SYNTHESIS AND SPECTRAL PROPERTIES OF 1-(6-METHOXY-2-BENZOTHIAZOLYL)-2-PYRIDONES

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Received January 19, 1996
Accepted February 24, 1996

Dedicated to the authors' colleague Dr Dusan Ilavsky who died unexpectedly on July 18, 1995.

Substituted 1-(6-methoxy-2-benzothiazolyl)-2-pyridones **5a**–**5f** have been prepared from *N*-(6-methoxy-2-benzothiazolyl)cyanoacetamide (**2**) which on reactions with 4-substituted benzaldehydes gives 3-aryl-2-cyano-*N*-(6-methoxy-2-benzothiazolyl)-2-propenamides **4a**–**4g**. Derivatives **4a**–**4f** were cyclized with malonodinitrile in the presence of piperidine to give the corresponding 2-pyridones **5a**–**5f**. The IR, UV, ^{1}H NMR and mass spectra of the substances synthesized are discussed.
Key word: 1-(6-Methoxy-2-benzothiazolyl)-2-pyridones.

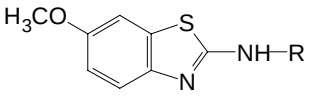
Interesting biological properties as well as accessibility of precursors initiated our interest in the chemistry of both benzothiazoles[1–3] and 2-pyridones[4].

In continuation of ref.[5], the present paper deals with synthesis and study of properties of some substituted 1-(6-methoxy-2-benzothiazolyl)-2-pyridones prepared from 2-amino-6-methoxybenzothiazole[6] (**1**).

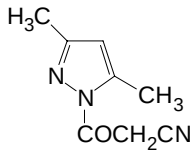
1-Cyanoacetyl-3,5-dimethylpyrazole[7] (**3**) is an efficient reagent for cyanoacetylation of various amino derivatives[5,8], giving the respective cyanoacetamide **2** in the yield of 88% by boiling with arylamine **1** in toluene.

3-Aryl-2-cyano-*N*-(6-methoxy-2-benzothiazolyl)-2-propenamides **4a**–**4g** were obtained in yields of 79–92% (Table I) by the Knoevenagel reaction of C–H acid **2** with 4-substituted benzaldehydes. The condensation was carried out in boiling solution of potassium acetate in acetic acid (**4a–4d**, **4f–4g**) or 15% aqueous sodium hydroxide in ethanol (**4e**). 2-Cyano-2-propenamides **4** actually are activated nitriles which generally are suitable precursors for syntheses of other derivatives, e.g., 2-pyridones[9,10], 1,4-dihydropyridines[11], 4*H*-pyranes[12] etc.

6-Amino-4-aryl-3,5-dicyano-1-(6-methoxy-2-benzothiazolyl)-2-pyridones **5a**–**5f** were prepared by reactions of malonodinitrile with *N*-(6-methoxy-2-benzothiazolyl)-2-propenamides **4a**–**4f** in boiling ethanol with piperidine as a catalyst (yields 29–34%; Table I). Also in this case[5] the reaction most probably goes as a Michael addition of the



	R
1	H
2	$COCH_2CN$



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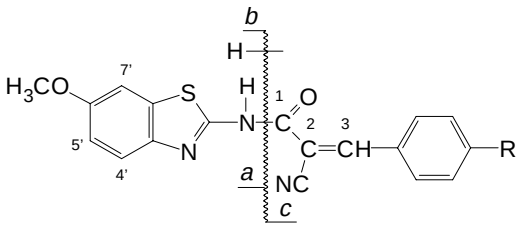
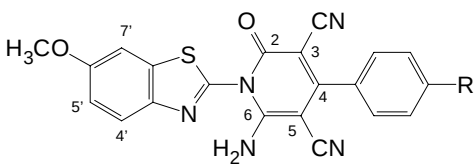


4

	R		R
a	H	**e**	NO_2
b	CH_3	**f**	CN
c	OCH_3	**g**	$N(CH_3)_2$
d	Cl		



5

	R		R
a	H	**d**	Cl
b	CH_3	**e**	NO_2
c	OCH_3	**f**	CN

dinitrile to α,β-unsaturated system with subsequent cyclization and splitting off of hydrogen.

Both the spectral data and elemental analyses (Tables I–V) confirm the structure of *N*-(6-methoxy-2-benzothiazolyl)cyanoacetamide (**2**), substituted 2-cyano-2-propenamides **4** and 1-(6-methoxy-2-benzothiazolyl)-2-pyridones **5**. The IR spectra of derivatives **4** show beside the characteristic bands (Table II) also a weak band of the newly formed multiple bond at 1 595–1 611 cm^{-1}. All the derivatives **4** and **5** exhibit $\nu(CH_3)_{as}$ and $\nu(CH_3)_s$ of the 6-methoxy group in benzothiazole in the regions from 2 936 to 2 996 and from 2 831 to 2 845 cm^{-1}, respectively. The corresponding $\delta(CH_3)_{as}$ and $\delta(CH_3)_s$ are found at 1 428–1 439 and 1 329–1 395 cm^{-1}, respectively.

The UV spectra of *N*-(6-methoxy-2-benzothiazolyl)-2-propenamides **4** (Table II) reflect the lengthening of conjugated system as compared with cyanoacetamide **2** by a bathochromic shift of λ_{max} corresponding the electron distribution in the whole molecule, the substituent having a distinct effect on this maximum. The pyridone grouping in derivatives **5** is characterized by the absorption maximum in the region of 367–385 nm.

The ^1H NMR data unambiguously confirm the structure of compounds **4** and **5**. In the spectra of substituted 2-propenamides **4** (Table III) the olefinic proton H-3 makes itself felt as a singlet at δ 8.49–8.23. The ^1H NMR spectra of 1-(6-methoxy-2-benzothiazolyl)-2-pyridones **5** (Table IV) show a signal of the amino group formed by the cyclization at δ 8.96–8.65. In both the series studied, as it was expected, the effect of substituent R was most distinct on the chemical shifts of protons of the benzene ring at 4-position of pyridone. The proton signals H-4′, H-5′, and H-7′ of benzothiazole ring as well as those of the respective methoxy group in substituted 2-pyridones **5a**–**5f** were shifted downfield as compared with the corresponding amides **4a**–**4f**, to the regions δ 7.94–7.93 (H-4′), δ 7.76–7.75 (H-7′), δ 7.15 (H-5′), and δ 3.82 (OCH_3).

The EI mass spectra of the compounds **4a**–**4g** studied contain relatively intense peaks of molecular ions (Table V). The main direction of their fragmentation is splitting of N–C bond at β-position with respect to the benzothiazole ring. Splitting of this bond with retention of charge at the fragment containing the benzothiazole nucleus produces fragment ions type *a* (without hydrogen rearrangement, *m/z* 179) or *b* (with hydrogen rearrangement, *m/z* 180). If the charge becomes localized at the opposite (other) side of the molecule, the fragment ions type *c* are formed.

Also the EI mass spectra of the investigated substituted 2-pyridones **5** contain relatively intense peaks of molecular ions (Table V). In all the cases, except for **5e** (R = NO_2), the basic peak in spectra is that of the $(M - H)^{\bullet+}$ ion. Decomposition of C–N bond between benzothiazole and pyridone nuclei in the molecular ion with rearrangement of hydrogen produces the fragment ion with *m/z* 165.

TABLE I
Characteristic data of compounds **4a**–**4g** and **5a**–**5f**

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found		
			%C	%H	%N
4a	220–222[a]	$C_{18}H_{13}N_3O_2S$	64.46	3.91	12.53
	90	(335.4)	64.26	4.01	12.50
4b	219–221[a]	$C_{19}H_{15}N_3O_2S$	65.31	4.33	12.03
	86	(349.4)	64.40	4.54	12.12
4c	218–220[a]	$C_{19}H_{15}N_3O_3S$	62.45	4.14	11.50
	82	(365.4)	62.29	4.21	11.62
4d	236–239[a]	$C_{18}H_{12}ClN_3O_2S$	58.46	3.27	11.36
	81	(369.8)	57.75	3.11	11.36
4e	265–267[a]	$C_{18}H_{12}N_4O_4S$	56.83	3.18	14.73
	92	(380.4)	56.06	3.42	14.29
4f	279–281[a]	$C_{19}H_{12}N_4O_2S$	63.32	3.36	15.55
	90	(360.4)	63.99	3.99	15.61
4g	284–286[a]	$C_{20}H_{18}N_4O_2S$	63.47	4.79	14.81
	79	(378.4)	63.86	5.45	14.88
5a	284–287[a]	$C_{21}H_{13}N_5O_2S$	63.15	3.28	17.54
	30	(399.4)	62.95	3.15	17.52
5b	286–290[a]	$C_{22}H_{15}N_5O_2S$	63.91	3.66	16.94
	30	(413.4)	63.27	3.84	17.02
5c	300–305[a]	$C_{22}H_{15}N_5O_3S$	61.53	3.52	16.31
	34	(429.4)	61.40	3.66	16.42
5d	310–312[b]	$C_{21}H_{12}ClN_5O_2S$	58.13	2.79	16.14
	29	(433.9)	58.36	2.97	15.42
5e	313–317[a]	$C_{21}H_{12}N_6O_4S$	56.75	2.72	18.91
	30	(444.4)	57.16	2.84	19.08
5f	336–338[c]	$C_{22}H_{12}N_6O_2S$	62.25	2.85	19.80
	34	(424.4)	62.52	3.30	19.85

Recrystallized from: [a] acetic acid, [b] dioxane, [c] acetic acid–dimethylformamide (10 : 1).

TABLE II
IR spectra (KBr) and UV spectra (dioxane, *c* 1 . 10^{-4} mol l^{-1}) of compounds **2**, **4a**–**4g**, and **5a**–**5f**

Compound	IR spectrum			UV spectrum	
	ν(NH)[a]	ν(C≡N)	ν(C=O)	λ_{max}	log ε
2	3 216	2 263	1 705	252	2.81
				290	3.12
				308	3.08
4a	3 198	2 228	1 673	313	3.34
				363	3.22
4b	3 177	2 224	1 624	328	3.35
				360[b]	3.27
4c	3 196	2 222	1 671	269	2.93
				360	3.54
4d	3 206	2 224	1 674	320	3.31
				365	3.19
4e	3 198	2 226	1 682	310	3.34
				383	3.14
4f	3 206	2 224	1 674	306	3.40
				380	3.18
4g	3 179	2 216	1 663	266	3.12
				429	3.69
5a	3 426	2 211	1 673	272	3.52
				336	3.18
				370	3.14
5b	3 289	2 222	1 671	276	3.52
		2 206		332	3.22
				372	3.13
5c	3 430	2 226	1 671	277	3.49
		2 218		341	3.44
				385[b]	3.20
5d	3 438	2 227	1 680	276	3.53
		2 211		342	3.22
				367[b]	3.13
5e	3 441	2 226	1 686	273	3.62
		2 216		345	3.18
				383[b]	3.15
5f	3 438	2 228	1 680	268	–[c]
		2 211		385	–[c]

[a] ν(NH_2) for compounds **5a**–**5f**; [b] shoulder; [c] measured in saturated solution.

TABLE III
^{1}H NMR spectra of compounds **4a**–**4g**

Compound	NH (s)	H-3 (s)	H-7′ (d) *J*(7′,5′)	H-4′ (d) *J*(4′,5′)	H-5′ (dd)	OCH_3 (s)	4-Substituted phenyl
4a	12.71	8.42	7.54 2.8	7.50 8.8	7.03	3.76	8.15–7.80 m and 7.70–7.39 m, 2 H and 3 H
4b	13.22	8.38	7.54 2.4	7.50 8.8	7.02	3.76	7.89 d and 7.36 d, 2 H and 2 H, *J* = 8.2; 2.35 s, 3 H
4c	12.73	8.35	7.52 2.6	7.50 8.9	7.01	3.76	8.00 d and 7.11 d, 2 H and 2 H, *J* = 8.9; 3.82 s, 3 H
4d	12.52	8.39	7.52 2.6	7.60 8.8	7.02	3.76	7.98 d and 7.48 d, 2 H and 2 H, *J* = 8.8
4e	12.84	8.49	7.52 2.6	7.49 8.1	7.03	3.77	8.35 d and 8.14 d, 2 H and 2 H, *J* = 8.7
4f	13.17	8.45	7.54 2.4	7.48 8.7	7.04	3.76	8.08–8.01 m, 4 H
4g	12.33	8.23	7.50 2.6	7.51 8.8	6.99	3.76	7.88 d and 8.00 d, 2 H and 2 H, *J* = 9.0; 3.21 s, 6 H

TABLE IV
^{1}H NMR spectra of compounds **5a**–**5f**

Compound	NH_2 (s)	H-4′ (d) *J*(4′,5′)	H-7′ (d) *J*(7′,5′)	H-5′ (dd)	OCH_3 (s)	4-Substituted phenyl
5a	8.65	7.94 8.8	7.75 2.4	7.15	3.82	7.65–7.33 m, 5 H
5b	8.96	7.93 9.0	7.75 2.6	7.15	3.82	7.50–7.29 m, 4 H; 2.36 s, 3 H
5c	8.66	7.93 9.1	7.75 2.5	7.15	3.80	7.49 d and 7.07 d, 2 H and 2 H, *J* = 8.8; 3.80, 3 H
5d	8.72	7.93 9.1	7.75 2.6	7.15	3.82	7.67–7.54 m, 4 H
5e	8.79	7.94 9.0	7.76 2.6	7.15	3.82	8.40 d and 7.81 d, 2 H and 2 H, *J* = 8.8
5f	8.84	7.94 8.9	7.75 2.5	7.15	3.82	8.04 d and 7.71 d, 2 H and 2 H, *J* = 8.3

EXPERIMENTAL

The melting points were determined with a Kofler apparatus. The IR spectra were measured with a FTIR PU 9800 (Philips) spectrometer, the UV spectra (λ, nm; log ε) were recorded with a Specord UV-VIS M-40 apparatus. The ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured with a Tesla BS 587 (80 MHz) spectrometer in hexadeuteriodimethyl sulfoxide with hexamethyldisiloxane as the internal standard. The EI mass spectra were recorded with an MS 902 S (A.E.I. Manchester) spectrometer with direct inlet system, electron energy 70 eV, trap current 100 μA, ion source temperature 220–240 °C (for compounds **2**, **4a**–**4g**) or 150–200 °C (for compounds **5a**–**5f**).

TABLE V
Mass spectra (EI) of **2**, **4a–4g**, **5a–5c**, and **5e–5f** derivatives. For each compound 10 most abundant peaks are given

Compound	*m/z* (rel. abundance, %)
2	248 (15), 247 ($M^{+\bullet}$, 100), 207 (44), 181 (10), 180 (84), 179 (14), 166 (10), 165 (89), 138 (9), 135 (11)
4a	336 (20), 335 ($M^{+\bullet}$, 99), 334 (20), 180 (37), 179 (37), 156 (100), 128 (83), 101 (30), 77 (53), 51 (23)
4b	350 (21), 349 ($M^{+\bullet}$, 85), 348 (17), 180 (23), 171 (14), 170 (100), 142 (28), 116 (17), 115 (66), 65 (14)
4c	366 (10), 365 ($M^{+\bullet}$, 42), 364 (8), 188 (16), 187 (13), 186 (100), 165 (12), 158 (27), 143 (10), 115 (8)
4d	371 (43), 370 (30), 369 ($M^{+\bullet}$, 100), 192 (29), 190 (77), 180 (37), 179 (46), 162 (37), 127 (38), 126 (30)
4e	380 ($M^{+\bullet}$, 75), 351 (27), 207 (33), 180 (68), 179 (100), 171 (84), 165 (40), 143 (29), 135 (28), 116 (20)
4f	361 (23), 360 ($M^{+\bullet}$, 93), 359 (25), 258 (20), 207 (30), 181 (33), 180 (39), 179 (100), 153 (31), 135 (25)
4g	378 ($M^{+\bullet}$, 16), 200 (15), 199 (100), 185 (16), 180 (7), 171 (40), 159 (9), 156 (9), 155 (7), 128 (8)
5a	400 (22), 399 ($M^{+\bullet}$, 82), 398 (100), 383 (9), 371 (8), 355 (9), 165 (31), 138 (9), 77 (8), 45 (15)
5b	414 (22), 413 ($M^{+\bullet}$, 78), 412 (100), 398 (10), 207 (11), 206 (10), 180 (13), 179 (11), 165 (28), 145 (11)
5c	430 (18), 429 ($M^{+\bullet}$, 55), 428 (100), 223 (13), 206 (18), 191 (24), 183 (16), 180 (18), 165 (32), 149 (18)
5e	445 (27), 444 ($M^{+\bullet}$, 100), 443 (90), 414 (43), 413 (72), 397 (55), 206 (21), 191 (25), 180 (25), 165 (45)
5f	425 (30), 424 ($M^{+\bullet}$, 84), 423 (100), 191 (12), 190 (19), 180 (13), 165 (37), 138 (12), 110 (11), 63 (12)

N-(6-Methoxy-2-benzothiazolyl)cyanoacetamide (**2**)

A solution of 2-amino-6-methoxybenzothiazole[6] (**1**; 6.1 g, 34 mmol) in anhydrous toluene (150 ml) was added to a solution of 1-cyanoacetyl-3,5-dimethylpyrazole[7] (**3**; 5.3 g, 34 mmol) in the same solvent (100 ml) and the mixture was refluxed 4 h. After cooling, the solid portion was isolated and recrystallized from acetic acid; yield 7.4 g (88%), m.p. 224–226 °C. The IR, UV, and mass spectra are given in Tables II and V. ^{1}H NMR spectrum: 7.66 d, 1 H, J(4,5) = 8.9 (H-4); 7.59 d, 1 H, J(7,5) = 2.5 (H-7); 7.04 dd, 1 H (H-5); 4.08 s, 2 H (CH_2); 3.81 s, 3 H (OCH_3). For $C_{11}H_9N_3O_2S$ (247.3) calculated: 53.43% C, 3.67% H, 16.99% N; found: 53.58% C, 3.40% H, 17.21% N.

General Procedure for Preparation of 3-Aryl-2-cyano-*N*-(6-methoxy-2-benzothiazolyl)-2-propenamides **4a**–**4d** and **4f**–**4g**

A mixture of 4-substituted benzaldehyde (6 mmol), *N*-(6-methoxy-2-benzothiazolyl)cyanoacetamide (**2**; 1.48 g, 6 mmol), anhydrous potassium acetate (1.48 g, 15 mmol), and acetic acid (30 ml) was stirred while refluxing 3 h. After pouring on ice, the raw product was collected by filtration, washed with water, dried, and recrystallized from a suitable solvent. The yields, melting points, and elemental analyses are presented in Table I.

2-Cyano-*N*-(6-methoxy-2-benzothiazolyl)-3-(4-nitrophenyl)-2-propenamide (**4e**)

A solution of 4-nitrobenzaldehyde (0.6 g, 4 mmol) in ethanol (30 ml) and 15% aqueous sodium hydroxide (5 drops) were added to a hot solution of *N*-(6-methoxy-2-benzothiazolyl)cyanoacetamide (**2**; 1 g, 4 mmol) in the same solvent (50 ml) with stirring. The reaction mixture was refluxed 1 h, whereupon it was gradually cooled to room temperature with stirring. The solid portion was filtered off and recrystallized from acetic acid. The yield, melting point, and elemental analyses are given in Table I.

General Procedure for Preparation of 6-Amino-4-aryl-3,5-dicyano-1-(6-methoxy-2-benzothiazolyl)-2-pyridones **5a**–**5f**

A mixture of 3-aryl-2-cyano-*N*-(6-methoxy-2-benzothiazolyl)-2-propenamide **4a**–**4f** (1.5 mmol), malonodinitrile (0.13 g, 2 mmol), and piperidine (4 drops) in anhydrous ethanol (30 ml) was stirred at boiling temperature 3 h, whereupon it was left to cool to room temperature with stirring. The solid portion was filtered off and recrystallized from a suitable solvent. The yields, melting points, and elemental analyses are given in Table I.

The authors are indebted to Mrs M. Hrobonova and Mrs S. Markusova for measuring the UV and IR spectra, respectively. The research was supported by the Grant Agency of Ministry of Education of the Slovak Republic (Grant No. 1/1415/94).

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