Ultrasonic or Microwave Modified Continuous Flow Chemistry for The Synthesis of Tetrahydrocannabinol: Observing Effects Of Various Solvents And Acids

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Abstract

Synthesizing tetrahydrocannabinol is a lengthy process with minimal yields and little applicability on an industrial scale. To close the gap between bench chemistry and industry process chemistry, this paper introduces a small-scale flow chemistry method that utilizes a microwave or ultrasonic medium to produce major tetrahydrocannabinol isomers. This process produces excellent yields and minimal side products, which leads to more efficient large-scale production of desired cannabinoids.

Keywords: Flow-chemistry, Synthesis, THC, Microwave, Sonication

1. Introduction

Chemical synthesis in the laboratory has been carried out in standardized glassware, and the use of glassware as the primary batch-type laboratory scale reactor has remained vastly unchanged for over 200 years. By contrast, continuous-flow processes are not common in bench laboratories and are generally found in larger, industrial-scale systems. Production process aspects such as facile automation, reproducibility, safety, and process reliability due to constant reaction parameters are associated with larger, industrial-scale flow process systems.[1-5] Though there has been tremendous progress in the development of new chemical methodologies over the past several decades, there is now a quest for new technologies that would allow those reactions to be scaled up. The combination thereof would allow for quicker synthesis and simplify the purification or isolation of desired products.

Most cannabinoid production firms currently use batch-style processes to produce large quantities of materials under long reaction durations. These conditions are usually not environmentally friendly and can produce undesired side products. Flow chemistry have shown to be useful to produce cannabinoids, albeit at small scales.[6-8] Flow chemistry is beneficial by closing the gap between small-scale bench chemists and large-scale process engineers by mimicking large-scale production in a laboratory environment through continuous production with limited need to

interact with the system. As shown in figure 1, the simple flow design provides the ability to tailor the flow path and add additional sites that lead to the final product (i.e., purification, hydrogenation, sample taking, etc.). Synthetic procedures developed in bench laboratories frequently fail to meet large-scale production needs without substantial modification, creating lengthy optimization processes. Small-scale flow processes provide an opportunity to bridge the gap between bench-scale, and large-scale production processes. By employing flow chemistry processes to produce cannabinoids, smaller-scale flow productions can be implemented and more rapidly scaled up to larger processes. There exists a need in the cannabinoid production industry for flow chemistry methodologies that provide simplified and expedited links to accessing large-scale processes.[9-11]

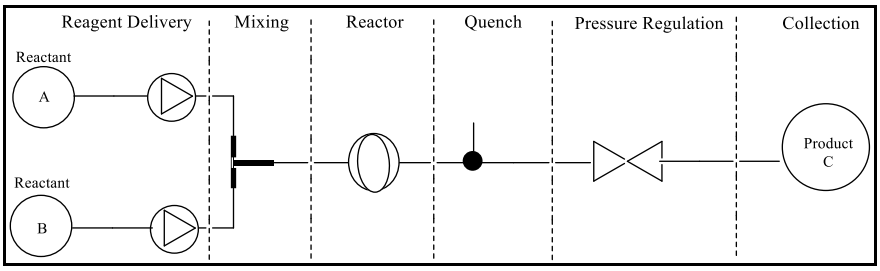


Figure 1: Six component breakdown of a basic flow system with coil reactor

A flow chemistry module establishes a stable set of conditions through which reagents are passed. The key advantages of flow chemistry, including the correlation between reaction time and position within the reactor and ease of replication, allow for a flow module to be tailored and adapted. In addition, the flow conditions could provide short dispersal paths and improved mass transference rates, deriving in better yields and selectivity.[12-15] Microwave irradiation and sonication can be used to address kinetic problems. While microwave irradiation addresses kinetic problems when relatively narrow flow channels create solid phase/solution phase mixing problems, Sonication addresses kinetic problems by producing cavitation bubbles where high temperatures and pressures are experienced within the microenvironment of the cavitation bubbles produced. As the ultrasound intensity increases, the reaction rate increases due to an increase in the number of cavitation bubbles and an increase in the temperature within the cavitation bubbles as depicted in figure 2a.[16-18]The traditional method of heating, heats the reaction mixture outside in, which can cause uneven heating and inconsistent reaction kinetics with the need for stirring. The microwave radiation provides deeper penetration and heats the solvent and sample evenly while maintaining consistent reaction kinetics, as depicted in figure 2b.[19] Combining microwave irradiation with flow reactors can be advantageous since microwave irradiation allows one to create heat inside continuous-flow devices at locations where interactions between two phases occur. Due to the difficulty microwave chemistry can present in scale up of batch environments, microwave-flow can possibly solve those issues as depicted in figure 2c-d. Combining a sonicator with flow reactors can be advantageous in creating reactive microenvironments during the

circulation around the sonicating field, and expediting reaction kinetics creates a greener way of producing product than in standard bench reactions.[20-26]

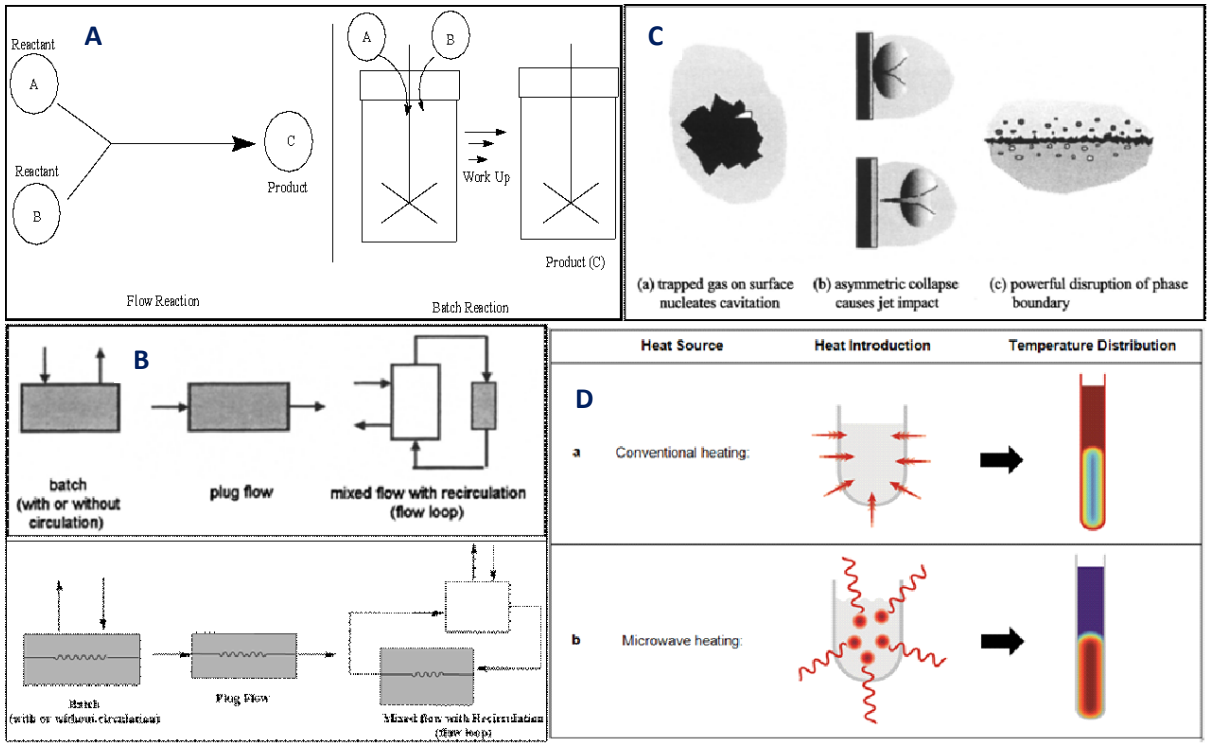


Figure 2: (A) comparison of the two various methods of either flow or batch chemistry. (B) The various modifications of either the top with sonication in flow or batch, bottom with microwave flow or batch (C) Microenvironments of solvated compounds caused by sonication (D) comparison of conventional heating (top) compared to microwave heating (bottom).

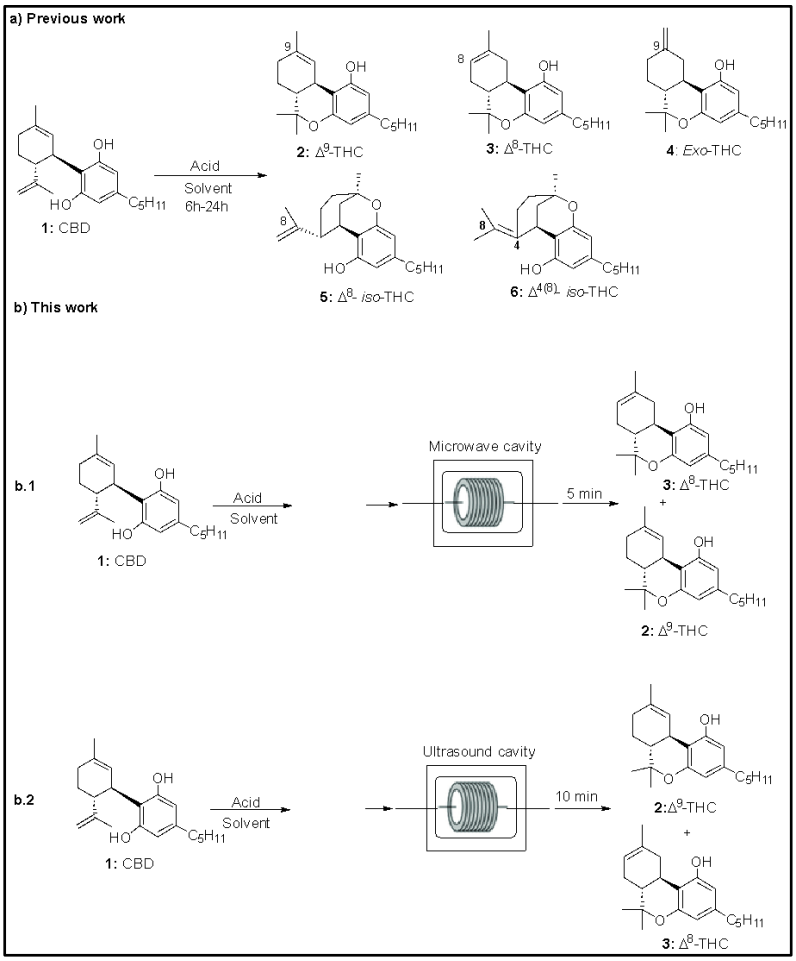


Figure 3: (a) Flow synthesis of cannabinoids, (b.1)-(b.2) Our work using modified flow systems to produce Δ^8-THC and Δ^9-THC

Tetrahydrocannabinol is a partial agonist at the cannabinoid type 1 receptor and has been approved as a therapeutic treatment for a myriad of conditions.[27] It is also available to recreational and medical consumers depending on state laws.[27] The goal of this work is to combine the application of non-ionizing ultrasound or microwave radiation with novel flow chemistry process techniques and reactor systems to produce various cannabinoid products, while also determining the implication of various types of solvents and acids in the conversion of CBD to THC. The use of CBD as the starting material is to mimic industrial starting points, as the total synthesis or coupling of terpenes to resorcinol is limited to THC or HHC products. As shown in Figure 3 (a) Flow synthesis of cannabinoids, (b.1)-(b.2) our work using modified flow systems to produce Δ8-THC and Δ9-THC. Our work presents variable yields and ratios, dependent on acid and solvent with scalable methodologies.

2. Methods

General Remarks: All commercial acids and solvents were ACS and HPLC grade, respectively. Acids and solvents were all purchased from Sigma Aldrich and were used without further purification. CBD isolate was purchased in bulk from GVB Biopharma. Quantification was performed using high performance liquid chromatography (HPLC) on an Agilent 1100 series

equipped with Next Leaf CBX for Potency C_{18} RP column 2.7uM, 150x4.6mm. MeOH with CH_2O_2:H_20 with CH_2O_2 is used for quantification of reactions. HPLC data can be found in the SI. Omegasonics 1900BT (40KHz), Rovsun 410HT (40KHz) ultrasonicator were used with the former used in scaled up reactions. A modified GE JES2051SN5SS 1200W domestic microwave (SI Scheme 1) was used for the microwave reactions.

Experimental Section

General procedure to obtain tetrahydrocannabinol (THC) assisted by microwave.

To an open vessel was added CBD (0.5 g), 1.5 mL of solvent, and 5% mol catalytic amount of acid. Reaction was irradiated in a modified commercial microwave (SI Scheme 1) oven for 5 min. Reaction progress was monitored by high performance liquid chromatography (HPLC) with a diode array detector and the readings were taken at 230 nm wavelength, two HPLC peaks between 7 and 7.5 minutes correspond to Δ^9-THC and Δ^8-THC, respectively. The temperature of the reactions was monitored using a Teflon braided thermocouple beaded thermometer. The reaction mixture was poured into a sodium bicarbonate-saturated solution and extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with brine (10 ml), dried over Na_2SO_4, and evaporated under vacuum. ^{1}H NMR (500 MHz, CDCl3) δ 6.33 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 1.6 Hz, 1H), 5.53 (s, 1H), 5.49 – 5.44 (m, 1H), 3.28 (dd, J = 16.4, 4.7 Hz, 1H), 2.76 (td, J = 10.9, 4.5 Hz, 1H), 2.44 (td, J = 7.5, 2.9 Hz, 3H), 2.18 (ddt, J = 11.5, 5.5, 2.8 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.56 (dq, J = 14.2, 7.2 Hz, 3H), 1.43 (s, 3H), 1.33 (qq, J = 7.4, 4.3 Hz, 5H), 1.14 (s, 3H), 0.96 – 0.87 (m, 4H).

General procedure to obtain Tetrahydrocannabinol (THC) assisted by sonication.

To an open vessel was added CBD (0.5 g), 1.5 mL of solvent, and 5% catalytic amount of acid. Reaction was sonicated using ultrasonic bath for 2 min at 60°C. Reaction progress was monitored by high performance liquid chromatography (HPLC) with a diode array detector and the readings were taken at 230 nm wavelength, two HPLC peaks between 7 and 7.5 minutes correspond to Δ^9-THC and Δ^8-THC, respectively. The temperature of the reactions was monitored using a Teflon braided thermocouple beaded thermometer. The reaction mixture was poured into a sodium bicarbonate-saturated solution and extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with brine (10 ml), dried over Na_2SO_4, and evaporated under vacuum. ^{1}H NMR (500 MHz, CDCl3) δ 6.33 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 1.6 Hz, 1H), 5.53 (s, 1H), 5.49 – 5.44 (m, 1H), 3.28 (dd, J = 16.4, 4.7 Hz, 1H), 2.76 (td, J = 10.9, 4.5 Hz, 1H), 2.44 (td, J = 7.5, 2.9 Hz, 3H), 2.18 (ddt, J = 11.5, 5.5, 2.8 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.56 (dq, J = 14.2, 7.2 Hz, 3H), 1.43 (s, 3H), 1.33 (qq, J = 7.4, 4.3 Hz, 5H), 1.14 (s, 3H), 0.96 – 0.87 (m, 4H).

Scaled synthesis of Δ^9THC and Δ^8THC using microwave-assisted flow conditions

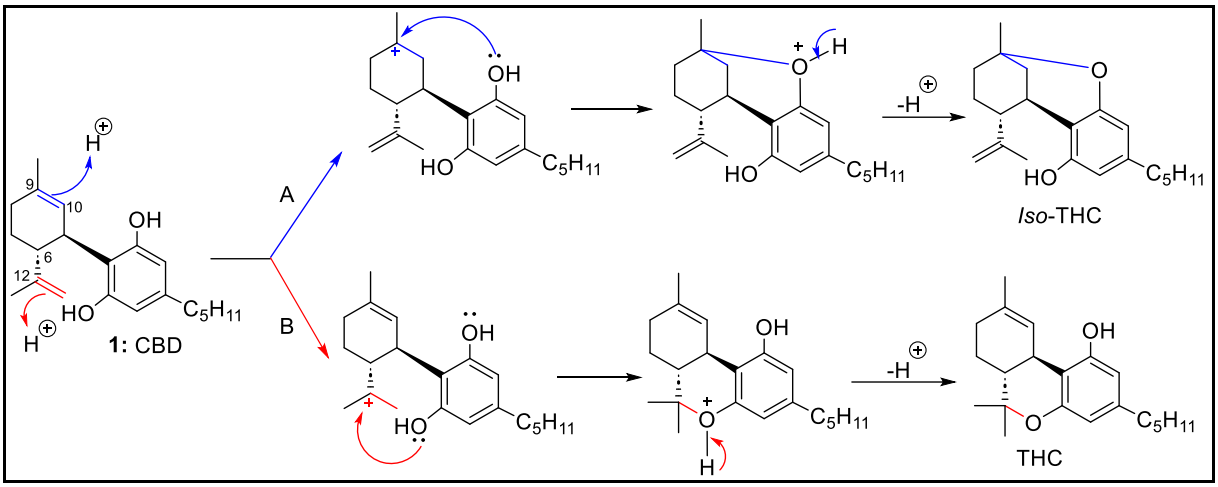
A microwave-assisted continuous flow reactor 100 (SI Figure 1) was used to synthesize a mixture of (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-

ol (Δ^8THC) and (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol (Δ^9THC) from (1'*S*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (CBD). CBD (500 g, 1.6 mol) was dissolved in hexanes (1L) to obtain a 1.6M solution in a holding tank (110). *p*-Toluensulfonic acid (15.22 g, 0.008 mol) was added to the solution. A diaphragm pump (120) was utilized to push the reaction mixture through the flow path (130) into a 1,200-watt microwave reactor (140) and back into the holding tank (110). The reaction reached completion after five minutes; the HPLC showed that CBD had been completely consumed and that an 82% total THC yield had been achieved, prior to purification. A plot of the reaction progress over time is depicted in SI Figure 4, where the THC data points indicate combined amounts of Δ^8-THC and Δ^9-THC produced. The HPLC traces in SI Figures 5A-5C show the reaction progress at t = 0 minutes (SI Figure 5A), t = 2.5 minutes (SI Figure 5B), and t = 7.5 minutes (SI Figure 5C). The HPLC peak at approximately 4.2 minutes corresponds to CBD, and the two HPLC peaks between 7 and 7.5 minutes correspond to Δ^9-THC and Δ^8-THC, respectively. ^{1}H NMR (500 MHz, CDCl3) δ 6.33 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 1.6 Hz, 1H), 5.53 (s, 1H), 5.49 – 5.44 (m, 1H), 3.28 (dd, J = 16.4, 4.7 Hz, 1H), 2.76 (td, J = 10.9, 4.5 Hz, 1H), 2.44 (td, J = 7.5, 2.9 Hz, 3H), 2.18 (ddt, J = 11.5, 5.5, 2.8 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.56 (dq, J = 14.2, 7.2 Hz, 3H), 1.43 (s, 3H), 1.33 (qq, J = 7.4, 4.3 Hz, 5H), 1.14 (s, 3H), 0.96 – 0.87 (m, 4H).

Scaled synthesis of Δ^9THC and Δ^8THC using sonication-assisted flow conditions

A sonication-assisted continuous flow reactor 500 (SI Figure 2) was used to synthesize a mixture of Δ^8-THC and Δ^9-THC from CBD. CBD (6,000g, 19.11 mol) was dissolved in toluene (12 L) to obtain a 1.6M solution in a holding tank (510). *p*-Toluensulfonic acid (181.53 g, 0.96 mol) was added to the solution. A diaphragm pump (520) was utilized to push the reaction mixture through the flow path (530) into the ultrasound bath, which was heated at 60°C (540) and flowed back into the holding tank (510). The reaction was run for 10 minutes at room temperature with final reaction temperature at 60°C. The reaction reached completion after 20 minutes; the HPLC showed that CBD had been completely consumed and that an 85% total THC yield had been achieved. The HPLC traces in SI Figures 6A-6C show the reaction progress at 5 minutes (SI Figure 6A), 10 minutes (SI Figure 6B), and 15 minutes (SI Figure 6C). The HPLC peak at approximately 4.2 minutes corresponds to CBD, and the two HPLC peaks between around 6.9 and 7.3 minutes correspond to Δ^9THC and Δ^8THC, respectively. ^{1}H NMR (500 MHz, CDCl3) δ 6.33 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 1.6 Hz, 1H), 5.53 (s, 1H), 5.49 – 5.44 (m, 1H), 3.28 (dd, J = 16.4, 4.7 Hz, 1H), 2.76 (td, J = 10.9, 4.5 Hz, 1H), 2.44 (td, J = 7.5, 2.9 Hz, 3H), 2.18 (ddt, J = 11.5, 5.5, 2.8 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.56 (dq, J = 14.2, 7.2 Hz, 3H), 1.43 (s, 3H), 1.33 (qq, J = 7.4, 4.3 Hz, 5H), 1.14 (s, 3H), 0.96 – 0.87 (m, 4H).

3. Results and Discussion



Scheme 1: Two pathways for the cyclization of CBD in acid conditions.

Acid-promoted cyclization of CBD occurs via activation of a specific double bond[28] (Scheme 1). CBD scaffold has two exocyclic double bonds, one in the cyclohexyl ring (Δ^9), and another in the propenyl chain (Δ^{12}). When the activation occurs on Δ^{12}, the chromene ring forms to afford the THC scaffold (path B, scheme 1). Moreover, activation at the Δ9 double bond turns the cyclization toward the oxocine ring formation to furnish Δ^8-*iso*-THC (path A, scheme 1). The chromene ring is bonded linearly between the resorcinol and the terpenyl moiety, whereas the oxocin ring is "connected".[28] Therefore, THC-core can be the presumed major product because it is more energetically stable. Several refined methodologies to produce THC have been reported[28-32] using acid catalysis or various synthetic pathways. These conventional synthetic approaches describe the formation of not only Δ^9THC and Δ^8THC isomers, but also around 3-15% of Δ^8-*iso*-THC (Figure 3, previous work). Kappe *et.al.*[5] developed a procedure to obtain Δ^9-THC and Δ^8-THC using flow chemistry with excellent yield and the ability to control reaction factors that have a significant impact on product selectivity. The acid-mediated cyclization is limited by reaction rate as well as variable factors (i.e., Temperature, Moisture content, etc.). The use of microwave and sonication was observed to increase the reaction rates either through direct intervention through heating and polarization of reactants and solvent (Figure 4 A), or through acoustic manipulation such as causing cavitation bubbles (Figure 4 B) creating microenvironments of pressure and temperature differences. Due to the short reaction times with noticeable conversions, MW and SN through data collections are observed to provide commensalistic benefits by decreasing reaction times and increasing conversions with commonly used acids.

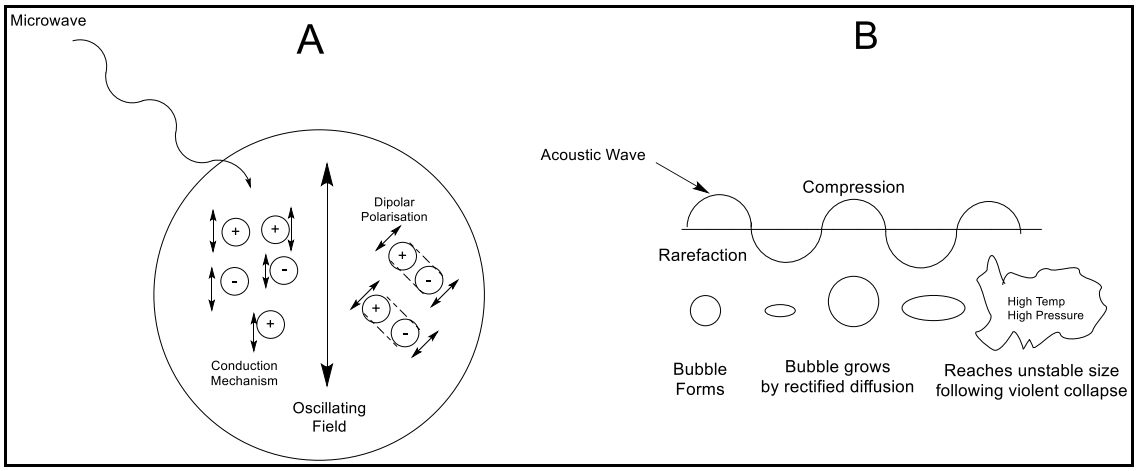


Figure 4: (A) Microwave effects on the polarizability of polar solvents, as well as local heating or superheating causing increased reaction rates. (B) Acoustic waves (sonicator) causing compression and rarefaction causing increased mechanical effects causing increased reaction kinetics.

To examine the selectivity of CBD cyclization, diverse reactions involving the use of organic and inorganic acids in various solvents were accomplished using microwave energy (SI Table 1). The reactions were carried out in a modified commercial microwave oven using an open-vessel technique with modified temperature monitoring. Solvents used are described in SI Figure 10.

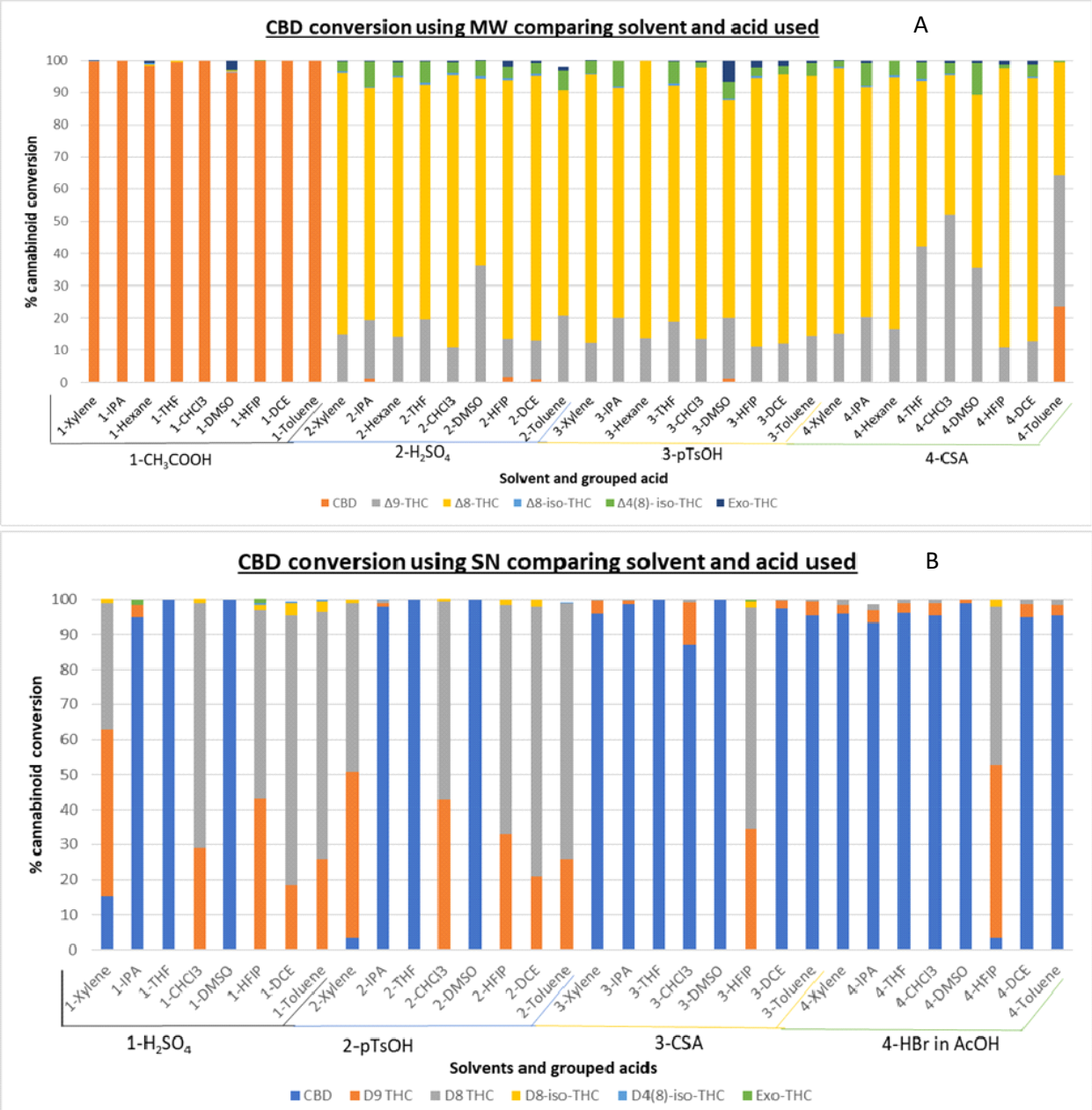


Figure 5: (Top) Microwave Reaction conditions: 0.5g CBD, 1.5 mL of solvent , 5% catalytic amount of acid, MW (1200W), 5 min reaction time. [a]The percentage ratios of the THC isomers were determined using HPLC. [b]The Temperature baseline was 110°C as original scaled flow setup was done at this temperature for constant reaction time. **(Bottom) Sonication Reaction conditions:** 0.5g CBD, 1.5 mL of solvent , 5% catalytic amount of acid, SN (40KHz), 2 min reaction time. [a]The percentage ratios of the THC isomers were determined using HPLC. [b]The temperature baseline was 60°C as original scaled flow setup was done at this temperature for constant reaction time.

The results indicate that acetic acid is not a good catalyst for the cyclization of CBD (Figure 5 A). Although reaction times generally took two minutes, the reactions were microwaved for a total of five minutes in an effort to influence conversion, and almost 100% of CBD was recovered in all cases. Using sulfuric acid as catalyst, Δ^8-THC and Δ^9-THC were afforded as the main products, but other THC isomers were also obtained (SI Table 1, entries 10-18). $\Delta^{4(8)}$- *iso*-THC

was accomplished with 8.0%, 6.7%, and 6.0% when the reaction was carried out in isopropanol (IPA), Tetrahydrofuran (THF), or toluene as solvent, respectively (SI Table 1, entries 11, 13, and 18). *p*TsOH in hexane converted CBD into Δ^8- and Δ^9-THC mixture in a better yield than sulfuric acid and CSA with no isomer formation (SI Table 1, entry 21). The use of other solvents performed different grades of regioselectivity. CSA, an aprotic acid, arises as an attractive cyclization inducer because in combination with HFIP, a polar, strongly hydrogen bond-donating solvent, the regioselectivity of the CBD cyclization moved toward the generation of Δ^8-THC with an 86.8% yield (SI Table 1, entry 34). The combination of CSA as catalyst and toluene as solvent the reaction was not completed, obtaining 23.7% CBD with 40.6 and 35.0% of Δ^9- and Δ^8-THC, respectively (SI Table 1, entry 36). Then, we probed the effects of modifying microwave power in the conversion of CBD into THC isomers using *p*TsOH in hexane (Table 1). The results show that microwave power can affect the heating rate during the reaction and therefore influences the formation ratios of THC isomers during the cyclization of CBD. When performing the reaction at a setup microwave power of 240W only 2.5% of Δ^9-THC afforded (Table 1, entry 1). When the microwave power is increased, the CBD conversion is higher and increases the ratio of Δ^8-THC. At 960W, CBD fully converted into Δ^9- and Δ^8-THC with a ratio of 28.8 and 71.2%, respectively (Table 2, entry 4). These outcomes prove the premise that Δ^8-THC is thermodynamically more stable than its isomer Δ^9-THC.

Table 1: Effect of microwave power on microwave-assisted CBD acid-catalyzed cyclization.

Entry	MW Power (W)	THC isomer yields (%) in the final reaction mixture[a]					
		CBD	Δ^9-THC	Δ^8-THC	Δ^8-*iso*-THC	$\Delta^{4(8)}$- *iso*-THC	*Exo*-THC
1	240	97.5	2.5		0	0	0
2	480	83.1	15.1	1.8	0	0	0
3	720	6.2	46.1	47.7	0	0	0
4	960	0	28.8	71.2	0	0	0
5	1200	0	13.6	86.4	0	0	0

Reaction conditions: 0.5g CBD, 1.5 mL of Hexane, 5% catalytic amount of *p*TsOH, MW, 5 min reaction time
[a]The percentage ratios of the THC isomers were determined using HPLC.

The best conditions found for the conversion of CBD in the mixture of Δ^8THC and Δ^9THC (*p*TsOH and hexane: SI Table 1, entry 19) were applied to a continuous flow chemistry system assisted by microwave. The reaction comprises adding *p*TsOH to a CBD solution in hexane and feeding the reaction mixture through a continuous flow loop which is inside the microwave reactor as an energizing component (Scheme 2-b.1). The reaction finished in five minutes and yielded a mixture of 91% and 9% Δ8-THC and Δ9-THC, respectively, as determined by HPLC. The treatment of this reaction in a continuous flow system enables more accurate management of reaction factors and is more suitable for optimization and scale-up.

To prove that the technique established for CBD cyclization is not restricted only to a small scale, we decided to scale up this reaction to develop a procedure to produce THC in kilograms. A microwave-assisted continuous flow reactor was designed (SI Figure 1) to carry out the conversion of 500 g CBD into THC catalyzed by in hexane as the solvent. Figures 2 and 3 show the evolution of demonstrating that the reaction was completed after five minutes, and afforded an 82 % yield of Δ^8-THC and Δ^9-THC as an isolated mixture (94:6 regioselectivity ratio). The details of the procedure are explained in the method section. Encouraged by these results, we further extended the scope of our methodology to sonochemistry. We combined ultrasound with flow synthesis to promote the acid-cyclization of CBD using *p*TsOH in the presence of hexane (Scheme 2-b.2). To our knowledge, this is the first time that sonochemistry has been merged with flow chemistry for the synthesis of THC. The use of ultrasound as an unconventional energy source has been widely described in the literature in the development of new synthetic methodologies in organic and medicinal chemistry.[19-23]

Results from the use of sonication to influence the acid cyclization of CBD were varied. The use of acetic acid within the microwave proved to be inefficient within the cyclization, since heat was involved, the acid was not strong enough to induce cyclization. 33% HBr in acetic acid was used in the sonication trial as shown in Figure 5 (bottom) CBD conversion remained low with minute amounts of THC or isomers were created. The use of HFIP as a solvent produced almost 1:1 ratio of Δ^9-THC and Δ^8-THC with some CBD still unconverted. Use of other polar and non-polar solvents did not contribute to the cyclization. The use of Camphor sulfonic acid (CSA) in various solvents did not produce the desired product except HFIP where less than 1% CBD was detected, and Δ^8-THC and Δ^9-THC was detected with minimal unwanted isomer formation. Xylene, IPA, THF, and DMSO were the solvents that did not convert CBD to THC. Xylene did convert the CBD, but a detectable amount of CBD remained within the reaction. The use of H_2SO_4 in DMSO, IPA, and xylene had detectable amount of unconverted CBD, although in xylene Δ^8-THC and Δ^9-THC was produced, was not efficient compared to $CHCl_3$, HFIP, DCE, and toluene. Although the results differ from the microwave, the sonicator had a stable 60°C temperature, not having various heating spots or localized superheating spots as would be produced with the microwave. Without the additional heating, reaction kinetics might differ.

Similar to the microwave scaled reaction, a scaled sonicator flow reactor was created and based off the data collected from the small scale, toluene with pTsOH was used, since the cost of industrial solvent and acid is relatively cheap. We decided to scale up this reaction to develop a procedure to produce THC in kilograms. A sonication-assisted continuous flow reactor was designed (SI Figure 2) to carry out the conversion of 6000 g of CBD into THC, using pTsOH as the acid (5%) with toluene as the solvent heated at 60°C. Figure 4 shows the evolution of the reaction, demonstrating that after twenty minutes the reaction was completed. (SI Figure 2) displays the reactor designed to accomplish the acid-cyclization of CBD (6 kg) inside of the ultrasound bath cavity using a continuous flow process technique[14]. As shown in Figure 6, CBD

was completely converted to Δ8-THC and Δ9-THC after 10 minutes (83:17 regioselectivity ratio), with 85% isolated yield. The details of the procedure are explained in the method section.

It is interesting to point out that using the sonochemistry technique at room temperature, Δ^9-THC afforded better ratios than microwave-assisted reaction as well as less unwanted isomers. A higher temperature reached in the microwave experiments led to the isomerization of Δ^9-THC into Δ^8-THC, which is a thermodynamically more stable isomer[24].

The MW and SN assisted flow process demonstrated the ability to scale past milligram and gram scale affording a mixture of isomers compared to the current methodology in the literature. This mixture is perfect feedstock for hydrogenation conditions to make hexahydrocannabinol.[32] These methods also afford 300g/min of THC compared to Kappe et al. process that yields 1 g/h and 4 g/h of THC isomers.

4. Conclusions

We have developed unique reactor systems and techniques for producing cannabinoids in large quantities with decreased reaction times using the combination of flow conditions with microwave- and ultrasound reactors. The flow chemistry processes disclosed in this article enable a high degree of precision in the delivery of reagents/solutions and excellent control over the conditions to which the solutions are exposed. Precise control results in excellent reproducibility and safety, thereby making these methods amenable to larger scales. The processes disclosed herein can also be used in tandem, thereby providing a means to perform multi-step syntheses under flow conditions. The continuous flow processes can be used to produce the desired products at kilogram scales within minutes. Quick and clean production of cannabinoids are important as well within the industrial sector but also pharmaceutical sector with ongoing research of cannabinoids and their analogs uses in treatment of diseases and cancers.[32-35]

Abbreviations

Δ^9-THC: (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol

Δ^8-THC: (6a*R*,10a*S*)-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol

Δ^8-*iso*-THC: (2*R*,5R,6*S*)-2-methyl-9-pentyl-5-(prop-1-en-2-yl)-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[*b*]oxocin-7-ol

$\Delta^{4(8)}$-*iso*-THC: (2*R*,6*S*)-2-methyl-9-pentyl-5-(propan-2-ylidene)-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[*b*]oxocin-7-ol

Exo-THC: (6a*R*,10a*S*)-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol

MW: Microwave

US: Ultrasound

SN: Sonicator

IPA: Isopropyl alcohol

THF: Tetrahydrofuran

$CHCl_3$: Chloroform

DCE: 1,2-Dichlorethane

HFIP: 1,1,1,3,3,3-Hexafluoroisopropanol

DMSO: Dimethyl sulfoxide

*p*TsOH: *p*-Toluenesulfonic acid

CSA: Camphorsulfonic acid

HCl: Hydrochloric acid

HHC: Hexahydrocannabinol

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