Synthesis of Cyclopentanone from an Alkyne Having an Active Methyne Using Chromium Carbene Complex

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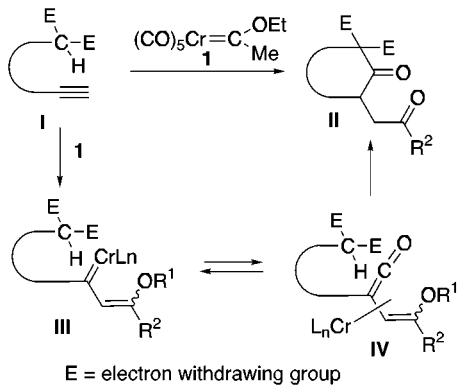
Chromium carbene complex is very useful in synthetic organic chemistry, and it has been used in various carbon−carbon bond forming reactions.[1] We have already shown novel lactone and lactam syntheses from an alkyne having a hydroxyl or a tosylamide group in a tether using chromium carbene complex.[2] In these reactions, the important intermediate is chromium vinylketene complex **IV** derived from chromium vinylcarbene complex **III**, which is attacked by a hydroxyl and a tosylamide group intramolecularly to give the lactone and lactam in good yields (Scheme 1). If a carbanion can attack the vinylketene moiety of this complex **IV** intramolecularly, cyclic ketone **II** would be formed.

Here, we want to report a novel synthesis of a five-membered ketone[3] from an alkyne having an active methyne proton in a tether using chromium carbene complex.

When a CH_3CN solution of alkyne **2a** and chromium carbene complex **1** was refluxed for 6 h and then the reaction mixture was treated with 10% HCl, none of the desired product was obtained. Instead, ester **4** and lactone **5**, which were produced by the reaction of the ethoxy group with the ketene part in complex **6** intramolecularly, were obtained in 15% and 26% yields, respectively (Scheme 2). This means that the active methyne part did not react with the vinyl ketene moiety. To generate a carbanion from the active methyne, a base was used for this reaction. It is already known that a proton of the methyl group on chromium carbene complex **1** is acidic and that a carbanion is generated upon treatment with a base. Moreover, the added base should coordinate with chromium. Thus, it is important to select the appropriate base. Bases such as NaH, pyridine, DABCO, Proton Sponge (1,8-bis(dimethylamino)naphthalene, Aldrich) and K_2CO_3 did not give good results. However, a small amount of the cyclized product was obtained in the presence of diisopropylethylamine and Et_3N (runs 2 and 3). Thus, the reaction was carried out under various conditions in the presence of Et_3N. The results are shown in Table 1. As a solvent, THF can be used, but benzene did not give the cyclized product.

The use of EtCN as a solvent improved the yield of the desired product (runs 3 and 6), and a higher reaction temperature gave a good result (run 7). The amount of Et_3N affected the yield of **3a** (runs 7 and 10−12), since Et_3N coordinates with chromium carbene complex and it would retard the reaction rate, and 10 mol % of Et_3N gave a good result (run 11).

Scheme 1



Scheme 2

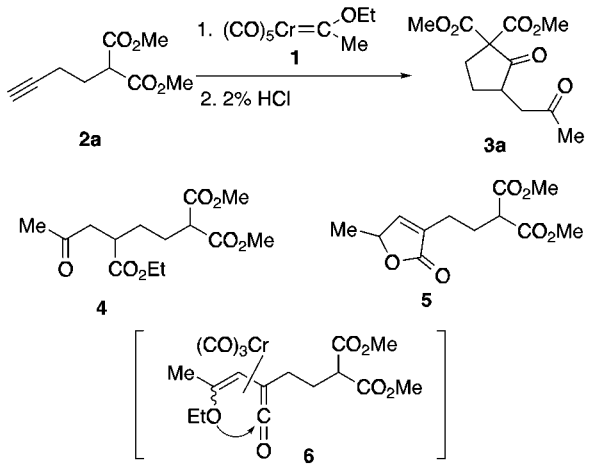


Table 1 Reaction of 2a with 1 under Various Conditions

run	2	solvent	base (eq)	temp (°C)	time (h)	yield (%)
1	**2a**	MeCN	none	70	6.0	0
2	**2a**	MeCN	iPr_2NEt (1.3)	70	2.5	5
3	**2a**	MeCN	Et_3N (1.5)	70	1.5	11
4	**2a**	THF	Et_3N (1.5)	reflux	0.5	28
5	**2a**	benzene	Et_3N (1.5)	reflux	0.5	0
6	**2a**	EtCN	Et_3N (1.5)	70	1.0	27
7	**2a**	EtCN	Et_3N (1.5)	90	0.5	35
8	**2a**	EtCN	Et_3N (1.5)	reflux	0.5	29
9	**2a**	PrCN	Et_3N (1.5)	90	0.5	30
10	**2a**	EtCN	Et_3N (1.0)	90	0.5	36
11	**2a**	EtCN	Et_3N (0.1)	90	0.5	46
12	**2a**	EtCN	Et_3N (0.01)	90	0.5	23
13	**2b**	EtCN	Et_3N (0.1)	90	0.5	48
14	**2c**	EtCN	Et_3N (0.1)	90	0.5	16[a]
15	**2d**	EtCN	Et_3N (0.1)	90	0.5	77[b]

[a] 1.5 equiv of Et_3N was used. [b] **3d** was isolated.

Various substrates **2** having an active methyne proton were used for this reaction, and the corresponding ketones, **3b**, **3c**, and **3d**, were obtained in 48%, 16%, and 77% yields, respectively (runs 13−15) (Figure 1). The reaction of **2d** with **1** gave deacetylated product **3d**. In order to examine whether deacetylation occurred under the reaction conditions, the reaction mixture was concentrated and the NMR and mass spectra were measured. However, measurement of the spectra indicates that the deacetylation did not occur. The spectral data after treatment of **7** with 2% HCl also indicated that the acetyl group remained unchanged. It is clear that deacetylation occurred during the purification, since **3d**

(1) (a) Fischer, E. O.; Maasbol, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580. For general reviews, see: (b) Dotz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (c) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, pp. 209−393. (d) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 1065−1113.

(2) (a) Ochifuji, N.; Mori, M. *Tetrahedron Lett.* **1995**, *36*, 9501. (b) Ishibashi, T.; Ochifuji, N.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 6165.

(3) Formation of a five-membered ketone using chromium carbene complex: Aumann, R.; Meyer, A. G.; Frohlich, R. *Organometallics* **1996**, *15*, 5018 and references cited therein.

S0022-3263(97)00806-2 CCC: $14.00

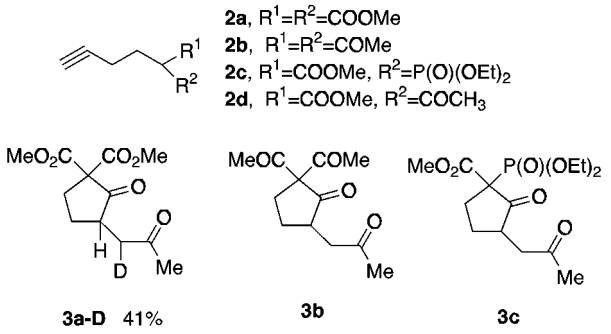
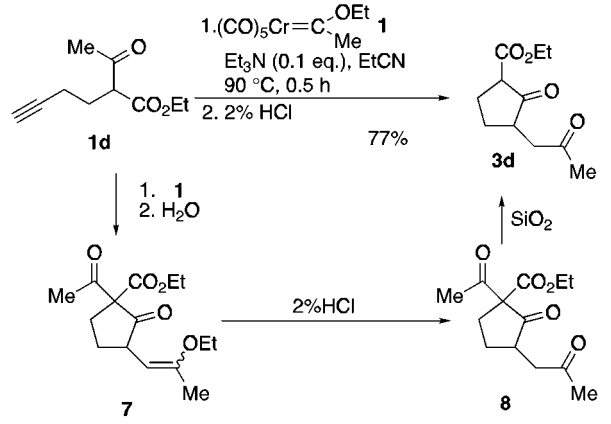
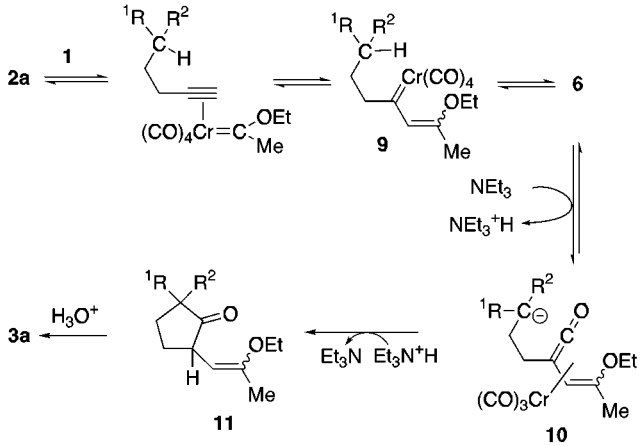


Figure 1.

Scheme 3



Scheme 4

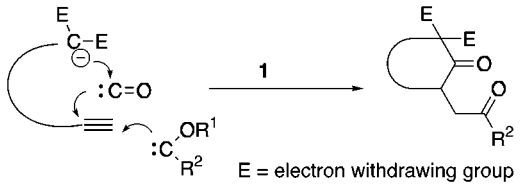


was obtained after the crude product **8** was purified by column chromatography on silica gel (Scheme 3).

The reaction mechanism is shown in Scheme 4. Chromium carbene complex **1** is coordinated by the alkyne part of **2** and then converts into chromium vinylcarbene complex **9**, which is in a state of equilibrium with chromium vinylketene complex **6**. Then, the carbanion generated from the active methyne by Et_3N attacks the vinylketene moiety intramolecularly to give cyclized product **11**, which is hydrolyzed to give cyclic ketone **3**. This mechanism was confirmed by the fact that the α-proton of the cyclic ketocarbonyl group was not deuterated when the reaction mixture of **1** with **2a** was treated with 10% DCl, and **3a-D** was obtained in 41% yield.

These results indicate that the reaction of chromium carbene complex with alkyne, having an active methyne proton in a tether, in the presence of a base gives the cyclic ketone in moderate yields. This means that the

Scheme 5



carbene carbon of **1** is introduced on the terminal alkyne carbon, and that carbon monoxide on the chromium carbene complex is inserted between the other alkyne carbon and the active methyne carbon to produce a five-membered ketone. Three carbon−carbon bonds are formed in this process (Scheme 5).

Experimental Section

General. Solvents were distilled under an argon atmosphere from sodium benzophenone ketyl (THF and benzene) or CaH_2 (CH_3CN, EtCN, and PrCN). All other reagents and solvents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70−230 mesh, 60 Å), and flash chromatography was performed on silica gel 60 (230−400 mesh, 60 Å) using the indicated solvent.

General Procedures for Cyclizations Using Chromium Carbene Complex. A EtCN solution of the substrate **2** (0.1 M), Et_3N, and chromium carbene complex **1** (1.2 equiv) was stirred at 90 °C. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel to give the desired cyclized product **3**.

2,2-Bis(methoxycarbonyl)-5-(2-oxopropyl)cyclopentan-1-one (3a). A crude product which was prepared from **2a** (49.5 mg, 0.269 mmol), **1** (86.0 mg, 0.326 mmol), and Et_3N (4.0 μL, 0.029 mmol) was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give **3a** (31.3 mg, 45%) as a pale yellow oil: IR (neat) 1740, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3 H), 3.77 (s, 3 H), 2.97 (dd, J = 3.4, 18.3 Hz, 1 H), 2.77−2.71 (m, 2 H), 2.61 (dd, J = 7.7, 18.3 Hz, 1 H), 2.41 (ddd, J = 7.0, 11.5, 13.5 Hz, 1 H), 2.33−2.26 (m, 1 H), 2.15 (s, 3 H), 1.62−1.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.2, 205.4, 167.7, 166.8, 67.3, 53.3, 53.2, 44.6, 43.8, 31.0, 29.8, 26.3; MS m/z 256 (M^+), 224, 213, 192, 181, 43; HRMS calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0939. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.18; H, 6.35.

2,2-Diacetyl-5-(2-oxopropyl)cyclopentan-1-one (3b). A crude product which was prepared from **2b** (29.7 mg, 0.195 mmol), **1** (62.7 mg, 0.237 mmol), and Et_3N (3.0 μL, 0.022 mmol) was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give **3b** (21.2 mg, 48%) as a pale yellow oil: IR (neat) 1753, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.91 (dd, J = 3.5, 18.6 Hz, 1 H), 2.79 (dd, J = 6.2, 18.6 Hz, 1 H), 2.59−2.53 (m, 1 H), 2.50−2.46 (m, 1 H), 2.29 (s, 3 H), 2.20 (s, 3 H), 2.13 (s, 3 H), 2.22−2.15 (m, 2 H), 1.61−1.54 (m, 1 H); MS m/z 209 (M^+ − Me), 182, 139, 124, 43.

2-(Diethylphosphono)-2-(ethoxycarbonyl)-5-(2-oxopropyl)cyclopentan-1-one (3c). A crude product which was prepared from **2c** (69.5 mg, 0.252 mmol), **1** (79.9 mg, 0.302 mmol), and Et_3N (53 μL, 0.380 mmol) was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/2) to give **3c** (14.1 mg, 16%) as a pale yellow oil. IR (neat) 1751, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (isomer a) δ 4.25−4.13 (m, 6 H), 3.02 (dd, J = 3.7, 18.1 Hz, 1 H), 2.95−2.82 (m, 1 H), 2.79−2.74 (m, 1 H), 2.55 (dd, J = 7.7, 18.1 Hz, 1 H), 2.56−2.48 (m, 1 H), 2.17 (s, 3 H), 1.77−1.69 (m, 1 H), 1.66−1.56 (m, 1 H), 1.35−1.25 (m, 9 H); (isomer b) δ 4.25−4.13 (m, 6 H), 2.94 (dd, J = 3.7, 18.1 Hz, 1 H), 2.95−2.82 (m, 1 H), 2.71−2.66 (m, 1 H), 2.44 (dd, J = 8.6, 18.1 Hz, 1 H), 2.56−2.48 (m, 1 H), 2.14 (s, 3 H), 1.77−1.69 (m, 1 H), 1.66−1.56 (m, 1 H), 1.35−1.25 (m, 9 H); MS m/z 348 (M^+), 320, 302, 43.

2-(Ethoxycarbonyl)-5-(2-oxopropyl)cyclopentan-1-one (3d). A crude product which was prepared from **2d** (42.4 mg, 0.233 mmol), **1** (73.6 mg, 0.279 mmol), and Et_3N (3.5 μL, 0.025 mmol) was purified by column chromatography on silica gel

(hexane/ethyl acetate, 2/1) to give **3d** (37.8 mg, 77%) as a pale yellow oil: IR (neat) 1752, 1725, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.21−4.17 (m, 2 H), 3.30 (dd, J = 8.3, 11.3 Hz, 1 H), 2.93−2.89 (m, 1 H), 2.68 (dd, J = 6.9, 18.4 Hz, 1 H), 2.57−2.51 (m, 1 H), 2.37−2.20 (m, 3 H), 2.15 (s, 3 H), 1.59−1.54 (m, 1 H), 1.28 (t, J = 7.0 Hz, 3 H); MS m/z 212 (M^+), 169, 166, 138, 123, 43. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.96; H, 7.42.

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