FlowSyn™ Application Note 15: Bohlmann-Rahtz Pyridine Synthesis[1,2]

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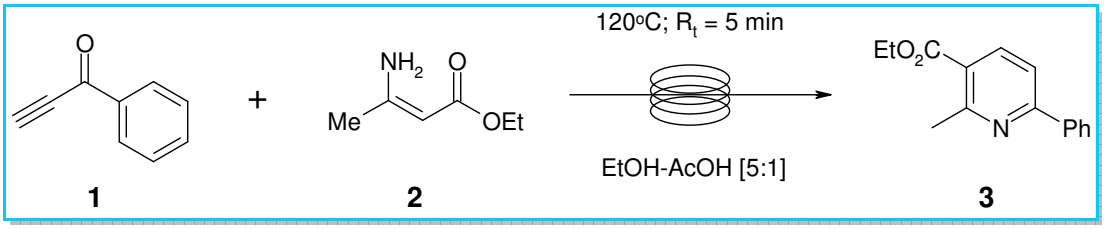

Method:

System solvent: EtOH–AcOH (5:1)
Stock solution A: 1-Phenyl-2-propyn-1-one **1**[3] (0.16 g, 1.23 mmol), ethyl 3-aminocrotonate **2** (0.2 mL, 1.6 mmol) in EtOH–AcOH (5:1) (12 mL).
Stock solution B: Empty.

FlowSyn was fitted with a 250 psi BPR.

a. Flow Reaction using FlowSyn™ 'Automated Experiment' Interface

1. FlowSyn™ was fitted with a 5 mL stainless steel (SS) tubing reactor, and the heating unit was tensioned to ensure optimal thermal contact.
2. The outflow from the collection valve was directed into a collection bottle containing a stirred solution of saturated aqueous $NaHCO_3$.
3. The selection valves were set to 'Reagent' and the reagent lines were primed.
4. The selection valves were set to 'Solvent' and the system was primed to remove all air bubbles.
5. The following flow parameters were entered into 'Setup Experiment'.

Reactors:	Coil	**Reaction time:**	5.00 min
Coil type:	Steel 5.0 mL	**Total Flow Rate:**	1 mL/min
Coil Temp:	120 °C	**Volume A:**	12 mL
Col. Temp:	0 °C	**Volume B:**	0 mL
Inlet A:	Bottle	**A:B Ratio:**	12:inf
Inlet B:	Bottle	**Post Collect:**	10 mL
Pre Collect:	2.0 mL	**Wash:**	5.0 mL

Total FlowSyn™ operation time = 38 min

6. By selecting 'Run Experiment', the FlowSyn™ equilibrated to the set temperature and then ran the flow reaction, before cleaning the system by flushing with system solvent ('Post Wash').
7. The collected outflow was extracted with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give **3** (0.25 g, 86%) as a yellow solid, mp 44–45 °C (Lit.[2] mp 44 °C).

b. Batch Reaction using Microwave Irradiation[4] in a CEM Discover®

A solution of 1-phenyl-2-propyn-1-one **1**[3] (40 mg, 0.31 mmol), ethyl 3-aminocrotonate **2** (52 mg, 0.40 mmol) in EtOH–AcOH (5:1) (3 mL) was irradiated for 5 min at 120 °C in a CEM Discover® microwave synthesizer at an initial power of 90 W (which was moderated to maintain constant temperature, as determined by the in-built IR sensor). The solution was allowed to cool in a stream of compressed air, evaporated *in vacuo* and partitioned between a saturated aqueous solution of $NaHCO_3$ (25 mL) and EtOAc (25 mL). The aqueous layer was further extracted with EtOAc (2 x 15 mL) and the organic extracts were combined, washed with brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude product. Purification by column chromatography on silica, eluting with light petroleum–ethyl acetate (4:1), gave **3** (64 mg, 86%) as a pale yellow solid, with identical physical and spectroscopic properties.[3]

c. Flow Reaction using Microwave Irradiation[5] in a CEM Discover®

A solution of 1-phenyl-2-propyn-1-one **1**[3] (40 mg, 0.31 mmol), ethyl 3-aminocrotonate **2** (52 mg, 0.40 mmol) in EtOH–AcOH (5:1) (3 mL) was irradiated at 120 °C in a pressure rated glass tube (10 mL) at a flow rate of 0.6 mL min^{-1} in a CEM Discover® microwave synthesizer pre-charged at an initial power of 120 W (which was moderated to maintain constant temperature, as determined by the in-built IR sensor). The flow cell was cleaned by washing with further batches of EtOH–AcOH (5:1) and the collected outflow was poured immediately into a stirred solution of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated *in vacuo* to give the crude product. Purification by column chromatography on silica, eluting with light petroleum–ethyl acetate (4:1), gave **3** (56 mg, 76%) as a pale yellow solid, with identical physical and spectroscopic properties.[3]

Conclusions:

Use of the FlowSyn™ faithfully reproduced the outcome of a batch reactor or flow reactor with continuous processing using microwave dielectric heating, offering an alternative means to scale up these microwave-assisted procedures for the Bohlmann-Rahtz pyridine synthesis.

Supplementary Information:

Ethyl 2–methyl–6–phenylpyridine–3–carboxylate 3[2,3]

HRMS: Found MH^+, 242.1176. $C_{15}H_{16}NO_2$ [MH^+] requires 242.1176.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.20 (1H, d, *J* 8.2), 7.98 (2H, m), 7.56 (1H, d, *J* 8.2), 7.39 (3H), 4.32 (2H, q, *J* 7.1), 2.85 (3H, s), 1.35 (3H, t, *J* 7.1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 167.0 (C), 160.3 (C), 159.4 (C), 139.8 (CH), 139.0 (C), 130.1 (CH), 129.2 (CH), 127.8 (CH), 124.1 (C), 117.9 (CH), 61.6 (CH_2), 25.6 (CH_3), 14.7 (CH_3).

IR (nujol) 1717, 1581, 1277, 1090, 1022.

MS (EI): *m/z* (rel. intensity) 241 (90, $M^{\cdot+}$), 213 (50), 196 (100), 168 (65), 141 (35), 115 (25), 77 (8).

References

1. For an account of the Bohlmann-Rahtz reaction, see *The Bohlmann–Rahtz pyridine synthesis: from discovery to applications*, Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459.
2. Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
3. Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.
4. For the use of a microwave irradiation to promote the Bohlmann-Rahtz reaction, see *A new one-step synthesis of pyridines under microwave-assisted conditions*, Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331
5. For the use of a microwave flow reactor in the Bohlmann-Rahtz reaction, and for details of the apparatus set up, see Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. *J. Org. Chem.* **2005**, *70*, 7003