Continuous Flow Microwave Chemistry

Introduction

Microwave chemistry has long been known to accelerate chemical transformations and provide a simple means to access more rigorous reaction conditions. Flow chemistry has demonstrated similar benefits, with the added bonus of being able to increase the reaction scale simply by prolonging the reaction. The combination of the two technologies opens the door to a quick optimization and easy scale-up of virtually unlimited types of chemical transformations. The Discover® 2.0 microwave synthesizer provides the means to perform both types of reactions simultaneously or sequentially within the same system.

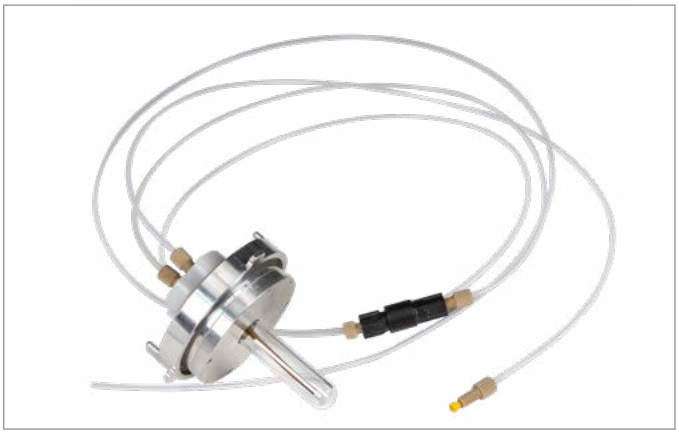


Figure 1: 10 mL Flow Cell for Discover 2.0 Microwave Synthesizer

Heck Reaction

The ability to form C-C bonds through transition metal catalyzed reactions has proven to be an invaluable tool for the synthetic chemist.[1] The scalability of these transformations has provided significant benefit to the pharmaceutical industry in particular.[2] While performing reactions at elevated temperatures and pressures conventionally often requires the design of specialized equipment, the use of a microwave reactor allows simple and safe access to harsh reaction conditions. Batch microwave methods are restricted in scale by the size of the microwave cavity itself, however, the ability to perform microwave reactions in flow provides the same advantages as microwave chemistry with the ability to increase the scale.

Price et al. have demonstrated the efficiency of the Heck reaction in flow using low loadings of $Pd(OAc)_2$ and conventional heating.[3] Translation of this protocol to a microwave method for both batch and flow methods allowed for fast and convenient synthesis of the Heck coupled product.

Procedure

In the batch reaction, all reagents were combined in a 10 mL microwave vial and irradiated for 5 minutes at 190 °C using 175 W of power. Following completion, the reaction was purified using flash column chromatography (20:1 hexanes : EtOAc).

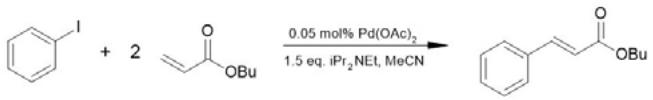


Table 1: Heck Reagents Required

Reagent	Batch	Flow
Iodobenzene	0.101 g	2.02 g
Butyl acrylate	0.127 g	2.54 g
$Pd(OAc)_2$	0.06 mg	1.2 mg
DIPEA	0.096 g	1.92 g
MeCN	1 mL	20 mL

In the flow reaction, the flow vessel was loaded with pure acetonitrile and heated to 190 °C using 230 W of power, at which time the reaction mixture was added to an Erlenmeyer flask and pumped through the microwave using an HPLC pump at a flow rate of 1.0 mL/minute. Once the entire solution had been pumped through the flow vessel, it was flushed with acetonitrile. Following completion, the reaction was purified by flash column chromatography (20:1 hexanes : EtOAc).

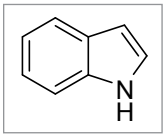
Table 2: Heck Coupling Conditions

Mode	Temperature	Time	Scale	Isolated Yield
Batch	190 °C	5 minutes	0.5 mmol	89%
Flow	190 °C	30 minutes	10 mmol	91%

Results

Use of microwave heating allowed access to a temperature of 190 °C, well above the boiling point of acetonitrile. This increased temperature resulted in a pressure of nearly 200 psi during the batch reaction. Despite these forcing conditions, the reaction proved suitable for synthesis in flow, providing a modest increase in yield with a 20-fold increase in scale.

Fisher Indole Synthesis



indole

The indole functionality, an aromatic heterocyclic compound consisting of a benzene ring fused to a pyrrole ring, is found in several biologically relevant compounds.[4] Synthesis of these compounds can be performed using several different approaches, including the Fisher Indole Synthesis.

This approach, developed in 1883, involves reaction of a phenylhydrazine derivative with an aldehyde or ketone under Brønsted or Lewis acidic conditions. Fisher Indole Synthesis often requires elevated temperatures and pressures, making its microwave assisted synthesis particularly attractive. The benefit of microwave assisted synthesis has recently been applied to this transformation using a specially designed flow reactor.[5] Conversion of this method to both batch and flow synthesis on CEM's Discover 2.0 microwave synthesizer provided the desired indole in high yield.

Procedure

In the batch reaction, reagents were loaded into a 10 mL microwave vial equipped with a stir bar. The solution was heated to 210 °C for 3 minutes using 200 W of power. After cooling, the reaction was poured into 3 mL of cold water and the product isolated by suction filtration.

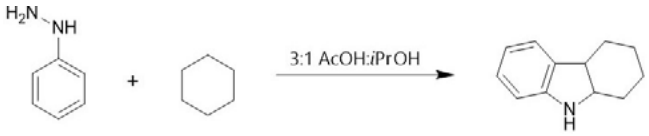


Table 3: Fisher-Indole Reagents Required

Reagent	Batch	Flow
Phenylhydrazine	0.216 g	2.16 g
Cyclohexanone	0.216 g	2.16 g
Acetic Acid	1.5 mL	15 mL
isopropanol	0.5 mL	5 mL

In the flow reaction, the flow vessel was loaded with a 3:1 mixture of acetic acid : isopropanol and heated to 210 °C using 225 W of power. Upon reaching temperature, the reaction solution was added to an Erlenmeyer flask and pumped through the microwave using an HPLC pump at a flow rate of 2.5 mL/minute. Once the entire solution had been pumped through the flow vessel, it was flushed with the solvent mixture.

Upon cooling, the reaction mixture was poured into 100 mL of ice water and the product isolated by suction filtration.

Table 4: Fisher-Indole Coupling Conditions

Mode	Temperature	Time	Scale	Isolated Yield
Batch	210 °C	3 minutes	2 mmol	90%
Flow	210 °C	15 minutes	20 mmol	88%

Results

The use of microwave irradiation enabled the reaction to quickly attain 210 °C and up to 160 psi, in the case of the batch reaction. Both procedures generated the desired indole in good yields. The ability to quickly translate a batch reaction to a flow system has allowed for the large scale synthesis of the biologically important indole framework.

Conclusion

The combination of microwave and flow technologies has enabled the quick and easy synthesis, as well as subsequent upscaling of both Heck and Fisher Indole reactions in the Discover 2.0 microwave synthesizer. The use of a flow vessel with the same type of setup and in the same system as the batch reaction meant translating to a larger scale was as simple as using more starting materials and allowing the reaction to proceed for a longer period of time; no further optimization was required.

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[3] Cyr, P.; Deng, S. T.; Hawkins, J. M.; Price, K. E. *Org. Lett.* **2013**, 15, 4342.

[4] Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, 47, 491.

[5] Öhrngren, P.; Fardost, A.; Russo, F.; Schanche, J.-S.; Fagrell, M.; Larhed, M. *Org. Process Res. Dev.* **2012**, 16, 1053.

United States (Headquarters)
800-726-3331
704-821-7015
info@cem.com

France
33 (01) 69 35 57 80
info.fr@cem.com

Germany, Austria, Switzerland
(49) 2842-9644-0
info@cem.de

Ireland
+353 (0) 1 885 1752
info.ireland@cem.com

Italy
(39) 35-896224
info.srl@cem.com

Japan
+81-3-5793-8542
info@cemjapan.co.jp

United Kingdom
(44) 1280-822873
info.uk@cem.com

www.cem.com