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Effective stereoselective approach to substituted 1,4-dioxane-2,5-diones as prospective substrates for ring-opening polymerization

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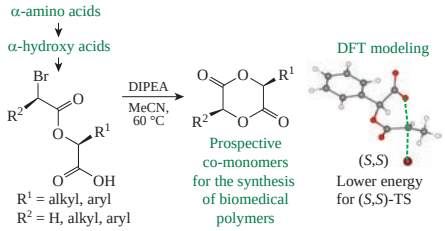
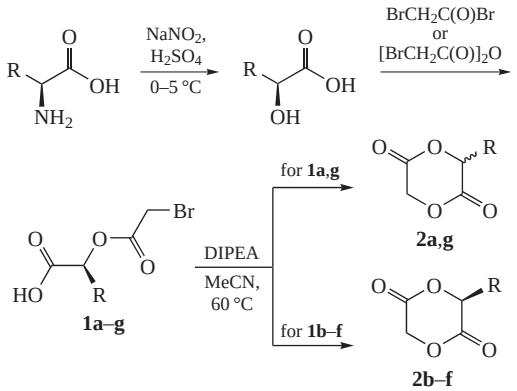
Intramolecular cyclization of α-bromoacyl derivatives of α-hydroxy acids affords 1,4-dioxane-2,5-diones. The method is suitable to obtain mono- and disubstituted products, the latter being formed stereoselectively as (*S*,*S*)-diastereomers, as confirmed by DFT modeling.



The development of biomedical polymers is one of the most highly demanded fields of modern chemistry. These materials should possess regulated biodegradability and hydrophilicity, full biocompatibility and specifically programmed mechanical properties. The most frequently used biomedical polymers comprise homo- and copolymers of 1,4-dioxane-2,5-dione (glycolide, GL), 3,5-dimethyl-1,4-dioxane-2,5-dione (lactide, LA) and other cyclic esters obtained *via* catalytic ring-opening polymerization (ROP).[1–8] The GL / LA ratio in copolymers determines the entire spectrum of their properties. The fundamental chemical challenge in GL/LA copolymer synthesis is the difference in GL and LA reactivities.[9] High reactivity of GL leads to formation of non-statistic copolymers with lower strength and elasticity due to the presence of extended poly-GL blocks. The preparation of GL/LA statistic copolymers with the desired characteristics requires elevated temperatures and moderately active catalyst, toxic tin(II) 2-ethylhexanoate $Sn(Oct)_2$.[10–12] A promising synthetic approach to statistic GL copolymer, which allows one to apply modern efficient ROP catalysts as well as vary polymer product properties, uses monosubstituted 1,4-dioxane-2,5-diones as substrates. Several methods of obtaining mono- and disubstituted derivatives of 1,4-dioxane-2,5-diones have been described.[13–19] Regularly, the synthetic approach includes acylation of α-hydroxy acids by α-halo carboxylic acids or their derivatives with subsequent cyclization. The first stage proceeds smoothly in high yields, while the main difficulties arise during the second stage. Moreover, DMF used in all cases as a solvent hampers separation and purification of cyclization products.

Herein, we have developed an effective method for the synthesis of mono-substituted 1,4-dioxane-2,5-diones. We studied the influence of the solvent on the cyclization of compound **1a**, a mandelic acid/α-bromoacetyl bromide conjugate (R = Ph, Scheme 1). We found that acetonitrile MeCN was the best solvent (Table 1) for cyclization of **1a** into 3-phenyl-1,4-dioxane-



a R = Ph
b R = Me
c R = Pr^i
d R = Bu^i
e R = Bn
f R = 4-$BnOC_6H_4CH_2$
g R = $BnOCH_2$

Scheme 1

Table 1 Cyclization of 2-(2-bromoacetoxy)-2-phenylacetic acid **1a** into lactide **2a** at 60 °C in different solvents.[a]

Solvent	30 min yields (%)		90 min yields (%)	
	2a	Oligomers	**2a**	Oligomers
DMF	68	32		
DMSO	15	31	43	57
THF	25	41		
1,4-dioxane	0	5	0	19
Acetone	8	14	21	48
MeCN	96	4		

[a] Cyclization protocol: substrate (10 mmol) in appropriate solvent (24 ml) was added dropwise at 60 °C to the solution of DIPEA (10 mmol) in 12 ml of the solvent. Conversion of **1** and **2**/oligomers ratio were determined by ^{1}H NMR spectroscopy.

† A possible reason for the efficiency of MeCN lies in the extremely high nucleophilicity of the carboxylate anion in this solvent. This fact was experimentally confirmed.[20]

Table 2 Synthesis of 3-R-1,4-dioxane-2,5-diones **2a–g**.

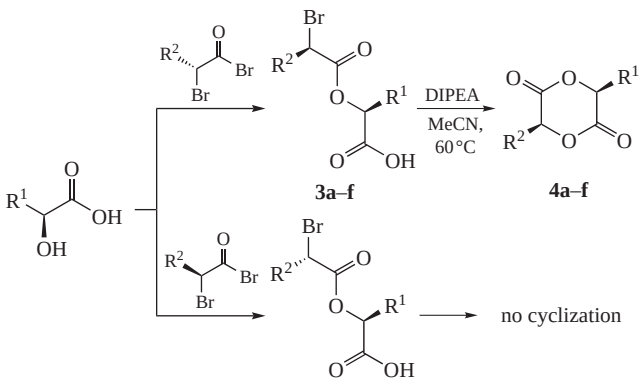
R	Diazotization and acylation[a]		Cyclization			
	Product	Yield[b] (%)	Product	Yield (%)	mp/°C	$[\alpha]_D^{20}$ [c]
Ph	**1a**	–	**2a**	88	119	–5.2
Me	**1b**	–	**2b**	62	66	not determined
Pr^i	**1c**	88	**2c**	86	63	–138.4
Bu^i	**1d**	86	**2d**	80	78	–146.6
Bn	**1e**	78	**2e**	87	108	–142.2
4-$BnOC_6H_4CH_2$	**1f**	60	**2f**	74	114	+20.8
$BnOCH_2$	**1g**	82	**2g**	76	oil	+1.2

[a]For compound **1a**,**c–e** $BrCH_2C(O)Br$ was used, for compounds **1f**,**g** $[BrCH_2C(O)]_2Br$ was used. [b]Yield of the diazotization step. [c]In $CHCl_3$.

2,5-dione **2a** and significantly surpassed other solvents such as DMF, DMSO, acetone and etheral solvents. After 30 min at 60 °C, full conversion of **1a** was achieved with formation of **2a** and insignificant (~4%) admixtures of oligomeric products.† An additional advantage of MeCN is the simplicity of separation of the product with 'polymerization grade' purity.

We used natural (*S*)-lactic and (*S*)-mandelic acids as starting compounds for the synthesis of a range of mono-substituted 1,4-dioxane-2,5-diones. We also prepared a number of α-hydroxy acids *via* diazotization of α-amino acids securing the initial configuration at the asymmetric carbon atom.[21] Acylation of these α-hydroxy acids with bromoacetyl bromide or bromoacetic anhydride afforded products **2b–g** which were subjected to cyclization in MeCN in the presence of *N*,*N*-diisopropyl-*N*-ethyl amine (DIPEA, see Scheme 1) without additional purification. Compounds **2a–g** were obtained in high yields (Table 2) and characterized by ^1H and ^{13}C NMR spectroscopy (see Online Supplementary Materials). Synthesis of lactides **2a** and **2g** was accompanied by racemization, while alkyl derivatives **2c–e** were determined to be enantiomerically pure (*S*)-isomers (the values of specific rotation $[\alpha]_D^{20}$ are given in Table 2).

In the synthesis of disubstituted 1,4-dioxane-2,5-diones from (*S*)-α-hydroxy acids we used racemic α-bromopropionyl and α-bromo-α-phenylacetyl bromides. Precursors **3a–f** formed at the acylation stage (Scheme 2) were found to be ~1 : 1 mixtures of diastereomers (for ^1H NMR spectra, see Online Supplementary Materials). We have discovered that in the presence of a base a dynamic resolution occurs, namely, one of the diastereomers



	R^1	R^2	Yield of **4** (%)
a	Me	Me	46
b	Pr^i	Me	41
c	Ph	Me	48
d	Bn	Me	48
e	4-$BnOC_6H_4CH_2$	Me	38
f	Ph	Ph	43

Scheme 2

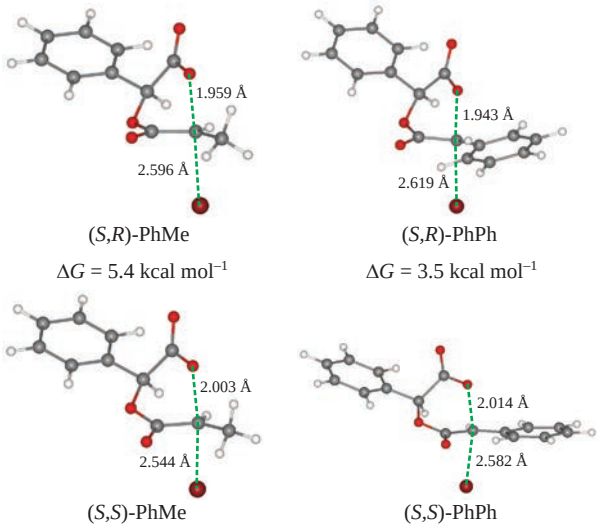
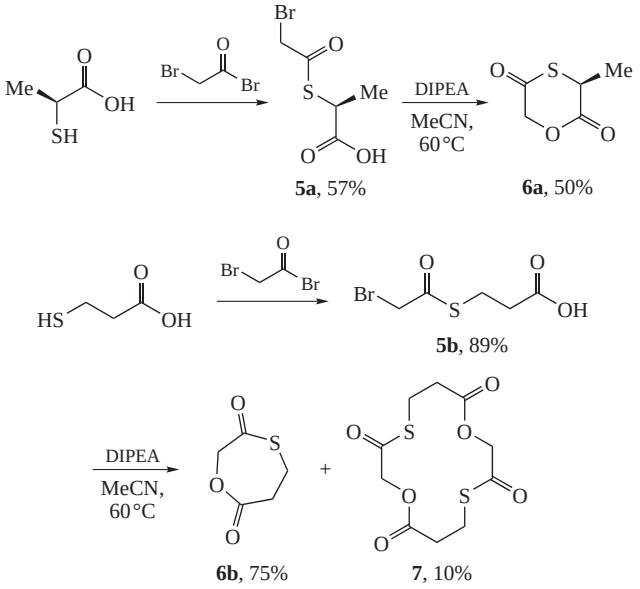


Figure 1 Calculated geometries of the transition states of intramolecular S_N cyclization for (*S*,*S*)- and (*S*,*R*)-diastereomers of BrCHRC(O)OCH(Ph)C(O)O-anions derived from **3c** (R = Me) and **3f** (R = Ph).

undergoes cyclization more rapidly. As a result, spectrally pure products **4a–f** were isolated. The (*S*,*S*)-configuration of **4a** was proven by measurement of its specific rotation, which corresponded to the table values for commercial (*S*,*S*)-lactide. Enantiomeric purity of compounds **4b–f** was monitored by chromatography using a column with a chiral stationary phase. Compounds **4b**,**d**,**e** turned to be enantiomerically pure (see Online Supplementary Materials), while **4c** and **4f** were mixtures of enantiomers (although one diastereomer). Formation of (*R*,*R*)-**4c** and (*R*,*R*)-**4f** was most likely due to the ease of enolization of mandelate fragment in **3c** and **3f**.

To illustrate the preference for (*S*,*S*)-isomer formation, we conducted DFT calculations‡ for **3c** and **3f** anions, and the corresponding intramolecular cyclization transition states. Calculations have shown that activation barriers for (*S*,*R*)-isomers are higher than those for (*S*,*S*)-isomers by 5.4 and 3.5 kcal mol^{-1}, respectively. The difference in energy is due to various reasons. In the case of **3c**, the increase in $TS_{(S,R)}$ energy is owing to van der Waals repulsion between the H atom and methyl group in an energetically



Scheme 3

‡ DFT calculations were performed using Gaussian 09 program package (B3PW91/DGTZVP level of theory).

unfavorable axial position. In the case of cyclization of **3f**, the relative decrease of $TS_{(S,S)}$ energy is caused by the conjugation with the π-system of the benzene ring, in $TS_{(S,R)}$ this conjugation is less effective (Figure 1).

The developed method is applicable to sulfur-containing analogues of 1,4-dioxane-2,5-diones (Scheme 3). Using 2- and 3-mercaptopropionic acids as reactants, we obtained precursors **5a**,**b** which were further cyclized into thio esters **6a**,**b**. In the synthesis of **6b**, a 14-member cyclic byproduct **7** was also formed.

The efficiency of mono-substituted 1,4-dioxane-2,5-diones in the preparation of statistic glycolide-based copolymers was demonstrated by synthesizing copolymer of **2b** and GL. Polymerization in the presence of magnesium-containing phenolate catalyst[22] at 80 °C afforded a low crystallinity product.

In conclusion, we have elaborated an effective method of synthesis of mono- and disubstituted 1,4-dioxane-2,5-diones and their heteroanalogs based on the acylation of α-hydroxy acids and derivates of α-bromoalkanoic acids with a subsequent cyclization in MeCN solution. For aliphatic α-hydroxy acids, which are less susceptible to enolization, the method is diastereo- and enantioselective. The obtained cyclic esters serve as promising substrates for obtaining a wide range of glycolide-based biomedical grade copolymers. The synthesis and study of these polymers is an object of our further research.

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Online Supplementary Materials

Supplementary data associated with this article (experimental details, ^{1}H and ^{13}C NMR spectra of compounds, results of DFT calculations) can be found in the online version at doi: 10.1016/j.mencom.2018.01.020.

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