ACS Macro Letters

Letter

pubs.acs.org/macroletters

Facile Synthesis of Functionalized Lactones and Organocatalytic Ring-Opening Polymerization

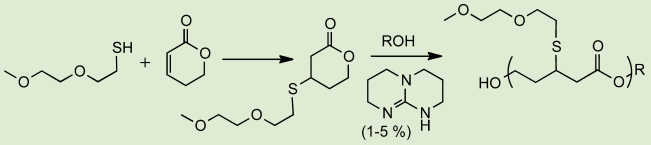
Hyunuk Kim,[†] Johan V. Olsson,[†] James L. Hedrick,[‡] and Robert M. Waymouth*,[†]

[†]Department of Chemistry, Stanford University, Stanford, California 94305, United States

[‡]IBM Almaden Research Center, 650 Harry Road, California 95120, United States

Supporting Information

ABSTRACT: A facile one-step synthesis of functionalized valerolactones was carried out by the conjugate addition of thiols to the α,β-unsaturated valerolactone 5,6-dihydro-2*H*-pyran-2-one. The resultant 3-mercaptovalerolactones undergo ring-opening polymerization in solution or in the melt to generate polyesters functionalized either with benzyl mercaptans or oligoethylene glycol pendant groups. The copolymerization of the 3-mercaptovalerolactones with ε-caprolactone generates random copolymers.



Biodegradable aliphatic polyesters are versatile thermoplastics and a useful class of biomedical materials.[1−3] Their increasing use in biomedical applications has stimulated the development of new synthetic strategies to minimize residual toxic metals[4−7] and to generate functionalized polyesters to broaden the range of chemical, physical, and biological properties of these materials.[4,8−17]

The synthesis and ring-opening polymerization of functionalized lactones has proven to be a particular powerful strategy for generating functionalized polyesters, notwithstanding the often cumbersome and multistep syntheses required to prepare these monomers.[3,4,8,9,17−20] Herein, we report a mild and facile method for generating functional lactones by a one-step Michael addition[21−24] of thiol compounds to the α,β-unsaturated valerolactone 5,6-dihydro-2*H*-pyran-2-one (Figure 1). While the conjugate addition of thiols to α,β-unsaturated lactones is known,[22−24] its application for the synthesis of functionalized valerolactones is a novel strategy for generating polymerizable lactones.

Despite the presence of the β-thioether group, these functionalized valerolactones could be polymerized in solution or in the melt with organic catalysts derived from 1,5,7-triazabicyclo-[4,4,0]dec-5-ene (TBD).[5,25] In addition, aliphatic polyesters with pendant functional groups were successfully copolymerized by the organocatalytic reaction of VL derivatives and caprolactone (CL).

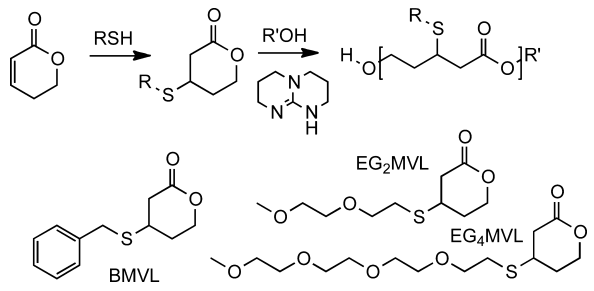


Figure 1. Synthesis of substituted valerolactones and subsequent organocatalytic ring-opening polymerization.

Table 1. Homopolymerization of 3-Mercaptovalerolactones with TBD (5 mol %) in Toluene[a]

run	monomer	[M]/[I]	time	conv.[c]/%	M_n[d] (GPC)	M_w/M_n
1	BMVL	25	1 h	30	2500	1.27
2		50	1 h	29	2700	1.37
3		100	1 h	23	3000	1.30
4	EG_2MVL	25	5 h	58	500[e]	1.64
5		50[b]	8 h	59	4600	1.35
6[f]		100	24 h	11	1000	1.41
7	EG_4MVL	25	5 h	32	980[e]	1.30

[a][Monomer]$_0$ = 1.0 M, *I* = $PhCH_2OH$, 25 °C. [b][Monomer]$_0$ = 1.1 M. [c]Determined by ^1H NMR. [d]Determined by gel permeation chromatography (GPC). [e]GPC analysis prior to dialysis. [f]1 mol % TBD was used.

The conjugate addition of benzyl mercaptan to 5,6-dihydro-2*H*-pyran-2-one (DHP) was performed in the presence of triethyl amine at 80 °C.[22] BMVL was obtained in high yield (76%) as an odorless solid product. The ethylene-glycol functionalized monomers were prepared analogously by addition of either 2-(2-methoxyethoxy)ethanethiol or 1-mercapto-3,6,9,12-tetraoxotridecane[26] to DHP to generate the substituted valerolactones EG_2MVL (54% yield) or EG_4MVL (44% yield), respectively (Figure 1).

Attempts to carry out the ring-opening polymerization of BMVL with 5 mol % TBD in the presence of an alcohol initiator in dichloromethane were unsuccessful, even at high

Received: March 22, 2012
Accepted: June 12, 2012
Published: June 19, 2012

Table 2. Melt Polymerization of 3-Mercaptovalerolactones[a]

run	mon.	cat.	cond. time h/T °C	[M]/[I]	conv.[b]/%	yield/%	M_n (theoretical)	M_n[c] (GPC)	M_w/M_n[c]
7	BMVL		12/45	47	0				
8		TBD, 5 mol %	24/45	100	60	62	13000	4050	1.85
9		TBD, 1 mol %	24/45	100	36	37	8000	8900	1.45
10		$Sn(oct)_2$ 5 mol %	24/100	26	16	8	1200	2200	1.31
11	EG_2MVL	TBD 5 mol %	24/25	25	65	3	3802	3300	1.55
12		TBD 5 mol %	24/25	100	53	35	12676	6700	1.43
13		TBD 1 mol %	24/25	100	28	35	6826	6100	1.37
14	EG_4MVL	TBD 5 mol %	24/25	25	60	4	4830	3800	1.32

[a] I = pyrene butanol. [b] Determined by ^{1}H NMR. [c] Determined by GPC.

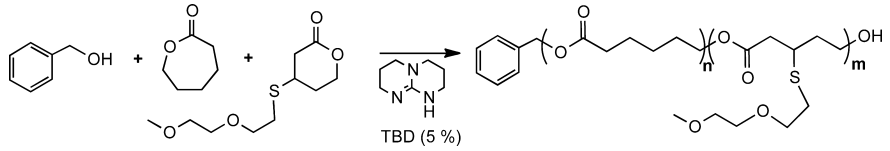


Figure 2. Random copolymerization of EG_2MVL and CL.

Table 3. Copolymerization of 3-Mercaptovalerolactones with ε-Caprolactone[a]

run	monomers	[M]/[I]	conv.[b] of MVL/CL, %	composition[c] MVL/CL, %	M_n[d]	M_w/M_n[d]
15	BMVL-CL	25	94/76	51/49	5800	1.47
16	EG_2MVL-CL	15	87/84	48/52	6900	1.27
17	EG_4MVL-CL	15	83/79	51/49	6800	1.21

[a] $[Monomer]_0$ = ([CL] + [MVL]) = 1.0 M in toluene, [CL]/[MVL] = 1.0, I = $PhCH_2OH$, 25 °C. [b] Determined by ^{1}H NMR. [c] ^{13}C NMR. [d] Determined by GPC.

monomer concentrations (0.45−5.0 M). However in toluene the polymerization of BMVL (1.0 M) initiated by benzyl alcohol with 5 mol % TBD catalyst proceeded to 20−30% conversion to afford the functionalized polymer p(BMVL) with yields of 13−20% and molecular weights of 2500−3000 Da, after purification by dialysis. The ring-opening of EG_2MVL proceeded to higher conversions (58%) in toluene, but only oligomers were generated at initiating alcohol concentrations of 0.04 M ($[M]_0/[I]_0$ = 25). Higher molecular weights (M_n = 4600 Da) could be generated at lower initiator concentrations (0.02 M, $[M]_0/[I]_0$ = 50) after 8 h (Table 1).

The ring-opening polymerizations of the mercapto-substituted valerolactones BMVL, EG_2MVL, and EG_4MVL in toluene solution are not very efficient; they are considerable slower and proceed to lower conversion than analogous reactions of the unsubstituted valerolactone under similar conditions (90% conversion within 30 min for valerolactone with 5 mol % TBD in dichloromethane).[25] This is likely due to the less favorable thermodynamics of ring-opening of the substituted lactones,[27−30] as might be expected on the basis of the Thorpe−Ingold effect.[30−32] The reticence of the mercapto-substituted lactones to undergo polymerization in methylene chloride was unexpected;[25] we switched to toluene on the basis of suggestions that the polarity of the solvent can influence the thermodynamics of ring-opening.[33,34]

Higher monomer conversions (60−70%) were observed in the absence of solvent: melt polymerization of BMVL, EG_2MVL, and EG_4MVL were performed in the presence of TBD catalyst at 25−45 °C. No conversion was observed in the absence of catalysts under the same conditions. The high activity of the organocatalyst TBD is evident from the higher conversions observed at 45 °C than that obtained with tin octoate $Sn(Oct)_2$ (5 mol %) at 100 °C. Conversions in the melt are higher with 5 mol % TBD, but under these conditions, competitive retro-Michael reactions can occur,[24] leading to lower molecular weights than predicted from the initial monomer to initiator ratio $[M]_0/[I]_0$ (entries 8 and 12). Retro-Michael reactions were evidenced by the formation of 4−6% DHP in the crude NMR samples prepared in the melt (see Figures S13, S15, and S16, Supporting Information (SI)). Lowering the TBD loadings to 1 mol % produced polymers with more predictable molecular weights, more closely resembling the theoretically predicted M_n (entries 9 and 13, Table 2). Nevertheless, at 1 mol % TBD, polymerization of EG_2MVL led to a small amount of elimination (Figure S14 of the SI), likely as a consequence of the basicity of TBD.

The 3-mercaptovalerolactones could also be copolymerized with other lactones. The copolymerization of a 1:1 mixture of the mercaptovalerolactones and ε-caprolactone was carried out with 5 mol % TBD in toluene solution at room temperature. The copolymerizations were both more rapid and proceeded to higher conversions (76−94%) than the MVL homopolymerizations.[34] An analysis of the microstructure of the copolymers by ^{13}C NMR analysis (see SI) revealed them to be random copolymers[35] with compositions closely approximate to that of the initial feed ratio (Figure 2, Table 3).

The homopolymers p(BMVL) and p(EG_2MVL) and copolymers are soluble in tetrahydrofuran, aromatic, and chlorinated solvents. The homopolymer pEG_4MVL (M_n = 3800 Da) is highly soluble in water (Figure S17, SI). Analysis of these materials by differential scanning calorimetry (DSC) revealed that pBMVL with M_n = 8900 g/mol exhibits a glass transition temperature T_g = −14.3 °C (Figure S24, SI), whereas the copolymer with caprolactone, $pBMVL_{34}$-r-CL_{33}, exhibited a single glass transition temperature T_g = −28 °C (Figure S25, SI). A glass transition temperature T_g = −52.8 °C was observed for the mercaptovalerolactone with a pendant ethylene glycol

dx.doi.org/10.1021/mz3001397 | ACS Macro Lett. 2012, 1, 845−847

group pEG_2MVL (M_n = 6100, Figure S26 of the SI). The thermal stability of pBMVL and pEG_2MVL was investigated by thermal gravimetric analysis (TGA); these polymers showed no significant weight loss until 250 °C (Figure S27, SI).

In summary, we report a facile strategy for generating functionalized lactones by the conjugate addition of thiols to α,β-unsaturated lactones. Organocatalytic ring-opening polymerization of these 3-mercaptovalerolactones generates homopolymers or copolymers decorated with hydrophobic or hydrophilic functional groups. Further studies on the scope and generality of this strategy are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental section, NMR spectra, and DSC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: waymouth@stanford.edu. Tel.: (650) 723-4515.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge support from the NSF (GOALI CHE-0957386) and the DOE (DE-FG-02-10ER16198). This work was also supported by the NRF (NRF-2010-C00059) of the Korean Ministry of Education, Science and Technology (H.K.) and The Marcus and Amalia Wallenberg Foundation (postdoctoral funding (V.O.)).

■ REFERENCES

(1) Albertsson, A. C.; Varma, I. K. *Adv. Polym. Sci.* **2002**, *157*, 1−40.
(2) Guo, B. L.; Finne-Wistrand, A.; Albertsson, A. C. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 2097−2105.
(3) Tian, H.; Tang, Z.; Zhuang, X.; Chen, X.; Jing, X. *Prog. Polym. Sci.* **2012**, *37*, 237−280.
(4) Jerome, C.; Lecomte, P. *Adv. Drug Delivery Rev.* **2008**, *60*, 1056−1076.
(5) Kiesewetter, M. K.; Shin, E. J.; Hedrick, J. L.; Waymouth, R. M. *Macromolecules* **2010**, *43*, 2093−2107.
(6) Kamber, N. E.; Jeong, W.; Waymouth, R. M.; Pratt, R. C.; Lohmeijer, B. G. G.; Hedrick, J. L. *Chem. Rev.* **2007**, *107*, 5813−5840.
(7) Bourissou, D.; Moebs-Sanchez, S.; Martin-Vaca, B. *Compt. Rend. Chim.* **2007**, *10*, 775−794.
(8) Williams, C. K. *Chem. Soc. Rev.* **2007**, *36*, 1573−1580.
(9) Seyednejad, H.; Ghassemi, A. H.; van Nostrum, C. F.; Vermonden, T.; Hennink, W. E. *J. Controlled Release* **2011**, *152*, 168−176.
(10) Parrish, B.; Emrick, T. *Macromolecules* **2004**, *37*, 5863−5865.
(11) Parrish, B.; Breitenkamp, R. B.; Emrick, T. *J. Am. Chem. Soc.* **2005**, *127*, 7404−7410.
(12) Taniguchi, I.; Mayes, A. M.; Chan, E. W. L.; Griffith, L. G. *Macromolecules* **2004**, *38*, 216−219.
(13) Prime, E. L.; Cooper-White, J. J.; Qiao, G. G. *Aust. J. Chem.* **2006**, *59*, 534−538.
(14) Taniguchi, I.; Kuhlman, W. A.; Mayes, A. M.; Griffith, L. G. *Polym. Int.* **2006**, *55*, 1385−1397.
(15) Du, J.-Z.; Du, X.-J.; Mao, C.-Q.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 17560−17563.
(16) Riva, R.; Schmeits, S.; Jérôme, C.; Jérôme, R.; Lecomte, P. *Macromolecules* **2007**, *40*, 796−803.
(17) du Boullay, O. T.; Saffon, N.; Diehl, J.-P.; Martin-Vaca, B.; Bourissou, D. *Biomacromolecules* **2010**, *11*, 1921−1929.
(18) Trollsas, M.; Lee, V. Y.; Mecerreyes, D.; Lowenhielm, P.; Moller, M.; Miller, R. D.; Hedrick, J. L. *Macromolecules* **2000**, *33*, 4619−4627.
(19) Jiang, X.; Vogel, E. B.; Smith, M. R.; Baker, G. L. *Macromolecules* **2008**, *41*, 1937−1944.
(20) Jiang, X.; Smith, M. R.; Baker, G. L. *Macromolecules* **2007**, *41*, 318−324.
(21) Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E. *Prog. Polym. Sci.* **2006**, *31*, 487−531.
(22) Calvet, S.; Courillon, C.; Malacria, M. *ARKIVOC (Gainesville, FL, U.S.)* **2002**, *v*, 189−195.
(23) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; González, L. *Eur. J. Org. Chem.* **2004**, *2004*, 1492−1499.
(24) Kupchan, S. M.; Giacobbe, T. J.; Krull, I. S.; Thomas, S. M.; Eakin, M. A.; Fessler, D. C. *J. Org. Chem.* **1970**, *35*, 3539−3543.
(25) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556−4557.
(26) Snow, A. W.; Foos, E. E. *Synthesis* **2003**, 509−512.
(27) Save, M.; Schappacher, M.; Soum, A. *Macromol. Chem. Phys.* **2002**, *203*, 889−899.
(28) Matsuo, J.; Aoki, K.; Sanda, F.; Endo, T. *Macromolecules* **1998**, *31*, 4432−4438.
(29) Martello, M. T.; Burns, A.; Hillmyer, M. *ACS Macro Lett.* **2012**, *1*, 131−135.
(30) Zhang, D. H.; Hillmyer, M. A.; Tolman, W. B. *Biomacromolecules* **2005**, *6*, 2091−2095.
(31) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1766.
(32) Wheeler, O. H.; de Rodriguez, E. E. G. *J. Org. Chem.* **1964**, *29*, 1227−1229.
(33) Aleman, C.; Betran, O.; Casanovas, J.; Houk, K. N.; Hall, H. K. *J. Org. Chem.* **2009**, *74*, 6237−6244.
(34) Szymanski, R. *Prog. Polym. Sci.* **1992**, *17*, 917−951.
(35) In contrast, copolymerization of caprolactone with unsubstituted valerolactones with *N*-heterocyclic carbene catalysts yields gradient copolymers: Shin, E. J.; Brown, H. A.; Gonzalez, S.; Jeong, W.; Hedrick, J. L.; Waymouth, R. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6388−6391.