JOC*Note*

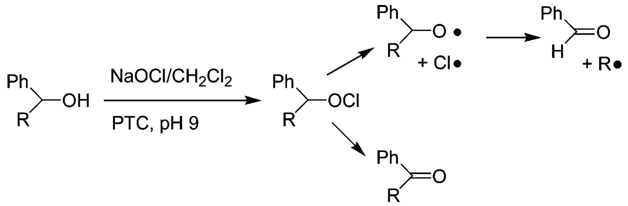
Competing Reactions of Secondary Alcohols with Sodium Hypochlorite Promoted by Phase-Transfer Catalysis

Zack R. Bright, Cedric R. Luyeye,
Angela Ste. Marie Morton, Marina Sedenko,
Robert G. Landolt,* Matthew J. Bronzi,
Katherine M. Bohovic, M. W. Alex Gonser,
Theodore E. Lapainis, and William H. Hendrickson

Department of Chemistry, Texas Wesleyan University, Fort Worth, Texas 76105, and Department of Chemistry, University of Dallas, Irving, Texas 75060

rlandolt@txwes.edu

Received June 3, 2004

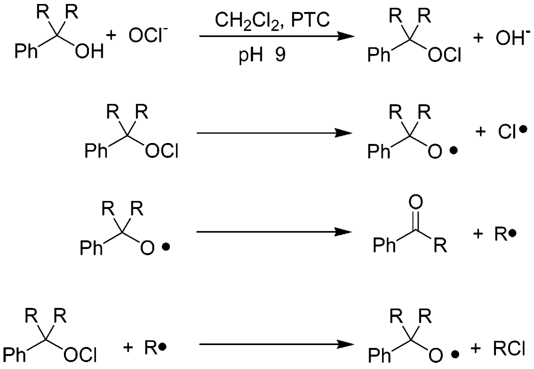


With aqueous hypochlorite and a phase transfer catalyst, secondary alcohols undergo hitherto unreported free radical reactions that compete with and effectively limit traditional ketone syntheses. Product mixture profiles are determined by reactant ratios, organic cosolvent, and availability of oxygen to the system. Under argon, over half of substrate alcohols, PhCH(OH)R, are converted to benzaldehyde and free radical products through β-scission of intermediate alkyl hypochlorites. Secondary alcohols with R containing three or more carbons also may undergo δ chlorination.

Aqueous sodium hypochlorite has been cited widely as an effective oxidant in the transformation of secondary alcohols to ketones as well as for a range of other reactions.[1] Under basic conditions, the utilization of a phase transfer catalyst (PTC) such as tetra-*n*-butylammonium hydrogen sulfate (TBAHS) facilitates secondary alcohol to ketone transformation in two phase systems, with ethyl acetate exhibiting better results than dichloromethane as the organic phase.[2] Kinetic studies, conducted in air, of substituted 1-phenylethanols[3] as well as benzyl alcohols[4] have shown that such oxidations are facilitated by electron withdrawing substituents and point toward an ionic reaction mechanism.

Phase transfer catalysts also are known to enable two-phase chlorinations of hydrocarbons by aqueous hypochlorite, with research indicating free radical pathways to be operable and dichlorine monoxide (Cl_2O) suggested as a reactive intermediate.[5] With PTC under biphasic conditions, bromo- and iodoaromatics undergo substitution reactions with aqueous hypochlorite, yielding chlorinated aromatics.[6]

SCHEME 1



Tertiary alcohols, when treated with aqueous hypochlorite under phase transfer catalytic conditions, are subject to radical chain decomposition of intermediate alkyl hypochlorites.[7] Products are formed by β-scission of an intermediate alkoxy radical, leading to a ketone and chloroalkane, as shown in Scheme 1. Similar to most phase transfer reactions with hypochlorite, tertiary alcohol reactions are facilitated by the aqueous phase being maintained at pH 8−9. Radical pathways are inhibited by oxygen.

Significantly, hitherto unrecognized β-scission and other free radical reactions may compete under conditions routinely utilized for two-phase oxidations of secondary alcohols with aqueous hypochlorite. The degree to which these processes successfully compete will reduce the efficiency of alcohol to ketone syntheses, and the competing processes themselves provide insight into the role of solvents, pH, PTC, and structural features. The present paper identifies a series of substrates subject to this competition and identifies control parameters that may be employed to impact yields from competing pathways.[8]

At ambient temperatures, using dichloromethane, TBAHS, and aqueous hypochlorite at pH ~9, secondary alcohols PhCH(OH)R (**1**) produced substantial benzaldehyde (**2**) as well as the expected ketones (**3**, Table 1). Benzaldehyde yields reflect lower limits of substrates undergoing β-scission, since under the same conditions the aldehyde is subject to conversion to benzoic acid.

---

* Address correspondence to this author at Texas Wesleyan University.

[1] Skarzewski, J.; Siedlecka, R. *Org. Prep. Proced. Int.* **1992**, *24*, 623−647.

[2] (a) Lee, G. A.; Freedman, H. H. *Isr. J. Chem.* **1985**, *26*, 229−234. (b) Mirafzal, G. A.; Lozeva, A. M. *Tetrahedron Lett.* **1998**, *39*, 7263−7266.

[3] Sakai, A.; Hendrickson, D.G.; Hendrickson, W. H. *Tetrahedron Lett.* **2000**, *41*, 2759−2763.

[4] Bradley, L. M.; Lesica, J. M.; Albertson, K. B. *React. Kinet. Catal.* Lett. **1997**, *62*, 3−7.

[5] (a) Fonouni, H. E.; Krishnan, S.; Kuhn, D. G.; Hamilton, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 7672−7676. (b) Dneprovskii, A. S.; Eliseenkov, E. V. *Russ. J. Org. Chem.* **1994**, *30* (2), 235−240.

[6] (a) O'Connor, K. J.; Burrows, C. J. *J. Org. Chem.* **1991**, *56*, 1344−1346. (b) Arnold, J. T.; Bayraktaroglu, T. O.; Brown, R. G.; Heiermann, C. R.; Magnus, W. W.; Ohman, A. B.; Landolt, R. G. *J. Org. Chem.* **1992**, *57*, 391−393. (c) Bayraktaroglu, T. O.; Gooding, M. A.; Khatib, S. F.; Lee, H.; Kourouma, M.; Landolt, R. G. *J. Org. Chem.* **1993**, *58*, 1264−1265.

[7] Dailey, J. I.; Hays, R. S.; Lee, H.; Mitchell, R. M.; Ries, J. J.; Landolt, R. G.; Hussmann; H. H.; Lockridge, J. B.; Hendrickson, W. H. *J. Org. Chem.* **2000**, *65*, 2568−2571.

10.1021/jo0490651 CCC: $30.25 © 2005 American Chemical Society
Published on Web 12/18/2004

TABLE 1. Secondary Alcohol−Hypochlorite/PTC Reactions

Ph-CH(OH)R + OCl^- → Ph-C(=O)H + Ph-C(=O)R + [RCl]

1, R	residual **1**, %	**2**, %	**3**, %	time, min
ethyl[a]	14−16	50−73	12−14	40−60
propyl[a]	8−10	70−85	5−10	60−80
butyl[a]	5−13	50−60	15−30	40−60
2,2-dimethylethyl[a,b]	5−15	70−85	trace	30
1-methylethyl[c,d]	0−13	42−61	23−36	120
1-methylpropyl[a,b,d]	trace	65−70	6	30

[a] Except as noted, 1.3×10^{-3} mol of substrate and Ph-Cl in 40−50 mL of CH_2Cl_2; aq 6% NaOCl, in 2−10 mL increments (1.6×10^{-2} mol); TBAHS, 0.010−0.013 g (3×10^{-5} mol); under argon; pH adjusted to 8.5−9 with aq NaOH or HCl. [b] One portion of 40 mL aq NaOCl (3.2×10^{-2} mol) employed. [c] Substrate (6.15×10^{-3} mol) and Ph-Cl (3.07×10^{-3} mol) in 15 mL of CH_2Cl_2 stirred with 40 mL of aq NaOCl (3.2×10^{-2} mol) containing $NaHCO_3$ (8.0×10^{-3} mol) and TBASH (0.029 g, 3.6×10^{-5} mol) at pH 9.0. [d] Air atmosphere.

Simple flushing of reaction mixtures with argon prior to and during reactions proved effective in enhancing conversion of 1-phenyl-1-propanol to benzaldehyde.[9] Two experimental approaches lead to maximization of benzaldehyde production: (A) addition of hypochlorite to 1-phenyl-1-propanol in increments (Table 1) and (B) treatment of relatively high concentrations (2.0 M) of 2-methyl-1-phenyl-1-propanol with 20% excess bleach under either air or argon, yielding 67−97% benzaldehyde and only 2−4% ketone.

Simple R−Cl cleavage products projected to result from β-scission of phenyl alkyl hypochlorite were indistinguishable from solvents by GC/GCMS under conditions employed for these reactions. However, dichlorinated cleavage byproducts were detected (1,3-dichloropropane from 1-phenyl-1-butanol and 1,3-dichlorobutane from 1-phenyl-1-pentanol and 2-methyl-1-phenyl-1-butanol), arising from δ-hydrogen abstraction-promoted chlorination (see below) followed by a second chlorination resulting after β-scission. Moreover, in air, hypochlorite/PTC reactions of 1-phenyl-2-propanol in dichloromethane produced 54−60% benzyl chloride, the expected chlorinated β-scission product, and less than 15% ketone (Scheme 2).[10]

SCHEME 2

$$PhCH_2CH(OCl)CH_3 \rightarrow [PhCH_2CH(O\bullet)CH_3] \rightarrow PhCH_2Cl + PhCH_2C(=O)CH_3$$

Key reaction variables impacting β-scission include reactant/PTC concentration ratios, solvent, pH, and employment of an inert vs an air atmosphere. When reactions were maintained at pH > 11, no β-scission was detected; substrates essentially were inert. Table 2 provides results of comparative reactions of 1-phenyl-1-propanol (**1**) wherein the levels of reactants and PTC were constant at pH 8.5−9.5, but the organic solvent and atmosphere were varied. Results showed clearly that benzaldehyde formation/β-scission was favored by an inert atmosphere. When an air atmosphere was employed with either ethyl acetate or dichloromethane, ketone formation was favored, but more aldehyde formed early, along with limited ketone, when exposure to air was minimized in either of these solvents.

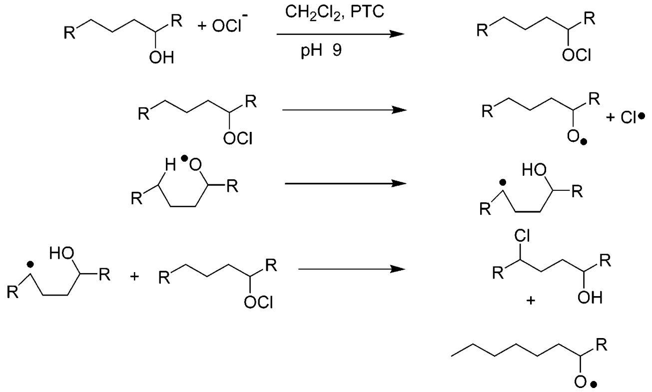
TABLE 2. Impact of Solvent and Atmosphere on Reactions of 1-Phenyl-1-propanol

solvent	atmosphere	time, min	benzaldehyde, %	propiophenone, %
CH_2Cl_2	air	15	10−22	54−56
		30	trace	47−58
	Ar	15	19−30	44−51
		30	trace	39−48
ethyl acetate	air	30	0	84−90
	Ar	10−30	38−44	19−37

The ability of ethyl acetate to facilitate higher ketone yields relative to reactions in dichloromethane, previously attributed to formation of a reactive intermediate,[2a] is likely derived from the ester's more aerated state as the top layer in the two-phase system, enhancing its capacity to supply radical-inhibiting oxygen to the system. With ethyl acetate in air, hypochlorite treatment of 1-phenyl-2-propanol produced 1-phenyl-2-propanone in modest amounts (20−50%) and no benzyl chloride in 1 h. In contrast, using argon, β-scission resulted in greater than 60−78% benzyl chloride production in 30 min, along with a substantial amount of chloroethyl acetate.

The occurrence of β-scission products along with ketones in these reactions suggests that alkyl hypochlorites are intermediates in the reactions of secondary alcohols as well as for tertiary alcohols. Additional evidence for alkyl hypochlorite intermediates is provided by the reactions of secondary aliphatic alcohols having side chains of three or more carbon atoms. Alkyl hypochlorites formed from such alcohols undergo radical chain decompositions to produce δ-chloro alcohols (Scheme 3).[11] Under conditions of excess hypochlorite, the δ-chloro alcohols would be oxidized to δ-chloroketones. In addition to

SCHEME 3



---

[8] Preliminary reports: (a) Angela Ste. Marie, DFW/ACS Section Meeting-In-Miniature, April, 1994; (b) Marina Sedenko, DFW/ACS Section Meeting-In-Miniature, April 2000; M. W. Alex Gonser, National ACS Meeting, New Orleans, April 2003.

[9] In attempts to enhance β-scission by rigorously excluding air through freeze−thaw under vacuum and working under a blanket of nitrogen, the conversion level to benzaldehyde and to ketone averaged 45% and 26% yields, respectively.

[10] The β-scission product acetaldehyde (ethanal) would not have been detected by the GC conditions employed.

[11] (a) Walling, C.; Bristol, D. *J. Org. Chem.* **1972**, *37*, 3514−3516. (b) Nedelec, J.Y.; Gruselle, A.; Triki, A.; LeFort, D. *Tetrahedron* **1977**, *33*, 39−44. (c) Cekovic, Z.; Djokic, G. *Tetrahedron* **1981**, *37*, 4263−4268.

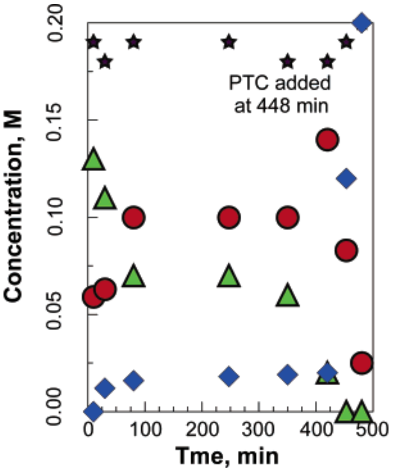


FIGURE 1. Addition of 5.0 × 10^{-5} mol PTC to a reaction mixture of 25 mL of 0.20 M 1-phenyl-1-ethanol in CH_2Cl_2 with 20 mL of bleach at pH 9 after 448 min: [1-phenyl-1-ethanol] (▲), [1-phenylethyl hypochlorite] (●), [acetophenone] (◆), total (★).

dichlorinated cleavage products from 1-phenyl-1-butanol, 1-phenyl-1-pentanol, and 2-methyl-1-phenylbutanol, δ-hydrogen abstractions were observed for reactions of both 5-nonanol and 2-octanol. For example, in reactions of 2-octanol in dichloromethane in air, both 2-octanone (42–74%) and 5-chloro-2-octanone (18–26%) were produced. Reactions of aliphatic alcohols showed the same effects of solvent and atmosphere as seen with aromatic alcohols, e.g., higher amounts of radical products in dichloromethane compared to ethyl acetate and under an argon atmosphere compared to air.

Additional evidence for alkyl hypochlorite involvement in biphasic reactions of secondary alcohols was derived when aqueous hypochlorite at pH 8–9 was mixed with dichloromethane solutions of secondary alcohols with no PTC present. Similar to tertiary alcohols,[7] titrimetric analysis showed that a substantial portion of substrate was converted to the secondary alkyl hypochlorite that proved to be quite stable under ambient conditions, especially in dichloromethane, until addition of the phase-transfer catalyst (Figure 1). It is projected that PTC-mediated participation by intermediates such as chlorine monoxide and its precursor, hypochlorite ion, effects decomposition of the alkyl hypochlorite.

To demonstrate further that alkyl hypochlorites are reactive intermediates, a reaction of 1-phenyl-1-ethanol with bleach in $CDCl_3$ was monitored by ^1H NMR, GC, and iodometric titration. The results given in Figure 2 show good agreement between alkyl hypochlorite measured by titration and ^1H NMR. Also, the similarity of the concentrations of alcohol and ketone determined by ^1H NMR and GC indicates that KI treatment of the reaction samples provides reliable GC analysis.

Reactions of secondary alcohols with aqueous hypochlorite shared a significant characteristic with tertiary alcohols.[7] With no catalyst present, solutions of the secondary alkyl hypochlorite from 1-phenyl-1-propanol underwent thermally promoted β-scission in the inlet and on columns during gas chromatographic analysis: 38–40% to benzaldehyde as well as oxidation, 13% to 1-phenyl-1-propanone, with ~30% substrate remaining.

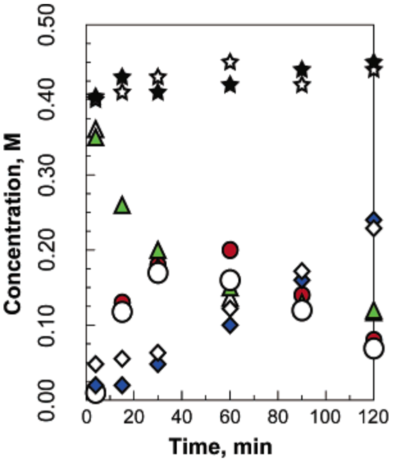


FIGURE 2. Reaction of 10 mL of 0.40 M 1-phenylethanol in $CDCl_3$ with 20 mL of bleach at pH 9.0 catalyzed by 1.3 × 10^{-5} mol PTC: [1-phenyl-1-ethanol]$_{gc}$ (△), [1-phenyl-1-ethanol]$_{NMR}$ (▲), [1-phenylethyl hypochlorite]$_{tit}$ (○), [1-phenylethyl hypochlorite]$_{NMR}$ (●), [acetophenone]$_{gc}$ (◇), [acetophenone]$_{nmr}$ (◆), [total]$_{gc}$ (☆), [total]$_{NMR}$ (★). See the Experimental Section for details.[7]

In contrast, acidified aqueous potassium iodide pretreatment, prior to GC and GCMS analysis, induced reduction of secondary alkyl hypochlorites back to the starting alcohol.

In summary, PTC-catalyzed reactions of secondary alcohols with sodium hypochlorite form alkyl hypochlorite intermediates. These intermediates may either eliminate HCl to form ketones or undergo radical chain decompositions typical of alkyl hypochlorites to give β-scission or δ-hydrogen abstraction. Oxygen inhibits the chain decomposition and favors ketone formation, while the chain decomposition is enhanced by inert atmosphere or by higher alcohol/oxidant ratios. β-Scission is more likely when the alkyl radical that is split off is benzyl or more highly substituted, while δ-hydrogen abstraction is likely to occur for alcohols with a side chain of more than three carbon atoms.

Experimental Section

Materials and General Procedures. All organic compounds employed were secured from commercial suppliers. Aqueous hypochlorite, unless specified otherwise, was obtained in the form of commercial Ultra Clorox, "6.0%". In all cases the phase transfer catalyst (PTC) used was tetrabutylammonium hydrogen sulfate (TBAHS). Gas chromatographic (GC) instruments were equipped with capillary columns and flame ionization detectors. Except where noted, the pH values of aqueous layers of biphasic systems were set and maintained at desired levels by the addition of aqueous NaOH or HCl, and the pH was monitored by pH meters. Progress of reactions was followed by GC, using chlorobenzene or *tert*-butylbenzene as an internal standard. All reactions were conducted at ambient temperatures.

Potassium iodide (KI) treatments consisted of mixing reaction aliquots with 5% aqueous KI acidified with concentrated HCl. The presence of active oxidants was clearly indicated by dark pink to pinkish brown color development in both layers, concentrated in the organic phase.

Reactions of 1-Phenyl-2-propanol. Conditions given in footnotes a and b of Table 1 were employed, except that 100 mg of TBAHS was used.

Comparative Reactions of 1-Phenyl-1-propanol (Table 2). Aqueous hypochlorite (100 mL, 6.00 g, 8.1 × 10^{-2} mol) containing 0.200 g (5.8×10^{-4} mol) of PTC was adjusted to pH 8.5−9.5 that was maintained with concentrated HCl and the solution was stirred magnetically with the substrate alcohol (0.700 g, 5.14×10^{-3} mol) and chlorobenzene(0.579 g, 5.13×10^{-3} mol) dissolved in 50 mL of organic cosolvent. Reactions under Ar were conducted in a sidearm flask fitted for gas inlet and exit, with each layer separately sparged with Ar for 20 min prior to and during mixing. Aliquots were split and analyzed with and without KI treatment prior to GC analysis. The identity of all products was confirmed by GCMS.

Reaction of 2.0 M 2-Methyl-1-phenyl-1-propanol in Dichloromethane. Sodium bicarbonate (3.78 g, 4.50×10^{-2} mol) was added to 45 mL of aqueous hypochlorite (2.70 g, 3.6×10^{-2} mol) containing 0.025 g (7.4×10^{-5} mol) of PTC. The pH of this solution was 8.4. The 2-methyl-1-phenyl-1-propanol (4.55 g, 3.03×10^{-2} mol) and chlorobenzene (0.338 g, $3.01 \times 10^{-4-}$mol) in 15 mL of dichloromethane were added to the magnetically stirred bleach solution. After 15 min, an aliquot was taken and quenched with KI. Analysis by GC showed 3% remaining alcohol, 2% isobutyrophenone, and 67% benzaldehyde. Reactions under argon were done with the bleach solution in a three-necked round-bottom flask equipped with a gas inlet connected to a Firestone valve and an addition funnel containing the dichloromethane solution. Both solutions were sparged with Ar for 20 min prior to mixing.

^{1}H NMR Analysis of 1-Phenyl-1-ethanol Reaction (Figure 2). The chemical shifts of the methyl hydrogens of 1-phenyl-1-ethanol (d, 1.44 ppm) and 1-phenylethyl hypochlorite (d, 1.54 ppm) overlapped on the 60 MHz instrument to yield a triplet centered at 1.49 ppm. However, the concentrations of the alcohol and hypochlorite could be determined by integration of the resolved outer peaks at 1.39 and 1.59 ppm, using *tert*-butylbenzene (1.29 ppm) as an internal standard. The 1-phenyl-1-ethanol (0.494 g, 4.04 mmol), PTC (0.0044 g, 1.3×10^{-5} mol), and *tert*-butylbenzene (0.137 g, 1.02×10^{-3} mol) were dissolved in 10 mL of $CDCl_3$. The solution was stirred with 20 mL of bleach buffered with 0.2 M $NaHCO_3$ at pH 9.0. At intervals, 0.20-mL aliquots of the organic layer were removed, diluted to 1.0 mL with $CDCl_3$, washed with D_2O, dried over $MgSO_4$, and analyzed by NMR. After NMR analysis, the aliquot was divided. Alkyl hypochlorite concentration in one part was determined by iodometric titration; the other part was quenched with KI and analyzed by GC. Since treatment of KI converts alkyl hypochlorite to alcohol, the $[\text{alcohol}]_{gc}$ points in Figure 2 were calculated by subtracting the alkyl hypochlorite concentration from the alcohol concentration after KI treatment.

Reaction of 2-Octanol. A 20.0 mL dichloromethane solution of 2-octanol (0.264 g, 2.04×10^{-3} mol), PTC (0.034 g, 1.0×10^{-4} mol), and chlorobenzene (0.118 g, 1.05×10^{-3} mol) was stirred with 20 mL of bleach buffered at pH 9 with 0.2 M $NaHCO_3$. Aliquots were quenched with KI and analyzed by GC. The 5-chloro-2-octanol was identified by GCMS and by the comparison of retention times of products formed in the decomposition of 1-methylheptyl hypochlorite by iron(II) sulfate according to the procedure of Cekovic and Djokic.[11c] Oxidation of the 5-chloro-2-octanol solution with bleach in ethyl acetate gave a solution of 5-chloro-2-octanone.[2b] Retention times of chlorination products in reactions of 5-nonanol were assigned in a similar manner.

Acknowledgment. All phases of this work were supported by Chemistry Departmental Research Grants from the Robert A. Welch Foundation (AZ0003, Texas Wesleyan, and BA0015, University of Dallas) and by the O'Hara Chemical Sciences Institute of the University of Dallas. The effort was made possible in part by instrumentation supplied by the National Science Foundation under an Instrumentation and Laboratory Improvement Grant to Texas Wesleyan (USE-9250391).

JO0490651