Preparation of Dihalobenzophenones by Oxidation under Phase-Transfer-Catalysis Conditions

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Received March 15, 1988

Introduction

The utilization of the hydroxide ion under phasetransfer-catalysis conditions ("PTC/OH-") has been applied to a wide range of useful base-catalyzed organic reactions.¹ Diarylmethanes have been oxidized to benzophenones by oxygen under PTC/OH⁻ conditions.² The catalysts used were "accessible"³ quaternary ammonium ("quat") salts, containing two or more ethyl groups. We report the PTC/OH⁻ oxidation of dihalodiphenylmethanes to dihalobenzophenones, useful as monomers. We shall show that employing more organophilic rather than accessible quats for the oxidation of dihalodiphenylmethane yields more favorable results. This work represents a successful application of PTC/OH⁻ guidelines.¹ In addition, we wish to report a Freidel-Crafts alkylation with enhanced para, para selectivity as part of a two step one-pot route to dihalobenzophenones.

In a previously reported process,⁴ dihalodiphenylmethane was oxidized to dihalobenzophenone by using NaNO₂ as the oxidizing agent, in a highly exothermic reaction, liberating N₂O gas as an undesirable byproduct. The oxidation of dihalodiphenylmethane to dihalobenzophenone may be performed under PTC conditions with NaOH as the base, oxygen as the oxidizing agent, and water as the byproduct.

Results and Discussion

Dichlorodiphenylmethane and bromochlorodiphenylmethane were prepared by a Friedel-Crafts alkylation of chlorobenzene or bromobenzene with p-chlorobenzyl chloride in the presence of $AlCl_3$ (see Figure 1). When the reaction was performed in the temperature range 3-10 °C, the attack of the carbonium ion was 58% ortho, 27% para, and 15% meta to the chlorine atom of chlorobenzene. The para selectivity may be doubled (achieving 61% para, 39% ortho, and <1% meta) by maintaining the temperature of the reaction mixture at -4 °C or at -22 °C. Under similar conditions the reaction of bromobenzene with p-chlorobenzyl chloride in the presence of AlCl₃ gave an 85% para-, 14% ortho-, and <1% meta-product distribution. Thus, the selectivity toward the kinetic products was achieved by lowering the temperature of the Freidel-Crafts reaction. In all cases, quantitative conversion was achieved, and only 1–7% of the products were dialkylation materials and other higher boiling species. Flash distillation of the crude product at 142 °C (0.4 mmHg) afforded the corresponding mixture of para- and ortho-alkylated products.

The effects of various reaction variables on the PTC/ OH⁻ oxidation of dihalodiphenylmethane were investigated under the following standard conditions: A 2 M solution of dichlorodiphenylmethane (61% 4,4'-dichloro and 39%



Where X = CI, Br

Figure 1. Preparation of dihalobenzophenone.

Table I. E	ffect of	Quat	Structure	and	Counterion
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catalyst name	quat	counterion	maximum conversion, %
Aliquat 336	$\sim Oct_3 NMe^+$	Cl-	98
TOA Br	Oct_4N^+	Br ⁻	9 3
TBA HSO_4	Bu₄N+	HSO₄⁻	90
TBA Br	Bu_4N^+	Br⁻	67
TEBA Cl	Et ₃ NCH ₂ Ph ⁺	Cl-	44
no quat			0 (3 days)

Table II. Effect of Counteranion on PTC/OH⁻ Oxidation Reactivity

	conversion (standard conditions), %				
time	TBA HSO ₄	TBA Br			
 4 min	56	2			
9 min	66				
27 min	79	32			
184 min	86				
276 min	87				
18 h		65			

Table III. Effect of Base Concentration on PTC/OH-Oxidation

	conversion at 17 min, %	
	50% NaOH	NaOH pellets
10 mol % catalyst	40	56
20 mol % catalyst	74 (20 min)	83

2,4'-dichloro) in toluene was reacted with 9.6 molar equiv of 50% NaOH and an initial pressure of 200 psi of oxygen in the presence of 20 mol % Aliquat 336 (trademark of Henkel Corp.) at 40–50 °C for approximately 18 h. The results are shown in Tables I–III.

It has been reported⁵ that "the oxidation of diphenylmethane in basic solutions involves a process where rate is limited by and equal to the rate of ionization of diphenylmethane". The first step in the base-catalyzed oxidation of dihalodiphenylmethane may be expected to be deprotonation. The pK_a of diphenylmethane is 33^6 and the p K_a of dihalodiphenylmethane is expected to be 31–32. According to the PTC/OH⁻ guidelines,¹ the deprotonation of a substrate in the pK_a range 23-37 is more likely to proceed via the extraction mechanism.⁷ The preferred quats for extraction mechanism reactions are more organophilic than accessible and/or have hydrophilic counteranions. Examination of Table I reveals that, given a constant anion, the more organophilic quats indeed induce higher conversions than the more hydrophilic quats. For example, TOA Br (93%) is better than TBA Br (67%), and Aliquat 336 (98%) is better than TEBA Cl (44%). Historically, alkyltriethylammonium salts, such as TEBA Cl or those used for the oxidation of diarylmethanes,² have

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been the classic PTC/OH⁻ interfacial catalysts.⁸ The behavior exhibited here is consistent with the extraction mechanism according to which the increased organophilicity of the quat results in enhanced solubility of the more organophilic ion pair, [Q⁺OH⁻]org, in the organic phase (see eq 1).⁹

rate of oxidation = $k_{\text{chem}}[Q^+OH^-]_{\text{org}}[XPhCH_2PhCl]$ (1)

$$k_{\rm obsd} = k_{\rm chem} [Q^+ O H^-]_{\rm org}$$

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It should be noted that fluorene and substrates more acidic $(16 < pK_a < 23)$ would be expected to be deprotonated by an interfacial mechanism.¹ Thus, the PTC base-catalyzed oxidation of fluorene may be expected to be catalyzed more effectively by accessible quats.

Other reaction variables were investigated, such as counteranion, kinetics, form of base used, and temperature, which support the application of reaction conditions consistent with the extraction mechanism.

One of the reasons that this PTC/OH⁻ oxidation proceeds so well is that hydroxide acts as a true catalyst, with water as the byproduct rather than an anionic leaving group (which could potentially poison the catalyst). In the absence of leaving groups, the only other anion in this oxidation system is the catalyst counteranion. Comparison of TBA HSO_4 with TBA Br as shown in Tables I and II illustrates that the system is more reactive in the presence of hydrogen sulfate (actually hard dianionic sulfate) relative to bromide, as would be expected from an extractive OH⁻ system.¹⁰

The kinetics of the reaction of bromochlorodiphenylmethane with oxygen at atmospheric pressure in chlorobenzene in the presence of 10 mol % tetraoctylammonium (TOA) bromide and 50% NaOH at room temperature obeyed pseudo-first-order kinetics through at least 0.6 half-life. Furthermore, when the volume of the added solvent was doubled (corresponding to a decrease in substrate concentration by a factor of 1.7, from ca. 1.3 M to ca. 0.76 M), the initial pseudo-first-order rate constant, $k_{\rm obsd}$, decreased from $1.9 \times 10^{-3} \text{ min}^{-1}$ to $1.0 \times 10^{-3} \text{ min}^{-1}$. These results indicate at least approximate first-order kinetics with respect to both substrate and catalyst (see eq 1). This is consistent with the extraction mechanism behavior and is in contrast to the fractional-order kinetics observed in interfacial PTC/OH⁻ systems.¹¹

NaOH pellets induced a higher initial reactivity than 50% NaOH on the oxidation of the 4,4'-dichlorodiphenylmethane isomer under standard conditions. The conversions at 17 min are shown in Table III.

Temperature and oxygen pressure both effect the maximum conversion in the oxidation. A 0.8 M toluene solution of a mixture of bromochlorodiphenylmethanes was oxidized with oxygen at atmospheric pressure in the presence of 10 mol % TOA Br and 50% NaOH. The reaction, at 70 °C, was initially rapid (32% at 40 min) and then ceased at about 2 h, probably due to catalyst deactivation, attaining a maximum conversion of 37%. At room temperature the reaction commenced more slowly as expected (5% at 50 min), but the catalyst did not deactivate as rapidly (>6 h) to afford a slightly higher maximum conversion of 44%.

It is worthy to note that dichlorobenzophenones may be prepared in a two-step process without the isolation of intermediates or removal of aluminum salts. The excess chlorobenzene used in the Freidel-Crafts alkylation serves as an excellent solvent for the PTC/OH⁻ oxidation. The oxidation is performed on the crude Freidel-Crafts reaction mixture (including aluminum salts) by heating the mixture to 45 °C in the presence of Aliquat 336, excess NaOH, and 210 psi of oxygen.

In summary, the oxidation of dihalodiphenylmethane to dihalobenzophenone has been performed under very mild phase-transfer-catalysis conditions with NaOH as the base, oxygen as the oxidizing agent, and water as the major byproduct. Reaction conditions were chosen with the aid of previously reported PTC guidelines,¹ including the effect of quat structure, counteranions, and kinetics. Enhanced para, para selectivity of the Freidel-Crafts alkylation was achieved by using subambient temperatures.

Experimental Section

4-Chlorobenzyl chloride, chlorobenzene, aluminum chloride, phase-transfer catalysts, oxygen, and NaOH were commercially available and were used without further purification. Gas chromatography was performed on a DB5-15N fused silica cappilary column, 15 m, $0.25 \,\mu$ m, installed in a Hewlett-Packard HP 5890A gas chromatograph. Then temperature was programmed from 100 to 300 °C at 20°/min. The carrier gas was nitrogen at a flow of 3.5 mL/min. The injector temperature was 200 °C and the FID detector at 300 °C. Standards of authentic samples of 4,4'-dichlorobenzophenone, 4,4'-dichlorodiphenylmethane and 2,4'-dichlorodiphenylmethane were prepared, and the molar response factors were determined to be 1.13 ($t_{\rm R}$ = 5.41 min), 1.00 (4.69 min), and 1.00 (1.49 min), respectively. NMR spectra of the dichlorodiphenylmethanes prepared were run on an IBM NR-80 80-MHz spectrometer. The methylene protons appeared as follows: 3,4'-dichlorodiphenylmethane, 4.34 ppm; 2,4'-dichlorodiphenylmethane, 4.17 ppm; 4,4'-dichlorodiphenylmethane, 3.98 ppm.

Freidel-Crafts Alkylation. In a 1-L four-necked roundbottomed flask equipped with a mechanical stirrer, dropping funnel, nitrogen gas inlet topped by a calcium chloride drying tube, and a thermal well were placed 2.0 g (0.015 mol) of aluminum chloride and 356 g (3.14 mol) of chlorobenzene. The flask was immersed in an ethylene glycol/water bath cooled to -6 °C. A solution of 128.8 g (0.80 mol) of 4-chlorobenzyl chloride in 266 g (2.36 mol) of chlorobenzene was added dropwise over 33 min to the cooled slurry. The reaction temperature was maintained at -2 to -5 °C throughout the reaction. After an additional 27 min reaction time, the reaction mixture was washed with water and dried over MgSO₄, and the solvent was evaporated. Distillation of the crude product yielded a fraction collected at 142 $^{\circ}C/(0.4 \text{ mmHg})$, which weighed 144.9 g (76%). The ratio of 4,4'-dichlorodiphenylmethane to 2,4'-dichlorodiphenylmethane was 61:39.

Oxidation Kinetics. A solution was prepared by dissolving 10.9 g (0.020 mol) of tetraoctylammonium bromide and 23.7 g (0.10 mol) of a 61:39 mixture of 4,4'-dichlorodiphenylmethane-2,4'dichlorodiphenylmethane, respectively, in 30 mL of toluene. This solution and 50 mL (0.96 mol) of 50% NaOH were placed in a 350-mL stainless steel Parr bomb equipped with a sampling port, thermocouple, mechanical stirrer, oxygen inlet tube, pressure gauge $(\pm 10 \text{ psi})$, and a heating mantle equipped with a thermocouple external to the bomb. The bomb was sealed and pressurized to 200 psi with oxygen. The temperature of the reaction was maintained in the range 40-50 °C with vigorous stirring. Samples were taken at regular intervals for GC analysis. The reaction was allowed to proceed for 18-22 h, after which the product was analyzed after total dissolution of the reaction mixture in methylene chloride-water (1:1 v/v).

Alkylation and Oxidation without Isolation of Intermediates. To the vessel described in the alkylation procedure were added 1.0 g (0.0075 mol) of AlCl₃ and 178 g (1.57 mol) of chlorobenzene. The mixture was cooled to -5 °C, and a solution of $64.4~{\rm g}~(0.40~{\rm mol})$ of 4-chlorobenzyl chloride in 133 g (2.9 mol) of chlorbenzene was added dropwise during 30 min, maintaining a reaction temperature of 0-5 °C. After an additional 80 min at

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-3 to 5 °C, 230 mL (4.9 mol) of 50% NaOH was added to neutralize the HCl and decompose the remaining aluminum salts. The conversion of 4-chlorobenzyl chloride was 100% containing 66% of the 4,4'-isomer and 7% dialkylation products. The contents of the flask were transferred to a 1-L steel bomb equipped with a magnetically driven efficient stirring rod with baffles and gas dispersion capability, an oxygen inlet, pressure gauge, rpm meter, heating unit with external and internal thermocouples, and a sampling port. To the mixture was added 15.8 g (0.039 mol) of Aliquat 336. The bomb was sealed and charged with 210 psig of oxygen at 25 °C. The vessel was heated, and the reaction mixture was maintained at 46-50 °C and 150-210 psig for 92 h (83% conversion at 92 h and 70% conversion of the 4,4'-dichlorodiphenylmethane at 26.2 h). The product was treated with methylene chloride and water, and the organic phase solvent was evaporated to yield 135 g of crude product. Of this crude product, 106 g were triturated with 100 mL of hexane and washed with an additional 100 mL of hexane to yield 48 g of material after filtration. This material was 85% 4,4'-dichlorobenzophenone by GC analysis.

Acknowledgment. We wish to thank Alan J. Williams, Lab Director of the Organic Specialties Laboratory in the Dow Chemical Co., for his generous and patient support of this research project.

Registry No. Oct₃NMe⁺Cl⁻, 5137-55-3; Oct₄N⁺Br⁻, 14866-33-2; Bu₄N⁺HSO₄⁻, 32503-27-8; Bu₄N⁺Br⁻, 1643-19-2; Et₃NCH₂Ph⁺Cl⁻, 56-37-1; bromochlorodiphenylmethane, 118631-45-1; chlorobenzene, 108-90-7; 4-chlorobenzyl chloride, 104-83-6; 4,4'-dichlorodiphenylmethane, 101-76-8; 2,4'-dichlorodiphenylmethane, 52094-02-7; 4,4'-dichlorobenzophenone, 90-98-2; bromobenzene, 108-86-1.

Trimethylsilyl Azide/Triflic Acid, a Highly **Efficient Electrophilic Aromatic Amination** Reagent¹

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Received August 3, 1988

Introduction

Aromatic amines are important synthetic intermediates. Usually they are prepared by nitration of the aromatics followed by the reduction of the corresponding nitro compounds.² Direct one-step aminations of aromatics are known but so far give only moderate yields ($\leq 75\%$).^{2,3}

The direct electrophilic amination of aromatics has its origin in Graebe and Jaubert's work of 1901.⁴ They discovered the amination of aromatic hydrocarbons with hydroxylammonium chloride in the presence of Friedel-Crafts catalysts. Kovacic and co-workers systematically investigated aminations with different reagents such as hydroxylamine and its salts,⁵ alkylhydroxylamines,⁶ hydroxylamine-O-sulfonic acid,⁷ and hydrazoic acid.⁸ Usu-

Scheme I. Protonation of Hydrazoic Acid



ally a 2-fold molar excess of a Friedel-Crafts halide was necessary to provide sufficient reactivity. The catalysts coordinate with the reagent and increase the polarization of the nitrogen-oxygen bond and thus increase the electrophilic nature of the nitrogen.⁵⁻⁸ The yields of these reactions vary between 5 and 70%.5-8 The reported isomer distributions confirm the electrophilic nature of the reactions, but an involvement of the free nitrenium ion NH2⁺ seems unlikely.

Olah and co-workers investigated the structure and properties of the aminodiazonium ion prepared by protonation of hydrazoic acid in superacids.⁹ In contrast to the stable aromatic diazonium ions, aliphatic diazonium ions generally can only be obtained in highly acidic media due to elimination of nitrogen. Olah was able to show by NMR spectroscopy that hydrazoic acid, as well as methyl or ethyl azides, was protonated under superacidic stable ion conditions. Regarding the mesomeric structures of azides $(1 \Rightarrow 2)$, the protonation could take place either on N-1 or on N-2. The former would lead to the mesomeric aminodiazonium ion (3-5) and the latter to the iminodi-¹⁵N NMR spectroscopy azenium ion (6) (Scheme I). showed evidence only for the formation of the aminodiazonium ion.

A convenient in situ preparation of the aminodiazonium ion allowing its use for the amination of aromatics was also reported.⁹ For this purpose sodium azide (or trimethylsilyl azide) was reacted with anhydrous aluminum chloride and subsequently with dry hydrogen chloride gas to form the aminodiazonium tetrachloroaluminate. This intermediate reacts with aromatic hydrocarbons and leads to the corresponding aminoarenes in relatively good yields (e.g. toluene $\sim 73\%$, chlorobenzene $\sim 25^{\circ}$). The observed isomer distributions are typical for electrophilic aromatic substitutions.

In continuation of our studies we now have found in trimethylsilyl azide/triflic acid a highly efficient improved reagent system that allows simple and nearly quantitative amination of aromatics.

Results and Discussion

On the basis of our earlier work,⁹ trimethylsilyl azide is a suitable and improved synthon for aromatic amination, because it is a well-known source of azide, soluble in most organic solvents, and should not form cumbersome insoluble salts after cleavage of the silicon-nitrogen bond. In order to improve the homogeneity of the system and to provide stable ion conditions, a protic superacid should

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