View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Kyutacar : Kyushu Institute of Technology Academic Repository

九州工業大学学術機関リポジトリ
Kyutacar
Kyushu Institute of Technology Academic Repository

A Simple Synthetic Route for the Preparation of Tetramethylglycolide from Lactic Acid

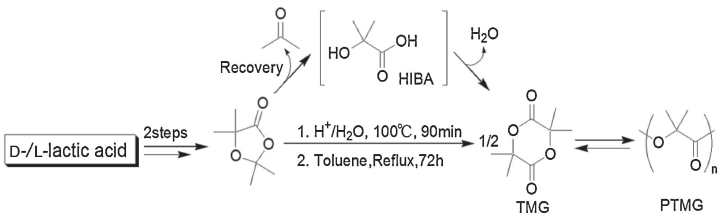
著者	Watanabe Kohtaro, Andou Yoshito, Shirai Yoshihito, Nishida Haruo
journal or publication title	Chemistry Letters
volume	42
number	2
page range	159-161
year	2013-02-01
URL	http://hdl.handle.net/10228/00006648

doi: info:doi/10.1246/cl.2013.159

A Simple Synthetic Route for the Preparation of Tetramethylglycolide from Lactic Acid

Kohtaro Watanabe,[1] Yoshito Andou,*[2] Yoshihito Shirai,[1,2] and Haruo Nishida*[1,2]
[1]*Department of Biological Functions and Engineering, Kyushu Institute of Technology, 2-4 Hibikino, Wakamatsu-ku, Kitakyushu, Fukuoka 808-0196*
[2]*Eco-Town Collaborative R&D Center for the Environment and Recycling, Kyushu Institute of Technology, 2-4 Hibikino, Wakamatsu-ku, Kitakyushu, Fukuoka 808-0196*

(Received October 18, 2012; CL-121068; E-mail: yando@life.kyutech.ac.jp)



REPRINTED FROM

Chemistry Letters

Vol.42 No.2 2013 p.159–161
CMLTAG
February 5, 2013

The Chemical Society of Japan

Published on the web February 2, 2013; doi:10.1246/cl.2013.159

doi:10.1246/cl.2013.159
Published on the web February 2, 2013

A Simple Synthetic Route for the Preparation of Tetramethylglycolide from Lactic Acid

Kohtaro Watanabe,[1] Yoshito Andou,*[2] Yoshihito Shirai,[1,2] and Haruo Nishida*[1,2]
[1]*Department of Biological Functions and Engineering, Kyushu Institute of Technology, 2-4 Hibikino, Wakamatsu-ku, Kitakyushu, Fukuoka 808-0196*
[2]*Eco-Town Collaborative R&D Center for the Environment and Recycling, Kyushu Institute of Technology, 2-4 Hibikino, Wakamatsu-ku, Kitakyushu, Fukuoka 808-0196*

(Received October 18, 2012; CL-121068; E-mail: yando@life.kyutech.ac.jp)

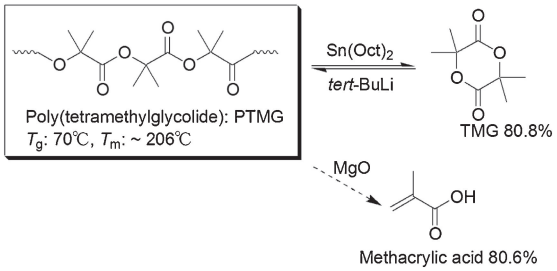
Poly(tetramethylglycolide), a chemical recyclable polymer, is currently attracting a lot of interest as a substitute for poly(L-lactic acid). We report here a simple and convenient route for the synthesis of tetramethylglycolide (TMG) from lactic acid. This method involves three steps: (1) one-step protection of lactic acid by cyclic acetalization employing acetone; (2) α-methylation of the obtained 2,2,5-trimethyl-1,3-dioxolan-4-one; and (3) one-pot synthesis of TMG including the hydrolysis of 2,2,5,5-tetramethyl-1,3-dioxolan-4-one. We found significant advantages of the incorporation of existing reactions in the synthesis of TMG.

Poly(L-lactic acid) [poly(L-lactide), PLLA], a well-known, bioabsorbable, biodegradable, and recyclable material, is an attractive raw material produced from renewable resources rather than petrochemical products. It is anticipated that it may be used in many applications in the future owing to its environmental compatibility, excellent thermoplasticity, transparency, and crystallinity, and high melting point ($T_m = 170\,^\circ$C).[1] PLLA is generally produced through the ring-opening polymerization of L,L-lactide (LLA) as a cyclic monomer, and during its thermal degradation, LLA is recovered as a result of the depolymerization of PLLA.

However, one important issue affecting monomer recovery is racemization,[2] which results in the recovery of diastereoisomers, meso, and D,D-lactides, leading to decreases in the crystallinity and melting point of the reproduced PLLA.[3] As a solution to the important issue of the racemization of PLLA, poly(tetramethylglycolide) (PTMG) has been reported as a racemization-free polymer from lactic acid.[4] PTMG has been depolymerized selectively with the aid of appropriate catalysts (Scheme 1). Thus, PTMG has attracted attention as a possible candidate because it is a sustainably recyclable plastic while maintaining its particular thermal properties.

In spite of the development of a synthetic method, the multistep synthesis procedure for tetramethylglycolide (TMG) as a racemization-free monomer is one of the serious problems associated with the sustained recycling of PTMG, because hydroxy and carboxy groups, as highly reactive groups in lactic acid, have to be protected before the substitution of the α-methine proton by a methyl group. α-Hydroxyisobutyric acid (HIBA) has been synthesized through the α-methylation reaction via protection/deprotection processes of the functional groups of lactic acid. TMG is a cyclic diester of HIBA and can be polymerized into PTMG, which is an optically nonactive polyester with higher thermal properties ($T_g = 70\,^\circ$C, $T_m \approx 206\,^\circ$C) than PLLA.[5]

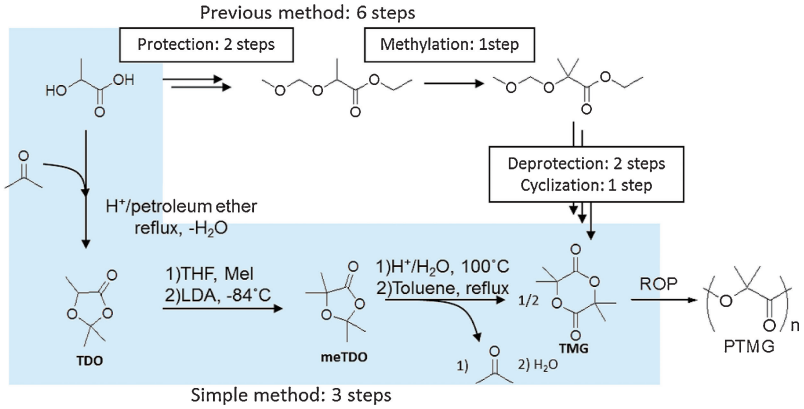
For the avoidance of the bothersome processes of the protection/deprotection of acyclic derivatives, the methylation of a cyclic derivative from lactic acid was examined to obtain TMG in a simple manner. In this article, we report that a simplified synthetic route of TMG was developed for the preparation of PTMG as more general use (Scheme 2). This TMG synthetic route was conveniently modified by using a one-step cyclization reaction with acetone as a protecting agent. This synthetic route, albeit a combination of basic synthetic methods, can suppress the use of toxic reagents and solvents, making it a "greener" synthetic method. As a result, 2,2,5-trimethyl-1,3-dioxolan-4-one (TDO) was converted successfully into 2,2,5,5-tetramethyl-1,3-dioxolan-4-one (meTDO) as a methylated derivative.



Scheme 1. Selective thermal depolymerization of PTMG.

For the synthesis of HIBA from lactic acid, the functional groups of lactic acid must be protected. If TMG could be prepared by methylation from lactide, which protects both functional groups by itself, this would be the simplest synthetic route for obtaining TMG. However, the direct methylation of lactide hardly occurs under basic conditions (such as with lithium diisopropylamide (LDA)), because the ring-opening reaction is induced. Bhaw-Luximon et al. reported that the polymerization of lactide with LDA is induced by the nucleophilic reaction of lithium enolate anions generated in the cause of α-deprotonation.[6] In this study, the six-membered ring of lactide was opened easily to produce oligo(lactic acid) by using LDA. On the other hand, the bidentate protection method has been developed for the asymmetric synthesis of α-hydroxycarboxylic acid and amino acid.[7–10] Moreover, various carbonyl compounds having bulky side groups have been used as protection reagents and chiral templates. The present approach permits the one-step protection of lactic acid through cyclic acetalization. Acetone was selected to protect the functional groups of lactic acid because it is easy to handle, stable, and commonly available. Moreover, acetone can also be derived from biomass resources through acetone–butanol fermentation.[11] When D-/L-lactic acid was reacted with acetone in the presence of acidic catalysts under azeotropic dehydration conditions,[12,13] 2,2,5-trimethyl-1,3-dioxolan-4-one (D-/L-lactic acid derivative,

 © 2013 The Chemical Society of Japan



Scheme 2. Total synthetic route of TMG from D/L-lactic acid.

Table 1. Cyclization of D/L-lactic acid and HIBA[a]

Entry	Substrate	Reactant (equiv)	Catalysts (equiv)	Yield /%
1	D-/L-lactic acid	Acetone (4.0)	MSA (0.016)	44
2	D-/L-lactic acid	Acetone (4.0)	*p*-TSA (0.016)	49
3	D-/L-lactic acid	Acetone (10)	*p*-TSA (0.016)	52
4	HIBA	Acetone (4.0)	MSA (0.016)	67

[a]All reactions were carried out in petroleum ether (reflux, 48 h).

Table 2. α-Methylation of TDO[a]

Entry	Base (equiv)	Temp /°C	Time	Yield /%
1	LDA (1.1)	−84	75 min	63
2	LHMDS (1.2)	−84	90 min	45
3	LTMP (1.2)	−84	90 min	50
4	$LiNH_2$ (1.2)	0–r.t.	24 h	—
5	KH(1.1)/Et_3B(1.1)	−84–r.t.	24 h	—

[a]All reactions were carried out in THF. Methylating agent is methyl iodide (CH_3I, 3.0 equiv).

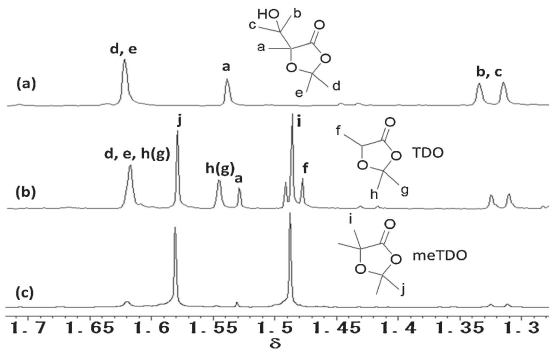


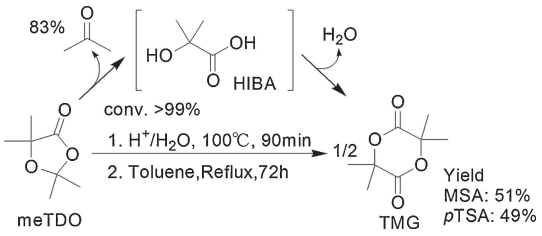
Figure 1. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of (a) TDO with LDA, (b) TDO with LDA after addition of MeI, and (c) TDO with MeI after addition of LDA.

TDO) was obtained (the yield is listed in Table 1). The results show that *p*-toluenesulfonic acid (*p*-TSA) was an effective catalyst, giving a slightly higher yield than methanesulfonic acid (MSA), and the optimum amount of acetone was 10 molar equivalents to lactic acid. We hardly obtained TDO with over 50% yield, because the deprotection reaction during the distillation of TDO for purification caused the competitive regeneration of lactic acid. However, this reaction gave no by-product except for the oligomer of lactic acid, which can be hydrolyzed; therefore, lactic acid regenerated from TDO or the oligomer can be reused as a starting material for the synthesis of TDO.

Moreover, HIBA was also protected easily by acetone under acidic conditions, to yield 2,2,5,5-tetramethyl-1,3-dioxolan-4-one (methylated cyclic compound, meTDO) in 67% yield after distillation under reduced pressure (see Supporting Information[18]).

α-Methylation of TDO was carried out by using various bases with methyl iodide (Table 2). In this reaction, it is expected that the α-methine hydrogen as a proton is abstracted by the dialkylamide anion having bulky side groups as the proper bases, in the same manner as the α-methylation of the acyclic lactic acid derivative.[4] In the case of TDO, the side reaction occurred preferentially in comparison with the methylation reaction of the previous acyclic derivative. As a result,[14] we suggested that the by-product was reacted between TDO and acetone as a deprotecting component, as shown in Figure 1a. It is supposed that the by-product was produced as a result of the α-position carboanion of TDO attacking the carbonyl group of the deprotected acetone. Figure 1 shows the ^{1}H NMR spectra of (a) the by-product, (b) the mixture of TDO with LDA after the addition of MeI, and (c) the mixture of TDO and MeI after the addition of LDA. This means that TDO was accompanied by the deprotection and addition reaction with LDA and a small amount of water faster than the methylation reaction with methyl iodide. In attempts to find the optimum conditions, we succeeded in suppressing the side reaction by adding LDA to the THF solution containing MeI and TDO. The TDO was first mixed with 3.0 molar equivalents of methyl iodide in THF, and then, LDA (1.1 molar equivalents) was added dropwise into the

 © 2013 The Chemical Society of Japan



Scheme 3. One-pot synthesis of TMG from meTDO.

solution over 45 min at −84 °C. The reaction mixture was stirred for another 30 min, and then warmed up to 25 °C to give the corresponding adduct meTDO (Figure S1).[18] The yield was 63% after quenching with an aqueous solution of NH_4Cl (10%) (Entry 1 in Table 2). As a result, the reaction with lithium hexamethyldisilazane (LHMDS) and lithium 2,2,6,6-tetramethylpiperizide (LTMP), which has similar bulky side groups, gave meTDO under the improved procedure.

These are strong bases, as demonstrated by the pK_a values of the conjugate acids LDA, LHMDS, and LTMP, which are 35.7, 25.8, and 37.3, respectively.[15] TDO was stable in these strongly basic conditions under dehydration compared with lactide, so the methylation proceeded preferentially. On the other hand, meTDO was hardly obtained with the general strong bases KH and $LiNH_2$ after the addition of the bases at 25 °C in the same way as the reactions at −84 °C (Entries 4 and 5 in Table 2). These bases are as strongly basic as LDA, but gave no methylated product because of their low solubility in THF compared with the bulky lithium dialkylamide base. In particular, $LiNH_2$, having compact side groups, showed a high activity that caused some side reaction. In other words, this result demonstrates the steric hindrance effect of bulky lithium amide bases, which suppresses side reactions so that the α-methine proton of TDO is abstracted selectively.

To obtain TMG with ease, we succeeded in designing a shorter process involving the conversion of meTDO through the hydrolysis reaction as a one-pot process (Scheme 3). First, the meTDO was hydrolyzed easily in distilled water by using MSA or *p*-TSA as a catalyst at 100 °C in a convenient time (90 min, conversion to HIBA: >99%),[16] with reproduction of acetone after deprotection. Acetone was recovered simultaneously as a volatile portion in high yield (83%) by using the Dean–Stark trap (Figure S4).[18] As an advantage of this synthesis route, the recovered acetone can be reused as the protection reagent for lactic acid. After the recovery of acetone, toluene was added to the flask for the condensation reaction as the second step. The reaction mixture was heated at reflux in toluene to remove azeotropic water by distillation; the resulting TMG product was formed in moderate yield (49–51%), and the acyclic dimer or oligomer of HIBA was observed as a by-product. Generally, Brønsted acids such as MSA and *p*-TSA are employed for the cyclic dimerization of HIBA to TMG.[5,17] Therefore, acidic catalysts for the hydrolysis of meTDO can be used continuously for the cyclic dimerization of HIBA.

The obtained TMG was polymerized smoothly to PTMG through the typical procedure with alkyl and alkoxyl lithium (Table 3). This simplified synthetic method for TMG is promising for the reduction in production processes for the sustainable recycling of PTMG.

Table 3. Ring-opening polymerizationa of TMG[a]

Entry	Initiator	M/I[b]	Temp/°C	M_n[c]	M_w/M_n	Yield/%
1	*t*-BuLi	340	120	46000	1.4	97
2	*t*-BuOLi	10	130	6800	1.5	84
3	*t*-BuOLi	135	130	25700	1.6	89
4	*i*-PrOLi	290	120	7600	1.4	46

[a]Reaction time: 24 h. [b]Molar ratio: Monomer/Initiator. [c]Based on PS standard calibration.

In conclusion, we have succeeded in developing a shorter process for the preparation of TMG as a monomer in the sustainable system of poly(tetramethylglycolide) (PTMG). Our approach for the synthesis of TMG involves the one-step protection and deprotection reactions for two functional groups of lactic acid, with the protection agent recovered for sustainable use. Moreover, TMG is formed by a condensation reaction via the deprotection reaction of the cyclic compound in a one-pot reaction under acidic conditions. We believe that this route provides a simple, convenient, and environmental friendly method for sustainable production from biomass. Although we preliminarily described a shorter synthesis route consisting of a simple reaction for PTMG based on biomass, we are studying in detail various possibilities for achieving a simple process for the production of PTMG as a sustainable material.

This work was supported by JSPS Grant-in-Aid for Scientific Research (A) No. 23241030 and Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation R2217.

References and Notes

1 Y. Fan, H. Nishida, T. Mori, Y. Shirai, T. Endo, *Polymer* **2004**, *45*, 1197.
2 Y. Fan, H. Nishida, Y. Shirai, T. Endo, *Green Chem.* **2003**, *5*, 575.
3 M. Ajioka, K. Enomoto, K. Suzuki, A. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2125.
4 K. Watanabe, Y. Andou, Y. Shirai, H. Nishida, *Chem. Lett.* **2010**, *39*, 698.
5 H. Nishida, Y. Andou, K. Watanabe, Y. Arazoe, S. Ide, Y. Shirai, *Macromolecules* **2011**, *44*, 12.
6 A. Bhaw-Luximon, D. Jhurry, N. Spassky, S. Pensec, J. Belleney, *Polymer* **2001**, *42*, 9651.
7 J.-W. Chang, D.-P. Jang, B.-J. Uang, F.-L. Liao, S.-L. Wang, *Org. Lett.* **1999**, *1*, 2061.
8 P. T. Grover, N. N. Bhongle, S. A. Wald, C. H. Senanayake, *J. Org. Chem.* **2000**, *65*, 6283.
9 T. Misaki, S. Ureshino, R. Nagase, Y. Oguni, Y. Tanabe, *Org. Process Res. Dev.* **2006**, *10*, 500.
10 J. Spengler, C. Böttcher, F. Albericio, K. Burger, *Chem. Rev.* **2006**, *106*, 4728.
11 S. C. Beesch, *Ind. Eng. Chem.* **1952**, *44*, 1677.
12 M. Farines, J. Soulier, *Bull. Soc. Chim. Fr.* **1970**, 332.
13 T. Miyagawa, F. Sanada, T. Endo, *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 1861.
14 FT-IR (Figure S2) and ^{13}C NMR spectrum (Figure S3) of by-product are shown in Supporting Information.[18]
15 R. R. Fraser, T. S. Mansour, *J. Org. Chem.* **1984**, *49*, 3442.
16 Calculated from integration ratio of ^1H NMR spectra in acetone-d_6 as a solvent.
17 H. Deibig, J. Geiger, M. Sander, *Makromol. Chem.* **1971**, *145*, 123.
18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

 © 2013 The Chemical Society of Japan

View publication stats