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An Efficient Method for the Synthesis of 5-Aryl Substituted Isoxazoles by Thermolysis of the Related Benzyl and Heteroaromatic Cobaloximes

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Thermolysis of benzyl- and heteroaromatic methyl cobaloximes in boiling *m*-xylene, afforded the corresponding 5-arylisoxazoles in moderate to good yields.

Key Words: Synthesis, 5-arylisoxazoles, Cobaloximes, Heteroaromatic.

INTRODUCTION

Varhelyi *et al.*[1] investigated a range of hydrated sulfito-bis-dimethylglyoxime complexes of cobalt, mainly focusing on the kinetics of their decomposition processes. Simultaneously, Miyokawa *et al.*[2] commenced a series of kinetic and thermodynamic studies on alkyl salicylideneiminato complex of cobalt(III). They reported that in the cases of RCo(salen)py, a three stage decomposition occurred, with loss of pyridine preceding detachment of the alkyl group. Owing to their relative ease of preparation and purification, most thermochemical studies on organo-cobalt complexes have involved cobaloximes. These were first discovered by Schrauzer and Kohnle[3] and their chemistry has been extensively reviewed[4].

Benedetti *et al.*[5] found that heating methylcobaloxime (base ligand = H_2O) resulted in the loss of water or CH_3 and nitrous acid in the first step of the three stage decomposition pathways. Brown *et al.*[6] investigated on 43 examples of alkyl, aryl and benzyl cobaloximes (base ligand = H_2O or pyridine); they proposed that (at least for alkyl derivatives) decomposition occurs *via* sequential loss of the bottom axial ligand, the top axial ligand and finally breakdown of the 'core' of the cobaloxime, $(dmgh)_2Co$. Detailed examination of the benzyl cobaloximes by Brown *et al.*[7] revealed that, like their alkyl counterparts, decomposition was a three stage process, but that the sequence of steps and the nature of decomposition was quite different. They reported that the base axial ligand was detached in the final stage of the decomposition. The heterocycles,

3,4-dimethyl-5-arylisoxazoles, were removed at each of the three stages[8]. Interception of the benzyl radical by the carbon atom of the C=N bond in the dimethylglyoxime monoanions constituting the equatorial plane of the complex, is a key stage in the isoxazole formation and is not unexpected in the light of Finke's earlier studies[9].

An attempt by Brown *et al.*[10] to synthesize 3,4-dimethyl-5-vinylisoxazoles from allyl and cinnamyl cobaloximes failed. Allyl cobaloximes provide low yield of the corresponding 2,3-dimethyl pyridines. Subsequently, Brown *et al.*[11] with mass spectroscopic studies have clarified the stages of the thermal decomposition of alkyl cobaloximes. They reported that for the thermolysis of complexes containing pyridine as the base ligand, primary and secondary alkyl as the top axial ligand, lose the top axial alkyl ligand first, followed by pyridine at a higher temperature. For alkyl cobaloximes with water as base ligand, primary alkyl compounds lose water first, but in the cases of secondary alkyl complexes, the hydrocarbon group leaves at the low temperature. In the final stage of thermal disruption, equatorial ligands undergo symmetrical cleavage and dehydration to form the corresponding nitriles.

Here, a thermolysis of benzyl- and heteroaromatic methyl-cobaloximes has been reported. Our interest in thermolysis of benzyl and heteroaromatic methyl cobaloximes arose from most broadly useful heteroaromatic precursor and intermediate in preparative organic chemistry and biodynamic heterocycles[12].

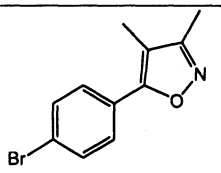
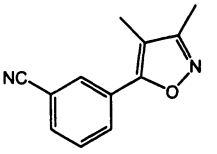
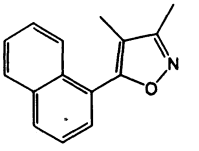
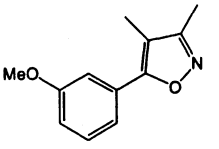
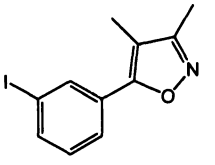
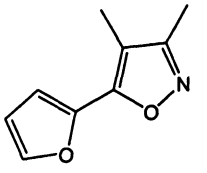
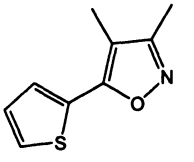
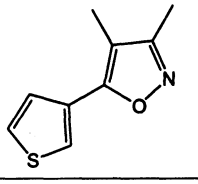
EXPERIMENTAL

IR spectra were recorded on spectrophotometer Shimadzu 460. ^1H spectra were registered on spectrometer Bruker DRX500 Avance in $CDCl_3$, internal reference TMS. GC-Mass spectra were measured on Shimadzu Mass-QP1100EX instrument.

1-chloromethyl thiophene was prepared by the chlorination of thiophene[13]. 3-bromomethyl thiophene was obtained by bromination of 3-methyl thiophene with N-bromosuccinimide[14]. Furfuryl alcohol was brominated with PBr_3 in ether as outlined by Zanett[15]. Since furfuryl bromide is unstable, its ethereal solution was used in cobaloxime preparation. Organo bis(dimethylglyoximato)pyridine Co(III) complexes were synthesized using the procedure reported in the literature[16] from bis(dimethylglyoximato)(pyridine) cobalt(I) which was generated *in situ* by $NaBH_4$ reduction of chlorocobaloxime, $CoCl(DH)_2py$ under strict inert atmosphere.

Procedure for synthesis of 5-arylisoxazoles: The benzyl cobaloximes **(1–8)** (10 mmol) were heated in boiling *m*-xylene until TLC indicated complete consumption of the starting material. A reflux period of 24–48 h was normally required. The solvent was removed under reduced pressure and the residue purified by column chromatography. Evaporation of the solvent gave corresponding isoxazoles in 31–69% yield (Table-1).

TABLE-1
THERMAL DECOMPOSITION OF BENZYL- AND HETEROAROMATIC METHYL COBALOXIMES [$RCH_2Co(DH)_2py$]

Compd.	R	Isoxazole	Yield (%)
1	4-BrC_6H_4		31
2	3-CNC_6H_4		32
3	1-Naphthyl		34
4	3-$MeOC_6H_4$		39
5	3-IC_6H_4		36
6	2-Furyl		67
7	2-Thienyl		69
8	3-Thienyl		65

5-(4-Bromophenyl)-3,4-dimethyl isoxazole (1): Beige solid; m.p.: 83–84°C; IR (KBr) ν (cm^{-1}): 1661, 1613, 1573, 1065, 627; ^1H NMR ($CDCl_3$): 2.16 (s, 3H, C—CH_3), 2.29 (s, 3H, C—CH_3), 7.56–7.62 (m, 4H, Ar—H); GC-Mass (m/e, (%)): 251 (M^+, 20), 253 (M + 2, 20), 183 (40), 103 (100), 68 (25), 42 (35).

3-(3,4-Dimethylisoxazole-5-yl) benzonitrile (2): White solid; m.p.: 197–198°C; IR (KBr) ν (cm^{-1}): 2190, 1694, 1625, 1590, 1091; ^1H NMR ($CDCl_3$): 2.21 (s, 3H, C—CH_3), 2.32 (s, 3H, C—CH_3), 7.62 (t, 1H, J = 7.8, Ar—H), 7.71 (d, 1H, J = 7.8, Ar-H), 7.96 (d, 1H, J = 7.8, Ar-H), 7.98 (s, 1H, Ar-H); GC-Mass (m/e, (%)): 198 (M^+, 100), 199 (M + 1, 55), 169 (36), 129 (88), 102 (90), 76 (22), 55 (60), 41 (89).

3,4-Dimethyl-5-naphthalen-1-yl isoxazole (3): Yellow solid, m.p.: 53–55°C; IR (KBr) ν (cm^{-1}): 1658, 1619, 1595, 1105; ^1H NMR ($CDCl_3$): 1.97 (s, 3H, C—CH_3), 2.38 (s, 3H, C—CH_3), 7.53–7.56 (m, 4H, Ar—H), 7.88 (m, 1H, Ar—H), 7.92 (m, 1H, Ar—H), 7.97 (t, 1H, J = 4.7, Ar—H); GC-Mass (m/e, (%)): 223 (M^+, 49), 224 (M + 1, 35), 180 (45), 155 (85), 153 (90), 127 (100), 103 (22), 68 (63), 41 (77).

5-(3-Methoxyphenyl)-3,4-dimethyl isoxazole (4): Yellow oil; IR (neat) ν (cm^{-1}): 1696, 1654, 1587, 1226, 1083, 1019; ^1H NMR ($CDCl_3$): 2.13 (s, 3H, C—CH_3), 2.25 (s, 3H, C—CH_3), 3.87 (s, 3H, Ar—O—CH_3), 6.93 (dd, 1H, J = 2.4, J = 8.0, Ar—H), 7.22 (d, 1H, J = 1.7, Ar—H), 7.24 (d, 1H, J = 8.0, Ar—H), 7.35 (t, 1H, J = 8.0, Ar—H); GC-Mass (m/e, (%)): 203 (M^+, 37), 204 (M + 1, 32), 160 (78), 134 (100), 119 (60), 77 (69), 63 (53), 42 (50).

5-(3-Iodophenyl)-3,4-dimethyl isoxazole (5): White solid; m.p.: 47–49°C; IR (KBr) ν (cm^{-1}): 1663, 1574, 1541, 1061, 613; ^1H NMR ($CDCl_3$): 2.17 (s, 3H, C—CH_3), 2.29 (s, 3H, C—CH_3), 7.21 (t, 1H, J = 7.8, Ar—H), 7.66 (d, 1H, J = 7.8, Ar—H), 7.75 (d, 1H, J = 7.8, Ar—H), 8.05 (s, 1H, Ar—H); GC-Mass (m/e, (%)): 299 (M^+, 12), 300 (M + 1, 10), 231 (M + 2, 18), 203 (28), 103 (100), 144 (42), 76 (56), 50 (35).

5-(2-Furyl)-3,4-dimethyl isoxazole (6): Yellow solid; m.p.: 30–31°C; IR (KBr) ν (cm^{-1}): 1609, 1087; ^1H NMR ($CDCl_3$): 2.17 (s, 3H, C—CH_3), 2.27 (s, 3H, C—CH_3), 6.53 (q, 1H, J = 1.7, furfuran-H), 6.80 (d, 1H, J = 3.4, furfuran-H), 7.54 (d, 1H, J = 3.4, furfuran-H); GC-Mass (m/e, (%)): 163 (M^+, 100), 164 (M + 1, 10), 95 (20), 134 (16), 66 (14).

3,4-Dimethyl-5-(2-thienyl) isoxazole (7): Yellow solid; m.p.: 75–76°C; IR (KBr) ν (cm^{-1}): 1612, 1225, 842; ^1H NMR ($CDCl_3$): 2.16 (s, 3H, C—CH_3), 2.28 (s, 3H, C—CH_3), 7.15 (dd, 1H, J = 3.8, J = 4.9, thiophen-H), 7.46 (d, 1H, J = 5.2, thiophen-H), 7.47 (d, 1H, J = 3.61, thiophen-H); GC-Mass (m/e, (%)): 179 (M^+, 100), 180 (M + 1, 26), 181 (M + 2, 18), 136 (22), 111 (66).

3,4-Dimethyl-5-(3-thienyl) isoxazole (8): Yellowish solid; m.p. 81–82°C; IR (KBr) ν (cm^{-1}): 1616, 1222, 847; ^1H NMR ($CDCl_3$): 2.16 (s, 3H, C—CH_3), 2.28 (s, 3H, C—CH_3), 7.44 (dd, 1H, J = 2.9, J = 5.0, thiophen-H), 7.49 (dd, 1H, J = 1.1, J = 5.0, thiophen-H), 7.67 (dd, 1H, J = 1.0, J = 2.8, thiophen-H); GC-Mass (m/e, (%)): 179 (M^+, 100), 180 (M + 1, 15), 181 (M + 2, 5), 136 (10), 111 (58), 84 (12).

RESULTS AND DISCUSSION

The heterocycles were detached at each of the three stages of thermal decomposition in overall yield to make this an attractive small-scale, one-pot route to these materials[8, 9]. Results of the thermolysis of benzyl- and heteroaromatic methyl cobaloximes are shown in Table-1. The difference in yield of isoxazoles is attributed to the greater stability of the heteroaromatic methyl radicals than benzyl radicals, which were associated with a lifetime sufficiently long to permit interception by the dimethylglyoxime mono-anion under the conditions of the thermolysis.

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