Two-Stage Flow Synthesis of Coumarin via *O*-Acetylation of Salicylaldehyde

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Continuous-flow synthesis of coumarin was realized in a tandem microflow system containing two microreactors in this study. Generally, better reaction yield (91%) and less side reaction were obtained in the flow system compared with conventional method. Interestingly, different reaction pathways were observed between continuous-flow system and batch methods.

Keywords: coumarin, continuous-flow approach

1. Introduction

Flow chemistry, as a rapidly emerging technology, is exploited to provide an efficient, scalable route for the fine chemical coumarin. By the two connected coil reactors design, the reaction mechanism is proved to be *O*-acylation followed by intramolecular aldol-type condensation. The *O*-acetylation of salicylaldehyde reduced the generation of phenolic resin and resulted in highly increased yield and safety.

Recently, coumarin (Figure 1) and its derivatives, including 5,6-benzopyrone, 1,2-benzopyrone, became more and more attractive for chemists because of their clinical medical values, such as anti-HIV, antitumor, antihypertension, anti-arrhythmia, anti-inflammatory, anti-osteoporosis, antiseptic, and analgesic [1]. Coumarin itself is found in many plants, such as *Dipteryx odorata*, *Anthoxanthum odoratum*, and *Galium odoratum*, and has been used in perfume, tobacco, and certain alcoholic drinks. Various strategies for the synthesis of coumarin and its derivatives, including Pechmann, Perkin, Knoevenagel, Claisen–Reformatsky, and Wittig reactions, have been developed by several groups [2]. Traditionally, the most accessible route to produce coumarin on industrial scale involves a Perkin reaction between salicylaldehyde and acetic anhydride at 150–200 °C for 6–8 h. Acetic acid generated should be removed to keep the reaction at high temperature and the resin generated during the reaction causes an increase in viscosity. Thus, we turned our attention in developing a concise and efficient synthesis of coumarin.

Continuous-flow synthesis has been proved to be a practical technique with many advantages over the conventional batch reactions [3]. It offers precise control of stoichiometry, reaction time, temperature, high reproducibility, and often better reaction yields due to the higher surface area to volume ratio under flow conditions [4]. Especially, it offers enhanced safety for superheated or pressurized reactions and hazardous reagents containing obnoxious intermediates producing reactions [4]. It can be used not only in the major classes of organic transformation but also in the others, including polymerizations [3], photochemical reactions [5], precipitate-forming reactions [6], electrosyntheses [7], and enzymatic reaction [8]. Herein, the flow chemistry methodology for the synthesis of coumarin was developed, with less acetic anhydride and simple procedure.

2. Results and Discussion

2.1. Generation Flow Design. Our initial objective was to minimize the reaction time for the production of coumarin. To achieve this, we started our investigation by simply transferring the reported method [9] to a Vapourtec R4/R2+ flow reactor at 240 °C with residence time of 5 min on a 100 mL scale. The back-pressure regulator was located at the end of the heated zone to offer a 21–25 bar press for the reaction system to prevent the gasification of reactant mixture at high temperature (Scheme 1). However, the conversion was improved from 6.4% up to only 21.1% with residence time increasing from 5 min to 30 min (Table 1). One undesired product, which was assigned to be the *O*-acetylsalicylaldehyde (**3**) [10], was yielded within significant quantities. The compound **3** indicated that the process of this reaction could contain *O*-acetylation. The reported mechanism for the reaction contains Perkin condensation followed by intramolecular esterification, in which the intermediate compound **2** was supposed to be detected (Scheme 2). However, compound **2** was not detected. In order to confirm the process of the reaction, a series of reactions at the temperature in the range between 110 °C and 200 °C was performed on the microreactor. Monitoring on thin-layer chromatography (TLC) showed that two compounds, including compound **3** and coumarin, were generated during the reaction, and coumarin did not show up at the temperature lower than 180 °C. On the basis of the result, we presumed that the temperature might alter the mechanism of the reaction, in which the mild condition benefited the acetylation, while high temperature preferred aldol condensation or Perkin process. Also, no compound **2** was produced when the reaction temperatures

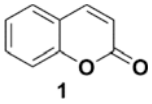

Figure 1. Structure of coumarin

Scheme 1. Schematic of the flow configuration used for the synthesis of coumarin

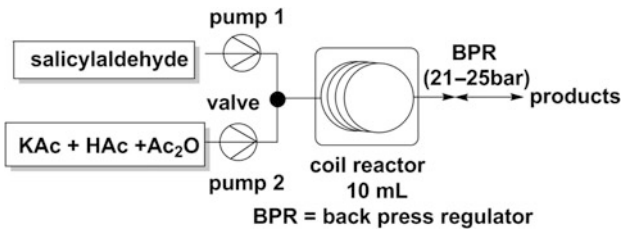

Table 1. Synthesis of coumarin in microreactor with various residence times

Reaction time (min)	5	10	15	20	25	30
Conversion to coumarin (%)	6.4	10.6	14.7	16.5	20.3	21.1

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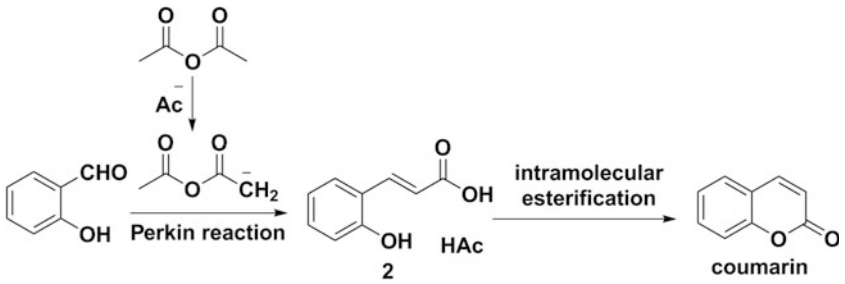
Scheme 2. Reported mechanism of formation of coumarin via the Perkin reaction



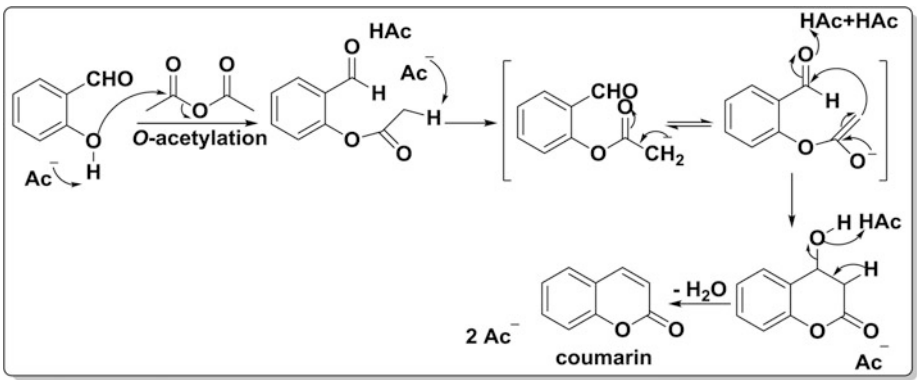
were 180 °C, 190 °C, 200 °C, and 240 °C. That means the reported "perkin process" was not suitable to explain the process of the reaction in microreactor. As shown in Scheme 3, the reaction process was described as *O*-acetylation and intramolecular aldol-type condensation followed by dehydration.

In order to confirm the proposal mechanism, we constructed a standard PFA coiled tube reactor coupled to a high-temperature coiled tube reactor, considering the generally reported mild conditions for acetylation [11] and Majumder's report [12] on the formation of coumarin at 175–180 °C from *O*-acetylsalicylaldehyde. The construction, in which the two coils could be heated to the desired temperature individually, enabled us to achieve better controlled temperatures for the two staged reaction.

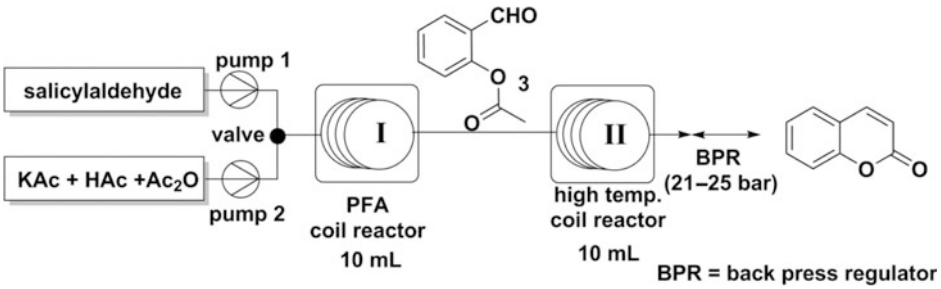
Firstly, the synthesis of coumarin by passing the reaction mixture through the connected coil reactors of 150 °C and 240 °C was examined with the residence time of 15 min (Scheme 4). The conversion to coumarin increased significantly to 78%. The exciting results demonstrated that the individually controlled temperatures finished each stage of the reaction completely and encouraged us to continue our work by optimizing the conditions of two stages of the reaction.

2.2. Optimization of *O*-Acetylation and Intramolecular Aldol-Type Condensation. The optimization of *O*-acetylation of salicylaldehyde was investigated as follows. Firstly, the reactions were performed by varying the temperature in the range between 110 °C and 170 °C while keeping residence time as 25 min. High-performance liquid chromatography (HPLC) analysis illustrated that the compound **3** was the sole product in the reaction at temperature beneath 180 °C. As shown in Figure 2, the conversion of salicylaldehyde to **3** increased upon increasing the temperature up to 150 °C but decreased upon further increasing temperature. It indicated that gently heating below 150 °C contributes to *O*-acetylation of salicylaldehyde but not formation of coumarin. Moreover, it explained why the reactions at 240 °C afforded low conversion to coumarin (Table 1) as that high temperature afforded less intermediate **3**, which resulted in less coumarin produced. Therefore, the optimal temperature for the synthesis of compound **3** was 150 °C. We next explored the optimal residence time of the *O*-acetylation stage by running the reactions with the various residence times ranging from 10 to 30 min. As presented by the results in Figure 3, the reactions with residence time of 22.5 min and 25 min afforded similar conversion of salicylaldehyde to **3**. Unexpectedly, long residence time did not give high conversion. The ratio of compound **3**–salicylaldehyde increased as the residence time increased up to 25 min, as listed in Table 2. Additionally, the ratio of compound **3**–salicylaldehyde decreased significantly 5 days after reaction, as shown in Figure 5. We believe that the unstability of compound **3** with H_2O is the main reason for this phenomenon.

Scheme 3. Proposal mechanism of formation of coumarin via *O*-acetylated salicylaldehyde



Scheme 4. Schematic of the flow configuration with the two connected coil reactors



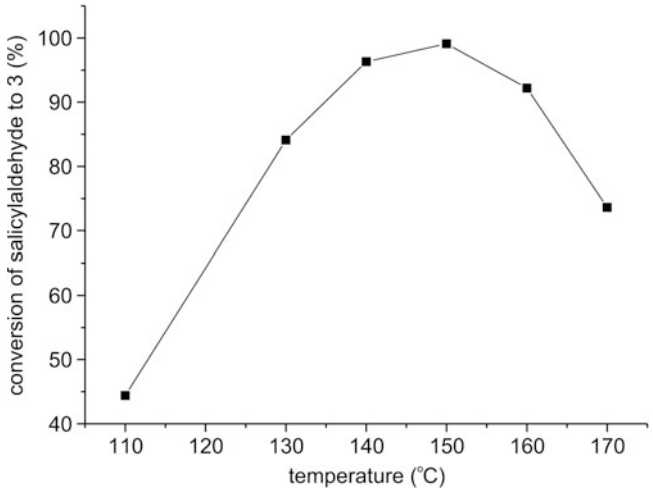


Figure 2. Conversion to **3** at various temperatures with 25 min of residence time

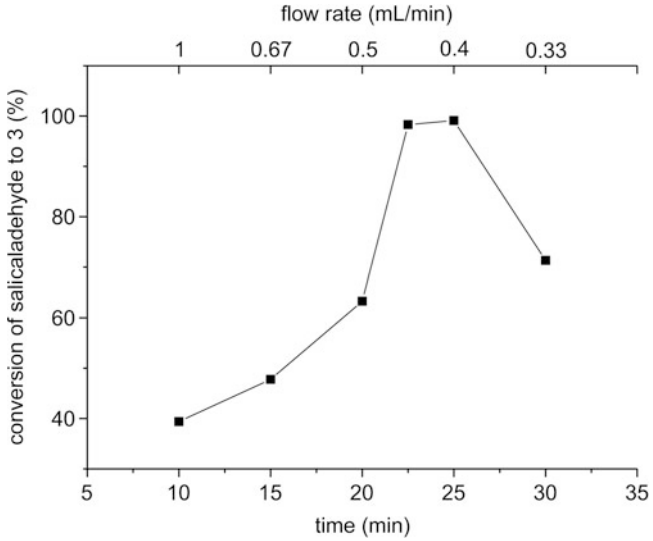


Figure 3. Conversion to **3** at 150 °C with various residence times

Table 2. Ratio of compound **3** to salicyaldehyde with different residence time

Time (min)	10	15	20	22.5	25	30
R^a	0.7	1.66	1.91	11.67	29.5	9.31

[a] Ratio between compound **3** and salicylaldehyde. It was attained by comparing HPLC peak area of two compounds.

It was reported that, when *O*-acetylsalicylaldehyde was heated in the presence of fused NaOAc at 175–180 °C for 8 h, it afforded coumarin as the sole condensation product in ca. 40% yield [12]. Thus, the effluent mixture from reactor **I** was directly added to the coil reactor **II** heated to the temperatures ranged from 170 °C to 250 °C. The conversion to coumarin from **3** increased with the temperature increased (Figure 4). Notably, by-product phenolic resin also increased with the temperature increasing, which made effluent thick and would clog the coil reactor. This can explain why the reaction at 250 °C failed with blockage issues. Finally, the optimal temperature of intramolecular aldol condensation was identified to be 240 °C. Consequently, the reactions at 240 °C with residence time varied from 5 to 25 min were investigated. As shown in Figure 6, the conversion to coumarin increased with the residence time increased up to 25 min. We consider the resin, formed as a result of the back mixing in flow reactors due to the extended reaction at high temperature, as the reason for the decreased conversion. This was reflected by the dark effluent mixture collected after reaction. Finally, 22.5 min was identified to be the optimal residence time of the conversion from **3** to coumarin.

Finally, the flow synthesis of coumarin under the optimized conditions above starting from salicylaldehyde was successfully performed with a 91% conversion in the coil configuration

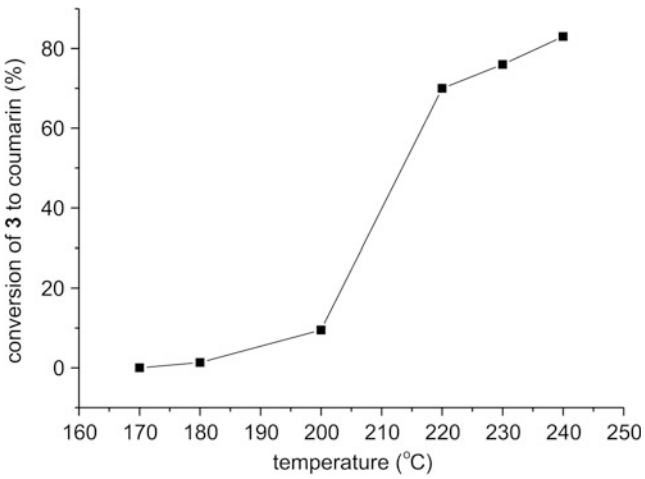


Figure 4. Conversion to coumarin from **3** at various temperatures with 25 min of residence time

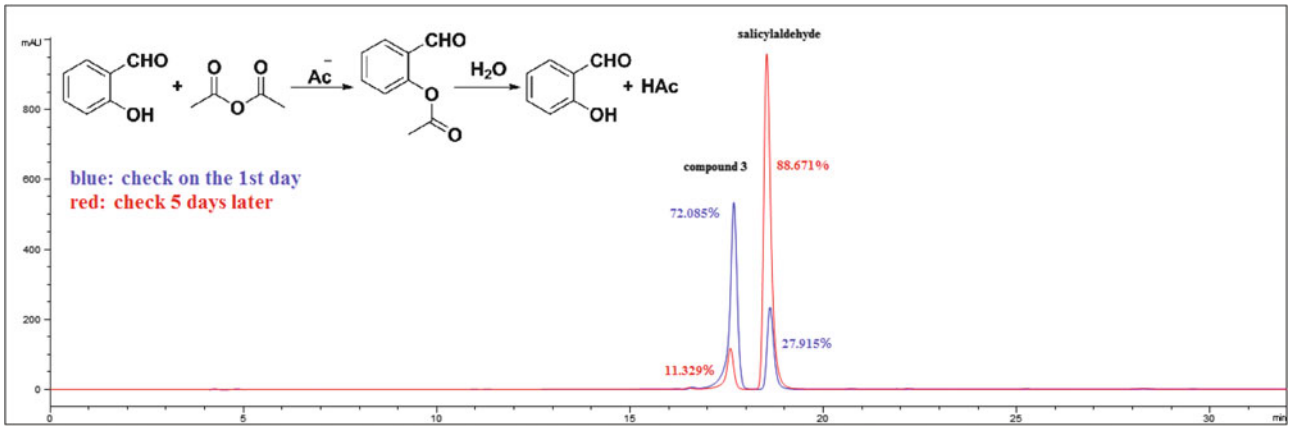


Figure 5. HPLC spectra for the reaction mixture of *O*-acetylation of salicylaldehyde

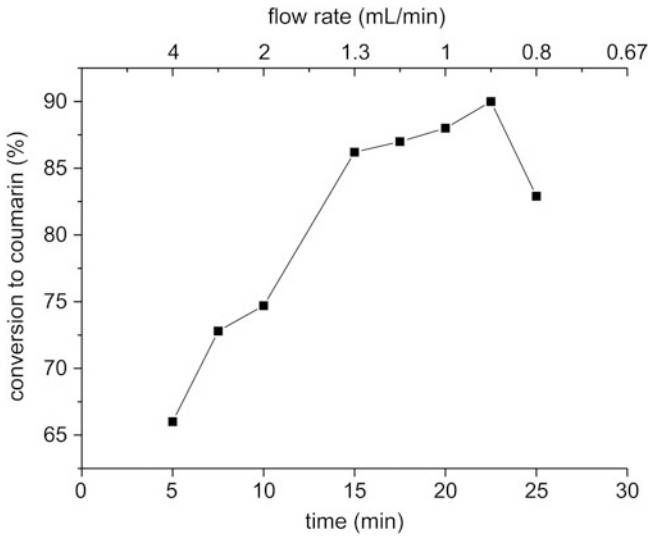


Figure 6. Conversion to coumarin from **3** at 240 °C with various residence times

(Table 2, entry 2). It is worth mentioning that the residence time of the coil reactor **I** was adjusted to 22.5 min to adapt the residence time of the coil reactor **II**, confined to the same volume of coil reactors on the device. With simple reduced pressure distillation, the pure coumarin could be obtained. This methodology worked successfully for up to at least 120 g scale in laboratory by continuous operation. With a straightforward modification, it can be applied on industrial scale. Notably, the back mixing in flow reactors under continuous operation is supposed to be a technical barrier for large-scale manufacturing process. We believe that the effective mixer installed in the microreactor or a gradual size increase of the reactor will overcome this problem.

2.3. Comparison with Conventional Synthesis of Coumarin by Perkin Reaction. As the further investigation, the comparison between the synthesis in batch and that in microreactor was performed (Table 3). By flow synthetic methodology, coumarin was yielded in 91% in 22.5 min, whereas, in batch, it frequently requires several hours under reflux condition. On the other hand, the continuous production of coumarin without an acid-removing procedure during the reaction could raise the productive efficiency in the further manufacture. More importantly, less acetic anhydride used in the reaction means economical application on potential industrial scale. All features mentioned above can bring a potentially cost-effective manufacture in the future.

In summary, a continuous-flow approach to the synthesis of coumarin was developed. The new reactor employed in this methodology consists of two coils, which were heated individually to the desired temperatures. By this methodology, coumarin was synthesized in 91% conversion via two-staged reaction including the *O*-acetylation and intramolecular aldol-type condensation followed by dehydration. By a continuous operation, it was amenable to scale-up to 120 g. It is believed that with straightforward modification, including parallel running and mixer set, the approach has a potential application on manufacturing scale.

3. Experimental Section

3.1. General Experimental Methods

3.1.1. Description of the Apparatus. All the experiments were performed on a Vapourtec R4/R2+ flow reactor. The system was equipped with one or two reactor coils. The "reagent out" port on

Table 3. Comparison between the synthesis of coumarin in batch and microreactors

Entry	Option	Time (min)	Acid removing	Temperature (°C)	Ac_2O	Conversion
1	Batch	480	Yes	180	2 eq.	68%
2	Microreactor	22.5	No	150 + 240	1.1 eq.	91%

the first reactor coil was connected to the "reagent in" port on second reactor coil using a 32-mm length of tubing. The "reagent out" port on the second reactor was equipped with a 250 bar back-pressure regulator, after which there was a length of tubing leading to a waste or collection flask. The system was initially primed using the equipment manufacturer's suggested startup sequence.

3.1.2. General Procedure. A solution of potassium acetate (0.01 equiv.), acetic anhydride (1.1 equiv.), and acetic acid (0.26 equiv.) was prepared, where acetic acid was added to improve the solubility of KAc in acetic anhydride. The solution was thoroughly mixed until it became a completely homogeneous clear solution. The solution and salicylaldehyde were pumped into the coil reactors, respectively. Product collection was commenced after three cycles of residence time, and the time for the collection was recorded for the further calculation. After reaction, the reactor was flushed with pure ethanol at the temperature higher than 150 °C. The collected effluent could then be detected by HPLC or further purified. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Ascend (400 MHz) spectrometer in $CDCl_3$ (7.26 ppm and 77.1 ppm).

3.1.3. Purification Methods

3.1.3.1. Compound ***3****.* The reaction mixture was neutralized by saturated Na_2CO_3 solution followed by extraction with CH_2Cl_2 (3 × 30 mL). Removal of solvent and purification by column chromatography on silica gel with hexane–EtOAc (5:1) afforded **3** (94%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.11 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.66–7.60 (m, 1H), 7.42–7.37 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 188.9, 169.4, 151.6, 135.4, 131.5, 128.1, 126.5, 123.6, 21.0. It is in good agreement with the reported data [10].

3.1.3.2. Coumarin. The reaction mixture was neutralized by saturated Na_2CO_3 solution. Extraction with CH_2Cl_2 (3 × 30 mL), removal of solvent and purification by column chromatography on silica gel with hexane/EtOAc (5:1) afforded 3 (94%) as an oil. The combined organic extracts were washed with saturated Na_2CO_3 solution (20 mL) and evaporated in vacuum. Flash chromatography on silicagel with hexane–EtOAc (10:1) gave coumarin as a white solid: mp69-71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 9.5 Hz, 1H), 7.54–7.47 (m, 2H), 7.32–7.26 (m, 2H), 6.41 (d, J = 9.5 Hz, 1H) ^{13}C NMR ($CDCl_3$, 400 MHz) δ 160.8, 154.1, 143.5, 131.9, 127.9, 124.5, 118.9, 116.9, 116.7.

3.2. HPLC Analysis.

(a) HPLC analysis for coumarin was performed by loading samples into the injector of an Agilent Technologies 1260 Infinity HPLC system (Eclipse XDB-C18 column [length: 250 mm, ID: 4.6 mm]) with a flow rate of 1.0 mL/min; acetonitrile–aqueous acetic acid (0.5% v/v): initial (20/80); 20 min (20/80); 25 min (45/55), using an ultraviolet (UV) detector with analysis channel at 275 nm.

(b) HPLC analysis for salicylaldehyde was performed by loading samples into the injector of an Agilent Technologies 1260 Infinity HPLC system (Eclipse XDB-C18 column [length: 250 mm, ID: 4.6 mm]) with a flow rate of 0.6 mL/min; acetonitrile–aqueous acetic acid (0.5% v/v): initial (20/80); 25 min (20/80); 35 min (60/40); 40 min (90/10); 50 min (90/10), using a UV detector with analysis channel at 257 nm.

(c) The product ratios and conversion were calculated by calibration curve method. Standard curve was made by checking the commercially available analytical grade of coumarin and salicylaldehyde (detection at 275 and 257 nm).

Supporting Information

Electronic Supplementary Material is available in the online version at doi: 10.1556/1846.2014.00043.

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