

Short Note

(E)-3-[4-(Pent-4-en-1-yloxy)phenyl]acrylic Acid

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Abstract: (E)-3-[4-(Pent-4-en-1-yloxy)phenyl]acetic acid is one of the useful components of liquid crystal materials which can be produced through Williamson ether synthesis by synthesizing 4-hydroxy-cinnamic acid and 5-bromo-1-pentene. Although Williamson ether synthesis is generally slow under conventional external heating conditions, microwave irradiation was effective for significant acceleration of the etherification. Furthermore, we demonstrated the rapid and continuous synthesis of (E)-3-[4-(pent-4-en-1-yloxy)phenyl]acetic acid, using a microwave-assisted flow reactor developed by us, in which the blockage by salt precipitation was suppressed by the continuous addition of an aqueous methanol solution after the reaction cavity.

Keywords: aryl alkyl ether; Williamson ether synthesis; microwave; flow chemistry

1. Introduction

(E)-3-[4-(Pent-4-en-1-yloxy)phenyl]acrylic acid is utilized as a component of liquid crystal materials [1]. This compound is usually produced through Williamson ether synthesis by synthesizing 4-hydroxy-cinnamic acid and 5-bromo-1-pentene under basic conditions. Williamson ether synthesis is recognized as a representative method for carbon-oxygen bond formation to provide ethereal compounds, and a huge number of examples have been reported to date [2,3]. In general, however, a long reaction time and a number of additives used to activate electrophiles in S_N2 reactions are required for Williamson ether synthesis. Starting from 4-hydroxy-cinnamic acid (1) and 5-bromo-1-pentene (2), (E)-3-[4-(pent-4-en-1-yloxy)phenyl]acrylic acid (3) was reportedly prepared with KOH as a base and KI as an activator at high reaction temperature; the reaction needed 24 h for completion [1].

Rapid heating by MicroWave (MW) irradiation is often used for the acceleration of target reactions, and tremendous efforts have been made towards microwave-assisted organic synthesis [4,5]. Not surprisingly, the application of MW heating to Williamson ether synthesis has been investigated by using simple microwave applicators [6–9]. However, the application of MW chemistry to a scale-up synthesis is difficult because of the limited penetration depth of MW. On the other hand, flow chemistry has benefits in terms of safe on-demand synthesis, and thus various types of reactions have been demonstrated successfully in a continuous manner [10–14]. In this context, some flow-microwave systems have been reported [15,16]. Wang reported a continuous-flow system with a domestic microwave oven and examined some organic reactions, including Williamson ether synthesis between benzyl chloride and phenol [17]. Strauss and colleagues developed their continuous microwave reactor, equipped with a pressure control valve to increase the reaction temperature, and its applications revealed that Strauss's system allowed for improved productivity in comparison with Wang's prototype

system [18]. However, the reported yields (49% and 67%) were not adequate, and only a single example was demonstrated. Thus, these reactions have much room for improvement, in terms of the reaction efficiency and the number of reaction examples.

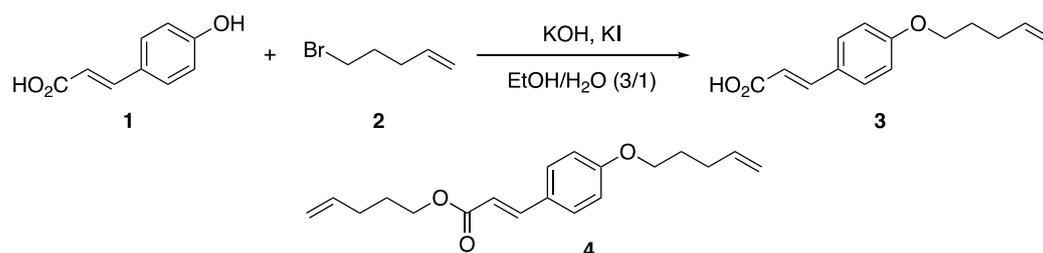
In 2015, we reported a highly efficient single-mode microwave applicator with a resonance cavity and demonstrated the synthetic application of our apparatus, in which two well-known reactions (the Fischer indole synthesis and the Diels-Alder reaction) were performed on a large scale (e.g., 100 g h⁻¹ for the Fischer indole synthesis) continuously at high reaction temperature [19,20]. It is known that MW is absorbed directly by polarized organic molecules, and the resulting molecular vibration enables rapid heating of the reaction mixture. Therefore, we expected that rapid heating by MW irradiation would be effective in flow chemistry with starting materials having a good electrostatic property, since the residence time of the reactants is normally limited. Herein, we disclose the continuous-flow synthesis of (*E*)-3-[4-(pent-4-en-1-yloxy)phenyl]acrylic acid via Williamson ether synthesis using the flow-microwave applicator.

2. Results and Discussion

2.1. Initial Screening of the Reaction Conditions Using a Batch Reactor

To check the effect of MW irradiation, we first examined the reaction between 4-hydroxy-cinnamic acid (**1**) and 5-bromo-1-pentene (**2**) under the batch conditions (Table 1). According to the literature [1], the reaction was carried out at 90 °C under oil bath heating, and the desired compound **3** was obtained in 96% yield, although the reaction required 24 h for completion (entry 1). When the reaction time was changed to 10 min, the yield dropped dramatically to only 23% (entry 2). Even though the reason is not clear at present, MW heating increased the yield slightly even at 90 °C (entry 3). Interestingly, it was found that KI was not essential for this reaction, and the etherification was further accelerated when the temperature was raised up to 150 °C (entry 4). In this case, ester compound **4** was also formed in 19% yield as a byproduct, suggesting that substitution by the carboxylate anion could occur at high temperature. Therefore, we reduced the amount of **2** to minimize the overreaction, and 3.0 equivalents of KOH was added for promoting hydrolysis of the resultant ester **4**. As we expected, the desired ether **3** was selectively obtained in 91% yield (entry 5). MeOH was slightly less effective for this reaction in comparison with EtOH (entry 6).

Table 1. Williamson ether synthesis under batch conditions ¹.



Entry	Heat Source	Time	KOH (equiv)	KI (equiv)	Temp. (°C)	Yield of 3 (%) ²
1	oil bath	24 h	2.0	0.5	90	96
2	oil bath	10 min	2.0	0.5	90	23
3	microwave	10 min	2.0	0.5	90	32
4	microwave	10 min	2.5	0	150	78 ³
5 ⁴	microwave	10 min	3.0	0	150	91
6 ^{4,5}	microwave	10 min	3.0	0	150	86

¹ The reactions were carried out with 4-hydroxy-cinnamic acid (**1**) (1.0 equiv), 5-bromo-1-pentene (**2**) (1.5 equiv), KOH, and KI in EtOH/H₂O (3/1) on a 1.0 mmol scale, unless otherwise mentioned; ² Determined by ¹H-NMR analysis; ³ Ester **4** was obtained in 19% yield; ⁴ Run with 1.2 equiv of **2**; ⁵ MeOH was used instead of EtOH.

2.2. Continuous Williamson Ether Synthesis Using our Flow-Microwave Applicator

On the basis of the results obtained in Table 1, we needed to devise a flow-microwave system for this Williamson ether synthesis (Figure 1). The carboxylate form of **3** was found to precipitate quite easily from the reaction mixture, when the solution was cooled to ambient temperature. Thus, a mixed solvent of MeOH/H₂O was continuously added, using the second pump just after the reaction cavity to dissolve the potassium salt of **3**, so that potential clogging by the precipitate would be prevented. The detailed conditions are listed in Scheme 1. The volume of the reaction vessel in the microwave cavity was approximately 6 mL. The desired product **3** was quantitatively obtained, when the flow rate was 1.2 mL/min and the irradiation power was 120 W. In addition, over 90% chemical yield was retained even when the flow rate was increased to 4.0 mL/min (the residence time in the reaction vessel was 1.5 min), while higher MW irradiation power (170 W) was required to elevate the reaction temperature. These results suggest that the reaction reaches completion quickly (less than 1.5 min) at more than 160 °C. In this case, about 300 g of **3** can be produced by this system theoretically, if the continuous reaction is operated for 1 day.

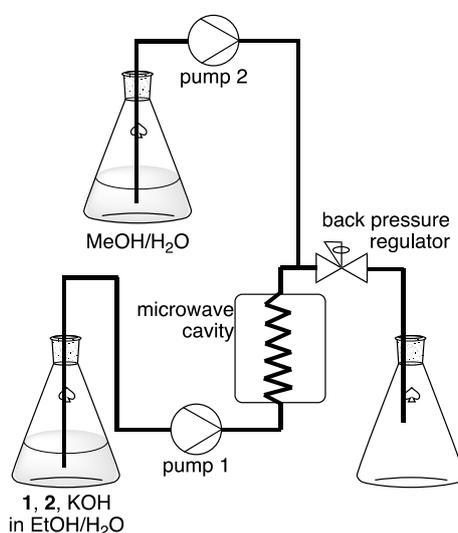
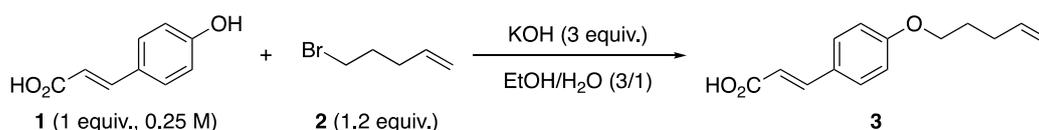


Figure 1. Outline of our flow-microwave system.



Pump 1 (mL/min)	Pump 2 (mL/min)	Irradiation power (W)	Temp. (°C)	Yield of 3 (%) ¹
1.2	4.8	120	155-160	99
2.0	8.0	130	160-165	93
4.0	6.0	170	160	91 (91) ²

¹ NMR yield. ² Isolated yield.

Scheme 1. Williamson ether synthesis between **1** and **2** using flow-microwave applicator.

3. Experiments

3.1. General

The ¹H-NMR spectrum was measured on a JEOL JNM-ECA-500 spectrometer (JEOL, Tokyo, Japan) at 500 MHz, and the ¹³C-NMR spectrum was recorded on a JEOL JNM-ECA-500 spectrometer

at 125 MHz. Chemical shifts were reported in parts per million (ppm) downfield from residual chloroform in CDCl₃ for ¹H-NMR. For ¹³C-NMR, chemical shifts were reported in a scale relative to CDCl₃. Column chromatography was performed with silica gel N-60 (40–100 mm) purchased from Kanto Chemical Co., Inc., (Tokyo, Japan). A thin layer chromatography (TLC) analysis was performed on Silica gel 60 F₂₅₄-coated glass plates (Merck, Darmstadt, Germany). The visualization of TLC plates was carried out by means of UltraViolet (UV) irradiation at 254 nm, or by spraying a 12-molybdo(VI)phosphoric acid ethanol solution. Reagents and solvents were purchased from commercial suppliers and were used without purification.

3.2. Typical Procedure of Williamson Ether Synthesis Using Flow-Microwave System

A stock solution of 4-hydroxy-cinnamic acid (2.05 g, 12.5 mmol), 5-bromo-1-pentene (2.23 g, 15.0 mmol) and KOH (2.10 g, 37.4 mmol) in EtOH/H₂O (3/1, 50 mL) was pumped into the microwave applicator at a flow rate of 4.0 mL/min, and the irradiation power of the microwave reactor was set at 170 W. Meanwhile, the MeOH/H₂O (5/1) solution was pumped into the line between the reaction vessel and the backpressure regulator at 6.0 mL/min. To stabilize the applicator, the solution was first run for 5 min. After the exit temperature reached 155–160 °C, the reaction mixture was collected for 1 min. The organic solvent was evaporated in vacuo, and the resultant residue was neutralized with 1 N HCl. The organic materials were extracted with EtOAc, and the combined organic layers were dried over Na₂SO₄. After filtration, the filtrate was concentrated, and the ¹H-NMR was measured to determine the yield (91%). The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10/1 to 3/1) to give **3** (211 mg, 91%) as a colorless solid.

¹H-NMR (500 MHz, CDCl₃): δ = 7.74 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.85 (tdd, *J* = 6.9, 10.3, 17.2 Hz, 1H), 5.07 (dd, *J* = 1.7, 17.2 Hz, 1H), 5.01 (dd, *J* = 1.7, 10.3 Hz, 1H), 4.01 (t, *J* = 6.3 Hz, 2H), 2.27–2.23 (m, 2H), 1.93–1.88 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃): δ = 172.4, 161.3, 146.8, 137.6, 130.1, 126.6, 115.4, 114.9, 114.5, 67.3, 30.0, 28.3.

The NMR spectra were consistent with the previous paper [1].

4. Conclusions

We have demonstrated Williamson ether synthesis using a flow-microwave applicator. Our system is effective for the continuous synthesis of (*E*)-3-[4-(pent-4-en-1-yloxy)phenyl]acrylic acid (**3**), and we believe that this method would be applicable to the synthesis of other ethereal compounds. Further applications of this flow-microwave system is being investigated in our group.

Supplementary Materials: The following are available online, flow-microwave applicator and NMR spectra of (*E*)-3-[4-(pent-4-en-1-yloxy)phenyl]acrylic acid.

Author Contributions: Y.H. and H.E. conceived the idea for this work and designed the experiments; T.S. and S.T. performed the experiments. N.O., T.O., and H.O. set up the flow-microwave applicator for this transformation. H.E., H.O., and Y.H. prepared the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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