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Aryl-substituted cyclohexadienyl complexes: novel intermediates for an organometallic approach to Sceletium and Amaryllidaceae alkaloid synthesis.

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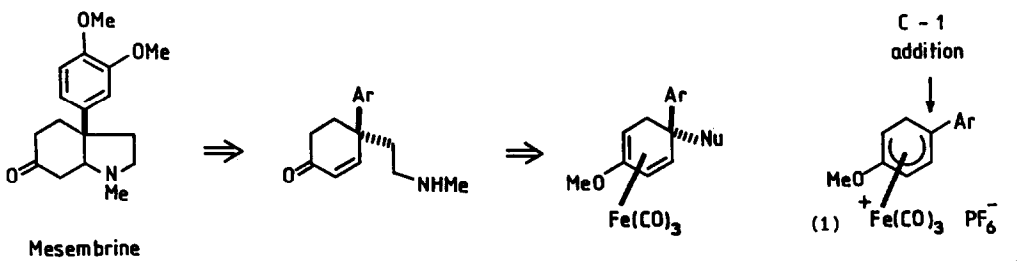
Abstract: A new method for the synthesis of 1-phenyl substituted tricarbonyl(η^5-cyclohexadienyl)iron(1+) complexes is described. Although 1-phenyl substituents were found to direct nucleophiles to the far end of the π-system, this effect could be overcome by a methoxyl substituent at C-4, permitting a regio- and stereocontrolled alkylation step that forms a quaternary centre required in Sceletium and Amaryllidaceae alkaloid synthesis.

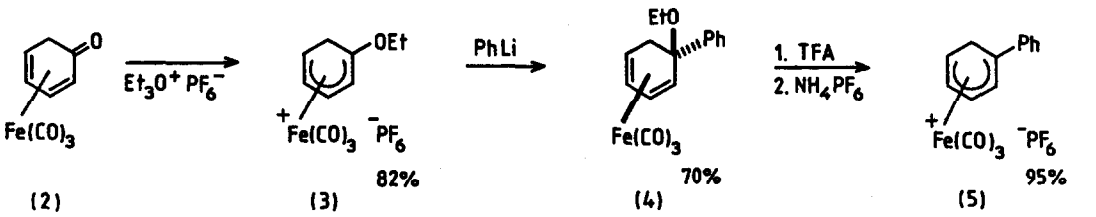
C-1 alkylation of 1-aryl substituted tricarbonyl(η^5-cyclohexadienyl)iron(1+) complexes offers prospects for the stereocontrolled formation of a quaternary centre at the junction between aromatic and partially saturated six-membered rings, a structural feature common to Sceletium and Amaryllidaceae alkaloids of types that possess important biological activity. In this paper we describe a versatile new route for the efficient preparation of η^5-1-arylcyclohexadienyl complexes, and define, for the first time, the directing influence of the 1-aryl group in alkylation reactions. By combining 1-phenyl and 4-methoxyl directing groups within the same cationic η^5-dienyl complex (1) we have been able to promote the C-1 mode of alkylation required for alkaloid synthesis.



Mesembrine

While the tricarbonyl(η^5-1-phenylcyclohexadienyl)iron(1+) cation has been prepared before in low yield,[1] the directing influence of the 1-phenyl group in cationic η^5 complexes had not been examined prior to the

commencement of our investigation. To define this effect, we first sought an efficient synthesis of the simple 1-phenyl salt. Recent work in this laboratory has demonstrated that 1-substituted complexes are conveniently accessible through the alkylation of η^5-1-alkoxycyclohexadienyl complexes.[2] We now report the use of a related arylation procedure in a regiocontrolled route (Scheme 1) to the 1-phenyl substitution pattern.

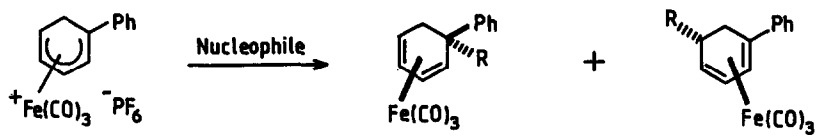


(2) (3) (4) (5)

Scheme 1

The 1-ethoxy salt (3), prepared from the dienone complex (2)[3] by a modification of a procedure described by Birch,[4] reacted with phenyllithium in dichloromethane at -78°C to produce the adduct (4).[5] This complex could be de-alkoxylated by treatment with trifluoroacetic acid.[6] Addition of ammonium hexafluorophosphate precipitated the 1-phenyl salt (5) in 95% yield.

The reactivity of this 1-phenyl substituted salt towards nucleophiles was then examined. The results, shown in Table 1, indicate a general preference for nucleophile addition to the C-5 terminus. The required C-1 alkylation product, however, was observed with sodio dimethyl malonate as the nucleophile. This afforded a minor product of the required type (6).

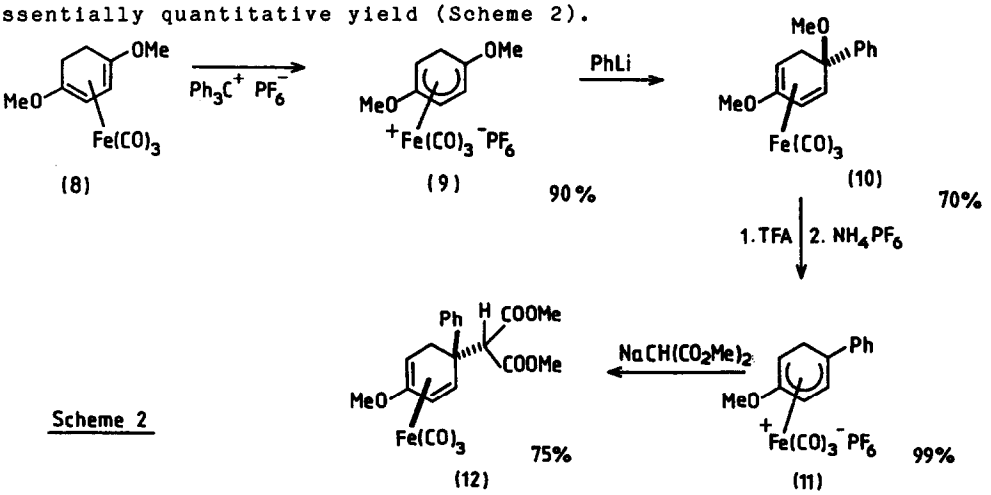


(5) (6) (7)

Nucleophile	R	Yield	Ratio (6):(7)
Me_2CuLi	Me	83%	<1 : >99
$NaBH_4$	H	86%	10 : 90
$NaCH(CO_2Me)_2$	$CH(CO_2Me)_2$	83%	15 : 85

Table 1

In order to promote C-1 addition it is necessary to de-activate the C-5 terminus towards nucleophilic attack. By placing a methoxyl substituent in competition[7] with the phenyl directing group, this objective might be achieved, whilst introducing, at the same time, useful functionality that would lead to the correct oxygenation pattern required for a synthesis of mesembrine, a suitable initial target molecule to test the viability of this approach. Our attention thus turned to the 1-phenyl-4-methoxy substituted salt (11). This complex could be prepared by the same alkylation/demethoxylation sequence that was used to prepare the 1-phenyl salt. The 1,4-dimethoxy complex (8)[8] was treated with triphenylcarbenium hexafluorophosphate to give the 1,4-dimethoxy salt (9) (Scheme 2), which was arylated with phenyllithium to produce the complex (10) in 70% yield. De-alkoxylation provided the 1-phenyl-4-methoxy salt (11) in essentially quantitative yield (Scheme 2).



Scheme 2

For a convenient entry for mesembrine synthesis, the directing influence of the 4-OMe group must be stronger than the directing influence of the 1-Ph group, indicated by the data presented in Table 1. From this table it is clear that the best prospects for success would arise with the malonate nucleophile. In the event, reaction of the salt (11) with sodio dimethyl malonate proceeded exclusively by C-1 addition. No trace of the C-5 adduct could be detected in the crude reaction product by 250MHz ^{1}H-NMR spectroscopy. The pure complex (12) was obtained as a single regio- and stereoisomer in 75% yield, by crystallization from hexane. N.O.e measurements on this product revealed a clear enhancement between the malonate -CH- and H-6α on the ring, indicating that the normal stereochemistry of nucleophile addition (trans to the metal) had been followed.

In this work we have demonstrated that, by the use of an OMe directing group it is possible to overcome the normal regiocontrol preference of a phenyl substituent and so form the quaternary centre as required for our studies on alkaloid synthesis.[9] With this approach, aryl and alkyl groups are added by means of a series of two metal mediated nucleophile addition steps, which make efficient use of the iron centre to provide both activation and stereocontrol in a sequence of reactions.[10]

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