Synthesis of Hydrazides Through an Enzymatic Hydrazinolysis Reaction

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Amano PS lipase catalyzes the reaction of formic hydrazide, acetic hydrazide and methyl carbazate with various esters: $\alpha,\beta$-unsaturated hydrazides were obtained by using methyl acrylate or vinyl crotonate. The reaction with ethyl $(\pm)$-2-chloropropionate yields the corresponding hydrazide in good yield but with moderate enantiomeric excess.

The ability of lipases to catalyze acylation reactions in organic solvents has provided the synthetic chemist with an additional and very useful tool for the preparation of optically active compounds. This is clearly indicated by the increasing number of papers published in this field during the last years.¹

Lipase-catalyzed esterification and transesterification reactions have been widely applied to the resolution of racemic alcohols² and esters.³ Nevertheless, most of the reports of the studies involving nitrogen compounds as acyl-acceptors in lipase-catalyze acylation reactions have been limited to those of peptide synthesis.⁴ Recently, we have described the aminolysis of a racemic ester using Candida cylindracea lipase as catalyst; in these reactions, chiral amides from aliphatic or aromatic amines, were obtained.⁵ Aminolysis processes involving racemic amines⁶ and a double enantioselectivity with both racemic ester and amines⁷ have also been described.

Moreover, the lipases have a broader range of applications in organic synthesis. Because lipase-catalyzed reactions are carried out in mild conditions, they are of great use in the preparation of achiral compounds which are obtained by chemical methods in drastic conditions and, in most cases, impurified by byproducts.

In a preliminary communication,⁸ we have described that Amano PS lipase⁹ catalyzes the reaction between ethyl acetate and different hydrazines. The hydrazides 3a–c were obtained as a sole product in high yields.

In this paper it is shown that not only was ethyl acetate an adequate substrate in the hydrazinolysis reaction, but ethyl butyrate and unsaturated esters are also suitable for this kind of reaction. In these cases, hydrazines with electron-withdrawing groups and Amano PS lipase as catalyst were used because they led to the best results in the reaction with ethyl acetate. The results with ethyl butyrate (see Table) are close to those of the ethyl acetate. The highest yields of hydrazides 3 were obtained when the ester was used as solvent.

In the reactions involving $\alpha,\beta$-unsaturated esters and basic compounds, such as hydrazines, the corresponding Michael addition compounds, 6, should be the major products obtained. However, the lipase may catalyze the reaction of hydrazinolysis to yield the corresponding hydrazides 5.

We report herein that $\alpha,\beta$-unsaturated hydrazides are obtained when the reactions between methyl acrylate or vinyl crotonate and hydrazines are catalyzed by Amano PS lipase. If the enzyme is omitted, the Michael adduct is obtained in the case of methyl acrylate, and a complex mixture of compounds in the case of vinyl crotonate. From these results we can deduce that these esters are excellent substrates for the enzyme and the influence of the hydrazine on the catalytic activity of the lipase seems to be important because poor results were obtained when methyl acrylate was used as acylation reagent of amines in the presence of lipases.¹₀

Finally, we have studied the enantioselectivity of the hydrazinolysis reaction of ethyl $(\pm)$-2-chloropropionate using Amano PS lipase. The reactions were carried out in diisopropyl ether as solvent and the hydrazides 8 were obtained with good yields but moderated enantiomeric excess. The configuration was determined by analogy with the optically active hydrazide obtained from the (S)-$(\pm)$-ester and the corresponding hydrazine.
<table>
<thead>
<tr>
<th>Product</th>
<th>Reaction Time (d)*</th>
<th>Yield (%)</th>
<th>mp b (°C)</th>
<th>Molecular Formula</th>
<th>IR (Nujol)c (ν cm⁻¹)</th>
<th>¹H-NMR d δ</th>
<th>¹²C-NMR e δ</th>
<th>MS (70 eV)f m/z (%)</th>
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<tbody>
<tr>
<td>3a</td>
<td>2</td>
<td>90</td>
<td>72–74</td>
<td>C₆H₈N₂O₃</td>
<td>1650</td>
<td>2.1 (s, 3H), 3.7 (s, 3H), 7.7 (brs, 1H), 8.7 (brs, 1H) 20 (c), 53 (c), 157 (s), 170 (s) 132 (M⁺, 11), 90 (100), 43 (32)</td>
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<td></td>
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<tr>
<td>3b</td>
<td>2</td>
<td>60</td>
<td>74–76</td>
<td>C₆H₈N₂O₅</td>
<td>1660</td>
<td>2.1 (s, 3H), 8.1 (s, 1H), 9.2 (brs, 1H), 9.3 (brs, 1H) 20 (c), 159 (d), 168 (s) 102 (M⁺, 13), 60 (57), 43 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>2</td>
<td>78</td>
<td>137–139</td>
<td>C₆H₁₂N₂O₅</td>
<td>1657</td>
<td>2.1 (s, 6H), 8.9 (brs, 2H) 20 (c), 168 (s) 116 (M⁺, 8), 74 (54), 43 (100)</td>
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<tr>
<td>3d</td>
<td>3</td>
<td>95 (oil)</td>
<td></td>
<td>C₆H₁₂N₂O₅</td>
<td>1650</td>
<td>0.9 (t, 3H), 1.7 (m, 2H), 2.3 (t, 2H), 3.8 (s, 3H), 8.3 (brs, 1H), 9.2 (brs, 1H) 13 (c), 19 (t), 35 (t), 52 (c), 157 (s), 173 (s) 160 (M⁺, 9), 71 (50), 90 (100)</td>
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</tr>
<tr>
<td>3e</td>
<td>3</td>
<td>92</td>
<td>76–78</td>
<td>C₆H₁₂N₂O₅</td>
<td>1650</td>
<td>0.8 (t, 3H), 1.5 (s, 2H), 2.1 (t, 2H), 8.0 (s, 1H), 9.8 (brs, 2H) 14 (c), 19 (t), 35 (t), 159 (d), 171 (s) 130 (M⁺, 6), 71 (4), 60 (100)</td>
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<tr>
<td>3f</td>
<td>3</td>
<td>96</td>
<td>98–100</td>
<td>C₆H₁₂N₂O₅</td>
<td>1590</td>
<td>1.0 (t, 3H), 1.7 (c, 2H), 2.1 (s, 3H), 2.3 (t, 2H), 8.7 (brs, 1H), 8.9 (brs, 1H) 14 (c), 19 (t), 21 (t), 35.3 (c), 168 (s), 171 (s) 144 (M⁺, 9), 71 (8), 43 (100)</td>
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<tr>
<td>5a</td>
<td>1</td>
<td>87</td>
<td>92–94</td>
<td>C₆H₁₂N₂O₇</td>
<td>1672</td>
<td>3.8 (s, 2H), 5.8 (d, 1H), 6.2 (dd, 1H), 6.4 (dd, 1H), 7.4 (t, 2H), 8.4 (brs, 1H) 53 (t), 128 (d), 129 (s), 158 (s), 165 (s) 144 (M⁺, 12), 55 (100)</td>
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<tr>
<td>5b</td>
<td>4</td>
<td>57</td>
<td>97–99</td>
<td>C₆H₁₂N₂O₇</td>
<td>1683</td>
<td>5.7 (d, 1H), 6.2 (dd, 1H), 6.4 (d, 1H), 8.0 (s, 1H), 10.2 (brs, 1H) 127 (d), 129 (s), 159 (d), 163 (s) 114 (M⁺, 7), 55 (100)</td>
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<tr>
<td>5c</td>
<td>3</td>
<td>63</td>
<td>146–148</td>
<td>C₆H₈N₂O₂</td>
<td>1641</td>
<td>2.1 (s, 3H), 5.8 (d, 1H), 6.2 (dd, 1H), 6.4 (dd, 1H), 9.4 (brs, 2H) 21 (c), 127 (d), 130 (d), 164 (s), 168 (s) 128 (M⁺, 7), 55 (82), 43 (100)</td>
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<td></td>
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<tr>
<td>5d</td>
<td>3</td>
<td>46</td>
<td>131–133</td>
<td>C₆H₁₀N₂O₄</td>
<td>1681</td>
<td>1.9 (d, 3H), 3.8 (s, 3H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (brs, 1H), 8.0 (brs, 1H) 18 (t), 53 (t), 122 (d), 143 (d), 157 (s), 166 (s) 158 (M⁺, 8), 69 (100)</td>
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<td></td>
</tr>
<tr>
<td>5e</td>
<td>3</td>
<td>53</td>
<td>125–127</td>
<td>C₆H₈N₂O₂</td>
<td>1671</td>
<td>2.0 (d, 3H), 5.8 (d, 1H), 7.1 (m, 1H), 8.6 (s, 1H), 10.6 (brs, 1H) 18 (c), 123 (d), 140 (d), 159 (d), 163 (s) 128 (M⁺, 11), 69 (100)</td>
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<td></td>
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<tr>
<td>5f</td>
<td>3</td>
<td>58</td>
<td>176–178</td>
<td>C₆H₈N₂O₂</td>
<td>1655</td>
<td>1.8 (d, 3H), 1.9 (s, 3H), 5.9 (d, 1H), 6.8 (m, 1H), 9.8 (brs, 2H) 18 (c), 21 (c), 123 (d), 140 (d), 164 (s), 168 (s) 142 (M⁺, 4), 69 (100), 43 (99)</td>
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<td></td>
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<tr>
<td>8a</td>
<td>2</td>
<td>53</td>
<td>55–57</td>
<td>C₆H₈N₂O₄Cl</td>
<td>1680</td>
<td>1.7 (d, 2H), 3.8 (s, 3H), 4.5 (c, 1H), 7.2 (brs, 1H), 8.6 (brs, 1H) 22 (c), 52 (c), 157 (s), 170 (s) 180 (M⁺, 9), 90 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>3</td>
<td>51</td>
<td>92–94</td>
<td>C₆H₁₂N₄O₄Cl</td>
<td>1615</td>
<td>1.6 (d, 3H), 4.6 (c, 1H), 8.1 (s, 1H), 10.2 (brs, 1H), 10.5 (brs, 1H) 21 (c), 52 (d), 159 (d), 167 (s) 150 (M⁺, 4), 60 (100)</td>
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<td></td>
</tr>
<tr>
<td>8c</td>
<td>3</td>
<td>58</td>
<td>142–144</td>
<td>C₆H₁₂N₄O₄Cl</td>
<td>1620</td>
<td>1.8 (d, 3H), 2.1 (s, 3H), 4.5 (c, 1H), 8.6 (brs, 1H), 9.2 (brs, 1H) 21 (c), 22 (c), 53 (d), 166 (s), 167 (s) 164 (M⁺, 5), 122 (46), 43 (100)</td>
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</tbody>
</table>

a Reactions were carried out at 25°C.
b Uncorrected, measured with a Gallenkamp melting point apparatus.
c Recorded on a Perkin-Elmer 170-X Infrared Fourier transform spectrophotometer.
d Compounds 3a–3d, 3f, 5a, 5c–5e, 8a, 8c, were measured in CDCl₃/TMS and 3e, 5b, 5f, 8b, were measured in DMSO-d₆, at 300 MHz on a Bruker AC-300 spectrometer.
e Compounds 3a–d, 5a, 5d, 8a, 8c, were measured in CDCl₃ and 3e–f, 5b–c, 5e–f, 8b, were measured in DMSO-d₆, at 75.5 MHz on a Bruker AC-300 spectrometer.
f Recorded on a Hewlett-Packard 5897A spectrometer.
In conclusion, the strategy described here provides an easy method to obtain hydrazides which, we believe, is an improved synthetic method for acylation of hydrazines. The important applications of hydrazides in pharmaceutical field are noteworthy.

![Chemical structure](image)

$\text{N}^{\text{S}}\text{(-)-Formyl-2-chloropropionohydrazide (8b); Typical Procedure:}

Hydrazine 1b (0.3 g, 5 mmol) is added to a stirred solution of ethyl ($\pm$)-2-chloropropionate (1.36 mL, 10 mmol), $t$-Pr$_2$O (30 mL) and Amano PS lipase (2 g). The mixture is stirred for 3 d at 25 $^\circ$C; then it is filtered and solvents are evaporated under reduced pressure to give 8b after recrystallization; yield: 0.39 g (51%).

$8a: [\alpha]_D^{22} = 25.1\degree$ (c = 0.7, EtOH); ee 40%.

$8b: [\alpha]_D^{22} = 21.3\degree$ (c = 0.2, EtOH); ee 61%.

$8c: [\alpha]_D^{22} = 26.9\degree$ (c = 0.3, EtOH); ee 42%.

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(9) An improved method for the identification of enzymes developed by Amano Pharmaceutical Co. has shown that Amano P lipase from Pseudomonas fluorescens is now more similar to lipase from Pseudomonas cepacia. For this reason it is convenient to change the trade name to amano PS lipase.

(10) Unpublished results obtained in our laboratory.

<table>
<thead>
<tr>
<th>R¹</th>
<th>CO₂Me</th>
<th>CHO</th>
<th>COMe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 8</td>
<td>a</td>
<td>b</td>
<td>c</td>
</tr>
</tbody>
</table>

Ethyl ($\pm$)-2-chloropropionate, ethyl (S)-(−)-2-chloropropionate, formic hydrazide, methyl carbamate, hydrazine hydrate, vinyl crotonate and methyl acrylate were purchased from Aldrich Chemical Co. $t$-Pr$_2$O, ethyl butyrate and EtOAc were purchased from Merck. Reagent quality solvents were used without further purification. Observed rotations at the Na-D line were obtained at 22 $^\circ$C using a Perkin-Elmer 241 Polarimeter.

**N-Formylobutyrohydrazide (3e); Typical Procedure:**

Formic hydrazide (0.30 g, 5 mmol) is dissolved in ethyl butyrate (20 mL) and then Amano PS lipase (2 g) is added. After being stirred at r.t. for 3 d, the enzyme is filtered and the resulting solution is evaporated to give 3e after recrystallization in CHCl$_3$/hexane or CHCl$_3$/CCl$_4$; yield: 0.6 g (92%).

**Acrylohydrazides 5a–c and Crotonohydrazides 5d–f; General Procedures:**

Method A: Hydrazine 1a–e (2.5 mmol) is dissolved in methyl acrylate (10 mL) and then Amano PS lipase (1 g) is added. After stirring at r.t. in absence of light for 1–4 d, IR showed that the reaction is complete, and then the enzyme is filtered. Solvent is evaporated in vacuo and products 5a–c are obtained after recrystallization in CHCl$_3$/CCl$_4$.

Method B: In a dried, nitrogen-filled round bottom flask protected from light and fitted with stirrer, hydrazine 1d–f (2.5 mmol) is added over a stirred mixture of vinyl crotonate (0.9 mL, 7.5 mmol), Amano PS lipase (1 g) and $t$-Pr$_2$O (30 mL) at 25 $^\circ$C. The mixture is stirred for 3 d and then filtered when IR shows that the reaction is complete. Solvent is evaporated and products 5d–f are obtained after recrystallization in CHCl$_3$/CCl$_4$. 

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