A two-phase bromination process using tetraalkylammonium hydroxide for the practical synthesis of α-bromolactones from lactones

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Abstract

A simple and efficient method for α-brominating lactones that affords α-bromolactones under mild conditions using tetraalkylammonium hydroxide (R₄N⁺OH⁻) as a base was developed. Lactones are ring-opened with Br₂ and a substoichiometric amount of PBr₃, leading to good yields of the corresponding α-bromocarboxylic acids. Subsequent intramolecular cyclization over 1 h using a two-phase system (H₂O/CHCl₃) containing R₄N⁺OH⁻ afforded α-bromo lactones in good yields. This method can be applied at the 10 mmol scale using simple operations. α-Bromo-δ-valerolactone, which is extremely reactive and difficult to isolate, could be isolated and stored in a freezer for about one week using the developed method. Optimizing the solvent for environmentally friendly large-scale syntheses revealed that methyl ethyl ketone (MEK) was as effective. In addition, in situ-generated α-bromo-δ-valerolactone was directly converted into a sulfur-substituted functional lactone without difficulty by reacting it with a sulfur nucleophile in one pot without isolation. This new bromination system is expected to facilitate the industrial use of α-bromolactones as important intermediates.

Introduction

Lactones are important heterocycles in the organic chemistry, materials science, and medicinal chemistry fields, and bromolactones are important synthetic intermediates for selectively, effectively, and practically introducing lactone units into organic molecules [1-18]. Among brominated lactones, the α-bromolactone, in which the bromine atom is located at the
**Scheme 1:** General procedure for α-bromination of δ-valerolactone (1a) and the method described in this work.

a) general procedure for α-brominating δ-valerolactone

1a \[\text{LDA (excess)} \rightarrow \text{TMSCI} \rightarrow \text{Br}_2, \text{Et}_3\text{N} \rightarrow 3a\]

b) this work

1a \[\text{Br}_2 (2 \text{ equiv}) \rightarrow \text{PBr}_3 \text{ cat.} \rightarrow \text{2a} \rightarrow \text{Br} \rightarrow \text{R}_2\text{N}^+\text{OH}^- (1.2 \text{ equiv}) \rightarrow 3a\]

**Results and Discussion**

We begin by first discussing the properties and stabilities of industrially important five- and six-membered lactones. γ-Butyrolactone and its α-brominated derivative are both stable at room temperature; α-bromo-γ-butyrolactone is readily synthesized by brominating the five-membered lactone under basic conditions. In sharp contrast, the corresponding six-membered α-bromo-δ-valerolactone has a more-distorted ring and is extremely unstable, even at room temperature [39-41]. In fact, it must be stored in a freezer because ring-opening polymerization and ring-contraction reactions occur readily at room temperature (see Supporting Information File 1). Therefore, in this study, we chose unstable δ-valerolactone (1a) as a model compound during the development of a new and innovative method for the synthesis of α-bromolactones, and investigated the reaction conditions in detail.

We first examined the Hell–Volhard–Zelinsky-type ring-opening reaction of 1a (Table 1). In this reaction, the corresponding acid bromide is formed in situ by heating with Br₂ and
Table 1: Ring-opening reactions of lactones with Br₂ in the presence of a substoichiometric amount of PBr₃.

| Entry | 1 (mmol) | Br₂ (equiv) | PBr₃ (mol %) | Temp. (°C) | Time (h) | Yield 2 (%) |
|-------|----------|-------------|--------------|------------|----------|-------------|
| 1     | 5a: n = 1 | 5           | 2.0          | 5          | 80       | 24          | 2a: 90 |
| 2     | 5a: n = 1 | 5           | 2.0          | –          | 80       | 24          | 2a: 1  |
| 3     | 5a: n = 1 | 31          | 2.0          | 10         | 80       | 24          | 2a: 89 |
| 4     | 5b: n = 0 | 31          | 2.0          | 10         | 90       | 24          | 2b: 76 |
| 5     | 5c: n = 2 | 31          | 2.0          | 10         | 90       | 24          | 2c: 70 |

*Yields were determined by ¹H NMR spectroscopy using 1,3,5-trioxane as an internal standard.*

Since we successfully synthesized carboxylic acid 2a from lactone 1a in good yield, we next investigated the ring-closing reaction of 2a. Various acids and bases (PTSA, hydrochloric acid, NaOH, KOH, and NaHCO₃) were used to promote the intramolecular cyclization of 2a; however, no reaction was observed using any of these acids/bases. Interestingly, 2a was converted into 3a in very low yield when 1.2 equiv of n-Bu₄N⁺F⁻ was used, despite n-Bu₄N⁺F⁻ itself being less basic than the other bases (Scheme 2a) [42,43]. These results suggest that the properties of the counter cation may be important for the intramolecular cyclization of 2a. Based on this observation, we next examined n-Bu₄N⁺O⁻H⁻, a more-basic R₄N⁺X⁻ system, for the ring-closure of 2a. Surprisingly, the reaction proceeded...
smoothly to give α-bromo-δ-valerolactone (3a) in 52% yield in 43 h (Scheme 2b). However, further extending the reaction time to 72 h resulted in a dramatically lower yield of 3a (8%), most likely because 3a is unstable to base at room temperature and may decompose or polymerize (see Supporting Information File 1).

To avoid decomposition or polymerization, 3a produced in situ by the intramolecular cyclization of 2a should be separated immediately from the reaction mixture containing n-Bu₄N⁺OH⁻. Tetraalkylammonium salts are used as phase-transfer catalysts as they are soluble in both organic solvents and water. With these properties in mind, we next investigated the ring-closure of 2a using a two-phase CHCl₃/H₂O system (Table 2). Intramolecular cyclization of the salt forms 3a, which is extracted into the organic layer due to its low solubility in water. Because n-Bu₄N⁺OH⁻ is less-soluble in organic solvents than water, 3a is phase-separable from the base. To our delight, 2a was smoothly converted into 3a in 74% yield in this two-phase system, with the reaction time successfully reduced to 1 h (Table 2, entries 1–5). The use of a co-solvent to increase the solubility of 2a was investigated in detail; DMSO was found to be the most effective solvent, with 3a produced in 82% yield (Table 2, entries 5–12).

| Table 2: Optimizing the intramolecular cyclization of 2a in a two-phase systema. |
|-------------------|-------------------|-------------------|
| Entry | Solvent | Time (h) | Yield 3a (%) |
|-------|---------|----------|--------------|
| 1     | CH₂CN   | 24       | 29           |
| 2     | CH₃CN   | 18       | 38           |
| 3     | CH₃CN   | 9        | 58           |
| 4     | CH₃CN   | 3        | 65           |
| 5     | CH₃CN   | 1        | 74           |
| 6     | MeOH    | 1        | 29           |
| 7     | EtOH    | 1        | 51           |
| 8     | iPrOH   | 1        | 68           |
| 9     | THF     | 1        | 61           |
| 10    | DMSO    | 1        | 82           |
| 11    | DMF     | 1        | 64           |
| 12    | none    | 1        | 65           |

aYields were determined by ¹H NMR spectroscopy using 1,3,5-trioxane as an internal standard.

We next optimized the base used to cyclize 2a in the two-phase system under the optimized conditions (entry 10, Table 2), the results of which are summarized in Table 3. The use of tetraalkylammonium hydroxides with longer alkyl chains tended to increase the yield of 3a (Table 3, entries 1–5), while the use of diisopropylethylamine, triethylamine, DBU, or Cs₂CO₃ was

| Table 3: Optimizing the base for the intramolecular cyclization of 2a to 3a. |
|-------------------|-------------------|-------------------|
| Entry | Base | Yield 3a (%) |
|-------|------|--------------|
| 1     | n-Bu₄N⁺OH⁻ (40% in H₂O) | 82 |
| 2     | n-Pr₄N⁺OH⁻ (40% in H₂O) | 67 |
| 3     | Et₄N⁺OH⁻ (40% in H₂O) | 36 |
| 4     | (10% in H₂O) | 37 |
| 5     | Me₄N⁺OH⁻ (40% in H₂O) | 21 |
| 6     | Et₃N | 34 |
| 7     | Et₂N | 34 |
| 8     | Cs₂CO₃ | 39 |
| 9     | none | – |

aYields were determined by ¹H NMR spectroscopy using 1,3,5-trioxane as an internal standard.
less effective (Table 3, entries 6–9); furthermore, the reaction did not proceed in the absence of a base (Table 3, entry 10). This investigation revealed that medium-chain tetraalkylammonium hydroxides, namely $n$-Bu$_4$N$^+$OH$^-$ and $n$-Pr$_4$N$^+$OH$^-$, effectively transform $2a$ into $3a$ through intramolecular cyclization.

We next investigated the effect of the size of the lactone ring on the $\alpha$-bromination reaction in this two-phase system. Table 4 shows that $2a$ and $2b$ were transformed to $3a$ and $3b$ in good yields, but $2c$ did not react under these conditions due to the entropic cost associated with forming a seven-membered ring. Lactones $3a$ and $3b$ were obtained in good yields even when $n$-Pr$_4$N$^+$OH$^-$ was used as the base [44].

### Table 4: Reaction scope for the the intramolecular cyclization of $2$ in a two-phase system

| Entry | $n$ | Base                  | Yield $3$ (%) |
|-------|----|-----------------------|---------------|
| 1     | 2a: $n = 1$ | $n$-Bu$_4$N$^+$OH$^-$ | 74            |
|       | 2b: $n = 0$ | $n$-Pr$_4$N$^+$OH$^-$ | 75$^b$        |
| 2     | 2c: $n = 2$ | $n$-Bu$_4$N$^+$OH$^-$ | 69            |
|       |           | $n$-Pr$_4$N$^+$OH$^-$ | 73 (61)       |

$^a$Yields were determined by $^1$H NMR spectroscopy using 1,3,5-trioxane as an internal standard (isolated yield). $^b$See reference [44].

While the developed two-phase CHCl$_3$/H$_2$O system performed well for the syntheses of $\alpha$-bromolactones, the use of CHCl$_3$ as the reaction solvent should ideally be avoided because it is toxic and an environmental pollutant. Therefore, we further optimized the solvent combination to construct an eco-friendlier reaction system (Table 5). Various solvents were used as the organic layer instead of CHCl$_3$, with $3a$ produced in good yield using methyl ethyl ketone (MEK) as the solvent (Table 5, entries 1–5). Although the use of other ketones as solvents also afforded $3a$ in moderate yields, MEK proved to be the most suitable replacement for CHCl$_3$ (Table 5, entries 5–8).

### Table 5: Optimizing the organic solvent in the two-phase system

| Entry | Solvent       | Yield $3a$ (%) |
|-------|---------------|---------------|
| 1     | CHCl$_3$      | 74            |
| 2     | FC-72         | 56            |
| 3     | BTF           | 43            |
| 4     | 2-bromopropane| 33            |
| 5     | MEK           | 75            |
| 6     | acetylacetone | 64            |
| 7     | 3-methyl-2-butanol | 55 |
| 8     | pinacolone    | 49            |

$^a$Yields were determined by $^1$H NMR spectroscopy using 1,3,5-trioxane as an internal standard.

This environmentally friendly procedure was used to synthesize other lactones. For instance, this method was used to prepare $3b$ from $2b$ in 84% yield on a 10 mmol scale (Scheme 3a). Furthermore, this system also provided 2,2-
diphenyl-γ-butyrolactone (3d), which bears two phenyl groups at the α-position, in 78% yield (Scheme 3b).

α-Bromolactones were obtained without any handling difficulties using our developed system, with synthesis scale-up tolerated under mild conditions. To facilitate the construction of various functional scaffolds using this system, lactones were subsequently α-functionalized via the corresponding α-bromolactones using this two-phase system. Interestingly, 3b synthesized using this method was smoothly substituted at the α-position with benzenethiol (4) in the presence of K₂CO₃ to afford the unsymmetrically functionalized sulfide 5 in 86% yield; 5 is a precursor to some pharmaceutical cores (Scheme 4) [45-48].

However, α-bromo-δ-valerolactone (3a) was extremely unstable under ambient conditions, and its purity quickly deteriorated even when stored in a freezer with shading (see Supporting Information File 1), resulting in trace amounts of α-functionalized lactones using the above-mentioned two-step method. Hence, we focused on sequential nucleophilic substitution in a two-phase system based on this bromination protocol. After ring-closing 2a, the generated α-bromolactone 3a was extracted into the organic layer, whereas the formed n-Bu₄N⁺Br⁻ dissolved in both the aqueous and organic layers. N-Bu₄N⁺Nu⁻ is formed when Na⁺Nu⁻ (Nu⁻: nucleophile) is added to the reaction mixture, which is then phase-transferred into the organic phase, with subsequent nucleophilic substitution at the α-position of 3a proceeding directly to produce a variety of α-substituted lactones, along with the regeneration of n-Bu₄N⁺Br⁻ (Scheme 5).

To demonstrate the applicability of this protocol, we investigated the synthesis of 2-phenylthio-α-valerolactone (6). Carboxylic acid 2a (2.0 mmol) directly reacted with n-Bu₄N⁺OH⁻ (1.2 equiv) and PhS⁻Na⁺ in the two-phase system under the optimized conditions for the synthesis of α-bromolactones, and 6 was successfully obtained in 72% yield (Scheme 6). These results demonstrate that this novel system facilitates the easy syntheses of functional molecules via α-bromolactones as key synthetic intermediates.

### Conclusion

In this study, we developed a facile and efficient method for α-brominating lactones using tetraalkylammonium hydroxide (R₄N⁺OH⁻) as the base under mild conditions. Lactones were ring-opened with Br₂ and a substoichiometric amount of PBr₃, which led to the corresponding α-bromocarboxylic acids in

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**Scheme 4:** Synthesis of unsymmetrically functionalized sulfide 5 via the two-phase system-promoted intramolecular cyclization of 2b.

**Scheme 5:** Sequential nucleophilic substitution in the two-phase system.
good yields. These carboxylic acids subsequently underwent intramolecular cyclization in 1 h using a two-phase system (H$_2$O/CHCl$_3$) with R$_4$N$^+$OH$^-$ to afford α-bromolactones in excellent yields. The use of methyl ethyl ketone (MEK) in the two-phase system led to an eco-friendly system amenable to large-scale synthesis. Furthermore, the α-bromolactones generated in situ by this method were transformed into functional molecules, such as α-thiolated lactones, in good yields without any handling difficulties. We expect that this new bromination system will lead to the use of various α-bromolactones as synthetic intermediates in organic chemistry.

**Experimental**

**General comments.** Unless otherwise stated, all starting materials and catalysts were purchased from commercial sources and used without further purification. All solvents were used without distillation. $^1$H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) FT NMR system or a JEOL JNM-ECX400 (400 MHz) FT NMR system in CDC$_3$ with Me$_4$Si as an internal standard. $^{13}$C ($^1$H) NMR spectra were recorded on a JEOL JNM-ECX400 (100 MHz) FT NMR or JEOL JNM-ECS400 (100 MHz) FT NMR system in CDC$_3$.

**Ring-opening reaction of δ-valerolactone (1a) with Br$_2$ in the presence of a catalytic amount of PBr$_3$ (entry 1, Table 1).** To a 50 mL three-neck flask were added δ-valerolactone (1a, 5 mmol) and PBr$_3$ (5 mol %), then Br$_2$ (1.0 equiv) was added dropwise for 2 h at 0 °C. After adding Br$_2$, another amount of Br$_2$ (1.0 equiv) was added to the reaction mixture for 30 min at 70 °C. The resulting solution was then stirred for 24 h at 80 °C. After the reaction was completed, the mixture was dissolved in CH$_2$CN (30 mL) and bubbling N$_2$ gas to remove excess amount of Br$_2$ and the formed HBr (under open-air) then filtered. The filtrate was concentrated under reduced pressure to produce 2,5-dibromopentanoic acid 2a in 90% yield with trace amount of 1a. The purity of 2a was determined by $^1$H and $^{13}$C NMR spectroscopy, and 2a was used for the subsequent intramolecular cyclization without any further purification.

**General procedure for the synthesis of α-substituted lactones 3 via intramolecular cyclization of 2 with R$_4$N$^+$OH$^-$ in two-phase system (Table 4, Table 5 and Scheme 3b).** To a 30 mL flask were added 2 (1.0 mmol, 2a–c: synthesized and used without further purification; 2d: purchased from commercial sources), CH$_3$CN (1.0 mL), H$_2$O (4 mL), CHCl$_3$ (5.0 mL) or MEK (5.0 mL), and R$_4$N$^+$OH$^-$ (1.2 equiv in aqueous solution). The mixture was stirred vigorously at 25 °C overnight. After the reaction was completed, the mixture was extracted with CHCl$_3$ (15 mL × 3). The organic layer was washed with H$_2$O (10 mL × 2), dried by anhydrous Na$_2$SO$_4$, then filtered. The filtrate was concentrated under reduced pressure. Finally, the residue was purified by gel permeation chromatography (eluent: CH$_2$Cl$_2$) or distillation to give pure product 3.

**Gram-scale synthesis of α-bromolactone 3b in two-phase system with n-Pr$_4$N$^+$OH$^-$ (Scheme 3a).** To a 300 mL flask were added 2b (10 mmol, synthesized by the procedure above mentioned and used without further purification), CH$_3$CN (10 mL), H$_2$O (40 mL), MEK (50 mL), and n-Pr$_4$N$^+$OH$^-$ (1.2 equiv in aqueous solution). The mixture was stirred vigorously at 25 °C for 3 h. After the reaction was completed, the solvent was removed under reduced pressure. The residue was extracted with CHCl$_3$ (20 mL × 3). The organic layer was washed with H$_2$O (10 mL × 2), dried by anhydrous Na$_2$SO$_4$, then filtered. The filtrate was concentrated under reduced pressure. Finally, the residue was purified by distillation to give pure product 3b in 64% yield (1.05 g).

**Cascade synthesis of 5 via two-phase ring closing of 3b and following substitution with benzenethiol 4 in the presence of K$_2$CO$_3$ (Scheme 4).** To a 100 mL flask were added 2b (4.0 mmol), CH$_3$CN (4 mL), H$_2$O (16 mL), MEK (20 mL), and n-Pr$_4$N$^+$OH$^-$ (1.2 equiv in aqueous solution). The mixture was stirred vigorously at 25 °C for 1 h. After the reaction was completed, the mixture was extracted with CHCl$_3$ (15 mL × 3). The organic layer was washed with H$_2$O (10 mL × 2), dried by anhydrous Na$_2$SO$_4$, then filtered. The filtrate was concentrated under reduced pressure to give crude 3b. To a 50 mL flask were added 3b (used without isolation), benzenethiol 4 (2.4 mmol), DMF (5 mL), and K$_2$CO$_3$ (0.45 mmol), and the mixture was stirred at 25 °C overnight. The resulting mixture was extracted with CH$_2$Cl$_2$ (15 mL × 3). The organic layer was washed with H$_2$O (10 mL × 2), dried by anhydrous Na$_2$SO$_4$, then filtered. The filtrate was concentrated under reduced pressure. Finally, the residue was purified by silica-gel column chromatography (AcOMe/isohexane) to give pure product 5.

**One-pot synthesis of a functional lactone 6 using PhS$^-$Na$^+$ as the nucleophiles in the two-phase system (Scheme 6).** To a three-necked flask were added 2a (2.0 mmol), DMSO (2 mL), H$_2$O (4 mL), CHCl$_3$ (10 mL), and n-Bu$_4$N$^+$OH$^-$ (1.2 equiv in aqueous solution), and stirred vigorously for 10 min at 25 °C. Then, a solution of PhS$^-$Na$^+$ (1.2 mmol) in H$_2$O (4 mL) was slowly added over 30 min. After the addition, the solution was further stirred for 80 min. The resulting mixture was extracted with Et$_2$O (15 mL × 3), and the organic layer was washed with 1% HCl aq (10 mL), H$_2$O (10 mL × 2), and dried by anhydrous MgSO$_4$. The filtration was carried out, and the filtrate was concentrated under reduced pressure. Finally, the residue was purified by silica-gel column chromatography (Et$_2$O/isohexane) to give pure product 6.
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Although we tried to isolate α-bromo-δ-valerolactone 3a synthesized by using n-Pr4N+OH− as the base (entry 1 in Table 4), 3a was very unstable and some decomposition of 3a was observed during the isolation using a recycling GPC (eluent: CH2Cl2). Finally, we could be isolated pure 3a in 20% yield. The details of the stability of 3a under ambient conditions and the characterization data of 3a are given in Supporting Information File 1.