Improved Synthesis of 2-Substituted 4-Chlorothiazole-5-carbaldehydes

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An improved method for the reaction of 2,4-dichlorothiazole-5-carbaldehyde (**2**) with secondary amines was established using potassium carbonate in acetonitrile at room temperature instead of deprotonation with butyllithium in tetrahydrofuran at -78°. The method is convenient and the yields of **3** even higher. Compound **2** could also be reacted by this method with thiophenols to yield 4-chloro-2-phenylthiothiazole-5-carbaldehydes **4**.

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In the course of our investigations on aldose reductase inhibitors of the 3-aminorhodanine type those compounds revealed the highest efficiency in the test system which where condensed in the 5-position of the aminorhodanine with heteroaromatic aldehydes [1]. To provide such aldehydes of the thiazole type we had to improve methods known from the literature and can now report on the preparation of some 2-amino- and 2-arylthio-4-chlorothiazole-5-carbaldehydes **3** and **4**.

In the literature some methods for the preparation of 2-substituted thiazole-5-carbaldehydes are known. One of these methods [2] starts with 2,4-dichlorothiazole **2**, resulting from the treatment of thiazolidine-2,4-dione **1** with dimethylformamide and phosphoryl chloride [3]. Compound **2** is deprotonated with lithium dipropylamide in 5-position at -78° in tetrahydrofuran and then reacted with either dimethylformamide or *N*-formylpiperidine to yield 4-chloro-2-dimethylaminothiazole-5-carbaldehyde (**3i**) respectively the 2-piperidino-derivative **3f**. Another method [4] starts with 2,4-dichlorothiazole-5-carbaldehyde **2** which is reacted with 4-methylpiperazine and butyllithium in tetrahydrofuran at -78° to yield **3g**.

We now could improve the synthesis of compounds **3** considerably by replacing the handling with butyllithium at -78° under strict protection from moisture by simple treatment of **2** with the amine in acetonitrile in the presence of potassium carbonate at room temperature. As can be seen from Scheme 1, yields are in most cases better than those from the other methods. Furthermore we were able to extend the scope of this method to the synthesis of the new 2-arylthio-4-chlorothiazole-5-carbaldehydes **4** by using thiophenols instead of amines.

EXPERIMENTAL

Instrumental equipment and chromatografic conditions are those already described [5].

General Procedure for the Synthesis of the 2-Amino-4-chlorothiazole-5-carbaldehydes **3** and the 2-Arylthio-4-chlorothiazole-5-carbaldehydes **4**.

To a stirred suspension of 0.91 g (0.005 mole) of 2,4-dichlorothiazole-5-carbaldehyde (**2**) prepared from thiazolidine-2,4-dione according to [3] and 1.38 g (0.010 mole) of potassium carbonate in 50 ml of acetonitrile, 0.005 mole of the amine and the thiophenol were added, respectively. After stirring for twelve hours at room temperature the salts were filtered, washed with 50 ml of acetonitrile and the filtrate was evaporated *in vacuo* to dryness. The residue was recrystallized from light petroleum.

4-Chloro-2-pyrrolidinothiazole-5-carbaldehyde (**3a**).

This compound was obtained as colorless needles, 1.01 g (84%), mp 118°; ir: ν CO 1643 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.04-2.17 (br m, 4H, 3'- and 4'-H), 3.30-3.80 (br m, 4H, 2'- and 5'H), 9.79 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 25.6 (C-3', C-4'), 49.9 (C-2', C-5'), 118.8 (C-5), 148.4 (C-4), 168.3 (C-2), 179.9 ppm (CO); ms: m/z 218 (36, M^++1), 217 (20, M^+), 216 (100), 188 (78).

Anal. Calcd. for $C_8H_9ClN_2OS$ (216.69): C, 44.34; H, 4.19; Cl, 16.36; N, 12.93; S, 14.80. Found: C, 44.27; H, 4.21; Cl, 16.28; N, 12.70; S, 15.09.

4-Chloro-2-((*S*)-(+)-1-phenylethylamino)thiazole-5-carbaldehyde (**3b**).

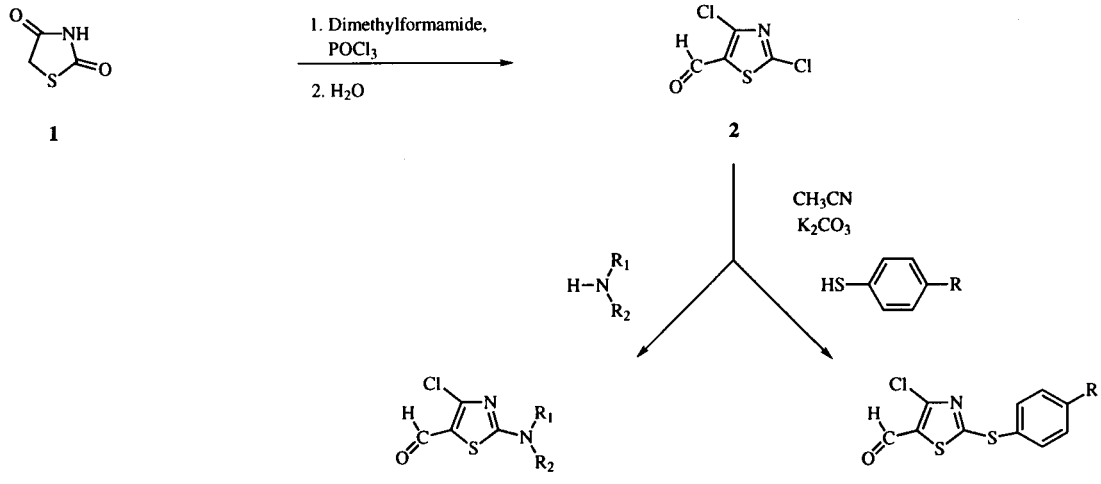
This compound was obtained as colorless crystals (light petroleum/ethyl acetate), 0.65 g (60%), mp 141°; ir: ν NH 3199, CO 1642 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.66 (d, 3H, CH_3), 4.58 (m, 1H, NHC*H*), 7.26-7.38 (m, 5H, phenyl protons), 7.64 (m, 1H, NH), 9.71 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 23.2 (CH_3), 56.3 (CH), 119.4 (C-5), 126.1 (C-2', C- 6'), 128.2 (C-4'), 129.0 (C-3', C-5'), 140.5 (C-1'), 147.3 (C-4), 172.3 (C-2), 180.1 ppm (CO); ms: m/z 267 (1, M), 105 (100); [α]: + 27.4° (λ = 598 nm, T 22°, methylene chloride).

Anal. Calcd. for $C_{12}H_{11}ClN_2OS$ (266.74): C, 54.03; H, 4.16; Cl, 13.29; N, 10.50, S, 12.02. Found: C, 54.10; H, 4.16; Cl, 13.30; N, 10.35; S, 12.13.

4-Chloro-2-((*R*)-(-)-1-phenylethylamino)thiazole-5-carbaldehyde (**3c**).

This compound was obtained as colorless crystals (light petroleum/ethyl acetate), 0.80 g (63%), mp 138°; ir: ν NH 3196, CO 1642 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.66 (d, 3H, CH_3), 4.58 (m, 1H, CH), 7.26-7.38 (m, 5H, phenyl protons), 7.64 (m,

Scheme 1



3	R_1	R_2	% yield	% yield [lit]
a			84	
b	H		60	
c	H		63	
d			54	
e	H		67	
f			83	78,70 [3]
g			76	52 [4]
h			78	90 [3]

4a: R = H yield 71%
4b: R = Cl 65%

1H, NH), 9.71 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 23.1 (CH_3), 56.3 (CH), 119.3 (C-5), 126.1 (C-2', C-6'), 128.2 (C-4'), 129.0 (C-3', C-5'), 140.5 (C-1'), 147.3 (C-4), 172.3 (C-2), 180.1 ppm (HCO); ms: m/z 268, (10, M^++1), 266 (11), 105 (100); [α]: -27.4° (λ = 598 nm, T = 22°, methylen chloride).

Anal. Calcd. for $C_{12}H_{11}ClN_2OS$ (266.74): C, 54.03; H, 4.16; Cl, 13.29; N, 10.50; S, 12.02. Found: C, 54.32; H, 4.15; Cl, 13.29; N, 10.49; S, 12.11.

4-Chloro-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)thiazole-5-carbaldehyde (**3d**).

This compound was obtained as colorless powder, (toluene/light petroleum), 1.92 g (54%), mp 131°; ir: ν CO 1622 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.85-3.05 (m, 2H, 4'-H), 3.71-3.88 (m, 2H, 3'-H), 4.65-4.80 (m, 2H, 1'-H), 7.18-7.29 (m, 4H, aromatic H), 9.78 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 28.4 (C-4'), 46.1 (C-3'), 49.3 (C-1'), 119.1 (C-5),

126.4, 127.1, 127.5, 128.4, 131.2, 133.8 (aromatic C), 148.1 (C-4), 171.4 (C-2), 180.1 ppm (HCO); ms: m/z 280 (29, M^++1), 279 (M^+), 278 (79), 117 (100).

Anal. Calcd. for $C_{13}H_{11}ClN_2OS$ (278.76): C, 56.01; H, 3.98; Cl, 12.72; N, 10.05; S, 11.50. Found: C, 56.28; H, 3.94; Cl, 12.51; N, 9.88; S, 11.64.

4-Chloro-2-*tert*-butylaminothiazole-5-carbaldehyde (**3e**).

This compound was obtained as brown-red crystals (light petroleum/ethyl acetate), 0.68 g (67%), mp 125°; ir: ν NH 3300, CO 1633 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (s, 9H, 3 CH_3), 6.30 (bs, 1H, NH), 9.76 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 28.4 ($(CH_3)_3$), 54.3 ($NHC(CH_3)_3$), 119.0 (C-5), 147.8 (C-4), 170.1 (C-2), 180.2 ppm (HCO); ms: m/z 219 (2, M^+), 218 (20), 162 (100).

Anal. Calcd. for $C_8H_{11}ClN_2OS$ (218.71): C, 43.93; H, 5.07; Cl, 16.21; N, 12.81; S, 14.66. Found: C, 43.94; H, 4.90; Cl, 16.25; N, 12.79; S, 14.68.

4-Chloro-2-piperidinothiazole-5-carbaldehyde (**3f**).

This compound was obtained as colorless needles, 0.60 g (83%), mp 88-90°; (lit [2] mp 91-92°, yield 71%); all analytical data agrees with the literature [2].

4-Chloro-2-(4-methylpiperazino)thiazole-5-carbaldehyde (**3g**).

This compound was obtained as colorless needles, 0.84 g (76%), mp 135-137°; (lit [4] mp 140-141°, yield 52%); all analytical data agrees with the literature [4].

4-Chloro-2-morpholinothiazole-5-carbaldehyde (**3h**).

This compound was obtained as shining crystals, 1.6 g (78%), mp 200°; (lit [3] mp 200°, yield 90%); all analytical data agrees with the literature [3].

4-Chloro-2-phenylthiothiazole-5-carbaldehyde (**4a**).

This compound was obtained as colorless crystals, 0.51 g (71%), mp 96°; ir: ν CO 1669 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.51-7.62 (m, 3H, 3',4',5'-H), 7.68-7.70 (m, 2H, 2',6'-H), 9.84 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 127.9 (C-5), 129.9 (C-1'), 130.7 (C-3', C-5'), 131.8 (C-4'), 135.6 (C-2', C-6'), 147.1 (C-4), 180.0 (C-2), 180.4 ppm (HCO); ms: m/z 257 (44, M^++1), 256 (34, M^+), 255 (100).

Anal. Calcd. for $C_{10}H_6ClNOS_2$ (255.74): C, 46.97; H, 2.36; Cl, 13.86; N, 5.48; S, 25.07. Found: C, 47.13; H, 2.23; Cl, 13.99; N, 5.53; S, 24.84.

4-Chloro-2-(4-chlorophenylthio)thiazole-5-carbaldehyde (**4b**).

This compound was obtained as a yellow oil, 1.13 g (65%); ir: ν CO 1666 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.47-7.52 (m, 2H, 2',6'-H), 7.58-7.64 (m, 2H, 3',5'-H), 9.83 ppm (s, 1H, HCO); ^{13}C nmr (deuteriochloroform): δ 126.3 (C-5), 129.6 (C-1'), 130.2 (C-3',5'), 136.8 (C-2',6'), 138.6 (C-4'), 147.1 (C-4), 178.8 (C-2), 180.5 ppm (HCO); ms: m/z 291 (23, M^++1), 290 (22, M^+), 250 (100).

Anal. Calcd. for $C_{10}H_5Cl_2NOS_2$ (290.18): C, 41.39; H, 1.74; Cl, 24.43; N, 4.83; S, 22.10. Found: C, 41.44; H, 1.83; Cl, 24.45; N, 4.91; S, 22.31.

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