Ring Cleavage of 3,5-Disubstituted 2-Isoxazolines by Molybdenum Hexacarbonyl and Water to β-Hydroxy Ketones

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An efficient method for preparing β-hydroxy ketones from 2-isoxazolines by N-O bond cleavage promoted by molybdenum hexacarbonyl is described.

Isoxazolines are increasingly used as precursors for the synthesis of various classes of acyclic compounds. The so-called „isoxazoline route" (cycloaddition-reductive opening) has become a standard tool for natural products synthesis.[1,2]

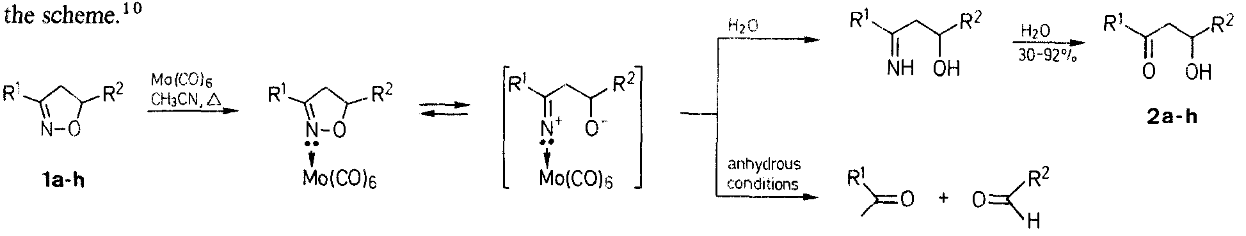
Among the vast array of functionalities which can be revealed by reductive cleavage of the heterocyclic ring, γ-amino alcohols and β-hydroxy ketones are the most relevant ones. The ability of an isoxazoline to serve as a masked β-amino alcohol has been amply demonstrated.[3]

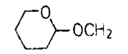
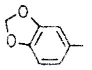
On the other hand the transformation of an isoxazoline to a β-hydroxy ketone, originally pioneered by Torsell[4] and occasionally by others,[5,6] was then greatly expanded mainly by Curran[7] and Kozikowski.[8] A number of procedures are found in the literature to bring about this operation but the most precise conditions for converting isoxazolines to β-hydroxy ketones consist in their hydrogenation in the presence of W-2 Raney nickel and four equivalents of aluminium chloride in 5:1 methanol-water solution. However these conditions cannot be applied to molecules containing additional unsaturation or protective groups sensitive to hydrogenolysis. In such cases selective N-O bond cleavage can be achieved by chemical reduction promoted by Ti^{3+}.[9]

More recently it has been reported that N-O bond cleavage of isoxazolines occurred in the presence either of iron pentacarbonyl, both thermally or photochemically, of molybdenum hexacarbonyl to produce a mixture of products depending on substituent pattern.[10] We have now successfully utilized molybdenum hexacarbonyl in wet acetonitrile for cleavage of a 3,5-disubstituted isoxazole, obtaining a clean transformation to the corresponding β-enamino ketone in high yield.[11]

This result prompted us to apply the same reaction condition to 3,5-disubstituted isoxazolines **1a–h**. We have found that simply refluxing these compounds in the presence of 0.5 eq. of molybdenium hexacarbonyl in wet acetonitrile resulted in smooth cleavage of the N-O bond forming the corresponding β-hydroxy ketones **2a–h**.

The ring cleavage is best explained by the mechanism outlined in the scheme.[10]



1, 2	R^1	R^2
a	$(CH_3)_2C(OH)$	n-C_8H_{17}
b	$(CH_3)_2C(OH)$	$C_6H_5CH_2$
c	$CH_3OOC(CH_2)_2$	n-$C_{10}H_{21}$
d	$HOOC(CH_2)_2$	n-$C_{10}H_{21}$
e	$CH_3OOC(CH_2)_2$	n-$C_{12}H_{25}$
f	CH_3CH_2	
g		$(CH_3)_2C(OH)$
h	$CH_3(CH_2)_5$	(Z)-$CH_3(CH{=}CH)$

The complex initially formed between the isoxazolines and molybdenum hexacarbonyl undergoes N-O bond cleavage to give a nitrene-complex. This complex undergoes retroaldol cleavage in the absence of water, while in the presence of water, it is converted to a β-imino-alcohol through protonation-reduction, which is subsequently hydrolyzed to the β-hydroxy ketone.

A molar ratio of 1 : 0.5 [substrate/molybdenum hexacarbonyl] is enough to complete the reaction because the $[Mo^{2+}(CO)_5]$ species is also taking part in the N-O ring cleavage.

Table. Isoxazolines **1** and Their Cleavage Products **2**

Compound	m.p. (°C)	Yield[a] (%)	Molecular Formula[b] or Lit. m.p. (°C)	IR ($CHCl_3$) ν (cm^{-1})	^1H-NMR ($CDCl_3$/TMS)[c] δ (ppm)
1a	oil	85	$C_{14}H_{27}NO_2$ (241.4)	3400, 1600	0.9 (br t, 3H); 1.25 (br s, 14H); 1.47 (s, 6H); 2.5 (br, 1H); 2.9 (ddd, 2H, J = 17, 10 and 8 Hz); 4.3–4.75 (m, 1H)
1b	103–105	70	$C_{13}H_{17}NO_2$ (219.3)	3400, 1600, 1590	1.37 (s, 6H); 2.4 (br s, 1H); 2.5–2.9 (m, 4H); 4.8 (m, 1H); 7.2 (s, 5H)
1c	51–52		[12]	–	–
1d	94–95[d]		[12]	–	–
1e	74–75	72	$C_{19}H_{35}NO_3$ (325.5)	1740, 1610	0.9 (br t, 3H); 1.1–1.6 (m, 22H); 2.5–3.0 (m, 6H); 3.7 (s, 3H); 4.6 (m, 1H)
1f	oil	70	[13]	1610	1.1 (t, 3H, J = 7 Hz); 1.3–1.9 (m, 6H); 2.4 (q, 3H, J = 7 Hz); 2.9–3.1 (m, 2H); 3.3–3.45 (m, 2H); 3.5–3.9 (m, 2H); 4.5–4.8 (m, 2H)
1g	93–94	65	$C_{13}H_{15}NO_4$ (249.3)	3400, 1600, 1590	1.2 (s, 3H); 1.35 (s, 3H); 2.1 (s, 1H); 3.1–3.37 (m, 2H); 4.3–4.6 (m, 1H); 5.6 (s, 2H); 6.6–7.25 (m, 3H)
1h	oil	76	$C_{12}H_{21}NO$ (195.3)	1650, 1620	0.9 (br t, 3H); 1.1–1.5 (m, 8H); 1.7 (d, 3H, J = 6 Hz); 2.35 (t, 2H, J = 7 Hz); 3.0 (ddd, 2H, J = 17.10 and 8 Hz); 5.0–5.8 (m, 3H)
2a	oil	55	$C_{14}H_{28}O_3$ (244.4)	3400, 1710	0.9 (br t, 3H); 1.25 (br s, 14H); 1.37 (s, 6H); 2.7 (m, 2H), 3.05 (br, 1H); 3.7 (br, 1H); 4.05 (br, 1H)
2b	oil	60	$C_{13}H_{18}O_3$ (222.3)	3400, 1710	1.37 (s, 6H); 2.76–3 (m, 4H); 3.3 (br, 2H); 4.3 (m, 1H); 7.2 (s, 5H)
2c	52–54	90	$C_{17}H_{32}O_4$ (300.4)	3400, 1740, 1700	0.9 (br t, 3H); 1.1–1.6 (m, 20H); 2.5–3.0 (m, 5H); 3.6 (s, 3H); 4.05 (m, 1H)
2d	90–91	80	$C_{16}H_{30}O_4$ (286.4)	3400, 1700	0.9 (br t, 3H); 1.07–1.5 (m, 20H); 2.65 (m, 4H); 4.05 (m, 1H); 5.87 (br, 2H)
2e	50–51	90	$C_{19}H_{36}O_4$ (328.5)	3400, 1740, 1700	(0.9 (br t, 3H); 1.1–1.6 (m, 24H); 2.4–2.8 (m, 5H); 3.6 (s, 3H); 4.05 (m, 1H)
2f	oil	92	$C_{11}H_{20}O_4$ (216.3)	3400, 1710	1.05 (t, 3H, J = 7 Hz); 1.3–1.97 (m, 6H); 2.3–2.75 (m, 4H); 3.3–4.0 (m, 5H); 4.02–4.37 (br, 1H); 4.5 (br s, 1H)
2g	oil	30	$C_{13}H_{16}O_5$ (252.3)	3400, 1670, 1600	1.25 (s, 3H); 1.3 (s, 3H); 2.1 (s, 1H); 2.9–3.15 (m, 2H); 3.7 (br, 1H); 4.0 (m, 1H); 5.6 (s, 2H); 6.6–7.25 (m, 3H)
2h	oil	70	$C_{12}H_{22}O_2$ (198.3)	3400, 1700	0.9 (br t, 3H); 1.1–1.5 (m, 8H); 1.7 (d, 3H, J = 6 Hz); 2.3–2.7 (m, 4H); 2.95 (br s, 1H); 4.7–5.0 (m, 1H); 5.2–5.7 (m, 2H)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.10, N ±0.33.
[c] Recorded on a Bruker WP80 spectrometer.
[d] Prepared by saponification of **1c**.

The yields are usually lower than obtained by hydrogenolytic conditions, but we believe that this procedure is both more efficient and experimentally more convenient than Ti^{3+} reduction, in virtue of its simplicity, rapidity and effectiveness.

The starting isoxazolines were prepared by cycloaddition on the appropriate alkenes of nitrile oxides generated from the corresponding nitroalkanes[14] (**1a–f**) of from the hydroximoyl chloride[15] (**1g–h**).

Ring opening to β-hydroxy-ketones; Typical Procedure:

To a mixture of isoxazoline (0.1 mol) in acetonitrile (50 ml) containing water (50 drops), molybdenum hexacarbonyl (13 g, 0.05 mol) is added and heated at reflux until no more starting material is detected by TLC (silica gel, eluent: ethyl acetate/*n*-hexane; 1:1). On completion of the reaction, silica gel (10 g) is added to the cooled mixture. After removal of the solvent *in vacuo* (20 mbar), the residue is chromatographed on a silica gel column with ethyl acetate as eluent to yield pure β-hydroxy ketones (Table).

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