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OXIDATIVE FREE-RADICAL CYCLISATIONS VIA COBALT(I) REAGENTS. NOVEL APPROACH TO FUNCTIONALISED BUTYROLACTONES.

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Summary: Radical cyclisation of (1) in the presence of Co(I) species leads to the cis-ring fused alkyl cobalt complex(6) which can be converted, in a preparative manner, into (8) following 1,2-elimination [to (7)] and hydrolysis/oxidation, and into (12) following photo-oxygenation [to (15)], reduction [to (16)], and hydrolysis/oxidation.

The overwhelming majority of free radical cyclisation reactions are performed under reductive conditions, with the result that ring formation is invariably accomplished at the expense of two functional groups; i.e. the radical precursor group X, and the radical acceptor (unsaturated functionality)(Scheme)[1]. Although illustrations of free-radical trapping by, for example, oxygen[2], nitroxides[2], isonitriles[3], Michael acceptors[4], alkyl radicals[5] abound in the literature, the generality of these methods in synthesis has not been established. Single electron transfer has been implicated in the reactions of many transition metal complexes with organic halides[6], and it is our contention that transition metal reagents offer a great potential in free-radical trapping methodologies. In this Letter we describe methods for achieving oxidative free-radical cyclisation by means of nucleophilic cobalt(I) reagents[7]. In one procedure, the method leads via hydrogen atom loss to an alkene at the product radical site. The second method leads, through isolatable alkyl and alkylperoxycobalt intermediates to an alcohol at the same product radical centre (Scheme 1). By oxidation of the alkene, both methods constitute novel approaches to the synthesis of γ^1-hydroxy-(α-methylene)γ-butyrolactone units present in a wide range of biologically active natural products. In the accompanying Letter we outline an extension of the general methods in the synthesis of functionalised reduced heterocycles.

Reductive cyclisation of the bromo-acetal(1a) derived from cyclohex-2-enol($EtOCH{=}CH_2$, Br_2 at -100°C, then $C_6H_5NMe_2$ at 0°C) in the presence of tributyltin hydride has been shown to lead to high yields of the cis-fused adduct(2a), which by hydrolysis and oxidation (Jones) produces the butyrolactone(3a)[8]. The same general chemistry, using the corresponding enol ether(1b) provides an expeditious synthesis of theβ-oxy-γ--butyrolactone unit(3b) present in alliacolide and related natural

products[9]. We have now found that treatment of (1a) under catalytic conditions (~10%) with the Co(I) species generated by electrochemical reduction of the cobaloxime(4) [chloro(pyridino)bis-(dimethylglyoximato)cobalt(III)] (-1.8V; $LiClO_4$, MeOH) produces a good yield (60-70%) of the cis-fused adduct(7) containing unsaturation in the six-membered ring[10,11]. This adduct results from trapping of the product radical centre(5) by Co(II) leading to the cobalt complex(6) which then suffers 1,2-elimination of H-Co in situ. The same product(7) can be produced in similar yield under identical conditions using Vitamin B_{12}, but alternative reducing conditions, e.g. ZnHg, MeOH/H_2O; Zn, MeOH/H_2O; $NaBH_4$, NaOH/MeOH, using either Vitamin B_{12} or the cobaloxime(4) led to (7) contaminated by small amounts (~20%) of the corresponding trans-fused adduct[7]. Hydrolysis and oxidation of the acetal(7) in the presence of Jones reagent then provided the known unsaturated lactone(8)[12]. In a similar manner, using Co(I)-catalytic procedures, cyclisation of the bromo-acetal(9) led to almost entirely the endo-unsaturated acetal(10), which could be converted into the lactone(11).

Epoxidation of (8)(mcpba, CH_2Cl_2, 0°C), followed by reduction of the resulting β-epoxide using sodium cyanoborohydride in the presence of boron trifluoride etherate, gave rise to the β-hydroxybutyrolactone(12)[13]. The isomeric α-hydroxybutyrolactone(14a) was easily produced from (8) following saponification, iodolactonisation(to 13), and reduction(Bu_3SnH)[12a].

When the bromoacetal(1a) was treated with 1.2 equivalents of Co(I) [generated from the cobaloxime(4)], chromatography(silica G, $CHCl_3$) separated the alkyl cobaloxime(6)(60%) as a heat and light sensitive orange powder[14]. Irradiation of the alkylcobaloxime(6) in acetonitrile in the presence of oxygen(450W Hg lamp; Pyrex filter) then led to the alkylperoxy cobalt complex (15; dark red brown)(53%) which after reduction ($NaBH_4$, MeOH) provided a 2:1 mixture (65%) of the β- and α-carbinols(16) and (17). Hydrolysis and oxidation of the separatedβ-epimer(16) using Grieco's conditions(mcpba, catalytic $BF_3.OEt_2$)[15] then produced the β-hydroxy lactone(12) identical with that produced earlier. The t--butyldimethylsilyl ether(14b) of the isomeric lactone was produced from (17), following protection (t-$BuMe_2SiCl$, DBU, CH_2Cl_2) and oxidation with Jones reagent; this material correlated with an authentic sample produced from (14a) in this work and by others[12a].

Further studies are now in progress to exploit the use of these cobalt(I) catalysed oxidative free-radical reactions in other areas of synthesis.

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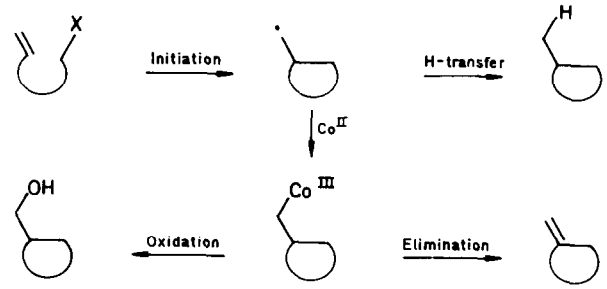
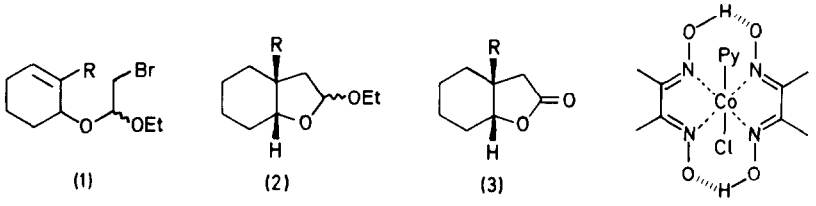
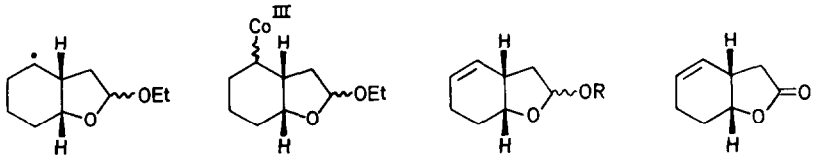


Scheme



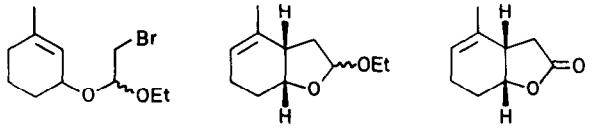
(1) (2) (3) (4)

a R = H; *b* R = Oalkyl

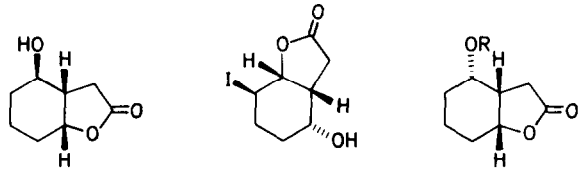


(5) (6) (7) (8)

a R = Me; *b* R = Et

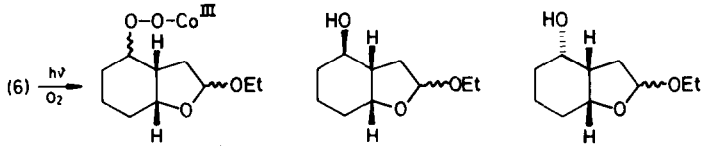


(9) (10) (11)



(12) (13) (14)

a R = H; *b* R = *t*BuMe$_2$Si



(15) (16) (17)

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10. Satisfactory spectroscopic data, together with microanalytical and/or mass spectroscopic data, were obtained for all new compounds.
11. Predominantly one anomer of (7) was produced showing: δ5.78(dm, J 9, :CH), 5.54(dm, J 9, :CH), 5.01(dd, J8 and 2, OCHO), 4.32(dt, J12 and 6, CHO), 3.36 and 3.38(OMe, anomers), 2.8(m, 1H), 2.18-1.65(m, 6H).
12. a) P.A. Grieco, N. Marinovic and M. Miyashita, J.Org.Chem., 1975, 40, 1670; b) E.J. Corey and T. Ravindranathan, Tetrahedron Letters, 1971, 4753.
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16. See: S. Torii, T. Inokuchi and T. Yukawa, J.Org.Chem., 1985, 50, 5875, for some contemporaneous studies.

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