35 (3H, t, *J* 7.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6 (C), 159.9 (C), 159.1 (C), 139.4 (CH), 138.4 (C), 129.7 (CH), 128.8 (CH), 127.4 (CH), 123.7 (C), 117.4 (CH), 61.2 (CH_2), 25.2 (CH_3), 14.3 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 242 (MH^+, 100%), 214 (10).

Ethyl 2-methyl-6-(4-chlorophenyl)pyridine-3-carboxylate (4b). Obtained as a pale yellow solid, mp 46–47 °C (aq. EtOH) (lit.[24] mp 47–48 °C) (Found: MH^+, 276.0787. $C_{15}H_{15}{}^{35}ClNO_2$ [*MH*] requires 276.0786); R_f 0.68 (light petroleum–EtOAc, 1 : 1); IR (nujol)/cm^{-1} ν_{max} 1725, 1588, 1497, 1465, 1362, 1258, 1185, 1163, 1091, 1015, 899, 828, 784, 742, 701; ^1H NMR (400 MHz; $CDCl_3$) δ 8.31 (1H, d, *J* 8.0, 4–H), 7.98 (2H, app d, *J* 8.4, 2′,6′-Ph*H*), 7.49 (1H, d, *J* 8.0, 5–H), 7.43 (2H, app d, *J* 8.4, 3′,5′-Ph*H*), 4.42 (2H, q, *J* 7.1, OCH_2CH_3), 1.63 (3H, s, CH_3), 1.37 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.4 (C), 160.8 (C), 158.2 (C), 139.1 (CH), 134.2 (C), 136.0 (C), 128.9 (CH), 128.3 (CH), 124.4 (C), 117.8 (CH), 60.7 (CH_2), 24.6 (CH_3), 14.5 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 278 (MH^+, 33%), 276 (MH^+, 100), 250 (18), 248 (56).

Ethyl 2,6-dimethylpyridine-3-carboxylate (4c). Obtained as a pale yellow solid, mp 59–60 °C (EtOH) (lit.[20a] mp 60 °C) (Found: MH^+, 180.1020. $C_{10}H_{14}NO_2$ [*MH*] requires 180.1019); R_f 0.44 (light petroleum–EtOAc, 1 : 1); IR (nujol)/cm^{-1} ν_{max} 1730, 1593, 1272, 1236, 1148, 1079, 770, 722; ^1H NMR (400 MHz; $CDCl_3$) δ 8.05 (1H, d, *J* 8.1, 4–H), 7.05 (1H, d, *J* 8.1, 5–H), 4.33 (2H, q, *J* 7.1, OCH_2CH_3), 2.78 (3H, s, CH_3), 2.52 (3H, s, CH_3), 1.34 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.9 (C), 161.5 (C), 159.0 (C), 138.3 (CH), 122.5 (C), 120.9 (CH), 61.8 (CH_2), 25.1 (CH_3), 24.4 (CH_3), 13.7 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 180 (MH^+, 95%), 152 (100), 134 (20).

***tert*-Butyl 2,6-dimethylpyridine-3-carboxylate (4d).** Obtained as a pale yellow oil[23] (Found: MH^+, 208.1329. $C_{12}H_{18}NO_2$ [*MH*] requires 208.1332); R_f 0.59 (light petroleum–EtOAc, 1 : 1); IR (film)/cm^{-1} ν_{max} 2925, 2850, 1721, 1598, 1464, 1377, 1281, 1177, 1140, 1083, 775, 722; ^1H NMR (400 MHz; $CDCl_3$) δ 7.94 (1H, d, *J* 8.0, 4–H), 6.89 (1H, d, *J* 8.0, 5–H), 2.71 (3H, s, CH_3), 2.44 (3H, s, CH_3), 1.56 (9H, s, CMe_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.9 (C), 161.2 (C), 158.4 (C), 139.3 (CH), 124.1 (C), 120.8 (CH), 82.0 (C), 27.9 (CH_3), 25.4 (CH_3), 24.8 (CH_3); MS (APcI) *m*/*z* (rel. intensity) 208 (MH^+, 10%), 152 (100), 134 (10).

Conclusions

The Bohlmann–Rahtz synthesis of 2,3,6-trisubstituted pyridines by cyclodehydration of the corresponding aminodienone was originally reported using traditional conductive heating methods. Following the discovery that this process can be facilitated using microwave irradiation, heating these precursors in the presence of a Brønsted acid gives excellent yields of the product in a very short time without the need for chromatographic purification. Using a Syrris microreactor platform, optimum residence times were established for efficient reaction and these parameters transferred well to microwave-assisted batch, stop-flow and continuous flow regimes, as well as to continuous flow conductive heating apparatus. Differences in how the temperature of the reactor was measured, being either the internal or external temperature of the cell, gave small variations in the required residence time. Of the

apparatus investigated, microwave-assisted batch processes in a single-mode cavity were found mostly to be highly efficient and were transferred successfully to continuous stop-flow production in the Voyager system, continuous processing in the single-mode Discover system and batch processing in a multimode synthesizer on <4 mmol scale. Finally, through reaction dilution and small adjustments in residence time, this reaction was transferred successfully to mesoscale production using a continuous flow multimode microwave reactor. This shows that current technology does have the means to scale-up or scale-out microwave batch experiments and that the reaction parameters for the Bohlmann–Rahtz cyclodehydration reaction transfer reliably between different technology platforms for mesoscale production.

It is premature to say whether these same design rules hold for other systems and reactions of study. It could be anticipated that, in a similar fashion, discoveries made in microwave batch experiments, in particular for homogenous mixtures, will follow similar principles. One would expect the scale up of these methods would be relatively straightforward using a stop-flow microwave platform, a single- or multi-mode microwave flow reactor or a multimode batch reactor, providing with the latter that there was not much more than a ten-fold increase in scale. Continuous flow conductive heating platforms, on the other hand, operating on either micro- or mesoscale production, would seem to give rise to small but significant differences in the chemical efficiency of reaction, that one could attribute to variations in heating profile or temperature measurement. Whether these design rules hold for the scale up of heterogeneous processes, such as reactions over a catalyst bed, procedures with solid precipitation or crystallization or for the processing of slurries, is another matter entirely and one that will continue to provide significant challenges for continuous flow platforms and microwave-assisted synthesis for some time to come.

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