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SYNTHESIS AND ENANTIOSELECTIVE LIPASE-CATALYZED KINETIC RESOLUTION OF METHYL 6-(METHOXYCARBONYL-METHYL)SULFANYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLATES

A series of methyl 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridine-3-carboxylates as more lipophilic derivatives of biologically active 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylic acid esters have been prepared by alkylation of 6-thioxo-1,4-dihydropyridines with methyl bromoacetate. Kinetic resolution catalyzed by *Candida antarctica* lipase B (Novozym 435®) has been investigated; enantiomeric excess of the target products reached 70%. The experiments revealed that 6-(methoxycarbonylmethyl)sulfanyl group is an essentially new activating group, which being removed by 5 bonds from chiral center undergoes easy enzymatic hydrolysis and could be used for kinetic resolution of racemic 1,4-dihydropyridines.

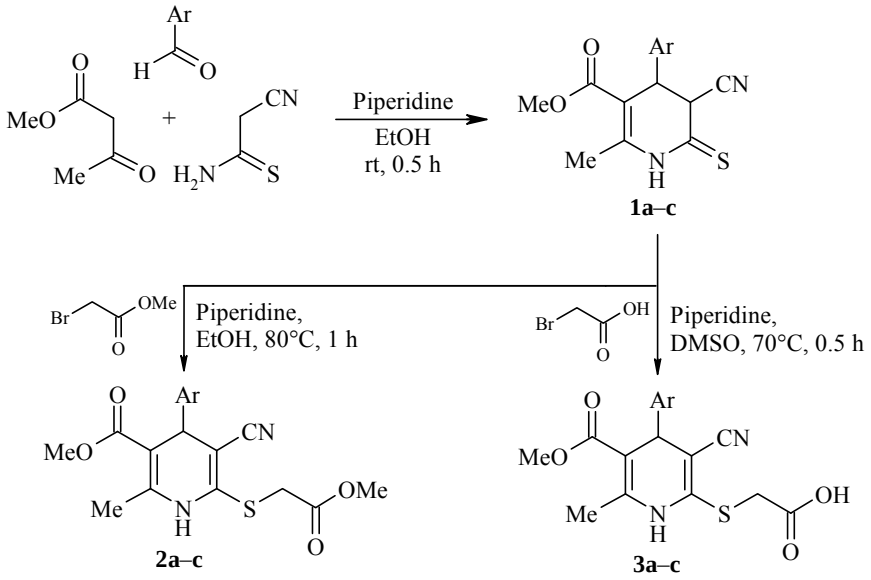
Keywords: dihydropyridines, *Candida antarctica* lipase B, enzymatic kinetic resolution.

1,4-Dihydropyridines (1,4-DHPs) are known as calcium channel effectors and antagonists. Many cardiovascular drugs on their basis are currently in use in the clinics or still are in different stages of development [1–4]. Pharmacology of 1,4-DHPs is at the eve of a novel boom: the academic interest is growing towards pharmacological activities which are not related (or are only partially related) to their L-type calcium channel antagonist properties: neurotropic (antiamnestic, anticonvulsant, neuroregulatory) [5], membrane protecting [6–8], radioprotecting [9], analgesic [10], antidiabetic [11], antitumor [12], antitubercular [13], anti-inflammatory [14], gene-transfection [15], and as uroselective agents for treatment of benign prostatic hyperplasia [16]. Some 1,4-DHPs have also shown the ability to modulate N-type calcium channel, and have been studied as anticonvulsants [17], stress protective agents [18], and cardio depressants [19].

6-Alkylsulfanyl-substitued 1,4-DHPs display cardiovascular [20–24], hepatoprotective [25], antioxidant [26], and antiradical [27] activities, however, these compounds are still insufficiently studied.

The enantiomers of chiral 1,4-DHPs usually differ in their biological activities, and can even have an opposite action profile [28–30]. Chemoenzymatic methods for preparation of optically pure drugs have a number of advantages: it is simple, direct, efficient, mild, and cheap in case of repeated use of the enzyme. Incorporation of an enzymatically labile functional group, which allow kinetic resolution of monocyclic 1,4-DHPs, has been used as a conventional technique for the last decade [30–32].

The objective of this work was the preparation of enantiopure 1,4-DHPs containing lipophilic (methoxycarbonylmethyl)sulfanyl group at position 6. We expected that the enzymatic hydrolysis of this group could promote kinetic resolution of the target 1,4-DHPs. The starting 4-aryl-5-cyano-3-methoxycarbonyl-2-methyl-1,4-dihydropyridine-6-thiones **1a**–**c** were prepared by a one-pot three-component condensation of the methyl acetoacetate, aromatic aldehyde and 2-cyanothioacetamide according to the previously described synthetic protocol [33, 34].



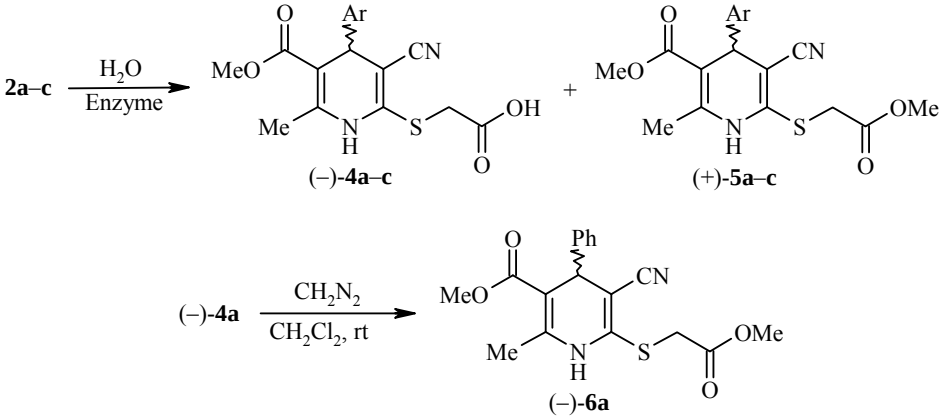
1–**3** **a** Ar = Ph; **b** Ar = 2-ClC_6H_4; **c** Ar = 2-$F_2HCOC_6H_4$

Alkylation of thiones **1a**–**c** bearing several nucleophilic reaction centres (C-5, S, N atoms) under mild reaction conditions with methyl bromoacetate proceeds preferably at the sulfur atom giving methyl 4-aryl-5-cyano-6-(methoxycarbonyl-methyl)sulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylates **2a**–**c**. Carboxylic acids **3a**–**c** as references compounds for the investigation of enzyme catalyzed hydrolysis were prepared by alkylation of thiones **1a**–**c** with bromoacetic acid in the presence of piperidine.

Enzymatic screening of the substrates **2a**–**c** was performed in water-saturated diisopropyl ether (DIPE), water-saturated *tert*-butyl methyl ether and phosphate buffer pH 7.5, modified (or not) with 15% MeCN at 20 to 50°C by using protease P6 (*Aspergillus melleus*), acylase 30,000 (*Aspergillus* sp.), *Candida rugosa* lipase (CRL) and *Candida antarctica* lipase B (CAL-B, Novozym 435®). In the case of methyl 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridine-3-carboxylates **2a**–**c**, protease P6 and acylase 30,000 were inactive. CRL-catalyzed hydrolysis of the (methoxycarbonylmethyl)sulfanyl group in phosphate buffer was rather slow, but Novozym 435® showed significant hydrolytic activity both in water-saturated DIPE and in phosphate buffer.

Kinetic resolution of methyl 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydro-pyridine-3-carboxylates **2a**–**c** in the presence of Novozym 435® were investigated in more detail. As we have found, the concentration of substrate in water-saturated DIPE had to be less than 0.01%, otherwise precipitation took place. To increase the solubility of methyl 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridine-3-carboxylates **2a**–**c**, 1–3% of dichloromethane (DCM) was added to the reaction mixture. It increased the reaction rate, but decreased the enantioselectivity.

The formed acid **4a**–**c** and the remaining ester **5a**–**c** were separated by column chromatography. Yields and the enantiomeric excess (*ee*) of esters **5a**–**c** were determined by HPLC equipped with Whelk O1 and Lux Cellulose-2 (Table). The enantiomeric excess values ranged between 10 to 70%, depending on the substituent at position 4. The reaction time is longer and the enantioselectivity is better at room temperature than at 45°C.



4, **5** **a** Ar = Ph; **b** Ar = 2-ClC_6H_4; **c** Ar = 2-$F_2HCOC_6H_4$

Reaction conditions and yields of enzymatic hydrolysis*

Substrate	DCM–DIPE ratio, v/v	T, °C	Time, h	Yield, %		*ee* of compound **5**, %
				Compound **4**	Compound **5**	
2a	1:57	rt	1.5	46	49	53
2b	1:33	rt	1.5	47	46	70
2c	1:100	rt	1.5	45	46	10
2a	1:16	rt	1.5	46	46	43
2b	1:16	rt	1.5	48	47	51
2c	1:16	rt	1.5	44	45	10
2a	1:57	45	1.0	45	48	49
2b	1:33	45	1.0	45	45	67
2c	1:100	45	1.0	47	46	8

* Isolated yields and enantiomeric excess values were measured after column chromatography.

Since the enantiomeric excess of carboxylic acids **4a**–**c** could not be determined by given HPLC methods, acid (–)-**4a** was methylated with diazomethane and enantiomeric excess was measured for the corresponding methyl (–)-6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridine-3-carboxylate (–)-**6a**, which appeared to be 25%. Absolute configurations of the obtained enantioenriched esters **5a**–**c** and **6a** are still unknown because we have not succeeded in growing crystals for the X-ray analysis.

In conclusion, new methyl 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridine-3-carboxylates as more lipophilic derivatives of biologically active methyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates have been prepared by alkylation of 1,4-dihydropyridine-6-thiolates with methyl bromoacetate, and their kinetic resolution catalyzed by *Candida antarctica* lipase B has been investigated. Our experiments allowed to the characterize 6-(methoxycarbonylmethyl)sulfanyl group as an essentially new activating group, which being removed by 5 bonds from the chiral center could be used for kinetic resolution of racemic 1,4-DHPs. The stereoselectivity of the immobilized *Candida antarctica* lipase B under the studied conditions (water-saturated DIPE, 25–45°C, excess of substrate with regard to lipase) toward the methyl 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridine-3-carboxylates was moderate.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 580 B spectrometer in nujol. ^{1}H NMR spectrum of compound **1c** was recorded on a Varian Mercury 200BB spectrometer (200 MHz), ^{1}H and ^{13}C NMR spectra of remaining compounds were recorded on a Varian 400-MR spectrometer (400 and 100 MHz respectively). DMSO-d_6 was used as solvent for compounds **3b**,**c**, $CDCl_3$ – for remaining compounds. HMDSO was used as internal standard (δ 0.055 ppm). Mass spectral data were determined on an Acquity UPLC system (Waters) connected to a micrOTOF-Q mass spectrometer operating in the ESI positive or negative ion mode on an Acquity UPLC BEH C18 column (1.7 μm, 2.1 × 50 mm) using a gradient elution with MeCN–HCOOH (0.1%) in water. The enantiomeric excesses were analyzed by HPLC on a Lux Cellulose-2 phase column (4 μm, 4.6 × 150 mm), eluent 0.1% AcOH in 2-PrOH–hexane, 50:50, flow rate 1 ml/min, detection at 254 nm. Elemental analyses were determined on an EA 1106 (Carlo Erba Instruments). Melting points were determined on an OptiMelt (SRS Stanford Research Systems). Optical rotation values were measured with a Rudolph Research Analytical autopol VI automatic polarimeter. TLC was performed on 20 × 20 cm Silica gel TLC-PET F254 foils (Fluka). All reagents were purchased from Aldrich, Acros, Fluka or Merck and used without further purification.

Preparation of compound **1a** was described in [33], compound **1b** – in [34], compounds **2a** and **3a** – in [35].

Methyl 5-cyano-4-(2-difluoromethoxyphenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (1c). A mixture of 2-(difluoromethoxy)benzaldehyde (0.69 g, 4.0 mmol), methyl acetoacetate (0.46 g, 4.0 mmol), and piperidine (0.04 ml, 0.4 mmol) in EtOH (20 ml) was stirred for 5 min at room temperature. Then 2-cyanothioacetamide (0.40 g, 4.0 mmol) and piperidine (0.40 ml, 4.0 mmol) were added, and the reaction mixture was stirred for 30 min. The resulting reaction mixture was acidified with 2.4 ml of 3N hydrochloric acid in EtOH. The precipitate was separated by filtration, washed with cold (–10°C) MeOH (5 ml) and water (20 ml). Yield 0.94 g (67%). Yellow powder. Mp 121–122°C. IR spectrum, ν, cm^{-1}: 3309 (N–H), 2198 (C≡N), 1714 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (1.5H, s) and 2.53 (1.5H, s, 2-CH_3 (*cis*- and *trans*-)); 3.59 (1.5H, s) and 3.61 (1.5H, s, $COOCH_3$ (*cis*- and *trans*-)); 4.11 (0.5H, d, *J* = 7.4) and 4.80 (0.5H, d, *J* = 1.8, H-5 (*cis*- and *trans*-)); 4.17 (0.5H, d, *J* = 7.4) and 5.00 (0.5H, d, *J* = 7.4, H-4 (*cis*- and *trans*-)); 6.58 (1H, t, *J* = 73.2, $OCHF_2$); 6.84–7.30 (4H, m, H Ar); 8.81 (1H, br. s, NH). Found, %: C 54.40; H 4.11; N 7.87. $C_{16}H_{14}F_2N_2O_3S$. Calculated, %: C 54.54; H 4.00; N 7.95.

Methyl 4-(2-chlorophenyl)-5-cyano-6-(methoxycarbonylmethyl)sulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate (2b). A mixture of thione **1b** (0.32 g, 1.0 mmol) and piperidine (0.10 ml, 1.0 mmol) in EtOH (20 ml) was stirred 10 min at room temperature. Then methyl bromoacetate (0.12 ml, 1.3 mmol) was added and the reaction mixture was stirred at 80°C for 1 h. The precipitate was separated by filtration, washed with cold (–10°C) MeOH (5 ml) and water (20 ml). Yield 0.35 g (90%). White powder. Mp 159–161°C. IR spectrum, ν, cm^{-1}: 3309 (N–H), 2198 (C≡N), 1714 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, 2-CH_3); 3.54 (2H, AB system, *J* = 16.0, SCH_2); 3.54 (3H, s, 3-$COOCH_3$); 3.78 (3H, s, $CH_2COOC\underline{H}_3$); 5.24 (1H, s, H-4); 7.00–7.30 (4H, m, H Ar); 8.51 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 19.3 (2-CH_3); 34.7 (SCH_2); 39.2 (C-4); 51.2 ($CH_2COO\underline{C}H_3$); 53.7 (3-$COO\underline{C}H_3$); 90.9 (C-3); 101.3 (C-5); 117.9 (C≡N); 127.4 (C Ar); 128.4 (C Ar); 129.7 (C Ar); 130.2 (C Ar); 132.3 (C Ar); 141.9 (C Ar); 145.4 (C-6); 145.5 (C-2); 167.0 (3-$\underline{C}OOCH_3$); 173.1 ($CH_2\underline{C}OOCH_3$). Mass-spectrum, *m/z* (I_{rel}, %): 393 $[M+H]^+$ (100), 281 $[M–Ar]^+$ (47). Found, %: C 55.23; H 4.21; N 7.02. $C_{18}H_{17}ClN_2O_4S$. Calculated, %: C 55.03; H 4.36; N 7.13.

Methyl 5-cyano-4-(2-difluoromethoxyphenyl)-6-(methoxycarbonylmethyl)sulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate (2c). Compound **2c** was prepared in the same manner as compound **2b** using thione **1c** instead of thione **1b**. Yield 0.32 g (76%). Mp 180–181°C. IR spectrum, ν, cm^{-1}: 3309 (N–H), 2198 (C≡N), 1714 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, 2-CH_3); 3.50 (3H, s, 3-$COOCH_3$); 3.51 (2H,

AB system, J = 16.0, SCH_2); 3.78 (3H, s, $CH_2COOC\underline{H}_3$); 5.00 (1H, s, H-4); 6.48 (1H, dd, J = 73.2, J = 2.7, $OCHF_2$); 7.00–7.30 (4H, m, H Ar); 8.36 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 19.4 (2-CH_3); 34.7 (SCH_2); 37.2 (C-4); 51.1 ($CH_2COO\underline{C}H_3$); 53.7 (3-$COO\underline{C}H_3$); 90.5 (C-3); 100.6 (C-5); 116.6 (t, J = 259.2, $OCHF_2$); 118.1 (C≡N); 125.7 (C Ar); 128.4 (C Ar); 130.3 (C Ar); 132.3 (C Ar); 135.4 (C Ar); 142.0 (C Ar); 145.6 (C-6); 148.8 (C-2); 167.1 (3-$\underline{C}OOCH_3$); 173.0 ($CH_2\underline{C}OOCH_3$). Mass-spectrum, *m/z* (I_{rel}, %): 447 $[M+Na]^+$ (100), 425 $[M+H]^+$ (35), 296 $[M–Ar]^+$ (53). Found C 53.64; H 4.42; N 6.55. $C_{19}H_{18}F_2N_2O_5S$. Calculated, %: C 53.77; H 4.27; N 6.60.

Methyl 6-(carboxymethyl)sulfanyl-4-(2-chlorophenyl)-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylate (3b). A mixture of thione **1b** (0.32 g, 1.0 mmol) and piperidine (0.1 ml, 1.0 mmol) in DMSO (20 ml) was stirred 10 min at room temperature. Then bromoacetic acid (0.14 g, 1.0 mmol) was added and the reaction mixture was stirred at 70°C for 30 min. Resulting mixture was diluted with water (30 ml) and extracted with EtOAc (3 × 30 ml). The combined organic extracts were evaporated and crystallized from CH_2Cl_2. The precipitate was separated by filtration, washed with cold (–10°C) MeOH (5 ml) and water (20 ml). Yield 0.33 g (87%). White powder. Mp 165–167°C. IR spectrum, ν, cm^{-1}: 3225 (N–H), 3175 (O–H), 2216 (C≡N), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, 2-CH_3); 3.44 (3H, s, $COOCH_3$); 3.81 (2H, AB system, J = 15.6, SCH_2); 5.07 (1H, s, H-4); 7.17–7.39 (4H, m, H Ar); 9.59 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 18.5 (2-CH_3); 34.7 (SCH_2); 39.2 (C-4); 53.7 (3-$COO\underline{C}H_3$); 90.0 (C-3); 101.3 (C-5); 118.9 (C≡N); 127.2 (C Ar); 128.3 (C Ar); 129.5 (C Ar); 130.2 (C Ar); 132.1 (C Ar); 141.7 (C Ar); 145.4 (C-6) 145.5 (C-2); 166.9 (3-$\underline{C}OOCH_3$); 172.8 ($CH_2\underline{C}OOH$). Mass spectrum, *m/z* (I_{rel}, %): 401 $[M+Na]^+$ (21), 379 $[M+H]^+$ (100), 267 $[M–Ar]^+$ (68). Found, %: C 53.80; H 3.81; N 7.22. $C_{17}H_{15}ClN_2O_4S$. Calculated, %: C 53.90; H 3.99; N 7.39.

Methyl 6-(carboxymethyl)sulfanyl-5-cyano-4-(2-difluoromethoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (3c). Compound **3c** was prepared in the same manner as compound **3b** using thione **1c** instead of thione **1b**. Yield 0.33 g (81%). Mp 122–124°C. IR spectrum, ν, cm^{-1}: 3225 (N–H), 3175 (O–H), 2216 (C≡N), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, 2-CH_3); 3.45 (3H, s, $COOCH_3$); 3.80 (2H, AB system, J = 15.6, SCH_2); 4.90 (1H, s, H-4); 6.58 (1H, t, J = 73.9, $OCHF_2$); 7.08–7.31 (4H, m, H Ar); 9.50 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 19.3 (2-CH_3); 34.7 (SCH_2); 37.1 (C-4); 53.7 (3-$COO\underline{C}H_3$); 90.5 (C-3); 100.4 (C-5); 118.1 (C≡N); 116.3 (t, J = 259.2, $OCHF_2$); 125.5 (C Ar); 128.3 (C Ar); 130.1 (C Ar); 132.2 (C Ar); 135.4 (C Ar); 141.9 (C Ar); 145.4 (C-6); 148.7 (C-2); 167.0 (3-$\underline{C}OOCH_3$); 173.0 ($CH_2\underline{C}OOH$). Mass-spectrum, *m/z* (I_{rel}, %): 433 $[M+Na]^+$ (85), 411 $[M+H]^+$ (100), 267 $[M–Ar]^+$ (24). Found, %: C 52.40; H 3.82; N 6.73. $C_{18}H_{16}F_2N_2O_5S$. Calculated, %: C 52.68; H 3.93; N 6.83.

Preparative hydrolysis of esters 2a–c catalysed by *Candida antarctica* lipase B (CAL-B, Novozym 435®) (General Method). To a solution of ester **2a–c** (1 mmol) in dichloromethane (2 ml) an appropriate amount of diisopropylether was added to reach the desired solvent ratio, as mentioned in the Table. Then Novozym 435® (≥10,000 U/g, 0.4 g) was added and the reaction mixture was stirred (300 rpm) at the appropriate temperature. Probe samples (10–20 μl) were taken with syringe every 10–20 min, diluted with 75% aq. MeCN solution (1 ml) and analyzed by HPLC. The reaction was stopped when ~50% of acid **4a–c** was formed (HPLC). Blank reactions without enzyme showed no conversion of substrate. Then enzyme was filtered off, the filtrate was evaporated under reduced pressure at 50°C to dryness and the residue was separated by flash chromatography to give acids **4a–c** and esters **5a–c**, which were analyzed on HPLC. The spectral characteristics of optically active acids **4a–c** and esters **5a–c** correspond to that of the corresponding racemates **3a–c** and **2a–c**.

Methyl 6-(carboxymethyl)sulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((–)-4a). Yield 0.16 g (46%). Mp 122–123°C. $[\alpha]_D^{20}$ –2.9° (*c* 1, MeOH).

Methyl 5-cyano-6-(methoxycarbonylmethyl)sulfanyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((+)-5a). Yield 0.18 g (49%). Mp 160–161°C. $[\alpha]_D^{20}$ +55.1° (*c* 1, MeOH).

Methyl 5-cyano-6-(methoxycarbonylmethyl)sulfanyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((–)-6a). A mixture of acid (–)-**4a** (0.1 g, 0.3 mmol), 0.5M diazomethane solution in Et_2O (1.0 ml), and CH_2Cl_2 (7 ml) was stirred for 10 min at room temperature. The precipitate was separated by filtration, washed with cold (–10°C) MeOH (5 ml) and water (20 ml). Yield 0.10 g (97%). White powder. Mp 159–161°C. $[\alpha]_D^{20}$ –19.2° (*c* 1, MeOH). IR spectrum, ν, cm^{-1}: 3309 (N–H), 2198 (C≡N), 1714 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, 2-CH_3); 3.50 (3H, s, 3-$COOCH_3$); 3.51 (2H, AB system, *J* = 16.0, SCH_2); 3.78 (3H, s, $CH_2COOC\underline{H}_3$); 5.24 (1H, s, H-4); 7.06–7.28 (5H, m, H Ph); 8.37 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 19.4 (2-CH_3); 34.8 (SCH_2); 42.4 (C-4); 51.2 ($CH_2COO\underline{C}H_3$); 53.7 (3-$COO\underline{C}H_3$); 91.5 (C-3); 101.5 (C-5); 118.5 (C≡N); 127.2 (C Ph); 127.3 (C Ph); 128.7 (C Ph); 141.5 (C Ph); 144.3 (C-6); 145.0 (C-2); 167.2 (3-$\underline{C}OOCH_3$); 173.0 ($CH_2\underline{C}OOCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 359 $[M+H]^+$ (100), 281 $[M–Ph]^+$ (61). Found, %: C 60.22; H 5.11; N 7.86. $C_{18}H_{18}N_2O_4S$. Calculated, %: C 60.32; H 5.06; N 7.82.

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