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Note

The application of microwave heating to the synthesis of 6-amino-6-deoxycellulose

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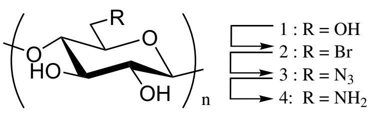
Abstract—Microwave heating was applied to the reactions involved in the synthesis of 6-amino-6-deoxycellulose, **4**. These included, cellulose solubilization, bromination at C-6, displacement of bromine with azide ion, and reduction of the azido group to an amino group. Compared to conventional heating, this approach had the advantages of shortening reaction times and retaining the degree of polymerization of **4**.

Keywords: 6-Amino-6-deoxycellulose; 6-Bromo-6-deoxycellulose; 6-Azido-6-deoxycellulose; Microwave heating; Conventional heating

For the last decade it has been accepted that microwave heating has an advantage of shortening reaction times, compared with conventional heating (an oil bath method).[1] Indeed, there are a few reports concerning the reactions of cellulose by microwave heating.[2–4] Recently, we have reported a facile synthesis of 6-amino-6-deoxycellulose (6-aminocellulose, **4**) by three reaction steps from cellulose (**1**) as shown in Scheme 1.[5] However, the number-average degree of polymerization (DPn) of the final product, **4**, was lower than that of the starting cellulose. In other words, depolymerization occurred during the preparation of **4**; however, depolymerization in each reaction step was not investigated. Because one of the reasons for such depolymerization was thought to be the long reaction times of these reaction steps, the application of microwave heating was attractive. This report describes a comparison of microwave heating and conventional heating in the reactions, including cellulose solubilization, in the synthesis of **4**.



Scheme 1.

The results of the reactions in the preparation of 6-aminocellulose, **4**, from cellulose, **1**, by microwave heating and conventional heating are summarized in Table 1. The heating cycle in Table 1 is described in Section 1 and Figure 1.

The use of microwave heating for cellulose solubilization in LiBr–Me_2NCOMe has not been reported to date. Although there were two reports concerning cellulose solubilization in LiCl–Me_2NCOMe by microwave heating, a detailed experimental procedure was not described.[3,6] Cellulose solubilization in LiBr–Me_2NCOMe was performed in an oil bath by the following process: heating of the suspension of cellulose in Me_2NCOMe at 130 °C for 2 h for cellulose activation, addition of LiBr to the suspension at 100 °C, additional heating at 100 °C for 15 min and keeping at 60 °C overnight. The DPn of cellulose triacetate (CTA) prepared from cellulose dissolved by the conventional method was 112 (Table 1, entry A-1). Then, we tried to replace only the conventional heating before the addition of LiBr with microwave heating. Microwave irradiation at 250 W for 32 s led to complete cellulose dissolution within 1 h after the addition of LiBr (Table 1, entry

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Table 1. Results of the reactions using microwave heating and conventional heating

Entry	Reaction step	Heating method	Reaction temperature (°C)	Heating cycle[a]						Product		
				Ramp time		Hold time		Cooling time	Number of cycles	Yield (%)	DS[b]	DPn[c]
				Time (s)	Irradiation power (W)	Time (min)	Irradiation power (W)	Time (min)				
A-1	Solubilization	Oil-bath	130	—	—	120	—	—	—	—	—	112
A-2	Solubilization	MW	140	32	250	0	—	10	1	—	—	113
B-1	a	Oil-bath	70	—	—	120	—	—	—	93	0.98	66
B-2	a	MW	70	60	70	5	5 (3 Pulses)	5	1	88	0.86	—
B-3	a	MW	70	60	70	7.5	5 (4 Pulses)	5	1	88	0.92	91
B-4	a	MW	70	60	70	10	5 (5 Pulses)	5	1	87	0.91	63
C-1	b	Oil-bath	70	—	—	2880	—	—	—	79	0.96	88
C-2	b	MW	95	12	200	0	—	5	20	—	0.72[d]	—
C-3	b	MW	80	60	20	30	5–10 (Continuous)	5	1	94	0.81[d]	—
C-4	b	MW	80	60	20	40	5–10 (Continuous)	5	1	94	0.91[d]	—
C-5	b	MW	80	60	20	50	5–10 (Continuous)	5	1	91	0.92	122
D-1	c	Oil-bath	60	—	—	2880	—	—	—	88	0.96	59
D-2	c	MW	70	60	15	40	5–10 (Continuous)	5	1	71	0.49[d]	—
D-3	c	MW	70	60	15	50	5–10 (Continuous)	5	1	75	0.65[d]	—
D-4	c	MW	70	60	15	60	5–10 (Continuous)	5	1	65	0.82[d]	—
D-5	c	MW	80	60	50	15	5–10 (Continuous)	5	3	91	0.92	106

[a] The heating cycle is described in Figure 1.

[b] The degree of substitution (DS) was determined by elemental analyses, unless otherwise noted.

[c] The degree of polymerization (DPn) was determined by GPC measurements (polystyrene standard).

[d] The DS was determined by FT-IR spectroscopy.

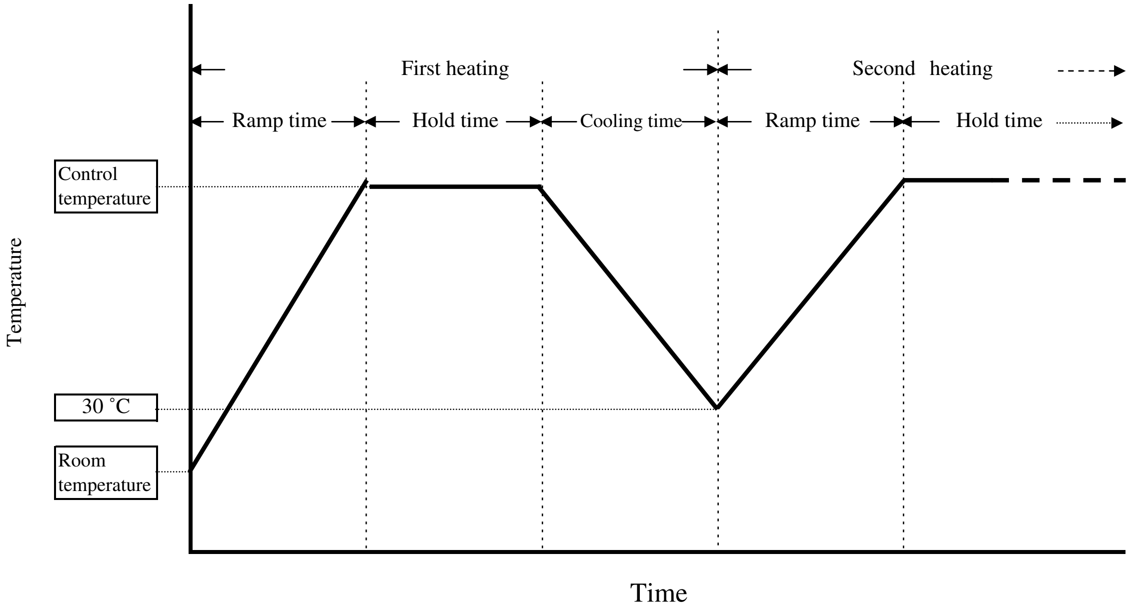

Figure 1. Heating cycle in microwave heating.

A-2). In this case, the DPn of CTA prepared from the cellulose was 113. On the other hand, microwave irradiation, even at low output power, after the addition of LiBr gave a dark brown cellulose solution, which might be due to the instability of LiBr.

Bromination of cellulose (**1**) was performed in an oil bath according to the method in the previous paper[5] (NBS, Ph_3P, LiBr–Me_2NCOMe, 70 °C, 2 h) to give 6-bromo-6-deoxycellulose (6-bromocellulose, **2**) with a degree of substitution (DS) of 0.98 and a DPn of 66 in 93% yield (Table 1, entry B-1), indicating that bromination was mainly responsible for the decrease of DPn during the synthesis of **4**. Then, microwave heating was applied to bromination of cellulose dissolved by microwave heating (Table 1, entry A-2). Microwave heating for 5 min at the hold time gave 6-bromocellulose, **2**, with a DS of 0.86 in 88% yield (Table 1, entry B-2), whereas microwave heating for 7.5 min afforded **2** with a DS of 0.92 and a DPn of 91 in 88% yield (Table 1, entry B-3). The DPn of **2** decreased remarkably at a hold time of 10 min (Table 1, entry B-4). Consequently, it was difficult to attain a high DS while retaining the DPn of **2**, even by microwave heating, although many reaction conditions aside from those in Table 1 were tried.

Singh et al. have reported that microwave heating accelerated the reaction of haloarylketones with sodium azide in DMSO to the corresponding azidoarylketones.[7] A similar effect was also expected for the nucleophilic displacement of 6-bromocellulose **2** by NaN_3. Azidation of 6-bromocellulose **2** of DS 0.98 with DPn of 66 (from Table 1, entry B-1) was performed in an oil bath according to our method[5] (NaN_3, n-Bu_4NI, DMSO, 70 °C, 48 h) to give 6-azido-6-deoxycellulose (6-azidocellulose, **3**) with a DS 0.96 and a DPn of 88 in 81% yield (Table 1, entry C-1). In this reaction, the reaction mixture was a suspension at the beginning of the reaction, and became a clear solution as the reaction proceeded. The increase of DPn of the cellulose derivative before and after the reaction might be due to elimination of a low molecular weight fraction of the product during purification of **3**. Azidation of **2** with a DS of 0.92 and a DPn of 91 (from Table 1, entry B-3) was performed by microwave heating. First, the reaction at 180 °C by microwave heating was done as a preliminary experiment, but **3** was obtained in low yield (data not shown). In the reaction at 95 °C using microwave at 200 W irradiation for 12 s, 20 heating cycles were required for the solution to become clear, and the DS of **3** obtained was only 0.72 (Table 1, entry C-2). The DS of **3** increased with increasing the hold time, and leveled off at 80 °C. Microwave irradiation for 50 min afforded **3** with a DS of 0.92 and DPn of 122 in 91% yield (Table 1, entry C-5), indicating that azidation of 6-bromocellulose **2** by microwave heating proceeded quantitatively in a very short time. The yield of 6-azidocellulose **3** by microwave heating was higher than that by conventional heating. The increase of DPn before and after the reaction might be explained by the same reason described above in the conventional heating.

The reduction of 6-azidocellulose **3** with a DS of 0.96 and a DPn of 88 (from Table 1, entry C-1) was performed in an oil bath according to our method[5] ($NaBH_4$, DMSO, 60 °C, 48 h) to give 6-aminocellulose **4** with a DS of 0.96 and DPn of 59 in 88% yield (Table 1, entry D-1), indicating that the depolymerization of the cellulose derivative occurred partially in this reaction. Then, microwave heating was used for reduction of **3** with a DS of 0.92 and a DPn of 122 (from Table 1, entry C-5). The reaction at 180 °C by microwave heating gave no satisfactory results (data not shown). When carried out at 70 °C, the DS of 6-aminocellulose **4** was 0.82, even when the hold time was 60 min (Table 1, entry D-4). Finally, it was found by a trial–error method that **4** with a DS of 0.92 and a DPn of 106 was obtained in 91% yield under the heating conditions listed in Table 1, entry D-5, although the three heating cycles were required. The ^{13}C NMR spectrum of **4** by microwave heating (Table 1, entry D-5) was in agreement with the data of **4** obtained by conventional heating.[5]

The microwave heating sequence (Table 1, entries A-2, B-3, C-5, and D-5) afforded 6-aminocellulose **4** from cellulose with a DS of 0.92 and a DPn of 106 in 73% overall yield, whereas the conventional heating process,[5] gave **4** with a DS of 0.96 and a DPn of 59 in 65% total yield. Therefore, microwave heating had the advantages of shortening the reaction time, increasing the overall yield and retaining the DPn of **4**, compared with conventional heating.

1. Experimental

1.1. General methods

Microcrystalline cellulose (Avicel®, DP = 114) and LiBr were purchased from Merck (Darmstadt, Germany), and Sigma–Aldrich (St. Louis, USA), respectively. Other reagents were purchased from Nakalai Tesque (Kyoto, Japan) or Wako Pure Chemical Industries (Osaka, Japan). All chemicals and reagents, unless otherwise specified, were used without further purification. Me_2NCOMe was purified by distillation at reduced pressure from KOH. *N*-Bromosuccinimide (NBS) was recrystallized from CCl_4–1,4-dioxane. Microcrystalline cellulose and LiBr were dried in vacuo at 100 °C for 1.5 h and at 130 °C for 3 h, respectively, before use.

Microwave heating was conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The apparatus consists of a continuous focused microwave power delivery system with power output from 0 to 300 W at 2.45 GHz. The reactions were performed in a 50 mL round-bottom flask (an open-type reaction vessel). The reaction temperature of the content in the flask was monitored using a calibrated infrared temperature control of the apparatus. One heating cycle consisted of heating from room temperature (or 30 °C) to a control temperature at ramp time, keeping at the control temperature for a hold time, and then cooling from the control temperature to 30 °C, shown as Figure 1. The control temperature was used as reaction temperature.

The work-up methods were performed according to the method given previously.[5] ^{1}H and ^{13}C NMR spectra were recorded with a Varian INOVA300 FT-NMR (300 MHz, 75 MHz) spectrometer. FT-IR spectra were measured in KBr pellets with a Shimadzu FTIR-8600 spectrophotometer. The DS of the cellulose derivatives **2**–**4** were determined by elemental analysis, unless otherwise noted. The DS of 6-azidocellulose, **3**, and 6-aminocellulose, **4**, were easily calculated from the calibration curves for DS with a high correlation coefficient (0.9939). This curve was obtained from the absorbance at 2111 cm^{-1}, assigned to azido group stretching, normalized by the absorbance at 2967 cm^{-1}, derived from CH stretching, and the DS determined by elemental analysis. Cellulose **1** and the cellulose derivatives **2**–**4** were acetylated with Ac_2O–pyridine–*N*,*N*-dimethylaminopyridine (DMAP) at 60 °C for 24 h before GPC measurements, and their DPn were determined by GPC analyses with a Shimadzu LC-10 system, equipped with Shodex columns (KF802, KF802.5, and K805) and a Shimadzu refractive index detector (RID-10A), in $CHCl_3$ at the flow rate (1.0 mL/min) at 40 °C. Calibration curves were obtained by using polystyrene standards (Shodex).

1.2. Dissolution of cellulose (1)

Microcrystalline cellulose (200 mg, 1.23 mM) was suspended in Me_2NCOMe (12 mL). The reaction mixture was activated by microwave heating under the appropriate conditions (Table 1, entry A-2), and kept at 100 °C in an oil bath. LiBr (2.8 g, 537 mM) was added to the mixture. The mixture was kept at the same temperature for 15 min and then the temperature was lowered to 60 °C. The mixture became a slightly yellow solution within 30 min, and was kept at this temperature overnight.

1.3. Bromination of cellulose (1)

To the cellulose solution in LiBr–Me_2NCOMe, Ph_3P (0.81 g, 3.09 mM), and NBS (0.55 g, 3.09 mM) were added at 0 °C. The reaction solution was irradiated by microwave under the conditions (Table 1, entry B-3), and worked-up to give 6-bromo-6-deoxycellulose (**2**) as a slightly brown powder (244 mg, yield: 88%, DS = 0.92).

1.4. Azidation of 6-bromo-6-deoxycellulose (2)

6-Bromo-6-deoxycellulose (**2**) (200 mg, 0.89 mmol, DS = 0.92), NaN_3 (289 mg, 4.45 mmol), and *n*-Bu_4NI (16.5 mg, 0.04 mmol) were suspended in DMSO (10 mL) in a flask. The solution was irradiated in the microwave (Table 1, entry C-5) and then the reaction mixture was worked-up to afford 6-azido-6-deoxycellulose (**3**) as a slightly brown powder (151 mg, yield: 91%, DS = 0.92).

1.5. Reduction of 6-azido-6-deoxycellulose (3)

6-Azido-6-deoxycellulose (**3**) (50 mg, 0.27 mmol, DS = 0.92) was added to DMSO (10 mL). Microwave irradiation of the mixture at 15 W for 2 min afforded a clear solution. After the addition of $NaBH_4$ (202 mg, 5.35 mmol), the solution was heated by microwave heating under the conditions (Table 1, entry D-5), and worked-up to give 6-amino-6-deoxycellulose (**4**) as a slightly brown powder (39 mg, yield: 91%, DS = 0.92). ^{13}C NMR (1% DCl in D_2O at 20 °C) δ: 105.3 (C-1), 82.2 (C-4), 76.5 (C-3), 75.7 (C-2), 74.0 (C-5), 42.8 (C-6) ppm.

References

1. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
2. Satgé, C.; Verneuil, B.; Branland, P.; Granet, R.; Krausz, P.; Rozier, J.; Petit, C. *Carbohydr. Polym.* **2002**, *49*, 373–376.
3. Satgé, C.; Granet, R.; Verneuil, B.; Branland, P.; Krausz, P. *C. R. Chim.* **2004**, *7*, 135–142.
4. Antova, G.; Vasvasora, P.; Zlantanov, M. *Carbohydr. Polym.* **2004**, *57*, 131–134.
5. Matsui, Y.; Ishikawa, J.; Kamitakahara, H.; Takano, T.; Nakatsubo, F. *Carbohydr. Res.* **2005**, *340*, 1403–1406.
6. Mocanu, C.; Pielichowski, K.; Murariu, A.; Ciovică, S.; Pielichowski, J.; Polaczek, J. In *Modern Polymeric Materials for Environmental Applications, International Seminar, 1st, Krakow, Poland, December 16–18, 2004*; Pielichowski, K., Ed.; Wydawnictwo Naukowo-Techniczne TEZA: Krakow, 2004; pp 101–104.
7. Singh, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdóttir, A. D. *Tetrahedron Lett.* **2003**, *44*, 9169–9171.