Preparation of *m*-Acylaniline Derivatives by the Reaction of Tricarbonyl(cyclohexadienone *O*-benzyloxime)iron Complex and Higher Order Cuprates

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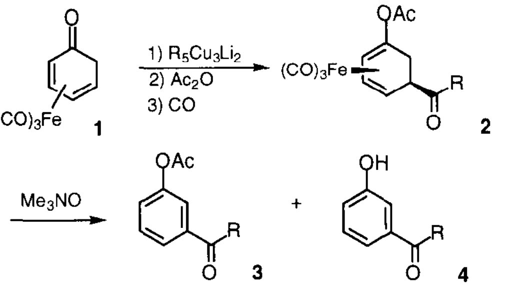
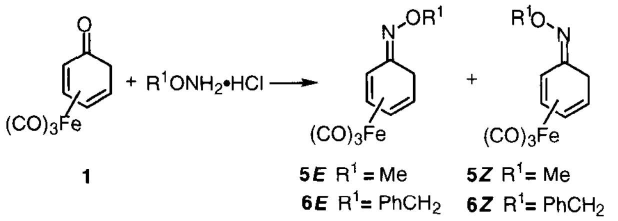
Reaction of tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one *O*-benzyloxime]iron and organocuprates, followed by the treatment with acetic anhydride and carbon monoxide, affords [(1,2,3,4-η)-1-(*N*-acetoxy-*N*-benzyloxyamino)-5-*endo*-acyl-1,3-cyclohexadiene]tricarbonylirons, which are converted to *m*-acylaniline derivatives by treating with potassium carbonate.

Although Friedel-Crafts acylation is considered as one of the most powerful synthetic tools for the introduction of an acyl substituent to an aromatic ring system, direct *m*-acylation of phenol or aniline derivatives is still a difficult transformation in organic synthesis.[1] In the previous paper, we have reported the regioselective preparation of *m*-acylphenol derivatives using tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one]iron (**1**) as a phenol equivalent.[2] In this method, higher order cuprates ($R_5Cu_3Li_2$) react with the coordinated carbon monoxide of the iron complex **1**, and the addition of acetic anhydride and the successive bubbling of carbon monoxide afford stable tricarbonyl complexes **2**. The complexes **2** are converted to *m*-acylphenol derivatives **3** and **4** by the oxidation with trimethylamine *N*-oxide.



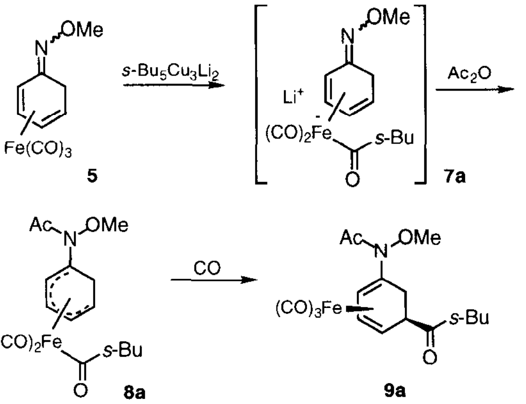
Since *m*-acylaniline derivatives were expected to be synthesized in the same way by the use of *O*-alkyloxime derivatives of **1**, the preparation of tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one *O*-alkyloxime]iron (**5**, **6**) and their reaction with organocuprates were examined.



The oximes, (*E*) and (*Z*)-tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one *O*-methyloxime]irons (**5*E***, **5*Z***) and their *O*-benzyl analogs (**6*E***, **6*Z***), were prepared by the reaction of **1**[3] and *O*-methyl or *O*-benzylhydroxylamine hydrochloride in the presence of sodium carbonate in ethanol and water (1/1) at 70 °C for 8 h. Separation of the *E* and *Z* isomers was easily performed by silica gel column chromatography to afford **5** and **6** in good yield (**5*E*** 75%, **5*Z*** 13%; **6*E*** 80%, **6*Z*** 14%).

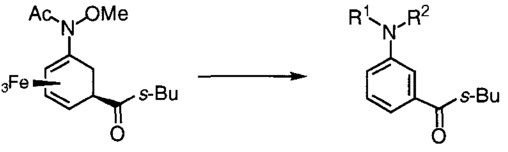
Treatment of the (*E*)-*O*-methyloxime **5*E*** with a higher order cuprate[4] (s-$Bu_5Cu_3Li_2$) for 1 h at -78 °C, followed by the addition of acetic anhydride for 10 min at 0 °C and then water, afforded a thermally unstable and acid sensitive iron complex, which was extracted with ether at 0 °C after removal of inorganic salts by filtration through a Celite pad.[5] The low field carbonyl peak (263.6 ppm) of ^{13}C-NMR of **8a**[6] indicates the existence of iron acyl functional group,[7] which suggests the structure of **8a** as [(1,2,3,4,5-η)-1-(*N*-acetoxy-*N*-methoxyamino)cyclohexadienyl]-dicarbonyl(2-methylbutanoyl)iron.

In an ethereal solution of **8a**, the acyl group of **8a** migrated to the C_5 position of the cyclohexadienyl ligand under carbon monoxide atmosphere at room temperature, affording [(1,2,3,4-η)-1-(*N*-acetoxy-*N*-benzyloxyamino)-5-*endo*-(2-methylbutanoyl)-1,3-cyclohexadiene]tricarbonyliron (**9a**). The tricarbonyliron complex **9a**[8] was isolated in 72% yield from **5*E*** after Florisil column chromatography and the structure was assigned by the comparison of its NMR and IR data with those of the 1-acetoxy-derivatives **2** (R = *s*-Bu).[2]



As shown in Table 1, the iron complex **9a** was converted to *m*-acylaniline derivatives **10a**, **11a** in 70% total yield by the oxidation with cerium(IV) ammonium nitrate (CAN). It is noteworthy that the tricarbonyliron complex **9a** can also be converted to *m*-acylaniline derivatives **11a** and **12a** by the treatment with a base. That is, when **9a** was treated with potassium carbonate in methanol for 1 h at room temperature, **11a** and **12a** were obtained in 86% total yield.

As the tricarbonyliron complex **9a** was not stable enough and gradually decomposed during the purification, the synthesis of the *m*-acylaniline derivatives **11a** and **12a** from the oxime **5*E*** was investigated without the isolation of **9a**. An ethereal solution of the crude dicarbonyliron **8a** which was prepared from **5*E*** by the above procedure was stirred under carbon monoxide atmosphere. After removal of the solvent, the crude tricarbonyliron complex **9a** was immediately treated with potassium carbon-



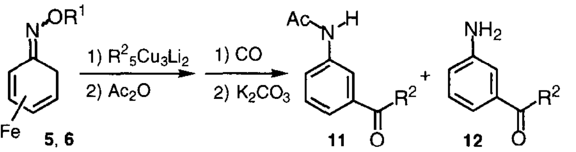
9a

10a (R^1=Ac, R^2=OMe)
11a (R^1=Ac, R^2=H)
12a (R^1=H, R^2=H)

Table 1. Transformation of the tricarbonyliron complex **9a** to *m*-acylaniline derivatives

Reagent	Yield / %		
	10a	**11a**	**12a**
Me_3NO	4	18	0
I_2	22	17	0
CAN	50	20	0
K_2CO_3	0	62	24

ate in methanol. Though the acetyl group was partially cleaved by this procedure, the *m*-acylaniline derivatives **11a** and **12a** were obtained in 48 and 11% yield, respectively (Table 2, entry 1). It became apparent that the *m*-acylanilines **11a** and **12a** were obtained in better yield (52%, 20%) by employing the *O*-benzyloxime **6*E*** instead of the *O*-methyloxime **5*E*** (Table 2, entry 3).



5, 6 **11** **12**

Table 2. Reaction of the tricarbonyl iron complex **5**, **6** with organocuprates

Entry	R^1	R^2	Yield / %	
1	Me (**5*E***)	*s*-Bu	48 (**11a**)	11 (**12a**)
2	Me (**5*Z***)	*s*-Bu	48 (**11a**)	10 (**12a**)
3	CH_2Ph (**6*E***)	*s*-Bu	52 (**11a**)	20 (**12a**)
4	CH_2Ph (**6*Z***)	*s*-Bu	53 (**11a**)	20 (**12a**)
5	CH_2Ph (**6*E***)	Me	72 (**11b**)	4 (**12b**)
6	CH_2Ph (**6*E***)	*n*-Bu	62 (**11c**)	10 (**12c**)
7[a]	CH_2Ph (**6*E***)	Ph	45 (**11d**)	2 (**12d**)

a) $Ph_2Cu(CN)Li_2$ was used instead of $Ph_5Cu_3Li_2$.

As shown in Table 2, various *m*-acylaniline derivatives could be synthesized from benzyloxime **6*E*** and **6*Z***. Not only *s*-butyl but also methyl and *n*-butyl cuprates reacted with **6** to afford *m*-acylaniline derivatives in good yield (entry 5, 6). *m*-Benzoylaniline derivatives were also synthesized by using $Ph_2Cu(CN)Li_2$[9] as a nucleophile (entry 7). As both *E* and *Z* isomers of the *O*-alkyloxime derivatives (**5*E*** and **5*Z***, or **6*E*** and **6*Z***) react with a higher order cuprate (*s*-$Bu_5Cu_3Li_2$) to afford *m*-acylanilines **11a** and **12a** in the same yield (entry 1-4), it is not synthetically necessary to separate both isomers.

m-Alkylaniline derivative has been regioselectively synthesized from tricarbonyl(η^6-*N*,*N*-dimethylaniline)chromium by the action of soft anions, which directly attack the *meta*-position of the aniline-chromium complex.[10] In the present method, *m*-acylaniline derivatives are regioselectively formed from the readily available iron complex of cyclohexadienone *O*-benzyloxime **6**.

General experimental procedure (Table 2, entry 3) is as follows: To 400 mg (2.1 mmol) of CuI in a mixture of ether (5 ml) and THF (5 ml) was added *s*-BuLi (1.50 mol dm^{-3}; 2.35 ml, 3.53 mmol) at -30 °C. After being stirred for 10 min at -30 °C, the reaction mixture was cooled to -78 °C and 339 mg (1.0 mmol) of **6*E*** was added. After 1 h, 432 mg (4.0 mmol) of acetic anhydride in ether (2 ml) was added. After being warmed to 0 °C, the mixture was poured into 10 ml of brine. The organic materials were extracted with ether at 0 °C after removal of inorganic salts by filtration through a Celite pad. The ether extracts were dried over magnesium sulfate. The ether layer was stirred for 16 h under carbon monoxide atmosphere at room temperature. After the solvent was evaporated, the crude product was treated with potassium carbonate (553 mg, 4 mmol) in MeOH (10 ml) at room temperature for 1 h. After removal of MeOH in vacuo and then addition of water, the organic materials were extracted with ethyl acetate and organic phase was dried over magnesium sulfate. The crude products were purified by thin-layer chromatography (Silica gel, hexane:ethyl acetate=3:1) to afford **11a** (113.5 mg, 52 %) and **12a** (36.0 mg, 20 %).

References and Notes

1 H. Heaney, "The Bimolecular Aromatic Friedel-Crafts Reaction," in "Comprehensive Organic Synthesis," ed by B. M. Trost, Pergamon Press, Oxford (1991), Vol. 2, p 733.

2 S. H. Ban, H. Sakurai, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, **1997**, 699.

3 A. J. Birch, L. F. Kelly, and D. J. Thompson, *J. Chem. Soc., Perkin Trans. I*, **1981**, 1006.

4 When *s*-butyllithium was employed as an alkylation reagent, *N*-aceyl- *N*-benzyloxyaniline was obtained in 20% yield along with a recovery of the starting material (60%). When *s*-butylmagnesium chloride was employed, no reaction proceeded.

5 It is necessary to remove inorganic salts at this stage. The presence of inorganic salts disturbed the acyl migration from **8a** to **9a**.

6 **8a**, ^{1}H NMR (500MHz, $CDCl_3$) $\delta = 0.78$-0.82 (7H, m), 0.90-1.00 (1H, m), 2.15 (3H, s), 2.15-2.22 (1H, m), 2.75-2.85 (1H, m), 3.40-3.50 (1H, m), 3.69 (3H, s), 3.68-3.75 (1H, m), 4.65-4.75 (2H, m), 6.14 (1H, br s); ^{13}C NMR (125MHz, $CDCl_3$, -10 °C) 263.6 (RC=O), 219.9, 209.1 (CO); IR (KBr) 1999, 1940, 1689, 1639 cm^{-1}. In the previous paper,[2] we assigned the structure of the product of *s*-$Bu_5Cu_3Li_2$ and **1** after quenching with acetic anhydride as [(1,2,3,4-η)-1-acetoxy-5-*endo*-(2-methylbutanoyl)-1,3-cyclohexadiene]dicarbonyliron based on the IR spectrum. By the examination of the ^{13}C NMR, the structure should be assigned as [(1,2,3,4,5-η)-1-acetoxycyclohexadienyl]dicarbonyl(2-methylbutanoyl)-iron, which will be disclosed in a full paper.

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 **9a**, ^{1}H NMR (500MHz, $CDCl_3$) $\delta = 0.82$ (1.5H, t, $J = 7.4$ Hz), 0.83 (1.5H, t, $J = 7.4$ Hz), 1.03 (3H, d, $J = 6.8$ Hz), 1.29-1.35 (1H, m), 1.61-1.70 (1H, m), 1.76-1.86 (1H, m), 2.15 (3H, s), 2.52-2.55 (1H, m), 2.61-2.64 (1H, m), 2.72-2.78 (1H, m), 3.23-3.27 (1H, m), 3.81 (3H, s), 5.22-5.25 (1H, m), 5.83-5.86 (1H, m); IR (KBr) 2048, 1982, 1711, 1676 cm^{-1}.

9 J. M. Klunder, T. Onami, and K. B. Sharpless, *J. Org. Chem.*, **54**, 1295 (1989). The use of $Ph_5Cu_3Li_2$ instead of $Ph_2Cu(CN)Li_2$ gave **11d** and **12d** in low yield.

10 M. F. Semmelhack, "Nucleophilic Addition to Arene-Metal Complexes," in "Comprehensive Organic Synthesis," ed by B. M. Trost, Pergamon Press, Oxford (1991), Vol. 4, p 517.