Preparation of 2,5-Disubstituted Furans from Terminal Ynones and Aldehydes with CrCl₂, Me₃SiCl, and H₂O

Kazuhiko Takai,* Ryotaro Morita, Shuji Sakamoto

Department of Applied Chemistry Faculty of Engineering, Okayama University, Tsushima, Okayama 700-8530, Japan Fax +81(86)2518094; E-mail: ktakai@cc.okayama-u.ac.jp

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Abstract: Treatment of α , β -acetylenic ketones with chromium(II) in the presence of aldehydes, Me₃SiCl and water in THF gives 2,5-disubstituted furans in good to excellent yields.

Keywords: ynone, furan, chromium(II)

One-electron transfer to α , β -unsaturated ketones produces radical enolate species which can undergo further reactions. Among the possible reductants, chromium(II) has a mild reducing ability, and so the one-electron reduction of enones proceeds without affecting the coexisting aldehydes. This enables chromium(II) to be used in cross-coupling reactions of enones and aldehydes.^{1a,b,2} In this communication, we report on reactions between ynones and aldehydes initiated with chromium(II). When the reactions are conducted in the presence of Me₃SiCl and water, 2,5-disubstituted furans are produced via crosscoupling of the two carbonyl compounds.³

A mixture of ynone **1a** and nonanal was treated with $CrCl_2$ in DMF at 25 °C. The aldehyde was consumed in 30 min, and the Baylis-Hillman-type adduct **2a** was obtained as a major product (37% yield) after hydrolysis (Equation 1). In the case of the internal ynone **1b**, the coupling product **2b**, having a Z-configuration, was obtained in 44% yield.⁴ The reaction was accelerated and the yield increased to 66% by addition of Et₂AlCl.



Equation 1

The reaction course changed markedly when Me₃SiCl was present in the reaction mixture.^{2b} For example, treatment of a mixture of **1a** (2.0 equiv) and nonanal with CrCl₂ (8.0 equiv) in the presence of Me₃SiCl (6.0 equiv) in DMF at 0 °C for 4 h, followed by desilylation with Bu₄NF (4.0 equiv), gave the cross Pinacol-type diol **3a** as

a major product, and **2a** was not observed (Equation 2). In addition, the 2,5-disubstituted furan **4a** was obtained unexpectedly in 5% yield. Because such a one-pot formation of a furan via cross-coupling of an ynone and an aldehyde is useful,³ we explored the optimum reaction conditions for the synthesis.





The yield of the furan **4a** increased to 51% by changing the solvent from DMF to THF and stirring the mixture for 24 h.⁵ Moreover, addition of 1.0 equiv of water to the mixture increased the yield to 80% (Equation 3). Further addition of water (5.0 equiv), however, resulted in a decrease in the yield (31%). When D₂O was used in the reaction, deuterium was incorporated at the 3 position of **4a** in 70% content.



Equation 3

The results of the synthesis of 2,5-disubstituted furans from ynones and aldehydes are shown in the Table. Because organochromium reagents add selectively to aldehydes, the furan formation can be accomplished without affecting the coexisting ketone group (Table, entry 5).⁶ Because reduction of the substituted ynone **1b** with CrCl₂ did not proceed in THF at 25 °C (95% recovery after stirring for 24 h), a 2,3,5-trisubstituted furan could not be obtained. In order to reduce the amount of the chromium salt, a catalytic cycle with manganese as a reductant of chromium(III) was examined.⁷ However, the yield of **4a**

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Table Synthesis of 2,5-Disubstituted Furansa

		CrCl ₂ , Me ₃ SiCl, H ₂ O	R ¹	_R ²
K CHU 4	• // · R ² —	THF, 25 °C, 24 h		
Entry	R ¹	R ²		Yield /% ^b
1	<i>n</i> -C ₈ H ₁₇	Ph(CH ₂) ₂	(4 a)	80
2				31 ^c
3	$c-C_{6}H_{11}$	$Ph(CH_2)_2$		65
4	Ph	Ph(CH ₂) ₂		73
5	MeCO(CH ₂) ₈	$Ph(CH_2)_2$		79
6	$Ph(CH_2)_2$	$c - C_6 H_{11}$		72
7	$c-C_{6}H_{11}$	$c - C_6 H_{11}$		57
8	Ph	$c - C_6 H_{11}$		70

^a Reactions were conducted on a 1.0 mmol scale. Ynone (2.0 mmol), $CrCl_2$ (8.0 mmol), Me_3SiCl (6.0 mmol), and water (1.0 mmol) were used per mmole of an aldehyde.

^b Isolated yields.

^c CrCl₂ (0.8 mmol), Mn (8.0 mmol), Me₃SiCl (6.0 mmol), and water (1.0 mmol) were used per mmole of nonanal.

became 31% yield, probably due to the slow reaction (Table, entry 2).

A plausible mechanism for the formation of the Baylis-Hillman-type adduct and furan, promoted by chromium(II), is shown in Scheme 1. One-electron reduction of the acetylenic ketone 5 with Cr(II) gives the allenyl enolate radical 6. Under anhydrous conditions, an aldol reaction of 6 with an aldehyde proceeds and a second oneelectron reduction gives 7. In contrast to the case of enone, cyclopropanol formation from 7 does not occur,^{2a} and the Baylis-Hillman type adduct 8 is produced as a major product after hydrolysis. When Me₃SiCl and water are added to the reaction mixture, hydrochloric acid is generated in situ.⁸ Protonation of the enolate 6 followed by a second one-electron reduction proceeds to give the β chromioenone 10. When the amount of protons is insufficient, 8 and 9 are obtained as byproducts.⁵ Addition of 10 to an aldehyde⁹ followed by ring closure and elimination produces the 2,5-disubstituted furan 13.10 This mechanism explains the incorporation of deuterium at the 3-position of **13** when D₂O was used.^{11,12}

In conclusion, α , β -acetylenic ketones are reduced with chromium(II) in DMF to give allenyl enolate radicals, which add to aldehydes to give Baylis-Hillman-type products. When the reductions are conducted in the presence of Me₃SiCl and water in THF, 2,5-disubstituted furans are produced in good to excellent yields.

Typical Procedure

(Table 1, entry 1) To a mixture of $CrCl_2$ (0.98 g, 8.0 mmol) in THF (14 mL) was added Me₃SiCl (0.76 mL, 6.0 mmol) and a THF solution of water (1.0 mmol), and the mixture was stirred at 25 °C for 20 min. A solution of nonanal (0.14 g, 1.0 mmol) and 5-phenyl-1-



Scheme 1

pentyn-3-one (0.32 g, 2.0 mmol) in THF (10 mL) was added at 25 °C. After stirring for 24 h at 25 °C, the reaction mixture was poured into water (10 mL). The mixture was extracted with ether (3 × 20 mL) and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification by column chromatography on silica gel (hexane) gave 2-octyl-5-(2-phenyleth-yl)furan **4a** in 80% yield (0.23 g, 0.80 mmol). **4a**: bp 130 °C (bath temp, 0.2 Torr); IR (neat): 3028, 2953, 2926, 2855, 1567, 1497, 1455, 1015, 780, 749, 698, 666 cm⁻¹; ¹H NMR (CDCl₃): δ 0.89 (t, *J* = 6.8 Hz, 3 H), 1.28–1.32 (m, 10 H), 1.58–1.65 (m, 2 H), 2.57 (t, *J* = 7.7 Hz, 2 H), 2.86–2.96 (m, 4 H), 5.84 (s, 2 H), 7.17–7.30 (m, 5 H); ¹³C NMR (CDCl₃): δ 14.1, 22.7, 28.1, 28.2, 29.2, 29.2, 29.3, 30.0, 31.9, 34.5, 104.9, 105.5, 125.9, 128.3, 128.4, 141.5, 153.4, 154.9.

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References and Notes

- (a) For intramolecular carbon-carbon bond formation between α,β-acetylenic ketones and carbonyl groups with chromium(II), see: Smith, A. B. III *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: Orlando, **1984**, 252. (b) See also: Smith, A. B. III; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184.
- (2) (a) Toratsu, C.; Fujii, T.; Suzuki, T.; Takai, K. Angew. Chem. Int. Ed. 2000, 39, 2725. (b) Takai, K.; Morita, R.; Toratsu, C. Angew. Chem. Int. Ed. 2001, 40, 1116.
- (3) (a) Holand, S.; Mercier, F.; Le Goff, N.; Epsztein, R. Bull. Soc. Chim. Fr. 1972, 4357. (b) Nishio, T.; Omote, Y. J. Chem. Soc., Perkin Trans. 1 1979, 1703. (c) Sato, F.; Katsuno, H. Tetrahedron Lett. 1983, 24, 1809.
- (4) The stereochemistry was assigned by an NOE experiment.

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(5) The compounds **2a**, **14** (a mixture of stereoisomers), and **15** were also obtained in addition to the furan **4a** (Figure).



Figure

- (6) The following functional substrates were recovered under the standard reaction conditions (Table, entry 1)due to the mild nucleophilicity of the organochromium reagent: 1dodecene (94%); 1-dodecyne (95%); 1-chlorododecane (99%); ethyl octanoate (92%); nonanenitrile (97%); 3phenylpropyl acrylate (89%); nonanal ethylene acetal (92%); 4-phenyl-2-butanone (98%).
- (7) Fürstner, A.; Shi, N. J. Am. Chem. Soc. 1996, 118, 12349.
- (8) When the reaction of 1a and nonanal was conducted with 1.0 equiv of hydrochloric acid in ether instead of Me₃SiCl and water, only the furan 4a was obtained in 19% yield along with 14 and 15 both in 15% yield, and 59% of 1a was recovered. The result suggests that Me₃SiCl accelerates the reduction of 1a with chromium(II), and also suppresses the formation of 14. The latter effect of Me₃SiCl is still obscure.
- (9) Knochel, P.; Rao, J. Tetrahedron 1993, 49, 29.
- (10) When the *E*-isomer of γ-hydroxy α,β-enone **15** was left to stand for several hours in CDCl₃ (an NMR tube), it spontaneously isomerized and cyclized to furan **4a** (Equation 4).



Equation 4

(11) The pathway for the formation of a furan can be written as in Scheme 2. However, the allenylic chromium species 17, which is similar to 16, usually adds to an aldehyde at the γ-position via a six-membered transition state to give a propargylic product selectively (Equation 5). For reactions of allenylic chromium reagents with carbonyl compounds, see: (a) Delbecq, F.; Baudouy, R.; Goré, J. *Nouv. J. Chim.* 1979, *3*, 321. (b) Place, P.; Venière, C.; Goré, J. *Tetrahedron Lett.* 1981, *37*, 1359.



Scheme 2



Equation 5

(12) In the case of SmI₂, one-electron transfer to a ketone proceeds smoothly. Thus, carbon-carbon bond formation at the β-position of an α,β-unsaturated ester occurred via radical addition with a proton source. See: (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* 1986, *27*, 5763. (b) Fukuzawa, S.-I.; Seki, K.; Tatsuzaka, M.; Mutoh, K. *J. Am. Chem. Soc.* 1997, *119*, 1482.