melting point apparatus and are uncorrected. Elemental analyses were obtained on a Perkin-Elmer 240 EA instrument. Mass spectra were carried out on a JEOL JMS-D300 mass spectrometer.

Oxidation of 1. To a solution of trifluoroacetic acid (25 mL) containing 0.1 M lithium chloride was added **1** (1.90 g, 10.0 mmol), lead tetraacetate (7.76 g, 17.5 mmol), and methylene chloride (25 mL). The solution was stirred for 24 h in the dark at room temperature and then quenched with 5% NaOH. The reaction mixture was extracted with three portions of 40 mL of ether, and the organic extracts were combined, washed with saturated aqueous sodium carbonate (3 × 40 mL) and brine (3 × 40 mL), dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure left a mixture of trifluoroacetate adducts which were hydrolyzed by refluxing with 10% aqueous sodium hydroxide for 16 h. The crude mixture was extracted with ether (3 × 40 mL). The ether extracts were combined, washed with brine, and dried over anhydrous magnesium sulfate. Evaporation of solvent produced white solids identified as a mixture of **1**, **3**, and **4**. Separation was completed on a silica gel chromatographic column for the yields of **1** (1.48 g), **3** (80 mg, 0.37 mmol), and **4** (320 mg, 1.60 mmol, 70% yield corrected for recollected starting material). Physical data of **4**: mp 208–208.5 °C; ^{1}H NMR (CDCl$_3$) 1.75–1.80 (3 H, m), 1.93 (1 H, s, OH), 2.05 (1 H, dd, J = 1.5 and 12 Hz), 2.20 (1 H, t, J = 5 Hz), 2.3–2.6 (9 H, m), 2.73 (1 H, m); ^{13}C NMR (CDCl$_3$) 40.74 (t), 42.59 (t), 48.79 (d), 49.49 (d), 50.45 (d), 50.88 (d), 51.54 (d), 51.76 (d), 52.76 (d), 53.38 (d), 55.11 (d), 57.82 (d), 63.41 (d), 98.50 (d); MS, m/z (relative intensity) 200 (M$^+$, 100), 172 (2.5), 159 (3.4), 143 (2.6), 133 (8.6); IR (CDCl$_3$) 3605, 3450 (OH), 2958, and 2867 cm^{-1}. Anal. Calcd for C$_{14}$H$_{16}$O: C, 83.96, H, 8.05. Found: C, 83.95; H, 8.17.

14-Iodohexacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}]tetradecan-10-one (5). To dry benzene (200 mL, freshly distilled over sodium) were added **4** (1.00 g, 5.00 mmol), lead tetraacetate (4.44 g, 10.0 mmol), and iodine (2.54 g, 10.0 mmol) under nitrogen. The solution was heated to reflux for 20 min and then stirred at 70–75 °C for 1.5 h. It was cooled and filtered, and the precipitates were washed with ether. The liquid portions were combined and shaken with saturated sodium thiosulfate (100 mL) until the color of the solution faded. The organic layer was separated, washed with water (2 × 50 mL) and saturated sodium bicarbonate (2 × 50 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure yielded a light yellow oil which was purified by column chromatograph. Compound **5** was collected in 60% yield (1.03 g, 3.15 mmol): mp 77–78 °C; ^{1}H NMR (CDCl$_3$) 1.74 (2 H, s), 1.90 (1 H, dt, J = 7 and 13 Hz), 2.49 (1 H, d, J = 13 Hz), 2.59–2.66 (3 H, m), 2.8–3.1 (3 H, m), 3.16 (3 H, m), 3.41 (1 H, m), 4.03 (1 H, d, J = 2 Hz, CHI); ^{13}C NMR (CDCl$_3$) 31.80 (d, CHI) 43.90 (t), 45.85 (t), 46.24 (d), 47.56 (d), 51.70 (d), 51.98 (d), 53.34 (d), 55.55 (d), 56.16 (d), 57.21 (d), 64.54 (d), 65.21 (d), 227.20 (s, C=O); MS, m/z (relative intensity) 326 (M$^+$, 0.4), 199 (M$^+$ – I, 100), 171 (45), 129 (26), 105 (42), 91 (26); IR (CDCl$_3$) 1738 cm^{-1} (C=O). Anal. Calcd for C$_{14}$H$_{15}$IO: C, 51.55; H, 4.64. Found C, 51.55; H, 4.61.

Hydrolysis of 5. The iodide **5** (1.03 g, 3.15 mmol) was hydrolyzed by refluxing in 10% NaOH for 16 h to yield the hemiketal **6** (640 mg, 3.0 mmol) in 94%: mp 261–262 °C dec; ^{1}H NMR (CDCl$_3$) 1.53 (1 H, dt, J = 3.5 and 11 Hz), 1.70 (2 H, s), 2.07 (1 H, d, J = 11 Hz), 2.20 (1 H, m), 2.30–2.65 (6 H, m), 2.67–2.72 (2 H, m), 2.75–2.80 (1 H, m), 3.87 (1 H, d, J =6 Hz, OH), 4.40 (1 H, t, J = 9.5 Hz); ^{13}C NMR (CDCl$_3$) 33.00 (t), 37.41 (d), 42.84 (t), 47.05 (d), 49.15 (d), 49.77 (d), 51.37 (d), 53.95 (d), 54.12 (d), 54.40 (d), 54.56 (d), 57.35 (d), 77.69 (d), 106.12 (s); MS, m/z (relative intensity) 216 (M$^+$, 100), 198 (9), 188 (11), 175 (12), 171 (24), 170 (24); IR (CDCl$_3$) 3581, 3370 (OH), 2958, and 2871 cm^{-1}. Anal. Calcd for C$_{14}$H$_{16}$O$_2$: C, 77.74; H, 7.45. Found C, 77.48; H, 7.44. The iodide **5** (33 mg, 0.10 mmol) was also hydrolyzed in trifluoroacetic acid/methylene chloride (v/v 1/1) by stirring for 24 h at room temperature to produce **7a** (23 mg) in nearly quantitative yield: mp 291–292 °C dec; ^{1}H NMR (CDCl$_3$) 1.70 (2 H, s), 2.06 (1 H, m), 2.25 (1 H, br s, OH), 2.4–2.7 (5 H, m), 2.87 (2 H, m), 2.9–3.2 (4 H, m), 3.77 (1 H, s, CHOH); ^{13}C NMR (CDCl$_3$) 42.69 (t), 43.27 (d), 46.28 (t), 47.91 (d), 51.58 (d), 52.10 (d), 53.96 (d), 56.44 (d), 57.20 (2 C, d), 59.82 (d), 60.31 (d), 81.23 (CHOH, d), 228.45 (C=O, s); MS, m/z (relative intensity) 216 (M$^+$, 100), 198 (M$^+$ – 18, 33), 170 (34), 129 (60), 121 (52); IR (CDCl$_3$) 3610 (OH) and 1722 (CO) cm^{-1}.

11-Oxohexacyclo[6.6.0.0^{3,7}.0^{4,14}.0^{5,12}.0^{6,10}]tetradecanyl *p*-Toluenesulfonate (7b). In a round-bottom flask a solution of **5** (180 mg, 0.55 mmol) and silver *p*-toluenesulfonate (155 mg, 0.56 mmol) in acetonitrile (13 mL) was stirred at 0 °C for 2 h. The solution was allowed to warm up to room temperature and stirred for another 18 h. It was quenched with water and was extracted with ether. The organic layers were combined, washed, dried, and evaporated as usual. The white solids collected were purified by column chromatography to yield **7b** (147 mg, 0.40 mmol, 72%) and **6** (8.4 mg, 0.04 mmol, 7%). Compound **7b**: mp 141–142 °C; ^{1}H NMR (CDCl$_3$) 1.68 (2 H, m), 1.95 (1 H, dt, J = 7 and 13 Hz), 2.20 (1 H, d, J = 13 Hz), 2.37 (1 H, m), 2.44 (3 H, s), 2.55–2.61 (3 H, m), 2.75–2.90 (3 H, m), 2.90–3.05 (1 H, m), 3.05–3.20 (2 H, m), 4.28 (1 H, d, J = 2 Hz), 7.34 (2 H, d, J = 8 Hz), 7.74 (2 H, d, J = 8 Hz); ^{13}C NMR (CDCl$_3$) 21.56, 42.22, 42.73, 46.21, 47.76, 51.51, 52.09, 53.92, 56.17, 56.76, 57.07, 57.26, 65.73, 90.79, 127.80, 129.74, 133.4, 144.54, 226.83; MS, m/z (relative intensity) 370 (M$^+$, 1.0), 215 (2.8), 198 (100), 170 (30), 155 (10); IR (CDCl$_3$) 1722 (CO), 1601, and 1361 cm^{-1}.

Hexacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}]tetradecane-10,14-dione (2). The oxidation was completed by mildly heating at 55 °C a solution of **6** (500 mg, 2.32 mmol) with potassium dichromate (1.36 g, 4.63 mmol) in 1.0% sulfuric acid (50 mL). The reaction mixture was neutralized with 5% NaOH, followed by extractions with ether. The diketone **2** was purified by column chromatograph, yield 78% (385 mg, 1.80 mmol): mp 293.5–294.5 °C dec; IR (CCl$_4$) 1760 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) 1.85 (2 H, t, J = 1.2 Hz), 2.15 (1 H, dt, J = 8 and 12 Hz), 2.63–2.80 (6 H, m), 2.9–3.1 (3 H, m), 3.38 (2 H, m); ^{13}C NMR (CDCl$_3$) 42.55, 43.20, 46.99, 47.65, 52.31, 54.08, 56.14, 57.35, 223.42 (CO); MS, m/z (relative intensity) 214 (M$^+$, 100), 196 (2.2), 186 (15), 168 (3.5), 158 (5.5), 148 (13). Anal. Calcd for C$_{14}$H$_{14}$O$_2$: C, 78.48; H, 6.59. Found: C, 78.40; H, 6.57.

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Registry No. **1**, 17872-39-8; **2**, 112533-27-4; **3**, 112533-28-5; **4**, 112533-29-6; **5**, 112533-30-9; **6**, 112533-31-0; **7a**, 112533-33-2; **7b**, 112533-32-1.

Supplementary Material Available: 2D ^{1}H–^{13}C NMR COSY spectrum of **4** (1 page). Ordering information is given on any current masthead page.

Optimization of a Simple System for the Oxidation of Octan-2-ol with Sodium Bromate, Mediated by Ruthenium Tetraoxide Generated in Situ

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1. Introduction

Ruthenium tetraoxide has, for many years, been recognized as a powerful oxidizing agent for the conversion of secondary alcohols to ketones.[1] Initially it was used in stoichiometric amounts[2–4] as an alternative to the more toxic and expensive compound, osmium tetraoxide, since,

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(1) Lee, D. G.; van den Engh, M. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1973; Part B, Chapter 4, p 177.

(2) Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682.

(3) Beynon, P. J.; Collins, P. M.; Doganges, P. T.; Overend, W. G. *J. Chem. Soc. C* **1966**, 1131.

(4) Lee, D. G.; Spitzer, U. A.; Cleland, J.; Olson, M. E. *Can. J. Chem.* **1976**, *54*, 2124.

0022-3263/88/1953-1103$01.50/0

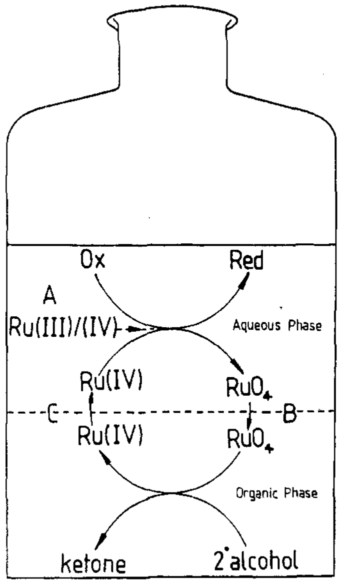

Figure 1. Schematic diagram illustrating the processes which occur in the cyclic, biphasic system during the oxidation of a water-insoluble, secondary alcohol using an oxidizing agent (Ox) mediated by RuO_4, generated in situ.

like osmium tetraoxide, it was found to generate no side-reaction products, a problem frequently encountered with other common oxidants such as chromium and methyl sulfoxide reagents.[5]

The search for cheaper, more convenient and lower risk procedures for alcohol oxidation led to the development of cyclic systems in which catalytic amounts of RuO_4 were generated in situ by using mainly periodate[6-9] or hypochlorite[10] as the stoichiometric oxidizing agent. Although some work was carried out in a single aqueous phase, the majority of systems employed an aqueous/organic biphasic medium in which a catalytic amount of RuO_4 was produced in the aqueous phase but would subsequently partition largely into the organic phase, thus allowing it to oxidize water-insoluble secondary alcohols to ketones.

Following a renewed interest in these biphasic, catalytic systems, recent attempts have been made to improve the rate of alcohol oxidation and increase the product yield by using phase-transfer catalysts[11,12] and anticomplexing agents such as acetonitrile.[5] In addition, some workers have investigated the use of cheaper oxidizing agents including sodium bromate[12] and electrochemically generated $Cl_2/[Cl^+]$[13] as an alternative to periodate or hypochlorite.

We have carried out a detailed study of the factors affecting the rate of oxidation of a water-insoluble secondary alcohol (octan-2-ol) in a typical cyclic, biphasic system, mediated by RuO_4, using sodium bromate as the stoichiometric oxidizing agent. In this paper we report our results and discuss the optimization of this simple system. The use of oxidizing agents other than sodium bromate is also discussed.

2. Results and Discussion

2.1. Principles of the Biphasic System. Figure 1 represents schematically the processes which occur within the biphasic system. Initially, a Ru(III) or Ru(IV) starting material (A) is oxidized in the aqueous phase by the oxidizing agent (Ox) to RuO_4 (B) which then partitions between the two phases, favoring strongly the organic phase. The RuO_4 oxidizes the non-water-soluble secondary alcohol present only in the organic phase and in doing so, is itself reduced to an insoluble Ru(IV) species (C) probably a partially hydrated form of RuO_2. When this Ru(IV) species is transferred into the aqueous phase it is reoxidized to RuO_4 by the excess oxidizing agent present. The RuO_4 then partitions into the organic phase and the catalytic cycle involving RuO_4 mediating the oxidation of the secondary alcohol by the strong oxidizing agent continues (see Figure 1).

It has been suggested[5,12] that the addition of phase-transfer catalysts such as Aliquat 336 to the biphasic system will produce an improved rate of oxidation of the alcohol by allowing the oxidizing agent (Ox) to pass into the organic phase, thereby facilitating reoxidation of the Ru(IV) species to RuO_4. However, in our work, we found no significant increase in the rate of oxidation of the alcohol in the presence of a phase-transfer catalyst such as Aliquat 336.

2.2. Ruthenium Starting Materials. The function of the Ru starting material is to generate a fixed amount of RuO_4 which initiates the catalytic cycle. It is essential, therefore, that it is rapidly and completely oxidized to RuO_4 by the oxidizing agent.

Many of the biphasic systems[8,10-12] of the type described in section 2.1 employed $RuCl_3{\cdot}nH_2O$ as the Ru starting material; however, under certain conditions, this material can cause problems. For example, we have found that when $RuCl_3{\cdot}nH_2O$ (0.014 mmol) is added to unbuffered 0.8 mol dm^{-3} $NaBrO_3$ solution (7.5 cm^3) at pH 5, an orange solution is obtained instead of the usual yellow/green color of RuO_4. Addition of CCl_4 (15 ml) to the solution followed by vigorous stirring produces only a slight green coloration of the CCl_4 layer due to RuO_4 whereas the aqueous layer remains orange. The absorption spectrum of this orange-colored solution shows a broad peak (λ_{max} 470 nm) as well as characteristic peaks due to RuO_4 (λ_{max} 310 and 385 nm).

A test system (see section 4.2.3) was used to measure the % RuO_4 generated when $RuCl_3{\cdot}nH_2O$ (dissolved in 0.5 mol dm^{-3} H_2SO_4) was injected into a strong $Ce(SO_4)_2$ solution.[14] Once again, the orange-colored species appeared to be generated and its color persisted for at least 1 h. Despite the generation of this orange-colored species, RuO_4 was produced, albeit slowly, and the measured overall % RuO_4 was found to be high, ca. 84%. From this work it appears that $RuCl_3{\cdot}nH_2O$ reacts with strong oxidizing agents such as BrO_3^- and Ce^{4+} in acidic solution to give, initially, an orange species, possibly a Ru(IV) chloro aquo complex,[15] which has some resistance to corrosion but is gradually oxidized completely to RuO_4 by the oxidizing agent.

Octan-2-ol (6 mmol) was injected into the biphasic, aqueous/CCl_4 system containing the orange species in $NaBrO_3$ to illustrate this further, and its rate of oxidation to octan-2-one was found to be very slow (complete conversion was achieved in ca. 12 h). Interestingly, where $RuCl_3{\cdot}nH_2O$ was used successfully by previous workers, the

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[5] Morris, P. E.; Kiely, D. E. *J. Org. Chem.* **1987**, *52*, 1149.

[6] Nakato, H. *Tetrahedron* **1963**, *19*, 1959.

[7] Parikh, V. M.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 3452.

[8] Caputo, J. A.; Fuchs, R. *Tetrahedron Lett.* **1967**, 4729.

[9] Moriarty, R. M.; Gopal, H.; Adams, T. *Tetrahedron Lett.* **1970**, 4003.

[10] Wolfe, S.; Hasan, S. K.; Campbell, J. R. *J. Chem. Soc. D* **1970**, 1420.

[11] Carlsen, H. J.; Tsutomu, K.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

[12] Yamamoto, Y.; Suzuki, H.; Moro-oka, Y. *Tetrahedron Lett.* **1985**, *26*, 2107.

[13] Torii, S.; Inokuchi, T.; Sugiura T. *J. Org. Chem.* **1986**, *51*, 155.

[14] Mills, A.; Giddings, S.; Patel, I. *J. Chem. Soc., Faraday Trans. 1* **1987**, 83, 2317.

[15] Seddon, E. A.; Seddon, K. R. *The Chemistry of Ruthenium*; Elsevier: Oxford, 1984; Chapter 8, Section 8.3.

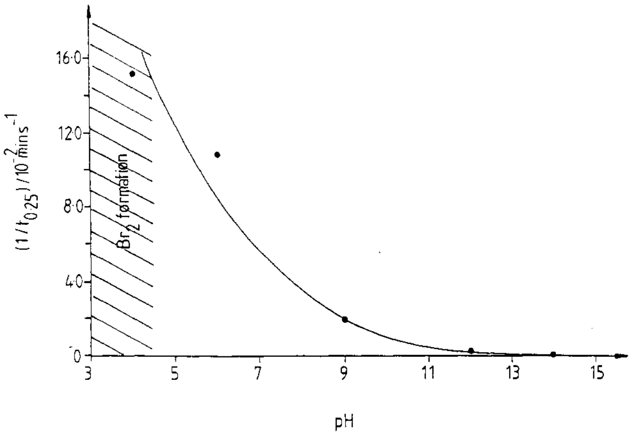

Figure 2. Plot of $1/t_{0.25}$ versus pH over the range pH 4 to 14. ($t_{0.25}$ = time for 25% of the octan-2-ol to be oxidized).

reactions were carried out by using a neutral or alkaline aqueous phase. However, under these conditions, $RuCl_3{\cdot}nH_2O$ is unstable, undergoing rapid and extensive hydrolysis and air oxidation to form $RuO_2{\cdot}xH_2O$. Therefore, in this other work it was likely that the latter Ru compound and not $RuCl_3{\cdot}nH_2O$ was the effective starting material. As a result, under the pH conditions, where the orange-colored species is formed (usually pH <5),[15] $RuCl_3{\cdot}nH_2O$ is not a good starting material to use in the biphasic system.

$RuO_2{\cdot}xH_2O$ is a common, relatively cheap Ru compound and has several advantages over $RuCl_3{\cdot}nH_2O$ as a starting material: (i) it is stable and relatively insoluble in acid, neutral, and alkaline media, (ii) it can be oxidized quickly and completely to RuO_4[14] in acidic or neutral conditions or to RuO_4^- and/or RuO_4^{2-} in alkaline conditions[16-18] by strong oxidizing agents, and (iii) it contains no Cl^- ions capable of being oxidized to Cl_2 under strong oxidizing conditions which could result in undesirable side reactions. Consequently, $RuO_2{\cdot}xH_2O$ was chosen as the Ru starting material in our further experiments.

2.3. Variation of pH. A series of experiments were carried out in which the aqueous phase was buffered at different pHs in the range pH 4–12, and the amounts of $NaBrO_3$ (6 mmol), $RuO_2{\cdot}xH_2O$ starting material (0.014 mmol), and octan-2-ol (3 mmol) were fixed. Details of the buffers and the procedure are described in the Experimental Section.

For each pH, decay curves of peak height for octan-2-ol versus time were plotted and values for $t_{0.25}$ (the time for 25% of the octan-2-ol to be oxidized) were obtained. The results of this work are illustrated in Figure 2 which shows a plot of $1/t_{0.25}$ versus pH over the range pH 4–14. From this plot, it can be seen that there is a significant decrease in $1/t_{0.25}$ (i.e. the rate of oxidation is slower) with increasing pH, and this trend can be interpreted in the following way.

In the reactions carried out at pH >9, any RuO_4 produced in the aqueous phase is unstable, being reduced by OH^- ions to perruthenate (RuO_4^-) and subsequently to ruthenate (RuO_4^{2-}).[16-18] Unlike RuO_4, these latter species are insoluble in CCl_4 and, as a result, the aqueous layer in these reactions was normally orange in color and gave the characteristic absorption spectrum[16,17] of RuO_4^{2-}. Although both RuO_4^- and RuO_4^{2-} are capable of oxidizing most secondary alcohols,[19,20] the octan-2-ol is dissolved in the CCl_4 layer, thus the phase boundary between the oxidant and the alcohol prevents their reaction and the rate of oxidation is therefore very slow.

Table I. Variation of Stirrer Speed

stirrer speed, rpm	$t_{0.25}$, min	stirrer speed, rpm	$t_{0.25}$, min
0	394	500	10
300	183	725	9
400	72		

Between pH 5 and pH 8, any RuO_4 generated in the aqueous layer is stable and a large proportion partitions into the CCl_4 layer (as evidenced by a green coloration) where it is able to oxidize the octan-2-ol. Thus, under these conditions, the rate of alcohol oxidation is quite fast.

There is a further increase in reaction rate at pH's less than 5 and this appears to be largely due to the fact that BrO_3^- is reduced to Br_2 rather than Br^- under these pH conditions.[21] The generation of Br_2 allows the possibility of bromination and/or oxidation of the octan-2-ol to occur and so enhances the rate of disappearance of the alcohol. In support of this, at pH 4, a reddish brown coloration of the CCl_4 was observed about 20 min after injecting the octan-2-ol, indicating that Br_2 was being produced and this was later confirmed by UV/vis spectrophotometry.

From these results, it appears that the optimum pH of the aqueous layer for the oxidation of octan-2-ol to octan-2-one using $NaBrO_3$ lies between pH 5 and pH 8 since, in this region, RuO_4 is stable and no Br_2 is generated.

2.4. Variation of Sodium Bromate Concentration. The effect of variation of sodium bromate concentration on the rate of oxidation of octan-2-ol was studied in a series of experiments in which the aqueous phase was buffered at pH 6. The amounts of octan-2-ol (3 mmol) and $RuO_2{\cdot}xH_2O$ starting material (0.014 mmol) were fixed and the concentration of sodium bromate was varied from 0.2 to 1.4 mol dm^{-3} to give a 2- to 10-fold excess over the octan-2-ol. The values of $t_{0.25}$ obtained showed only a slight variation over a fivefold increase in bromate concentration, i.e., from 11.8 min for 0.27 mol dm^{-3} $NaBrO_3$ to 9.7 min for 1.33 mol $dm^{-3}NaBrO_3$, implying that the rate of oxidation is almost independant of the bromate concentration when it is in excess.

2.5. Variation in Stirrer Speed. In another set of experiments, the stirrer speed was varied from 0 to 725 rpm using fixed amounts of sodium bromate (6 mmol) and $RuO_2{\cdot}xH_2O$ (0.014 mmol) in an aqueous phase buffered at pH 6 to oxidize the octan-2-ol (3 mmol). The values of $t_{0.25}$ obtained as a function of stirrer speed are given in Table I. It is clear that the stirrer speed, and hence the degree of mixing of the aqueous and organic phases, has a significant effect on the rate of alcohol oxidation in a two-phase system. From this work it was apparent that at low stirrer speeds (<300 rpm) stirring caused little disruption of the single boundary between the two phases and thus the rate of alcohol oxidation remained slow. At stirrer speeds <300 rpm the single-phase boundary was broken up into many as droplets of one phase passed into the other. Under these conditions the interfacial area available for transfer of the Ru mediators (B and C in Figure 1) was significantly increased and, therefore, not surprisingly this resulted in a significant increase in reaction rate. At a stirrer speed >650 rpm no increase in reaction rate was

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(16) Connick, R. W.; Hurley, C. R. *J. Am. Chem. Soc.* **1952**, *74*, 5012.

(17) Larsen, R. P.; Ross, L. E. *Anal. Chem.* **1959**, *31*, 176.

(18) Griffith, W. P. *The Chemistry of Rarer Platinum Metals*; Interscience: New York, 1967; Chapter 4, p 147.

(19) Lee, D. G.; Spitzer, V. A.; Cleland, J.; Olson, M. E. *Can. J. Chem.* **1976**, *54*, 2124.

(20) Burke, L. D.; Healy, J. F. *J. Chem. Soc., Dalton Trans.* **1972**, 1091.

(21) Duonghong, D.; Erbs, W.; Shuben, L.; Grätzel, M. *Chem. Phys. Lett.* **1983**, *95*, 266.

observed, indicating that no improvement in mixing of the two phases can be achieved at these higher stirrer speeds.

From the work of others[22] it appears possible to improve on the mixing of the two phases, and thus produce grater reaction rates, through the use of continuous ultrasound or more efficient mechanical agitation methods such as vigorous shaking.

2.6. Alternative Oxidizing Agents. Unlike $NaBrO_3$, other oxidizing agents such as $KMnO_4$ and $Ce(SO_4)_2$ can be used as the stoichiometric oxidizing agent in the biphasic system when the pH of the aqueous phase is very low (pH <3). From Figure 2 it appears likely that the rate of oxidation of octan-2-ol would increase with decreasing pH. However, no significant improvement in the rate of oxidation of the alcohol was found when either $Ce(SO_4)_2$ or $KMnO_4$ were used as the oxidizing agent. This result may be associated with the much lower (up to 10 times) concentrations of these oxidizing agents which had to be used, due to their low solubilities.

It was observed when using $Ce(SO_4)_2$ which is less highly colored than $KMnO_4$, that, in addition to $RuO_2 \cdot xH_2O$, a red-orange species was produced in the CCl_4, following reduction of the RuO_4. This red-orange species was very water-soluble and readily oxidized to RuO_4 by $Ce(SO_4)_2$. These properties, including color, are very similar to those exhibited by the ruthenium species (RuO^{2+}).[23] Thus, at low pH, it appears that this red-orange species acts as the Ru(IV) mediator in the biphasic system as well as $RuO_2 \cdot xH_2O$, and it is likely that its rate of return from the CCl_4 to the aqueous phase is faster than $RuO_2 \cdot xH_2O$, due to its high water solubility.

Interestingly, these observations suggest that, since the red-orange species is insoluble in CCl_4, an appreciable part of the catalytic cycle takes place at the interface of the aqueous microdroplets, dispersed in the organic phase.

3. Conclusion

The results of this work have established what appear to be the major factors affecting the oxidation of a water-insoluble alcohol such as octan-2-ol by a strong oxidizing agent such as sodium bromate in a biphasic system, mediated by ruthenium tetraoxide. These factors include the choice of ruthenium starting material, the pH of the aqueous phase, and the degree of dispersion of the two phases.

$RuO_2 \cdot xH_2O$ is an efficient starting material, with significant advantages over the commonly used $RuCl_3 \cdot nH_2O$. It generates RuO_4 quickly ($t_{1/2}$ = ca. 104 s) and in stoichiometric quantities when exposed to BrO_3^- ions. Using this oxidant there is an optimum pH range (pH 5–8) in which fast oxidation of octan-2-ol occurs with no formation of Br_2. In this system it is crucial to have a maximum degree of mixing of the two phases in order that there should be rapid transfer of RuO_4 from the aqueous phase into the CCl_4 and, upon reduction, return of the $RuO_2 \cdot xH_2O$ back into the aqueous phase. Under these conditions a fast oxidation of octan-2-ol can be achieved ($t_{0.25}$ = 9 min) which is significantly greater (ca. 4 times) than the rate reported by Suzuki et al.[12] using a similar system with $NaBrO_3$ as the oxidizing agent.

4. Experimental Section

4.1. Materials. Octan-2-ol (GPR) and carbon tetrachloride (Spectrosol) were obtained from BDH. Many biphasic systems described in the literature used chloroform as the organic phase. However, a lengthy procedure of washing and distillation is required for removal of the ethanol present to produce a nonreducing medium. In contrast, we found that RuO_4 was stable in CCl_4, after simply washing the CCl_4 thoroughly with water; thus it was used as the organic phase in all our experiments.

The oxidizing agents sodium bromate (GPR), potassium permanganate (AnalaR) and cerium(IV) sulfate (0.5 mol dm^{-3} ConVol solution in 1 mol dm^{-3} H_2SO_4) were all purchased from BDH. Ruthenium trichloride hydrate ($RuCl_3 \cdot nH_2O$) with a quoted Ru content of 41.28% was supplied by Johnson Matthey. The ruthenium dioxide hydrate ($RuO_2 \cdot xH_2O$) was obtained in its highly hydrated form from Aldrich Chemicals and had a water content of 25% (measured by TGA). In a previous paper[14] we established that samples of $RuO_2 \cdot xH_2O$ with a water content less than 20% can be only partially oxidized to RuO_4 by a strong oxidant and if the water content is less than 10% then they are not coroded at all. Therefore, only $RuO_2 \cdot xH_2O$ samples with a water content greater than 20% are suitable as the ruthenium starting material for this work. $RuO_2 \cdot xH_2O$ in this highly hydrated form is available from a number of commercial suppliers, e.g. Aldrich, Johnson Matthey, Strem, and Engelhard, or it can be prepared by the alkaline hydrolysis of $RuO_2 \cdot xH_2O$.[14]

All buffers were prepared by using AnalaR or GPR reagents and doubly distilled and deionized water.

4.2. Methods. 4.2.1. The Biphasic System. Experiments were carried out in a 30 cm^3 straight-sided bottle with a narrow neck, over which a rubber septum could be fitted. The oxidizing agent, usually sodium bromate, dissolved in aqueous, buffered solution (7.5 cm^3) was placed in the bottle with the ruthenium starting material and the mixture was sonicated for 5 min to aid the dispersion and complete oxidation of the Ru starting material to RuO_4 by the oxidizing agent. Carbon tetrachloride (15 cm^3) was then added and the bottle was sealed using the septum. The two phases were stirred vigorously throughout the experiment by means of a magnetic stirrer and octan-2-ol (3 mmol) was injected through the septum into the reaction mixture.

Samples from the organic phase were taken at regular intervals over a 1–2-h period after allowing the two layers to separate by stopping the stirrer for a short time. Oxidation of octan-2-ol to octan-2-one was monitored by gas chromatography (GC) using a Pye Model 104 gas chromatograph incorporating a Carbowax column (2.4 m) and a flame ionization detector (FID). The carrier gas was nitrogen. Calibration of the GC was carried out by injecting in known amounts of octan-2-ol in CCl_4 and measuring the peak heights obtained. It was found that the peak height was directly proportional to the number of moles of octan-2-ol injected.

4.2.2. Preparation of Buffers. The following buffers were prepared to produce aqueous solutions with a pH range of 4 to 12: pH 4, 0.2 mol dm^{-3} $CH_3COO^-Na^+$ (10 cm^3)/0.2 mol dm^{-3} CH_3COOH (40 cm^3); pH 6, 0.2 mol dm^{-3} $CH_3COO^-Na^+$ (47.5 cm^3)/0.2 mol dm^{-3} CH_3COOH (2.5 cm^3); pH 9, [0.05 mol dm^{-3} $NaHCO_3$ (25 cm^3)/0.1 mol dm^{-3} NaOH (2.5 cm^3)]; and pH 12, [0.1 mol dm^{-3} KCl (25 cm^3)/0.1 mol dm^{-3} NaOH (6 cm^3)] [the pH 9 and 12 buffers were made up to 50 cm^3 with water]. For each experiment, 7.5 cm^3 of buffer (chosen from the above list) was used as the aqueous phase to which was added the oxidizing agent, $NaBrO_3$, and the Ru starting material.

4.2.3. Test System To Determine the Percentage Conversion of Ru Starting Material to RuO_4. A test system was used to determine the percentage conversion of ruthenium starting material to RuO_4. It consisted of two Dreschel bottles (each 125 cm^3) connected in series, through which was passed a continuous stream of N_2, provided by a N_2 cylinder (flow rate ~180 cm^3/min). The first Dreschel bottle, the reaction vessel, contained 100 cm^3 of a stirred $Ce(SO_4)_2$ solution (3.6×10^{-3} mol dm^{-3} in 0.5 mol dm^{-3} H_2SO_4) and was fitted with a rubber septum through which a sample of the ruthenium starting material, dissolved or dispersed in 10 cm^3 of 0.5 mol dm^{-3} H_2SO_4, could be injected. The second Dreschel bottle, the RuO_4 trap, contained 100 cm^3 of 0.1 mol dm^{-3} NaOCl in 1 mol dm^{-3} NaOH and was used to collect, in the form of perruthenate ions (RuO_4^-), any RuO_4 produced in the reaction vessel and carried over by the N_2 stream. A detailed account of this flow system has been given in a previous paper.[14] Owing to the high solubility of RuO_4 (ca. 20.3 g dm^{-3} at 20 °C), a long period of time (6–8 h) was required to flush out all the RuO_4 produced in the reaction vessel.

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[22] Lorimer, J. P.; Mason, T. *J. Chem. Soc. Rev.* **1987**, *16*, 239 and references therein.

[23] Gortsema, F. P.; Cobble, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 4317.

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The percentage conversion of the ruthenium starting material injected to RuO_4 was calculated by using eq 1, where $N(RuO_4^-)$

$$\% \, RuO_4 = [N(RuO_4^-)/N(Ru_{St})] \times 100 \qquad (1)$$

is the number of moles of RuO_4^- collected in the RuO_4 trap (a quantity determined spectrophotometrically) and $N(Ru_{St})$ is the number of moles of Ru starting material injected into the reaction vessel (calculated using the % Ru content of the sample). The observed value for the % RuO_4 represents a minimum, since some RuO_4 reacted with the rubber septum and the glassware (shown by blackening of both) before reacting in the hypochlorite trap.

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Registry No. RuO_4, 20427-56-9; octan-2-ol, 123-96-6; octan-2-one, 111-13-7.

1-(1-Ethoxyethyl): An Effective Protecting Group for Imidazole Nitrogen

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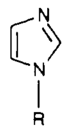
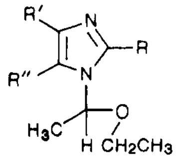
Introduction

Given the importance of substituted imidazoles in biological and pharmaceutical chemistry, it is understandable that 1-N protecting groups are continually being developed.[1-12] A large variety of these are known (**1a–g**). All allow formation of a C_2 or a C_5 anion, but each suffers from one or more disadvantage which precludes its general applicability. These may include: (1) incomplete lithiation of C_2, sometimes competitive with lithiation of the protecting group;[3,4] (2) deprotection[3-5] or protection[6,11] problems; (3) lack of reactivity of corresponding C_2 or C_5 anions with weaker electrophiles;[6-10] (4) expense.[11,12]



1a, $R = CH_2Ph^{1a,2-4}$
b, $R = CH_2OR^{3-5}$
c, $R = CH(OR)_2{}^{6,7}$
d, $R = SO_2Ar^{6,8,9}$
e, $R = SO_2N(CH_3)_2{}^{3,10}$
f, $R = CPh_3{}^{6,11}$
g, $R = CH_2OCH_2CH_2Si(CH_3)_3{}^{12}$

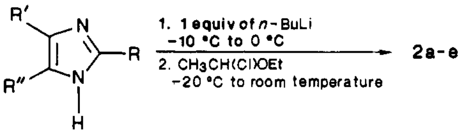


2a, $R = R' = R'' = H$
b, $R = CH_3$; $R' = R'' = H$
c, $R = Ph$; $R' = R'' = H$
d, $R = CH(OCH_3)_2$; $R' = R'' = H$
e, $R = H$; $R' = R'' = CH_3$

During the course of our work on imidazole-containing models for various enzymes,[13] we required an Im protecting group that was inexpensive, readily introduced and removed, but able to tolerate a variety of acidic and basic conditions, and allowed lithiation of C_2 or C_5 (if C_2 is blocked) with subsequent electrophilic additions proceeding in high yield. We believe the 1-ethoxyethyl[14] protecting group (EE) in **2** satisfies all these criteria.

Results and Discussion

(a) Synthesis. The protecting group is introduced simply by dropwise addition of 1-chloro-1-ethoxyethane[15] to a THF solution of the N-anion of the parent imidazole (**3a–e**) as in eq 1. While they are not optimized, the



(1)

3a-e

isolated yields (all distilled) range from 70% to 86%. Physical data for **2a–e** are given in Table I (^1H NMR data are given as supplementary material) and a representative procedure is given in the Experimental Section.

Metalation of the ring positions (C_2 in **2a** or C_5 in **2d**) is accomplished in dry THF at −40 °C to −30 °C by treatment with *n*-butyllithium using standard syringe techniques. In the case of **2c**, C_5 metalation occurred only with *sec*-BuLi at −10 °C to 0 °C; at lower temperatures kinetic lithiation occurs both at C_5 and on the phenyl ring. The thermodynamic C_5 anion was obtained by adding first $^3/_4$ of the required 1.1 equiv of *sec*-BuLi at −10 °C to the THF solution of **2c** and stirring the resulting mixture at −5 °C for 30 min. The remaining *sec*-BuLi was then added over 15 min after which time the solution was stirred at 0 °C for 10 min. In the case of **2d** → **10** (see Table II), the initial lithiation was carried out without problems at −40 °C in THF by the addition of 1 equiv of *n*-BuLi followed by stirring for 30 min.

We have unsuccessfully attempted the formation of the dianion (C_2, C_5) of **2a** in THF by treatment with 2.1 equiv of *n*-BuLi at 0 °C. Even after prolonged stirring, a D_2O quench of the solution indicated that only the C_2 anion was formed.

A standard procedure including workup is given in the Experimental Section. Given in Table II are the isolated yields of the various products along with mp/bp data. (^1H NMR data is given as supplementary material.) While we have not attempted to optimize any case, the yields are good to excellent and the procedures are simple and

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[1] (a) Shirley, D. A.; Alley, P. W. *J. Am. Chem. Soc.* **1957**, *79*, 4922. (b) Iversen, P. E.; Lund, H. *Acta Chem. Scand.* **1966**, *20*, 2649.

[2] (a) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 383. (b) Roe, A. M. *J. Chem. Soc.* **1963**, 2195.

[3] Chadwick, D. J.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans 1* **1984**, 481.

[4] Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

[5] Brown, R. S.; Huguet, J. *Can. J. Chem.* **1980**, *58*, 889.

[6] Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038.

[7] Brown, R. S.; Ulan, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 2382.

[8] (a) Sakakibara, S.; Fujii, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1466. (b) Fujii, T.; Sakakibara, S. *Ibid.* **1970**, *43*, 3954; **1974**, *47*, 3146.

[9] van der Eijk, J. M.; Nolte, R. J. M.; Zwikker, J. W. *J. Org. Chem.* **1980**, *45*, 547.

[10] In our hands, several attempts to react the C_2 anion of 1-(*N*,*N*-dimethylsulfonamido)imidazole with DMF at −20 °C or 0 °C in THF produced only starting material.

[11] (a) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381. (b) Kelley, J. L.; Miller, C. A.; McLean, E. W. *J. Med. Chem.* **1977**, *20*, 721. (c) Current cost of triphenylmethyl chloride (Aldrich) is $58.30 (U.S.)/500 g or $32.50/mol.

[12] (a) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891. (b) Current cost of [2-(trimethylsilyl)ethoxy]methyl chloride (Aldrich) is $107.50 (U.S.)/25 g or $716.80/mol.

[13] (a) Street, J. P.; Skorey, K. I.; Brown, R. S.; Ball, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 7669. (b) Slebocka-Tilk, H.; Cocho, J. L.; Frakman, Z.; Brown, R. S. *Ibid.* **1984**, *106*, 2421. (c) Somayaji, V.; Skorey, K. I.; Brown, R. S.; Ball, R. G. *J. Org. Chem.* **1986**, *51*, 4866.

[14] Insofar as we are aware, use of the EE group has not been reported in the open literature. After completion of the experimental work, we discovered that it has been mentioned in the patent literature although its method of introduction is different (with $CH_2{=}CHOEt$; Whitney, J. G. U.S. Pat. Appl. 109 923, 07 January, 1980. Adolphi, H.; et al. U.S. Pat. 3 681/375, 1972. Fr. Pat. 1 486 817, June 30, 1967) and generalities of removal were not described.

[15] Grummitt, O.; Budewitz, E. P.; Chudd, C. C. *Organic Syntheses*; Wiley: New York, 1963, Collect. Vol. IV, p 748.

0022-3263/88/1953-1107$01.50/0 © 1988 American Chemical Society