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SPECIAL ISSUE PAPER

Synthesis of coumarin derivatives in a microfluidic flow system employing the Pechmann condensation: A case study

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Abstract

For the synthesis of coumarin derivatives using the Pechmann condensation scheme, an acidic ionic liquid catalyst, abbreviated as **[EBsImH][HSO$_4$]**, was prepared from the ring opening of 1,4-butanesultone by 1-ethylimidazole, followed by the addition of 1 equiv. H_2SO_4(*c*). The **[EBsImH][HSO$_4$]**-catalyzed Pechmann condensation reactions proceeded smoothly in a batch setup, with recyclable **[EBsImH][HSO$_4$]** showing great catalytic activity. The acidic ionic liquid catalyst **[EBsImH][HSO$_4$]** was recovered from EtOAc/H_2O extraction of the product mixture, where the H_2O layer was worked up and dried for reuse in consecutive runs of the Pechmann condensation reactions, maintaining >85% conversion for four times. The catalytic reactions were also carried out in a microfluidic flow setup. The flow parameters, the reactant molar amounts, and the additional H_2SO_4 as a modifying acid catalyst were optimized in the current case study. A minimum conversion rate of 2.8 g/hr of coumarin derivatives was demonstrated.

KEYWORDS

catalyst recovery and reuse, Coumarin derivatives, ionic liquid, microfluidic flow reactions, Pechmann condensation

1 | INTRODUCTION

Coumarin is a fragrant organic chemical compound, found naturally in many plants. Although coumarin itself does not have anticoagulant properties, it is transformed, in the biological world, into natural anticoagulant dicoumarol, a material known to be responsible for bleeding disease.[1] Coumarin laser dyes are efficient for pulsed- and continuous-wave operations in laser applications.[2] For instance, coumarin 102 has been well studied.[3] They are also used as a fluorescent dye to stain biological specimens. Coumarin tetramethyl laser dyes are used as an active medium in coherent organic light emitting diode emitters. For example, coumarin 545T serves as the gain medium on widely tunable green laser emission due to enhanced solubility and increased laser conversion efficiency.[4] The structures of coumarin 102 and 545 T are shown in Scheme 1. Alternatively, coumarin derivatives serve in the pharmaceutical industry as a precursor in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to dicoumarol, exhibiting a wide range of biological activities, for example, (a) antileishmanicidal,[5] (b) anticoagulant,[6] (c) anti-inflammatory,[7] (d) antimicrobial,[8] (e) antioxidant,[7] (f) antitumoral,[9] and (g) anti-HIV agents;[10] (h) enzyme inhibition properties;[11] and (i) pharmacological effects on the central nervous system.[12]

Routine aldol condensation between salicylaldehyde and acetic anhydride generates coumarin easily in the laboratory.[13] In much greater usage for the preparation of

Dedicated to the memory of Professor Jun-ichi Yoshida.

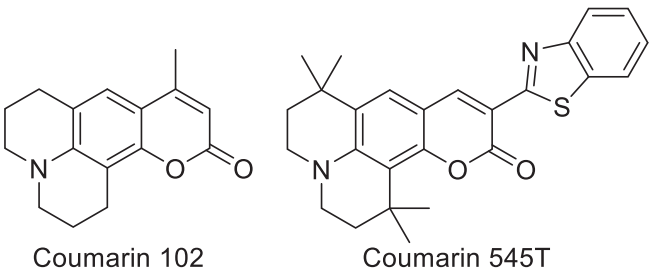
the coumarin derivatives are the many named reactions, for instance, (a) Knoevenagel, (b) Perkin, (c) Kostanecki-Robinson, (d) Pechmann, or (e) Reformatskii methods.[14]

Several reviews on coumarin were compiled on the green methods, for example, its catalytic reactions using ionic liquids or deep eutectic solvents, microwave- or ultrasound-induced reactions, solvent-free synthesis, and mechanosynthesis. Recently, Sangshetti et al. reviewed[15] the Pechmann condensation, the chemical reaction used to obtain coumarin derivatives from phenols and carboxylic acids or esters containing a β-carbonyl group under acidic conditions, employing a batch process in general.[16] The Pechmann condensation was first discovered in 1883 by Hans von Pechmann[17] and is also referred to as Pechmann-Duisberg when acetoacetic esters and derivatives are used.

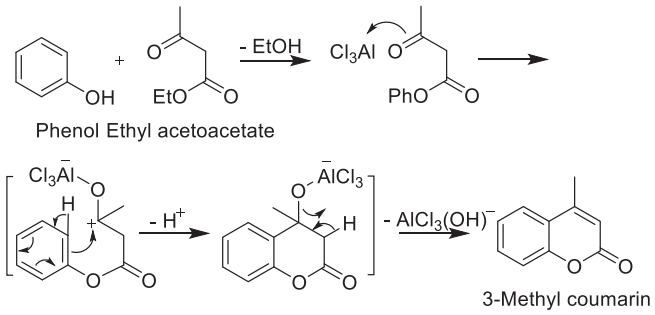
Shown in Scheme 2 is the mechanism of the Pechmann condensation using the Lewis acid catalyst $AlCl_3$ for the purpose of illustration. The various catalysts covered in Sangshetti's 2016 review are (a) classical acid, (b) diatomic nonmetal, (c) ionic liquid, (d) Lewis acids, (e) sulfated metal oxide, (f) metal halide, (g) mixed catalyst, (h) metal nitrate/sulfate, (i) zeolite, (j) triflate, etc.[15]

Noticed here is the ionic liquid, which is composed completely of charged particles, with each cation immediately surrounded by anions and each anion immediately by cations, where cations are organic in nature.[18] Given only the embedded cationic and anionic charged particles, ionic liquids have unique physical properties. These solvents exhibit negligible vapor pressure, high thermal stability, and tunable polarity. They have found applications in the synthesis of coumarin derivatives. The use of a hybrid of N-doped carbon-wrapped polyoxometalate and ionic liquid as a catalyst under solvent-free conditions was reported.[19] Also reported was the use of an ionic liquid $[Et_3N(CH_2)_4OSO_3H][HSO_4]$ as the catalyst under solvent-free conditions.[20] A facile and green methodology was documented using noncorrosive ionic liquid $[Et_3NH][HSO_4]$ as an efficient catalyst.[21] The methods have further been studied under solvent-free conditions.[22] Extension to the preparation of bis-coumarins was successful using ionic liquid immobilized on nanoparticles.[23]

Taking advantage of the abundant literature, we wished to study the acidic ionic liquid-catalyzed Pechmann condensation to produce coumarin using a flow reactor. A microfluidic flow setup can influence the essence of a chemical reaction, attributed from the small size and flow nature. The advantages are (a) fast mixing to achieve homogeneity in solution, thanks to the shortening of the diffusion path in a microreactor; (b) the enhanced heat transfer and hence the greater temperature control capability as a result of larger surface-to-volume ratios, along with more efficient phase–boundary reactions; and (c) the easy control of the residence time by length of the channel and by flow speed.[24] We thought that it worthwhile to study the synthesis of coumarin derivatives under microfluidic flow conditions, which have not been detailed in the literature. In order to make use of the advantages mentioned above and to conform to the principles of green chemistry,[25] our goal was thus to convert the synthesis of coumarin derivatives from batch reaction to microfluidic flow reaction, with reaction parameters optimized.



SCHEME 1 Structures of coumarin 102 and coumarin 545T



SCHEME 2 Mechanism of lewis acid-catalyzed pechmann condensation reaction

2 | EXPERIMENTAL

2.1 | General

Starting chemicals, organic solvents, and reagents used were from commercial sources, for example, Aldrich, Merck, etc., and were used directly without further purification. ^{1}H NMR spectra were recorded using 400-MHz or 500-MHz machines, with chemical shifts in δ units, downfield positive, and referenced to the residual peak of deuterated solvents ($CDCl_3$ δ 7.24, d_6-DMSO δ 2.50).

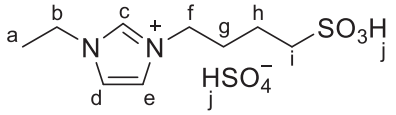
2.2 | 3-Ethyl-1-(butane sulfonic acid) imidazolium hydrogen sulfate ([EBsImH][HSO_4])

The ionic liquid catalyst **[EBsImH][HSO_4]** was prepared in two stages according to the procedure given in the

literature.[26] Into a 150-ml round-bottomed flask, 1-ethylimidazole (2.00 g, 21.0 mmol) and 1,4-butanesultone (2.86 g, 21.0 mmol) were added, followed by toluene (40 ml). The reaction mixture was stirred at 40°C for 24 hr using a magnetic bar. A white precipitate formed, which was filtered and then washed with toluene prior to being pumped dry under reduced pressure, ending in white zwitterion 3-ethyl-1-(butane sulfonic acid) imidazolium (**EBsIm**, 4.03 g, 82.6%). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 9.23 (s, 1H, H_c), 7.80 (s, 2H, H_e, H_d), 4.22–4.16 (m, J = 7.6 Hz, 4H, H_b, H_f), 2.47 (t, J = 7.2 Hz, 2H, H_i), 1.92–1.85 (m, J = 7.4 Hz, 2H, H_h), 1.58–1.50 (m, J = 7.4 Hz, 2H, H_g), 1.43–140 (t, J = 7.6 Hz, 3H, H_a). The zwitterion intermediate **EBsIm** was further mixed well with H_2SO_4(*c*), in a 1:1 M ratio, and then heated to 100°C until the mixture gave a uniformly colorless liquid that was placed under vacuum for 24 hr to obtain the ionic liquid **[EBsImH][HSO$_4$]** (Scheme 3). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 4.90 (br, 2H, H_j), 9.20 (s, 1H, H_c), 7.79 (s, 1H, H_e), 7.78 (s, 1H, H_d), 4.21–4.15 (m, *J* = 7.72 Hz, 4H, H_b, H_f), 2.51–2.48 (t, *J* = 7.8 Hz, 2H, H_i), 1.92–1.86 (m, *J* = 7.4 Hz, 2H, H_h), 1.58–1.50 (m, *J* = 7.3 Hz, 2H, H_g), 1.43–1.39 (t, *J* = 7.0 Hz, 3H, H_a).

2.3 | Batch reactions

The ionic liquid catalyst **[EBsImH][HSO$_4$]** (0.49 g, 1.5 mmol) was added to ethyl acetoacetate (1.30 g, 10.0 mmol); then, the mixture was heated to and then maintained at 70°C, with enough stirring, before the addition of 1,3-benzendiol (**1**, 1.10 g, 10.0 mmol). The reaction mixture was further stirred for 30 min, followed by EtOAc/H_2O (20 ml:10 ml) extraction. The organic layer was rotary evaporated to yield a crude product that was recrystallized from EtOH/H_2O to give the coumarin derivative **A.** Similar batch Pechmann condensation reactions using acidic ionic liquid **[EBsImH][HSO$_4$]** as a catalyst for phenol reactants with ethyl acetoacetate, for example, 1,3,5-trihydroxybenzene (**2**), 1,2,3-trihydroxybenzene (**3**), 3,5-dihydroxytoluene (**4**), and 3-methoxyphenol (**5**), were conducted in order to yield the coumarin derivatives **B**–**E**. All these Pechmann condensation reactions were performed under solvent-free conditions. The structures of coumarin derivatives **A**–**E** are displayed in Scheme 4, with the conversion data given in the Results and Discussion sections.



SCHEME 3 Structure of **[EBsImH][HSO$_4$]**

A (82.1%, mp: 182–184°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51 (d, *J* = 9.6 Hz, 1H, H_b), 6.88–6.82 (m, 2H, H_c, H_d), 6.16 (s, 1H, H_a), 2.42 (s, 3H, H_e).[19,27]

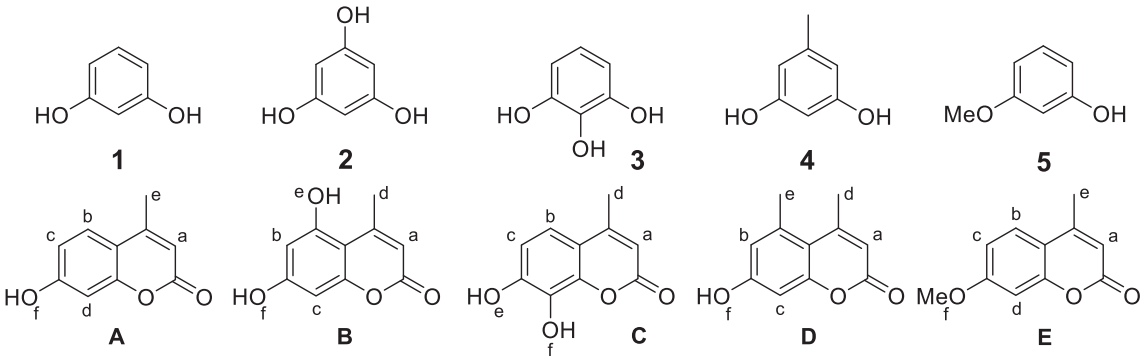
B (96.1%, mp: 282–284°C). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 10.57 (s, 1H, H_f), 10.36 (s, 1H, H_e), 6.24–6.24 (d, 1H, H_b), 6.16–6.15 (d, 1H, H_c), 5.83 (s, 1H, H_a), 2.47 (s, 3H, H_d).[19,27]

C (76.9%, mp: 240–242°C). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 10.03 (s, 1H, H_e), 9.27 (s, 1H, H_f), 7.10–7.08 (d, 1H, H_b), 6.82–6.80 (d, 1H, H_c), 6.12 (s, 1H, H_a), 2.35(s, 3H, H_d).[19,27]

D (94.3%, mp: 249–251°C). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 10.52 (s, 1H, H_f), 6.62(d, 1H, H_b), 6.57 (s, 1H, H_c), 6.04 (s, 1H, H_a), 2.54(s, 3H, H_e), 2.27 (s, 3H, H_d).[19,27]

E (42.8%, mp: 160–162°C)[56]. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.69–7.67 (d, *J* = 8.4 Hz, 1H, H_b), 6.98 (s, 1H, H_d), 6.95 (d, *J* = 2.48 Hz, 1H, H_c), 6.21 (s, 1H, H_a), 3.86(s, 3H, H_f), 2.39 (s, 3H, H_e).[19,27]

For comparison, batch reactions using H_2SO_4(*c*) instead of **[EBsImH][HSO$_4$]** as the catalyst were also performed under solvent-free conditions, with each using the catalyst H_2SO_4(*c*) (0.14 g, 1.5 mmol), reactant ethyl acetoacetate (1.30 g, 10.0 mmol), and phenol reactants **1**–**5** (1.10–1.26 g, 10.0 mmol) to produce the corresponding coumarin derivatives **A**–**E**.



SCHEME 4 Structures of phenol reactants **1–5** and coumarin derivatives **A–E**

2.4 | Recycling use of the ionic liquid catalyst [EBsImH][HSO_4]

The ionic liquid catalyst **[EBsImH][HSO_4]** (0.49 g, 1.5 mmol) was mixed well with ethyl acetoacetate (1.30 g, 10.0 mmol) at 70°C; then, the phenol reactant was added (using **1** as example, 1.10 g, 10.0 mmol). The reaction mixture was further stirred for 30 min, followed by EtOAc/H_2O (20 ml:10 ml) extraction. The H_2O layer was further extracted with EtOAc (20 ml × 2) before rotary evaporation and then vacuum dried at 120°C for 24 hr. The recovered ionic liquid catalyst [EBsImH][HSO_4] was then mixed well with ethyl acetoacetate and **1** in the same molar ratio for the next Pechmann condensation reactions, with similar activity observed. The recovery and reuse experiments were conducted four times.

2.5 | Microfluidic flow reactions

One syringe (12 ml) was prepared, each containing, in different experiments, an individually homogeneous solution of phenol reactants **1**–**5** (1.10–1.26 g, 10.0 mmol) plus a varying amount of ethyl acetoacetate (1.30–5.20 g, 10.0–40.0 mmol), with flow controlled by a Fusion 100 syringe pump (syringe size 0.5–60 ml).[28] A second syringe (12 ml) of simple ionic liquid catalyst **[EBsImH][HSO_4]** (0.49–3.30 g, 1.5–10.0 mmol) was set up, which was also controlled with a Fusion 100 syringe pump. The ionic liquid catalyst **[EBsImH][HSO_4]** may require slight heating to assist its transfer from the mother liquor to the inside volume of the syringe. The syringe outlet was connected to polytetrafluoroethylene (PTFE) fittings and tubing [1/16″ od (= outside diameter), 0.18 or 0.50 mm id (= interior diameter), typically 10 cm]. The first inlet of the PTFE Tee was connected to the tube through which the phenol reactants plus ethyl acetoacetate flowed, and the second inlet was connected to the tube through which the ionic liquid catalyst **[EBsImH][HSO_4]** flowed, whereas the outlet of PTFE Tee was connected to a reaction tubing (1/16″ od, 0.18 or 0.50 mm id, typically 100 cm). The tube outlet was connected to PTFE fittings, and the product mixture was received by a third syringe (12 ml) for convenience in handling samples. The reaction tubing was experimentally immersed in a sand bath, typically at 70°C for constant temperature.

3 | RESULTS AND DISCUSSION

The batch Pechmann condensation reactions of ethyl acetoacetate and **1** to produce **A** were optimized under solvent-free conditions; based on this, the temperature of the reaction chosen was 70°C (Table 1); the time of reaction was 30 min (Table 1); and the ionic liquid catalyst **[EBsImH][HSO_4]** was greater than 15 mol% (Table 2). Concerning the reaction conditions, a conversion greater than 80% was chosen to be used as the starting point for later optimization on the microfluidic flow experiments.

TABLE 1 Conversions of **1** to **A** in the batch Pechmann condensation at various temperatures (condition: **1** 10 mmol; ethyl acetoacetate 10 mmol; **[EBsImH][HSO_4]** 15 mol%)

Entry	Time/min	50°C conversion (%)	60°C conversion (%)	70°C conversion (%)
1	5	16.4	36.2	48.3
2	10	33.0	48.6	59.2
3	15	40.7	56.4	67.1
4	20	47.7	68.8	73.4
5	25	53.9	75.9	78.3
6	30	58.8	80.6	82.1

Entry	Mol %	Temperature (°C)	Time (min)	Conversion (%)
1	2	70	30	62.3
2	5	70	30	64.2
3	15	70	30	82.1
4	50	70	30	84.3
5	100	70	30	90.2

TABLE 2 Conversions of **1** to **A** in the batch Pechmann condensation at various **[EBsImH][HSO_4]** amounts (condition: **1** 10 mmol; ethyl acetoacetate 10 mmol; temp. 70°C; time 30 min)

TABLE 3 Comparison of the conversions in batch Pechmann condensation reactions using **[EBsImH][HSO$_4$]** or H_2SO_4(*c*) as catalyst (15 mol%) for ethyl acetoacetate and different phenol reactants **1**–**5** to produce **A**–**E** (condition: substrate 10 mmol; ethyl acetoacetate 10 mmol; temp. 70°C; time 30 min)

Entry	Phenol reactant	Coumarin derivative	[EBsImH][HSO$_4$], conversion/%	H_2SO_4(*c*), conversion/%
1	**1**	**A**	82.1	74.1
2	**2**	**B**	96.1	94.2
3	**3**	**C**	76.9	72.2
4	**4**	**D**	94.3	50.2
5	**5**	**E**	42.8	28.8

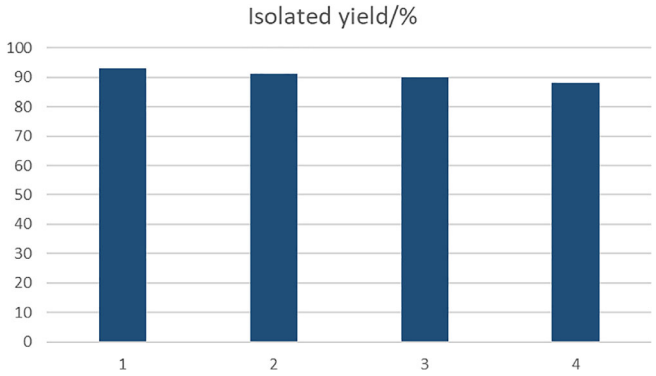


FIGURE 1 Results on yields for four consecutive runs of Pechmann condensation reaction reusing recovered acidic ionic liquid catalyst **[EBsImH][HSO$_4$]**

Maintaining the batch reaction conditions at 70°C and 30 min for respective phenol reactants **1**–**5** (10 mmol) and common ethyl acetoacetate (10 mmol) using acidic ionic liquid **[EBsImH][HSO$_4$]** as the catalyst (15 mol%), the results of the produced coumarin derivatives **A**–**E** are shown in Table 3. The conversion of coumarin derivative **E** is the lowest (42.8%), and that of **C** is also lower (76.9%) than that of the remaining coumarin derivatives (**A** 82.1%; **B** 96.1%; **D** 94.3%). A comparison of the catalyst activity was also made between **[EBsImH][HSO$_4$]** and H_2SO_4(*c*), as shown in Table 3. Using H_2SO_4(*c*) as the catalyst, the conversion of coumarin derivative **B** is fine (94.2%), but not the conversions of the remaining coumarin derivatives (**A** 74.1%; **C** 72.2%; **D** 50.2%; **E** 28.8%). Thus, for the batch Pechmann condensation reactions of ethyl acetoacetate and different phenol reactants **1**–**5** used to produce **A**–**E**, the ionic liquid **[EBsImH][HSO$_4$]** is more compatible under solvent-free conditions than the H_2SO_4(*c*) as a catalyst.

Using recovered acidic ionic liquid **[EBsImH][HSO$_4$]** as the catalyst, the results of its reuse four consecutive times are shown in Figure 1 for the production of **A**, as an example, maintaining >85% conversion at all times. The batch Pechmann condensation reactions gave, at final stage, the coumarin derivative product in the EtOAc layer and the catalyst in the H_2O layer. The acidic ionic liquid catalyst **[EBsImH][HSO$_4$]** was easily recovered from the H_2O layer and then reapplied in an identical Pechmann condensation reaction with the introduction of the same amounts of phenol reactant and ethyl acetoacetate, under solvent-free conditions.

In this study, the Pechmann condensation reactions have been modified from a batch setup to a microfluidic flow setup. The basic idea behind this was to calibrate the PTFE Tee position to be the starting point along the reaction coordinate and the PTFE tubing outlet position to be the ending point, that is, at approximately 0 and 30 min correspondingly in the flow, provided that the microfluidic flow reaction could be completed by a reaction time similar to the duration in the batch Pechmann condensation reaction. We found that the ethyl acetoacetate reaction with different phenol reactants **1**–**5** did not proceed with the same time in a microfluidic flow setup to produce coumarin derivatives **A**–**E**. Throughout the series, the reaction temperature was maintained at 70°C. The reaction times completing the microfluidic flow are shown in Table 4. The suggested 30-min reaction time worked for **B**, **C**, and **D** (entries 4–10), whereas an extension to 60-min reaction time worked for **A** (entries 1–3) and **E** (entries 11–13). The reactant mixtures (phenol reactants + ethyl acetoacetate) were varied by the molar ratio. The flow rate of the reactant mixtures and the flow rate of the catalyst were also varied. At a 1:1 phenol reactants/ethyl acetoacetate molar ratio, the conversions were not satisfactory: **A** 51.2% (entry 1), **D** 33.2% (entry 8), and **E** 5.6% (entry 11). In addition, the viscous nature of the flow did not allow **B** and **C** to run on the microfluidic flow system. A change of the phenol reactant/ethyl acetoacetate molar ratio from 1:1 to 1:2–1:4 allowed the microfluidic flow reactions to proceed (entries 2, 4, 6, 9, and 12), taking advantage of the fact that the extra ethyl acetoacetate modifies the original viscosity of the flow that is intrinsically solvent free. The result of **E** was not yet satisfactory (entry 12). Furthermore, we attempted mixing 1:1 ionic liquid **[EBsImH][HSO$_4$]** and H_2SO_4(*c*) as a catalyst for the microfluidic

TABLE 4 Comparison of the conversions of microfluidic flow Pechmann condensation for different phenol reactants **1**–**5** at 70°C, using **[EBsImH][HSO$_4$]** as catalyst

Entry	Product	Time (min)	Reactant flow rate (μl/min)	Phenol: EAA	Catalyst flow rate (μl/min)	Conversion (%)
1	**A**	60	48	1:1	24	51.2
2	**A**	60	54	1:2	18	94.1
3	**A**	60	73	1:1	73[a]	96.2
4	**B**	30	120	1:4	24	97.3
5	**B**	30	146	1:4	146[a]	98.1
6	**C**	30	108	1:2	36	80.2
7	**C**	30	146	1:2	146[a]	94.7
8	**D**	30	96	1:1	48	33.2
9	**D**	30	108	1:2	38	88.5
10	**D**	30	146	1:1	146[a]	90.2
11	**E**	60	48	1:1	24	5.6
12	**E**	60	54	1:2	18	5.2
13	**E**	60	73	1:1	73[a]	66.6

[a]Modified catalyst **[EBsImH][HSO$_4$]**/H_2SO_4(*c*) (1:1) was used.

TABLE 5 The optimum rates of microfluidic flow Pechmann condensation for coumarin derivatives **A**–**E**, using 1:1 **[EBsImH][HSO$_4$]**/H_2SO_4(*c*) as catalyst at 70°C

Entry	Product	Reactant flow rate (μl/min)	Phenol: EAA	Catalyst flow rate (μl/min)	Conversion (%)	Hourly yield (g/hr)
1	**A**	73	1:1	73	96.2	3.7
2	**B**	146	1:4	146	98.1	3.9
3	**C**	146	1:2	146	94.7	5.3
4	**D**	146	1:1	146	90.2	7.5
5	**E**	73	1:1	73	66.6	2.8

flow reactions, achieving the results of **A** 96.2% (entry 3), **B** 98.1% (entry 5), **C** 94.7% (entry 7), **D** 90.2% (entry 10), and **E** 66.6% (entry 13). The result of **E** at 66.6% in conversion is a more-than-10× increase compared to that at 5.6% (entry 11) or at 5.2% (entry 12), but it still has room to improve.

Table 5 lists the hourly yields of coumarin derivatives **A**–**E** for this case study on the microfluidic flow Pechmann condensation reactions, where the lowest hourly yield of 2.8 g/hr for **E** is noted, whereas the hourly yields of **A**–**D** are between 3.7 g/hr (low) and 7.5 g/hr (high), all being greater than that of **E**. The ionic liquid **[EBsImH][HSO$_4$]** mixing with equal molar H_2SO_4(*c*) has been utilized in the microfluidic flow Pechmann condensation reactions under solvent-free conditions.

To summarize the case study on the microfluidic flow Pechmann condensation reactions, the hourly yields of coumarin derivatives above were achieved, not by using the simple acidic ionic liquid **[EBsImH][HSO$_4$]** as a catalyst but rather by using a 1:1 mixed ionic liquid **[EBsImH][HSO$_4$]** and H_2SO_4(*c*), under solvent-free conditions.

The summary on conversions in producing **A**–**E** is as follows: with batch 82.1, 96.1, 76.9, 94.3, and 42.8%, respectively (Table 3) and with flow 96.2, 98.1, 94.7, 90.2, and 66.6%, respectively (Table 5). The microfluidic flow reaction indeed shows advantages of a short diffusion path length, enhanced heat transfer, and easy residence time control in this case study on the synthesis of coumarin derivatives. For demands of greater quantity, similar modules of the microfluidic flow reaction setup could be replicated. A batch reaction has to go through pilot stages in order to scale up production.

The current study analyzed the ^{1}H NMR spectroscopic data of coumarin derivative product mixtures in order to calculate the degree of product formation. A benefit of targeting coumarin derivatives in a microfluidic flow reaction is that the reactant mixtures have no

luminescence, but the product mixtures would self-report the degree of formation of coumarin derivative because of the inherent photoluminescence property, which would greatly help in the future in the development of the microfluidic flow reaction system. Taking, for example, structure **A** without the 3-methyl substituent, 7-hydroxycoumarin shows a characteristic emission peak at 387 nm and an absorption maximum at 326 nm, with the quantum yield being 0.08.[29]

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