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Generation of Thiazoles by Column Dehydrogenation of Thiazolidines with MnO_2

Sabine Mensching and Markus Kalesse

Hannover, Institut für Organische Chemie, Universität

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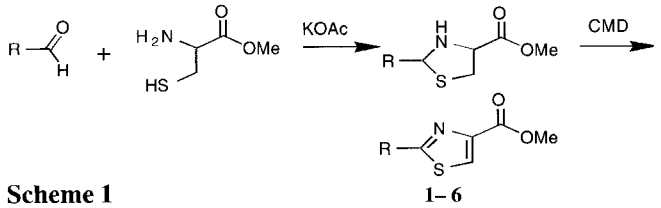
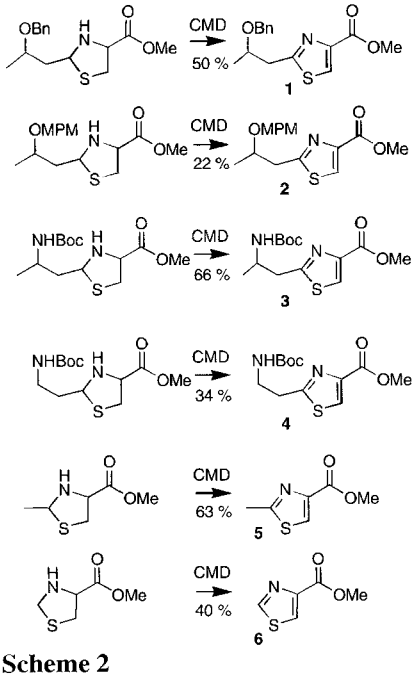
Thiazoles are essential groups in a variety of different natural products. Among those biologically very potent compounds are epothilones [1], bleomycin [2] or renin inhibitors [3]. Even though the mode of action of epothilones has not been unraveled yet, it seems that the thiazole moiety is essential for the biological activity. The thiazole groups of bleomycin are neces- sary for minor groove binding. Since we were interested in the design of new minor groove binding compounds based on thiazole moieties, we had to establish a route that enabled us to have easy access to substituted thiazole derivatives.



Scheme 1 **1–6**



Scheme 2

Herein we describe a convenient method for the dehydrogenation of thiazolidines to thiazoles (Scheme 1) by a modification of the method described by Sheppard [4]. Starting from cysteine we converted substituted aldehydes in two steps to the corresponding thiazole derivatives. The first step involves the generation of the thiazolidine. In the second step the crude material was transferred on a dry MnO_2 column, and the column was eluted with dioxane. The fractions containing the thiazole derivative were concentrated and the residue was purified via flash-chromatography if necessary (Scheme 2, yield over two steps). With this column-dehydrogenation we were able to obtain the thiazole moiety of epothilone (**5**) in 63% yield.

Experimental

All reagents were of analytical grade quality. Solvents were distilled in glass. – IR: Perkin Elmer FT 1710. – NMR: Bruker WP 200, AM 400. – ^{13}C NMR spectra were measured with ^{1}H-broadband decoupling. The signal multiplicities were determined by means of the DEPT 135 (CH or CH_3 give positive signals (+), while CH_2 gives negative signals) or APT technique (CH and CH_3 give negative signals (–), while quaternary C and CH_2 give positive signals (+)). – Low-resolution mass spectra: Finnigan MAT 312. High-resolution and FAB mass spectra: VG Autospec. – Flash chromatography: J. T. Baker silica gel (0.03–0.06 mm). – Elemental Analyses: Heraeus CHN-Rapid (Institut für Organische Chemie der Universität Hannover). – CMD is the abbreviation for chemical manganese dioxide and is a generous gift from the Sedema company [5].

General method for the thiazolidine formation

To a solution of 1.0 g (10 mmol) of KOAc and 1.84 g (10 mmol) L-cysteine methyl ester hydrochloride in 30 ml H_2O/MeOH (1:1) was added 9 mmol of the appropriate aldehyde (dissolved in 3 ml MeOH). The solution was stirred at RT for 3.5 h. After that time the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The

thiazolidine was used in the next step without further purification.

General method for the dehydrogenation of thiazolidines

A column was filled with 91 g (1 mol) CMD. 7 mmol of the thiazolidine derivative in 30 ml dioxane was transferred to the dry CMD column. The substance was eluted with 270 ml dioxane when 0.2–0.4 bar pressure was applied to the column. By flashing the MnO_2 with dioxane the temperature of the column increased and at approximately 50 °C the best yields were obtained. The fractions containing the thiazole derivatives were collected and purified via flash chromatography.

Methyl 2-(2-Benzyloxy-)propylthiazole-4-carboxylate (**1**)

Yield 50%. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm= 8.1 (s, 1H); 7.3 (m, 5H); 4.61 (d, 1H, J = 12 Hz); 4.45 (d, 1H, J = 12 Hz); 3.42–3.28 (m, 1H); 3.39 (s, 3H); 3.26 (m, 2H); 1.3 (d, 3H, J = 6 Hz). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ/ppm= 168.31 (+); 161.93 (+); 145.86 (+); 138.10 (+); 128.33 (–); 128.2 (–); 127.65 (–); 127.58 (–); 74.0 (–); 70.8 (+); 52.32 (–); 40.59 (+); 19.36 (–). – IR ($CHCl_3$): ν/cm^{-1}= 3124; 3000; 2928; 1724; 1452; 1376; 1232; 1128; 1028; 916. – MS (70 °C): *m/z* (%): 260 [M$^+$–31] (1.3); 185 (21.9); 170 (16.2); 110 (1.9); 107 (1.4); 91 (100.0); 83 (1.2); 77 (5.3); 65 (16.2). – $C_{15}H_{17}NO_3S$ (291.36): calcd. C 61.83 H 5.88 N 4.8; found C 61.78 H 5.82 N 5.19.

Methyl 2-(2-(4-Methoxy-)benzyloxy-)propylthiazole-4-carboxylate (**2**)

Yield 22%. – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 8.10 (s, 1H); 7.23 (m, 2H); 6.85 (m, 2H); 4.51 (d, 2H, J = 11 Hz); 4.37 (d, 2H, J = 11 HZ); 3.95 (m, 4H); 3.80 (s, 3H); 3.23 (m, 2H); 1.28 (d, 3H, J = 6 Hz). – ^{13}C NMR (100 MHz, DEPT, $CDCl_3$): δ/ppm= 168,40 (C); 161.96 (C); 159.13 (C); 145.82 (C); 130.14 (C); 129.97 (+); 129.36 (+); 128.20 (+); 113.77 (+); 73.69 (+); 70.54 (–); 55.26 (+); 52.39 (+); 40.64 (–); 19.43 (+). – IR (cap. film): ν/cm^{-1} = 3454; 3116; 2953; 2867; 2838; 1738; 1614; 1587; 1515; 1485; 1341; 1325; 1249; 1211; 1098; 1034. – MS (90 °C): *m/z* (%): 321 [M$^+$] (2.0); 290 (3.6); 200 (1.7); 185 (97.0); 170 (81.8); 153 (35.9); 138 (27.3); 125 (17.4); 121 (100.0); 111 (2.1); 109 (6.1); 91 (10.1); 77 (19.5). – HRMS calcd. for $C_{16}H_{19}NO_4S$ (321.39) 321.10348, found 321.10311.

Methyl 2-(2-N-tert-Butoxycarbonylamino-)propylthiazole-4-carboxylate (**3**)

Yield 66%. – ^{1}H NMR (200 MHz; $CDCl_3$): δ/ppm = 8.13 (s, 1H); 4.72 (br. s, 1H) 4.05 (m, 1H); 3.95 (s, 3H); 3.24 (m, 2H); 1.42 (s, 9H); 1.22 (d, 3H, J = 6 Hz). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ/ppm = 167.98 (+); 161.73 (+); 154.94 (+); 146.25 (+); 127.88 (–); 79.34 (+); 52.27 (–); 40.03 (+); 28.30 (–); 20.45 (–). – IR ($CHCl_3$): ν/cm^{-1} = 3436; 3124; 2980; 2932; 1708; 1600; 1540; 1368; 1232; 1168; 1104; 1060; 992; 908. – MS (50 °C): *m/z* (%): 300 [M$^+$] (1.9); 269 (1.1); 227 (16.9); 199 (3.8); 195 (12.7); 175 (15.2); 160 (35.01); 157 (100.9); 144 (36.1); 142 (16.7); 132 (17.6); 130 (40.2); 121 (88.); 116 (42.2); 112 (11.1); 103 (57.0); 99 (22.9); 88 (79.5). – $C_{13}H_{20}N_2O_4S$ (300.37): calcd. C 51.98 H 6.71 N 9.32; found C 51.50 H 6.70 N 8.55.

Methyl 2-(2-N-tert-Butoxycarbonylamino-)ethylthiazole-4-carboxylate (**4**)

Yield 34%. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 8.11 (s, 1H); 5.06 (m, 1H); 3.95 (s, 3H); 3.57 (q, 2H, J = 6 Hz); 3.27 (tr, 2H, J = 6 Hz); 1.42 (s, 9H). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ/ppm = 168.88 (+); 161.79 (+); 155.84 (+); 146.61 (+); 128.22 (–); 127.71 (–); 79.56 (+); 52.42 (–); 40.02 (+); 33.81 (+); 28.36 (–). – IR ($CHCl_3$): ν/cm^{-1} = 3692; 3672; 3492; 3060; 2952; 2840; 1724; 1484; 1436; 1344; 1328; 1236; 1116; 1024; 908. – MS (FAB): *m/z* (%): 287 [M$^+$+1] (100.0); 273 (7); 245 (4); 231 (27); 213 (7); 33.81 (+); 28.36 (–). – $C_{12}H_{18}N_2O_4S$ (286.35): calcd. C 50.34 H 6.34 N 9.78; found C 50.59 H 6.36 N 9.54.

Methyl 2-Methylthiazole-4-carboxylate (**5**)

Yield 63%. – ^{1}H NMR ($CDCl_3$, 200 MHz) δ/ppm = 8.08 (s, 1H); 3.97 (s, 3H); 2.79 (s; 3H). – ^{13}C NMR ($CDCl_3$; 50 MHz) δ/ppm = 166.65 (+); 161.6 (+); 146.23 (+); 127.30 (–); 52.18 (–); 19.13 (–). – IR ($CHCl_3$): ν/cm^{-1} = 3000; 2956; 1724; 1488; 1436; 1344; 1324; 1244; 1176; 1100. – MS (RT): *m/z* (%): 157 [M$^+$](42.07); 145 (4.34); 133 (11.65); 126 (100.0); 116 (9.33); 105 (12.87); 99 (90.33). – $C_6H_7NO_2S$ (157.19): calcd. C 45.84 H 4.48 N 8.81; found C 45.70 H 4.49 N 8.60.

Methyl Thiazole-4-carboxylate (**6**)

Yield 40%. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 8.88 (d, 1H, J = 2 Hz); 8.27 (d, 1H, J = 2 Hz); 3.97 (s, 3H). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ/ppm = 161.75 (+); 147.84 (+); 127.40(–); 52.50 (–).03 (–); 70.86 (+); 66.24 (+); 40.63 (+); 19.41 (–); 15.11 (–). – IR ($CHCl_3$): ν/cm^{-1} = 3420; 3112; 3057; 1727; 1503; 1434; 1279; 1217; 1093; 980. – MS (60 °C): *m/z* (%): 145 [M$^+$+2] (2.1); 144 [M$^+$+1] (2.8); 143 [M$^+$] (33.3); 112 (100.0); 85 (58.8); 84 (25.9). – HRMS calcd for $C_5H_5NO_2S$ (143.16) 143.00410, found 143.00412.

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[5] Type Faradizer M; Sedema; B 1050 Brussels; Belgium

Address for correspondence:
Dr. M. Kalesse
Universität Hannover
Institut für Organische Chemie
Schneiderberg 1B
D-30167 Hannover
Telefax: Int. code +(511)762-3011
Email: Kalesse@mbox.oci.uni-hannover.de