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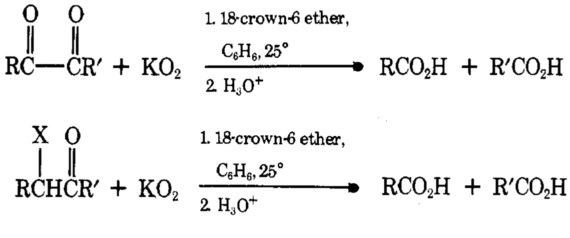
Oxidative Cleavage of α-Keto, α-Hydroxy, and α-Halo Ketones, Esters, and Carboxylic Acids by Superoxide[1]

Summary: The reaction of α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids with potassium superoxide in benzene in the presence of 18-crown-6 ether results in the oxidative cleavage of these compounds to carboxylic acids in a reaction which, in several respects, is reminiscent of the behavior of certain dioxygenases.

Sir: In previous reports we have demonstrated that superoxide is a potent and synthetically useful oxygen nucleophile.[2,3] This communication describes the results of our continuing investigation of the reactivity of this reagent and in particular its reactions with α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids. These studies reveal that such substrates undergo facile oxidative cleavage to produce the respective carboxylic acids in fair to excellent yields. A summary of the results obtained on treatment of various representative substrates is given in Table I.



$$\overset{O}{\overset{\|}{RC}}-\overset{O}{\overset{\|}{C}}R' + KO_2 \xrightarrow[2.\ H_3O^+]{1.\ 18\text{-crown-6 ether},\ C_6H_6,\ 25°} RCO_2H + R'CO_2H$$

$$R\overset{X}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}R' + KO_2 \xrightarrow[2.\ H_3O^+]{1.\ 18\text{-crown-6 ether},\ C_6H_6,\ 25°} RCO_2H + R'CO_2H$$

R′ = OH, OR, alkyl, aryl; X = OH, Cl, Br

The following description is typical of the experimental procedures employed in the reaction of potassium superoxide[4] with α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids. *dl*-Camphoroquinone (0.831 g, 5.00 mmol) was added to a mixture of 18-crown-6 ether[5] (0.528 g, 2.00 mmol) and powdered potassium superoxide (1.42 g, 20.0 mmol) in dry benzene.[6] The resulting mixture was vigorously stirred for 12 h, then cautiously poured into 20 ml of water. The aqueous layer was separated and acidified with 3 M HCl and subsequently extracted with three 40-ml portions of ethyl ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The residual white solid was recrystallized from aqueous ethanol to give 0.87 g (87%) of *dl*-camphoric acid, mp 205–206° (lit.[7] mp 208°).

Certain aspects of this reaction deserve brief comment. First, the results shown in Table I indicate that the oxidative cleavage of α-substituted ketones, esters, and carboxyl-

Table I. Reactions of Potassium Superoxide with Various α-Keto, α-Hydroxy, and α-Halo Ketones, Esters, and Carboxylic Acids

Substrate	mM of KO_2/mM of substrate[a]	Product[b]	Yield,[c] %
Benzil	3/1	Benzoic acid	87
Camphoroquinone	4/1	Camphoric acid	87
1,2-Cyclohexadione	4/1	Adipic acid	53
2-Ketoglutaric acid	4/1	Succinic acid	42[d]
2-Ketophenylacetic acid	4/1	Benzoic acid	93
Ethyl 2-ketophenylacetate[e]	4/1	Benzoic acid	93
Benzoin	3/1	Benzoic acid	98
2-Hydroxycyclohexanone	4/1	Adipic acid	69
Mandelic acid	4/1	Benzoic acid	94 (81)[f]
2-Hydroxystearic acid	12/1	Heptadecanoic acid	77
1-Hydroxycycloheptanecarboxylic acid	4/1	1-Hydroxycycloheptanecarboxylic acid	[g]
1-Cyclohexylmandelic acid	4/1	1-Cyclohexylmandelic acid	[g]
Ethyl Mandelate	4/1	Benzoic acid	93
2-Chlorocyclohexanone	4/1	Adipic acid	60
2-Chlorocyclooctanone	4/1	Octanedioic acid	62
3-Bromocamphor	4/1	Camphoric acid	54
Phenacyl chloride	4/1	Benzoic acid	72
2-Bromo-2-phenyl-acetic acid	4/1	Benzoic acid	90
2-Bromooctanoic acid	4/1	Heptanoic acid	58[h]
Methyl 2-bromo-2-cyclohexane acetate	4/1	Cyclohexanecarboxylic acid	54[h]

[a] Unless otherwise indicated, all reactions were carried out for 24 h using a 1:10 ratio of 18-crown-6 to KO_2. Understandably, reaction times were noticeably shorter at higher ratios. [b] Products were characterized by comparison of spectral data. Solids were further characterized by their melting points and liquids by their GLC retention times. [c] Unless otherwise indicated, reported values refer to isolated, recrystallized product yields, based on substrate. [d] Because of its solubility characteristics, considerable difficulty was experienced in isolating this material from the crude reaction mixture. Control experiments suggest that the values given represent minimal isolated yields. Conversion yields generally ranged from 20 to 30% higher. [e] For a discussion of the cleavage of esters by superoxide, see ref 2b. [f] Carried out in dry DMSO. [g] A nearly quantitative recovery of starting material was obtained in this instance. [h] Determined by GLC analysis.

ic acids by superoxide seems applicable to a spectrum of substrates, including not only α-keto and α-hydroxy carbonyl compounds but α-halo ketones, esters, and acids as well. This latter reaction, in particular, provides a convenient and unique procedure for the degradative cleavage of α-halo carbonyl compounds. Second, the fact that both 1-hydroxycycloheptanecarboxylic acid and α-cyclohexylmandelic acid can be quantitatively recovered after treatment with potassium superoxide suggests that the successful oxidative cleavage of α-hydroxy carbonyl compounds requires the presence of an α hydrogen on the hydroxy-bearing carbon. Third, the reaction of superoxide with α-keto and α-hydroxy carbonyl compounds resembles, in several respects, the behavior of certain dioxygenases. Specifically, the oxidative cleavage of α-keto carboxylic acids is reminiscent of the reaction of those enzymes which use α-ketoglutarate as a cosubstrate.[8] This oxygenase catalyzes the overall reaction

$$S + O_2 + HO_2CCH_2CH_2C(O)CO_2H \xrightarrow{\text{enzyme}} SO + HO_2CCH_2CH_2CO_2H + CO_2$$

where one atom of oxygen is introduced into the substrate (S) and another into the resulting succinic acid. Typical substrates oxidized by such enzymes are alkane derivatives such as proline peptides, betaines, and the methyl group of thiamine. Hamilton[9] has proposed that these reactions proceed through the intermediacy of persuccinic acid formed by the oxidative decarboxylation of α-ketoglutaric acid. The attractiveness of this proposal is enhanced by the fact that peracids are putative intermediates resulting from the demonstrated reaction of superoxide with carboxylic esters.[2b] What relevancy, if any, these observations have to the mechanism of dioxygenase action in these instances remain uncorroborated and is currently under further investigation. However, the possibility that superoxide, either free or coordinated, is involved in these processes is made more reasonable by the fact that these oxygenases are Fe(II)-containing enzymes whose reaction with molecular oxygen provides a plausible means for the biosynthesis of the requisite superoxide.

Aside from their synthetic utility[10] and their possible relevancy to the mechanisms of oxidation by certain dioxygenase enzymes, the results reported here may offer some insight into the role of superoxide in biological disorders. Further observations related to the scope and mechanism(s) of these reactions will be presented in future papers.

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(10) The principal reagents used for the selective cleavage of α-keto and α-hydroxy carbonyl compounds are periodic acid and lead tetraacetate. Unlike lead tetraacetate, periodic acid requires an aqueous solvent media; however, lead tetraacetate has the disadvantage that the side reactions which frequently accompany the use of this reagent can sometimes become the dominant reaction pathway. The oxidative cleavage of α-halo carbonyl compounds has not been reported for either of these reagents. For a discussion and comparison of the relative merits of both periodic acid and lead tetraacetate in oxidative cleavage reactions, see H. O. House in "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1971, Chapter 7.

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Synthesis of Unsymmetrical Conjugated Diynes via the Reaction of Lithium Dialkynyldialkylborates with Iodine

Summary: Unsymmetrical conjugated diynes may be prepared in satisfactory yield by the reaction of iodine in tetrahydrofuran with lithium dialkynyldisiamylborates, $Li^+[Sia_2BC\equiv CR(C\equiv CR')]$; a convenient, essentially one-pot procedure for the preparation of unsymmetrical conjugated diynes from commercially available borane–methyl sulfide and acetylenes is presented.

Sir: Treatment of lithium 1-alkynyltrialkylborates and lithium ethynyltrialkylborates with iodine under very mild conditions produces the corresponding acetylenes in essentially quantitative yields (eq 1).[1,2] More recently, it has been reported that symmetrical diynes and enynes may be prepared in excellent yield from lithium dialkynyldialkylborates (eq 2)[3] or lithium alkynylalkenyldialkylborates (eq 3),[4] respectively.

$$Li^+[R_3BC\equiv CR']^- \xrightarrow[\text{THF, }-78°]{I_2} RC\equiv CR' \qquad (1)$$

$$Li^+[R_2B(C\equiv CR')_2]^- \xrightarrow[\text{THF, }-78°]{I_2} R'C\equiv CC\equiv CR' \qquad (2)$$

$$Li^+[R_2B(C\equiv CR')(CH\!=\!CHR'')]^- \xrightarrow[\text{THF, }-78°]{I_2} R'C\equiv CCH\!=\!CHR'' \qquad (3)$$

Investigations in our laboratory into the synthesis and reactions of alkynyldialkylboranes have led to the development of a convenient, general, and quantitative method for the synthesis of base-free alkynyldialkylboranes from methyl dialkylborinates. Treatment of the 1-alkynyldisiamylboranes with lithium alkynes produces cleanly the corresponding lithium dialkynyldisiamylborates. This procedure, in contrast to the earlier one,[3] makes possible the synthesis of lithium dialkynyldisiamylborates containing two different alkynyl groups. Treatment of this "ate" complex with iodine gives the corresponding diyne, symmetrical or unsymmetrical as desired, in excellent yield (eq 4).

$$Sia_2BC\equiv CR + LiC\equiv CR' \xrightarrow[-78°]{\text{THF}} Li^+[Sia_2B(C\equiv CR)(C\equiv CR')]^-$$