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Preliminary communication

Anomalous deprotonation of tricarbonyl(η^5-1-arylcyclohexadienyl)iron complexes

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Abstract

1-Aryl substituted cyclohexadienyl complexes provide the first examples of deprotonation from C-6 of tricarbonyl(cyclohexadienyl)iron(1 +) complexes, and, in the case of ortho-substituted aryl substituents, a reversed regiocontrol of nucleophile addition.

Keywords: Iron; Carbonyl; Cyclohexadienyl; Biaryl; Deprotonation

The utility of tricarbonyl(η^5-cyclohexadienyl)iron(1 +) complexes in organic synthesis is sometimes limited by competing deprotonation reactions from side-chain positions. This side-reaction has been examined in detail for a series of sterically hindered bicyclic complexes [1]. We have previously shown that even quite a small change in the substitution pattern of the dienyl complex (e.g. the introduction of an additional methyl group on the dienyl unit, at a location remote from the site of nucleophile addition) can be enough to switch the reaction from nucleophile addition to side-chain deprotonation [2]. In all the cases reported to date, however, deprotonation has taken place at a methyl or methylene group next to the dienyl moiety, to form an exocyclic triene complex. The alternative deprotonation from C-6 of the cyclohexadienyl ligand, which might be expected to be favoured by the formation of a stable metal-free aromatic product, does not compete with side-chain deprotonation. Indeed, selective side-chain deprotonation has been used in the chemical separation of a mixture of regioisomeric η^5-cyclohexadienyl complexes [3].

1. Anomalous deprotonation reactions

In this paper, we report the first examples of deprotonation from C-6 of tricarbonyl(η^5-cyclohexadienyl)iron(1 +) complexes. Our work is directed towards the development of stereocontrolled C–C bond formation for alkaloid synthesis, in which electrophilic 1-aryl substituted cyclohexadienyl complexes are used as key intermediates. Cyanoacetate ester addition has been used to introduce (after decarboxylation) a two atom side-chain, to form a quaternary centre at the junction of the two six-membered rings. The reaction works well when the aryl substituent is a simple phenyl group or *p*-substituted arene and is a key step in our synthesis of *O*-methyljoubertiamine [4]. We have now examined vinyl and acetylide [5] addition in search of alternative sources of two atom units. Organoiron complexes bearing *o*-substituted aromatics ($MeOCH_2C_6H_4$ and $(CHO)C_6H_4$) at C-1 (see Scheme 1 and Table 1) have been employed in this work, since a substituent is required at this position in our target structures. Nucleophile addition in these cases has proved to be less efficient, and dimeric and aromatic by-products have been identified.

Solvent effects were found to influence of the course of the nucleophile addition reaction. When the divinylcuprate reagent was used as the nucleophile in reactions with the simple phenyl-substituted salt **1a**, the reaction was slightly more efficient when performed in DME at −40°C (Table 1, entry 2), than in THF at −78°C (entry 1), in which the majority of the product consisted of dimeric metal complexes and 4-methoxybiphenyl. In DME, however, the mass balance of the reaction was rather poor (52%). The use of THF was

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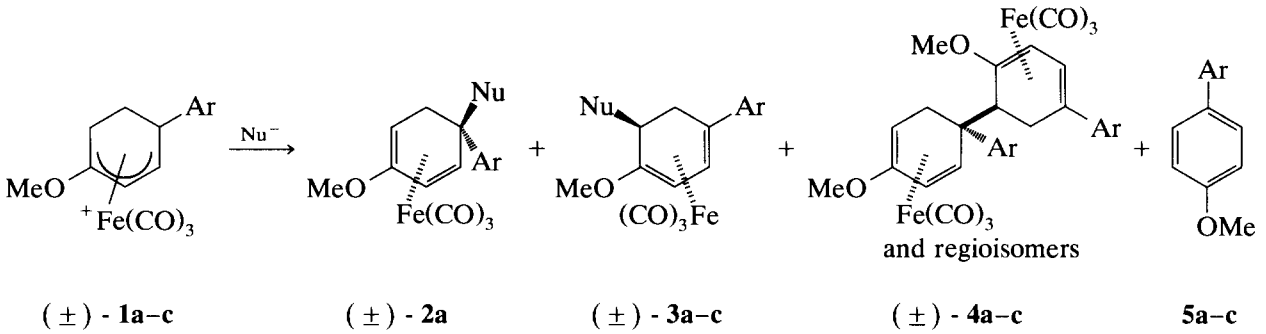


(±) - **1a–c** (±) - **2a** (±) - **3a–c** (±) - **4a–c** **5a–c**

Ar: **a** - Ph; **b** - *o*-$MeOCH_2C_6H_4$; **c** - *o*-$(CHO)C_6H_4$
Nu: CH_2=CH–; PhC≡C–; $CH(CN)CO_2Me$

Scheme 1. Nucleophile addition to 1-aryl substituted organoiron cations.

improved (entry 3) by preparing the cuprate reagent from the dimethyl sulfide complex of copper(I) bromide. In this case, the mass balance was 90%, but deprotonation slightly predominated over nucleophile addition. Similar results were obtained with Grignard, lithiocuprate and vinyllithium reagents (entries 4, 5, and 6), and with the ortho substituted salts **1b** and **1c** (entries 7 and 8). In all cases, when nucleophile addition occured, it was the ω-addition product **3** that was obtained, not the expected [4] ipso adduct **2**, and aromatisation was consistently encountered as a side reaction.

The formation of dimers is a common side reaction for cationic organometallic complexes, especially when organomagnesium nucleophiles are employed [6], but deprotonation to form aromatic structures has not been observed before. Since tricarbonyliron complexes can be envisaged as equivalents of aryl cation synthons [7], methods to gain convenient direct access to aromatic products are of potential importance in synthetic applications [8].

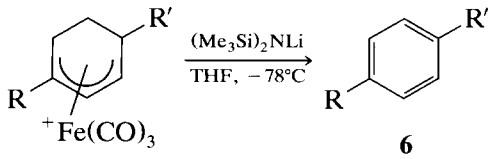
2. Application to biaryl synthesis

The original work on aryl cation synthons combined decomplexation of neutral η^4 complexes with conventional aromatisation steps, using DDQ or Pd/C, to complete the aromatic targets [7]. This methodology has been found to be unsatisfactory when sensitive structures are present in the target molecule [9]. A one-step aromatisation by deprotonation of cationic cyclohexadienyl complexes might offer an attractive alternative. In view of this, we have examined the

Table 1

Entry	Dienyl salt	Nu-M	Solvent [a] T, °C	Yield, %			
				2	3[d]	4	5[d]
1	**1a**	$(CH_2$=$CH)_2CuMgBr$ [b]	THF, −78	0	20	29	30
2	**1a**	$(CH_2$=$CH)_2CuMgBr$ [b]	DME, −40	0	29	−[e]	23
3	**1a**	$(CH_2$=$CH)_2CuMgBr$ [c]	THF, −78	0	42	−[e]	48
4	**1a**	CH_2=$CHMgBr$	DCM, −78	0	27	−[e]	22
5	**1a**	$(CH_2$=$CH)_2CuLi$ [c]	THF, −78	0	25	0	24
6	**1a**	CH_2=$CHLi$	DCM, −78	0	26	0	49
7	**1b**	$(CH_2$=$CH)_2CuMgBr$ [c]	THF, −78	0	25	23	17
8	**1c**	$(CH_2$=$CH)_2CuMgBr$ [c]	THF, −78	0	17	7[f]	20
9	**1a**	$(PhC$≡$C)_2CuLi$ [c]	THF, −20	0	0	0	29
10	**1a**	PhC≡CLi	DCM, −20	0	0	0	32
11	**1b**	PhC≡CLi	DCM, −20	0	0	0	23
12	**1a**	$NaCH(CN)CO_2Me$	THF, 0	82	0	0	0
13	**1b**	$NaCH(CN)CO_2Me$	THF, 0	0	71	0	0
14	**1c**	$NaCH(CN)CO_2Me$	THF, 0	0	72[g]	0	0

[a] THF—tetrahydrofuran; DME—dimethoxyethane; DCM—dichloromethane. [b] Cuprate was prepared using CuI. [c] Cuprate was prepared using $CuBr \cdot Me_2S$. [d] Ratio of products **3** and **5** was estimated from the ^1H NMR spectra of their mixtures. [e] Identified by TLC, too little to quantify. [f] Product **4c** was characterised only by ^1H NMR and IR spectra. [g] Second molecule of methyl cyanoacetate added to the aldehyde group.



Scheme 2. Deprotonation of cationic organoiron complexes (See Table 2).

generality and utility of the deprotonation reaction. Deliberate deprotonation of **1a** by reaction with $(Me_3Si)_2NLi$ afforded 4-methoxybiphenyl in 59% yield (Scheme 2 and Table 2, entry 1). Comparison of reactions of 1-phenyl substituted salts (Table 2, entries 1,2) with 1,4-dimethoxy- and 2-methoxydienyl complexes (Table 2, entries 3,4) shows that the deprotonation reaction requires the presence of the 1-aryl group for success. The reaction allows novel access to biaryl structures, and demonstrates for the first time that this type of deprotonation is possible.

3. Control of selectivity between nucleophile addition and deprotonation

The deprotonation reaction can be prevented by the choice of a less basic nucleophile, so opening the way for C–C bond formation by nucleophile addition. Regiocontrol of the nucleophile addition depends markedly on the nature of the nucleophile. The product ratios reported in Table 1 indicate that in the case of nucleophiles of middle strength, such as vinyllithium, magnesium or copper reagents, the directing effect of 1-aryl substituent overcomes that of 4-methoxy group [10], and only adducts **3** (Scheme 1) are obtained. In the case of milder nucleophiles, such as the sodium enolate of methyl cyanoacetate, complex **2** normally predominates (Table 1, entry 12) [4], but introduction of an ortho substituent on the aryl group was found to reverse the regiocontrol of nucleophile addition, and regioisomer **3** was the only product (Table 1, entries 13 and 14). This difference was attributed to steric blocking of the approach of the nucleophile by the ortho substituent. It seemed possible that a less bulky nucleophile might penetrate this steric blockade, and the phenylacetylide ion was chosen as a model nucleophile to explore this possibility. Surprisingly, no nucleophile addition products could be isolated (Table 1, entries 10 and 11), even with the simple phenyl substituted salt **1a**. With both lithium and the less basic copper acetylides, biaryls were the only products from the attempted nucleophile additions.

Table 2

Entry	Organoiron salt		Yield of **6** (%)
	R	R'	
1	OMe	Ph	59
2	H	Ph	40
3	OMe	OMe	0 [a]
4	OMe	H	0 [b]

[a] Only the corresponding 4-methoxycyclohexadien-1-one tricarbonyliron complex was isolated. [b] Starting salt was recovered.

4. Conclusions

This investigation has shown that the chemistry of aryl-substituted tricarbonyl(cyclohexadienyl)iron(1 +) complexes differs from the reactions of simple cyclohexadienyl complexes through the accessibility of deprotonation reactions, and that regiocontrol is strongly influenced by the presence of additional substituent groups. Of the nucleophiles examined, only methyl cyanoacetate is suitable for introducing two-atom units for the construction of quaternary centres at the carbon carrying a phenyl substituent. The process cannot be simply extended to ortho-functionalised aromatic systems of type **1b,c**, nor to other nucleophiles. Alternative synthetic routes will be needed to give access to more elaborately substituted alkaloids. Either the ortho substituent must be added at a later stage, or the order of introduction of aryl and C_2 unit must be reversed.

In the course of this work the first examples of C-6 deptotonation have been observed. This unusual reaction is particular to the 1-aryl series of cyclohexadienyl salts and can be effected in synthetically useful yields by the use of a strong base, affording a novel route to biaryls.

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