Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 7, pp. 853-856, 1996

0960-894X/96 $15.00 + 0.00

S0960-894X(96)00133-3

LIPASE-CATALYZED CHEMOSPECIFIC *O*-ACYLATION OF 3-MERCAPTO-1-PROPANOL AND 4-MERCAPTO-1-BUTANOL

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Abstract: The lipase-catalyzed chemospecific *O*-acylation of 3-mercapto-1-propanol and 4-mercapto-1-butanol by several aliphatic carboxylic acid ethyl esters are described. Similar treatment on 1-mercapto-2-propanol and 3-mercapto-2-butanol did not yield the expected *O*-acyl derivatives. Copyright © 1996 Elsevier Science Ltd

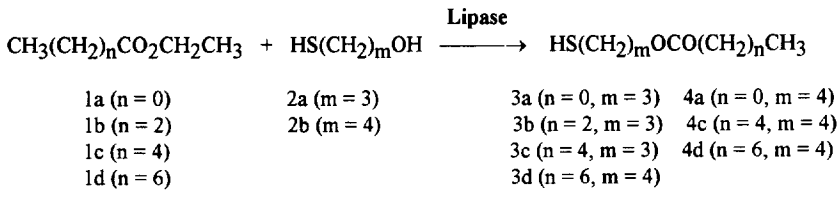
It is well known that compounds containing a thiol group develop multiple biological actions. Molecules bearing free-SH are considered important protectors against radiation-induced damage to DNA[1] by gamma[2] and fast neutron radiation.[3] If tumor cells absorb less drug than the normal ones, thiol compounds can be used in cancer radiotherapy.[4] It has been shown that thiols protect according to their global electrical charge.[5] In case of uncharged thiols, they protect by scavenging of hydroxyl radicals both near DNA and in the bulk. Moreover, these compounds are also employed in cosmetic preparations to reduce actinic damage to human skin due to over-exposure to sunlight.[6]

Considering the above mentioned characteristics, we sought to prepare molecules with free -SH group and acylated -OH groups as potential radioprotectors. The strategy must involve selective transformations; synthetic procedures for the preparation of such compounds are described very little in literature. Some reports deal with the synthesis of 3-mercaptopropyl- and 4-mercaptobutyl acetate by chemical methods, though involve several steps and proceed with both low yield and chemoselectivity.[7,8]

This selectivity, sometimes difficult to achieve using traditional methods, can be accomplished through application of enzymes. Among them, lipases in organic media are well-known to be useful in many reactions.[9-11] Lipase-catalyzed esterifications and transesterifications have been used successfully in the selective acylation of various kind of bi- and polyfunctional compounds, such as sugars and aminoalcohols.[12-16]

In previous papers we have described the chemospecific lipase-catalyzed acylation of 2-mercaptoethanol[17,18] and the chemoselective lipase-catalyzed acylation of 3-mercaptopropane-1,2-diol.[19] We now report a simple procedure to obtain in a chemoselective way O-acyl esters of 3-mercapto-1-propanol and 4-mercapto-1-butanol.

Scheme 1 shows the lipase-catalyzed transesterification reaction between these two hydroxyalkanethiols and the respective ethyl carboxylates.



Scheme 1

Lipases from three different sources were employed: porcine pancreatic lipase (PPL), Lipozyme^{TM} IM60 (LIP), a *Mucor miehei* immobilized lipase, and a lipase from the yeast *Candida cylindracea* (CCL). Ethyl carboxylates were use as acylating agents and solvents.

The reaction of 3-mercapto-1-propanol (**2a**) and 4-mercapto-1-butanol (**2b**) with ethyl carboxylates, catalyzed by the above mentioned lipases, afforded exclusively the *O*-acyl esters in every case tested, as shown in Tables 1 and 2.

Table 1 . Lipase-catalyzed *O*-acylation of 3-mercapto-1-propanol

Acylating agent	Time (h)	Temp. / °C	Enzyme	Product	Yield (%)
1a	24	28	PPL	**3a**	95.4
	48	28	LIP		73.8
	192	28	CCL		81.5
1b	24	28	PPL	**3b**	87.8
	24	28	LIP		92.4
	24	28	CCL		93.5
1c	720	27	PPL	**3c**	87.9
	16	27	LIP		94.5
	30	27	CCL		87.4
1d	168	31	PPL	**3d**	95.5
	46	31	LIP		95.0
	46	31	CCL		92.8

Reactions were carried out under standard conditions (see text) unless noted otherwise.
Enzyme:Substrate ratio: 1.1 for PPL and LIP and 3.3 for CCL.

Table 2 . Lipase-catalyzed *O*-acylation of 4-mercapto-1-butanol

Acylating agent	Time (h)	Temp. / °C	Enzyme	Product	Yield (%)
1a	168	30	PPL	**4a**	91.9
	48	30	LIP		88.1
	48	30	CCL		52.7
1c	168	30	PPL	**4c**	66.1
	168	30	LIP		56.3
	168	30	CCL		66.2
1d	48	30	PPL	**4d**	83.7
	48	30	LIP		76.4
	48	30	CCL		88.4

Reactions were carried out under standard conditions (see text) unless noted otherwise. Enzyme:Substrate ratio: 0.94 for PPL and LIP and 2.8 for CCL.

The general procedure involves addition of the lipase to a solution of the mercaptoalcohol (10 mmol) and the ethyl carboxylate (ratio A/S = 15 for ethyl acetate, 5 for the remaining esters). The suspension was shaken at 200 rpm at the indicated temperature and the progress of the reaction was monitored by GLC. At the completion of the reaction, the enzyme was removed by filtration and the products were isolated by flash chromatography on silica gel and identified by GC-MS and by ^{1}H and ^{13}C NMR spectroscopy. Control experiments were set up in which only the mercaptoalcohol and the ethyl carboxylate were incubated.

The three enzymes chemospecifically acylated the two substrates in high yields, producing better yields for the three-carbon α,ω--hydroxyalkanethiol derivatives (**3a-d**). In general, PPL proved to be slower than the other two lipases. In contrast with the results reported with 2-mercaptoethanol[17] no reaction was observed with ethyl decanoate (n = 8) and ethyl dodecanoate (n = 10) with either substrate and in the presence of any of the enzymes.

Although the specificity exhibited with the three and four carbon thiols is in accordance with the results previously described for 2-mercaptoethanol[17,18] the nature of the hydroxyl and thiol groups, primary or secondary, affects dramatically the enzymatic behavior.

Thus, when 1-mercapto-2-propanol, a position isomer of 3-mercapto-1-propanol, was treated with ethyl acetate in presence of LIP, only 13.2 % of the O-acetate was formed after 7 days of reaction. No reaction was observed with the remaining lipases. The possibility of

an enantioselective catalysis developed by the lipases was ruled out since the purified product did not exhibit any optical rotation. 3-Mercapto-2-butanol, a position isomer of 4-mercapto-1-butanol in which both functional groups are secondary, did not react with ethyl acetate in the presence of any of the three enzymes, even after much longer periods of time.

As far as we know the reported compounds have not been prepared previously in a chemospecific manner. Considering that current protective methods for alcohols involve the concomitant reaction of other functional groups, such as thiols and carboxylic acids, also present in the molecule,[20] the enzymatic procedure here presented offers a convenient method for selective protection of alcohols.

Acknowledgments. We thank Novo-Nordisk for a generous gift of Lipozyme^{TM} IM60 and UMYMFOR for the GLC analyses and spectra. We are indebted to CONICET and UBA for partial financial support.

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(*Received in USA* 3 *November* 1995; *accepted* 27 *February* 1996)