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SYNTHESIS OF NEW THIAZOLES FROM α-HALOHETARYL KETONES

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Reactions of α-bromoacetylphenoxathiin, α-bromoacetylphenoxathiin 10,10-dioxide, or α-bromoacetylthianthrene with certain p-(arylsulfonyl)thiobenzamides lead to the formation of the corresponding 2,4-disubstituted thiazoles. The new compounds were characterized through elemental analysis and spectral data (IR, ^{1}H NMR, and ^{13}C NMR).

Keywords: 2,4-disubstituted thiazoles, α-bromo ketones, *p*-(arylsulfonyl)thiobenzamides.

The continuous interest in the chemistry of thiazole derivatives is mainly due to the specific pharmacological activities recently proved for such compounds, e.g., anti-inflammatory [1, 2], anesthetic [3], antihypertensive [4], hypoglycemic [5, 6], antimicrobial [7], and even anti-HIV [8] and antitumor activities [9]. As in other related cases [10, 11], introduction of an (arylsulfonyl)phenyl substituent in the thiazole ring may be interesting keeping in mind the known pharmacological activities of compounds bearing diaryl sulfone moieties [12, 13]. On the other hand, polynuclear derivatives (e.g., phenoxathiin, thianthrene) show a large variety of interesting biological activities [14-17].

In this paper we describe the syntheses and physical characterization of some new thiazoles **1-9**, substituted at $C_{(2)}$ with *p*-(arylsulfonyl)phenyl groups and at $C_{(4)}$ with phenoxathiin, phenoxathiin 10,10-dioxide, and thianthrene groups by a Hantzsch-type condensation of the corresponding *p*-(arylsulfonyl)thiobenzamides **10, 11**, or **12** with α-bromoacetylphenoxathiin (**13**), α-bromoacetylphenoxathiin 10,10-dioxide (**14**), or α-bromoacetylthianthrene (**15**) in refluxing ethanol (Scheme).

All the new compounds were characterized by elemental analyses and IR, UV, ^{1}H NMR, and ^{13}C NMR spectral data.

The IR spectra of all the new thiazoles (Table 3) differ strongly from the spectra of the coressponding starting thioamides and α-bromoacetylhetarenes; thus, the strong absorptions of 1640 cm^{-1} (attributed to coupled δNH_2 and $\nu C{=}N$ vibrations) from the thioamides and of 1699 cm^{-1} (attributed to $\nu C{=}O$) from the bromoacetyl derivatives are lacking, suggesting the cyclization. However, the thiazole ring cannot be directly identified through its ring vibrations (ca. 1450 cm^{-1}) due to the overlap with benzene ring absorptions. All the IR spectra indicated the presence of the sulfonyl SO_2 group by two strong absorptions at ~1160 cm^{-1} (νSO_2 sym.) and ~1320 cm^{-1} (νSO_2 asym.). Additionally, the phenoxathiin and the phenoxathiin 10,10-dioxide derivatives **1-6** presented the characteristic C–O–C frequencies at ~1230-1080 cm^{-1}.

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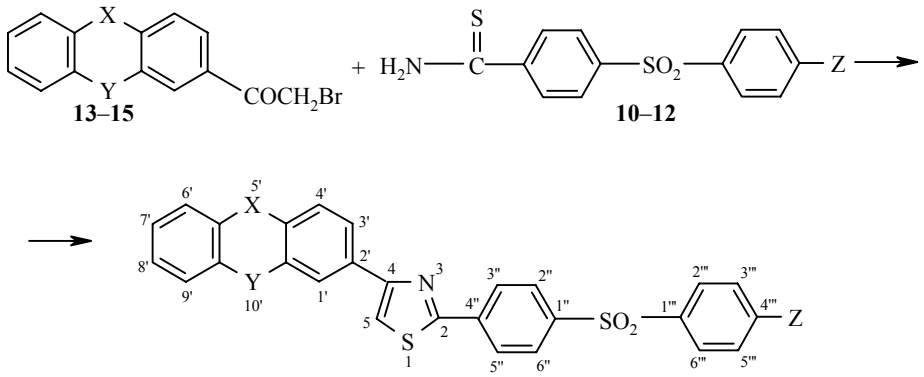
Scheme



13–15 **10–12** **1–9**

Com-pound	X	Y	Z	Com-pound	X	Y	Z	Com-pound	X	Y	Z
1	O	S	H	**4**	O	SO_2	H	**7**	S	S	H
2	O	S	Cl	**5**	O	SO_2	Cl	**8**	S	S	Cl
3	O	S	Br	**6**	O	SO_2	Br	**9**	S	S	Br

Naturally, all the discussed spectra showed the characteristic absorptions of phenyl rings, e.g., the νC=C ring vibrations at 1440-1600 cm^{-1} and the γ-2CH and γ-4CH frequencies characteristic of monosubstituted heterocyclic rings (828-858 cm^{-1} and 750-764 cm^{-1}). In addition to these bands, the *p*-chlorophenyl derivatives **2**, **5**, and **8** showed the aromatic νC–Cl frequency at ~620 cm^{-1}, whereas the *p*-bromophenyl compounds **3**, **6**, and **9** indicated two aromatic νC–Br bands at ~572-689 cm^{-1}.

The electronic spectra of the new thiazoles (Table 3) generally present three absorptions, situated at ~250-274 nm (ε ~4×10^4), 275-294 nm (ε ~3×10^4), and 305-340 nm (ε ~2×10^4). The first two bands are due to benzene rings whereas the absorption of 305-340 nm could be attributed to the conjugated thiazole ring.

The ^{1}H NMR spectra (Table 1) are in perfect agreement with the suggested structures of all new thiazoles [18]. The thiazole proton, H-5, occurs as a singlet at 7.67-7.87 ppm.The electron-withdrawing effect of the thiazole ring influences the resonances of H-1' and H-3' from the 2-substituted hetaryl rings (7.4-8.67 ppm) and of H-2" and H-3" from the disubstituted benzene nucleus (8.01-8.18 ppm).

The ^{13}C NMR spectra, including the APT (Attached Proton Test) sequences [19] and the two-dimensional connectivity experiments (^{1}H–^{13}C-,^{1}H–^{1}H-, and ^{13}C–^{13}C COSY [20-23]) permitted a better characterization of the new thiazoles. The positions of ^{13}C NMR signals are presented in Table 2. The C-5 tertiary atom from the thiazole ring indicates signals between 116.7-117.3 ppm in phenoxathiin derivatives, between 115.2-115.4 ppm in phenoxathiin 10,10-dioxide derivatives and between 117.2-117.9 ppm in thianthrene derivatives. The quaternary carbon atoms of thiazole ring, C-4 and C-2, present signals at 142.7-153.1 and at 164.8-171.2 ppm, respectively.

EXPERIMENTAL

The IR spectra were recorded in KBr pellets on a FTS 135 Biorad apparatus (Table 3), the UV spectra on a Specord UV-VIS C, Zeiss Jena apparatus (Table 3), and the NMR spectra on a Varian Gemini 300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C, using TMS as internal standard). Melting points were determined on a Boetius apparatus and are uncorrected.

TABLE 1. ^{1}H NMR Data for compounds **1-9** (δ, ppm, *J*, Hz, $CDCl_3$ and TFA)

Com-pound	H-1'	H-3'	H-4'	H-6'	H-7'	H-8'	H-9'	H-5	H-3''	H-2''	H-2'''	H-3'''	H-4'''
1	7.39d (2.2)	7.44 dd (8.4; 2.2)	7.08 d (8.4)	7.00 br. d (7.9)	7.16 m	7.05-7.12 m		7.84 s	8.10 d (8.8)	8.16 d (8.8)	7.96 dd (8.8; 1.4)	7.60 dd (8.8; 1.4)	7.70 tt (7.4; 1.4)
2	7.39 d (2.2)	7.44 dd (8.4; 2.2)	7.08 d (8.4)	7.00 dd (7.7; 1.2)	7.13-7.20 m		7.06 dd (7.4; 1.2)	7.77 s	8.10 d (8.7)	8.15 d (8.7)	7.90 d (8.9)	7.55 d (8.7)	–
3	7.40 d (2.2)	7.45 dd (8.4; 2.2)	7.08 d (8.5)	7.00 d (7.6; 1.6)	7.13-7.20 m		7.05 dd (7.5; 1.2)	7.73 s	8.10 d (8.9)	8.14 d (8.9)	7.82 d (8.8)	7.72 d (8.8)	–
4	8.67 d (2.20)	8.28 dd (8.8; 2.2)	7.47 d (8.8)	7.42 dd (7.9; 1.9)	7.68 td (7.8; 1.7)	7.54 m	8.1 dd (8.1; 1.6)	7.67 s	8.05 d (8.5)	8.18 d (8.5)	7.99 dd (7.9; 1.7)	7.56 br. t (7.9)	7.58 tt (7.9; 1.7)
5	8.66 dd (2.20)	8.3 dd (8.8; 2.2)	7.50 d (8.8)	7.42 br. d (8.1)	7.58-7.72 td (8.3; 1.7)		8.07 dd (8.5; 1.9)	7.87 s	8.03 d (8.4)	8.20 d (8.4)	7.93 d (8.7)	7.62 d (8.7)	–
6	8.63 d (2.2)	8.25 dd (8.8; 2.2)	7.45 d (8.8)	7.40 dd (7.9; 1.0)	7.65-7.70 m		8.09 dd (8.0; 1.7)	7.69 s	8.01 d (8.7)	8.17 d (8.7)	7.84 d (8.8)	7.67 d (8.8)	–
7	7.85 br. s	7.59 br. s	7.59 br. s	7.28 m	7.46 m	7.46 m	7.28 m	7.81 s	8.14 s	8.14 s	7.96 dd (7.3; 1.4)	7.58 t (7.3)	7.69 br. t (7.3)
8	7.80 br. s	7.58 br. s	7.58 br. s	7.26 m	7.46 m	7.46 m	7.26 m	7.71 s	8.09 d (9.0)	8.11 d (9.0)	7.89 d (8.7)	7.53 d (8.7)	–
9	7.83 d (1.3)	7.60 br. s	7.60 br. s	7.29 m	7.49 m	7.49 m	7.29 m	7.78 s	8.11 d (9.0)	8.14 d (9.0)	7.83 d (8.8)	7.72 d (8.8)	–

TABLE 2. ^{13}C NMR Data for Compounds **1-9** (δ, ppm, *J*, Hz, $CDCl_3$ and TFA)

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
C-1'	125.6	125.5	125.3	121.0	121.1	120.0	127.1	127.0	127.0
C-2'	129.8	130.1	129.6	128.7	128.2	130.4	126.6	126.7	126.9
C-3'	126.9	126.8	126.8	132.0	132.1	131.3	126.4	126.2	126.1
C-4'	118.9	118.4	118.7	119.4	119.5	118.8	129.8	129.5	129.3
C-4a'	155.0	154.7	151.0	154.2	151.4	150.5	137.8	137.5	137.6
C-5a'	151.0	150.9	150.5	151.3	151.1	150.2	134.0	134.0	131.4
C-6'	118.0	117.6	117.6	118.9	118.9	118.3	128.4	128.3	128.3
C-7'	128.5	128.4	128.4	134.2	134.3	133.7	128.7	128.9	128.9
C-8'	125.8	125.4	125.5	125.0	125.1	124.4	128.8	128.8	128.8
C-9'	126.8	126.8	126.9	123.4	123.5	122.4	128.4	128.3	128.3
C-9a'	122.3	118.0	118.1	124.7	125.2	123.9	133.8	131.0	134.1
C-10a'	123.0	122.6	118.7	125.2	126.4	124.8	134.0	134.2	134.3
C-4	149.7	145.5	145.3	151.1	142.7	153.1	149.9	150.8	151.2
C-5	117.3	116.9	116.7	115.3	115.2	115.4	117.9	117.4	117.2
C-2	170.4	170.1	169.9	165.8	171.2	164.8	170.6	170.0	169.9
C-1"	149.6	150.0	145.2	141.2	141.3	141.3	145.9	145.2	144.9
C-2"	129.2	129.3	128.7	127.4	127.3	126.6	129.5	129.2	129.1
C-3"	129.4	129.1	128.2	128.4	128.5	127.6	129.2	129.1	129.0
C-4"	129.9	130.1	133.1	137.6	137.4	136.9	138.5	137.7	138.2
C-1"'	138.3	137.2	138.0	140.3	133.1	139.0	140.7	141.7	140.1
C-2"'	127.9	129.3	129.3	129.2	127.7	129.0	127.9	129.3	129.4
C-3"'	130.1	130.3	129.2	132.7	129.4	128.4	130.0	130.3	133.2
C-4"'	135.2	141.9	123.2	136.9	133.4	135.1	134.9	140.3	130.2

TABLE 3. IR and UV Spectra of the Synthesized Compounds **1-9**

Compound	IR spectra, cm^{-1}								UV spectra	
	νSO_2 (as)	νSO_2 (sym)	νC=C	νC–X	νC–O–C	νC–O–C	γ-2CH	γ-4CH	λ_{max}, nm	$\varepsilon \cdot 10^4$
1	1304, 1267	1157, 1106	1635, 1559, 1468	—	1229	1071	822	750	275, 305	4.22, 1.62
2	1326, 1303, 1265	1159, 1107	1576, 1467	623	1230	1089	834	764	273, 305	4.4, 1.8
3	1325, 1303, 1265	1159, 1103	1635, 1626, 1559, 1467	689, 573	1230	1069	828	758	272, 305	4.1, 1.6
4	1298, 1275	1156	1636, 1625, 1559, 1472	—	1228	1087	842	750	272, 298, 340	4.2, 2.7, 1.37
5	1319, 1299, 1275	1156, 1105, 1106	1635, 1626, 1470	622	1229	1089	858	764	273, 294, 340	3.95, 2.75, 1.4
6	1322, 1300, 1274	1156, 1104	1635, 1626, 1560, 1469	609, 562	1230	1087	835	758	274, 294, 340	4.35, 2.9, 1.55
7	1318, 1261	1155, 1093	1636, 1558, 1541, 1473	—	—	—	830	749	251, 278, 326	3.2, 3.5, 1.95
8	1325	1158, 1106	1636, 1624, 1558, 1473	620	—	—	835	764	250, 278	2.8, 3.35
9	1326	1159, 1105	1636, 1558, 1521, 1474	612, 573	—	—	832	757	250, 275	3.4, 3.97

TABLE 4. Characteristics of the Synthesized Compounds **1-9**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Retention time, min	Yield, %
		N	S			
1	$C_{27}H_{17}NS_3O_3$	1.85 / 2.08	19.03 / 19.21	257-258	6.13	37
2	$C_{27}H_{16}ClNO_3S_3$	2.37 / 2.62	17.28 / 17.97	273-274	9.33	21
3	$C_{27}H_{17}BrNO_3S_3$	2.16 / 2.42	16.28 / 16.59	275-276	10.49	27
4	$C_{27}H_{17}NO_5S_3$	2.52 / 2.61	17.82 / 18.04	265-266	4.02	33
5	$C_{27}H_{16}ClNO_5S_3$	2.11 / 2.47	16.04 / 16.96	232-233	4.58	57
6	$C_{27}H_{16}BrNO_5S_3$	1.92 / 2.29	15.25 / 15.73	235-236	4.77	59
7	$C_{27}H_{17}NO_2S_4$	2.36 / 2.71	18.85 / 18.06	262-263	5.65	34
8	$C_{27}H_{16}ClNO_2S_4$	2.75 / 2.54	17.83 / 17.45	275-276	6.19	43
9	$C_{27}H_{16}BrNO_2S_4$	2.01 / 2.35	16.38 / 16.14	280-281	7.15	50

HPLC was performed on a Beckman-Gold liquid chromatograph with UV-Diode Array 168 detector; stationary phase octadecylsilane (ODS, 5 μm); 25 cm × 4.6 mm column. Detection was made at 300 nm. The mobile phase was methanol–water (80:20) for **1-3** and methanol–water (95:5) for **4-9**.

The starting compounds **10–15** were obtained according to the literature [24–26].

General procedure for the preparation of 2-(*p*-arylsulfonylphenyl)-4-hetarylthiazoles 1-9. A solution of thiobenzamide **10-12** (1 mmol) and α-halo ketone **13-15** (1 mmol) in anhydrous ethanol (20 ml) was refluxed for 8 h. The precipitate obtained on cooling was filtered off and recrystallized from chloroform–petroleum ether (Table 4).

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