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Selective reversible protection of ethylenediamine for the synthesis of methacryl-based monomers

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SUMMARY

The hydrophilic monomers, 2-aminoethylmethacrylamide (AEMA), N,N-bis(2-hydroxypropyl)aminoethylmethacrylamide (HPAEMA) and N,N,N'-tris(2-hydroxypropyl)ethylenediamine methacrylate (HPEDM), were prepared through selective and reversible protection of ethylenediamine. Ethylenediamine was selectively protected by trimethylsilylation to give N,N,N'-tris- and N,N-bis(trimethylsilyl)ethylenediamine. Stoichiometric addition of methacryloyl chloride to N,N,N'-tris(trimethylsilyl)ethylenediamine gave exclusively N,N-bis(trimethylsilyl)aminoethylmethacrylamide (BTAEMA) in quantitative yield. Desilylation with methanol also produced AEMA in quantitative yield. Treatment of AEMA with propylene oxide produced HPAEMA monomer in 92.4% yield. N,N-Bis(trimethylsilyl)ethylenediamine was treated with propylene oxide, and desilylated to give 92.8% yield of N,N-bis(2-hydroxypropyl)ethylenediamine. Upon treatment with glycidyl methacrylate, HPEDM monomer was produced in 75.6% yield. The selective and reversible protection of ethylenediamine provides a convenient and efficient method for generating asymmetrically substituted ethylenediamine-based monomers.

INTRODUCTION

Positively charged hydrophilic hydrogel polymers can be used as support matrices for cultured cells (1). Copolymers containing either Quadrol methacrylate or 2-aminoethyl-methacrylate and hydroxyethylmethacrylate actively support the growth of cultured fibroblasts (2). Quadrol methacrylate was prepared from the alkylation of N,N,N'-tris(2-hydroxypropyl)ethylenediamine by glycidyl methacrylate (3-4) and 2-aminoethylmethacrylamide from acylation of excess ethylenediamine with methacryloyl chloride (2). Problems with these synthetic approaches have included: 1) low yield synthesis and fractional distillation

of N,N,N'-tris(2-hydroxypropyl)ethylenediamine, 2) formation of N,N'-bis-methacrylamide byproducts and 3) formation of Michael addition products. These problems could be eliminated by utilizing a selectively reversible substituted ethylenediamine (ED) which can only undergo stoichiometric mono-acylation or alkylation. Once the monomer is formed, the protecting group could be removed to allow for further alkylation with propylene oxide. Currently, no simple method is available to selectively and reversibly protect one of the two amino groups on ED. West et al. (5) have prepared in high yield N,N,N'-tris(trimethysilyl)ethylene diamine (TTED) and N,N-bis(trimethylsilyl)ethylenediamine (BTED) for use in a mechanistic study of anionic rearrangements. Use of these reagents were potentially attractive for synthesis because the selectively protected EDs could be readily prepared in high yield and the reactions were potentially reversible upon addition of alcohol under mild conditions. Herein, we report the use of TTED and BTED to selectively and quantitatively synthesize 2-aminoethyl-methacrylamide (AEMA), N',N'-bis(2-hydroxypropyl)amino-ethylmethacrylamide (HPAEMA) and N,N,N'-tris(2-hydroxy-propyl)ethylenediamine methacrylate (HPEDM).

EXPERIMENTAL

Materials and Methods

Ethylenediamine, glycidyl methacrylate, hexamethyl-disilazane (HMDS), methacryloyl chloride, propylene oxide, and trimethylchlorosilane (TMCS) were purchased from Aldrich Chemical Co. (Milwaukee, WI) and distilled prior to use. N-butyllithium (1.6M) in hexanes and ρ-methoxylphenol were used as purchased from Aldrich. Ethyl ether, THF and triethylamine (Fisher) were dried over sodium metal and distilled before use. All glassware was oven dried before use. All reactions were performed in an atmosphere of dry nitrogen.

Preparation of Silylated Ethylenediamines

N,N'-Bis(trimethylsilyl)ethylenediamine, TTED and BTED were prepared on a large scale following a modified procedure reported by West et al. (5).

N,N'-Bis(trimethylsilyl)ethylenediamine

Ethylenediamine (191.2g, 3.2 mol) was mixed with (540.0g, 3.3 mol) of hexamethyldisilazane and twenty drops of trimethylchlorosilane as catalyst. The mixture was heated to 150°C for 2 days. An additional 30g of hexamethyldisilazane was added and maintained at 150°C for 12 hr, then fractionally distilled at reduced pressure to give 501g

(77.2%) of colorless liquid, N,N'-Bis(trimethylsilyl)-ethylenediamine, bp 35°C (0.9 torr) [lit. bp 70°C (8 torr)] (5).

N,N,N'-Tris(trimethylsilyl)ethylenediamine (TTED)

N,N'-Bis(trimethylsilyl)ethylenediamine (164.0g, 0.8 mol) was dissolved in 500mL of dry ethyl ether and cooled in a dry ice bath. To the ice cold solution was added 500mL of 1.6M n-butyllithium in hexane. The mixture was stirred for 1 day at room temperature. Following the change of the mixture from colorless to cherry red and finally to dark red, the mixture was again cooled and 84.0g (0.8 mol) of trimethylchlorosilane was added. After stirring at room temperature for 24 hrs, the mixture was filtered. The filtrate was concentrated and fractionally distilled to give 199.5g (87.5%) of TTED, bp 56°C (0.5 torr) [lit. bp 103-4°C (18 torr)] (5).

N,N-Bis(trimethylsilyl)ethylenediamine (BTED)

To 68.9g (0.25 mol) of TTED in 100mL of dry THF was added 9g (0.28 mol) of methanol with stirring. The mixture was maintained at room temperature for 40 hr, then concentrated and fractionally distilled at reduced pressure to give 50.0g (94.4%) of BTED, bp 43°C (0.2 torr) [lit. bp 107-8°C (24 torr)] (5).

N,N-Bis(2-hydroxypropyl)N',N'-bis(trimethylsilyl)-ethylenediamine

A 500mL round bottom flask fitted with a dry ice reflux condenser was charged with N,N-bis(trimethylsilyl)ethylenediamine (83.2g, 0.4 mol), and propylene oxide (142.0g, 2.5 mol) with 5g alumina added as catalyst. The mixture was stirred and refluxed at 50-70°C for 7 days. The mixture was filtered and the filtrate concentrated and fractionally distilled to give 117.0g (89.2%) of the colorless liquid, N,N-Bis(2-hydroxypropyl)-N',N'-bis(trimethylsilyl)ethylenediamine, bp 100°C (0.2 torr).

^{1}H NMR ($CDCl_3$): δ 0.06 (s, 18H), 1.10 (d, 6H), 2.3-2.5 (m, 6H), 2.75 (m, 2H), 3.75 (m, 2H). Elemental Anal. $C_{14}H_{36}N_2O_2Si_2$: C, 52.45%; H, 11.32%; N, 8.74%. Found: C, 52.66%; H, 11.39%; N, 8.70%. FT-IR: strong O-H stretching band at 3360 cm^{-1}.

N,N-Bis(2-hydroxypropyl)ethylenediamine

N,N-Bis(2-hydroxypropyl)-N',N'-bis(trimethysilyl)ethylenediamine (23.12g, 0.07 mol) was dissolved in 30mL of methanol and refluxed under nitrogen overnight. After removal of methanol and volatile by-products, the viscous oil was

distilled at reduced pressure to yield 9.62g (92.8%) of colorless oil, N,N-bis(2-hydroxypropyl)ethylenediamine collected at 118°C/0.2 mmHg.

^{1}H NMR ($CDCl_3$): δ 1.06 (d, 6H), 2.3-2.5 (m, 6H), 2.75 (t, 2H), 3.80 (m, 2H). Elemental Anal. $C_8H_{20}N_2O_2$: C, 54.52%; H, 11.44%; N, 15.89%. Found: C, 54.44%; H, 11.39%; N, 15.71%. FT-IR: strong O-H stretching band at 3360 cm^{-1}.

N,N,N'-Tris(2-hydroxypropyl)ethylenediamine methacrylate (HPEDM)

N,N-Bis(2-hydroxypropyl)ethylenediamine (5.1g, 0.03 mol) and glycidylmethacrylate (4.5g, 0.03 mol) were mixed in 20mL chloroform with 3mL of 2-propanol and 30mg of p-methoxylphenol as inhibitor. The mixture was stirred under the protection of nitrogen at 40°C for two days. After cooling to room temperature, the mixture was washed twice with 10mL water, dried over magnesium sulfate and filtered. To the filtrate, 40-50mL of pentane was added and the mixture was set aside overnight. The product phased-out and settled to the bottom of the flask. The top liquid was decanted and the product was washed four times with a 5mL pentane/chloroform mixture (6:1). After removal of solvent in vacuo, 7.4g (75.6%) oil, HPEDM, was obtained.

^{1}H NMR ($CDCl_3$): δ 1.10 (d, 6H), 1.91 (s, 3H), 2.2-2.8 (m, 10H), 3.85 (m, 2H), 4.05 (m, 1H), 4.12 (d, 2H), 5.55 (s, 1H), 6.11 (s, 1H). Elemental Anal. $C_{15}H_{30}N_2O_5$: C, 56.58%; H, 9.50%; N, 8.80%. Found: C, 56.44%; H, 9.32%; N, 8.07%.

N,N-Bis(trimethylsilyl)aminoethylmethacrylamide

To a stirred, ice cold mixture of N,N,N'-tris(trimethylsilyl)ethylenediamine (59.4g, 0.23 mol) and triethylamine (22.9g, 0.23 mol) in 200mL of dry ethyl ether, methacryloyl chloride (23.7g, 0.23 mol dissolved in 60mL of dry ethyl ether) was added dropwise. After addition, the stirred reaction mixture was allowed to warm to room temperature and was maintained for 2 days. The insoluble product was collected by filtration and dried in vacuo to give 61.0g (99%) of N,N-bis(trimethylsilyl)aminoethylmethacrylamide, mp 83-84°C.

^{1}H NMR ($CDCl_3$): δ 0.10 (s,18H), 1.95 (s, 3H), 2.90 (m, 2H), 3.20 (m, 2H), 5.30 (s, 1H), 5.65 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 2 (Me_3-Si), 19 (CH_3C=), 33 (C-N), 34.4 (C-N), 119.7 (CH_2=), 140.2 (=CR_2) 169.5 (C=O). Elemental Anal. $C_{12}H_{28}N_{20}Si_2$: C, 52.89%; H, 10.35; N, 10.28%. Found: C, 52.73%; H, 10.28%; N, 10.03%.

2-Aminoethylmethacrylamide (AEMA)

N,N-Bis(trimethylsilyl)aminoethylmethacrylamide (16.5g, 0.06 mmol) was dissolved in 80mL of methanol and set aside at room temperature overnight. Upon removal of solvent and volatile by-products, a clear oil, N-2-aminoethylmethacrylamide, 7.6g (98.3%) was obtained.

^{1}H NMR (D_2O): δ 1.75 (s, 3H), 2.60 (t, 2H), 3.15 (t, 2H), 5.25 (s, 1H), 5.55 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 19 (CH_3C=), 31 (C-N), 32 (C-N), 119 (CH_2=), 139.8 (=CR_2), 168.4 (C=O). Elemental Anal. $C_6H_{12}N_2O$: C, 56.22%; H, 9.44%; N, 21.86%. Found: C, 56.25%; H, 9.40%; N, 21.86%. FT-IR: weak N-H stretching band at 3325 cm^{-1}.

N,N-Bis(2-hydroxypropyl)aminoethylmethacrylamide (HPAEMA)

A mixture of (6.3g, 0.05 mol) of 2-aminoethylmethacrylamide and propylene oxide (14.4g, 0.25 mol) in 100mL of ethanol was refluxed with stirring overnight under nitrogen. After removal of solvent and unreacted propylene oxide, a clear viscous oil, N,N-Bis(2-hydroxypropyl)aminoethylmethacrylamide, 11.3g (93.4%) was obtained.

^{1}H NMR ($CDCl_3$): δ 1.05 (d, 6H), 1.80 (s, 3H), 2.35 (m, 4H), 2.65 (m, 2H), 3.25 (m, 2H), 3.70 (m, 2H), 5.15 (s, 1H), 5.60 (s, 1H). ^{13}C NMR (D_2O): δ 18 (CH_3C=), 20 (CH_3COH-), 38.8 (-CH_2-N), 54 (-CH_2-N), 62 (N-CH_2COH-), 65 (-COH-), 124 (CH_2=), 142 (=CR_2), 175 (C=O). Elemental Anal. $C_{12}H_{24}N_2O_3$: C, 58.99%; H, 9.90%; N, 11.47%. Found: C, 58.93%; H, 9.92%; N, 11.43%. FT-IR: strong O-H stretching band at 3360 cm^{-1}.

RESULTS AND DISCUSSION

Ethylenediamine-based monomers are commonly used in the synthesis of a variety of polymers. In most cases, both nitrogen atoms of ethylenediamine (ED) are utilized in the polymerization reaction and incorporated into the polymer chain. For example, in the synthesis of epoxide-based resins, ED is mixed with bis-epoxides to form the appropriate polymer. Presently, no simple methods are available to produce asymmetrically substituted ED which could generate unique monomers for polymer synthesis. In this study, ED was selectively silylated and asymmetrically alkylated either prior to or following methacryl monomer synthesis.

Two selectively silylated ethylenediamines, TTED and BTED, were used to prepare three monomers, HPEDM, HPAEMA and AEMA. The reaction scheme for the synthesis of HPEDM is shown in

Figure 1. HPEDM was prepared in 75.6% yield from the stoichiometric mixture of glycidyl methacrylate with the asymmetrically substituted N,N-bis-(2-hydroxypropyl) ethylenediamine, a diaminodiol prepared by the asymmetrical alkylation of ED with propylene oxide. The asymmetrical alkylation of ED was achieved by initially protecting one of the nitrogen atoms on ED with a removable trimethylsilyl blocking group. BTED, a bis-trimethylsilylated ED, was prepared in 94.4% yield by a modified version of the procedure described by West et al. The primary amine in BTED was slowly alkylated in a neat mixture containing propylene oxide resulting in a 89.2% yield of N,N-bis(2-hydroxypropyl)-N',N'-bis(trimethyl- silyl)ethylene diamine. Overnight reflux of N,N-bis(2-hydroxypropyl)-N',N'-bis(trimethylsilyl)ethylene in methanol resulted in methanolysis of the trimethylsilyl group, and a 92.8% yield of N,N-bis-(2-hydroxypropyl)ethylenediamine.

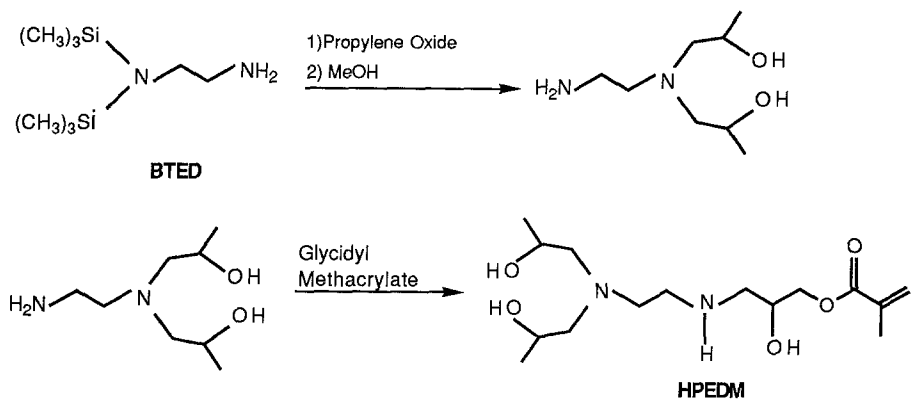

Figure 1

TTED and BTED were also used directly in the synthesis of N,N-bis(trimethylsilyl)aminoethylmethacrylamide which was subsequently used to prepare AEMA and HPAEMA. The reactions are show on Figure 2. N,N-Bis(trimethylsilyl)aminoethyl-methacrylamide was produced in quantitative yield from the stoichiometric reaction of TTED with methacryloyl chloride. The N'-trimethylsilyl group was not retained in the product. The desired product was also quantitatively prepared from the stoichiometric reaction of BTED with methacryloyl chloride, however, NMR evidence suggested that the product had undergone traces of desilylation. Since BTED is prepared from TTED, direct synthesis of the methacryloyl monomer from TTED would be preferred. The addition of

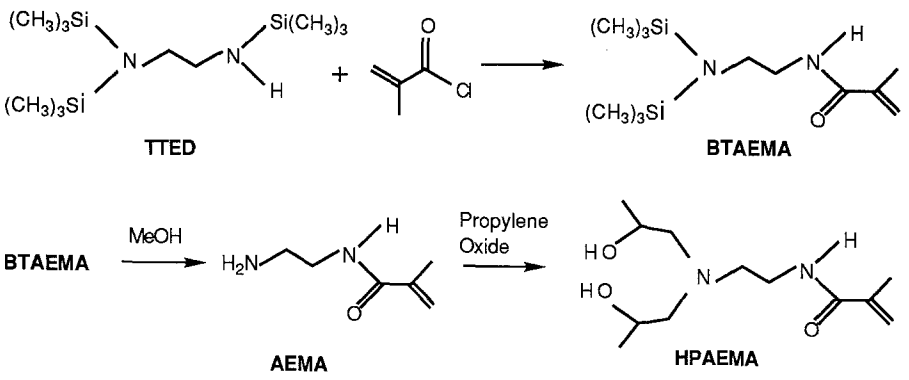

Figure 2

methanol to the methacryloyl monomer at room temperature generated quantitative yields of AEMA. Treatment of AEMA with excess propylene oxide produced HPAEMA in 93.4% yield.

The two synthetic schemes described demonstrate the utility of BTED and TTED in the synthesis of asymmetric ED-based monomers. This study is now being extended to use TTED and BTED in the synthesis of epoxy-based hydrogels. The active (unblocked) amino group is incorporated into the polymer chain and, upon removal of the protecting group, a desirable pendant aminoethyl arm can be generated.

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