Chemoenzymatic Syntheses of Optically Active Polyacrylates

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Received February 17, 1999; Revised Manuscript Received May 28, 1999

ABSTRACT: Different primary alcohols were transesterified using Mucor meihei lipase. 2,3-Butanedione monoxime acrylate was used efficiently as an acrylating agent to synthesize optically active acrylates. The effects of substrate substituition and solvent on the reaction rate were studied. The results showed that the reaction rates in nonpolar solvents were the fastest for acryloylating reactions reported until now. The enantiomeric excess (ee) and enantiomeric purity (*E* value) of all the acrylate monomers were evaluated and compared. The synthesized optically active acrylate monomers were polymerized by the free-radical initiation technique.

Introduction

Optically active polymers have found applications in asymmetric synthesis, as chiral adsorbents for separation of racemates and in liquid crystals.[1] The synthesis of optically active acrylate monomer is an important step in the synthesis of optically active polyacrylates. Optically active acrylates and methacrylates have usually been synthesized from optically active alcohols.

Recent advances in enzyme catalysis in nonaqueous media have shown that enzymes are useful catalysts for the resolution of alcohols.[2−4] Although a few reports[5,6] are available about the lipase catalyzed acryloyl ester synthesis, a detailed study has not yet been reported. Vinyl acrylates are found to be efficient acyl transfer agents for this purpose.[7] Even though the reaction is irreversible, the yields reported are quite low (40−60%).

The fast reaction rate of oxime esters[8,9] and the easy availability of the oximes, used as the starting material for the oxime ester, have prompted us to use oxime acrylate as an acrylating agent for the syntheses of optically active acrylates.

In the present study, different primary alcohols were transesterified with 2,3-butanedione monoxime acrylate in diisopropyl ether solvent using Mucor meihei lipase catalyst (Scheme 1).

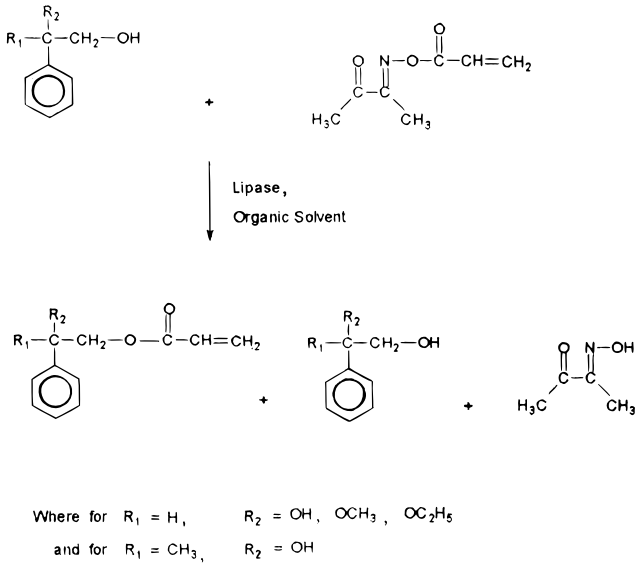
Experimental Section

Chemicals. 2,3-Butanedione monoxime acrylate was synthesized by the condensation of 2,3-butanedione monoxime (s.d. fine Chemicals, Mumbai, India) and acryloyl chloride (Sisco Research Laboratory, Mumbai, India). Among the alcohols used only 2-phenyl-propane-1,2-diol was obtained from Aldrich Chemical Co. All the other alcohols were synthesized by the ring opening reaction of styrene oxide. The solvents used were of analytical grade. Dodecatungstosilicic acid was obtained from Sisco.

Lipase. Lipozyme IM 20 (41 Iug^{-1}), a commercially available lipase (from fungus Mucor meihei immobilized on a macroporous anion-exchange resin) was obtained from Novo Nordisk and used as received.

Synthesis of Reactants. The detailed procedure for syntheses of (1) 2,3-butanedione monoxime acrylate and (2) optically active acrylates by lipase catalysis and their polymerization procedure are given elsewhere.[9]

Scheme 1



Syntheses of Alcohols by Ring Opening Reaction of Styrene Oxide. By this method 1-phenylethane-1,2-diol, 2-methoxy-2-phenylethanol, and 2-ethoxy-2-phenylethanol were synthesized.

General Procedure. Styrene oxide (0.1 mol) in water or alcohol (150 mL) was taken in a 250 mL round-bottomed flask fitted with an addition funnel. The mixture was stirred in an ice bath. When the temperature of the reaction mixture reached 0 °C, dodecatungstosilicic acid catalyst (10 mg) dissolved in 25 mL of cold water or alcohol was added dropwise for a period of 15 min. After 2 h of stirring the ice bath was removed, and stirring was continued for a further 8 h at room temperature. Extraction was carried out in chloroform, and the organic layer was washed with water and freed from traces of water by drying over anhydrous sodium sulfate, and then the solvent chloroform was evaporated to recover the product alcohol.

Alcohols. The boiling point and yield of the alcohols are as follows:

alcohol	bp/mp (°C)	yield (%)
1-phenylethane-1,2-diol	65−66 (mp)	96
2-methoxy-2-phenylethanol	237	98
2-ethoxy-2-phenylethanol	70−72 0.1 mmHg	98

The purity of all the alcohols, 1-phenylethane-1,2-diol (reten-

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10.1021/ma990222l CCC: $18.00
Published on Web 08/31/1999

Table 1. ^{1}H NMR Spectral Data (δ, ppm) of Acrylate Monomers Derived from Primary Alcohols[a]

acrylates	C(=O)OCH$_2$−	OC(=O)CH=CH$_2$	aromatic	PhCH	−CH$_3$	−OCH$_3$	−OCH$_2$−
A1	4.29	5.75−6.58	7.3	4.96			
A2	4.29	5.7−6.6	7.3		1.48		
A3	4.30	5.76−6.35	7.34	4.41		3.30	
A4	4.30	5.20−6.31	7.34	4.50	1.19		3.5

[a] A1 = 1-phenylethane-1,2-diol monoacrylate, A2 = 2-phenylpropane-1,2-diol monoacrylate, A3 = 2-methoxy-2-phenylethyl acrylate, and A4 = 2-ethoxy-2-phenylethyl acrylate.

Table 2. Results of Elemental Analysis of Acrylate Monomer

	theoretical (%)			found (%)		
acrylate monomer	C	H	O	C	H	O
1-phenylethane-1,2-diol monoacrylate	68.75	6.25	25.0	68.48	6.22	25.30
2-phenylpropane-1,2-diol monoacrylate	69.90	6.80	23.30	69.92	6.78	23.30
2-methoxy-2-phenylethyl acrylate	69.90	6.80	23.30	69.87	6.83	23.30
2-ethoxy-2-phenylethyl acrylate	70.94	7.22	21.88	70.89	7.22	21.89

tion time, rt, = 5.88 min), 2-methoxy-2-phenylethanol (rt = 5.17 min), and 2-ethoxy-2-phenylethanol (rt = 5.75 min), was confirmed by GC analysis.

Acrylate Monomers. The purity of the synthesized acrylate monomers was confirmed by gas chromatography.

(a) ^{1}H NMR Spectroscopy. The δ ppm values of the NMR spectra of the acrylates obtained from the primary alcohols are listed in Table 1.

(b) Elemental Analysis. The elemental composition of the monomers was found and compared with the theoretical values of the respective acrylates (Table 2).

Polyacrylates. IR Spectroscopy. The IR spectra of all the polyacrylates showed the following characteristic bands: 3030 (broad, −CH stretching), 2950 (strong, −CH stretching), 1740 (very strong, C=O stretching), 1600 cm^{-1} (weak, aromatic).

Results and Discussion

Transesterification of Primary Alcohols by Lipase Catalysis. Scheme 1 shows the reaction of primary alcohol (I) with 2,3-butanedione monoxime acrylate (II).

The reaction of primary alcohols with oxime acrylate was found to be quite fast. Complete conversion with respect to oxime acrylate was observed within 4−6 h (Table 3). In the case of 2-phenylpropane-1,2-diol the time taken for completion of the reaction is highest, probably due to steric effects.

Samples were removed at different intervals of time from the reaction mixture, filtered, and subjected to GC analysis. The GC products showed different retention times. In all cases it was observed that the peak due to oxime acrylate disappears first (3.0−5.0 h). After the disappearance of the oxime acrylate peak the peak area of oxime remains constant, but the area of the product peak increases slowly. These observations lead to following type of mechanism.

$$\text{oxime acrylate} + \text{lipase} \xrightarrow{\text{step I}} \text{(lipase:acrylate) complex} + \text{oxime}$$

$$\text{(lipase:acrylate) complex} + \text{ROH} \xrightarrow{\text{step II}} \text{R−O−acrylate} + \text{lipase}$$

In the first step, lipase must be binding the acrylate temporarily to give free oxime leading to the increase in peak area due to oxime at retention time 2.1 min and simultaneous decrease in peak area of oxime acrylate at retention time 4.2 min. In the second step the lipase: acrylate complex reacts with alcohol to give the desired acrylate monomer, which is manifested by an increase in the peak area of product acrylate monomer at 6.6 min, whereas a proportionate decrease in the peak area due to alcohol at 5.1 min is clearly observed, as expected.[4,10]

Table 3. Stereochemical Data of Substituted Acrylates

product code[a]	yield (%)	reacn time (h)	$[\alpha]_D^{20}$ (c = 1 CHCl$_3$)	absolute config	ee (%)	E value
A	46.0	4	−22.5	*R*	32.8	2.70
B	48.0	6	−12.5	*R*	28.0	2.72
C	47.0	4	−18.8	*R*	26.3	2.10
D	48.0	4.5	−19.5	*R*	27.6	2.20

[a] A = 1-phenylethane-1,2-diol monoacrylate, B = 2-phenylpropane-1,2-diol monoacrylate, C = 2-methoxy-2-phenylethyl acrylate, and D = 2-ethoxy-2-phenylethyl acrylate.

Since the racemic alcohol used was double the quantity (% mol) of oxime acrylate, the faster reacting enantiomer will be converted preferentially into the corresponding acrylate. This method proved to be the best method for resolution of the alcohol because of the following:

(1) The reaction cannot proceed beyond 50% conversion (limiting reagent); hence, the highest enantiomeric ratio is expected in the present studies.[11]

(2) Since the reactant oxime acrylate is getting consumed completely under these conditions, the separation of product acrylate monomer from the reaction mixture is easy (Scheme 1). The consumption of the alcohol stops after a certain time (approximately 4−6 h), as expected. The side product oxime is not taking part in the reverse reaction.

Effect of Substrate Substitution on Reaction. Figure 1 represents the plot of percent conversion with time of 2-methoxy-2-phenylethanol and 2-ethoxy-2-phenylethanol into corresponding acrylate monomers, whereas Figure 2 represents the percent conversion of 1-phenylethane-1,2-diol and 2-phenylpropane-1,2-diol into the corresponding acrylates at different intervals of time.

From Figure 1, it is clear that 2-methoxy-2-phenylethanol and 2-ethoxy-2-phenylethanol exhibit only a marginal change in their reactivity.

The reaction of 1-phenylethane-1,2-diol with oxime acrylate completes in 4 h, whereas for 2-phenylpropane-1,2-diol it takes 6 h. The difference in the rate of conversion exhibited in Figure 2 can be accounted for by the substitution of the hydrogen on 1-phenylethane-1,2-diol by a bulkier methyl group which has increased the crowding considerably and thus negatively affects the reactivity of 2-phenylpropane-1,2-diol. On comparing

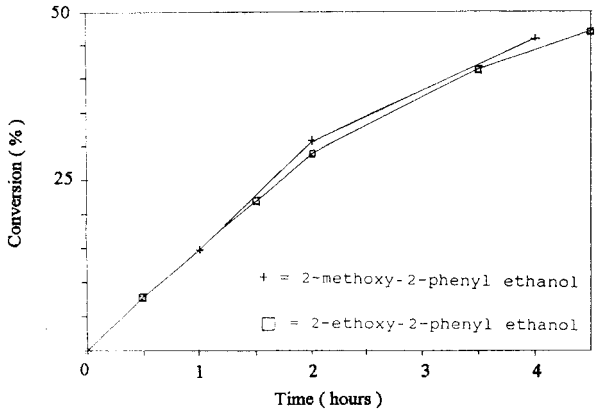

Figure 1. Comparison between the rate of transesterification of 2-methoxy-2-phenylethanol and 2-ethoxy-2-phenylethanol with oxime acrylate.

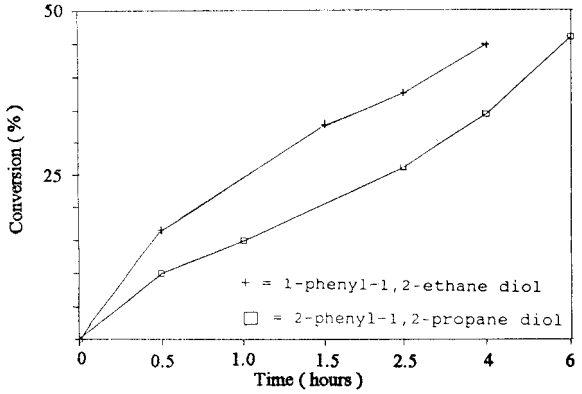

Figure 2. Comparison between the rate of transesterification of 1-phenylethane-1,2- diol and 2-phenylpropane-1,2-diol with oxime acrylate.

Figures 1 and 2, it is evident that the overall rate of conversion of each of the alcohols is not very different, probably because the reactive site in each case is away from the substituition. The observation could be explained on the basis of the inertness of the hydroxyl group in 2-phenylpropane-1,2-diol toward the lipase catalyzed transesterification reaction, which is quite obvious since it is a tertiary hydroxyl group. However, 1-phenylethane-1,2-diol monoacrylate formation needs further explanation. Since primary alcohols react many-fold faster than secondary alcohols, the 2-phenylpropane-1,2-diol monoacrylate must have formed first. As a consequence, the secondary hydroxyl group becomes highly crowded after monoester formation, restricting the reaction to a monoester stage only.

Effect of Solvent. A model reaction of 1-phenylethane-1,2-diol with 2,3-butanedione monoxime acrylate was selected to study the effect of solvent on the rate of lipase catalyzed transesterification. Solvents of different log *P* values were used for the model reaction. The log *P* values for tetrahydrofuran (THF), diethyl ether, diisopropyl ether, and hexane are 0.49, 0.89, 2.00, and 3.50, respectively.[12]

It is well-known[13] that hydrophobicity increases from THF to hexane. From Figure 3 it is observed that, in general, the rate of reaction increases as the hydrophobicity of the solvent increases except for hexane. The reversal of this general trend observed in the case of hexane is due to poor solubility of reactant 1-phenylethane-1,2-diol in hexane.

Thus, solvent plays a vital role in controlling the rate of the lipase catalyzed transesterification. It can be

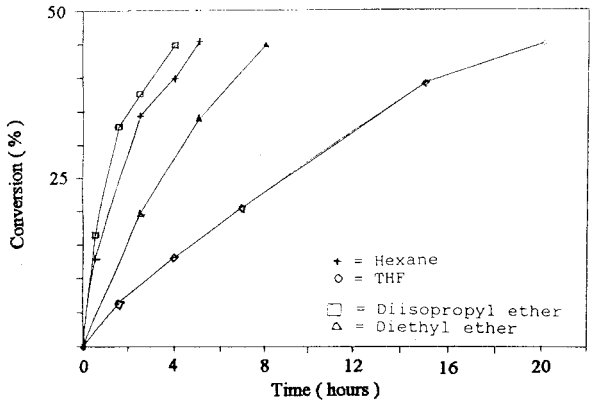

Figure 3. Effect of solvent on the rate of transesterification of 1-phenylethane-1,2-diol.

Table 4. Polymerization Data of Acrylate Monomers

monomer code[a]	poly-acrylate	reacn time (h)	yield (%)	$\bar{M}_W$	$[\alpha]_D^{20}$ (c = 1 $CHCl_3$)	MWD[b]
A	Poly (A)	6.0	85.5	88200	−18.5	1.6
B	Poly (B)	6.5	88.5	68600	−10.5	1.5
C	Poly (C)	7.0	90.0	44400	−16.5	1.3
D	Poly (D)	7.5	92.0	45500	−17.5	1.4

[a] A = 1-phenylethane-1,2-diol monoacrylate, B = 2-phenylpropane-1,2-diol monoacrylate, C = 2-methoxy-2-phenylethyl acrylate, and D = 2-ethoxy-2-phenylethyl acrylate. [b] MWD = molecular weight distribution.

inferred that a high rate of reaction could be achieved if (1) both the reactants are completely soluble in the solvent and (2) the solvent used is highly hydrophobic in nature. This accounts for the very slow rate of transesterification reaction[14] of alcohol with oxime acrylate using THF as solvent.

Separation of Optically Active Acrylate Monomers. All the acrylates were separated from the reaction mixture by column chromatography technique. The optical rotations of alcohols, obtained by the alkaline hydrolysis of the acrylate monomers, were compared with authentic enantiomers obtained from Aldrich. It was observed that the absolute configuration of acrylate A and C is *R*. (Literature value of $[\alpha]_D^{20}$ for the *R*-isomer of 1-phenylethane-1,2-diol is −39 (c = 1% (w/v) in $CHCl_3$) and for the *R*-isomer of 2-methoxy-2-phenylethanol is −133 (c = 1% (w/v) in acetone). By analogy with A and C one can assume that the absolute configuration of B and D is *R* (Table 3).

The "ee" of all the transesterification reactions is about 25−30%. Similarly, the *E* values of all the reactions of primary alcohols were around 2, indicating that there was no significant difference in enantioselectivity between substituted primary alcohols.

The synthesized acrylate monomers were polymerized by free-radical initiation reaction, and the results are as tabulated (Table 4). It is clearly seen from Table 4 that the hydroxy functional polymers have shown relatively higher weight average molecular weight in comparison with other polyacrylates. This is probably due to the higher activation of the double bond by the relatively more electronegative −OH group as compared to the −OR group (where R = $-CH_3$ or $-C_2H_5$). The specific rotation data showed that the rotations observed for polyacrylates were slightly less than their respective acrylate monomers (Tables 3 and 4).

Conclusions

The preliminary studies showed that the lipase catalyzed transesterification of primary alcohols in the presence of diisopropyl ether was quite fast, but enantioselectivity was limited to 30%. Solvent plays a major role in the rate of transesterification reaction. Thus, the present methodology can be applied advantageously to synthesize optically active acrylate monomers even from sterically hindered alcohols where other reagents fail.

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MA990222L