Microwave Reaction Tutorial

Reaction Examples for the Teaching Laboratory

Biotage®

Microwave Reaction Tutorial

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Initiate Success in Chemical Education with Microwave Assisted Organic Synthesis

Microwave irradiation is a well-established method of increasing the reaction rate of chemical processes. By employing microwaves to generate high temperatures and pressures under carefully controlled conditions, chemistry that may have taken hours is routinely achieved in minutes.

Every year, more pharmaceutical and industrial laboratories make use of microwave assisted organic synthesis (MAOS) to trial new reactions and rapidly develop new molecules. However, university undergraduates rarely have the opportunity to gain hands-on experience in MAOS as teaching laboratories do not typically invest in such systems. Biotage is now bridging this gap by providing the innovative market-leading Biotage® Initiator+ systems specifically for teaching laboratories. Initiator+ allows students to gain experience with MAOS and to investigate a large number of reactions in a very short amount of time.

Pathfinder – Your Blueprint for Microwave Synthesis

Our Pathfinder reaction database puts a world of cited reactions at the user's fingertips. Pathfinder is a host of industrially relevant MAOS reactions accessible online to your students. Search for structures and find peer-reviewed papers that detail the synthesis conditions required, allowing you to contrast MAOS with traditional synthesis approaches.

Success in Chemical Education

Microwave synthesis provides an excellent method for vastly increasing the speed of chemical reactions in a safe and controllable way. In the educational environment, this means you can expose students to an unprecedented range of multi-step chemical reactions in a compressed timescale, making the most of available time in a busy teaching schedule. In addition, because reaction times are routinely less than five minutes, several student groups can share a single microwave instrument.

With increasing numbers of companies employing MAOS in their laboratories, students with experience in microwave synthesis are gaining knowledge directly relevant to the industrial world, giving them a head-start in their chemical careers.

Overcome the Time Hurdle

Chemical synthesis takes time. Many reactions need to run for several hours at the least, so fitting more than one reaction into a student's laboratory day is impractical. As a result, many of the most interesting chemical processes – such as the multi-step reactions that are mainstay of pharmaceutically-relevant small molecule drug design – are not accessible in university teaching laboratories. This means that new chemists are leaving academia without experience of the kinds of reactions and processes that are common in the chemical industry.

Microwave synthesis alleviates this problem. Using microwave assisted organic synthesis (MAOS), a reaction that might originally have taken hours can be reduced to a few minutes, with increased reaction efficiency and therefore compound purity at the same time. Using MAOS, multistep reactions become accessible, giving students the grounding in chemistry that industry values. Imagine being able to complete multi-step reactions in a single laboratory period rather than over a week or more.

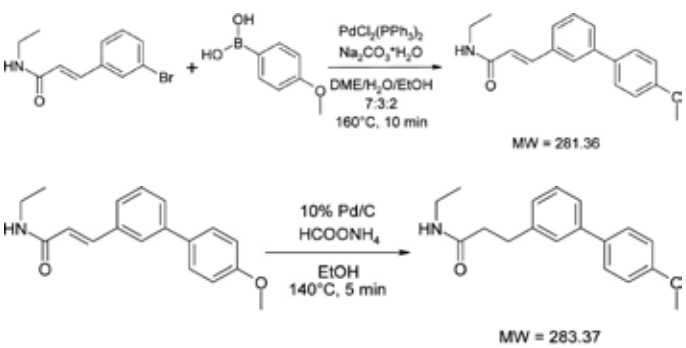


Figure 1. A typical multi-step reaction involving MAOS.

Self-directed Learning

In education, self-directed learning is described as a process whereby an individual takes the initiative either alone or in a group to understand their learning requirements, identify a path and create a strategy to achieve their learning goal. In chemical education within the teaching laboratory, self-directed learning is focused on creativity. In chemical synthesis such creativity can be described as an iterative cycle of developing synthetic routes, performing them, evaluating the results and then re-designing the experiment as necessary. Self-directed learning is seen as the most effective way of developing real understanding of a subject.

Unfortunately, in a many chemical teaching laboratories, chemical creativity has given way to textbook learning due to the time restrictions inherent in traditional organic synthesis. Students are often presented with a problem, the method to solve it, and a way to assess if they were successful. Students may also be told the conditions required for the synthesis, leaving little room for creativity. However, with MAOS, reactions times are shortened and so iterative experimental design can be performed and probed. This self-directed process is recognized as being one of the most effective methods of teaching, and produces chemists with a clear understanding of the requirements of the chemical industry.

Suitable Reaction Examples

The following pages contain example reactions that could be adapted for use in the teaching laboratory. Pathfinder, our microwave synthesis reference software, details thousands of reactions that make use of MAOS, which may serve as inspiration to educators seeking to develop new teaching laboratory courses that showcase industrially-important syntheses.

Figure 2. Biotage® Initiator+ is the standard tool for lab scale microwave assisted organic synthesis.

Oxidation of Alcohol to Ketone with MnO_2

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
1-Phenylethanol	122.17	2.5	1	305.4 mg	302 µL	
Manganese(IV)oxide (MnO_2)	86.94	3.0	1.2	260.8 mg		
1,2-Dichloroethane (DCE)	98.96				2.5 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add MnO_2, 1-phenylethanol, and then 1,2-dichloroethane. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

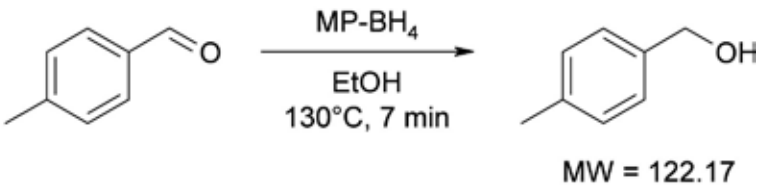
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS, with the best information from the absorbance at 208 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
15 minutes	200 °C	Normal	On

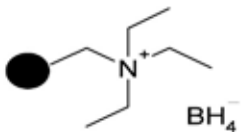
The reaction mixture was analyzed by HPLC-MS and showed a product purity of 70% at 208 nm. The mixture was filtered through Celite, the solid remains were washed with added DCE and the combined clear solutions were concentrated under reduced pressure and dried. A sample was analyzed by ^{1}H NMR, which showed 65% conversion from alcohol to ketone.

Reduction of Aldehyde to Alcohol with MP-BH_4



MW = 122.17

MP-BH_4, Polystyrene-supported Borohydride:



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
p-Tolualdehyde	120.15	1	1	120 mg	118 µL	
MP-BH_4 (3.2 mmol/g)		0.75	0.75	234 mg		
Ethanol (EtOH)	46.07				3.0 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add MP-BH_4, p-tolualdehyde and then ethanol. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

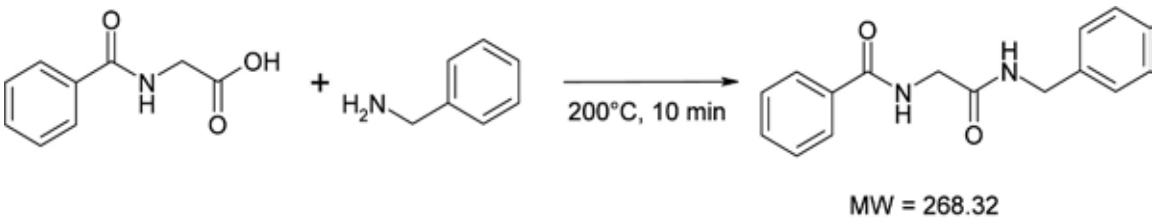
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 215 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
7 minutes	130 °C	High	On

The reaction mixture was analyzed by HPLC-MS and showed complete conversion at 215 nm. After the reaction, the solid material was filtered off and washed with dichloromethane. The combined solutions were concentrated under reduced pressure and dried to give the product in 95% yield and >97% purity according to HPLC-MS and ^{1}H NMR.

Solvent-Free Amide Bond Formation



MW = 268.32

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
Hippuric acid	179.18	2.75	1	492.0 mg		
Benzylamine	107.16	2.75	1	294.3 mg	300 µL	

To a 0.5–2 mL (conical) reaction vial containing a magnetic stir bar, add the hippuric acid and the benzylamine. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

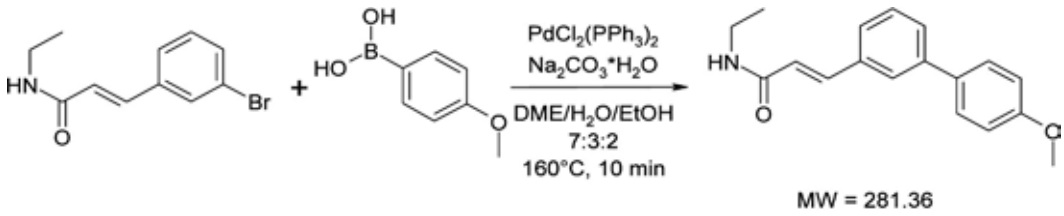
The resulting solid can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 254 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
10 minutes	200 °C	Very High	On

The reaction mixture was analyzed by HPLC-MS and showed a product purity of 69% at 254 nm. The product was purified by recrystallization from dichloromethane-methanol, giving a yield of 82% with 97% purity according to HPLC-MS, ^{1}H NMR and ^{13}C NMR.

2-Step Reaction 1: Suzuki reaction and Catalytic Transfer Hydrogenation



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
trans-3-Bromo-*N*-ethylcinnamamide	254.13	0.410	1	104.2 mg		
4-Methoxyphenylboronic acid	151.96	0.615	1.5	93.5 mg		
Bis(triphenylphosphine) palladium(II) chloride($(Ph_3P)_2PdCl_2$)	701.89	0.005	0.01	3.5 mg		
Sodium carbonate monohydrate (Na_2CO_3*H_2O)	124.00	0.615	1.5	76.3 mg		
Dimethoxyethanol/water/ethanol (DME/H_2O/EtOH) 7:3:2					2.5 mL (1.59:0.68:0.46)	

To a 2–5 mL reaction vial containing a magnetic stir bar, add *trans*-3-bromo-*N*-ethylcinnamamide, 4-methoxyphenylboronic acid, Na_2CO_3*H_2O and the catalyst. Finally, add the solvent mixture. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 254 nm.

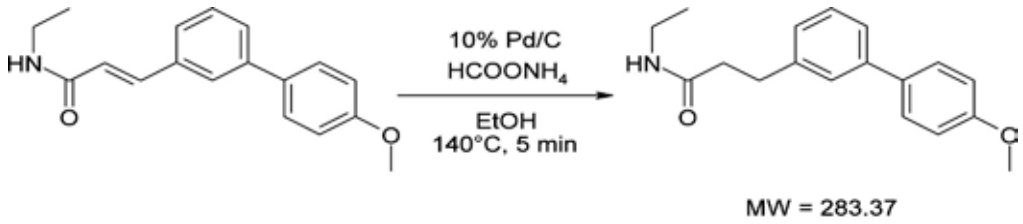
Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
10 minutes	160 °C	High	On

The reaction mixture was analyzed by HPLC-MS and showed a product purity of 86% at 254 nm. The reaction mixture was filtered, the solvent evaporated, and the residue was dissolved in dichloromethane and washed with first a saturated Na2CO3 water solution and then water. The organic layer was dried over Na_2SO_4 concentrated under reduced pressure and dried. The solid residue was re-crystallized from ethyl acetate yielding the product in 70% yield and >95% purity according to HPLC-MS and ^{1}H NMR.

This product is used in the subsequent step.

Step 2: Catalytic Transfer Hydrogenation



MW = 283.37

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
trans-3-(4-Methoxyphenyl)-*N*-ethylcinnamamide	281.36	0.3	1	84.4 mg		
10% Pd on charcoal (Pd/C) (0.94 mmol/g)		0.009	0.03	9.6 mg		
Ammonium formate ($HCOONH_4$)	63.06	1.5	5	94.6 mg		
Ethanol (EtOH)	46.07				2.5 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add *trans*-3-(4-methoxyphenyl)-*N*-ethylcinnamamide, ammonium formate and palladium on charcoal. Finally, add the ethanol. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

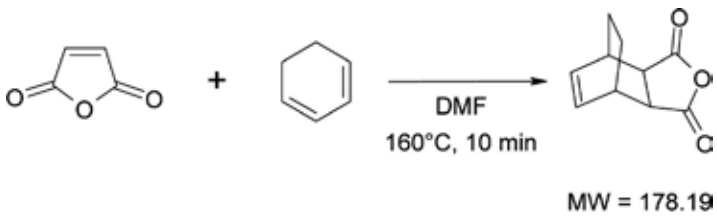
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 220 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
5 minutes	140 °C	Normal	Off

The reaction mixture was analyzed by HPLC-MS and showed a product purity of 95% at 220 nm. Filtration through Celite, washing of the solids with ethanol and removal of solvent and drying, gave the pure (›99% according to ^{1}H NMR) product in 98% yield.

2-Step Reaction 2: Diels-Alder Cycloaddition and Imide Formation



MW = 178.19

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
Maleic anhydride	98.06	1.250	1	122.6 mg		
1,3-Cyclohexadiene	80.13	1.875	1.5	150.2 mg	179 µL	
N,*N*-Dimethylformamide (DMF)	73.09				2.5 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add maleic anhydride, 1,3-cyclohexadiene and DMF. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened the reaction vial can be uncapped.

The reaction mixture can be monitored and analyzed by HPLC-MS with the best information from the absorbance at 200 nm.

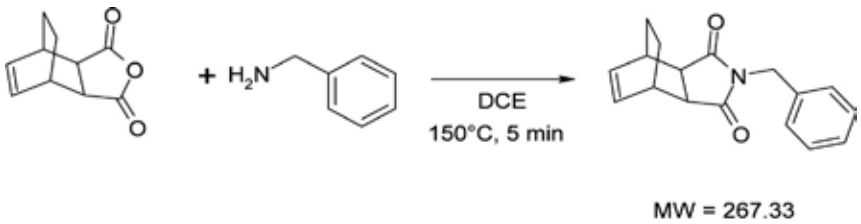
Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
10 minutes	160 °C	Normal	On

The isolated yield of the product was 99% and the purity 97% according to HPLC-MS and ^{1}H NMR.

After the reaction, the solvent and remaining cyclohexadiene must be evaporated (reduced pressure and high temperature are needed) before the following step.

Step 2: Imide formation



MW = 267.33

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
Diels-Alder product	178.19	1	1	178.2 mg		
Benzylamine	107.16	1	1	107.2 mg	109 µL	
1,2-Dichloroethane (DCE)	98.96				2.5 mL	

TTo a 2–5 mL reaction vial containing a magnetic stir bar, add the Diels-Alder product from Step 1, benzylamine and 1,2-dichloro-ethane. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

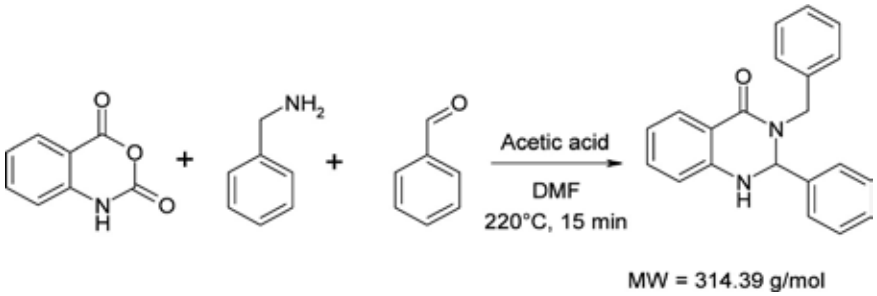
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 208 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
5 minutes	100 °C	Normal	Off

When the benzylamine is added at room temperature, a solid, consisting of ring-opened amide, precipitates. A clear solution was obtained after the heating. The solution was concentrated and dried. The product was obtained in 92% purity and quantitative yield.

3-Component Reaction



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
Isatoic anhydride	163.13	1.7	1	277 mg		
Benzylamine	107.16	1.7	1	182 mg	186 µL	
Benzaldehyde	106.12	1.7	1	180 mg	173 µL	
Acetic acid	60.05	1.7	1	102 mg	97 µL	
N,*N*-Dimethylformamide (DMF)	73.09				3.0 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add isatoic anhydride, benzylamine, benzaldehyde and acetic acid. Finally, add the DMF. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

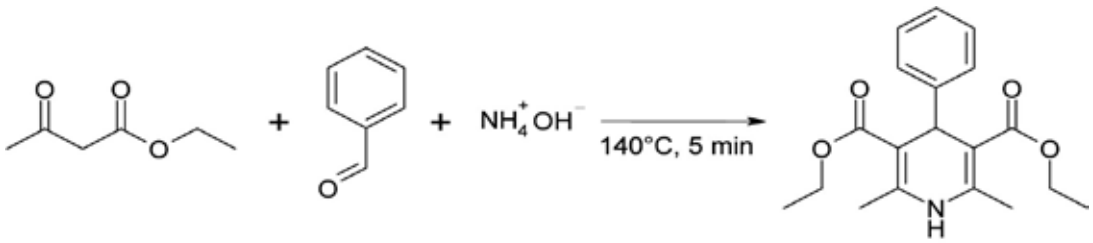
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 235 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
15 minutes	220 °C	Normal	On

The reaction mixture was analyzed by HPLC-MS and showed a product purity of 78% at 235 nm. The solvent of the reaction mixture was evaporated under reduced pressure and the residue adsorbed onto silica. The product was then purified using a Biotage automated flash chromatography system (SP4), using an ethyl acetate/heptane gradient. The pure product (>97% according to 1H NMR) was isolated in 70% yield.

Hantzsch, 3-Component Reaction



MW = 329.40

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
Ethyl acetoacetate	130.14	12.5	5	1.63 g	1.59 mL	
Benzaldehyde	106.12	2.5	1	265.3 mg	254 µL	
Ammonia (14.0 M NH_3 in H2O)	35.05	10	4		714 µL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add ethyl acetoacetate, benzaldehyde, and ammonia. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

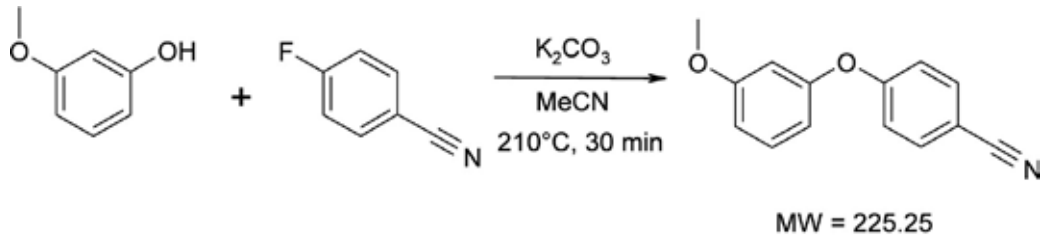
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 215 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time	Pre-stirring
5 minutes	140 °C	High	On	20 s

The reaction mixture was analyzed by HPLC-MS and showed a product purity of 75% at 215 nm. The water was evaporated and the residue was recrystallized from ethanol and water, giving the pure product (97% according to HPLC-MS) in 59% yield.

Nucleophilic Aromatic Substitution



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
3-Methoxyphenol	124.14	1	1	124.1 mg	108 µL	
4-Fluorobenzonitrile	121.11	1	1	121.1 mg		
Potassium carbonate (K_2CO_3)	138.20	1.2	1.2	165.8 mg		
Acetonitrile (MeCN)	41.05				3 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add potassium carbonate, 4- fluorobenzonitrile, 3-methoxyphenol, and acetonitrile. Cap the vial and heat it as described using Initiator. The pressure value needs to be set as well as the temperature, and the instrument will regulate the power so that it stays at the first value (210 °C or 20 bar) it reaches. This is because this reaction gives a high pressure in the vial, and if it's allowed to reach 22 bar, the system will be shut down in order not to risk the personal safety of the user. In order to do this, you need to go into advanced edit mode: Press advanced edit (either below the list of reactions on an instrument with a robot, or in the upper left corner of an instrument without a robot), and then in the new window, press Edit. In the new window that opens, you can set all the parameters you want to, including pressure. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

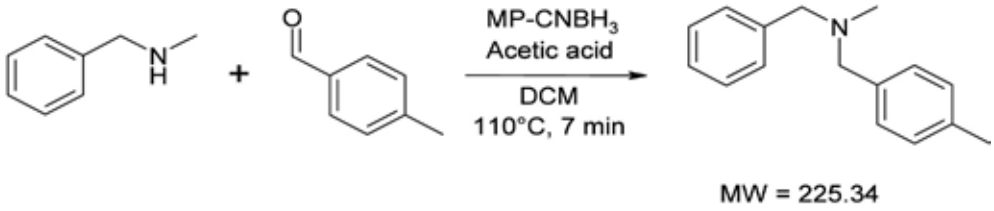
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 235 nm.

Instrument Settings

Time	Temperature	Pressure	Absorption level	Fixed Hold Time
30 minutes	210 °C	20 bar	Normal	Off

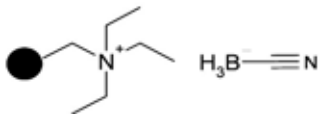
After heating, the reaction mixture was filtered and the solid material was washed with acetonitrile. The combined organic phases were concentrated under reduced pressure and the product was purified on a Biotage® SP4 using flash column chromatography on silica eluted with an ethyl acetate-heptane gradient (0-20% ethyl acetate). The product was obtained in 98% purity (according to HPLC-MS and ^{1}H-NMR) and 96% yield.

Reductive Amination



MW = 225.34

MP-$CNBH_3$, Polystyrene-supported Cyanoborohydride:



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
N-Benzylmethylamine	121.18	0.5	1	60.6 mg	65 µL	
p-Tolualdehyde	120.15	0.6	1.2	72.1 mg	71 µL	
MP-$CNBH_3$ (2.4 mmol/g)		1.25	2.5	520 mg		
Acetic acid	60.05	2.5	5	150 mg	143 mL	
Dichloromethane (DCM)	84.93				2.5 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add MP-$CNBH_3$, *N*-benzylmethylamine, acetic acid, p-tolualdehyde and dichloromethane. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

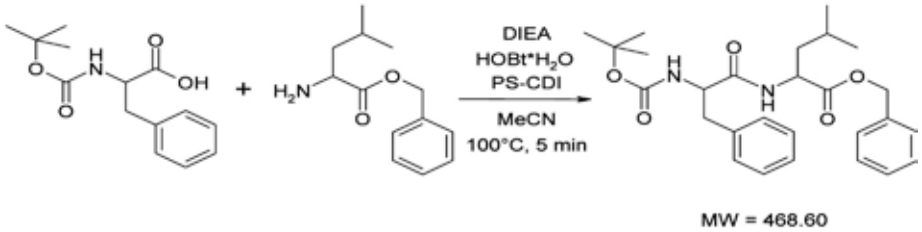
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 220 nm.

Instrument Settings

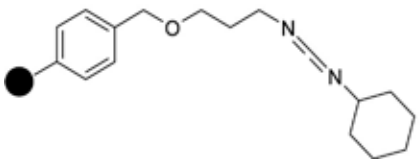
Time	Temperature	Absorption level	Fixed Hold Time
7 minutes	110 °C	Normal	Off

The solid phase material was filtered off and washed with DCM. The combined organic phases were washed, first with saturated NaHCO3, then with water, and finally dried with Na_2SO_4. After filtration to remove the drying agent and evaporation of the solvent, the product was purified by column chromatography on silica eluted with toluene-ethyl acetate 10:1. After purification, the yield was 95% and the purity was 96% according to HPLC-MS and ^{1}H NMR.

Peptide Coupling



PS-CDI, Polystyrene-supported Carbodiimide:



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
N-tert-Butoxycarbonylphenylalanine (Boc-Phe-OH)	265.31	1.845	1.3	489 mg		
Leucine benzyl ester (H-Leu-OBzl)	221.30	1.419	1	314 mg		
Diisopropylethylamine (DIEA)	129.25	1.845	1.3		316 µL	
1*H*-1,2,3-Benzotriazol-1-ol hydrate (HOBt*H_2O)	153.14	1.845	1.3	283 mg		
PS-CDI (1.35 mmol/g)		2.412	1.7	179 g		
Acetonitrile (MeCN)	41.05				1.3 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add Boc-Phe-OH, H-Leu-OBzl, HOBt*H_2O, PS-CDI and diisopropylethylamine. Finally, add the acetonitrile. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

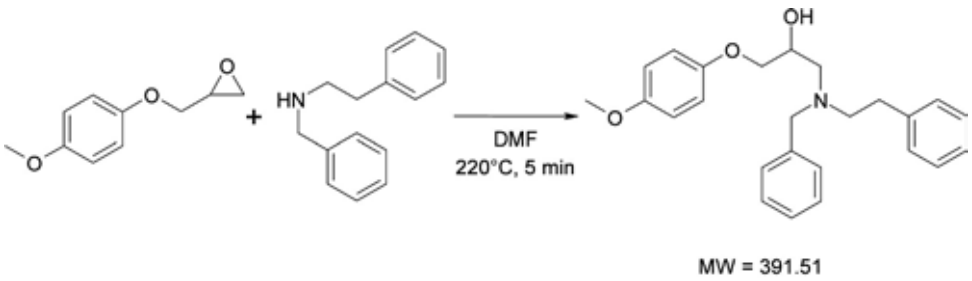
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 254 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time	Pre-stirring
5 minutes	100 °C	High	On	25 s

The solid material was filtered off and washed with dichloromethane. The combined organic phases were concentrated under reduced pressure, the remaining material re-dissolved in dichloromethane and washed; first with saturated $NaHCO_3$, then with water, and finally dried with Na_2SO_4. After filtration to remove the drying agent and evaporation of the solvent, the product was purified by silica column chromatography on a Biotage® SP4, using a heptane/ethyl acetate gradient.

Epoxide Opening



MW = 391.51

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
2,3-Epoxypropyl-4-methoxyphenyl ether	180.20	1.43	1.1	258 mg		
N-Benzyl-*N*-2-phenylethylamine	211.31	1.3	1	275 mg		
N,*N*-Dimethylformamide (DMF)	73.10				150 µL	

To a 0.5–2 mL (conical) reaction vial containing a magnetic stir bar, add 2,3-epoxypropyl-4-methoxyphenyl ether, *N*-benzyl-*N*-2-phenylethylamine and DMF. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

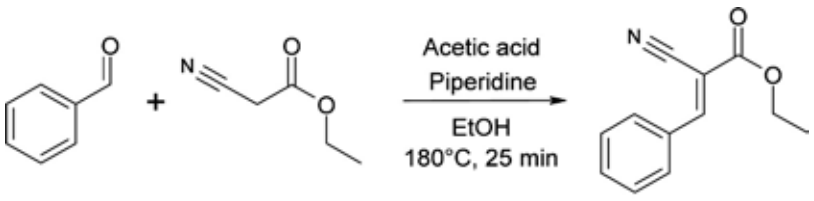
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 254 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
5 minutes	220 °C	Normal	Off

The reaction mixture was analyzed with HPLC-MS at 254 nm (72% purity) and the product was purified using preparative HPLC-MS.

Knoevenagel Condensation



MW = 201.23

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
Benzaldehyde	106.12	0.5	1	53.1 mg	51 µL	
Ethyl cyanoacetate	113.12	0.6	1.1	67.9 mg	64 µL	
Piperidine	85.15	0.1	0.2	8.5 mg	10 µL	
Acetic acid	60.05	0.1	0.2	6 mg	6 µL	
Ethanol (EtOH)	46.07				2.1 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add benzaldehyde, ethyl acetoacetate, piperidine, acetic acid, and ethanol. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

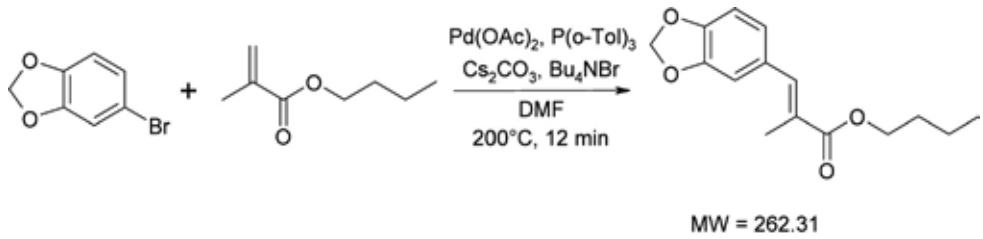
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 254 nm.

Instrument Settings

Time	Temperature	Absorption Level	Fixed Hold Time
25 minutes	180 °C	Normal	Off

The reaction mixture showed a product purity of 92% according to HPLC-MS at 254 nm. After the reaction, the solvent was removed from the reaction mixture and the residue was purified on a Biotage® SP4 by column chromatography on silica eluted with ethyl acetate-heptane, 1:2. The product was characterized by HPLC-MS and ^{1}H NMR.

Heck Coupling



MW = 262.31

Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
4-Bromo-1,2-(methylenedioxy) benzene	201.02	0.1	1	20.1 mg	12 µL	
Butyl methacrylate	142.20	0.15	1.5	21.3 mg	24 µL	
Palladium(II) acetate ($Pd(OAc)_2$)	224.49	0.004	0.04	0.9 mg		
Tri-ortho-tolylphosphine ($P(o\text{-}Tol)_3$)	304.37	0.1	1	3.0 mg		
Cesium carbonate (Cs_2CO_3)	325.82	0.12	1.2	39.1 mg		
Tetrabutylammonium bromide (Bu_4NBr)	322.37	0.1	1	32.2 mg		
N,*N*-Dimethylformamide (DMF)	73.10				1.12 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add cesium carbonate, palladium(II) acetate, tetrabutylammonium bromide and tri-*o*-tolylphosphine. Then add 4-bromo-1,2-(methylenedioxy)benzene, butyl methacrylate, and finally DMF. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

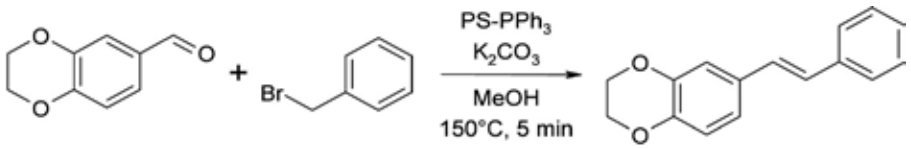
The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 254 nm.

Instrument Settings

Time	Temperature	Absorption Level	Fixed Hold Time
12 minutes	200 °C	Normal	Off

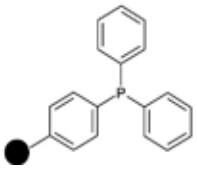
After the reaction, 3.0 mL water saturated with sodium chloride was added to the reaction mixture. It was then extracted with 5 x 2.5 mL ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered through Celite and concentrated on a rotary evaporator. The remaining mixture was purified on preparative TLC, ethyl acetate-heptane 1:10, giving the product in 83% yield.

Wittig Reaction



MW = 238.29

PS-PPh_3, Polystyrene-supported Triphenylphosphine:



Chemical Name	MW (g/mol)	Amount (mmol)	Equiv.	Theoretical Weight	Theoretical Volume	Real Weight or Volume
2,3-Dihydro-1,4-benzodioxane-6-carbaldehyde	164.16	0.3	1	49.2 mg		
Benzylbromide	171.04	1.2	4	205 mg	144 µL	
PS-Triphenylphosphine (1.8 mmol/g)		0.9	3	500 mg		
Potassium carbonate (K_2CO_3)	138.20	1.2	4	166 mg		
Methanol (MeOH)	32.04				2.1 mL	

To a 2–5 mL reaction vial containing a magnetic stir bar, add potassium carbonate, PS-triphenylphosphine, 2,3-dihydro-1,4-benzodioxane-6-carbaldehyde and benzylbromide. Finally, add the methanol. Make sure the solid material is within the solution; rinse the walls with the solvent if necessary. Cap the vial and heat it as described using Initiator. After the vial has been cooled to below 50 °C and the lid has opened, the reaction vial can be uncapped.

The reaction mixture can be monitored and analyzed by TLC or HPLC-MS with the best information from the absorbance at 280 nm.

Instrument Settings

Time	Temperature	Absorption level	Fixed Hold Time
5 minutes	150 °C	Normal	Off

The reaction was monitored by HPLC-MS at 280 nm and the product purity in the reaction mixture was 80%. The reaction mixture was filtered through a pad of silica and concentrated. The product was purified by preparative HPLC-MS.

Getting Started with Microwave Synthesis

Although microwave synthesis often renders unique results, the outcome is largely governed by a few, well-known phenomena. With knowledge about these phenomena, your benefits of using microwave synthesis will be greatly enhanced.

Creating Your Own Reactions

As well as the reactions listed here and the thousands of experiments listed on the Biotage Pathfinder software, chemists can create their own procedures. The most common method is to adapt existing synthetic procedures to make use of the microwave assistance. Below are listed some of the parameters to consider when adapting a synthetic route to make best use of the performance of a microwave system

Appropriate Conditions

Microwave synthesis is normally conducted under conditions that vary considerably from what is conventionally used in today's chemistry laboratories. Biotage microwave systems support a wide variety of reaction conditions accommodating different solvents, volumes, concentrations and phases, and are characterized by reproducible results.

Solvents

Common Solvents

Acetonitrile, DMF, and alcohols are commonly used for microwave-assisted organic synthesis.

Stick with Your Solvent

It might not be necessary to change from the reaction solvent specified for traditional chemistry conditions. First, try using the solvent that you would normally use.

Polar Solvents

Polar solvents (e.g. DMF, NMP, DMSO, methanol, ethanol, and acetic acid) work well with microwaves due to their polarity. Set the absorption level to Normal or High when using polar solvents.

Non-polar Solvents

Non-polar solvents (e.g. toluene, dioxane, and THF) can be heated more efficiently if other components in the reaction mixture respond to microwave energy, i.e. if the reaction mixture contains either polar reactants or ions (see ionic liquids below). When using less polar solvents, more concentrated reaction mixtures might be preferable. Set the absorption level to Low when using nonpolar solvents.

Ionic Liquids

Ionic liquids consist entirely of ions and therefore absorb microwave irradiation very efficiently. They also have low vapor pressure, further enhancing their suitability. Ionic liquids dissolve in a wide range of organic solvents and can therefore be used to increase the microwave absorption of low-absorbing reaction mixtures. Set the absorption level to Very High when using ionic liquids.

Volume

Do not exceed or fall below the microwave vial's specified volume range. Too low a volume will give an incorrect temperature measurement; while too high a volume does not leave sufficient head space for pressure build-up. When using low-absorbing or non-polar solvents, e.g. toluene and dioxane, always fill the microwave vial to the specified maximum volume.

Concentration

The concentration depends on the type of chemistry that is performed. A unimolecular reaction is independent of concentration and can be performed in very dilute solutions. Bi- or tri-molecular reactions on the other hand are highly dependent on the concentration; a higher concentration gives a faster reaction. The maximum obtainable concentration is dependent on the properties of the substrates and reagents as well as the properties of the solvent(s) used.

Phase

Different phases can be used, i.e. solution phase, solid phase, solid supported reagents, scavenger resins, and solvent free reactions.

Temperature

Reactions can be performed in a temperature range between 40 °C and 250 °C (Initiator) or 40 °C and 300 °C (Initiator+). Optimally the used reaction temperature should be as high as substrates and products allow before they start decomposing or as high as the reaction solvent allows, whichever is lowest.

Pressure

The reactions can safely be performed at pressures of up to 20 bar (Initiator) or 30 bar (Initiator+). If the pressure in a microwave vial becomes higher, the heating is automatically stopped and cooling begins. For an indication of the expected pressure of a reaction, please use a solvent table or the vapor pressure calculator at www.biotagepathfinder.com.

Additional reactions can be found in the reference book *Microwave Assisted Organic Synthesis*, Edited by J.P. Tierney and P. Lidström.

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For details on our academic starter packages visit www.biotage.com.

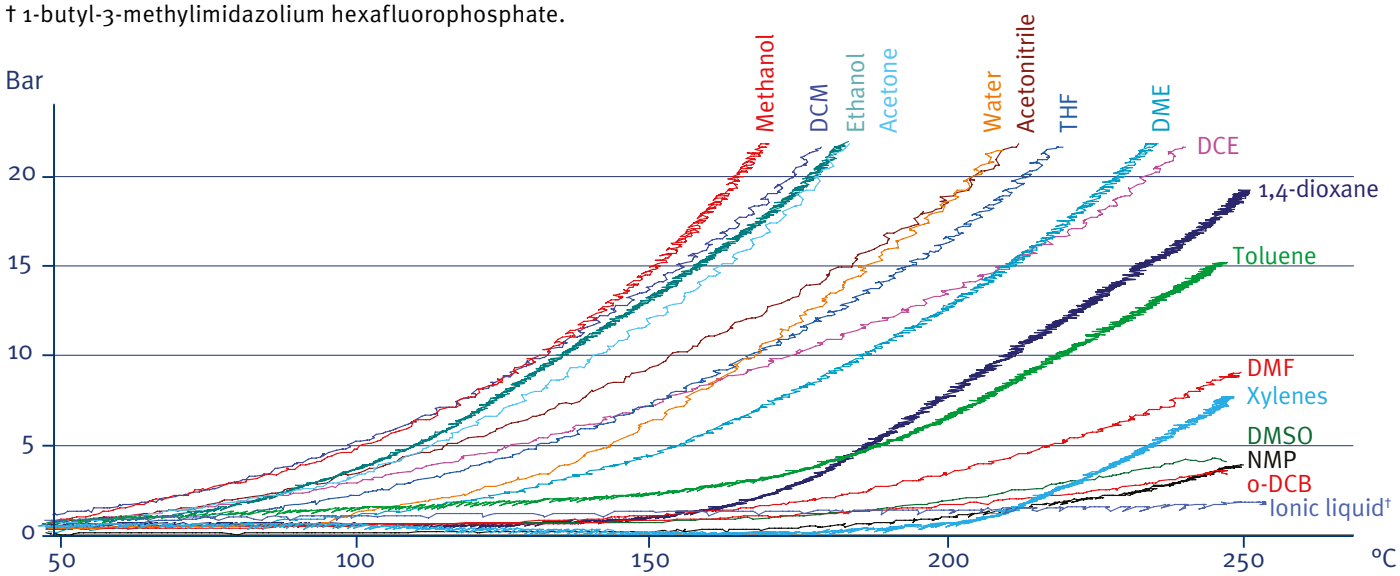
Solvent Boiling Points

To show the responses of various solvents to microwave irradiation, we measured the temperature and pressure of pure solvents during irradiation in an Initiator system. 5 ml solvent was heated in a 2-5 ml microwave vial, and the attained time, temperature, and pressure were noted when 20 bar or 250°C was reached. Temperature was set to 250°C and Absorption Level to Normal, unless otherwise indicated.

Solvent (Volume = 5 ml)	Boiling Point (1 atm) (°C)	Time (seconds)	Temperature (°C)	Pressure (bar)
1-methyl-2-pyrrolidinone (NMP)	202	83	250	4.5
1,2-dichloroethane (DCE)	83	69	240	20
1,2-dimethoxyethane (DME)*	85	166	233	20
1,4-dioxane*	100	628	250	18
Acetone*	56	273	179	20
Acetonitrile	81	45	207	20
Dichloromethane (DCM)	40	67	176	20
Dimethylsulfoxide (DMSO)	189	44	250	3.5
Ethanol*	78	58	180	20
Ionic liquid†	n/a	71	250	0.8
Methanol*	65	85	167	20
N,N-dimethylformamide (DMF)	153	68	250	8.9
o-dichlorobenzene (*o*-DCB)	180	63	250	2.3
Tetrahydrofuran (THF)*	65	94	215	20
Toluene*	111	488	250	15.2
Water (deionized)*	100	66	205	20
Xylenes*	137	459	250	7.7

* These solvents were heated using the Low absorption setting. The time stated is approximate, large variations can occur for low-absorbing solvents.

† 1-butyl-3-methylimidazolium hexafluorophosphate.



Biotage® Initiator+

Microwave Synthesizer

Rapid, Microwave-Assisted Organic Synthesis for Processing and Method Development

Biotage® Initiator+ represents a new generation of instruments for organic, medicinal, materials, nano and polymer chemistry professionals. It is an upgradable and reliable platform for chemists to make great discoveries. The Initiator+ is a flexible system that utilizes all Biotage vials, from 0.2 to 20 mL, in any order or combination, at any time without system modifications, delivering great flexibility and direct scale-up from milligrams to grams.

Initiator+ can also be upgraded with automation solutions to achieve higher throughput to save time and cost. Higher temperatures and pressures of up to 300 °C and 30 bar open new possibilities to perform difficult reactions. Even solvents with low boiling points can be run at higher temperatures. This allows for more flexibility in choosing a solvent.

Learn more at www.biotage.com.

Biotage® Initiator+ is a compact, safe and reliable microwave synthesizer for organic chemistry. Contact your Biotage representative to learn more.

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Biotage is a worldwide supplier of instruments and accessories designed to facilitate the work of laboratory chemists. With our deep knowledge of the industry, academic contacts and in-house R&D teams, we can deliver the best solutions to your challenges. We take great pride in our flexibility and ability to meet our customer's individual needs. With strong foundations in both analytical and organic chemistry, we can offer the widest range of solutions available on the market.

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