Lipase-supported Preparation of Optically Active 2-Amino Alcohols of Biological Interest

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(Received May 15, 1997, Accepted July 10, 1997)

Abstract: Transesterification of racemic N-acetylated 2-amino alcohols with vinyl acetate was investigated in the presence of inexpensive commercial porcine pancreatic lipase. The enzymatic kinetic resolution occurred with high reactivity and enantioselectivity to give optically pure N,O-diacyl and N-monooacyl. This result clearly indicates that the biocatalytic route can be efficiently used in the preparation of enantiopure 2-amino alcohol.

1. Introduction

The asymmetric synthesis utilizing chiral catalytic properties of enzymes is at present a well-defined method in the preparation of enantiomerically pure alcohols, acids, esters, amines, and amino acids[1-7]. Chiral amino alcohols have also received interest because they are important structural units of many pharmaceutical compounds and bioactive natural products[8, 9]. For example, (S)-(+)2-amino-1-butanol is a precursor to antitubercular drug Ethambutol[10]. The compound has previously been prepared through enzymatic transesterification of either 2-amin-1-butanol or N-ethoxycarbonyl-2-amino-1-butanol with ethyl acetate[11, 12] The former seems to be simple, but results in a mixture of N-monooacyl, N,O-diacyl and the remaining racemic substrate. Thus, it is judged that the latter method via protection of the amino group would be more desirable in achieving an useful transesterification. In this paper we wish to present an efficient kinetic resolution of 2-amino alcohol based on the lipase-catalyzed transesterification of the N-acetylated 2-amino alcohol with vinyl acetate.

2. Experimental

General. Reagent grade chemicals were used as received. Porcine pancreatic lipase and candida cylindracea lipase were purchased from Aldrich Chemical Co. Spectroscopic measurements utilized the following instrumentations: 1H NMR spectra were taken on a Brucker FT-NMR AC 250 spectrometer; NMR chemical shifts are reported in δ with respect to Me4Si as an internal standard. Infrared spectra were recorded on a Brucker IFS 48. GLC analyses were carried out on HP 5390 II chromatograph with a 15 m × 0.32 mm SPB-1 column at 150°C and with a flame-ionization detector. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. Melting points measured with Aldrich Mel-Temp II were not corrected. All transesterifications were performed at room temperature.

Preparation of 2-[N-(Alkylcarbonyl)amino]-1-Alcohol.
A THF (25 ml) solution of 2-amino-1-butanol (2.5 g, 28.1 mmol) was treated with acetic anhydride (3.15 g, 30.9 mmol). The mixture was stirred at room temperature for 1 h and then heated to 65°C for additional 10 h. The mixture was diluted with water (25 ml) and Et2O (25 ml) and the layers separated. The organic layer was washed with H2O (25 ml) and brine (25 ml). The organic layer was dried (K2CO3), filtered, and the solvent removed under reduced pressure. Purification was achieved by bulb-to-bulb distillation to afford pure compound.
in 85% yield.

2-[N-(Ethylcarbonyl)amino]-1-butanol 2: 1H NMR (CDCl3); δ 6.35 (br s, 1H), 4.28 (br s, 1H), 3.75 (m, 1H), 3.59 (dd, J = 11.2, 3.7 Hz, 1H), 3.49 (dd, J = 11.2, 5.7 Hz, 1H), 1.94 (s, 3H), 1.45 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); IR (CHCl3) (cm⁻¹) 3280, 1650, 1554.

2-[N-(Ethylcarbonyl)amino]-1-propanol 4: 1H NMR (CDCl3); δ = 6.55 (br s, 1H), 3.92 (m, 1H), 3.81 (br s, 1H), 3.59 (dd, J = 11.1, 3.9 Hz, 1H), 3.49 (dd, J = 11.1, 5.9 Hz, 1H), 1.91 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H); IR (CHCl3) (cm⁻¹) 3292, 1651, 1552.

**Lipase-Supported Transesterification of 2-[N-(Alkylcarbonyl)amino]-1 Alcohol.**

Powdered PPL (Aldrich, 3.2 g) was added to a solution of N-acetyl-2-amino-1-butanol (1.0 g, 7.6 mmol) and vinyl acetate (2.8 g, 32.5 mmol) in THF (15 mL). The suspension was stirred at RT for the time necessary to conversion to diacetate. The reaction was monitored by GC and was terminated by filtration of the reaction mixture to remove the enzyme. After usual work-up, the organic residue was chromatographed on silica gel with a gradient eluant of 15% ethyl acetate in hexanes (V/V) and with methanol in sequence. Fractions containing the desired compound were combined, and the solvents removed under reduced pressure to yield (S)-2 and (R)-4. An analytical sample was purified by bulb-to-bulb distillation. The materials were identical by 1H NMR spectroscopy with an authentic sample.

2-[N-(Ethylcarbonyl)amino]butyl acetate 4: mp 96-98°C; 1H NMR (CDCl3); δ 5.664 (br s, 1H), 4.05 (m, 3H), 2.07 (s, 3H), 1.94 (s, 3H), 1.50 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H); IR (CHCl3) (cm⁻¹) 3284, 1724, 1639, 1558.

2-[N-(Ethylcarbonyl)amino]propyl acetate 5: mp 40-45°C; 1H NMR (CDCl3); δ 5.76 (br s, 1H), 4.22 (m, 1H), 4.06 (dd, J = 11.1, 3.9 Hz, 1H), 3.96 (dd, J = 11.1, 5.9 Hz, 1H), 2.04 (s, 3H), 1.93 (s, 1H), 1.12 (d, J = 6.8 Hz, 3H); IR (CHCl3) (cm⁻¹) 3286, 1741, 1655, 1549.

The above acylates were treated with 6N NaOH at 70°C, respectively. Several extractions with methylene chloride, followed by vacuum distillation afforded the chiral 2-amino alcohols in ca. 80% yield.

**3. Results and Discussion**

Our approach to the synthesis of enantiomerically pure 2-amino-1-butanol 1 is outlined in Scheme 1. The acetylation was attempted for the N-protection of 2-amino-1-butanol 1, which was selectively acetylated by simple treatment of 1 with Ac₂O. We then conducted the PPL (porcine pancreatic lipase)-catalyzed transesterification of N-acetyl-2-amino-1-butanol 2 with vinyl acetate to obtain enantiomerically enriched product (R)-3 and the unreacted (S)-2 in very short reaction time. The reactions were carried out in tetrahydrofuran and vinyl acetate as the reaction medium with the powdered enzyme. Vinyl acetate appears to be efficiently used as an irreversible acylating reagent. The reaction was periodically monitored by GC in order to obtain optimal conversion, and was terminated by filtration of the reaction mixture. The enantiomeric excesses of 3 and 2 were obtained in 93% and 92% at conversion of 50% (Table 1). This shows that the R enantiomer of substrate 2 is much more reactive with PPL than its S counterpart. In contrast to the previous enzymatic transesterifications [11, 12], our method was at least 10~20 times faster under similar reaction condition. The reaction with *candida cylindracea* lipase was examined in a same manner. However, it did not give satisfactory reactivity.

![Scheme 1](image-url)

To obtain enantiomerically enriched (S)-2 and (R)-3 the reaction was stopped at ca. 46% and 60% conversion, respectively. After filtration of the reaction mixture and usual work-up, the organic residue was purified by column chromatography on silica gel and bulb-to-bulb distillation. The acylates (S)-2 and (R)-3 were hydrolysed in aqueous NaOH to yield the two chiral 2-amino-1-butanol (S)-1 and (R)-1 with ≥94% ee, respectively. The enantiomeric excesses and absolute configurations were based on comparison of the optical rotation with the value of optically pure authentic samples. 2-Amino-1-propanol as well as 2-amino-1-butanol was also chosen a model substrate for enzymatic resolution of amino alcohols. 2-Amino-1-propanol was also easily acetylated by the treatment with acetic anhydride to give N-acetyl-2-amino-1-propanol 4 in 85% yield. The kinetic resolution of the racemate
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Table 1. PPL-Catalyzed Transesterification of N-Acetyl-2-amino-1-butanol 2

<table>
<thead>
<tr>
<th>time (min)</th>
<th>conversion (%)</th>
<th>(+)-3</th>
<th>(-)-2</th>
</tr>
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<tbody>
<tr>
<td>30</td>
<td>30</td>
<td>40.2</td>
<td>96</td>
</tr>
<tr>
<td>50</td>
<td>46</td>
<td>39.4</td>
<td>94</td>
</tr>
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<td>55</td>
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<td>39.0</td>
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<td>60</td>
<td>53</td>
<td>37.7</td>
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</tr>
<tr>
<td>90</td>
<td>60</td>
<td>27.2</td>
<td>65</td>
</tr>
</tbody>
</table>

a) Based on starting material consumed, which was determined by GC analysis. Isolated yield was slightly lower than the conversion.
b) Determined on the basis of comparison of the optical rotations with the values of chemically synthesized optically pure authentic samples [(+)-2: \([\alpha]_{D}^{20} = -25.1\) (c = 1.0, EtOH), (+)-3: \([\alpha]_{D}^{20} = +41.9\) (c = 1.0, EtOH)].

4 was carried out through the same procedure. High reactivity and high enantioselectivity were still observed in the transesterification (Table 2). Both (R) form of diacetyl 5 and (S) form of monoacetyl 4 were \(\geq 94\%\) ee at 49% conversion.

![Chemical structure](attachment:image)

Table 2. PPL-Catalyzed Transesterification of N-Acetyl-2-amino-1-propanol 4

<table>
<thead>
<tr>
<th>time (min)</th>
<th>conversion (%)</th>
<th>(+)-5</th>
<th>(-)-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>35</td>
<td>36.9</td>
<td>96</td>
</tr>
<tr>
<td>40</td>
<td>49</td>
<td>36.1</td>
<td>94</td>
</tr>
<tr>
<td>65</td>
<td>60</td>
<td>25.7</td>
<td>67</td>
</tr>
</tbody>
</table>

a) The conversion refers to the amount of starting material consumed, which was determined by GC analysis.
b) Determined on the basis of comparison of the optical rotations with the values of chemically synthesized optically pure authentic samples [(+)-4: \([\alpha]_{D}^{20} = -19.2\) (c = 1.0, EtOH), (+)-5: \([\alpha]_{D}^{20} = +38.4\) (c = 1.0, EtOH)].

In conclusion, PPL-catalyzed transesterifications of N-acetyl-2-amino-1-butanol and N-acetyl-2-amino-1-propanol with vinyl acetate can be effectively used for the preparation of enantiomerically pure 2-amino-1-butanol and 2-amino-1-propanol, respectively. This result clearly indicates that the biocatalytic route can be efficiently used in the preparation of enantiorich 2-amino alcohols. We are continuing our investigation to expand the scope and synthetic application of this process.

Acknowledgment

We appreciate the financial support of this work by Ministry of Education (Biochem. Eng. C-06) in 1995.

References
