Medium Buffer Effects on the Condensation of L-Cysteine and Aryl Nitriles to (*R*)-2-Aryl-4,5-dihydrothiazole-4-carboxylic Acids

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Abstract: The condensation of L-cysteine and aryl nitriles to (*R*)-2-aryl-4,5-dihydrothiazole-4-carboxylic acids in buffered media was reinvestigated. Pure products (yields of 58–95%; up to 99% ee) were obtained in a $NaHCO_3$/NaOH-buffered aqueous alcoholic medium.

Key words: amino acids, heterocycles, nitriles, nucleophilic addition, thiols

The title compounds 2-aryl-4,5-dihydrothiazole-4-carboxylic acids **1** or their derivatives are naturally occurring heterocyclic compounds. Some of them are microbial siderophores like desferrithiocin (**2**),[1] micacocidin (**3**),[2] yersiniabactin (**4**)[3] or pyochelin (**5**).[4] Other notable cases are the potent and selective histone deacetylase inhibitor largazole (**6**)[5] and the well-known firefly luciferin (**7**), the biomolecular substrate in the generation of firefly bioluminescence (Figure 1).[6] The acids **1** possess antibiotic,[2] iron chelating,[7] histone deacetylase inhibiting,[8] anticancer,[9] metallo-β-lactamase inhibiting,[10] and other biological activities. The ready oxidation of the dihydrothiazole ring of **1** produces thiazolecarboxylic acids,[11,12a] an important family of pharmacophores themselves.[12]

Established synthetic approaches to acids **1** are the condensation of ethyl benzimidates with cysteine[13] or its esters, followed by saponification;[14] the reaction of 2-haloacrylic acids with thiobenzamides,[15] and other methods.[2,16] A convenient approach is the condensation of aryl nitriles with cysteine,[7d,f,h,8–10,11b,12,13b–d,17] which is often carried out in buffered reaction media, apparently with an intent to avoid racemization of the products **1** when starting from L-cysteine.[7d] The stereospecifity of this process has been implied by reported optical activity of the reaction products,[7d,8a,13b,c,18] but we are not aware of an analytical proof of the enantiomeric purity of the product. The procedures in buffer require prolonged reaction times of three days or longer,[9,12b] and heating up to 70 °C.[17a] These conditions still generate side-products, necessitating purification by gel filtration[13c] or after derivatization.[13c,17c] Alternatively, refluxing an alcoholic solution of nitrile and cysteine with base ($NaHCO_3$ or amines) furnishes acids **1** within a few hours,[8,11b] but with concomitant racemization.[18]

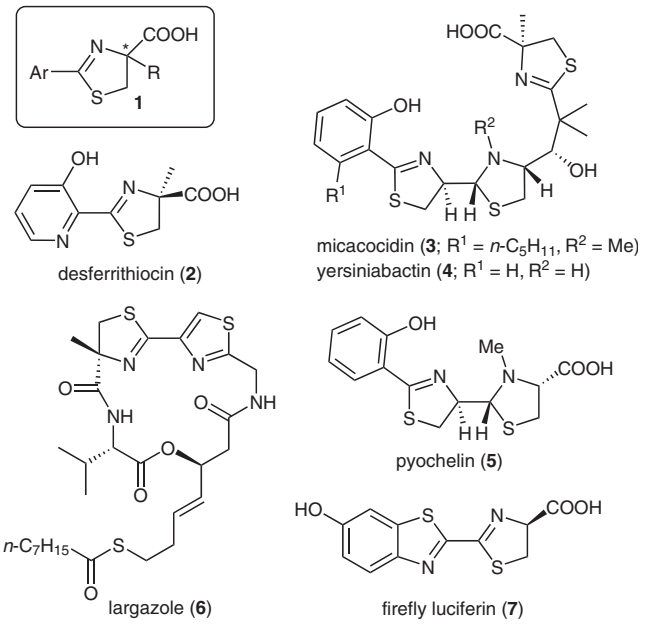
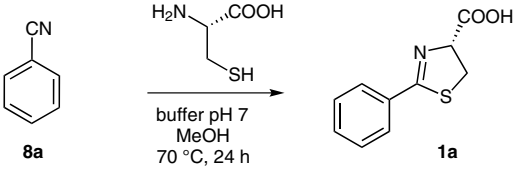


Figure 1 Examples of naturally occurring 2-aryl-4,5-dihydrothiazole-4-carboxylic acids or their derivatives

For our ongoing studies of the chemistry of firefly oxyluciferin,[19] 2-phenyl-4,5-dihydrothiazole-4-carboxylic acid (**1a**) was required as a simplified analogue[20] of firefly luciferin. The popular condensation of benzonitrile (**8a**) with L-cysteine in buffered (pH 7) solution at 70 °C was adopted (Scheme 1).[17a]



Scheme 1 Synthesis of 2-aryl-4,5-dihydrothiazole-4-carboxylic acids in a buffered, aqueous alcoholic medium

A near quantitative yield of product was obtained, but the ^{1}H NMR spectrum of the crude material[21] invariably displayed signals of a side-product, in addition to those of unreacted nitrile. According to LC-MS analysis, the side-product (m/z = 226) exceeds the mass of the desired **1a** (m/z = 208) by 18 units. The ^{1}H NMR spectrum displays a doublet of triplets at 5.09 ppm (1 H) and a multiplet at 3.18 ppm (2 H). Based on those data, the side product was

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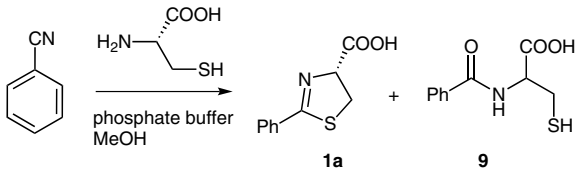
identified as *N*-benzoylcysteine (**9**), which arises from hydrolysis of **1a**. Unfortunately, **9** could not be removed from bulk **1a** by either recrystallization or silica gel chromatography. We therefore analyzed the effects of various buffers on the synthesis of **1a**, in the hope of finding reaction conditions that prevent the concomitant hydrolysis of **1a** to **9** (Table 1).

Table 1 Optimization of the Reaction Conditions[a]



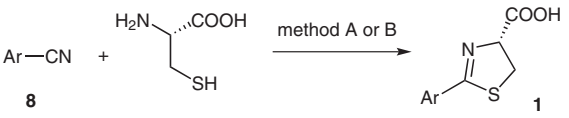
1a **9**

Entry	Temp (°C)	Time (h)	pH[b]	**1a** (%)[c] in crude	**1a**/**9**[c]
1	70	24	6.0	70	76:24
2	70	24	6.5	83	88:12
3	70	24	7.0	83	92:8
4	70	24	7.5	93	95:5
5	70	24	8.0	96	98:2
6	r.t.	24	7.5	87	100:0
7	50	24	7.5	88	96:4
8	90	24	7.5	51	56:44
9	90	96	7.5	–	0:100
10	r.t.	24	8.0	82	100:0
11	r.t.	96	8.0	92	100:0
12[d]	r.t.	24	–	95	100:0

[a] Reaction of PhCN (1 mmol) and L-cysteine (1.5 mmol) in 0.1 M buffer (1.7 mL) and MeOH (2.6 mL).
[b] pH of the aqueous phosphate buffer, measured by pH meter.
[c] Mol% of **1a** and ratio **1a**/**9** in the crude, based on ^{1}H NMR spectroscopy.
[d] No buffer; with $NaHCO_3$/NaOH as base, cf. method A (Table 2).

Either slightly acidic pH (Table 1, entries 1–5), higher temperatures (entries 6–8), or prolonged reaction time (entry 9) generated increased levels of **9**, supporting its nature as secondary hydrolysis product of **1a**. At prolonged heating, **9** became the main product (entry 9). At room temperature and with faintly basic phosphate buffer (pH 8.0), **1a** was obtained free of **9** in consistently high crude yields (entries 10 and 11), but still admixed with unreacted benzonitrile. Eventually, almost full conversion was attained by performing the reaction in the presence of an equivalent amount of $NaHCO_3$ relative to cysteine, and with addition of a catalytic amount (5 mol%) of aqueous NaOH (method A). Remaining benzonitrile in the reaction mixture could be removed by extraction with hexane, and subsequent acidification precipitated **1a** in high yield (Table 1, entry 12, and Table 2, entry 1).

Table 2 2-Aryl-4,5-dihydrothiazole-4-carboxylic Acids



8 **1**

Entry	Aryl	Method[a]	Time (h)	Yield (%)
1	Ph (**1a**)	A	24	88
2	4-ClC_6H_4 (**1b**)	A	24	78
3	4-FC_6H_4 (**1c**)	A	24	91
4	4-$CO_2MeC_6H_4$ (**1d**)	A	24	78
5	4-$MeCOC_6H_4$ (**1e**)	A	48	95
6	4-$NO_2C_6H_4$ (**1f**)	A	24	83
7	4-MeC_6H_4 (**1g**)	A	24	58
8	2-Py (**1h**)	A	24	81
9	3-Py (**1i**)	A	24	86
10	4-HOC_6H_4 (**1j**)	B	48	84[b]
11	4-$MeOC_6H_4$ (**1k**)	B	4	83

[a] Reaction conditions: method A: L-cysteine (1.5 equiv), $NaHCO_3$ (1.5 equiv), 1 M aq NaOH (5 mol%), H_2O, MeOH, r.t.; method B: L-cysteine (2 equiv), $NaHCO_3$ (4 equiv), EtOH, 100 °C.
[b] Isolated as the monohydrate.

The enantiomeric purity of **1a** was analyzed by normal phase chiral HPLC (chiralcel OD) with addition of CF_3CO_2H to the eluent and found to be in excess of 99% ee;[21] a racemic reference sample of **1a** for the analysis had been obtained from *rac*-cysteine according to the same synthetic method. Gratifyingly, the slightly basic reaction conditions had not induced any racemization in the condensation with L-cysteine. The use of near neutral buffers, which had been recommended in earlier protocols is no requirement for preventing racemization, but promotes the undesired hydrolysis of **1a** to **9** instead.

The synthetic method A could be applied to various aryl nitriles bearing electron-donating (methyl), electron-withdrawing functional groups (halogen, ester, acyl, nitro), or heterocyclic nitriles. The thiazolinic acids were obtained in 58–95% yields and high purity (Table 2, entries 2–9). In contrast, aryl nitriles bearing π-donating substituents (hydroxyl, methoxy) do not readily react under these or even harsher (heating to 60 °C) conditions. Their conversion into thiazolinic acids occurred only upon refluxing with excess L-cysteine and $NaHCO_3$ in ethanol (entries 10, 11; method B). However, chiral HPLC analysis of **1k** showed that partial racemization of the product had occurred (80% ee) in its synthesis.

In conclusion, we have studied the preparation of 2-aryl-4,5-dihydrothiazole-4-carboxylic acids **1** from aryl nitriles and L-cysteine. The reaction is best performed under mildly basic conditions to give the desired products in high yield (up to 95%) and purity (>99%) in less than a

day. Previously established and widely used protocols relying on reactions in near neutral phosphate buffer at extended reaction times offer no advantage, but suffer from concomitant hydrolysis of the products to *N*-aroylcysteines. Limitations of the protocol were nevertheless seen with electron-rich nitriles, which required thermally more forcing reaction conditions suffering from partial racemization. On the other hand, thiazolinic acid **1a** can now be considered a readily available enantiopure building block for asymmetric synthesis.

Reactions were performed in Schlenk flasks under argon to avoid oxidation to thiazoles. Solvents and reagents were obtained from commercial suppliers and used without further purification. NMR spectra were recorded at r.t. using $SiMe_4$ as an internal standard for ^1H NMR. ^{13}C NMR spectra were referenced to solvent signals ($CDCl_3$, δ = 77.16; DMSO, δ = 39.52). Chiral HPLC analyses were performed on a Chiralcel OD column with *n*-hexane–EtOH–CF_3CO_2H (90:10 + 0.1%, v/v) as an eluent (flow 1 mL/min), using UV detection. Melting points were measured on a metal heating block with a digital thermometer.

Condensation of L-Cysteine and Aryl Nitriles; General Procedure

Method A: Aryl nitrile (1.0 equiv), L-cysteine (1.5 equiv), and $NaHCO_3$ (1.5 equiv) were subsequently added to a degassed mixture of MeOH (2.6 mL/mmol), H_2O (1.7 mL/mmol), and a catalytic amount of 1 M NaOH (5 mol%). The reaction mixture, which remained suspended throughout, was stirred at r.t. until TLC analysis [*n*-hexane–EtOAc (1:1) + ca 2% of AcOH] indicated disappearance of the nitrile. MeOH was then removed from the mixture by evaporation under reduced pressure (40–50 °C/300 to 50 mbar).

Method B: A mixture of aryl nitrile (1.0 equiv), L-cysteine (2.0 equiv), and $NaHCO_3$ (4.00 equiv) in EtOH (1.5 mL/mmol) was stirred at 100 °C under argon, until TLC analysis indicated disappearance of the nitrile. The solvent was evaporated under reduced pressure and H_2O (5 mL/mmol) was added to the residual white solid.

Depending on the solubility of the crude sodium salt of the product in water, the following workup procedures were used:

Workup A, for water-soluble sodium salts: The cold (0 °C) solution was acidified with aq 2 M HCl to pH 2 (indicator paper). The precipitated solid was collected by filtration and washed with a small amount of H_2O.

Workup B, for alkali-soluble sodium salts: aq 2 M NaOH was added until the product was completely dissolved. The cooled (0 °C) solution was acidified with aq 2 M HCl to pH 2, precipitating a solid, which was collected by filtration and washed with H_2O.

Workup C, for non-water-soluble sodium salts: The mixture was acidified with aq 2 M HCl to pH 2 and the suspension vigorously stirred at r.t. The solid was collected by filtration and washed with H_2O.

Workup D, for hot water-soluble sodium salts: The hot (50–60 °C) solution was acidified with aq 2 M HCl to pH 2. The precipitated solid was collected by filtration and washed with H_2O.

In case the final product still contained sodium salt or inorganic salts, it was dissolved in hot EtOAc and filtered to remove insoluble solid. After evaporation of the solvent, pure product remained.

Additional product (10–15%) could be isolated from the mother liquors by extraction with EtOAc (TLC monitoring). The purity of this material was at times lower than that of the bulk material, and thus it was not included in the final yield (Table 2).

(*R*)-2-Phenyl-4,5-dihydrothiazole-4-carboxylic Acid (1a)

Reaction performed according to method A (9.7 mmol), workup A; yield: 1.77 g (88%); white solid; >99% ee; mp 114–115 °C; HPLC: t_R = 6.8 (major, *R*), 8.9 min (minor, *S*).

^1H NMR (250 MHz, $CDCl_3$): δ = 3.67–3.80 (m, 2 H, CH_2), 5.37 (t, $^3J_{H,H}$ = 9.4 Hz, 1 H, CH), 7.40–7.56 (m, 3 H, Ph-H), 7.84–7.89 (m, 2 H, Ph-H), 8.94 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 35.0 (CH_2), 78.4 (CH), 128.1 (2 C, Ph-C), 128.9 (2 C, Ph-C), 131.8 (Ph-C), 132.3 (Ph-C), 168.3 (C=N), 171.8 (CO_2H).

Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 57.73; H, 4.40; N, 6.76; S, 15.24.

(*R*)-2-(4-Chlorophenyl)-4,5-dihydrothiazole-4-carboxylic Acid (1b)

Reaction performed according to method A (7.3 mmol), workup B; yield: 1.37 g (78%); white solid; mp 165–166 °C (dec.).

^1H NMR (250 MHz, $CDCl_3$): δ = 3.75 (d, $^3J_{H,H}$ = 9.5 Hz, 2 H, CH_2), 5.35 (t, $^3J_{H,H}$ = 9.5 Hz, 1 H, CH), 7.41 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, Ar-H), 7.80 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, Ar-H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 35.3 (CH_2), 78.3 (CH), 129.0 (2 C, Ar-C), 129.8 (2 C, Ar-C), 131.1 (Ar-C), 136.5 (Ar-C), 167.2 (C=N), 171.6 (CO_2H).

Anal. Calcd for $C_{10}H_8ClNO_2S$: C, 49.69; H, 3.34; N, 5.80; S, 13.27. Found: C, 49.31; H, 3.29; N, 5.86; S, 13.19.

(*R*)-2-(4-Fluorophenyl)-4,5-dihydrothiazole-4-carboxylic Acid (1c)

Reaction performed according to method A (3.0 mmol), workup B; yield: 0.62 g (91%); white solid; mp 121–123 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.75 (d, $^3J_{H,H}$ = 9.6 Hz, 2 H, CH_2), 5.35 (t, $^3J_{H,H}$ = 9.6 Hz, 1 H, CH), 7.09–7.16 (m, 2 H, Ph-H), 7.84–7.90 (m, 2 H, Ph-H), 8.85 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 35.5 (CH_2), 77.8 (CH), 116.0 (d, $J_{C,F}$ = 22.1 Hz, 2 C, Ar-C), 128.4 (d, $J_{C,F}$ = 3.2 Hz, Ar-C), 131.1 (d, $J_{C,F}$ = 9.0 Hz, 2 C, Ar-C), 165.2 (d, $J_{C,F}$ = 253.6 Hz, Ar-CF), 172.1 (C=N), 173.9 (CO_2H).

Anal. Calcd for $C_{10}H_8FNO_2S$: C, 53.32; H, 3.58; N, 6.22; S: 14.24. Found: C, 53.26; H, 3.73; N, 6.88; S, 14.51.

(*R*)-2-[4-(Methoxycarbonyl)phenyl]-4,5-dihydrothiazole-4-carboxylic Acid (1d)

Reaction performed according to method A (6.2 mmol), workup C; yield: 1.29 g (78%); white solid; mp 161–163 °C (dec.).

^1H NMR (250 MHz, DMSO-d_6): δ = 3.66 (dd, ^2J = 11.3 Hz, ^3J = 8.3 Hz, 1 H, CH_2), 3.77 (dd, ^2J = 11.3 Hz, ^3J = 9.5 Hz, 1 H, CH_2), 5.35 (dd, ^3J = 8.3 and 9.5 Hz, 1 H, CH), 7.93 (d, ^3J = 8.4 Hz, 2 H, Ar-H), 8.07 (d, ^3J = 8.4 Hz, 2 H, Ar-H), 13.10 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 35.2 (CH_2), 52.4 (CH_3), 78.5 (CH), 128.4 (2 C, Ar-C), 129.6 (2 C, Ar-C), 132.1 (Ar-C), 136.2 (Ar-C), 165.5 (CO_2Me), 167.6 (C=N), 171.6 (CO_2H).

Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.46; H, 4.20; N, 5.36; S, 12.27.

(*R*)-2-(4-Acetylphenyl)-4,5-dihydrothiazole-4-carboxylic Acid (1e)

Reaction performed according to method A (6.9 mmol), workup A; yield: 1.63 g (95%); white solid; mp 151–152 °C (dec.).

^1H NMR (250 MHz, DMSO-d_6): δ = 2.63 (s, 3 H, CH_3), 3.67 (dd, ^2J = 11.2 Hz, ^3J = 8.3 Hz, 1 H, CH_2), 3.78 (dd, ^2J = 11.2 Hz, ^3J = 9.5 Hz, 1 H, CH_2), 5.37 (dd, ^3J = 8.3 and 9.5 Hz, 1 H, CH), 7.93 (d, ^3J = 8.4 Hz, 2 H, Ar-H), 8.06 (d, ^3J = 8.4 Hz, 2 H, Ar-H), 13.05 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 26.9 (CH_3), 35.2 (CH_2), 78.5 (CH), 128.4 (2 C, Ar-C), 128.7 (2 C, Ar-C), 136.0 (Ar-C), 138.9 (Ar-C), 167.7 (C=N), 171.6 (CO_2H), 197.5 (C=O).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}NO_3S$: 249.0454; found: 249.0452.

(*R*)-2-(4-Nitrophenyl)-4,5-dihydrothiazole-4-carboxylic Acid (1f)
Reaction performed according to method A (6.8 mmol), workup A; yield: 1.42 g (83%); yellow solid; mp 136–137 °C (dec.).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.71 (dd, ^2J = 11.3 Hz, ^3J = 8.3 Hz, 1 H, CH_2), 3.81 (dd, ^2J = 11.2 Hz, ^3J = 9.6 Hz, 1 H, CH_2), 5.40 (dd, ^3J = 8.3 and 9.6 Hz, 1 H, CH), 8.05 (d, ^3J = 8.9 Hz, 2 H, Ar-H), 8.34 (d, ^3J = 8.9 Hz, 2 H, Ar-H), 13.13 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 35.6 (CH_2), 78.5 (CH), 124.1 (2 C, Ar-C), 129.4 (2 C, Ar-C), 137.6 (Ar-C), 149.2 (Ar-C), 166.9 (C=N), 171.4 (CO_2H).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_8N_2O_4S$: 252.0199; found: 252.0184.

(*R*)-2-(4-Methylphenyl)-4,5-dihydrothiazole-4-carboxylic Acid (1g)
Reaction performed according to method A (8.6 mmol), workup A; yield: 1.10 g (58%), white solid; mp 150–153 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.36 (s, 3 H, CH_3), 3.59 (dd, ^2J = 11.2 Hz, ^3J = 8.2 Hz, 1 H, CH_2), 3.69 (dd, ^2J = 11.2 Hz, ^3J = 9.4 Hz, 1 H, CH_2), 5.27 (dd, ^3J = 8.2 and 9.4 Hz, 1 H, CH), 7.30 (d, ^3J = 8.1 Hz, 2 H, Ar-H), 7.69 (d, ^3J = 8.1 Hz, 2 H, Ar-H), 12.99 (s, 1 H, CO_2H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.0 (CH_3), 34.9 (CH_2), 78.3 (CH), 128.1 (2 C, Ar-C), 129.4 (2 C, Ar-C), 129.7 (Ar-C), 141.8 (Ar-C), 168.1 (C=N), 171.8 (CO_2H).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.80; H, 5.02; N, 6.39; S, 14.63.

(*R*)-2-(Pyridin-2-yl)-4,5-dihydrothiazole-4-carboxylic Acid (1h)
Reaction performed according to method A (9.6 mmol), workup A; yield: 1.62 g (81%); white solid; mp 133–134 °C (dec.).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.51 (dd, ^2J = 11.4 Hz, ^3J = 8.3 Hz, 1 H, CH_2), 3.62 (dd, ^2J = 11.4 Hz, ^3J = 9.8 Hz, 1 H, CH_2), 5.39 (dd, ^3J = 8.3 and 9.8 Hz, 1 H, CH), 7.58 (ddd, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 4.8 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H, 5-Ar-H), 7.95 (td, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.7 Hz, 1 H, 4-Ar-H), 8.06 (dt, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.3, 1 H, 3-Ar-H), 8.67 (ddd, $^3J_{H,H}$ = 4.8 Hz, $^4J_{H,H}$ = 1.7 Hz, $^3J_{H,H}$ = 1.3 Hz, 1 H, 6-Ar-H), 13.03 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 33.6 (CH_2), 78.8 (CH), 121.3 (Ar-C), 126.3 (Ar-C), 137.2 (Ar-C), 149.4 (Ar-C), 149.9 (Ar-C), 171.5 (C=N), 171.6 (CO_2H).

Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 51.91; H, 3.84; N, 13.38; S, 15.60.

(*R*)-2-(Pyridin-3-yl)-4,5-dihydrothiazole-4-carboxylic Acid (1i)
Reaction performed according to method A (9.6 mmol), workup A; yield: 1.72 g (86%); white solid; mp 179–181 °C (dec.).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.67 (dd, ^2J = 11.3 Hz, ^3J = 8.2 Hz, 1 H, CH_2), 3.77 (dd, ^2J = 11.3 Hz, ^3J = 9.5 Hz, 1 H, CH_2), 5.34 (dd, ^3J = 8.2 and 9.5 Hz, 1 H, CH), 7.55 (ddd, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 4.8 Hz, $^5J_{H,H}$ = 0.9 Hz, 1 H, 5-Ar-H), 8.15 (ddd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 2.3 Hz, $^4J_{H,H}$ = 1.7 Hz, 1 H, 4-Ar-H), 8.74 (dd, $^3J_{H,H}$ = 4.8 Hz, $^4J_{H,H}$ = 1.7 Hz, 1 H, 6-Ar-H), 8.94 (dd, $^4J_{H,H}$ = 2.3 Hz, $^5J_{H,H}$ = 0.9 Hz, 1 H, 2-Ar-H), 13.12 (br s, 1 H, CO_2H).

^{13}C NMR (91 MHz, DMSO-d_6): δ = 35.2 (CH_2), 78.3 (CH), 124.0 (Ar-C), 128.2 (Ar-C), 135.6 (Ar-C), 148.5 (Ar-C), 152.4 (Ar-C), 166.1 (C=N), 171.5 (CO_2H).

Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 51.83; H, 3.89; N, 13.43; S, 15.59.

(*R*)-2-(4-Hydroxyphenyl)-4,5-dihydrothiazole-4-carboxylic Acid Monohydrate (1j)
Reaction performed according to method B (8.4 mmol), workup A; yield: 1.71 g (84%); white solid; mp 151–153 °C (dec.).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.54 (dd, ^2J = 11.2 Hz, ^3J = 8.1 Hz, 1 H, CH_2), 3.65 (dd, ^2J = 11.2 Hz, ^3J = 9.3 Hz, 1 H, CH_2), 5.21 (dd, ^3J = 8.1 and 9.3 Hz, 1 H, CH), 6.84 (d, ^3J = 8.7 Hz, 2 H, Ar-H), 7.63 (d, ^3J = 8.7 Hz, 2 H, Ar-H), 10.28 (br s, 1 H, OH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 34.9 (CH_2), 78.3 (CH), 115.5 (2 C, Ar-C), 123.6 (Ar-C), 130.1 (2 C, Ar-C), 160.6 (Ar-C), 167.6 (C=N), 172.1 (CO_2H).

Anal. Calcd for $C_{10}H_9NO_3S·H_2O$: C, 49.78; H, 4.60; N, 5.81; S, 13.29. Found: C, 49.50; H, 4.66; N, 5.81; S, 13.40.

(*R*)-2-(4-Methoxyphenyl)-4,5-dihydrothiazole-4-carboxylic Acid (1k)
Reaction performed according to method B (1 mmol), workup B; yield: 0.20 g (83%); white solid; 80% ee; mp 165–168 °C (dec.); HPLC: t_R = 10.0 (major, *R*), 20.9 min (minor, *S*).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.70–3.74 (m, 2 H, CH_2), 3.86 (s, 3 H, CH_3), 5.33 (t, $^3J_{H,H}$ = 9.2 Hz, 1 H, CH), 6.92 (d, ^3J = 8.9 Hz, 2 H, Ar-H), 7.81 (d, ^3J = 8.9 Hz, 2 H, Ar-H), 10.31 (br s, 1 H, CO_2H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 35.0 (CH_2), 55.6 (CH_3), 76.7 (CH), 114.2 (2 C, Ar-C), 124.7 (Ar-C), 130.7 (2 C, Ar-C), 163.1 (C=N), 172.9 (2 C, Ar-C, CO_2H).

Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.75; H, 4.70; N, 5.92; S, 13.62.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Naegli, H. U.; Zaehner, H. *Helv. Chim. Acta* **1980**, *63*, 1400.
(2) Ino, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron Lett.* **1998**, *39*, 3509.
(3) Perry, R. D.; Balbo, P. B.; Jones, H. A.; Fetherston, J. D.; Demoll, E. *Microbiology* **1999**, *145*, 1181.
(4) Rinehart, K. L.; Staley, A. L.; Wilson, S. R.; Ankenbauer, R. G.; Cox, C. D. *J. Org. Chem.* **1995**, *60*, 2786.
(5) Taori, K.; Paul, V. J.; Luesch, H. *J. Am. Chem. Soc.* **2008**, *130*, 13506.
(6) White, E. H.; McCapra, F.; Field, G. F. *J. Am. Chem. Soc.* **1963**, *85*, 337.
(7) (a) Elliott, G. T.; Nagle, W. A.; Kelly, K. F.; McCollough, D.; Bona, R. L.; Burns, E. R. *J. Med. Chem.* **1989**, *32*, 1039. (b) Bergeron, R. J.; Liu, C. Z.; McManis, J. S.; Xia, M. X. B.; Algee, S. E.; Wiegand, J. *J. Med. Chem.* **1994**, *37*, 1411. (c) Bergeron, R. J.; Wollenweber, M.; Wiegand, J. *J. Med. Chem.* **1994**, *37*, 2889. (d) Bergeron, R. J.; Wiegand, J.; McManis, J. S.; McCosar, B. H.; Weimar, W. R.; Brittenham, G. M.; Smith, R. E. *J. Med. Chem.* **1999**, *42*, 2432. (e) Bergeron, R. J.; McManis, J. S.; Bussenius, J.; Brittenham, G. M.; Wiegand, J. *J. Med. Chem.* **1999**, *42*,

2881. (f) Zamri, A.; Schalk, I. J.; Pattus, F.; Abdallah, M. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1147. (g) Noel, S.; Guillon, L.; Schalk, I. J.; Mislin, G. L. A. *Org. Lett.* **2011**, *13*, 844. (h) Yoganathan, S.; Sit, C. S.; Vederas, J. C. *Org. Biomol. Chem.* **2011**, *9*, 2133.

(8) (a) Bowers, A. A.; West, N.; Newkirk, T. L.; Troutman-Youngman, A. E.; Schreiber, S. L.; Wiest, O.; Bradner, J. E.; Williams, R. M. *Org. Lett.* **2009**, *11*, 1301. (b) Souto, J. A.; Vaz, E.; Lepore, I.; Pöppler, A.; Franci, G.; Alvarez, R.; Altucci, L.; Lera, A. R. *J. Med. Chem.* **2010**, *53*, 4654.

(9) Li, W.; Lu, Y.; Wang, Z.; Dalton, J. T.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4113.

(10) Chen, P.; Horton, L. B.; Mikulski, R. L.; Deng, L.; Sundriyal, S.; Palzkill, T.; Song, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6229.

(11) See the most recent examples and references cited therein: (a) Dawsey, A. C.; Li, V.; Hamilton, K. C.; Wang, J.; Williams, T. J. *Dalton Trans.* **2012**, *41*, 7994. (b) Li, Z.; Ma, L.; Xu, J.; Kong, L.; Wu, X.; Yao, H. *Chem. Commun.* **2012**, *48*, 3763.

(12) See selected recent examples: (a) Lu, Y.; Li, C.-M.; Wang, Z.; Ross, C. R.; Chen, J.; Dalton, J. T.; Li, W.; Miller, D. D. *J. Med. Chem.* **2009**, *52*, 1701. (b) Li, F.; Lu, Y.; Li, W.; Miller, D. D.; Mahato, R. I. *J. Controlled Release* **2010**, *143*, 151. (c) Lu, Y.; Li, C.-M.; Wang, Z.; Chen, J.; Mohler, M. L.; Li, W.; Dalton, J. T.; Miller, D. D. *J. Med. Chem.* **2011**, *54*, 4678.

(13) (a) Elliott, G. T.; Kelly, K. F.; Bonna, R. L.; Burns, E. R. *Cancer Chemother. Pharmacol.* **1988**, *21*, 233. (b) Loughlin, W. A.; Knevitt, S. A.; Hosking, R. E.; Marshall, R. L. *Austr. J. Chem.* **2000**, *53*, 457. (c) Bergeron, R. J.; Wiegand, J.; Weimar, W. R.; Vinson, J. R. T.; Bussenius, J.; Yao, G. W.; McManis, J. S. *J. Med. Chem.* **1999**, *42*, 95. (d) Bergeron, R. J.; Wiegand, J.; Wollenweber, M.; McManis, J. S.; Algee, S. E.; Ratliff-Thompson, K. *J. Med. Chem.* **1996**, *39*, 1575.

(14) Kline, T.; Fromhold, M.; McKennon, T. E.; Cai, S.; Treiberg, J.; Ihle, N.; Sherman, D.; Schwan, W.; Hickey, M. J.; Warrener, P.; Witte, P. R. *Bioorg. Med. Chem.* **2000**, *8*, 73.

(15) (a) Effenberger, F.; Beisswenger, T.; Dannenhauer, F. *Chem. Ber.* **1988**, *121*, 2209. (b) Eidem, A. *Acta Chem. Scand.* **1971**, *25*, 1.

(16) (a) Suzuki, N.; Izawa, Y. *Tetrahedron Lett.* **1974**, 1863. (b) Suzuki, N.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3155.

(17) (a) Moraski, G. C.; Markley, L. D.; Chang, M.; Miller, M. J.; Cho, S.; Franzblau, S. G.; Hwang, C. H.; Boshoff, H. *Bioorg. Med. Chem.* **2012**, *20*, 2214. (b) Rodriguez-Lucena, D.; Rivault, F.; Schalk, I. J.; Mislin, G. L. A.; Gaboriau, F.; Lescoat, G. *Bioorg. Med. Chem.* **2010**, *18*, 689. (c) Rivault, F.; Schons, V.; Liébert, C.; Burger, A.; Sakr, E.; Abdallah, M. A.; Schalk, I. J.; Mislin, G. L. A. *Tetrahedron* **2006**, *62*, 2247.

(18) Zamri, A.; Abdallah, M. A. *Tetrahedron* **2000**, *56*, 249.

(19) Rebarz, M.; Kukovec, B.-M.; Maltsev, O. V.; Ruckebusch, C.; Hintermann, L.; Naumov, P.; Sliwa, M. *Chem. Sci.* **2013**, *4*, in press; DOI: 10.1039/c3sc50715g.

(20) Adam, W.; Ehrig, V. *Synthesis* **1976**, 817.

(21) See the Supporting Information for NMR spectra and HPLC traces. A racemic reference sample of **1a** for chiral HPLC was obtained from racemic cysteine according to method A.

