Synthesis of 3-Acyl-1,2-benzisoxazoles

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A convenient method for the synthesis of 3-acyl-1,2-benzisoxazoles, which are unstable toward bases, is described. Base-catalyzed cyclization of 2-alkyl- and aryl-1,3-dithian-2-yl *o*-chlorophenylketoximes **4a-l** gave 3-(2-alkyl- and aryl-1,3-dithian-2-yl)-1,2-benzisoxazoles **8a-l**, which were converted into the corresponding 3-acyl-1,2-benzisoxazoles **1a-l**.

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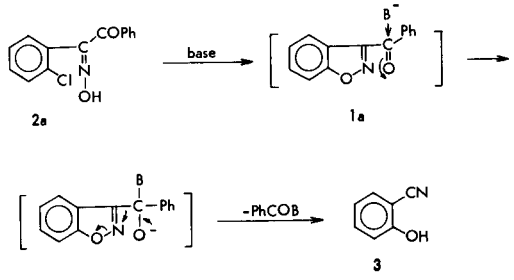
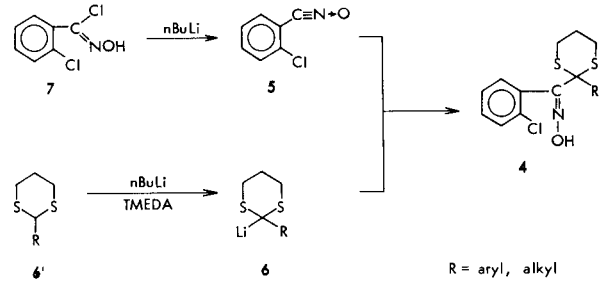
In relation to studies on chemistry and utilization of isoxazole derivatives, we attempted to synthesize a series of 3-acyl-1,2-benzisoxazoles **1**. The most generally applicable method of synthesis of 1,2-benzisoxazoles is base-catalyzed cyclization of *o*-halogenophenylketoximes (1). However, 3-acyl-1,2-benzisoxazoles are difficult to prepare in this way because of their instability toward alkali (2,3); with *o*-chlorophenylbenzoylketoxime **2a** in alkaline medium, the reaction proceeds with debenzoylation and ring cleavage to yield salicylonitrile **3**. Only a few examples of 3-acyl-1,2-benzisoxazoles such as 3-benzoyl-6-nitro- and perfluoro-3-benzoyl-1,2-benzisoxazoles have



been synthesized by unusual methods (2,4).

We recently reported the preparation of 2-substituted-1,3-dithian-2-yl *o*-chlorophenylketoximes **4** by the 1,3-addition reaction of *o*-chlorobenzonitrile oxide **5** with 2-aryl- and alkyl-2-lithio-1,3-dithianes **6** (5). The adducts **4** structurally build up a masked form of the acyl *o*-chlorophenylketoximes **2**, and therefore may be able to cyclize in alkaline medium to the 1,2-benzisoxazoles without ring cleavage. Using the adducts **4**, we have now successfully synthesized a series of 3-acyl-1,2-benzisoxazoles **1**.



Heating a solution of 2-phenyl-1,3-dithian-2-yl *o*-chlorophenylketoxime **4a** with potassium hydroxide in ethanol afforded a cyclization product, 3-(2-phenyl-1,3-dithian-2-yl)-1,2-benzisoxazole **8a**, in 98.4% yield. The structure of **8a** was assigned from its analytical and spectral data. The product **8a** was subsequently treated with mercuric oxide and boron trifluoride (6) in tetrahydrofuran (THF) to give a quantitative yield of a crystalline product **1a**, which was assigned the structure of 3-benzoyl-1,2-benzisoxazole by the spectral features showing the infrared (ir) band attributable to the carbonyl group at 1640 cm^{-1} and the aromatic proton signals in nuclear magnetic resonance (nmr) spectra at δ 7.98 and 7.45 (in deuteriochloroform). However, these structure assignments of **8a** and **1a** are not reliable since, in the cyclization of the *o*-chlorophenylketoxime **4a** in alkaline medium, another reaction course via a Beckmann rearrangement (7) to yield 2-benzoylbenzoxazole **9**, an isomer of **1a**, may exist and the difference between structures **1a** and **9** is difficult to recognize from the analytical and spectral data. Thus, the structure of **1a** was confirmed by an unequivocal synthesis which involved the 1,3-dipolar cycloaddition reaction of benzoylnitrile oxide **10** with benzyne **11** to 3-benzoyl-1,3-benzisoxazole **1a** (8). Further evidence of the structural assignment was also obtained by the ring cleavage of **1a** with potassium hydroxide to salicylonitrile **3** (9).

Similarly, the base catalyzed cyclization reactions of the various *o*-chlorophenylketoximes **4b-l** gave 3-(2-substituted 1,3-dithian-2-yl)-1,2-benzisoxazoles **8a-l**, which were subsequently treated with mercuric oxide and boron trifluoride in THF to give the corresponding 3-acyl-1,2-benzisoxazoles **1** in good yields. The conversion of **8** into **1** was also carried out successfully by the treatments with *N*-bromosuccinimide (10) as well as formaline with trifluoroacetic acid (5) in chloroform. The products **8** and **1**, characterized by their analytical and spectral data, are listed in Tables I and II, respectively.

Since a convenient method for the synthesis of 3-acyl-1,2-benzisoxazoles was established as described above, work was undertaken to synthesize biologically active derivatives. The results will be presented in the next paper.

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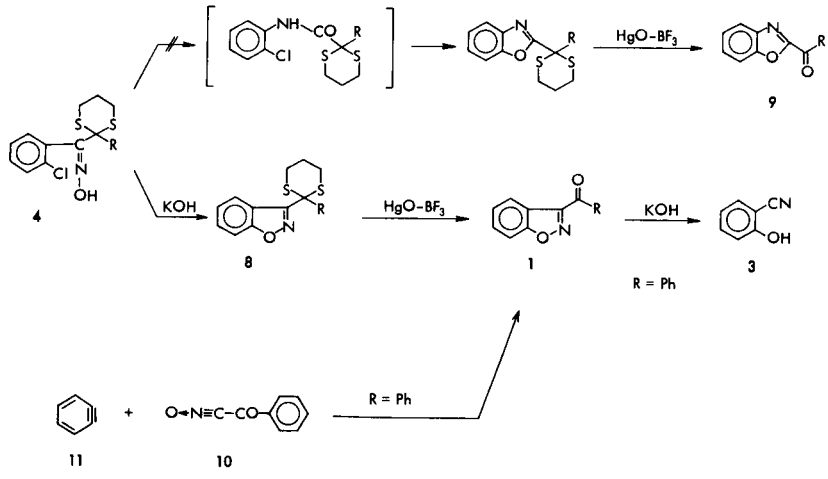
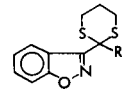


Table I

3-(2-Aryl- and Alkyl-1,3-dithian-2-yl)-1,2-benzisoxazoles (a)

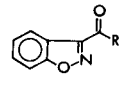


Compound No.	R	Recrystallization Solvent	M.p. °C	Yield %	Formula	Calcd., % C	H	N	Found, % C	H	N
8a	C_6H_5	isopropyl ether	144-146	98.4	$C_{17}H_{15}NOS_2$	65.15	4.79	4.48	65.23	4.81	4.41
8b	p-ClC_6H_4	*n*-hexane	125-126	99.0	$C_{17}H_{14}ClNOS_2$	58.69	4.05	4.02	58.66	3.94	3.99
8c	p-$MeOC_6H_4$	isopropyl ether	165-166	99.0	$C_{18}H_{17}NO_2S_2$	62.94	4.78	4.07	63.12	4.89	3.99
8d	p-$(Me)_2NC_6H_4$	ethyl acetate	200-201	80.3	$C_{19}H_{20}N_2OS_2$	64.02	5.65	7.85	64.12	5.63	7.72
8e	p-HOC_6H_4	isopropyl ether	205-206	98.2	$C_{15}H_{15}NO_2S_2$	61.98	4.59	4.25	62.07	4.59	4.16
8f	4-HO-3,6-$Me_2C_6H_2$	carbon tetrachloride	108-109	92.4	$C_{19}H_{19}NO_2S_2$	63.84	5.36	3.92	63.72	5.31	3.88
8g	1-naphthyl	isopropyl ether	201-202	95.4	$C_{21}H_{17}NOS_2$	69.39	4.71	3.85	69.21	4.74	3.84
8h	3-pyridyl	isopropyl ether	141-142	95.5	$C_{16}H_{14}N_2OS_2$	61.14	4.49	8.91	61.24	4.55	8.76
8i	2-thienyl	isopropyl ether	152-153	78.1	$C_{15}H_{13}NOS_3$	56.40	4.10	4.38	56.43	4.11	4.35
8j	Me	*n*-hexane	101-102	88.9	$C_{12}H_{17}NOS_2$	57.34	5.21	5.57	57.39	5.25	5.61
8k	Me_2CH	*n*-hexane	104-105	98.3	$C_{14}H_{17}NOS_2$	60.18	6.13	5.01	60.13	6.12	4.91
8l	$C_6H_5CH_2$		viscous	97.8	$C_{18}H_{17}NOS_2$	66.02	5.23	4.28	66.24	5.29	4.37

(a) Nmr, ir and mass spectra of the compounds in the Table agreed with the proposed structures.

Table II

2-Acyl-1,2-benzisoxazoles



Compound No.	R	Method	Recrystallization Solvent	M.p. °C	Yield %	Formula	Calcd., % C	H	N	Found, % C	H	N
1a	C_6H_5	A	hexane	85-86	99.0	$C_{14}H_9NO_2$	75.32	4.06	6.28	75.69	4.05	6.23
1b	p-ClC_6H_4	A	hexane	91-92	99.0	$C_{14}H_8ClNO_2$	65.43	3.13	5.43	65.48	3.07	5.49
1c	p-$MeOC_6H_4$	A	isopropyl ether	107-108	99.0	$C_{15}H_{11}NO_3$	71.14	4.37	5.52	71.18	4.37	5.45
1d	p-$Me_2NC_6H_4$	A	isopropyl ether	148-150	94.7	$C_{16}H_{14}N_2O_2$	72.17	5.29	10.51	72.43	5.29	10.50
1e	p-HOC_6H_4	B	carbon tetrachloride	125-127	96.2	$C_{14}H_9NO_3 \cdot \frac{1}{2}H_2O$	67.74	4.06	5.63	67.97	3.99	5.63
1f	4-HO-3,6-$Me_2C_6H_2$	B	carbon tetrachloride	175-176	91.8	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.71	4.83	5.22
1g	1-naphthyl	B	hexane	132-133	91.5	$C_{18}H_{11}NO_2$	79.11	4.06	5.12	79.33	4.04	5.09
1h	3-pyridyl	C	hexane	69-70	17.6	$C_{13}H_8N_2O_2$	69.64	3.60	12.50	69.39	3.42	12.25
1i	2-thienyl	D	hexane	139-140	65.5	$C_{12}H_7NO_2S$	62.89	2.08	6.11	62.98	3.10	6.21
1j	Me	A	hexane	33-35	93.1	$C_9H_7NO_2$	67.08	4.38	8.69	67.08	4.42	8.82
1k	Me_2CH	A		100-105/ 0.1 mm	95.0	$C_{11}H_{11}NO_2$	69.83	5.86	7.40	69.85	5.91	7.38
1l	$C_6H_5CH_2$	A	hexane	54-56	94.9	$C_{15}H_{11}NO_2$	75.94	4.67	5.90	75.97	4.67	5.85

EXPERIMENTAL

All melting and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer in deuteriochloroform using tetramethylsilane (TMS) as an internal standard. Infrared (ir) spectra were recorded on a JASCO IRA-I spectrometer. Mass spectra were recorded on a RMU-6 mass spectrometer.

2-Aryl- and 2-Alkyl-1,3-dithian-2-yl *o*-Chlorophenylketoximes (**4a-l**).

These compounds were prepared from *o*-chlorobenzonitrile oxide **5** and the corresponding 2-substituted 2-lithio-1,3-dithianes **6** by the procedure described in a previous paper (5).

3-(2-Alkyl- and 2-Aryl-1,3-dithian-2-yl)-1,2-benzisoxazoles (**8a-l**).

A solution of **4** (1 mmole) and potassium hydroxide (3 mmoles) in ethanol (30 ml.) was refluxed for 20 hours. After cooling, the reaction mixture was neutralized with 10% hydrochloric acid and concentrated under reduced pressure. The residue was extracted with chloroform and the extract was chromatographed on silica gel with chloroform to give a solid, which was recrystallized to afford the crystalline product **8** shown in Table I.

3-Acyl-1,2-benzisoxazoles (**1a-l**).

Method A.

To a solution of **8** (1 mmole) with mercuric oxide (2 mmoles) in 15% aqueous THF (10 ml.), was added dropwise boron trifluoride etherate (3 mmoles) at room temperature. After stirring for 16 hours, diethylether (20 ml.) was added and the mixture was filtered. The filtrate was washed with 5% aqueous sodium bicarbonate then water, dried over anhydrous sodium sulfate, and filtered. Removal of the solvent gave a crystalline residue, which was chromatographed on silica gel with benzene to give the product **1** shown in Table II.

a) Method B.

A mixture of **8** (1 mmole), mercuric oxide (2 mmoles) and 35% hydrochloric acid (0.5 ml.) in acetone (10 ml.) was stirred at room temperature for 2 days. This mixture was then treated in a manner similar to that described in Method A.

b) Method C.

A mixture of **8** (1 mmole) and *N*-bromosuccinimide (4 mmoles) in acetonitrile (10 ml.) was stirred at room temperature for 4 days. This mixture was then treated in a manner similar to that described in Method A.

c) Method D.

A mixture of **8** (1 mmole), 37% aqueous formaline (1 ml.) and trifluoroacetic acid (4 ml.) in chloroform (10 ml.) was stirred at room temperature for 2 days. This mixture was then treated in a manner similar to that described above.

Reaction of Benzoylnitrile Oxide **10** with Benzyne **11**.

Preparation of 3-Benzoyl-1,2-benzisoxazole (**1a**).

To a solution of anthranilic acid (1.78 g., 13 mmoles) and iso-amylnitrite (1.6 g., 13 mmoles) in tetrachloroethane (40 ml.) was added ω-isonitrosophenacylchloride (1.84 g., 10 mmoles) (11) and sodium bicarbonate (1.26 g., 15 mmoles). The mixture was stirred for 16 hours at room temperature and then evaporated. The residue was extracted with benzene and the extract was washed with water then dried over anhydrous sodium sulfate. Removal of the solvent and chromatography of the residue on silica gel with benzene gave a crystalline solid, which was recrystallized from *n*-hexane to give colorless prisms of **1a**, m.p. 85-86°, 1.00 g. (45.3%).

Reaction of 3-Benzoyl-1,2-benzisoxazole (**1a**) with Potassium Hydroxide.

A mixture of **1a** (0.223 g., 1 mmole) and potassium hydroxide (0.28 g., 5 mmoles) in ethanol (20 ml.) was stirred for 16 hours at room temperature. Next, the ethanol was evaporated and the residue was extracted with benzene. The solution was washed with water, dried over anhydrous sodium sulfate and chromatographed on silica gel. Elution with benzene gave ethylbenzoate, 0.135 g. (90%). Elution with chloroform gave *o*-hydroxybenzonitrile, m.p. 97-98°, 0.113 g. (95%).

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Table III

Spectral Data for **1a-l**

Compound No.	Nmr (deuteriochloroform) δ Assignment (a)		Ir (Nujol) cm^{-1}	Ms m/e
	Aromatic proton	Others	ν C=O	M^+
1a	7.20-8.15 (9H, m)		1670	223
1b	7.22-8.46 (8H, m)		1660	257
1c	6.90-8.53 (8H, m)	3.92 (Me, S)	1642	253
1d	6.53-8.33 (8H, m)	3.07 (2Me, S)	1650	266
1e	6.80-8.43 (8H, m)		1633	239
1f	7.23-8.25 (6H, m)	2.32 (2Me, S) 5.37 (OH, b)	1635	267
1g	7.37-8.73 (11H, m)		1660	273
1h	7.23-9.67 (8H, m)		1665	224
1i	7.10-8.60 (7H, m)		1633	229
1j	7.23-8.37 (4H, m)	2.8 (Me, S)	1700	161
1k	7.20-8.37 (4H, m)	1.33 (2Me, S) 3.8 (CH, m)	1700	189
1l	6.97-8.30 (9H, m)	4.5 (CH_2, S)	1705	237

(a) Abbreviations: s = singlet; m = multiplet; b = broad.

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