SYNTHESES OF CHIRAL N-SUBSTITUTED MALEIMIDES BEARING TWO POLYMERIZABLE GROUPS

Gao Huajing, Sun Jian, Xie Ning, Jin Zhaohui*

Institute of Petrochemical Engineering, Jilin Institute of Chemical Technology, Chengde Street 45, Jilin, China.

*Corresponding Author Email: 1224158505@qq.com

This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

ARTICLE DETAILS

Article History:

Received 26 June 2018

Accepted 2 July 2018

Available online 1 August 2018

ABSTRACT

Chiral (*S*)-*N*-maleoyl-L-leucine propargyl ester with a specific rotation of $[\alpha]_{435} = -27.5^\circ$ and chiral (*S*)-*N*-maleoyl-L-leucine allyl ester with a specific rotation of $[\alpha]_{435} = -36.2^\circ$, two monomers of *N*-substituted maleimide (RMI), were successfully synthesized from maleic anhydride, L-leucine, and propargyl alcohol or allyl alcohol accordingly. Both of them simultaneously have an olefinic group of the maleimide moiety and another polymerizable group (double or triple bond) in the ester moiety. ^1H NMR, ^{13}C NMR and FT-IR analysis confirmed the structures of them. And their model compounds of (*S*)-*N*-succinoyl-L-leucine propargyl ester and chiral (*S*)-*N*-succinoyl-L-leucine allyl ester were obtained respectively. The syntheses routes and results of them were reported in detail.

KEYWORDS

Propargyl ester, Allyl ester, N-Substituted maleimide, Synthesis.

1. INTRODUCTION

In the past three decades, Oishi et al. have systematically investigated on polymerization of *N*-substituted maleimides (RMIs) with various *N*-substituents (such as achiral amine, chiral amine, and chiral amino acid derivatives) and chiroptical properties of the polymers and copolymers [1-6]. Most polymerizations of these RMIs proceed through the reaction of the olefinic group in the imide ring, and the *N*-substituent did not participate in the construction of the polymer-main-chain because of the absence of polymerizable groups. Some RMI monomers possessing two reactive groups with different polymerization reactivities, such as an olefinic group and an ethynyl group, open a new field for polymer reactions and macromolecular networks. The authors have focused on the introduction of an unsaturated group as another polymerizable moiety to the *N*-substituent of a chiral RMI.

When the asymmetric anionic and/or radical polymerizations occur on the olefinic groups of chiral RMIs, the poly (RMI)s with pendant unsaturated groups are expected to show chirality induction and thermostable characteristics because of the cyclic polymer backbone. At the same time, the pendant unsaturated group could be available for further polymer design. Because (*S*)-*N*-maleoyl-L-leucine propargyl ester ((*S*)-PLMI) and (*S*)-*N*-maleoyl-L-leucine allyl ester ((*S*)-ALMI) both have one olefinic group in the maleimide ring and one unsaturated group in the *N*-substituted group simultaneously, they could be polymerized under anionic, or radical conditions. Herein, we report the synthesis routes of the two RMI monomers and their model compounds, (*S*)-*N*-succinoyl-L-leucine propargyl ester ((*S*)-PLSI) and (*S*)-*N*-succinoyl-L-leucine allyl ester ((*S*)-ALSI)

2. EXPERIMENTAL

2.1 Materials

Solvents used for syntheses, and measurements were purified in the usual manner.

2.2 Measurement

Specific rotations were measured in THF at 25°C using a quartz cell ($l = 0.5$ or 10 cm) with a JASCO DIP-140 polarimeter (JASCO Co. Ltd.). ^1H (270 MHz) and ^{13}C NMR (68 MHz) spectra were measured on a JEOL-EX270 apparatus (JEOL, Ltd.). FT-IR spectra were recorded in KBr phase using FTIR-8100A fourier transform infrared spectrophotometer (Shimadzu). CD (circular dichroism) spectra were recorded in THF at 25°C using a quartz cell of 1mm with a JASCO J-805 spectropolarimeter (JASCO Co. Ltd.).

2.3 Syntheses of Monomers (Scheme 1)

2.3.1 (*S*)-*N*-maleamic acid-L-leucine ((*S*)-LMA)

A solution of maleic anhydride (11.2 g, 0.11 mol) in acetic acid (60 mL) was dropwise added to a solution of L-leucine (15.0 g, 0.11 mol) in acetic acid (190 mL) at room temperature. After being stirred for 24 h at the same temperature, the reaction mixture was distilled under reduced pressure to remove acetic acid, and then crystallized from diethyl ether. After filtered and dried under vacuum, (*S*)-LMA was obtained as a white powder [yield: 20.1 g (76%), mp: 134-136.5°C (lit.35 141°C)]. ^1H NMR (δ in ppm from TMS in $\text{DMSO}-d_6$): 9.22-9.20 (d, 1H, NH), 6.51-6.34 (dd, 2H, $J = 12.54, 12.21$ Hz, $-\text{CH}=\text{CH}-$), 4.43-4.34 (dd, 1H, $J = 7.92, 7.92$ Hz, $-\text{CH}-$), 1.92-1.62 (m, 3H, $-\text{CH}_2-\text{CH}-$), 0.99-0.93 (dd, 6H, $J = 6.27, 5.93$ Hz, $-\text{CH}_3$).

Scheme 1: Synthesis of (*S*)-PLMI

2.3.2 (S)-N-maleoyl-L-leucine ((S)-LMI)

(S)-LMA (10.0 g, 44 mmol) was suspended into dry toluene (250 mL), H_3PO_4 (85%, 1.3 mL) and triethylamine (12.3 mL, 87 mmol) were added in sequence. Then the reaction mixture was refluxed for 1.5 h with vigorous stirring. The mixture was cooled to room temperature and organic solution was concentrated. The obtained residue was neutralized with 0.5 N HCl aq. to pH = 3 and extracted with ethyl acetate (100 mL $\times$ 3). The organic phase was fully washed with water (100 mL $\times$ 3), and saturated NaCl aq. (100 mL) in sequence, dried over Na_2SO_4 , and concentrated under reduced pressure, crystallized in *n*-hexane to afford (S)-LMI as a white powder [yield: 6.6 g (72%), mp: 88~89.5°C (lit.35 87~90°C), $[\alpha]_{435} = -41.2^\circ$ ($c = 1.0$ g/dL, $l = 10$ cm, THF)]. ^1H NMR (δ in ppm from TMS in CDCl_3): 6.74 (s, 2H, $-\text{CH}=\text{CH}-$), 4.82-4.77 (dd, 1H, $J = 4.29, 4.62$ Hz, $-\text{CH}$), 2.31-1.81 (m, 2H, $-\text{CH}_2$), 1.58 (m, 1H, $-\text{CH}$), 0.94-0.91 (dd, 6H, $J = 2.97, 2.97$ Hz, $-\text{CH}_3$).

2.3.3 (S)-PLMI

(S)-LMI (6.0 g, 28.4 mmol) was dissolved into thionyl chloride (SOCl_2) (30 mL), and the solution was refluxed for 2.5 h. After cooling to room temperature, excess SOCl_2 was removed under reduced pressure, the residue ((S)-LMI-Cl) was dissolved into dry toluene (80 mL). Propargyl alcohol (2.0 mL, 33.8 mmol) and triethylamine (4.8 mL, 33.8 mmol) were dissolved into dry toluene (100 mL), and the solution was cooled to 0°C. (S)-LMI-Cl in dry toluene was added dropwise into the above solution. Then the reaction solution was heated to 80°C and stirred for 11 h. After cooling to room temperature, the solution was washed with 1 N hydrochloric acid, water, saturated brine and dried over Na_2SO_4 . The solution was concentrated by rotary evaporator to obtain crude (S)-PLMI. The residue was purified by column chromatography (eluent: ethyl acetate / *n*-hexane = 1/3, v/v) and vacuum distillation to obtain (S)-PLMI as a yellow liquid [yield: 4.8 g (67%), bp: 160°C/0.6 mmHg, $[\alpha]_{435} = -27.5^\circ$ ($c = 1.0$ g/dL, $l = 10$ cm, THF)]. ^1H NMR (δ in ppm from TMS in CDCl_3): 6.75 (s, 2H, $-\text{CH}=\text{CH}-$), 4.83-4.77 (dd, 1H, $J = 4.3, 4.3$ Hz, $-\text{CH}$), 4.72-4.71 (d, 2H, $J = 2.3$ Hz, $-\text{CH}_2$), 2.50-2.49 (t, 1H, $J = 2.5$ Hz, $\text{CH}\equiv$), 2.31-1.84 (m, 2H, $-\text{CH}_2$), 1.53-1.38 (m, 1H, $-\text{CH}$), 0.94-0.91 (dd, 6H, $J = 2.0, 2.0$ Hz, $-\text{CH}_3$), ^{13}C NMR (δ in ppm from TMS in CDCl_3): 169.9 (N-C=O), 168.9 (C=O), 134.2 ($-\text{CH}=\text{CH}-$), 76.8 ($\equiv\text{C}-\text{CH}_2$), 75.5 ($\equiv\text{CH}$), 53.0 ($\text{CH}_2-\text{C}=\text{O}$), 50.4 (N-CH-), 36.9 ($-\text{CH}_2$), 24.9 ($-\text{CH}$), 23.0 ($-\text{CH}_3$), 20.8 ($-\text{CH}_3$). IR (KBr, cm^{-1}): 3300

($\text{HC}\equiv$), 3100, 2960, 2110 ($\text{C}\equiv\text{C}$), 1750, 1710, 1400, 1250, 840, 700. Anal. (%), Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 63.0; H, 6.30; N, 5.83.

2.3.4 (S)-ALMI

The synthetic route for the (S)-ALMI is approximate to the (S)-PLMI in Scheme 1. (S)-LMI (10.0 g, 47.4 mmol) was dissolved into thionyl chloride (SOCl_2) (50 mL), and the solution was refluxed for 2.5 h. After cooling to room temperature, excess SOCl_2 was removed under reduced pressure. The residue ((S)-LMI-Cl) was dissolved into dry toluene (150 mL). Allyl alcohol (4.5 mL, 66.4 mmol) and triethylamine (8.6 mL, 61.6 mmol) were dissolved into dry toluene (150 mL), and the solution was cooled to 0°C. (S)-LMI-Cl in dry toluene was added dropwise into the above solution. The reaction solution was then heated to 80°C and stirred for 11 h. After cooling to room temperature, the solution was washed with 1 N hydrochloric acid, water, and saturated brine, and dried over Na_2SO_4 . The solution was concentrated by rotary evaporator to obtain crude (S)-ALMI. The residue was purified by vacuum distillation to obtain (S)-ALMI as a yellow liquid [yield: 7.8 g (65.7%), bp: 130°C/0.5 mmHg, $[\alpha]_{435} = -36.2^\circ$ ($c = 1.0$ g/dL, $l = 10$ cm, THF)]. ^1H NMR (δ in ppm from TMS in CDCl_3): 6.74 (s, 2H, $-\text{CH}=\text{CH}-$), 5.94-5.80 (m, 1H, $-\text{CH}=\text{CH}_2$), 5.32-5.21 (m, 2H, $\text{CH}_2=\text{CH}-$), 4.81-4.75 (dd, 1H, $J = 4.62, 4.29$ Hz, $-\text{CH}-\text{N}$), 4.63-4.61 (m, 2H, $-\text{CH}_2-\text{O}$), 2.32-1.83 (m, 2H, $-\text{CH}_2-$), 1.52-1.37 (m, 1H, $-\text{CH}-\text{CH}_3$), 0.94-0.90 (dd, 6H, $J = 2.64, 2.31$ Hz, $-\text{CH}_3$). ^{13}C NMR (δ in ppm from TMS in CDCl_3): 170.15 (C=O in imide ring), 169.38 (C=O in ester group), 134.25 ($-\text{CH}=\text{CH}-$), 131.42 ($=\text{C}-\text{CH}_2$), 118.67 ($\text{CH}_2=$), 66.29 ($-\text{CH}_2-\text{O}$), 50.69 ($-\text{CH}-\text{N}$), 37.02 ($-\text{CH}_2$), 25.05 ($-\text{CH}$), 23.09 ($-\text{CH}_3$), 20.88 ($-\text{CH}_3$). IR (KBr, cm^{-1}): 3100, 2970, 2880, 1745, 1710, 1464, 1405, 1390, 1255, 1214, 1175, 1128, 1025, 985, 930, 835, 700. Anal. (%), Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.37; H, 6.94; N, 5.79.

2.4 Syntheses of Model Compounds

2.4.1 (S)-PLSI

The synthetic route for the (S)-PLSI is depicted in Scheme 2.

Scheme 2: Synthesis of (S)-PLSI

(S)-LMI (4 g, 18.9 mmol) was dissolved in ethyl acetate (30 mL) in a Schlenk reaction tube, 10 wt% palladium-activated carbon (Wako Pure Chemical Industries, Ltd., 0.04 g) was added. The solution was evacuated by aspirator and replaced by hydrogen gas. After stirring under hydrogen atmosphere for 24 h, the reaction tube was evacuated by aspirator, replaced by nitrogen gas, and then filtered to remove palladium-activated carbon. Filtrate was concentrated under reduced pressure to afford (S)-LSI as a yellow liquid [yield: 3.6 g (89%)]. (S)-PLSI was synthesized from (S)-LSI and propargyl alcohol by the same method as (S)-PLMI [yield: 55.7%, yellow liquid, bp: 175°C/0.6 mmHg, $[\alpha]_{435} = -98.0^\circ$ ($c = 1.0$ g/dL, $l = 10$ cm, THF)]. ^1H NMR (δ in ppm from TMS in CDCl_3): 4.87-4.81 (dd, 1H, $J = 4.3, 4.6$ Hz, $-\text{CH}$), 4.72-4.71 (d, 2H, $J = 2.3$ Hz, $-\text{CH}_2$), 2.77 (s, 4H, $-\text{CH}_2-\text{CH}_2-$), 2.50-2.49 (t, 1H, $J = 2.5$ Hz, $\text{CH}\equiv$), 2.23-1.86 (m, 2H, $-\text{CH}_2$), 1.51-1.31 (m, 1H, $-\text{CH}$), 0.94-0.91 (d, 6H, $J = 6.6$ Hz, $-\text{CH}_3$). ^{13}C NMR (δ in ppm from TMS in CDCl_3): 176.5 (N-C=O), 168.4 ($-\text{C}=\text{O}$), 76.9 ($\equiv\text{C}-\text{CH}_2$), 75.5 ($\text{CH}\equiv$), 53.0 ($\text{CH}_2-\text{C}=\text{O}$), 50.9 (N-CH-), 36.2 ($-\text{CH}_2$), 27.9 ($-\text{CH}_2$), 24.9 ($-\text{CH}$), 22.9 ($-\text{CH}_3$), 21.0 ($-\text{CH}_3$). IR (KBr, cm^{-1}): 3300 ($\text{HC}\equiv$), 2960, 2110 ($\text{C}\equiv\text{C}$), 1750, 1710, 1400, 1250. Anal. (%), Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.10; H, 7.12; N, 5.76.

2.4.2 (S)-ALSI

(S)-ALSI was synthesized from (S)-LSI and allyl alcohol by the same method as (S)-ALMI (yield: 52.9%, yellow liquid, bp: 146°C/0.5 mmHg, $[\alpha]_{435} = -92.6^\circ$ ($c = 1.0$ g/dL, $l = 10$ cm, THF)). ^1H NMR (δ in ppm from TMS in CDCl_3): 5.95-5.80 (m, 1H, $-\text{CH}=\text{CH}_2$), 5.33-5.22 (t, 2H, $J = 14.33$ Hz, $\text{CH}_2=\text{CH}-$), 4.85-4.79 (dd, 1H, $J = 4.32, 4.32$ Hz, $-\text{CH}-\text{N}$), 4.63-4.61 (d, 2H, $J = 5.68$ Hz, $-\text{CH}_2-\text{O}$), 2.76 (s, 4H, $-\text{CH}_2-\text{CH}_2-$), 2.25-1.86 (m, 2H, $-\text{CH}_2$), 1.49-1.34 (m, 1H, $-\text{CH}-\text{CH}_3$), 0.94-0.91 (d, 6H, $J = 6.49$ Hz, $-\text{CH}_3$). ^{13}C NMR (δ in ppm from TMS in CDCl_3): 176.41 (C=O in imide ring), 168.79 (C=O in ester

group), 131.45 ($=\text{C}-\text{CH}_2$), 118.51 ($\text{CH}_2=$), 66.15 ($-\text{CH}_2-\text{O}$), 51.14 ($-\text{CH}-\text{N}$), 36.32 ($-\text{CH}_2-$), 27.98 ($-\text{CH}_2-\text{CH}_2-$), 25.00 ($-\text{CH}$), 22.97 ($-\text{CH}_3$), 21.04 ($-\text{CH}_3$). IR (KBr, cm^{-1}): 2957, 2871, 1779, 1745, 1710, 1465, 1395, 1260, 1190, 1135, 1029, 980, 930, 822, 664. Anal. (%), Calcd. $\text{C}_{13}\text{H}_{19}\text{NO}_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.92; H, 7.78; N, 5.62.

3. RESULTS

To investigate the structures of monomers and model compounds, NMR, and FT-IR spectra were measured. Figure 1 illustrates the ^1H NMR spectra of (S)-PLMI and (S)-PLSI obtained. The ^1H NMR spectrum of (S)-PLMI (a in Figure 1) showed the olefinic protons of the maleimide ring at 6.75 ppm and the ethynyl proton at 2.50 ppm. And the olefinic protons of the maleimide ring at 6.75 ppm disappeared in the spectrum of (S)-PLSI (b in Figure 1).

Figure 1: ^1H NMR spectra of monomer (S)-PLMI (a) and model compound (S)-PLSI(b)

Figure 2 shows the FT-IR spectra of (S)-PLMI, (S)-PLSI, (S)-ALMI and (S)-ALSI. The IR spectra (in Figure 2) of (S)-PLMI and (S)-PLSI exhibited the characteristic absorptions assigned to the stretching vibrations of $\text{C}\equiv\text{C}$ -H and $\text{C}\equiv\text{C}$ bonds of the ethynyl group at 3300 cm^{-1} and 2110 cm^{-1} . (S)-ALMI and (S)-ALSI exhibited the characteristic absorptions assigned to the

stretching vibrations of $\text{C}=\text{C}$ -H and $\text{C}=\text{C}$ bonds of the olefinic group in the ester moiety at 2880 cm^{-1} and 1460 cm^{-1} in the IR spectra (in Figure 2).

Figure 2: FT-IR spectra of (S)-PLMI, (S)-PLSI(b), (S)-ALMI and (S)-ALSI

Information on chiroptical properties for (S)-RLMI was given by CD and UV spectra. Typical CD and UV spectra of (S)-PLMI, (S)-PLSI, (S)-ALMI and (S)-ALSI are depicted in Figure 3. The CD spectra of them exhibited a positive Cotton effect around 230-260 nm (Figure 3), which were mainly attributable to $n\rightarrow\pi^*$ transition of the carbonyl group in the *N*-substituent.

Figure 3: CD and UV spectra of (S)-PLMI(a), (S)-PLSI(b), (S)-ALMI(1) and (S)-ALSI(2)

4. CONCLUSIONS

Chiral (S)-*N*-maleoyl-L-leucine propargyl ester with a specific rotation of $[\alpha]_{435} = -27.5^\circ$, and chiral (S)-*N*-maleoyl-L-leucine allyl ester with a specific rotation of $[\alpha]_{435} = -36.2^\circ$, were successfully synthesized. They are the kind of chiral monomer (S)-RLMI, which simultaneously has an olefinic group of the maleimide moiety and another polymerizable group (such as double or triple bond) in the ester moiety. Such monomers will be able to open a new field for polymer reactions and macromolecular networks. ^1H NMR, ^{13}C NMR and IR analysis confirmed the structures of the (S)-PLMI and (S)-ALMI. Their model compounds, chiral (S)-PLSI and (S)-ALSI, were obtained at the same time.

REFERENCES

- [1] Oishi, T., Yamasaki, H., Fujimoto, M. 1991. Asymmetric polymerization of *N*-substituted maleimides. *Polymer Journal*, 23, 795-804. doi: 10.1295/polymj.23.795*
- [2] Onimura, K., Tsutsumi, H., Oishi, T. 1998. Asymmetric anionic polymerization of *N*-substituted maleimides with *n*-butyllithiummethylene-bridged 2,2-bis(oxazoline) complexes. *Macromolecules*, 31, 5971-5976. doi: 10.1021/ma980432i*
- [3] Isobe, Y., Onimura, K., Tsutsumi, H., Oishi, T. 2001. Asymmetric polymerization of *N*-1-naphthylmaleimide with chiral anionic initiator: preparation of highly optically active poly (*N*-1-naphthylmaleimide). *Macromolecules*, 34, 7617-7623. doi: 10.1021/ma010845a*
- [4] Zhou, H., Onimura, K., Tsutsumi, H., Oishi, T. 2001. Synthesis and chiroptical properties of (S)-(-)-*N*- α -methylbenzylmaleimide polymers containing crystallinity. *Polymer Journal*, 33, 227-235. doi:10.1295/polymj.33.227*
- [5] Zhang, Y., Onimura, K., Tsutsumi, H., Oishi, T. 2004. Asymmetric anionic polymerization of (S)-(-)-*N*-maleoyl-L-valine methyl ester. *Polymer Journal*, 36, 878-887. doi: 10.1295/polymj.36.878*
- [6] Oishi, T., Gao, H., Nakamura, T., Isobe, Y., Onimura, K. 2007. Asymmetric polymerizations of *N*-substituted maleimides bearing l-leucine ester derivatives and chiral recognition abilities of their polymers. *Polymer Journal*, 39, 1047-1059. doi: 10.1295/polymj.PJ2007022*

ABOUT THE AUTHORS

GAO Huajing (1971-), Doctor of Engineering, associate professor in Jilin Institute of Chemical Technology, E-mail: 364641193@qq.com.
 SUN Jian (1984-), Doctor of Engineering, lecturer in Jilin Institute of Chemical Technology.
 XIE Ning (1995-), Postgraduate in Jilin Institute of Chemical Technology.
 JIN Zhaohui (1970-), Doctor of Engineering, professor in Jilin Institute of Chemical Technology, E-mail: 1224158505@qq.com.