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Lipase-catalyzed conversions of trimethylsilyl ethers: deprotection, acetylation, epoxidation and one-pot-multi-step reactions

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Abstract

Unsaturated trimethylsilyl ethers are converted by lipase-catalyzed hydrolysis of ethyl acetate directly to alkenol acetates; the hydrolysis of diethyl carbonate yields unstable carbonic acid monoethylester, which deprotects trimethylsilyl ethers under mild conditions and without remaining acid. By the analogous lipase-catalyzed perhydrolysis of these esters with hydrogen peroxide, epoxyalkanol acetates and epoxyalkanols are obtained in one-pot reactions with selectivities of 90–97%. Using longer chain peroxy fatty acids, generated in-situ by lipase-catalyzed reaction of fatty acid and hydrogen peroxide, trimethylsilyl ethers are selectively (83–95%) epoxidized without removal of the protecting trimethylsilyl group.

Keywords: Trimethylsilyl ethers; Lipase; Perhydrolysis; Epoxidation; Carbonic acid esters

1. Introduction

The trialkylsilyl group is probably the most widely used protecting group. Originally introduced to increase the volatility and stability of hydroxyl compounds, it is today widely applied in organic synthesis as well [1]. One of the advantages of silyl ethers as protecting groups is that they can be removed under well-defined acidic conditions. The sensitivity of the silyl ether to acidity is determined by the substituents on the silicon; thus the trimethylsilyl (TMS) group is the most sensitive to acid-catalyzed hydrolysis and can be removed, e.g., by dilute acetic acid. If the protected molecule contains a C=C-bond which is to be epoxidized by peroxy acids, TMS is therefore not the protecting group of choice, although it has been reported to be stable enough for *m*-chloroperbenzoic acid (mcpba) epoxidation [2].

Lipases are used as biocatalysts for all kinds of esterifications and ester hydrolyses in organic synthesis [3]. Because they catalyze these reactions, they can also be applied for the selective protection (and deprotection) of alcohols and carboxylic acids as esters [4]. Some lipases, in particular, Novozym® 435, an immobilized lipase from *Candida antarctica*, are also able to catalyze the generation of peroxy acids from

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either carboxylic acids [5] or carboxylic acid esters [6] and hydrogen peroxide; these peroxy acids can be used in-situ for the epoxidation of C=C-bonds in olefins [5,7], unsaturated fatty acids [8] or plant oils [9]. Whereas the Novozym® 435-catalyzed reaction of hydrogen peroxide with carboxylic acids is restricted to straight fatty acids, the analogous reaction of carboxylic acid esters ('perhydrolysis') has a broader substrate range. It includes the generation of peroxyacetic acid from, e.g., ethyl acetate [10] and the generation of peroxycarbonic acid derivatives from, e.g., diethyl carbonate [11]. Recently, we found that the chemo-enzymatic epoxidation of unsaturated alcohols by perhydrolysis leads selectively to epoxyalkanol acylates in a one-pot-three-step reaction [12].

We now report the lipase-mediated conversion of trimethylsilyl ethers (TMSEs) to alcohols and acylates, the direct conversion of unsaturated TMSEs to epoxy alkanols and epoxy acylates by perhydrolysis as well as the epoxidation of unsaturated TMSEs by peroxy fatty acids without removal of the protecting group.

2. Experimental

2.1. Materials

Novozym® 435 was kindly supplied by Novo Nordisk Biotechnologie, Mainz, Germany and 60% hydrogen peroxide was supplied by Solvay, Hannover, Germany. Oleylalcohol (9-octadecenol, 99%) was purchased from Nu-Chek-Prep, Elysian, MN, USA. All others chemicals were standard synthesis grade and were used as such with the exception of diethyl carbonate. Diethyl carbonate was percolated prior to use over a 40-cm column filled with Al_2O_3 (Puralox SCCa 150/145 N; Condea Brunsbüttel, Germany). This was found to be essential to get any lipase-catalyzed conversions of this material. We suspect that there are impurities of chloroformic acid ester because we found it to be a powerful lipase inhibitor in separate experiments and its presence in diethyl carbonate could be easily caused by the industrial production process.

2.2. Analysis

Gas chromatography was performed on a Hewlett Packard Model 5890 Series II instrument equipped with a flame ionisation detector and a Chromatography Service SE-54 column of 25-m length. Retention times (temperature: 70°C isotherm for 5 min; 12–40°C; column head pressure 60 bar N_2) for the C_{11}-products were: 10-undecenol 11.8 min; 10-undecenyl TMSE 13.1 min; 10-undecenyl acetate 13.6 min; 10,11-epoxyundecanol 14.6 min; 10,11-epoxyundecyl TMSE 15.6 min; 10,11-epoxyundecyl

Table 1
Chemo-enzymatic one-pot conversions of trialkysilyl ethers

No.	Substrate	Reagent	Yield/product
1/1	10-undecenyl TMSE	ethyl acetate/H_2O[a]	89% 10-undecenyl acetate
1/2	10-undecenyl TMSE	diethyl carbonate/H_2O[a]	87% 10-undecenol
1/3	10-undecenyl TMSE	stearic acid/H_2O[b]	no reaction
1/4	undecyl TMSE	ethyl acetate/H_2O[a]	87% undecanol acetate
1/5	undecyl TMSE	diethyl carbonate/H_2O[a]	92% undecanol
1/6	10-undecenyl TESE	ethyl acetate/H_2O[a]	no reaction
1/7	9-octadecenyl TMSE	ethyl acetate/H_2O[a]	78% 9-octadecenyl acetate
1/8	9-octadecenyl TMSE	diethyl carbonate/H_2O[a]	98% 9-octadecenol
1/9	9-octadecenyl TMSE	myristic acid/H_2O[b]	no reaction

TMSE: trimethylsilyl ether; TESE: triethylsilyl ether.
[a] 1 mmol substrate in 10 ml ester, 5 mmol H_2O, 100 mg Novozym® 435, 24 h at 40°C.
[b] 1 mmol substrate and 1 mmol acid in 10 ml toluene, 5 mmol H_2O, 100 mg Novozym® 435, 24 h at 40°C.

Table 2
Chemo-enzymatic one-pot epoxidations of trialkysilyl ethers with various peroxy acids in-situ

No.	Substrate	Reagent	Yield/product (selectivity)
2/1	10-undecenyl TMSE	ethyl acetate/H_2O_2[a]	76% 10,11-epoxyundecyl acetate
2/2	10-undecenyl TMSE	diethyl carbonate/H_2O_2[a]	61% 10,11-epoxyundecanol (97%)
2/3	10-undecenyl TMSE	stearic acid/H_2O_2[b]	50% 10,11-epoxyundecyl TMSE (83%)
2/4	10-undecenyl TMSE	mcpba/H_2O[c]	69% 10,11-epoxyundecanol 31% 10,11-epoxyundecyl TMSE
2/5	10-undecenyl TESE	ethyl acetate/H_2O_2[a]	57% 10,11-epoxyundecyl TMSE (95%)
2/6	9-octadecenyl TMSE	ethyl acetate/H_2O_2[a]	69% 9,10-epoxyoctadecyl acetate
2/7	9-octadecenyl TMSE	diethyl carbonate/H_2O_2[a]	70% 9,10-epoxyoctadecanol (97%)
2/8	9-octadecenyl TMSE	myristic acid/H_2O_2[b]	86% 9,10-epoxyoctadecyl TMSE (95%)
2/9	9-octadecenyl TESE	ethyl acetate/H_2O_2[a]	87% 9,10-epoxyoctadecyl TESE (94%)

TMSE: trimethylsilyl ether; TESE: triethylsilyl ether.
[a]1 mmol substrate in 10 ml ester, 5 mmol H_2O_2 (24×10 μl, 60%), 100 mg Novozym® 435, 16 h at 40°C.
[b]1 mmol substrate and 1 mmol acid in 10 ml toluene, 5 mmol H_2O_2 (24×10 μl, 60%), 100 mg Novozym® 435, 16 h at 40°C.
[c]1 mmol substrate, 5 mmol mcpba and 5 mmol H_2O in 10 ml toluene, 24 h at 40°C.

acetate 16.0 min; 10-undecenyl TESE 16.5 min; 10,11-epoxyundecyl TESE 18.7 min. The corresponding data for the C_{18}-products were: 9-octadecenol 19.0 min; 9-octadecenyl TMSE 19.7 min; 9-octadecenyl acetate 20.1 min; 9,10-epoxyoctadecanol 20.7 min; 9,10-epoxyoctadecyl TMSE 21.6 min; 9,10-epoxyoctadecyl acetate 22.1 min; 9-octadecenyl TESE 22.0 min; 9,10-epoxyoctadecyl TESE 27.1 min. Saturated and unsaturated components are generally not distinguishable under these conditions. All free carboxylic and peroxycarboxylic acids were converted by CH_2N_2 to their methyl esters before GC analysis. The identity of the products was confirmed by comparison with authentic samples and/or GC-MS spectra. Yields and conversions were measured with the help of an internal standard (phthalic acid diethylester).

2.3. Synthesis of trialkylsilyl ethers [13]

Preparation of 9-octadecenyl TMSE: 10 mmol 9-octadecenol (2.69 g), 15 mmol triethylamine (2.5 ml) and 15 mg 4-dimethylamino pyridine were dissolved in 30 ml abs. diethyl ether. 10.5 mmol trimethylsilyl chloride (1.37 ml) were slowly added at room temperature. After 4 h of stirring, the mixture was hydrolyzed by the addition of 50 ml water. Phases were separated, the organic layer was dried over $MgSO_4$ and the solvent was evaporated—Yield: 91% (3.10 g) 9-octadecanol TMSE of 99% purity.

10-undecenyl TMSE, undecyl TMSE, 10-undecenyl TESE, undecyl TESE, octadecyl TMSE, octadecyl TESE and 9-octadecenyl TESE were prepared accordingly with yields of 91–99% and purities of 95% or more.

2.4. Lipase-catalyzed conversions of trialkylsilyl ethers

Conversion of 10-undecenyl TMSE to 10-undecenyl acetate: 1 mmol 10-undecenyl TMSE (252.6 mg; 97%) was dissolved in 10 ml ethyl acetate. 100 mg Novozym® 435 and 5 mmol water (0.1 ml) were added. After 24 h of stirring at 40°C, the lipase was removed by filtration and the reaction product was dried over Na_2SO_4 and finally analyzed by GC. The yield was 89% 10-undecenyl acetate; no further signals were detected.

All reactions in Table 1 were carried out accordingly.

Conversion of 9-octadecenyl TMSE to 9,10-epoxyoctadecanol: 1 mmol 9-octadecenyl TMSE (342.1 mg; 99%) was dissolved in 10 ml percolated diethyl carbonate and 100 mg Novozym® 435 was added. After stirring for 15 min, 15 μl

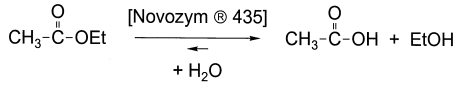
of 60% hydrogen peroxide were added by a Methrom 715 Dosimat, which has been modified to function automatically and time dependently. Every 15 min, the addition was repeated until all H_2O_2 (5 mmol, 240 μl) was added. After a further 16 h of stirring at 40°C, the lipase was removed by filtration and the reaction mixture was washed with water to remove the excess H_2O_2. The organic layer was dried over Na_2SO_4 and finally analyzed by GC. The yield was 70% 9,10-epoxyoctadecanol. As a by-product, 2% 9-octadecenol were detected; thus the selectivity was calculated to be 97%.

All reactions in Table 2 were carried out accordingly.

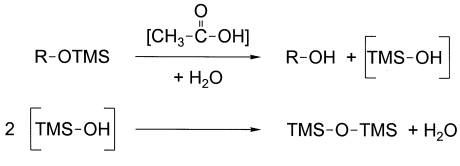
3. Results and discussion

In the first step of our investigations, we examined the reaction of unsaturated trimethylsilyl ethers (TMSEs) with various carboxylic acid esters (or carboxylic acids) in the presence of water and Novozym® 435. Throughout this study, trialkylsilyl ethers of 10-undecenol and 9-octadecenol were used as substrates.

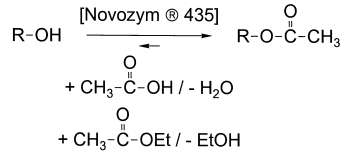
These TMSEs were selectively converted by ethyl acetate/H_2O/Novozym® 435 to the corresponding acetates with yields of 78–89% Table 1, Nos. 1/1 and 1/7). The reaction does not proceed in the absence of the lipase and/or without water and may therefore be understood as a one-pot-three-step reaction via the following steps:



(1)



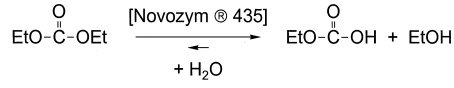
(2)



(3)

In the first step, the ethyl acetate is hydrolyzed to acetic acid, which is in turn capable of catalyzing the cleavage of the TMSE [1]; in the third step, the resulting alcohol is either esterified by acetic acid or transesterified by ethyl acetate.

In contrast to these reactions, the treatment of TMSEs with diethyl carbonate/H_2O/Novozym® 435 leads to deprotection yielding 87–98% of the free alcohols (Table 1, Nos. 1/2, 1/5 and 1/8). The first reaction step (4) is analogous to reaction (1):



(4)

Obviously, the intermediate carbonic acid monoethylester is acidic enough to cleave the TMSEs. However, it is unstable and decomposes to ethanol and carbon dioxide:

(5)

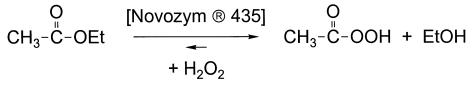
No esterification (analogous to (3)) occurs in this case, although in a water-free environment,

lipase-catalyzed transesterification of alcohols with diethyl carbonate is possible [14]. Neither such a lipase-mediated deprotection nor a replacement of the protecting group, as described above, have been reported in the literature before.

TMSEs are not attacked by longer-chain carboxylic acids (Table 1, Nos. 1/3 and 1/9). Furthermore, triethylsilyl ethers (TESEs) are not attacked even by ethyl acetate/H_2O/Novozym® 435 (Table 1, No. 1/6), which is easily understood, because they are estimated to be roughly 64 times less sensitive towards acid-catalyzed solvolysis [1]. Saturated TMSEs, of course, react in the same way as their unsaturated counterparts (Table 1, Nos. 1/4 and 1/5 vs. Nos. 1/1 and 1/2).

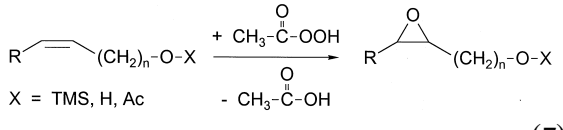
All these reaction open up possibilities for various chemo-enzymatic epoxidations leading to different products. Therefore in the next set of experiments (Table 2), the protecting group conversions were combined with epoxidation of the C=C-bonds, essentially by replacing water with hydrogen peroxide. Unsaturated TMSEs were now converted by ethyl acetate/H_2O_2/Novozym® 435 to the corresponding epoxyalkanol acetates (Table 1, Nos. 2/1 and 2/6) with yields of 69–76%. In addition to reactions (1), (2) and (3), the following steps take place.

(6) Lipase-catalyzed perhydrolysis of ethyl acetate to peroxy acetic acid [6,10]



(6)

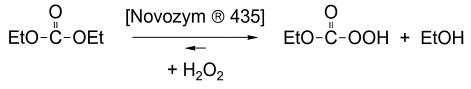
(7) Prileshajev-epoxidation of the C=C-bond by peroxy acetic acid which may occur in all stages of the reaction:



(7)

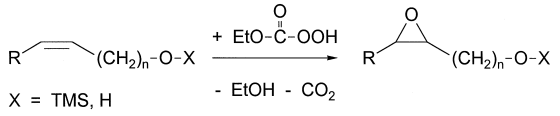
In toto, this represents a five-step-one-pot reaction with an overall selectivity of more than 90%.

By reaction with diethyl carbonate/H_2O_2/Novozym® 435, unsaturated TMSEs yield 61–70% epoxyalkanols (Table 2, Nos. 2/2 and 2/7). Hence, we conclude that by perhydrolysis of diethyl carbonate:



(8)

monoperoxy carbonic acid monoethylester is formed. It decomposes to carbon dioxide and ethanol, but only after acting as the oxidant in the Prileshajev reaction:



(9)

The use of peroxy carbonic acid derivatives as 'acid-free peracids' is currently investigated in detail.

Long-chain peroxy acids have been rarely used for epoxidation before, but because long chain carboxylic acids do not attack the TMSE-group (Table 1, Nos. 1/3 and 1/9), we are now able to epoxidize TMSEs with peroxy stearic acid (Table 2, No. 2/3) or peroxy myristic acid (Table 2, No. 2/8) generated in-situ from the fatty acid and hydrogen peroxide by lipase catalysis. 9-octadecenyl TMSE yields 86% epoxide with a selectivity of 95%; in the case of 10-undecenyl TMSE the yield is only 50%, but selectivity is still high (83%). Obviously, the reaction time of 16 h is to short to allow the complete epoxidation of the less reactive terminal C=C-bond. However, to facilitate comparison, we used the same reaction conditions throughout our study. At least under these conditions (16 h, 40°C, fivefold excess of oxidant, presence of water), TMSEs are not stable against mcpba (Table 2, No. 2/4); the reaction product is predominantly an epoxyalkanol. The more

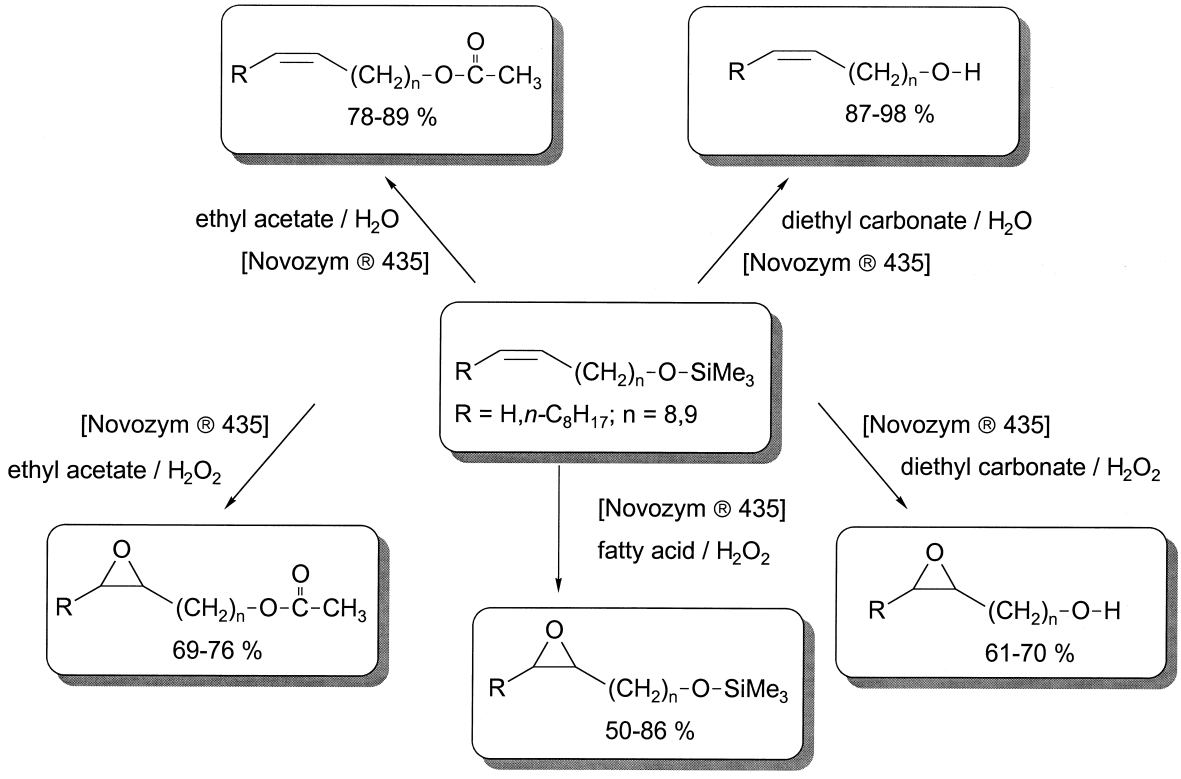


Fig. 1. Lipase-catalyzed one-pot-conversions of unsaturated trimethyl silyl ethers.

stable TESEs can be epoxidized selectively by ethyl acetate/H_2O_2/Novozym® 435 without an attack on the TESE group and with yields of 57–87% (Table 2, Nos. 2/5 and 2/9).

In conclusion, unsaturated TMSEs can be converted selectively by indirect lipase catalysis to a variety of products (Fig. 1). Chemo-enzymatic epoxidation rivals any other epoxidation method regarding selectivity, safety, easiness of procedure and work-up but is much more versatile and therefore these new one-pot reactions may provide useful shortcuts for many a complex synthesis.

Acknowledgements

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