Direct Synthesis of Polysubstituted Cyclopentenones from Ketones and Aldehydes Catalyzed by Zirconium Compounds

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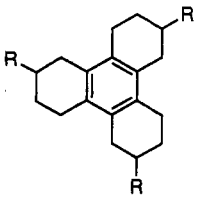
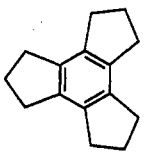
Polysubstituted cyclopentenones, such as 2,3,4,5-tetramethyl-2-cyclopenten-1-one and 2,3,4,5-tetraphenyl-2-cyclopenten-1-one, are important compounds as precursors for pentamethyl- and pentaphenylcyclopentadienes which are versatile ligands of various organometallic complexes.[1,2] Although there are many reports on the synthesis for polysubstituted cyclopentadiene ligands, the preparation of these ligands is generally troublesome and requires a multistep synthesis.[3] On the other hand, alkyl-substituted cyclopentenone derivatives are synthesized as perfume chemicals and pharmaceutical intermediates.

In a previous paper, we showed that Cp_2ZrCl_2 and $ZrCl_4$ efficiently catalyze the cyclotrimerization of cyclohexanone or cyclopentanone to form trisannelated benzene derivatives **1** or **2**, respectively.[4]



1 (R=H, CH_3, t-Bu)

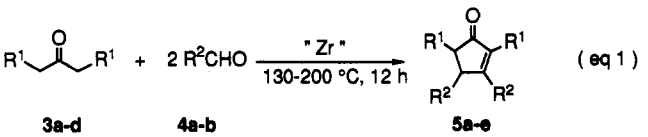


2

We have now found that the extension of this method to the cross-condensation reaction between acyclic ketones and aldehydes provides a one-pot preparation of polysubstituted cyclopentenone derivatives. In this paper, we report a one-pot synthesis of 2,3,4,5-tetrasubstituted 2-cyclopenten-1-ones, **5a–5e**, from the corresponding ketones, **3a–3d**, and aldehydes, **4a–4b**, by the action of zirconium chloride catalysts.

Table I shows the representative results for the reaction of diphenylacetone (**3a**) with benzaldehyde (**4a**) in the presence of several zirconium chlorides.

A mixture of **3a** and 3 equiv of **4a** was allowed to react in the presence of a catalytic amount of $ZrOCl_2 \cdot 8H_2O$ (0.1 equiv) without solvent in a sealed tube at 200 °C for 12



(eq 1)

3a-d **4a-b** **5a-e**

3	R^1
a	Ph
b	Me
c	Et
d	Pr

4	R^2
a	Ph
b	Me

5	R^1	R^2
a	Ph	Ph
b	Me	Ph
c	Et	Ph
d	Pr	Ph
e	Me	Me

h. Surprisingly, the double cross-aldol condensation and Nazarov cyclization simultaneously took place in the same pot to give *trans*-2,3,4,5-tetraphenyl-2-cyclopenten-1-one (**5a**) in 62% yield. From the comparison of the spectroscopic data of **5a** with those of literature values,[5] the phenyl groups on the C-4 and C-5 positions of **5a** were found to have a trans relationship. Conventionally, **5a** is prepared by the reaction of **3a** with benzoin in basic medium in 50% yield.[3] Recently, it has been reported that **5a** can be prepared from diphenylacetylene under pressure of carbon monoxide in the presence of various metal carbonyl catalysts, such as $Co_4(CO)_{12}$[6] and $Ni(CO)_4$.[7]

Among the catalysts examined, zirconium oxychloride, $ZrOCl_2 \cdot 8H_2O$, was found to be the best catalyst. $ZrCl_4$ and Cp_2ZrCl_2, which are favorable for the trisannelated benzene synthesis, were less efficient than $ZrOCl_2 \cdot 8H_2O$ in this reaction.

In the same manner as the reaction of **3a** and **4a**, the condensation of 3-pentanone (**3b**) with **4a** catalyzed by $ZrOCl_2 \cdot 8H_2O$ or $ZrCl_4$ produced *trans*-2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one (**5b**) in 63% yield. In this case, the reaction proceeded smoothly at a lower temperature (150 °C) than that of **3a** with **4a**, probably because of the facile enolization of **3b**. Similarly, the reaction of 4-heptanone (**3c**) with **4a** produced 2,5-dimethyl-3,4-diphenyl-2-cycopenten-1-one (**5c**) in slightly lower yield. Since the one-pot preparation of 2,3,4,5-tetraphenyl-2-cyclopenten-1-one (**5e**) seemed to be very attractive from the synthetic point of view, the reaction of **3b** with acetaldehyde (**4b**) was examined using $ZrCl_4$ as the catalyst. However, the reaction gave **5e** in 17% yield because of the facile self-condensation of **4b**.

Since mixed polysubstituted cyclopentadienes appear to be interesting ligands in organometallic chemistry, 1,2,3-trimethyl-4,5-diphenylcyclopentadiene (**6**) was prepared by the use of **4a** (eq 2).

The reaction of **5b** with MeLi in THF at −40 °C followed by quenching with acid at room temperature produced **6** without a dehydration operation. The double bond position of **6** was established by the ^1H NMR spectrum in which the methine proton appeared at δ 3.46 as singlet signal. Similarly, the reaction of **5b** with PhLi provided 2,5-dimethyl-1,3,4-triphenylcyclopentadiene (**7**) which appears to be an interesting ligand. The configuration was determined from the doublet signal of methyl group at δ 0.99 (eq 3).

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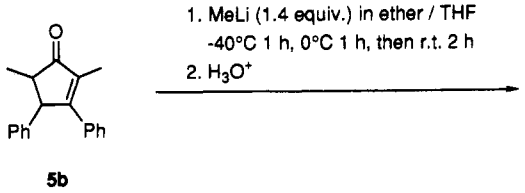
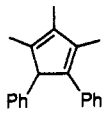


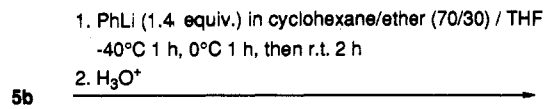
5b



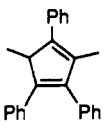
6

23 %

(eq 2)



5b



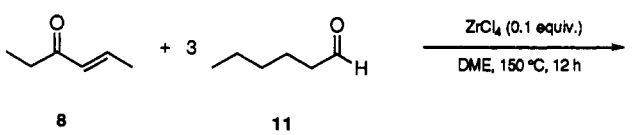
7

41 %

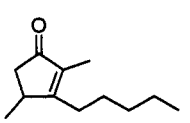
(eq 3)

Since the cyclopentenone synthesis by the present strategy is believed to involve the formation of α,β-unsaturated ketone as an intermediate, the reaction of α,β-unsaturated ketone with aldehyde under the influence of zirconium chlorides may provide an alternative direct route for the preparation of substituted cyclopentenone derivatives. Thus, 4-hexen-3-one (**8**) was allowed to react with an equal amount of **4a** at 130 °C in the presence of $ZrOCl_2 \cdot 8H_2O$ (Scheme I). As expected, the reaction afforded 2,4-dimethyl-3-phenylcyclopentenone (**9**) in 70% yield together with a small amount of the double condensate product **10**, which was formed by the subsequent condensation of the resulting **9** with **4a**. When the same reaction was carried out using 3 equiv of **4a** without solvent, **10** was obtained in 54% yield as a principal product.

The condensation of **8** with aliphatic aldehydes such as hexanal (**11**) under these conditions produced 2,4-dimethyl-5-pentylcyclopentenone (**12**) in low yield. However, when the reaction was carried out in DME, **12** was formed in fair yield (35%) (eq 4). The DME added seems



8 11



12

35 %

(eq 4)

to depress the self-condensation of **8** and **11**.

In conclusion, the present method, involving the double cross-condensation of ketones or α,β-unsaturated ketones with aldehydes and the Nazarov cyclization of the resulting condensates in one pot, provides a new strategy for the preparation of polysubstituted cyclopentenone derivatives.

Table I. Polysubstituted Cyclopentenone (5) Syntheses from Ketones (3) and Aldehydes (4) by Zirconium Chlorides[a]

ketone	aldehyde	temp/°C	catalyst	product,[b] %
3a	**4a**	150	$ZrOCl_2 \cdot 8H_2O$	**5a**, 39
			$ZrCl_4$	44
			Cp_2ZrCl_2	25
		200	$ZrOCl_2 \cdot 8H_2O$	62
			$ZrCl_4$	45
			Cp_2ZrCl_2	33
		250	$ZrOCl_2 \cdot 8H_2O$	73
3b	**4a**	130	$ZrOCl_2 \cdot 8H_2O$	**5b**, 39
			$ZrCl_4$	50
			Cp_2ZrCl_2	41
		150	$ZrOCl_2 \cdot 8H_2O$	63
			$ZrCl_4$	59
			Cp_2ZrCl_2	41
3c	**4a**	200	$ZrCl_4$	**5c**, 34
3d	**4a**	200	$ZrCl_4$	**5d**, 34
3b	**4b**	200	$ZrCl_4$	**5e**, 17

[a] **3** (3 mmol) was allowed to react with **4** (9 mmol) in the presence of zirconium chloride (0.3 mmol) without solvent. [b] Based on the amount of **3** used.

Experimental Section

Instruments. Melting points were uncorrected. ^1H- and ^{13}C-NMR spectra were recorded on a 400-MHz spectrometer with TMS as an internal reference in $CDCl_3$. IR spectra were measured by FT-IR. GC analyses were performed by a SE-30 or a SE-52 capillary column (0.2 mm × 25 m).

General Procedure. To a mixture of ketone (3 mmol) and aldehyde (9 mmol) was added $ZrOCl_2 \cdot 8H_2O$ (0.3 mmol) in a sealed tube. The mixture was allowed to react with shaking at 130–200 °C for 12 h. Aftr removal of the catalyst by filtration, the reaction mixture was extracted with chloroform (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in a rotary evaporator. The residue was purified by column chromatography on silica gel or recrystallization to give the corresponding cyclopentenone derivatives.

2,3,4,5-Tetraphenyl-2-cyclopenten-1-one (5a):[6] white solid; mp 162–163 °C; ^1H NMR δ 3.75 (d, 1H, J = 2.6 Hz), 4.55 (d, 1H, J = 2.6 Hz), 7.13–7.36 (m, 20H); ^{13}C NMR δ 57.6 (d), 63.1 (d), 127.0 (d), 127.2 (d), 127.6 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.9 (d), 129.0 (d), 129.5 (d), 129.8 (d), 131.7 (s), 134.6 (s), 139.3 (s), 140.1 (s), 141.5 (s), 169.0 (s) 206.0 (s); IR (KBr) 3061, 3024, 1693, 1621, 1492, 1348, 755, 695 cm^{-1}.

2,5-Dimethyl-3,4-diphenyl-2-cyclopenten-1-one (5b):[9] white solid; mp 116–117 °C; ^1H NMR δ 1.34 (d, 3H, J = 7.3 Hz), 2.02 (d, 3H, J = 2.2 Hz), 2.39 (dq, 1H, J = 7.3, 2.9 Hz), 3.97–3.98 (m, 1H), 7.06–7.38 (m, 10H); ^{13}C NMR δ 10.1 (q), 15.3 (q), 51.3 (d), 56.3 (d), 126.6 (d), 127.5 (d), 128.3 (d), 128.4 (d), 128.7 (d), 128.9 (d), 135.2 (d), 136.7 (s), 142.0 (s), 167.0 (s), 210.9 (s); IR (KBr) 2966, 1692, 1625, 1341, 755, 725, 696 cm^{-1}.

2,5-Diethyl-3,4-diphenyl-2-cyclopenten-1-one (5c): white solid; mp 92–93 °C; ^1H NMR δ 1.03 (t, 3H, J = 7.3 Hz), 1.15 (t, 3H, J = 7.3 Hz), 1.65–1.76 (m, 1H), 1.88–1.98 (m, 1H), 2.33–2.47 (m, 3H), 4.05 (m, 1H), 7.06–7.30 (m, 10H); ^{13}C NMR δ 11.3 (q), 13.3 (q), 17.4 (t), 24.6 (t), 54.3 (d), 57.3 (d), 126.5 (d), 127.5 (d), 127.7 (d), 128.2 (d), 128.6 (d), 128.7 (d), 135.5 (s), 142.2 (s), 142.8 (s), 167.8 (s), 210.8 (s); IR (KBr) 2969, 1682, 1624, 1452, 1357, 752, 722, 702, 694 cm^{-1}.

2,5-Dipropyl-3,4-diphenyl-2-cyclopenten-1-one (5d): ^1H NMR δ 0.89 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz), 1.43–1.64 (m, 5H), 1.84–1.89 (m, 1H), 2.33–2.45 (m, 3H), 4.04 (m, 1H), 7.05–7.29 (m, 10H); ^{13}C NMR δ 14.1 (q), 14.2 (q), 20.4 (t), 21.8 (t), 26.0 (t), 34.1 (t), 55.1 (d), 55.8 (d), 126.5 (d), 127.5 (d), 127.6 (d), 128.2 (d), 128.6 (d), 135.7 (d), 141.2 (s), 142.2 (s), 168.4 (s), 211.0 (s); IR (KBr) 2958, 2931, 2871, 1694, 1626, 1601, 1495, 1454, 1358, 756, 723, 700 cm^{-1}.

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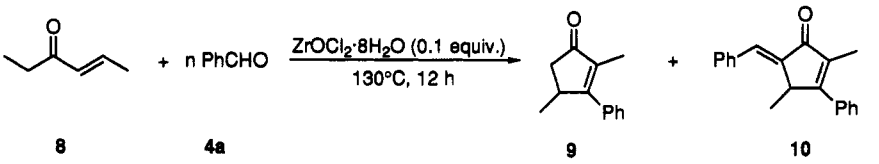
Scheme I



8 4a 9 10

n	Yield, % 9	10
1 (DME)	70	11
3	7	54

2,3,4,5-Tetramethyl-2-cyclopenten-1-one (5e): ^{1}H NMR δ 1.16 (d, 3H, J = 7.3 Hz), 1.18 (d, 3H, J = 7.3 Hz), 1.68 (m, 3H), 1.89 (dq, 1H, J = 2.6, 7.3 Hz), 1.98 (s, 3H), 2.24–2.26 (m, 1H); ^{13}C NMR δ 8.1 (q), 14.5 (q), 15.0 (q), 17.6 (q), 46.3 (d), 48.3 (d), 134.4 (s), 171.6 (s), 211.0 (s); IR (KBr) 2962, 2929, 2873, 1699, 1651, 1456, 1386, 1324 cm^{-1}.

Preparation of 1,2,3-Trimethyl-4,5-diphenylcyclopentadiene (6).[8] To a solution of **5b** (13.1 g, 50 mmol) in anhydrous THF (100 mL) was added dropwise an ether solution of 1.17 M MeLi (59.8 mL, 70 mmol) at −40 °C. The mixture was stirred for 1 h at that temperature and then at 0 °C for 1 h. After the temperature was maintained at room temperature for 2 h, the reaction was quenched with 0.25 M HCl. The solution was extracted with diethyl ether (3 × 50 mL), dried over $MgSO_4$, and evaporated. The residue was recrystallized from hexane/2-propanol (2:1) to afford **6** (3.0 g, 23%) as a white solid (mp 78–79 °C): ^{1}H NMR δ 1.73 (s, 3H), 1.90 (s, 3H), 2.10 (d, 3H, J = 1.8 Hz), 4.23 (s, 1H), 6.94–7.24 (m, 10H); ^{13}C NMR δ 11.3 (q), 12.2 (q), 12.9 (q), 62.6 (d), 125.4 (d), 126.0 (d), 127.9 (d), 128.2 (d), 128.3 (d), 136.1 (s), 136.9 (s), 139.5 (s), 139.6 (s), 140.9 (s), 142.0 (s); IR (KBr) 2910, 2854, 1597, 1490, 1438, 767, 698, 693 cm^{-1}.

Preparation of 2,5-Dimethyl-1,3,4-triphenylcyclopentadiene (7). To a solution of **5b** (2.6 g, 10 mmol) in anhydrous THF (20 mL) was added dropwise a cyclohexane/ether (7:3) solution of 1.8 M PhLi (7.8 mL, 14 mmol) at −40 °C. After a similar workup as above, recrystallization from methanol afforded **7** (1.3 g, 41%) as a white solid (mp 126–127 °C): ^{1}H NMR δ 0.99 (d, 3H, J = 7.7), 1.98 (d, 3H, J = 1.5 Hz), 4.09 (dq, 1H, J = 7.7, 1.8 Hz), 7.09–7.42 (m, 15H); ^{13}C NMR δ 14.0 (q), 16.1 (q), 48.8 (d), 126.0 (d), 126.1 (d), 126.8 (d), 128.0 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.7 (d), 135.8 (s), 136.6 (s), 137.0 (s), 143.3 (s), 145.9 (s), 146.4 (s); IR (KBr) 3049, 2959, 1594, 1493, 768, 699 cm^{-1}.

Preparation of 2,4-Dimethyl-3-phenylcyclopenten-1-one (9) and 5-Benzylidene-2,4-dimethyl-3-phenylcyclopenten-1-one (10). To a mixture of 4-hexen-3-one (0.294 g, 3 mmol) and benzaldehyde (0.318 g, 3 mmol) in DME (0.6 mL) was added $ZrOCl_2$·$8H_2O$ (0.096 g, 0.3 mmol) in a sealed tube. The mixture was allowed to react with shaking at 130 °C for 12 h. After removal of the catalyst by filtration, the reaction mixture was extracted with chloroform (30 mL × 3). The combined organic extract was dried over $MgSO_4$ and evaporated in a rotary evaporator. The residue was purified by column chromatography (hexane/ethylacetate = 7/1) on silica gel to give **9**: ^{1}H NMR δ 1.07 (d, 3H, J = 7.0 Hz), 1.86 (d, 3H, J = 1.8 Hz), 2.14 (dd, 1H, J = 1.9, 18.7 Hz), 2.81 (dd, 1H, J = 6.6, 18.7 Hz), 3.33–3.38 (m, 1H), 7.36–7.51 (m, 5H); ^{13}C NMR δ 9.2 (q), 19.7 (q), 35.1 (d), 42.6 (t), 127.3 (d), 128.1 (d), 128.5 (d), 134.9 (s), 135.7 (s), 172.0 (s), 208.2 (s); IR (NaCl) 2962, 2925, 1698, 1627, 1341, 772, 702 cm^{-1}.

Compound **10** was prepared by the same method as **9**. Recrystallization from ether gave **10** as a white solid (mp 100–101 °C): ^{1}H NMR δ 1.10 (d, 3H, J = 7.0 Hz), 2.03 (d, 3H, J = 1.1 Hz), 4.29–4.34 (m, 1H), 7.35–7.63 (m, 11H); ^{13}C NMR δ 10.0 (q), 16.6 (q), 39.1 (d), 128.0 (d), 128.6 (d), 128.7 (d), 129.0 (d), 129.2 (d), 130.6 (d), 130.9 (d), 134.7 (s), 135.0 (s), 137.0 (s), 138.8 (s), 167.2 (s), 196.8 (s); IR (KBr) 2982, 1682, 1674, 1641, 1610, 1348, 1042, 772, 696 cm^{-1}.

Preparation of 2,4-Dimethyl-3-pentylcyclopenten-1-one (12). To a mixture of 4-hexen-3-one (0.294 g, 3 mmol) and benzaldehyde (0.954 g, 9 mmol) in DME (0.6 mL) was added $ZrCl_4$ (0.070 g, 0.3 mmol) in a sealed tube and the resulting mixture allowed to react by shaking at 150 °C for 12 h. The mixture was treated by a similar method as decribed above. The product was purified by column chromatography (hexane/ethyl acetate = 7/1) on silica gel to afford **12**: ^{1}H NMR δ 0.91 (t, 3H, J = 7.3 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.29–1.47 (m, 6H), 1.69 (s, 3H), 1.96 (dd, 1H, J = 18.7, 1.8 Hz), 2.31–2.36 (m, 1H), 2.44–2.51 (m, 1H), 2.61 (dd, 1H, J = 6.6, 18.7 Hz), 2.84 (m, 1H); ^{13}C NMR δ 8.03 (q), 13.9 (q), 19.1 (q), 22.4 (t), 26.8 (t), 26.8 (t), 28.5 (t), 31.8 (t), 34.9 (d), 42.9 (t), 135.6 (s), 177.7 (s), 209.1 (s); IR (NaCl) 2959, 2932, 2872, 1704, 1644 cm^{-1}.

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Supplementary Material Available: Copies of spectra (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.