Notes

General Preparation of Arylacetic Acid Precursors. A Further Example of the Fe(CO)$_3$ Group as an Agent for Lateral Control and Activation in Reactivity of Cyclohexa-1,3-dienes

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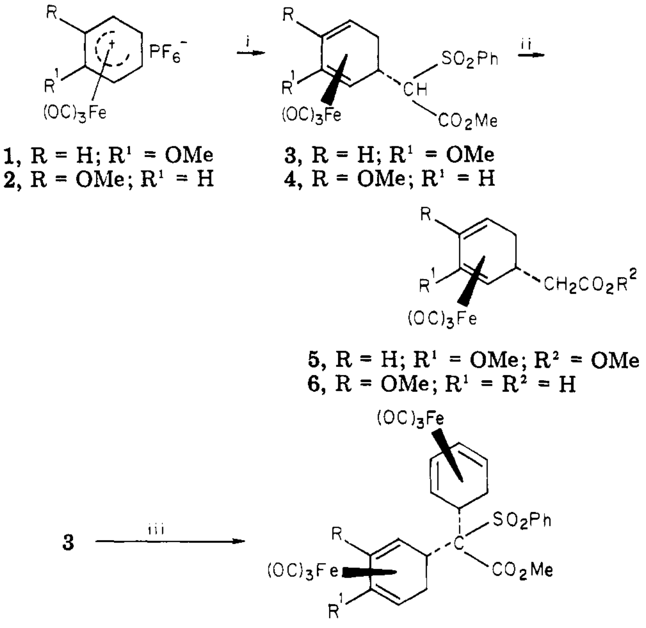
Received December 9, 1981

In general terms, classical protecting and blocking groups used in organic synthesis act by distinguishing functionalities within a molecule on a steric and/or electronic basis.[2] Differentiation by the alternative process of activation can be provided by so-called control groups.[3] Both modes of action have in common the attachment of the temporary, influential group in an endogenous manner, most often by direct σ-bonding, although p-orbital interactions are commonly supportive, e.g., in stabilizing charge on adjacent atoms.

In contrast to this, temporary attachment of Fe(CO)$_3$ to the π-electron network of dienes provides a means of attaining steric and electronic moderation (deactivation) as well as activation toward nucleophiles via derived cations.[4] Consequences and utilization of this process of lateral control of reactivity have been discussed in some detail, including the operational equivalency of tricarbonylcyclohexadienyliron cation complexes to positionally specific metal-free organic cations of formally mesomeric systems, e.g., 5-cation of cyclohexa-1,3-dienes, aryl cations, and 4- or 5-cation of cyclohex-2-en-1-one.[5] Resolved organometallic cation salts can lead to stereo- as well as regiospecifically defined equivalents.[5]

Included as part of the above-mentioned definition of cyclohexadienyliron cations as aryl cation equivalents was a general method for introduction of an aryl group in the α-position of a carbonyl compound.[6] The process here made use of the ready reaction of these organometallic salts with trimethylsilyl enol ethers. Not available, however, by that method were adducts of simple acetic acid derivatives, the appropriate Me$_3$Si compound not being conveniently available.[7] Compounding this, tricarbonylcyclohexadienyliron cations were shown to react with the stable lithium enolate from *tert*-butyl acetate to furnish complex mixtures, including dimeric iron complexes.[8]

Scheme I[a, b]



1, R = H; R^1 = OMe
2, R = OMe; R^1 = H

3, R = H; R^1 = OMe
4, R = OMe; R^1 = H

5, R = H; R^1 = OMe; R^2 = OMe
6, R = OMe; R^1 = R^2 = H

7, R = OMe; R^1 = H

[a] (i) NaH/CH$_2$(SO$_2$Ph)CO$_2$Me/THF, (ii) Na(Hg)/MeOH/Na$_2$HPO$_4$, (iii) NaH/[C$_6$H$_7$Fe(CO)$_3$]$^+$ PF$_6^-$/THF. [b] 1 → 3, 60%; 3 → 5, 81%; 2 → 4, 83%; 4 → 6, 80%; 4 → 7, 59%.

In order for one to make maximum use of the lateral control ability of organometallic complexes, these should preferably to stable to most classical reagents, to enable synthetic manipulations to be carried out elsewhere in the molecule. The cyclohexadiene–Fe(CO)$_3$ derivatives are stable to not unduly severe conditions with complex hydrides, Grignard reagents, bases, and acids, although more severe conditions with acids produce isomerizations.[5] They are unstable to most oxidizing agents.

We have now further employed the concept of lateral control and activation in a process amounting to directed nucleophilic aromatic substitution and leading to precursors in the important arylacetic acid group. The method consists of reacting a cyclohexadienyliron cation salt with preformed THF solution of the anion of methyl phenylsulfonyl acetate at 0 °C. Dissolution of the initially insoluble salt indicates reaction, which is generally complete in less than 15 min. The mixture is poured into water and then extracted into ether. Isolation by silica gel chromatography gives the sulfonylated complexes as mixtures of diastereomers which can often be at least partially separated by crystallization from hexane or methanol.[9] Desulfonylation[10] with sodium amalgam

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(2) For example see: McOmie, J. F. W. "Protective Groups in Organic Chemistry"; Plenum Press: London, 1973.

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(4) Birch, A. J.; Jenkins, I. D. In "Transition Metal Organometallics in Organic Synthesis"; Alper, H.; Ed.; Academic press: New York, 1976; Vol. 1, p 1.

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(6) Kelly, L. F.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1980**, *21*, 2455.

(7) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59.

(8) Birch, A. J.; Kelly, L. F.; unupublished result. See also: Birch, A. J. Kelly, L. F.; Narula, A. S. *Tetrahedron*, in press.

(9) By analogy with other additions of carbon nucleophiles,[4] addition here is assumed to take place at the metal-free face of the complex. Also the formation of diastereomers is of little consequence since the subsequent desulfonylation step removes the element of asymmetry from the acetate α-carbon atom. The separated pair of diastereomers of 4 were similarly converted to 6 (R^2 = OMe).

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proceeds cleanly at room temperature to produce the acetic acid derivative in good yield, demonstrating further the general compatibility of the $Fe(CO)_3$ protecting unit with common reagents and sequences.[11] Alternatively, the sulfonylated adduct can be treated with a further equivalent of sodium hydride and another equivalent of electrophile, such as a different dienyl iron cation, giving unsymmetrical diarylacetic acid precursors by a tandem arylation process.

The sequences so far examined are given in Scheme I.[12]

A recent paper[13] reports the conversion of a malonate adduct of a similar cyclohexadienyliron cation to the corresponding acetate as proceeding in 51% yield. The present method should therefore allow for some improvement in this result.

Experimental Section

General Procedures. Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. IR samples were measured on a Perkin-Elmer 257 spectrometer with deuteriochloroform as the solvent. Matched sodium chloride cells were used for this purpose. NMR spectra were recorded on a Varian HA-100 spectrometer with deuteriochloroform containing 1% tetramethylsilane as the solvent. Mass spectra were obtained on an AEl MS902 spectrometer operating at 70 eV. Tetrahydrofuran (THF) was dried prior to use by distillation from sodium-benzophenone ketyl. Methanol was dried by distillation from magnesium in the presence of iodine. Tricarbonylcyclohexadienyliron salts 1 and 2 were prepared by literature procedures.[14,15] The anion of methyl (phenylsulfonyl)acetate was prepared in THF by using a stoichiometric quantity of sodium hydride as the base. Complete deprotonation required 15 min at room temperature.

Procedure for Alkylation of Salts 1 and 2. By use of typical syringe techniques, a THF solution of methyl sodio(phenylsulfonyl)acetate (5.5 mmol) was added dropwise to a stirred suspension of the cation salt 1 or 2 (1.97 g, 5 mmol) in THF (20 mL) at 0 °C. After being stirred for 15 min the homogeneous solution was poured into water and then extracted with ether in the usual way. After being dried ($MgSO_4$), the organic phase was evaporated to leave a yellow oil which was chromatographed on silica gel with toluene–ethyl acetate (9:1) as the eluent. Isolation of the yellow band gave 3 or 4 as mixtures of diastereomers. By this process (methoxycyclohexadienyl)iron salt 1 gave sulfone 3 as an oil, 1.37 g (59%). A single diastereomer crystallized from methanol: mp 115–125 °C; NMR δ 7.94–7.42 (m, 5 H), 5 .16 (dd, J = 6, 2 Hz, 1 H), 3.87 (d, J = 7 Hz, 1 H), 3.60 (s, 3 H), 3.57 (d, J = 2 Hz, 1 H), 3.48 (s, 3 H), 3.18–2.54 (m, 2 H), 2.1–1.42 (m, 2 H); IR ν_{max} 2055, 1980, 1740 cm^{-1}; mass spectrum, m/e 462 (M^+). Anal. Calcd for $C_{19}H_{18}FeO_8S$: C, 49.4; H, 3.9. Found: C, 49.4; H, 4.1.

Likewise, salt 2 gave sulfone 4 as an oil, 1.93 g (83%). A single diastereomer crystallized from hexane: mp 140–155 °C; NMR δ 7.9–7.44 (m, 5 H), 4.98 (dd, J = 6, 2 Hz, 1 H), 3.61 (s, 3 H), 3.59 (s, 3 H), 3.52 (d, J = 7 Hz, 1 H), 3.38 (m, 1 H), 2.18 (dd, J = 6, 3 Hz, 1 H), 2.13 (m, 2 H), 1.27 (br s, 1 H); IR ν_{max} 2042, 1975, 1735 cm^{-1}; mass spectrum, m/e 462 (M^+). Anal. Calcd for $C_{19}H_{18}FeO_8S$: C, 49.4; H, 3.9. Found: C, 49.2; H, 4.0. A sample crystallized from MeOH (mp 135–145 °C) was shown by NMR to consist of a mixture of diastereomers.

Sulfonated adduct 4 (0.23 g, 0.5 mmol) was treated with NaH (0.5 mmol, room temperature, 15 min), and the resultant clear solution was added to a slurry of unsubstituted cyclohexadienyliron salt (1, R = R^1 = H; 0.5 mmol) in the manner just described. Chromatography over silica gel gave 7 initially as an oil which crystallized from hexane: 0.2 g (59%); mp 85–125 °C; the NMR of this material showed the expected structural features although the spectrum was complicated by the presence of diastereomers; IR ν_{max} 2045, 1975, 1735 cm^{-1}; mass spectrum, m/e 680 (M^+), together with six successive losses of CO. These data support structure 7.

Desulfonation Procedure. Sodium amalgam 5%, (2.7 g) was added in three portions over 30-min period to a stirred suspension of anhydrous sodium monohydrogen phosphate (0.28 g, 2 mmol) in dry MeOH (15 mL) containing the sulfonated complex 3 or 4 (0.23 g, 0.5 mmol). TLC (toluene–SiO_2) after this time indicated disappearance of the starting material and formation of one, faster running material. The mixture was decanted into water and then extracted with ether. A yellow oil was obtained after drying and concentration of the organic phase. Chromatography (toluene–SiO_2) gave the desulfonated complex as a yellow oil. In this manner sulfone 3 gave acetic ester 5: 0.13 g (81%); NMR δ 5.16 (dd, J = 6, 2 Hz, 1 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.36 (m, 1 H), 2.5 (m, 1 H), 2.42–2.10 (m, 3 H), 1.94 (m, 1 H), 1.18 (br d, J = 16 Hz, 1 H); IR ν_{max} 2050, 1975, 1730 cm^{-1}; mass spectrum, m/e 322 (M^+). Anal. Calcd for $C_{13}H_{14}FeO_6$: C, 47.9; H, 5.6. Found: C, 47.8; H, 5.6.

By a similar process 4 gave 6 (R = R^2 = OMe; R^1 = R^2 = OMe; R^1 = H): 0.144 (90%); NMR δ 5.02 (dd, J = 6, 2 Hz, 1 H), 3.57 (s, 6 H), 3.23 (m, 1 H), 2.63 (dd, J = 7, 3 Hz, 1 H), 2.4–1.9 (m, 4 H), 1.39 (br d, J = 16 Hz, 1 H); IR ν_{max} 2045, 1975, 1735 cm^{-1}; mass spectrum, m/e 322 (M^+). Satisfactory combustion values were not obtained in this case. However, saponification of the ester with KOH/MeOH gave a yellow solid (88%), shown to be the corresponding acid 6: mp 103–105 °C; NMR δ 10.95 (s, 1 H) and 3.6 (s, 3 H) were the only features that differed from the spectrum of the ester (see above); IR ν_{max} 2045, 1970, 1700 cm^{-1}; mass spectrum, m/e 308 (M^+). Anal. Calcd for $C_{12}H_{12}FeO_6$: C, 46.8; H, 3.9. Found: C, 46.5; H, 4.1.

Acknowledgment. It is a pleasure to acknowledge Professor A. J. Birch, under whose direction this work was carried out.

Registry No. 1, 74883-20-8; 1 (R = R^1 = H), 42535-11-5; 2, 51508-59-9; 3, 81857-44-5; 4, 81857-45-6; 5, 81857-46-7; 6, 81857-47-8; 6 (R = R^2 = OMe; R^1 = H), 81857-48-9; 7, 81875-68-5.

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[11] A useful compilation of reagents compatible with diene–$Fe(CO)_3$ complexes is given by: Pearson, A. J. *Acc. Chem. Res.* **1980**, *13*, 463.

[12] The yields quoted refer to pure, isolated materials. All complexes gave satisfactory ^1H NMR, IR, and mass spectra, as well as combustion values. The mass spectral fragmentations of the sulfonyl-containing complexes 3 and 4 differed from the usual patterns observed in that a peak for M − 28 was in relatively low abundance. In the adduct related to 4 having a Me group at position 5, the mass spectrum shows a disproportionate relative abundance of the M − 56 fragment.

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Catalysts for Silylations with 1,1,1,3,3,3-Hexamethyldisilazane

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Received December 2, 1981

Trimethylsilylation of organic compounds having labile hydrogen atoms finds increasing use in analytical and in preparative organic chemistry.[1] Several methods have become available for silylation of alcohols, mercaptans, carboxylic acids, amides, heterocyclic nitrogen compounds, etc., using a variety of silylating agents.[2]

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0022-3263/82/1947-3966$01.25/0