Tetrahedron Letters,Vol.30,No.20,pp 2607-2610,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

TRANSITION METAL MEDIATED ORGANIC SYNTHESIS, PART 11:[1] 2-ARYL SUBSTITUENTS: NEW DIRECTING GROUPS IN CYCLOHEXADIENYL π-COMPLEXES

David A. Owen and G. Richard Stephenson*,

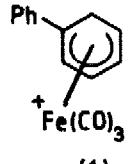
School of Chemical Sciences, University of East Anglia, Norwich, Norfolk, NR4 7TJ, U.K.

and Harry Finch and Stephen Swanson

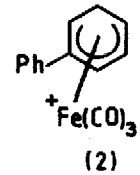
Glaxo Group Research Limited, Ware, Hertfordshire, SG12 0DJ, U.K.

Abstract: The regioselective formation and alkylation of tricarbonyl(η^5-2-arylcyclohexadienyl)iron(1+) salts provides a new, controlled route to intermediates for the preparation of 5-substituted 2-arylcyclohexadienes. The best regiocontrol was obtained when an electron donating group was placed on the arene substituent.

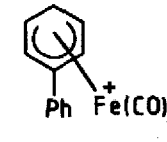
Regiocontrolled alkylation reactions are required for the efficient use of unsymmetrically substituted π-complexes as intermediates in organic synthesis. In the design of synthetic applications, the analysis of established patterns of regiocontrol is an essential step in the planning process.[2] There has been extensive examination of the tricarbonyliron series of π-complexes, through the development of synthetic routes employing 1-CO_2Me[3] and 2-OMe[4] groups to direct nucleophiles to the far end of the dienyl π-system. Similar control effects have been identified[5] in other metal π-complexes. Future synthetic work employing these control groups is thus on a firm footing.



(1)



(2)



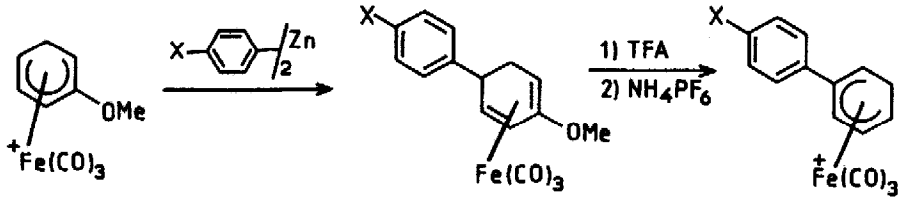
(3)

For phenyl directing groups in cationic tricarbonyl(η^5-cyclohexadienyl)iron(1+) complexes such as (1) and (2), the directing effects have not previously been examined, despite the fact that successful alkylation would lead to products with phenyl substituted cyclohexadienes containing chiral centres at the site of nucleophile addition. Since aryl substitution in multiply substituted six-membered rings is a common element within the structures of natural products, successful alkylation, controlled by planar chirality,[2] offers a new approach to the enantioselective synthesis of such substances. Although phenyl substituted complexes (1), (2), and (3) have been prepared previously,[6] the synthetic methods used were low yielding and formed mixtures of regioisomers. The alkylation of the dienyl cations has not been reported.

This paper describes a both new and general route for the regiocontrolled preparation of 2-aryl substituted cyclohexadienyl complexes, and an investigation of the regiodirecting effects of aryl substituents bearing electron withdrawing and electron donating groups. Our findings demonstrate that the introduction of a methoxy group onto the phenyl substituent can lead to a completely regiocontrolled alkylation, which, in common with other reactions of this type, also proceeds with complete stereocontrol.

Preparation of 2-arylcyclohexadienyl complexes

Acid catalysed demethoxylation[7] has found general use for regiocontrolled access to tricarbonyl(η^5-cyclohexadienyl)iron(1+) salts. In view of the accessibility[8] of 5-phenyl substituted neutral complexes such as (5a)[9] and (5b),[9] we have examined their conversion into (**6a,b**) by reaction in TFA. In common with other examples,[7] the process exhibited complete regiocontrol, a terminus of the dienyl moiety of the product arising at the site of OMe substitution in (5). The reaction has provided the first preparation of (**6a**) (79% overall yield) free from regioisomers and proved convenient for the formation of the substituted derivatives[10] (**6b**) and (**6c**) required for our regiocontrol studies. The CF_3-C_6H_4- substituent was introduced by addition of the diarylzinc reagent to the cationic dienyl complex (4). The product (**5c**) could be isolated in 94% yield by chromatography. Generally in the formation of (**6a,b,c**), crude alkylation products do not require purification before conversion to the salts, since by-products from the alkylation step (aryls and biphenyls) can easily be removed from the final product by washing with ether. In this way (**6c**) was obtained in 73% overall yield based on (4).



(4)

(5) a: X = H
b: X = OMe
c: X = CF_3

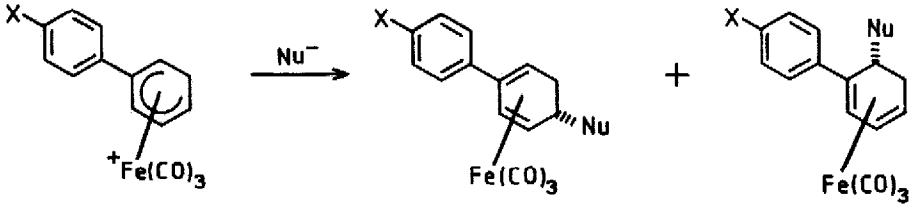
(6) a: 79%
b: 77%
c: 73%
(overall yields)

Alkylation of 2-arylcyclohexadienyl complexes

Alkylation of tricarbonyl(η^5-2-phenylcyclohexa-1,3-dienyl)iron(1+) PF_6(1-) (**6a**) was examined first. Hydride addition from sodium borohydride produced, in 99% yield, an 85:15 mixture of the known compounds (**7a**) and (**8a**),[6] indicating a substantial preference for reaction at the terminus remote from the phenyl substitution. Similar product ratios were obtained for the addition of cyanide and malonate anions. Addition of a further

phenyl group from lithium diphenylcuprate, a reaction performed at lower temperature, proceeded with marginally better regiocontrol. In all four cases, essentially similar results were obtained.

The influence of electron withdrawing (CF_3) and electron donating (OMe) substituents on the arene ring was then examined to explore the relationship between electronic effects and regiocontrol of alkylation.



(6) (7) (8)

SCHEME

	Nu = H	Nu = CN	Nu = $CH(CO_2Et)_2$	Nu = Ph
X = H	a	d	f	i
X = OMe	b	e	g	j
X = CF_3	c	—	h	—

Of all the cases (see Table), $F_3CC_6H_4$ substitution in (**6c**) proved least effective in promoting regiocontrol, producing, for example, an 80:20 mixture of (**7c**) and (**8c**). Addition of malonate to the $MeOC_6H_4$ substituted complex (**6b**), on the other hand, was completely selective, forming only the 5-substituted adduct (**7g**) in 80% yield.

TABLE: Ratio of products from nucleophile additions*

(Expt.) (see Scheme)	H (a)	H (d)	H (f)	H (i)	OMe (b)	OMe (e)	OMe (g)	OMe (j)	CF_3 (c)	CF_3 (h)
Ratio (7):(8)	85:15	85:15	85:15	90:10	86:14	88:14	100:0	95:5	80:20	89:11
(Yield)	(92%)	(92%)	(78%)	(83%)	(99%)	(80%)	(80%)	(80%)	(97%)	(78%)

* Regioisomer ratios reported in the Table were measured from integration of ^1H n.m.r. spectra recorded at 400 MHz. In these measurements, care was taken to avoid separation of products before examination by NMR (see Ref.10).

Conclusions

For 2-aryl substitution, the overall picture is a pronounced preference for alkylation at C-5. When transmitted through the arene ring, the influence of regio-directing control groups is attenuated, but OMe substitution still favours C-5, as it does in complex (4) itself. In synthetic applications where regiocontrol is required, methoxy substitution on the aryl group is appropriate. By the use of well controlled[11] nucleophiles such as malonate, completely regiocontrolled alkylation can be achieved.

Alkoxy and methylenedioxy substitution is common on arene rings in natural products. Our demonstration of an efficient means of access to intermediate complexes, and the establishment of the compatibility of electron-donating substituents on the arene with complete regiocontrol in alkylation reactions, indicates the suitability of the methods reported here for further development for use in natural product synthesis.

Acknowledgments. G.R.S. thanks the Royal Society for a 1983 University Research Fellowship. D.A.O. thanks Glaxo Group Research for financial support.

References

1. For part 10, see: P.W. Howard, G.R. Stephenson, and S.C. Taylor J. Organomet. Chem., in press.
2. G.R. Stephenson, R.P. Alexander, C. Morley, and P.W. Howard, Phil. Trans. R. Soc Lond. A, 1988, 326, 545.
3. B.M.R. Bandara, A.J. Birch, and L.F. Kelly, J. Org. Chem., 1984, 49, 2496; A.J. Birch, L.F. Kelly, and D.V. Weerasuria, J. Org. Chem., 1988, 53, 278.
4. A.J. Pearson and Y.-S. Chen, J. Org. Chem., 1986, 51, 1939; A.J. Pearson and P. Ham, J. Chem. Soc., Perkin Trans. 1, 1983, 1421; M. Chandler, E. Mincione, and P.J. Parsons, J. Chem. Soc., Chem. Commun., 1985, 1233; A.J. Pearson and T.R. Perrior, J. Organomet. Chem., 1985, 285, 253.
5. T.C.T. Chang and M. Rosenblum, Israel J. Chem., 1984, 24, 99; T.C.T. Chang, T.S. Coolbaugh, B.M. Foxman, M. Rosenblum, N. Simms, and C. Stockman, Organometallics, 1987, 6, 2394; M. Green, S. Greenfield, and M. Kersting, J. Chem. Soc., Chem. Commun., 1985, 18.
6. T.H. Whitesides and J.P. Neilan, J. Am. Chem. Soc., 1976, 98, 66.
7. A.J. Birch and M.A. Haas, J. Chem. Soc. C, 1971, 2465; A.J. Birch, B. Chauncy, L.F. Kelly, and D.J. Thompson, J. Organomet. Chem., 1985, 286, 37.
8. A.J. Birch and A.J. Pearson, Tetrahedron Lett., 1975, 2379.
9. I.M. Palotai and G.R. Stephenson, unpublished results.
10. All new compounds gave satisfactory microanalytical and spectroscopic data. The regioisomers (7) and (8) were characterised as mixtures.
11. A.J. Birch and G.R. Stephenson, J. Organomet. Chem., 1981, 218, 91.

(Received in USA 23 February 1989)