Efficient Method for Varying the Anions in Quaternary Onium Halides

Jong Yeob Jeon,[a] Jobi Kodiyan Varghese,[a] Ji Hae Park,[a] Suck-Hyun Lee,[a] and Bun Yeoul Lee*[a]

Quaternary onium salts of halides can be efficiently converted into the corresponding quaternary onium salts of various anions [NO_3^-, BF_4^-, PF_6^-, $CF_3SO_3^-$, $CH_3SO_3^-$, ClO_4^-, p-$CH_3C_6H_4SO_3^-$, $CF_3CO_2^-$, $2,4$-$(NO_2)_2C_6H_3O^-$] by treating the onium halide with trimethyl phosphate under neat condition in the presence of an equivalent amount of conjugate acid of the desired anion.

Introduction

A wide variety of applications of quaternary ammonium salts have been found in modern chemistry.[1] These salts have drawn attention not only as greener ionic liquid solvents[2] but also as components in catalytic reactions such as CO_2/epoxide coupling[3] or CO_2/epoxide copolymerization.[4] The properties of ionic liquids, such as solubility and viscosity, can be tuned through suitable choice of the cation/anion combination. Some anions are toxicophores that influence the biological effects of the ionic liquids.[5] Quaternary ammonium salts are typically prepared by S_N2 reaction of a neutral amine with an alkyl halide, and hence, the most common anions in quaternary ammonium salts are halides. Exchange of the halide anion with another anion is frequently required. This can be easily carried out by using the silver salt of the desired anion, but silver complexes are expensive and can cause prohibitive costs for large-scale preparations. Moreover, the silver halide by-product cannot be easily converted into a valuable silver metal or silver reagent. Anion exchange can be inexpensively achieved through salt metathesis by using the alkaline metal salt of the desired anion, but this approach is successful only in a limited number of situations. The desired product should precipitate in water from the water-soluble quaternary ammonium halide after the addition of the alkaline metal salt of the desired anion.[6] For example, an ionic liquid ([bmim]$^+$$PF_6^-$; [bmim]$^+$ = 1-butyl-3-methylimidazolium) can be prepared directly from [bmim]$^+$$Br^-$ by mixing with $NaPF_6$ in water. Contamination with a certain amount of halide ions, along with the loss of some product into the water phase, may be inevitable in this salt metathe-

sis reaction. Recently, a method using ion-exchange resins was introduced, but this method may not be feasible for large-scale synthesis either.[7] In this method, the exchange is driven by statistics and requires an excess amount of anions on the stationary resin. To reuse the resin, the halide ions collected on the resin should be thoroughly rinsed out by using copious amounts of solution containing the desired anion.

Recently, we developed a very efficient catalyst for CO_2/epoxide copolymerization, a salen-cobalt(III) complex tethered by quaternary ammonium salts [**3** in Equation (1)].[8] A synthetic route for large-scale production of the complex was also developed (100 kg-scale).[9] The most costly step in this synthesis is iodide exchange with nitrate anions by using expensive $AgNO_3$ [i.e., conversion of **1** into **2** in Equation (1)]. Because the polymer chain grows from the nitrate anions in **3**, a silver atom must be consumed to prepare a polymer chain. The catalyst activity is very sensitive not only to the ligand structure[10] but also to the anion of the quaternary ammonium salt.[11] In particular, the complex prepared from a ligand bearing halide ions does not show

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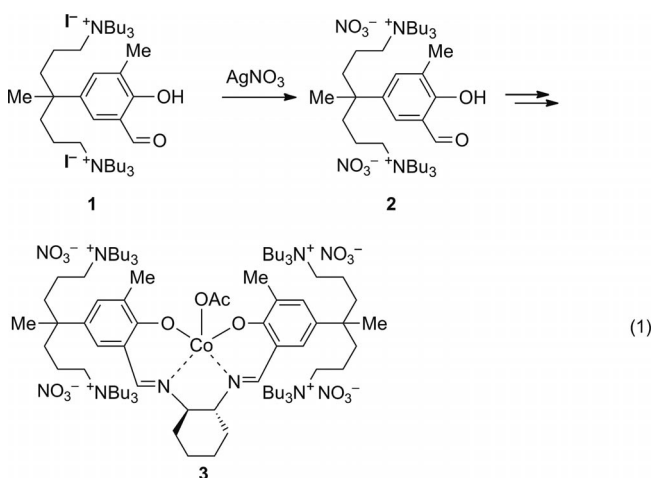
[a] Department of Molecular Science and Technology,
Ajou University,
Suwon 443-749 Korea
Fax: 82-31-219-2394
E-mail: bunyeoul@ajou.ac.kr

any activity, so halide exchange to another active anion is necessarily demanded. In this work, we report an efficient method for the conversion of quaternary ammonium halides into the salts of various anions. The method can be cost-effectively carried out with reactants under neat conditions on a large scale.

Results and Discussion

The strategy involves treating the quaternary ammonium halide with trimethyl phosphate. In the reaction, the halide anion attacks the methyl group of trimethyl phosphate, generating a fairly stable dimethyl phosphate anion (pK_a = 1.54).[12] One byproduct is produced, that is, a volatile halomethane, which can be easily removed with weak N_2 purging. Trimethyl phosphate is an inexpensive chemical available in large quantities. Similarly, it was reported that the hydroxide anion in tetrabutylammonium hydroxide attacks trimethyl phosphate at 100 °C to produce methanol, generating a dimethyl phosphate anion.[13] The generated dimethyl phosphate anion can be converted into other desired anions through the addition of the conjugate acid of the desired anion. Contrary to expectation, the reaction between quaternary ammonium iodide **1** and trimethyl phosphate is sluggish. When a homogeneous solution of **1** in trimethyl phosphate (1:4 ratio by weight, 1:25 ratio by mol) is heated under neat conditions at 60 °C for 15 h under weak N_2 purging, the reaction does not go to completion. Addition of an aliquot of the reaction mixture into a solution of $AgNO_3$ in methanol gives rise to white AgI precipitates, indicating the presence of iodide anions in the reaction pot. When the reaction temperature is increased to 100 °C, all of the iodide anions disappear, but some side reactions occur. The phenol moiety is methylated to form methyl ether.

The strategy is finally realized through the simultaneous addition of an equivalent amount of HNO_3 to the reaction pot. This addition accelerates the reaction, and all iodide anions are completely converted into iodomethane even at 60 °C, without any side reactions. The byproduct, iodomethane, is volatile (b.p. 42 °C) and is easily removable with weak N_2 purging during the reaction [Equation (2)]. No solid precipitates when an aliquot of the reaction pot, taken after 15 h of the reaction at 60 °C, is added to a $AgNO_3$ solution in methanol. The action of nitric acid enhances the electrophilicity of trimethyl phosphate, enabling nucleophilic attack by the iodide anion even at a low temperature of 60 °C. Because nitric acid is a stronger acid (pK_a = –1.3) than dimethyl phosphoric acid (pK_a = 1.54), the nitrate anion can directly counter the quaternary ammonium cation with the formation of dimethyl phosphoric acid [HOP-(O)(OMe)$_2$] as a byproduct. The reaction is carried out with the reactants of **1** and trimethyl phosphate in 1:1 ratio by weight under neat conditions without any additional solvent. The byproduct, dimethyl phosphoric acid, remains in the residue with product **2** even after evacuation at temperatures as high as 100 °C. An equivalent amount of dimethyl

phosphoric acid can be detected in the ^1H NMR spectrum. It can be completely removed by washing with water after neutralization with aqueous NH_4OH solution. Thus, the reaction mixture is dissolved in CH_2Cl_2 (5 mL per gram of **1**) and treated with aqueous NH_4OH (two molar amount of **1**, 3 mL of water solution per gram of **1**). By neutralization, dimethyl phosphoric acid becomes the dimethyl phosphate anion, which is highly hygroscopic and hence stays completely in the water phase. However, product **2** stays in both the CH_2Cl_2 and water phases in a ratio of approximately 7:3 at this stage. When $NaNO_3$ (two molar amount of **1**) is dissolved in the water phase, the product in the water phase moves to the CH_2Cl_2 phase because of the common-ion effect. Pure **2** can be isolated in an almost quantitative yield by collecting the CH_2Cl_2 phase. The catalyst synthesized from **2** prepared in this way shows exactly the same performance that was shown by the catalyst prepared by using $AgNO_3$.
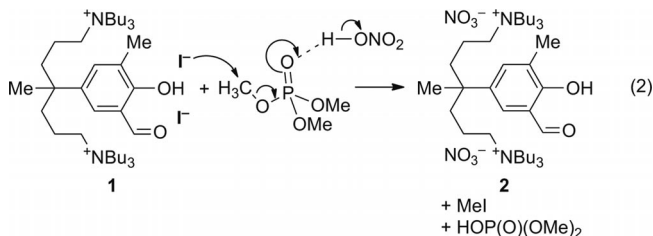
Through this strategy, quaternary onium salts of various anions can be prepared from the corresponding quaternary onium halide (Table 1). Tetrabutylammonium iodide is almost quantitatively converted into tetrabutylammonium nitrate under the same conditions and procedures employed for the preparation of **2** (Table 1, Entry 1). Quaternary ammonium bromide is a more attractive substrate than the iodide salt, because it is cheaper and available in larger quantities. Tetrabutylammonium bromide is also converted almost quantitatively into tetrabutylammonium nitrate through this method (Table 1, Entry 2). This method is easily scalable: tetrabutylammonium nitrate can be prepared on a 30-g scale in a laboratory by using a 100-mL glass reactor. Tetrabutylammonium bromide is available in kilogram quantities from Aldrich, but tetrabutylammonium nitrate is expensive and sold only in small amounts (10 g). This method is also applicable to tetrabutylammonium chloride (Table 1, Entry 3), but tetrabutylammonium chloride is not an attractive substrate, because it is much more expensive than tetrabutylammonium bromide. Tetrabutylammonium salts of various anions [BF_4^-, PF_6^-, $CF_3SO_3^-$, $CH_3SO_3^-$, ClO_4^-, p-$CH_3C_6H_4SO_3^-$, $CF_3CO_2^-$, 2,4-$(NO_2)_2C_6H_3O^-$ (2,4-dinitrophenolate)] can be prepared from tetrabutylammonium bromide by adding various acids instead of nitric acid [Equation (3); Table 1, Entries 4–11]. The isolated yields are high in all cases (>90%). Complete conversion was proved in each reaction by a negative $AgNO_3$ test. In all cases, formation of white AgBr precipitates is not observed at the $AgNO_3$ treatment. The high quality of each product is proved by ^1H, ^{13}C, ^{17}F, and ^{31}P NMR spectroscopy and elemental analysis. The products

are off-white-colored solids and the melting points are in agreement with the reported values. When acetic acid is used instead of nitric acid, conversion of bromide anions into bromomethane is accelerated, but the generated dimethyl phosphate anion is not protonated by acetic acid. Complete evacuation after the reaction eliminates the added acetic acid to give the pure tetrabutylammonium salt of the dimethyl phosphate anion $\{[Bu_4N]^+[(MeO)_2P(O)O]^-\}$ in high yield (96%). Tetrabutylphosphonium bromide is also converted into tetrabutylphosphonium salts of various anions without any problems under the same procedure and conditions (Table 1, Entries 12–14).
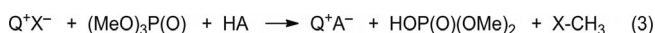
$$Q^+X^- + (MeO)_3P(O) + HA \longrightarrow Q^+A^- + HOP(O)(OMe)_2 + X\text{-}CH_3 \quad (3)$$

Table 1. Conversion of quaternary onium halides into their onium salts of various anions.[a]

Entry	Q^+	X^-	A^-	Yield [%]	M.p.[b] [°C]
1	Bu_4N^+	I^-	NO_3^-	96	117–118 (116–118)
2	Bu_4N^+	Br^-	NO_3^-	95 (98.5[c])	117–118 (116–118)
3	Bu_4N^+	Cl^-	NO_3^-	90	117–118 (116–118)
4	Bu_4N^+	Br^-	BF_4^-	90	161–162 (155–161)
5	Bu_4N^+	Br^-	PF_6^-	96	246–247 (244–246)
6	Bu_4N^+	Br^-	$CF_3SO_3^-$	93	111–112 (112–113)
7	Bu_4N^+	Br^-	$CH_3SO_3^-$	90	76–77 (70–80)
8	Bu_4N^+	Br^-	ClO_4^-	95	214–215 (211–215)
9	Bu_4N^+	Br^-	pTsO$^-$	95	70–71 (70–72)
10	Bu_4N^+	Br^-	$CF_3CO_2^-$	92	57–58
11	Bu_4N^+	Br^-	DNP^{-}[d]	91	101–103
12	Bu_4P^+	Br^-	NO_3^-	90	71–72
13	Bu_4P^+	Br^-	BF_4^-	94	95–98 (96–99)
14	Bu_4P^+	Br^-	$CF_3SO_3^-$	96	107–108
15	bbim$^+$[e]	Br^-	NO_3^-	92	liquid
16	bbim$^+$	Br^-	BF_4^-	96	liquid
17	bbim$^+$	Br^-	$CF_3SO_3^-$	91	liquid

[a] Reaction conditions: Q^+X^- (3.10 mmol), HA (3.10 mmol), trimethyl phosphate (37 mmol), 60 °C, 15 h. [b] Values in parentheses are the ones reported in the Aldrich catalogue. [c] Yield for 30-g scale synthesis. [d] 2,4-Dinitrophenolate. [e] 1,3-Dibutylimidazolium.

When 1-butyl-3-methylimidazolium bromide ([bmim]$^+$Br$^-$) is treated with trimethyl phosphate in the presence of nitric acid, the bromide anions are completely converted into volatile bromomethane, but the product [bmim]$^+$NO$_3^-$ is highly soluble in water, hampering its isolation through extraction with dichloromethane. The byproduct, dimethyl phosphoric acid, cannot be completely removed by evacuation even at a temperature as high as 120 °C. However, hydrophobic 1,3-dibutylimidazolium ([bbim]$^+$) salts of various anions can be prepared from [bbim]$^+$Br$^-$ according to this protocol with high yields (>90%; Table 1, Entries 15–17). For other hydrophilic quaternary ammonium halides such as N-butylpyridium bromide or tetraethylammonium bromide, the reaction with trimethyl phosphate in the presence of nitric acid is successful, but isolation of the nitrate salt is impossible because of the high solubility of the product in water.

Conclusions

The halide anion in a quaternary onium salt attacks trimethyl phosphate in the presence of an equivalent amount of strong acid under neat and mild conditions (60 °C, 15 h). Through this reaction, the halide anion in the quaternary onium salt can be efficiently exchanged with various anions [NO_3^-, BF_4^-, PF_6^-, $CF_3SO_3^-$, $CH_3SO_3^-$, ClO_4^-, p-$CH_3C_6H_4SO_3^-$, $CF_3CO_2^-$, 2,4-$(NO_2)_2C_6H_3O^-$]. This protocol can be applied to large-scale syntheses, allowing for economical preparation of key intermediates for a highly active catalyst for CO_2/epoxide copolymerizations.

Experimental Section

Typical Procedure for Conversion of Q^+X^- into Q^+A^- (Small Scale): HA (3.10 mmol) was slowly added to a flask containing trimethyl phosphate (5.21 g, 37.2 mmol) at 0 °C. Q^+X^- (3.10 mmol) was added to this solution with stirring. After the mixture was stirred at 60 °C for 15 h under weak N_2 bubbling, the excess amount of trimethyl phosphate was removed by vacuum distillation (37 °C/ 0.07 Torr). The residue was dissolved in dichloromethane (5 mL) and 10% aqueous NH_4OH solution (3.10 mmol, ≈4 mL) was added dropwise to make the solution neutral. NaA (3.10 mmol) was dissolved in the water phase. The two phases were stirred at room temperature for 2 h. The organic phase was collected, and the aqueous layer was extracted with an additional amount of dichloromethane (2 mL). The organic phases were combined, and the solvent was removed with a rotary evaporator. A small amount of residual trimethyl phosphate was completely removed through evacuation at 100 °C for 2 h.

Conversion of $Bu_4N^+Br^-$ into $Bu_4N^+NO_3^-$ (30-g Scale): Nitric acid (69%, 8.50 g, 93.1 mmol) was slowly added to a flask containing trimethyl phosphate (30.0 g, 214 mmol) at 0 °C. $Bu_4N^+Br^-$ (30.0 g, 93.1 mmol) was added to this solution with stirring. After the mixture was stirred at 60 °C for 15 h under weak N_2 bubbling, the resulting mixture was dissolved in dichloromethane (150 mL) and 10% aqueous NH_4OH solution (93.1 mmol, ≈120 mL) was added dropwise to make the solution neutral. NaNO$_3$ (7.91 g, 93.1 mmol) was dissolved in the water phase. The two phases were stirred at room temperature for 2 h. The organic phase was collected, and the solvent was removed with a rotary evaporator. A small amount of residual trimethyl phosphate was completely removed through evacuation at 100 °C for 2 h. The product was an off-white solid and the yield was 97.4% (27.6 g).

Conversion of 1 into 2: Nitric acid (69%, 2.10 g, 23.0 mmol) was slowly added to a flask containing trimethyl phosphate (10.0 g, 71.4 mmol) at 0 °C. {3-Methyl-5-[{Bu$_3$N$^+$(CH$_2$)$_3$}$_2$CMe]salicylaldehyde}(I$^-$)$_2$ (1; 10.0 g, 11.5 mmol) was added to this solution with stirring. After the mixture was stirred at 60 °C for 20 h under weak N_2 bubbling, the resulting oily mixture was dissolved in dichloromethane (50 mL) and 10% aqueous NH_4OH solution (23.0 mmol, ≈30 mL) was added dropwise to make the solution neutral. NaNO$_3$ (1.95 g, 23.0 mmol) was dissolved in the water phase. The two phases were stirred at room temperature for 2 h. The organic phase was collected, and the solvent was removed with a rotary evaporator to obtain a yellowish oil. A small amount of residual trimethyl phosphate was completely removed through evacuation at 100 °C for 2 h. The yield was 97% (8.50 g).

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra of new compounds and elemental analysis data.

Acknowledgments

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