One-Pot Synthesis of *E*-Alkylidene Derivatives of 3*H*-Furan-2-ones from 4-Pentynoic Acid and Aldehyde

Sung-Gon Lim, Bong-Il Kwon, Moon-Gun Choi, Chul-Ho Jun*

Center for Bioactive Molecular Hybrid (CBMH) and Department of Chemistry, Yonsei University, Seoul 120-749, Korea
Fax +82(2)31472644; E-mail: junch@yonsei.ac.kr

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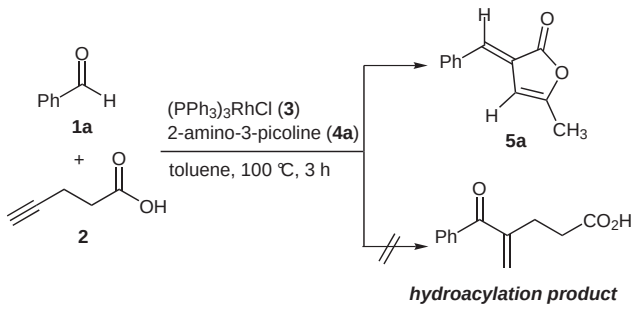
Abstract: 4-Pentynoic acid reacts with aldehyde under the co-catalyst system of Wilkinson's complex and 2-aminopyridine to give *E*-alkylidene derivatives of 3*H*-furan-2-one through the transition metal-catalyzed cyclization of 4-pentynoic acid followed by condensation of the resulting lactone with aldehyde.

Key words: lactone, lactam, Wilkinson's complex, aldehyde, 4-pentynoic acid

Interest in the chemistry of 5-substituted *E*-alkylidene derivatives of 3*H*-furan-2-one has recently emerged because of its potential antifungal uses such as preserving agricultural crops and wooden products.[1] However, only a few synthetic methods for these compounds have been reported,[2–4] and many individual reaction steps[2] or high pressure reaction conditions[3] are required to obtain these compounds.

Recently, we developed an efficient co-catalytic system of Wilkinson's complex and 2-amino-3-picoline for the intermolecular hydroacylation of alkenes or alkynes with aldehydes giving ketones or α,β-enones.[5,6] During the course of our studies on this intermolecular hydroacylation of various functionalized alkynes, we found that the reaction of benzaldehyde (**1a**) with 4-pentynoic acid (**2**) in the presence of Wilkinson's complex (**3**) and 2-amino-3-picoline (**4**a) resulted in (*E*)-3-benzylidene-3*H*-furan-2-one (**5a**) exclusively instead of the expected hydroacylation product, α,β-enone[6] (Equation 1). Herein, we report an unprecedented one-pot synthesis of *E*-alkylidene derivatives of 3*H*-furan-2-one derived from 4-pentynoic acid and aldehyde using a co-catalyst system of Wilkinson's complex and 2-aminopyridine.



Equation 1

The reaction of benzaldehyde (**1a**) and 4-pentynoic acid (**2**) in the presence of $(PPh_3)_3RhCl$ (**3**, 5 mol%) and 2-amino-3-picoline (**4a**, 40 mol%) was performed at 100 °C in toluene for 3 hours to afford (*E*)-3-benzylidene-3*H*-furan-2-one (**5a**)[7] in a 74% isolated yield (82% yield by GC) after chromatographic isolation (Table 1, entry 1). When the reaction was carried out without **4a** under identical reaction conditions, only 5-methylenedihydrofuran-2-one (**6**)[8] was obtained.

From these results, the reaction mechanism can be inferred as described in Scheme 1. Initially 4-pentynoic acid (**2**) undergoes cyclization under catalyst **3** to furnish **6**. The rhodium-catalyzed cyclization of alkynoic acid **2** to alkylidene lactone **6** was previously reported.[9] Lactone **6** might be further isomerized to the more stable lactone **7**.[10] Subsequent condensation of **7** with benzaldehyde (**1a**) in the presence of base **4a** leads to loss of water and **5a**. Since condensation of **7** with aldehydes was known to proceed via the basic metal salt, sodium acetate,[11] various bases including sodium acetate were applied to the one-pot transformation of **1a** and **2** to **5a** (Table 1). All bases except 2-aminopyridine derivatives were ineffective. Among various 2-aminopyridine derivatives (Table 1, entries 1–3), 2-aminopyridine showed the best reactivity. Interestingly, 4-aminopyridine (Table 1, entry 4) or sodium acetate (entry 8) did not show any reactivity.

Table 1 Reaction of Benzaldehyde (**1a**) and 4-Pentynoic Acid (**2**) with Various Bases **4**[a]

Entry	Base **4**	**5a** (%)[b]
1	2-Amino-3-picoline (**4a**)	74
2	2-Amino-6-picoline (**4b**)	45
3	2-Aminopyridine (**4c**)	75
4	4-Aminopyridine (**4d**)	0
5	Pyridine (**4e**)	0
6	Aniline (**4f**)	0
7	Cyclohexylamine (**4g**)	0
8	Sodium acetate (**4h**)	0

[a] Reagents: **1a** (0.216 mmol), **2** (0.432 mmol), **3** (0.011 mmol), **4** (0.086 mmol) in toluene at 100 °C for 3 h.
[b] Isolated yields.

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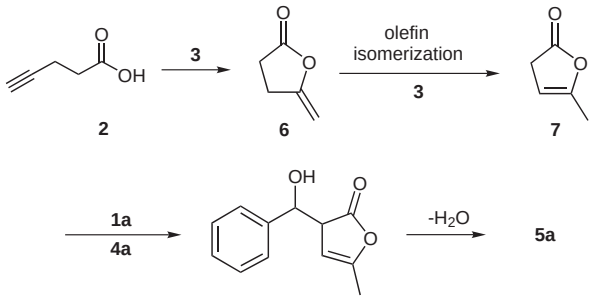
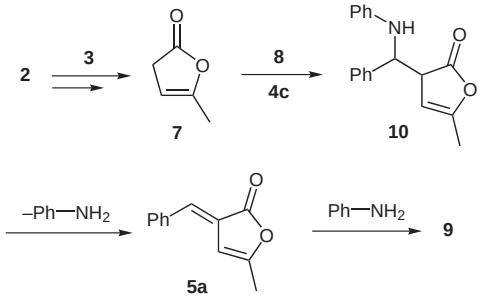


Scheme 1 Proposed mechanism for the reaction of **1a** and **2** under the co-catalyst systems of **3** and **4a.**

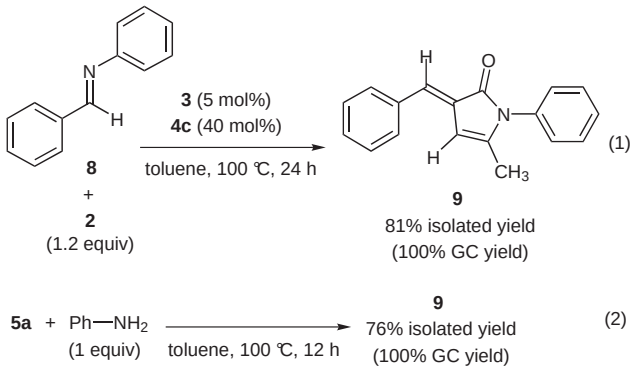


Scheme 2 Proposed reaction mechanism of aldimine **8** and **2**.

When the reaction was carried out with various aldehydes **1** (Table 2, entries 1–6), corresponding (*E*)-3-arylidene-5-methyl-*3H*-furan-2-one **5** was isolated in fairly good yields.

It is interesting to note that even with ferrocenecarboxaldehyde (**1g**), a good yield of the corresponding compound **5g** was obtained (Table 2, entry 7). However, with an aliphatic aldehyde such as cyclohexanecarboxaldehyde (**1h**), only a trace amount (4%) of **5h** was produced (Table 2, entry 8). The reason must be that the reaction of aromatic aldehyde with **2** leads to an extended conjugation of lactone **7** with the aromatic group of the aldehyde through condensation while that of aliphatic aldehyde with **2** does not. This hypothesis can be proven by the reaction of **2** with 1-cyclohexenecarboxaldehyde (**1i**), which gives an 81% isolated yield of the extended conjugation compound **5i** (Table 2, entry 9).

Another interesting thing to note was that the use of aldimine instead of aldehyde led to the formation of lactam: aldimine **8** reacted with **2** at 100 °C for 24 hours to give lactam **9** in 82% isolated yield (Equation 2).



Equation 2

The reaction mechanism of this transformation is shown in Scheme 2. After the initial formation of **7** from **2**, it reacts with **8** under base **4c** to generate **10**. The intermediate **10** undergoes β-elimination to afford aniline and lactone **5a**, which reacts further with aniline to produce lactam **9**.[12] The transformation mechanism of **5a** with aniline to **9** was confirmed when compound **5a** was allowed to react with aniline at 100 °C for 12 hours to give **9** in 76% isolated yield (Equation 2).

In conclusion, we have demonstrated a highly efficient one-pot synthesis of *E*-alkylidene derivatives of 3*H*-furan-2-one from 4-pentynoic acid and aldehyde under a Rh(I) catalyst and 2-aminopyridine. In addition, a novel direct one-pot synthesis of lactam was achieved by use of aldimine instead of aldehyde. Detailed mechanistic studies on the role of 2-aminopyridine, and further applications of this one-pot reaction with various alkynoic acids and aldehydes are underway.

Acknowledgment

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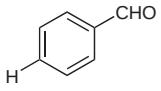
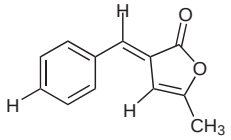
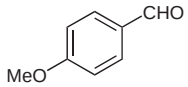
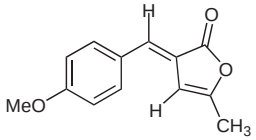
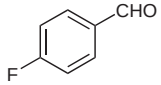
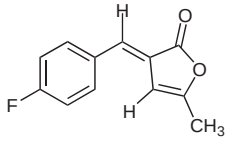
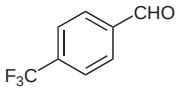
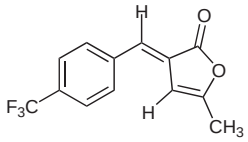
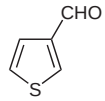
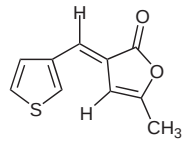
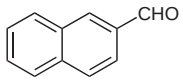
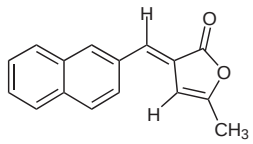
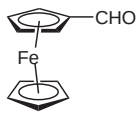
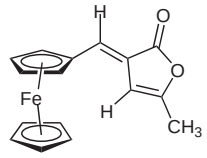
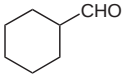
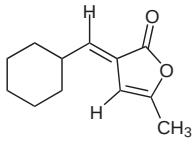
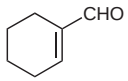
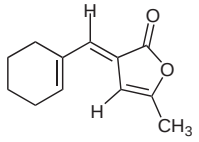
(7) The *E*-stereochemistry of compounds **5a**, **5c**, and **5d** was determined by NOESY spectroscopic analysis.
(8) The reaction of 4-pentynoic acid (**2**) and $(PPh_3)_3RhCl$ (**3**, 5 mol%) was performed in benzene-d_6 at 100 °C for 3 h to afford a 100% yield of 5-methylenedihydrofuran-2-one (**6**); the structure was confirmed by ^1H NMR spectroscopy. ^1H NMR (benzene-d_6): δ = 4.60–4.58 (m, 1 H), 4.03–4.01 (m, 1 H), 2.29–2.20 (m, 2 H), 2.12–2.03 (m, 2 H).

Table 2 Reaction of Aldehydes **1** with **2**[a]

Entry	Aldehyde **1**	Product **5**[13]	Isolated yield (%)[b]
1	 **1a**	 **5a**	83 (100)
2	 **1b**	 **5b**	91 (100)
3	 **1c**	 **5c**[6]	88 (95)
4	 **1d**	 **5d**[6]	72 (81)
5	 **1e**	 **5e**	82 (95)
6	 **1f**	 **5f**	75 (82)
7[c]	 **1g**	 **5g**	78 (93)
8[c]	 **1h**	 **5h**	4 (7)
9[c]	 **1i**	 **5i**	81 (94)

[a] Reagents: **1** (0.216 mmol), **2** (0.432 mmol), **3** (0.011 mmol), **4c** (0.086 mmol) in toluene at 100 °C for 12 h.
[b] GC yields are given in parentheses.
[c] The reaction was carried out at 100 °C for 24 h.

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(13) General Procedure for One-Pot Synthesis of (*E*)-Alkylidene Derivatives of 3*H*-Furan-2-ones from 4-Pentynoic Acid and Aldehyde

A screw-capped pressure vial (1 mL) was charged with benzaldehyde (**1a**, 22.9 mg, 0.216 mmol), 4-pentynoic acid (**2**, 42.3 mg, 0.432 mmol), $(PPh_3)_3RhCl$ (**3**, 10 mg, 0.011 mmol), 2-aminopyridine (**4c**, 8.1 mg, 0.086 mmol), and toluene (0.2 mL). The reaction mixture was stirred at 100 °C for 12 h. After the reaction reached completion, the mixture was purified by column chromatography (*n*-hexane–ethyl acetate, 5:1) to give **5a** (33.3 mg, 83%).

Compound **5a**: IR (KBr): 3058, 2982, 2931, 1770, 1734, 1668, 1602, 1424, 1266, 899, 746 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 6.29 (s, 1 H), 7.28 (s, 1 H), 7.46–7.34 (m, 3 H), 7.56–7.53 (m, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.0, 102.1, 125.5, 128.5, 129.1, 130.1, 134.0, 135.2, 158.4, 170.0. MS (EI, 70 eV): *m*/*z* (%) = 43 (100), 63 (9), 89 (9), 115 (54), 158 (21), 186 (84) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{12}H_{10}O_2$ $[M + H]^+$: 186.0681; found: 186.0683.

Compound **5b**: IR (KBr): 3058, 2987, 2839, 1770, 1638, 1601, 1510, 1428, 1266, 899, 746 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 3.85 (s, 3 H), 6.26 (s, 1 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 7.23 (s, 1 H), 7.51 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.9, 55.6, 102.0, 114.7, 123.1, 128.0, 131.9, 134.0, 157.3, 161.2, 170.0. MS (EI, 70 eV): *m*/z (%) = 43 (11), 102 (11), 115 (3.6), 145 (100), 173 (4.3), 188 (17.3), 216 (62.6) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{13}H_{12}O_3$ $[M + H]^+$: 216.0786, found: 216.0782. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.36; H, 5.48.

Compound **5c**: IR (KBr): 3053, 2986, 1770, 1632, 1509, 1418, 1263, 895, 737 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 6.24 (s, 1 H), 7.16–7.04 (m, 2 H), 7.23 (s, 1 H), 7.56–7.51 (m, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.0, 101.8, 116.3, 116.6, 125.3, 131.6, 131.9, 132.1, 132.7, 161.6, 165.6, 170.0. MS (EI, 70 eV): *m*/*z* (%) = 43 (60), 83 (5), 107 (6), 133 (48), 176 (21), 204 (100) $[M + H^+]$. Anal. Calcd for $C_{12}H_9FO_2$: C, 70.58; H, 4.44; found: C, 70.44; H, 4.51.

Compound **5d**: IR (KBr): 3053, 2990, 1778, 1638, 1601, 1510, 1426, 1327, 899, 746 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 6.27 (m, 1 H), 7.28 (s, 1 H), 7.70–7.58 (m, 4 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.2, 102.0, 126.0, 126.1, 126.2, 127.8, 130.0, 131.7, 138.7, 160.2, 169.4. MS (EI, 70 eV): *m*/*z* (%) = 43 (85), 133 (8), 164 (7), 183 (10), 235 (6), 254 (100) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{13}H_9O_2F_3$ $[M + H]^+$: 254.0555; found: 254.0557. Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.57. Found: C, 61.34; H, 3.47.

Compound **5e**: IR (KBr): 3058, 2987, 1765, 1638, 1424, 1266, 894, 746 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 6.19 (s, 1 H), 7.27 (s, 1 H), 7.41–7.31 (m, 2 H), 7.59 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.9, 102.2, 124.1, 127.2, 127.4, 127.4, 129.7, 137.3, 157.5, 170.3. MS (EI, 70 eV): *m*/*z* (%) = 18 (8), 43 (41), 77 (8), 96 (4), 121 (78), 164 (21), 192 (100) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{10}H_8O_2S$ $[M + H]^+$: 192.0245, found: 192.0249. Anal. Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19. Found: C, 62.51; H, 4.28.

Compound **5f**: IR (KBr): 3053, 2992, 1770, 1632, 1424, 1266, 1169, 930, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 6.40 (s, 1 H), 7.44 (s, 1 H), 7.57–7.49 (m, 2 H), 7.65 (dd, *J* = 1.6, 7.0 Hz, 1 H), 7.89–7.82 (m, 3 H), 7.99 (s, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.1, 102.4, 125.6, 126.1, 127.1, 127.8, 128.0, 128.9, 129.0, 131.2, 132.9, 133.5, 134.0, 134.2, 158.5, 170.2. MS (EI, 70 eV): *m*/*z* (%) = 43 (29), 115 (7.7), 139 (5.2), 165 (100), 208 (23.6), 236 (58.2) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{16}H_{12}O_2$ $[M + H]^+$: 236.0837; found: 236.0817. Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.36; H, 5.13.

Compound **5g**: IR (KBr): 3053, 2987, 1755, 1638, 1617, 1424, 1271, 889, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 4.18 (s, 5 H), 4.57–4.52 (m, 4 H), 6.02 (s, 1 H), 7.16 (s, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.0, 70.1, 70.5, 72.0, 100.2, 102.5, 121.8, 136.3, 155.0, 170.0. MS (EI, 70 eV): *m*/*z* (%) = 43 (7), 56 (14), 121 (42), 223 (55), 229 (22), 266 (52), 294 (100) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{16}H_{14}O_2Fe$ $[M + H]^+$: 294.0343; found: 294.0311. Anal. Calcd for $C_{16}H_{14}FeO_2$: C, 65.33; H, 4.80. Found: C, 63.63; H, 5.00.

Compound **5h**: IR (KBr): 3052, 2984, 2933, 2853, 1776, 1648, 1421, 1267, 913, 704 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.71–0.89 (m, 10 H), 2.11 (s, 3 H), 2.36–2.32 (m, 1 H), 5.83 (s, 1 H), 6.44 (d, *J* = 9.84 Hz, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.8, 25.6, 25.8, 32.2, 39.8, 101.1, 126.4, 144.8, 155.7. MS (EI, 70 eV): *m*/*z* (%) = 43 (42), 67 (10), 82 (38), 110 (100), 124 (7), 149 (5), 192 (29) $[M + H^+]$.

Compound **5i**: IR (KBr): 2941, 2859, 1779, 1632, 1602, 1439, 1296, 909, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.77–1.60 (m, 4 H), 2.13 (s, 3 H), 2.36–2.26 (m, 4 H), 6.06 (s, 1 H), 6.33 (t, *J* = 3.98 Hz, 1 H), 6.87 (s, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.8, 21.6, 22.4, 26.9, 27.1, 99.8, 102.8, 122.0, 136.5, 138.4, 142.4, 155.3. MS (EI, 70 eV): *m*/*z* (%) = 43 (79), 80 (100), 91 (53), 111 (24), 119 (31), 147 (61), 190 (79) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{12}H_{14}O_2$ $[M + H]^+$: 190.0994; found: 190.0993.

Compound **9**: IR (KBr): 3062, 1772, 1701, 1622, 1498, 1367, 1161, 910, 733 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 6.19 (s, 1 H), 7.35–7.32 (m, 2 H), 7.58–7.37 (m, 7 H), 7.72–7.69 (m, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.0, 99.6, 128.0, 128.1, 129.0, 129.3, 129.4, 130.0, 130.2, 131.1, 135.1, 136.1, 146.3, 169.5. MS (EI, 70 eV): *m*/*z* (%) = 51 (6), 77 (43), 118 (67), 218 (17), 232 (34), 261 (100) $[M + H^+]$. HRMS: *m*/*z* calcd for $C_{18}H_{15}NO$ $[M + H]^+$: 261.1154; found: 291.1154. Registry Number: 165263-88-7.