DOI: 10.1002/ejoc.200900982

Preparation of Arylmercapturic Acids by *S*-Arylation of *N*,*N*′-Diacetylcystine

Jan Krouželka[a] and Igor Linhart*[a]

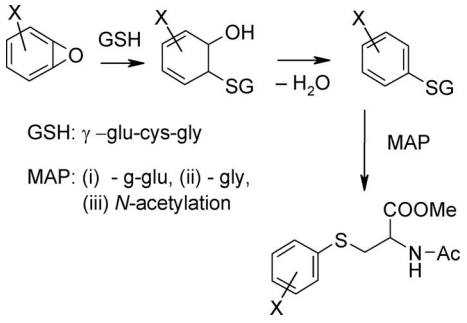
Keywords: Arylation / Sulfides / Copper / Amino acids / Reaction mechanisms

A simple convenient method has been developed for the preparation of *N*-acetyl-*S*-arylcysteines based on the Chan–Lam–Evans arylation of *N*,*N*′-diacetylcystine dimethyl ester with arylboronic acids and used to synthesize a series of arylmercapturic acids. Unlike copper-mediated *N*-arylation, the *S*-arylation of neither cysteine nor cystine derivatives proceeded satisfactorily in the presence of air.

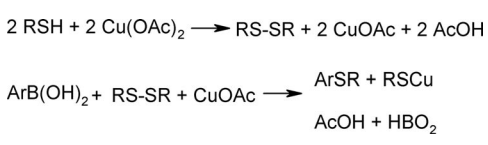
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

Electrophilic arene oxides react in vivo with glutathione, a cellular tripeptide that provides first-line protection against the attack of electrophiles and free radicals. The glutathione (GSH) conjugates formed undergo subsequent aromatization and biotransformation by the mercapturic acid pathway (MAP) to afford *N*-acetyl-*S*-arylcysteines, mercapturic acids, as metabolic end-products excreted in urine (Scheme 1).[1] The presence of mercapturic acids indicates internal exposure to potentially mutagenic and carcinogenic compounds, for example, phenylmercapturic acid has been used in occupational medicine as a biomarker of exposure to benzene, reflecting its metabolic activation to benzene oxide.[2] A traditional method for the synthesis of arylmercapturic acids was based on the addition of arenethiols to 2-acetamidopropenoate.[3] Another approach used the reaction of arenediazonium salts with *N*-acetylcysteine.[4] However, recent developments in organometallic chemistry have provided new possibilities for aryl–sulfur bond-forming reactions by using palladium[5] or copper[6] complexes. Aryl iodides can be used as substrates for copper- or palladium-mediated arylation of the thiol group of *N*-acetylcysteine to give mercapturic acids.[7] Over the last two decades a wide range of arylboronic acids have become readily commercially available so that nowadays they are reactants of choice for various arylation reactions including *S*-arylation. They have also been used successfully for Cu^{II}-mediated *S*-arylation of *N*-protected cysteine derivatives.[8] Although various *S*-arylation procedures have been developed for the preparation of unsymmetrical sulfides, that of Guy and co-workers[8] seems to be exceptional because of its ability to arylate aliphatic thiols in high yields by using arylboronic acids as the starting material. Interestingly, more than 1 equiv. of Cu^{II} was needed in this procedure. Liebeskind and co-workers noted that thiols are easily oxidised by Cu^{II} to disulfides, which are actually the ultimate substrates for *S*-arylation.[9] They found that, indeed, dialkyl disulfides react with arylboronic acids in the presence of at least a stoichiometric amount of Cu^{I} salts to give the corresponding alkyl aryl sulfides and 1 equiv. of Cu^{I} thiolate, which is inactive as a catalyst (Scheme 2).



Scheme 1. In vivo formation of mercapturic acids from arene oxides.



Scheme 2. Stoichiometry of the arylation of thiols with arylboronic acids according to Liebeskind and co-workers.[9]

The aim of this work was to develop a suitable *S*-arylation procedure for the synthesis of mercapturic acids bearing a wide range of aryl groups.

[a] Department of Organic Chemistry, Faculty of Chemical Technology, Institute of Chemical Technology Prague,
Technická 1905, 166 28 Prague, Czech Republic
Fax: +420-220-444-288
E-mail: linharti@vscht.cz

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

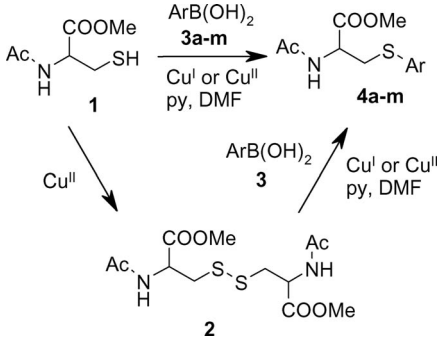
Results and Discussion

In our early attempts to arylate *N*-acetylcysteine methyl ester (**1**) with phenylboronic acid (**3a**) under the conditions of Guy and co-workers[8] (2.2 equiv. of boronic acid, 1.5 equiv. of Cu^{II} acetate and 3 equiv. of pyridine) we found that the yield of **4a** was 63% based on **1** (Table 1, entry 1). This represents significantly more than a quantitative yield when the stoichiometry outlined in Scheme 2 is taken into account. To explain this discrepancy and to gain an insight into the reaction mechanism we performed a series of experiments using **1** or *N*,*N*′-diacetylcystine dimethyl ester (**2**) with various amounts of Cu^{I} or Cu^{II} acetates (Scheme 3); the results are shown in Table 1.

Table 1. Preparation of *S*-phenylmercapturic acid (**4a**) by copper-mediated arylation. Optimization of the reaction conditions.[a]

Entry	Starting material	Mediator		Pyridine	% Yield[b] of **4**
		Cu cat.	Amount		
1	**1**	$Cu(OAc)_2$	1.5 equiv.	3 equiv.	63
2	**1**	CuOAc	1.0 equiv.	3 equiv.	3
3	**1**	CuOAc	1.5 equiv.	3 equiv.	53
4	**1**	CuOAc	2.0 equiv.	3 equiv.	55
5	**1**	$Cu(OAc)_2$	1.5 equiv.	3 equiv.	13[c]
6	**1**	$Cu(OAc)_2$	1.5 equiv.	10 equiv.	0[d]
7	**1**	$Cu(OAc)_2$	1.5 equiv.	–	0[e]
8	**2**	CuOAc	3.0 equiv.	–	0[f]
9	**2**	CuOAc	3.0 equiv.	6 equiv.	23[c]
10	**2**	CuOAc	3.0 equiv.	6 equiv.	96
11	**2**	CuOAc	2.0 equiv.	6 equiv.	69
12	**2**	$Cu(OAc)_2$	3.0 equiv.	6 equiv.	78

[a] The reactions were performed in DMF at 100 °C. [b] Isolated yields. [c] In the presence of dry air. [d] Methyl 2-acetamidopropenoate was isolated as the sole product. [e] NaH (1 equiv.) was added as a base. [f] K_2CO_3 (3 equiv.) was used instead of pyridine.



Scheme 3. Arylation of *N*-acetylcysteine methyl and *N*,*N*′-diacetylcystine dimethyl esters.

DMF was used as the solvent and pyridine (3 equiv.) was added to act as a ligand. Thiol **1** with 1.0 equiv. of Cu^{I} gave only 3% of **4a** due to the strong binding of Cu^{I} to the cysteine thiol group leading to an inactive Cu^{I} thiolate. The optimal amount of Cu^{I} for this reaction appears to be 1.5 equiv. Addition of more than 1.5 equiv. of Cu^{I} did not further improve significantly the yield of **4a** (Table 1, entries 2–4). These results strongly suggest that Cu^{I} thiolate formed upon reaction with Cu^{I} acetate in the presence of pyridine as the base serves as a substrate for arylation, however, additional Cu^{I} ions are needed to catalyse the reaction. Replacement of pyridine by phenanthroline as a stronger ligand as well as by potassium carbonate as a simple inorganic base led to elimination to yield methyl 2-acetamidopropenoate, and no arylation product was formed. Similarly, increasing the amount of pyridine to 10 equiv. gave the eliminated acetamidopropenoate.

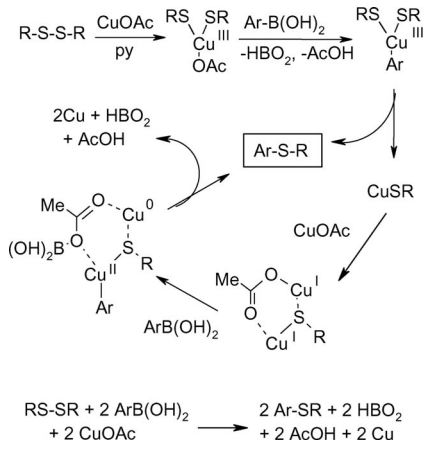
N,*N*′-Diacetylcystine dimethyl ester (**2**) was tested as another starting material for the *S*-arylations. Its reaction with 3 equiv. of Cu^{I} acetate and 6 equiv. of pyridine (corresponding to 1.5 equiv. of Cu^{I} acetate and 3 equiv. of pyridine for each sulfur in **2**) gave an almost quantitative yield with phenylboronic acid (**3a**). Decreasing the amount of Cu^{I} to 2 equiv. led to a marked decrease in the yield (Table 1, entries 10 and 11). With Cu^{II} acetate the reaction also proceeded satisfactorily (Table 1, entry 12). Nevertheless, the optimum yield was obtained with cystine **2** as the starting material and 3.0 equiv. of Cu^{I} as the mediator.

Although Cu^{I} thiolates were not active either as catalysts or as mediators of the reaction, they could be used as starting materials provided that an additional copper salt, Cu^{I} acetate, was added. Thus, Cu^{I} butanethiolate and 1.5 equiv. of phenylboronic acid with 1 equiv. of CuOAc and 3 equiv. of pyridine gave a 47% yield of butyl phenyl sulfide. Similarly, the Cu^{I} salt of **1** under the same conditions gave 62% of **4a**. The reaction appears to be rather non-selective as far as the starting material is concerned.

Unlike copper-catalysed *N*-arylations, which require air oxygen to proceed,[6a] the *S*-arylation required anoxic conditions. In the presence of dry air the yields were much lower (Table 1, compare entries 1 and 5 and 9 and 10). Similarly, the addition of water (3% in DMF) to the reaction mixture decreased the yield of **4d** from 50 to 28%. Tolylboronic acid **3d** was chosen for this experiment because it was expected that the addition of water might improve the solubility of the catalytic species and thereby measurably increase the yield. A possible mechanism for the arylation of disulfides is outlined in the Scheme 4. Pyridine ligands are not shown for the sake of simplicity, although the reaction did not proceed at all when pyridine was omitted from the reaction mixture (Table 1, entries 6 and 7). Pyridine acts as a ligand rather than a base and seems to play an important role in tuning the reactivity of the intermediary Cu complex. The reaction sequence begins with an oxidative addition of the disulfide to Cu^{I} followed by transmetallation of the boronic acid with Cu^{III} and reductive elimination to yield alkyl aryl sulfide and Cu^{I} thiolate, which is arylated in the presence of Cu^{I} acetate. The mechanism for this second arylation is not clear but it has been proved that Cu^{I} thiolates can be arylated under the reaction conditions used. The role of Cu^{I} acetate seems to be crucial and can be explained by the formation of a six-membered-ring complex followed by oxidative addition of arylboronic acid and reductive elimination of the aryl sulfide, as outlined in Scheme 4. With most of the arylboronic acids used this second arylation step apparently did not proceed well so that the yields were only around 50% when the arylation of both sulfur atoms in **2** is considered. Nevertheless, yields of more than 50%, which represents more than 100% when a single

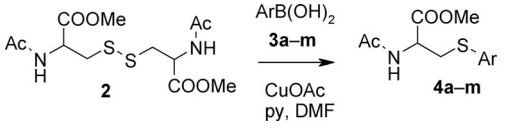
 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

arylation step is considered, were obtained with eight out of the thirteen boronic acids tested, two of them giving nearly quantitative yields (Table 2). Theoretically, 2 equiv. of Cu^{I} should suffice for the arylation of **2**, however, an excess of Cu^{I} acetate led to a better yield (Table 1, entries 10 and 11). A precipitate of Cu^{I} thiolate and/or Cu^{0} was formed in the course of reaction, which may explain this observation. Part of the catalytic species may be removed with the precipitate and thereby made unavailable for the reaction.



Scheme 4. Proposed mechanism for the arylation of disulfides and the overall stoichiometry of the reaction.

Table 2. Arylation of *N*,*N*′-diacetylcystine dimethyl ester (**2**) by arylboronic acids $ArB(OH)_2$ **3a**–**3m** in DMF at 100 °C in the presence of Cu(OAc) (3 equiv.) and pyridine (6 equiv.).[a]



Entry	Ar	Boronic acid	Product	% Yield[a]
1	phenyl	**3a**	**4a**	96
2	2-tolyl	**3b**	**4b**	48
3	3-tolyl	**3c**	**4c**	53
4	4-tolyl	**3d**	**4d**	50
5	3-vinylphenyl	**3e**	**4e**	56
6	4-vinylphenyl	**3f**	**4f**	56
7	4-methoxyphenyl	**3g**	**4g**	48
8	3-chlorophenyl	**3h**	**4h**	52
9	4-chlorophenyl	**3i**	**4i**	63
10	4-cyanophenyl	**3j**	**4j**	36
11	2-methoxycarbonylphenyl	**3k**	**4k**	24
12	3-methoxycarbonylphenyl	**3l**	**4l**	98
13	4-methoxycarbonylphenyl	**3m**	**4m**	56

[a] Isolated yields.

Unlike the reactions with *N*-arylsulfanylsuccinimides, which were used by Liebeskind and co-workers[9] as disulfide equivalents, the reactions with disulfides do not proceed catalytically, requiring at least 2 equiv. of Cu^{I} acetate, that is, 1 equiv. for each sulfur of the disulfide. Undoubtedly, this is a disadvantage of our procedure. Therefore, we tested another *S*-arylation process, that described by Taniguchi.[10] This procedure was reported to give good yields with diverse diaryl disulfides. Dibutyl disulfide was the only aliphatic compound in this series. Its arylation by phenylboronic acid yielded 29% of butyl phenyl sulfide.[10] Under the same conditions ($DMSO/H_2O$, 2:1, 5 mol-% CuI-bpy, 24 h in air), the reaction of **2** with **3a** yielded nearly 20% of **4a**, as determined analytically by ^1H NMR spectroscopy. The isolated yield was 9%, which indicates some catalytic turnover but, anyway, such a result is unsatisfactory.

The procedure described in this paper appears to be, despite the need for an excess of Cu^{I}, more suitable for the preparation of arylmercapturic acids than the catalytic process of Taniguchi.[10] It is also a convenient alternative to the Pd-catalysed arylation of *N*-acetylcysteine by aryl iodides.[7a]

Conclusions

Copper-mediated arylation of disulfides by arylboronic acids is an efficient tool for the preparation of arylmercapturic acids. Although both thiols and disulfides can be arylated by arylboronic acids in the presence of either CuOAc or $Cu(OAc)_2$, the use of disulfides as the starting materials and CuOAc as the mediator proved to be the most suitable for achieving high yields of arylmercapturic acids.

Experimental Section

General: Column chromatography was performed on silica gel 60 purchased from Fluka, particle size 0.063–0.200 mm. For thin-layer chromatography Merck silica gel 60 F_{254} plates were used. Retention factors (R_f) are given for chloroform/methanol (40:1) unless otherwise noted. *N*,*N*′-Dimethylformamide (DMF) was dried by distillation from phosphorus pentoxide in a vacuum and stored over molecular sieves. Other chemicals obtained from commercial sources were of analytical or synthetic grade and were used as received. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DRX500 (500 MHz for ^1H) or Varian Mercury 300 (300 MHz for ^1H) Fourier transform NMR spectrometer. High-resolution mass spectra were measured on a Q-TOF Micromass instrument.

***N*,*N*′-Diacetylcystine Dimethyl Ester (2):**[11] A mixture of *N*-acetylcysteine methyl ester (**1**) (2 mmol) and copper(II) acetate (4 mmol) in pyridine (10 mL) was heated in an oil bath at 40 °C for 1 h. During this time the colour of the solution turned from green to dark blue. Pyridine was then distilled off in a vacuum, dichloromethane (25 mL) was added and the resulting solution was washed three times with water. The organic layer was dried with magnesium sulfate, filtered and the solvent was evaporated in a vacuum. The crude product was purified by column chromatography on silica gel using $CHCl_3$/MeOH (20:1) to yield 61% of **2**. Crystallization from chloroform/cyclohexane afforded white crystals. R_f = 0.41 ($CHCl_3$/MeOH, 20:1); m.p. 125–126 °C. ^1H NMR ($CDCl_3$): δ = 2.07 (s, 6 H, CH_3CO), 3.21 (m, 4 H, CH_2), 3.78 (s, 6 H, $COOCH_3$), 4.88 (m, 1 H, $CHCOOCH_3$), 6.59 (d, J = 7.2 Hz, 1 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1 (CH_3CO), 40.7 (CH_2), 51.7 (*C*H), 52.8 (CH_3O), 170.0 ($COOCH_3$), 170.9 (CH_3CO) ppm. $C_{12}H_{20}N_2O_6S_2$ (352.42): calcd. C 40.90, H 5.72, N 7.95, S 18.20; found C 40.90, H 5.94, N 7.94, S 18.32.

General Procedure for the Arylation of 2: A mixture of *N*,*N*′-diacetylcystine dimethyl ester (**2**; 0.2 mmol), arylboronic acid (0.6 mmol), copper(I) acetate (0.6 mmol) and pyridine (1.2 mmol)

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

in DMF (2.5 mL) was heated in an oil bath at 100 °C under argon for 3 h. DMF was then distilled off in a vacuum, methanol was added to the residue and the resulting suspension was filtered through a paper filter. After evaporation of the solvent in a vacuum, column chromatography on silica gel using $CHCl_3$/MeOH (40:1) or $CHCl_3$/EtOAc (3:1) as eluent afforded the corresponding *N*-acetyl-*S*-arylcysteinates **4a**–**m**. A further purification step by column chromatography on silica gel was needed in several cases to obtain pure samples. As most of the mercapturic acid esters obtained were oils the sample homogeneity was checked by ^1H and ^{13}C NMR spectroscopy rather than by elemental analysis.

Methyl *N*-Acetyl-*S*-phenylcysteinate (4a): A mixture of *N*-acetylcysteine methyl ester (**1**; 76 mg, 0.4 mmol), phenylboronic acid (**3a**; 107 mg, 0.88 mmol), copper(II) acetate (110 mg, 0.6 mmol) and pyridine (95 mg; 1.2 mmol) in DMF (2.5 mL) was heated with an oil bath at 100 °C under argon for 3 h. DMF was then distilled off in vacuum, the residue was suspended in methanol and filtered through a paper filter. Evaporation of the solvent in vacuum followed by column chromatography on silica gel with $CHCl_3$/EtOAc (20:1) as eluent yielded 67 mg (63%) of a yellowish liquid. Compound **4a** (48.5 mg, 96%) was obtained by arylation of **1** or **2** with **3a** as described in the general procedure and identified by comparing its NMR spectra with published data.[12] Compound **4a** (48.5 g, 96%) was also obtained from **2** as described in the general procedure.

Methyl *N*-Acetyl-*S*-(2-tolyl)cysteinate (4b): Yellowish liquid (26 mg, 48%); R_f = 0.31. ^1H NMR ($CDCl_3$): δ = 1.90 (s, 3 H, CH_3CO), 2.41 (s, 3 H, CH_3-Ar), 3.32 (dd, J = 4.7, 14.0 Hz, 1 H, CH_2), 3.44 (dd, J = 4.7, 14.0 Hz, 1 H, CH_2), 3.57 (s, 3 H, COOCH_3), 4.85 (m, 1 H, CHCOOCH$_3$), 6.36 (d, J = 6.7 Hz, 1 H, NH), 7.16 (m, 3 H, Ar-H), 7.39 (m, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5 (*C*H$_3$-Ar), 22.8 (*C*H$_3$CO), 35.7 (*C*H$_2$), 52.3 and 52.4 (*C*H and *C*H$_3$O), 126.5, 127.1, 130.4, 130.9 (Ar *C*-H), 133.6 (Ar *C*-C), 139.1 (Ar *C*-S), 169.8 (*C*OOCH$_3$), 170.7 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{13}H_{17}NO_3S$ 267.0929; found 267.0938.

Methyl *N*-Acetyl-*S*-(3-tolyl)cysteinate (4c): Yellowish liquid (28 mg, 53%); R_f = 0.30. ^1H NMR ($CDCl_3$): δ = 1.81 (s, 3 H, CH_3CO), 2.25 (s, 3 H, CH_3-Ar), 3.28 (dd, J = 4.5, 14.2 Hz, 1 H, CH_2), 3.40 (dd, J = 4.5, 14.2 Hz, 1 H, CH_2), 3.51 (s, 3 H, COOCH_3), 4.80 (m, 1 H, CHCOOCH$_3$), 6.16 (d, J = 6.0 Hz, 1 H, NH), 6.96 (m, 1 H, Ar-H), 7.13 (m, 3 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2 (*C*H$_3$-Ar), 22.9 (*C*H$_3$CO), 36.6 (*C*H$_2$), 52.4 and 52.4 (*C*H and *C*H$_3$O), 127.9, 127.9, 128.9, 131.5 (Ar *C*-H), 134.4 (Ar *C*-C), 138.9 (Ar *C*-S), 169.7 (*C*OOCH$_3$), 170.7 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{13}H_{17}NO_3S$ 267.0929; found 267.0940.

Methyl *N*-Acetyl-*S*-(4-tolyl)cysteinate (4d): Yellowish liquid (27 mg, 50%); R_f = 0.33. ^1H NMR ($CDCl_3$): δ = 1.89 (s, 3 H, CH_3CO), 2.30 (s, 3 H, CH_3-Ar), 3.30 (dd, J = 4.7, 14.2 Hz, 1 H, CH_2), 3.41 (dd, J = 4.7, 14.2 Hz, 1 H, CH_2), 3.56 (s, 3 H, COOCH_3), 4.83 (m, 1 H, CHCOOCH$_3$), 6.40 (d, J = 7.0 Hz, 1 H, NH), 7.10 (d, J = 8.0 Hz, 2 H Ar-H), 7.31 (d, J = 8.0 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0 (*C*H$_3$-Ar), 22.8 (*C*H$_3$CO), 37.0 (*C*H$_2$), 52.4 and 52.4 (*C*H and *C*H$_3$O), 129.9 (Ar *C*-H), 130.9 (Ar *C*-C), 131.6 (Ar *C*-H), 137.4 (Ar *C*-S), 170.0 (*C*OOCH$_3$), 170.8 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{13}H_{17}NO_3S$ 267.0929; found 267.0928.

Methyl *N*-Acetyl-*S*-(3-vinylphenyl)cysteinate (4e): Yellowish liquid (31 mg, 56%); R_f = 0.33. ^1H NMR ($CDCl_3$): δ = 1.81 (s, 3 H, CH_3CO), 3.30 (dd, J = 4.5, 14.3 Hz, 1 H, CH_2), 3.41 (dd, J = 4.5, 14.3 Hz, 1 H, CH_2), 3.50 (s, 3 H, COOCH_3), 4.81 (m, 1 H, CHCOOCH$_3$), 5.22 (d, J = 10.9 Hz, 1 H, =CH_2), 5.70 (d, J = 17.6 Hz, 1 H, =CH_2), 6.25 (d, J = 6.5 Hz, 1 H, NH), 6.59 (dd, J = 10.9, 17.6 Hz, 1 H, CH=CH$_2$), 7.21 (m, 3 H, Ar-H), 7.37 (s, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8 (*C*H$_3$CO), 36.2 (*C*H$_2$), 52.3 and 52.4 (*C*H and *C*H$_3$O), 115.0 (=*C*H$_2$), 124.9, 128.4, 129.1, 130.0 (Ar *C*-H), 135.0 (Ar *C*-S), 135.9 (=*C*H), 138.4 (Ar *C*-C), 169.8 (*C*OOCH$_3$), 170.7 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{14}H_{17}NO_3S$ 279.0929; found 279.0928.

Methyl *N*-Acetyl-*S*-(4-vinylphenyl)cysteinate (4f): Yellowish liquid (31 mg, 56%); R_f = 0.35. ^1H NMR ($CDCl_3$): δ = 1.81 (s, 3 H, CH_3CO), 3.28 (dd, J = 4.5, 14.3 Hz, 1 H, CH_2), 3.41 (dd, J = 4.5, 14.3 Hz, 1 H, CH_2), 3.51 (s, 3 H, COOCH_3), 4.80 (m, 1 H, CHCOOCH$_3$), 5.18 (d, J = 10.9 Hz, 1 H, =CH_2), 5.66 (d, J = 17.6 Hz, 1 H, =CH_2), 6.17 (d, J = 5.9 Hz, 1 H, NH), 6.59 (dd, J = 10.9, 17.6 Hz, 1 H, CH=CH$_2$), 7.26 (d, J = 8.4 Hz, 2 H, Ar-H), 7.29 (d, J = 8.4 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.9 (*C*H$_3$CO), 36.5 (*C*H$_2$), 52.4 and 52.5 (*C*H and *C*H$_3$O), 114.4 (=*C*H$_2$), 126.8, 131.0 (Ar *C*-H), 134.0 (Ar *C*-S), 135.9 (=*C*H), 136.5 (Ar *C*-C), 169.7 (*C*OOCH$_3$), 170.7 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{14}H_{17}NO_3S$ 279.0929; found 279.0937.

Methyl *N*-Acetyl-*S*-(4-methoxyphenyl)cysteinate (4g): Yellowish liquid (27 mg, 48%); R_f = 0.28. ^1H NMR ($CDCl_3$): δ = 1.84 (s, 3 H, CH_3CO), 3.17 (dd, J = 4.9, 14.2 Hz, 1 H, CH_2), 3.27 (dd, J = 4.9, 14.2 Hz, 1 H, CH_2), 3.49 (s, 3 H, COOCH_3), 3.71 (s, 3 H, CH_3-O-Ar), 4.74 (m, 1 H, CHCOOCH$_3$), 6.22 (d, J = 6.7 Hz, 1 H, NH), 6.77 (d, J = 8.9 Hz, 2 H, Ar-H), 7.31 (d, J = 8.9 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.9 (*C*H$_3$CO), 38.0 (*C*H$_2$), 52.2 and 52.4 (*C*H and *C*H$_3$O), 55.3 (*C*H$_3$-O-Ar), 114.6 (Ar *C*-H), 124.7 (Ar *C*-S), 134.3 (Ar *C*-H), 159.4 (Ar *C*-O), 169.7 (*C*OOCH$_3$), 170.8 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{13}H_{17}NO_4S$ 283.0878; found 283.0867.

Methyl *N*-Acetyl-*S*-(3-chlorophenyl)cysteinate (4h): Colorless liquid (30 mg, 52%); R_f = 0.50. ^1H NMR ($CDCl_3$, 25 °C): δ = 1.92 (s, 3 H, CH_3CO), 3.37 (dd, J = 4.4, 14.1 Hz, 1 H, CH_2), 3.51 (dd, J = 4.4, 14.1 Hz, 1 H, CH_2), 3.62 (s, 3 H, COOCH_3), 4.88 (m, 1 H, CHCOOCH$_3$), 6.22 (br. s, 1 H, NH), 7.16–7.29 (m, 3 H, Ar-H), 7.37 (s, 1 H, Ar-H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 23.2 (*C*H$_3$CO), 36.3 (*C*H$_2$), 52.5 and 52.9 (*C*H and *C*H$_3$O), 127.3, 128.7, 130.2, 130.3 (Ar *C*-H), 134.9 and 137.2 (Ar *C*-S and Ar *C*-Cl), 170.0 (*C*OOCH$_3$), 170.8 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{12}H_{14}ClNO_3S$ 287.0383; found 287.0374.

Methyl *N*-Acetyl-*S*-(4-chlorophenyl)cysteinate (4i): White solid (36 mg, 63%); R_f = 0.49. ^1H NMR ($CDCl_3$, 25 °C): δ = 1.91 (s, 3 H, CH_3CO), 3.32 (dd, J = 4.4, 14.4 Hz, 1 H, CH_2), 3.47 (dd, J = 4.4, 14.4 Hz, 1 H, CH_2), 3.59 (s, 3 H, COOCH_3), 4.85 (m, 1 H, CHCOOCH$_3$), 6.22 (br. s, 1 H, NH), 7.24 (d, J = 8.8 Hz, 2 H Ar-H), 7.35 (d, J = 8.8 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 23.2 (*C*H$_3$CO), 36.9 (*C*H$_2$), 52.5 and 52.8 (*C*H and *C*H$_3$O), 129.4 (Ar *C*-H), 132.5 (Ar *C*-H), 133.4 and 133.5 (Ar *C*-S and Ar *C*-Cl), 170.0 (*C*OOCH$_3$), 170.9 (CH$_3$*C*O) ppm. HRMS (EI): calcd. for $C_{12}H_{14}ClNO_3S$ 287.0383; found 287.0372.

Methyl *N*-Acetyl-*S*-(4-cyanophenyl)cysteinate (4j): White solid (20 mg, 36%); R_f = 0.29 ($CHCl_3$/EtOAc, 3:1). ^1H NMR ($CDCl_3$, 25 °C): δ = 1.93 (s, 3 H, CH_3CO), 3.42 (dd, J = 4.7, 14.1 Hz, 1 H, CH_2), 3.59 (dd, J = 5.0, 14.1 Hz, 1 H, CH_2), 3.68 (s, 3 H, COOCH_3), 4.88 (m, 1 H, CHCOOCH$_3$), 6.40 (br. d, J = 6.4 Hz, 1 H, NH), 7.4 (d, J = 8.2 Hz, 2 H Ar-H), 7.55 (d, J = 8.2 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.2 (*C*H$_3$CO), 34.7 (*C*H$_2$S), 52.3 (*C*H$_3$O), 53.1 (*C*HCH$_2$), 118.7 (*C*N), 128.6, 132.6 (Ar *C*-H), 142.9 (Ar *C*-S), 109.6 (Ar *C*-CN), 170.1, 170.7 (*C*O) ppm. HRMS (EI): calcd. for $C_{13}H_{14}N_2O_3S$ 278.0725; found 278.0729.

Methyl *N*-Acetyl-*S*-(2-methoxycarbonylphenyl)cysteinate (4k): White solid (15 mg, 24%); R_f = 0.45. ^1H NMR ($CDCl_3$, 25 °C): δ = 1.91 (s, 3 H, CH_3CO), 3.40 (dd, J = 5.0, 13.8 Hz, 1 H, CH_2),

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

3.48 (dd, J = 5.0, 13.8 Hz, 1 H, CH_2), 3.67 (s, 3 H, COOCH_3), 3.91 (s, 3 H, Ar-COOCH_3), 4.90 (dt, J = 5.0, 7.6 Hz, 1 H, CHCOOCH$_3$), 6.57 (d, J = 7.6 Hz, 1 H, NH), 7.22 (m, 1 H Ar-H), 7.44 (m, 2 H, Ar-H), 7.84 (m, 1 H Ar-H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 23.2 (CH_3CO), 35.3 (CH_2), 52.0, 52.6 and 52.9 (CH, CH_3O and CH_3O), 125.7, 128.8 (Ar C-H), 130.4 (Ar C-C), 131.0, 132.5 (Ar C-H), 138.5 (Ar C-S), 167.5 (Ar C-COO), 170.2 (COOCH$_3$), 170.9 (CH$_3$CO) ppm. HRMS (EI): calcd. for $C_{14}H_{17}NO_5S$ 311.0827; found 311.0825.

Methyl *N*-Acetyl-*S*-(3-methoxycarbonylphenyl)cysteinate (4l): White solid (61 mg, 98%); R_f = 0.26 ($CHCl_3$/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.89 (s, 3 H, CH_3CO), 3.28 (dd, J = 4.3, 14.2 Hz, 1 H, CH_2), 3.50 (dd, J = 4.7, 14.2 Hz, 1 H, CH_2), 3.55 (s, 3 H, COOCH_3), 3.80 (s, 3 H, Ar-COOCH_3), 4.84 (m, 1 H, CHCOOCH$_3$), 6.39 (d, J = 7.1 Hz, 1 H, NH), 7.35 (t, J = 7.8 Hz, 1 H Ar-H), 7.55 (dt, J = 1.9, 7.8 Hz, 1 H, Ar-H), 7.85 (d, J = 7.8 Hz, 1 H Ar-H), 8.02 (t, J = 1.9 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 23.1 (CH_3CO), 36.5 (CH_2), 52.5, 52.6 (CH_3O), 52.8 (CHCH$_2$), 128.3, 129.3, 131.5, 135.0 (Ar C-H), 131.2 (Ar C-C), 135.9 (Ar C-S), 166.5 (Ar-CO), 170.1 and 170 (COOCH$_3$ and CH$_3$CO) ppm. HRMS (EI): calcd. for $C_{14}H_{17}NO_5S$ 311.0827; found 311.0835.

Methyl *N*-Acetyl-*S*-(4-methoxycarbonylphenyl)cysteinate (4m): White solid (35 mg, 56%); R_f = 0.44. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.86 (s, 3 H, CH_3CO), 3.41 (dd, J = 4.7, 14.4 Hz, 1 H, CH_2), 3.56 (dd, J = 4.7, 14.4 Hz, 1 H, CH_2), 3.60 (s, 3 H, COOCH_3), 3.87 (s, 3 H, Ar-COOCH_3), 4.88 (dt, J = 4.7, 7.4 Hz, 1 H, CHCOOCH$_3$), 6.36 (d, J = 7.4 Hz, 1 H, NH), 7.36 (d, J = 8.2 Hz, 2 H Ar-H), 7.91 (d, J = 8.3 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 23.2 (CH_3CO), 35.0 (CH_2), 52.4, 52.4 and 52.9 (CH, CH_3O and CH_3O), 128.1 (Ar C-C), 128.6, 130.2 (Ar C-H), 142.0 (Ar C-S), 166.7 (Ar C-COO), 170.1 and 170.8 (COOCH$_3$ and CH$_3$CO) ppm. HRMS (EI): calcd. for $C_{14}H_{17}NO_5S$ 311.0827; found 311.0818.

Acknowledgments

Financial support from the Ministry of Education, Youth and Sports of the Czech Republic (grant nos. LC06070, MSM 604 613 73 01 and 2B08051) is gratefully acknowledged.

[1] a) B. Mennervick, *Adv. Enzymol. Relat. Areas Mol. Biol.* **1985**, *57*, 357–406; b) A. M. Medeiros, M. G. Bird, G. Witz, *J. Toxicol. Environ. Health* **1997**, *51*, 519–538; c) V. Haufroid, D. Lison, *Int. Arch. Occup. Environ. Health* **2005**, *78*, 343–354; d) J. Angerer, U. Ewers, M. Wilhelm, *Int. J. Hyg. Environ. Health* **2007**, *210*, 201–228.

[2] a) F. J. Jongeneelen, H. A. A. M. Dirven, C.-M. Leijdekkers, P. T. Henderson, R. M. E. Brouns, K. Halm, *J. Anal. Toxicol.* **1987**, *11*, 100–104; b) M. Stommel, G. Muller, W. Stucker, C. Verkoyen, S. Schobel, K. Norpoth, *Carcinogenesis* **1989**, *10*, 279–282; c) P. J. Boogaard, N. J. van Sittert, *Occup. Environ. Med.* **1995**, *52*, 611–620; d) A. A. Melikian, Q. Qu, R. Shore, G. Li, H. Li, X. Jin, B. Cohen, L. Chen, Y. Li, S. Yin, R. Mu, X. Zhang, Y. Wang, *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci.* **2002**, *778*, 211–221.

[3] a) H. Behringer, E. Fackler, *Justus Liebigs Ann. Chem.* **1949**, *564*, 73–78; b) R. P. Hanzlik, P. E. Weller, J. Desai, J. Zheng, L. R. Hall, D. E. Slaughter, *J. Org. Chem.* **1990**, *55*, 2736–3742; c) B. Cossec, F. Cosnier, M. Burgart, *Molecules* **2008**, *13*, 2394–2407.

[4] a) D. V. Parke, R. T. Williams, *Biochem. J.* **1951**, *48*, 624–629; b) H. D. West, G. R. Mathura, *J. Biol. Chem.* **1954**, *208*, 315–318; J. Angerer, M. Schildbach, A. Kramer, *J. Anal. Toxicol.* **1998**, *22*, 211–214.

[5] a) T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205–3220; b) J. M. Baskin, Z. Wang, *Org. Lett.* **2002**, *4*, 4423; c) F. Y. Kong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517–3520; d) W. Deng, Y. Zou, Y.-F. Wang, L. Liu, Q.-X. Guo, *Synlett* **2004**, 1254–1258; e) H. Zhang, W. Cao, D. Ma, *Synth. Commun.* **2007**, *37*, 25–35.

[6] a) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) J.-P. Finet, A. Y. Fedorov, S. Combes, G. Boyer, *Curr. Org. Chem.* **2002**, *6*, 567–626; c) U. Schopfer, A. Schlapbach, *Tetrahedron* **2001**, *57*, 3069; d) M. Murata, S. L. Buchwald, *Tetrahedron* **2004**, *60*, 7397–7403; e) M. A. Fernandez-Rodrigez, Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181; f) M. Carril, R. SanMartin, E. Domínguez, I. Tellitu, *Chem. Eur. J.* **2007**, *13*, 5100–5105.

[7] a) P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* **1995**, *36*, 4133–4136; b) R. J. S. Hickman, B. J. Christie, R. W. Guy, T. J. White, *Aust. J. Chem.* **1985**, *38*, 899–904.

[8] P. S. Herradura, K. A. Pendola, R. K. Guy, *Org. Lett.* **2000**, *2*, 2019–2022.

[9] C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2002**, *4*, 4309–4312.

[10] a) N. Taniguchi, *Synlett* **2006**, 1351–1354; b) N. Taniguchi, *J. Org. Chem.* **2007**, *72*, 1241–1245.

[11] K. Kuramochi, S. Yukizawa, S. Ikeda, T. Sunoki, S. Arai, R. Matsui, A. Morita, Y. Mizushina, K. Sakaguchi, F. Sugawara, M. Ikekita, S. Kobayashi, *Bioorg. Med. Chem.* **2008**, *16*, 5039–5049.

[12] A. L. J. Beckwith, C. J. Easton, *Tetrahedron* **1983**, *39*, 3995–4001.

Received: August 28, 2009
Published Online: November 11, 2009

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim