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SELECTIVE CATALYTIC OXIDATION OF ALCOHOLS USING HYDROGEN PEROXIDE

J. H. Wynne^a; C. T. Lloyd^a; D. R. Witsil^a; G. W. Mushrush^a; W. M. Stalick^a

^a Department of Chemistry, George Mason University, Fairfax, VA, USA

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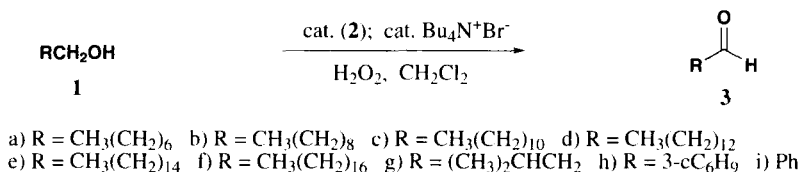
Submitted by J. H. Wynne, C. T. Lloyd, D. R. Witsil, G. W. Mushrush and W. M. Stalick*
(06/13/00)

Department of Chemistry
George Mason University, Fairfax, VA 22030, USA

The incorporation of a variety of aldehydes in the synthesis of many biologically active molecules is well documented.¹ There are many examples in the current literature, which employ copper or chromium salts that are either low yielding, non-atom economical, require complex starting materials, or involve multi-step syntheses.² Larock states that most general aldehyde forming oxidation reactions require stoichiometric quantities of an inorganic oxidant and proceed under non-neutral or extreme thermal conditions and therefore limit the substrates that can be subjected to oxidative processes.³ Although much attention has been given to the use of catalytic organometallic ruthenium species in the oxidation process, most are ineffective on aliphatic alcohols, frequently leading to over-oxidation to the carboxylic acids.⁴ Drago made use of an oxotriruthenium complex oxidation catalyst,

with varying success, on alcohols of low molecular weight, when employed under 40 psi of oxygen.⁵ Our group recently required a variety of aldehydes for use in other syntheses.⁶ We now report the synthesis of a triruthenium compound and its use as a catalyst in a novel method for the synthesis of a variety of aldehydes. It provides a new, efficient oxidative method, which proceeds under neutral, mild conditions and complements existing non-metallic oxidative reactions such as the Swern oxidation, which proceeds under mild, basic conditions.⁷ The results of these experiments are summarized in **Table 1**.

We selected hydrogen peroxide as the oxidant of choice due to its ability to function under ambient mild conditions as well as its low cost. Not only does this method exhibit atom-economical properties, but it also eliminates the need for disposal of the toxic heavy metal expended waste; in our case water is the only by-product from this process. The oxotruthenium catalyst, $[\text{Ru}_3\text{O}(\text{OAc})_6(\text{MeOH})_3]^+ \text{OAc}^-$ (**2**), was synthesized in our lab according to a modified procedure reported in the literature.^{8,9} In our hands, the Fouda⁸ and Bergbreiter⁹ methods afforded the desired product in high purity, albeit low yield. Their methods of purification appeared inefficient and moreover, involved the use of expensive ion exchange resins. We discovered that the crude complex could easily be purified in high yield, through simple crystallization.



An array of primary alcohols were subjected to a catalytic amount of tetrabutylammonium bromide (a PTC), and an excess of hydrogen peroxide. The reaction proceeded efficiently under neutral, ambient conditions in the presence of the trioxoruthenium catalyst (**2**). The progress of the reaction was monitored by periodic GC sampling employing an internal standard. Upon completion of the reaction, the ruthenium and phase transfer catalysts were easily removed by filtration through a plug of silica gel. The desired aldehydes were obtained in moderate yield upon purification. A variety of straight-chain aliphatic alcohols were oxidized in 54-72% yields (trials 1-6). When a branched alcohol, isoamyl alcohol, was subjected to the same reaction conditions, the reaction proceeded in a similar yield (Entry 7). When a primary alcohol containing a non-conjugated olefin functionality was subjected to the same reaction conditions, the yield was slightly lower; with very little epoxide formation, confirming the mild selectivity of this method as seen in Entry 8. Furthermore, when benzyl alcohol was subjected to the same reaction conditions, benzaldehyde was formed in high yield (Entry 9). Kinetic studies are currently underway to provide additional insight into this oxidation process.

Table 1: Selective Oxidation of Primary Alcohols with Hydrogen Peroxide.

Entry	Aldehyde	Yield (%)	mp (bp) (°C)	lit. (°C)	Time (hrs)	¹ H NMR (δ)
1	3a	67	166-167	168-170 ^a	24	9.80 (s, 1H), 2.47 (t, 2H), 2.28-2.21 (m, 10H), 1.02 (t, 3H)
2	3b	64	209	207 ^b	24	9.76 (s, 1H), 2.45 (t, 2H), 1.65-1.56 (m, 12H), 0.90 (t, 3H)
3	3c	70	41-42	43 ^c	24	9.79 (s, 1H), 2.42 (t, 2H), 1.67-1.61 (m, 14H), 1.15 (t, 3H)
4	3d	72	24-26	23 ^d	24	9.77 (s, 1H), 2.44 (t, 2H), 1.65-1.60 (m, 16H), 0.88 (t, 3H)
5	3e	61	31-33.5	32-34 ^e	24	9.76 (s, 1H), 2.44 (t, 2H), 1.66-1.59 (m, 18H), 0.86 (t, 3H)
6	3f	54	35-37	37-38 ^f	24	9.73 (s, 1H), 2.45 (t, 2H), 1.67-1.60 (m, 20H), 0.78 (t, 3H)
7	3g	69	(93)	(92) ^g	24	9.76 (s, 1H), 2.31 (d, 2H), 2.25-2.18 (m, 1H), 0.98 (d, 6H)
8	3h	45	(162)	(164) ^h	24	9.47 (s, 1H), 5.58 (s, 2H), 2.75-1.12 (m, 7H)
9	3i	96	(180)	(178-180) ⁱ	2	10.02 (s, 1H), 7.90 (d, 2H), 7.66-7.61 (m, 1H), 7.56-7.51 (m, 2H)

a) Ref. 12 b) Ref. 13 c) Ref. 14 d) Ref. 11 e) Ref. 15 f) Ref. 16 g) Ref. 17 h) Ref. 18 i) Ref. 19

EXPERIMENTAL SECTION

Ruthenium (III) chloride hydrate was obtained from Alfa Aesar in 99.9% purity and was used without further purification. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were taken on a Bruker 300 MHz spectrometer. FTIR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. GC analyses were performed on a Hewlett-Packard 6890 capillary chromatograph with FID (0.32 mm x 30 m, HP-5, 0.25 μm, column programmed to hold 100° for one min. with a 20° ramp to 250°). UV/vis spectra were recorded on a Hewlett-Packard 8453 spectrophotometer equipped with an HP power station.

tris(Methanol)hexa-μ-acetato-μ₃-oxo-triruthenium(II) Acetate (2).- To a 50 mL round-bottom flask fitted with a reflux condenser and a magnetic stir bar was added RuCl₃·3H₂O (0.50 g, 2.085 mmol), NaOAc (1.00 g, 12.19 mmol), then 12.5 mL of glacial acetic acid and 12.5 mL of absolute ethanol. The stirred solution was heated and allowed to reflux vigorously for 4 hr. Heating was stopped, and the resulting solution was allowed to cool to room temperature for 45 min. The cooled solution was diluted with 35 mL of methanol and filtered through a pad of Celite 545® (2.0 cm x 4.6 cm). The resulting dark green solution was then concentrated to form a thick oil by removing the volatiles *in vacuo*, using a rotary evaporator. The viscous, blue-green oil was again diluted with 35 mL of methanol, filtered, and re-concentrated as previously described to ensure complete ligand

exchange. The oil was evaporated further using a vacuum pump for 1 hr to remove any remaining traces of solvent prior to purification. Warm acetone (15 mL) was added and the mixture was mixed thoroughly. The resulting crystalline oxotriruthenium complex, $[\text{Ru}_3\text{O}(\text{OAc})_6(\text{MeOH})_3]^+ \text{AcO}^-$ (**2**), was collected on a Büchner funnel. The crystals were washed with an additional 5 mL of cold acetone, and allowed to dry in air for 10 min. The desired product was obtained in a 70-85% yield with respect to starting ruthenium salt. The subsequent crops contained impurities and were not as effective in the oxidation process. The IR (Nujol) 1715, 1580, 1457, 1377, 1312, 1030; and UV-vis λ_{max} 940 nm (MeOH) are consistent with literature values.¹⁰ We have used the catalyst for periods in excess of six months without signs of deterioration when stored at RT, under nitrogen.

Warning: H_2O_2 (30%) was transferred using a syringe and the reactions were carried out behind an explosion proof safety screen.

Typical Procedure. Tetradecanal (3d).- To a 50 mL round-bottom flask fitted with a condenser and magnetic stir bar was added $[\text{Ru}_3\text{O}(\text{OAc})_6(\text{MeOH})_3]^+ \text{AcO}^-$ (**2**) (0.13 g, 0.23 mmol), 1-tetradecanol (**1**) (1.00 g, 4.66 mmol), tetrabutylammonium bromide (0.15 g, 0.47 mmol), 25 mL CH_2Cl_2 , 3 equivalents of H_2O_2 (30% w/v; 1.60 mL, 13.98 mmol) and tetradecane (0.092 g, 0.047 mmol) as internal standard. The mixture was allowed to stir at room temperature and was monitored by GC sampling. Samples were withdrawn with the aid of a micro glass pipet, deposited onto a 1.5 cm plug of silica gel in a 1 mL glass pipet, and washed with 2 mL of ether to afford a sample suitable for GC injection. The reaction afforded the maximum product after 24 hr. The reaction mixture was filtered through a plug of silica gel (40 μm ; 2.5 cm x 5.0 cm) and washed with ether (3 x 50 mL). The resulting organic layer was dried over MgSO_4 and concentrated using rotary evaporation. The crude product was then purified by Kügelrohr distillation to afford 0.71 g (72%) of the desired tetradecanal. ^1H and ^{13}C spectroscopic data of the aldehydes were consistent with those reported in the literature.¹¹ The catalyst (**2**) can be recovered easily by washing it free from the silica gel onto which it was absorbed, using 100 mL MeOH. Concentration under reduced pressure, and purification by recrystallization as described above, results in a catalyst suitable for reuse in these oxidation reactions.

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