A Novel Reactive Polymer Having 2-Azetidinone-structure on the Main Chain: Development of Its Convenient Synthetic Method Based on [2 + 2]Cycloaddition of Bisketene with Bisimine

Atsushi Sudo and Takeshi Endo*

Research Laboratory of Resources Utilization, Tokyo
Institute of Technology, Nagatsuta-cho 4259,
Midori-ku, Yokohama, 226-8503 Japan

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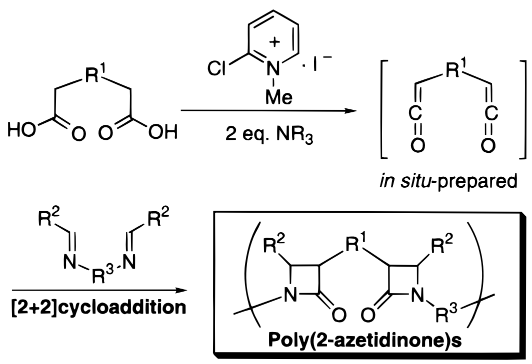
In the course of our research on applications of distinctive reactivities of cumulenes to the syntheses of various kinds of reactive polymers,[1] we focused our attention on [2 + 2]cyclization of ketenes with imines, to afford 2-azetidinones.[2] Since 2-azetidinones have relatively high reactivities due to their ring strain, they may be effectively applied not only as useful precursors for various β-amino acid derivatives[3] but also as monomers for ring opening polymerization.[4] This communication preliminarily communicates the synthesis and application of a polymer having the 2-azetidinone structure in the main chain.[5]

A novel polymerization system was designed, in which the bisketene was directly generated from the corresponding bis(carboxylic acid) by treatment with 2-chloro-1-methylpyridinium salt and tertiary amine to avoid perplexing isolation and purification of a bisketene (Scheme 1).[6]

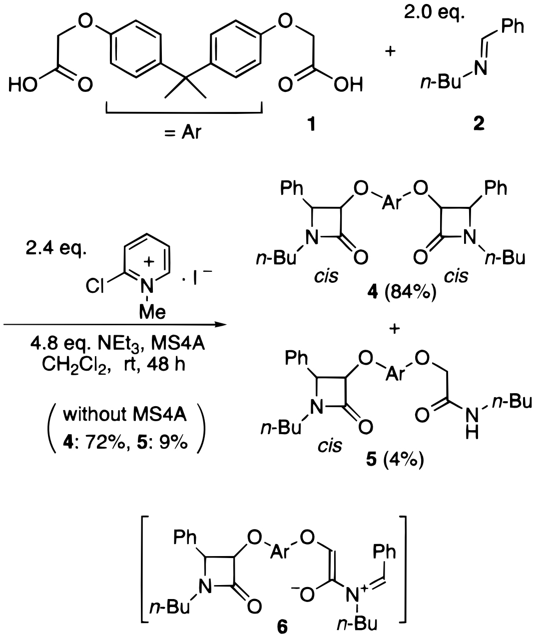
As a precursor for a bisketene, a bisphenol A derived bis(carboxylic acid), **1**, was synthesized according to the procedure reported in the literature.[7] A monofunctional imine, **2**, for the model reaction and a bisimine, **3**, for the polymerization were synthesized by condensation of benzaldehyde with butylamine and 1,12-diaminododecane, respectively, in the presence of magnesium sulfate as a dehydrating agent.

A model reaction using monofunctional imine **2** was carried out using dichloromethane and triethylamine as solvent and base, respectively, in which the desired bis(2-azetidinone) **4** was obtained, accompanied by mono(2-azetidinone) monoamide **5** (Scheme 2). [2 + 2] Cycloaddition of ketenes with imines proceeds through two stages, i.e., *N*-acylation of imines with ketenes, and cyclization of the resulting zwitterionic intermediates. Thus, the amide moiety of **5** is supposed to result from hydrolysis of intermediate **6**, of which one zwitterionic part remains uncyclized. Effects of solvent (acetonitrile, DMF, THF), reaction temperature, and amines (diisopropylethylamine, DBU) and ratio of reactants on the selectivities of the reaction products were examined; however, the yield of **4** was not improved and the generation of **5** was not suppressed. Finally, addition of molecular sieves (MS) was found to remarkably improve the reaction.[8] Among several types of molecular sieves examined, MS3A and MS4A improved the reaction, while MS5A did not. From these results, molecular sieves may work not only to remove trace amounts of water, but also to promote the cyclization of zwitterionic intermediate **6**, although its mechanism is not clear at the present time. It is also noteworthy that the relative stereochemistries of the substituents at positions 3 and 4 of the 2-azetidinone ring of **4** and **5** were found to be all cis by ^{1}H NMR spectroscopy.[2,6,9]

Scheme 1



Scheme 2



Under the reaction conditions thus optimized in the model reaction, the polymerization using bifunctional substrates **1** and **3** was carried out to obtain the corresponding polymer, **7**, in high yield. Its number-average molecular weight (M_n) was estimated to be approximately 15 400 by its analysis with SEC (eluent: DMF solution of LiBr, polystyrene standards) (Scheme 3).[10] The comparison of the ^{1}H NMR spectrum of **7** with those of the model compounds showed that the polymer was composed of two components, bis(2-azetidinone) and mono(2-azetidinone) monoamide, in a ratio of 93:7 on the basis of the integration values of ^{1}H NMR (Figure 1). This ratio is in good agreement with the result in the model reaction, in which the ratio between the model compounds **4** and **5** was 95:5. The clear AB-quartet-type signals with coupling constants of approximately 5 Hz of the model compounds and those of the obtained polymer indicate selective formation of *cis*-2-azetidinones.

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* To whom correspondence should be addressed. Telephone: +81-45-924-5244. Fax: +81-45-924-5279. E-mail: tendo@res.titech.ac.jp.

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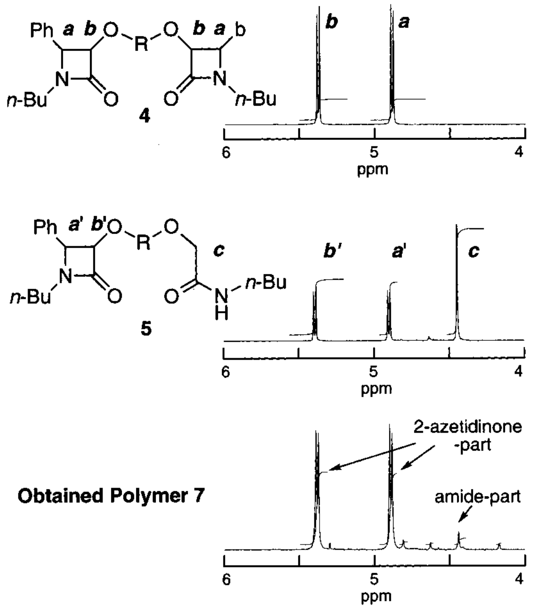
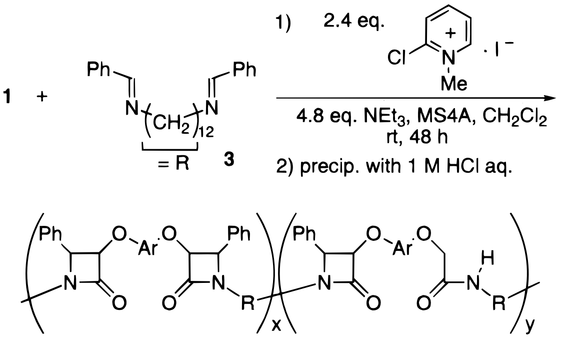


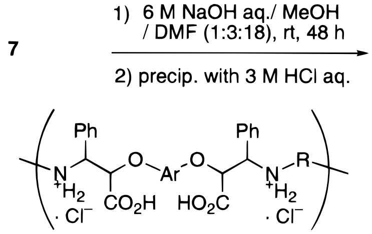
Figure 1. ^{1}H NMR spectra (270 MHz, CDCl$_3$, 25 °C, δ 4−6 ppm) of the model compounds **4** and **5**, and the obtained polymer **7**.

Scheme 3



7 88%, x:y=93:7, *cis*:*trans*>95:5, *M*n=15400, *M*w/*M*n=1.3

Scheme 4



8
ca. 40% conversion of
azetidinone moieties

To evaluate the potential of the obtained polymer **7** as a reactive polymer, hydrolysis of the 2-azetidinone moiety of the obtained polymer was carried out. After **7** was exposed to the basic conditions as depicted in Scheme 4, the mixture was poured into aqueous hydrochloric acid (3 M) to obtain a precipitate. The ^{1}H NMR spectrum of the obtained polymer suggested partial conversion (ca. 40%) of the 2-azetidinone moiety of **7** to the corresponding β-amino acid moiety (Figure 2(a)). This conversion was also supported by a decrease in the IR absorption at 1760 cm^{-1} and appearance of absorptions at 3200, 1740, and 1600 cm^{-1}. By means of repeating hydrolysis of the resulting polymer, 90% conversion of the 2-azetidinone moiety was accomplished (Figure 2b). In the ^{1}H NMR study of the hydrolyzed polymer, shapes and chemical shifts of the signals were found to depend on solvents for the measurement of ^{1}H NMR and the acidic treatment of the obtained precipitate. Serious fission of the main chain was not observed by ^{1}H NMR analysis. SEC analysis of **8** could not be carried out due to its gelation in DMF solution of LiBr. These preliminary results may indicate that poly(2-azetidinone)s such as **7** might be useful polymeric precursors for various poly(ether amine) derivatives by means of appropriate choice of the specific conditions of functional group interconversions.

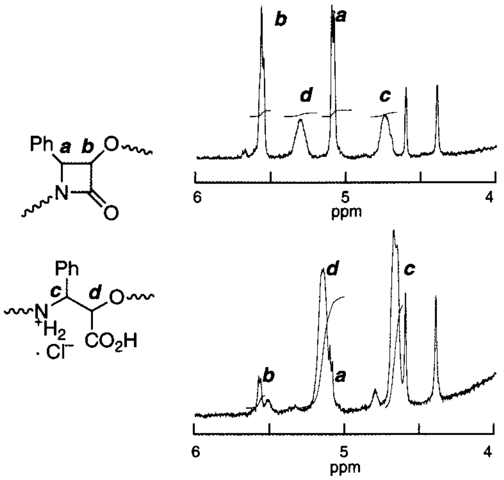


Figure 2. ^{1}H NMR spectra (270 MHz, DMSO-d_6, 25 °C, δ 4−6 ppm) of the obtained polymer by hydrolysis of **7**: (a) ca. 40% conversion; (b) ca. 90% conversion.

In summary, a bisketene, which was generated directly from a bisphenol A derived carboxylic acid by treatment with 2-chloropyridinium iodide and triethylamine, reacted with a bisimine smoothly in a [2 + 2] cycloaddition to afford the corresponding poly(2-azetidinone) efficiently. For a preliminary study concerning the application of the resulting polymer as a reactive polymer, its hydrolysis under basic conditions was examined to obtain the corresponding poly(ether amine) bearing carboxyl group. Further application of this synthetic strategy to obtain various poly(2-azetidinone)s and various functional group interconversions of the resulting polymers is now under investigation.

References and Notes

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(8) The procedure for the model reaction is as follows: Under Ar, to a stirred suspension of dicarboxylic acid **1** (114 mg, 0.330 mmol), 2-chloro-1-methylpyridinium iodide (205 mg, 0.802 mmol), imine **2** (106 mg, 0.660 mmol), and finely powdered molecular sieves 4A (1.0 g) in CH_2Cl_2 (8 mL) at 0 °C was added triethylamine (0.22 mL, 1.6 mmol). The mixture was stirred at 20 °C for 48 h. The reaction mixture was filtered, 1 M aqueous HCl was added (10 mL), and the result extracted with CH_2Cl_2 (3 × 10 mL). Usual workup and thin-layer chromatography (silica gel, eluent: CH_2Cl_2) gave **4** (175 mg, 0.277 mmol, 84%) and **5** (7.1 mg, 0.013 mmol, 4%). **4**: IR (KBr, cm^{-1}) 1760. **5**: IR (KBr, cm^{-1}) 1760, 1680.

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(10) The procedure for the polymerization reaction is similar to that for the model reaction, in which bisimine **3** (0.330 mmol) was used instead of 0.660 mmol of imine **2**. After the reaction mixture was stirred at 20 °C for 48 h, the mixture was filtered and concentrated under reduced pressure. The resultant mixture was dissolved in DMF (10 mL) and precipitated with 1 M aqueous HCl (100 mL) to obtain the corresponding polymer **7**, which was collected by filtration with suction and dried under vacuum.

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