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Syntheses of optically active γ-ketothiols and the esters by lipase-catalyzed hydrolysis via α-acetylthiomethylation of ketones

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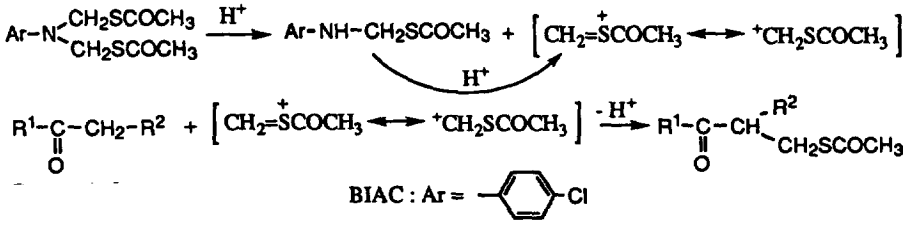
Abstract: The α-acetylthiomethylation of ketones was achieved by the reaction of ketones or the enamines with *N,N*-bis-(acetylthiomethyl)-*p*-chloroaniline in the presence of trifluoroacetic acid. The resulting thiolesters were hydrolyzed enantioselectively by catalysis of lipases. © 1997 Elsevier Science Ltd

Hydroxymethylation of an active methylene compound with formaldehyde is widely used in synthetic chemistry. However, mercaptomethylation with labile thioformaldehyde is unknown because of the formation of more stable 1,3,5-trithiane.[1] From the viewpoint of the synthetic importance of thiols,[2] we have investigated acylthiomethylation which leads to mercaptomethylation on subsequent deacylation. The α-acetylthiomethylation of ketones was achieved by the reaction of a ketone or the derived enamine with *N,N*-bis(acetylthiomethyl)-*p*-chloroaniline (BIAC)[3] in the presence of trifluoroacetic acid. Our strategy also includes synthesis of optically active γ-ketothiols and the esters by lipase-catalyzed hydrolysis of α-acetylthiomethyl ketones.

Based on the idea that from an *N,S*-formal, BIAC, it is possible to produce the acetylthiomethyl cation attacking an anionic carbon in an acidic medium, we examined the reaction of ketones with BIAC (Scheme 1).



Scheme 1.

According to the information obtained from initial experiments for acetylthiomethylation of *N,N*-dimethylaniline,[4] we carried out the reaction with trifluoroacetic acid in acetonitrile at reflux. Although cyclohexanone was acetylthiomethylated in good yield, we could not obtain the desired product for acyclic ketones. Therefore, we carried out the reaction of the corresponding enamine instead of the ketone. Although nucleophilicity of an enamine was recognized to be lower in an acidic medium, we succeeded in the synthesis of α-acetylthiomethyl ketone by means of addition of the enamine to a solution of BIAC and trifluoroacetic acid in acetonitrile at reflux.[5] The experimental results are summarized in Table 1.

Because an organosulfur compound with a thiol group such as cysteine plays an important role in vital functions, it was considered reasonable that an enzyme might catalyze efficiently the hydrolysis

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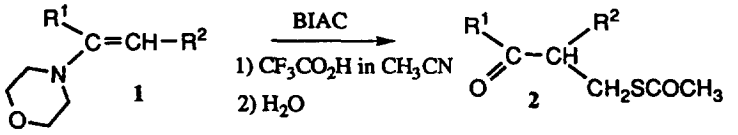
Table 1.



R^1	R^2	No.	Yield (%)	R^1	R^2	No.	Yield (%)
Ph	CH_3	**2a**	70	Ph	$CH_2CH(CH_3)_2$	**2e**	41
Ph	CH_2CH_3	**2b**	59	*p*-CH_3-Ph	$CH(CH_3)_2$	**2f**	35
Ph	$CH_2CH_2CH_3$	**2c**	60	Ph	CH_2Ph	**2g**	37
Ph	$CH(CH_3)_2$	**2d**	37	$CH_2(CH_2)_2CH_2$		**2h**	76[a]

a) Obtained by the direct reaction with cyclohexanone.

of a thiolester. However, there have been only a few examples of lipase-catalyzed hydrolysis of thiolesters[6] although ordinary esters are well known to be hydrolyzed enantioselectively by use of lipases.[7]

After preliminary screenings of commercially available lipases, we employed lipase PL (*Alcaligenes* sp.), AH (*Pseudomonas* sp.), PS (*Pseudomonas cepacia*) and OF (*Candida cylindracea*) as lipases and isopropyl ether (IPE) saturated with water as solvent[8] for the hydrolysis of these thiolesters.

The general procedure is as follows. A mixture of thiolester (2.5 mmol) and lipase (70 mg) in IPE (10 ml) saturated water was stirred at room temperature. After half the amount of substrate had been consumed, the lipase was removed by filtration through Celite. The filtrate was concentrated under reduced pressure to give an oily residue, which was subjected to silica gel column chromatography to give the thiol[9] and the unreacted ester. The enantiomeric excess was determined by HPLC analysis using a column packed with Chiralcel OD.

The experimental results are summarized in Table 2. For the investigation of the catalytic effect of lipases on the hydrolysis of *S*-2-benzoylbutyl acetothioate, **2b** was examined by using four lipases (entries 1–4). Lipase AH is well suited for this hydrolysis giving enantiomerically pure (*R*)-2-benzoylbutane thiol **3b*** and (*S*)-*S*-2-benzoylbutyl acetothioate **2b***. It is of interest that only lipase OF showed the opposite enantioselectivity (entry 4). We examined the catalytic effect of lipase AH and PL on the hydrolysis of further seven thiolesters. Lipase AH showed high enatioselectivity for the thiolesters with a blanched alkyl moiety or a benzene ring as well as with a normal alkyl. Lipase PL also gave good results in the enantioselectivity. In particular, in the hydrolyses of **2e** and **2g** it worked more effectively than lipase AH (entries 10 and 13). The cyclic ketone such as cyclohexanone derivative **2h** was not a good substrate for these lipases (entry 14).[10] The absolute configurations of **2b***, **2c*** and **2g*** and the corresponding antipode thiolesters, **3b***, **3c*** and **3g***, were assigned by comparison of the rotatory of the desulfurized ketones with those described previously.[11]

Thiols are usually prepared from thiolesters by hydrolysis under basic conditions, or by reduction with metal hydrides.[12] However, in the case of the ketothiolesters described above, such methods cannot be applied. We suggest that lipase-catalyzed hydrolysis is a fairly useful method for the synthesis of thiols from the thiolesters with chemically sensitive groups even if they have no stereogenic center.

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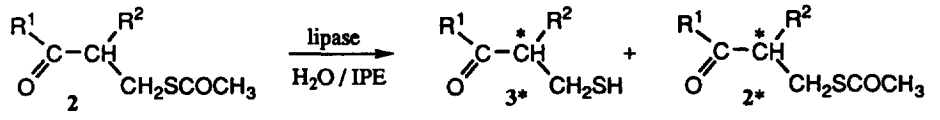
3. BIAC was prepared as follows: a solution of thiolacetic acid (0.1 mol) in 95% ethanol (15 ml) was added dropwise to a solution of *p*-chloroaniline (0.05 mole) and 37% formaldehyde (12 ml) in 95% ethanol (50 ml) with stirring at 45–50°C. The solution was stirred for 3 h and cooled in an ice-bath. The deposited pale yellow crystals were collected and washed with cold 95% ethanol.

Table 2. Lipase-catalyzed hydrolysis of thiolesters



Entry	R^1	R^2	No.	Lipase	Time (hour or day)	Thiol (3*) Chem. y. %	Thiol (3*) Opt. y., %ee[a] ($[\alpha]_D$[b] config.)	Ester (2*) Chem. y. %	Ester (2*) Opt. y., %ee[a] ($[\alpha]_D$[b] config.)
1	Ph	CH_2CH_3	**2b**	AH	32 h	43	> 99 (36, *R*)	41	> 99(- 92, *S*)
2	Ph	CH_2CH_3	**2b**	PL	7 d	34	70 (*R*)	49	53 (*S*)
3	Ph	CH_2CH_3	**2b**	PS	14 d	25	> 99 (*R*)	51	60 (*S*)
4	Ph	CH_2CH_3	**2b**	OF	7 d	33	21(- 8, *S*)	42	21(23, *R*)
5	Ph	CH_3	**2a**	AH	25 h	43	> 99 (81)	41	> 99 (-111°)
6	Ph	CH_3	**2a**	PL	7 d	41	> 99	40	> 99
7	Ph	$CH_2CH_2CH_3$	**2c**	AH	30 h	42	> 99 (32, *R*)	45	> 99(- 65, *S*)
8	Ph	$CH(CH_3)_2$	**2d**	AH	12 d	42	> 99 (- 1.1)	45	> 99(- 97)
9	Ph	$CH_2CH(CH_3)_2$	**2e**	AH	14 d	30	82	50	64
10	Ph	$CH_2CH(CH_3)_2$	**2e**	PL	14 d	35	93 (24)	44	76 (- 41)
11	*p*-Me-Ph	$CH(CH_3)_2$	**2f**	AH	4 d	42	> 99 (- 10)	44	90 (- 92)
12	Ph	CH_2Ph	**2g**	AH	20 d	25	> 99 (*R*)	55	68 (*S*)
13	Ph	CH_2Ph	**2g**	PL	24 h	39	> 99 (- 25, *R*)[c]	40	> 99 (- 37, *S*)[c]
14	$-CH_2(CH_2)_2CH_2-$		**2h**	AH	6 d	35	23	49	14

a) Determined by HPLC using a column packed with Chiralcel OD. b) $[\alpha]_D^{22}$ (c = 1.0, MeOH). c) $[\alpha]_D^{22}$ (c = 1.0, $CHCl_3$).

Yield 93%, mp 84–85°C. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (6H, s, 2 $COCH_3$), 5.05 (4H, s, 2 CH_2), 6.68 (2H, d, *J*=9.2 Hz, ArH), 7.21 (2H, d, *J*=9.2 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 31.1 (2C), 52.7 (2C), 115.8 (2C), 125.4, 129.2 (2C), 142.5, 195.4 (2C). Anal. Calcd for $C_{12}H_{14}ClNO_2S_2$: C,47.44; H, 4.64; Cl, 11.67; N, 4.61; S, 21.11. Found: C, 47.43; H, 4.58; Cl, 11.96; N, 4.61; S, 21.17.

4. Electron rich aromatic compounds such as *N,N*-dimethylaniline have also been demonstrated to react with PCAA to afford acetylthiomethyl compounds. These results will be reported elsewhere.
5. A typical procedure is as follows: a solution of morpholine enamine of butyrophenone (50 mmol) in acetonitrile (100 ml) was added dropwise to a refluxing solution of BIAC (25 mmol) and trifluoroacetic acid (25 mmol) in acetonitrile (100 ml) with stirring during 2 h. After 1 h of stirring, the reaction mixture is condensed under reduced pressure to give an oily residue, a benzene solution of which is washed with 5% hydrochloric acid, aqueous sodium bicarbonate and brine, and then dried over $MgSO_4$. After removal of the solvent, the resultant oil is subjected to silica gel column chromatography using hexane–AcOEt as an eluent to give an oily product (72%). *S*-2-Benzoylbutyl acetothioate **2b**: MS *m/z*: 236 (M^+), 193 ($M-COCH_3)^+$, 161 ($M-SCOCH_3)^+$. ^{1}H-NMR δ: 0.98 (3H, t, *J*=7.6 Hz, CH_3), 1.61–1.90 (2H, m, CH_2), 2.30 (3H, s, $COCH_3$), 3.14 (1H, dd, *J*=6.1, 13.4 Hz, SC*H*AHB), 3.21 (1H, dd, *J*=7.7, 13.4 Hz, SCHA*H*B), 3.59–3.69 (1H, m,

COCH), 7.44–7.51 (2H, m, ArH), 7.55–7.61 (1H, m, ArH), 7.94–7.98 (2H, m, ArH). ^{13}C-NMR δ: 11.4, 25.7, 30.1, 30.7, 47.7, 128.5 (2C), 128.8, 133.4 (2C), 137.0, 196.2, 202.4.

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9. The structure of thiols obtained was determined on the basis of the spectral data. For an example, **3b***: MS *m/z*: 194 (M^+), 161 $(M-SH)^+$. ^{1}H-NMR δ: 0.90 (3H, t, *J*=7.4 Hz, CH_3), 1.48 (1H, dd, *J*=8.2, 8.9 Hz, SH), 1.61–1.88 (2H, m, CH_2CH_3), 2.65 (1H, ddd, *J*=5.3, 8.9, 13.4 Hz, SCHAHB), 3.01 (1H, ddd, *J*=5.3, 8.9, 13.4 Hz, SCHA*H*B), 3.57–3.66 (1H, m, COCH), 7.45–7.52 (2H, m, ArH), 7.55–7.62 (1H, m, ArH), 7.96–7.99 (2H, m, ArH). ^{13}C-NMR δ: 11.5, 25.4, 25.5, 51.5, 128.5 (2C), 128.9, 133.4 (2C), 137.4, 202.4.
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11. The specific rotation of (*S*)-2-methylbutyrophenone prepared from the recovered thiolester in entry 1 by treatment with Raney nickel: $[\alpha]_D^{22}$ 35 (c=1.0, Et_2O), lit. $[\alpha]_D^{20}$ 36.6 (c=4.7, Et_2O); Enders, D., Eichenauer, H. Baus, U., Schubert, H. and Kremer, K. A. M., *Tetrahedron*, **1984**, 40, 1345–1359. (*S*)-2-methylvalerophenone from the thiolester in entry 7: $[\alpha]_D^{22}$ 25 (c=0.8, EtOH), lit. $[\alpha]_D$ −26.1 c=0.31, EtOH) for the *R*-isomer; Sayo, N., Kitahara, I. and Nakai, T., *Chem. Lett.*, **1984**, 259–262. (*S*)-2-methyl-3-phenylpropiophenone from the thiolester in entry 13: $[\alpha]_D^{22}$ 79 (c=0.8, EtOH), lit. $[\alpha]_D$ 87.5 (c=2.669, EtOH): Conant, J. B. and Carlson, G. H., *J. Am. Chem. Soc.*, **1932**, 54, 4054–4060.
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