ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 8, pp. 1855–1861. © Pleiades Publishing, Ltd., 2015.
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Synthesis of 2,5-Di(hydroxyalkyl)-1,3-thiazoles

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Received April 23, 2015

Abstract—A general approach towards synthesis of 2(5)-hydroxyalkyl-substituted 1,3-thiazole derivatives has been proposed. The method includes lithiation of 1,3-thiazole ring followed by reacting the formed thiazole lithium derivatives with electrophiles.

Keywords: 1,3-thiazole, *n*-butyllithium, electrophile, diol

DOI: 10.1134/S1070363215080113

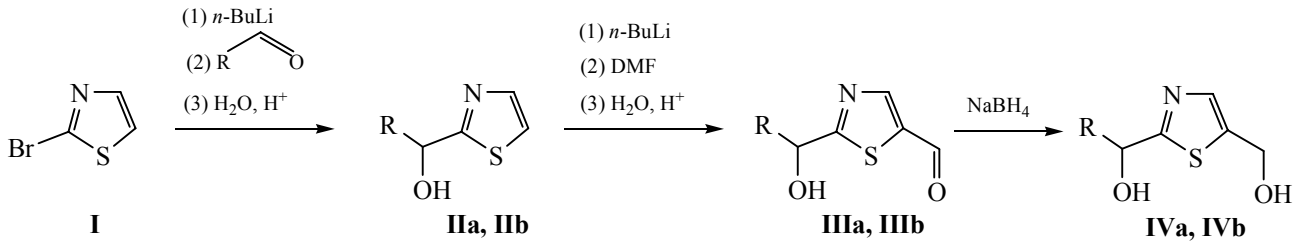
Natural and synthetic derivatives of 1,3-thiazole exhibit a range of biological activities and play significant part in the processes in living organisms [1–5]. Compounds possessing psychotropic [6–11] and nerve blocking [12] effects as well as anticancer drugs with cytotoxic activity against HT-1080 and MG-22A cancer cell lines [13] have been found among representatives of this class. The above-mentioned 1,3-thiazole derivatives with antitumor activity contain hydroxyl groups in the molecules; many compounds of this series are drugs with broad range of the biological effects [14–20]. Therefore, synthesis of such compounds is a fairly topical issue.

The earlier reported methods of hydroxyalkyl-1,3-thiazoles [14–23] are not preparative. Herein, we propose a suitable approach towards synthesis of the compounds containing hydroxyalkyl substituents at positions 2 and 5 of the 1,3-thiazole ring. This method affords the diols containing primary as well as secondary alcohol groups.

Commercially available 2-bromo-1,3-thiazole **I** was used as the starting reagent. It is known to react with *n*-butyllithium to form 2-thiazolyllithium, the latter being highly reactive towards various electrophiles [24–27] including aldehydes and *N*,*N*-dimethylformamide. For example, sequential treatment of thiazole **1** with *n*-butyllithium and aldehydes as described in [28] afforded compounds **IIa** and **IIb** in high yield. For further functionalization of 1,3-thiazole ring, the products **IIa** and **IIb** were treated with *n*-butyllithium, and then DMF was added. As a result, previously unknown aldehydes **IIIa** and **IIIb** were obtained. Their reduction with sodium borohydride gave diols **IVa** and **IVb** (Scheme 1).

Isomeric diols **IXa** and **IXb** were prepared via a series of transformations. Initially, 1,3-thiazole-2-

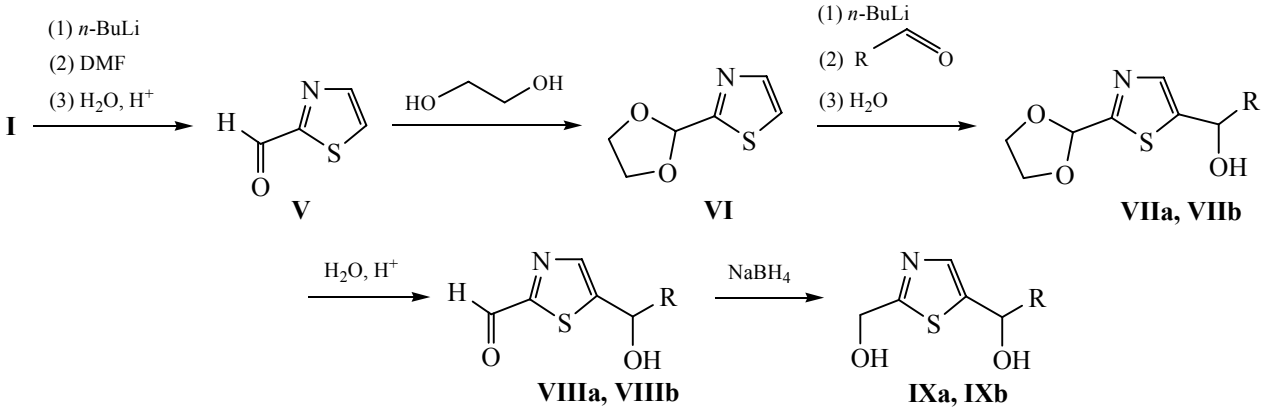
Scheme 1.



I **IIa, IIb** **IIIa, IIIb** **IVa, IVb**

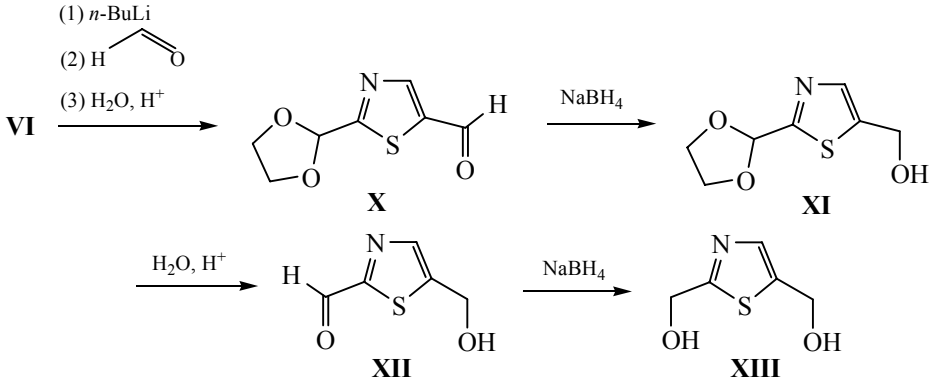
R = Me (**a**), Ph (**b**).

Scheme 2.

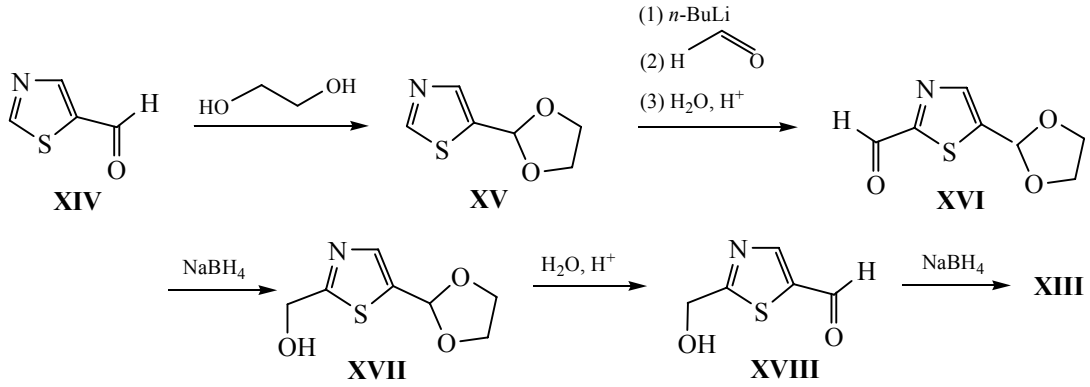


R = Me (**a**), Ph (**b**).

Scheme 3.



Scheme 4.



carbaldehyde **V** [24] and synthon **VI** [29] were prepared; they are capable of selectively reacting with *n*-butyllithium to form 5-lithiated 1,3-thiazole [28, 29]. Herein we report for the first time that the lithium derivative reacted with acetaldehyde or benzaldehyde to give the secondary alcohols **VIIa** and **VIIb**. Hydrolysis of the latter in the presence of *p*-toluenesulfonic acid yielded aldehydes **VIIIa** and **VIIIb**, structural isomers of compounds **IIIa** and **IIIb**. In turn, aldehydes **VIIIa** and **VIIIb** were reduced into the corresponding diols **IXa** and **IXd** with sodium borohydride (Scheme 2).

Table 1. Yields, melting points, and elemental analysis data for compounds **III–XVIII**

Comp. no.	Yield, %	mp, °C (eluent)	Found, %		Formula	Calculated, %	
			N	S		N	S
IIIa	58	78–80 (CH_2Cl_2–EtOAc, 75 : 25)	9.11	20.61	$C_6H_7NO_2S$	8.91	20.40
IIIb	74	68–71 (CH_2Cl_2–EtOAc, 90 : 10)	6.60	14.83	$C_{11}H_9NO_2S$	6.39	14.62
IVa	60	Oil (EtOAc)	8.95	20.28	$C_6H_9NO_2S$	8.80	20.14
IVb	80	111–113 (CH_2Cl_2–EtOAc, 50 : 50)	6.56	14.67	$C_{11}H_{11}NO_2S$	6.33	14.49
VIIa[a]	75	Oil (CH_2Cl_2–EtOAc, 60 : 40)	7.08	16.04	$C_8H_{11}NO_3S$	6.96	15.93
VIIb	83	Oil (CH_2Cl_2–EtOAc, 60 : 40)	5.61	12.48	$C_{13}H_{13}NO_3S$	5.32	12.18
VIIIa[b]	42	Oil (CH_2Cl_2–EtOAc, 90 : 10)	9.11	20.53	$C_6H_7NO_2S$	8.91	20.40
VIIIb	64	Oil (CH_2Cl_2–EtOAc, 85 : 15)	6.52	14.72	$C_{11}H_9NO_2S$	6.39	14.62
IXa	95	Oil (EtOAc–MeOH, 90 : 10)	9.02	20.31	$C_6H_9NO_2S$	8.80	20.14
IXb	79	96–98 (EtOAc)	6.62	14.19	$C_{11}H_{11}NO_2S$	6.33	14.49
XII	60	Oil (CH_2Cl_2–EtOAc, 85 : 15)	9.85	22.56	$C_5H_5NO_2S$	9.78	22.40
XIII	69[c]	Oil (EtOAc)	9.79	22.28	$C_5H_7NO_2S$	9.65	22.09
XV	89	–[d]	9.05	20.49	$C_6H_7NO_2S$	8.91	20.40
XVI	85	Oil (CH_2Cl_2–EtOAc, 90 : 10)	7.72	17.38	$C_7H_7NO_3S$	7.56	17.31
XVII	95	Oil (EtOAc)	7.69	17.26	$C_7H_9NO_3S$	7.48	17.13
XVIII	30	105–106 (CH_2Cl_2–EtOAc, 75 : 25)	9.95	22.57	$C_5H_5NO_2S$	9.78	22.40

[a] The substance was earlier obtained as described in [28]. [b] Compound was earlier with 39% yield as described in [28]. [c] Yield for the method *a*. [d] bp 63°C (0.6 mmHg).

The simplest representative of the diols obtained, 2,5-di(hydroxymethyl)-1,3-thiazole **XIII**, was synthesized as follows. Initially, compound **VI** was converted into aldehyde **XII** and then reduced to diol **XIII** with sodium borohydride (Scheme 3).

Similar reaction starting from the available 1,3-thiazole-5-carbaldehyde **XIV** [31] afforded 2-(hydroxymethyl)-1,3-thiazole-5-carbaldehyde **XVIII**, a structural isomer of aldehyde **XII**. Aldehyde **XVIII** was reduced into 2,5-di(hydroxymethyl)-1,3-thiazole **XIII** with yield of 83% (Scheme 4).

Composition and structure of the products was confirmed by elemental analysis (Table 1), ^{1}H, ^{13}C NMR, and IR spectroscopy data as well as chromato–mass spectrometry (Table 2).

In summary, we have elaborated a convenient method to prepare 2,5-di(hydroxyalkyl)-1,3-thiazoles as well as isomeric pairs **III** and **VIII**, **X** and **XVI**, **XI** and **XVII**, **XII** and **XVIII**, **IV** and **IX**, potential biologically active substances. Their chemical and biological properties are currently under study and will be discussed in the upcoming reports.

EXPERIMENTAL

NMR spectra of the solutions in DMSO-d_6 were recorded using a Bruker AVANCE DRX-500 spectrometer [500 (^{1}H), 125 MHz (^{13}C)] relative to internal TMS. IR spectra (KBr) were registered with a Vertex 70 spectrometer. Melting points were determined using a Fisher Johns instrument. GC–MS spectra were registered using a liquid chromatography–mass spectrometry system for an Agilent 1100 Series high-performance chromatograph equipped with a diode array and an Agilent LC\MSD SL mass-selective detector with rapid ionization mode switching (positive/negative). Parameters of the GC–MS analysis: Zorbax SB-C18 column (1.8 μm, 4.6 × 15 mm, PN 821975-932); solvent A, acetonitrile–water (95 :5) + 0.1% trifluoroacetic acid, solvent B, 0.1% aqueous solution of trifluoroacetic acid; eluent rate 3 mL min^{-1}; injection volume 1 μL; UV detector at 215,

Table 2. Spectral data for compounds **IV**–**XVIII**

Comp. no.	ν, cm^{-1}	δ_H, ppm	δ_C, ppm	m/z, $[M+1]^+$
IIIa	3204 (O–H), 1672 (C=O)	1.46 d (3H, CH_3, J_{HH} 6.3 Hz), 4.98 q (1H, C<u>H</u>OH, J_{HH} 6.3 Hz), 6.38 s (1H, OH), 8.58 s (1H, $C^4H_{thiazole}$), 10.0 s (1H, CHO)	187.16 ($C^2_{thiazole}$), 184.3 (C=O), 152.83 ($C^4_{thiazole}$), 138.43($C^5_{thiazole}$), 67.23 (COH), 23.78 (CH_3)	158
IIIb	3191 (O–H), 1667 (C=O)	6.04 s (1H, CH), 7.14 s (1H, OH), 7.30 t (1H, C_6H_5, J_{HH} 7.2 Hz), 7.37 t (2H, C_6H_5, J_{HH} 7.2 Hz), 7.49 d (2H, C_6H_5, J_{HH} 7.5 Hz), 8.56 s (1H, $C^4H_{thiazole}$), 10.02 s (1H, CHO)	184.9 ($C^2_{thiazole}$), 184.29 (C=O), 152.78 ($C^4_{thiazole}$), 138.52 ($C^5_{thiazole}$), 141.83, 128.46, 128.00, 126.74 (C_6H_5), 72.9 (CHOH)	220
IVa	3248 (O–H)	1.42 d (3H, CH_3), 4.62 s (2H, CH_2), 4.87 q (1H, C<u>H</u>OH, J_{HH} 6.6 Hz), 5.45 s (1H, OH), 6.01 s (1H, OH), 7.49 s (1H, $C^4H_{thiazole}$)	177.55 ($C^2_{thiazole}$), 139.69 ($C^4_{thiazole}$), 139.00 ($C^5_{thiazole}$), 66.92 (COH), 55.91 (COH), 24.27 (CH_3)	160
IVb	3338 (O–H)	4.66 s (2H, CH_2), 5.93 s (1H, C<u>H</u>OH), 6.74 s (1H, OH), 7.28 t (1H, C_6H_5, J_{HH} 7.4 Hz), 7.36 t (2H, C_6H_5, J_{HH} 7.4 Hz), 7.48 d (2H, C_6H_5, J_{HH} 7.1 Hz), 7.53 s (1H, $C^4H_{thiazole}$)	175.68 ($C^2_{thiazole}$), 143.01 ($C^5_{thiazole}$), 139.11 ($C^4_{thiazole}$), 140.25, 128.28, 127.56, 126.49 (C_6H_5), 72.75 (CH_2OH), 55.96 (CHOH)	222
VIIa	3258 (O–H)	1.42 d (3H, CH_3, J_{HH} 6.3 Hz), 3.93–4.09 m (4H, OCH_2CH_2O), 4.97–5.04 m (1H, C<u>H</u>OH), 5.72 s (1H, OH), 7.62 s (1H, $C^4H_{thiazole}$)	166.36 ($C^2_{thiazole}$), 147.97 ($C^5_{thiazole}$), 137.88 ($C^4_{thiazole}$), 99.68 (OCHO), 65.15 (CH_2CH_2), 62.60 (CHOH), 25.81 (CH_3)	202
VIIb	3240 (O–H)	3.93–4.06 m (4H, OCH_2CH_2O), 5.96 s (1H, OCHO), 6.04 d (1H, C<u>H</u>OH, J_{HH} 4.0 Hz), 6.44 d (1H, OH, J_{HH} 4.0 Hz), 7.27 t (1H, C_6H_5, J_{HH} 6.9 Hz), 7.36 t (2H, C_6H_5, J_{HH} 7.9 Hz), 7.44 d (2H, C_6H_5, J_{HH} 7.9 Hz), 7.63 s (1H, $C^4H_{thiazole}$)	167.35 ($C^2_{thiazole}$), 144.33 ($C^5_{thiazole}$), 138.95 ($C^4_{thiazole}$), 146.75, 128.43, 127.55, 125.96 (C_6H_5), 99.62 (OCHO), 68.56 (CH_2CH_2), 65.18 (CHOH)	264
VIIIa	3262 (O–H), 1679 (C=O)	1.47 d (3H, CH_3, J_{HH} 6.3 Hz), 5.07–5.15 m (1H, C<u>H</u>OH), 6.03 d (1H, OH, J_{HH} 3.9 Hz), 8.07 s (1H, $C^4H_{thiazole}$), 9.87 s (1H, CHO)	184.98 (C=O), 163.91 ($C^2_{thiazole}$), 155.47 ($C^5_{thiazole}$), 141.30 ($C^4_{thiazole}$), 62.88 (CHOH), 25.70 (CH_3)	158
VIIIb	3348 (O–H), 1684 (C=O)	6.15 d (1H, C<u>H</u>OH, J_{HH} 4.2 Hz), 6.72 d (1H, OH, J_{HH} 4.2 Hz), 7.29 t (1H, C_6H_5, J_{HH} 7.4 Hz), 7.37 t (2H, C_6H_5, J_{HH} 7.4 Hz), 7.46 d (2H, C_6H_5, J_{HH} 7.4 Hz), 8.03 s (1H, $C^4H_{thiazole}$), 9.86 s (1H, CHO)	184.94 (C=O), 164.57 ($C^2_{thiazole}$), 153.75 ($C^5_{thiazole}$), 142.09 ($C^4_{thiazole}$), 143.7, 128.6, 127.85, 126.09 (C_6H_5), 68.69 (CHOH)	220
IXa	3236 (O–H)	1.41 d (3H, CH_3, J_{HH} 6.6 Hz), 4.65 d (2H, CH_2, J_{HH} 5.8 Hz), 5.00–4.92 m (1H, CH), 5.58 d (1H, OH, J_{HH} 4.4 Hz), 5.93 t (1H, OH, J_{HH} 5.7 Hz), 7.48 s (1H, $C^4H_{thiazole}$)	172.11 ($C^2_{thiazole}$), 145.65 ($C^5_{thiazole}$), 137.26 ($C^4_{thiazole}$), 62.62 (COH), 61.03 (COH), 25.85 (CH_3)	160
IXb	3315 (O–H)	4.63 s (2H, CH_2), 5.93 s (1H, OH), 5.99 s (1H, C<u>H</u>OH), 6.3 s (1H, OH), 7.26 t (1H, C_6H_5, J_{HH} 6.9 Hz), 7.35 t (2H, C_6H_5, J_{HH} 6.9 Hz), 7.42 d (2H, C_6H_5, J_{HH} 7.5 Hz), 7.49 s (1H, $C^4H_{thiazole}$)	173.27 ($C^2_{thiazole}$), 144.43 ($C^5_{thiazole}$), 138.41 ($C^4_{thiazole}$), 144.64, 128.32, 127.38, 125.95 (C_6H_5), 68.67 (CH_2OH), 61.04 (CHOH)	222
XII	3211 (O–H), 1682 (C=O)	4.8 s (2H, CH_2), 5.9 s (1H, OH), 8.07 s (1H, $C^4H_{thiazole}$), 9.88 s (1H, CHO)	184.87 (C=O), 164.54 ($C^2_{thiazole}$), 149.97 ($C^5_{thiazole}$), 142.3 ($C^4_{thiazole}$), 56.21 (CH_2OH)	144
XIII	3227 (O–H)	4.63 s (2H, CH_2), 4.67 s (2H, CH_2), 5.48 s (1H, OH), 5.96 s (1H, OH), 7.52 s (1H, $C^4H_{thiazole}$)	173.14 ($C^2_{thiazole}$), 140.01 ($C^5_{thiazole}$), 139.00 ($C^4_{thiazole}$), 61.05 (COH), 55.85 (COH)	146
XV	–	3.98–4.13 m (4H, OCH_2CH_2O), 6.17 s (1H, CH), 7.93 s (1H, $C^4H_{thiazole}$), 8.77 s (1H, $C^2H_{thiazole}$)	157.17 ($C^2_{thiazole}$), 134.85 ($C^4_{thiazole}$), 134.34 ($C^5_{thiazole}$), 97.30 (OCHO), 68.38 (CH_2CH_2)	158

Table 2. (Contd.)

Comp. no.	ν, cm^{-1}	δ_H, ppm	δ_C, ppm	*m*/*z*, $[M+1]^+$
XVI	1687 (C=O)	3.96–4.09 m (4H, OCH_2CH_2O), 6.26 s (1H, CH), 8.3 s (1H, $C^4H_{thiazole}$), 9.92 s (1H, CHO)	185.04 (C=O), 166.13 ($C^2_{thiazole}$), 144.43 ($C^4_{thiazole}$), 144.41 ($C^5_{thiazole}$), 97.3 (OCHO), 65.17 (CH_2CH_2)	186
XVII	3236 (O–H)	3.96–4.09 m (4H, OCH_2CH_2O), 4.83 s (2H, CH_2), 5.9 s (1H, OH), 5.96 s (1H, OCHO), 7.60 s (1H, $C^4H_{thiazole}$)	163.45 ($C^2_{thiazole}$), 145.63 ($C^5_{thiazole}$), 135.95 ($C^4_{thiazole}$), 98.61 (OCHO), 67.56 (CH_2CH_2), 67.17 (CHOH)	188
XVIII	3244 (O–H), 1661 (C=O)	4.79 s (2H, CH_2), 6.35 s (1H, OH), 8.56 s (1H,$C^4H_{thiazole}$), 10.01 s (1H, CHO)	184.16 (C=O), 183.44 ($C^2_{thiazole}$), 152.85 ($C^4_{thiazole}$), 138.35 ($C^5_{thiazole}$), 61.36 (CH_2OH)	144

254, 265 nm; ionization method – chemical ionization at atmospheric pressure (APCI), scan range *m*/*z* 80–1000. Elemental analysis was performed in the Institute of Bioorganic Chemistry and Petrochemistry of National Academy of Sciences of Ukraine. The reaction progress was monitored by TLC on Silufol UV-254 plates eluting with CH_2Cl_2–EtOAc mixture and detecting with UV light. The obtained compounds were purified via column chromatography (Silica gel 60, 230–400 mesh).

1-(1,3-Thiazol-2-yl)ethanol **IIa** [30], phenyl(1,3-thiazol-2-yl)methanol **IIb** [28], 1,3-thiazole-2-carbaldehyde **V** [24], 2-(1,3-dioxolan-2-yl)-1,3-thiazole **VI** [29], 2-(1,3-dioxolan-2-yl)-1,3-thiazole-5-carbaldehyde **X**, and [2-(1,3-dioxolan-2-yl)-1,3-thiazol-5-yl]-methanol **XI** [28] were prepared via the earlier reported methods.

2-(1-Hydroxyethyl)-1,3-thiazole-5-carbaldehyde (IIIa). A solution of *n*-butyllithium in hexane (68 mL, 2.5 mol/L) was added dropwise to a solution of 0.077 mol of compound **IIa** in 150 mL of tetrahydrofuran at –80 to –70°C over 0.5 h. The mixture was stirred during 1 h, and then 0.116 mol of dimethylformamide was added dropwise at –70 to –60°C. The reaction mixture was stirred during **XII** h. Then, 170 mL of 15% acetic acid solution was added dropwise. The mixture was extracted with ethyl acetate; the organic layer was dried over sodium sulfate. After the solvent removal, the residue was purified via chromatography (CH_2Cl_2–EtOAc, 75 : 25).

2-[Hydroxy(phenyl)methyl]-1,3-thiazole-5-carbaldehyde (IIIb) was prepared similarly from phenyl(1,3-thiazol-2-yl)methanol **IIb**.

1-[5-(Hydroxymethyl)-1,3-thiazol-2-yl]ethan-1-ol (IVa). 0.004 mol of sodium borohydride was added portionwise to a solution of 0.008 mol of compound **IIIa** in 6 mL of tetrahydrofuran and 3 mL of methanol cooled at 5°C. The mixture was stirred during **XII** h; the solvent was removed under reduced pressure. The residue was purified by chromatography (EtOAc).

[5-(Hydroxymethyl)-1,3-thiazol-2-yl](phenyl)-methanol (IVb) was prepared similarly to thiazole **IIIb** from aldehyde **IVa**.

1-[2-(1,3-Dioxolan-2-yl)-1,3-thiazol-5-yl]ethan-1-ol (VIIa). A solution of *n*-butyllithium in hexane (70.4 mL, 2.5 mol/L) was added dropwise to a solution of 0.146 mol of compound **VI** in 250 mL of tetrahydrofuran at –80 to –70°C over 0.5 h. The mixture was stirred during 1 h, and then 0.22 mol of acetaldehyde was added dropwise at –70 to –60°C. The reaction mixture temperature was adjusted to –20°C for 0.5 h. Next, 68 mL of water was added dropwise, and the mixture was stirred during 2 h at 20–25°C. The organic layer was separated; the aqueous layer was extracted with ethyl acetate and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography (CH_2Cl_2–EtOAc, 60 : 40).

[2-(1,3-Dioxolan-2-yl)-1,3-thiazol-5-yl](phenyl)-methanol (VIIb) was prepared similarly from 0.366 mol of compound **VI**, 176 mL of 2.5 mol/L *n*-butyllithium hexane solution, and 0.55 mol of benzaldehyde.

5-(1-Hydroxyethyl)-1,3-thiazole-2-carboxaldehyde (VIIIa). 0.0006 mol of *p*-toluenesulfonic acid was added to a solution of 0.006 mol of compound **VIIa** in 10 mL of acetonitrile and 4 mL of water. The mixture was refluxed during 9 h. After cooling to 20°C, 20 mL of ethyl acetate was added. The organic layer was separated, the solvent was removed under reduced

pressure, and the residue was purified by chromatography (CH_2Cl_2–EtOAc, 80 : 20).

5-[Hydroxy(phenyl)methyl]-1,3-thiazole-2-carbaldehyde (VIIIb) was prepared similarly from [2-(1,3-dioxolan-2-yl)-1,3-thiazol-5-yl](phenyl)methanol **VIIb**.

1-[2-(Hydroxymethyl)-1,3-thiazol-5-yl]ethan-1-ol (IXa) and [2-(hydroxymethyl)-1,3-thiazol-5-yl]-(phenyl)methanol (IXb) were synthesized from aldehydes **VIIIa** and **VIIIb** according to the procedure described for compound **IVa**.

5-(Hydroxymethyl)-1,3-thiazole-2-carbaldehyde (XII) was prepared similarly to compound **VIIIa** from the thiazole **XI**.

2,5-Di(hydroxymethyl)-1,3-thiazole (XIII). *a*. 0.005 mol of sodium borohydride was added portionwise to a solution of 0.01 mol of compound **XII** in 6 mL of tetrahydrofuran and 3 mL of methanol cooled to 5°C. The mixture was stirred during 9 h, the solvent was removed under reduced pressure, and the residue was purified by chromatography (EtOAc).

b. Compound **XIII** was also prepared from compound **XVIII** according to the above procedure in 83% yield.

5-(1,3-Dioxolan-2-yl)-1,3-thiazole (XV). 0.0215 mol of *p*-toluenesulfonic acid was added to a solution of 0.43 mol of 1,3-thiazole-5-carbaldehyde **XIV** [31] and 1.5 mol of ethylene glycol in 500 mL of benzene. The mixture was heated during 8 h with a Dean–Stark trap, and then 500 mL of water was added. The mixture was extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated. The residue was distilled in vacuum.

5-(1,3-Dioxolan-2-yl)-1,3-thiazole-2-carbaldehyde (XVI) was prepared similarly to compound **IIIa** from 5-(1,3-dioxolan-2-yl)-1,3-thiazole **XV**.

[5-(1,3-Dioxolan-2-yl)-1,3-thiazol-2-yl]methanol (XVII) was obtained from 5-(1,3-dioxolan-2-yl)-1,3-thiazole-2-carbaldehyde **XVI** following the procedure described for compound **IVa**.

5-(Hydroxymethyl)-1,3-thiazole-2-carbaldehyde (XVIII) was prepared from compound **XVII** similarly to aldehyde **VIIIa**.

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