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SYNTHESIS AND HYDROLYSIS OF ETHOXYCARBONYLMETHYL AND CYANOETHYL 5-CYANO-6-METHYLSULFANYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLATES

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Abstract: Ethoxycarbonylmethyl and 2-cyanoethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates were synthesized by making use of one-pot four- and five-component method, and by alkylation of 1,4-dihydropyridine-3-carboxylic acid with ethyl bromoacetate. By basic hydrolysis of esters, both 1,4-dihydropyridine-3-carboxylic acids and (1,4-dihydropyridine-3-carbonyloxy)acetic acids were prepared. *Candida antarctica lipase* B catalysed hydrolysis of ethoxycarbonylmethyl 1,4-dihydropyridine-3-carboxylates proceeded with low enantioselectivity yielding both type of acids as slightly enantioenriched compounds.

Keywords: Ethoxycarbonylmethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates, 2-cyanoethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates, one-pot four-component synthesis, hydrolysis, alkylation, *Candida antarctica* lipase B.

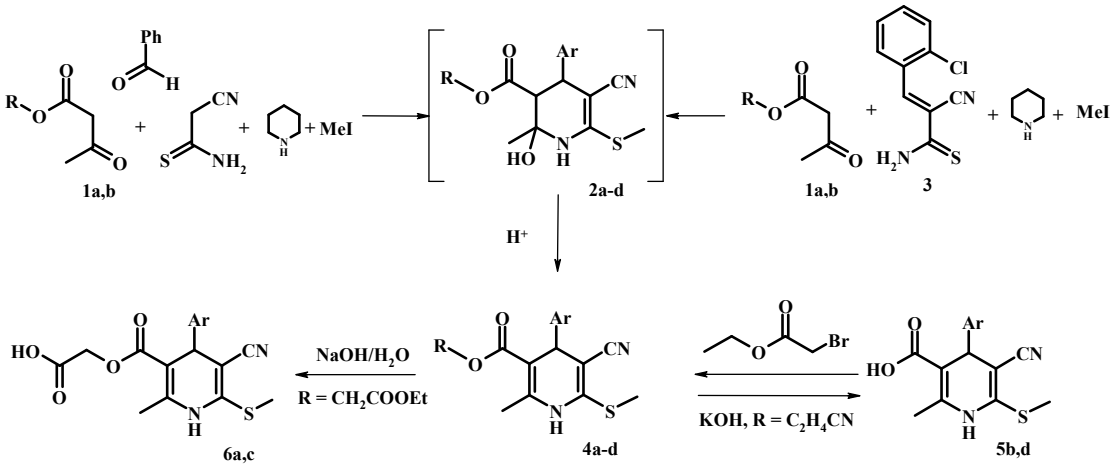
Introduction

1,4-Dihydropyridines (1,4-DHPs) are known as effective calcium channel modulators, especially antagonists[1-5]. 1,4-DHPs, bearing different carbofunctionalities at the positions 3 and 5, possess a stereogenic carbon at position 4 in the 1,4-DHP ring, and enantiomers often show different biological activities[3]. Amongst the methods for preparation of enantiopure compounds, the biotechnological approach based on enzyme-catalysed enantiomeric differentiation has become a promising way for the enantioseparation of 1,4-DHPs[6]. In most cases, the alkoxycarbonyl groups, which are directly attached to the 1,4-DHP ring, do not undergo enzymatic hydrolysis as their reactivity is diminished due to β-aminovinylcarbonyl type conjugation. To get enantiopure compounds, the modification of 1,4-DHP-3-carboxylates with enzymatically labile groups is necessary. The ethoxycarbonylmethyl esters at the position 3 of the 1,4-DHP are readily cleavable by lipases with high enantioselectivity[7,8]. Racemic 6-methylsulfanyl-1,4-DHP-3-carboxylates display antihypertensive or vasodilating activities and low toxicity[9]. Their modification to carboxymethyl 1,4-DHP-carboxylates, enzymatic hydrolysis and alkylation could lead to the desired enantiopure or enantioenriched 6-methylsulfanyl-1,4-DHP-3-carboxylates.

Results and discussion

The choice of methods for synthesis of ethoxycarbonylmethyl 6-methylsulfanyl-1,4-DHP-3-carboxylates **4** was based on our previous work[7,9] and literature data[10]. Bis(ethoxycarbonylmethyl) 1,4-DHP-3,5-carboxylates were prepared by Hantzsch synthesis of ethoxycarbonylmethyl acetoacetate, aromatic aldehyde and ammonia in ethanol in 42-67% yields. By making use of *Candida antarctica* lipase B (CAL-B), they were enzymatically hydrolysed reaching 93% enantiomeric excess[7]. On the other hand, six methods for preparation of 6-methylsulfanyl-1,4-DHP-3-carboxylates are known[9].

To prepare ethoxycarbonylmethyl esters **4**, first of all ethoxycarbonylmethyl 3-oxobutyrate **1a** as key building block was synthesized by esterification of ethyl hydroxyacetate with 4-methyleneoxetan-2-one[11]. 6-Methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylates **4a,b** (see Scheme 1) were prepared in 59% and 41% yields by condensation of ethoxycarbonylmethyl or 2-cyanoethyl 3-oxobutyrates **1**, benzaldehyde, 2-cyanothioacetamide, piperidine and iodomethane (one-pot five-component, method A). In case of 4-(2-chlorophenyl) substituent, isolation of compound **4c** from reaction mixture by making use of column chromatography is rather complicated. By carrying out the condensation of ethoxycarbonylmethyl or 2-cyanoethyl 3-oxobutyrates **1**, 3-(2-chlorophenyl)-2-cyanothioacrylamide **3**, piperidine and iodomethane (one-pot four-component synthesis, method B), 1,4-DHP **4c** or **4d** crystallizes from reaction mixture in 65% and 64% yield, respectively.



a) Ar = C_6H_5, R = CH_2COOEt; b) Ar = C_6H_5, R = C_2H_4CN;
c) Ar = 2-Cl-C_6H_4, R = CH_2COOEt; d) Ar = 2-Cl-C_6H_4, R = C_2H_4CN

Scheme 1. Synthesis and hydrolysis of ethoxycarbonylmethyl and 2-cyanoethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates **4a-d**.

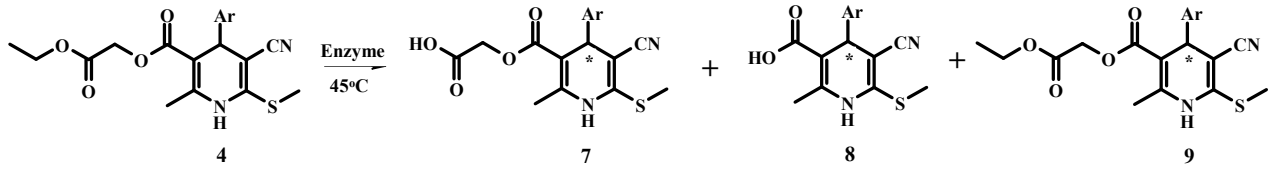
It should be noted that in case of the methods **A** and **B** 6-hydroxy-1,4,5,6-tetrahydropyridines **2** are formed as intermediates. By acidification of the reaction mixture containing compounds **2** and **4**, the dehydration of 6-hydroxy derivatives **2** takes place giving pure 1,4-dihydropyridines **4.**

Hydrolysis of cyanoethyl esters **4b,d** with KOH gave 1,4-DHP-3-carboxylic acids **5b,d** (96% and 92% yields, respectively), but hydrolysis of esters **4a,c** with $NaOH/H_2O$ – (1,4-DHP-3-carbonyloxy)acetic acids **6a,c** (82% and 63% yields, respectively). Acids **5** and **6** were authentic samples because enzymatic hydrolysis could proceed touching "inner" or "outer" ester groups (Scheme 1). Ethoxycarbonylmethyl ester **4a** in 71% yield was obtained also by

alkylation of 1,4-dihydropyridine-3-carboxylic acid **5b** in DMF with ethyl bromoacetate (method **C**).

The structures of the compounds were proved by spectroscopic methods. In the IR spectra of 1,4-DHPs **4, 5** and **6**, absorption bands for $\nu_{C\equiv N}$ at 2199-2204 cm^{-1} (5-cyano, β-amino vinyl conjugation) and at 2250-2260 cm^{-1} (3-$CO_2C_2H_4\underline{CN}$, no conjugation in case of **4b,d**) and bands corresponding to the type of conjugation for $\nu_{C=O}$ are observed. In the ^1H NMR spectra of **4, 5** and **6** the most characteristic are singlets from 4-H protons at 4.73-5.40 ppm, which confirm 1,4-dihydropyridine structure.

As we expected, enzymatic hydrolysis of ethoxycarbonylmethyl 6-methylsulfanyl-1,4-DHP-3-carboxylates **4a,c** yielded both type of acids **7** and **8** (Scheme 2). Hydrolysis of the substrates **4a,c** was performed in the most appropriate reaction conditions taking into account literature data[7] and our experience (phosphate buffer pH 7.5 modified with 15% acetonitrile or dimethyl sulfoxide, water-saturated diisopropyl ether - DIPE), using lipases *Candida antarctica (Novozym 435®* or CAL-B) and *Candida rugosa* (CRL). As the obtained acids and remaining esters are kinetically controlled products, enzyme catalysed hydrolysis was stopped when 45-50% conversion was occurred. When ester **4a** was hydrolysed in presence of CRL, less than 10% of enantiomeric excess was observed both for reaction product - "outer" acid **7a** and for the remaining ester **9a**. Using CRL, no enantioselective hydrolysis was observed for **4c**.



4 7 8 9

a) Ar = C_6H_5; c) Ar = 2-Cl-C_6H_4

Scheme 2. Enzymatic hydrolysis of ethoxycarbonylmethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates **4a,c**.

CAL-B is an efficient catalyst for the enantioselective transformations of various kinds of substrates and is widely used in practice[12-15]. When CAL-B was used for enantioseparation of **4a,c** in phosphate buffer pH 7.5 (modified with acetonitrile at 45 °C, Table 1), hydrolysis of both ester groups ("outer" and "inner") of compounds **4a,c** was observed, but contrary to above mentioned literature data for symmetric 1,4-DHPs (CAL-B hydrolyses only the "outer" ester giving 93% enantiomeric excess)[7], the enantiomeric excess for both acids **7** and **8**, and remaining ester **9** was again very low.

Table 1. Enzyme catalysed hydrolysis of **4a,c** in different solvents at 45 °C

Substrate **4**	Enzyme	Solvent	Time, h.	Acid **7**		Acid **8**		Remaining ester **9**	
				Chem. yield, %*	ee, %	Chem. yield, %*	ee, %	Chem. yield, %*	ee, %
4a	Novozym 435®	MeCN/ Buffer	24	33	10	15	2	46	11
4a	*Candida rugosa*	MeCN/ Buffer	110	45	6	-	-	48	5
4a	Novozym 435®	DIPE/ CH_2Cl_2	20	31	-	18	-	47	-
4a	Novozym 435®	DMSO/ Buffer	24	35	-	15	-	46	-
4c	Novozym 435®	MeCN/ Buffer	34	31	9	13	2	45	10
4c	*Candida rugosa*	MeCN/ Buffer	140	49	-	-	-	49	-

* Chemical yields were determined by HPLC.

When enzymatic hydrolysis of the substrates **4a,c** with CAL-B was carried in water-saturated diisopropyl ether or phosphate buffer modified with dimethyl sulfoxide, no enantioseparation was observed. So, new enzymatically labile groups have to be introduced to get enantioseparation for unsymmetrical sulfur containing 1,4-DHPs.

Conclusion

In conclusion, ethoxycarbonylmethyl and 2-cyanoethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates **4** were synthesized by making use of a one-pot four- and five-component method. Ethoxycarbonylmethyl ester **4a** was obtained also by alkylation of 1,4-dihydropyridine-3-carboxylic acid **5b** with ethyl bromoacetate. By basic hydrolysis of 2-cyanoethyl and ethoxycarbonylmethyl esters **4**, the 1,4-dihydropyridine-3-carboxylic acids **5** and (1,4-dihydropyridine-3-carbonyloxy)acetic acids **6** were prepared, subsequently.

Candida antarctica lipase B catalysed hydrolysis of the unsymmetrical sulfur containing ethoxycarbonylmethyl 1,4-dihydropyridine-3-carboxylates **4a,c** proceeded touching both "inner" and "outer" ester groups yielding slightly enantioenriched acids **7** and **8**.

Experimental

All reagents were purchased from Aldrich or Acros and used without further purification. Lipase B acrylic resin from *Candida antarctica (Novozym 435®)* ≥10,000 U/g, recombinant, expressed in *Aspergillus niger* was used. Melting points were determined on Optimelt MPA100 apparatus and are uncorrected. IR spectra were recorded on a "Shimadzu" IRPrstige-21 spectrometer (in nujol) and peak positions ν_{max} were expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury-200 (200 MHz) spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are expressed in δ (p.p.m. downfield from TMS) and coupling constants (*J*) in Hz. The course of the reactions and the individuality of substances were monitored by TLC on Kieselgel 60 F Merck plates with dichloromethane/hexane/methanol

(5:5:1) as eluent. Determination of enantiomeric excesses of the products **7**, **8** and **9** was performed by direct analysis on a chiral column (R,R)-Whelk-O 1, 4.6x250 mm, 5 μ (Regis) using Shimadzu LC-20AD pump, SPD-M20A diode array detector and Sil-20AC autosampler. The eluent was hexane/dichloromethane/isopropanol with 0.01% acetic acid (80:10:10) and flow rate 1.0 ml/min. Enzymatic reactions were carried out in a New Brunswick Scientific G24 environmental incubatory orbital shaker. Compounds were recrystallized from ethanol.

General procedure for synthesis of ethoxycarbonylmethyl (2-cyanoethyl) 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylates (4a,b) (Method A).

A mixture of 4 mmol of ethoxycarbonylmethyl 3-oxobutyrate **1a** or 2-cyanoethyl 3-oxo-butyrate **1b**, 4 mmol of aldehyde and 0.3 mmol of piperidine in 15 ml of ethanol was stirred for 5 min. Then 4 mmol of 2-cyanothioacetamide and 4.3 mmol of piperidine were added and the mixture was stirred for 25 min. After the 4.3 mmol of methyl iodide were added, the resulting reaction mixture was shortly heated till reflux, cooled to 30-40 ^{o}C and acidified with 1 ml of 3N hydrochloric acid in ethanol and stirred for 1 h at room temperature. The precipitate was filtered, washed with 5 ml of cold (ca. 5 °C) ethanol and 20 ml of water to give products **4a,b**.

Ethoxycarbonylmethyl 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4a). Yellow crystals, yield 59%, mp 129-130 °C. IR: 1681, 1756 (C=O); 2200 (C≡N); 3066, 3270 (NH). ^{1}H NMR ($CDCl_3$): 1.23 and 4.16 (t and q, J = 7 Hz, 5H, Et); 2.41 (s, 3H, 2-Me); 2.48 (s, 3H, SMe); 4.54 (AB quartet, J = 16 Hz, 2H, 3-$COOCH_2$); 4.75 (s, 1H, 4-H); 6.09 (s, 1H, NH); 7.20-7.38 (m, 5H, 4-Ph). Anal. Calcd. for $C_{19}H_{20}N_2O_4S$: C 61.27, H 5.41, N 7.52, S; 8.61 Found: C 60.75; H 5.40; N 7.46; S 8.69.

2-Cyanoethyl 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (**4b).** Yellow crystals, yield 41%, mp 160-162 °C. IR: 1675, (C=O); 2197, 2260 (C≡N); 3316 (NH). ^{1}H NMR ($CDCl_3$): 2.33 (s, 3H, 2-Me); 2.44 (s, 3H, SMe); 2.47 and 4.14 (t and t, J = 6.5 Hz, 4H, 3-$COOCH_2CH_2CN$); 4.59 (s, 1H, 4-H); 6.23 (s, 1H, NH); 7.16-7.27 (m, 5H, 4-Ph). Anal. Calcd. for $C_{18}H_{17}N_3O_2S$: C 63.70, H 5.05, N 12.38, S 9.45; Found: C 63.65, H 5.17, N 12.30, S 9.34.

General procedure for synthesis of ethoxycarbonylmethyl (2-cyanoethyl) 4-(2-chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates (4c,d) (Method B).

A mixture of 4 mmol of ethoxycarbonylmethyl 3-oxo-butyrate **1a** or 2-cyanoethyl 3-oxo-butyrate **1b**, 4 mmol of 3-(2-chlorophenyl)-2-cyanothioacrylamide and 4.3 mmol of piperidine in 15 ml of ethanol was stirred for 25 min. Then 4.3 mmol of methyl iodide was added, the resulting reaction mixture was shortly heated until reflux, cooled to 30-40 ^{o}C, acidified with 1 ml of 3N hydrochloric acid in ethanol and stirred for 1 h at room temperature. The precipitate was filtered, washed with 5 ml of cold (ca. 5 °C) ethanol and 20 ml of water to give products **4c,d**.

Ethoxycarbonylmethyl 4-(2-chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydro-pyridine-3-carboxylate (4c). White crystals, yield 65%, mp 144-145 °C. IR: 1684, 1728 (C=O); 2199 (C≡N); 3336, (NH). ^{1}H NMR ($CDCl_3$): 1.14 and 4.07 (t and q, J = 7 Hz, 5H, Et); 2.34 (s,

3H, 2-Me); 2.40 (s, 3H, SMe); 4.44 (AB quartet, J = 16 Hz, 2H, 3-$COOCH_2$); 5.29 (s, 1H, 4-H); 6.20 (s, 1H, NH); 7.05-7.30 (m, 4H, 4-C_6H_4). Anal. Calcd. for $C_{19}H_{19}ClN_2O_4S$: C 56.09, H 4.71, N 6.88, S 7.88; Found: C 56.01, H 4.79, N 6.81, S 7.92.

2-Cyanoethyl ester 4-(2-chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydropyridine-3-carboxylate (4d). White crystals, yield 64%, mp 151-153 °C. IR: 1654, (C=O); 2199, 2250 (C≡N); 3299 (NH). ^{1}H NMR ($CDCl_3$): 2.35 (s, 3H, 2-Me); 2.41 (s, 3H, SMe); 2.48 and 4.11 (t and t, J = 6.5 Hz, 2H, 3-$COOCH_2CH_2CN$); 5.23 (s, 1H, 4-H); 6.08 (s, 1H, NH); 7.10-7.34 (m, 4H, 4-C_6H_4). Anal. Calcd. for $C_{18}H_{16}ClN_3O_2S$: C 57.83, H 4.31, N 11.24, S 8.58; Found: C 57.80, H 4.36, N 11.16, S 8.51.

General procedure for synthesis of 4-aryl-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydropyridine-3-carboxylic acids (5b,d).

A mixture of 1 mmol of cyanoethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates **4b,d** and 1.3 mmol of KOH in 10 ml of absolute ethanol was stirred at ambient temperature. After 4 h the mixture was acidified until pH ~ 2 with 2M HCl/H_2O. The precipitate was filtered, washed with 5 ml of cold (ca. 5 °C) ethanol and 15 ml of water to give products **5b,d**.

5-Cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylic acid (5b). White crystals, yield 96%, mp 182-184 °C. IR: 1675 (C=O); 2211 (C≡N); 3198, 3267, (NH, OH). ^{1}H NMR (DMSO-d_6): 2.26 (s, 3H, 2-Me); 2.43 (s, 3H, SMe); 4.41 (s, 1H, 4-H); 7.07-7.28 (m, 5H, 4-Ph); 9.27 (s, 1H, NH); 11.95 (s, 1H, OH). Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C 62.92, H 4.93, N 9.78, S 11.20; Found: C 62.96, H 4.94, N 9.58, S 11.10.

4-(2-Chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydropyridine-3-carboxylic acid (5d). White crystals, yield 92%, mp 191-192 °C. IR: 1697, (C=O); 2194 (C≡N); 3326 (NH). ^{1}H NMR (DMSO-d_6): 2.28 (s, 3H, 2-Me); 2.41 (s, 3H, SMe); 5.00 (s, 1H, 4-H); 7.16-7.33 (m, 4H, 4-C_6H_4); 9.27 (s, 1H, NH); 11.87 (s, 1H, OH). Anal. Calcd. for $C_{15}H_{13}ClN_2O_2S$: C 56.16, H 4.08, N 8.73, S 10.00; Found: C 56.33, H 4.00, N 8.63, S 9.91.

Ethoxycarbonylmethyl 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 4a (method C). A mixture of 1 mmol of 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylic acid **(5b)** and 1 mmol of Et_3N in 10 ml of ethanol and 3 ml of DMF was shortly refluxed and stirred for 12 h at room temperature. The precipitate was flash chromatographed with chloroform/hexane/acetone (2:1:1) to give product **4a** as colourless crystals, yield 71%, mp 129-130 °C.

General procedure for synthesis of 4-aryl-5-cyano-2-methyl-6-methylsulfanyl-(1,4-dihydropyridine-3-carbonyloxy)acetic acids (6a,b).

A mixture of 1 mmol of ethoxycarbonylmethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates **4a,c** and 1 mmol of 3N $NaOH/H_2O$ in 10 ml of ethanol was stirred at the ambient

temperature. After 8 h the mixture was acidified until pH ~ 2 with 2M HCl/H_2O. The precipitate was filtered, washed with 5 ml of cold (ca. 5 °C) ethanol and 20 ml of water to give acid **6**.

5-Cyano-2-methyl-6-methylsulfanyl-4-phenyl-(1,4-dihydropyridine-3-carbonyloxy)acetic acid (6a). White crystals**,** yield 82%, mp 163-164 °C. IR: 1687, 1775 (C=O); 2200 (C≡N); 3188, 3273, (NH, OH). ^{1}H NMR ($CDCl_3$): 2.41 (s, 3H, 2-Me); 2.48 (s, 3H, SMe); 4.58 (AB quartet, J = 16 Hz, 2H, 3-$COOCH_2$); 4.73 (s, 1H, 4-H); 6.18 (s, 1H, NH); 7.10-7.38 (m, 5H, 4-Ph). Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C 59.29, H 4.68, N 8.13, S; 9.31 Found: C 59.75; H 4.57; N 8.03; S 9.27.

4-(2-Chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-(1,4-dihydropyridine-3-carbonyloxy)-acetic acid (6b). White crystals**,** yield 63%, mp 119-121 °C. IR: 1644, 1717 (C=O); 2193 (C≡N); 3325, 3625 (NH, OH). ^{1}H NMR (DMSO-d_6): 2.27 (s, 3H, 2-Me); 2.40 (s, 3H, SMe); 4.33 (AB quartet, J = 16 Hz, 2H, 3-$COOCH_2$); 5.05 (s, 1H, 4-H); 7.06-7.36 (m, 4H, 4-C_6H_4); 9.50 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{15}ClN_2O_4S$: C 53.90, H 3.99, N 7.39, S 8.46; Found: C 53.78, H 4.12, N 7.33, S 8.40.

General procedure for enzymatic hydrolysis of ethoxycarbonylmethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates 4a,c.

0.2 mmol of 1,4-dihydropyridine **4a,c** were dissolved in 20 ml of solvent system and heated to 45 ^{o}C, after which 80 mg of enzyme was added. The resulting mixture was shaken at 350 rpm and heated at 45 ^{o}C. Reactions were monitored by HPLC and were stopped when 45-50% of acids were formed. Solvent systems: 3 ml of acetonitrile or dimethyl sulfoxide and 17 ml of 20 mM K_2HPO_4/KH_2PO_4 buffer, pH 7.5, 3 ml of dichloromethane and 17 ml of water-saturated diisopropyl ether. The results are combined in Table 1.

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