



# Solvent-free Claisen and Cannizzaro reactions<sup>†</sup>

Kazuhiro Yoshizawa, Shinji Toyota and Fumio Toda\*

*Department of Chemistry, Okayama University of Science, Ridai-cho, Okayama 700-0005, Japan*

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**Abstract**—Claisen and Cannizzaro reactions were found to proceed efficiently under solvent-free conditions. The solvent-free Claisen reactions were especially effective for the ester substituted with sterically bulky groups, which does not react in solution. © 2001 Elsevier Science Ltd. All rights reserved.

We have been studying how molecules move quite easily and even selectively in the solid state.<sup>1</sup> When the molecular movements in the solid state are applied to organic reactions, selective and efficient solvent-free organic reactions can be designed.<sup>1</sup> Recently, we found that the title reactions also proceed efficiently under solvent-free conditions. In particular, the solvent-free Claisen reactions of the ester substituted with a sterically bulky group proceeded very efficiently, although these reactions did not occur in solution. These solvent-free reactions are important not only for their efficiency and simplicity, but also as green and sustainable procedures.

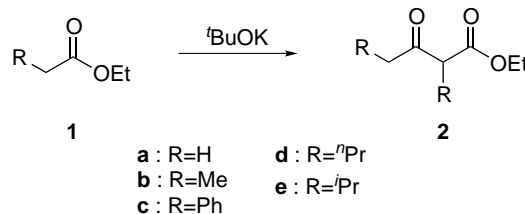
## Claisen condensation reactions<sup>2</sup>

For example, after a mixture of ethyl acetate (**1a**) (3.52 g, 40 mmol) and powdered <sup>t</sup>BuOK (3.68 g, 28 mmol) was kept at 80°C for 20 min, the reaction mixture was neutralized by addition of dil. HCl and extracted with ether. The oil left after evaporation of the solvent from the dried ether solution was distilled in vacuo by Kugelrohr apparatus to give **2a** (1.9 g, 73% yield). When the same reaction was carried out in EtOH containing EtONa for 8 h under reflux, **2a** was obtained in 36–76% yield.<sup>3</sup> For example, when a solution of **1a** (3.52 g, 40 mmol) and EtONa (1.9 g, 28 mmol) in EtOH (4 ml) was heated under reflux for 8 h, **2a** (1.17 g, 45%) was obtained after the usual work up procedure.

The same treatment of **1b** and **1c** with <sup>t</sup>BuOK for 2 h and 10 min, respectively, gave **2b** in 60% and **2c** in 73% yields, respectively. In contrast, reactions of **1b** and **1c** in solution for 16 and 6 h, respectively, gave **2b** and **2c** in 47 and 55% yields, respectively.<sup>3</sup> These data clearly show that solvent-free reactions are simpler and more efficient than solution reactions. For the ester substituted with a sterically bulky group, the difference in efficiency between solvent-free and solution reactions becomes larger. Treatment of ethyl pentanoate (**1d**) with <sup>t</sup>BuOK for 1 h gave **2d** in 61% yield, although its solution reaction for 32 h gave **2d** in 35% yield. Furthermore, solvent-free reaction of ethyl 3-methylbutanoate (**1e**) for 1 h gave **2e** in 33% yield; however, solution reaction for 48 h did not give any **2e**, and **1e** was recovered unchanged. A plausible explanation of

**Table 1.** Solvent-free Claisen condensation reactions of **3**

	R	Reaction conditions		Yield (%) of <b>4</b>
		Temperature (°C)	Time (min)	
<b>a</b>	H	100	30	75
<b>b</b>	Me	120	60	66
<b>c</b>	Et	120	30	64
<b>d</b>	Ph	90	20	84

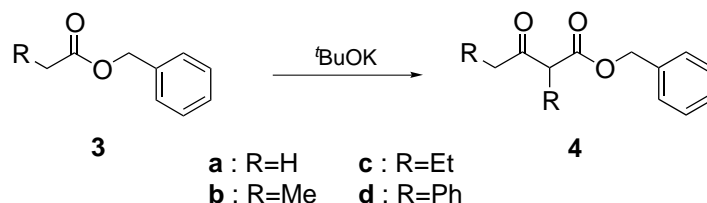


**Scheme 1.**

**Keywords:** solvent-free reaction; Claisen reaction; Cannizzaro reaction; green chemistry.

\* Corresponding author. Fax: +81 86 256 9604; e-mail: toda@chem.ous.ac.jp

<sup>†</sup> This paper is dedicated to Professor Masazumi Nakagawa on the occasion of his 85th birthday.



Scheme 2.

the inefficiency of the reaction in solution is that the reactant and reagent are solvated and their mutual approach to the condensation reaction becomes difficult for sterical reasons.

A similar steric effect was observed in the reaction of benzyl carboxylate (**3**). When **3a–d** were treated with <sup>t</sup>BuOK under solvent-free conditions at the reaction temperature and reaction time indicated in Table 1, **4a–d** were obtained in the moderate yields shown in Table 1. When the same reactions of **3a–e** were carried out in toluene and <sup>t</sup>BuOH under reflux for 16 h, no condensation product was obtained and **3a–e** were recovered unchanged. In solution reactions, exchange of the alkoxy group occurs among the substrate, reagent and solvent. Therefore, the alkoxy groups of

the ester, metal alkoxide and alcohol used as a solvent should be identical. In the solvent-free reactions, however, a strong base such as <sup>t</sup>BuOK can be used for any kind of ester substrate, since such exchange does not occur. This is also a considerable advantage (Schemes 1 and 2).

Cross-condensation reaction of benzyl benzoate (**5**) and benzyl carboxylate (**6**) was carried out under solvent-free conditions. Treatment of a 1:1 mixture of **5** and **6** with <sup>t</sup>BuOK under the conditions indicated in Table 2 gave the cross-condensed product **7** in the yield shown in Table 2. Although the cross-condensation between **5** and **6c** did not occur, cross-condensation products **7a** and **7b** were obtained in moderate yields. Because heating of **5**, **6** and <sup>t</sup>BuOK in toluene under reflux for 16 h did not give any product, it is clear that the solvent-free reaction is again effective even for the cross-condensation. In these cases, self-condensation of **6** itself did not occur probably because of the high reactivity of **5** (Scheme 3).

Table 2. Solvent-free cross-condensation reactions of **5** and **6**

R	Reaction conditions		Yield (%) of <b>7</b>
	Temperature (°C)	Time (h)	
<b>a</b> H	120	1	42
<b>b</b> Me	100	1	45
<b>c</b> Ph	120	1	0

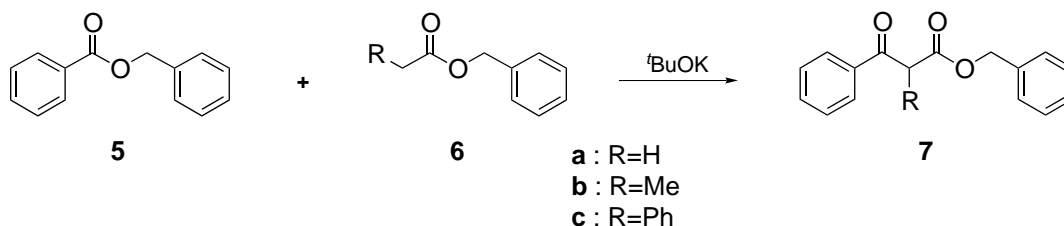
Table 3. Solvent-free Cannizzaro reactions

Aldehyde	Reaction conditions		Yield (%) of	
	Temperature (°C)	Time (min)	Acid	Alcohol
<b>8</b>	100	5	41	38
<b>11</b>	rt	10	43	39
<b>12</b>	80	3	51	18
<b>13</b>	80	5	46	38
<b>14</b>	100	5	49	41
<b>15</b>	100	30	46	27
<b>16</b>	rt	10	48	45
<b>17</b>	rt	10	53	33
<b>18</b>	0	10	40	36

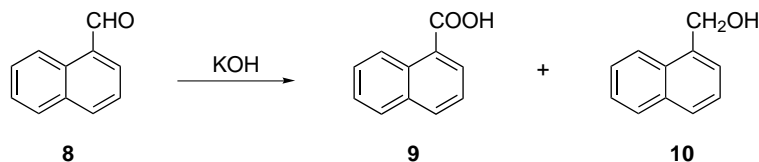
#### Cannizzaro reactions<sup>4</sup>

After a mixture of powdered 1-formylnaphthalene (**8**) (4.68 g, 30 mmol) and powdered KOH (2.52 g, 45 mmol) was kept at 100°C for 5 min, water was added to the reaction mixture, and was filtered to give 1-(hydroxymethyl)naphthalene (**10**), after Kugelrohr distillation, (0.485 g, 38% yield). The filtrate was acidified by conc. HCl and filtered to give 1-naphthoic acid (**9**) (0.57 g, 41% yield). For liquid aldehydes, a similar method can be applied. When the alcohol formed by the solvent-free reaction is an oily material, the product was extracted with ether. Finally, treatment of aldehydes **11–18** by these procedures gave the corresponding alcohols and acids in the yields indicated in Table 3.

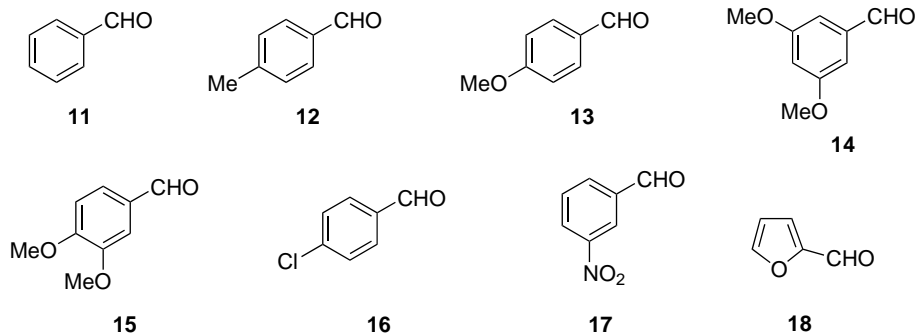
In the case of crystalline *p*-methylbenzaldehyde (**16**), the yield of *p*-methylbenzoic acid exceeded 50%, probably due to air oxidation of **16** during the reaction at 80°C. When the reaction was carried out at room temperature in nitrogen atmosphere under ultrasound



Scheme 3.



Scheme 4.



Scheme 5.

irradiation, *p*-methylbenzoic acid and *p*-methylbenzyl alcohol were obtained in 43 and 33% yield, respectively (Table 3). In all cases shown in Table 3, solvent-free Cannizzaro reactions proceeded efficiently under milder conditions, and the products were obtained in moderate yields by a simple separation method (Schemes 4 and 5).

The solvent-free Cannizzaro reaction has some advantages. In addition to simplicity and cleanness of the procedure, the solvent-free reaction proceeds much faster than a solution reaction. For example, reaction of **11** in 60% aq. KOH takes 24 h to complete,<sup>5</sup> although the solvent-free reaction is completed within 5 min. In all other cases indicated in Table 3, all reactions are completed within 30 min.

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