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SYNTHESIS OF AZASPIROCYCLIC COMPOUNDS VIA ORGANOIRON COMPLEXES. POTENTIAL SYNTHETIC ROUTES TO HISTRIONICOTOXIN AND CEPHALOTAXUS ALKALOIDS.[1]

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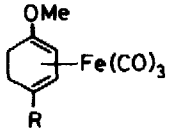
Abstract

Reaction of cyclohexadienylium-Fe(CO)$_3$ complexes (7) and (8) with sodiomalononitrile gives the carbo-spirocyclic derivatives (9) and (10), whilst reaction with benzylamine and removal of iron leads to the azaspirocyclic enones (15) and (16), respectively.

Our current research is directed towards the development of actual synthetic applications of cyclohexadiene-Fe(CO)$_3$ complexes, within the framework of well-defined natural product target molecules. Our recent work on the synthesis of spirocyclic compounds[2] led us to examine the possibility of constructing azaspirocyclic molecules. To this end we required a cyclohexadienylium complex which would react with 'divalent' nucleophiles regiospecifically at a position carrying a substituent in which a leaving group was present, suitably disposed for further reaction with the nucleophile. We describe herein our initial results in this area.

The ester complexes (1) and (2), available from our previous work,[2] were both smoothly reduced to the oily primary alcohols[3] (3) $\nu_{max}(CCl_4)$ 3645, 2045, 1970 cm^{-1}, and (4) ν_{max} 3615, 3410, 2035, 1960 cm^{-1}, respectively, in 98-100% yield (diisobutylaluminium hydride, 2.2 - 2.5 equiv., THF, -78° to 20°C, overnight). Conversion to the p-toluenesulphonate esters was accomplished in 98-100% yield under the usual conditions (1.7 equiv. p-MeC$_6$H$_4$SO$_2$Cl, pyridine, 0°C, 24 h) to give (5), ν_{max} 2040, 1965, 1602, 1370, 1180 cm^{-1}, and (6) ν_{max} 2045, 1965, 1602, 1363, 1178 cm^{-1}, respectively, both obtained as syrups.

Regiospecific hydride abstraction to give the hexafluorophosphates (7) (68%), $\nu_{max}(CH_2Cl_2)$ 2115, 2060, 1602, 1500, 1362, 1180 cm^{-1}, as a gum which could not be crystallised, and (8) (90%) as a pale yellow solid, ν_{max} 2108, 2055, 1600, 1500, 1360, 1176 cm^{-1}, was achieved using the following sequence: (i) 1.3 equiv. Ph_3CBF_4, CH_2Cl_2, reflux (reaction progress followed by I.R. spectroscopy); (ii) evaporation of CH_2Cl_2 and wash the tetrafluoroborate with ether by decantation; (iii) dissolve salts in CH_2Cl_2 and shake vigorously with aqueous NH_4PF_6; (iv) separate layers, extract aqueous with CH_2Cl_2 and precipitate the hexafluorophosphates from the organic extracts by the addition of ether.



(1) R = $(CH_2)_3CO_2Me$

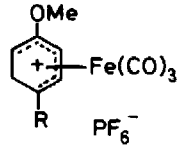
(2) R = $(CH_2)_2CO_2Me$

(3) R = $(CH_2)_3CH_2OH$

(4) R = $(CH_2)_2CH_2OH$

(5) R = $(CH_2)_3CH_2OTs$

(6) R = $(CH_2)_2CH_2OTs$

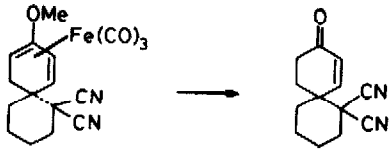


(7) R = $(CH_2)_3CH_2OTs$

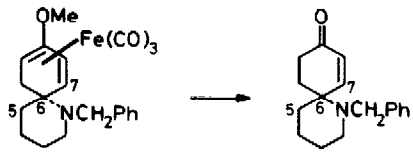
(8) R = $(CH_2)_2CH_2OTs$

Reaction of (7) with an excess of sodiomalononitrile (from NaH and $CH_2[CN]_2$) in THF (0°C) gave, after preparative layer chromatography, the spiro[5.5]undecane derivative (9), m.p. 116-117°C (53%). Similar treatment of the salt (8), gave the spiro[4.5]decane derivative (10); m.p. 91-92°C (59%). Oxidative removal of the metal (anhydrous Me_3NO,[4] benzene, 20°C overnight) followed by acidic hydrolysis (oxalic acid, MeOH, H_2O, 20°C, 45 min) gave the spirocyclic enones (11), $\nu_{max}(CHCl_3)$ 2260, 1690, 1605 cm^{-1}, and (12), ν_{max} 2260, 1695, 1615 cm^{-1}, both obtained as colourless oils after preparative layer chromatography. In our experience the dienylium cation is considerably more reactive towards sodiomalononitrile than is a primary tosylate, so that this reaction occurs by initial addition to the substituted cyclohexadienylium terminus, followed by regeneration of the bisnitrile anion and intramolecular tosylate displacement.

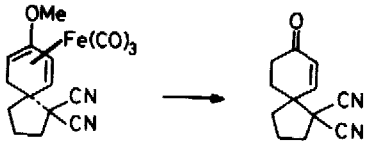
These results prompted us to investigate the synthesis of azaspirocyclic compounds <u>via</u> the salts (7) and (8). Accordingly, a solution of (7) in nitromethane was added slowly to a stirred solution of benzylamine (10 equiv.) in nitromethane under nitrogen, and the resulting mixture was stirred for a further 0.5 h., after which time the solvent was removed <u>in vacuo</u> and the



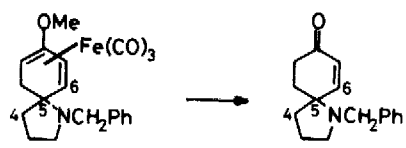
(9) (11)



(13) (15)



(10) (12)



(14) (16)

product separated by preparative layer chromatography to give (13) as a yellow oil (90%) ν_{max} ($CHCl_3$) 2050, 1977, 1605, 1485 cm^{-1}; δ($CDCl_3$), 7.25 (5H, s), 5.27 (1H, dd, J 6.5, 2.5 Hz, 8-H), 3.67 (3H, s, OMe), 3.45 and 3.32 (each 1H, d, ABq, J_{AB} 15 Hz, $C\underline{H}_2Ph$), 3.25 (1H, m, 10-H), 2.71 (1H, d, J 6.5 Hz, 7-H), 2.3 (2H, m, $-C\underline{H}_2-N$), 1.9-1.2 (8H). Similar treatment of the salt (8), but using only 2 equivalents of benzylamine, afforded the azaspirocycle (14) as a yellow oil (98%), ν_{max} 2050, 1970, 1605, 1488 cm^{-1}; δ($CDCl_3$) 7.26 (5H, s), 5.25 (1H, dd, J 6.5, 2.4 Hz, 7-H), 3.66 (3H, s, MeO), 3.35 (2H, narrow ABq, $C\underline{H}_2Ph$), 3.3 (1H, m, 9-H), 2.45 (3H, m, 6-H and $C\underline{H}_2-N$), 1.97-1.57 (6H). Removal of iron from these complexes as above, followed by acidic hydrolysis (oxalic acid, MeOH, H_2O, 20°C, 1 h) and preparative layer chromatography, afforded the azaspirocyclic enones (15), ν_{max} 1680, 1605 cm^{-1}, and (16), ν_{max} 1685, 1608 cm^{-1}, both obtained chromatographically pure as colourless oils which become discoloured on exposure to air or chlorinated solvents.

We envisage that intermediates of type (15) will have considerable potential in the synthesis of histrionicotoxin derivatives,[5] whilst compounds related to (16), in which the cyclohexenone unit is converted to a five-membered ring, may be useful as intermediates for the synthesis of Cephalotaxus alkaloids.[6]

These possibilities are currently under investigation.

Acknowledgements

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References

1. Organoiron Complexes in Organic Synthesis. Part 14. Part 13, A.J. Pearson and C.W. Ong, J.C.S. Perkin I, submitted.

2. A.J. Pearson, J.C.S. Perkin I, 1979, 1255; 1980, 400.

3. All new compounds, obtained as racemic mixtures, gave satisfactory spectroscopic and analytical data.

4. Y. Shvo and E. Hazum, J.C.S. Chem. Comm., 1974, 336.

5. E.J. Corey and R.A. Ruden, Tetrahedron Lett., 1973, 1495; E.J. Corey, Y. Ueda and R.A. Ruden, ibid., 1975, 4347; E.J. Corey, M. Petrzilka and Y. Ueda, ibid., 1975, 4343; E.J. Corey, J.F. Arnett, and G.N. Widiger, J. Amer. Chem. Soc., 1975, 97, 430; E.J. Corey and R.D. Balanson, Heterocycles, 1976, 5, 445; E. Gossinger, R. Imhof and H. Wehrli, Helv. Chim. Acta, 1975, 58, 96; T. Fukuyama, L.V. Dunkerton, M. Aratani and Y. Kishi, J. Org. Chem., 1975, 40, 2011; M. Aratani, L.V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura and S. Inone, ibid., 1975, 40, 2009; H.E. Schoemaker and W.N. Speckamp, Tetrahedron Lett., 1978, 1515.

6. S.M. Weinreb and M.F. Semmelhack, Acc. Chem. Res., 1975, 8, 158; L. Duhamel, J.M. Poirier and P. Granger, J. Org. Chem., 1979, 44, 3576.

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