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REACTIONS OF ARYL BROMIDES WITH COBALOXIME(I). REDUCTIVE ARYLATION

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Summary

Successful arylations of both cobaloximes(I) and hydridocobaloximes with aryl halides with electron-withdrawing substituents have been demonstrated. The scope, utility and possible mechanisms of these useful synthetic reactions are discussed.

Introduction

Arylcobalt complexes have traditionally been prepared, sometimes in high yield, by reaction of aryllithium or arylmagnesium halides with cobalt(III) complexes [1—3]. Unfortunately, these reactions are limited in scope to Grignard and/or organolithium compatible aryl groups and require an inconvenient reverse addition due to the extremely poor solubility of most cobalt(III) chelates in ethereal solvents. In contrast, the traditional route to alkylcobalt complexes, reductive alkylation [4], is convenient, rapid and versatile, and can frequently be carried out on cobalt(II) complexes generated in situ, thus obviating the need for prior synthesis and work-up of the cobalt reagent. We first published the successful reductive arylation of cobaloximes in 1978 [5] and subsequently demonstrated the reductive arylation of cob(I)inamide (albeit in very low yield) [6]. We would now like to report additional arylation reactions in order to define the scope and limitations of this useful synthetic procedure.

Results and discussion

All aryl(pyridine)cobaloximes migrated as a single spot on silica gel thin layer chromatograms and were positively identified by their ^{1}H NMR spectra and satisfactory elemental analysis. In addition, all aryl(pyridine)cobaloximes were converted to the aquo complexes by either of two methods. Method I

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involved intermediate conversion to the equatorially protonated chlorocobaloximes (eq. 1, yields 81—97%) [7—9] followed by treatment of the solid with

$$XC_6H_4Co(D_2H_2)py + 2\ HCl \xrightarrow{MeOH/HOH} XC_6H_4Co(D_2H_3)Cl + pyH^+Cl^- \quad (1)$$

dibasic potassium phosphate in aqueous methanol (eq. 2, yields >90%). Method

$$XC_6H_4Co(D_2H_3)Cl + HPO_4^{2-} \xrightarrow{MeOH/HOH} XC_6H_4Co(D_2H_2)OH_2 + H_2PO_4^- + Cl^- \quad (2)$$

II involved treatment of an aqueous methanolic solution of aryl(pyridine)-cobaloxime with Dowex-50 ion exchange resin in the H^+-form (eq. 3, yields 70—80%) [5,10]. The aryl(aquo)cobaloximes thus obtained were also charac-

$$XC_6H_4Co(D_2H_2)py + Dowex\text{-}SO_3H \xrightarrow{MeOH/HOH} XC_6H_4Co(D_2H_2)OH_2 + Dowex\text{-}SO_3^-\ pyH^+ \quad (3)$$

terized by ^1H NMR spectroscopy and elemental analysis. In addition *p*-$CF_3C_6H_4$-$Co(D_2H_2)py$ was independently synthesized from chloro(pyridine)cobaloxime-(III) [3] and *p*-$CF_3C_6H_4MgBr$ in THF in 75% yield and was in all respects identical to that obtained by reductive arylation.

TABLE 1

ATTEMPTED REDUCTIVE ARYLATIONS OF COBALOXIMES [a]

Aryl halide	Cobaloxime reagent	Ratio [b]	Solvent	Conditions
C_6H_5Br	$Co^I(D_2H_2)py^-$	1.4—10 [e]	MeOH	Base
C_6H_5Br	$Co^I(D_2H_2)S(CH_3)_2^-$	1.4	MeOH	Base
C_6H_5Br	$Co^I(D_2H_2)py^-$	3.75	t-BuOH	Base
C_6H_5Br	$HCo(D_2H_2)py$	5.0	MeOH	Neutral
C_6H_5Br	$HCo(D_2H_2)py$	10.0	DMF	Neutral
C_6H_5I	$Co^I(D_2H_2)py^-$	2.5	MeOH	Base
p-$CF_3C_6H_4Br$	$Co^I(D_2H_2)py^-$	1.5	MeOH	Base
p-$CF_3C_6H_4Br$	$HCo(D_2H_2)py$	2.5	MeOH	Neutral
p-$CH_3OOCC_6H_4Br$	$Co^I(D_2H_2)py^-$	2.0	MeOH	Base
m-$CH_3OOCC_6H_4Br$	$Co^I(D_2H_2)py^-$	2.5	MeOH	Base
p-$CH_3C(=O)C_6H_4Br$	$Co^I(D_2H_2)py^-$	2.0	MeOH	Base
p-$(CH_3)_2NC_6H_4Br$	$Co^I(D_2H_2)py^-$	2.0	MeOH	Base
p-$(CH_3)_2H^+NC_6H_4Br$	$HCo(D_2H_2)OH_2$	2.0	MeOH/HAc	Acid
p-$(CH_3)_2NC_6H_4Br$	$HCo(D_2H_2)py$	2.0	MeOH	Neutral

[a] For procedures, see text. [b] Ratio of arylating agent to cobaloxime. [c] All products were identified by ^1H NMR spectroscopy and elemental analysis as well as conversion to the aryl(aquo)cobaloximes (see text). [d] Yields of purified product, based on cobalt. [e] Represents several experiments at various ratios, times and temperatures.

All attempts to obtain phenylcobaloximes by reductive arylation with bromobenzene or iodobenzene under a variety of conditions were unsuccessful (Table 1). Similarly, *p*-bromo-*N*,*N*-dimethylaniline was unreactive. However, reductive arylations (via both cobaloxime(I) and hydridocobaloxime species) with aryl bromides with electron-withdrawing substituents (including *p*-CF_3, σ_I = 0.42, *p*- and *m*-CH_3OOC—, σ_I = 0.34 and *p*-$CH_3C(=O)$—, σ_I = 0.29 [11]) produce substantial amounts of products (Table 1). It should be pointed out, however, that Grignard arylation of cobalt(III) complexes nearly always proceeds in much higher yield [3,9] so that this route should always be preferred for Grignard compatible aryl groups. Additionally, arylation of cobalt with Grignard incompatible aryl groups can also be achieved by reaction of arylhydrazines with cobalt(II) complexes in the presence of oxygen as suggested by Goedken et al. [12]. However, we have been unable to get this reaction to occur in appreciably higher yield than those shown in Table 1 and the work-up is considerably more difficult. Considering additionally the relatively poor availability of arylhydrazine reagents, the reductive arylation route is always to be preferred.

We have found that increasing the reaction times listed in Table 1 do not significantly change the yields of arylcobaloximes. The yields are thus apparently limited by side reactions. These side reactions probably do not involve the aryl halide since the yields are not very sensitive to the amount of excess aryl

Reducing agent	Temperature (°C)	Time (h)	Product [c]	Yield [d] (%)
BH_4^-	r.t. —50 [e]	18—24 [e]	none	0
BH_4^-	r.t	19	none	0
BH_4^-	50	18	none	0
H_2	r.t.	18	none	0
H_2	50	48	none	0
BH_4^-	r.t.	10	none	0
BH_4^-	r.t.	23	*p*-$CF_3C_6H_4Co(D_2H_2)py$	5
H_2	r.t.	20	*p*-$CF_3C_6H_4Co(D_2H_2)py$	4
BH_4^-	50	40	*p*-$CH_3OOCC_6H_4Co(D_2H_2)py$	10
BH_4^-	50	48	*m*-$CH_3OOCC_6H_4Co(D_2H_2)py$	7.5
BH_4^-	50	16	*p*-$CH_3C(=O)C_6H_4Co(D_2H_2)py$	11.5
BH_4^-	50	16	none	0
H_2	50	24	none	0
H_2	50	24	none	0

halide employed, no major organic products have been detected in the reaction mixtures, and large amounts of unreacted aryl halide can always be obtained from the reaction mixtures. However, cobaloxime(II) is known to undergo hydrogenation of coordinated dimethylglyoxime in the absence of good hydridocobaloxime trapping reagents [13—15]. Although a similar equatorial ligand reduction by borohydride has not been demonstrated it seems reasonable that the prolonged reaction with excess borohydride also causes such reduction. This, in fact, may explain why the color of cobaloxime(I) slowly disperses in such reaction mixtures despite the rigorous exclusion of air, requiring periodic readditions of borohydride (see Experimental). It seems likely then, that arylcobaloxime yields in these preparations are limited by reductive destruction of the cobalt reagent.

The mechanism of these reductive arylations is unknown. However, an atom transfer mechanism (eq. 4 and 5) which is well documented for reactions of cobalt(II) reagents with alkyl halides [16—22] can be ruled out since prolonged

$$Co^{II}(Chelate)L + ArX \rightarrow XCo(Chelate)L + Ar\cdot \quad (4)$$

$$Co^{II}(Chelate)L + Ar\cdot \rightarrow ArCo(Chelate)L \quad (5)$$

reaction of cobaloxime(II) reagents with various aryl halides in the absence of added reducing agents failed to produce any detectable amounts of arylcobaloximes. Tucker [23] has studied the reactions of $Co^{I}(BAE)^{-}$ and $Co^{I}(SALEN)^{-}$ with various *p*- and *o*-substituted aryl halides in tetrahydrofuran to produce *p*- and *o*-substituted arylcobalt complexes in yields ranging from 2.6 to 64%, although most yields were below 20%. Tucker found the relative rates of halide displacement to vary in the order I >> Br >> Cl >> F and found that significant amounts of arene by-products were formed. Based on these observations Tucker concluded the reactions occur via an electron-transfer mechanism (eq. 6 and 7). However, considering the extremely high nucleophilicity of cobaloxime(I)

$$Co^{I}(Chelate)L^{-} + ArX \rightarrow Co^{II}(Chelate)L + Ar\cdot + X^{-} \quad (6)$$

$$Co^{II}(Chelate)L + Ar\cdot \rightarrow ArCo(Chelate)L \quad (7)$$

reagents [24] and our observation of the requirement for an electron-withdrawing substituent, nucleophilic aromatic substitution cannot be ruled out. In fact an earlier polarography and cyclic voltammetry study of the kinetics of the interaction of $Co^{I}(SALEN)^{-}$ with bromobenzene by Costa and coworkers [25] concluded that the reaction was an S_N2 displacement. These apparent discrepancies are somewhat reminiscent of the current situation with respect to reductive alkylation of cobalt chelates. Early kinetic studies by Schrauzer and Deutsch [26] led to the conclusion that an S_N2 mechanism was operative. This conclusion was soon supported by stereochemical investigations showing inversion of configuration for both secondary [27] and primary [28,29] alkylating agents. However, subsequent studies have shown that at least in some cases of highly strained alkylating agents [30,31] and possibly more generally [32—35] an S_N2 mechanism cannot occur and reductive alkylation must proceed via an electron-transfer mechanism analogous to eq. 6 and 7. It thus seems reasonable to conclude at the present time that reductive alkylation of cobalt chelates may occur either via an S_N2 or an electron-transfer mechanism depending upon conditions

and reagent structure. A similar dichotomy of mechanism may also occur for reductive arylation.

Experimental

All operations were performed in dim light. ^{1}H NMR spectra were recorded on a Varian T-60 NMR spectrometer. Elemental analyses were made by Galbraith Laboratories, Knoxville, Tennessee.

Methyl-*m*-bromobenzoate was obtained by sulfuric acid catalyzed esterification of *m*-bromobenzoic acid with methanol.

Reductive arylations

Reductive arylations were generally carried out as follows: 75 ml of solvent (Table 1) were purged with argon for 30 min in a three-necked round-bottomed flask. Following addition of 0.02 mol of cobaltous chloride hexahydrate and 0.04 mol of dimethylglyoxime the argon purge was continued for 30 min. 0.04 moles of sodium hydroxide and 0.022 mol of axial ligand (pyridine or dimethyl sulfide) were then added. For reductions to hydridocobaloximes with hydrogen, the aryl halide was then added, the atmosphere was replaced with hydrogen under an atmospheric pressure hydrogen reservoir, and the mixture was vigorously stirred throughout the reaction time. For reductions to cobaloxime(I) nucleophiles, excess base and aryl halide were added followed by a solution of sodium borohydride, dropwise, under continuous argon purge. As the dark green color of cobaloxime(I) slowly dispersed, additional borohydride was added periodically to keep the cobalt reagent reduced.

After completion of the reaction time (Table 1) the reaction mixtures were filtered and crude product was removed from the filtered solids by stirring with chloroform. Additional crude product was obtained by concentration of the reaction supernatant and addition of water. Pooled crude products, which were substantially contaminated with unreacted aryl halide, were dried and purified by silica gel chromatography. Elution with chloroform or methylene chloride removed contaminating aryl halide, while the arylcobaloximes could be eluted with acetone, unarylated cobaloxime remaining on the column. When necessary, the final products were recrystallized from methanol/water or methylene chloride/cyclohexane.

p-$CF_3C_6H_4Co(D_2H_2)py$. Elemental anal. Found C, 46.54; H, 4.28; N, 13.50. $C_{20}H_{23}CoF_3N_5O_4$ calcd.: C, 46.79; H, 4.52; N, 13.64%. NMR ($CDCl_3$) δ (ppm, Me_4Si) 2.04 (s, 12 H), 7.01—8.86 (m, 9.4 H).

p-$CH_3OOCC_6H_4Co(D_2H_2)py$. Elemental anal. Found C, 49.85; H, 5.01; N, 13.96. $C_{21}H_{26}CoN_5O_6$ calcd.: C, 50.10; H, 5.21; N, 13.91%. NMR ($CDCl_3$) δ (ppm, Me_4Si) 2.03 (s, 12 H), 3.82 (s, 2.9 H), 7.17—8.87 (m, 9.0 H).

m-$CH_3OOCC_6H_4Co(D_2H_2)py$. Elemental anal. Found C, 50.02; H, 5.10; N, 14.07. $C_{21}H_{26}CoN_5O_6$ calcd.: 50.10; H, 5.21; N, 13.91%. NMR ($CDCl_3$/methanol-d_4) δ (ppm, Me_4Si) 2.03 (s, 12 H), 3.87 (s, 3.1 H), 6.70—9.03 (m, 8.8 H).

p-$CH_3C(=O)C_6H_4Co(D_2H_2)py$. Elemental anal. Found C, 51.50, H, 5.49, N, 14.21. $C_{21}H_{26}CoN_5O_5$ calcd.: C, 51.75; H, 5.38; N, 14.37%. NMR ($CDCl_3$) δ (ppm, Me_4Si) 2.02 (s, 12 H), 2.47 (s, 3.0 H), 7.21—8.84 (m, 9.3 H).

Hydrolyses to Aryl(aquo)cobaloximes

Method I. Aryl(pyridine)cobaloximes were converted to the equatorially protonated chlorocobaloximes (eq. 1) as follows: 5.0 mmol of aryl(pyridine)-cobaloxime was dissolved in 200 ml of 3.0 *N* methanolic HCl with slight warming, if necessary, to effect solution. After stirring for 30 min 100 ml of water was added and the product was precipitated by reduction in volume to 100 ml on a rotary flash evaporator. The product was collected by vacuum filtration, washed with cold water and dried in vacuo over P_2O_5.

The equatorially protonated chlorocobaloximes were converted to the aryl-(aquo)cobaloximes (eq. 2) as follows: approximately 5.0 mmol of protonated chlorocobaloxime was dissolved in 150 ml of methanol. 100 ml of 0.1 *M* aqueous dibasic potassium phosphate was added gradually with stirring. After further stirring for 1 h the volume was reduced to 100 ml by rotary flash evaporation. The solid product was collected by vacuum filtration, washed with cold water and dried in vacuo over P_2O_5.

p-$CF_3C_6H_4Co(D_2H_2)OH_2$. Yield 95%. Elemental anal. Found C, 39.61; H, 4.32; N, 12.20; F, 12.71. $C_{15}H_{20}CoF_3N_4O_5$ calcd.: C, 39.83; H, 4.46; N, 12.39; F, 12.60%. NMR ($CDCl_3$) δ (ppm, Me_4Si) 2.01 (s, 12 H), 6.81—7.74 (m, 4.4 H).

p-$CH_3OOCC_6H_4Co(D_2H_2)OH_2$: Yield 75%. Elemental anal. Found C, 43.15; H, 5.26; N, 12.58%. $C_{16}H_{23}CoN_4O_7$ calcd.: 43.44; H, 5.24; N, 12.67. NMR ($CDCl_3$/methanol-d_4) δ (ppm, Me_4Si) 2.15 (s, 12 H), 3.81 (s, 3.1 H), 7.10—7.60 (m, 4.2 H).

Method II (equation 3). 1.5 mmoles of aryl(pyridine)cobaloxime was dissolved in 150 ml of methanol. 1.33 g of Dowex-50-X-8 ion exchange resin (H^+-form) and 75 ml of water were added, and the mixture was stirred overnight. The ion exchange resin was removed by vacuum filtration and the supernatant was refiltered by gravity. The solvent volume was reduced to about 30 ml by rotary flash evaporation and the precipitated solid was collected by vacuum filtration, washed with water and dried in vacuo over P_2O_5.

m-$CH_3OOCC_6H_4Co(D_2H_2)OH_2$. Yield 72%. Elemental anal. Found C, 43.31; H, 5.40; N, 12.72%. $C_{16}H_{23}CoN_4O_7$ calcd.: C, 43.44; H, 5.24; N, 12.67. NMR ($CDCl_3$/methanol-d_4) δ (ppm, Me_4Si) 2.15 (s, 12 H), 3.84 (s, 3.1 H), 6.72—7.82 (m, 4.3 H).

p-$CH_3C(=O)C_6H_4Co(D_2H_2)OH_2$. Yield 87%. Elemental anal. Found C, 44.85; H, 5.55; N, 13.25. $C_{16}H_{23}CoN_4O_6$ calcd.: C, 45.07; H, 5.44; N, 13.14%. NMR ($CDCl_3$/methanol-d_4) δ (ppm, Me_4Si) 2.14 (s, 12 H), 2.46 (s, 2.9 H), 7.28 (m, 4.2 H).

Grignard preparation of p-$CF_3C_6H_4Co(D_2H_2)py$

p-$CF_3C_6H_4MgBr$ was prepared from 0.047 mol of *p*-$CF_3C_6H_4Br$ and 0.048 g-atom of magnesium in 60 ml of tetrahydrofuran which had been freshly distilled from excess $LiAlH_4$. The THF solution of the Grignard reagent was added dropwise to a slurry of 0.015 moles of chloro(pyridine)cobaloxime [4] in 60 ml of freshly distilled THF with cooling in ice. After the addition was complete the mixture was refluxed for 15 min. The reaction mixture was cooled in ice and hydrolyzed with 100 ml of 10% HCl. The mixture was extracted several times with petroleum ether, neutralized, and the solid product was recovered by vacuum filtration. The product was air dried and recrystallized from chloroform. Yield 75%.

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