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Ozonization of Thioketones and Aryl Arenedithiocarboxylates, a Novel Route to Sterically Hindered Sulfines

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Table. Comparison of Reactant Proportions in the Sodium/Liquid Ammonia Reduction of 2-(Tetradec-9-ynyl)-tetrahydropyran (1) to *E*-2-(Tetradec-9-enyl)-tetrahydropyran (2)

Conditions	Alkyne 1 (mol)	Sodium (g-atom)	Liquid NH ₃ (ml)	Ether (ml)	Ratio of <i>trans</i> -2:1
A	0.038	0.18	400	20	1.21:1
B	0.045	0.21	1000	50	8.55:1
C	0.038	0.18	1000	100	8.55:1

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Ozonization of Thioketones and Aryl Arenedithiocarboxylates, a Novel Route to Sterically Hindered Sulfines¹

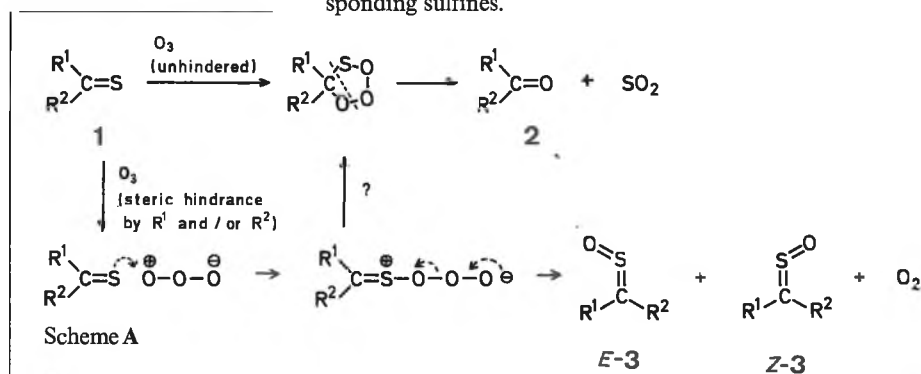
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We have earlier reported that the oxidation of thiocarbonyl compounds with peroxyacids provides a general route to a variety of sulfines^{2,3}. Ozonization is generally recognized as a clean, mild, and selective method of oxidation and therefore would be attractive for the preparation of sulfines. In the present communication, we report our results obtained in the ozonization of thioketones and aryl arenedithiocarboxylates.

When ozone was passed through a solution of thiobenzophenone (1a) in dichloromethane, rapid decolorization of the mixture was observed and benzophenone was isolated as the only product. The same result was obtained under strictly controlled reaction conditions (1 equiv of ozone in dichloromethane at -78°). 4,4'-Dimethoxythiobenzophenone (1b) reacts analogously. With sterically hindered thioketones (1c-f, Table 1), however, the reaction takes a different course giving rise to the formation of sulfines. Thus, from the ozonization of 2,4,6-trimethylthiobenzophenone (1c) using 1 equiv of ozone in dichloromethane at -78° phenyl-(2,4,6-trimethylphenyl)-sulfine was obtained in 61% yield as a mixture of the *Z*- and *E*-isomers.

Similar results were obtained with aryl arenedithiocarboxylates (Table 2). Whereas ozonization of phenyl dithiobenzoate (1g) affords *S*-phenyl thiobenzoate as the only product, ozonization of the sterically hindered dithioesters 1h-1 using 1 equiv of ozone gives fair to good yields of the corresponding sulfines.



The remarkable difference in the behavior of unhindered and sterically hindered substrates may be rationalized by the following assumption (Scheme A). In the case of un-

¹ Paper XIII is M. Jacobson, K. Ohinata, D. L. Chambers, W. A. Jones, M. Fujimoto, *J. Med. Chem.* **16**, 248 (1973).

² Mention of a commercial or proprietary product in this paper does not constitute an endorsement of this product by the USDA.

³ J. S. Read, F. L. Warren, P. H. Hewitt, *Chem. Commun.* **1968**, 792.

W. L. Roelofs, R. Carde, G. Benz, G. von Salis, *Experientia* **27**, 1438 (1971).

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M. Jacobson, R. E. Redfern, W. A. Jones, M. H. Aldridge, *Science* **170**, 542 (1970).

⁴ M. Jacobson, *Science* **163**, 190 (1969).

M. Jacobson, *Insect Sex Pheromones*, Academic Press, New York, 1972.

⁵ H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, Inc., New York, 1965, p. 71.

K. N. Campbell, L. T. Eby, *J. Amer. Chem. Soc.* **63**, 216 (1941).

⁶ L. Crombie, S. H. Harper, *J. Chem. Soc.* **1950**, 1707.

⁷ C. Litchfield, R. D. Harlow, A. F. Isbell, R. Reiser, *J. Amer. Oil Chem. Soc.* **42**, 73 (1965).

⁸ D. Warthen, N. Green, *J. Amer. Oil Chem. Soc.* **46**, 191 (1969).

⁹ D. Warthen, M. Jacobson, *J. Med. Chem.* **11**, 373 (1968).

¹⁰ D. Warthen, M. Jacobson, *J. Med. Chem.* **10**, 1190 (1967).

¹¹ D. Warthen, *J. Med. Chem.* **11**, 371 (1968).

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¹³ N. Green, J. D. Warthen, C. L. Mangum, *J. Econ. Entomol.* **64**, 1381 (1971).

hindered thiocarbonyl compounds, the thiocarbonyl group of **1** undergoes cycloaddition with ozone⁴ with subsequent loss of sulfur dioxide to give⁵ the carbonyl compound (**2**). In the case of sterically hindered substrates, the cycloaddition of ozone is rendered difficult or even impossible; instead, nucleophilic attack of the thiocarbonyl sulfur⁶ on the ozone molecule may take place; subsequent elimination of oxygen yields the sulfine (**3**).

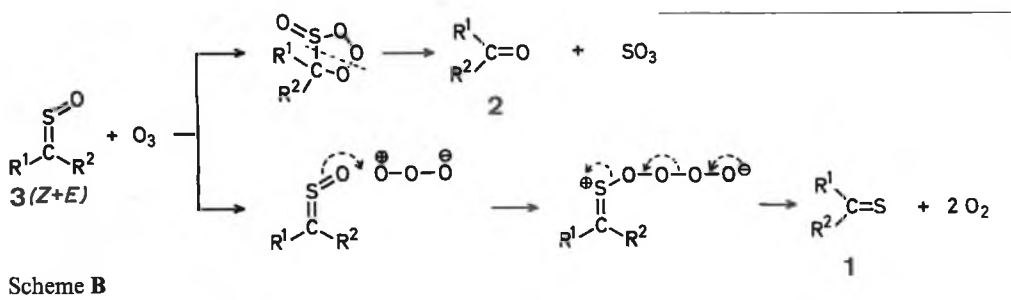
As sulfines are themselves sensitive to oxidizing agents⁷, we also investigated the reaction of these compounds with ozone. Upon treatment with 1 equiv of ozone, almost all of the sulfines listed in Table 3 (sulfine *Z*-**3h** is an exception) reacted smoothly to give the corresponding carbonyl compounds as the main products. In some cases reduction products, viz. the thiocarbonyl compounds (**1**) were also isolated. The predominant formation of carbonyl compounds (**2**) in this reaction may be explained by cycloaddition of ozone to the sulfine (**3**) and elimination of sulfur trioxide from the cycloaddition product, whereas the formation of thiocarbonyl compounds (**1**) could proceed via nucleophilic attack of the sulfine oxygen on the ozone molecule followed by elimination of oxygen.

thiocarboxylates, respectively, are found in the product mixture. This apparent loss of ozone is not caused by obvious reasons such as escape from the reaction vessel or thermal degradation⁸ of ozone. The isolation of reduction products during ozonization of sulfines (Scheme B) may account for this unexpected ozone consumption.

The mechanism proposed in Scheme B is also supported by the fact that the ozonization product obtained from *Z*-**3h** contains a considerable amount of the opposite isomer (*E*-**3h**).

Although the proposed Schemes A and B are rather speculative it is evident that the conversion of thiobenzophenone (**1a**) to benzophenone (**2a**) by ozonization does not proceed via the intermediacy of a sulfine since this would not be compatible with the observed consumption of only 1 equiv of ozone for quantitative conversion. The difference in the mechanisms of the ozonization of unhindered and hindered thiocarbonyl compounds (Scheme A) is related to the differences encountered in the ozonization of sterically unhindered and hindered alkenes⁹.

Although all of the sulfines listed in Tables 1 and 2 may be

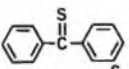
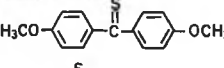
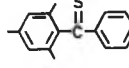
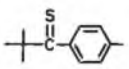




Scheme B

In all ozonization experiments with sterically hindered thioketones and dithioesters using 1 equivalent of ozone considerable amounts of starting material can be recovered, while only small quantities of the corresponding ketones or *S*-aryl

prepared by peroxyacid oxidation^{2,3} of thioketones, the present simple ozonization method provides an attractive alternative, particularly in view of the considerably different *Z/E* ratio of the products obtained.

Table 1. Ozonization of Thioketones using One Equivalent of Ozone

Substrate	Sulfine			Recovered Substrate (%)	Ketone Yield (%)
	Yield (%)	<i>Z/E</i> Ratio	m. p.		
1a 	0	—	—	0	100
1b 	0	—	—	9	47 (+40% tar)
1c 	61	60/40	<i>Z</i> : 98–101° <i>E</i> : 58–59°	29	0
1d 	32	70/30	<i>Z</i> : 70.8–71.5° <i>E</i> : oil	0 ^a	35
1e 	43	one isomer ^b	oil, crystals at 0°	40	3
1f 	27	one isomer ^b	49.5–51°	58	5

^a This substrate is unstable and is rapidly converted to the ketone during chromatography.

^b The geometry could not be established.

Table 2. Ozonization of Aryl Arenedithiocarbonylates using One Equivalent of Ozone

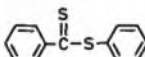
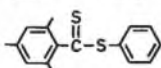
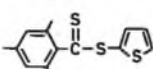
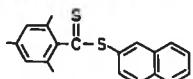
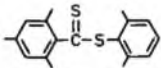
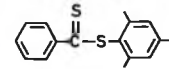
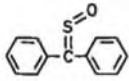
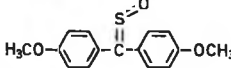
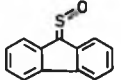
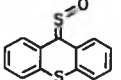
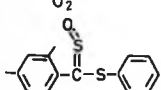
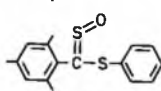
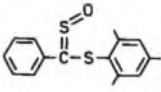
Substrate	Sulfine			Recovered Substrate (%)	<i>S</i> -Aryl Thio-carboxylate (%)
	Yield (%)	<i>Z/E</i> Ratio	m. p.		
1g 	0	—	—	—	100
1h 	41	65/35	<i>Z.</i> : 98–100° <i>E.</i> : 69.5–70.5°	51	0
1i 	37	45/55	<i>Z.</i> : 124–125° <i>E.</i> : 27–28.5°	54	0
1j 	59	55/45	<i>Z.</i> : 117–118° <i>E.</i> : 102–104°	27	12
1k 	38	40/60	<i>Z.</i> : 197–199° <i>E.</i> : 130.1–130.2°	59	0
1l 	23	80/20	<i>Z.</i> : 102–103° <i>E.</i> : 62–63°	60	9

Table 3. Ozonization of Sulfines using One Equivalent of Ozone

Substrate	Carbonyl Compound	Recovered Substrate		
	Yield (%)	%	<i>Z/E</i> Ratio	By-products
3a 	69	2	—	
3b 	64	0	—	3.5% 1b
3m 	86	10	—	
3n 	100	0	—	
<i>E</i> -3h 	84	1	?	9% 1h
<i>Z</i> -3h 	3	48	10/90	27% 1h
3l 	72	23	only <i>Z</i>	

Ozonization of Thiocarbonyl Compounds; General Procedure:

The reactions were carried out on a 0.4–2.0 mmol scale. Ozone was prepared by passing a stream of dried oxygen through a "Fischer ozone generator". The ozone thus formed was led into a known volume of dichloromethane at -78° . According to Rubin¹¹, a saturated solution of ozone in dichloromethane at -78° contains 0.04 mol/l; this was checked by iodometric titration. Ozone was transferred from this saturated solution into a solution of the substrate (1 equiv) in dichloromethane at -78° within 20 min using a slow stream of nitrogen¹². When the ozone transfer was completed the reaction mixture was allowed to warm

to room temperature. The solvent was removed in vacuo and the residue was subjected to thick-layer chromatography on silica gel using benzene/petroleum ether as eluent. The pure *Z*- and *E*-isomers were thus obtained, except in the case of 3i and 3k. The products were characterized by elemental analysis. I.R., and ¹H-N.M.R. spectrometry.

The above procedure was also used for the ozonization of the sulfines.

The use of more than 1 equiv of ozone in the above procedure leads to a raise in yield of sulfine; on the other hand, however, this also leads to increased formation of the corresponding ketone

or *S*-aryl thiocarboxylate, respectively, which usually are difficult to separate from the sulfine.

All sulfines listed in Tables 1 and 2 were also prepared by oxidation of the thiocarbonyl compounds with 3-chloroperbenzoic acid. The geometry of the *Z*- and *E*-isomers was established as described in Ref. ³ and Ref. ¹⁰.

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¹ Part XX in the series "Chemistry of Sulfines"; Part XIX: A. Tangerman, B. Zwanenburg, *Tetrahedron Lett.* **1973**, 79.

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³ B. Zwanenburg, L. Thijs, J. Strating, *Rec. Trav. Chim.* **90**, 614 (1971).

⁴ Formation of primary ozonide from an alkene and ozone, see R. Huisgen, *Angew. Chem.* **75**, 604 (1963).

⁵ Cf. Criegee mechanism for the ozonolysis of alkenes, R. Criegee, *Record Chem. Progr.* **18**, 111 (1957).

⁶ Cf. Formation of sulfoxides from sulfides and ozone, P. S. Bailey, *Chem. Rev.* **58**, 925 (1958).

⁷ B. Zwanenburg, L. Thijs, J. Strating, *Rec. Trav. Chim.* **86**, 577 (1967).

⁸ R. L. Augustine, *Oxidation*, Marcel Dekker, Inc., New York, 1969, Vol. I, p. 291.

⁹ R. W. Murray, *Accounts Chem. Res.* **1**, 313 (1968).

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Synthesis of 1,2,3-Trimethyl-, 1,2,3,7-Tetramethyl-, and 1,2,3,5,6,7-Hexamethylnaphthalenes

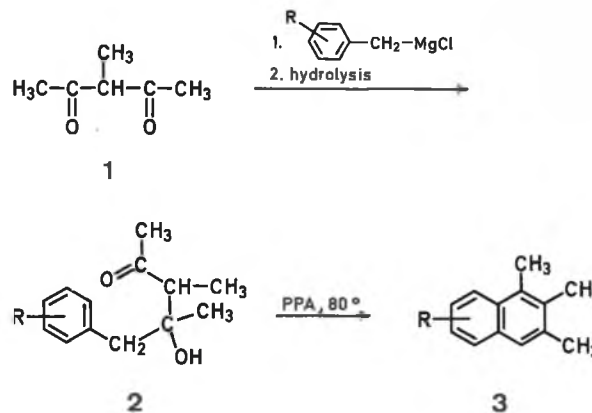
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This report concludes our work on the synthesis of polymethylnaphthalenes from β -hydroxyketones by describing the synthesis of the title compounds from the appropriate Grignard reagents and 3-methylpentanedione.

According to Kohler and Erickson¹, β -diketones of the type $R^1-CO-CH(R^2)-CO-R^3$ are cleaved by Grignard reagents. It has now been found, contrary to the results of these authors, that β -hydroxyketones (**2**) can in fact be obtained in 45–60% yields from 3-methylpentanedione (**1**) and benzylmagnesium chloride or its homologues by the method reported earlier by us². The yields are generally somewhat lower than those obtained with 2,4-pentanedione but the method is nevertheless quite suitable for preparing these otherwise inaccessible compounds.

The α -methyl- γ -phenyl- β -hydroxyketones (**2**) synthesized in this manner underwent cyclodehydration to polymethylnaphthalenes (**3**) in 50–55% yields. Here again, the yields are somewhat lower than those obtained with β -hydroxyketones unsubstituted in the CH_2 group. Perhaps the presence of a methyl substituent facilitates *trans* dehydration of the hydroxyketone prior to carbocation formation and cyclization.



3-Methylpentanedione (1):

This diketone was prepared as described by Johnson, Markham, and Price³.

2,3-Dimethyl-2-hydroxy-4-oxo-1-phenylpentane (2, R = H):

This β -hydroxyketone was prepared by the method described earlier by us from 3-methylpentanedione (**1**; 0.8 mol) and benzylmagnesium chloride (2.0 mol). It was isolated by bulb-to-bulb distillation; yield: 95 g (57%); b. p. 80–85°/0.02 torr.

$C_{13}H_{18}O_2$ calc. C 75.69 H 8.79
(206.3) found 75.62 8.58

I.R.: $\nu_{OH} = 3586$ (shoulder), $\nu_{C=O} = 1700^{-1}$.

¹H-N.M.R. ($CDCl_3$): $\delta = 7.23$ (m, 5H_{arom}), 1.10 (s, 3H, CH_3), 2.16 (s, 3H, $COCH_3$), 2.72 ppm (s, 1H, OH).

1,2,3-Trimethylnaphthalene (3, R = H):

Hydroxyketone **2**, R = H, (70 g, 0.3 mol) was dissolved in polyphosphoric acid (320 ml) and the solution heated at 80° for 2 hr with stirring. The cold reaction mixture was poured into ice-cold 10% sodium hydroxide solution (3 l) and the oil was extracted with ether. The extract was freed of acid by washing with water, 5% aqueous sodium-hydrogen carbonate, and again water, and was dried with potassium carbonate. The ether was evaporated and the residue dissolved in acetone-free methanol (200 ml) and treated with Girard's reagent T (30 g) and Rexyn 102 (H)[®] (Fisher Amberlite-IRC-150) resin (2.0 g) as catalyst. The alcohol was evaporated and the residue extracted with pentane. Pentane was distilled off and the crude product purified by bulb-to-bulb distillation to give a pale yellow oil; yield: 30 g (52%); m. p. 27 to 28°; m. p. of picrate (orange needles, from ethanol): 144–145° (Ref. ⁴, m. p. 142.5°; Ref. ⁵, m. p. 141–142°).

$C_{13}H_{14}$ calc. C 91.67 H 8.33
(170.2) found 91.62 8.39

¹H-N.M.R. ($CDCl_3$): $\delta = 6.87$ –8.06 (m, 5H_{arom}), 2.24, 2.32, 2.48 ppm (3s, 9H, 3 CH_3).

2,3-Dimethyl-2-hydroxy-1-(4-methylphenyl)-4-oxopentane (2, R = 4- CH_3):

This compound was prepared from 3-methylpentanedione (**1**) and 4-methylbenzylmagnesium chloride by the same procedure as described above for **2**, R = H; yield: 46%; b. p. 85–90°/0.02 torr.

$C_{14}H_{20}O_2$ calc. C 76.34 H 9.17
(220.3) found 76.75 8.83

I.R.: $\nu_{C=O} = 1707$, $\nu_{OH} = 3505$, 3578 cm^{-1} (shoulder).

¹H-N.M.R. ($CDCl_3$): $\delta = 7.09$ (m, 4H_{arom}), 2.77 (s, 2H, $CH_2C_6H_5$), 2.32 (s, 3H, $CH_3-C_6H_4$), 2.18 (s, 3H, $COCH_3$), 1.11 ppm (s, 3H, CH_3).