Hypochlorite-Induced Ipso-Substitution Reactions of Aromatic Alcohols and Related Compounds

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Abstract: Organic solvent extracts derived from aqueous hypochlorite/phase-transfer catalyst solutions induce rapid and efficient ipso substitution of aromatic carbinols and related substrates. The key parameter impacting rates and yields is pH of the original hypochlorite/phase-transfer catalyst component.

Key words: alcohols, electrophilic aromatic substitution, halogenation, phase-transfer catalysis, solvent effects

For oxidation,¹ chlorination,² disinfection,³ or chemical warfare agent decontamination,⁴ the reagent of choice could be aqueous hypochlorite (OCl⁻). In addition to serving as a halogenating/oxidizing agent, hypochlorite is the conjugate base of a weak acid, HOCl ($pK_a = 7.5$).⁵ When delivered as a basic aqueous solution, it is immiscible with many organics, and reactions with the latter readily may be achieved using phase-transfer catalysts (PTC). However, as well as the reagent, water may react with organic substrates or reaction intermediates either by competing or consecutive pathways, giving rise to secondary products.

Reactivity and selectivity have been managed by adjusting the pH value of aqueous solutions in hypochlorite-induced reactions of polynuclear aromatics and chloroform precursors, oxidative decarboxylations, competing oxidation and β -scission of alcohols, and ipso substitutions of aromatic halides.⁶ These reactions generally proceed more rapidly at pH 8–9 than at pH >11, except for the haloform reaction, whose heightened reactivity at high pH has been attributed to the role of slow formation of precursor enolate.⁷ When the inverse PTC catalyst β -cyclodextrin was employed for haloform reactions with aqueous hypochlorite to achieve miscibility with methyl ketones,⁸ no attempt was made to adjust or monitor the pH value. Other efforts involving special technologies specifically have used hypochlorite at approximately pH 9 for ruthenium-catalyzed oxidation of ethers and alcohols,⁹ polymerimmobilized TEMPO for aerobic oxidation of alcohols,¹⁰ and selective oxidation of benzyl alcohols in ionic liquids.11

Under inert atmosphere at optimum pH, β -scission results from hypochlorite/PTC reactions with 3° alcohols, where-

SYNLETT 2011, No. 14, pp 2069–2071 Advanced online publication: 10.08.2011 DOI: 10.1055/s-0030-1261178; Art ID: S03711ST © Georg Thieme Verlag Stuttgart · New York as conventional oxidation to ketones and β -scission reactions occur competitively with 2° alcohols.^{6j,k} The catalyst does more than bring ionic material into the organic phase. Specifically, β -scission conversion of the ROCl from 2-phenyl-2-propanol and oxidation of the ROCl from 1-phenylethanol to acetophenone were delayed until the PTC was added to a two-phase alcohol–hypochlorite mixture.

In the present work, electrophilic ipso-substitution reactions¹² initially were observed to compete with oxidation in dual phase, OCI⁻/PTC reactions of 4-methoxybenzyl alcohol (**1a**), facilitated by the electron-donating effect of the methoxy group.¹³ Significantly, this substituent has been found to have a deactivating effect on the OCI⁻/PTC oxidation of benzyl alcohols.¹⁴ Reaction of **1a** with aqueous NaOCl at pH 8–9, PTC and dichloromethane resulted in ca. 30–40% yield of 4-methoxychlorobenzene [4-chloroanisole (**2a**)] through ipso substitution in addition to 4-methoxybenzaldehyde [anisaldehyde (**3**)], the expected oxidation product.

In contrast, use of a nontraditional, homogeneous 'monophasic', PTC-facilitated system was found to consume the starting material much more rapidly than in the two-phase approach, to yield **2a** as the predominant product (Scheme 1).





Effective ipso substitutions were initiated by mixing the phase-transfer reagent, tetra-*n*-butylammonium bisulfate with aqueous hypochlorite, and adjusting the pH value to 8–9. A portion of dichloromethane was added, the dual phase mixture was shaken, and the organic layer was physically separated to provide a reactive, ipso-chlorinating solution. When this extract was added to a separate dichloromethane aliquot containing **1a**, GC analysis revealed rapid production up to 80% of **2a**, with only modest formation of byproducts **3** and 2,4-dichloromethoxybenzene. Alternately, dual-phase reactions with

bleach layers pH > 11, with or without PTC, resulted in exclusive oxidation to aldehyde **3**.

In less than 5 minutes, 'monophasic' reaction of **1a** with an extract derived from pH 8–9 hypochlorite induced the ipso substitution at ambient temperatures. Subsequently, similar monophasic treatment showed 75–79% ipso-product **2a** from 4-methoxybenzoic acid [anisic acid (**4**)] within the same time frame; however, the aldehyde **3** was relatively inert to these conditions (Scheme 2).



Scheme 2

Evidence that ipso-product **2a** was derived directly from **1a** also came from isolation of formaldehyde as the dimedone derivative, (1,3,1',3'-tetraketo-5,5,5',5'-tetramethyl-4,4'-dicyclohexylmethane)¹⁵ from aqueous extracts of dichloromethane reaction solutions.

The ipso-enhancing effect of the methoxy and other electron-donating substituents also was evidenced in monophasic reactions of methoxy-substituted secondary and tertiary aromatic alcohols **1b–f** and carboxylic acid and acid derivatives **1g–j**, as indicated as 1-X-4-Y-benzenes in Table 1. Ketones expected from secondary alcohol oxidations were detected as minor products.

Other substrates thought to be plausible candidates for ipso substitution were subjected to reaction under conditions shown in Table 1. Those with electron-donating substituents, including 4-acetoxybenzoic acid, 4-methoxybenzamide, 4-methoxybromobenzene, 4-*tert*-butylbenzoic acid, 2-methoxybenzyl alcohol, 4-methoxybenzylamine, methoxytrityl alcohol, and 4-methylbenzoyl chloride showed trace production of ipso products to GC analysis. Benzoic acid, benzoyl chloride, and 2-phenyl-2-propanol were inert. These reactions typically exhibited poor mass balances, involving either substrates and/or potential non-ipso products not characterizable by GC. Further mechanistic studies are in progress

Heightened reactivity near pH 9 in biphasic systems with PTC has lead others to propose either the intermediacy of chlorine monoxide $(Cl_2O)^{1,2}$ or enhanced efficiency of coextraction of hypochlorous acid with hypochlorite by catalyst at bleach pH near the pK_a of HOCl.¹⁶ β -Scission products and other evidence from both secondary- and tertiary-alcohol reactions with hypochlorite are indicative of the active involvement of alkyl hypochlorites, ROCl, as intermediates in these processes.¹⁷

We suggest that the monophasic processes occurred via electrophilic aromatic substitution involving arenium ions resulting from attack potentially by any of several chlorinating agents.¹⁸ The latter include but are not limited to

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HOCl, Cl₂O, or a PTC complex of HOCl and its conjugate base. With suitably activated aromatics, research has revealed that, for substrates lacking *para*-ipso leaving groups, electrophilic substitution occurred under the mild, monophasic conditions described above. Methoxybenzene (anisole), or 1,3,5-trimethylbenzene (mesitylene), yielded relatively clean, ring-chlorination products, conclusively identified by GC-MS to be **2a** and 2-chloro-1,3,5-trimethylbenzene, respectively. Reactivity of these substrates also depended on pH of PTC solutions in aqueous hypochlorite used to provide CH₂Cl₂ extracts. This opens the prospect that monophasic chlorination may be feasible for a variety of substances that respond to control parameters in degree yet to be determined.

 Table 1
 Hypochlorite-Induced Ipso-Substitutions of 1-X-4-Y-benzenes

1	Y	Х	Yield of 2a (%)	Yield of ketone (%)
1b	OMe	CH(OH)Me	53-73	2–20
1c	OMe	CH(OH)Et	67–92	6–10
1d	OMe	CH(OH)Ph	73–75 ^b	1–10
1e	OMe	CH(OH)(4-MeOC ₆ H ₄)	69–70 ^c	21–23
1f	OMe	C(OH)Me ₂	34–47	
1g	OMe	C(=O)Cl	70-80	
1h	OMe	C(=O)O(=O)(4-Ans) ^a	48	
1i	OPh	CO ₂ H	100	
1j	t-Bu	C(C=O)Cl	95	

^a Anisic anhydride; co-products (fate of X).

^b Recovered benzaldehyde (from leaving group): 71-75%.

^c Recovered 4-methoxybenzaldehyde (from leaving group): 57–65%; pH 8–9 of bleach/PTC aqueous layer.

General Procedure

Tetra-*n*-butylammonium bisulfate (0.6082 g, $1.79 \cdot 10^{-3}$ mol) and NaCl (10 g) were dissolved in 6% aq hypochlorite (50 mL, Clorox bleach, ca. $4 \cdot 10^{-2}$ mol, pH 11.45). The pH value was adjusted with 6 M HCl to 8–9. This solution and CH₂Cl₂ (20 mL) were shaken thoroughly using a separatory funnel. The CH₂Cl₂ extract layer was added to a CH₂Cl₂ solution (20 mL) containing substrate alcohol (2.6 · 10⁻³ mol) and chlorobenzene (2.6 · 10⁻³ mol, internal standard) previously analyzed by capillary gas chromatography (GC) to establish a starting material concentration. Progress of reactions was followed by GC and GC-MS. All reactions were conducted at ambient temperatures. Best results were obtained using distilled CH₂Cl₂.

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