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SYNTHESES OF NEW CARBONYL DERIVATIVES FROM α-HALOHETARYL KETONES

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The Kröhnke reaction of 2ω-bromoacetylphenoxathiin and 2-ω-bromophenoxathiin 10,10-dioxide, through N-ylide and S-ylide intermediates, leading to the corresponding glyoxals, was described. The condensation reaction of 2-ω-bromoacetylphenoxathiin with aromatic o-hydroxy aldehydes and further cyclization to new furan derivatives was also performed. The new compounds were characterized through elemental analysis and spectral data (IR, ^{1}H NMR and ^{13}C NMR).

Keywords: 2-ω-bromoacetylphenoxathiin, 2-ω-bromophenoxathiin 10,10-dioxide, glyoxals, α-halohetaryl ketones, N-ylides, S-ylides, cyclization, Kröhnke reaction.

The continuous interest in phenoxathiin chemistry is not only due to the large variety of biological activities but also to the diversified theoretical aspects concerning the reactivity of this polynuclear heterocyclic system [1-4].

On the other hand, N-ylides and S-ylides are highly reactive compounds used as intermediates in the synthesis of numerous heterocyclic systems [5-8].

This paper describes the synthesis of phenoxathiin carbonyl derivatives **1**, **2** starting from 2-ω-bromoacetylphenoxathiin **3** and the corresponding 10,10-dioxide **4** (Schemes 1 and 2).

In the first step of the Kröhnke reaction, N-(phenoxathiin-2-carbonylmethyl)- or N-(phenoxathiin-10,10-dioxide-2-carbonylmethyl)pyridinium halides **5-8** reacted with *p*-nitrosodimethylaniline, under basic conditions, leading to the corresponding nitrones **9**, **10**. The pyridinium N-ylide intermediates were not isolated. In the classical Kröhnke reaction, NaOH was used as base (mode A for **7**); the use of triethylamine as catalyst increases the reaction yield by 40% (mode B, Table 1). The analogous reactions of S-[(phenoxathiin-2-carbonyl)methyl]tetrahydrothiophenium bromide (**11**), the corresponding 10,10-dioxide **12**, and dimethylsulfonium chloride **13** (triethylamine as a catalyst) through nonisolated S-ylide intermediates were also carried out (modes C, D). The reaction yields are lower than in the case of N-ylide intermediates, showing the comparatively lower reactivity of S-ylides (Table 1).

In the second step of the Kröhnke reaction, the obtained nitrones **9**, **10** were hydrolyzed under acid catalysis to the corresponding glyoxals **14**, **15** having the same characteristics as previously reported in the literature [9, 10].

New benzofuran derivatives **16-18** were obtained in very good yields by cyclocondensation of 2-ω-bromoacetylphenoxathiin (**3**) with 2-hydroxybenzaldehyde (**19**), 5-formyl-2-hydroxy-3-methoxybenzaldehyde (**20**), and 1-formyl-2-hydroxynaphthalene (**21**) under K_2CO_3 catalysis in refluxing ethanol (Scheme 2).

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Scheme 1

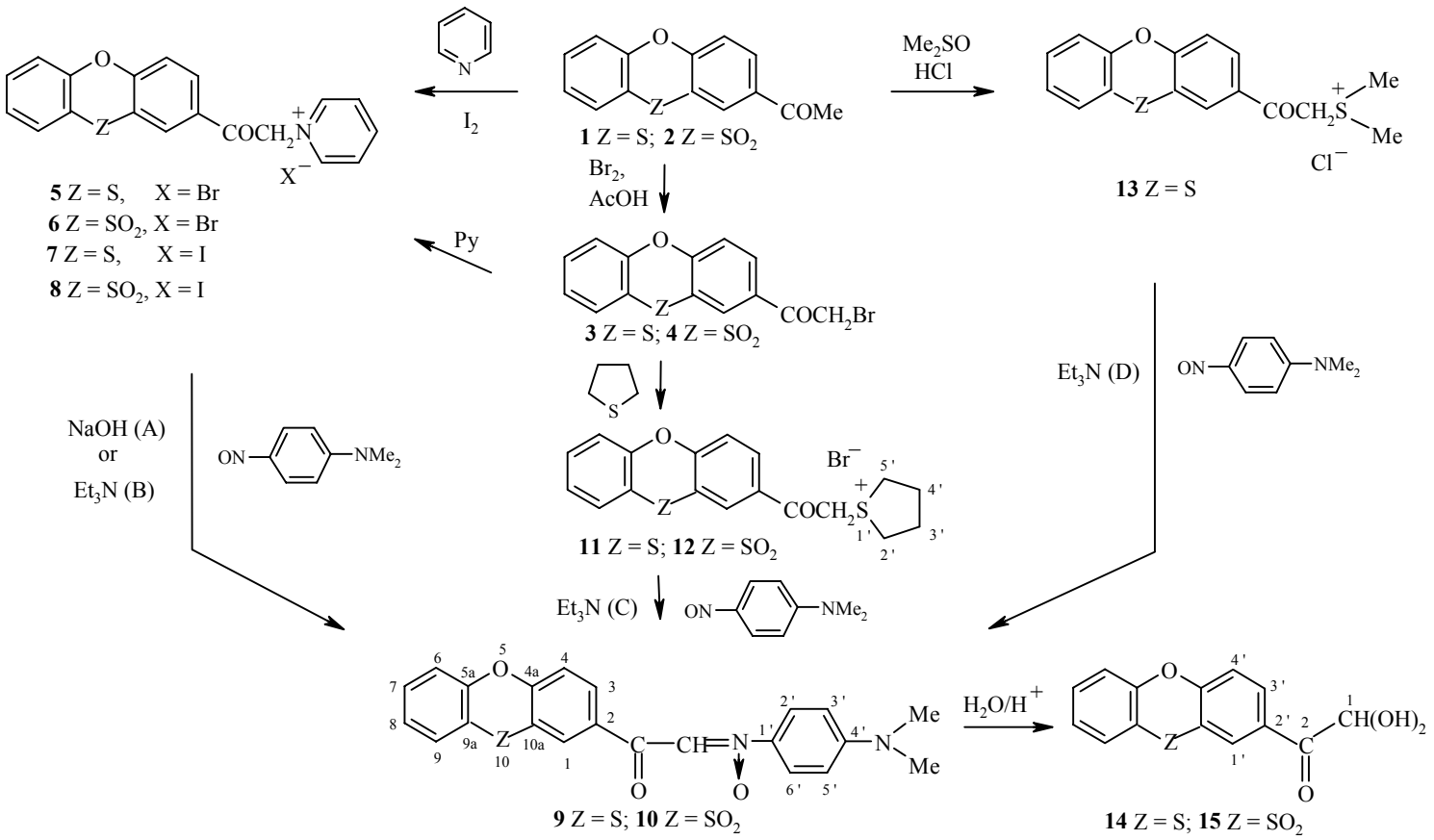

Me2SO
HCl
I2
Br2,
AcOH
Py
NaOH (A)
or
Et3N (B)
Et3N (D)
Et3N (C)
H2O/H+
1 Z = S; 2 Z = SO2
3 Z = S; 4 Z = SO2
5 Z = S, X = Br
6 Z = SO2, X = Br
7 Z = S, X = I
8 Z = SO2, X = I
9 Z = S; 10 Z = SO2
11 Z = S; 12 Z = SO2
13 Z = S
14 Z = S; 15 Z = SO2

TABLE. Characteristics of the Synthesized Products **9-12**, **16-18**

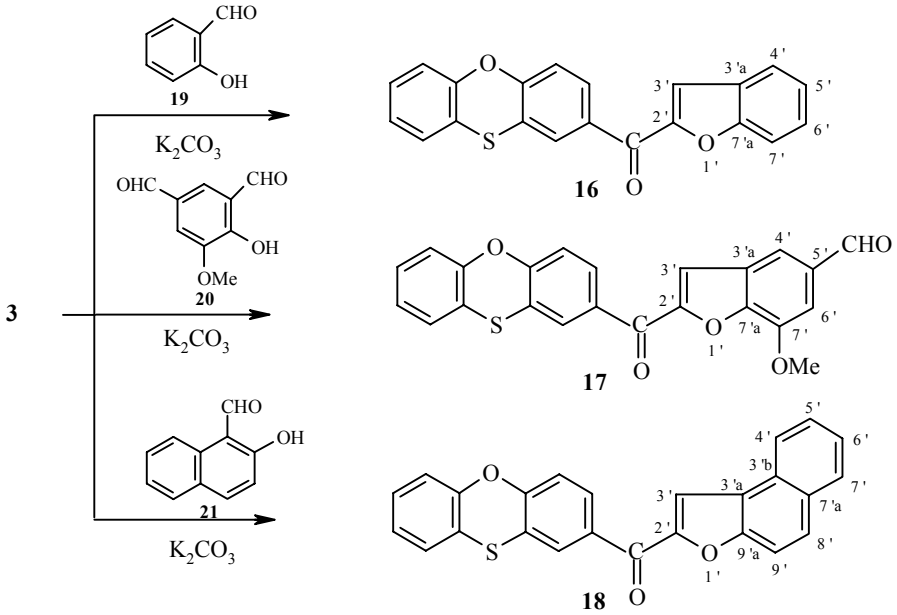
Com-pound	Name	Empirical formula	S, %		Yield, %	mp, °C (solvent)	RT, min.
			Calc.	Found			
9	N-(Phenoxathiin-2-carbonylmethylene)-4'-(N,N-dimethyl-amino)aniline N-oxide	$C_{22}H_{18}N_2O_3S$	8.19	8.43	*	120-121 (toluene–petr. ether)	3.7
10	N-(Phenoxathiin-10,10-dioxide-2-carbonylmethylene)-4'-(N,N-dimethylamino)aniline N-oxide	$C_{22}H_{18}N_2O_5S$	7.57	7.24	*[2]	171-173 (toluene–petr. ether)	2.4
11	S-(Phenoxathiin-2-carbonylmethyl)tetrahydrothiophenium bromide	$C_{18}H_{17}BrO_2S_2$	15.63	15.34	95	144-146	4.0
12	S-(Phenoxathiin-10,10-dioxide-2-carbonylmethyl)tetra-hydrothiophenium bromide	$C_{18}H_{17}BrO_4S_2$	14.50	14.68	86	188-189	2.3
16	2'-Benzo[*b*]furyl 2-phenoxathiinyl ketone	$C_{21}H_{12}O_3S$	9.31	9.39	96.5	155-156 (ethanol)	7.2
17	2'-(5'-Formyl-7'-methoxy)benzo[*b*]furyl 2-phenoxathiinyl ketone	$C_{23}H_{16}O_5S$	7.97	8.28	86.0	188–189 (toluene)	5.6
18	2'-Naphto[1,2-*b*]furyl 2-phenoxathiinyl ketone	$C_{25}H_{16}O_3S$	8.13	8.27	88.1	186-187 (toluene)	11.2

* Yield, %: 30.8 – mode A, 83.3 – mode B, 65.4 – mode C, 42.5 – mode D.

*[2] Yield, %: 85.6 – mode B, 66.8 – mode C.

The new compounds **9-12**, **16-18** were characterized by elemental analyses, IR, UV, ^{1}H NMR, and ^{13}C NMR spectral data (Tables 2-4).

Scheme 2



The ^{1}H NMR and ^{13}C NMR spectra (Table 3 and 4) are in perfect agreement with the suggested structures of all the new compounds. The bidimensional connectivity experiments (^{1}H–^{1}H- and ^{1}H–^{13}C-COSY) allowed more accurate assignments of aromatic and heteroaromatic H- and C-signals.

TABLE 2. IR and UV Spectra of the Synthesized Compounds **9-12**, **16-18**

IR, cm^{-1}	Compound						
	9	**10**	**11**	**12**	**16**	**17**	**18**
νC=O	1661 vs	1647 vs	1662 vs	1674 vs	1634 vs	1649 s	1635 s
νC–O–C_{as} (phenox.)	1262 s	1269 vs	1264 vs	1275 vs	1271 vs	1267 vs	1272 vs
νC–O–C_{sym} (phenox.)	1063 s	1063 s	1080 s	1064 s	1080 m	1079 m	1081 m
γ2CH	818 m	829 m	818 m	832 m	836 s	831 s	832 s
γ4CH	736 m	753 s	750 s	763 m	735 s	746 s	742 vs
Others	1257 vs (νN→O) 1603 s (νC=N)	1240 vs (νN→O) 1603 s (νC=N) 1297 vs (νSO_{2as}) 1155 vs (νSO_{2sym})	2929 m (νCH_{2as}) 2853 m (νCH_{2sym})	1309 vs (νSO_{2as}) 1156 vs (νSO_{2sym}) 2926 m (νCH_{2as}) 2858 m (νCH_{2sym})	furan: 3128 w (νCH) 745 vs (γCH)	1150 vs (νO-CH_3) 1699 vs (νCHO) furan: 3135 w (νCH) 749(γCH)	furan: 3116 w (νCH) 749 vs (γCH)
λ, nm	235 280 318 451	218 291 323 469	222 270	212 264 288	226 277 314	226 284 316	222 272 318 363

vs – very strong, s – strong, m – medium, w – weak.

TABLE 3. ^{1}H NMR Data for Compounds **9-12**, **16-18** (δ, ppm, *J*, Hz, DMSO-d_6)

Atom	**9**	**10**	**11**	**12**	**16**	**17**	**18**
H(1)	7.89, d, J_{13} = 1.7	8.61, s	7.90, s	8.71, s	7.86-7.88, m, 3H (+H(5'))	7.97, s	7.91-7.93, m, 3H (+H(10'))
H(3)	7.83, d, J_{34} = 8.6	8.36, d, J_{34} = 8.6	7.82, d, J_{34} = 8.8	8.44, d, J_{34} = 8.8		7.84, d, J_{34} = 8.6	
H(4)	7.18, d, J_{43} = 8.5	7.71, d, J_{43} = 8.8	7.24, d, J_{43} = 8.7	7.81, d J_{43} = 8.7	7.24, d, J_{43} = 8.4	7.24, d J_{43} = 8.6	7.25, d, J_{43} = 8.3
H(6)	7.10-7.14, m, 2H	7.64, bd, J_{67} = 8.3	7.11-7.16, m, 2H	7.94, bd J_{67} = 7.7	7.13, dd J_{67} = 7.8 , J_{68} = 1.2	7.10-7.14 m, 2H	7.13-7.16, m, 2H
H(8)		7.57, bt, J = 7.3		7.63,d, J_{89} = 7.8	7.14, bd, J_{89} = 7.7		
H(7)	7.22-7.28, m, 2H	7.86, bd, J = 8.5	7.27-7.30 m, 2H	7.92, t J_{78} = 7.8 J_{76} = 7.7	7.21-7.28, m, 2H	7.23-7.28 m, 2H	7.28-7.31, m, 2H
H(9)		8.11, d, J_{98} = 7.8		8.19, d, J_{98} = 8.1			
H(2')	7.82, d, $J_{3'2'}$ = 9.3	7.85, d, $J_{3'2'}$ = 8.8	3.55-3.69, m, 4H	3.56-3.69 m, 4H	—	—	—
H(3')	6.75, d, $J_{3'2'}$ = 9.3	6.75, d, $J_{3'2'}$ = 8.8	2.25-2.36, m, 4H	2.24-2.37 m, 4H	7.84, s	8.02, s	8.55, s
H(6')	—	—	—	—	7.39, bt. $J_{6'5'}$ = 7.6 $J_{6'7'}$ = 7.4	—	8.50, d, $J_{6'7'}$ = 8.0
H(7')	—	—	—	—	7.57, td, $J_{7'8'}$ = 8.4 $J_{7'6'}$ = 7.4, $J_{7'5'}$ = 1.1	7.52, s	7.60, t, $J_{7'8'}$ = 7.3 $J_{7'6'}$ = 7.9
Others	8.75, s (CH=N) 3.00, s (2CH_3)	8.89, s (CH=N) 3.07, s (2CH_3)	5.30, s (CH_2)	5.72, s (CH_2)	7.77, d, $J_{7'8'}$ = 8.5 (H(8'))	10.02, s (CHO) 7.83, s (H(5')) 4.04, s (OCH_3)	7.70, t, $J_{8'7'}$ = 7.3; $J_{8'9'}$ = 7.6, (H(8')) 8.09, d, 2H (H(9'), H(11'))

TABLE 4. ^{13}C NMR Data for Compounds **9-12**, **16-18** (δ ppm, DMSO-d_6)

Atom	**9**	**10**	**11**	**12**	**16**	**17**	**18**
C(1)	127.08	123.42	128.75	124.20	128.12	128.15	128.16
C(2)	134.50	134.36	130.91	131.01	133.49	133.05	133.70
C(3)	128.75	134.36	129.23	134.25	129.94	129.98	129.97
C(4)	117.83	119.70	117.91	120.52	117.86	117.84	117.87
C(4a)	154.38	153.32	155.54	154.47	154.66	154.77	154.60
C(5a)	150.40	150.48	149.97	150.45	150.43	150.30	150.50
C(6)	117.79	119.26	117.51	119.72	117.86	117.84	117.87
C(7)	127.02	135.33	127.13	135.57	127.11	127.08	127.14
C(8)	126.59	126.08	125.86	126.40	125.66	125.65	128.61
C(9)	128.55	123.08	127.84	123.15	128.72	128.59	128.61
C(9a)	118.18	124.32	118.11	124.66	118.83	118.07	118.36
C(10a)	119.49	124.44	119.85	124.83	119.90	119.86	119.90
CO	181.41	185.06	190.0	197.05	181.33	192.16	180.72
C(2')	122.89	122.99	42.71	42.81	155.30	152.40	153.87
C(3')	110.85	110.83	28.22	28.32	117.11	117.51	116.6
C(4')	152.14	152.26	28.22	28.32	128.60	120.89	124.07
C(5')	110.85	110.83	42.71	42.81	124.17	133.05	127.56
C(6')	122.89	122.99	—	—	112.30	107.46	125.74
C(7')	—	—	—	—	126.84	146.05	130.32
C(7'a)	—	—	—	—	151.15	147.91	127.88
Others	136.91 (C(1')) 125.56 (CH=N) 39.87 (CH_3)	136.78 (C(1')) 125.66 (CH=N) 39.84 (CH_3)			123.88 (C(3'a))	128.47 (C(3'a)) 192.16 (CHO) 56.22 (OCH_3)	122.71 (C(3'a)) 130.17 (C(3'b)) 112.80 (C(8')) 128.97 (C(9')) 150.96 (C(9'a))

EXPERIMENTAL

The IR spectra were recorded in KBr pellets on a FTS-135 Biorad instrument (Table 2), the UV spectra on a Specord UV-vis C. Zeiss Jena apparatus (Table 1), and the NMR spectra (Tables 3 and 4) on a Jeol-LAMBDA 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6, using TMS as internal standard. Melting points were determined on a Boetius apparatus and are uncorrected. The HPLC analysis were performed on a Beckman liquid chromatograph, Gold-126 system equipped with a UV-Diode Array Gold-168 detector; stationary phase octylsilane (5 μm); 25 cm × 4.6 mm column. Detection was made at 270 nm, and the mobile phase was methanol–water (80:20) at 1.5 ml/min.

The starting compounds **1-8**, **13**, **14** were obtained according to the literature [10-13]. The characteristics of the products **9-12**, **16-18** are given in Table 1.

Tetrahydrothiophenium Bromides 11, 12. A solution of tetrahydrothiophene (2 mmol) and α-bromo ketone **3**, **4** (2 mmol) in anhydrous toluene (15 ml) was refluxed for 5 h. The resulting solid was filtered after 24 h and washed with petroleum ether.

Nitrones 9, 10. A. To a cooled (-2°C) suspension of N-(phenoxathiin-2-carbonylmethyl)pyridinium iodide (**7**) (33 mmol) in water (5ml), a solution of *p*-nitrosodimethylaniline (37 mmol) in ethanol (20 ml) was added in small portions with stirring. To the reaction mixture an ice-cooled 1N solution of NaOH (4 ml) was added dropwise and stirring was continued for 2 h at room temperature. The red precipitate was filtered off and then washed with 3 ml ethanol.

B. To an ice-cooled suspension of pyridinium halide **5-8** (33 mmol) in ethanol (15 ml), a solution of triethylamine (15 mmol) in ethanol (5 ml) was added dropwise for 15 min with stirring. A solution of *p*-nitrosodimethylaniline (12 mmol) in 5 ml of ethanol was added to the reaction mixture and the stirring was continued for another 2 h at room temperature. The red precipitate was filtered off. Using the same procedure, nitrones **9**, **10** were obtained starting from tetrahydrothiophenium bromides **11**, **12** or from S-(phenoxathiin-2-carbonylmethyl)dimethylsulfonium chloride (**13**).

Phenoxathiinyl Glyoxal Hydrates 14, 15. To a suspension of nitrone **9**, **10** (15 mmol) in water (2 ml), H_2SO_4 5N (5 ml) was added. The reaction mixture was maintained at room temperature for 6 h with stirring and then was extracted with ether (3 × 10 ml). After the ether was removed by evaporation, the obtained solid was recrystallized from 80% AcOH giving crystals of 2-(2'-phenoxathiinyl)glyoxal hydrate (**14**) (mp 132-134°C; 24% yield) and 2-(2'-phenoxathiinyl-10,10-dioxide)glyoxal hydrate (**15**) (mp 128.5-129.5°C; 35% yield).

Furan Derivatives 16-18. To 2-ω-bromoacetylphenoxathiine (**3**) (2.5 mmol) a solution of aldehydes **19-21** (2.5 mmol) in ethanol (20 ml) and anhydrous K_2CO_3 (3.5 g) were added. The reaction mixture was refluxed for 90 min (**16**, **18**) and 4 h respectively (**17**). After removing the solvent by vacuum distillation, water was poured over the residue and the resulting solid was filtered off, washed with water, and dried.

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