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Efficient aldol condensation in aqueous biphasic system under microfluidic conditions

Katsunori Tanaka[a], Shinya Motomatsu[a,b], Koichi Koyama[b], Koichi Fukase[a,*]

[a] *Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama-cho, Toyonaka-shi, Osaka 560-0043, Japan*
[b] *Kishida Chemical Co., Ltd, Technopark 14-10, Sanda, Hyogo 669-1339, Japan*

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Abstract

A microfluidic system was applied to aldol reaction in aqueous biphasic medium. Advantageous aspects of microfluidic conditions, that is, efficient mixing, fast heat transfer, and residence time control led to the high-yielding reaction of acetone enolate with even α-proton-containing aldehydes in biphasic aqueous-acetone system, by minimizing the formation of self-condensation products.

A continuous flow microreactor, which is reported to realize efficient mixing and fast heat transfer, is recognized as an innovative technology in recent organic syntheses.[1] The flow system also allows the control of the residence time, namely, the reaction mixture can be subjected to the subsequent reaction in appropriate intervals; hence the method is well-suited for the reactions dealing with the unstable intermediates.[2] Furthermore, once the reaction conditions are optimized for small-scale operation, the same conditions are directly applicable to large-scale synthesis under the flow process. By taking advantage of these aspects, we have recently applied a microfluidic system to the cation-mediated reactions and improvements have been realized for glycosylations,[3a,b] dehydration,[3c] and the reductive opening of benzylidene acetal groups.[3d] We herein report the efficient aldol condensation of acetone in an aqueous biphasic system.

Aldol condensation is one of the most fundamental C–C bond forming reactions and a variety of efficient procedures, including the metal- or organic molecule-catalyzed asymmetric variants, have actively been investigated.[4] β-Hydroxy α-methyl ketones are useful synthetic intermediates and prepared by using acetone as a precursor of enolate.[3c] This acetone-based aldol reaction is conveniently performed by slowly adding the aldehydes to biphasic solution of acetone and sodium hydroxide below 10 °C. For this conventional reaction, acetone is used as a solvent in order to achieve the efficient condensation. However, the efficiency of this protocol under the batch conditions significantly decreases when the reaction is performed in a large-scale, since (i) inefficient mixing of the biphasic solution, (ii) difficulty in maintaining the reaction temperature, and (iii) a long time exposure of base-sensitive starting materials and products to the highly basic reaction media lead to the aldehyde-polymerization. The situation becomes miserable particularly when the reaction is applied to the aldehydes containing the α-protons. For example, the reaction with decyl aldehyde **1** resulted in the production of a large amount of aldehyde-polymer gel, and the desired 4-hydroxy-2-tridecanone **6** is obtained only in less than 20% yield (Fig. 1).

We therefore expected that the aqueous biphasic aldol condensation is a good case where the advantageous aspects of microfluidic reaction can be featured at maximum. We have designed the microfluidic system as shown in Figure 1 by integrating two micromixers.[5,6] The appropriate flow rates and residence time were optimized for these two micromixing processes. In the first mixer, acetone

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[*] Corresponding author. Tel.: +81 6 6850 5388; fax: +81 6 6850 5419.
E-mail address: koichi@chem.sci.osaka-u.ac.jp (K. Fukase).

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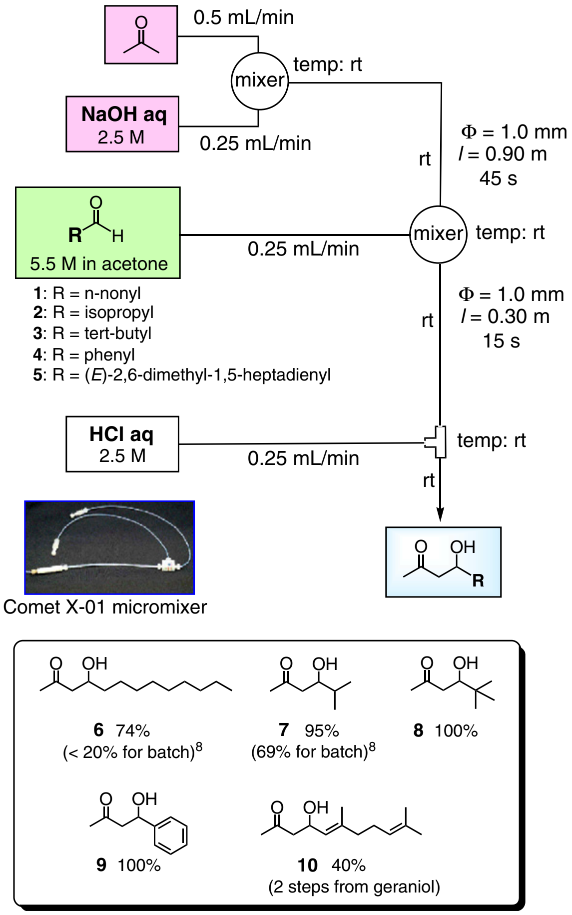

Fig. 1. Biphasic aldol condensation of acetone with aldehydes **1**–**5** under the microfluidic conditions.

enolate should be formed from acetone and aqueous NaOH solution,[7] while the enolate can be rapidly reacted with aldehydes, owing to the efficient mixing by the second micromixer. Undesired polymer formation of the base-sensitive aldehydes was effectively suppressed with this sequential process. In addition, the aldol products, which are also susceptible to the base-mediated polymerization, can be readily removed from the system after quenching with hydrochloric acid by the use of T-shaped mixer (Fig. 1).

We examined the decyl aldehyde **1**, isobutyraldehyde **2**, pivalaldehyde **3**, benzaldehyde **4**, and geranyl aldehyde **5** as the representative aldehydes, which contain different number of α-protons. Gratefully, the reaction with decyl aldehyde **1** under the conditions optimized in Figure 1 resulted in the significant increase of the aldol product formation; 4-hydroxy-2-tridecanone **6** was obtained in 74% yield, which is about fourfold increase in the yield compared with the conventional batch conditions (ca. 20%).[8] In comparison, the direct mixing of the 5.5 M aldehyde solution in acetone and the aqueous 2.5 M NaOH solution gave a significant amount of the polymerized products, similar to the results obtained by the batch reaction.[8] Furthermore, the use of lower concentrations of the aldehyde solution than that optimized in Figure 1 resulted in incomplete conversion. These results clearly show the success for applying the sequential micromixing systems, as well as the importance of the reaction concentration for the efficient micromixing. Not only the efficiency for the aldol process, but also the 'room temperature-reaction' makes the established microfluidic procedure to be quite attractive method for the β-hydroxyketone derivatives, such as for industrial-scale preparation. The reaction with isobutyraldehyde **2**, which contains a single α-proton, also gave the β-hydroxycarbonyl compound **7** in 95% yield.[9] The comparison experiment under the conventional batch reaction gave 69% of **7**;[8,10] hence the efficiency of microfluidic system to the biphasic aldol reaction can thus be proved. As expected from these two examples, the reaction with the simpler pivalaldehyde **3** and benzaldehyde **4**, which have no α-proton, gave the aldol product **8** and **9** in nearly quantitative yields. It is noted that the dehydrated product of the labile 4-hydroxy-4-phenyl-2-butanone **9** could not be detected from the reaction mixtures, since the reaction was quenched immediately after the formation of **9** under the flow process of Figure 1. The relatively unstable (*E*)-3,7-dimethyl-2,6-octadienal **5** (geranyl aldehyde) also reacted with acetone enolate under the conditions in Figure 1, providing a 40% yield of β-hydroxyketone **10** (two steps yield from geraniol)[11] together with the recovery of aldehyde **5**. Any other byproducts could not be detected from the reaction mixtures.

In summary, we have achieved the efficient aldol condensation of acetone in aqueous biphasic system even with α-proton-containing aldehydes under the microfluidic conditions. The success of the present method owes to the integration of all favorable aspects of microfluidic reactions, namely, efficient mixing, precise temperature control, and the 'easy handling' of the reactive intermediate (enolate) and the aldol adducts by controlling the residence time. The efficiency of microfluidic system for both aldol condensation and other acid-mediated reactions reported previously[3] provokes the need to re-investigate the traditional reactions, which have not been throughout utilized for organic synthesis. The research in this line is now in progress in this laboratory.

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7. The treatment of acetone with aqueous NaOH solution affords a biphasic mixture at a high concentration of NaOH. Micromixing should promote efficient transfer of NaOH from aqueous layer to organic layer and consequently form sufficient amount of acetone enolate, in spite of the large differences in their pK_a (~16 for H_2O and ~20 for α-proton of carbonyls).
8. In order to compare the microfluidic and the batch conditions, the same concentrations of the aldehydes (in acetone) and the aqueous NaOH solution were used for the batch reaction: A 5.5 M solution of the aldehyde (1.5 mol scale) in acetone was added to the premixed biphasic solution of acetone and 2.5 M NaOH (2.7:1) at 8.5 °C over 1.5–3 h.
9. Typical procedure of microfluidic aldol condensation: Acetone and 2.5 M NaOH solution were injected to the first micromixer (Comet X-01) at room temperature, by using syringe-pumps at a flow rate of 0.5 mL/min for acetone and 0.25 mL/min for NaOH solution. After the mixture was allowed to flow for 45 s through a Teflon reactor tube ($\varnothing = 1.0$ mm, $l = 0.9$ m) at this temperature, the intermediary enolate was mixed with a solution of isobutyraldehyde **2** (10 g, 139 mmol, 5.5 M) in acetone (25 mL) through the second micromixer (Comet X-01) by another syringe-pump at a flow rate of 0.25 mL/min at room temperature. After the reaction mixture was allowed to flow at the same temperature for additional 15 s through a Teflon reactor tube ($\varnothing = 1.0$ mm, $l = 0.3$ m), the mixture was quenched by another flow of 2.5 M HCl solution (0.25 mL/min) using the T-shaped mixer at room temperature. It takes about 20 min to consume 10 g of substrate **2** under the above conditions. The mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product. The residue was purified by distillation under reduced pressure (50–70 °C/20 mm Hg) to afford **7** (17 g, 95%). The spectrum data were in good agreement to those reported in Ref. 10. The conditions established herein can be readily applicable to the scale-up synthesis simply by preparing the stock solutions of substrate and reagents and pumping them continuously into the micromixing system.
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