Chemistry of Heterocyclic Compounds, Vol. 38, No. 7, 2002

THIOCYANATION, HALOGENATION, DEHALOGENATION, TRANSHALOGENATION, AND NITRATION OF 2-SUBSTITUTED 4-(2-FURYL)THIAZOLES

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Bromination and thiocyanation of 2-amino- and 2-acetylamino-4-(2-furyl)thiazoles when 1 mol of reagent is used at 10°C are directed to the 5 position. Formation of 5'-bromo-substituted derivatives when the reaction temperature is raised is the result of a secondary, thermodynamically controlled process. Monohalogenation and mononitration of 4-(2-furyl)-2-methylthiazole are directed to the 5' position. Nitration of 2-acetylamino-4-(5-nitro-2-furyl)thiazole by a nitrating mixture is accompanied by oxidative cleavage of the 5-nitrofuran moiety and leads to formation of 5,5'- and 3',5'-dinitro derivatives.

Keywords: 2-R-4-(2-furyl)thiazoles (R = NH_2, NHAc, Me), bromination, iodination, nitration, oxidative cleavage of 5-nitro-2-furyl group, transbromination, thiocyanation.

It was shown earlier that 4-(2-furyl)thiazoles with electron-donor groups in the position 2 of the thiazole ring form 5,5'-dibromo-substituted derivatives upon bromination [1]. Thiocyanation products of 2-amino- and 2-acetamino-4-(2-furyl)thiazoles were assigned the structure of the 5-thiocyano derivative substituted on the thiazole ring [2]. However, as was demonstrated by ^{1}H NMR spectra, treating the same compounds with 1 mol of bromine in an acetic acid medium at 40-65°C and also holding the reaction mixture at room temperature for many hours leads to the 5'-bromo derivative substituted on the furyl group [1]. Moreover, according to data in [3], treatment of the thienyl analogs of the above-indicated heterocycles with 1 mol of bromine leads to substitution at the thiazole ring.

The aim of this work was to refine the reactivity with respect to electrophilic substitution for furan and thiazole rings in 2-amino- (**1a**), 2-acetylamino- (**1b**), and 2-methyl-4-(2-furyl)thiazoles (**1c**).

We found that thiocyanation of compounds **1a,b** upon treatment with 1 mol of dithiocyanogen in fact leads to the 5-thiocyano derivatives substituted on the thiazole ring **2a,b**, which was confirmed by ^{1}H NMR spectra. Monosubstitution is highly selective; the yields of monothiocyano-substituted derivatives are almost quantitative. When we use 2 mol of dithiocyanogen, subsequent substitution occurs at the position 5' of the furyl group, but the reaction proceeds slowly, competing with polymerization of the dithiocyanogen. Complete conversion of compounds **1a,b** to the 5,5'-substituted **5a,b** occurs only when we use 4-5 mol of dithiocyanogen. The thiocyano group in compounds **2b, 5b** is not exchanged for the nitro group upon heating with $NaNO_2$ in acetic acid but remains unchanged, in contrast to the 5,5'-dibromo analog [4].

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: dzsile@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 983-991, July, 2002. Original article submitted February 28, 2001.

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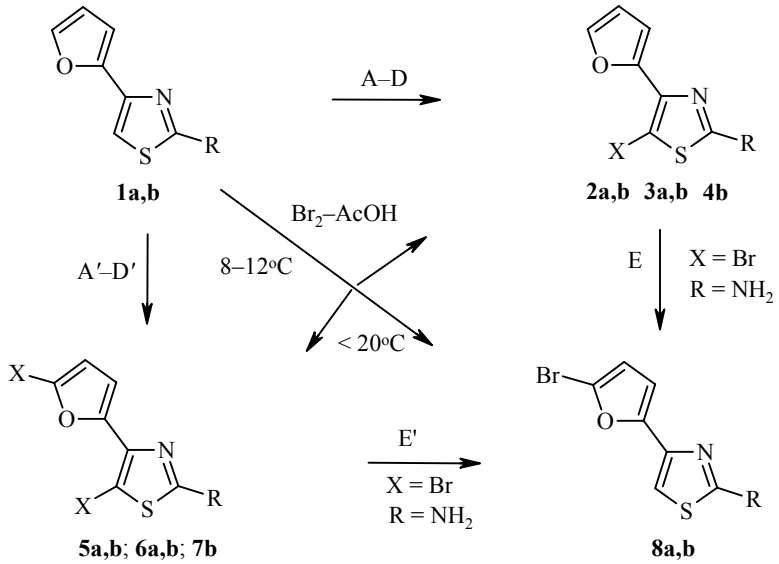


2a,b, **5a,b** X = SCN; **3a,b**, **6a,b** X = Br; **4b**, **7b** X = I; **1–3**, **5**, **6**, **8a** R = NH_2; **1–8 b** R = NHAc

A $(SCN)_2$–AcOH, B Br_2–AcOH, ~10°C, C NBS–AcOH, D $2I_2$–DMSO,
E 1HBr–AcOH, 100°C; A' $4(SCN)_2$–AcOH, B' $2Br_2$–AcOH, C' 2NBS–AcOH,
D' $3I_2$–DMSO, E' 2HBr–AcOH, 100°C

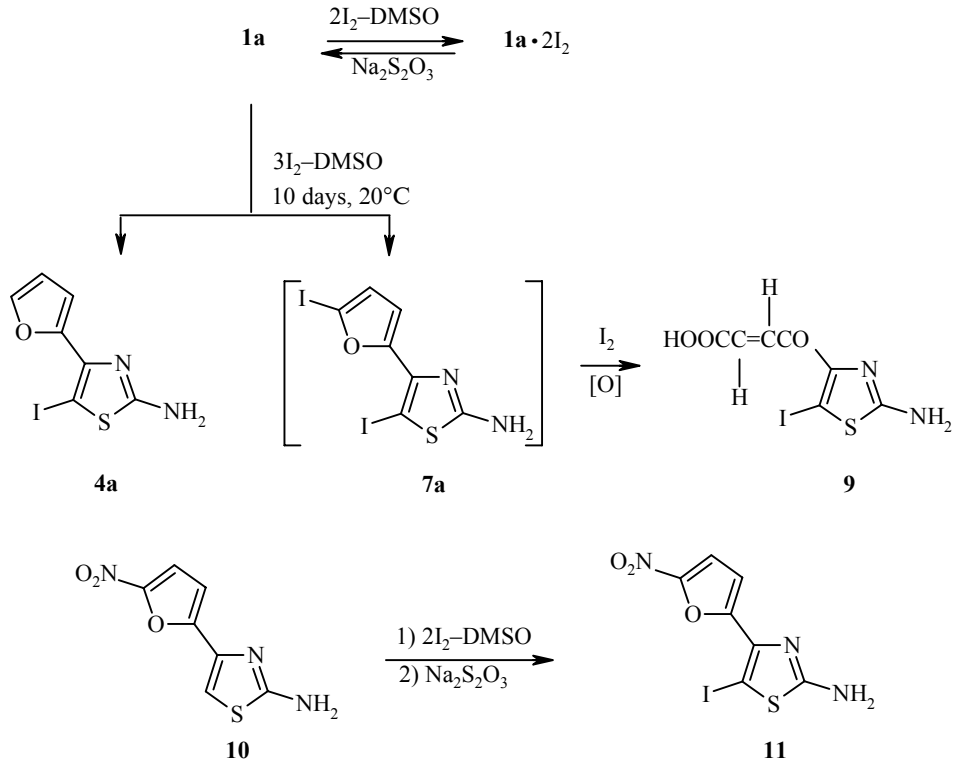
Since 2-amino-5-bromo(iodo)-4-methylthiazoles are easily dehalogenated [5], the question arose about whether monobromination products of compounds **1a,b** substituted at the position 5' of the furan moiety (**8a,b**), described in [1], are products of a secondary reaction.

We found that when compounds **1a,b** are treated with 1 mol of bromine in acetic acid at a temperature of 8-12°C, judging from the ^{1}H NMR spectrum, the products formed are ~80% 5-bromo derivatives substituted on the thiazole ring **3a,b** and ~10% dibromo-substituted derivatives **6a,b**. When the reaction temperature is raised to 20°C, compounds **8a,b** also appear.

From this it follows that the kinetically controlled process leads to substitution on the thiazole ring, while transhalogenation is a thermodynamically more favorable secondary process. This is confirmed experimentally. Thus when heated for 1 h on a steam bath with 1 mole of hydrobromic acid in glacial acetic acid medium, 5-bromothiazole **3a** is 90% converted to 5'-bromofurylthiazole **8a**, while when treated with 2 mol of hydrobromic acid, 5,5'-dibromofurylthiazole **6a** is 70% converted to the same compound **8a**.

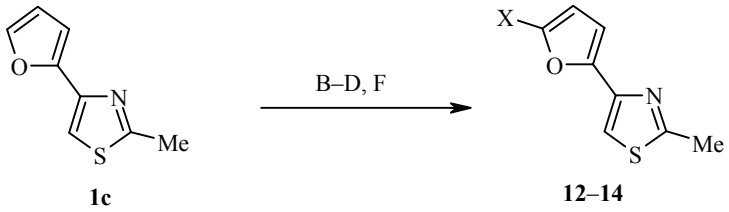
The 5-bromofurylthiazoles **3a,b** are obtained in purer form when compounds **1a,b** are treated with 1 mol N-bromosuccinimide (method C), since strong acids are not isolated in the reaction. But even in this case, the products contain ~5% dibromo-substituted **6a,b**.

Amine **1a**, when reacted with 2 moles of iodine in DMSO, forms a stable liquid complex and only traces of 5-iodofurylthiazole **4a** (according to the ^{1}H NMR spectrum). With 3 mol of iodine and a prolonged reaction time (10 days) followed by treatment with $Na_2S_2O_3$ and NaOH, from amine **1a** we obtained a mixture of 5-iodo-substituted **4a**, 5,5'-diiodo-substituted **7a**, and the sodium salt of 3-(2-amino-5-iodo-4-thiazoloyl)acrylic acid **9** in 6:1:4 ratio (according to the ^{1}H NMR spectrum). The acid **9** is the product of oxidative cleavage by iodine of the 5-iodo-2-furyl group in the 5,5'-diiodo derivative **7a**. Although iodine is a weak oxidizing agent, in this case the exposure time to it was prolonged. Such cleavage has already been observed for 2-(5-bromo-2-furyl)- and 2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridines [4, 6]. In the 1H NMR spectrum of acid **9**, we observe 2 doublets with chemical shifts δ 6.90 ppm and 8.0 ppm (J = 16 Hz), i.e., in regions characteristic for the resonance of protons of the *trans* vinyl group in HetCOCH=CHCOOH [4, 6].



Iodination of amide **1b** using 2 mol of iodine in DMSO for 30 min goes to completion, and leads to formation of 5-iodothiazole **4b** and 10% 5,5'-diiodo derivative **7b**. Since the HI isolated in the reaction is oxidized by DMSO to I_2, we do not see transiodination from the position 5 to the position 5' in the case of compound **4b** or deiodination in the case of the diiodo-substituted derivative **7b** at the position 5. 2-Amino-4-(5-nitro-2-furyl)thiazole (**10**) is easily iodized in the presence of 2 mol of iodine, forming the 5-iodo derivative **11**.

2-Methyl-4-(2-furyl)thiazole (**1c**) is halogenated only in the position 5' of the furan moiety when treated with 1 mol of reagent. Upon iodination of heterocycle **1c** using 2 mol of iodine in DMSO, we note only further partial iodination of the methyl group of the compound.



B–D (see Scheme 1), F – N-chlorosuccinimide–AcOH
12 X = Br, **13** X = I, **14** X = Cl

In contrast to the reactions of thiocyanation and halogenation of compound **1b**, occurring at 8-12°C on the thiazole ring upon reaction with 1 mol of reagent, its nitration with 1 mol of 70% HNO_3 in a mixture of conc. H_2SO_4 and glacial acetic acid (or in just H_2SO_4) leads to the 5'-nitro derivative substituted on the furan ring **15b** in 85-90% yield, i.e., without involving the thiazole ring, since nitration of 2-acetylamino-4-phenylthiazole is directed to the *para* position of the phenyl substituent [7].

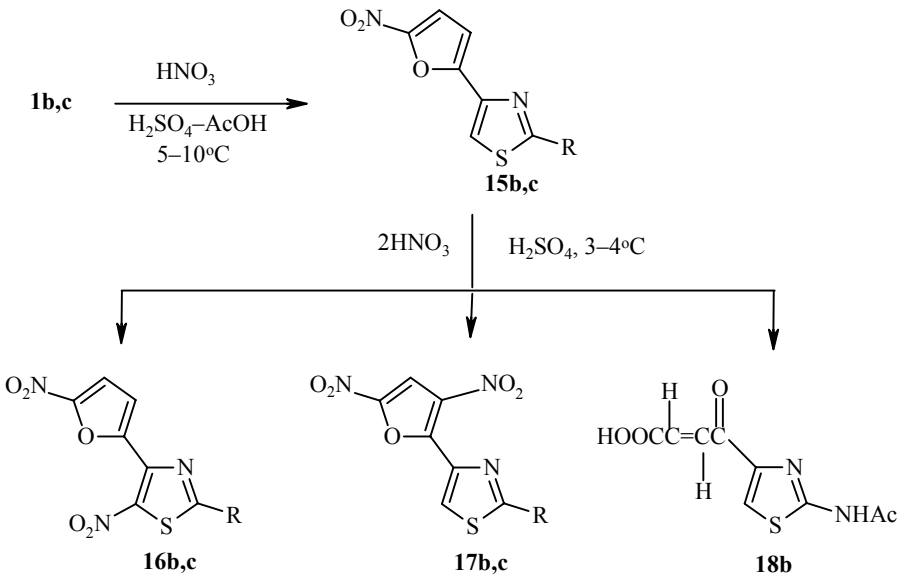
TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
2a	$C_8H_5N_3OS_2$	43.22 / 43.03	2.01 / 2.26	19.05 / 18.82	184-185	99 (A)
2b	$C_{10}H_7N_3O_2S_2$	45.03 / 45.27	2.40 / 2.66	15.63 / 15.84	219-220	98 (A)
3a	$C_7H_5BrN_2OS$	34.14 / 34.31	2.18 / 2.06	11.56 / 11.43	140-142	75 (B) 80 (C)
3b	$C_9H_7BrN_2O_2S$	37.41 / 37.65	2.38 / 2.46	9.50 / 9.76	218-220	80 (C)
4a	$C_7H_5IN_2OS$	29.03 / 28.78	1.60 / 1.73	9.30 / 9.59	167-170	60
4b	$C_9H_7IN_2O_2S$	32.34 / 32.35	1.81 / 2.11	8.22 / 8.38	227-230	87 (D)
5a*	$C_9H_4N_4OS_3$	38.68 / 38.56	1.56 / 1.44	19.71 / 19.99	183-185	
5b*	$C_{11}H_6N_4O_2S_3$	40.60 / 40.98	1.60 / 1.88	17.70 / 17.38	> 250 (dec.)	
6a*	$C_7H_4Br_2N_2OS$	25.71 / 25.95	1.11 / 1.24	8.42 / 8.65	138-139	88 (C')
6b	$C_9H_6Br_2N_2O_2S$	29.37 / 29.53	1.61 / 1.65	7.47 / 7.65	225-226	95 (C')
7b	$C_9H_6I_2N_2O_2S$	24.00 / 23.50	1.59 / 1.32	6.03 / 6.09	228-231	98 (D')
8a*	$C_7H_5BrN_2OS$	34.15 / 34.30	2.03 / 2.06	11.63 / 11.43	163-164 [1]	90 (E) 70 (E')
11	$C_7H_4IN_3O_3S$	25.35 / 24.94	1.03 / 1.19	12.80 / 12.46	280 (dec.)	90-95
12	C_8H_6BrNOS	39.02 / 39.36	2.20 / 2.48	5.63 / 5.74	74-75 [4]	91 (B) 90 (C)
13	C_8H_6INOS	32.73 / 33.01	1.90 / 2.08	4.48 / 4.81	84-87	92 (D)
14*	C_8H_6ClNOS	47.81 / 48.13	3.27 / 3.03	7.15 / 7.02	65-68	88 (E)
15b	$C_9H_7N_3O_4S$	42.42 / 42.69	2.80 / 2.79	16.53 / 16.59	295-296 (dec.) [8]	85-90
15c	$C_8H_6N_2O_3S$	45.43 / 45.71	2.68 / 2.88	13.60 / 13.32	142-143 [8]	65
16b	$C_9H_6N_4O_6S$	35.98 / 36.25	2.14 / 2.03	18.48 / 18.79	287-288	40
17b	$C_9H_6N_4O_6S$	36.13 / 36.25	2.02 / 2.03	18.53 / 18.79	220 (dec.)	13
18b*[2]	$C_9H_8N_2O_4S$	44.61 / 45.00	3.23 / 3.36	11.48 / 11.66	> 300	14

* Compound **14** was purified by vacuum sublimation, **5a,b** was purified by crystallization from aqueous DMF, **6a** and **8a** from AcOH, the rest from EtOH or dilute EtOH.

*[2] IR spectrum (vaseline oil), ν, cm^{-1}: 1695 (COOH), 1680 (C=O), 980 (*trans*-CH=CH).

4-(2-Furyl)-2-methylthiazole **1c** is nitrated similarly. The yield of the 5'-nitro derivative is 65%, i.e., the same as described earlier for nitration of this compound in acetic anhydride [8].



15–17 **b** R = NHAc, **c** R = Me

Nitration of phenylazoles, in particular 2-, 4-, and 5-phenylthiazoles [9] and phenylpyrazole [10], when treated with 1 mol of HNO_3 in conc. H_2SO_4 medium, which is directed to the *para* position of the phenyl substituent and not to the heterocycle, is explained by the fact that the indicated compounds do not react in the form of the base but rather as the "conjugate acid" (i.e., in the protonated form). However, in the case of 2-(2-furyl)imidazo[1,2-*a*]pyridine, it was established earlier that "dissolution" in conc. H_2SO_4 is accompanied by formation of 3,5'-disulfonic acids. Further addition of HNO_3 leads to the nitrodesulfonation product [6]. In our case, the ^{1}H NMR spectrum of the solution of compound **1b** in conc. H_2SO_4 did not give a clear idea of the site and degree of sulfonation.

Further introduction of a nitro group into the 5'-nitro compound **15b** is hindered. Therefore the reaction of compound **15b** with 1 mol of HNO_3 in conc. H_2SO_4 does not go to completion, but according to TLC and the ^{1}H NMR spectrum, treatment with 2 mol HNO_3 leads to three products (**16b-18b**) in 3:1:1 ratio. The same products are obtained upon reaction of compound **1b** with 3 mol of HNO_3. The products were separated using preparative chromatography. In addition to the expected 5,5'-dinitro-substituted **16b**, prepared previously from 5,5'-dibromo-substituted **6b** and $NaNO_2$ in acetic acid [4], we obtained the 3',5'-dinitro derivative substituted at the furyl group **17b** and the product of oxidative cleavage of the nitrofuryl group in compound **15b**: *trans*-3-(2-acetylamino-4-thiazoloyl)acrylic acid **18b**. Formation of the 3,5-dinitrofuryl-substituted derivatives was noted earlier only upon nitration of some 2-(2-heterylvinyl)furans (Het = 2-amino-4-thiazolyl [11], 2-imidazo[1,2-*a*]-pyridinyl [6]). Oxidative cleavage of the nitrofuryl group was accompanied by further nitration of 2-(5-nitro-2-furyl)-substituted imidazo[1,2-*a*]pyridine [6] and imidazo[1,2-*a*]pyrimidine [12].

Further nitration of methylthiazole **15c** with 1.1 mol of HNO_3 led to 5,5'- and 3',5'-dinitro-substituted **16c, 17c** (1:3) with total yield 9% (according to the ^{1}H NMR spectrum). The major products were the products of exhaustive oxidation, which could not be separated. Due to the small amounts of the dinitro derivatives, only the ^{1}H NMR spectra were determined.

TABLE 2. ^{1}H NMR Spectra of Substituted 4-(2-Furyl)thiazoles

Compound	Chemical shifts, δ, ppm*				
	H-5	Furyl group			Other protons
		H-3'	H-4'	H-5'	
2a	—	6.89	6.60	7.82	7.8 (2H, br. s, NH_2)
2b	—	7.00	6.68	7.90	2.17 (3H, s, Me); 12.75 (1H, s, NH)
3a	—	6.77	6.57	7.83	7.3 (2H, br. s, NH_2)
3b	—	6.85	6.57	7.76	2.10 (3H, s, Me); 12.50 (1H, s, NH)
4a	—	6.85	6.63	7.76	4.5 (2H, br. s, NH_2)
4b	—	6.95	6.64	7.81	2.13 (3H, s, Me); 12.56 (1H, s, NH)
5a	—	7.11	7.33	—	7.18 (2H, br. s, NH_2)
5b	—	7.19	7.38	—	2.07 (3H, s, Me); 12.93 (1H, s, NH)
6a	—	6.89	6.71	—	7.10 (2H, br. s, NH_2)
6b	—	6.93	6.74	—	2.16 (3H, s, Me); 12.66 (1H, s, NH)
7a	—	6.85	6.63	—	7.1 (2H, br. s, NH_2)
7b	—	6.85	7.03	—	2.13 (3H, s, Me); 12.60 (1H, s, NH)
8a	6.78	6.62	6.65	—	7.16 (2H, br. s, NH_2)
8b	7.36	6.69	6.70	—	2.15 (3H, s, Me); 12.36 (1H, s, NH)
12	7.68	6.81	6.69	—	2.69 (3H, s, Me)
13	7.65	6.77	6.72	—	2.69 (3H, s, Me)
14	7.68	6.88	6.60	—	2.70 (3H, s, Me)
15b	7.82	7.05	7.78	—	2.03 (3H, s, Me); 12.55 (1H, s, NH)
15c	8.13	7.16	7.85	—	2.77 (3H, s, Me)
16b	—	7.85	7.84	—	2.26 (3H, s, Me); 13.22 (1H, s, NH)
16c	—	7.71	7.87	—	2.77 (3H, s, Me)
17b	8.46 s (8.56)	—	8.56 s (8.46)		2.18 (3H, s, Me); 12.74 (1H, s, NH)
17c	8.46 s (8.79)		8.79 s (8.46)		2.75 (3H, s, Me)
18b	8.29	—	—	—	2.17 (3H, s, Me); 6.76 and 7.93 (each 1H, 2d, *trans*-CH=CH)*[2]; 12.50 (1H, s, NH)

* Signals for 2-substituted furan: H-3, dd; H-4, q; H-5, dd; J(3-4) = 3.6-3.8, J(3-5) = 0.9, J(4-5) = 1.7-1.8 Hz; 2,5-disubstituted furan – 2d, J(3-4) = 3.6-4.0 Hz.

*[2] J = 16. Hz.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WH-90/DS (90 MHz) in DMSO-d_6, internal standard TMS; the IR spectra were recorded on a Perkin-Elmer 580 B in vaseline oil. TLC was performed on Silufol UV-254 (visualization in UV light) in the system benzene–ethylacetate, 3:1; the R_f values increase in the order: starting compound < 5'-substituted derivative < 5-substituted derivative < 5,5'-disubstituted derivative. The melting points were determined on a Boetius apparatus.

The starting compounds **1a,b** were prepared based on 2-bromoacetylfuran according to the procedure in [2], and **1c** was prepared according to the procedure in [13]. N-Bromosuccinimide was purified by crystallization from water, dried over P_2O_5.

2-Amino- and 2-Acetylamino-4-(2-furyl)-5-thiocyanothiazoles (2a,b). A. NH_4SCN (3 g) were added to a solution of compounds **1a,b** (10 mmol) in AcOH (40 ml), and a solution of bromine (0.51 ml, 10 mmol) in AcOH (10 ml) was added with vigorous stirring at a temperature of 8-12°C over a 20 min period; this was

stirred for an additional 30 min, poured over ice, and neutralized with an aqueous solution of NH_4OH. The precipitate of compounds **2a,b** was filtered out and washed with water.

2-Amino- and 2-Acetylamino-5-thiocyano-4-(5-thiocyano-2-furyl)thiazoles (5a,b). A'. Obtained similarly to method A, from compounds **1a,b** (10 mmol) in AcOH (150 ml), NH_4SCN (12 g), adding bromine (2.1 ml, 40 mmol) in AcOH (30 ml) over a 1 h period.

2-Amino- and 2-Acetylamino-5-bromo-4-(2-furyl)thiazoles (3a,b). B. A solution of bromine (0.51 ml, 10 mmol) in AcOH (20 ml) was added to a solution of compounds **1a,b** (10 mmol) in AcOH (25 ml) at 8-12°C over a 40 min period. This was stirred for an additional 1 h at the same temperature, poured over ice, alkalinized with an aqueous solution of NH_4OH; the precipitate was filtered out. According to TLC and the ^1H NMR spectrum, the crude products contain as an impurity the starting materials and the 5,5'-dibromo-substituted derivatives.

C. NBS (1.78 g, 10 mmol) was added in very small portions to a solution of compounds **1a,b** (10 mmol) in AcOH (20 ml) at room temperature with vigorous stirring over a 30 min period. This was stirred for an additional 30 min, diluted with ice water (100 ml), and neutralized with an aqueous solution of NaOH. The precipitate of bromides **3a,b** was filtered out, with 5% impurity of the dibromides **6a,b**.

2-Amino- and 2-Acetylamino-5-bromo-4-(5-bromo-2-furyl)thiazoles (6a,b). B'. Obtained from compounds **1a,b** (10 mmol) as in method B, but using 20 mmol of bromine.

C'. Obtained from compounds **1a,b** (10 mmol) as described in method C, using 20 mmol of NBS.

2-Amino-4-(2-furyl)-5-iodothiazole (4a). A solution of iodine (7.62 g, 30 mmol) in DMSO (20 ml) was added to a solution of furylthiazole **1a** (1.66 g, 10 mmol) in DMSO (20 ml), the reaction mixture was held at room temperature for 10 days, diluted with a concentrated solution of $Na_2S_2O_3$, and slightly alkalinized with an NaOH solution. The precipitate was filtered out, washed with water, and dried. We obtained 1.9 g of a mixture consisting of amine **4a**, diiodo-substituted **7a**, and compound **9**. Compound **4a** was separated using TLC on a Kieselgel 60 UV-254 plate (eluent was benzene–ethylacetate, 3:1; middle fraction).

2-Acetylamino-4-(2-furyl)-5-iodothiazole (4b). D. Obtained from compound **1b** and iodine (2 mol), as described for amine **4a**, holding the reaction mixture for 30 min and treating it with an $Na_2S_2O_3$ solution.

2-Acetylamino-5-iodo-4-(5-iodo-2-furyl)thiazole (7b). D'. Obtained from compound **1b** (10 mmol) and iodine (30 mmol) in DMSO (50 ml), holding the reaction mixture for 20 h at room temperature. Then the mixture was poured into water; the precipitating diiodo-substituted derivative, which precipitated as the base and not as an iodine complex, was filtered out and washed with an $Na_2S_2O_3$ solution and water.

2-Amino-4-(5-bromo-2-furyl)thiazole (8a). E. Compound **3a** (0.54 g, 2.2 mmol) was heated with a solution of 40% HBr (0.36 ml, 2.2 mmol) in AcOH (10 ml) for 1 h on a steam bath and then neutralized with an aqueous ammonia solution; the precipitate was filtered out, washed with water, and dried. Yield of compound **8a** 0.47 g. According to the ^1H NMR spectrum, the reaction product contains 95% of substance **8a** and impurities of substances **1a** and **6a**.

E'. Obtained from dibromide **6a** (0.75 g, 2.3 mmol), as described above, using 40% HBr (0.73 ml, 4.6 mmol). We obtained 0.42 g of crude aminobromothiazole **8a**.

2-Amino-5-iodo-4-(5-nitro-2-furyl)thiazole (11). A solution of iodine (5.08 g, 20 mmol) in DMSO (15 ml) was added to a solution of compound **10** (2.11 g, 10 mmol) in DMSO (30 ml). The reaction mixture was held at room temperature in the dark for 7 days, then it was diluted with a concentrated aqueous solution of $Na_2S_2O_3$; the precipitate was filtered out, washed with water, and dried in the dark. We obtained 3.22 g of the 5-iodo-substituted derivative with traces of the starting compound.

2-Methyl-4-(5-bromo-2-furyl)thiazole (12) was obtained from compound **1c** (3.3 g, 20 mmol), treating it with brominating agent (Br_2, NBS) (20 mmol) by methods B and C described above.

2-Methyl-4-(5-iodo-2-furyl)thiazole (13) was obtained from compound **1c** (1.65 g, 10 mmol) and iodine (5.08 g, 20 mmol), as described in method D. The product was extracted with ether.

2-Methyl-4-(5-chloro-2-furyl)thiazole (14) was obtained from compound **1c** (1.65 g, 10 mmol) and N-chlorosuccinimide (1.33 g, 10 mmol) that had been stored for a long time, similarly to bromide **3a** according to method C. The reaction product **14** was extracted with ether and purified to remove unreacted starting **1c** by vacuum distillation.

2-Acetylamino-4-(5-nitro-2-furyl)thiazole (15b). Substance **1b** (2.08 g, 10 mmol) was dissolved in a mixture of conc. H_2SO_4 (50 ml) and glacial acetic acid (20 ml) at 15-20°C. A mixture of 70% HNO_3 (0.70 ml, 11 mmol) with conc. H_2SO_4 (5 ml) was added to the solution obtained over a period of 15 min at a temperature of 5-10°C, after which stirring was continued for 30 min at 0-5°C. The reaction mixture was poured over ice (500 g); the precipitate was filtered out and washed with water. Yield of nitro compound **15b** 2.16 g. The filtrate was alkalinized with a 40% aqueous NaOH solution until the yellow color changed to red-brown; it was held for 24 hours at room temperature, and another 0.1 g of nitro compound **15b** was filtered out.

The same reaction product was obtained by adding a solution of 70% HNO_3 (0.63 ml, 10 mmol) in conc. H_2SO_4 (3 ml) at 2-5°C over a 10 min period to a solution of compound **1b** (1.92 g, 9.2 mmol) in conc. H_2SO_4 (50 ml). The reaction mixture was additionally stirred for 1 h and then poured over ice (200 g); 2.06 g of nitro compound **15b** was filtered out.

2-Methyl-4-(5-nitro-2-furyl)thiazole (15c) was obtained from compound **1c** (20 mmol) in a mixture of conc. H_2SO_4 and glacial acetic acid, as described above. The reaction mixture was poured over ice (200 g) and the reaction product was separated by extraction with ether.

2-Acetylamino-5-nitro-4-(5-nitro-2-furyl)thiazole (16b), 2-Acetylamino-4-(3,5-dinitro-2-furyl)-thiazole (17b) and ***trans*-3-(2-Acetylamino-4-thiazoloyl)acrylic Acid (18b).** A solution of 70% HNO_3 (2.5 ml, 40 mmol) in conc. H_2SO_4 (10 ml) was added with vigorous stirring at a temperature of 3-4°C over a 40 min period to a solution of compound **15b** (5.06 g, 20 mmol) in conc. H_2SO_4 (100 ml). The reaction mixture was stirred for an additional 2 h at the same temperature and then poured over ice (800 g); the precipitate was filtered out, and a mixture of dinitro compound **16b** and **17b** (3.09 g) was obtained, with traces of acid **18b**. The mixture was separated on a Kieselgel 60 UV-254 plate in the system benzene–ethylacetate, 3:1. The compounds were extracted with acetone from the sorbent. The upper fraction was compound **17b**, the middle fraction was **16b**, and acid **18b** was at the starting line.

After removal of the dinitro compounds, acid **18b** (0.7 g) was precipitated from the filtrate by neutralization with a 40% NaOH solution to pH 6. In order to remove traces of the dinitro compounds, compound **18b** was recrystallized from DMF–ether.

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