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Lipase-Catalyzed Aminolysis and Ammonolysis of β-ketoesters. Synthesis of Optically Active β-ketoamides.

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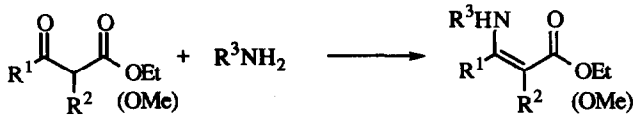
Abstract: *Aminolysis and ammonolysis reactions of β-ketoesters catalyzed by* Candida antarctica *lipase are very efficient methods for the preparation of β-ketoamides. When racemic amines are used in these processes, the corresponding optically active β-ketoamides are obtained with moderate-high enantiomeric excesses.*

INTRODUCTION

β-Ketoamides are highly versatile intermediates in organic synthesis,[1] and for this reason it is always of current interest to find new and simple procedures for the preparation of these compounds. Several methods to achieve 3-oxoamides have been put forth. In general these processes involve specific reactions and low yields are achieved[2] in many cases.

Chemoselective transformations of difunctional compounds is a critical problem in organic synthesis. Thus, when β-ketoesters (**1**), react with primary amines (**2**) at room temperature, enaminoesters (**3**) are mainly formed (Scheme I), and only in a few cases the selective preparation of the corresponding β-ketoamide is achieved. For instance, by using dimethylaminopyridine as catalyst it is possible to prepare 3-oxoamides if secondary amines are used as starting materials.[3] In other cases, the aminolysis of β-ketoesters requires high temperatures and long reaction times and often low yields of β-ketoamides are obtained due to the competitive enaminoester formation.[4] An interesting alternative is the room temperature aminolysis of the β-ketothioester derivatives,[5] but these substrates are not so readily available.[6]

Scheme I



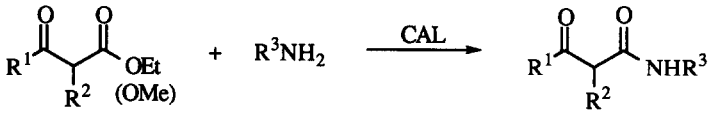
(1) **(2)** **(3)**

In recent years, our group has been investigating the potentiality of lipases to catalyze aminolysis reactions in organic media.[7] In our work, we have shown the usefulness of this kind of process for the preparation of a great variety of amides.[8] Taking into account the efficiency and mildness of these biocatalytic reactions, we thought it would be of interest to try the chemoselective enzymatic aminolysis of β-ketoesters.

In a preliminary communcation,[9] we described the synthesis of some β-ketoamides using *Candida antarctica* lipase (CAL) as catalyst. This lipase has also shown a very high catalytic efficiency in the ammonolysis of β-ketoesters. In this paper we have applied the aminolysis and ammonolysis processes to other β-ketoesters. Furthermore, the enantioselective properties of CAL when racemic amines are used as nucleophiles have been investigated.

RESULTS AND DISCUSSION

In order to widen the utility of CAL in the enzymatic aminolysis reactions, we have investigated the amidation of different β-ketoesters **1** with various different sized primary aliphatic amines and ammonia (**2**) (Table I). All the reactions of aminolysis have been carried out at room temperature using dioxane as the solvent and with a molar 1:1 ratio ester-amine. The ammonolysis reactions were performed using a 2% solution of ammonium in dioxane as reagent and solvent (see details in experimental part).



1 **2** **4**

Table I. Amidation reactions of β-ketoesters (**1**) with different amines and ammonia (**2**).

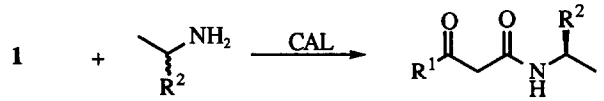
Entry	R^1	R^2	R^3	t(h)	yield(%)
4a	Me	H	Bu	16	90
4b	Me	H	$PhCH_2$	18	89
4c	Me	H	Allyl	16	91
4d	Me	H	H	24	59
4e	Et	H	Bu	24	98
4f	Et	H	Dodecyl	17	98
4g	Ph	H	Bu	36	96
4h	Ph	H	Allyl	22	98
4i	Ph	H	$PhCH_2$	93	73
4j	Ph	H	H	68	92
4k	Me	Me	Bu	144	41
4l	Me	Me	$PhCH_2$	144	42
4m	$-(CH_2)_3-$		Bu	48	81
4n	$-(CH_2)_3-$		$PhCH_2$	48	88
4p	$-(CH_2)_3-$		H	15	90

From the results collected in Table I, one can see that in most cases the yields are very high. However, the substrate has a strong influence on the catalytic activity of the CAL. For instance, if the reaction of benzylamine with ethyl 3-oxobutyrate (Entry **4b**) is compared to the analogue with ethyl 3-oxo-3-phenylpropionate (Entry **4i**), the decrease of the rate of reaction is noticeable. In addition, the poorer results were obtained with ethyl 2-methyl-3-oxobutyrate (entries **4k** and **4l**).

When the aminolysis reaction was investigated in the absence of the enzyme, the corresponding enaminoester **3** was obtained. Neverthleless, in these reaction conditions, with ethyl 3-oxo-3-phenylpropionate a small amount of the corresponding β-ketoamide was isolated too: **4f**(5%), **4g**(9%) and **4h**(6%). It noteworthy that enaminoesters **3** were not adequate substrates for the enzymatic amidation reaction because, when **3** was treated with an excess of amine in the presence of the enzyme, not reaction took place.

In the earlier communication,[9] we indicated that ammonium is an efficient nucleophile in the enzymatic reaction of β-ketoesters in organic media, this being the first reported example of an enzymatic ammonolysis reaction. Recently, this process has been applied for the resolution of some aryl esters.[10] In our case the corresponding *N*-unsubstituted β-ketoamides were obtained with high yields.

We checked the enantioselectivity of the CAL in the aminolysis of β-ketoesters with racemic amines. We have investigated the aminolysis of ethyl 3-oxobutyrate and 3-oxo-3-phenylpropionate with different racemic amines. These reactions are carried out in the same conditions as for the former cases and the results are collected in Table II. As it is shown in this Table, CAL catalyzes the amidation with the (*R*)-enantiomer of the amine obtaining the corresponding β-ketoamide with high enantiomeric excess in most cases. The configuration and ee of these β-ketoamides were determined by comparison of the optical rotation with that obtained from the appropriate optically active amine and the corresponding ester in the presence of the enzyme.



(±)-**5** **6**

Table II. Amidation reaction of β-ketoesters (**1**) with racemic amines (**5**).

Entry	R^1	R^2	t(h)	Conv.(%)[a]	$[\alpha]_D^{22}$(c)[b]	e.e.(%)
6a	CH_3	C_2H_5	0.75	46	-13.8 (0.92)	56
6b	CH_3	C_5H_{11}	0.25	38	-2.1 (1.33)	>98
6c	CH_3	Ph	9	43	+80.6 (0.64)	>98
6d	Ph	C_2H_5	65	25	-8.9 (1.60)	54
6f	Ph	C_5H_{11}	69	20	-4.4 (0.53)	93
6g	Ph	Ph	148	18	+46.4 (0.87)	>97

[a] Calculated with respect to the β-ketoesters **1**.

[b] In chloroform.

CONCLUSION

In the present work we have developed a very simple, practical and mild procedure for the preparation of β-ketoamides by the direct aminolysis and ammonolysis of β-ketoesters. The present method also allows the synthesis of optically active β-ketoamides with moderate to high enantiomeric excesses and yields.

EXPERIMENTAL

We used an immobilized lipase from *Candida antarctica* SP 435A (CAL) (gifted by Novo Nordisk). All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over a suitable desiccant and stored under nitrogen. 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 242 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.

General Procedure for the Enzymatic Aminolysis of β-ketoesters. 2.5 mmol of ester and 2.5 mmol of amine were added to a suspension of CA lipase (300 mg) in dioxane (20 ml) under nitrogen atmosphere. The mixture was shaken at 30°C and 250 rpm during the time indicated in the Tables. Then, the enzyme was filtered, washed with dichloromethane and the organic solvents were evaporated. If necessary, the residue was subjected to column chromatography using hexane-ethyl acetate 2:1 as eluent.

***N*-Butyl-3-oxobutyramide (4a)**: mp 38-39°C; IR (nujol) 1722, 1645 cm^{-1}; ^{1}H-NMR δ (ppm): 7.15 (bs, 1H, NH), 3.43 (s, 2H, CH_2), 3.21 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.71-1.22 (m, 4H, $2CH_2$), 0.85 (t,3H, CH_3); ^{13}C NMR δ (ppm): 203.46 (C=O), 165.70 (C=O), 50.01 (CH_2), 38.69 (CH_2), 30.76 (CH_2), 29.82 (CH_3), 19.41 (CH_2), 13.10 (CH_3); MS (70 eV) *m/z* 157 (M^+, 19), 43 (100).

***N*-Benzyl-3-oxobutyramide (4b)**: mp 101-102°C; IR (nujol) 1714, 1643 cm^{-1}; ^{1}H-NMR δ (ppm): 7.50-7.20 (m, 6H, Ph, NH), 4.43 (d, 2H, CH_2), 3.40 (s, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 203.95 (C=O), 165.64 (C=O), 137.65 ($C_{aromatic}$), 128.28, 127.26, 127.05 ($CH_{aromatic}$) 49.51 (CH_2), 43.02 (CH_2), 30.39 (CH_3); MS (70 eV) *m/z* 191 (M^+, 3), 106 (100).

***N*-Allyl-3-oxobutyramide (4c)**: oil; IR (neat) 1721, 1645 cm^{-1}; ^{1}H-NMR δ (ppm): 7.20 (bs, 1H, NH), 5.95-5.76 (m, 1H, CH=), 5.30-5.12 (m, 2H, $=CH_2$), 3.92 (m, 2H, CH_2), 3.46 (s, 2H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 203.60 (C=O), 165.74 (C=O), 133.34 (CH), 115.57 (CH_2),49.85 (CH_2), 41.32 (CH_2), 30.13 (CH_3); MS (70 eV) *m/z* 141 (M^+, 5), 56 (100).

***N*-Butyl-3-oxovaleramide (4e)**: mp 58-59°C; IR (nujol) 1709, 1643 cm^{-1}; ^{1}H-NMR δ (ppm): 7.10 (bs, 1H, NH), 3.41 (s, 2H, CH_2), 3.25 (m, 2H, CH_2), 2.59 (q, 2H, CH_2), 1.60-1.26 (m, 4H, $2CH_2$), 1.20 (t, 3H, CH_3), 0.92 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 206.26 (C=O), 165.74 (C=O), 48.89 (CH_2), 38.76 (CH_2), 36.05 (CH_2), 30.86 (CH_2), 19.51 (CH_2), 13.17 (CH_3), 6.86 (CH_3); MS (70 eV) *m/z* 171 (M^+, 15), 43 (100).

***N*-Dodecyl-3-oxovaleramide (4f)**: mp 87-88°C; IR (nujol) 1715, 1640 cm^{-1}; ^{1}H-NMR δ (ppm): 7.16 (bs, 1H, NH), 3.40 (s, 2H, CH_2), 3.25 (m, 2H, CH_2), 2.58 (q, 2H, CH_2), 1.70-1.19 (m, 18H, $9CH_2$), 1.09 (t, 3H, CH_3), 0.90 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 207.47 (C=O), 165.23 (C=O), 48.30 (CH_2), 39.33 (CH_2), 36.93 (CH_2), 31.66 (CH_2), 29.38 (CH_2), 29.34 (CH_2), 29.28 (CH_2), 29.10 (CH_2), 29.02 (CH_2), 26.66 (CH_2), 22.44 (CH_2),13.88 (CH_3), 7.15 (CH_3); MS (70 eV) *m/z* 283 (M^+, 44),129 (100).

***N*-Butyl-3-oxo-3-phenylpropionamide (4g)**: oil; IR (neat) 1691, 1651 cm^{-1}; ^{1}H-NMR δ (ppm): 8.05-7.11 (m, 6H, Ph, NH), 3.95 (s, 2H, CH_2), 3.29 (q, 2H, CH_2), 1.62-1.20 (m, 4H, $2CH_2$), 0.88 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 195.64 (C=O), 165.63 (C=O), 135.76 ($C_{aromatic}$), 133.60, 128.43, 128.17, 125.24 ($CH_{aromatics}$), 45.18 (CH_2), 39.05 (CH_2), 31.33 (CH_2), 19.68 (CH_2), 13.37 (CH_3); MS (70 eV) *m/z* 219 (M^+, 9), 105(100).

***N*-Allyl-3-oxo-3-phenylpropionamide (4h)**: mp 59-60 °C; IR (nujol) 1686, 1624 cm^{-1}; ^{1}H-NMR δ (ppm): 8.05-7.26 (m, 6H, Ph, NH), 5.95-5.77 (m, 1H, CH=), 5.30-5.10 (m, 2H, $=CH_2$), 3.96 (s, 2H, CH_2), 3.93 (m,2H, CH_2); ^{13}C NMR δ (ppm): 195.23 (C=O), 165.75 (C=O), 135.69 ($C_{aromatic}$), 133.82, 133.53, 133.39, 128.37, 128.10, 127.96, 125.27 ($CH_{aromatics}$, CH), 115.79 (CH_2), 45.24 (CH_2), 41.53 (CH_2); MS (70 eV) *m/z* 203(M^+, 17), 105 (100).

***N*-Benzyl-3-oxo-3-phenylpropionamide (4i)**: mp 88-89°C; IR (nujol) 1693, 1645 cm^{-1}; ^{1}H-NMR δ (ppm): 8.00 (d, 1H, NH), 7.80-7.17 (m, 10H, 2Ph), 4.49 (d, 2H, CH_2), 3.97 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 195.14 (C=O), 165.96 (C=O), 137.61, 135.68 ($C_{aromatics}$), 133.50, 128.19, 128.11, 127.17, 126.94, 125.31 ($CH_{aromatics}$), 45.24 (CH_2), 43.09 (CH_2); MS (70 eV) *m/z* 253 (M^+, 34), 106 (100).

***N*-Butyl-2-methyl-3-oxobutyramide (4k)**: oil; IR (neat) 1724, 1651 cm^{-1}; ^{1}H-NMR δ (ppm): 6.52 (bs, 1H, NH), 3.43 (q, 1H, CH), 3.27 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.67-1.18 (m, 7H, $2CH_2$, CH_3),

0.94 (t,3H, CH_3); ^{13}C NMR δ (ppm): 206.16 (C=O), 169.74 (C=O), 54.79 (CH), 38.60 (CH_2), 30.57 (CH_2), 30.02 (CH_3), 21.07 (CH_2), 15. 32 (CH_3), 13.30 (CH_3); MS (70 eV) *m/z* 171 (M^+, 7), 99 (100).

***N*-Benzyl-2-methyl-3-oxobutyramide (4l)**: mp 85-86°C; IR (nujol) 1720, 1631 cm^{-1}; ^1H-NMR δ (ppm): 7.31-7.15 (m, 5H, Ph), 6.46 (bs, 1H, NH), 4.35 (d, 2H, CH_2), 3.37 (q, 1H, CH), 2.18 (s, 3H, CH_3), 1.32 (d, 3H, CH_3); ^{13}C NMR δ (ppm): 206.64 (C=O), 169.54 (C=O), 137.72 ($C_{aromatic}$), 128.37, 127.23, 127.16 ($CH_{aromatics}$) 54.40 (CH), 43.25 (CH_2), 28.17 (CH_3), 14.02 (CH_3); MS (70 eV) *m/z* 205 (M^+, 10), 106 (100).

***N*-Butyl-2-oxocyclopentanecarboxamide (4m)**: oil; IR (neat) 1745, 1651 cm^{-1}; ^1H-NMR δ (ppm): 6.68 (bs, 1H, NH), 3.15 (m, 2H, CH_2), 2.88 (t, 1H, CH), 2.38-1.63 (m, 6H, $3CH_2$), 1.48-1.16 (m, 4H, $2CH_2$), 0.82 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 216.14 (C=O), 166.69 (C=O), 53.89 (CH), 38.86 (CH_2), 38.35 (CH_2), 31.03 (CH_2), 25.68 (CH_2), 20.06 (CH_2), 19.55 (CH_2), 13.28 (CH_3); MS (70 eV) *m/z* 183 (M^+, 3), 111 (100).

***N*-Benzyl-2-oxocyclopentanecarboxamide (4n)**: mp 85-86°C; IR (nujol) 1737, 1656 cm^{-1}; ^1H-NMR δ (ppm): 7.35-7.16 (m, 5H, Ph), 7.05 (bs, 1H, NH), 4.45 (dd, 1H, CH_2PH), 4.31 (dd, 1H, CH_2Ph), 2.97 (t, 1H, CH), 2.34-1.73 (m, 6H, $3CH_2$); ^{13}C NMR δ (ppm): 216.17 (C=O), 166.59 (C=O), 137.80 ($C_{aromatic}$), 128.30, 127.27, 127.04 ($CH_{aromatics}$), 53.96 (CH), 43.20 (CH_2), 38.52 (CH_2), 25.65 (CH_2), 20.14 (CH_2); MS (70 eV) *m/z* 217 (M^+, 25), 106 (100).

***(R)*-(-)-*N*-(1-Methylpropyl)-3-oxobutyramide (6a)**: oil; IR (neat) 1722, 1643 cm^{-1}; ^1H-NMR δ (ppm): 6.81 (bs, 1H, NH), 3.92 (m, 1H, CH), 3.41 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 1.50 (m, 2H, CH_2), 1.13 (d,3H, CH_3), 0.90 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 203.92 (C=O), 164.76 (C=O), 49.92 (CH_2), 46.24 (CH), 30.08 (CH_3), 28.82 (CH_2), 19.65 (CH_3), 9.80 (CH_3); MS (70 eV) *m/z* 157 (M^+, 5), 44 (100).

***(R)*-(-)-*N*-(1-Methylhexyl)-3-oxobutyramide (6b)**: oil; IR (nujol) 1722, 1643 cm^{-1}; ^1H-NMR δ (ppm): 6.85 (bs, 1H, NH), 3.97 (m, 1H, CH), 3.39 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 1.52-1.20 (m, 4H, $2CH_2$), 1.12 (d, 3H, CH_3), 0.89 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 203.92 (C=O), 164.83 (C=O), 50.02 (CH_2), 44.98 (CH), 31.18 (CH_2), 30.09 (CH_2), 25.23 (CH_2), 20.71 (CH_2), 20.24 (CH_3), 13.54 (CH_3); MS (70 eV) *m/z* 199 (M^+, 2), 128 (100).

***(R)*-(+)-*N*-(1-Phenylethyl)-3-oxobutyramide (6c)**: oil; IR (nujol) 1714, 1651 cm^{-1}; ^1H-NMR δ (ppm): 7.44 (bs, 1H, NH), 7.30-7.15 (m, 5H, Ph), 5.10 (m, 1H, CH), 3.37 (s, 2H, CH_2), 2.22 (s, 3H, CH_3), 1.47 (d, 3H, CH_3); ^{13}C NMR δ (ppm): 204.55 (C=O), 164.67 (C=O), 142.84 ($C_{aromatic}$), 128.38, 127.07, 125.80 ($CH_{aromatics}$) 49.39 (CH_2), 48.62 (CH), 30.66 (CH_3), 21.83 (CH_3); MS (70 eV) *m/z* 205 (M^+, 17), 43 (100).

***(R)*-(-)-*N*-(1-Methylpropyl)-3-oxo-3-phenylpropionamide (6d)**: oil; IR (neat) 1695, 1645 cm^{-1}; ^1H-NMR δ (ppm): 8.10-7.43 (m, 5H, Ph), 6.85 (bs, 1H, NH), 4.16-3.85 (m, 3H, CH_2, CH), 1.55-1.43 (m, 2H, CH_2), 1.18 (d, 3H, CH_3), 0.89 (t, 3H, CH_3); ^{13}C NMR δ (ppm): 195.92 (C=O), 164.88 (C=O), 135.88 ($C_{aromatic}$), 133.71, 128.54, 126.57, 125.34 ($CH_{aromatics}$), 46.59 (CH), 45.37 (CH_2), 29.44 (CH_2), 20.19 (CH_3), 10.02 (CH_3); MS (70 eV) *m/z* 219 (M^+, 16), 77(100).

***(R)*-(-)-*N*-(1-Methylhexyl)-3-oxo-3-phenylpropionamide (6e)**: mp 84-85°C; IR (neat) 1693, 1645 cm^{-1}; ^1H-NMR δ (ppm): 8.10-7.32 (m, 5H, Ph), 6.85 (bs, 1H, NH), 4.26-3.93 (m, 3H, CH_2, CH), 1.73-1.55 (m, 11H, $4CH_2$, CH_3), 0.92 (t,3H, CH_3); ^{13}C NMR δ (ppm): 196.17 (C=O), 164.66 (C=O), 135.98 ($C_{aromatic}$), 133.86, 128.66, 128.39, 128.21 ($CH_{aromatics}$), 45.46 (CH), 45.35 (CH_2), 36.51 (CH_2), 31.43 (CH_2), 25.42 (CH_2), 22.34 (CH_2) 20.65 (CH_3), 13.87 (CH_3); MS (70 eV) *m/z* 261 (M^+, 6), 105 (100).

***(R)*-(+)-*N*-(1-Phenylethyl)-3-oxo-3-phenylpropionamide (6f)**: mp 90-91°C; IR (nujol) 1683, 1643 cm^{-1}; ^1H-NMR δ (ppm): 8.05-7.20 (m, 11H, 2Ph, NH), 5.16 (m, 1H, CH), 3.85 (s, 2H, CH_2), 1.53 (d, 3H, CH_3); ^{13}C NMR δ (ppm): 196.15 (C=O), 164.71 (C=O), 142.92, 136.01 ($C_{aromatics}$), 133.97, 128.73, 128.54, 128.41, 128.28, 127.16, 125.92, 125.56 ($CH_{aromatics}$), 48.91 (CH), 45.03 (CH_2), 22.03 (CH_3); MS (70 eV) *m/z* 267(M^+, 3), 120 (100).

General Procedure for the Enzymatic Ammonolysis of β-ketoesters. 2.5 mmol of β-ketoester was added to a suspension of CA lipase (300 mg) in a 2% solution of ammonia in dioxane (20 ml). The mixture was shaken at 30°C and 250 rpm during the time indicated in Table I. Then, the enzyme was filtered, washed with dichloromethane and the organic solvents were evaporated. If necessary, the residue was subjected to column chromatography using hexane-ethyl acetate 2:1 as eluent.

3-Oxobutyramide (4d): oil; IR (nujol) 1722, 1656 cm^{-1}; ^{1}H-NMR δ (ppm): 6.55 (bs, 2H, NH_2), 3.44 (s, 2H, CH_2), 2.27 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 204.05 (C=O), 168.71 (C=O), 49.51 (CH_2), 30.59 (CH_3); MS (70 eV) *m/z* 101 (M^+, 33), 59 (100).

3-Oxo-3-phenylpropionamide (4j): mp 94-95 °C; IR (nujol) 1647, 1633 cm^{-1}; ^{1}H-NMR δ (ppm): 8.02-7.43 (m, 5H, Ph, NH), 6.05 (bs, 2H, NH_2), 3.97 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 195.31 (C=O), 168.74 (C=O), 135.81 ($C_{aromatic}$), 135.85, 128.64, 128.36, 125.63 ($CH_{aromatics}$), 45.09 (CH_2); MS (70 eV) *m/z* 163 (M^+, 17), 105 (100).

2-Oxocyclopentanecarboxamide (4p): mp 97-98 °C; IR (nujol) 1736, 1655 cm^{-1}; ^{1}H-NMR δ (ppm): 6.85 (bs, 1H, NH_2), 6.15 (bs, 1H, NH_2), 3.16 (t, 1H, CH), 2.52-1.75 (m, 6H, $3CH_2$), ^{13}C NMR δ (ppm): 215.90 (C=O), 165.41 (C=O), 53.92 (CH), 38.53 (CH_2), 25.50 (CH_2), 20.10 (CH_2)); MS (70 eV) *m/z* 127 (M^+, 43), 72 (100).

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REFERENCES

1. a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P. *J. Am.Chem. Soc.* **1985**, *107*, 1777. b) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *ibid*, **1985**, *107*, 5219. c) Boeckman, Jr., R. K.; Starret, Jr.,J. E.; Nickell, D. G.; Sum, P. E.*ibid*, **1986**, *108*, 5549. d) Boeckman, Jr., R. K.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486. e) Shenin, Y. D. *Antibiot. Med. Biotechnol.* **1986**, *11*, 835.
2. a) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431. b) Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848. c) Pak, C. S.; Yang, H. C.; Choi, E. B. *Synthesis.* **1992**, 1213. d) Cossy, J.; Belotti, D.; Thellend, A.; Pete, J. P.; *Synthesis.* **1988**,721. e) Lasley, L. C.; Wright, B. B. *Synth. Commun.* **1989**, *19*, 59.
3. Cossy, J.; Thellend, A. *Synthesis.* **1989**, 753.
4. a) Couturier, M., Blanc, P. *Bull. Soc. Chim. Fr.* **1958**, 151. b) Williams, J. W.; Krynitsky, J. A. *Org. Synth. Coll. Vol. III*, **1955**, 10.
5. Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 3019.
6. a) Booth, P. M.; Fox, C. M. J.; Ley, S. V. Tetrahedron Lett. 1983, 24, 5143. b) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin I.* **1987**, 121. c) Clarke, T.; Ley, S. V. *ibid.* **1987**, 131. d) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 345.
7. Gotor, V. *Microbial Reagents in Organic Synthesis.* NATO ASI Series. **1992**, *381*, 199.
8. a) Brieva, R.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Chem. Commun.*, **1990**, 1386.b) Gotor, V.; Brieva, R.; González, C.; Rebolledo, F. *Tetrahedron*, **1991**, *47*, 9207. c) Puertas, S. Brieva, R.; Rebolledo, F.; Gotor, V. *Tetrahedron*, **1993**, *49*, 4007. d) García, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry*, **1992**, *3*,, 1519. e) Quirós, M.; Sánchez, V. M.; Brieva, R.; Rebolledo, F.; Gotor, V. *ibid*, **1993**, *4*,, 1105. f) García, M. J. ; Rebolledo, F.; Gotor, V. *ibid*, **1993**, *4*, 2199.
9. García, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron Lett.* **1993**, *4*, 2199.
10. de Zoete, M. C.; Kock-van Dalen, A. C.; van Rantxijk, F.; Sheldon, R. A. *J. Chem. Soc., Chem. Commun.*, **1993**, 1831.

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