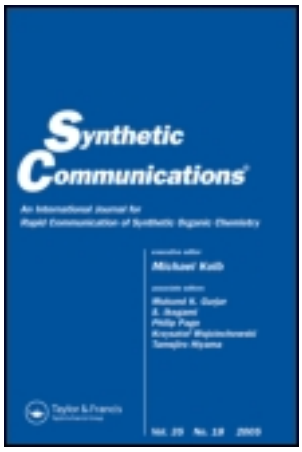

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One-Step Synthesis of *ortho*-Hydroxycinnamaldehyde

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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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INTRODUCTION

ortho-Hydroxycinnamaldehyde (**3a**) was isolated from the stem bark of *Cinnamomum cassia* Blume.[1] 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,[1] anti-angiogenic activity,[2] anti-tumor activity,[3] immunomodulatory effects,[4] and cyclin dependent kinases inhibitory activity.[5]

We previously reported an approach to *ortho*-hydroxycinnamaldehyde (**3a**) based on the functional group transformation of carboxylic acid to aldehyde.[2] 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.[6,7] 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.[8] 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.[8] 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 precusor 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 $KHCO_3$ or Na_2CO_3 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.

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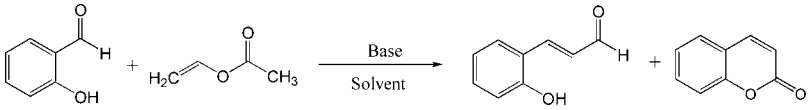
Table 1. Condensation of *ortho*-hydroxybenzaldehyde (**1a**) with vinyl acetate (**2**).



1a **2** **3a** **4**

Base	Yield (%) of **3a**
K_2CO_3	34[a]
$KHCO_3$	Side products[b]
$Ba(OH)_2$	No reaction[a]
Na_2CO_3	Side products[b]
t-BuOK	No reaction[c]

[a]CH_3CN at reflux.
[b]Coumarin (**4**).
[c]THF at 70°C.

Table 2. Effects of solvent on condensation of **1a** and **2** using K_2CO_3 as a base.

Solvent	Temperature (°C)	Yield (%) of **3a**
CH_3CN	80–85	34
Toluene	110–115	No reaction
THF	65–70	No reaction
DMF	155–160	Side product[a]
1,4-Dioxane	100–105	No reaction

[a]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

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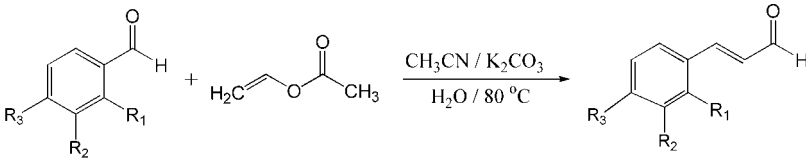
Table 3. Condensation of substituted benzaldehydes and vinyl acetate in K_2CO_3/CH_3CN.



1a-f **2** **3a-f**

Entry	R_1	R_2	R_3	Time (hr)	Yield (%)[a]
1a	OH	H	H	40	34
1b	OCH_3	H	H	40	No reaction[b]
1c	Cl	H	H	40	40
1d	Br	H	H	40	40
1e	H	OH	H	40	43
1f	H	H	OH	40	No reaction[b]

[a]Yields refer to isolated products.
[b]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.[1] m.p. 131–132°C]. ^{1}H NMR (300 MHz, acetone-d_6): 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).

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***ortho*-Chlorocinnamaldehyde (3c).** m.p.: 53–54°C, [lit.[9] m.p. 51–53°C]. ^{1}H NMR (300 MHz, acetone-d_6): 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.[10] m.p. 65–67°C]. ^{1}H NMR (300 MHz, $CDCl_3$): 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.[11] m.p. 118–120°C]. ^{1}H NMR (300 MHz, acetone-d_6): 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).

REFERENCES

1. Kwon, B.M.; Cho, Y.K.; Nam, J.Y.; Lee, S.H.; Bok, S.H.; Chun, S.K.; Kim, J.A.; Lee, I.R. 2′-Hydroxycinnamaldehyde from *Cinnamomum cassia* Blume. Planta Media **1996**, *62*, 183–184.
2. Kwon, B.M.; Lee, S.H.; Cho, Y.K.; Bok, S.H.; So, S.H.; Youn, M.R.; Chang, S.I. Synthesis and biological activity of cinnamaldehydes as angiogenesis inhibitors. Bioorg. Med. Chem. Letters **1997**, *7*, 2473–2476.
3. Lee, C.W.; Hong, D.H.; Han, S.B.; Park, S.H.; Kim, H.K.; Kwon, B.M.; Kim, H.M. Inhibition of human tumor growth by 2′-hydroxy- and 2′-benzoxycinnamaldehydes. Planta Medica **1999**, *65*, 263–266.
4. Koh, W.S.; Yoon, S.Y.; Kwon, B.M.; Jeong, T.C.; Nam, K.S.; Han, M.Y. Cinnamaldehydes inhibit lymphocyte proliferation and modulate T cell differentiation. Int. J. Immunpharm. **1998**, *20*, 643–660.
5. Jeong, H.W.; Kim, M.R.; Son, K.H.; Han, M.Y.; Ha, J.H.; Garnier, M.; Meijer, L.; Kwon, B.M. Cinnamaldehydes inhibit cyclin dependent kinase 4/cyclin D1. Bioorg. Med. Chem. Letters **2000**, *10*, 1819–1822.
6. Heathcock, C.H. The aldol reaction: acid and general base catalysis. In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Heathcock, C.H., Eds.; Pergamon: Oxford, 1991; Vol. 2, 132–156.
7. Saito, S.; Yamamoto, H. Directed aldol condensation. Chem. Eur. J. **1999**, *5*, 1959–1562.
8. Mahata, P.K.; Barun, O.; Ila, H.; Junjappa, H. Formation of acetaldehyde enolate from vinyl acetate and its reaction with aromatic and heterocyclic aldehydes: an efficient synthesis of enals and polyenals. Synlett. **2000**, *9*, 1345–1347.

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9. Nudelman, A.; Binnes, Y.; Shmueli-Broide, N.; Odessa, Y.; Hieble, J.P.; Sulpizio, A.C. "Vinylogs" and "acetylenylogs" of beta-adrenergic agents. Arch. Pharm. (Weinheim) **1996**, *329*, 125–132.
10. Wang, C.H.; Horng, J.M. Synthesis of 4-aryl-2-picolines. Heterocyles **1977**, *7*, 759–763.
11. Sung, N.D.; Kwon, B.M.; Lim, C.H.; Cho, Y.K. Inhibition of farnesyl protein transferase by ortho-substituted cinnamaldehyde derivatives. Agric. Chem. Biotechnol. **1998**, *41*, 218–221.

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