Conjugate substitution and addition of α-substituted acrylate: A highly efficient, facile, convenient and versatile approach to degradable polymer by dynamic covalent chemistry

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Electronic Supplementary Information

Experiments

Instruments

1H and 13C NMR spectra were recorded in CDCl3 (Across Organics) on an AVANCE 400 (Bruker) spectrometer. Chemical shifts in 1H and 13C NMR spectra were referred to the signal of tetramethylsilane (TMS) and solvent (CDCl3), respectively. Molecular weight and its distributions were determined at 40 °C by size-exclusion chromatography (SEC) on an EXTREMA chromatograph (JASCO) equipped with two SEC columns (PL-gel, Mixed C [300 mm × 7.5 mm], Polymer Laboratories), using tetrahydrofuran (THF, Wako Pure Chemical Industries, for HPLC grade) as an eluent (flow rate = 0.8 mL min\(^{-1}\)) and calibrated against standard polystyrene (PS) samples (TSK-gel oligomer kit, Tosoh, calibrated against standard polystyrene (PS) samples (TSK-gel oligomer kit, Tosoh, Japan)) using a Shimadzu HPLC grade) as an eluent (flow rate = 0.8 mL min\(^{-1}\)) and calibrated against standard polystyrene (PS) samples (TSK-gel oligomer kit, Tosoh, calibrated against standard polystyrene (PS) samples) using a Shimadzu HPLC grade) as an eluent (flow rate = 0.8 mL min\(^{-1}\)).

M. \(\alpha\)-(Chloromethyl)acryloyl chloride (10)\(^{-1,2}\)

Thionyl chloride (58 mL, 3.10 mmol) was added dropwise to a solution of 1,4-butanediol (3.61 g, 40.0 mmol) in THF (25 mL) under argon atmosphere at −10 °C. The reaction mixture was stirred for 45 h, diluted with diethyl ether (100 mL) and washed with sat. NaHCO3 aq (100 mL). The organic layer was concentrated, and the residue was purified by distillation under reduced pressure to afford \(\alpha\)-(chloromethyl)acryloyl chloride (10) (23.1 g) as colorless oil. Yield 72.3%; bp 62.5-67.0 °C / 11 mmHg.

1,4-butylene bis[\(\alpha\)-(chloromethyl)acrylate] (4)\(^{-1}\)

A solution of 10 (13.1 g, 94.0 mmol) in THF (25 mL) was added dropwise to a solution of 1,4-butanediol (3.61 g, 40.0 mmol) in THF (25 mL) under argon atmosphere at −10 °C. The reaction mixture was stirred for 24 h and concentrated. The residue was purified by distillation under reduced pressure to afford \(\alpha\)-(chloromethyl)acryloyl chloride (10) (23.1 g) as colorless oil. Yield 72.3%; bp 62.5-67.0 °C / 11 mmHg.

Methyl \(\alpha\)-(Chloromethyl)acrylate (11)\(^{-1}\)

Thionyl chloride (53.0 mL, 0.27 mol) was added to methyl \(\alpha\)-(hydroxymethyl)acrylate (57.6 g, 0.496 mol) dropwise. The reaction mixture was stirred for 15 h and concentrated. The residue was purified by distillation under reduced pressure to yield methyl \(\alpha\)-(chloromethyl)acrylate (11) as colorless oil (54.0 g). Yield: 80.1%; bp 58-60 °C / 7.5 mmHg; \(^1\)H NMR (400 MHz, 26 °C, CDCl3) δ/ppm 6.39 (s, 1H, CH=), 5.99 (d, J = 1.4 Hz, 1H, CHH=), 4.29 (d, J = 1.4 Hz, 2H, CH2Cl), 3.81 (s, 3H, OCH3).

Polymerization of 2a and 4 (Table 1, Runs 1–3)

Electronic Supplementary Material (ESI) for Polymer Chemistry.

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A typical procedure (Table 1, Run 3): A solution of Et$_3$N (0.10 g, 1.0 mmol) and 1,10-decanedithiol (2a) (83 mg, 0.40 mmol) in CHCl$_3$ (0.50 mL) was added dropwise to a solution of 4 (0.118 mg, 0.400 mmol) in CHCl$_3$ (0.50 mL). The reaction mixture was stirred for 24 h and poured into MeOH (50 mL). The precipitate was collected by filtration and dried in vacuo to yield the corresponding unsaturated polymer (153 mg) as white powder. Yield: 79%; $M_n$ = 58000, $M_w/M_n$ = 2.27.

Polymerization of 2b and 4 (Runs 4–6)

A typical procedure (Table 1, Run 4): Polymerization 2b (61 mg, 0.40 mmol) and 4 (0.118 mg, 0.400 mmol) was conducted in a similar manner to that of 2a and 4. After 24 h, the reaction mixture was washed with 1 M HCl aq (5.0 mL), and the organic layer was concentrated and dried in vacuo to yield the corresponding polymer (137 mg) as white powder. Yield: 84%; $M_n$ = 12000, $M_w/M_n$ = 1.43

Polymerization of 2e and 4 without end-capping (Run 7).

Polymerization of 2e (74 mg, 0.41 mmol) and 3 (0.118 mg, 0.400 mmol) was conducted in a similar manner to that of 2b and 3 described above to yield the corresponding polymer (131 mg) as a colorless elastomer. The product exhibited poor solubility in THF and CHCl$_3$.

Polymerization of 2e and 4 with end-capping (Run 8)

Polymerization of 2c (74 mg, 0.41 mmol) and 4 (0.118 mg, 0.400 mmol) was conducted in a similar manner to that of 2b and 4 described above. After 1 h, a solution of methyl α-(chloromethyl)acrylate (19 mg, 0.14 mmol) in CHCl$_3$ (0.40 mL) was added. The reaction mixture was stirred further 3 h and poured into MeOH (50 mL). The precipitate was collected by centrifugation to yield the corresponding polymer (137 mg) as a colorless sticky solid. Yield 84%; $M_n$ = 17000, $M_w/M_n$ = 2.08.

Polymerization of 4 and 5 (Table 2, Run 9)

A solution of Et$_3$N (0.102 g, 1.00 mmol) and adipic acid (5) (58 mg, 0.40 mmol) in N,N-dimethylformamide (DMF, 0.50 mL) was added dropwise to a solution of 4 (0.118 mg, 0.400 mmol) in DMF (0.30 mL). The reaction mixture was stirred for 1 h and CHCl$_3$ (10 mL) was added. The solution was washed with water (10 mL × 3) and the organic layer was dried over Na$_2$SO$_4$ and concentrated. The residue was poured into water (40 mL). The precipitate was collected by filtration and dried in vacuo to yield the corresponding unsaturated polymer (78 mg) as white powder. Yield: 53%; $M_n$ = 14000, $M_w/M_n$ = 1.86.

Polymerization of 4 and 6 (Runs 10 and 11)

A typical procedure (Table 2, Run 11): A solution of DBU (0.156 g, 1.02 mmol) and n-propyl amine (6, 24 mg, 0.41 mmol) in 1,4-dioxane (0.50 mL) was added dropwise to a solution of 4 (0.119 mg, 0.403 mmol) in 1,4-dioxane (0.30 mL). The reaction mixture was stirred for 24 h and water (10 mL) was added. The solution was extracted with CH$_2$Cl$_2$ (30 mL) and the organic layer was washed with water (30 mL), dried over Na$_2$SO$_4$ and concentrated. The residue was dried in vacuo to yield the corresponding unsaturated polymer (78 mg) as white powder. Yield: 90%; $M_n$ = 1900, $M_w/M_n$ = 1.92.

Polymerization of 4 and 7 (interfacial polymerization, Run 12)

A solution of 4 (0.122 g, 0.413 mmol) in CH$_2$Cl$_2$ (0.80 mL) was added to a solution of bisphenol A (7) (0.94 mg, 0.41 mmol) and benzyltriethylammonium chloride (BTEAC, 20 mg, 88 mmol) in ca. 0.6 M NaOH aq (1.5 mL). The reaction mixture was vigorously stirred for 24 h and water (10 mL) was added. The solution was extracted with CH$_2$Cl$_2$ (10 mL) and the organic layer was concentrated. The residue was dried in vacuo to yield the corresponding unsaturated polymer (137 mg) as white powder. Yield: 74%; $M_n$ = 2800, $M_w/M_n$ = 1.56.

Polymers of 4 and 7 (solution polymerization, Runs 13 and 14)

A typical procedure (Table 2, Run 14): A solution of Et$_3$N (0.105 g, 1.03 mmol) and 7 (91 mg, 0.40 mmol) in CHCl$_3$ (0.50 mL) was added dropwise to a solution of 4 (0.118 mg, 0.400 mmol) in CHCl$_3$ (0.50 mL). The reaction mixture was stirred for 24 h and water (5 mL) was added. The organic layer was concentrated and the residue was dried in vacuo to yield the corresponding unsaturated polymer (168 mg) as white powder. Yield: 93%; $M_n$ = 32000, $M_w/M_n$ = 1.98.

Synthesis of Prepolymer P7/12

A solution of adipoyl chloride (12, 0.293 g, 1.60 mmol) in CHCl$_3$ (2.0 mL) was added dropwise to a solution of 7 (0.457 g, 2.00 mmol) and Et$_3$N (0.508 g, 5.00 mmol) in CHCl$_3$ (2.0 mL). The reaction mixture was stirred for 2 h and water (4 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with CHCl$_3$ (5 mL × 3). The combined organic layer was concentrated and the residue was dried in vacuo at 60 °C for 3 h. The residue was dissolved in CHCl$_3$ (5 mL) and washed with 0.16 M HCl aq (6 mL). The organic layer was separated and the aqueous layer was extracted with CHCl$_3$ (5 mL × 3). The combined organic layer was washed with brine (5 mL), concentrated and dried in vacuo to yield prepolymer P7/12 as a mixture with Et$_3$N·HCl (0.847 g). The product was used in the next reaction without further purification. $M_n$ = 750, $M_w/M_n$ = 1.95 (SEC); $M_n$ = 675 (NMR).

Synthesis of Terpolymer P4/(7/13)

A solution of 4 (0.118 g, 0.400 mmol) in CHCl$_3$ (0.50 mL) was added dropwise to a solution of prepolymer P7/13 (0.328 g, 0.363 mmol) and Et$_3$N (0.108 g, 1.01 mmol) in CHCl$_3$ (0.30 mL). The reaction mixture was stirred for 1 h and water (1.5 mL) and 1 M HCl aq (0.5 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with CHCl$_3$ (5 mL × 3). The combined organic layer was washed with brine (5 mL), concentrated and dried in vacuo to yield terpolymer P4/(7/13) (0.403 g, 97%). $M_n$ = 6420, $M_w/M_n$ = 1.93 (SEC).

Model reaction for the polycondensation with dithiol monomer

A typical procedure (Table 1, Run 1): Model reaction of 11 (134 mg, 1.00 mmol) and benzyl mercaptan (A, 112 mg, 0.902 mmol) was conducted in a similar manner to the polymerization of 2a and 4. After 3 h, the reaction mixture was washed with 1 M HCl aq (0.5 mL), and the organic layer was concentrated in vacuo to yield a mixture of 5 and 6 (0.230 mg) as yellow oil.
Main-chain scission of obtained polymers

A typical procedure (Table 2, Run 7): A solution of Et₃N (15.2 mg, 0.150 mmol) and 13 (0.187 g, 1.50 mmol) in CH₃CN (0.6 mL) was added dropwise to a solution of P4/5 (0.110 g, 0.400 mmol/unit) in CHCl₃ (0.6 mL). The reaction mixture was stirred at room temperature, and small portions were sampled at the determined time. After 24 h, 0.1 M HCl aq (1 mL) was added, and the product was extracted with CHCl₃ (3 mL). The organic layer was washed with brine (3 mL), concentrated and dried in vacuo to give viscous colorless liquid (0.216 g).

Decrosslinking of P2a/4-gel

A solution of Et₃N (10 mg, 0.11 mmol) and 13 (0.124 g, 1.00 mmol) in CH₃CN (0.4 mL) was added dropwise to a suspension of P2a/4-gel (86 mg) in CHCl₃ (0.4 mL). The reaction mixture was stirred at room temperature for 46 h. The obtained solution was poured into hexane to recover the product, and the precipitate was collected by decantation and dried in vacuo to give pale yellow viscous liquid (0.125 g).

Additional Results and Discussion

Kinetic control toward selective SN₂ reaction

In advance to the polymerization, we first investigate the selectivity of conjugate substitution and addition reactions by a model reaction of 11 and benzyl mercaptan (13) (Scheme S1, Table S1). Since the substitution reaction release the hydrochloride, the reaction should be employed in the presence of weak base such as amine. However, amine compounds can catalyse the conjugate addition, the substitution reaction of 11 is competitive with the addition reaction against the product, 14. Figure 1 shows the ¹H NMR spectra of the products by the reaction of 11 and 14 with Et₃N. In addition to the signals assigned to 15 (labelled a-e), those of the addition product 16 (labelled c'-f') were observed. From the intensity ratio of signal a to signals d and d', the selectivity of substitution reaction against the subsequent addition reaction was evaluated. The products from an equimolar mixture of 1a and 11 in CH₃CN included 98% of 14 and 2% of 15 (Table 1, Run 1). An excess amount of 13 afforded the addition product quantitatively (Runs 2 and 3). These results indicated that the substitution reaction of 11 and 13 preferentially proceeded, and thereafter the addition reaction of 13 and 14 followed. In other words, the conjugate substitution proceeds at much faster reaction rate than the conjugate addition. Similar tendency was found among the reactions in CHCl₃ (Runs 4-6), and notably, the equimolar mixture of 11 and 13 yielded the substitution product (14) selectively. As the Michael addition-type thiol-ene reaction proceeds very slow in low polar solvents such as CHCl₃, these results seem to be reasonable. Therefore, CHCl₃ should be a suitable solvent and base to supress the crosslinking in the polymerization of 2 and 4.

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\text{Scheme S1. Model reaction of the polymerization of 2 and 3.}
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\text{Table S1 Model reaction of 11 and 13 under the ambient conditions.}
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* A: 1.00 mmol, [11]₀/[13]₀/[Et₃N]₀ = 1/1.00/2.50, solvent: 1 mL, 3 h.

* Determined by ¹H NMR spectrum of the product extracted with CHCl₃ (400 MHz, CDCl₃, 26 °C)

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\text{Figure S1 ¹H NMR spectra of the reaction products of 11 and 13 (400 MHz, CDCl₃, 26 °C).}
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The experimental codes were corresponding to Table 1. Labels for the assignments were corresponding to Scheme S1 except the followings: *CHCl₃ and ●CH₃CN.
Figure S2 $^1$H NMR spectra of (a) 4 and (b) P2a/4, (c) P2b/4, (d) P2c/4, (e) P2d/4 and (f) P2e/4 (400 MHz, CDCl$_3$, 26 °C). *: CHCl$_3$, #: tetramethylsilane and •: Et$_3$N·HCl.

Figure S3 $^1$C NMR spectra of (a) 4 and (b) P2a/4, (c) P2c/4, (d) P2d/4 and (e) P2e/4 (100 MHz, CDCl$_3$, 26 °C). *: CHCl$_3$, #: tetramethylsilane.
Figure S4 IR spectra of (a) P2a/4, (b) P2b/4, (c) P2c/4, (d) P2d/4, (e) P2e/4, (f) P4/5, (g) P4/6, and (h) P4/7 (ATR).
Figure S5 TGA/DTA charts of (a) P2a/4, (b) P2b/4, (c) P2c/4 and (d) P2d/4 (heating rate = 10 °C/min, under N₂ atmosphere).
Figure S6 TGA/DTA charts of (e) P2e/4, (f) P4/5, (g) P4/6, and (h) P4/7 (heating rate = 10 °C/min, under N$_2$ atmosphere).
Figure S7 DSC charts of (a) P2a/4, (b) P2d/4, (c) P4/5, and (d) P4/7 (heating rate = 10 °C/min, under N₂ atmosphere).
Figure S8: $^1$H NMR spectra of (a) P4/5, (b) P4/6, and (c) P4/7 (400 MHz, CDCl$_3$, 26 °C). *: Tetramethylsilane, **: CHCl$_3$.

Figure S9: $^{13}$C NMR spectra of (a) P4/5, (b) P4/6, and (c) P4/7 (100 MHz, CDCl$_3$, 26 °C). *: CHCl$_3$.

Figure S10: $^1$H NMR spectra of P2a/4 (a) before and (b) after the main-chain scission (400 MHz, CDCl$_3$, 26 °C).

Figure S11: $^1$H NMR spectra of P4/5 (a) before and (b) after the main-chain scission (400 MHz, CDCl$_3$, 26 °C).
Figure S12 $^1$H NMR spectra of P4/7 (a) before and (b) after the main-chain scission (400 MHz, CDCl$_3$, 26 °C).

Notes and references