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Article

One-Pot Synthesis of Monofunctionalized Oligoethylene Glycols through Ring-Opening and Heterogeneous Hydrolysis of Macrocyclic Sulfates

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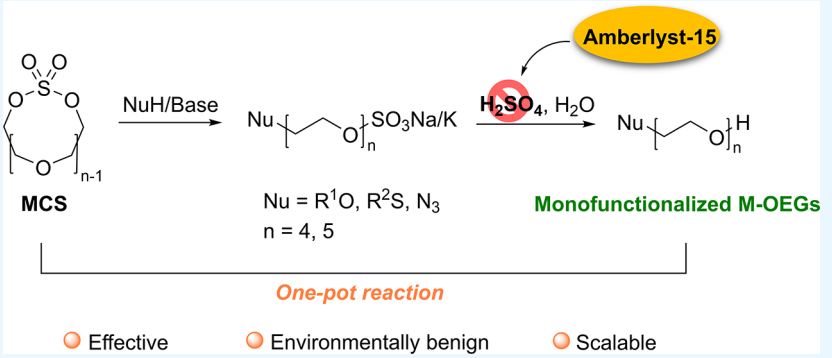

ABSTRACT: The one-pot nucleophilic ring-opening reaction of oligoethylene glycol macrocyclic sulfates provides an efficient strategy for the monofunctionalization of oligoethylene glycols without protecting or activating group manipulation. In this strategy, the hydrolysis process is generally promoted by sulfuric acid, which is hazardous, difficult to handle, environmentally unfriendly, and unfit for industrial operation. Here, we explored a convenient handling solid acid, Amberlyst-15, as a replacement for sulfuric acid to accomplish the hydrolysis of sulfate salt intermediates. With this method, 18 valuable oligoethylene glycol derivatives were prepared with high efficiency, and gram-scale applicability of this method has been successfully demonstrated to afford a clickable oligoethylene glycol derivative **1b** and a valuable building block **1g** for F-19 magnetic resonance imaging traceable biomaterial construction.

INTRODUCTION

Oligoethylene glycols (OEGs), short poly(ethylene glycol) (PEG) chains, have been extensively used as remarkable building blocks due to their hydrophilicity, flexibility, chemical stability, ion conductivity, and biocompatibility. Introducing suitable OEGs is a promising strategy to endow molecules/polymers with higher water solubility, improved pharmacokinetics, and better optoelectronic properties in drug development and material sciences.[1] Efforts have constantly been made to develop methods for the conjugation of OEGs, which mainly depends on the availability of activated OEGylation agents. Therefore, the efficient and scalable synthesis of functionalized OEGs with high purity is of great importance.

Monofunctionalized OEGs are the most used OEG derivatives in drug development and material sciences. However, as long linear molecules without sterical and electronic effects for selective modification, the monofunctionalization of OEGs is very challenging. Recently, a highly efficient synthesis of monodisperse PEGs (M-PEGs) and their derivatives through a macrocyclic sulfate-based strategy has been developed in this group.[2] In this strategy, the OEG macrocyclic sulfates (MCSs) were ring-opened with nucleophiles to give sulfate salt intermediates and then hydrolyzed with sulfuric acid to provide monofunctionalized OEGs in one pot (Scheme 1). Nevertheless, the sulfuric acid-catalyzed hydrolysis process suffers from several problems: the risk of concentrated sulfuric acid exposure, possible decomposition of the OEGs,[3] tedious neutralization and purification processes, and being environmentally unfriendly. In terms of safety and economic and environmental perspectives, the employment of an easy-handling and reusable acid for the hydrolysis process is essential.

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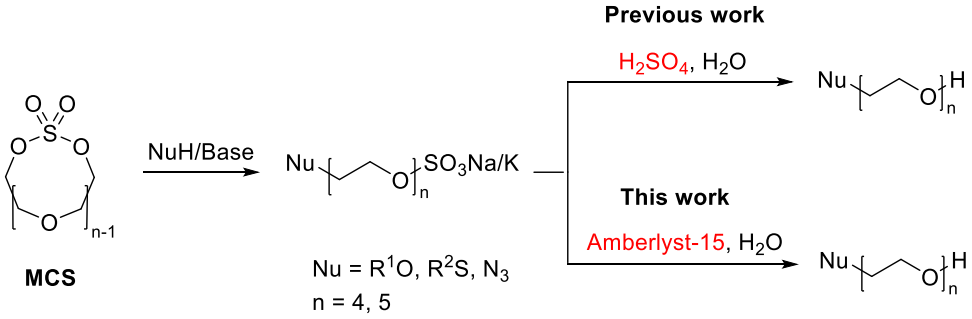
Scheme 1. Previous and Current Works on the Monofunctionalization of M-OEGs

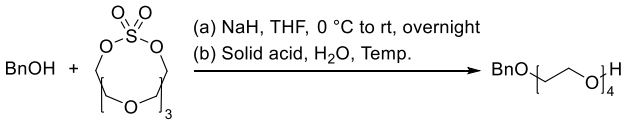


Solid acids with anionic charges on their surface can function as convenient heterogeneous acids, which are "green" alternatives to conventional liquid acids by allaying safety and environmental concerns.[4] Amberlyst-15, a commercially available cation exchange resin with strongly acidic sulfonic groups that can perform heterogeneous acid catalysis, has been effectively applied in a variety of acid-catalyzed reactions in organic synthesis, including acetylation, alkylation, Michael addition, esterification, etc.[5] Compared with sulfuric acid, the use of Amberlyst-15 is more desirable because it is safe and convenient to use, readily removed at the end of the reaction, easy to recycle, and needs no neutralization after the reaction, which may overcome the shortcomings of sulfuric acid that promoted the hydrolysis process mentioned above. Therefore, we investigated the employment of Amberlyst-15 as a potential heterogeneous acid to hydrolyze OEG macrocyclic sulfate salt intermediates during the one-pot nucleophilic ring-opening reaction of OEG macrocyclic sulfates to develop a green and scalable approach for monofunctionalized monodisperse OEG (M-OEG) preparation.

RESULTS AND DISCUSSION

Optimization studies were carried out using tetraethylene glycol macrocyclic sulfate **MCS-1** as the substrate and commercially available benzyl alcohol as the nucleophile, which can act as a UV active tag to facilitate reaction progress monitoring and product purification. It is worth noting that **MCS-1** can be conveniently prepared from tetraethylene glycol on multi-hundred-gram scales.[6] **MCS-1** was first treated with benzyl alcohol in the presence of 1.5 equiv of NaH to provide the sulfate salt intermediate. Then, 0.9 equiv of Amberlyst-15, a resin with sulfonic groups that can perform as an acid catalyst, and 2.0 equiv of H_2O were added. The resulting mixture was stirred at room temperature for 12 h. To our delight, monobenzylated tetraethylene glycol **1a** was isolated in an 84% yield (Table 1, entry 1). It was noteworthy that the reaction was very convenient to handle, during which Amberlyst-15 was removed by filtration, and the resulting solution was concentrated for chromatography purification without neutralization or extraction. When the equivalence ratio of Amberlyst-15 and benzyl alcohol was increased to 2.5, the yield of **1a** was decreased to 73% due to the potential adsorption capacity of Amberlyst-15 (Table 1, entry 2). Besides Amberlyst solid acid, we have screened HND series of solid acids, such as HND-8, HND-580, and HND-582. It was found that Amberlyst-15 gave the highest yield (Table 1, entries 3−5), so Amberlyst-15 is the solid acid of choice. When elevating the hydrolysis temperature to 45 °C, the yield was increased to 90% (Table 1, entry 6). Ground Amberlyst-15 has

Table 1. Optimization of the Nucleophilic Ring-Opening Reaction of MCS[a]



entry	solid acid	solid acid [equiv]	temp.[b]	yield [%][c]
1	Amberlyst-15	0.9	rt	84
2	Amberlyst-15	2.5	rt	73
3	HND-8	0.9	rt	69
4	HND-580	0.9	rt	50
5	HND-582	0.9	rt	62
6	Amberlyst-15	2.5	45 °C	90
7[d]	Amberlyst-15	0.5	rt	trace
8[d]	Amberlyst-15	0.9	rt	99
9[d]	Amberlyst-15	1.5	rt	92
10[d]	Amberlyst-15	2.5	rt	86

[a]Unless otherwise indicated, reactions were carried out with benzyl alcohol (1.0 equiv), NaH (1.5 equiv), and **MCS-1** (1.3 equiv) in THF and then hydrolyzed with solid acid and H_2O (2.0 equiv). [b]The reaction temperature of hydrolysis. [c]Isolated yields. [d]Ground Amberlyst-15 was used (particle size: 30−40 mesh).

higher surface areas, allowing sufficient contact with the reactant. Therefore, Amberlyst-15 was ground into powder before adding it to the reaction. The hydrolysis was almost stopped when 0.5 equiv of Amberlyst-15 was used because Amberlyst-15 would be neutralized to its sodium salt form in the presence of excess NaH (Table 1, entry 7). Satisfactorily, full conversion can be achieved by varying the amount of Amberlyst-15 (Table 1, entries 8−10), indicating the high efficacy of the reaction.

Under the optimized conditions, the substrate scope was further investigated for tetraethylene glycol macrocyclic sulfate **MCS-1** and pentaethylene glycol macrocyclic sulfate **MCS-2**. A wide range of nucleophiles is compatible with this hydrolysis procedure (Table 2). First, MCSs treated with O-nucleophiles, including alcohol and phenol, in the presence of NaH provided ether derivatives of M-OEGs **1a**−**1c** and **2a**−**2c** in excellent yields (Table 2, entries 1−3). Monobenzyl tetraethylene glycol **1a** and pentaethylene glycol **2a** are useful building blocks in M-PEG synthesis.[7] M-OEGs **1b** and **2b**, functionalized with alkyne groups, are ready for application in a click chemistry reaction. When salts like MeONa were applied, DMF was used as the solvent in the nucleophilic ring-opening step due to the poor solubility of alkoxides in THF. DMF was removed after the ring-opening reaction, and the sulfate salt intermediate was

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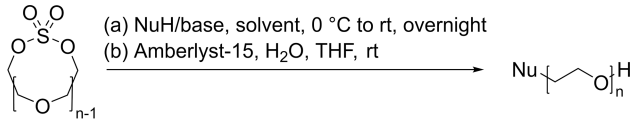
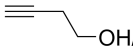
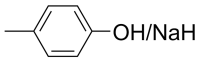
Table 2. Substrate Scope of the Nucleophilic Ring-opening Reaction of MCS



MCS-1, n = 4
MCS-2, n = 5

1, n = 4
2, n = 5

Entry	NuH/base	Solvent	Product	Yield[b]
1[a]	BnOH/NaH	THF	**1a**, n = 4 **2a**, n = 5	**1a**, 99% (93%[c]) **2a**, 90%
2[a]		THF	**1b**, n = 4 **2b**, n = 5	**1b**, 98% **2b**, 94%
3[a]		THF	**1c**, n = 4 **2c**, n = 5	**1c**, 99% (92%[c]) **2c**, 99%
4[d]	MeONa	DMF	**1d**, n = 4 **2d**, n = 5	**1d**, 88% (70%[c]) **2d**, 87%
5[e]	AcONa	DMF	**1e**, n = 4 **2e**, n = 5	**1e**, 85% (99%[c]) **2e**, 90%
6[e]	BzONa	DMF	**1f**, n = 4 **2f**, n = 5	**1f**, 99% (99%[c]) **2f**, 98%
7[e]	$(CF_3)_3COK$	DMF	**1h**, n = 4 **2h**, n = 5	**1g**, 99% (99%[c]) **2g**, 98%
8[e]	AcSK	DMF	**1g**, n = 4 **2g**, n = 5	**1h**, 95% (88%[c]) **2h**, 99%
9[e]	NaN_3	DMF	**1i**, n = 4 **2i**, n = 5	**1i**, 99% (97%[c]) **2i**, 95%

[a]Reactions were carried out with a nucleophile (1.0 equiv), NaH (1.5 equiv), and **MCS** (1.3 equiv) and then hydrolyzed with Amberlyst-15 (0.9 equiv) and H_2O (2.0 equiv) in THF. [b]Isolated yields. [c]Yields of the monofunctionalization of M-OEGs through a macrocyclic sulfate-based strategy employing sulfuric acid as the catalyst.[2] [d]Reactions were carried out with a nucleophile (1.5 equiv) and **MCS**s (1.0 equiv) and then hydrolyzed with Amberlyst-15 (1.0 equiv) and H_2O (2.0 equiv) in THF. [e]Reactions were carried out with a nucleophile (1.5 equiv) and **MCS**s (1.0 equiv) and then hydrolyzed with Amberlyst-15 (0.7 equiv) and H_2O (2.0 equiv) in THF.

hydrolyzed in THF at room temperature. Hydrolysis catalyzed with a lower equivalence ratio of Amberlyst-15 (0.7 equiv) did not compromise the reaction efficiency (Table 2, entries 5−9) since there are no acid consumption results from the presence of NaH. A slightly increased equivalence ratio of Amberlyst-15 (1.0 equiv) should be applied to accomplish the hydrolysis process, owing to the relatively strong alkalinity of MeONa (Table 2, entry 4). Perfluoro-*tert*-butylated derivatives **1g** and **2g** with 9 symmetrical fluorines, which are valuable building blocks in F-19 magnetic resonance imaging (^{19}F MRI) traceable biomaterials, were also conveniently prepared in quantitative yields (Table 2, entry 7).[8] From S-nucleophile potassium thioacetate, sulfur can be efficiently introduced into OEGs (Table 2, entry 8). Last but not least, the other two clickable OEGs **1i** and **2i** were obtained in excellent yields when NaN_3 was employed (Table 2, entry 9). Notably, this Amberlyst-15-catalyzed hydrolysis method provides higher or comparable yields than our previous study using sulfuric acid.[2]

To demonstrate the practicality of the current strategy, the gram-scale syntheses of M-OEG derivatives **1b** and **1g** were performed under the optimized conditions (Scheme 2). Satisfactorily, 6.1 g of M-OEG derivative **1b** and 14.7 g of M-OEG derivative **1g** were obtained with good yields on a 39 mmol scale.

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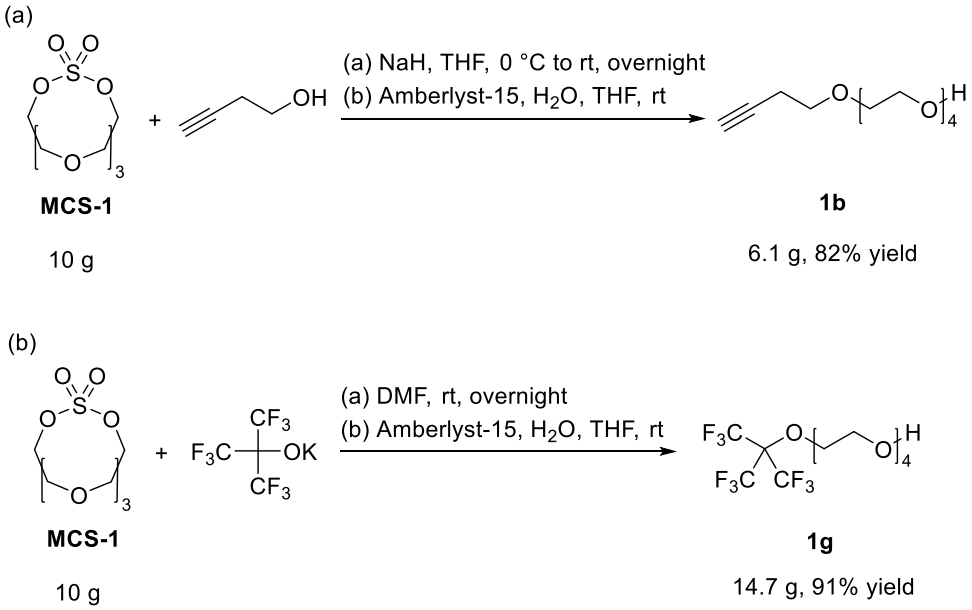
Scheme 2. Gram-Scale Synthesis of OEG Derivatives 1b and 1g



CONCLUSIONS

In this work, using a convenient handling solid acid, Amberlyst-15, to hydrolyze OEG sulfate intermediates, an efficient and scalable synthesis of monofunctionalized M-OEGs was developed with a one-pot procedure. The use of Amberlyst-15 instead of liquid acid H_2SO_4 in the hydrolysis process is a significant improvement over previous work, which is convenient, safe, and environmentally friendly. From easily available MCSs, a wide substrate scope for the strategy has been accomplished with good to excellent yields and provided various useful monofunctionalized OEGs. Besides, the strategy has been demonstrated in gram-scale production to afford a clickable OEG derivative **1b** and a valuable building block **1g** for F-19 MRI-traceable biomaterial construction. This strategy may promote the availability and industrial application of monofunctionalized M-OEGs to meet the urgent needs in drug development and material sciences.

EXPERIMENTAL SECTION

General Information. All commercially available reagents and solvents were used as received, unless otherwise mentioned. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker 400 or 500 MHz spectrometer. Chemical shifts were in ppm and coupling constants (J) were in Hertz (Hz). ^{1}H NMR spectra were referenced to solvent D-atom using $CDCl_3$ (s, 7.26 ppm) as a solvent. ^{13}C NMR spectra were referenced to solvent carbons (77.2 ppm for $CDCl_3$). ^{19}F NMR spectra were referenced to 2% perfluorobenzene (s, −164.90 ppm) in $CDCl_3$. The splitting patterns for ^{1}H NMR spectra were denoted as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and combinations thereof. High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific Q Exactive Focus.

Tetraethylene Glycol Macrocyclic Sulfate ***MCS-1***.[2] At 0 °C, $SOCl_2$ (30 mL, 411.88 mmol, in 100 mL of CH_2Cl_2) was added over 1 h to a stirring solution of tetraethylene glycol (40.00 g, 205.94 mmol), triethylamine (137.80 mL, 988.53 mmol), and DMAP (1.27 g, 10.30 mmol) in CH_2Cl_2 (2.5 L). After the addition, the mixture was stirred at 0 °C for 2 h and washed with water (1 L) three times. The combined organic layers were concentrated and purified by flash chromatography on silica gel with EtOAc/PE (1/1) as eluents to give the intermediate as a brown oil. The intermediate macrocyclic sulfite was dissolved in a mixture of CH_3CN (300 mL), CCl_4 (300 mL), and water (450 mL) at 0 °C. $NaIO_4$ (52.86 g, 247.13 mmol) and $RuCl_3{\cdot}3H_2O$ (0.27 g, 1.03 mmol) were sequentially added to the reaction mixture, and the resulting mixture was stirred at 0 °C for 1 h. The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (250 mL, twice). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by recrystallization with methanol to give 34.16 g of **MCS-1** as a white solid with 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64−3.69 (m, 8H), 3.83 (t, J = 7.5 Hz, 4H), 4.47 (t, J = 5.0 Hz, 4H).

Monobenzyl Tetraethylene Glycol ***1a***.[2] Under an atmosphere of Ar, to a suspension of NaH (36.0 mg, 60% dispersed in mineral oil, 0.90 mmol, in 2 mL of THF) was added a solution of benzyl alcohol (64.9 mg, 0.60 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 30 min and a solution of **MCS-1** (200.0 mg, 0.78 mmol) in THF (2 mL) was added at this temperature. The resulting mixture was stirred for 12 h at rt. Then, H_2O (21.6 μL, 1.20 mmol) and Amberlyst-15 (130.0 mg, 0.55 mmol) were added to the reaction mixture, and the resulting mixture was stirred for 12 h at rt. After the removal of Amberlyst-15 by filtration, the filtrate was collected and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with MeOH/CH_2Cl_2 (1/50−1/20) as eluents to give compound **1a** (168.9 mg, 99% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59−3.71 (m, 16H), 4.56 (s, 2H), 7.26−7.31 (m, 1H), 7.34 (d, J = 4.8 Hz, 4H).

Monomethoxy Tetraethylene Glycol ***1d***.[2] Under an atmosphere of Ar, to a suspension of sodium methoxide (63.2 mg, 1.17 mmol, in 3 mL of DMF) was added a solution of **MCS-1** (200.0 mg, 0.78 mmol) in DMF (2 mL) at rt. The mixture was stirred overnight, and then, the solvent was removed under vaccum. The residue was dissolved in THF and

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then H_2O (28.1 μL, 1.56 mmol) and Amberlyst-15 (185.7 mg, 0.78 mmol) were added to the reaction mixture, and the resulting mixture was stirred for 12 h at rt. After the removal of Amberlyst-15 by filtration, the filtrate was collected and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with MeOH/CH_2Cl_2 (1/50−1/20) as eluents to give compound **1d** (141.0 mg, 87% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.50−3.69 (m, 16H).

Monoacetyl-Tetraethylene Glycol ***1e***.[2] Under an atmosphere of Ar, to a suspension of sodium acetate (96.0 mg, 1.17 mmol, in 3 mL of DMF) was added a solution of **MCS-1** (200.0 mg, 0.78 mmol) in DMF (2 mL) at rt. The mixture was stirred overnight and then the solvent was removed under vaccum. The residue was dissolved in THF, and then H_2O (28.1 μL, 1.56 mmol) and Amberlyst-15 (130.0 mg, 0.55 mmol) were added to the reaction mixture, and the resulting mixture was stirred for 12 h at rt. After the removal of Amberlyst-15 by filtration, the filtrate was collected and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with MeOH/CH_2Cl_2 (1/50−1/20) as eluents to give compound **1e** (156.6 mg, 85% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.56−3.74 (m, 14H), 4.22 (t, J = 6.0 Hz, 2H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07319.

Additional experimental details and materials; ^{1}H/^{19}F/^{13}C NMR and HRMS spectra of the synthesized compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

OEGs, oligoethylene glycols; PEGs, poly(ethylene glycols); MCSs, macrocyclic sulfates; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; MRI, magnetic resonance imaging; rt, room temperature

■ REFERENCES

(1) (a) Wang, S.; He, W.; Xiao, C.; Tao, Y.; Wang, X. Synthesis of Y-Shaped OEGylated Poly(amino acid)s: The Impact of OEG Architecture. *Biomacromolecules* **2019**, *20*, 1655−1666. (b) Wang, X.; Liu, Y.; Wang, Z.; Lu, Y.; Yao, Z.; Ding, Y.; Yu, Z.; Wang, J.; Pei, J. Revealing the Effect of Oligo(ethylene glycol) Side Chains On n-doping Process in FBDPPV-Based Polymers. *J. Polym. Sci.* **2022**, *60*, 538−547. (c) Ajiro, H.; Haramiishi, Y.; Chanthaset, N.; Akashi, M. Polymer Design Using Trimethylene Carbonate with Ethylene Glycol Units for Biomedical Applications. *Polym. J.* **2016**, *48*, 751−760.

https://doi.org/10.1021/acsomega.2c07319
ACS Omega 2023, 8, 7684−7689

(d) Meng, B.; Liu, J.; Wang, L. Oligo(ethylene glycol) as Side Chains of Conjugated Polymers for Optoelectronic Applications. *Polym. Chem.* **2020**, *11*, 1261−1270. (e) Schantl, A. E.; Verhulst, A.; Neven, E.; Behets, G. J.; D'Haese, P. C.; Maillard, M.; Mordasini, D.; Phan, O.; Burnier, M.; Spaggiari, D.; Decosterd, L. A.; MacAskill, M. G.; Alcaide-Corral, C. J.; Tavares, A. A. S.; Newby, D. E.; Beindl, V. C.; Maj, R.; Labarre, A.; Hegde, C.; Castagner, B.; Ivarsson, M. E.; Leroux, J.-C. Inhibition of Vascular Calcification by Inositol Phosphates Derivatized with Ethylene Glycol Oligomers. *Nat. Commun.* **2020**, *11*, No. 721. (f) Harris, J. M.; Chess, R. B. Effect of Pegylation on Pharmaceuticals. *Nat. Rev. Drug Discovery* **2003**, *2*, 214−221.

(2) Zhang, H.; Li, X.; Shi, Q.; Li, Y.; Xia, G.; Chen, L.; Yang, Z.; Jiang, Z.-X. Highly Efficient Synthesis of Monodisperse Poly(ethylene glycols) and Derivatives through Macrocyclization of Oligo(ethylene glycols). *Angew. Chem., Int. Ed.* **2015**, *54*, 3763−3767.

(3) Székely, G.; Schaepertoens, M.; Gaffney, P.R.J.; Livingston, A. G. Beyond PEG2000: Synthesis and Functionalisation of Monodisperse PEGylated Homostars and Clickable Bivalent Polyethyleneglycols. *Chem. − Eur. J.* **2014**, *20*, 10038−10051.

(4) (a) Gupta, P.; Paul, S. Solid Acids: Green Alternatives for Acid Catalysis. *Catal. Today* **2014**, *236*, 153−170. (b) Thomas, S. J. M. Solid Acid Catalysts. *Sci. Am.* **1992**, *266*, 112−119.

(5) (a) Naikwadi, D. R.; Bankar, B. D.; Ravi, K.; Biradar, A. V. Efficient and Recyclable Solid Acid-Catalyzed Alkylation of Active Methylene Compound via Oxonium Intermediate for Atom Economical Synthesis of Organic Compounds. *Res. Chem. Intermed.* **2021**, *47*, 3691−3703. (b) Naikwadi, D. R.; Ravi, K.; Singh, A. S.; Advani, J. H.; Biradar, A. V. Gram-Scale Synthesis of Flavoring Ketones in One Pot via Alkylation-Decarboxylation on Benzylic Carbon Using a Commercial Solid Acid Catalyst. *ACS Omega* **2020**, *5*, 14291−14296. (c) Pal, R.; Sarkar, T.; Khasnobis, S. Amberlyst-15 in Organic Synthesis. *ARKIVOC* **2012**, *2012*, 570−609. (d) El-Nassan, H. B. Amberlyst 15: An Efficient Green Catalyst for the Synthesis of Heterocyclic Compounds. *Russ. J. Org. Chem.* **2021**, *57*, 1109−1134. (e) Fan, G.; Liao, C.; Fang, T.; Luo, S.; Song, G. Amberlyst 15 as a New and Reusable Catalyst for the Conversion of Cellulose into Cellulose Acetate. *Carbohydr. Polym.* **2014**, *112*, 203−209.

(6) Xia, G.; Li, Y.; Yang, Z.; Jiang, Z.-X. Development of a Scalable Process for α-Amino-ω-methoxyl-dodecaethylene Glycol. *Org. Process Res. Dev.* **2015**, *19*, 1769−1773.

(7) (a) Bohn, P.; Meier, M. A. R. Uniform Poly(ethylene glycol): a Comparative Study. *Polym. J.* **2020**, *52*, 165−178. (b) Maranski, K.; Andreev, Y. G.; Bruce, P. G. Synthesis of Poly(ethylene oxide) Approaching Monodispersity. *Angew. Chem., Int. Ed.* **2014**, *53*, 6411−6413. (c) Ahmed, S. A.; Tanaka, M. Synthesis of Oligo(ethylene glycol) toward 44-mer. *J. Org. Chem.* **2006**, *71*, 9884−9886. (d) French, A. C.; Thompson, A. L.; Davis, B. G. High-Purity Discrete PEG-Oligomer Crystals Allow Structural Insight. *Angew. Chem., Int. Ed.* **2009**, *48*, 1248−1252. (e) Székely, G.; Schaepertoens, M.; Gaffney, P. R. J.; Livingston, A. G. Beyond PEG2000: Synthesis and Functionalisation of Monodisperse PEGylated Homostars and Clickable Bivalent Polyethyleneglycols. *Chem. − Eur. J.* **2014**, *20*, 10038−10051.

(8) (a) Yue, X.; Feng, Y.; Yu, Y. B. Synthesis and Characterization of Fluorinated Conjugates of Albumin. *J. Fluorine Chem.* **2013**, *152*, 173−181. (b) Jiang, Z.-X.; Feng, Y.; Yu, Y. B. Fluorinated Paramagnetic Chelates as Potential Multi-Chromic ^{19}F Tracer Agents. *Chem. Commun.* **2011**, *47*, 7233−7235.

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