Acylation and Alkoxycarbonylation of Oximes Through an Enzymatic Oximolysis Reaction

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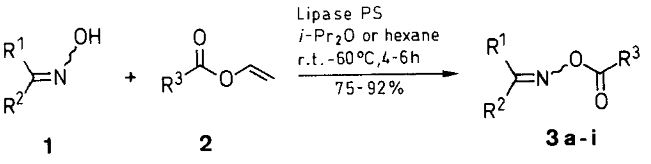
Ketone or benzaldehyde *O*-acyloximes and *O*-(*tert*-butoxycarbonyl)oximes can be prepared by reaction of oximes with vinyl esters and di-*tert*-butyl dicarbonate, respectively, using lipases as biocatalysts.

Over the last few years, the use of enzymes in organic solvents has occupied a position of particular prominence in asymmetric organic synthesis.[1] Lipases can be used for the preparation of organic compounds which are difficult to obtain by chemical methods. In these processes, the enzymatic esterification or transesterification reaction has been widely exploited;[2] however, the corresponding reaction with nitrogen organic compounds has been investigated much less. In this way, we have shown that lipases successfully catalyze amide[3] and hydrazide[4] formation. These enzymatic procedures are interesting alternatives to conventional methods due to the enantioselective and regioselective properties of these enzymes.

Oxime esters have great importance as chemoselective acylating reagents of bifunctional compounds such as amino alcohols.[5] In a preliminary communication, we have reported the enzymatic oximolysis reaction with synthetic aims.[6] We have now introduced some modifications into the substrate, lipase and reaction conditions in order to extend the synthetic applications of this oximolysis process, and the results are reported here.

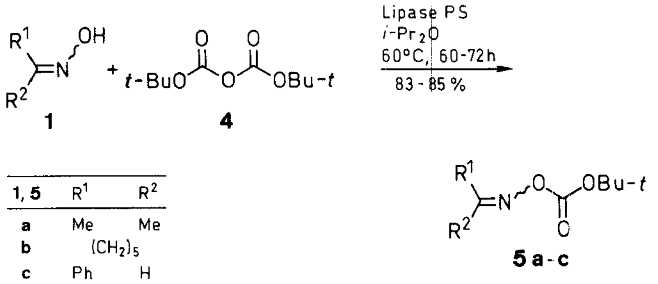
Lipase PS catalyzes the reaction between oximes **1** and vinyl acetate (**2a**), the corresponding oxime esters **3a–c** being obtained as the sole product in high yield.[6] We have now checked the reaction of acetone oxime with vinyl esters of different sizes and lipases. In this process four lipases, *Pseudomonas cepacia* (PS), *Candida cylindracea* (CC), porcine pancreatic (PP) and *Candida antarctica* (SP 435), showed a high catalytic activity, although the best results were obtained when *Candida antarctica* lipase[7] was used as the catalyst. With respect to the vinyl esters tested, vinyl acetate reacted much more rapidly than any others of longer chain length. These results are in accordance with those reported by other authors, for example, in the stereoselective acylation of binaphthol.[8] Oximes **1** did not react with vinyl esters in the absence of an enzyme.



3	R^1	R^2	R^3	3	R^1	R^2	R^3
a	Me	Me	Me	f	Ph	H	MeCH=CH$_2$
b	(CH$_2$)$_5$		Me	g	Me	Me	n-C$_{11}$H$_{13}$
c	Ph	H	Me	h	(CH$_2$)$_5$		n-C$_{11}$H$_{13}$
d	Me	Me	MeCH=CH$_2$	i	Ph	H	n-C$_{11}$H$_{13}$
e	(CH$_2$)$_5$		MeCH=CH$_2$				

In a preliminary communication,[6] we also reported that the enzymatic oximolysis reaction with ethyl and methyl esters is a reversible process, for this reason vinyl esters are used to shift the equilibrium to the product. We believe that the commercially available di-*tert*-butyl dicarbonate should be an adequate substrate for the preparation of oxime carbonates through the enzymatic oximolysis reaction, because the leaving bulky *tert*-butyl alcohol could favor an irreversible process.

The reaction of oximes **1** with di-*tert*-butyl dicarbonate (**4**) in the presence of lipases gave the carbonates **5** in high yield; in the absence of any enzyme, compound **4** did not react with oximes **1**. It is necessary to emphasize that if dimethyl dicarbonate is used, the corresponding oxime carbonates could not be isolated, probably because of the reversibility of the process.



1, 5	R^1	R^2
a	Me	Me
b	(CH$_2$)$_5$	
c	Ph	H

Table 1. Reaction Conditions

Product	Lipase	Solvent	Time (h)	Temp. (°C)	Yield (%)
3a	SP 435	hexane	3	30	90
3a	PS	i-Pr$_2$O	4	30	92
3a	CC	hexane	24	30	75
3a	PP	hexane	24	30	70
3b	PS	i-Pr$_2$O	6	30	86
3c	PS	i-Pr$_2$O	6	30	77
3d	PS	i-Pr$_2$O	12	60	90
3e	PS	i-Pr$_2$O	12	60	80
3f	PS	i-Pr$_2$O	12	60	88
3g	SP 435	hexane	60	60	89
3g	PS	i-Pr$_2$O	72	60	85
3g	CC	hexane	96	60	85
3h	PS	i-Pr$_2$O	72	60	75
3i	PS	i-Pr$_2$O	72	60	80
5a	SP 435	hexane	36	60	87
5a	PS	i-Pr$_2$O	60	60	85
5a	CC	hexane	72	60	80
5a	PP	hexane	120	60	70
5b	PS	i-Pr$_2$O	72	60	83
5c	PS	i-Pr$_2$O	72	60	85

On the other hand, the Boc group is one of the most common groups used in the protection of amines and can be introduced using *tert*-butoxycarbonyl azide,[9]

Table 2. Physical and Spectroscopic Data of *O*-Acyloximes **3a**–**i** and *O*-(*tert*-Butoxycarbonyl)oximes **5a**–**c**.

Product	mp[a] (°C)	Molecular Formula[b]	IR ($CHCl_3$)[c] ν (cm^{-1})	^1H NMR[d] δ	^{13}C NMR[d] δ	MS (70 eV)[e] *m*/*z* (%)
3a	oil	$C_5H_9NO_2$ (115.1)	1765	2.00 (s, 3H), 2.05 (s, 3H), 2.17 (s, 3H)	16.5 (q), 19.1 (q), 21.0 (q), 163.3 (s), 168.3 (s)	115 (M^+, 4), 57 (8), 43 (100)
3b	oil	$C_8H_{13}NO_2$ (155.2)	1762	1.68 (m, 6H), 2.27 (s, 3H), 2.38 (t, 2H), 2.52 (t, 2H)	19.3 (q), 25.1 (t), 25.3 (t), 25.5 (t), 26.5 (t), 31.8 (t), 168.1 (s), 168.6 (s)	155 (M^+, 2), 96 (27), 43 (100)
3c	oil	$C_9H_9NO_2$ (163.2)	1765	2.22 (s, 3H), 7.44 (m, 3H), 7.75 (m, 2H), 8.38 (s, 1H)	19.0 (q), 127.8 (d), 128.4 (d), 129.6 (d), 131.2 (s), 155.4 (d), 168.2 (s)	163 (M^+, 12), 10 (100), 43 (81)
3d	oil	$C_7H_{11}NO_2$ (141.2)	1747	1.84 (dd, 3H), 1.92 (d, 6H), 5.87 (dd, 1H), 7.04 (m, 1H)	15.8 (q), 17.1 (q), 20.8 (q), 119.3 (d), 145.1 (d), 163.1 (s), 168.8 (s)	69 ($M^+ - 72$, 100), 57 ($M^+ - 84$, 9)
3e	42–44	$C_{10}H_{15}NO_2$ (181.2)	1743	1.69 (m, 6H), 1.93 (dd, 3H), 2.49 (t, 2H), 2.57 (t, 2H), 5.92 (dd, 1H), 7.08 (m, 1H)	16.8 (q), 24.0 (t), 24.6 (t), 25.4 (t), 25.5 (t), 30.7 (s), 119.5 (d), 144.2 (d), 162.9 (s), 169.1 (s)	181 (M^+, 1), 96 (3), 69 (100)
3f	44–46	$C_{11}H_{11}NO_2$ (189.2)	1742	2.01 (dd, 3H), 6.02 (dd, 1H), 7.22 (m, 1H), 7.47 (m, 3H), 7.81 (m, 2H), 8.43 (s, 1H)	17.8 (q), 119.7 (d), 127.9 (d), 128.4 (d), 129.7 (s), 131.1 (d), 146.3 (d), 155.6 (d), 163.5 (s)	189 (M^+, 7), 77 (17), 69 (100)
3g	oil	$C_{15}H_{29}NO_2$ (255.4)	1762	0.88 (t, 3H), 1.29 (m, 16H), 1.68 (m, 2H), 2.03 (d, 6H), 2.41 (t, 2H)	13.6 (q), 16.3 (q), 21.4 (q), 22.2 (t), 24.4 (t), 28.6 (t), 28.7 (t), 28.8 (t), 29.0 (t), 29.1 (t), 29.1 (t), 31.4 (t), 32.4 (t), 163.0 (s), 170.6 (s)	183 ($M^+ - 72$, 98), 72 ($M^+ - 183$, 11), 41 (CH_3CN^+, 100)
3h	45–47	$C_{18}H_{33}NO_2$ (295.5)	1757	0.89 (t, 3H), 1.25 (m, 16H), 1.68 (m, 8H), 2.39 (m, 4H), 2.54 (t, 2H)	13.9 (q), 22.4 (t), 24.7 (t), 25.2 (t), 25.6 (t), 26.6 (t), 26.7 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.7 (t), 31.9 (t), 32.9 (t), 168.3 (s), 171.3 (s)	295 (M^+, 1), 183 (45), 96 (50), 41 (CH_3CN^+, 100)
3i	49–51	$C_{19}H_{29}NO_2$ (303.4)	1774	0.83 (t, 3H), 1.22 (m, 16H), 1.69 (m, 2H), 2.41 (t, 2H), 7.41 (m, 3H), 7.71 (m, 2H), 8.40 (s, 1H)	13.9 (q), 22.5 (t), 24.6 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 29.4 (t), 31.7 (t), 32.6 (t), 126.8 (d), 128.1 (d), 128.5 (d), 128.6 (d), 130.0 (s), 131.4 (d), 155.7 (d), 171.2 (s)	304 (M^+, 1), 183 (41), 77 (39), 43 (100)
5a	oil	$C_8H_{15}NO_3$ (173.2)	1772	1.56 (s, 9H), 2.02 (d, 6H)	16.2 (q), 21.3 (q), 27.2 (q), 82.5 (s), 151.8 (s), 162.0 (s)	57 ($C_4H_9^+$, 100), 56 ($M^+ - 117$, 30), 41 (CH_3CN^+, 24)
5b	oil	$C_{11}H_{19}NO_3$ (213.3)	1770	1.54 (s, 9H), 1.68 (m, 6H), 2.34 (t, 2H), 2.53 (t, 2H)	24.9 (t), 25.2 (t), 26.1 (t), 26.2 (t), 27.2 (q), 31.5 (s), 82.3 (s), 152.0 (s), 166.8 (s)	96 ($M^+ - 117$, 16), 57 ($C_4H_9^+$, 100), 41 (CH_3CN^+, 30)
5c	80–82	$C_{12}H_{15}NO_3$ (221.3)	1774	1.53 (s, 9H), 7.47 (m, 3H), 7.73 (m, 2H), 8.43 (s, 1H)	27.6 (q), 83.8 (s), 128.1 (d), 128.7 (d), 129.9 (s), 131.4 (d), 151.7 (s), 155.0 (d)	104 ($M^+ - 117$, 51), 77 ($C_6H_5^+$, 28), 57 ($C_4H_9^+$, 100)

[a] Uncorrected, measured with a Gallenkamp Melting Point apparatus.

[b] Microanalysis recorded on a Perkin-Elmer model 240 and a Carlo Erba model 1108 instruments. All compounds gave satisfactory microanalyses: C ± 0.28, H ± 0.18, N ± 0.23.

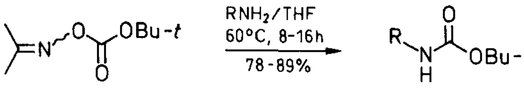
[c] Recorded on a Perkin-Elmer 170-X Infrared Fourier Transform Spectrophotometer.

[d] Compounds were measured in $CDCl_3$/TMS, at 300 MHz on a Bruker AC-300 Spectrometer.

[e] Recorded on a Hewlett Packard 5897 A Spectrometer.

di-*tert*-buyl dicarbonate[10] or an oxime reagent.[11] With respect to the last, the *tert*-butoxycarbonylated oximes are obtained by reaction of oxime chloroformates prepared by reaction of the oxime with phosgene or trichloromethyl chloroformate and *tert*-butyl alcohol in pyridine.[11] The procedure developed here allows the easy preparation of different oxime carbonates that may be of utility in the blocking of amino groups under mild conditions. It is noteworthy, that compounds **5** cannot be prepared by the conventional method from the corresponding oxime and *tert*-butyl chloroformate because this compound is thermally unstable.

We mentioned before that oxime esters can be used in the selective formation of amides from amino alcohols under mild conditions.[5] We have checked this reaction with acetone *O*-(*tert*-butoxycarbonyl)oxime (**5a**) and different amines and amino alcohols. In all cases, only the corresponding *tert*-butyl carbamate was obtained. This method, then, provides an interesting alternative to introduce the Boc group into amino alcohols in a chemoselective way, since *O*-carbonates were not detected.



5a **6a-d**

6	R	6	R
a	Bu	**c**	CH(Me)CH_2OH
b	CH_2CH(OH)Me	**d**	$(CH_2)_6$OH

In conclusion, we have shown the great utility of the use of enzymes in organic solvents for the preparation of nitrogen organic compounds. The enzymatic oximolysis reaction described here allows the easy preparation of oxime esters and oxime *tert*-butylcarbonates, which are excellent reagents for the chemoselective preparation of amides and carbamates from amino alcohols.

Acetone oxime, cyclohexanone, benzaldehyde, $NH_2OH \cdot HCl$, vinyl acetate, vinyl crotonate, di-*tert*-butyl dicarbonate, dimethyl dicarbonate, $BuNH_2$ and amino alcohols were purchased from Aldrich Chemical Co.; vinyl laureate was purchased from Fluka Chemika. Reagent quality solvents are used without further purification.

Acetone *O*-Acetyloxime (3a); Typical Procedure:

Acetone oxime (**1a**; 0.365 g, 5 mmol) was dissolved in hexane or i-Pr_2O (20 mL) and then, vinyl acetate (0.86 g, 10 mmol) and lipase PS (1.5 g) were added. After stirring at r.t. for 4 h, the enzyme was filtered and the solvent was evaporated in vacuo. Compound **3a** was purified by distillation in vacuo or by flash silica gel column chromatography using Et_2O/hexane/$CHCl_3$ (1:6:3) as eluant; yield: 0.53 g (92 %).

***O*-Acyloximes 3d–i; General Procedure:**

In a dried, N_2-filled round-bottom flask fitted with a magnetic stirrer, oxime (5 mmol) was added over a period mixture of i-Pr_2O (20 mL), vinyl ester (10 mmol) and lipase PS (1.5 g). The mixture was stirred at 60 °C until the TLC showed that the reaction was completed; then the enzyme was filtered and solvents evaporated in vacuo. Products **3d–i** are purified by flash silica gel column chromatography with Et_2O/hexane/$CHCl_3$ (1:6:3) as eluant or by distillation in vacuo.

Acetone *O*-(*tert*-Butoxycarbonyl)oxime (5a); Typical Procedure:

In a dried, N_2-filled round-bottom flask fitted with a magnetic stirrer, acetone oxime (0.365 g, 5 mmol) was added over a stirred mixture of i-Pr_2O (20 mL), $O(CO_2Bu$-$t)_2$ (2.18 g, 10 mmol) and lipase PS (1.5 g). After stirring at 60 °C for 60 h, the enzyme was filtered, the solvent was evaporated in vacuo and compound **5a** was obtained after purification by flash silica gel column chromatography with Et_2O/hexane (1:4) as eluant; yield: 0.75 g (87 %).

***tert*-Butyl Butylcarbamate (6a):**

$BuNH_2$ (5 mmol, 0.494 mL) was added to a solution of oxime carbonate **5a** (5 mmol, 0.865 g) in THF (15 mL). After being stirred at 60 °C for 8 h, the solvent was evaporated to give the carbamate **6a** and acetone oxime. Compound **6a** was purified by flash silica gel column chromatography using Et_2O/hexane (4:1) as eluant; yield: 0.77 g (89 %); oil.

IR (neat): $\nu_{C=O} = 1691\ cm^{-1}$.

^1H NMR ($CDCl_3$/TMS): δ = 0.51 (t, 3 H), 1.46 (m, 13 H), 3.12 (q, 2 H), 4.54 (br s, 1 H).

^{13}C NMR ($CDCl_3$/TMS): δ = 13.4 (q), 19.6 (q), 28.1 (t), 31.9 (t), 40.0 (t), 78.3 (s), 155.8 (s).

MS: m/z: 173 (M^+, 1), 57 (100).

***tert*-Butyl Hydroxyalkylcarbamates 6b–d; General Procedure:**

To a solution of oxime carbonate **5a** (5 mmol) in THF (15 mL), the corresponding amino alcohol was added; after stirring at 60 °C for 16 h, the solvent was evaporated under reduced pressure to give **6b–d** and acetone oxime. Products were purified by flash silica gel column chromatography with Et_2O/Hexane (1:4).

tert-Butyl 2-Hydroxypropylcarbamate (**6b**): yield: 0.73 g (84 %); oil.

IR (neat): $\nu_{C=O} = 1690\ cm^{-1}$.

^1H NMR ($CDCl_3$/TMS): δ = 1.19 (d, 3 H), 1.47 (s, 9 H), 2.48 (br s, 1 H), 2.95 (m, 1 H), 3.28 (m, 1 H), 3.93 (m, 1 H), 5.02 (br s, 1 H).

^{13}C NMR ($CDCl_3$/TMS): δ = 20.4 (q), 28.2 (q), 47.7 (t), 67.1 (d), 79 (s), 156 (s).

MS: m/z (%) = 57 (C_4H_9+, 100), 44 (C_2H_4O+, 51).

tert-Butyl 2-Hydroxy-1-methylethylcarbamate (**6c**): yield: 0.71 g (81 %); mp 50–52 °C.

IR ($CHCl_3$): $\nu_{C=O} = 1692\ cm^{-1}$.

^1H NMR ($CDCl_3$/TMS): δ = 1.14 (d, 3 H), 1.48 (s, 9 H), 2.47 (br s, 1 H), 3.62 (m, 3 H), 4.73 (br s, 1 H)

^{13}C NMR ($CDCl_3$/TMS): δ = 17.1 (q), 28.2 (q), 66.3 (d), 76.3 (t), 79.3 (s), 156.1 (s).

MS: m/z (%) = 59 (C_3H_7O+, 41), 57 (C_4H_9+, 100).

tert-Butyl 6-hydroxyhexylcarbamate (**6d**): yield: 0.85 g (79 %); mp 39–41 °C.

IR ($CHCl_3$): $\nu_{C=O} = 1691\ cm^{-1}$.

^1H NMR ($CDCl_3$/TMS): δ = 1.43 (m, 17 H), 1.32 (br s, 1 H), 3.22 (q, 2 H), 3.66 (t, 2 H), 4.61 (br s, 1 H).

^{13}C NMR ($CDCl_3$/TMS): δ = 25.1 (t), 26.2 (t), 28.2 (q), 29.8 (t), 32.3 (t), 40.1 (t), 62.2 (t), 78.8 (s), 156.0 (s).

MS: m/z (%) = 161 (M+ − 56, 8), 57 (C_4H_9+, 100).

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(7) The generous gift of *Candida antarctica* lipase (SP435) by NOVO-NORDISK is gratefully acknowledged.

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