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Lipase Catalyzed Aminolysis of Ethyl Propiolate and Acrylic Esters. Synthesis of Chiral Acrylamides

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Key Words: aminolysis; lipase; enantioselectivity; propiolamides; acrylamides.

Abstract: *Candida cylindracea lipase is a useful catalyst for the preparation of propiolamides. Candida antarctica lipase efficiently catalyzes the aminolysis of different acrylic esters and aliphatic amines; if racemic amines are used, the corresponding optically active acrylic amide is obtained in moderate-high enantiomeric excess.*

INTRODUCTION

Amidases such as carboxypeptidases, *N*-acylases, and acid proteases have been the most commonly used enzymes to catalyze amidation reactions[1] in both organic and aqueous media. Although at first these enzymes were only used for the resolution of α-aminoacids and in the peptide synthesis, Klibanov and co-workers.[2] have reported that subtilisin can catalyze the enantioselective amidation of simple racemic amines using 3-methyl-3-pentanol as solvent and 2,2,2-trifluoroethyl butyrate as acyl donor. Recently, this method has been applied to the continuous production of (*R*)-1-aminoindane and (*R*)-1-(1-naphthyl)ethylamine[3].

The use of lipases in the amidation reaction arose from the need to overcome certain shortcomings of amidases as catalysts for peptide synthesis in organic solvents, namely, narrow substrate specificity and undesirable proteolysis activity[4]. Lipases are active in a great variety of organic solvents and, in contrast to

amidases, have a broad substrate specificity and do not catalyze the secondary hydrolysis of the amide bond.

However, whilst there is a wealth of literature governing the use of lipases in esterification and transesterification reactions[5-7], the use of these enzymes in amidation reactions is less well documented. The synthesis of peptides from conveniently protected D or L aminoacids has been investigated using porcine pancreatic and *Candida cylindracea* lipases as catalysts[8,9]. In addition, we have shown that some lipases exhibit their enantioselective properties in the amidation of racemic esters such as ethyl (±)-2-chloropropionate and 2-methylbutyrate[10], and recently this methodology has been used for the preparation of lactams[11].

In this paper we investigate the catalytic potential of some lipases in the amidation of unsaturated esters. Some amides derived from propiolic acid have proven activity as bactericides[12]. Furthermore, α,β-unsaturated amides can be used in the synthesis of polymeric material.

RESULTS AND DISCUSSION

In a preliminary communication[13], we reported that *Candida cylindracea* lipase (CCL) is a useful catalyst in the amidation reaction of ethyl propiolate. The enzymatic reaction was faster than the competitive Michael addition when aromatic amines were used, and the corresponding propiolamides were obtained in very satisfactory yields (Table I). However, when aliphatic amines were used, the only compounds isolated were the Michael adducts even when the reaction was performed at low temperature.

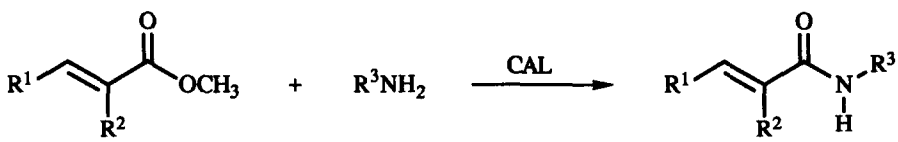
$$\underset{\mathbf{1}}{H-C\equiv C-CO_2Et} + \underset{\mathbf{2}}{ArNH_2} \xrightarrow{CCL} \underset{\mathbf{3}}{H-C\equiv C-CONHAr}$$

Table I. Amidation reaction of ethyl propiolate with amines (2)

Entry	Ar	t, h	T, °C	Yield, %
3a	C_6H_5	96	25	80
3b	*p*-CH_3O-C_6H_4	72	25	85
3c	*p*-CH_3-C_6H_4	96	25	82
3d	*p*-Cl-C_6H_4	96	60	60

We checked the catalytic potential of CCL in the amidation of other α,β-unsaturated esters such as acrylic esters. The enzyme did not show any catalytic activity towards these substrates when both aromatic and

aliphatic amines were used; in all cases the starting materials or the corresponding Michael adducts were isolated. Other lipases such as porcine pancreatic and *Pseudomonas cepacia* led to similar results. However, *Candida antarctica* lipase (CAL), which has proved to be an efficient catalyst in the amidation reaction[14], satisfactorily catalyzed the formation of acrylic amides with different acrylic esters and aliphatic amines. Of the different amines tested, the best results were obtained with *n*-butylamine and benzylamine; with allylamine and isopropylamine, the corresponding acrylic amide was detected in the ^{1}H-NMR spectrum of the reaction mixture but could not be isolated, the major compound being the Michael adduct. With respect to the solvent, we tried the amidation reaction in tetrahydrofuran, hexane and diisopropylether, and the best results were those shown in Table II.



4 **5** **6**

Table II. Amidation reaction of methyl acrylic esters (**4**) with amines (**5**)

Entry	R^1	R^2	R^3	Solvent	t, days	T, °C	Yield, %
6a	H	H	C_4H_9	THF	4	30	45
6b	H	H	C_6H_5-CH_2	THF	7	30	53
6c	CH_3	H	C_4H_9	THF	3	30	60
6d	CH_3	H	C_6H_5-CH_2	hexane	3	60	88
6e	H	CH_3	C_4H_9	*i*-Pr_2O	6	30	81
6f	H	CH_3	C_6H_5-CH_2	hexane	3	60	40

The synthesis of optically active acrylic amides is a significant operation in organic chemistry because these compounds can be used for the preparation of optically active polymers. For this reason, and taking into account the efficiency of CAL as a catalyst in the amidation of acrylic esters, we have investigated the amidation of acrylic esters with racemic amines. For these reactions, the best solvent was tetrahydrofuran, and the optimal reaction conditions are those indicated in Table III. As is shown in Table III, CAL preferably catalyzes the amidation with the (*R*)-enantiomer of the amine and the corresponding amide is obtained in good yield and in moderate to high enantiomeric excess. The configuration of these acrylic amides was determined by analogy with the optically active amide obtained from (*R*)-(-)-1-methylpropylamine or (*R*)-(-)-1-methylhexylamine and the corresponding acrylic ester using CAL as catalyst. The ee of amides **8a**, **8c** and **8e** was calculated by ^{1}H-NMR

spectroscopy using the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium (III). For amides **8b**, **8d** and **8f**, the ee was calculated by comparison of the optical rotation with that obtained for an authentic sample.

(±)-7 **8**

Table III. Amidation reaction of methyl acrylic esters (4) with racemic amines (7)

Entry	R^1	R^2	R^4	t, days	T, °C	Yield, %	ee, %
8a	H	H	C_2H_5	7	30	25	72
8b	H	H	C_5H_{11}	7	30	20	95
8c	CH_3	H	C_2H_5	7	30	30	72
8d	CH_3	H	C_5H_{11}	7	30	40	74
8e	H	CH_3	C_2H_5	11	30	27	95
8f	H	CH_3	C_5H_{11}	11	30	22	95

If we compare the enantioselectivity achieved in this process with the results obtained by Klibanov[2], CAL exhibits a high selectivity towards the R isomer of the amine whilst subtilisin is highly selective towards the S isomer of 2-aminobutane and 2-aminoheptane in the esterification reaction with 2,2,2-trifluoroethyl butyrate.

CONCLUSION

In the present work we describe a very easy procedure for the preparation of some propiolamides and acrylic amides. *Candida antarctica* lipase is an efficient catalyst for the preparation of chiral acrylic amides. The importance of the compounds obtained in certain areas of industrial interest is noteworthy.

EXPERIMENTAL

Candida cylindracea lipase, Type VII crude, was purchased from Sigma Chemical Co. *Candida antarctica* lipase (SP 435 A) was obtained from Novo Nordisk Co. All reagents were of commercial quality and

were purchased from Aldrich Chemie. Solvents were distilled over a suitable desiccant and stored under argon. For column chromatography, Merck silica gel 60/230-400 mesh was used. Melting points were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 170-X Infrared Fourier transform spectrophotometer. ^{1}H- and ^{13}C-NMR were obtained with TMS (tetramethylsilane) as internal standard, using a Bruker AC-300 (^{1}H- 300 MHz and ^{13}C- 75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 5897 A spectrometer. All the new compounds gave satisfactory elemental analysis and were performed by Microanalyses Perkin-Elmer 240.

***Candida cylindracea* lipase catalyzed aminolysis of ethyl propiolate.**

To a solution of 5 mmol of ethyl propiolate (**1**) and 4 mmol of the corresponding amine (**2**) in 25 mL of tetrachloromethane was added CCL (4 g). The suspension was stirred at 25°C or 60°C. Reaction was terminated by removal of the enzyme by filtration. Organic solvent was evaporated under reduced pressure to give amide (**3**) after recrystallization in hexane/CCl_4.

***N*-Phenylpropiolamide (3a)**: mp 81-83°C; IR (KBr) ν_{max}: 2110 (C≡C) and 1635 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.94 (s, 1H, CH), 7.10-7.50 (m, 5H, aromatic), 7.60 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 74.16 (CH), 77.46 (C), 120.03 (CH), 125.09 (CH), 128.99 (CH), 136.88 (C), 149.81 (C=O); MS m/z: 145 (M+, 95), 117 (100).

***N*-*p*-Methoxyphenylpropiolamide (3b)**: mp 96-98°C; IR (KBr) ν_{max}: 2110 (C≡C) and 1650 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.95 (s, 1H, CH), 3.80 (s, 3H, CH_3), 7.45-6.80 (m, 4H, aromatic), 7.60 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 55.28 (CH_3), 74.21 (C), 77.47 (CH), 113.95 (CH), 121.88 (CH), 130.06 (C), 149.94 (C), 156.67 (C=O); MS m/z: 175 (M+, 80), 122 (100).

***N*-*p*-Tolylpropiolamide (3c)**: mp 126-128°C; IR (KBr) ν_{max}: 2100 (C≡C) and 1640 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H, CH_3), 2.95 (s, 1H, CH), 7.10-7.40 (m, 4H, aromatic), 7.60 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.82 (CH_3), 73.97 (C), 77.56 (CH), 120.07 (CH), 129.46 (CH), 134.35 (C), 134.82 (C), 149.73 (C=O); MS m/z: 159 (M+, 82), 130 (100).

***N*-*p*-Chlorophenylpropiolamide (3d)**: mp 172-174°C; IR (KBr) ν_{max}: 2100 (C≡C) and 1640 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.00 (s, 1H, CH), 7.20-7.50 (m, 4H, aromatic), 7.60 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 74.39 (C), 77.36 (CH), 121.12 (CH), 129.15 (CH), 135.36 (C), 149.50 (C), 159.50 (C=O); MS m/z: 181 [(M+2)+, 33], 179 (M+, 100).

***Candida antarctica* lipase catalyzed amidation of acrylic esters (4) with amines (5).**

To a solution of 2 mmol of acrylic ester (**4**) and 2 mmol of amine (**5**) in 15 mL of solvent, CAL (100

mg) was added. When the reaction was terminated, the enzyme was removed by filtration and the solvent evaporated. The residue was dissolved in dichloromethane and washed with 3N HCl and distilled water. The evaporation of the dichloromethane yielded the corresponding amide.

***N*-Butylacrylamide (6a)**: oil; IR (neat) ν_{max}: 3261 (NH) and 1626 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (t, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 3.34 (q, 2H, CH_2), 5.62 (dd, 1H, =CH), 6.01 (bs, 1H, NH), 6.14 (dd, 1H, =C*H*H), 6.28 (dd, 1H, =CH*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.67 (CH_3), 20.00 (CH_2), 31.50 (CH_2), 39.24 (CH_2), 125.95 (CH_2), 130.95 (CH), 165.60 (C=O); MS m/z: 127 (M^+, 4), 55 (100).

***N*-Benzylacrylamide (6b)**: mp 57-59°C; IR (KBr) ν_{max}: 3287 (NH) and 1653 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.53 (d, 2H, CH_2), 5.68 (dd, 1H, =CH), 5.93 (bs, 1H, NH), 6.14 (dd, 1H, =C*H*H), 6.34 (dd, 1H, =CH*H*), 7.15-7.46 (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ (ppm): 43.49 (CH_2), 126.57 (CH_2), 127.38 (CH), 127.71 (CH), 128.55 (CH), 130.52 (CH), 137.90 (C), 165.34 (C=O); MS m/z: 161 (M^+, 100).

***N*-Butylcrotonamide (6c)**: oil; IR (neat) ν_{max}: 3291 (NH) and 1672 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (t, 3H, CH_3), 1.15-1.63 (m, 4H, CH_2), 1.85 (dd, 3H, CH_3), 3.28 (q, 2H, CH_2), 5.90 (dd, 1H, =CH), 6.53 (bs, 1H, NH), 6.83 (m, 1H, =CH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.50 (CH_3), 17.40 (CH_3), 19.85 (CH_2), 31.43 (CH_2), 38.98 (CH_2), 125.07 (CH), 139.01 (CH), 166.00 (C=O); MS m/z: 141 (M^+, 2), 69 (100).

***N*-Benzylcrotonamide (6d)**: mp 113-115°C; IR (KBr) ν_{max}: 3266 (NH) and 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.80 (dd, 3H, CH_3), 4.45 (d, 2H, CH_2), 5.70-5.95 (dd, 1H, =CH, and bs, 1H, NH), 6.84 (m, 1H, =CH), 7.15-7.38 (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ (ppm): 17.44 (CH_3), 43.02 (CH_2), 124.72 (CH), 126.95 (CH), 127.36 (CH), 128.23 (CH), 138.17 (C), 139.63 (CH), 165.88 (C=O); MS m/z: 175 (M^+, 30), 160 (100).

***N*-Butylmethacrylamide (6e)**: oil; IR (neat) ν_{max}: 3325 (NH) and 1657 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.97 (t, 3H, CH_3), 1.25-1.70 (m, 4H, CH_2), 1.98 (dd, 3H, CH_3), 3.31 (q, 2H, CH_2), 5.30 (m, 1H, =C*H*H), 5.68 (m, 1H, =CH*H*), 5.91 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.51 (CH_3), 18.45 (CH_3), 19.84 (CH_2), 31.37 (CH_2), 39.13 (CH_2), 118.89 (CH_2), 139.95 (C), 168.10 (C=O); MS m/z: 141 (M^+, 3), 39 (100).

***N*-Benzylmethacrylamide (6f)**: mp 73-75°C; IR (KBr) ν_{max}: 3295 (NH) and 1653 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.99 (dd, 3H, CH_3), 4.46 (d, 2H, CH_2), 5.35 (m, 1H, =C*H*H), 5.72 (m, 1H, =CH*H*), 6.10 (bs, 1H, NH), 7.20-7.45 (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ (ppm): 18.59 (CH_3), 43.64

(CH_2), 119.61 (CH_2), 127.45 (CH), 127.73 (CH), 128.62 (CH), 138.03 (C), 139.73 (C), 168.09 (C=O); MS m/z: 175 (M^+, 29), 39 (100).

***Candida antarctica* lipase catalyzed amidation of acrylic esters (4) with racemic amines (7).**

To a solution of 5 mmol of acrylic ester (4) and 5 mmol of amine (7) in 25 mL of tetrahydrofuran, CAL (250 mg) was added. When the reaction was terminated, the enzyme was removed by filtration and the solvent evaporated. The residue was subjected to flash chromatography on silica using hexane-ethyl acetate 2:1 as eluent.

(*R*)-(-)-*N*-(1-Methylpropyl)acrylamide (8a): oil; $[\alpha]_D^{25}$ -9.3 (c 0.79, chloroform), ee 72%; IR (neat) ν_{max}: 3279 (NH) and 1659 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.84 (t, 3H, CH_3), 1.09 (d, 3H, CH_3), 1.43 (m, 2H, CH_2), 3.93 (m, 1H, CH), 5.34 (bs, 1H, NH), 5.56 (dd, 1H, =CH), 5.99 (dd, 1H, =C*H*H), 6.22 (dd, 1H, =CH*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.23 (CH_3), 20.20 (CH_3), 29.46 (CH_2), 46.51 (CH), 125.83 (CH_2), 131.06 (CH), 164.82 (C=O); MS m/z: 127 (M^+, 8), 98 (100).

(*R*)-(+)-*N*-(1-Methylhexyl)acrylamide (8b): mp 46-48°C; $[\alpha]_D^{25}$ +11.5 (c 1.09, chloroform), ee 95%; IR (KBr) ν_{max}: 3293 (NH) and 1659 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (t, 3H, CH_3), 1.17 (d, 3H, CH_3), 1.22-1.55 (m, 8H, CH_2), 4.06 (m, 1H, CH), 5.37 (bs, 1H, NH), 5.63 (dd, 1H, =CH), 6.07 (dd, 1H, =C*H*H), 6.29 (dd, 1H, =CH*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.84 (CH_3), 20.71 (CH_3), 22.37 (CH_2), 25.55 (CH_2), 31.50 (CH_2), 36.67 (CH_2), 45.14 (CH), 125.72 (CH_2), 131.11 (CH), 164.64 (C=O); MS m/z: 169 (M^+, 2), 98 (100).

(*R*)-(-)-*N*-(1-Methylpropyl)crotonamide (8c): mp 84-86°C; $[\alpha]_D^{25}$ -14.0 (c 1.06, chloroform), ee 72%; IR (KBr) ν_{max}: 3233 (NH) and 1669 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (t, 3H, CH_3), 1.16 (d, 3H, CH_3), 1.49 (m, 2H, CH_2), 1.86 (dd, 3H, CH_3), 3.98 (m, 1H, CH), 5.42 (bs, 1H, NH), 5.79 (dd, 1H, =CH), 6.83 (m, 1H, =CH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.19 (CH_3), 17.50 (CH_3), 20.36 (CH_3), 29.59 (CH_2), 46.29 (CH), 125.19 (CH), 139.35 (CH), 165.10 (C=O); MS m/z: 141 (M^+, 5), 69 (100).

(*R*)-(+)-*N*-(1-Methylhexyl)crotonamide (8d): mp 58-60°C; $[\alpha]_D^{25}$ +2.9 (c 1.22, chloroform), ee 74%; IR (KBr) ν_{max}: 3289 (NH) and 1672 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (t, 3H, CH_3), 1.12 (d, 3H, CH_3), 1.20-1.50 (m, 8H, CH_2), 1.85 (dd, 3H, CH_3), 4.02 (m, 1H, CH), 5.47 (bs, 1H, NH), 5.82 (dd, 1H, =CH), 6.83 (m, 1H, =CH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.74 (CH_3), 17.34 (CH_3), 20.67 (CH_3), 22.29 (CH_2), 25.49 (CH_2), 31.46 (CH_2), 36.61 (CH_2), 44.81 (CH), 125.33 (CH), 138.77 (CH), 165.09 (C=O); MS m/z: 183 (M^+, 4), 69 (100).

(*R*)-(-)-*N*-(1-Methylpropyl)methacrylamide (8e): mp 56-58°C; $[\alpha]_D^{25}$ -19.8 (c 0.96, chloroform), ee 95%; IR (KBr) ν_{max}: 3293 (NH) and 1653 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.91 (t,

3H, CH_3), 1.15 (d, 3H, CH_3), 1.50 (m, 2H, CH_2), 1.95 (dd, 3H, CH_3), 3.96 (m, 1H, CH), 5.29 (m, 1H, =C*H*H), 5.43-5.71 (bs, 1H, NH and m, 1H, =CH*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.31 (CH_3), 18.69 (CH_3), 20.36 (CH_3), 29.64 (CH_2), 46.58 (CH), 118.86 (CH_2), 140.45 (C), 167.86 (C=O); MS m/z: 141 (M^+, 8), 69 (100).

(*R*)-(-)-*N*-(1-Methylhexyl)methacrylamide (8f): mp 51-53°C; $[\alpha]_D^{25}$ -6.8 (c 1.13, chloroform), ee 95%; IR (KBr) ν_{max}: 3298 (NH) and 1653 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (t, 3H, CH_3), 1.15 (d, 3H, CH_3), 1.21-1.54 (m, 8H, CH_2), 1.97 (dd, 3H, CH_3), 4.01 (m, 1H, CH), 5.31 (m, 1H, =C*H*H), 5.52 (bs, 1H, NH), 5.67 (m, 1H, =CH*H*); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.83 (CH_3), 18.56 (CH_3), 20.71 (CH_3), 22.37 (CH_2), 25.54 (CH_2), 31.49 (CH_2), 36.70 (CH_2), 45.11 (CH), 118.70 (CH_2), 140.30 (C), 167.59 (C=O); MS m/z: 183 (M^+, 5), 112 (100), 69 (98).

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