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Synthesis of New 1,3-Thiazolecarbaldehydes

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Abstract—H-Lithiation and Br-lithiation reactions of 1,3-thiazole were studied in order to obtain new thiazole derivatives. Four isomeric chloromethyl derivatives of 1,3-thiazole containing a protected aldehyde group like 2-(1,3-dioxolan-2-yl)-5-(chloromethyl)-1,3-thiazole, 5-(1,3-dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole, 4-(1,3-dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole, and 2-(1,3-dioxolan-2-yl)-4-(chloromethyl)-1,3-thiazole were synthesized. Their nucleophilic substitution reactions with dimethylamine and sodium methylthiolate were studied. New aldehydes of 1,3-thiazole series of low-molecular weight were obtained.

Keywords: 1,3-thiazole, 1,3-thiazole lithiation, aldehydes, 1,3-thiazole chloromethyl derivatives, nucleophilic substitution

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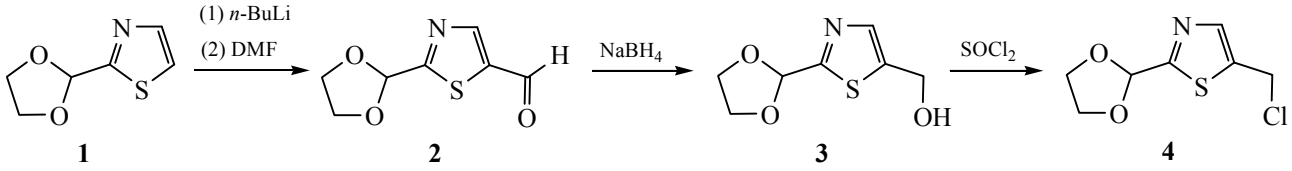
Synthesis of new low-molecular weight heterocyclic synthons, in particular, 1,3-thiazole derivatives, is an urgent task of modern organic chemistry. This, as has long been known, is caused by a wide spectrum of biological activity of both natural and synthetic related compounds. 2-, 4-, and 5-formyl-1,3-thiazoles are used as medications in the treatment of *E. coli*-induced Crohn's disease [1], as well as selective inhibitors of various enzymes [2–5], selective antagonists of sigma receptors [6 , 7], adenosine receptor [8, 9], and new T-type calcium channel blockers [10]. Their various biological activities have also been studied [11–15].

Here we report on a preparative method for new isomeric polyfunctional 1,3-thiazole derivatives containing chloromethyl and dioxolanyl protected aldehyde groups. The presence of both groups in one molecule makes it possible to obtain broad libraries of compounds for biological screening. An important factor is the synthesis of several different isomeric compounds, which provides a possibility to understand, as a result of biological studies, how the substrate interacts with a particular protein, which spatial placement of the substituents will be most beneficial for achieving the maximum biological effect.

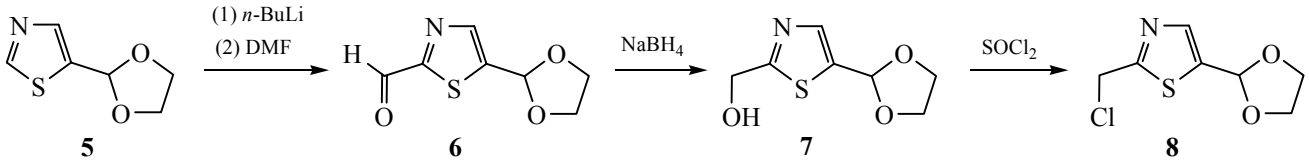
For the synthesis of chloromethyl derivatives **4** and **8**, we used the known 5-hydroxymethyl-2-(1,3-dioxolan-2-yl)-1,3-thiazole **3** [16] and 2-hydroxymethyl-5-(1,3-dioxolan-2-yl)-1,3-thiazole **7** [17], respectively, obtained by treating 2-(1,3-dioxolan-2-yl)-1,3-thiazole **1** [18] or 5-(1,3-dioxolan-2-yl)-1,3-thiazole **5** [17] in succession with butyl lithium and dimethylformamide. The initially formed aldehydes **2** [16] and **6** [17] were then reduced with sodium borohydride to yield alcohols **3** and **7** (Schemes 1, 2). The subsequent reaction of compounds **3** and **7** with thionyl chloride was carried out in dichloromethane at 5°C. Compounds **4** and **8** were isolated by column chromatography as oily substances in 89–90% yield.

Available ethyl 2-amino-1,3-thiazole-4-carboxylate **9** [19] was used to prepare 2-(chloromethyl)-4-(1,3-dioxolan-2-yl)-1,3-thiazole **16**. Under the action of copper bromide and *tert*-butyl nitrate in acetonitrile it was first converted to ethyl 2-bromo-1,3-thiazole-4-carboxylate **10** [20] in 88% yield (Scheme 3). Carboxylate **10** was reduced with lithium borohydride to (2-bromo-1,3-thiazol-4-yl)methanol **11** [21] in 78% yield. We first carried out the Swern oxidation of compound **11** to form 2-bromo-1,3-thiazole-4-carbaldehyde **12** in 92% yield. It should be noted that compound **12** has been previously obtained [22], but with the use of a large dilution of the reaction mixture and the use of expensive diisobutyl aluminum hydride. To replace the bromine atom with an aldehyde group, dioxolane protection **12**→**13** was performed according

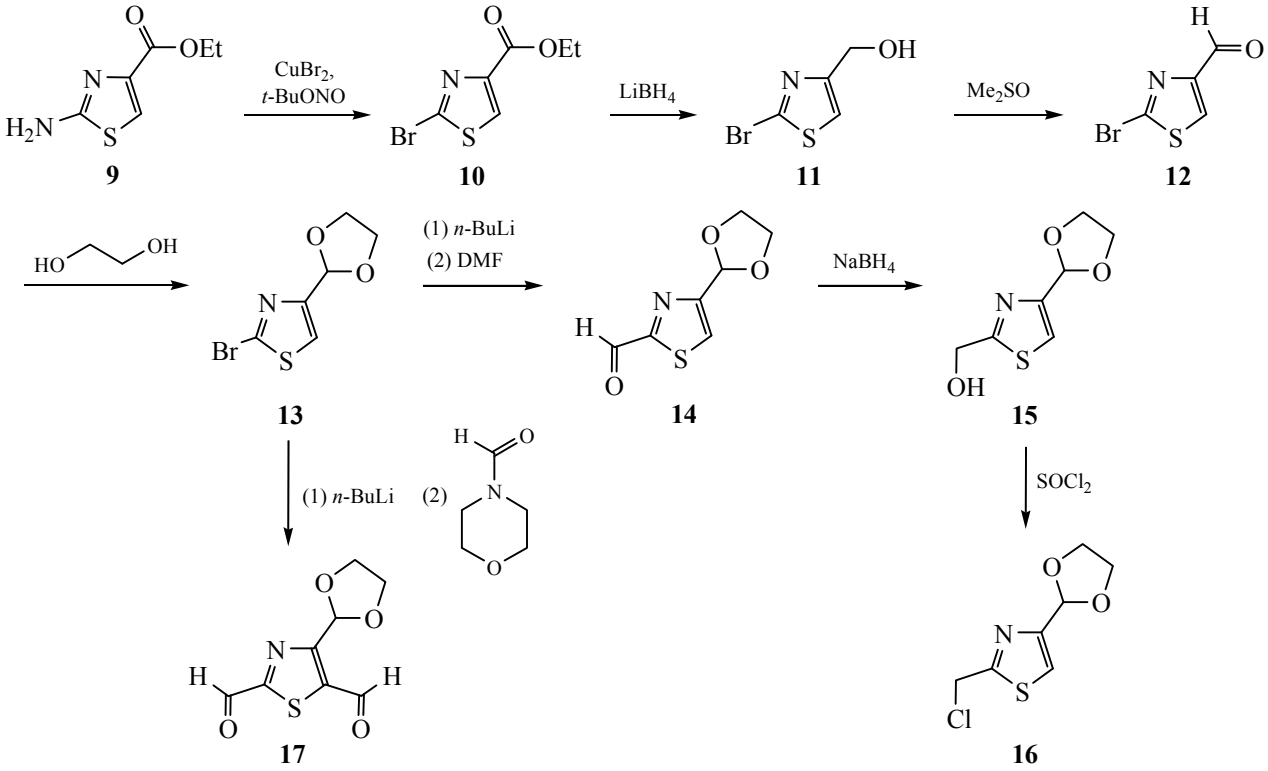
Scheme 1.



Scheme 2.



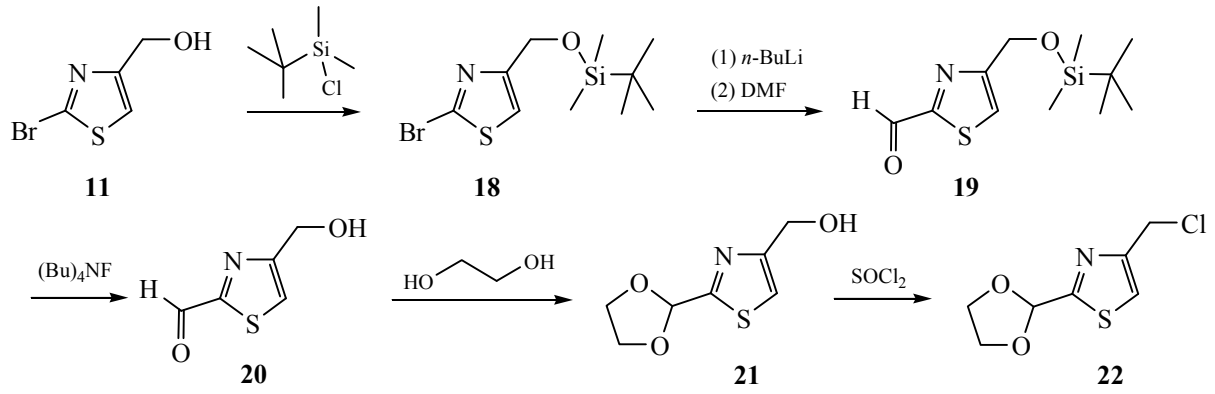
Scheme 3.



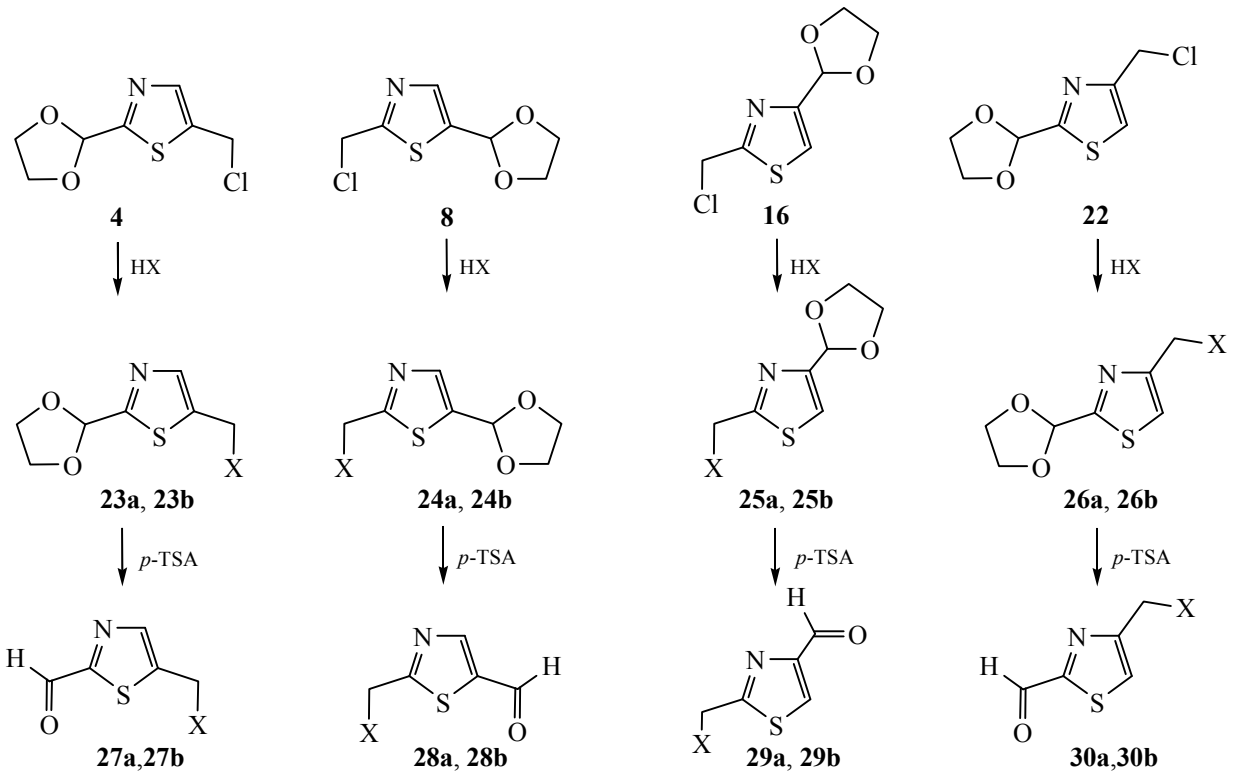
to the procedure described in [23]. Further reaction of **13** with *n*-butyllithium and DMF as an electrophile resulted in aldehyde **14** in 52% yield. Note that the lithiation of 2-bromo-4-(1,3-dioxolan-2-yl)-1,3-thiazole **13** strongly depends both on the nature of the lithiating reagent and on the solvent nature. Thus, the reaction with *tert*-butyllithium in THF involved double lithiation and the formation of dianion, which gave 4-(1,3-dioxolan-2-yl)-1,3-thiazol-2,5-dicarbaldehyde **17** when reacted with morpholine-4-carbaldehyde. Compound **17** is a promising reagent in organic synthesis. Next, aldehyde **14** was reduced to [4-(1,3-dioxolan-2-yl)-1,3-thiazol-2-yl]methanol **15**, and then converted to the desired 2-(chloromethyl)-4-(1,3-dioxolan-2-yl)-1,3-thiazole **16** (Scheme 3).

(2-Bromo-1,3-thiazol-4-yl)methanol **11** was used for the synthesis of 4-(chloromethyl)-2-(1,3-dioxolan-2-yl)-1,3-thiazole **22**. Lithiation of **11** with two equivalents of *n*-butyllithium failed, since the 1,3-thiazole

Scheme 4.



Scheme 5.



X = NMe_2 (**a**), SMe (**b**).

ring became inactive for further lithiation at the position 2 when a charge was formed on the alcohol group. Therefore, we first carried out the protection of the alcohol group and obtained 2-bromo-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole **18**. This made it possible to carry out the Br-lithiation reaction and to synthesize 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-2-carbaldehyde **19** by the subsequent treatment with dimethylformamide (Scheme 4). After removal of the *tert*-butyl(dimethyl)silyl protection, 4-(hydroxylmethyl)-1,3-thiazole-2-carbaldehyde **20** was obtained. Further protection of the aldehyde group with dioxolane group afforded 4-hydroxymethyl-2-(1,3-dioxolan-2-yl)-1,3-thiazole **21**. Subsequent treatment of **21** with thionyl chloride in dichloromethane solution gave 4-(chloromethyl)-2-(1,3-dioxolan-2-yl)-1,3-thiazole **22** (Scheme 4).

To study the synthetic potential of the synthesized chloromethyl derivatives of 1,3-thiazole, we carried out their reactions with sodium methylthiolate and dimethylamine. As a result, compounds **23**–**26** were obtained. After removal of dioxolane protection, they

Table 1. Yields, melting points, and elemental analysis data for compounds **4**–**30**

Comp. no.	Yield, %	mp, °C (eluent for chromatography)	Found, %		Formula	Calculated, %	
			N	S		N	S
4	90	Oil (CH_2Cl_2–EtOAc, 90 : 10)	6.97	15.77	$C_7H_8ClNO_2S$	6.81	15.59
8	89	Oil (CH_2Cl_2–EtOAc, 90 : 10)	6.89	15.82	$C_7H_8ClNO_2S$	6.81	15.59
12	92	121–122[a] (CH_2Cl_2)	7.38	16.89	C_4H_2BrNOS	7.29	16.70
14	52	81–83 (hexane–EtOAc, 70 : 30)	7.72	17.53	$C_7H_7NO_3S$	7.56	17.31
15	96	Oil (CH_2Cl_2–EtOAc, 70 : 30)	7.69	17.27	$C_7H_9NO_3S$	7.48	17.13
16	52	Oil (CH_2Cl_2–EtOAc, 90 : 10)	6.97	15.75	$C_7H_8ClNO_2S$	6.81	15.59
17	19	69–70 (hexane–EtOAc, 70 : 30)	6.78	15.19	$C_8H_7NO_4S$	6.57	15.04
19	76	Oil (hexane–EtOAc, 96 : 4)	5.62	12.64	$C_{11}H_{19}NO_2SSi$	5.44	12.46
20	71	Oil (CH_2Cl_2–EtOAc, 70 : 30)	9.89	22.51	$C_5H_5NO_2S$	9.78	22.40
21	64	Oil (EtOAc)	7.64	17.30	$C_7H_9NO_3S$	7.48	17.13
22	95	Oil (CH_2Cl_2–EtOAc, 90 : 10)	6.93	15.84	$C_7H_8ClNO_2S$	6.81	15.59
23a	84	Oil (CH_2Cl_2–MeOH, 90 : 10)	13.27	15.08	$C_9H_{14}N_2O_2S$	13.07	14.96
23b	92	Oil (hexane–EtOAc, 70 : 30)	6.61	29.59	$C_8H_{11}NO_2S_2$	6.45	29.51
24a	90	Oil (CH_2Cl_2–MeOH, 90 : 10)	13.19	15.09	$C_9H_{14}N_2O_2S$	13.07	14.96
24b	79	Oil (hexane–EtOAc, 70 : 30)	6.58	29.68	$C_8H_{11}NO_2S_2$	6.45	29.51
25a	77	Oil (CH_2Cl_2–MeOH, 95 : 5)	13.30	14.99	$C_9H_{14}N_2O_2S$	13.07	14.96
25b	85	Oil (hexane–EtOAc, 70 : 30)	6.56	29.72	$C_8H_{11}NO_2S_2$	6.45	29.51
26a	83	Oil (CH_2Cl_2–MeOH, 90 : 10)	13.23	15.10	$C_9H_{14}N_2O_2S$	13.07	14.96
26b	84	Oil (hexane–EtOAc, 70 : 30)	6.64	29.77	$C_8H_{11}NO_2S_2$	6.45	29.51
27a	63	Oil (EtOAc)	16.59	18.97	$C_7H_{10}N_2OS$	16.46	18.84
27b	70	Oil (CH_2Cl_2)	8.23	37.22	$C_6H_7NOS_2$	8.08	37.01
28a	80	Oil (EtOAc)	16.56	18.96	$C_7H_{10}N_2OS$	16.46	18.84
28b	94	Oil (CH_2Cl_2)	8.19	37.22	$C_6H_7NOS_2$	8.08	37.01
29a[b]	94	Oil (EtOAc)	16.67	19.02	$C_7H_{10}N_2OS$	16.46	18.84
29b	89	Oil (CH_2Cl_2)	8.17	37.18	$C_6H_7NOS_2$	8.08	37.01
30a[c]	89	Oil (EtOAc)	16.65	18.94	$C_7H_{10}N_2OS$	16.46	18.84
30b	88	Oil (CH_2Cl_2)	8.22	37.25	$C_6H_7NOS_2$	8.08	37.01

[a] According to [22]. [b] Compound **29a** was previously prepared by other method [24]. [c] Compound **30a** was previously prepared by other method [25].

were converted to the corresponding aldehydes **27**–**30** (Scheme 5), which are low-molecular weight synthons for the synthesis of new 1,3-thiazole derivatives for selection of various bioregulators among them. It should also be noted that most of the synthesized compounds are soluble in water, which is very useful in carrying out biological studies.

The composition and structure of the obtained compounds were proved by elemental analysis (Table 1), ^1H and ^{13}C NMR, IR spectroscopy, as well as chromatography-mass spectrometry (Table 2).

In conclusion, isomeric chloromethyl derivatives of 1,3-thiazole containing a protected aldehyde group

Table 2. IR, NMR, and mass spectral data for compounds **4**–**30**

Comp. no.	ν, cm^{-1}	δ_H, ppm	δ_C, ppm	*m*/z, $[M + 1]^+$
4	704, 789, 937, 1024, 1083, 1211, 2891	4.00–4.16 m (4H, OCH_2CH_2O), 4.76 s (2H, CH_2), 6.05 s (1H, OCHO), 7.69 s (1H, $C^4H_{thiazole}$)	170.02 ($C^2_{thiazole}$), 142.54 ($C^4_{thiazole}$), 136.68 ($C^5_{thiazole}$), 100.17 (OCHO), 65.62 (CH_2CH_2), 37.36 (CH_2Cl)	206
8	717, 868, 937, 1023, 1070, 1213, 2891	3.95–4.12 m (4H, OCH_2CH_2O), 4.79 s (2H, CH_2), 6.10 s (1H, OCHO), 7.73 s (1H, $C^4H_{thiazole}$)	167.34 ($C^2_{thiazole}$), 141.37 ($C^4_{thiazole}$), 138.95 ($C^5_{thiazole}$), 98.53 (OCHO), 65.36 (CH_2CH_2), 41.50 (CH_2Cl).	206
14	660, 786, 838, 984, 996, 1096, 1164, 1244, 1386, 1452, 1690 (CO), 2898, 3080	4.01–4.17 m (4H, OCH_2CH_2O), 6.04 s (1H, CH), 7.80 s (1H, $H_{thiazole}$), 9.95 s (1H, CHO)	183.79 (C=O), 166.55 ($C^2_{thiazole}$), 157.18 ($C^4_{thiazole}$), 123.99 ($C^5_{thiazole}$), 99.52 (OCHO), 65.52 (CH_2CH_2)	186
15	730, 760, 936, 990, 1027, 1085, 1142, 2887, 3266 (OH)	3.90–4.10 m (4H, OCH_2CH_2O), 4.62 s (1H, OH), 4.83 s (2H, CH_2), 5.88 s (1H, OCHO), 7.31 s (1H, $H_{thiazole}$)	173.86 ($C^2_{thiazole}$), 153.33 ($C^4_{thiazole}$), 117.24 ($C^5_{thiazole}$), 99.74 (OCHO), 65.28 (CH_2CH_2), 61.80 (CH_2OH)	188
16	759, 912, 1083, 1119, 1148, 1205, 2889	3.96–4.16 m (4H, OCH_2CH_2O), 4.83 s (2H, CH_2), 5.96 s (1H, OCHO), 7.44 (1H, $H_{thiazole}$)	167.54 ($C^2_{thiazole}$), 153.97 ($C^4_{thiazole}$), 118.97 ($C^5_{thiazole}$), 99.73 (OCHO), 65.36 (CH_2CH_2), 41.49 (CH_2Cl).	206
17	772, 1106, 1192, 1292, 1450, 1670 (C=O), 1696 (C=O), 2902	4.10–4.23 m (4H, OCH_2CH_2O), 6.24 s (1H, OCHO), 9.96 s (1H, C^2CHO), 10.42 s (1H, C^5CHO)	183.76 (C=O), 183.66 (C=O), 168.48 ($C^2_{thiazole}$), 159.58 ($C^4_{thiazole}$), 141.37 ($C^5_{thiazole}$), 99.81 (OCHO), 65.72 (CH_2CH_2)	214
19	648, 775, 834, 1099, 1133, 1255, 1692 (C=O), 2856, 2931	0.12 s (6H, $2CH_3$), 0.93 s [9H, $C(CH_3)_3$], 4.93 s (2H, CH_2), 7.63 s (1H, $H_{thiazole}$), 9.93 s (1H, CHO)	183.75 (C=O), 165.65 ($C^2_{thiazole}$), 160.75 ($C^4_{thiazole}$), 121.45 ($C^5_{thiazole}$), 62.00 (CH_2), 25.87 ($3CH_3$), 18.35 [$SiC(CH_3)_3$], –5.37 ($2CH_3$)	258
20	650, 750, 957, 1020, 1687 (C=O), 2833, 3237 (OH)	3.2 br.s (1H, OH), 4.86 s (2H, CH_2), 7.64 s (1H, $H_{thiazole}$), 9.92 s (1H, CHO)	183.61 (C=O), 166.02 ($C^2_{thiazole}$), 159.62 ($C^4_{thiazole}$), 122.31 ($C^5_{thiazole}$), 60.69 (CH_2OH)	144
21	754, 934, 1022, 1086, 1212, 2891, 3337 (OH)	3.30 s (1H, OH), 4.01–4.18 m (4H, OCH_2CH_2O), 4.76 s (2H, CH_2), 6.10 s (1H, OCHO), 7.23 s (1H, $H_{thiazole}$)	168.83 ($C^2_{thiazole}$), 157.17 ($C^4_{thiazole}$), 115.90 ($C^5_{thiazole}$), 100.03 (OCHO), 65.56 (CH_2CH_2), 60.76 (CH_2OH)	188
22	646, 719, 936, 1024, 1085, 1213, 2892	3.97-4.15 m (4H, OCH_2CH_2O), 4.66 s (2H, CH_2), 6.08 s (1H, OCHO), 7.32 s (1H, $H_{thiazole}$)	169.08 ($C^2_{thiazole}$), 152.85 ($C^4_{thiazole}$), 118.64 ($C^5_{thiazole}$), 99.94 (OCHO), 65.61 (CH_2CH_2), 40.69 (CH_2Cl)	206
23a	796, 839, 939, 1023, 1082, 1215, 1355, 1459, 2775, 2821, 2889, 2946	2.20 s (6H, $2CH_3$), 3.58 s (2H, CH_2), 3.94–4.13 m (4H, OCH_2CH_2O), 6.03 s (1H, OCHO), 7.52 s (1H, $C^4H_{thiazole}$)	168.28 ($C^2_{thiazole}$), 141.16 ($C^4_{thiazole}$), 138.35 ($C^5_{thiazole}$), 100.43 (OCHO), 65.49 (CH_2CH_2), 55.49 (CH_2), 45.03 ($2CH_3$)	215
23b	623, 789, 938, 1082, 1213, 1345, 2890	2.05 s (3H, CH_3), 3.84 s (2H, CH_2), 3.96–4.17 m (4H, OCH_2CH_2O), 6.05 s (1H, OCHO), 7.56 s (1H, $C^4H_{thiazole}$)	168.16 ($C^2_{thiazole}$), 141.25 ($C^4_{thiazole}$), 138.55 ($C^5_{thiazole}$), 100.34 (OCHO), 65.54 (CH_2CH_2), 29.79 (CH_2), 15.15 (CH_3)	218
24a	803, 851, 938, 1029, 1070, 1124, 1270, 1346, 1456, 2886, 2947	2.33 s (6H, $2CH_3$), 3.73 s (2H, CH_2), 3.95–4.13 m (4H, OCH_2CH_2O), 6.08 s (1H, OCHO), 7.68 s (1H, $C^4H_{thiazole}$)	172.23 ($C^2_{thiazole}$), 140.99 ($C^4_{thiazole}$), 136.96 ($C^5_{thiazole}$), 98.90 (OCHO), 65.28 (CH_2CH_2), 61.11 (CH_2), 45.59 ($2CH_3$)	215
24b	691, 801, 866, 937, 1069, 1214, 1379, 2887	2.13 s (3H, CH_3), 3.92 s (2H, CH_2), 3.97–4.13 m (4H, OCH_2CH_2O), 6.08 s (1H, OCHO), 7.67 s (1H, $C^4H_{thiazole}$)	170.93 ($C^2_{thiazole}$), 141.21 ($C^4_{thiazole}$), 137.43 ($C^5_{thiazole}$), 98.78 (OCHO), 65.33 (CH_2CH_2), 35.52 (CH_2), 15.67 (CH_3)	218

Table 2. (Contd.)

Comp. no.	ν, cm^{-1}	δ_H, ppm	δ_C, ppm	*m*/z, $[M+1]^+$
25a	757, 939, 1030, 1085, 1141, 1268, 1348, 1457, 2777, 2825, 2886, 2947	2.32 s (6H, $2CH_3$), 3.75 s (2H, CH_2), 3.96–4.13 m (4H, OCH_2CH_2O), 5.92 s (1H, OCHO), 7.34 s (1H, $H_{thiazole}$)	172.20 ($C^2_{thiazole}$), 153.13 ($C^4_{thiazole}$), 117.70 ($C^5_{thiazole}$), 99.99 (OCHO), 65.28 (CH_2CH_2), 61.00 (CH_2), 45.72 ($2CH_3$)	215
25b	757, 935, 1027, 1079, 1146, 1472, 2887	2.13 s (3H, CH_3), 3.97 s (2H, CH_2), 3.98–4.16 m (4H, OCH_2CH_2O), 5.93 s (1H, OCHO), 7.36 s (1H, $H_{thiazole}$)	171.00 ($C^2_{thiazole}$), 153.58 ($C^4_{thiazole}$), 117.93 ($C^5_{thiazole}$), 99.89 (OCHO), 65.30 (CH_2CH_2), 35.40 (CH_2), 15.74 (CH_3)	218
26a	763, 849, 937, 1027, 1085, 1214, 1344, 1457, 2771, 2819, 2889, 2944	2.26 s (6H, $2CH_3$), 3.57 s (2H, CH_2), 3.99–4.16 m (4H, OCH_2CH_2O), 6.10 s (1H, OCHO), 7.14 s (1H, $H_{thiazole}$)	167.85 ($C^2_{thiazole}$), 155.11 ($C^4_{thiazole}$), 117.00 ($C^5_{thiazole}$), 100.23 (OCHO), 65.52 (CH_2CH_2), 59.32 (CH_2), 45.43 ($2CH_3$)	215
26b	738, 935, 1024, 1084, 1212, 1343, 2890	2.07 s (3H, CH_3), 3.80 s (2H, CH_2), 4.00–4.17 m (4H, OCH_2CH_2O), 6.09 s (1H, OCHO), 7.15 s (1H, $H_{thiazole}$)	168.38 ($C^2_{thiazole}$), 154.29 ($C^4_{thiazole}$), 116.37 ($C^5_{thiazole}$), 100.13 (OCHO), 65.56 (CH_2CH_2), 33.67 (CH_2), 15.53 (CH_3)	218
27a	646, 788, 871, 1024, 1354, 1424, 1685 (C=O), 2775, 2822	2.25 s (6H, $2CH_3$), 3.69 s (2H, CH_2), 7.87 s (1H, $C^4H_{thiazole}$), 9.89 s (1H, CHO)	184.02 (C=O), 165.72 ($C^2_{thiazole}$), 145.87 ($C^5_{thiazole}$), 143.71 ($C^4_{thiazole}$), 55.54 (CH_2), 45.13 ($2CH_3$)	171
27b	650, 782, 1232, 1424, 1686 (C=O), 2854, 2916	2.09 s (3H, CH_3), 3.91 s (2H, CH_2), 7.90 s (1H, $C^4H_{thiazole}$), 9.91 s (1H, CHO)	183.91 (C=O), 165.47 ($C^2_{thiazole}$), 145.99 ($C^5_{thiazole}$), 143.98 ($C^4_{thiazole}$), 29.86 (CH_2), 15.42 (CH_3)	174
28a	665, 796, 960, 1131, 1227, 1339, 1437, 1514, 1670 (C=O), 2780, 2826	2.33 s (6H, $2CH_3$), 3.76 s (2H, CH_2), 8.26 s (1H, $C^4H_{thiazole}$), 9.96 s (1H, CHO)	182.35 (C=O), 180.51 ($C^2_{thiazole}$), 151.40 ($C^4_{thiazole}$), 139.63 ($C^5_{thiazole}$), 61.31 (CH_2), 45.76 ($2CH_3$)	171
28b	660, 792, 1221, 1426, 1662(C=O), 2828, 2917	2.14 s (3H, CH_3), 3.96 s (2H, CH_2), 8.26 s (1H, $C^4H_{thiazole}$), 9.97 s (1H, CHO)	182.15 (C=O), 178.32 ($C^2_{thiazole}$), 151.33 ($C^4_{thiazole}$), 140.12 ($C^5_{thiazole}$), 35.91 (CH_2), 15.89 (CH_3)	174
29a	715, 763, 849, 1037, 1123, 1485, 1691 (C=O), 2779, 2825	2.35 s (6H, $2CH_3$), 3.79 s (2H, CH_2), 8.13 s (1H, $H_{thiazole}$), 9.95 s (1H, CHO)	184.53 (C=O), 173.27 ($C^2_{thiazole}$), 154.65 ($C^4_{thiazole}$), 129.12 ($C^5_{thiazole}$), 60.73 (CH_2), 45.72 ($2CH_3$)	171
29b	699, 745, 965, 1093, 1481, 1687(C=O), 2829, 2916	2.12 s (3H, CH_3), 3.98 s (2H, CH_2), 8.13 s (1H, $H_{thiazole}$), 9.94 s (1H, CHO)	184.34 (C=O), 171.76 ($C^2_{thiazole}$), 154.68 ($C^4_{thiazole}$), 129.14 ($C^5_{thiazole}$), 35.29 (CH_2), 15.71 (CH_3)	174
30a	648, 730, 977, 1029, 1144, 1229, 1452, 1686 (C=O), 2955	2.27 s (6H, $2CH_3$), 3.64 s (2H, CH_2), 7.54 s (1H, $H_{thiazole}$), 9.95 s (1H, CHO)	183.93 (C=O), 165.66 ($C^2_{thiazole}$), 157.97 ($C^4_{thiazole}$), 123.42 ($C^5_{thiazole}$), 59.18 (CH_2), 45.44 ($2CH_3$)	171
30b	650, 748, 1234, 1438, 1676 (C=O), 2852, 2918	2.07 s (3H, CH_3), 3.85 s (2H, CH_2), 7.53 s (1H, $H_{thiazole}$), 9.92 s (1H, CHO)	183.66 (C=O), 165.86 ($C^2_{thiazole}$), 157.20 ($C^4_{thiazole}$), 122.78 ($C^5_{thiazole}$), 33.49 (CH_2), 15.59 (CH_3)	174

were synthesized through the H- and Br-lithiation reactions at the positions 2 and 5 of the 1,3-thiazole ring. Their reactions of nucleophilic substitution with dimethylamine and sodium methylthiolate furnished new aldehydes of the 1,3-thiazole series, which are low-molecular weight synthons for the synthesis of different 1,3-thiazole derivatives for selection of various bioregulators among them.

EXPERIMENTAL

The NMR spectra of the solutions in $CDCl_3$ were registered on a Bruker AVANCE DRX-500 [500 (^1H), 125 MHz (^{13}C)] spectrometer, internal reference TMS. The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. The melting points were determined on a Fisher Johns apparatus.

Chromato-mass spectra were recorded using a liquid chromatography-mass spectrometric system on a highly efficient liquid chromatograph Agilent 1100 Series equipped with a diode array with an Agilent LC MSD SL mass-selective detector with fast positive/negative ionization switching. Parameters of chromatography-mass spectrometry analysis: column Zorbax SB C18 1.8 μm 4.6 × 15 mm (PN 821975-932); solvents: A, acetonitrile–water (95 : 5), 0.1% trifluoroacetic acid; B, 0.1% aqueous trifluoroacetic acid; flow eluent 3 mL/min, injection volume 1 μL; UV detectors 215, 254, 265 nm, chemical ionization at atmospheric pressure (APCI), scanning range of *m*/*z* 80–1000 Da. Elemental analysis was carried out in the Analytical Laboratory of the Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine. The reaction progress was monitored by TLC on Silufol UV-254 plates,detection by UV exposure. The resulting compounds were purified by column chromatography (Silica gel 60, 230–400 mesh).

2-(1,3-Dioxolan-2-yl)-1,3-thiazole **1** [18], 2-(1,3-dioxolan-2-yl)-1,3-thiazole-5-carbaldehyde **2** [16], [2-(1,3-dioxolan-2-yl)-1,3-thiazol-5-yl]methanol **3** [16], 5-(1,3-dioxolan-2-yl)-1,3-thiazole **5** [17], 5-(1,3-dioxolan-2-yl)-1,3-thiazole-2-carbaldehyde **6** [17], 2-hydroxymethyl-5-(1,3-dioxolan-2-yl)-1,3-thiazole **7** [17], ethyl 2-amino-1,3-thiazole-4-carboxylate **9** [19], ethyl 2-bromo-1,3-thiazole-4-carboxylate **10** [20], (2-bromo-1,3-thiazol-4-yl)methanol **11** [21], 2-bromo-4-(1,3-dioxolan-2-yl)-1,3-thiazole **13** [23] were prepared according to the known procedures.

2-(1,3-Dioxolan-2-yl)-5-(chloromethyl)-1,3-thiazole (4). To a pre-cooled (5°C) solution of 0.01 mol of compound **3** in 10 mL of dichloromethane was added dropwise 0.015 mol of thionyl chloride. The mixture was stirred for 0.5 h, and then 20 mL of saturated aqueous sodium bicarbonate solution was added. The mixture was extracted with 20 mL of dichloromethane. The organic layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed at a reduced pressure, and the residue was chromatographed.

5-(1,3-Dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole (8) was prepared similarly from alcohol **7**.

2-Bromo-1,3-thiazole-4-carbaldehyde (12). A solution of 0.22 mol of dimethyl sulfoxide in 50 mL of dichloromethane was added dropwise to a solution of 0.11 mol of oxalyl chloride in 200 mL of dichloromethane in a temperature range of –75 to –65°C. The mixture was stirred for 0.5 h, and then a solution of 0.1 mol of **11** in 100 mL of dichloromethane was added dropwise at –75 to –65°C. The mixture was stirred for an additional 2 h, and then 0.5 mol of triethylamine was added dropwise at –75 to –65°C. After the temperature of the reaction mixture was raised to –10°C for 1 h, the mixture was poured into a solution of 0.4 mol of sodium bicarbonate in 400 mL of water, stirred for 0.5 h and extracted with dichloromethane. The organic layer was dried with sodium sulfate, the solvent was removed at a reduced pressure, and the residue was chromatographed.

4-(1,3-Dioxolan-2-yl)-1,3-thiazole-2-carbaldehyde (14). To 176 mL of a 2.5 M solution of *n*-butyllithium in hexane was added 900 mL of tetrahydrofuran. The mixture was cooled to –80°C, a solution of 0.4 mol of compound **13** in 450 mL of tetrahydrofuran was added dropwise within 0.5 h at a temperature of –80 to –70°C. The resulting mixture was stirred for 1 h, and then 0.64 mol of dimethylformamide was added dropwise at –70 to –60°C. The stirring was continued for 12 h at room temperature, then the mixture was poured into 1200 mL of ice water and 75 mL of acetic acid was added. The resulting mixture was stirred for 1 h and then extracted with ethyl acetate. The organic layer was dried with sodium sulfate, the solvent was removed at a reduced pressure, and the residue was chromatographed.

[4-(1,3-Dioxolan-2-yl)-1,3-thiazol-2-yl]methanol (15). To a pre-cooled (5°C) solution of 0.008 mol of **14** in 6 mL of tetrahydrofuran and 3 mL of methanol 0.004 mol of sodium borohydride was added in portions. The mixture was stirred for 12 h, then a solution of 0.008 mol of acetic acid in 10 mL of water was added. After stirring for an additional 1 h, the mixture was extracted with ethyl acetate. The organic layer was separated and dried with sodium sulfate. The solvent was removed at a reduced pressure, and the residue was chromatographed.

4-(1,3-Dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole (16) was prepared similarly to compound **4** from alcohol **15**.

4-(1,3-Dioxolan-2-yl)-1,3-thiazole-2,5-dicarbaldehyde (17). To a solution of 0.017 mol of compound **13** in 60 mL of tetrahydrofuran 22 mL of a 1.7 M solution of *tert*-butyllithium in pentane was added dropwise at –85 to –80°C within 0.5 h. The mixture was stirred for 0.5 h, then a solution of 0.036 mol of

morpholine-4-carbaldehyde in 10 mL of tetrahydrofuran was added dropwise at a temperature of –85 to –80°C. The resulting mixture was stirred for 0.5 h at the same temperature, then the temperature was raised to 0°C for 1 h. Next, 70 mL of water and 3.9 mL of conc. hydrochloric acid were successively added. The mixture was stirred for 10 min at 10°C, then the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic fractions were dried with sodium sulfate. The solvent was removed at a reduced pressure. The resulting mixture was separated by column chromatography, affording dialdehyde **17** (19%) and aldehyde **14** (16%).

4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-2-carbaldehyde (19). To 114 mL of a 2.5 M *n*-butyllithium solution in hexane was added 650 mL of diethyl ether. The mixture was cooled to –80°C, then a solution of 0.23 mol of compound **18** in 150 mL of diethyl ether was added dropwise over 0.5 h at a temperature of –80 to –70°C. The stirring was continued for an additional 1 h, then 0.36 mol of dimethylformamide was added dropwise at –70 to –60°C. The resulting mixture was stirred for 12 h at room temperature and then poured into 700 mL of ice water. Next, 86 mL of conc. hydrochloric acid was added, and the mixture was stirred for 0.5 h, after which sodium carbonate was added until pH ~ 9. The mixture was extracted with ethyl acetate, and the organic layer was dried with sodium sulfate. The solvent was removed at a reduced pressure, and the residue was chromatographed.

4-(Hydroxymethyl)-1,3-thiazole-2-carbaldehyde (20). To a solution of 0.05 mol of compound **19** cooled to 5°C 60 mL of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran was added. The reaction mixture was stirred for 5 min, then poured into 150 mL of a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed at a reduced pressure, and the residue was chromatographed.

[2-(1,3-Dioxolan-2-yl)-1,3-thiazol-4-yl]methanol (21). To a solution of 0.04 mol of compound **20** in 50 mL of benzene were added in succession 0.15 mol of ethylene glycol and 0.002 mol of *p*-toluenesulfonic acid. The mixture was heated for 8 h with a Dean–Stark trap, then 50 mL of water was added. The resulting mixture was extracted with ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate and dried with sodium sulfate. The solvent was removed at a reduced pressure, and the residue was chromatographed.

2-(1,3-Dioxolan-2-yl)-4-(chloromethyl)-1,3-thiazole (22) was prepared similarly to compound **4** from alcohol **21**.

1-[2-(1,3-Dioxolan-2-yl)-1,3-thiazol-5-yl]-*N*,*N*-dimethylmethanamine (23a). To a solution of 0.01 mol of compound **4** in 21 mL of tetrahydrofuran were added 7 mL of water and 3 mL of a 40% aqueous solution of dimethylamine. The mixture was stirred for 12 h, then a solution of 0.012 mol of sodium hydroxide in 25 mL of water was added. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed at a reduced pressure and the residue was chromatographed.

2-(1,3-Dioxolan-2-yl)-5-[(methylsulfanyl)methyl]-1,3-thiazole (23b). To a solution of 0.01 mol of compound **4** in 21 mL of tetrahydrofuran were added 7 mL of water and 6.7 mL of a 21% aqueous solution of sodium methylthiolate. The mixture was stirred for 12 h, then 25 mL of water was added. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed at a reduced pressure, and the residue was chromatographed.

1-[5-(1,3-Dioxolan-2-yl)-1,3-thiazol-2-yl]-*N*,*N*-dimethylmethanamine (24a) was prepared similarly to compound **23a** from 5-(1,3-dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole **8**.

5-(1,3-Dioxolan-2-yl)-2-[(methylsulfanyl)methyl]-1,3-thiazole (24b) was prepared similarly to compound **23b** from 5-(1,3-dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole **8**.

1-[4-(1,3-Dioxolan-2-yl)-1,3-thiazol-2-yl]-*N*,*N*-dimethylmethanamine (25a) was prepared similarly to compound **23a** from 4-(1,3-dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole **16**.

4-(1,3-Dioxolan-2-yl)-2-[(methylsulfanyl)methyl]-1,3-thiazole (25b) was prepared similarly to compound **23b** from 4-(1,3-dioxolan-2-yl)-2-(chloromethyl)-1,3-thiazole **16**.

1-[2-(1,3-Dioxolan-2-yl)-1,3-thiazol-4-yl]-*N*,*N*-dimethylmethanamine (26a) was prepared similarly to compound **23a** from 2-(1,3-dioxolan-2-yl)-4-(chloromethyl)-1,3-thiazole **22**.

2-(1,3-Dioxolan-2-yl)-4-[(methylsulfanyl)methyl]-1,3-thiazole (26b) was prepared similarly to compound **23b** from 2-(1,3-dioxolan-2-yl)-4-(chloromethyl)-1,3-thiazole **22**.

5-[(Dimethylamino)methyl]-1,3-thiazole-2-carbaldehyde (27a). To a solution of 0.005 mol of compound **23a** in 15 mL of tetrahydrofuran was added a solution of 0.006 mol of conc. sulfuric acid in 15 mL of water. The mixture was refluxed for 8 h, and then cooled to 20°C. A solution of 0.012 mol of sodium hydroxide in 10 mL of water was added. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed at a reduced pressure and the residue was chromatographed.

5-[(Methylsulfanyl)methyl]-1,3-thiazole-2-carbaldehyde (27b). To a solution of 0.01 mol of compound **23b** in 15 mL of acetonitrile and 6 mL of water was added 0.001 mol of *p*-toluenesulfonic acid. The mixture was refluxed for 12 h. After cooling to 20°C, 30 mL of ethyl acetate was added. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate, and dried with sodium sulfate. The solvent was removed at a reduced pressure, the residue was chromatographed.

2-[(Dimethylamino)methyl]-1,3-thiazole-5-carbaldehyde (28a) was prepared similarly to compound **27a** from 1-[5-(1,3-dioxolan-2-yl)-1,3-thiazol-2-yl]-*N*,*N*-dimethylmethanamine **24a**.

2-[(Methylsulfanyl)methyl]-1,3-thiazole-5-carbaldehyde (28b) was prepared similarly to compound **27b** from 5-(1,3-dioxolan-2-yl)-2-[(methylsulphanyl)methyl]-1,3-thiazole **24b**.

2-[(Dimethylamino)methyl]-1,3-thiazole-4-carbaldehyde (29a) was prepared similarly to compound **27a** from 1-[4-(1,3-dioxolan-2-yl)-1,3-thiazol-2-yl]-*N*,*N*-dimethylmethanamine **25a**.

2-[(Methylsulfanyl)methyl]-1,3-thiazole-4-carbaldehyde (29b) was prepared similarly to compound **27b** from 4-(1,3-dioxolan-2-yl)-2-[(methylsulfanyl)methyl]-1,3-thiazole **25b**.

4-[(Dimethylamino)methyl]-1,3-thiazole-2-carbaldehyde (30a) was prepared similarly to compound **27a** from 1-[2-(1,3-dioxolan-2-yl)-1,3-thiazol-4-yl]-*N*,*N*-dimethylmethanamine **26a**.

4-[(Methylsulfanyl)methyl]-1,3-thiazole-2-carbaldehyde (30b) was prepared similarly to compound **27b** from 2-(1,3-dioxolan-2-yl)-4-[(methylsulfanyl)methyl]-1,3-thiazole **26b**.

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