Cobaloximes. Part 3.[1] A Cobaloxime Synthesis for Use with Reactive Alkyl Halides

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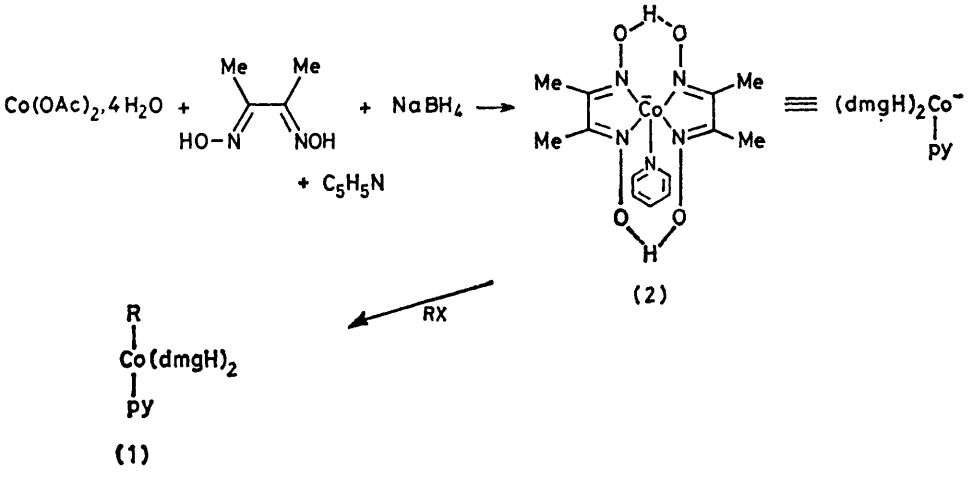
The reaction of (bisdimethylglyoximato)dipyridinecobalt(II) with alkyl iodides or α-bromo-esters and related compounds, in the presence of zinc and under aprotic anaerobic conditions, gives alkylcobaloximes in moderate to good yields.

In connection with studies on potential coenzyme B_{12} model compounds,[2] we required a series of (alkoxycarbonylmethyl)cobaloximes (1; R = CH_2CO_2-alkyl). Alkylcobaloximes are synthesised most often by the method of Schrauzer [3] or its recent variants,[4] which involve the *in situ* generation of a cobalt(I) species in aqueous methanol [3] or dimethylformamide [4] and reaction of this anion with an alkyl halide or similar reagent (Scheme 1). Under the Schrauzer conditions, α-bromo-esters are rapidly destroyed and yields of alkoxycarbonylcobaloximes are poor. We therefore sought an alternative synthesis which would be generally applicable, technically simple, and efficient.



SCHEME 1

One solution to the problem is to generate the pyridinecobaloxime(I) anion (2) in an aprotic medium, and we [1] have developed such an approach, as has Dolphin.[4] However, our method, although particularly useful for the substrates for which it was developed, was somewhat cumbersome in that cyanoethylcobaloxime was required as starting material.

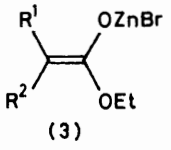
As the problem lies in the sensitivity of the substrates and/or the products to hydrolysis, we have examined neutral aprotic techniques for cobaloxime synthesis, and here report a method which is technically simple and particularly effective for use with α-halogeno-ester substrates.

It has been observed [5] that chloro(pyridine)cobaloxime (1; R = Cl) reacts with ethyl bromoacetate in the presence of zinc to give a 21% yield of ethoxycarbonylmethyl(pyridine)cobaloxime (1; R = CH_2CO_2Et); initially we examined the general synthetic utility of this reaction. The results were unpromising. Only the reactions of the simple α-bromo-esters were successful, and the yields were only moderate. Variations in temperature (up to 120 °C), pretreatment of zinc (with H_2SO_4 or HNO_3), and solvent variation had no beneficial effect. The use of bromo(pyridine)cobaloxime (1; R = Br) or bromo(tributylphosphine)cobaloxime also gave no improvement.

We then performed a series of control experiments aimed at elucidating the mechanism of the synthesis. We reasoned that the action of the zinc could have involved the formation of the Reformatsky reagent (3).[6] However, when this reagent was formed first and the chlorocobaloxime added subsequently, no alkylcobaloxime was produced. Furthermore, the corresponding potassium enolate [7] and the lithium enolate of acetone [8] gave no alkylcobaloxime. Indeed, yields were highest if the zinc and chlorocobaloxime were mixed and the bromo-ester was added later. These results indicate that the initial process is the reduction of chlorocobaloxime by zinc, a conclusion which was confirmed by the formation of cyanomethylcobaloxime (1; R = CH_2CN) in 64% yield from chloroacetonitrile (which is not reduced by zinc under our reaction conditions).

Zinc is reported to reduce cobaloxime(II) species to

cobaloxime(I) under basic conditions; [9] it was necessary, therefore, to determine the oxidation level of the reactive cobalt species here. The characteristic colour of cobaloxime(I) anions was not detected on reaction of zinc and halogenocobaloxime alone, and the absence



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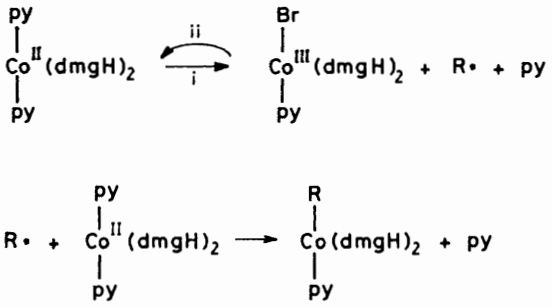

SCHEME 2 *Reagents*: i, RBr; ii, Zn, py

of such species was further indicated by the inertness of the system to nitrous oxide. Nitrous oxide is known [10] to destroy rapidly cobalt(I) complexes, but when ethyl 2-bromopropionate was treated with dipyridinecobaloxime and zinc in an atmosphere of nitrous oxide, 1-ethoxycarbonylethyl(pyridine)cobaloxime was formed in 90% yield (identical with that of the reaction run under nitrogen).

These results show that this cobaloxime synthesis is a variant of the reaction, studied in detail by Halpern, of cobaloxime(II) complexes with alkyl halides.[11] The function of the zinc is to regenerate cobalt(II) from halogenocobalt(III) product. The overall process is depicted in Scheme 2. The alkylcobaloxime-forming steps are an inner sphere redox process involving neutral, radical species; thus the process conforms to our original requirement for non-basic, non-nucleophilic conditions for sensitive substrates.

The Reformatsky reaction of zinc with the α-bromo-esters is an unwanted side-reaction; thus those halogeno-esters which react most rapidly with zinc [6] gave low yields of cobaloxime.

With these data to hand, it was possible to define better conditions for the various synthetic steps. Thus, it is unnecessary to use halogenocobaloxime as starting material; the air-sensitive cobaloxime(II) complex (1; R = py), preferably generated *in situ* (see Experimental section) in benzene, gave better yields. The involvement of carbon and cobalt radicals meant that the rigorous exclusion of oxygen was advantageous. The results of using the redefined reaction conditions, and an excess of zinc wool, are given in the Table, together with our results obtained by the Schrauzer method, for comparison.

It was evident from the mechanism that for the simple alkyl halides, iodides would be preferred to bromides [Table: runs 1, 2 (footnote *c*), 4, and 5). However, since in general iodides are less accessible than bromides, we have studied mainly the bromides.

Unactivated bromides (*e.g.* runs 2 and 3) do not react with cobaloxime(II), and if the substrate or product is base-sensitive then the iodide must be used (*e.g.* runs 4 and 5). α-Bromo-esters generally give high yields of alkylcobaloxime (runs 6—10), but for the more reactive or hindered analogues the yields are considerably reduced. This is ascribed to two factors. First, the rate of formation of the unwanted Reformatsky intermediate increases with increasing α-substitution, particularly by aryl groups (runs 11 and 12),[6] and secondly the more sterically crowded cobaloximes are much less stable and are more difficult to form.[12] Thus, the intermediate 2-nitropropyl radical of run 17 dimerises [13] and is not captured by cobalt.

We have also examined the effect of varying the

Alkylcobaloxime syntheses from dipyridinecobaloxime(II) generated *in situ*

Run no.	Substrate	*T*/°C	Reaction time (h)	Yield (%)	Lit. yield (%) [a]
1	MeI	40	24	95	74 [b]
2	Me_2CHBr	60	72	Trace [c]	33
3	$Br[CH_2]_2CO_2Me$	75	6	0 [d]	
4	$I[CH_2]_2CO_2Me$	75	2	45 [d]	
5	$ICH_2CH(CO_2Et)CH_2CO_2Me$	75	2	68 [d]	
6	$BrCH_2CO_2Et$	70	1	90	18
7	$MeCHBrCO_2Et$	70	1	90	18
8	$EtCHBrCO_2Et$	60	1	85	38
9	$Pr^nCHBrCO_2Et$	50	1.5	90	45
10	$Pr^iCHBrCO_2Et$	40—45	2	70	28
11	$PhCHBrCO_2Et$	35	1.5	Trace	36 [e]
12	$Me_2CCHBrCO_2Et$	40	1	0	
13	$PhCOCH_2Br$	45	1	31	17
14	$ClCH_2CN$	70	1	64	36
15	MeCHClCN	60—70	1	69	20
16	$BrCH_2NO_2$	45—60	1	24	19
17	$BrCMe_2NO_2$	40	2	0 [f]	

[a] As they are rarely reported, yields by the Schrauzer method in our hands are given for comparison. [b] Literature yield 99% using dimethyl sulphate (see ref. 3). [c] Isopropyl iodide gave a 57% yield without recycling (see G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, 1966, **88**, 3738). [d] Mr. A. P. F. Cook conducted these experiments. [e] Literature yield 40% (M. N. Ricroch and A. Gaudemer, *J. Organomet. Chem.*, 1974, **67**, 119). [f] Product 2,3-dimethyl-2,3-dinitrobutane.

reducing metal, but of those tried (aluminium powder, aluminium amalgam, zinc) none was superior to zinc wool.

If the halogenocobaloxime intermediate in Scheme 2 is readily separable from the alkylcobaloxime product, then the zinc may be omitted and two equivalents of cobaloxime(II) used. In most simple cases, however, we have found the separation to be difficult and tedious.

The method has proved to be most useful for the synthesis of alkylcobaloximes which require base-sensitive substrates, and for which the Schrauzer method frequently fails.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. T.l.c., both preparative and analytical, was carried out under carbon dioxide using GF_{254} silica plates unless stated to the contrary. Column chromatography was carried out on silica gel H (type 60) unless stated otherwise. A mixture of chloroform, ethyl acetate, and methanol (2 : 2 : 1 v/v/v) was used for the alkylcobaloximes for both column and thin-layer chromatography.

All solvents were purified and dried as described.[14]

Ethoxycarbonylmethyl(pyridine)cobaloxime (1; R = CH_2CO_2Et).—Chloro(pyridine)cobaloxime [3] (1 g, 2.48 mmol) and zinc wool (0.2 g, 3 mmol) were stirred in benzene (3 ml) under nitrogen at 75 °C. Ethyl bromoacetate (0.5 g, 3 mmol) was added, together with a small crystal of iodine. The mixture was heated at 80 °C for 2 h and then poured into 10% sulphuric acid (10 ml). The two layers were separated and the aqueous phase was extracted with chloroform (3 × 20 ml). The combined extracts were washed with water (30 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography gave the cobaloxime (1; R = CH_2CO_2Et) (0.23 g, 20%), identical with authentic material.

Similarly prepared were 1-ethoxycarbonylethyl(pyridine)-cobaloxime (54%), 1-ethoxycarbonylpropyl(pyridine)cobaloxime (30%), and benzyl(pyridine)cobaloxime (21%).

Reaction of Chloro(pyridine)cobaloxime with the Reformatsky Intermediate from Ethyl 2-Bromopropionate.—Ethyl 2-bromopropionate (1.18 g, 6.5 mmol) and zinc wool (0.4 g, 6 mmol) were stirred in benzene (7 ml) at 80 °C under nitrogen until all the zinc had dissolved.[5] Chloro(pyridine)-cobaloxime (2.0 g, 4.95 mmol) was added and the mixture heated for 2 h. The alkylcobaloxime was not formed (t.l.c.).

Reaction of Chloro(pyridine)cobaloxime with the Potassium Enolate of Ethyl Propionate.—Ethyl propionate (0.255 g, 2.5 mmol) was added to a suspension of potassium hydride (0.1 g, 2.5 mmol; oil-free) in tetrahydrofuran (THF) (10 ml) under nitrogen. Chloro(pyridine)cobaloxime (1.01 g, 2.5 mmol) in THF (10 ml) was added. The solution turned red and then slowly brown, and was stirred overnight at room temperature. After the usual work-up n.m.r. and t.l.c. analysis showed the absence of an alkylcobaloxime.

Reaction of Chloro(pyridine)cobaloxime with the Lithium Enolate of Acetone.—Isopropenyl acetate (0.230 g, 2.3 mmol) was added to a solution of methyl-lithium (4.6 mmol) in 1,2-dimethoxyethane (4.6 ml) under nitrogen at −78 °C. After 45 min, a suspension of chloro(pyridine)cobaloxime (1.0 g, 2.48 mmol) in 1,2-dimethoxyethane (20 ml) was added. The mixture was stirred at 40 °C for 12 h, then cooled and poured into 10% sulphuric acid (20 ml). The two layers were separated and the aqueous phase was extracted with chloroform (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue contained no alkylcobaloxime (n.m.r., t.l.c.).

Reaction of Pyridinecobaloxime(II) with Zinc.—Zinc wool (0.1 g, 1.5 mol) and pyridinecobaloxime(II) (0.5 g, 1.359 mmol) were mixed in benzene (3 ml) at 80 °C under nitrogen. After 3 h, the starting materials were unchanged.

Preparation of 1-Ethoxycarbonylethyl(pyridine)cobaloxime in the Presence of Nitrous Oxide.—Cobalt(II) acetate tetrahydrate (0.498 g, 2 mmol), dimethylglyoxime (0.464 g, 4 mmol), pyridine (0.474 g, 6 mmol), and zinc wool (in excess) were stirred in degassed benzene (10 ml) under nitrous oxide at 70 °C for 10 min. Ethyl 2-bromopropionate (0.724 g, 3 mmol) was added and the mixture heated for 1 h. The solvent was removed under reduced pressure and the residue dissolved in chloroform (20 ml) and washed with water (2 × 10 ml). The solution was dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatography afforded the cobaloxime (1; R = $CHMeCO_2Et$) (0.844 g, 90%), identical (n.m.r., i.r.) with that obtained from chloro(pyridine)cobaloxime.

Syntheses with Dipyridinecobalt(II) Generated in situ: General Procedure.—Cobalt(II) acetate tetrahydrate (0.5 g, 2 mmol), dimethylglyoxime (0.464 g, 4 mmol), and pyridine (0.474 g, 6 mmol) were stirred in degassed benzene (10 ml) at 70 °C under nitrogen for 2 min. The halogeno-compound (4 mmol) and zinc wool (in excess) were added, and the mixture was heated at 70 °C for 2 h. The solvent was removed under reduced pressure and the residue dissolved in chloroform (20 ml) and washed with water (2 × 10 ml). The chloroform solution was dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatography afforded the cobaloximes (1). Detailed results are given in the Table.

Use of aluminium amalgam. The foregoing general procedure was adapted using ethyl 2-bromobutyrate as the alkylating agent and aluminium amalgam as the reducing agent to give the cobaloxime (1; R = $CHPrCO_2Et$) (0.197 g, 33%), identical with authentic material. A similar experiment using 2-bromo-3-methylbutyrate (0.332 g, 1.5 mmol) gave the *alkylcobaloxime* (1; R = $CHPr^iCO_2Et$) (0.08 g, 3%); $\delta(CDCl_3)$ 0.8 (3 H, d, *J* 6 Hz), 0.9 (3 H, d, *J* 5 Hz), 1.2 (4 H, t, *J* 7 Hz), 2.22 (13 H, s), 3.95 (2 H, q, *J* 7 Hz), and 7.22—8.7 (5 H, m); $\nu_{max.}$ (Nujol) 3 120, 3 050, 1 685, 1 620, 1 565, and 1 500 cm^{-1} (Found: C, 48.0; H, 6.5; N, 13.85. $C_{20}H_{32}CoN_5O_4$ requires C, 48.25; H, 6.5; N, 14.1%).

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