Chemistry of Heterocyclic Compounds, Vol. 44, No. 9, 2008

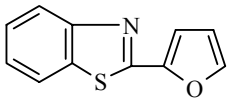
SYNTHESIS AND PROPERTIES OF 2-(2-FURYL)BENZOTHIAZOLE*

E. B. Melnikova[1], M. M. Elchaninov[1], A. A. Milov[2], and B. S. Lukyanov[3]

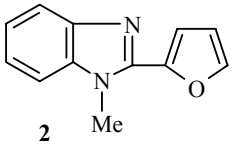
The electrophilic reactions (nitration, bromination, hydroxymethylation, formylation, acylation) and radical substitution reactions (nitration, arylation) of 2-(2-furyl)benzothiazole have been studied. It was found that all of the reactions occur at position 5 of the furan ring. Only nitration in PPA gave the 5',6-dinitro derivative. Quantum-chemical calculation data for the electron density distribution in the neutral and protonated 2-(2-furyl)benzothiazole molecules are given.

Keywords: 2-(2-furyl)benzothiazole, quantum-chemical calculations, substituents orientation, electrophilic and radical substitution reactions.

In continuing our search for novel biologically active compounds and organic luminophores amongst 2-hetaryl-substituted benzazoles we aimed to develop or select a convenient method for the synthesis and study of the relative reactivity of the 2-(2-furyl)benzothiazole (**1**) compared with its benzimidazole analog **2**.



1



2

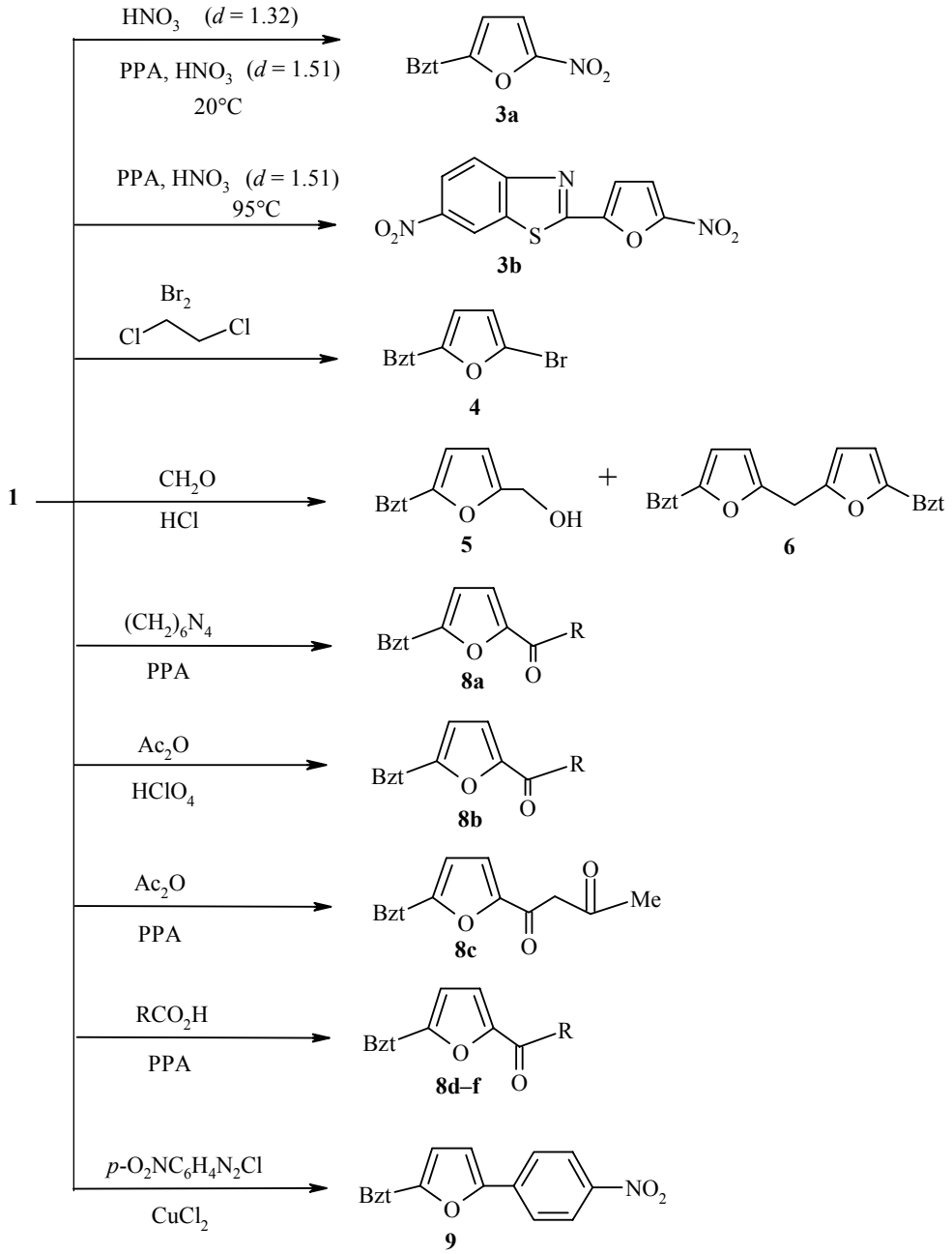
Only the results of bromination [1, 2] and formylation [3] of compound **1** were known at the beginning of our work. Hence it was of interest to broaden the range of electrophilic substitution reactions by carrying out some of these using radical and oxidative reagents.

It has previously been shown [4] that, in contrast to other methods [5, 6], the synthesis of 2-(2-furyl)-benzothiazole (**1**) gives best results *via* condensation of furoyl chloride with *o*-aminothiophenol in DMF. The work carried out by us has confirmed that this method permits the preparation of compound **1** in 85% yield. Compound **1** was then treated with electrophilic reagents including a mixture of nitric acid in PPA, bromine in dichloroethane, formalin in the presence of hydrochloric acid, hexamethylenetetramine in PPA, acetic anhydride in the presence of perchloric acid, and carboxylic acids in PPA. Radical substitution reactions were also carried out including nitration in dilute nitric acid and Meerwein arylation.

* Dedicated to Boris Aleksandrovich Trofimov on his 70th jubilee.

[1]South Russia State Technical University, Novocherkassk 346428; e-mail: katrin_novochek@mail.ru. [2]South Scientific Centre, Russian Academy of Sciences, Rostov-on-Don 344006. [3]Research Institute of Physical and Organic Chemistry, South Federal University, Rostov-on-Don 344104, Russia; e-mail: bluk@ipoc.rsu.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1331-1338, September, 2008. Original article submitted February 11, 2008.

In general the substitution reactions of 2-(2-furyl)benzothiazole (**1**) occur smoothly with quite high yields. Nitration by refluxing in dilute nitric acid (d = 1.32) gives the 2-(5-nitro-2-furyl)benzothiazole (**3a**) in 40% yield. As is known, it occurs in this case *via* a radical mechanism. Nitration using fuming nitric acid (d = 1.51) in PPA at 20ºC also gives compound **3a** and at 95ºC the 5',6-dinitro derivative **3b**. Both of the nitro compounds were formed in quantitative yields under these conditions. Compound **3a** was also prepared through a counter synthesis *via ipso* substitution of the bromine for a nitro group in the 2-(5-bromo-2-furyl)benzothiazole (**4**). Bromination using bromine in dichloroethane also gives substitution at position 5 of the furan ring. However, in contrast to the benzimidazole **2**, further substitution in the benzothiazole fragment does not occur even upon prolonged refluxing with a threefold excess of bromine.



8 a R = H, **b** R = Me, **d** R = Ph, **e** R = *p*-FC_6H_4, **f** R = *p*-$O_2NC_6H_4$; Bzt =2-benzothiazolyl

By contrast with the 2-(2-furyl)-1-methylbenzimidazole (**2**) the benzothiazole **1** does not participate in a chloromethylation using paraformaldehye in concentrated HCl hence we tried to bring about its hydroxymethylation by refluxing in a 40% solution of formaldehyde in the presence of a catalytic amount of hydrochloric acid (d = 1.19). The yield of the 5-hydroxymethyl derivative **5** was 42%. In addition to compound **5** a side product 2,2'-di(2-benzothiazolyl)-5,5'-difurylmethane (**6**) was formed in 18% yield. It should be noted that the furylbenzimidazole **2** does not generally react under these conditions. Oxidation of the hydroxymethyl derivative **5** using potassium permanganate gave the corresponding carboxylic acid **7** which seemed very stable (in contrast to the benzimidazole analog). This is evidently connected with the lower basicity of compound **1** compared with benzimidazole **2** which lowers the likelihood of an intermediate formation of a readily decarboxylating zwitterion.

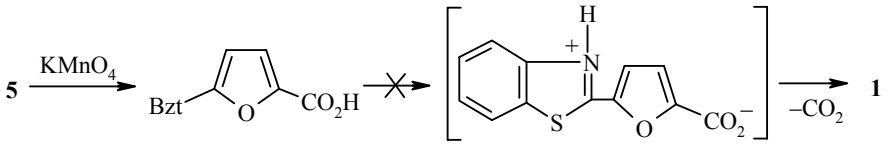


TABLE 1. Physico-Chemical Characteristics of the Compounds Synthesized **1, 3-9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (EtOH)	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N			
1	$C_{11}H_7NOS$	65.32 / 65.67	3.53 / 3.48	6.70 / 6.96	106-107	—	85
3a	$C_{11}H_6N_2O_3S$	53.33 / 53.65	2.41 / 2.46	11.63 / 11.38	227-228	1370 (NO_2)	40*, 96*[2]
3b	$C_{11}H_5N_3O_5S$	45.72 / 45.36	1.53 / 1.72	14.55 / 14.43	214-215	1370 (NO_2)	99
4	$C_{11}H_6BrNOS$	46.83 / 47.16	2.42 / 2.16	5.22 / 5.00	125-126	—	86
5	$C_{12}H_9NO_2S$	62.54 / 62.32	4.17 / 3.92	5.95 / 6.06	165-167 (dec.)	1130 (OH)	42
6	$C_{23}H_{14}N_2O_2S_2$	67.02 / 66.67	3.17 / 3.38	6.95 / 6.76	218-220 (dec.)	—	18
7	$C_{12}H_7NO_3S$	59.02 / 58.78	3.04 / 2.86	5.65 / 5.71	87-88 (dec.)	1700 (C=O), 2630 (OH)	28
8a	$C_{12}H_7NO_2S$	65.15 / 62.87	2.97 / 3.08	6.03 / 6.11	175-176 (174 [3])	1680 (C=O)	95
8b	$C_{13}H_9NO_2S$	63.97 / 64.18	4.02 / 3.73	5.54 / 5.76	191-192	1670	92
8c	$C_{15}H_{11}NO_3S$	63.44 / 63.14	4.17 / 3.89	5.03 / 4.91	209-210	1670 (C=O), 1610 (C=O)	54
8d	$C_{18}H_{11}NO_2S$	71.12 / 70.80	4.02 / 3.63	4.30 / 4.59	137-138	1680 (C=O)	47
8e	$C_{18}H_{10}FNO_2S$	67.32 / 66.87	2.95 / 3.10	4.57 / 4.33	184-185	1680 (C=O)	77
8f	$C_{18}H_{10}N_2O_4S$	62.12 / 61.71	3.15 / 2.86	7.85 / 8.00	234-235	1370 (NO_2), 1680 (C=O)	37
9	$C_{17}H_{10}N_2O_3S$	62.97 / 63.35	3.27 / 3.11	8.56 / 8.70	212-213	1370 (NO_2)	38

* Synthesis carried out by method A

*[2] Synthesis carried out by method B

TABLE 2. ^{1}H NMR Spectra of Compounds **1, 3-9**

Com-pound	Chemical shifts ($CDCl_3$), δ, ppm (J, Hz)						
	H-4' (1H, d)	H-3' (1H, d)	H-6 arom. (1H, t)	H-5 arom. (1H, t)	H-7 arom. (1H, d)	H-4 arom. (1H, d)	Other signals
1	6.59-6.62 (1H, m)	7.20 ($J_{4,3}$ = 3.6)	7.38 (J = 7.8)	7.49 (J = 7.7)	7.90 ($J_{7,6}$ = 8.0)	8.05 ($J_{4,5}$ = 7.9)	7.61 (1H, d, $J_{4,5}$ = 2.2, H-5')
3a	7.48 ($J_{3,4}$ = 3.9)	7.37 ($J_{4,3}$ = 3.9)	7.50 (J = 7.8)	7.58 (J = 7.8)	7.98 ($J_{7,6}$ = 7.5)	8.13 ($J_{4,5}$ = 7.7)	—
3b	7.52 ($J_{3,4}$ = 3.9)	7.48 ($J_{4,3}$ = 3.9)	—	8.44 (1H, d, J = 8.0)	8.92 (1H, s)	8.21 ($J_{4,5}$ = 8.0)	—
4	6.54 ($J_{3,4}$ = 3.6)	7.15 ($J_{4,3}$ = 3.6)	7.40 (J = 7.8)	7.51 (J = 7.8)	7.90 ($J_{7,6}$ = 8.0)	8.05 ($J_{4,5}$ = 7.9)	—
5	6.50 ($J_{3,4}$ = 3.5)	7.15 ($J_{4,3}$ = 3.5)	7.38 (J = 7.8)	7.49 (J = 8.0)	7.90 ($J_{7,6}$ = 7.8)	8.05 ($J_{4,5}$ = 8.0)	2.07 (1H. br. s, OH); 4.73 (2H, d, J = 3.6, CH_2)
6	6.40 (2H, $J_{3,4}$ = 3.5)	7.15 (2H, $J_{4,3}$ = 3.5)	7.38 (2H, J = 8.1)	7.49 (2H, J = 8.0)	7.90 (2H, $J_{7,6}$ = 7.8)	8.05 (2H, $J_{4,5}$ = 8.0)	4.30 (2H, s, CH_2)
7*	7.82 ($J_{3,4}$ = 3.7)	7.55 ($J_{3,4}$ = 3.7)	7.40-7.60 (m)	7.40-7.60 (m)	8.00-8.15 (m)	8.00-8.15 (m)	9.2 (1H, s, COOH)
8a	7.40 ($J_{3,4}$ = 3.7)	7.35 ($J_{4,3}$ = 3.7)	7.47 (J = 7.9)	7.55 (J = 8.0)	7.95 ($J_{7,6}$ = 8.0)	8.10 ($J_{4,5}$ = 7.9)	9.80 (1H, s, CHO)
8b	7.32 ($J_{3,4}$ = 3.7)	7.30 ($J_{4,3}$ = 3.7)	7.43 (J = 7.9)	7.53 (J = 8.0)	7.95 ($J_{7,6}$ = 8.0)	8.10 ($J_{4,5}$ = 7.9)	2.60 (3H, s, $COCH_3$)
8c	7.10 ($J_{3,4}$ = 3.7)	7.35 ($J_{3,4}$ = 3.7)	7.44 (J = 7.9)	7.55 (J = 8.0)	7.95 ($J_{7,6}$ = 8.0)	8.08 ($J_{4,5}$ = 7.9)	2.38 (3H, s, $COCH_3$); 6.17 (1H, d, J = 1.4, CH_2); 6.82 (1H, d, J = 2.2, CH_2)
8d	7.41 ($J_{3,4}$ = 3.7)	7.38 ($J_{4,3}$ = 3.7)	7.45 (J = 8.0)	7.52-7.59 (m)	7.96 ($J_{7,6}$ = 8.0)	8.04-8.13 (m)	7.52-7.59 (2H, m, C_6H_5); 7.65 (1H, t, C_6H_5, J =7.2); 8.04-8.13 (2H, m, C_6H_5)
8e	7.44 ($J_{3,4}$ = 3.7)	7.39 ($J_{4,3}$ = 3.7)	7.46 (J = 7.9)	7.56 (J = 7.9)	7.96 ($J_{7,6}$ = 8.0)	8.09-8.19 (m)	7.20-7.28 (2H, m, C_6H_4F); 8.09-8.19 (2H, m, C_6H_4F)
8f*	7.61 ($J_{3,4}$ = 3.8)	7.50 ($J_{4,3}$ = 3.8)	7.44-7.59 (m)	7.44-7.59 (m)	8.03-8.11 (m)	8.03-8.11 (m)	8.23 (2H, d, J = 8.8, $C_6H_4NO_2$); 8.41 (2H, d, J = 8.8, $C_6H_4NO_2$)
9	7.07 ($J_{3,4}$ = 3.5)	7.35 ($J_{4,3}$ = 3.5)	7.43 (J = 7.9)	7.54 (J = 8.0)	7.94 ($J_{7,6}$ = 7.8)	8.09 ($J_{4,5}$ = 7.9)	7.94 (2H, d, J = 8.8, $C_6H_4NO_2$); 8.32 (2H, d, J = 8.8, $C_6H_4NO_2$)

* The ^{1}H NMR spectra of compounds **7** and **8f** were recorded in DMSO-d_6 and the remaining compounds in $CDCl_3$.

Study [3] reported the formylation of the 2-(2-furyl)benzothiazole (**1**) using the Vilsmeier reagent in 72% yield. We have used another method previously successfully employed in the formylation of benzimidazoles *via* the action of hexamethylenetetramine in PPA on the benzothiazole **1**. In comparison with the benzimidazole **2** which forms the 5-formyl derivative in less than 31% yield [7] the benzothiazole **1** gives the corresponding aldehyde **8a** in almost quantitative yield (95%).

Different variants of the acetylation of compound **1** tried by us proved unsuccessful. In searching for the optimum conditions for carrying out the reaction and bearing in mind the successful experimental acylation of the furylbenzimidazole **2** [7] we have used the method of acylation of phenols and phenyl esters proposed by Gardner [8] through the action of acetic acid or its anhydride in PPA at 110-120ºC on compound **1**. However, the main acetylation product under these conditions was not the 5-acetyl derivative **8b** but evidently the diketone **8c** formed through acetylation of the COMe group in the monoketone **8b**. Column chromatography gave the 2-(5-acetoacetyl-2-furyl)benzothiazole (**8c**) in 54% yield and the acetyl derivative **8b** in only 5% yield. The IR spectrum of compound **8c** showed two C=O group stretching bands at 1610 and 1670 cm^{-1}. The 2-(5-acetyl-2-furyl)benzothiazole (**8b**) was obtained in 92% yield by refluxing the benzothiazole **1** in acetic anhydride in the presence of a catalytic amount of perchloric acid. Compound **2** does not react under these conditions.

Benzoylation of compound **1** using benzoic, *p*-fluorobenzoic, and *p*-nitrobenzoic acids was also carried out using the Gardner method but at higher temperature (170ºC). Formation of the 5-benzoyl derivatives **8d-f** takes place smoothly in this case and in good yields.

Meerwein arylation was performed by treating the benzothiazole **1** with *p*-nitrophenyldiazonium chloride in aqueous acetone solution in the presence of $CuCl_2$ as catalyst. The yield of the 2-[5-(*p*-nitrophenyl)-2-furyl]-benzothiazole (**9**) was 38%.

As evident from the experimental data the furan ring in compound **1** proved very stable to rigid reaction conditions (as in the analog **2**). However, in contrast to compound **2**, in strongly acidic medium a sharp lowering of its reactivity was observed. Hence we were unable to prepare a sulfo derivative of compound **1** despite many attempts at sulfonation under varying conditions (mixture of PPA and H_2SO_4, concentrated H_2SO_4, H_2SO_4 in acetic anhydride, and sodium benzenesulfonate in PPA). We were also unable to obtain a chloromethylation product using paraformaldehyde in conc. HCl and the starting benzothiazole **1**. This is evidently connected with the protonation of the benzothiazole fragment of compound **1** at the nitrogen atom and hence to an increase in its electron acceptor nature. This proposal is confirmed by quantum-chemical calculation data using the B3LYP/6-31G method with the help of the Gaussian 03 program [9]. Hence the overall positive charge of the furan ring in the protonated molecule of **1** is almost three times greater than the neutral form (0.32 and 0.11 relative to hydrogen).

EXPERIMENTAL

The IR spectra of the compounds studied were recorded on a Specord IR-75 spectrometer using vaseline oil. ^1H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) with the signals of the residual protons of the deuterated solvent ($CDCl_3$, 7.26 ppm) as standard. Monitoring of the reaction course and purity of the synthesized compounds was carried out by TLC on Brockmann activity grade II alumina plates in CH_2Cl_2 (revealed using iodine vapor) and on Silufol UV-254 plates in CH_2Cl_2. Yields, melting points, and spectroscopic characteristics the compounds obtained are given in Tables 1 and 2.

2-(2-Furyl)benzothiazole (1). Furoyl chloride (1 ml, 10 mmol) was added to a solution of *o*-amino-thiophenol (1.25 g, 10 mmol) in DMF (10 ml) and refluxed for 30 min. The cooled reaction product was poured into cold water (50 ml). The precipitate was filtered off, thoroughly washed with cold water, and recrystallized from alcohol, drying at room temperature. Yield 1.71 g.

2-(5-Nitro-2-furyl)benzothiazole (3a). A. A solution of the benzothiazole **1** (2.01 g, 10 mmol) in nitric acid (d = 1.32, 50 ml) was refluxed for 3 h. The reaction product was cooled and poured into cold water (250 ml). The precipitated compound **3a** was filtered off and washed 2-3 times with a small amount of cold water. Yield 0.98 g.

B. Nitric acid (d = 1.51, 0.42 ml, 10 mmol) was added to a solution of the benzothiazole **1** (2.01 g, 10 mmol) in PPA (40 g) and heated for 30 min at 20ºC with constant stirring. It was then poured into water (200 ml), neutralized with 25% ammonia solution, and the precipitate was filtered off. Yield 2.36 g.

6-Nitro-2-(5-nitro-2-furyl)benzothiazole (3b). Nitric acid (d = 1.51, 1.25 ml, 30 mmol) was added to a solution of the benzothiazole **1** (2.10 g, 10 mmol) in PPA (40 g) and heated for 3 h at 90-95°C with constant stirring. It was then poured into water (200 ml), neutralized with a 25% solution of ammonia, and the precipitate was filtered off. Yield 2.89 g.

2-(5-Bromo-2-furyl)benzothiazole (4). Bromine (0.53 ml, 10 mmol) was added to a solution of compound **1** (2.01 g, 10 mmol) in dichloroethane (50 ml) and refluxed for 4 h. The dichloroethane was evaporated in air and compound **4** was crystallized from alcohol. Yield 2.41 g.

2-(5-Hydroxymethyl-2-furyl)benzothiazole (5) and 2,2'-di(2-benzothiazolyl)-5,5'-difurylmethane (6). Hydrochloric acid (3-4 drops) was added to a mixture of the benzothiazole **1** (2.01 g, 10 mmol) in formalin (70 ml) and refluxed for 2 h, poured into cold water (200 ml), and neutralized with 25% ammonia solution until its odor remained in the mixture. The precipitate was filtered off and thoroughly washed with cold water. It was then suspended in water and refluxed for 5 min, cooled, and again filtered. The mixture of two compounds obtained was chromatographed on a 3 cm long aluminium oxide column using chloroform as eluent. Yield of compound **5** 0.97 g and of compound **6** 0.38 g.

2-(5-Carboxy-2-furyl)benzothiazole (7). Compound **5** (2.31 g, 10 mmol) was added to a solution of $KMnO_4$ (6.32 g, 40 mmol) in water (150 ml) and heated at 50-60°C to the disappearance of the permanganate color. The hot solution was filtered from MnO_2, cooled, and acidified using HCl to pH 1-2. The precipitated carboxylic acid was filtered off. Yield 0.69 g.

2-(5-Formyl-2-furyl)benzothiazole (8a). Hexamethylenetetramine (5.6 g, 40 mmol) was added to a solution of compound **1** (2.01 g, 10 mmol) in PPA (40 g) and heated for 3 h at 80-90°C with stirring. It was then poured into water (200 ml), neutralized with a 25% solution of ammonia, and the reaction product was filtered. The aldehyde obtained was crystallized from alcohol. Yield 2.18 g.

2-(5-Acetyl-2-furyl)benzothiazole (8b). Perchloric acid (2-3 drops) was added to a solution of compound **1** (2.01 g, 10 mmol) in acetic anhydride (30 ml) and refluxed for 1.5 h. It was then carefully poured into cold water (100 ml) and neutralized with a 25% solution of ammonia. The precipitate was filtered off and crystallized from alcohol. Yield 2.23 g.

2-(5-Acetoacetyl-2-furyl)benzothiazole (8c). Acetic anhydride (1.89 ml, 20 mmol) was added to a solution of compound **1** (2.01 g, 10 mmol) in PPA (40 g) and heated for 16 h at 110-120°C with constant stirring. It was then poured into water (200 ml), neutralized with a 25% ammonia solution, filtered off, and dried. The dried material was dissolved in methylene chloride and chromatographed on an alumina column (15 cm) using methylene chloride as eluent. Yield 1.54 g.

2-(5-Benzoyl-2-furyl)benzothiazole (8d). Benzoic acid (4.88 g, 40 mmol) was added to a solution of compound **1** (2.01 g, 10 mmol) in PPA (40 g) and heated for 3 h at 170-180°C with stirring. It was then poured into water (200 ml), neutralized with a 25% ammonia solution, filtered off, and dried. The dried material was dissolved in chloroform and chromatographed on an alumina column (5 cm) using chloroform as eluent. Compound **8d** was then crystallized from ethanol. Yield 1.43 g.

2-[5-(*p*-Fluorobenzoyl)-2-furyl]benzothiazole (8e). *p*-Fluorobenzoic acid (5.6 g, 40 mmol) was added to a solution of compound **1** (2.01 g, 10 mmol) in PPA (40 g) and was heated for 4 h at 170-180°C with constant stirring. It was then poured into water (200 ml), neutralized with a 25% solution of ammonia, filtered, and the precipitate was crystallized from ethanol. Yield 2.49 g.

2-[5-(*p*-Nitrobenzoyl)-2-furyl]benzothiazole (8f). *p*-Nitrobenzoic acid (0.67 g, 40 mmol) was added to a solution of compound **1** (2.01 g, 10 mmol) in PPA (40 g) and heated for 5 h at 170-180ºC with constant stirring. It was then poured into water (200 ml), neutralized with a 25% ammonia solution, filtered, and the precipitate was dried. The dried material was dissolved in chloroform and chromatographed on an alumina column (5 cm) using chloroform as eluent. Yield 1.29 g.

2-[5-(*p*-Nitrophenyl)-2-furyl]benzothiazole (9). *p*-Nitroaniline hydrochloride obtained from *p*-nitroaniline (1.38 g, 10 mmol), water (20 ml), and conc. HCl (8 ml) was diazotized using a solution of $NaNO_2$ (0.69 g, 10 mmol) in water (3 ml). The reaction product was stirred for 30 min at 5°C and the 2-(2-furyl)-benzothiazole (2.01 g, 10 mmol) in acetone (10 ml) and a solution of $CuCl_2$ (0.2 g) in water (1 ml) were added. The reaction product was stirred for 1 day at 20°C. The precipitated compound **9** was filtered and washed with a 50% aqueous solution of acetone. Yield 1.22 g.

This work was carried out with the financial support of the Russian fund for basic research (grant 07-03-0234).

REFERENCES

1. V. Fărcăsan, *Studii si Cercetări Chim.*, **13**, 103 (1962).
2. V. Fărcăsan and J. Mester, *Studia Univ. Babes-Bolyai*, **12**, 68 (1967).
3. M. Yu. Kornilov, E. M. Ruban, V. N. Fedchuk, E. V. Starinskaya, and M. V. Buznik, *Zh. Org. Khim.*, **9**, 2577 (1973).
4. A. I. Kiprianov and A. A. Shulezhko, *Zh. Obshch. Khim.*, **34**, 3932 (1964).
5. M. T. Bogert and A. Stull, *J. Am. Chem. Soc.*, **48**, 243 (1926).
6. V. Fărcăsan and C. Makkay, *Studii si Cercetări Chim.*, **10**, 145 (1959).
7. M. M. El'chaninov, A. M. Simonov, and L. Ya. Oleinikova, *Khim. Geterotsikl. Soedin.*, 1311 (1983). [*Chem. Heterocycl. Comp.*, **19**, 1041 (1983)].
8. P. D. Gardner, *J. Am. Chem. Soc.*, **76**, 4550 (1951).
9. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nacatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, *Gaussian 03,* Gaussian Inc., Pittsburgh PA (2003).