Supporting Information

Introducing Ugi Reaction into Polymer Chemistry as A Green Click Reaction to Prepare Middle-Functional Block Copolymers

Bin Yang, Yuan Zhao, Changkui Fu, Chongyu Zhu, Yaling Zhang, Shiqi Wang, Yen Wei, Lei Tao*

The Key Laboratory of Bioorganic Phophorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China.
leitao@mail.tsinghua.edu.cn.

Experimental Section

1. Materials

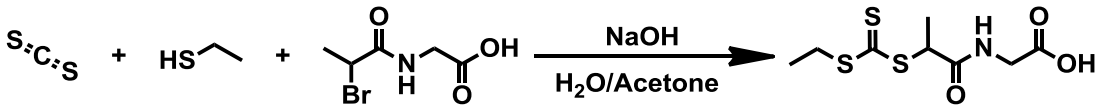
Methoxypolyethylene glycol (mPEG, Mn ~ 5000, Aldrich), carbon disulfide (J&K, 99.9%), ethanethiol (J&K, 98%), cyclohexyl isocyanide (J&K, 98%), Captopril (J&K, 97%), trifluoroacetic acid (J&K, 99.9%), N-isopropylacrylamide (NIPAAm, J&K, 99%), 2,2'-azobis(2-methylpropionitrile) (AIBN, J&K, 99.9%), dansylglycine (J&K, 98%), 4-formylbenzoic acid (Aladdin, 98%), N,N'-dicyclohexylcarbodiimide (DCC, Aladdin, ≥ 99.0%), 4-dimethylamiopryidine (DMAP, Aladdin, 99%), 1,4-butylene glycol (Aladdin, ≥ 99.0%), 2-bromoisobutyryl bromide (Maya, 97%), 1,1,4,7,7-pentamethyldiethylenetriamine (J&K, 98%), methyl methacrylate (MMA, Aladdin 99%), were used as purchased. CuBr was washed by acetic acid prior to use. 2-(4-((tert-butoxycarbonyl)amino)phenyl)acetic acid[1], 2-acrylamidoacetic acid[2], 2-(2-bromopropanamido)acetic acid[3], and 4-hydroxybutyl 2-bromo-2-methylpropanoate[4] were synthesized as previous literatures.

2. Instrumental Analysis

Gel permeation chromatography (GPC) analyses of polymers were performed using N,N-dimethyl formamide (DMF) containing 50 mM LiBr as the eluent. The GPC system was a Shimadzu LC-20AD pump system consisting of an auto injector, a MZ-Gel SDplus 10.0 μm guard column (50 × 8.0 mm, 10^2 Å) followed by a MZ-Gel SDplus 5.0 μm bead-size column (50 – 10^6 Å, linear) and a Shimadzu RID-10A refractive index detector. The system was calibrated with narrow molecular weight distribution polystyrene standards ranging from 200 to 10^6 g mol^{-1}. ^{1}H NMR and ^{13}C NMR spectra were obtained using a JEOL JNM-ECA400 (400MHz) spectrometer for all samples. The ESI-MS data were collected using a Micro TOF-QII Bruker. The FT-IR spectra were made in a transmission mode on a Perkin-Elmer Spectrum 100 spectrometer (Waltham, MA, USA). UV-Visible absorption spectra were recorded on UV/Vis/NIR Perkin-Elmer lambda750 spectrometer (Waltham, MA, USA) using quartz cuvettes of 1 cm path length. The fluorescence measurements were obtained on a Perkin-Elmer LS-55 spectrometer equipped with quartz cuvettes of 1 cm path length.

3. Method

3.1. Synthesis of 2-(2-(((ethylthio)carbonothioyl)thio)propanamido)acetic acid:



NaOH aq solution (50 %, 1.60 g) was added to ethanethiol (1.24 g, 20.0 mmol) and water (6.0 mL) mixture, followed by addition of acetone (2.0 mL) to give a colorless solution. The solution was stirred at 25 °C for 0.5 h, then carbon disulfide (1.40 mL, 1.76 g, 23.1 mmol) was added to obtain a clear orange solution. The reaction mixture was stirred for 0.5 h and then cooled in an ice-water bath. 2-(2-Bromopropanamido)acetic acid (4.31 g, 20.5 mmol) was added dropwise, followed by 1.60 g of 50 % aq NaOH solution at a rate to keep the temperature of

mixture not exceed 30 °C. After the exotherm reaction, water (6.0 mL) was added and the reaction was stirred at 25 °C for 24 hrs. The reaction mixture was diluted with 50 mL of water. Then, 12 M HCl was added at a rate to keep the temperature < 10 °C (using ice bath), and the obtained yellow oil was extracted by ethyl acetate. The organic layer was dried over $MgSO_4$ before evaporated, and the residue was purified via silica gel column chromatography eluting with ethyl acetate/petroleum ether (1/4) to get a bright yellow solid (3.64 g, 68%).

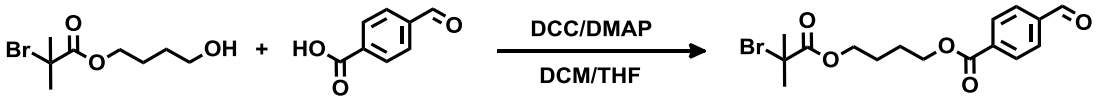
^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 6.93 (t, 1H, *J* = 4.7 Hz, NH), 4.82 (q, 1H, *J* = 7.4 Hz, CH), 4.18-3.99 (m, 2H, CH_2COOH), 3.38 (q, 2H, *J* = 7.4 Hz, CH_2CH_3), 1.59 (d, 3H, *J* = 7.4 Hz, CH_3CH), 1.37 (t, 3H, *J* = 7.4 Hz, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 223.60, 173.56, 171.48, 47.46, 41.67, 32.05, 16.17, 13.03.

IR (ν/cm^{-1}): 3124, 1732, 1662, 1532, 1438, 1418, 1371, 1299, 1225, 1203, 1124, 1084, 1071, 1036, 966, 945, 832.

ESI-MS: observed (expected): 289.9954 (289.9950) [M+Na$^+$].

3.2. Synthesis of 4-((2-bromo-2-methylpropanoyl)oxy)butyl 4-formylbenzoate:



4-Hydroxybutyl 2-bromo-2-methylpropanoate (1.62 g 6.76 mmol) was dissolved with 4-formylbenzoic acid (1.22 g, 8.13 mmol) and DMAP (25.0 mg, 0.2 mmol) in 40 mL of dry CH_2Cl_2 and 5 mL of anhydrous THF. DCC (2.79 g, 13.5 mmol) was added to the mixture under nitrogen atmosphere. The system was stirred at 25 °C for 24 h. After removing the solvents, 15 mL of toluene was added and the insoluble white solid was removed by filtration. The organic layer was dried over $MgSO_4$ before evaporated, and the residue was purified via silica gel column chromatography eluting with ethyl acetate/petroleum ether (1/9) to get a pale yellow oil (1.86 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 10.04 (s, 1H, CHO), 8.13 (d, 2H, *J* = 8.0 Hz, CHCCHO), 7.89 (d, 2H, *J* = 8.0 Hz, CHCCOO), 4.35 (t, 2H, *J* = 6.0 Hz, CH_2OCOAr),

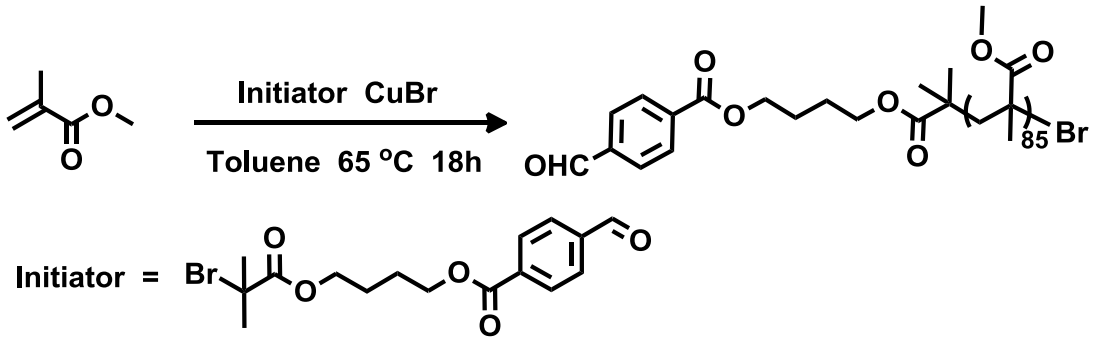
4.20 (t, 2H, *J* = 6.0 Hz, C<u>H</u>$_2$OCOC), 1.92-1.77 (m, 10H, CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_2$, CC<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 191.83, 171.82, 165.66, 139.27, 135.29, 130.31, 129.69, 65.50, 65.16, 55.93, 30.85, 25.37.

IR (ν/cm^{-1}): 2961, 2854, 2734, 1722, 1705, 1463, 1378, 1268, 1201, 1161, 1104, 1015, 947, 929, 758.

ESI-MS: observed (expected): 372.0511 (371.0489) [M+H$^+$].

3.3. Synthesis of benzaldehyde terminated polymethyl methacrylate (PMMA-CHO):



MMA (6.0 g, 60 mmol), 4-((2-bromo-2-methylpropanoyl)oxy)butyl 4-formylbenzoate as initiator (222 mg, 0.62 mmol), CuBr (22 mg, 0.15 mmol) and 1,1,4,7,7-pentamethyldiethylenetriamine (33 μL, 0.30 mmol) were charged into a dry Schlenk tube along with toluene (10 mL). The Schlenk tube was sealed with a rubber septum and degassed through three freeze-pump-thaw cycles. The tube was then put into an oil bath maintained at 65 °C for 18 hours. The crude was passed a short neutral alumina column to remove metal salt, and then precipitated from toluene to cold petroleum ether for 3 times. The collected white powder was dried under vacuum to obtain the pure polymer for characterizations and further use.

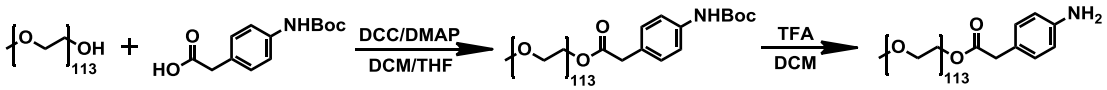
^{1}H NMR (400 MHz, CD_3CN, δ/ppm): 10.12 (s, C<u>H</u>O), 8.21 (d, *J* = 7.6 Hz, C<u>H</u>CCHO), 8.03 (d, *J* = 7.6 Hz, C<u>H</u>CCO), 4.40 (m, C<u>H</u>$_2$OCOAr), 4.08 (m, C<u>H</u>$_2$OCOC), 3.80-3.36 (m, COOC<u>H</u>$_3$), 2.02-1.74 (m, C<u>H</u>$_2$C), 1.08-0.71 (m, C<u>H</u>$_3$C).

The polymerization conversion (~ 80%) was calculated by ^{1}H NMR of the crude, comparing the peaks of the vinyl protons and the methoxy protons. The molecular

weight was obtained by the ester methylene protons ($C\underline{H_2}OCOAr$) on the polymer chain end compared to the methoxy protons on the polymer main chain (DP ~ 85, M_{nNMR} ~ 8800).

GPC was also used to evaluate the PDI and molecular weight of the final polymer (M_{nGPC} ~ 24200, PDI: 1.08).

3.4. Synthesis of phenylamine terminated methoxypolyetylene glycol (mPEG-NH_2):

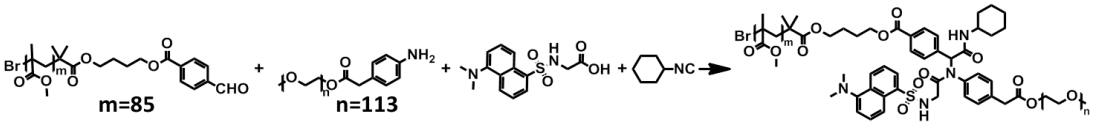


Methoxypolyethylene glycol (Mn ~ 5000, 2.00 g, 0.4 mmol) was azeotropic treated with toluene to remove the remaining water, then dissolved with 2-(4-((tert-butoxycarbonyl)amino)phenyl)acetic acid (0.20 g, 0.8 mmol) and DMAP (5.0 mg, 0.04 mmol) in 40 mL of dry CH_2Cl_2 and 10 mL of anhydrous THF. DCC (0.17 g, 0. 8 mmol) was added to the mixture under nitrogen atmosphere. The system was stirred at 25 °C for 10 h. After removing the solvents, 15 mL of toluene was added and the insoluble white solid was removed by filtration. The polymer was obtained by precipitation from toluene to diethyl ether for three times. Then, the polymer was dissolved in 0.5 mL of dry CH_2Cl_2 and 0.5 mL of trifluoroacetic acid, and stirred at 25 °C for 10 h. After removing the solvents, the trace residual trifluoroacetic acid was removed via a basic aluminum oxide column. The final polymer was obtained as a white solid after removing the solvent.

^{1}H NMR (400 MHz, CD_3CN, δ/ppm): 6.97 (d, *J* = 8.2 Hz, $C\underline{H}CCH_2$), 6.59 (d, *J* = 8.2 Hz, $C\underline{H}CNH_2$), 4.15 (t, $COOC\underline{H_2}$), 4.09 (s, NH_2), 3.75-3.35 (m, $OC\underline{H_2}C\underline{H_2}O$), 3.29 (s, OCH_3).

M_{nGPC} ~ 28000, PDI: 1.03

3.5. Synthesis of mid-fluorescent copolymer:

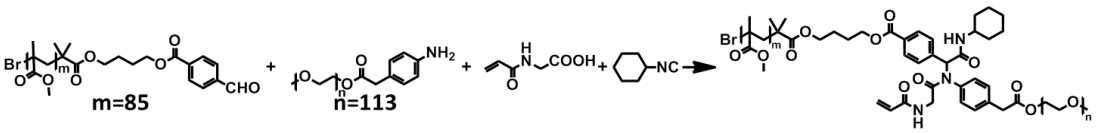


PMMA-CHO (86 mg, 0.01 mmol) and mPEG-NH_2 (50 mg, 0.01 mmol) were charged into a dry EP tube along with methanol (250 μL) and acetonitrile (250 μL). Then dansylglycine (15 mg 0.05 mmol) and cyclohexyl isocyanide (12 μL, 0.10 mmol) were added and reacted for next 0.5 hours. Samples were taken periodically for ^{1}H NMR and GPC analyses for conversion (**Figure S1, Figure 1c**) and molecular weight calculations, respectively. The mixture was dialyzed against DMSO using dialysis membrane (MWCO: 3500D) for 24 h. The final polymer (~ 125 mg) was obtained by precipitation in cold diethyl ether. The yield was ~ 90%.

^{1}H NMR (400 MHz, CD_3CN, δ/ppm): 8.57 (d, *J* = 8.4 Hz, C<u>H</u>CHCHCS), 8.26 (d, *J* = 8.6 Hz, C<u>H</u>CHCHCN), 8.03 (d, *J* = 7.2 Hz, CHCHC<u>H</u>CS), 7.75 (d, *J* = 7.6 Hz, C<u>H</u>CCOO), 7.65-7.53 (m, CHC<u>H</u>CHCS, CHC<u>H</u>CHCN), 7.29 (d, *J* = 7.5 Hz, CHCHC<u>H</u>CN), 7.17-6.97 (m, C<u>H</u>CHCCOO, C<u>H</u>CC<u>H</u>$_2$COO), 6.80-6.70 (m, C<u>H</u>CN), 6.40 (m, N<u>H</u>CO), 6.13 (m, N<u>H</u>SO_2), 5.83 (s, NC<u>H</u>CO), 4.29 (t, C<u>H</u>$_2$OCOAr), 4.16 (t, C<u>H</u>$_2$OCOCH$_2$), 4.05 (m, C<u>H</u>$_2$OCOC), 3.64-3.56 (m, COOC<u>H</u>$_3$), 3.56-3.52 (m, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.29 (s, OC<u>H</u>$_3$), 2.90 (s, NC<u>H</u>$_3$), 2.10-1.70 (m, C<u>H</u>$_2$C), 1.08-0.70 (m, C<u>H</u>$_3$C).

M_{nGPC} ~ 43800, PDI = 1.08.

3.6. Synthesis of mid-vinyl copolymer:

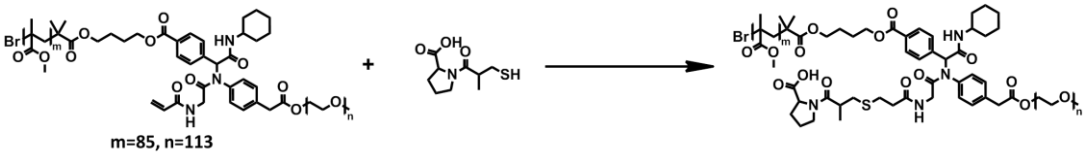


PMMA-CHO (86 mg, 0.01 mmol) and mPEG-NH_2 (50 mg, 0.01 mmol) were charged into a dry EP tube along with methanol (250 μL) and acetonitrile (250 μL). Then 2-acrylamidoacetic acid (6.5 mg 0.05 mmol) and cyclohexyl isocyanide (12 μL, 0.10 mmol) were added and reacted for next 0.5 hours. Samples were taken periodically for ^{1}H NMR and GPC analyses for conversion and molecular weight calculations (**Figure S5**), respectively. The mixture was dialyzed against DMSO using dialysis membrane (MWCO: 3500D) for 24 h. The final polymer (~ 124 mg) was obtained by precipitation in cold diethyl ether. The yield was ~ 90%.

^{1}H NMR (400 MHz, CD_3CN, δ/ppm): 7.79 (d, *J* = 7.9 Hz, C<u>H</u>CCOO), 7.25 (d, *J* = 7.9 Hz, C<u>H</u>CHCCOO), 7.20-7.11 (m, C<u>H</u>CCH$_2$COO), 6.92-6.85 (m, C<u>H</u>CN), 6.66 (m, N<u>H</u>CH), 6.27 (dd, C<u>H</u>CH$_2$), 6.15 (dd, CHC<u>H$_2$</u>), 6.06 (s, NC<u>H</u>CO), 5.62 (dd, CHC<u>H$_2$</u>), 4.29 (t, C<u>H$_2$</u>OCOAr), 4.16 (t, C<u>H$_2$</u>OCOCH$_2$), 4.05 (m, C<u>H$_2$</u>OCOC), 3.64-3.56 (m, COOC<u>H$_3$</u>), 3.56-3.52 (m, OC<u>H$_2$</u>C<u>H$_2$</u>O), 3.29 (s, OC<u>H$_3$</u>), 2.10-1.70 (m, C<u>H$_2$</u>C), 1.08-0.70 (m, C<u>H$_3$</u>C).

M_{nGPC} ~ 43800, PDI = 1.08.

3.7. Thiol-ene reaction between the Captopril and mid-vinyl copolymer:

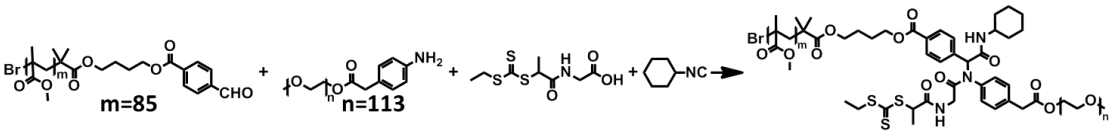


Mid-vinyl block copolymer (60 mg, 0.004 mmol), Captopril (20 mg, 0.08 mmol) were charged into a dry round bottom flask along with THF (4.0 mL). Then 2,2-Dimethoxy-2-phenylacetophenone (DMPA, 2 mg, 0.008 mmol) was added. The flask was sealed with a rubber septum and purged by nitrogen flow for 20 min. The tube was then put under a UV light (365 nm) for 4 h. The mixture was dialyzed against DMSO using dialysis membrane (MWCO: 3500D) for 24 h. The final polymer was obtained by precipitation in cold diethyl ether.

^{1}H NMR (400 MHz, CD_3CN, δ/ppm): 7.79 (d, *J* = 7.9 Hz, C<u>H</u>CCOO), 7.25 (d, *J* = 7.9 Hz, C<u>H</u>CHCCOO), 7.20-7.11 (m, C<u>H</u>CCH$_2$COO), 6.92-6.85 (m, C<u>H</u>CN), 6.66 (m, N<u>H</u>CH), 6.04 (s, NC<u>H</u>CO), 4.39 (m, C<u>H</u>COOH), 4.29 (t, C<u>H$_2$</u>OCOAr), 4.16 (t, C<u>H$_2$</u>OCOCH$_2$), 4.05 (m, C<u>H$_2$</u>OCOC), 3.64-3.56 (m, COOC<u>H$_3$</u>), 3.56-3.52 (m, OC<u>H$_2$</u>C<u>H$_2$</u>O), 3.29 (s, OC<u>H$_3$</u>), 2.10-1.70 (m, C<u>H$_2$</u>C), 1.08-0.70 (m, C<u>H$_3$</u>C).

M_{nGPC} ~ 43300, PDI = 1.08. (**Figure S6**)

3.8. Synthesis of mid-CTA copolymer:

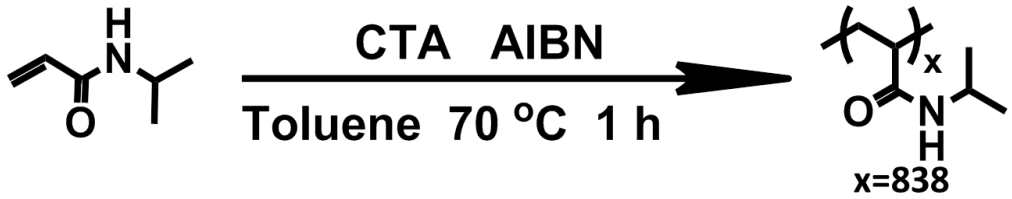


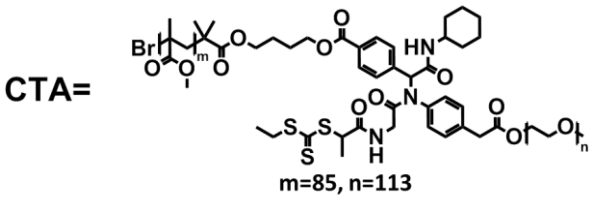
PMMA-CHO (86 mg, 0.01 mmol) and mPEG-NH_2 (50 mg, 0.01 mmol) were charged into a dry EP tube along with methanol (250 μL) and acetonitrile (250 μL). Then 2-(2-(((ethylthio)carbonothioyl)thio)propanamido)acetic acid (13.4 mg 0.05 mmol) and cyclohexyl isocyanide (12 μL, 0.10 mmol) were added and reacted for next 0.5 hours. Samples were taken periodically for ^{1}H NMR and GPC analyses for conversion and molecular weight calculations (**Figure S7**), respectively. The mixture was dialyzed against DMSO using dialysis membrane (3500D) for 24 h. The final polymer (~ 125 mg) was obtained by precipitation in cold diethyl ether. The yield was ~ 90%.

^{1}H NMR (400 MHz, CD_3CN, δ/ppm): 7.79 (d, *J* = 7.9 Hz, C<u>H</u>CCOO), 7.25 (d, *J* = 7.9 Hz, C<u>H</u>CHCCOO), 7.14 (m, C<u>H</u>CH_2COO), 6.88 (m, C<u>H</u>CN), 6.60 (m, N<u>H</u>CH), 6.05 (s, NC<u>H</u>CO), 4.79 (m, CHS), 4.29 (t, C<u>H_2</u>OCOAr), 4.16 (t, C<u>H_2</u>OCOCH_2), 4.05 (m, C<u>H_2</u>OCOC), 3.64-3.56 (m, COOC<u>H_3</u>), 3.56-3.52 (m, OC<u>H_2</u>C<u>H_2</u>O), 3.29 (s, OC<u>H_3</u>), 2.10-1.70 (m, C<u>H_2</u>C), 1.08-0.70 (m, C<u>H_3</u>C).

M_{nGPC} ~ 44000, PDI = 1.08.

3.9. Synthesis of miktoarm star copolymer:





NIPAAm (1.70 g, 15 mmol), mid-CTA copolymer (macro-CTA, 140 mg, 0.01 mmol)

and AIBN (1.0 mg, 0.006 mmol) were charged into a dry Schlenk tube along with toluene (3.0 mL). The Schlenk tube was sealed with a rubber septum and purged by nitrogen flow for 20 min. The tube was then put into an oil bath maintained at 70 °C for 1 h. The crude was precipitated from toluene to cold diethyl ether for 3 times, and then dried under vacuum to obtain the pure polymer for further characterizations and use.

The polymerization conversion (~ 50%) was calculated by ^{1}H NMR of the crude, comparing the peaks of the vinyl protons and the methyne protons. GPC was also used to evaluate the PDI and molecular weight of the final polymer.

^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 7.10-5.70 (m, CHN<u>H</u>CO), 4.14-3.88 (m, C<u>H</u>NHCO), 3.67-3.63 (m, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.62-3.58 (m, COOC<u>H</u>$_3$), 3.29 (s, OC<u>H</u>$_3$), 2.40-1.46 (m, C<u>H</u>$_2$C, C<u>H</u>$_2$C<u>H</u>), 1.40-1.00 (m, C<u>H</u>$_3$C, C<u>H</u>$_3$CC<u>H</u>$_3$).

M_{nGPC} ~ 196700, PDI = 1.30.

Supporting Data

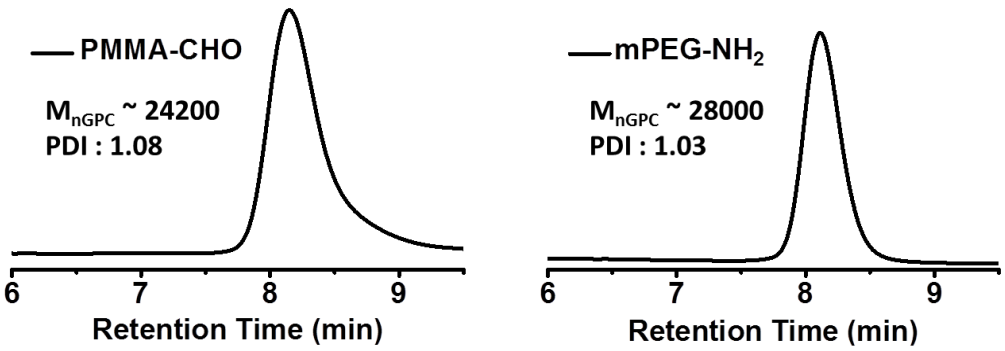


Figure S1. GPC curves of the two parent polymers: PMMA-CHO and mPEG-NH_2.

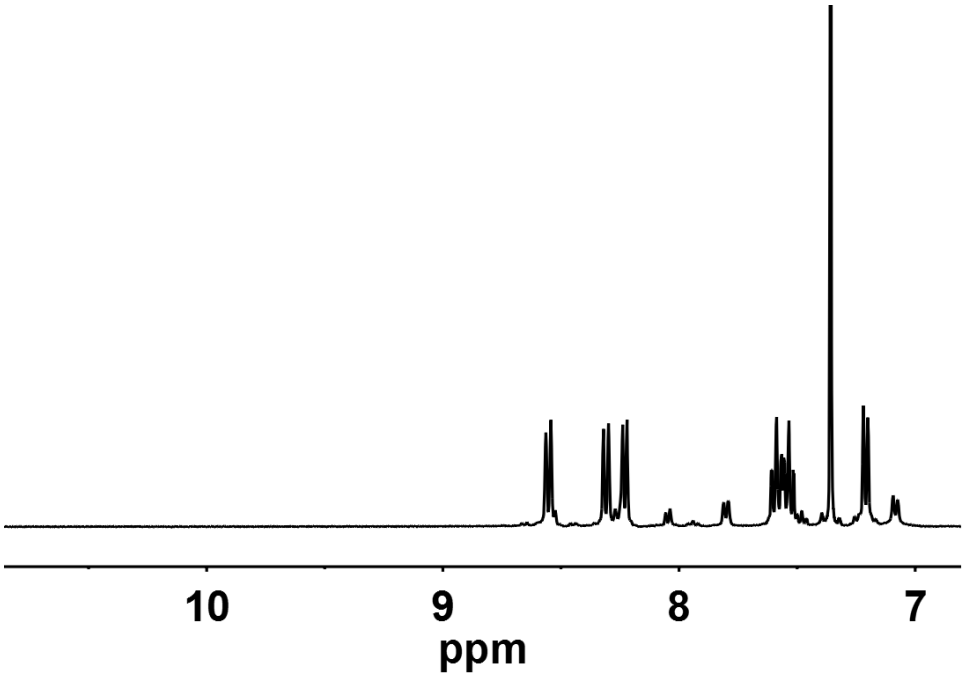


Figure S2. ^{1}H NMR analysis ($CDCl_3$-d, 400 MHz, portion) of the crude of Ugi coupling reaction after 0.5 h.

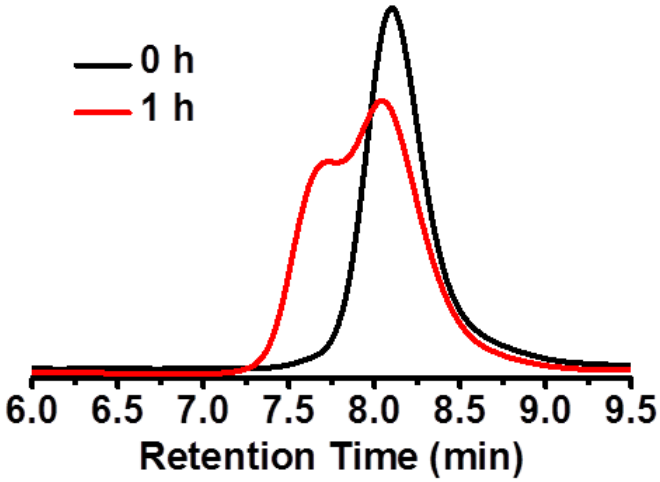


Figure S3. GPC tracking of the control reaction (mPEG-NH_2, PMMA-CHO and carboxylic acid, 1:1:5).

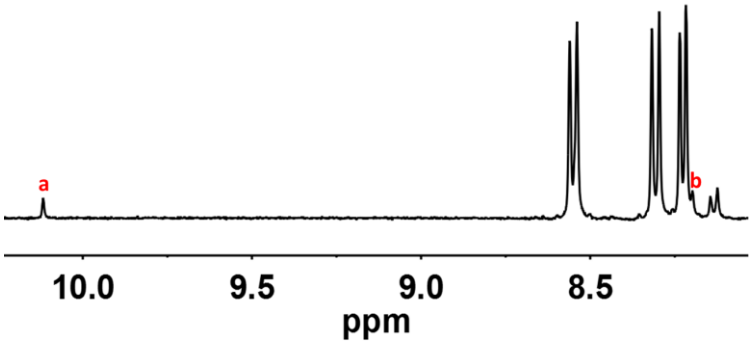


Figure S4. ^{1}H NMR analysis ($CDCl_3$-d, 400 MHz, portion) of the control reaction (mPEG-NH_2, PMMA-CHO and carboxylic acid, 1:1:5) (a: -C<u>H</u>O; b: -ArC<u>H</u>N-).

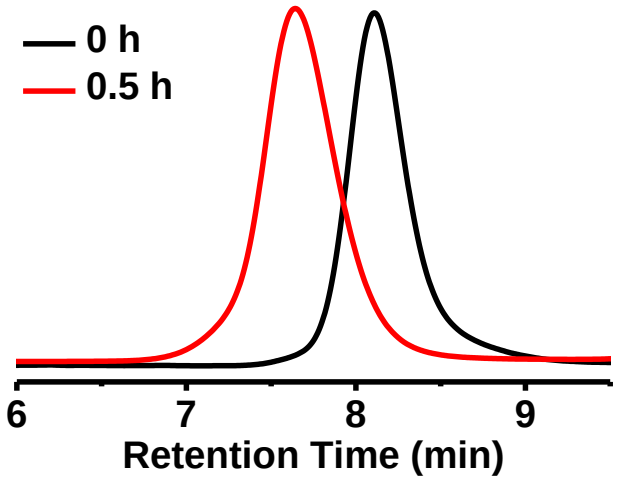


Figure S5. GPC tracking of the generation of Ugi-locked copolymer using 2-acrylamidoacetic acid (mid-vinyl copolymer).

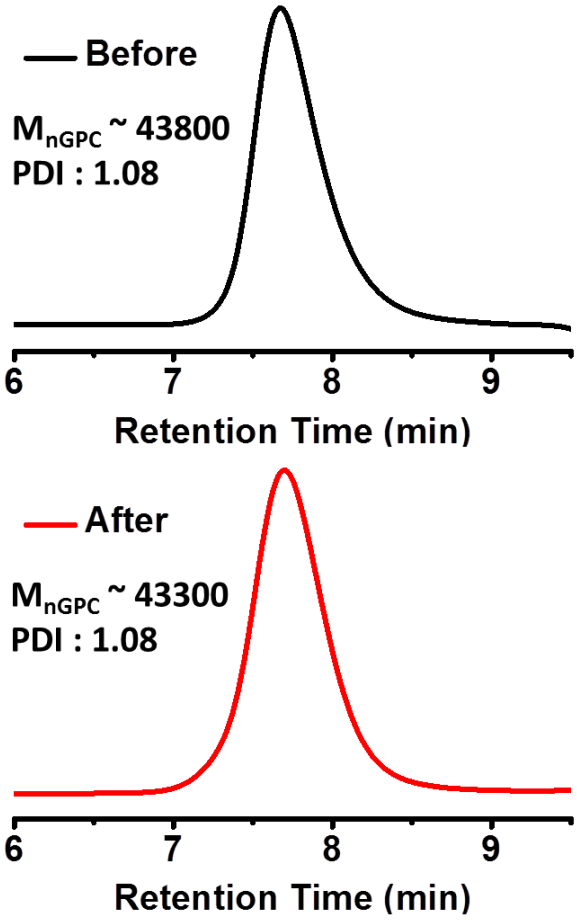


Figure S6. GPC curves of the 2-acrylamidoacetic acid locked block copolymer before and after thiol-ene click reaction. (Before: MnGPC ~ 43800, PDI=1.08; After: MnGPC ~ 43300, PDI=1.08)

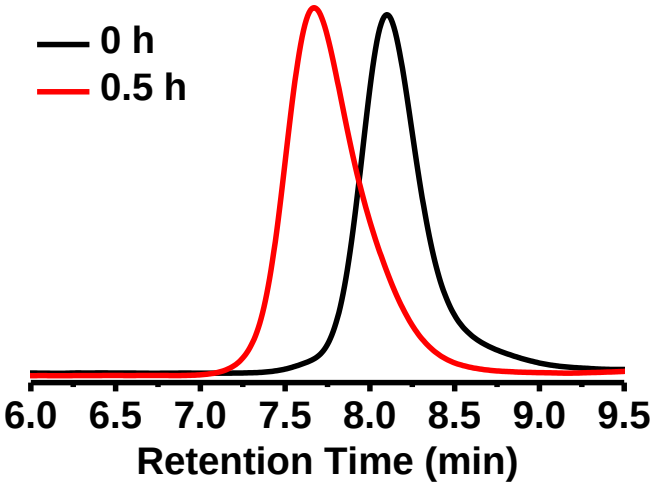


Figure S7. GPC tracking of the generation of Ugi-locked copolymer using 2-(2-(((ethylthio) carbonothioyl)thio)propanamido)acetic acid (mid-CTA copolymer).

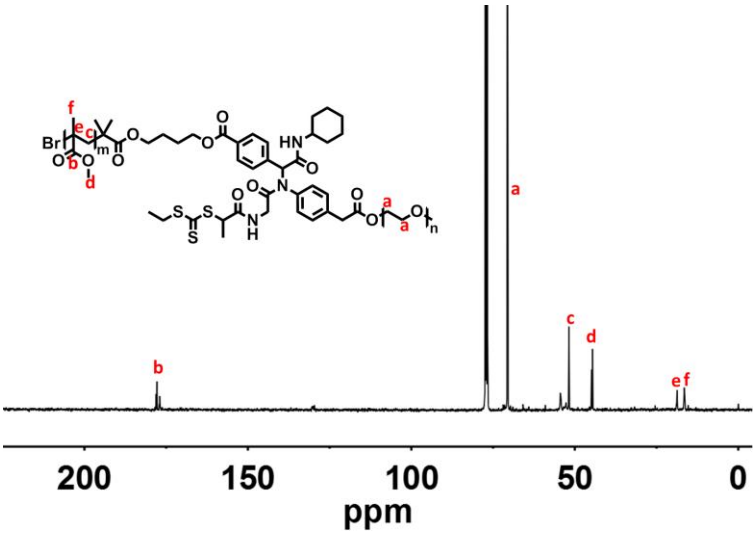


Figure S8. ^{13}C NMR analysis ($CDCl_3$-d, 100 MHz) of the mid-CTA block copolymer.

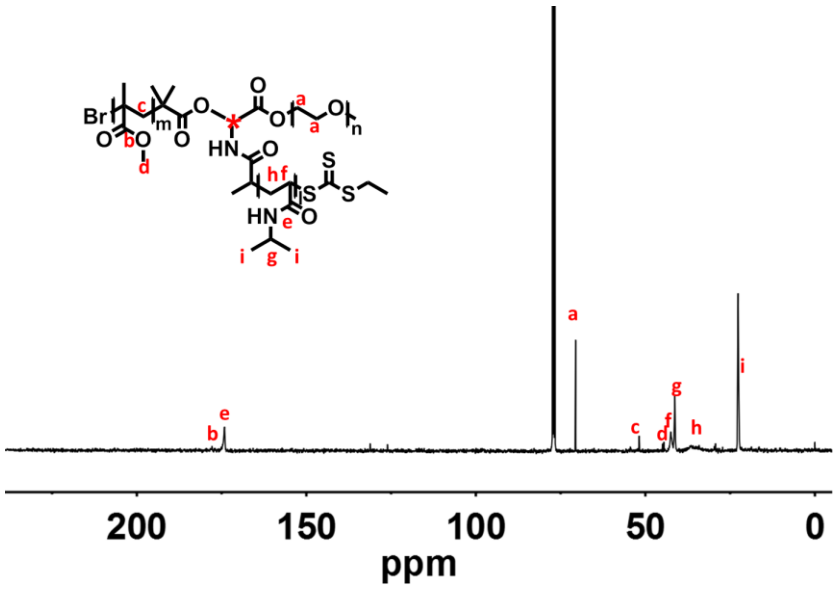


Figure S9. ^{13}C NMR analysis ($CDCl_3$-d, 100 MHz) of the miktoarm star copolymer.

Reference

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