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The Thermolysis of Benzyl Cobaloximes: A New One Step Synthesis of 5-Arylisoxazoles

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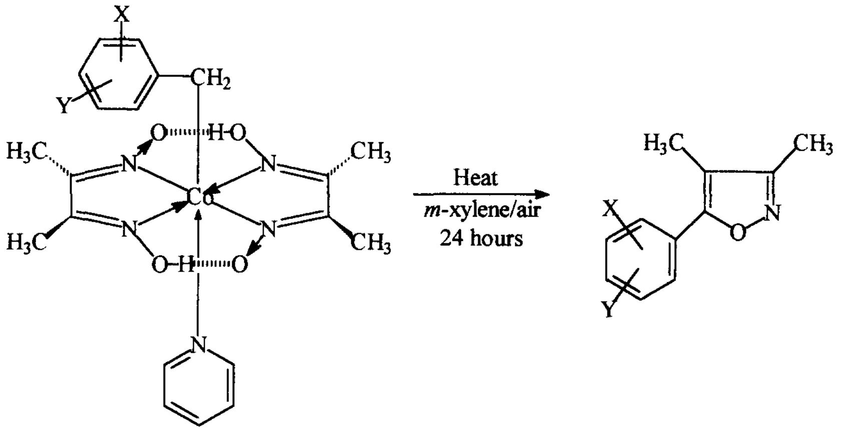
Abstract: *When benzyl cobaloximes are either dry-distilled or boiled in xylene solution they afford the corresponding 5-arylisoxazoles in moderate to good yields.*

Recently there has been a resurgence in the chemistry of isoxazoles arising from their use as molecular synthons. Whilst stable to a range of reactants, these heterocycles can nevertheless be cleaved in a predictable and synthetically useful manner under appropriate conditions. Thus it has been suggested that the isoxazole ring "...is the most broadly useful heteroaromatic precursor and intermediate in preparative organic chemistry."[1]

The thermolysis of alkyl cobaloximes is believed to proceed *via* detachment of the top ligands as carbon-centred radicals. These are then stabilised either by dimerisation or by H-atom abstraction to form alkanes and alkenes.[2] Thus the predominant volatile product (apart from pyridine) from the thermolysis of 2-phenylethyl cobaloxime (top axial ligand = $PhCH_2CH_2$-) is styrene. In contrast to the earlier studies on the thermochemistry of benzylic cobaloximes which failed to indicate the formation of any heterocyclic species,[3] we report that if the benzyl radicals are intercepted by the dimethylglyoxime mono-anion moieties which make up the equatorial plane of the cobaloxime (**1a-j**), then 5-arylisoxazoles (**2a-j**) are produced in significant yields (see Scheme 1). The conversion may be effected simply by dry distillation, but the use of boiling *m*-xylene gives a more controlled reaction with far fewer by-products. The benzylic CH_2 is incorporated in the heterocyclic ring at position 5. When the parent cobaloximes are prepared from dimethylglyoxime, the resulting isoxazoles have methyl groups at positions 3 and 4. Other cobaloximes, notably those prepared from diphenylglyoxime and 1,2-cyclohexanedione dioxime, afford isoxazoles with phenyl substitution at positions 3 and 4 or with a cyclohexane ring fused across the above positions (**3** and **4**).

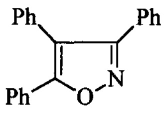
Yields of these products were lower than those derived from the dimethyl glyoxime at 10% and 15%, respectively.



1a X = H Y = H
b X = 3-chloro, Y = H
c X = 3-fluoro, Y = H
d X = 4-fluoro, Y = H
e X = 4-nitro, Y = H
f X = 3-methyl, Y = H
g X = 4-methyl, Y = H
h X = 4-^{t}butyl, Y = H
i X = 3-methyl, Y = 4-methyl
j X = 2-methyl, Y = 5-methyl

2a X = H, Y = H (44%)
b X = 3-chloro, Y = H (39%)
c X = 3-fluoro, Y = H (41%)
d X = 4-fluoro, Y = H (39%)
e X = 4-nitro, Y = H (35%)
f X = 3-methyl, Y = H (45%)
g X = 4-methyl, Y = H (47%)
h X = 4-tbutyl, Y = H (50%)
i X = 3-methyl, Y = 4-methyl (38%)
j X = 2-methyl, Y = 5-methyl (62%)

Scheme 1



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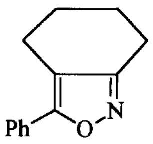

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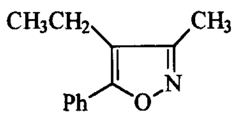
The use of glyoxime itself [HC(NOH)CH(NOH)] has so far failed to afford any parent 5-arylisoxazole. When an unsymmetrically substituted glyoxime [*e.g.* $CH_3C(NOH)C(NOH)CH_2CH_3$ (**5**)] was used to prepare the benzyl cobaloxime then thermolysis yielded the expected isomeric mixture of 4-ethyl-3-methyl-5-phenylisoxazole (**6**) and 3-ethyl-4-methyl-5-phenylisoxazole (**7**), together with a third product, 4-benzyl-3,5-dimethylisoxazole (**8**) which was, at the time, unanticipated.



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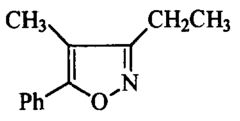

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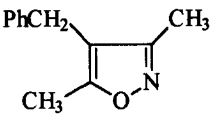

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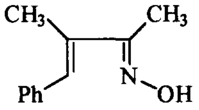
We believe that this is the first report of a free radical-based pathway for the construction of an isoxazole ring. The benzyl radical first attacks the dimethylglyoxime mono anion to yield a mixture of two monoximes (**9** and **10**) the latter an example of a new structural type. These may be isolated (more conveniently if a lower b.p. solvent such as toluene is used) and each subsequently converted into the isoxazole by further heating (in xylene).



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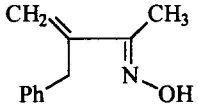

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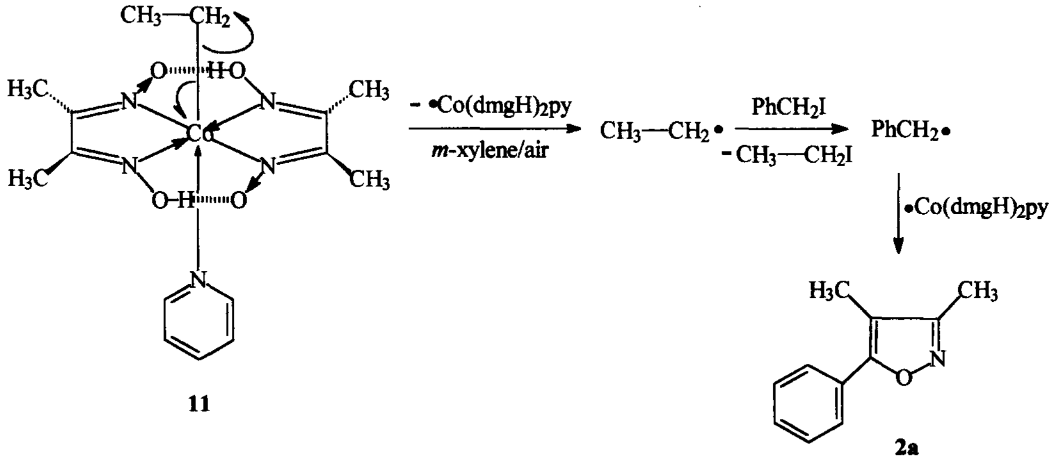
Attempts to form 5-alkylisoxazoles from alkyl cobaloximes failed. Thus when the top axial ligand = CH_3CH_2, no 3,4,5-trimethylisoxazole was produced. However, when ethyl cobaloxime (**11**) was boiled under reflux in a mixture of xylene and benzyl iodide, then a 5% yield of 3,4-dimethyl-5-phenylisoxazole (**2a**) was obtained. Presumably the highly reactive ethyl radicals produced by Co-C bond fission readily abstract iodine atoms from the $PhCH_2I$ releasing the relatively more stable benzyl radicals[4] which attack the equatorial ligand system in a more leisurely fashion (Scheme 2).



Scheme 2

A typical procedure is as follows: The benzyl cobaloximes[5] **1a-j** (10 mmol) were heated in boiling *m*-xylene (50cm^3) until TLC indicated complete consumption of the starting material (ethyl acetate as eluent). A reflux period of 24-48 hr was normally required. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel: 9/1 cyclohexane/ethyl acetate as eluent). Evaporation of the solvents gave the isoxazoles **2a-j** in the yields quoted in Scheme 1. Products were characterised by mass spectrometric comparison with library spectra, nmr spectroscopy and micro-analysis.

The mechanistic explanation (including quantitative thermochemical studies) of isoxazole formation from cobaloximes is the focus of our continuing investigations.

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References and notes

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4. Brown, T. M.; Cooksey, C. J.; Crich, D; Dronsfield, A. T.; Ellis, R. *J. Chem. Soc. Perkin Trans. 1,* **1993**, 2131.
5. The benzyl cobaloximes **1a-j** are known compounds and are easily prepared from the corresponding benzyl bromides in one-pot reactions: see Brown, T. M.; Cooksey,C. J. *Educ. Chem.*, **1987**, 24, 77 and references therein. For large-scale preparations of cobaloximes see Schrauzer, G. N. *Inorg. Synth.*, **1968**, 11, 61. The benzyl cobaloxime derived from **5** was prepared by Jeremy Stephens (University of Derby) who also (in part) investigated its conversion into isoxazoles **6**, **7**, and **8**.

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