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Jong Han Kim<sup>a</sup>, Sangku Lee<sup>a</sup>, Mu-Gil Kwon<sup>b</sup>, Yong Soo Park<sup>b</sup>, Sung-Kyu Choi<sup>a</sup> & Byoung-Mog Kwon<sup>a</sup>

<sup>a</sup> Korea Research Institute of Bioscience and Biotechnology, 52 Uendong, Yusonggu, Taejon, 305-600, Republic of Korea

<sup>b</sup> Kunwha Pharmaceutical, Ltd., Choongnam, Republic of Korea

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## One-Step Synthesis of *ortho*-Hydroxycinnamaldehyde

Jong Han Kim,<sup>1</sup> Sangku Lee,<sup>1</sup> Mu-Gil Kwon,<sup>2</sup>  
Yong Soo Park,<sup>2</sup> Sung-Kyu Choi,<sup>1</sup> and  
Byoung-Mog Kwon<sup>1,\*</sup>

<sup>1</sup>Korea Research Institute of Bioscience and Biotechnology,  
Taejeon, Republic of Korea

<sup>2</sup>Kunwha Pharmaceutical, Ltd., Choongnam,  
Republic of Korea

### ABSTRACT

An improved and convenient one-step procedure for the large scale synthesis of *ortho*-hydroxycinnamaldehyde (**3a**) using *ortho*-hydroxybenzaldehyde and vinyl acetate is described.

**Key Words:** Cinnamaldehyde, Cross aldol condensation; *ortho*-Hydroxycinnamaldehyde; One-step procedure.

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\*Correspondence: Byoung-Mog Kwon, Korea Research Institute of Bioscience and Biotechnology, 52 Uendong, Yusonggu, Taejeon 305-600, Republic of Korea; Fax: 82-42-8612675; E-mail: kwonbm@kribb.re.kr.

## INTRODUCTION

*ortho*-Hydroxycinnamaldehyde (**3a**) was isolated from the stem bark of *Cinnamomum cassia* Blume.<sup>[1]</sup> This plant has been used as a traditional medicine for various diseases including hypertension and indigestion in China and Korea. *ortho*-Hydroxycinnamaldehyde (**3a**) and its derivatives have been reported to exhibit a broad range of biological activities including farnesyl protein transferase inhibitory activity,<sup>[1]</sup> anti-angiogenic activity,<sup>[2]</sup> anti-tumor activity,<sup>[3]</sup> immunomodulatory effects,<sup>[4]</sup> and cyclin dependent kinases inhibitory activity.<sup>[5]</sup>

We previously reported an approach to *ortho*-hydroxycinnamaldehyde (**3a**) based on the functional group transformation of carboxylic acid to aldehyde.<sup>[2]</sup> However, the approach involved three reaction steps and expensive reagents such as diisobutylaluminum hydride. As we were interested in *in vivo* activities of **3a**, we needed to have a simple and convenient synthetic method that would bring a large quantity of **3a**.

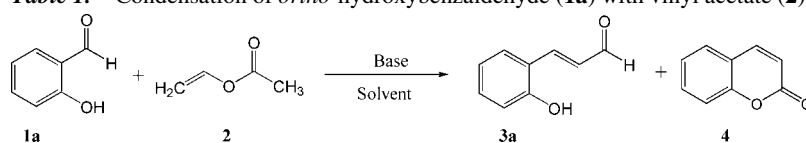
Cross aldol condensation between two different carbonyl compounds has long provoked interest to organic chemists due to its effectiveness for carbon–carbon bond formations.<sup>[6,7]</sup> The condensation reaction has traditionally been carried out by mixing two different carbonyl units under protic conditions in the presence of an acid or base as a catalyst. Recently, Junjappa et al. reported the generation of acetaldehyde enolate from vinyl acetate (**2**) by cleaving the acetyl group with barium hydroxide or potassium *t*-butoxide.<sup>[8]</sup> They also prepared several aromatic enals by the reaction of substituted benzaldehydes with acetaldehyde enolate generated *in situ* by cleaving vinyl acetate in high yields.<sup>[8]</sup> However, we could not detect *ortho*-hydroxycinnamaldehyde (**3a**) from *ortho*-hydroxybenzaldehyde (**1a**) under the same conditions as Junjappa et al. described.

In order to effect the condensation of *ortho*-hydroxybenzaldehyde with vinyl acetate as a precursor of acetaldehyde enolate, we screened bases and solvents (Table 1). When potassium carbonate was used as a base, *ortho*-hydroxycinnamaldehyde (**3a**) was obtained in 34% yield together with a trace amount of coumarin (**4**) and unidentified side products. Interestingly, upon heating a mixture of *ortho*-hydroxybenzaldehyde and vinyl acetate in the presence of KHCO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub> as a base, only coumarin (**4**) was isolated and no **3a** was detected.

Having successfully demonstrated the utility of potassium carbonate as a base, we examined the condensation of *ortho*-hydroxybenzaldehyde with vinyl acetate by changing solvents in order to improve the yield of **3a** (Table 2). However, all attempts were not rewarding. The feasibility of potassium carbonate/ acetonitrile in the condensation reaction of substituted benzaldehydes (**1a–f**) with vinyl acetate as a source of acetaldehyde enolate was examined (Table 3). Among the tested benzaldehydes, *ortho*-methoxybenzaldehyde (**1b**) and *para*-hydroxybenzaldehyde (**1f**) did not provide the corresponding enals.



**Table 1.** Condensation of *ortho*-hydroxybenzaldehyde (**1a**) with vinyl acetate (**2**).



Base	Yield (%) of <b>3a</b>
K <sub>2</sub> CO <sub>3</sub>	34 <sup>a</sup>
KHCO <sub>3</sub>	Side products <sup>b</sup>
Ba(OH) <sub>2</sub>	No reaction <sup>a</sup>
Na <sub>2</sub> CO <sub>3</sub>	Side products <sup>b</sup>
<i>t</i> -BuOK	No reaction <sup>c</sup>

<sup>a</sup>CH<sub>3</sub>CN at reflux.

<sup>b</sup>Coumarin (**4**).

<sup>c</sup>THF at 70°C.

**Table 2.** Effects of solvent on condensation of **1a** and **2** using K<sub>2</sub>CO<sub>3</sub> as a base.

Solvent	Temperature (°C)	Yield (%) of <b>3a</b>
CH <sub>3</sub> CN	80–85	34
Toluene	110–115	No reaction
THF	65–70	No reaction
DMF	155–160	Side product <sup>a</sup>
1,4-Dioxane	100–105	No reaction

<sup>a</sup>Coumarin (**4**) was only isolated product.

In conclusion, we have successfully employed potassium carbonate as a base for the cross aldol condensation of *ortho*-hydroxybenzaldehyde (**1a**) with vinyl acetate (**2**) to yield *ortho*-hydroxycinnamaldehyde (**3a**). This synthetic method was easily amenable to large scale in one pot chemical reaction step.

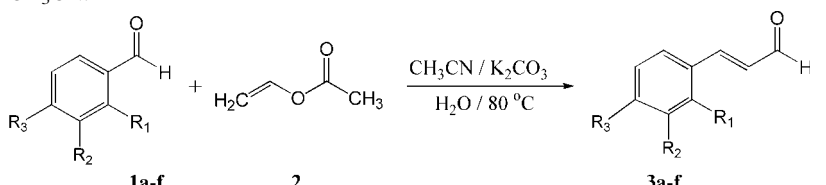
## EXPERIMENTAL

### General

Analytical TLC was performed on Kiesel gel 60 F254 (precoated silica gel plate, Merck, Art. 105715, NMRC, Palo Alto, CA). NMR spectra were



**Table 3.** Condensation of substituted benzaldehydes and vinyl acetate in  $K_2CO_3/CH_3CN$ .



Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Time (hr)	Yield (%) <sup>a</sup>
<b>1a</b>	OH	H	H	40	34
<b>1b</b>	OCH <sub>3</sub>	H	H	40	No reaction <sup>b</sup>
<b>1c</b>	Cl	H	H	40	40
<b>1d</b>	Br	H	H	40	40
<b>1e</b>	H	OH	H	40	43
<b>1f</b>	H	H	OH	40	No reaction <sup>b</sup>

<sup>a</sup>Yields refer to isolated products.

<sup>b</sup>No cinnamaldehydes **3b, f** were detected.

obtained on a Varian UNITY 300 MHz instrument. Column chromatography was performed on Merck silica gel 60 (230–400 mesh).

### General Procedure for the Synthesis of 3

A mixture of benzaldehyde (1 mol) and vinyl acetate (1.1 mol) in  $CH_3CN$  (300 mL) was added by dropwise using dropping funnel to a stirred suspension of  $K_2CO_3$  (1.2 mol) and  $H_2O$  (catalytic amount) in  $CH_3CN$ . The reaction mixture was refluxed for 40 hr. The reaction mixture after cooling was poured into cold water and diluted with EtOAc : *n*-hexane (2 : 1) mixture. The organic layer was washed with 10% NaOH solution, and the aqueous layer was separated, acidified with 10% HCl solution, and extracted with  $CH_2Cl_2$ . The resultant organic layer ( $CH_2Cl_2$ ) was dried over  $MgSO_4$  and concentrated in vacuo. The dark residue was purified by column chromatography on silica gel eluting with *n*-hexane-EtOAc to afford the cinnamaldehyde **3**. The following compounds were obtained.

**ortho-Hydroxycinnamaldehyde (3a).** m.p.: 129–131°C, [lit.<sup>[1]</sup> m.p. 131–132°C]. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): δ 9.68 (1H, d, *J* = 7.8 Hz), 7.89 (1H, d, *J* = 16.2 Hz), 7.63 (1H, dd, *J* = 7.7, 1.5 Hz), 7.30 (1H, dd, *J* = 7.7, 1.5 Hz), 7.00 (1H, d, *J* = 7.8 Hz), 6.92 (1H, dd, *J* = 7.5, 1.1 Hz), 6.84 (1H, dd, *J* = 7.8, 16.2 Hz).



***ortho*-Chlorocinnamaldehyde (3c).** m.p.: 53–54°C, [lit.<sup>[9]</sup> m.p. 51–53°C]. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): δ 9.79 (1H, d, *J* = 7.5 Hz), 8.01 (1H, d, *J* = 15.9 Hz), 7.91 (1H, t, *J* = 7.2 Hz), 7.54 (1H, d, *J* = 7.5 Hz), 7.48 (1H, dd, *J* = 7.2, 1.8 Hz), 7.42, (1H, dd, *J* = 7.2, 1.5 Hz), 6.80 (1H, dd, *J* = 7.5, 15.9 Hz).

***ortho*-Bromocinnamaldehyde (3d).** m.p.: 63–65°C, [lit.<sup>[10]</sup> m.p. 65–67°C]. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.75 (1H, d, *J* = 7.5 Hz), 7.87 (1H, d, *J* = 15.9 Hz), 7.63 (2H, d, *J* = 7.8 Hz), 7.35 (1H, t, *J* = 7.5 Hz), 7.27 (1H, dd, *J* = 7.2, 1.8 Hz), 6.80 (1H, dd, *J* = 7.5, 15.9 Hz).

***meta*-Hydroxycinnamaldehyde (3e).** m.p.: 119–120°C, [lit.<sup>[11]</sup> m.p. 118–120°C]. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): δ 9.69 (1H, d, *J* = 7.8 Hz), 7.60 (1H, d, *J* = 15.9 Hz), 7.29 (1H, t, *J* = 7.8 Hz), 7.20 (1H, s), 7.16 (1H, d, *J* = 2.4 Hz), 6.96 (1H, dd, *J* = 8.25, 2.4 Hz), 6.69 (1H, dd, *J* = 7.8, 15.9 Hz).

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