

Triethylborane-Mediated Atom Transfer Radical Cyclization Reaction in Water

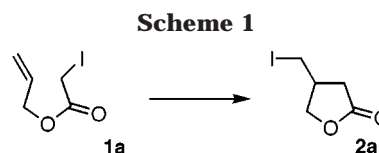
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The use of radicals in organic synthesis has increased dramatically within the last two decades.¹ During those years, many methods which lead to carbon-centered radicals have been developed. Among them, triethylborane proved to be an efficient radical initiator and has been widely used for synthetic radical reactions.² Triethylborane-induced radical reactions have several characteristic features. First, the reaction could take place at low-temperature such as $-78\text{ }^{\circ}\text{C}$ in the presence of a trace amount of oxygen. Second, various solvents including alcohol and water could be used because of the stability of Et_3B in aqueous media. Here we report that Et_3B -mediated radical cyclization reactions are much more efficient in water than in benzene or hexane.

We chose an atom-transfer cyclization³ of allyl iodoacetate as a model reaction in water. The indirect bromoacetal method was developed by Stork⁴ and Ueno⁵ because direct cyclization of α -halo esters into γ -butyrolactones is a relatively slow radical reaction.⁶ Lactones are usually produced from this strategy by oxidation of the products prepared from radical cyclization of bro-



moacetal. Indeed, treatment of allyl iodoacetate **1a** with triethylborane in benzene or hexane at room temperature gave no lactone **2a**. The iodide was consumed, and many products of high molecular weight were formed. In contrast, in water,⁷ **1a** cyclized much more rapidly and gave lactone **2a** in high yield. Treatment of allyl iodoacetate **1a** (1.0 mmol) in water (30 mL) with triethylborane (1.0 M methanol solution,⁸ 0.1 mL, 0.1 mmol) at $25\text{ }^{\circ}\text{C}$ for 3 h provided **2a** in 67% yield.⁹ At lower concentration (0.01 M, **1a** (1.0 mmol)/ H_2O (100 mL), the yield of **2a** increased to 78% (Scheme 1).

This powerful solvent effect also operates in a related system. Crotyl iodoacetate **1b** and 2-pentenyl iodoacetate **1c** provided the corresponding lactones **2b** and **2c** in 77% and 72% yield, respectively. 4-Hydroxy-2-butenyl iodoacetate **1d** also gave γ -butyrolactone **2d** in good yield (89%). In contrast, iodoacetate **1e**, which has a longer alkyl substituent (propyl group) on the terminal olefinic carbon, afforded the corresponding lactone **2e** in only 18% yield after stirring for 12 h upon treatment with Et_3B . More than half of the iodide **2e** (70%) remained at the end of the reaction. Moreover, 2-tridecenyl iodoacetate **1f** provided no cyclized γ -lactone **2f**, and **1f** was recovered completely. Similar results were obtained in the case of the reactions of iodoacetate **3a** and **3b**. Whereas **3a** provided the corresponding lactone **4a** in 67% yield, **3b** did not afford any lactone, and **3b** gave oligomeric products.¹⁰

3-Butenyl iodoacetate **5** (1.0 mmol) gave δ -lactone **6**, which is generated through 6-exo cyclization, in 42% yield upon treatment with Et_3B in water (30 mL). Again, the yield of **6** increased to 70% at lower concentration (0.01 M, **5** (1.0 mmol)/ H_2O (100 mL)).

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(8) The stability of Et_3B in MeOH was checked by the examination of ^1H NMR of CD_3OD solution of Et_3B . After standing at $25\text{ }^{\circ}\text{C}$ for one month, no change was observed on the NMR spectrum.

(9) The reaction was performed in a reaction flask equipped with a toy balloon which was filled with argon. Oxygen, which is necessary to produce an ethyl radical from Et_3B , could penetrate the balloon easily, and the concentration of oxygen in the balloon reaches 10% after 12 h. Alternatively, air could be introduced by a syringe (2 mL) every 30 min (three times) after an addition of Et_3B when the flask was kept strictly under argon atmosphere.

(10) The yields of lactone might be parallel to the solubility of α -iodoester in water. The solubility of **1a**–**f**, **3a**, and **3b** are as follows: **1a** (1.0×10^{-2} M); **1b** (4.4×10^{-3} M); **1c** (1.4×10^{-3} M); **1d** (1.7×10^{-1} M); **1e** (4.0×10^{-4} M); **1f** ($<1.0 \times 10^{-4}$ M); **3a** (5.1×10^{-3} M); **3b** (4.0×10^{-4} M). The solubility of α -iodoester in water was roughly determined as follows. Water (100 mL) was added to a 200-mL Erlenmeyer flask containing α -iodoester (2.0 mmol) and the mixture was stirred vigorously for 30 min. The resulting mixture was allowed to stand undisturbed for 30 min. During that time, α -iodoester that did not dissolve in water sank to the bottom of the flask. Half the volume of water (50 mL) was taken out from the water layer by a syringe, and the α -iodoester that dissolved in the water was extracted with ethyl acetate (3 \times 20 mL). The remaining α -iodoester after evaporation of the combined organic layer was weighed.

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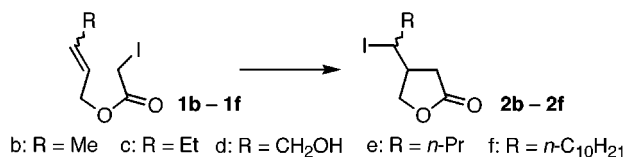
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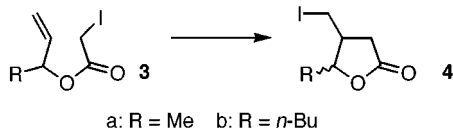
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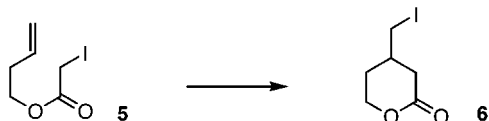
Scheme 2



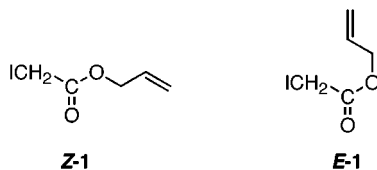
Scheme 3



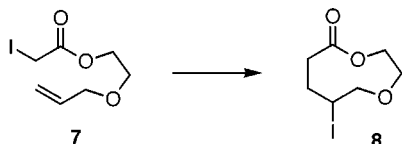
Scheme 4



Scheme 5



Scheme 6

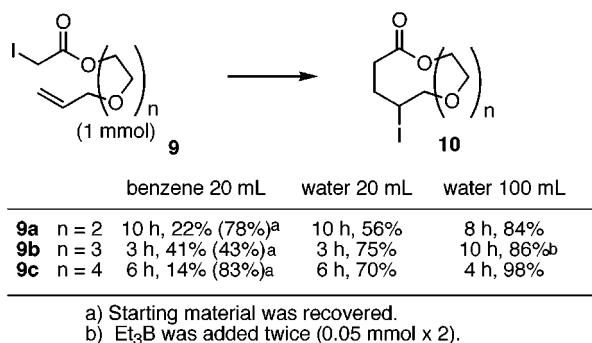


We speculate that water can effectively decrease the barrier to rotation between the major *Z*-rotamer and minor *E*-rotamer which can cyclize (Scheme 5).¹¹ Curran and Tamine have suggested that *Z* and *E* conformers of the radical are not sufficiently interconverting in benzene at 25 °C.^{6h} In water, however, the interconversion of the rotamers might occur as a result of the decrease of the barrier and cyclization from *E*-rotamer could afford lactone **2**.

Next, we examined the preparation of medium ring lactone (Scheme 6). Whereas treatment of α -iodoester **7** (1.0 mmol) with Et₃B (0.1 mmol) in water (100 mL) provided nine-membered lactone **8** in 69% yield, the atom transfer cyclization reaction of **7** in benzene (100 mL) afforded the corresponding lactone in only 27% yield. An endo cyclization product was obtained as a single isomer in each solvent without contamination by an exo product.

Water as a reaction solvent strikingly accelerated the reaction rate of the cyclization of a large-membered ring. Stirring a solution of **9a** (1.0 mmol) in water (30 mL) in the presence of Et₃B (1.0 M MeOH solution, 0.1 mL, 0.1 mmol) at 25 °C for 10 h provided a 12-membered ring **10a** in 56% yield (Scheme 7). In contrast, the reaction of **9a** in benzene in the presence of a hexane solution of Et₃B (1.0 M, 0.1 mL, 0.1 mmol) afforded the lactone in only 22% yield along with the recovered starting material

Scheme 7



9a (78%). Similar results were obtained in the reaction of **9b** (*n* = 3) and **9c** (*n* = 4). The exact role of water in these radical reactions is not clear at this stage. Nonetheless, the advantages of using water as a solvent are numerous from economical and environmental points of view.

Experimental Section

A Typical Procedure for Cyclization of Allyl Iodoacetate in Water. Allyl iodoacetate **1a** (224 mg, 1.0 mmol) was placed in a 50 mL flask, and distilled water (30 mL) was added. The mixture was flushed with argon in a toy balloon and stirred to suspend the starting material. A solution of triethylborane in methanol (1.0 M, 0.10 mL, 0.10 mmol) was then added dropwise. After stirring for 3 h at room temperature, the reaction mixture was extracted with ethyl acetate (20 mL × 3), and the organic layer was concentrated. Silica gel column purification (hexane:ethyl acetate = 3:1) of the crude product provided β -(iodomethyl)- γ -butyrolactone **2a** (150 mg, 0.67 mmol) in 67% yield, which showed the identical ¹H spectrum as reported in the literature.^{6h}

A Typical Cyclization Procedure for Large Ring Lactones in Water. To 3,6-dioxo-8-nonenyl iodoacetate **9a** (314 mg, 1.0 mmol) in a 50 mL flask was added distilled water (20 mL), and the resulting mixture was set under argon atmosphere with a toy balloon. With stirring to suspend the iodoacetate, triethylborane (1.0 M methanol solution, 0.10 mL, 0.10 mmol) was added dropwise to the resulting suspension. The suspension was stirred for 10 h at room temperature. Extraction with ethyl acetate (20 mL × 3) followed by silica gel column purification afforded endo-cyclized product 4-iodo-6,9-dioxo-11-undecanolid (10a, 176 mg, 0.56 mmol) in 56% yield: IR (neat) 2864, 1735, 1439, 1248, 1083 cm⁻¹; ¹H NMR (CDCl₃) δ 2.02–2.14 (m, 1H), 2.44–2.66 (m, 3H), 3.42–3.80 (m, 8H), 3.95–4.02 (m, 1H), 4.21–4.31 (m, 1H), 4.71–4.80 (m, 1H); ¹³C NMR (CDCl₃) δ 29.85, 33.49, 34.23, 62.17, 68.82, 70.38, 70.91, 76.89, 172.66; MS (peak match; calcd: 314, meas: EI) 314, 187, 143, 99, 55. Anal. Found: C, 34.16; H, 4.65%. Calcd for C₉H₁₅O₄: C, 34.41; H, 4.81%.

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Supporting Information Available: Experimental details and characterization data (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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