Facile One-Pot Synthesis of Cinnamamides from Aromatic Aldehydes and Acetonitrile with Me₃SiOK

Hyun Seung Lee, Sung Hwan Kim, and Jae Nyoung Kim[*]

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
[*]E-mail: kimjn@chonnam.ac.kr
Received February 28, 2011, Accepted March 15, 2011

α,β-Unsaturated amides are important because of their biological activities and their presence in the structure of natural products.[1] Thus, a variety of synthetic approaches have been reported including the hydration of α,β-unsaturated nitriles.[2-4] However, a one-pot synthesis of α,β-unsaturated primary amides from the corresponding aldehydes is rather limited.[2] SmI₂-mediated sequential reaction of samarium chloroacetamide enolate and an aldehyde followed by a β-elimination provided α,β-unsaturated primary amides in 53-64% (Scheme 1).[2a] PPh₃ and zinc-promoted Wittig reaction of bromoacetamide and aldehyde under solvent-free conditions is another one-pot procedure (Scheme 1).[2b] Besides these methods, there have been reported a palladium-catalyzed synthesis of cinnamamides from aryl halides and acrylamide.[4a,b]

During our recent studies for the development of an efficient hydration method of nitrile,[5] we envisioned that we could prepare various cinnamamides in a one-pot reaction from aromatic aldehydes and acetonitrile using Me₃SiOK, as shown in Scheme 1. Merchant reported an efficient synthesis of primary amides from nitriles mediated by potassium trimethylsilanolate.[6] Thus, if a Knoevenagel type condensation between aromatic aldehydes and acetonitrile could be efficient with Me₃SiOK, then an efficient one-pot synthesis of cinnamamide derivatives would be developed. Acetonitrile itself could also be converted to acetamide with Me₃SiOK; however, the hydration rates of aliphatic nitriles were much slower than aromatic or α,β-unsaturated nitriles.[6,7] Thus we presumed that synthesis of cinnamamides could be achieved.

In order to find an optimum condition, we examined some typical conditions, as shown in Table 1. Initially, we ex-

amined the reaction of benzaldehyde (**1a**) in CH₃CN in the presence of Me₃SiOK (3.0 equiv) at 40 °C (entry 1). The reaction was very fast and benzaldehyde disappeared within 20 min; however, cinnamamide (**3a**) was formed in low yield (10%). Instead, *trans*-cinnamonitrile (**2a**) was isolated as a major product (62%). The results stated that condensation between benzaldehyde and acetonitrile was very fast, but the hydration of **2a** to **3a** was sluggish at the temperature. The reaction at refluxing acetonitrile produced a low yield of **3a** (25%) along with many intractable side products (entry 2). The reaction in the presence of Cs₂CO₃ was ineffective for the formation of **3a** (entry 3). Thus we ran the reaction of **1a** in toluene in the presence of CH₃CN (5.0 equiv) at refluxing temperature (entry 4). To our delight, the yield of **3a** increased to 79% with complete disappearance of cinnamonitrile. In the reaction, appreciable amounts of potassium benzoate were formed by aerobic oxidation of benzaldehyde.[8] The reaction with 2.0 equiv of CH₃CN showed somewhat decreased yield of **3a** (entry 5).

Encouraged by the successful results we carried out one-pot synthesis of cinnamamides under the optimized conditions (entry 4 in Table 1), and the results are summarized in Table 2. The reactions of *p*-tolualdehyde (**1b**), mesitaldehyde

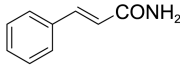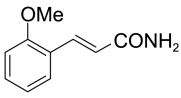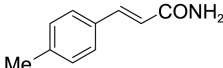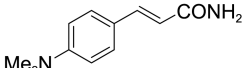**Table 1.** Optimization of reaction conditions for the conversion of **1a** to **3a**
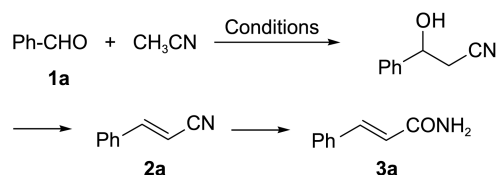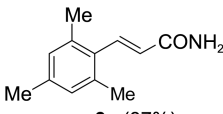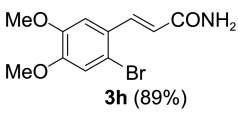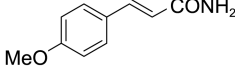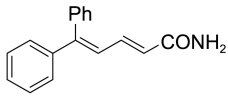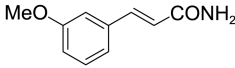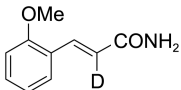
Entry	Conditions	Yields (2a/3a)[a,b]
1	CH₃CN (solvent), Me₃SiOK (3.0 equiv), 40 °C, 20 min	62/10
2	CH₃CN (solvent), Me₃SiOK (3.0 equiv), reflux, 3 h	0/25
3	CH₃CN (solvent), Cs₂CO₃ (3.0 equiv), reflux, 3 h	69/0
4	CH₃CN (5.0 equiv), Me₃SiOK (3.0 equiv), toluene, reflux, 3 h	0/79
5	CH₃CN (2.0 equiv), Me₃SiOK (3.0 equiv), toluene, reflux, 3 h	0/57

[a]In all entries, benzaldehyde was consumed completely. [b]Benzoic acid was observed in variable amounts (5-25%) after acidification.

Scheme 1

Notes

Bull. Korean Chem. Soc. **2011**, Vol. 32, No. 5   1749
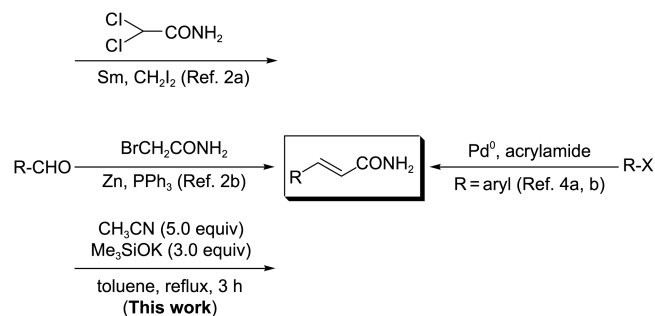
Table 2. One-pot synthesis of α,β-unsaturated primary amides[a]

Entry	Product (%)[b]	Entry	Product (%)[b]
1	**3a** (79%)	6	**3f** (82%)
2	**3b** (72%)	7	**3g** (79%)
3	**3c** (87%)	8	**3h** (89%)
4	**3d** (65%)	9	**3i** (63%)
5	**3e** (79%)	10	**3j** (67%)[c]

[a]Conditions: aldehyde (1.0 mmol), CH_3CN (5.0 equiv), Me_3SiOK (3.0 equiv), toluene, reflux, 3 h. [b]*Trans* isomer, and *cis* isomer was not formed. [c]CD_3CN was used and isolated as a mixture of **3j**:**3f** (2:1).

(**1c**), *p*-anisaldehyde (**1d**), *m*-anisaldehyde (**1e**), *o*-anisaldehyde (**1f**), 4-(dimethylamino)benzaldehyde (**1g**), and 2-bromo-4,5-dimethoxybenzaldehyde (**1h**) afforded the corresponding *trans*-cinnamamides **3b-h** in moderate to good yields (65-89%), as shown in entries 2-8. In most entries, variable amounts of the corresponding benzoic acid derivatives were formed by aerobic oxidation as their potassium salts.[8] The reaction of β-phenylcinnamaldehyde (**1i**) provided **3i** in moderate yield (entry 9). The reaction of **1f** and CD_3CN under the same conditions (entry 10) produced a mixture of α-D-cinnamamide (**3j**) and **3f** (*ca.* 2:1 ratio). The deuterium atom in CD_3CN might be exchanged to hydrogen atom by moisture under the reaction conditions in part, even though we used dry toluene as a solvent.

In summary, a facile one-pot procedure for the preparation of cinnamamides was developed. The reaction was carried out in refluxing toluene in the presence of CH_3CN and Me_3SiOK in short time.

Experimental Section

Typical Procedure for the Synthesis of Cinnamamide 3a. A mixture of benzaldehyde (106 mg, 1.0 mmol), Me_3SiOK (Tech. 90%, 428 mg, 3.0 mmol), CH_3CN (205 mg, 5.0 mmol) in toluene (2.0 mL) was heated to reflux for 3 h under N_2 balloon atmosphere. During the reaction some solid materials were deposited. After cooling to room temperature, the reaction mixture was poured into water (10 mL) and extracted with $CHCl_3$ (100 mL × 3). The organic layers were combined, dried with $MgSO_4$. After removal of solvent and column

chromatographic purification process (EtOAc/CHCl₃, 5:1) *trans*-cinnamamide (**3a**) was obtained as a white solid, 116 mg (79%). Other amides were prepared similarly. Known compounds were characterized by their mp, IR, and ^{1}H NMR spectra by comparison with the reported data, and unknown compounds were fully-characterized as follows.

Compound 3a:[2b,9a] 79%; white solid, mp 145-147 °C; IR (KBr) 3373, 3169, 1660, 1603, 1394 cm⁻¹; ^{1}H NMR (CDCl₃, 300 MHz) δ 5.77 (br s, NH), 5.92 (br s, NH), 6.47 (d, *J* = 15.6 Hz, 1H), 7.32-7.44 (m, 3H), 7.46-7.56 (m, 2H), 7.65 (d, *J* = 15.6 Hz, 1H).

Compound 3b:[2b,9a] 72%; white solid, mp 189-190 °C; IR (KBr) 3313, 3170, 1666, 1595, 1394, 1219 cm⁻¹; ^{1}H NMR (DMSO-*d₆*, 300 MHz) δ 2.32 (s, 3H), 6.58 (d, *J* = 15.9 Hz, 1H), 7.11 (br s, NH), 7.22 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.60 (br s, NH).

Compound 3c: 87%; white solid, mp 186-188 °C; IR (KBr) 3386, 3201, 1665, 1597, 1392 cm⁻¹; ^{1}H NMR (DMSO-*d₆*, 300 MHz) δ 2.22 (s, 3H), 2.26 (s, 6H), 6.21 (d, *J* = 16.2 Hz, 1H), 6.89 (s, 2H), 7.16 (br s, NH), 7.50 (d, *J* = 16.2 Hz, 1H), 7.64 (br s, NH); ^{13}C NMR (DMSO-*d₆*, 75 MHz) δ 20.65, 20.85, 127.00, 128.95, 131.31, 136.04, 136.94, 137.04, 166.82; ESIMS *m/z* 190 (M⁺+H). Anal. Calcd. For $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.01; H, 8.14; N, 7.22.

Compound 3d:[9a] 65%; white solid, mp 194-196 °C; IR (KBr) 3351, 3170, 1659, 1592, 1259 cm⁻¹; ^{1}H NMR (DMSO-*d₆*, 300 MHz) δ 3.78 (s, 3H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.03 (br s, NH), 7.37 (d, *J* = 15.9 Hz, 1H), 7.48 (br s, NH), 7.50 (d, *J* = 8.7 Hz, 2H).

Compound 3e:[9b] 79%; white solid, mp 175-177 °C; IR (KBr) 3337, 3187, 1670, 1600, 1269 cm⁻¹; ^{1}H NMR (CDCl₃, 300 MHz) δ 3.79 (s, 3H), 6.47 (d, *J* = 15.6 Hz, 1H), 6.16 (br s, NH), 6.49 (br s, NH), 6.89 (d, *J* = 8.1 Hz, 1H), 7.00 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.25 (dd, *J* = 8.1 and 7.8 Hz, 1H), 7.57 (d, *J* = 15.6 Hz, 1H).

Compound 3f:[2b,9b] 82%; white solid, mp 189-191 °C; IR (KBr) 3372, 3174, 1656, 1601, 1400, 1247 cm⁻¹; ^{1}H NMR (DMSO-*d₆*, 300 MHz) δ 3.84 (s, 3H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.08 (br s, NH), 7.35 (dd, *J* = 8.4 and 7.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.62 (br s, NH), 7.66 (d, *J* = 15.9 Hz, 1H); ESIMS *m/z* 178 (M⁺+H).

Compound 3g: 79%; white solid, mp 218-220 °C; IR (KBr) 3360, 3162, 1649, 1591, 1523, 1359 cm⁻¹; ^{1}H NMR (DMSO-*d₆*, 300 MHz) δ 2.93 (s, 6H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.91 (br s, NH), 7.31 (d, *J* = 15.9 Hz, 1H), 7.35 (br s, NH), 7.37 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (DMSO-*d₆*, 75 MHz) δ 39.80, 112.00, 116.68, 122.31, 128.93, 139.78, 151.11, 167.54; ESIMS *m/z* 191 (M⁺+H). Anal. Calcd. For $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.77; H, 7.68; N, 14.39.

Compound 3h: 89%; white solid, mp 236-238 °C; IR (KBr) 3339, 3178, 1663, 1599, 1503, 1262 cm⁻¹; ^{1}H NMR (DMSO-*d₆*, 300 MHz) δ 3.80 (s, 3H), 3.81 (s, 3H), 6.66 (d, *J* = 15.6 Hz, 1H), 7.17 (br s, NH), 7.19 (s, 1H), 7.23 (s, 1H), 7.60 (d, *J* = 15.6 Hz, 1H), 7.69 (br s, NH); ^{13}C NMR (DMSO-*d₆*, 75 MHz) δ 55.69, 56.05, 109.49, 115.61, 115.70, 123.19,

126.17, 137.13, 148.56, 150.68, 166.56; ESIMS *m/z* 286 (M$^+$+H), 288 (M$^+$+H+2). Anal. Calcd. For C$_{11}$H$_{12}$BrNO$_3$: C, 46.18; H, 4.23; N, 4.90. Found: C, 46.36; H, 4.54; N, 4.85.

Compound 3i:[9c] 63%; white solid, mp 159-162 °C; IR (KBr) 3330, 3162, 1660, 1598, 1398 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.55 (br s, NH), 5.82 (br s, NH), 6.07 (d, *J* = 15.0 Hz, 1H), 6.77 (d, *J* = 11.7 Hz, 1H), 7.18-7.43 (m, 11H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 124.01, 125.23, 128.02, 128.22, 128.30, 128.37, 128.51, 130.35, 138.57, 139.79, 141.47, 150.32, 168.21; ESIMS *m/z* 250 (M$^+$+H).

Compound **3j**: 67% (**3f:3j** = 1:2); white solid, mp 154-156 °C; IR (KBr) 3371, 3177, 1649, 1600, 1248 cm^{-1}; ^{1}H NMR (DMSO-*d$_6$*, 300 MHz) δ 3.85 (s, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.09 (br s, NH), 7.36 (dd, *J* = 8.4 and 7.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.60 (br s, NH), 7.66 (s, 1H); ESIMS *m/z* 178 (**3f**, M$^+$+H), 179 (**3j**, M$^+$+H).

References and Notes

1. For the examples of biologically active α,β-unsaturated amides, see: (a) Davies, I. R.; Cheeseman, M.; Niyadurupola, D. G.; Bull, S. D. *Tetrahedron Lett.* **2005**, *46*, 5547-5549. (b) Williams, P. G.; Asolkar, R. N.; Kondratyuk, T.; Pezzuto, J. M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 83-88. (c) Park Choo, H.-Y.; Peak, K.-H.; Park, J.; Kim, D. H.; Chung, H. S. *Eur. J. Med. Chem.* **2000**, *35*, 643-648.

2. For the synthesis of α,β-unsaturated primary amides, see: (a) Concellon, J. M.; Rodriguez-Solla, H.; Concellon, C.; Simal, C.; Alvaredo, N. *J. Org. Chem.* **2010**, *75*, 3451-3453. (b) Feng, S.; Zhang, Z.; Jiang, S.; Yu, X. *J. Chem. Res.* **2010**, 382-384. (c) Petrova, J.; Momchilova, S.; Vassilev, N. G. *Phosphorus, Sulfur and Silicon* **2000**, *164*, 87-94.

3. For the synthesis of α,β-unsaturated amides from aldehydes, see: (a) Kojima, S.; Inai, H.; Hidaka, T.; Ohkata, K. *Chem. Commun.* **2000**, 1795-1796. (b) Jiang, S.; Yang, K.; Yu, X. *Synth. Commun.*

2009, *39*, 1759-1767. (c) Zheng, J.; Wang, Z.; Shen, Y. *Synth. Commun.* **1992**, *22*, 1611-1617. (d) Kojima, S.; Kawaguchi, K.; Matsukawa, S.; Uchida, K.; Akiba, K.-y. *Chem. Lett.* **2002**, 170-171. (e) Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2669-2672. (f) Hernandez-Fernandez, E.; Fernandez-Zertuche, M.; Garcia-Barradas, O.; Munoz-Muniz, O.; Ordonez, M. *Synlett* **2006**, 440-444. (g) Kojima, S.; Inai, H.; Hidaka, T.; Fukuzaki, T.; Ohkata, K. *J. Org. Chem.* **2002**, *67*, 4093-4099. (h) Weidlich, T.; Prokes, L.; Ruzicka, A.; Padelkova, Z. *Monatsh Chem.* **2010**, *141*, 205-211.

4. For the other approaches of α,β-unsaturated amides including a Pd-catalyzed Heck reaction with acrylamides, see: (a) Borhade, S. R.; Waghmode, S. B. *Tetrahedron Lett.* **2008**, *49*, 3423-3429. (b) Tian, J.; Moeller, K. D. *Org. Lett.* **2005**, *7*, 5381-5383. (c) Botella, L.; Najera, C. *J. Org. Chem.* **2005**, *70*, 4360-4369. (d) Zapf, A.; Beller, M. *Chem. Eur. J.* **2001**, *7*, 2908-2915. (e) Concellon, J. M.; Bardales, E. *J. Org. Chem.* **2003**, *68*, 9492-9495. (f) Concellon, J. M.; Bardales, E. *Eur. J. Org. Chem.* **2004**, 1523-1526. (g) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346-4353. (h) Park, J. H.; Kim, S. Y.; Kim, S. M.; Chung, Y. K. *Org. Lett.* **2007**, *9*, 2465-2468. (i) Schleicher, K. D.; Jamison, T. F. *Org. Lett.* **2007**, *9*, 875-878. (j) Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem. Int. Ed.* **2005**, *44*, 1075-1078. (k) Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. *Org. Lett.* **2009**, *11*, 3810-3813. (l) Gartner, Z. J.; Grubina, R.; Calderone, C. T.; Liu, D. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 1370-1375.

5. For our recent studies on the hydration of nitriles, see: (a) Kim, E. S.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 1589-1591. (b) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973-2975. (c) Kim, E. S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 6286-6289.

6. Merchant, K. J. *Tetrahedron Lett.* **2000**, *41*, 3747-3749.

7. In most cases, a trace amount of acetamide was formed under the reaction conditions.

8. Actually, benzoic acid was isolated in 14% from the reaction mixture. For the air oxidation of aldehydes in the presence of base, see: (a) Ko, E. Y.; Lim, C. H.; Chung, K.-H. *Bull. Korean Chem. Soc.* **2006**, *27*, 432-434. (b) Chung, K.-H.; Moon, B.-C.; Lim, C. H.; Kim, J. P.; Lee, J. H.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 1203-1205. Such an aerobic oxidation occurred in most entries in variable amounts, and the reaction with *p*-nitrobenzaldehyde failed completely.

9. (a) Cai, M.-Z.; Zhao, H.; Hu, W.-Y. *Chin. J. Chem.* **2005**, *23*, 443-447. (b) Bernini, R.; Cacchi, S.; Salve, I. D.; Fabrizi, G. *Synlett* **2006**, 2947-2952. (c) Sasho, S.; Harakawa, H.; Kamisaka, N.; Miki, I.; Kuno, Y.; Kumazawa, T.; Sekine, S. 1997, JP 09087237A; *Chem. Abstr.* **1997**, *127*, 17675.