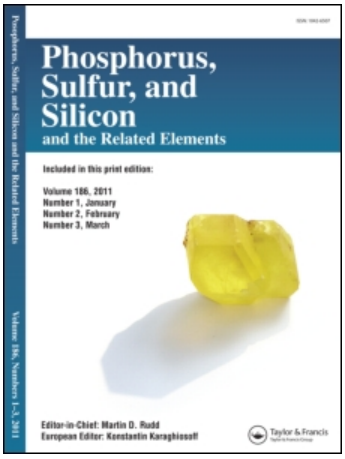

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REACTIONS OF *o*-CHLOROSUBSTITUTED β-KETOENOLATES WITH HETEROCUMULENES

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REACTIONS OF *o*-CHLOROSUBSTITUTED β-KETOENOLATES WITH HETEROCUMULENES

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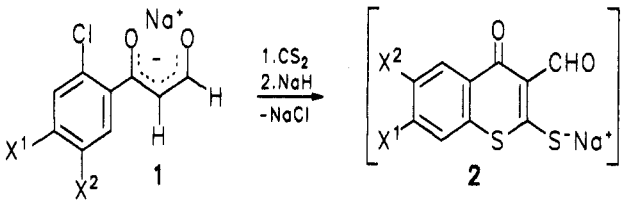
Treatment of *o*-chlorophenyl β-ketoenolates **1** with carbon disulfide in the presence of sodium hydride and subsequent alkylation with CH-acidic halocompounds affords the thieno[2,3-*b*]-4H-[1]benzothiin-4-ones **3**. Reaction of **1** with phenyl isothiocyanate leads to thiophenes **6** which undergo intramolecular cyclization yielding thieno[2,3-*b*]quinolin-4-ones **7**.

Key words: Heterocumulenes; thieno[2,3-*b*]-4H-[1]benzothiin-4-ones; thiophenes; thieno[2,3-*b*]quinolin-4-ones.

We have been investigating the reaction of various aroylacetaldehydes with heterocumulenes.[1,2] As an extension of this work, we have become interested in the reactions of *o*-chlorophenyl β-ketoenolates **1** with carbon disulfide and aryl isothiocyanates.

Thus, treatment of **1** with carbon disulfide in *N,N*-dimethylformamide (DMF) leads as expected [2,3] to the intermediately formed sodium salts **2**. Using for alkylation a haloactive compound Hal-CH_2-A with a methylene group sufficiently activated by a strong electron-withdrawing substituent A, thieno[2,3-*b*]-4H-[1]benzothiin-4-ones **3** are obtained. Obviously, the basic reaction conditions cause the immediate cyclization *via* aldehyde group with elimination of water.

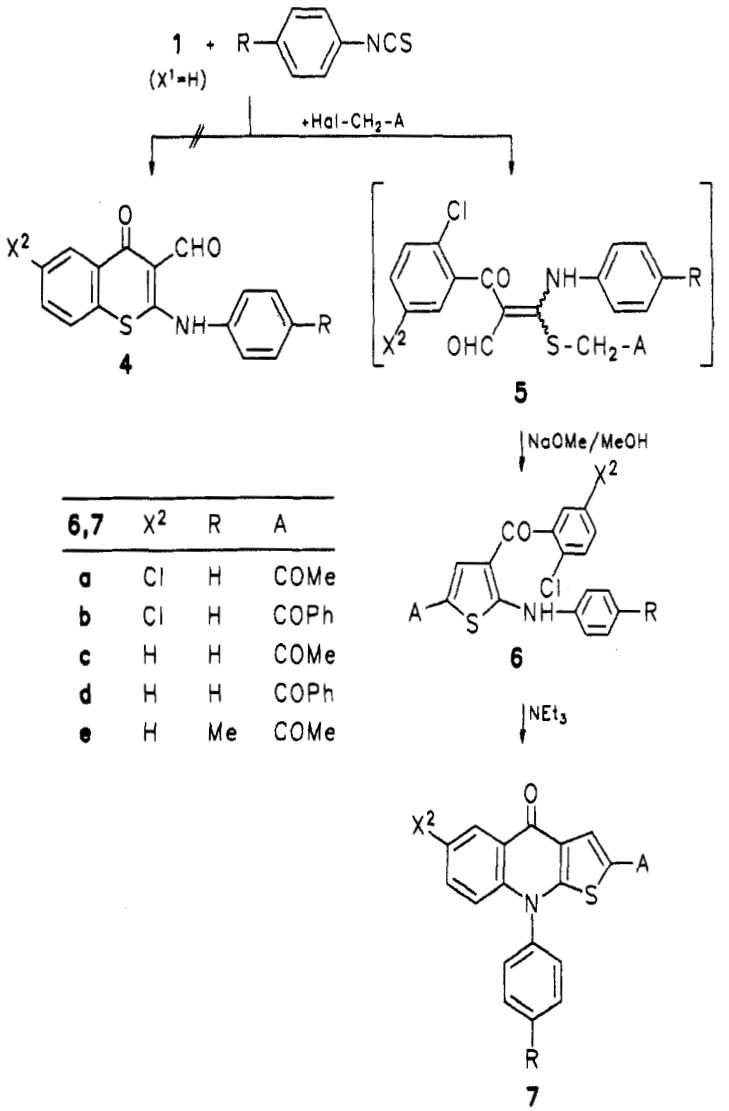


3	X^1	X^2	A
a	H	H	CO_2Et
b	H	Cl	CO_2Et
c	Cl	H	CO_2Et
d	H	Cl	COPh
e	H	Cl	COMe
f	H	Cl	CN

SCHEME 1

The ^{1}H NMR spectra of **3** are characterized by the typical downfield-shift of the aromatic H-5 proton caused by the ketocarbonyl group in *peri*-position[4] (Table IV). The mass spectra show an intensive molecular ion. The fragmentation is determined by the loss of carbon monoxide and the acceptor group from the molecular ion. In the IR spectra strong and sharp bands exist at $\tilde{\nu}$ = 1605–1630 cm^{-1}. They exhibit a conjugated ketocarbonyl stretching vibration.[4] Compounds of this structure are of pharmaceutical interest as potential schistosomicidal agents[5] or can be used for the treatment of psychotic disturbances.[6]

On the contrary, reaction of **1** with phenyl isothiocyanate does not afford 2-anilino-4-oxo-4H-1-benzothiin-3-carbaldehydes **4**. Alkylation with ω-bromoacetophenone leads to the ketene *S,N*-acetals **5** which undergo cyclization under mild



6,7	X^2	R	A
a	Cl	H	COMe
b	Cl	H	COPh
c	H	H	COMe
d	H	H	COPh
e	H	Me	COMe

SCHEME 2

TABLE I

Characteristic data of the compounds **3a–f**

Compd.	M.P. (°C) (Solvent)	Yield (%)	Molecular Formula (Molecular Weight)	Elemental Analysis (%) Calculated/Found				
				C	H	Cl	N	S
3a	156-157 (ethanol)	33	$C_{14}H_{10}O_3S_2$ (290.4)	57.91 / 57.86	3.47 / 3.46	- / -	- / -	22.08 / 21.96
3b	203-204 (1-butanol)	35	$C_{14}H_9ClO_3S_2$ (324.8)	51.77 / 51.67	2.79 / 2.94	10.92 / 10.97	- / -	19.74 / 19.99
3c	213-214 (1-butanol)	39	$C_{14}H_9ClO_3S_2$ (324.8)	51.77 / 51.77	2.79 / 2.94	10.92 / 10.97	- / -	19.74 / 19.99
3d	196-197 (ethanol)	30	$C_{18}H_9ClO_2S_2$ (356.8)	60.58 / 60.52	2.54 / 2.50	9.93 / 9.92	- / -	17.97 / 17.96
3e	308-310 (DMF)	32	$C_{13}H_7ClO_2S_2$ (294.8)	52.97 / 52.90	2.39 / 2.36	12.03 / 12.06	- / -	21.75 / 21.64
3f	273 (DMF)	27	$C_{12}H_4ClNOS_2$ (277.7)	51.89 / 51.80	1.45 / 1.44	12.76 / 12.55	5.04 / 5.08	23.09 / 22.90

TABLE II

Characteristic data of the compounds **6a–e**

Compd.	M.P. (°C) (Solvent)	Yield (%)	Molecular Formula (Molecular Weight)	Elemental Analysis (%) Calculated/Found				
				C	H	Cl	N	S
6a	170-172 (1-butanol)	51	$C_{19}H_{13}Cl_2NO_2S$ (390.3)	58.47 / 58.33	3.36 / 3.41	18.17 / 17.88	3.59 / 3.73	8.21 / 8.46
6b	164-166 (1-butanol)	58	$C_{24}H_{15}Cl_2NO_2S$ 452.4)	63.70 / 63.83	3.34 / 3.32	15.68 / 15.67	3.10 / 3.24	7.09 / 7.07
6c	130-132 (1-butanol)	37	$C_{19}H_{14}ClNO_2S$ (355.8)	64.13 / 63.84	3.97 / 3.93	9.96 / 10.23	3.94 / 3.64	9.01 / 9.02
6d	150-152 (1-butanol)	29	$C_{24}H_{16}ClNO_2S$ (417.9)	68.98 / 68.72	3.86 / 3.82	8.48 / 8.29	3.35 / 3.28	7.67 / 7.69
6e	143-145 (1-butanol)	57	$C_{20}H_{16}ClNO_2S$ (369.9)	64.94 / 65.07	4.36 / 4.39	9.58 / 9.60	3.79 / 3.79	8.67 / 8.63

TABLE III

Characteristic data of the compounds **7a–e**

Compd.	M.P. (°C) (Solvent)	Yield (%)	Molecular Formula (Molecular Weight)	Elemental Analysis (%) Calculated/Found				
				C	H	Cl	N	S
7a	>360 (DMF)	71	$C_{19}H_{12}ClNO_2S$ (353.8)	64.50 / 64.43	3.42 / 3.49	10.02 / 10.10	3.96 / 4.05	9.06 / 9.20
7b	288-290 (DMF)	84	$C_{24}H_{14}ClNO_2S$ (415.9)	69.29 / 69.12	3.39 / 3.30	8.52 / 8.54	3.37 / 3.51	7.70 / 7.78
7c	346-347 (DMF)	84	$C_{19}H_{13}NO_2S$ (319.4)	71.45 / 71.34	4.10 / 4.12	- / -	4.39 / 4.11	10.04 / 9.93
7d	258-260 (DMF)	92	$C_{24}H_{15}NO_2S$ (381.4)	75.57 / 75.53	3.96 / 3.90	- / -	3.67 / 3.59	8.40 / 8.40
7e	>360 (DMF)	89	$C_{20}H_{15}NO_2S$ (333.4)	72.05 / 72.27	4.53 / 4.51	- / -	4.20 / 4.38	9.62 / 9.62

TABLE IV
Spectral data of the compounds **3a–f**

Compd.	IR $\tilde{\nu}$ (cm^{-1})	^1H NMR δ (ppm); J (Hz)	MS m/z (%)
3a	1715 (CO) 1625 (CO)	1.39 (t, 3H, CH_3, J=7); 4.38 (q, 2H, CH_2, J=7); 7.55-7.64 (m, 3H, arom.); 8.44 (s, 1H, CH); 8.64 (m, 1H, H-5)	290 (100) 262 (39)
3b	1725 (CO) 1605 (CO)	1.48 (t, 3H, CH_3, J=7); 4.39 (q, 2H, CH_2, J=7); 7.53-7.62 (m, 2H, arom.); 8.41 (s, 1H, CH); 8.57 (dd, 1H, H-5; J=2, J=0.5)	324 (100) 296 (56)
3c	1725 (CO) 1605 (CO)	1.50 (t, 3H, CH_3, J=7); 4.45 (q, 2H, CH_2, J=7); 7.31-7.68 (m, 2H, arom.); 8.30 (s, 1H, CH); 8.40 (dd, 1H, H-5, J=9, J=0.5)	324 (100) 296 (59)
3d	1630 (CO) 1610 (CO)	7.45-7.98 (m, 7H, arom.); 8.27 (s, 1H, CH); 8.55 (dd, 1H, H-5, J=9, J=0.5)	356 (87) 105 (100)
3e	1665 (CO) 1630 (CO)	2.63 (s, 3H, CH_3); 7.27-7.64 (m, 2H, arom.); 8.32 (s, 1H, CH); 8.56 (d, 1H, H-5, J=9)	294 (100) 251 (15)
3f	2100 (CN) 1610 (CO)	7.48-7.65 (m, 2H, arom.); 8.31 (s, 1H, CH); 8.57 (dd, 1H, H-5, J=8.5, J=0.5)	277 (100) 249 (78)

TABLE V
Spectral data of the compounds **6a–e** and **7a–e**

Compd.	IR $\tilde{\nu}$ (cm^{-1})	^1H NMR δ (ppm); J (Hz)	MS m/z (%)
6a	3200 (NH) 1650 (CO)	2.36 (s, 3H, CH_3); 7.20-7.44 (m, 10H, 9H arom., 1CH); 11.67 [s, (br.), 1H, NH]	389 (71) 354 (100)
6b	3530 (NH) 1610 (CO)	7.21-7.74 (m, 14H, 13H arom., 1CH); 11.72 [s, (br.), 1H, NH]	451 (44) 105 (100)
6c	3350 (NH) 1645 (CO)	2.34 (s, 3H, CH_3); 7.40-7.50 (m, 10H, 9H arom., 1CH); 11.77 [s, (br.), 1H, NH]	355 (73) 320 (100)
6d	3210 (NH) 1610 (CO)	7.34-7.73 (m, 15H, 14H arom., 1CH); 11.82 [s, (br.), 1H, NH]	417 (100)

TABLE V (*Continued*)

6e	3400 (NH) 1650 (CO) 1605 (CO)	2.29 (s, 3H, CH_3); 2.31 (s, 3H, CH_3); 7.17-7.43 (m, 9H, 8H arom., 1CH); 11.62 [s, (br.), 1H, NH]	369 (70) 334 (100)
7a	1650 (CO) 1620 (CO)	2.54 (s, 3H, CH_3);7.40-7.71 (m, 2H, arom.); 8.20 (s, 1H, CH); 8.50 (d, 1H, H-5, J=2)	353 (100)
7b	1625 (CO) 1605 (CO)	6.83-7.85 (m, 12H, arom.); 8.09 (s, 1H, CH); 8.44 (d, 1H, H-5, J=2)	415 (100)
7c	1650 (CO) 1625 (CO)	3.33 (s, 3H, CH_3); 7.41-7.82 (m, 9H, arom.); 8.35-8.38 (m, 2H, H-5, 1CH)	319 (100)
7d	1625 (CO) 1610 (CO)	6.89-7.87 (m, 13H, arom.); 8.15 (s, 1H, CH); 8.52-8.57 (m, 1H, H-5)	381 (100)
7e	1650 (CO) 1625 (CO)	2.51 (s, 3H, CH_3); 2.55 (s, 3H, CH_3); 6.90-7.57 (m, 7H, arom.); 8.23 (s, 1H, CH); 8.54 (dd, 1H, H-5, J=2, J=8)	333 (97) 318 (100)

conditions in the presence of catalytic amounts of a base yielding thiophenes **6** as the only product. Similar to the *p*-chlorophenyl β-ketoenolates,[1] cyclization occurs regioselective *via* aldehyde group.

There is no peak for an aldehyde proton in the ^{1}H NMR spectra of **6**. A broad signal for the NH-proton at δ = 11.67–11.82 ppm is characteristic for an intramolecular hydrogen bond.

Heating **6** in dry *N,N*-dimethylformamide in the presence of triethylamine for 5 h gave thieno[2,3-*b*]quinolin-4-ones **7** in good yields (Scheme 2) which are of interest because of their bactericidal activity.[7-11] Similar to **3**, a downfield shift for the H-5 proton is observed in the ^{1}H NMR spectra. Mass spectra are characterized by an intensive peak for the molecular ion and by the loss of carbon monoxide.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Zeiss Specord 71 IR. ^{1}H NMR spectra were recorded on Bruker NMR Spectrometers WP 200 and AC 80 using TMS as an internal standard. Mass spectra were obtained on a M. v. Ardenne Mass Spectrometer (16 eV) and on a EI-MS (AMD Intectra GmbH, 70 eV). Microanalyses were carried out by the Department of Chemistry of the Martin Luther University Halle.

Thieno[2,3-b]-4H-[1]benzothiin-4-ones **3**; *General procedure:* The sodium salt of aroylacetaldehyde **1** (0.05 mol) was dissolved in dry DMF (100 ml). The cooled mixture was treated with carbon disulfide (0.05 mol) and subsequently with sodium hydride (0.05 mol). After stirring at room temperature for 4 h the appropriate alkylating reagent (0.055 mol) was added dropwise at −5°C. The mixture was stirred for another 5 h and poured into ice/water (300 ml). The resulting solids were filtrated and recrystallized.

2-Anilino-3-benzoyl-thiophenes **6**; *General procedure:* The sodium salt **1** (0.05 mol) was dissolved in dry DMF (100 ml). The mixture was cooled (0°C) and the aryl isothiocyanate (0.05 mol) was added dropwise. Stirring was continued at room temperature for 4 h. Then the alkylating reagent (0.055 mol) was added at −5°C. After stirring for 5 h the mixture was poured into ice/water (300 ml). Oils were extracted with methylene chloride and dried with sodium sulfate. The solvent was evaporated under reduced pressure, the residue dissolved in dry methanol (50 ml) and treated with 0.5 N methanolic solution of sodium methanolate (1 ml). The whole mixture was stirred for 3 h at 0°C. The resulting solid product was filtrated and recrystallized from 1-butanol.

Thieno[2,3-b]-quinolin-4-ones **7**; *General procedure:* A mixture of thiophene **6** (5 mmol) and triethylamine (10 mmol) in dry DMF (15 ml) was refluxed for 5 h. After cooling, the precipitate was filtrated and recrystallized.

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