Regioselective Acylation of (5-Alkylidene-1,3-cyclohexadiene)tricarbonyliron Complexes by the Reaction with Organometallic Reagents

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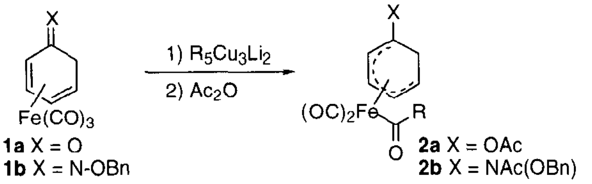
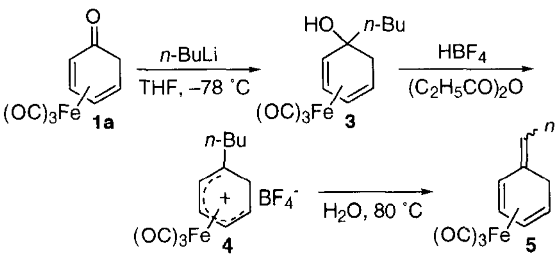
Reaction of [(1,2,3,4-η)-5-alkylidene-1,3-cyclohexadiene]tricarbonylirons and organometallic reagents generates acyl-[(1,2,3,4,5-η)-1-alkylcyclohexadienyl]dicarbonylirons. The acyl group in these complexes migrates to the cyclohexadienyl moiety under carbon monoxide atmosphere, providing [(1,2,3,4-η)-6-acyl-2-alkyl-1,3-cyclohexadiene]tricarbonylirons, which are further transformed to *m*-alkylphenyl ketones by the oxidation with trimethylamine *N*-oxide.

Recently, we have reported the generation of acyl(η^5-cyclohexadienyl)iron complexes **2a,b** by the reaction of tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one]iron **1a** and its *O*-benzyloxime **1b** with higher order cuprates.[1,2] In these reactions, **2a,b** are generated by nucleophilic attack of cuprates on the ligand carbon monoxide and the successive treatment with acetic anhydride. These complexes **2a,b** are synthetically important intermediates, and, in fact, they can be converted to *m*-acylated phenols and anilines, which are difficult to be prepared by the Friedel-Crafts acylation.

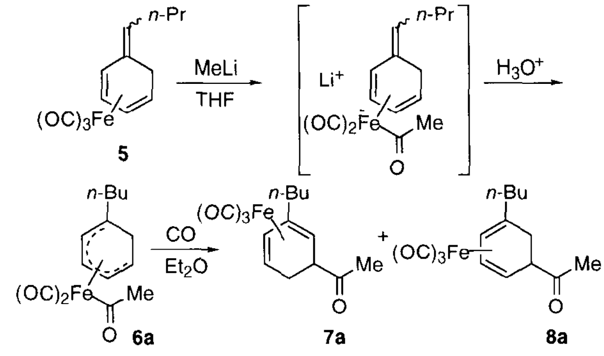


Generally acyl(η^5-cyclohexa, and cycloheptadienyl)iron complexes are synthesized by several steps from the readily available tricarbonyl(η^4-diene)iron derivatives.[3,4] As the acyl-(η^5-cyclohexadienyl)iron complexes **2** are generated from tricarbonyl(η^4-cyclohexadiene)iron derivatives **1** directly, similar acyl(η^5-cyclohexadienyl)iron complex is expected to be formed from [(1,2,3,4-η)-5-alkylidene-1,3-cyclohexadiene]tricarbonyliron. Based on this consideration, we have examined the conversion of [(1,2,3,4-η)-5-alkylidene-1,3-cyclohexadiene]tricarbonyliron derivatives to acyl(η^5-cyclohexadienyl)iron complexes, and this method was applied to the regioselective formation of *m*-substituted phenyl ketone derivatives.



[(1,2,3,4-η)-5-Butylidene-1,3-cyclohexadiene]tricarbonyliron (**5**) was easily prepared from tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadiene-1-one]iron (**1a**).[5] The reaction of **1a** with butyllithium at −78 °C for 1 h afforded an alcohol **3** in good yield. The alcohol **3** was treated with aq. HBF_4 in propionic anhydride, giving tetrafluoroborate **4**, which was converted to the triene complex **5** as an inseparable *E* and *Z* -mixture (*E* : *Z* = 3 : 1) after heating in H_2O at 80 °C for 3 h.

Reaction of [(1,2,3,4-η)-5-butylidene-1,3-cyclohexadiene]tricarbonyliron (**5**) and methyllithium in THF at −35 °C for 1 h, followed by the addition of aq. NH_4Cl, afforded a thermally unstable iron complex **6a** after extraction with Et_2O and evaporation of the solvent at 0 °C. The low field carbonyl peak (260.8 ppm) of ^{13}C-NMR of **6a**[6] indicates the existence of an acyliron moiety,[7] which suggests the structure of **6a** as acetyl[(1,2,3,4,5-η)-1-butylcyclohexadienyl]dicarbonyliron. The acetyl group of the dicarbonyliron complex **6a** migrated selectively to the C_5 position of the cyclohexadienyl ligand under carbon monoxide atmosphere in Et_2O at room temperature, and [(1,2,3,4-η)-6-acetyl-2-butyl-1,3-cyclohexadiene]tricarbonyliron (**7a**)[8] and its isomer **8a** were obtained in 83% total yield (**7a**:**8a**=>10:1) from **5** after Florisil column chromatography.



The dieneiron complexes **7a** and **8a** were transformed to *m*-butylphenyl methyl ketone by oxidation.[9] That is, when the mixture of **7a** and **8a** was treated with trimethylamine *N*-oxide in *N*,*N*-dimethylacetamide (DMA) at room temperature, *m*-butylphenyl methyl ketone (**9a**; R = Me) was obtained in 68% yield. On the whole, *m*-butylphenyl methyl ketone (**9a**) was synthesized in 56% total yield from **5** (method A). Alternatively, **9a** was also synthesized regioselectively from **5** almost in the same yield without the conversion of the acyl(dicarbonyl)iron complex **6a** to the tricarbonyliron complex **7a** and **8a**. That is, the direct oxidation of the crude **6a** with trimethylamine *N*-oxide afforded **9a** in 57% yield from **5** (method B).

Various *m*-butylphenyl ketones **9** were prepared by these two methods as listed in Table 1.[10] In addition to methyl and butyllithiums, bulky *s*-butyl and *t*-butyllithiums reacted with **5** to afford **9** in moderate yield. Phenyllithium could be also employed to give a benzophenone derivative **9e**. Except for the reaction of phenyllithium, methods A and B gave the similar results.

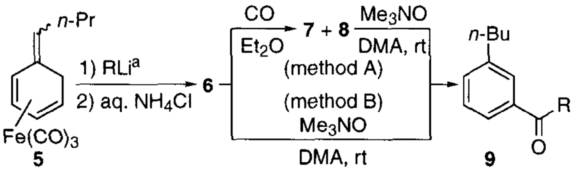
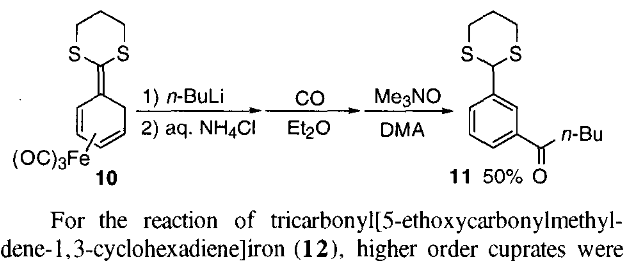


Table 1. Preparation of *m*-butylphenyl ketones **9** from **5**

	Yield / % by method A			Yield / % by method B
R	7+8	9	total yield	9
Me[b]	83	68	56	57
n-Bu	91	77	70	72
s-Bu	77	60	46	52
t-Bu	94	64	60	53
Ph	92	81	75	45

[a] In all cases reaction temperature is -78 °C unless otherwise noted.
[b] Reaction temperature is -35 °C.

The reaction of tricarbonyl[(1,2,3,4-η)-5-(1,3-dithian-2-ylidene)-1,3-cyclohexadiene]iron (**10**) and butyllithium was carried out by method A, giving butyl *m*-(1,3-dithian-2-yl)phenyl ketone **1 1** in 50% yield.



For the reaction of tricarbonyl[5-ethoxycarbonylmethylidene-1,3-cyclohexadiene]iron (**12**), higher order cuprates were found to be the choice of the nucleophile.[11] Higher order cuprates prepared from primary, secondary, and tertiary alkyllithiums and copper(I) iodide reacted with **12** to provide ethyl (*m*-acylphenyl)acetate derivatives **1 3** in moderate yield.

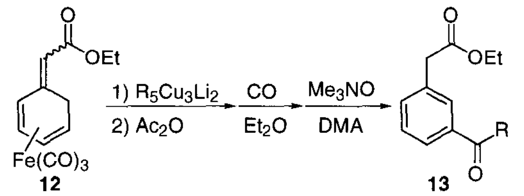


Table 2. Preparation of ethyl (*m*-acylphenyl)acetate **13** from **12**

R	Yield / %
Me	58
n-Bu	75
s-Bu	60
t-Bu	58

It has been reported that stabilized anions such as 2-lithio-2-methylpropionitrile or 2-lithio-1,3-dithiane react with tricarbonyl-(η^4-1,3-cyclohexadiene)iron to afford alkylated cyclohexenes by the attack of these anions to the diene moiety. Non-stabilized organolithiums such as butyllithium react with the same iron complex but give several products such as 4-pentenoylcyclohexene, 3-butylcyclohexene, and pentanal in low yield.[12] In the present reaction of [(1,2,3,4-η)-5-alkylidene-1,3-cyclohexadiene]tricarbonyliron, non-stabilized organolithiums or higher order cuprates attack not onto the triene moiety but onto the carbon monoxide of the tricarbonyliron complexes **5**, **10**, and **12** selectively. This acyl group migrates regioselectively to the C_5 position of the cyclohexadienyl ligand, affording *m*-alkylphenyl ketone or ethyl *m*-acylphenylacetate derivatives after the oxidation with trimethylamine *N*-oxide. It should be also mentioned that the obtained *m*-alkylphenyl ketone and ethyl *m*-acylphenylacetate derivatives are both difficult to be synthesized by the Friedel-Crafts acylation from alkylbenzenes and ethyl phenylacetate, respectively.[13]

References and Notes

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6 **6a**, ^{1}H NMR (500 MHz, $CDCl_3$, -10 °C) δ = 0.84 (3H, t, *J* = 6.9 Hz), 1.13-1.35 (3H, m), 1.51-1.70 (2H, m), 1.93-2.05 (1H, m), 1.99 (1H, d, *J* = 14.3 Hz), 2.32 (3H, s), 2.50 (1H, dd, *J* = 14.3, 5.7 Hz), 3.41-3.48 (1H, m), 4.26-4.35 (1H, m), 4.59-4.68 (1H, m), 6.12 (1H, t, *J* = 5.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, -10 °C) δ = 260.8 (RC=O), 220.1, 209.4 (CO); IR (KBr) 2000, 1940, 1645 cm^{-1}.

7 The ^{13}C-resonance of the acetyl carbon of acetyldicarbonylcyclopentadienyliron is reported to be 254.4 ppm. L. F. Farnell, E. W. Randall, and E. Rosenberg, *J. Chem. Soc., Chem. Commun.*, **1971**, 1078.

8 **7a**, ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, t, *J* = 7.34 Hz), 1.39-1.46 (2H, m), 1.52-1.60 (1H, m), 1.62-1.70 (1H, m), 1.86 (1H, ddd, *J* = 15.3, 8.8, 2.3 Hz), 2.05 (1H, ddd, *J* = 15.2, 5.3, 3.3 Hz), 2.12 (3H, s), 2.27 (2H, t, *J* = 7.7 Hz), 2.44 (1H, ddd, *J* = 8.9, 5.4, 1.5 Hz), 3.08-3.10 (1H, m), 3.23-3.24 (1H, m), 5.13 (1H, d, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.1, 206.8, 105.2, 85.4, 61.9, 58.9, 47.9, 36.2, 33.4, 28.3, 27.5, 22.5, 13.9; IR (KBr) 2038, 1969, 1709 cm^{-1}.

9 Other oxidation methods, such as cerium(IV) ammonium nitrate (CAN) in MeOH and iodine in THF gave **9a** in lower yield.

10 General experimental procedure is as follows: To a THF solution (4.5 ml) of **5** (103 mg, 0.38 mmol) was added *n*-BuLi (1.56 mol dm^{-3}; 0.61 ml, 0.95 mmol) at -78 °C. After 1 h, the reaction was quenched with aq. NH_4Cl (25 ml). The combined ether extracts (10 ml x 3) were washed with brine and dried over anhydrous Na_2SO_4 at 0 °C to afford an ether solution of the crude **6**.

Method A: The ether solution of the crude **6** was stirred under carbon monoxide atmosphere for 18 h at room temperature. After removal of the solvent, the mixture of **7b** and **8b** (122.9 mg, 0.34 mmol, 91%) was obtained by the purification by Florisil column chromatography. To a DMA solution (10 ml) of **7b** and **8b** was added Me_3NO (0.3g, 4 mmol) at 0 °C and the reaction mixture was stirred for 12 h at room temperature. The crude products were purified by TLC (hexane:ethyl acetate=10:1) to afford butyl *m*-butylphenyl ketone **9b** (57.2 mg, 0.26 mmol, 77% (70% for 2 steps)).

Method B: After removal of the solvent from the ether solution of the crude **6** at 0 °C, DMA (10 ml) and Me_3NO was added. The reaction mixture was stirred for 12 h. **9b** was obtained after the purification by TLC (48.1 mg, 0.22 mmol, 72% from **5** (83.3 mg, 0.30 mmol)).

11 Organolithium reagent reacts with ethoxycarbonyl group of **1 2**.

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