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Cobaloximes as Environmentally Advantageous Alternatives to Organotin Hydrides in Iodine Atom Abstraction Routes to Benzyl Radicals

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High yields of alkyl radicals derived from alkylcobaloximes have been achieved using tungsten light (or in some cases ultrasound) radiation in both organic and aqueous media. These improved yields are obtained when pyridine (the usual base ligand) is replaced by suitably bulky lone-pair donors or water. The alkyl radicals so generated take part in iodine abstraction reactions with benzyl iodides giving benzyl radicals which may be trapped in near-quantitative yield with 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) or in good yield with lepidinium (4-methylquinolinium) trifluoroethanoate or lepidinium camphor-10-sulphonate. The usual drawbacks of cost and tedious work-up procedures associated with the more commonly used organotin hydride reagents are avoided.

Keywords: cobaloxime; radicals; iodine atom abstraction; ultrasound; TEMPO-trapping

INTRODUCTION

The generation of structurally diverse carbon-centred radicals by halogen abstraction using reagents such as tributyl- (or triphenyl-) tin hydride, usually in the presence of 2,2′-azobisisobutyronitrile (AIBN), or by using tris(trimethylsilyl)silane has become a popular and highly effective procedure.[1] The use of alkylcobaloximes as convenient sources of alkyl radicals has been widely adopted over the last 25 years and is still of current interest.[2] We recently reported the generation and trapping of benzyl radicals from a variety of benzyl iodides by cobaloxime-mediated iodine atom abstraction.[3] The technique has the advantages over the use of tin hydride reagents in routes to benzyl radicals of cheapness and ease of removal of cobalt(II) by-products by simple silica-gel chromatography. Additionally there are significant environmental advantages. Whilst the convenience of the approach was demonstrated, an obvious barrier to widespread adoption was that yields were only moderate. In order to generate higher fluxes of abstracting radicals, the need for greater photolytic fragility in the alkylcobaloxime was recognized. The strategy adopted to achieve this end was to reduce the stabilizing influence conferred upon the structure by the pyridine ligand, whilst maintaining the 'shelf' stability of the reagent. Two possibilities were considered:

(1) to replace pyridine by more sterically demanding ligands such as phosphines or bulky nitrogen heterocycles, and
(2) to employ the pyridylcobaloxime in aqueous acid in which water–pyridine exchange was very likely. This new procedure has the added attraction of providing a route to radicals in aqueous media rather than the organic media demanded by the organotin hydride methods.

RESULTS AND DISCUSSION

Sterically demanding ligands

It has been shown that bulky base ligands can cause a considerable distortion of the equatorial ligand plane in cobaloximes.[4] We consider that an inevitable consequence of this distortion would be the weakening of the carbon–cobalt bond

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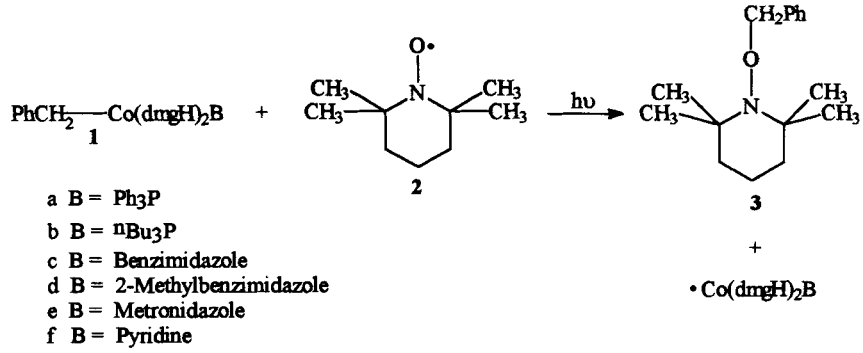


Scheme 1 Benzyl-TEMPO produced (in varying yields; see Table 1) from cobaloximes incorporating different base ligands **B**.

strength, which in turn would lead to a higher flux of alkyl radicals on photolysis. In order to pursue this idea a series of benzylcobaloximes (**1a–f**) were prepared (**1d** and **1e** are novel) with differing base ligands (**B**). These cobaloximes were then subjected to tungsten light photolysis in ethanol using commercial 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) (**2**) as a convenient radical trap so that yields could be quantified and compared (Scheme 1). The outcomes of these experiments are summarized in Table 1.

Benzimidazole was chosen as the preferred ligand for further work on the grounds of cheapness, reasonable solubility and lack of odour. In passing, it is worthy of note that a similar yield of benzyl-TEMPO (85%) was obtained from the benzimidazole complex when an ultrasound cleaning bath was used as the source of irradiation. However, the exposure time required is 18 h, rather than 1 h when tungsten light is used.

Table 1 Variation in yield of benzyl-TEMPO (**3**) with change of base ligand (**B**) in $PhCH_2Co(dmgH)_2B$[a]

Base ligand, **B**	Reaction time (h)	Benzyl-TEMPO (% yield)[c]
(a) Ph_3P	2.0	44
(b) nBu_3P	1.0	84
(c) Benzimidazole	1.0	91
(c) Benzimidazole	1.0	91
(d) 2-Methylbenzimidazole	1.0	90
(e) Metronidazole[b]	3.5	95
(f) Pyridine	1.0	58[3]

[a] EtOH as solvent; tungsten light photolysis.
[b] 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole.
[c] Yields determined by gas chromatography using an internal standard.

Photolysis studies in aqueous acid

The use of a water-based system has significant environmental advantages over an organic solvent medium. Tungsten light photolysis of $PhCH_2Co(dmgH)_2py$ (dmg, dimethylglyoximate; py, pyridine in the presence of TEMPO (**2**) was carried out over a range of pH values in buffered aqueous media. The results are summarized in Table 2.

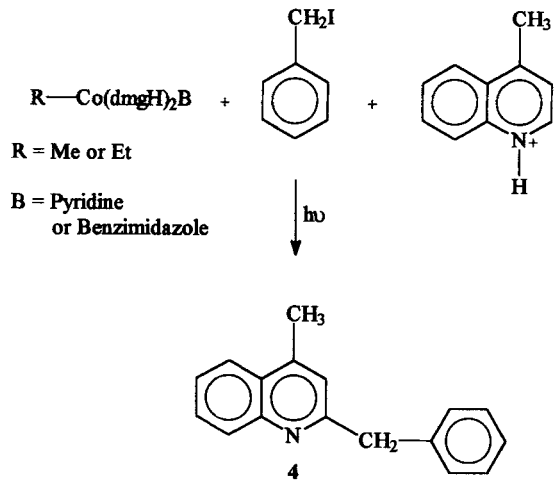
Even after long reaction times (20 h), yields are at best moderate (51% at pH 4). At lower pH the yields fall off sharply (8% at pH 2) due to the total decomposition of the cobaloxime, including the hydrolysis of the dimethylglyoxime to diacetyl.

The suggestion that a more fragile cobaloxime was being generated by the replacement of pyridine by water was tested by a single experiment using $PhCH_2(dmgH)_2H_2O$ at pH 6 under the same irradiation conditions. This gave an 85% yield of benzyl-TEMPO after 20 h. Although we have not pursued this system further in our present work, it may have potential application to aqueous radical reactions if the 20 h reaction time is acceptable.

Table 2 Variation in yield of benzyl-TEMPO (**3**) using aqueous media at different pH[a]

Solvent system	Reaction time (h)	Benzyl-TEMPO/ (% yield)[b]
Water/ethanol, 1 : 1(pH 6 buffer)	20	41
Water (pH 6 buffer)	20	32
Water (pH 4 buffer)	20	51
Water (pH 2 buffer)	20	8

[a] Substrate $PhCH_2Co(dmgH)_2py$; tungsten light photolysis.
[b] Yields determined by gas chromatography using an intenal standard.



Scheme 2 Iodine atom abstraction from benzyl iodide to form benzyl radicals which are then trapped by protonated lepidine.

The TEMPO-trapping studies established that the use of benzimidazole in place of pyridine as the base ligand in benzylcobaloxime greatly facilitates the homolysis of the carbon–cobalt bond and hence the more rapid release of radicals. It was therefore appropriate to study the performance of cobaloximes with benzimidazole as base ligand in iodine abstraction reactions. The proposed reaction sequence is shown in Scheme 2.

We have already reported on the effectiveness of $EtCo(dmgH)_2py$ in this context.[3] The results obtained for methyl or ethyl as the cobaloxime alkyl group (R) in either ethanol or propanone as solvent are shown in Table 3. Protonated lepidine is used, in various degrees of excess, as either the camphor-10-sulphonate or trifluoroethanoate salt (Scheme 2).

The yield of 2-benzyl-lepidine (57%) obtained using $EtCo(dmgH)_2$benzimidazole and a 10-fold excess of protonated lepidine is significantly better than that previously reported using $EtCo(dmgH)_2py$ under the same reaction conditions (10%).[3] The benzylated lepidine is obtained as the free base without need for basification of the reaction mixture, a finding consistent with our earlier report.[3] The use of an excess of lepidine salt as substrate for the radical attack is clearly an inconvenience in terms of purification of the benzylated product. However, if the excess is reduced, the yield of product falls off sharply. Near-quantitative results are obtained with 20-fold excess, 50–60% yield with 10-fold excess and < 10% yield with one equivalent of the lepidinium camphor-10-sulphonate. Conductivity measurements comparing lepidinium camphor-10-sulfonate and sodium chloride solutions of the same molarity suggest, from the markedly lower conductivity of the former, that much of the alleged lepidinium salt had reverted to free lepidine and undissociated camphor-10-sulphonic acid. To increase the proportion of protonated heterocycle present in the equilibrium a stronger acid (trifluoroethanoic acid) was used in place of camphor-1-sulphonic acid. A consequence of this was that a near-quantitative yield was obtained with a 10-fold excess of salt rather than the 20-fold excess required if the weaker camphor-10-sulphonic acid is employed.

In conclusion, we find that if benzimidazole is used instead of pyridine as the base ligand (**B**) in $EtCo(dmgH)_2\mathbf{B}$ then this leads to significantly higher yields of benzyl-lepidine in iodine abstraction reactions. This we believe is due to the higher flux of ethyl radicals produced from the photolytically more fragile cobaloxime which results

Table 3 Yields of 2-benzyl-lepidine (**4**) from excess protonated lepidine and one equivalent of benzyl iodide using iodine atom abstraction by alkyl radicals derived from one equivalent of $RCo(dmgH)_2\mathbf{B}$ under the influence of tungsten light

R	B	Solvent	Excess of protonated lepidine	Salt[a]	Time (h)	Yield of 4[b] (%)
Et	Pyridine	EtOH	10-fold	CS	3.0	10[3]
Et	Benzimidazole	EtOH	10-fold	CS	3.0	57
Et	Benzimidazole	EtOH	20-fold	CS	1.0	98
Et	Benzimidazole	Me_2CO	20-fold	CS	1.0	91
Et	Benzimidazole	Me_2CO	10-fold	TF	3.5	97
Me	Benzimidazole	EtOH	20-fold	CS	1.5	75

[a] CS, camphor-10-sulphonate; TF, trifluoroethanoate.
[b] Yields determined by gas chromatography using an internal standard.

when the relatively bulky benzimidazole is used as base ligand. In addition, the efficiency of protonated lepidine as a trap is enhanced when the trifluoroethanoate salt is used rather than the camphor-10-sulphonate since the tendency to dissociate back to free base is less extensive in the case of the former.

EXPERIMENTAL

General remarks

NMR spectra were recorded on JEOL PMX-60 and Varian AM-400 spectrometers. $CDCl_3$ was used as solvent with Me_4Si as internal standard. Shifts are expressed in ppm downfield from Me_4Si. Coupling constants (J) are given in Hz. Column chromatography was performed with Merck silica gel 100 (70–230 mesh) or Sorbsil flash silica gel C60 (mean pore diameter 60 Å). Solvents were standard Aldrich chemicals and were distilled prior to use. Benzyl bromide was converted into benzyl iodide by a standard Finkelstein procedure.[5] Cobaloximes were prepared according to literature methods and purified by crystallization from MeOH or column chromatography (ethyl acetate as eluent) immediately before use. Ultrasonic cleavage of cobaloximes was effected with a Langford model 1000 cleaning bath (25 MHz, 167 mW cm^{-2} rating). Photolysis reactions (under a flow of nitrogen) were performed using either 2×200 W tungsten filament household lamps maintained at 5 cm from the reaction flask, or a single 300 W halogen floodlamp positioned at 5 cm from the vessel. Both types of lamp provide a similar spectral distribution over the visible range (400–750 nm)). The small amount of ultraviolet light emitted by the tungsten halide lamp was absorbed by the glass lamp cover and the glass walls of the reaction vessel.

GC–MS was performed using a Hewlett–Packard GC 5890 Series II chromatograph in conjunction with mass spectrometer MS5971. Separations were achieved on a 12 m silicone-gum capillary column and products identified using a Wiley 138 library, where appropriate, or by comparison of their mass spectra with those of authentic samples. Quantification of products was achieved by GC (MS detection) using acetophenone as an internal standard. Microanalytical data were obtained on a Perkin–Elmer 240B elemental analyser. All infrared spectra were recorded on a Perkin–Elmer 881 spectrophotometer. Mass spectra were recorded on an AEI MS-902 or an MM-701CF instrument, using electron impact ionization at 70 eV unless stated otherwise. All reactions were monitored by TLC chromatography using Merck silica-gel 60 F_{254} precoated aluminium plates.

Preparation of benzylcobaloximes (1a–f)

Cobaloximes **1a**, **b**, **c** and **f** are known compounds and were prepared according to literature methods.[4,6] An example is described below.

Preparation of 1f

A 250 cm^3 round-bottom flask was fitted with a pressure-equalizing funnel and a nitrogen inlet. Pyridine (0.80 g, 11 mmol) and methanol (100 cm^3) were added to the flask and magnetically stirred under nitrogen for 5 min. Dimethylglyoxime (2.32 g, 20 mmol) was added, followed by cobalt chloride (2.37 g, 10 mmol). A deep red–brown colour developed. Sodium hydroxide solution (1.6 g, 40 mmol) dissolved in water (5 cm^3) was added dropwise over 20 s. The solution turned to a deep blue–black colour after 5–8 min. Benzyl bromide (0.855 g, 5 mmol) was then added dropwise over 20 s. After a further 2 min the colour had changed to yellow–brown and the mixture was added to a slush of ice/water (300 cm^3). The mixture was whisked with a glass rod to encourage crystallization. The yellow crystalline product was filtered, washed with several portions of water until the filtrate was not highly coloured and then dried in air. A typical yield was 65%.[3]

Preparation of benzylmetronidazole cobaloxime (1e)

This was prepared from $PhCH_2Co(dmgH)_2py$ (1.97 g, 4.29 mmol) by replacement of the pyridine ligand by H_2O using Dowex 50 (H^+) ion exchange resin, monitoring the reaction by TLC (ethyl acetate as eluent). The aquo complex was not usually isolated but converted *in situ* into the metronidazole derivative by the addition of metronidazole (0.513 g, 3.00 mmol) dissolved in the minimum volume of methanol (10 cm^3). Removal of the solvent followed by column chromatography on silica gel (ethyl ethanoate as eluent) afforded orange/brown crystals of the benzylmetronidazole cobaloxime **1e** (1.65 g, 70%); λ_{max}(nm) 273.9 (189 570); ν_{max}(cm^{-1})

(Nujol mull) 2924, 2854, 1546, 1344, 1268, 1232, 1188, 1086, 758 and 740; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (s, 1H), 7.27 (m, 1H), 6.97 (m, 4H), 4.42 (t, 2H), 3.89 (t, 2H), 2.84 (s, 2H), 2.46 (s, 3H), 1.96 (s, 12H); δ_C ($CDCl_3$, 100 MHz) 12.11 (s), 12.73 (s), 31.98 (s), 48.59 (s), 60.99 (s), 124.69 (s), 127.83 (s) 128.66 (s), 132.99 (s), 136.29 (s), 146.89 (s), 150.23 (s), 153.67 (s); *m/z* 551 (Found C, 45.48; H, 5.55; N, 17.60. $C_{21}H_{30}N_7O_7Co$ requires C, 45.74; H, 5.48, N, 17.78%).

Preparation of benzyl-2-methylbenzimidazole cobaloxime (1d)

This was prepared in an analogous manner (1.38 g, 63%); λ_{max}(nm) 272.8 (138 483); ν_{max}(cm^{-1}) (Nujol mull) 2866, 1420, 1310, 1086, 972 and 696. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (m, 2H), 7.26–7.20 (m, 5H), 6.99–7.19 (m, 2H), 2.92 (s, 2H), 2.63 (s, 3H), 1.94 (s, 12H)); δ_C($CDCl_3$, 100 MHz) 2.20, 12.57, 15.05, 114.59, 122.29, 124.64, 127.56, 127.97, 128.98, 129.10, 129.85, 147.23, 150.33, 152.86; *m/z* 513 (Found: C, 53.98; H, 5.75; N, 16.52; $C_{23}H_{29}N_6O_4Co$ requires C, 53.90; H, 5.70; N, 16.40%).

Preparation of an authentic sample of *N*-benzyloxy-2,2,6,6-tetramethylpiperidine (3) by photolysis of benzylcobaloxime with TEMPO

This was prepared according to the literature method.[3] [Tungsten light photolysis of an ethanolic solution of benzylcobaloxime and TEMPO in a 1 : 1 molar ratio was carried out until all the cobaloxime had been consumed (2 h). Removal of solvent followed by flash chromatography (silica gel, 9 : 1 cyclohexane/ethyl ethanoate) afforded the pure product]. The structure was confirmed by NMR spectroscopy: δ_H(400 MHz) 1.15 (6H, s), 1.25 (6H, s), 1.3–1.6 (6H, m), 4.82 (2H, s) and 7.37–7.34 (5H, m); δ_C(100 MHz) 17.11, 20.30, 33.09, 39.70, 60.00, 78.70, 127.29, 127.45, 128.22, 138.29 (Found: C, 77.6; H, 9.9; N, 5.6. $C_{16}H_{25}NO$ requires C, 77.65; H, 10.18; N, 5.66%).

Typical procedure for photolysis of benzylcobaloximes with different base ligands (1a–f) in the presence of TEMPO

The benzylcobaloxime **1a–f** (3.0 mmol) and TEMPO (0.47 g, 3.0 mmol) were dissolved in ethanol (100 cm^3). The stirred solution was degassed using nitrogen prior to irradiation with two 200 W tungsten-filament household lamps. The reaction was stopped when TLC indicated complete consumption of cobaloxime. The outcome was monitored by GC–MS and the yields (Table 1) evaluated using acetophenone as internal standard. Removal of solvent followed by column chromatography (using CH_2Cl_2 as eluent) afforded the benzyloxy-2,2,6,6-tetramethylpiperidine (**3**) (confirmed by MS and ^{1}H NMR spectroscopy) in isolated yields (as a colourless oil) only 5% lower than those reported in Table 1.

Ultrasonic cleavage of benzylbenzimidazole cobaloxime (1c) in the presence of TEMPO

The benzylcobaloxime **1c** (1.38 g, 3.0 mmol) and TEMPO (0.47 g, 3.0 mmol) were dissolved in propanone (100 cm^3) and the solution degassed with nitrogen prior to sonication at 25 °C (coolant water was required to maintain the constancy of the bath temperature). After 18 h, TLC showed that all the cobaloxime had been consumed. The mixture was worked up as described above to afford the same product (**3**) [85% by GC (internal standard), 0.586 g, 79% as isolated]. A control experiment conducted in the absence of ultrasound failed to afford any trace of the benzyl-TEMPO adduct (**3**).

Typical procedure for photolysis of benzylcobaloxime (1f) with TEMPO in buffered aqueous media (pH 2–6)

Benzylcobaloxime (**1f**) (1.38 g, 3.00 mmol) and TEMPO (0.47 g, 3.00 mmol) were dissolved in distilled water (100 cm^3) buffered to the appropriate pH using commercial buffer tablets. The stirred solution was degassed using nitrogen prior to irradiation with 2×200 W tungsten-filament household lamps. The reaction was stopped after TLC indicated complete consumption of the cobaloxime (0.5–20 h). The yields (Table 2) of benzyl-TEMPO adduct (**3**) were determined by GC using an internal standard and confirmed by isolation using the previous column chromatographic procedure. Isolated yields were typically 5% lower than those determined by GC analysis.

2-Benzyl-4-methylquinolines: standard protocol for the photolysis of benyl iodide with ethyl or methylcobaloxime in the presence of lepidinium salts (camphor-10-sulphonate/ trifluoroethanoate)

Benzyl iodide (0.327 g, 1.5 mmol), the ethyl- or methyl-cobaloxime (base ligand pyridine or benzimidazole) (1.5 mmol) and either lepidinium camphor-10-sulphonate (5.63 g, 15 mmol) or lepidinium trifluoroethanoate (3.85 g, 15 mmol) were dissolved in either ethanol (100 cm^3) or propanone (100 cm^3) according to Table 3. The stirred solution was degassed using nitrogen prior to irradiation with a 300 W tungsten halogen floodlamp. The reaction was monitored for the complete consumption of both cobaloxime (by TLC, ethyl ethanoate as eluent) and the benzyl iodide (GC–MS). Reaction times (1.0–3.5 h) were insufficiently long to permit any conversion of the benzyl iodide in to the corresponding alcohol (absence confirmed by GC–MS). The identity of the product, 2-benzyl-4-methylquinoline (**4**), was confirmed by GC–MS. Quantification of yields (Table 3) was achieved by GC using an internal standard. Further confirmation of yields was achieved by removal of the solvent under reduced pressure, extracting with diethyl ether (2×40 cm^3), washing with saturated brine solution (2×10 cm^3), drying (anhydrous $MgSO_4$) and evaporation of the ether (under reduced pressure) to give a brown oil. Column chromatography (using CH_2Cl_2 as eluent) gave **4** (confirmed by GC–MS and comparison of its ^1H NMR spectrum with that of an authentic sample) as a brown viscous oil. The isolated yield was 5% lower than that obtained by GC determination reported in Table 3.

2-Benzyl-4-methylquinoline (4)

This is a known compound[7] and was prepared by tungsten light photolysis of an ethanolic solution of benzylcobaloxime and lepedinium camphor-10-sulphonic acid in a 1 : 10 molar ratio until thin-layer chromatography indicated that all the cobaloxime had been consumed (24 h). The product was isolated by flash chromatograhy (silica gel, using 9 : 1 cyclohexane/ethyl ethanoate as eluent) and identified by NMR spectroscopy. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (ddd, 1H), 7.89 (ddd, 1H), 7.69 (td, 1H), 7.51 (td, 1H), 7.30–7.21 (m, 4H), 7.04 (s, 1H), 4.29 (s, 2H), 2.58 (s, 3H); *m/z* 233.12.

CONCLUSION

This work has demonstrated that benzylic radicals are attractively accessible from the corresponding iodides through cobaloxime-based mediation. These synthetically important intermediates can now be generated under conditions which have significant environmental advantages over those associated with the use of tributyltin hydride and related compounds in iodine atom abstraction.

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