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RUTHENIUM CATALYZED OXIDATION OF ALCOHOLS TO ALDEHYDES AND KETONES BY AMINE-N-OXIDES

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We have for several years been looking for a mild, transition metal catalyzed method for the oxidation of alcohols to carbonyl compounds. The hope was to find a catalytic procedure which employed an oxidant that was both inexpensive and unreactive toward most organic functional groups. A variety of likely oxidants were explored with every transition metal except technetium and gold. Some success was realized with tert-butyl hydroperoxide using either vanadium or ruthenium catalysts,[1a] and with Chloramine-T using ruthenium catalysts.[1b] We then discovered a much more effective combination. Under ruthenium catalysis, amine-N-oxides rapidly oxidize alcohols to aldehydes and ketones at room temperature (Table I).

Examination of Table I reveals that the results with olefinic alcohols are variable. Allylic alcohols are generally good substrates, whereas homoallylic cases (15, 16, and 17) are unpredictable and tend to give low conversions. For example, cholesterol is recovered completely unchanged from these oxidations (case 15). Moreover, when cholesterol, or other 3β-hydroxy-Δ^5-steroids, are present with an alcohol which normally reacts smoothly, they inhibit the oxidation of that alcohol. We speculate that certain homoallylic alcohols (note case 17 is an exception) form very stable alkoxyolefin complexes with ruthenium (II?) and thus tie up the catalyst; in the case of cholesterol this would presumably require prior isomerization to the 3α-hydroxy epimer.

As exemplified by the steroidal examples, simple 2° alcohols afford excellent yields of ketones. The crude yields were quantitative and those reported are for the recrystallized substances. With 1° alcohols aldehydes are produced in good yield, especially if more dilute conditions are used (compare cases 2 and 3).

Table I. Ruthenium Catalyzed Oxidation of Alcohols by N-Methylmorpholine-N-Oxide^{a}

	Alcohol	% Yield of Ketone or Aldehyde^{b}
1)	cyclododecanol	100
2)	1-dodecanol	80
3)	"	90^{c}
4)	citronellol	79
5)	geraniol	81^{d}
6)	*d*-carveol	$\underline{94}$
7)	*trans*-pinocarveol	80
8)	2-methyl-1-hepten-3-ol	73(18)
9)	*E*-3-octen-5-ol	75(15)
10)	1-nonen-3-ol	45(55)
11)	5α-cholestan-3β-ol^{e}	$\underline{87}$
12)	testosterone^{e}	$\underline{94}$
13)	17β-hydroxy-5α-Δ²-androstene^{e}	$\underline{83}$
14)	3α-hydroxy-5α-Δ¹-cholestene^{e}	$\underline{87}$
15)	cholesterol^{e}	0(100)
16)	1-nonen-4-ol	7(80)
17)	*ℓ*-isopulegol	73(17)
18)	*threo*-2-thiophenyl-cyclododecanol	$\underline{73}$
19)	4-dimethylaminocyclohexanol	65(25)
20)	β-3-indolylethanol	trace(95)
21)	3-hydroxy benzyl alcohol	65
22)	17β-hydroxy-5α-androstane-3-ethylene ketal^{e}	$\underline{86}$

a) Unless otherwise noted, these oxidations were carried out on from 1 to 100 mmol scales as described in detail for the oxidation of 1/10 mole of *d*-carveol (the most common scale was 2 mmol). b) The underlined figures refer to isolated yields (either recrystallization or distillation), otherwise yields were determined by glc relative to an internal standard. The figures in parentheses indicate the approximate yield of recovered, unreacted alcohol. c) Twice the volume of acetone solvent (i. e., 20 ml/mmol instead of 10 ml/mmol) was used in this case. d) Pure **geranial** (i. e., no *cis*-*trans* isomerization). e) Because of solubility problems, twice the usual volume of acetone solvent (as in case 3 above) was employed with all the steroid examples.

The following procedure reveals how the oxidation is performed on a 1/10 mole scale: a 2 l. one-necked round bottomed flask equipped with a magnetic stirrer and a drying tube was charged with 1 l. of dry acetone,[2] 15. 2 g (0. 1 mol) of *d*-carveol and 23. 4 g (0. 2 mol) of anhydrous N-methylmorpholine-N-oxide.[3] To this solution 800 mg (0. 84 mmol) of $RuCl_2(P\phi_3)_3$ (Strem Chem. Inc.) was added in one portion and the resulting gold solution was stirred for 2 hr at room temperature, after which time the reaction mixture was dark brown. The flask was attached to a rotary evaporator and most of the acetone was removed. The residue was transferred to a separatory funnel with the aid of several portions of CH_2Cl_2 (500 ml total). The organic layer was washed twice with 200 ml portions of 4% HCl, once with 200 ml of water, dried (Na_2SO_4) and concentrated to give 15. 3g of a brown oil. Distillation afforded 14. 1 g (94%) of *d*-carvone (bp 96–99°/10 mm) which was > 99% pure by glc.

Catalyst, N-oxide, and solvent, the three variables in this new oxidation procedure, were explored in detail. Although almost every transition metal was tried, only ruthenium compounds were active as catalysts. Even some ruthenium species were catalytically inactive (e. g., $RuO_2 \cdot xH_2O$, $Ru(acac)_3$, and $RuCl_3(NO)(P\phi_3)_2$). N-Methylmorpholine-N-oxide[4] was far superior to other N-oxides[5] tried. N,N-Dimethyl aniline-N-oxide, trimethyl amine-N-oxide, and N,N-dimethyl-n-dodecyl amine-N-oxide were all reactive but the oxidations stopped at 40–70% conversion. Pyridine-N-oxide and four substituted analogs were inactive as oxidants. Only acetone, DMF and HMPT were found to be good solvents for this reaction. Table II shows the outcome of oxidations of a 2° and 1° alcohol in both acetone and DMF using three different ruthenium catalysts. Hydrated ruthenium trichloride ($RuCl_3 \cdot xH_2O$) is the least expensive catalyst, but its poor solubility in acetone leads to lower yields and limits its use to DMF. In those instances where separation of the product from DMF would be a problem, the use of either $RuCl_2(P\phi_3)_3$ or $Ru_3(CO)_{12}$ as catalyst, and of acetone as solvent is recommended. In both acetone and DMF the activity of the catalyst diminishes as the reaction proceeds. In acetone a dark brown precipitate is usually formed; in DMF there is no precipitate, but activity is lost nonetheless.

Table II. Effect of Ruthenium Catalyst and Solvent[a]

Catalyst[b]	cyclododecanol as substrate % yield in acetone	cyclododecanol as substrate % yield in DMF	1-dodecanol as substrate % yield in acetone	1-dodecanol as substrate % yield in DMF
$RuCl_2(P\phi_3)_3$	100	100	80	78
$Ru_3(CO)_{12}$	100	100	79	80
$RuCl_3 \cdot xH_2O$	80	100	60	77

a) All reactions were run on a 2 mmol scale with N-methylmorpholine-N-oxide (4 mmol) as the oxidant. The amount of catalyst used was constant based on ruthenium content (i. e., 1/125 mmole Ru : mmol of alcohol). b) All three catalysts were purchased from Strem Chemicals Inc.

The mechanism of these oxidations probably involves formation of a ruthenium alkoxide which undergoes β-elimination to produce the carbonyl compound and a ruthenium hydride. The ruthenium hydride (or its equivalent) could be oxidized by the amine-N-oxide and then the cycle could be repeated. Although ruthenium catalyzed dehydrogenations of alcohols have been reported previously,[6] the conditions required were much more vigorous (i. e., temperatures of ~200°C). In fact, to the best of our knowledge, this new oxidation provides one[7] of the most facile examples of transition metal catalyzed dehydrogenation of alcohols yet reported. Determination of the precise role(s) played by the N-oxide in accelerating these reactions will require further study. However, it is worth pointing out that amine-N-oxides are rather basic substances and readily coordinate with metals. N-Methylmorpholine-N-oxide, in particular, has unique possibilities as a ligand.

Whereas most oxidants react more rapidly with 2° than with 1° alcohols, this new catalytic reagent shows a preference for 1° alcohols. For example, 1-decanol is oxidized three times faster than 2-dodecanol. In fact, the oxidations of 1° alcohols were mildly exothermic even on a 2 mmol scale; this might explain why dilution improved the yield (case 3, Table I). Benzylic and allylic alcohols are more reactive than their saturated counterparts. Thus, α-phenethyl alcohol reacts at 4 times the rate of 2-dodecanol. Both cis- and trans-4-tert-butyl cyclohexanol are oxidized at comparable rates, indicating little discrimination between axial and equatorial alcohols.

Like the Moffatt oxidation, this new reagent reveals a tolerance for functional groups which are sensitive to oxidation (cases 18, 19, and 21). However, unlike the Moffatt reagent it fails in the presence of indoles (case 20); the indole moiety seems to inhibit the ruthenium catalyst, since in case 20 the starting alcohol was recovered largely unchanged.

As the first mild homogeneous catalytic oxidation of alcohols to aldehydes and ketones, this new procedure should prove a valuable addition to the methods for oxidizing alcohols.

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References

1. a) K. Akashi, A. O. Chong, K. Oshima and K. B. Sharpless, unpublished results; b) K. Oshima and K. B. Sharpless, unpublished results.
2. Reagent grade acetone was allowed to stand over drierite for ~3–10 hr and then distilled and stored over drierite. When DMF was employed as solvent it was simply stored over 4Å molecular sieves prior to use.
3. Hydrated N-methyl morpholine-N-oxide (Eastman Kodak) was dried for 2–3 hr at 90° under high vacuum. Use of the hydrated N-oxide led to slower and often incomplete oxidations, especially in acetone.
4. Chemists at Upjohn were the first to discover the unique effectiveness of this N-oxide as the oxidant in a transition metal catalyzed process (see V. VanRheenen, R. C. Kelly, and C. Y. Cho, Tetrahedron Lett., in press). We are indebted to Dr. Robert Kelly for informing us of their results (Os catalyzed conversion of olefins to vicinal diols) prior to publication.
5. The anhydrous N-oxides were used in all cases.
6. a) Y. Sasson and J. Blum, Tetrahedron Lett., 2167 (1971); b) S. L. Regan and G. M. Whitesides, J. Org. Chem., **37**, 1832 (1972).
7. Another effective catalytic system involves the potent oxidant RuO_4 (for a recent review, see "Oxidation in Organic Chemistry," Part B, W. S. Trahanovsky, Ed., Academic Press, 1973, Chapter 4).