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REACTIONS OF COORDINATED LIGANDS

IX *. CHROMIUM(0)-PROMOTED INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTION OF AN ARYL HALIDE: A PREPARATION OF CHROMAN

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Summary

When treated with potassium t-butoxide in dimethyl sulphoxide the chromium tricarbonyl complex of 3-(2-fluorophenyl)propan-1-ol underwent a rapid intramolecular nucleophilic substitution to give the corresponding complex of chroman, from which the heterocycle was obtained by oxidation with iodine. With metal alkoxides the chromium tricarbonyl complex of 2-(2-fluorophenyl)ethanol gave either mixtures (from which the product of intramolecular nucleophilic substitution was not isolated) or the products of intermolecular nucleophilic substitution.

Introduction

A limited number of heterocyclic systems can be prepared by intramolecular nucleophilic substitutions with *o*-substituted aryl halides in which the substituent contains a nucleophilic nitrogen, oxygen or sulphur atom. Some of these substitutions are known to proceed via benzyne intermediates, while others proceed by an addition-elimination mechanism with a carbanion as an intermediate [2]. The latter substitutions, like the analogous intermolecular reactions, are accelerated by substituents in the arene ring which increase the stability of the intermediate carbanion. However, it has been known for a number of years that with nucleophiles such as amines [3,4], carbanions [5], alkoxide [6,7], and thiolate [8] anions the intermolecular nucleophilic substitutions of aryl halides are also accelerated when the aryl halide is

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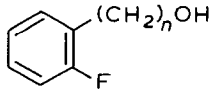
coordinated with a chromium tricarbonyl residue, and, in the case of methoxide, the acceleration is because of a similar stabilisation of the intermediate carbanion [9]. We now report an example of a rapid intramolecular nucleophilic substitution with the chromium tricarbonyl complex of an aryl halide, and show that it can be used in a preparation of the six-membered heterocycle, chroman [10]. A further example of the same type of process, but which gave rise to a seven-membered heterocycle, was reported briefly after the present work was commenced [11].

Results and discussion

A Wittig reaction with 2-fluorobenzaldehyde and (ethoxycarbonylmethylene)triphenylphosphorane gave ethyl 3-(2-fluorophenyl)propenoate whose ^{1}H NMR spectra indicated a mixture of the *E*- and *Z*-isomers in a ratio of approximately 2/1 (presumably the material prepared previously [12] by esterification of 2-fluorocinnammic acid was almost entirely the *E*-isomer). Hydrogenation of this mixture over a palladium/charcoal catalyst gave ethyl 3-(2-fluorophenyl)propanoate which was reduced with lithium aluminium hydride to give 3-(2-fluorophenyl)-propan-1-ol (Ia).

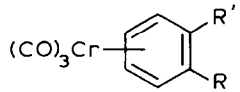
Of the various methods available for preparing the chromium tricarbonyl complexes of arenes [13], those in which the arene is heated for several hours with chromium hexacarbonyl in a high-boiling solvent were considered unsuitable for the present work. The method devised by Öfele [14] seemed very suitable, however, and was shown to be applicable to *o*-substituted aryl fluorides by use of the model compound, 2-fluorotoluene. Treatment of this arene with tricarbonyl(trispyridine) chromium(0) [15] and boron trifluoride etherate gave the complex IIa which was identical with a sample prepared by heating the arene with chromium hexacarbonyl as described in the literature [8]. Application of Öfele's method to the fluoroalcohol Ia and to chroman gave the complexes IIb and III respectively. The latter complex was separated readily from the excess of arene by column chromatography on alumina, but this technique was found to be unsuitable for the complex IIb which was finally separated and purified by HPLC. A comparison of the ^{1}H NMR spectra of the two complexes and their parent ligands indicated that, as expected [13,16], complex formation had caused the signals arising from the aromatic protons to be shifted to higher field (ca. 1–2 ppm).

Because of the difficulties which had been encountered in the separation of the



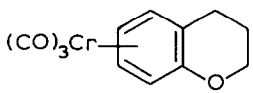
(I)

(Ia, *n* = 3;
Ib, *n* = 2)



(II)

(a, R = F, R' = Me;
b, R = F, R' = $(CH_2)_3OH$;
c, R = F, R' = CH_2CO_2Et;
d, R = F, R' = $(CH_2)_2OH$;
e, R = H, R' = $(CH_2)_2OH$;
f, R = $OCHMe_2$, R' = $(CH_2)_2OH$;
g, R = OC^2H_3, R' = $(CH_2)_2OH$)



(III)

complex IIb from unchanged fluoroalcohol Ia it was thought that in the preparation of the lower homologue IId it might be preferable to attach the chromium tricarbonyl residue to the arene ring before the primary hydroxyl group was generated. Accordingly, the complex IIc was prepared from the parent arene and then reduced by addition to an excess of lithium aluminium hydride in diethyl ether at room temperature. The ^{1}H NMR spectrum of the reduction product showed that not only had the ester group been reduced, but that further reduction to give the phenyl complex IIe had also partly occurred. Presumably, as aryl fluorides are normally inert towards lithium aluminium hydride in diethyl ether [17], this reduction is the result of the aryl fluoride being activated towards attack by hydride because of coordination with a chromium tricarbonyl residue. Inverse addition of lithium aluminium hydride to an excess of the ester at 0°C afforded the primary alcohol complex IId which was readily separated from unchanged ester by column chromatography.

No cyclisation was observed (^{1}H NMR) when a solution of the complex IIb and t-butylamine in dimethyl sulphoxide-d_6 was kept at room temperature for 20 h and then at 40°C for 5 h. However, when the complex was treated with sodium isopropoxide in propan-2-ol at room temperature the ^{1}H NMR signal characteristic of the ArOCH_2 group in the cyclised product III slowly appeared and after 15 h had a relative intensity which indicated that cyclisation had occurred to the extent of about 75%. Use of the very strong base, potassium t-butoxide in dimethyl sulphoxide, resulted in complete cyclisation within 10 min at room temperature, and subsequent workup and purification afforded the chroman complex III in 75% yield. Mild oxidation of this complex with iodine in ether gave chroman in quantitative yield. No changes in the ^{1}H NMR spectrum were observed when a solution of the fluoroalcohol Ia and potassium t-butoxide in dimethyl sulphoxide was kept at room temperature for 100 h.

In contrast with the result obtained with the complex IIb no pure compound was isolated when the lower homologue IId was treated with potassium t-butoxide in dimethyl sulphoxide. Column chromatography on alumina of the resultant complex mixture afforded a number of fractions, none of which showed the ^{1}H NMR spectrum expected of a complexed 2,3-dihydrobenzfuran. With the sodium alkoxides prepared from propan-2-ol and methanol-d_4 the complex IId afforded the products of intermolecular reactions, i.e. IIf and IIg respectively, which were characterised by their ^{1}H NMR and mass spectra. The apparent reluctance of the complex IId to undergo the base-promoted cyclisation exhibited by the higher homologue IIb is probably due to the strain which would attend the formation of the complexed five-membered ring intermediate formed initially in the reaction. In this context it should be noted that although under basic conditions the chromium tricarbonyl complex of 4-phenyl-1-cyanobutane readily undergoes intramolecular cyclisation to give (after subsequent oxidation) a 1,2,3,4-tetrahydronaphthalene system, the complex of 3-phenyl-1-cyanopropane gives a dimeric product which is formed from an initial intermolecular reaction [18].

Experimental

^{1}H NMR spectra were recorded on a Perkin–Elmer R32 (90 MHz) instrument with Me_4Si as internal standard and, unless stated otherwise, for solutions in $CDCl_3$.

Mass spectra were recorded with Varian CH 5D and Finnigan 4000 instruments. IR spectra were measured on a Pye Unicam SP200 spectrometer. All experiments involving chromium tricarbonyl complexes were carried out in deoxygenated solvents under dry, purified nitrogen and, whenever possible, in the absence of light. Ether refers to diethyl ether throughout. Light petroleum refers to the fraction with b.p. 40–60°C. Chroman [19] and ethyl (2-fluorophenyl)acetate [20] were prepared by the methods described in the literature.

Ethyl 3-(2-fluorophenyl)propanoate

Sodium ethoxide (from sodium, 1.85 g) in dry ethanol (160 ml) followed by 2-fluorobenzaldehyde (10 g) was added to (ethoxycarbonylmethyl)triphenylphosphonium bromide [21] (34.6 g) in dry ethanol and the mixture was kept for 48 h and then heated under reflux for 30 min. The precipitate (NaBr) was removed by filtration and the bulk of the solvent was removed from the filtrate under reduced pressure. Light petroleum (200 ml) was added to the residual solution and the precipitate (Ph_3PO) was removed by filtration. Fractionation of the filtrate gave ethyl 3-(2-fluorophenyl)propenoate (13.7 g, 88%), b.p. 72–80°C/0.2 mmHg (lit. [12], b.p. 140–141°C/11 mmHg), δ (ppm) 7.79 (1H, d, J 16 Hz, ArC*H*) and 6.50 (1H, d, C*H*CO) (*E*-isomer), and 7.30 (1H, d, J 12.5 Hz, ArC*H*) and 6.04 (1H, d, C*H*CO) (*Z*-isomer). This ester (13.5 g) in ethanol (100 ml) was hydrogenated over a 10% palladium/charcoal catalyst (110 mg) to give the saturated ester (12.6 g, 92%), b.p. 80–83°C/0.65 mmHg, ν_{max} 1745 cm^{-1}; δ (ppm) 7.08 (4H, m, ArH), 4.09 (2H, q, OCH_2), 2.96 (2H, t, $ArCH_2$), 2.58 (2H, t, CH_2O) and 1.18 (3H, t, CH_3) (Found: C, 67.1; H, 6.4; M^+ 196. $C_{11}H_{13}FO_2$ calcd.: C, 67.3; H, 6.7%; M 196).

3-(2-Fluorophenyl)propan-1-ol (Ia)

Ethyl 3-(2-fluorophenyl)propanoate (10 g) in dry ether (30 ml) was added dropwise with stirring to lithium aluminium hydride (1.3 g) in dry ether (60 ml). The mixture was stirred for a further 30 min and then ethyl acetate (1 ml) followed by water (10 ml) was added. The mixture was filtered and the filtrate was dried ($MgSO_4$) and fractionated to give the alcohol (7.1 g, 90%), b.p. 88–89°C/1.5 mmHg, ν_{max} 3380 cm^{-1}; δ (ppm) 7.06 (4H, m, ArH), 3.61 (2H, t, CH_2OH), 2.70 (2H, t, $ArCH_2$), 2.0 (1H, s, OH), and 1.86 (2H, m, CH_2CH_2OH) (Found: C, 70.2; H, 7.1; M^+ 154. $C_9H_{11}FO$ calcd.: C, 70.1; H, 7.2%; M 154).

Tricarbonyl(2-fluorotoluene)chromium (IIa)

Freshly distilled boron trifluoride etherate (3 g, 22 mmol) was added dropwise with stirring to a mixture of 2-fluorotoluene (19.2 g, 170 mmol), tricarbonyl(trispyridine)chromium (2.6 g, 7mmol), and ether (10 ml). The mixture was stirred for a further 1 h, diluted with ether (40 ml), cooled to 0°C, and shaken with water (30 ml). The ether layer was separated and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on a column of alumina (Grade III) with light petroleum as the eluent to give the complex (0.55 g, 32%) which was identical (m.p. and mixed m.p. 72°C; IR) with a sample prepared from 2-fluorotoluene and hexacarbonylchromium [8] (Found: C, 49.0; H, 3.0; M^+ 246. $C_{10}H_{10}CrFO_3$ calcd.: C, 48.8; H, 2.9%; M 246); δ (ppm) (acetone-d_6) 5.75 (3H, m, ArH), 5.25 (1H, m, ArH), and 2.21 (3H, s, Me).

The following complexes were prepared in a similar manner: tricarbonyl[3-(2-flu-

orophenyl)propan-1-ol]chromium (IIb, 23%) m.p. 52–54°C, δ (ppm) (acetone-d_6) 5.74 (3H, m) and 5.20 (1H, m) due to Ar–H, 3.61 [3H (2H after ^2H_2O shake), t, CH_2OH], 2.95–2.25 (2H, m, $ArCH_2$), and 1.78 (2H, m, $ArCH_2CH_2$) (Found: C, 49.45; H, 3.85; M^+ 290. $C_{12}H_{11}CrFO_4$ calcd.: C, 49.7; H, 3.8%; M 290; tricarbonyl[ethyl (2-fluorophenyl)acetate]chromium (IIc, 34%) as a yellow oil, δ (ppm) (acetone-d_6) 5.75 (3H, m) and 5.23 (1H, m) due to Ar–H, 4.14 (2H, q, CH_2CH_3), 3.57 (2H, dd, $ArCH_2$), and 1.19 (3H, t, CH_2CH_3), ν_{max} 1735, 1910, and 1995 cm^{-1}, M^+ 318 ($C_{13}H_{11}CrFO_4$ calcd.: M 318); and tricarbonyl(chroman)chromium (III, 49%), m.p. 82–84°C, δ (ppm) (acetone-d_6) 5.73 (1H, d), 5.64 (1H, t), 5.30 (1H, d), and 5.11 (1H, t) due to ArH, 4.17 (2H, t, CH_2O), 2.69 (2H, m, $ArCH_2$), and 2.14 (2H, m, $CH_2CH_2CH_2$) Found: C, 53.4; H, 3.8; M^+ 270. $C_{12}H_{10}CrO_4$ calcd.: C, 53.3; H, 3.7%; M 270).

Tricarbonyl[2-(2-fluorophenyl)ethanol]chromium (IId)

(a) Lithium aluminium hydride (28 mg) in dry ether (10 ml) was added dropwise with stirring to the complex IIc (470 mg) in dry ether (10 ml) at 0°C. The mixture was stirred at 0°C for a further 30 min and then water (2 ml) was carefully added followed by hydrochloric acid (1 M) (30 ml). The ether layer was separated and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on a column of alumina (Grade 3) using 10% (v/v) ethyl acetate/light petroleum as the eluent to give unchanged complex IIc (54 mg). Further elution of the column with 25% (v/v) ethyl acetate/light petroleum gave the complex (330 mg, 92%), m.p. 45–50°C, ν_{max} 3350, 1985, and 1885 cm^{-1}; δ (ppm) 5.75 (3H, m, ArH), 5.21 (1H, m, ArH), 3.78 [3H (2H after ^2H_2O shake), m, CH_2OH], and 2.7 (2H, m, $ArCH_2$) (Found: C, 47.65; H, 3.0; M^+ 276. $C_{11}H_9CrFO_4$ calcd.: C, 47.8; H, 3.3%; M 276).

(b) The complex IIc (400 mg) in dry ether (10 ml) was added dropwise with stirring to lithium aluminium hydride (60 mg) in dry ether (15 ml). After 2 h the organic material was isolated as described above to give a yellow gum (200 mg) which had a ^1H NMR spectrum almost identical to that of the complex IId but which also showed a strong signal with δ 5.5(s) ppm. The mass spectrum (chemical ionisation, NH_3) showed m/e 276 (complex IId) and 258 (complex IIe; calcd. for $C_{11}H_{10}CrO_4$, 258).

Preparation of chroman via the complex III

Potassium (5 g) was allowed to react with dry t-butanol (150 ml) and then the excess of alcohol was removed by distillation and the residue was heated at 90°C in vacuo for 20 h. A portion (272 mg) of the residual solid was dissolved in DMSO-d_6 (5 ml), and a portion (0.80 ml) of the solution was added to the complex IIb (66 mg) in DMSO-d_6 (0.8 ml). After 10 min the ^1H NMR spectrum of the mixture showed no signal at δ 3.6. After a further 10 min the mixture was diluted with hydrochloric acid 1 M (30 ml) and then extracted with ether (3 × 10 ml). The ether and the residual volatile material (free arenes?) were removed under reduced pressure from the extract to leave the complex III as a yellow solid (46 mg, 75%) whose ^1H NMR and IR spectra were identical with those of the authentic sample.

Iodine (80 mg) was added to the complex III (40 mg) in ether (10 ml), and after 1 h the mixture was extracted with aqueous sodium metabisulphite until colourless, washed with water (20 ml) and dried ($MgSO_4$). Removal of the ether under reduced

pressure afforded chroman (20 mg, 100%) whose ^1H NMR spectrum was indistinguishable from that of an authentic sample.

Intermolecular substitutions with the complex IId

(a) Sodium (4 mg) was allowed to react with methanol-d_4 (0.2 ml) and the resultant solution was added to the complex (35 mg) in methanol-d_4 (0.4 ml). After 24 h the mixture showed δ (ppm) 5.72 (1H, d), 5.61 (1H, t), 5.35 (1H, d), and 5.01 (1H, t) due to aromatic protons, 3.68 (2H, t, CH_2O), and 2.8–2.4 (2H, m, $ArCH_2$). The mixture was added to hydrochloric acid 1 *M* (5 ml) and the organic material was extracted with ether (2 × 5 ml) to give the complex IIg as a yellow gum (37 mg), M^+ 291 ($C_{12}H_9{}^2H_3CrO_5$ requires *M* 291).

(b) The complex (50 mg) in propan-2-ol (10 ml) was treated with sodium propan-2-oxide (from sodium, 4 mg) in propan-2-ol (10 ml), and after 15 h the mixture was processed as in experiment (a) to give the complex IIf (56 mg) as a yellow gum which showed δ (ppm) (acetone-d_6) 5.85 (1H, d), 5.70 (1H, t), 5.46 (1H, d), and 5.07 (1H, t) due to aromatic protons, 4.50 (1H, m, CHO), 3.73 (3H, m, CH_2OH), 2.9 and 2.45 (2H, m, $ArCH_2$), and 1.33 (6H, m, Me_2); M^+ 316 ($C_{14}H_{16}CrO_5$ requires *M* 316).

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