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Fine-tuning electrophilicity of cationic tricarbonyliron complexes

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Abstract

Solvent effects can be used to switch aryllithium addition to η^5-cyclohexadienyl tricarbonyliron complexes between novel formation of an acyl product, and the synthetically more valuable direct addition to the dienyl ligand. This gives efficient access to o-functionalised 1-arylcyclohexadienyl complexes for use in alkaloid synthesis.

Keywords: Iron; Carbonyl; Cyclohexadienyl; Solvent effects

Not all nucleophiles add efficiently to electrophilic η^5-cyclohexadienyl $Fe(CO)_3^+$ complexes, and in cases in which nucleophile addition fails, attack at a metal-bound carbonyl ligand has sometimes been invoked to account for the problem [1]. The resulting adduct would be a metal acyl complex, but since no examples have been satisfactory characterised, these species have been assumed to be unstable. We report below the first example of the formation of a stable metal acyl species. By examining in detail the factors that inhibit direct nucleophile addition to the dienyl ligand, optimisation of this synthetically more useful mode of addition has been achieved [2]. We show how the selection of an appropriate solvent switches the course of the reaction between carbonyl- and dienyl-adduct formation.

Cationic 1-arylcyclohexadienyltricarbonyliron complexes are a valuable source of C_{12} building blocks for alkaloid synthesis [3], and have been used in a model synthesis of *O*-methyljoubertiamine [3,4]. We have developed [5] a convenient route to arylcyclohexadienyl complexes via aryllithium (C_6H_4Li and 4-$MeOC_6H_4Li$) addition to 1-alkoxydienyl complexes. After the addition of the nucleophile, removal of the alkoxy leaving group with acid affords the substituted dienyl complex. This reaction sequence employs the Birch dichloromethane conditions [6] for the use of organolithium reagents with cationic tricarbonyliron complexes. Our examination of the extension of these methods with 2-substituted aryl nucleophiles and the cation **1** (Scheme 1) has revealed that the expected adducts **3** are formed in much lower yields (14%–58%) as mixtures with other compounds (Table 1). The reaction has also been examined in ether-based solvents that are more normal for organolithium chemistry [7]. Again, mixtures of products were usually obtained, but in one case (Table 1, entry 2) a single compound was formed. This product exhibited an unusual IR feature in the metal carbonyl region (ν_{CO} 1999 and 1942 cm^{-1}; Fig. 1(a)), could be isolated in low yield, and was clearly not the expected η^4-diene product. The IR spectrum also showed an absorption band at 1607 cm^{-1}, which is characteristic [8,9] of an iron–acyl bond. In the ^1H NMR spectrum of the compound, the pattern of signals was similar to that of the starting salt **1** though, as expected for a neutral complex, the resonances appeared at higher field than those for the cationic complex.

On the basis of the spectral data, this complex was identified as the novel [10] metal acyl adduct **2**. This structural assignment was later confirmed by high resolution MS. The yield of **2** could be improved to 30% by changing from THF to DME as solvent (Table 1, entry 4) though, under these conditions the acyl product was formed as a mixture with the known dienone complex **5**. Lowering the reaction temperature (entry 3) did not improve the yield of **2**; instead, a new complex **4** appeared as the major product. Although the overall efficiency of the conversion was increased to 55%, the yield of **2** was reduced again, to 10%. The new product

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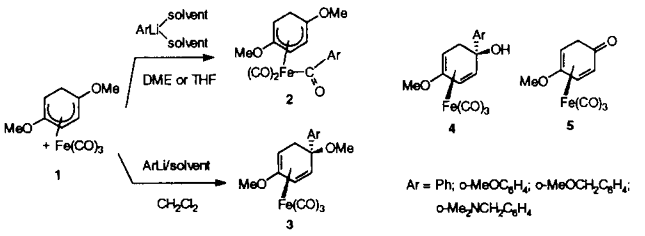


Scheme 1. Effects of the changes in the solvent on the regiochemistry of nucleophile addition.

4 proved also to be a by-product when the reaction was performed in dichloromethane.

The formation of 2 is the first example of the isolation and characterisation of an acyl product arising from the formation of a C–C bond to the carbonyl ligand of a cationic η^5 tricarbonyliron complex, though such reactions are known [11] for other organometal-carbonyl electrophiles, and have been studied [12] for neutral η^4-cyclohexadiene tricarbonyliron complexes. The acyl species 2 was more unstable than η^4-diene complexes, but this mode of nucleophile addition appears general with o-substituted aryllithium reagents in ether solvents, and can be identified from the IR and ^{1}H NMR spectra of the products. In one case ($MeOC_6H_4Li$, Table 1, entries 6 and 7), the acyl adduct could not be purified sufficiently for full characterisation because of extreme instability. Reaction of 1 with the simple aryllithium reagent PhLi [5] was investigated in DME, but none of the acyl product was formed. Acyl formation by aryllithium compounds is restricted to the substituted reagents. The yield of the alcohol 4, however, was raised to 60% when the reaction was performed in DME in the presence of TMEDA. The results presented in Table 1 reveal the profound influence of solvent effects in switching the regioselectivity of reaction.

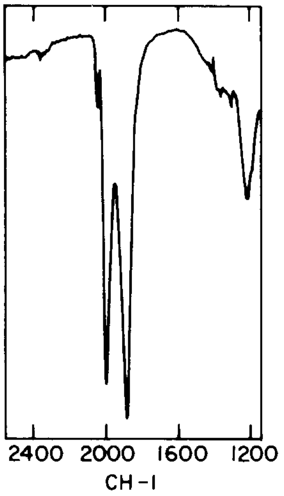


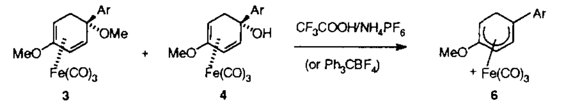
Fig. 1. IR spectra (metal carbonyl region) of acyl products 2: (a) Ar = $MeOCH_2C_6H_4$ (illustrated) (1999, 1942, 1607 cm^{-1}); (b) Ar = $Me_2NCH_2C_6H_4$ (1998, 1940, 1611 cm^{-1}); (c) Ar = $MeOC_6H_4$ (1996, 1937, 1597 cm^{-1}).

In view of the unexpected formation of the alcohol 4 as a by-product of reaction in dichloromethane, our well established [3–5] reaction using phenyllithium was re-examined. Along with the known compound 3, small amounts of the alcohol and dienone products were also

Table 1
Adduct yield

Entry	Nucleophile	Solvent [a]	T (°C)	Yield (%)			
				2	3	4	5
1	o-$MeOCH_2C_6H_4Li$	THF [b]	−78	0	0	0	– [c]
2	o-$MeOCH_2C_6H_4Li$	THF [b]	0	10	0	0	– [c]
3	o-$MeOCH_2C_6H_4Li$	DME [b]	−78	10	0	35	10
4	o-$MeOCH_2C_6H_4Li$	DME [b]	0	30	0	0	5
5	o-$Me_2NCH_2C_6H_4Li$	DME [b]	0	5	0	0	10
6	o-$MeOC_6H_4Li$	DME [b]	−60	1	0	0	6
7	o-$MeOC_6H_4Li$	DME [b]	0	1	0	0	– [c]
8	PhLi	DME [b]	−78	0	0	37	10
9	PhLi	DME [b]	0	0	0	0	– [c]
10	PhLi · TMEDA	DME [b]	−78	0	0	60	10
11	PhLi	DCM [d]	−78	0	72	13	9
12	o-$MeOC_6H_4Li$	DCM [d]	−78	0	43	24	17
13	o-$MeOCH_2C_6H_4Li$	DCM [d]	−78	0	58	15	10
14	o-$MeOCH_2C_6H_4Li$	DCM [e]	−78	0	0	0	50
15	o-$Me_2NCH_2C_6H_4Li$	DCM [d]	−78	0	0	0	42
16	o-$Me_2NCH_2C_6H_4Li$	DCM [d]	−110	0	14	4	5

[a] THF, tetrahydrofuran;
DME, dimethoxymethane;
DCM, dichloromethane;
[b] nucleophile was prepared in the solvent used for the reaction;
[c] traces were identified by TLC – yield not estimated;
[d] nucleophile was prepared in diethyl ether / hexane;
[e] nucleophile was prepared in DME.



Scheme 2. Formation of o-functionalised arylsubstituted cyclohexadienyl complexes.

detected. The conditions of preparation of the organolithium reagent was an important factor in these reactions. In the case of conditions of the $MeOCH_2$-substituted nucleophile, the selectivity was switched from **3** to **5** by changing from ether/hexane to DME for the preparation of the nucleophile. The nature of the ortho substituent was also critical. In the Me_2NCH_2 case, only the dienone **5** was obtained under normal reaction conditions at −78° (entry 15). Even when the temperature was lowered to −110° (entry 16), **3** was isolated in a low (14%) yield, though this was now the major product.

At this stage it was clear that both the choice of solvent and the nature and position of the substituent in the nucleophile, were crucial factors to consider when choosing synthetically efficient systems. On the basis of these results, a revised approach was adopted to provide access to the substituted arylcyclohexadienyl complexes needed for use in alkaloid synthesis. Benzylamine-based nucleophiles had proved unsatisfactory, but the benzyl ether species prepared in Et_2O/hexane were suitable. Since removal of OMe from **3**, or OH from **4**, would give the same dienyl complex, entries 12 and 13 indicate satisfactory conditions for preparing the required dienyl intermediates. Either **3** or **4** was easily converted into the salt **6** (Scheme 2) by reaction with TFA followed by addition of NH_4PF_6, or by using Ph_3CBF_4 in CH_2Cl_2. Separation of **3** and **4** was unnecessary. Nucleophile addition, followed by removal of the dienone by chromatography on a short silica column afforded a mixture of **3** and **4** which could be used directly to give **6** in 77% yield. The corresponding dienyl salts were also prepared in the o-OMe (80% yield) and unsubstituted series (85% yield).

These investigations confirm earlier speculations by other research groups that nucleophile addition at carbonyl ligands of cationic η^5-cyclohexadienyl complexes can account for poor yields of adducts arising from the normal mode of addition to the dienyl unit [1]. We have also shown how choice of reaction conditions, particularly of solvent, can be employed to overcome such side reactions, and have in this way been able to make the series of o-functionalised aryl-substituted cyclohexadienyl complexes that we need [3] as intermediates in alkaloid synthesis. In the course of this work, we have isolated and fully characterised the first examples of stable acyl products from carbanion addition to a carbonyl ligand of a cationic (cyclohexadienyl) $Fe(CO)_3$ complex.

1. Typical experimental procedures

1.1. Preparation of the acyl products 2

n-Butyllithium (2 ml of 1.27 M solution in n-hexane, 2.54 mmol) was added to a solution of the aryl bromide (2.6 mmol) in freshly distilled THF or DME at −78°C. The mixture was stirred at that temperature for 30 min then added to a solution of salt **1** (1 mmol) in freshly distilled THF or DME (25–30 ml) at the temperature specified (Table 1). The mixture was stirred for 1 h then water was added. The mixture was extracted with ether (3 × 30 ml) and the combined extracts were dried over magnesium sulphate and concentrated under reduced pressure. Chromatography on silica gel (or alumina in the case of the nitrogen-containing nucleophile) with 5% ethyl acetate in hexane as eluant, gave complex **4**, and that with 25% ethyl acetate in hexane as eluant gave (in order of elution) the acyl complex **2** and ketone **5**.

1.2. Preparation of salts 6

The nucleophile addition was performed as described above except that the nucleophile was prepared in hexane/ether and CH_2Cl_2 was used as solvent for the addition reaction. After the work-up, chromatography on silica gel with 5% ethyl acetate in hexane as eluent gave, in order of elution, complexes **3** and **4**. The mixture of complexes **3** and **4** was stirred with trifluoroacetic acid (molar ratio 1:10) at 0°C for 30 min. Addition of saturated aqueous ammonium hexafluorophosphate afforded the corresponding salt as a yellow powder, which was reprecipitated from acetonitrile/ether.

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