Tetrahedron Vol. 49, No. 20, pp. 4321-4326, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Chiral Carbamates through an Enzymatic Alkoxycarbonylation Reaction.

Marcos Pozo and Vicente Gotor*

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain.

(*Received in UK* 12 *March* 1993)

Keywords: Vinyl carbonates, enzymatic alkoxycarbonylation, chiral carbamates, enantioselectivity, lipases.

Abstract: *Chiral carbamates could be obtained by enzymatic alkoxycarbonylation with vinyl carbonates and racemic amines using Candida antarctica lipase. The enantioselectivity achieved depended on the substrate nature and the solvent.*

INTRODUCTION

Carbamate derivatives are products of considerable interest in some areas of Medicinal Chemistry.[1] An alkaloid, physostigmine, which has a carbamate moiety in its structure, is currently undergoing clinical trials for the treatment of Alzheimer's Disease.[2] The preparation of carbamate analogues of physostigmine has recently been reported[3] and one of these compounds has been found to be a potent cholinesterease inhibitor. Some carbamates have been exploited in chemotherapy,[1b] and others were orally effective as peptidoleukotriene antagonists.[1a] Moreover, the carbamate derivatives are also useful intermediates for the synthesis of insecticides.[4] In addition, the alkoxycarbonylation of the amine group in amino acid derivatives is a fundamental task in peptide synthesis.[5]

In the last few years, many reagents and synthetic procedures to achieve the alkoxycarbonylation of amines have been reported due to a rising interest in this functional group.[6] In general this kind of process involves specific reactions and, in some cases, toxic reagents such as phosgene[7] or organometallic compounds.[8] Recently, Ghost *et al.*[9] have developed an efficient synthesis of carbamates with *N,N'*-disuccinimidyl carbonate.

To the best of our knowledge the enzymatic alkoxycarbonylation of amines using lipases in organic solvents has not been achieved. We believed that vinyl carbonates could be suitable reagents to achieve an efficient method for the preparation of chiral carbamates. We have already reported the utility of vinyl carbonates[10] in the synthesis of chiral carbonates and different *N*-butyl carbamates through an enzymatic alkoxycarbonylation reaction. Herein we report the synthesis of chiral carbamates from racemic amines. In addition, we checked the

influence of solvent and the starting carbonates on enantioselectivity.

RESULTS AND DISCUSSION

Our experimental strategy was based on the ability of CAL (*Candida antarctica* lipase SP 435A immobilized on acurrell) to catalyze the reaction between vinyl carbonates and butylamine.[10] Because the best results had previously been achieved with *n*-octyl carbonate, alkyl carbonates were used in this work. *n*-Octyl vinyl carbonate (**1a**) and *n*-butyl vinyl carbonate (**1b**) were prepared from the appropriate alcohol and vinyl chloroformate.

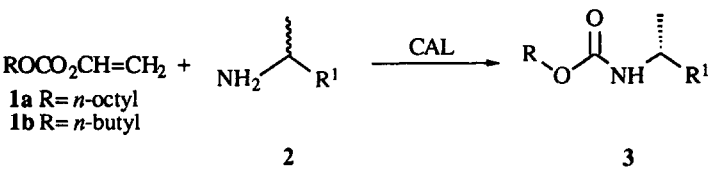
The alkoxycarbonylation procedure was applied to a series of racemic amines (**2**) (2-butyl amine, 2-heptyl amine and 1-phenylethyl amine). The reactions of the amines with the carbonates (**1**) (Scheme I) were carried out in different solvents, so that the solvent effect on the enantioselectivity of the process could be studied. The result are shown in the Table I.

It is known that enzymatic properties can be markedly altered simply by switching from one such solvent to another.[11] In general, the catalytic efficiency of enzymes diminishes as the polarity of the solvent increases.[12] Normally, the catalytic activity is low in polar solvents having a log P< 2, is moderate in solvents having a log P between 2 and 4, and is high in apolar solvents having a log P>4. With these data in mind four different solvents were chosen: hexane (log P= 3.5, apolar solvent, suitable for reactions in which dry enzymes powders are used), diisopropyl ether (which had been used successfully, in conjunction with other solvents such as trichlorotrifluoroethane and *tert*-butyl ether),[12] tetrahydrofuran (log P= 0.49) and dioxane (log P=-1.1) where immobilization is recommended for optimal activity.[12]

The enantioselectivity and activity of the enzyme changed only when 2-butyl amine and 1-phenylethyl amine were used (Table I, entries **3a-3l**). The best results were achieved with hexane and diisopropyl ether. We believe the lack of difference in the enantioselectivity, between both former solvents, was caused by our use of an immobilized enzyme. On the other hand, when the reactions were carried out in THF or dioxane, the enantiomeric excesses were the lowest (as predicted by Sih).[12] When 2-heptyl amine was used, changes in the solvent had no effect on enantioselectivity (Table I, entries **3e-3h**).

As reported in a previous paper, the lipase was enantioselective towards the *R* enantiomer, as in the reaction of vinyl carbonates with racemic alcohols.[10]

Scheme I.



Following the success of the synthesis with *n*-octyl vinyl carbonate, the effect of switching the alkyl group on the carbonate was investigated. Thus we chose *n*-butyl carbonate (**1b**), and hexane and diisopropyl ether as solvents.The best catalytic activity was achieved when hexane rather than diisopropyl ether was used as the solvent (Table I, entries **3m-3r**).

Table I. Carbamates (**3**) from (**1**) and racemic amines.

Entry	R	R[1]	Time, h	Conv.(%)[a]	e.e.%(Conf.)	$[\alpha]_D^{25}$ (c.)[b]	Solvent
3a	*n*-Octyl	Ethyl	20	40	62 (*R*)	-3.8 (0.4)	$^iPr_2O$
3b	*n*-Octyl	Ethyl	50	40	<5	0 (0.5)	Dioxane
3c	*n*-Octyl	Ethyl	27	45	62 (*R*)	-3.8 (0.6)	Hexane
3d	*n*-Octyl	Ethyl	48	43	48 (*R*)	-3.0 (1.2)	THF
3e	*n*-Octyl	Pentyl	29	39	40 (*R*)	-1.1 (0.3)	$^iPr_2O$
3f	*n*-Octyl	Pentyl	72	38	46 (*R*)	-1.3 (1.6)	Dioxane
3g	*n*-Octyl	Pentyl	30	40	42 (*R*)	-1.2 (0.4)	Hexane
3h	*n*-Octyl	Pentyl	54	41	40 (*R*)	-1.1 (3.5)	THF
3i	*n*-Octyl	Phenyl	24	41	98 (*R*)	+41.2 (0.2)	$^iPr_2O$
3j	*n*-Octyl	Phenyl	70	43	81 (*R*)	+34.0 (0.6)	Dioxane
3k	*n*-Octyl	Phenyl	26	39	98 (*R*)	+41.2 (1.0)	Hexane
3l	*n*-Octyl	Phenyl	52	42	83 (*R*)	+34.9 (1.8)	THF
3m	*n*-Butyl	Ethyl	24	40	20 (*R*)	-2.8 (0.9)	$^iPr_2O$
3n	*n*-Butyl	Ethyl	24	39	31 (*R*)	-4.3 (2.6)	Hexane
3o	*n*-Butyl	Pentyl	32	45	68 (*R*)	-2.0 (1.4)	$^iPr_2O$
3p	*n*-Butyl	Pentyl	24	42	73 (*R*)	-2.2 (1.9)	Hexane
3q	*n*-Butyl	Phenyl	22	45	70 (*R*)	+42.1 (0.3)	$^iPr_2O$
3r	*n*-Butyl	Phenyl	22	41	85 (*R*)	+51.1 (1.0)	Hexane

[a] Calculated with respect to the amine **2** by capillary gas chromatography and NMR.

[b] In chloroform.

From the results presented in Table I, we can conclude that the small difference in the enantioselectivity by switching the solvent in the case of 2-heptyl amine (entries **3e-3h**) and the poor results with the 2-butyl amine (entries **3m-3n**), were extreme cases. In the former, both the carbonate and amine had a long alkyl moiety whilst in the latter both carbonate and amine alkyl chains were short. For these reasons we suggest the CAL best catalyzed these alkoxycarbonylations when both carbonate and amine have neither a long nor a short alkyl chain at the same time. Thus good results were achieved when carbonate (**1b**) was used with 2-heptyl amine instead of carbonate (**1a**), or carbonate (**1a**) with 2-butyl amine. In the case of 1-phenylethyl amine, which was intermediate in length, the best results were achieved with a long alkyl chain in the carbonate, and with hexane or diisopropyl ether as solvent (see entries **3i-3l**).

CONCLUSIONS

Herein we reported a mild procedure to obtain chiral carbamates from racemic amines through an enzymatic alkoxycarbonylation. This method overcomes some of the operational problems of chemical methods which require the use of phosgene or organometallic compounds. The present method also allows the resolution of racemic amines. With a convenient combination of long-medium length of the amine and carbonate alkyl chains high e.e.'s could be achieved.

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 an adequate desiccant and stored under argon. For column chromatography, Merck silica gel 60/230-400 mesh was used. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Mattson 3000 Infrared Fourier Transform spectrophotometer. Gas chromatography was carried out with a Hewlett-Packard Model 5890 Series II gas chromatograph with flame ionization detection (FID) and a 25 m HP-1 capillary column coated with methylsilicone gum using N_2 as carrier gas. ^1H and ^{13}C-NMR were obtained with TMS (tetramethylsilane) as internal standard; using a Brucker AC-300 (^1H-300 MHz and ^{13}C-75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 5897 A spectrometer. Microanalyses were performed on a Perkin-Elmer 240B elemental analyzer.

Determination of enantiomeric excess and absolute configuration was as follows: All the e.e.'s and configurations were calculated in comparison with the optically active carbamate prepared from the appropriate chiral amine and *n*-octyl or *n*-butyl chloroformate. (All these compounds gave satisfactory ^1H-, ^{13}C-NMR and mass spectra).

Synthesis of carbonates (1). General procedure.[10]

Vinyl chloroformate (50 mmol) was slowly added to a solution of the appropriate alcohol (35 mmol) in dry pyridine (4 mL) under argon at 0° C. The solution was stirred for 2 h and then was acidified with HCl (3N) and extracted with dichloromethane; the organic layer was dried over sodium sulphate and submitted to flash chromatography on silica using hexane-ethyl ether 95:5 (**1a**) or 9:1 (**1b**). The final yields were 71% and 70% for (**1a**) and (**1b**) respectly. (**1a**) was characterized in our foregoing paper.[10]

***n*-Butylvinyl carbonate (1b):** oil; Rf=0.61 (Hexane:ethyl ether 9:1); IR (neat): $\upsilon_{c=o}$= 1763 cm^{-1}; (Found: C, 58.17; H, 8.41. $C_7H_{12}O_3$ requires C, 58.30; H, 8.39); ^1H-NMR ($CDCl_3$) δ (ppm): 7.10 (dd,1H,CH), 4.90 (dd, 1H, CH), 4.60 (dd, 1H, CH), 4.20 (t, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.00 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 152.68 (C=O), 142.52 (CH), 97.39 (CH_2), 68.63 (CH_2), 36.40 (CH_2), 18.73 (CH_2), 13.47 (CH_3); MS (EI, 70 eV), m/z: 144 (M^+), 57 (100).

Synthesis of carbamates (3a-3r). General procedure.

To a solution of carbonates (**1a**) or (**1b**) (1.2 mmol) and racemic amine (2mmol) in the appropriate solvent (15 mL) with molecular sieves (4Å) (1.5 mg), CAL (200 mg) was added (see Table I). The reaction was monitored by TLC or gas chromatography and was terminated by filtering off the enzyme. The organic solvent was evaporated under reduced pressure and chromatographic separation on silica gel of the resulting residue gave

the carbamate.

***R*-(-)-2-*N*-Butyl-*n*-octyl carbamate (3a-3d):** oil; Rf= 0.41 (Hexane:ethyl ether 7:3); IR (neat): $\upsilon_{c=o}$= 1693 cm^{-1}; (Found: C, 69.72; H, 8.25; N, 6.77. $C_{13}H_{27}NO_2$ requires C, 69.52; H, 8.27; N, 6.76); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.45 (bs, 1H, NH), 4.05 (t, 2H, CH_2), 3.60 (m, 1H, CH), 1.60 (m, 2H, CH_2), 1.45 (m, 2H, CH_2); 1.40-1.20 (m, 10H), 1.10 (d, 3H, CH_3), 0.90 (m, 6H, $2CH_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 156.17 (C=O), 64.69 (CH_2), 48.18 (CH), 31.71 (CH_2), 29.85 (CH_2), 29.18 (CH_2), 29.14 (CH_2), 28.98 (CH_2), 25.82 (CH_2), 22.57 (CH_2), 20.68 (CH_3), 14.03 (CH_3), 10.21 (CH_3); MS (EI, 70 eV), m/z: 214 (M^+–15, 2.77), 200 (100), 57 (37.86).

***R*-(-)-2-*N*-Heptyl-*n*-octyl carbamate (3e-3h):** oil; Rf= 0.36 (Hexane:ethyl ether 4:1); IR (neat): $\upsilon_{c=o}$= 1694 cm^{-1}; (Found: C, 70.72; H, 12.28; N, 5.16. $C_{16}H_{33}NO_2$ requires C, 70.78, H, 12.26; N, 5.16); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.40 (bs, 1H, NH), 4.00 (t, 2H, CH_2), 3.65 (bs,1H, CH), 1.60 (m, 2H, CH_2), 1.50-1.20 (m, 18H), 1.10 (d, 3H, CH_3), 0.90 (t, 6H, $2CH_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 156.10 (C=O), 64.64 (CH_2), 46.85 (CH), 37.08 (CH_2), 31.69 (CH_2), 31.59 (CH_2), 29.17 (CH_2), 29.12 (CH_2), 28.96 (CH_2), 25.80 (CH_2), 25.53 (CH_2), 22.54 (CH_2), 22.48 (CH_2), 21.18 (CH_3), 13.99 (CH_3), 13.93 (CH_3); MS (EI, 70 eV), m/z: 199 (11.93), 57 (13.55), 55(18.18).

***R*-(+)-*N*-1-Phenylethyl-*n*-octyl carbamate (3i-3l):** oil; Rf= 0.37 (Hexane:Ethyl ether 7:3); IR (neat): $\upsilon_{c=o}$= 1696 cm^{-1}; (Found: C, 73.69; H, 9.81; N, 5.06. $C_{17}H_{27}NO_2$ requires C, 73.59; H, 9.82; N, 5.05); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.30 (m, 5H, ar.), 5.00 (bs, 1H, NH), 4.85 (bs, 1H, CH), 4.00(m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.50 (d, 3H, CH_3), 1.40-1.20 (m, 10H) 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.85 (C=O), 143.61 (C), 128.47 (2xCH), 127.12 (2xCH), 125.80 (CH), 64.95 (CH_2), 50.40 (CH), 31.66 (CH_2), 29.12 (CH_2), 29.09 (CH_2); 28.89 (CH_2), 25.73 (CH_2), 22.53 (CH_2), 22.34 (CH_3), 13.99 (CH_3); MS (EI, 70 eV), m/z: 277 (M^+), 120 (10.21), 104 (31.40), 77 (24.56).

***R*-(-)-2-*N*-Butyl-*n*-butyl carbamate (3m-3n):** oil; Rf= 0.42 (Hexane:Ethyl ether 4:1); IR (neat): $\upsilon_{c=o}$= 1693 cm^{-1}; (Found: C, 62.29; H, 11.04; N, 8.10. $C_9H_{19}NO_2$ requires C, 62.38; H, 11.06; N, 8.09); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.60 (bs, 1H, NH), 4.05 (t, 2H, CH_2), 3.60 (m, 1H, CH), 1.70-1.30 (m, 6H), 1.10 (d, 3H, CH_3), 0.90 (m, 6H, $3CH_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 156.04 (C=O), 64.17 (CH_2), 48.02 (CH), 30.87 (CH_2), 29.66 (CH_2), 20.46 (CH_3), 18.85 (CH_2), 13.49 (CH_3), 10.02 (CH_3); MS (EI, 70 eV),m/z: 173 (M^+), 158 (3.06), 57 (32.10), 44 (40.59).

***R*-(-)-2-*N*-Heptyl-*n*-butyl carbamate (3o-3p):** oil; Rf= 0.39 (Hexane:Ethyl ether 7:3); IR (neat): $\upsilon_{c=o}$= 1694 cm^{-1}; (Found: C, 66.79; H, 11.69; N, 6.52. $C_{12}H_{25}NO_2$ requires C, 66.92; H, 11.71; N, 6.51); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.45 (bs, 1H, NH), 4.05 (t, 2H, CH_2), 3.65 (m, 1H, CH), 1.60 (m, 2H, CH_2), 1.50-1.20 (m, 10H), 1.10 (d, 3H, CH_3), 0.90 (m, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 156.13 (C=O), 64.73 (CH_2), 46.89 (CH), 37.11 (CH_2), 31.61 (CH_2), 31.05 (CH_2), 25.54 (CH_2), 22.48 (CH_2), 21.21 (CH_3), 19.03 (CH_2), 13.93 (CH_3), 13.67 (CH_3); MS (EI, 70 eV), m/z: 215 (M^+), 200 (1.65), 57 (16.17).

***R*-(+)-*N*-1-Phenylethyl-*n*-butyl carbamate (3q-3r):** oil; Rf= 0.32 (Hexane:Ethyl Ether 7:3); IR

(neat): $\upsilon_{c=o}$= 1692 cm^{-1}; (Found: C, 70.45; H, 8.67; N, 6.34. $C_{13}H_{19}NO_2$ requires C, 70.54; H, 8.66; N, 6.33); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40 (m, 5H, ar.), 5.20 (bs, 1H, NH), 4.80 (bs, 1H, CH), 4.00 (m, 2H, CH_2), 1.70-1.20 (m, 7H), 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.84 (C=O), 143.62 (C), 128.36 (2xCH), 126.98 (2xCH), 125.73 (CH), 64.51 (CH_2), 50.34 (CH), 30.86 (CH_2), 22.27 (CH_3), 18.85 (CH_2), 13.53 (CH_3); MS (EI, 70 eV), m/z: 221 (M^+), 106 (100), 77 (29.08).

***R*-(-)-2-*N*-Butyl-*n*-octyl carbamate:** $[\alpha]_D^{25}$= -6.1 (c= 0.3, $CHCl_3$).

***R*-(-)-2-*N*-Heptyl-*n*-octyl carbamate:** $[\alpha]_D^{25}$= -2.8 (c= 3.1, $CHCl_3$).

***R*-(+)-*N*-1-Phenylethyl-*n*-octyl carbamate:** $[\alpha]_D^{25}$=+42.0 (c= 1.1, $CHCl_3$).

***R*-(-)-2-*N*-Butyl-*n*-butyl carbamate:** $[\alpha]_D^{25}$= -13.8 (c= 2.4, $CHCl_3$).

***R*-(-)-2-*N*-Heptyl-*n*-butyl carbamate:** $[\alpha]_D^{25}$= -3.0 (c= 2.8, $CHCl_3$).

***R*-(+)-*N*-1-Phenylethyl-*n*-butyl carbamate:** $[\alpha]_D^{25}$=+60.1 (c= 5.5, $CHCl_3$).

ACKNOWLEDGEMENTS

Financial support of this work by DGICYT (project PB88-0499), is gratefully acknowledged. M.P. is the recipient of a predoctoral scholarship from the Ministerio de Educación y Ciencia, which is acknowledged. We also thank the Novo Nordisk Company for the generous donation of the lipase.

REFERENCES

1. (a) Matassa, V. G.; Maduskuie, T. P.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D. and Keith, R. A. *J. Med. Chem.* **1990**, *33*, 1781; (b) Firestone, R. A.; Pisano, J. M.; Falck, J. R.; McPhaul, M. M. and Krieger, M. *J. Med. Chem.* **1984**, *27*, 1037.
2. *Script* **1991** *No. 1634*, 22.
3. Allen, R. C.; Fink, D. M. *Tetrahedron Lett.* **1992**, *33*, 2103.
4. Khur, R. J. and Dorough, H. W.; *Carbamate Insecticides: Chemistry, Biochemistry and Toxicology*; C. R. C. Press, Cleveland, Ohio, **1976**.
5. Bodanszky, M., in: *Principles of Peptide Synthesis*, Hafner, Rees, Trost, Lehn, von Ragué Schleyer, Zahradnik (eds), Springer Verlag, Berlin, **1984**, p. 82.
6. Shute, R. E. and Rich, D. H.*Synthesis* **1987**, 346.
7. Denarié, M.; Grenouillat, D.; Malfroot, T.; Senet, J.; Sennyey, G. and Wolf, P. *Tetrahedron Lett.* **1987**, *28*, 5823.
8. Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1987**, *28*, 2005.
9. Ghosh, A. K.; Duong, T. T.; McKee, S. P. and Thompson, W. J. *Tetrahedron Lett.* **1992**, *33*, 2781.
10. Pozo, M.; Pulido, R. and Gotor, V. *Tetrahedron* **1992**, *48*, 6477.
11. Klibanov, A. M. *Trends Biochem. Sci.* **1989**, *14*, 141. Dordick, J. S. *Enzyme Microb. Technol.* **1989**, *11*, 194.
12. Chen, C. S. and Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695 and references cited therein.