Alkylcobaloxime Synthesis for Reactive Alkyl Halides

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Summary The reaction of bisdimethylglyoximatocobalt-(II) with α-halogenoesters and related compounds in the presence of zinc in non-aqueous solvent gives alkylcobaloximes, for which a mechanism is proposed; the yields are generally superior to those of conventional syntheses for the title compounds.

ALKYLCOBALOXIMES are of particular interest because of their use as simple models for the reactions of cobalamin dependent enzymes.[1] Alkylcobaloxime synthesis is dominated by two approaches: the addition of hydridocobaloxime to olefins[2] and the alkylation of bis(dimethylglyoximato-pyridinato)cobalt(I) anions, the Schrauzer method.[3] The latter is the more frequently used technique and involves the *in situ* generation of the cobalt(I) anion in aqueous methanolic solution at high pH. Although yields are high for simple alkyl halides, the method is less successful with reactive halides such as α-halogenoesters. We report here a synthesis which is technically simple, particularly effective for α-bromoesters, and which complements the Schrauzer method.

$$2Co(dmgH)_2py_2 + RX \rightarrow RCo(dmgH)_2py + XCo(dmgH)_2py$$

SCHEME 1. dmgH = dimethylglyoximato. py = pyridinato.

The reaction of bisglyoximatocobalt(II) complexes with alkyl halides has been studied mechanistically[4] (overall process as Scheme 1) but not further developed presumably because of the adverse stoicheiometry and the tedious separation of the mixed cobalt(III) complexes resulting. These reactions can be conducted in a non-nucleophilic medium and therefore offer potential for alkylcobaloxime synthesis from highly electrophilic halides provided that the halogenocobaloxime can be recycled.

Of the reducing agents which will selectively reduce halogenocobaloxime in the presence of α-halogenoesters (aluminium powder, aluminium amalgam, and zinc), we have found zinc wool to be the most effective. In a typical experiment, cobalt acetate (2 mmol), dimethylglyoxime (4 mmol), and pyridine (6 mmol) in degassed benzene (10 ml) at 60 °C under nitrogen were mixed with the alkyl halide (4 mmol) and an excess of zinc wool. After 1 h, work up *via* column chromatography on silica gel generally gave moderate to good yields of the alkylcobaloxime (Table).

In order to define the reaction more precisely, a number of control experiments were carried out. Firstly, the role of zinc in the process could be either as a reductant for the halogenocobaloxime or as a reductant for the α-halogenoester.[5] When preformed zinc enolates[5] were used, no cobaloxime was produced. Furthermore, lithium and potassium enolates were equally ineffective. The reduction of the α-halogenoester by zinc is therefore a competitive side reaction. This is not important in the simple α-halogenoesters, but may be the predominant reason for the lower yields of the more substituted compounds. This interpretation is confirmed by the reaction of chloroacetonitrile with chloropyridinatocobaloxime in the presence of zinc to give cyanomethylcobaloxime in 89% yield. Chloroacetonitrile is inert to zinc under the conditions of this reaction.

The reduction of vitamin B_{12a} with zinc gives vitamin B_{12s}[6] at the cobalt(I) oxidation level. The question arises, therefore, of the exact oxidation state of cobalt in the cobaloxime synthesis. Treatment of cobaloxime(II) with zinc alone did not generate the cobalt(I) anion. It appears therefore that cobaloxime(II) is the intermediate in the recycling of the halogenocobaloxime and the overall mechanism is plausibly expressed in Scheme 2.

$$Co(dmgH)_2py_2 + RX \rightarrow XCo(dmgH)_2py + R^{\cdot} + py$$
$$R^{\cdot} + Co(dmgH)_2py_2 \rightarrow RCo(dmgH)_2py + py$$
$$2XCo(dmgH)_2py + Zn \rightarrow 2Co(dmgH)_2py + 2X^- + Zn^{2+}$$

SCHEME 2

The scope for the synthesis is defined by the examples in the Table. Simple alkyl halides (nos. 1 and 2) give comparable (or worse) yields to those of the Schrauzer method. The elusive tertiary alkylcobaloximes[7] are not produced by this approach (*e.g.* no. 14) presumably because of steric congestion. The only α-halogenoesters which do not give high yields are those rapidly reduced by zinc[5] (no. 8) or

TABLE. Cobaloxime syntheses

No.	RX	T/°C	Reaction time/h	Yield/%	Reference yield[a]/%
1	MeI	40	24	95	74[b]
2	Me_2CHBr	60	72	Trace[c]	33
3	$BrCH_2CO_2Et$	70	2	90	18
4	$MeCHBrCO_2Et$	70	1	90	18
5	$EtCHBrCO_2Et$	60	1	85	38
6	$Pr^nCHBrCO_2Et$	50	1	90	45
7	$Pr^iCHBrCO_2Et$	40—45	1·5	70	28
8	$PhCHBrCO_2Et$	35	2	Trace	36[d]
9	$Me_2CCHBrCO_2Et$	40	1·5	0	—
10	$PhCOCH_2Br$	45	1	31	17
11	$ClCH_2CN$	70	1	64	36
12	MeCHClCN	60—70	1	69	20
13	$BrCH_2NO_2$	45—60	1	24	19
14	$BrCMe_2NO_2$	40	2	0[e]	—

[a] As they are rarely reported in the literature, yields by the Schrauzer method in our hands are given for comparison. [b] Literature yield 99% using dimethyl sulphate (see G. N. Schrauzer, *Inorg. Synth.*, 1968, **11**, 61). [c] Isopropyl iodide gave a 57% yield for the unrecycled reaction (see G. N. Schrauzer and R. J. Windgassen, *J. Amer. Chem. Soc.*, 1966, **88**, 3738). [d] Literature yield 40% (see M. N. Ricroch and A. Gaudemer, *J. Organometallic Chem.*, 1974, **67**, 119). [e] Product: 2,3-dimethyl-2,3-dinitrobutane.

prohibited by steric congestion (no. 9). Iodides react faster than bromides (see no. 2 footnote c) but are generally less accessible. Within these limitations, the method offers excellent scope for non-aqueous, non-nucleophilic alkylcobaloxime synthesis under mild conditions.

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