

Reactions of 9-Phenylthioxanthene 10-Oxide with Organometallic Reagents

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Reactions of 9-phenylthioxanthene 10-oxide (**1**) with a variety of Grignard reagents afforded 9-substituted 9-phenylthioxanthenes (**2**). Similarly, organolithiums reacted with the sulfoxide **1** to give the corresponding thioxanthenes **2**. The structures of 9-aryl-9-phenylthioxanthenes (**2d–i**) were confirmed by the alternative synthesis of the samples *via* the acid-catalyzed cyclization of triarylmethanol derivatives **5**. A possible mechanism by way of a 9-phenylthioxanthylum ion intermediate is proposed for the reaction of the sulfoxide **1** with organometallic reagents.

Keywords 9-phenylthioxanthene 10-oxide; organometallic reagent; Grignard reagent; organolithium; 9-phenylthioxanthene; 9-phenylthioxanthylum ion

Sulfoxides bearing a hydrogen atom at the α -position react with a variety of reagents such as acid chloride,¹⁾ Grignard reagents²⁾ and acid anhydrides³⁾ to give the corresponding Pummerer-type reaction products. However, the sulfoxides having no α -hydrogen, for example diaryl sulfoxides, do not react with acetic anhydride,^{3a)} and afford triarylsulfonium salts by the reaction with aromatic Grignard reagents followed by addition of a strong acid such as hydrogen bromide or perchloric acid.⁴⁾ There is no report on the reaction of cyclic sulfoxides bearing a hydrogen atom at the γ -position to the sulfur atom with organometallic reagents such as Grignard reagents or organolithiums.

We have investigated reactions of a cyclic sulfoxide bearing an active hydrogen atom at the γ -position, 9-phenylthioxanthene 10-oxide, with a variety of Grignard reagents or organolithiums.

Results and Discussion

Reaction of 9-phenylthioxanthene 10-oxide (**1**) with

Grignard reagents was conducted in refluxing benzene under a nitrogen atmosphere (Chart 1). Methyl-, ethyl-, and propylmagnesium halides were used as alkyl Grignard reagents. The reaction products were the corresponding 9-alkyl-9-phenylthioxanthenes (**2**) as major products and 9-phenylthioxanthene (**3**) as a minor product. The latter compound is a reduced product of the sulfoxide moiety of **1**. Under similar conditions, the reactions with aryl and aralkyl Grignard reagents such as phenyl-, 4-tolyl-, 2-methoxyphenyl-, 4-methoxyphenyl-, 4-chlorophenyl-, benzyl-, and β -phenethylmagnesium halides also afforded the corresponding **2** as major products. These results are summarized in Table I. The reaction with alkyl and aralkyl Grignard reagents afforded the reduction product **3** in higher yields compared to those with aryl Grignard reagents.

We previously reported that there are two diastereomeric isomers (*cis* and *trans*) in **1**,⁵⁾ so we carried out the reaction of pure *cis*-**1** with phenylmagnesium bromide. However, we could not find any marked difference of

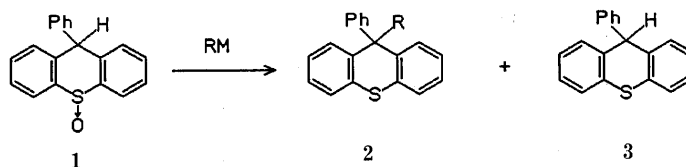


Chart 1

TABLE I. Reactions of 9-Phenylthioxanthene 10-Oxide (**1**) with Organometallic Reagents

Entry	Organometallic reagent	Product (2)				Product (3)
		Compound	R	Yield (%)	mp (°C)	Yield (%)
1	MeMgI	2a	Me	71	139	19
2	EtMgBr	2b	Et	48	Oil	35
3	PrMgBr	2c	Pr	51	101	16
4	PhMgBr	2d	Ph	81	217	2
5	4-ClC ₆ H ₄ MgBr	2e	4-ClC ₆ H ₄	69	196	4
6	4-MeC ₆ H ₄ MgBr	2f	4-MeC ₆ H ₄	61	174	8
7	2-MeC ₆ H ₄ MgBr	2g	2-MeC ₆ H ₄	55	207	10
8	4-MeOC ₆ H ₄ MgBr	2h	4-MeOC ₆ H ₄	69	218	7
9	2-MeOC ₆ H ₄ MgBr	2i	2-MeOC ₆ H ₄	51	185	9
10	PhCH ₂ MgCl	2j	PhCH ₂	46	139	31
11	Ph(CH ₂) ₂ MgBr	2k	Ph(CH ₂) ₂	37	183	33
12	MeLi	2a	Me	40		24
13	PhLi	2d	Ph	53		1

results between the *cis* and *trans* diastereoisomers of **1**.

The structures of the products (**2**) were determined by elemental analyses and spectroscopy. Furthermore, the 9-aryl-9-phenylthioxanthenes (**2d–i**) were identical, by comparison of melting points and spectroscopic data, with the materials which were synthesized by an unambiguous method (Chart 2). Reaction of 2-phenylthiobenzophenone (**4**)⁶ with Grignard reagents gave triarylmethanol derivatives (**5**). The alcohols (**5**) were subjected to cyclization by refluxing in acetic acid in the presence of a catalytic amount of concentrated sulfuric acid to afford the desired

9-substituted 9-phenylthioxanthenes (**2d–i**) in 70–90% yields.

Interestingly, from the reaction of **1** with equimolar phenylmagnesium bromide, small amounts of 9-phenylthioxanthenol (**6**) (10%) and bis(9-phenylthioxanthen-9-yl) peroxide (**7**) (2.3%) were isolated along with 9,9-diphenylthioxanthene (**2d**) (17%). The formation of these two products, **6** and **7**, provides strongly suggestive information about the reaction mechanism of **1** and Grignard reagents.

We next carried out the reaction of **1** with organolithium reagents and obtained similar results to those in the

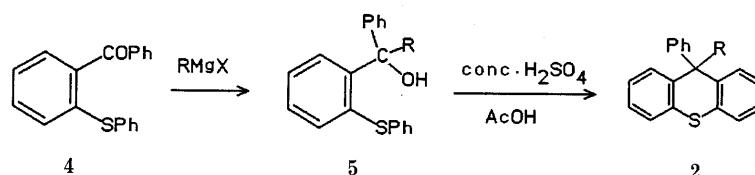


Chart 2

TABLE II. Elemental Analyses and Spectral Data for Compounds **2**

Compound	Formula	Analysis (%)		¹ H-NMR δ (CDCl ₃) ^{a)}	MS (<i>m/z</i>)
		Calcd	Found		
		C	H		
2a	C ₂₀ H ₁₆ S	83.28 (83.02)	5.59 (5.80)	2.40 (3H, s, Me), 6.70–7.50 (13H, m, ArH)	288 (M ⁺), 273 (base)
2b	C ₂₁ H ₁₈ S	83.40 (83.44)	6.00 (6.21)	0.78 (3H, t, <i>J</i> = 7.5 Hz, CH ₂ Me), 2.35 (2H, q, <i>J</i> = 7.5 Hz, CH ₂ Me), 6.70–7.50 (13H, m, ArH)	302 (M ⁺), 273 (base)
2c	C ₂₂ H ₂₀ S	83.48 (83.71)	6.37 (6.48)	0.86 (3H, t, <i>J</i> = 6 Hz, CH ₂ CH ₂ Me), 1.20 (2H, m, CH ₂ CH ₂ Me), 2.30 (2H, t, <i>J</i> = 6.5 Hz, CH ₂ CH ₂ Me), 6.70–7.50 (13H, m, ArH)	316 (M ⁺), 273 (base)
2d	C ₂₅ H ₁₈ S	85.67 (85.54)	5.18 (5.36)	6.70–7.50 (m, ArH)	350 (M ⁺), 273 (base)
2e	C ₂₅ H ₁₇ ClS	78.01 (78.17)	4.45 (4.74)	6.62–7.53 (m, ArH)	384 (M ⁺), 273 (base)
2f	C ₂₆ H ₂₀ S	85.67 (85.75)	5.53 (5.72)	2.30 (3H, s, Me), 6.60–7.50 (17H, m, ArH)	364 (M ⁺), 287 (base)
2g	C ₂₆ H ₂₀ S	85.67 (85.41)	5.53 (5.74)	1.65 (3H, s, Me), 6.50–7.50 (17H, m, ArH)	364 (M ⁺), 287 (base)
2h	C ₂₆ H ₂₀ OS	82.07 (81.77)	5.30 (5.51)	3.78 (3H, s, OMe), 6.70–7.50 (17H, m, ArH)	380 (M ⁺), 303 (base)
2i	C ₂₆ H ₂₀ OS	82.07 (81.97)	5.30 (5.54)	3.30 (3H, s, OMe), 6.39–7.60 (17H, m, ArH)	380 (M ⁺), 303 (base)
2j	C ₂₆ H ₂₀ S	85.67 (85.80)	5.53 (5.44)	3.63 (2H, s, –CH ₂ –), 6.25–6.50 (2H, m, ArH), 6.80–7.50 (16H, m, ArH)	273 (base), 91
2k	C ₂₇ H ₂₂ S	85.68 (85.57)	5.86 (6.02)	2.55 (4H, brs, –CH ₂ CH ₂ –), 6.80–7.40 (18H, m, ArH)	378 (M ⁺), 273 (base)

a) At 60 MHz, expressed in δ -value. Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

TABLE III. Preparation of Triarylmethanol **5** from the Reaction of 2-Phenylthiobenzophenone (**4**) with Grignard Reagents

Compound	R	Yield (%)	mp (°C)	Formula	Analysis (%)				MS (<i>m/z</i>)	IR (KBr) ν_{OH} (cm ^{−1})
					Calcd		Found			
					C	H	C	H		
5d	Ph	58	144	C ₂₅ H ₂₀ OS	81.48	5.46	81.69	5.34	368 (M ⁺), 350 (base)	3420
5e	4-ClC ₆ H ₄	36	Oil	C ₂₅ H ₁₉ ClOS	High resolution MS 402.0820 (402.0817)				402 (M ⁺), 181 (base)	3440 ^{a)}
5f	4-MeC ₆ H ₄	87	126	C ₂₆ H ₂₂ OS	81.64	5.80	81.39	5.78	382 (M ⁺), 181 (base)	3330
5g	2-MeC ₆ H ₄	25	133	C ₂₆ H ₂₂ OS	81.64	5.80	81.84	5.85	382 (M ⁺), 181 (base)	3460
5h	4-MeOC ₆ H ₄	44	119	C ₂₆ H ₂₂ O ₂ S	78.62	5.57	78.46	5.65	398 (M ⁺), 213 (base)	3445
5i	2-MeOC ₆ H ₄	23	148	C ₂₆ H ₂₂ O ₂ S	78.62	5.57	78.52	5.76	398 (M ⁺), 213 (base)	3470

a) The IR spectrum was measured on NaCl plates.

TABLE IV. Preparation of 9-Aryl-9-phenylthioxanthene **2** by Cyclization of **5** in the Presence of Concentrated Sulfuric Acid

Compound	R	Yield (%)	Analysis (%)	
			Calcd (Found)	
			C	H
2d	Ph	90	85.67 (85.72)	5.18 (5.31)
2e	4-ClC ₆ H ₄	88	78.01 (78.07)	4.45 (4.49)
2f	4-MeC ₆ H ₄	76	85.67 (85.59)	5.53 (5.80)
2g	2-MeC ₆ H ₄	70	85.67 (85.51)	5.53 (5.30)
2h	4-MeOC ₆ H ₄	80	82.07 (82.01)	5.30 (5.50)
2i	2-MeOC ₆ H ₄	85	82.07 (81.88)	5.30 (5.12)

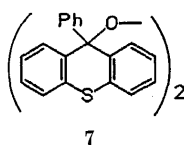
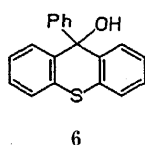


Chart 3

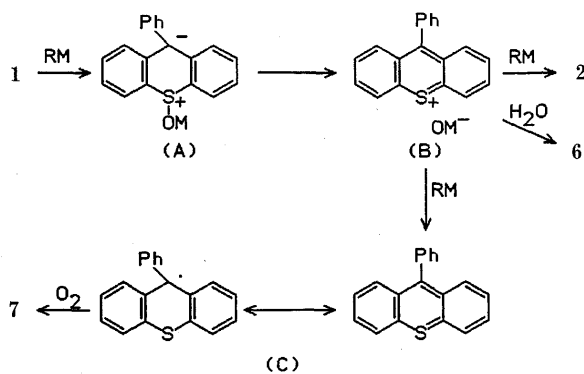


Chart 4

Grignard reactions. The reaction with methyl lithium gave **2a** and **3** in 40 and 24% yields, respectively. Similarly, from the reaction with phenyllithium, **2d** and **3** were obtained in 53 and 1% yields, respectively along with unidentified materials. These results are also listed in Table I.

A possible mechanism for the reaction of **1** with organometallic reagents giving 9-substituted 9-phenylthioxanthene (**2**) as a major reaction product is shown in Chart 4. Compound **1** reacts with organometallic reagents to form the zwitterionic intermediate (**A**), which is converted into 9-phenylthioxanthylum ion intermediate (**B**). The intermediate (**B**) is again attacked by organometallic reagents to give the 9-substituted 9-phenylthioxanthene (**2**). One of the minor products, 9-phenylthioxanthanol (**6**) is produced by an attack of water on the intermediate (**B**). Another minor product, **7** may be afforded via the formation of 9-phenylthioxanthene-9-yl radical (**C**) by single-electron transfer from the organometallic reagent to the intermediate (**B**), followed by trapping with an oxygen molecule. It has been reported that single-electron reduction of 9-phenylthioxanthylum perchlorate with a metal such as

zinc, copper or potassium provided the radical (**C**), whose structure was determined by ESR spectroscopy, and that treatment of the radical (**C**) with oxygen afforded the peroxide (**7**).⁷⁾

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a JASCO IR A-1 infrared spectrometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Hitachi R-20B spectrometer. Mass spectra (MS) were recorded with a JEOL JMSD-300 spectrometer and high-resolution MS with the JMA 2000 on-line system.

General Procedure for the Reaction of 9-Phenylthioxanthene 10-Oxide (1) with Grignard Reagents Grignard reagents were prepared in a usual manner by reaction of 21 mmol of organic halide with 520 mg of magnesium turnings in anhydrous ether under an atmosphere of nitrogen. After addition of the halide, the solution was refluxed for 3–4 h. Then 30 ml of anhydrous benzene was introduced to the Grignard reagent prepared as above and ether was removed by distillation until the temperature of the distillate vapor had reached 70 °C. A solution of 1 g of **1** in 20 ml of anhydrous benzene was added to the Grignard reagent solution and the mixture was refluxed under nitrogen for 10 h. The reaction mixture was cooled to 0–10 °C and hydrolyzed with a solution consisting of 10 ml of hydrobromic acid (*d* 1.48) and 10 ml of water. The benzene layer was separated and the aqueous layer was extracted with benzene. The benzene extract and the benzene layer were combined, washed twice with water and dried over anhydrous MgSO₄. The solvent was removed and the residue was chromatographed on silica gel using petroleum ether as a solvent to give the crude compounds **2** and 9-phenylthioxanthene (**3**). Compound **2** was purified by recrystallization from benzene–methanol in the case of solids and by vacuum distillation in the case of liquids. Compound **3** was recrystallized from methanol and characterized. The data from these experiments are tabulated in Tables I and II.

General Procedure for the Synthesis of Triarylmethanol Derivatives 5 A solution of 3 g of 2-phenylthiobenzophenone (**4**)⁶⁾ in 10 ml of anhydrous ether was added dropwise to a stirred ethereal solution of Grignard reagent prepared from 760 mg of magnesium turnings and 31 mmol of organic halide in a usual manner, and the mixture was refluxed for 5 h. The cooled reaction mixture was hydrolyzed with cold aqueous NH₄Cl solution and stirred for 0.5 h. The mixture was extracted with ether and the ether extract was washed with water and dried over anhydrous MgSO₄. The ether was distilled off and the residue was purified by chromatography on alumina using benzene–petroleum ether, followed by recrystallization from methanol in the case of solids. In the case of liquid, it was used as such for further reaction after confirmation of the characteristic IR absorption due to the hydroxy function. The yields, melting points, analytical and spectral data of the products are shown in Table III.

General Procedure for the Synthesis of 2 from 5 A few drops of concentrated sulfuric acid was added with stirring to a refluxing solution of 1.7 mmol of compound **5** in 20 ml of acetic acid. The resulting red-brown or violet solution was refluxed for 10 min and cooled. The cooled reaction mixture was poured into ice-cold aqueous sodium carbonate solution and the resulting solid was collected by filtration. The filtrate was extracted twice with ether and the ether extract was washed with water, then dried over anhydrous MgSO₄. The solvent was evaporated to give the crude product, which was combined with the solid collected by filtration and recrystallized from a mixture of benzene and methanol to give an analytically pure sample as indicated in Table IV.

Reaction of 1 with an Equimolar Phenylmagnesium Bromide A 1 N solution of phenylmagnesium bromide in ether (3.45 ml) was slowly added by syringe under nitrogen to a stirred solution of 1 g of **1** in 30 ml of anhydrous benzene. The mixture was stirred overnight at room temperature, refluxed for 1 h, then cooled to 0 °C and hydrolyzed with 6 ml of 47% hydrobromic acid. The benzene layer was separated, washed with water and dried over anhydrous MgSO₄. The solvent was evaporated and the resulting red oily substance was chromatographed on silica gel using petroleum ether as the eluent. The first fraction gave 200 mg (16.6%) of 9,9-diphenylthioxanthene (**2d**). From the second fraction, 96 mg (9.6%) of 9-phenylthioxanthanol (**6**), mp 105 °C (lit.⁸⁾ mp 106 °C) was obtained and the third fraction gave 23 mg (2.3%) of 9-bis(9-phenylthioxanthene-9-yl)peroxide (**7**), mp 186 °C (lit.^{7,9)} mp 188 °C). Unchanged starting sulfoxide (352 mg) was recovered finally by

elution with benzene.

Reactions of 1 with Organolithiums With Methyllithium: A solution of **1** (1 g) in anhydrous benzene (10 ml) was added to 25 ml of an ethereal solution of 0.64N methyllithium under a nitrogen atmosphere and the mixture was refluxed for 12 h. The reaction mixture was hydrolyzed with aqueous NH_4Cl solution and extracted with benzene. The extract was washed with water, dried over anhydrous MgSO_4 , and evaporated to dryness. The residue was chromatographed on silica gel using petroleum ether as the solvent to give 400 mg (40.3%) of 9-methyl-9-phenylthioxanthene (**2a**) and 225 mg (24.1%) of 9-phenylthioxanthene (**3**).

With Phenyllithium: A solution of **1** (500 mg) in anhydrous benzene (10 ml) was added to 6.7 ml of an ethereal solution of 1.5N phenyllithium under a nitrogen atmosphere. After ether was removed by distillation, the mixture was refluxed for 10 h. The reaction mixture was worked up as above to give a crude product, which was subjected to chromatography on silica gel using benzene-petroleum ether (1:10) as the solvent to afford 324 mg (53%) of **2d**, 5 mg (1.1%) of **3** and 54 mg of an unidentified amorphous solid.

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