Simultaneous copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) and living radical polymerization

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4.0 References
1.0 General

1.1 Materials. Copper(I) bromide (Aldrich, 98%) was purified according to the method of Keller and Wycoff.[1] N-(n-Propyl)-2-pyridylmethanimine,[2] 2-bromo-2-methyl-propionic acid benzyl ester initiator, propargyl methacrylate (1),[3] and 2′-azidoethyl-mannopyranoside (4)[4] were prepared as described earlier. Triethylamine (Fischer, 99%) was stored over sodium hydroxide pellets. All other reagents and solvents were obtained at the highest purity available from Aldrich Chemical Company and used without further purification unless stated.

1.2 Analysis. NMR spectra were obtained on a Bruker DPX400 spectrometer. All reactions were carried out using standard Schlenk techniques under an inert atmosphere of oxygen-free nitrogen, unless otherwise stated. Molar mass distributions of polymers were measured by size exclusion chromatography (SEC) with a system equipped with a differential refractive index detector and 2 mixed D columns, using CHCl₃ at 1.0 mL min⁻¹ as the mobile phase. Poly(MMA) standards (200 – 3 x 10⁵ Da) were used to calibrate the SEC. Sugar polymers were analysed by SEC using a system equipped with a guard column and two mixed C columns (200 - 2,000,000 g mol⁻¹) using N,N-dimethylformamide (DMF)/ 0.1M LiBr at 0.8 mL min⁻¹ as eluent. TLC plates were initially rinsed in the chamber solvent prior to sample application. Compounds were visualized by use of UV light (λ = 254 nm) or a basic aqueous solution (10 % w/w K₂CO₃ in water) of KMnO₄. Merck 60 (230-400 mesh) silica gel was used for column chromatography.

2.0 Synthesis of the organic azides

1-Azidoctane (2)

\[
\begin{array}{c}
\text{Br} \\
7
\end{array} \xrightarrow{\text{a}} \begin{array}{c}
\text{N}_3 \\
7
\end{array}
\]


1-Bromoctane (5.01 g, 25.9 mmol) and sodium azide (5.04 g, 48.6 mmol) were dissolved in a mixture of acetone (50 mL) and deionised water (10 mL). The resulting solution was heated to reflux and stirred at this temperature overnight. After cooling to ambient temperature, most of the acetone was removed under reduced pressure. Water (75 mL) was then added and the resulting mixture was then extracted with diethyl ether (3 x 50 mL). The organic
layers, collected, were dried over magnesium sulfate, filtered and the volatiles removed under reduced pressure to give (2) (3.61 g, 23.3 mmol, 90 % yield) as colourless oil.

Spectroscopic data was in agreement with that previously reported.[5]

1-Azido-triethylene glycol monomethyl ether (3)

\[
\begin{align*}
\text{Reagents and conditions:} & \quad a. \text{ TsCl, pyridine, } 4 \, ^\circ\text{C}; \quad b. \text{ NaN}_3, \text{ acetone/H}_2\text{O } 5:1 \text{ vol/vol, reflux.}
\end{align*}
\]

a: Triethylene glycol monomethyl ether (30.0 mL, 187 mmol) was dissolved in pyridine (200 mL). Solid p-toluene-sulfonyl chloride (42.88 g, 224.9 mmol) was added in small portions and the resulting solution was kept overnight at 4 °C. The resulting pyridinium hydrochloride crystals were filtered and the solvent removed under reduced pressure.

\[\text{CH}_2\text{Cl}_2 (500 \text{ mL}) \text{ was added and the solution was washed with ice-cold 0.1 M HCl (100 mL) and water (2 x 100 mL).} \]

The organic layer was dried over magnesium sulfate, filtered and the volatiles removed under reduced pressure. Obtained 38.1 g (120 mmol, 64 % yield) of spectroscopically pure[6] toluene-4-sulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester that was used for the next step without further purification (note: no residual TsCl was detected in the reaction crude product).

b: Toluene-4-sulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester (38.1 g, 119.4 mmol) and sodium azide (15.52 g, 238.8 mmol) were dissolved in a mixture of acetone (150 mL) and deionised water (30 mL). The resulting mixture was refluxed at 60 °C overnight. Most of the volatiles were then removed under reduced pressure. Then the salts were precipitated in ethyl acetate (300 mL) and after filtration H_2O (30 mL) was added and the mixture extracted with ethyl acetate (2 x 100 mL). The organic layer was dried over magnesium sulfate, filtered and the volatiles removed under reduced pressure. The crude residue was purified by flash chromatography (CC, SiO_2, ethyl acetate/petroleum ether 1:2 vol/vol). The relevant fractions were collected, combined and concentrated to dryness under reduced pressure to give (3) as colourless oil (20.2 g, 107 mmol, 89 % yield).

\[\begin{align*}
\text{H NMR (400.03 MHz, CDCl3, 298 K)} & \quad \delta = 3.37 \text{ (m, 2H, CH}_2\text{N}_3\text{); 3.38 (s, 3H, CH}_3\text{); 3.68 (m, 2H, OCH}_2\text{); 3.69 (m, 2H, CH}_2\text{O); 3.70(m, 2H, OCH}_2\text{); 3.71 (m, 2H, CH}_2\text{O); 3.75 (m, 2H, CH}_3\text{OCH}_2\text{); 15C}^1\text{H (100.59 MHz, CDCl}_3\text{, 298 K)} & \quad \delta = 50.77 (1C, CH}_3\text{N}_3\text{); 59.11 (1C, CH}_3\text{); 70.12 (1C, CH}_2\text{); 70.70 (1C, CH}_2\text{); 70.75 (1C, CH}_2\text{); 70.79 (1C, CH}_2\text{); 72.02 (1C, CH}_2\text{); IR (neat): } \tilde{\nu} = 2876, 2100, 1450, 1300, 1199, 1107, 853, 633. \text{ Anal. Calcd. for C}_7\text{H}_ {15}\text{N}_3\text{O}_3\text{: C, 44.43; H, 7.99; N, 22.21; Found: C, 44.35; H, 7.89; N, 22.01. MS(ESI): 189 (M+H) (2) 228 (M+K) (100).}
\end{align*}\]
3.0 CuAAC/LRP reactions

3.1 One-pot $^1$H NMR experiment. General procedure: A solution of mannose azide (4) (0.101 g, 0.401 mmol), propargyl methacrylate (1) (0.025 g, 0.20 mmol), 2-bromo-2-methyl-propionic acid benzyl ester initiator (8.0 µL, 3.8 µmol), propyl-pyridin-2-ylmethylene-amine ligand (1.2 µL, 7.6 µmol), triethylamine (2.8 µL, 19 µmol), mesitylene (internal NMR standard) and DMSO-$d_6$ (1.0 mL) were placed in an NMR tube and the resulting solution was analysed by $^1$H NMR. This solution was then transferred into a small vial and degassed for 10 minutes under nitrogen. This solution was then cannulated into a Youngs-tap NMR tube, previously evacuated and filled with nitrogen, containing CuBr (0.6 mg, 4 µmol). The mixture was finally placed into an NMR spectrometer set at the required temperature, and analysed by $^1$H NMR at regular intervals of time (5 to 7 minutes).

At the end of the reaction, the brown reaction solution was passed through a short neutral alumina pad and subsequently washed with the minimum amount of an appropriate solvent (in the case reported in this specific example DMSO was employed). 300 µL of this solution was diluted with an appropriate solvent suitable for SEC analysis (DMF in this case. CHCl$_3$ was employed for the CuAAC/LRP reactions in toluene-$d_8$ and DMF-$d_7$) up to a total volume of 2 mL.
Table S1. Characterisation data for the polymers prepared in this work

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<th>Cu (eq.)</th>
<th>Ligand (eq.)</th>
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<th>T/°C</th>
<th>ATRP/%</th>
<th>Click/%</th>
<th>PDI</th>
<th>Mₙ(SEC)/kDa</th>
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* Reaction time was 10 h 50 min for all the catalytic runs. Characterisation data, ATRP/% and click/% are relative to the final isolated polymers. 

b As determined by SEC using CHCl₃/Et₃N 95:5 vol/vol at 1.0 mL min⁻¹ as eluent.

c As determined by SEC using N,N-dimethylformamide (DMF)/ 0.1M LiBr at 0.8 mL min⁻¹ as eluent.
3.2 Influence of the ligand/CuBr concentration

Figure S1. Polymerisation first order kinetic plots for catalytic runs carried out in DMSO-\textit{d}_6 at different L_2CuBr concentrations. CuAAC/LRP: alkyne monomer (1) and trietyleneglycol azide (3) in toluene-\textit{d}_8. Reaction conditions: [initiator]:[(1)]:[(3)]:[Et$_3$N] = 1 : 50 : 100 : 5; T = 60 °C. [L$_2$CuBr] = 0.5, 1, 2, 4. "M" here indicates the concentration of the methacrylic moieties in solution, ((1) and the corresponding clicked monomer analogue).
Figure S2. CuAAC/LRP in toluene-\textit{d}_8 at different \textit{L}_2Cu\textsuperscript{Br} concentrations. CuAAC/LRP: alkyne monomer (1) and octy azide (2) in toluene-\textit{d}_8. Reaction conditions: [initiator]:[\textcolor{red}{(1)}]:[\textcolor{red}{(2)}]:[Et\textsubscript{3}N] = 1 : 50 : 100 : 5; T = 60 °C. [L\textsubscript{2}Cu\textsuperscript{Br}] = 0.5, 1, 2. "Click conversion" refers to the conversion of 1-alkyne units, both in the monomer (1) and in the polymer backbone into 1,2,3-triazole moieties. "LRP conversion" refers to the polymerisation of both (1) and the corresponding clicked monomer analogue.
Figure S3. Polymerisation first order kinetic plots for catalytic runs carried out in toluene-\(d_8\) at different L\(_2\)Cu\(^{1}\)Br concentrations. CuAAC/LRP: alkyne monomer (1) and octyl azide (2) in toluene-\(d_8\). Reaction conditions: [initiator]:[(1)]:[(2)]:[Et\(_3\)N] = 1 : 50 : 100 : 5; T = 60 °C. [L\(_2\)Cu\(^{1}\)Br] = 0.5, 1, 2. “[M]” here indicates the concentration of the methacrylic moieties in solution, [(1) and the corresponding clicked monomer analogue).
Figure S4. CuAAC/LRP at different catalyst concentrations. CuAAC/LRP: alkyne monomer (1) and α-2’-azidoethyl mannopyranoside (4) in DMSO-d₆. Reaction conditions: [initiator]:[(1)]:[((2)]:[Et₃N] = 1 : 50 : 100 : 5; T = 60 °C. [L₂CuBr] = 1, 2. “Click conversion” refers to the conversion of 1-alkyne units, both in the monomer (1) and in the polymer backbone into 1,2,3-triazole moieties. “LRP conversion” refers to the polymerisation of both (1) and the corresponding clicked monomer analogue.
Figure S5. Polymerisation first order kinetic plots for catalytic runs carried out in DMSO-\textit{d}_6 at different catalyst concentrations. CuAAC/LRP: alkyne monomer (1) and \(\alpha\)-2'-azidoethyl mannopyranoside (4) in DMSO-\textit{d}_6. Reaction conditions: [initiator]:[(1)]:[(4)]:[Et\textsubscript{3}N] = 1 : 50 : 100 : 5; \(T = 60\) °C. \([L\textsubscript{2}CuBr] = 1, 2. \("M"\) here indicates the concentration of the methacrylic moieties in solution, ((1) and the corresponding clicked monomer analogue).
3.3 Influence of the azide derivative

![Graph showing LRP and click conversion over time for two different azides: octylazide and triethyleneglycol azide.]

Figure S6. CuAAC/LRP in toluene-$d_8$ using different organic azides: octylazide (2) and triethyleneglycol azide (3). Reaction conditions: [initiator]:[(1)]:[(2) or (3)]:[Et$_3$N]:[L]:[CuBr] = 1 : 50 : 100 : 5 : 2 : 1, T = 60 °C. "Click conversion" refers to the conversion of 1-alkyne units, both in the monomer (1) and in the polymer backbone into 1,2,3-triazole moieties. "LRP conversion" refers to the polymerisation of both (1) and the corresponding clicked monomer analogue.
Figure S7. CuAAC/LRP in DMSO-d6 using different organic azides: triethyleneglycol azide (3) and 2’-azidoethyl-α-mannopyranoside (4). Reaction conditions: [initiator]:[(1)]:[(3) or (4)]:[Et3N]:[L]:[CuBr] = 1 : 50 : 100 : 5 : 2 : 1 in DMSO-d6, T = 60 °C. “Click conversion” refers to the conversion of 1-alkyne units, both in the monomer (1) and in the polymer backbone into 1,2,3-triazole moieties. “LRP conversion” refers to the polymerisation of both (1) and the corresponding clicked monomer analogue.
3.4 CuAAC/LRP in the absence of the iminopyridine ligand

Figure S8. CuAAC/LRP in DMSO-$d_6$ using triethyleneglycol azide (3), in the absence of the $N$-(n-propyl)-2-pyridylmethyleneimine bidentate ligand. Reaction conditions: [initiator]:[(1)]:[(3)]:[Et$_3$N]:[CuBr] = 1 : 50 : 100 : 5 : 1, T = 60 °C. "Click conversion" refers to the conversion of 1-alkyne units, both in the monomer (1) and in the polymer backbone into 1,2,3-triazole moieties. "LRP conversion" refers to the polymerisation of both (1) and the corresponding clicked monomer analogue.
References


