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The Formation and Reactions of α-Keto Sulfoxide

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The reactions of α-keto sulfoxide, produced by the oxidation of thiolester, were studied. It was established that the oxidation of *S*-ethyl thiobenzoate with *N*-bromosuccinimide and isopropyl alcohol afforded benzoyl ethyl sulfoxide. Similarly, butyryl ethyl sulfoxide was produced by the oxidation of *S*-ethyl thiobutyrate with iodosobenzene. α-Keto sulfoxide, produced by the above-mentioned oxidations, reacts with alcohols, phenols, amines or sodium carboxylates to afford acylated products such as esters, amides or carboxylic anhydrides in good yields.

It has been found that hexahydrophthalic anhydride is obtained in good yield by the reaction of sodium hexahydrophthalate with benzenesulfenyl chloride at room temperature. This result can be explained by assuming an initial formation of a condensation product, sodium benzenesulfenyl hexahydrophthalate, which in turn cyclizes to yield acid anhydride by the elimination of sodium benzenesulfenate.

Based on this finding, the oxidation of thiolesters was investigated with the assumption that α-keto

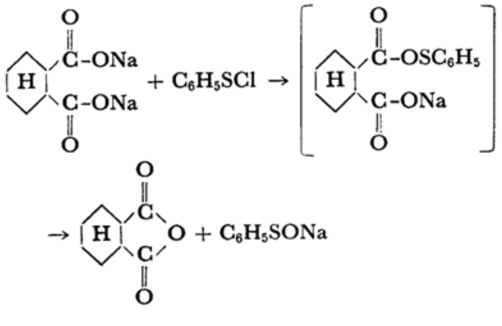


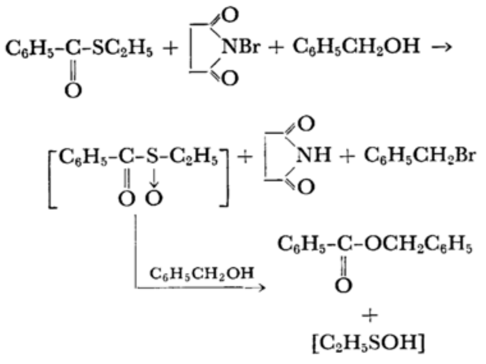
TABLE 1. THE REACTION OF 1 mol OF THIOLESTER WITH 1 mol of *N*-BROMOSUCCINIMIDE AND 2 mol OF ALCOHOL

Thiol ester	Alcohol	Ester Yield	Ester Bp	Yield of succinimide
$C_6H_5\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_2H_5$	C_2H_5OH	72%	88—91°C/12 mmHg	92%
$C_6H_5\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_2H_5$	$C_6H_5CH_2OH$	61%	120—122°C/3 mmHg	99%
$C_6H_5\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_6H_5$	C_2H_5OH	60%	96—100°C/20 mmHg	60%
$C_6H_5\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_6H_5$	$n\text{-}C_4H_9OH$	65%	122—124°C/14 mmHg	84%

sulfoxide, an isomer of sulfenyl carboxylate, would be an active acylating reagent when it was treated with active hydrogen compounds.

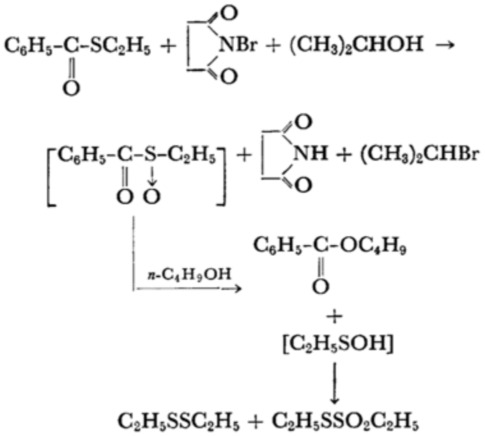
The oxidation of thiolester with either aqueous peracetic acid[1] or potassium permanganate[2] as an oxidant resulted in the formation of carboxylic acid, instead of the expected α-keto sulfoxide. In order to perform the above mentioned acylation reaction by the use of thiolester through α-keto sulfoxide, it is necessary to explore a convenient method for the oxidation of thiolester under anhydrous condition.

Recently, it has been reported that the treatment of *N*-bromosuccinimide with sulfide in hydrous dioxane at room temperature afforded sulfoxide.[3] In the present investigation, a modified oxidation of thiolester was tried by the use of alcohol instead of water in the above reaction as shown in the following equation. It was expected that oxidation by this procedure would be successfully carried out under anhydrous condition. Indeed, when 2 mol of benzyl alcohol was added to a mixture of 1 mol of *S*-ethyl thiobenzoate and 1 mol of *N*-bromosuccinimide, benzyl benzoate (61%), succinimide (99%) and benzyl bromide (64%) were obtained.



In a similar manner, various esters were obtained from the reaction of 1 mol each of thiolester and *N*-bromosuccinimide, and 2 mol of alcohols (see Table 1).

In order to extend this type of acylation to various active hydrogen compounds, such as amines or phenols, the oxidation of thiolester with equimolar amounts of *N*-bromosuccinimide and alcohol was investigated. The reaction of equimolar amounts of *S*-ethyl thiobenzoate, *N*-bromosuccinimide and isopropyl alcohol under ice-cooling, followed by the addition of butyl alcohol, resulted in the formation of butyl benzoate (93%), succinimide (88%), diethyl disulfide (68%) and *S*-ethyl thioethyl sulfonate (65%). Diethyl disulfide and *S*-ethyl thioethyl sulfonate would be the products resulted by the decomposition of ethanesulfenic acid formed. Of importance in this reaction is the fact that isopropyl benzoate, an undesirable by-product, was not obtained at all.



In a similar manner, various esters were obtained in good yields by the reactions of α-keto sulfoxide, produced from thiolester, *N*-bromosuccinimide and isopropyl alcohol, with various alcohols (see Table 2).

The existence of the α-keto sulfoxide, an intermediate, was confirmed by the infrared spectra of

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[1] C. J. Carallito and D. M. Freuhauf, *J. Am. Chem. Soc.*, **71**, 2248 (1949).

[2] R. Otto and R. Luders, *Ber.*, **13**, 1285 (1880).

[3] W. Tagaki, K. Kikukawa, K. Ando and S. Oae, *Chem. Ind.*, **38**, 1624 (1964).

TABLE 2. THE REACTION OF BENZOYL ETHYL SULFOXIDE WITH ALCOHOLS

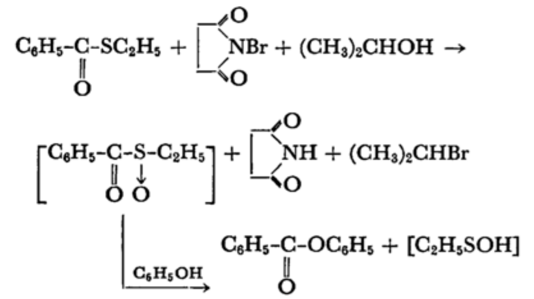
ROH	$C_6H_5CO_2R$		Yield of succinimide	Yield of $(C_2H_5S)_2$	Yield of $C_2H_5SSO_2C_2H_5$
	Yield	Bp °C/mmHg			
n-C_4H_9OH	93%	126—128/20	88%	68%	65%
n-$C_8H_{17}OH$	74%	128—132/1	93%	69%	—
$C_6H_5CH_2OH$	55%	127—128/2	91%	—	—
cyclo-$C_6H_{11}OH$	65%	109—113/1	91%	55%	—

TABLE 3. THE REACTION OF α-KETO SULFOXIDE, PRODUCED BY THE OXIDATION OF THIOLESTER WITH IODOSOBENZENE, WITH ALCOHOLS

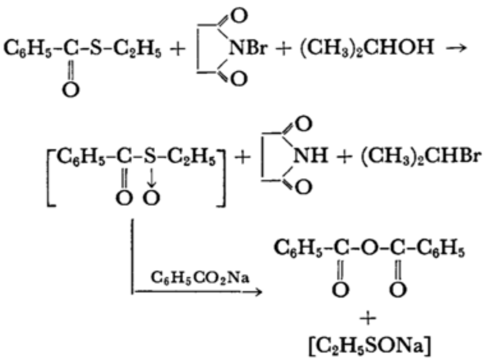
Thiol ester	Alcohol	Ester		Yield of iodobenzene
		Yield	Bp °C/mmHg	
$C_3H_7\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_2H_5$	C_2H_5OH	72%	101—110/760	94
$C_3H_7\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_2H_5$	i-C_3H_7OH	48%	110—115/760	80%
$C_3H_7\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_2H_5$	n-$C_8H_{17}OH$	65%	120—126/24	—
$C_6H_5\text{-}\underset{\underset{O}{\|}}{C}\text{-}SC_2H_5$	n-$C_8H_{17}OH$	37%	130—132/2	75%

the reaction mixture which was obtained from the reaction of the S-ethyl thiobenzoate, N-bromosuccinimide and isopropyl alcohol: 1720 cm^{-1}, 1780 cm^{-1} ($\rangle$C=O), 1180 cm^{-1} ($\rangle$S$\rightarrow$O). This spectrum was identical with that of the reaction mixture which was obtained from the reaction of S-ethyl thiobenzoate and iodosobenzene mentioned below.

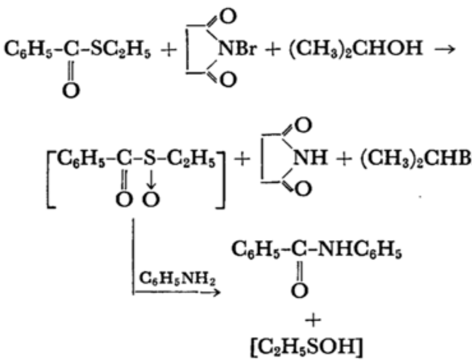
Next, α-keto sulfoxide, produced by the above mentioned procedure, was treated with phenol, phenyl benzoate (56%) and succinimide (87%) were obtained. The reactions of benzoyl ethyl sulfoxide with substituted phenol, such as p-chlorophenol and p-nitrophenol gave p-chlorophenyl benzoate and p-nitrophenyl benzoate in 34% and 10% yields, respectively along with a tarry product.



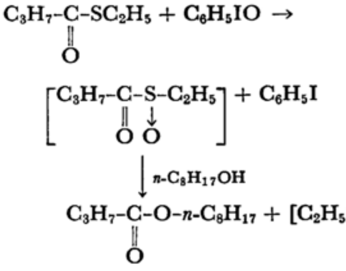
When benzoyl ethyl sulfoxide was allowed to react with benzoic acid, benzoic anhydride could not be obtained, while benzoic acid was recovered quantitatively along with unidentifiable tarry materials. However, when sodium benzoate was used instead of benzoic acid in the above reaction, benzoic anhydride was obtained in 65% yield.



In addition, benzoyl ethyl sulfoxide was found to react vigorously with aniline to afford benzanilide (70%) and succinimide (72%).



Then, the oxidation of thiolesters was tried by the use of iodosobenzene. When a mixture of *S*-ethyl thiobutyrate and iodosobenzene was refluxed in chloroform for 45 min, a precipitates of iodosobenzene disappeared. Successive addition of *n*-octyl alcohol to the reaction mixture at room temperature resulted in the formation of *n*-octyl butyrate in 65% yield.



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\begin{gathered}
C_3H_7\text{-}\underset{O}{\underset{\|}{C}}\text{-}SC_2H_5 + C_6H_5IO \rightarrow \\
\left[C_3H_7\text{-}\underset{O}{\underset{\|}{C}}\text{-}\underset{O}{\underset{\downarrow}{S}}\text{-}C_2H_5\right] + C_6H_5I \\
\Big\downarrow n\text{-}C_8H_{17}OH \\
C_3H_7\text{-}\underset{O}{\underset{\|}{C}}\text{-}O\text{-}n\text{-}C_8H_{17} + [C_2H_5SOH]
\end{gathered}
$$

Various esters were obtained in a similar manner by the reaction of thiolesters, iodosobenzene and alcohols (see Table 3).

Experimental

The Reaction of Sodium Hexahydrophthalate with Benzenesulfenyl Chloride. A mixture of sodium hexahydrophthalate (2.16 g, 0.01 mol) and benzenesulfenyl chloride (2.89 g, 0.02 mol) was stirred in tetrahydrofuran for 6 hr at room temperature. After the precipitates formed was removed by filtration, the residue was evapolated under reduced pressure. Distillation *in vacuo* gave hexahydrophthalic anhydride (1.00 g, 65%, bp 100—106°C/0.15 mmHg) with much amount of tarry product.

The Reaction of 1 mol of *S*-Ethyl Thiobenzoate with 1 mol of *N*-Bromosuccinimide and 2 mol of Benzyl Alcohol. Into a mixture of *S*-ethyl thiobenzoate (1.66 g, 0.01 mol) and *N*-bromosuccinimide (1.78 g, 0.01 mol) in carbon tetrachloride (20 m*l*), a solution of benzyl alcohol (2.16 g, 0.02 mol) in carbon tetrachloride (10 m*l*) was added drop by drop under stirring. After stirring had been continued for 3 hr, white precipitates were collected, washed with carbon tetrachloride; succinimide was obtained, 0.92 g (93%), mp 122—123°C. The filtrate was concentrated, and the distillation under reduced pressure gave a mixture of benzyl bromide and benzyl alcohol (bp 80—89°C/12 mmHg) and benzyl benzoate (bp 120—122°C/12 mmHg), 1.21 g (61%). The mixture of benzyl bromide and benzyl alcohol was refluxed with thiourea (1 g) in ether for 2 hr, and benzyl thioureyl bromide 1.53 g was obtained. From the weight of benzyl thioureyl bromide, the yield of benzyl bromide was estimated to be 1.06 g (62%).

Similarlly, various esters were obtained by the reaction of thiolesters and *N*-bromosuccinimide and alcohols. The results are listed in Table 1. All the esters were identified by the direct comparison of their IR spectra with those of corresponding authentic samples.

The Oxidation of *S*-Ethyl Thiobenzoate with *N*-Bromosuccinimide and Isopropyl Alcohol, and Reaction of Benzoyl Ethyl Sulfoxide, produced by the Oxidation, with Butyl Alcohol. Into a mixture of *S*-ethyl thiobenzoate (1.66 g, 0.01 mol) and *N*-bromosuccinimide (1.78 g, 0.01 mol) in carbon tetrachloride (10 m*l*), a solution of isopropyl alcohol (0.60 g, 0.01 mol) in carbon tetrachloride (10 m*l*) was added drop by drop under ice-cooling. After stirring for 2 hr, butyl alcohol (0.74 g, 0.01 mol) was added to the reaction mixture. The reaction mixture was stirred for 30 min. The succinimide, which precipitated, was filtered and was washed with carbon tetrachloride, 0.87 g (88%), mp 124—125°C. After removal of solvent, distillation under reduced pressure gave diethyl disulfide, (40—55°C/20 mmHg), 0.21 g (68%), *S*-ethyl thioethyl sulfonate, (90—100°C/20 mmHg), 0.25 g (65%) and butyl benzoate, (126—128°C/20 mmHg), 1.65 g (93%). Diethyl disulfide and butyl benzoate were identified by direct comparison of their IR spectra with those of corresponding authentic sample.

By a similar procedure, various esters were obtained by the reaction of benzoyl ethyl sulfoxide, produced by the reaction of *S*-ethyl thiobenzoate and *N*-bromosuccinimide and isopropyl alcohol, with various alcohols. The results are listed in Table 2. Butyl benzoate and benzyl benzoate were identified by direct comparison of their IR spectra with those of the authentic samples. The elemental analyses of octyl benzoate and cyclohexyl benzoate are as follows;

Found: C, 76.59; H, 9.43%. Calcd for $C_{15}H_{22}O_2$: ($C_6H_5CO_2n\text{-}C_8H_{17}$): C, 76.88; H, 9.46%.

Found: C, 76.34; H, 8.14%. Calcd for $C_{15}H_{16}O_2$ ($C_6H_5CO_2C_6H_{11}$): C, 76.44; H, 7.90%.

Reaction of Benzoyl Ethyl Sulfoxide with Sodium Benzoate. Sodium benzoate (1.44 g, 0.01 mol) was added to the carbon tetrachloride solution of benzoyl ethyl sulfoxide produced by the above mentioned procedure. After stirring for 30 min, white precipitates were collected. The solution was concentrated and distillation under reduced pressure gave benzoic anhydride (bp 140—142°C/1 mmHg) 1.46 g (65%).

Reaction of Benzoyl Ethyl Sulfoxide with Aniline. Similarly, *S*-ethyl thiobenzoate (1.66 g, 0.01 mol), *N*-bromosuccinimide (1.78 g, 0.01 mol) and isopropyl alcohol (0.60 g, 0.01 mol) were allowed to react under ice cooling. After removal of precipitated succinimide (0.70 g, 71% yield), excess amount of aniline (1.86 g, 0.02 mol) was added to the filtrate and a vigorous reaction took place in a short time. The reaction mixture was concentrated and the residue was washed with water and recrystallization from alcohol gave benzanilide, 1.38 g (70%), mp 162°C.

The Oxidation of *S*-Ethyl Thiobutyrate with Iodosobenzene and Reaction of Butyryl Ethyl Sulfoxide with Ethyl Alcohol. A mixture of *S*-ethyl thiobutyrate (1.32 g, 0.01 mol) and iodosobenzene (2.20 g, 0.01 mol) was refluxed in chloroform for 45 min. Ethyl alcohol (0.46 g, 0.01 mol) was added to the reaction mixture at room temperature. Distillation gave ethyl butyrate (bp 112—116°C/760 mmHg), 0.81 g (72%) and iodobenzene (bp 89—92°C/28 mmHg), 1.92 g (94%).

By a similar procedure, various esters were obtained by the reaction of butyryl ethyl sulfoxide, produced from thiolesters and iodosobenzene, with alcohols. Results are listed in Table 3.