Tetrahedron Letters No. 37, pp 3183 - 3186, 1975. Pergamon Press. Printed in Great Britain.

SUPEROXIDE ION AS A SYNTHETICALLY USEFUL OXYGEN NUCLEOPHILE

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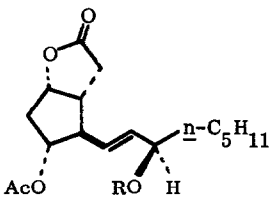
(Received in USA 10 June 1975; received in UK for publication 22 July 1975)

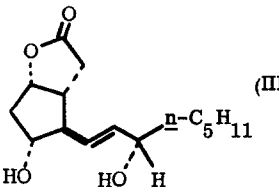
For a number of years we have been interested in the development of reagents for the S_N2 delivery of nucleophilic oxygen which are superior to conventional reactants such as OH^- and $RCOO^-$. One of the more crucial stimuli for studies in this area was the finding that existing methodology did not allow the realization of a very important synthetic objective in the prostaglandin field, namely the efficient conversion of 15-R (unnatural) prostaglandins to the 15-S (natural) isomers by nucleophilic displacement.

The use of the inexpensive, commercially available potassium superoxide (KO_2) as a nucleophilic reagent is sharply limited by its instability in hydroxylic solvents and its insolubility in aprotic solvents. Recently, it has been observed that KO_2 is appreciably soluble in dimethyl sulfoxide (DMSO)[1,2] and also that the solubility can be increased considerably in the presence of stoichiometric amounts of "dicyclohexyl-18-crown-6".[3] We have found that the readily available polyether 18-crown-6[4] is a superior agent for dissolving KO_2 in organic solvents, allowing the preparation of highly reactive solutions of superoxide not only in DMSO but also in dimethylformamide (DMF), dimethoxyethane (DME), and even in diethyl ether. Further, reactions of organic substrates with KO_2 can proceed satisfactorily in DMSO without added crown ether or with relatively small amounts of 18-crown-6. In solution KO_2 is an exceedingly reactive and effective oxygen nucleophile. The occurrence of nucleophilic displacement could readily be demonstrated with a variety of simple substrates. Interestingly, the products from displacement with halides were the corresponding alcohols, not hydroperoxides. For example, the following bromides were converted cleanly to the corresponding primary alcohols by KO_2 (4 equiv) and 18-crown-6 (2 equiv): (1) 1-decyl (DMSO, 25°, 2 hr, 80% yield[5]); (2) geranyl (DMSO--DMF, 1:1, 0°, 0.5 hr, 70%); (3) benzyl (DMSO--DMF, 1:1, 0°, 0.5 hr, 75%). Approximately 4 equiv of KO_2 were needed for complete reaction. A catalytic amount (ca. 0.1 equiv) of 18-crown-6 was sufficient, although larger amounts were usually employed in order to obtain more rapid reaction.

The conversion of a 15-R-prostanoid structure (I) to the 15-S-prostanoid system (III) was accomplished as follows. Reaction of the acetoxy alcohol I[6,7] ($[\alpha]^{25}D$ -33.5°, c = 1 in $CHCl_3$) with 1.2 equiv of methanesulfonyl chloride and 1.2 equiv of triethylamine in methylene chloride at -20° for 1 hr afforded the highly reactive mesylate II which was isolated and treated directly (without purification) with 4 equiv of



(I, R = H)
(II, R = SO_2CH_3)



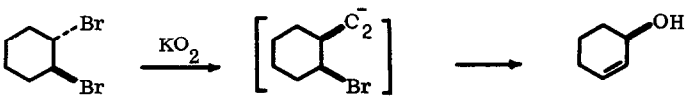
(III)

KO_2 and 4.5 equiv of 18-crown-6 in DMSO--DMF--DME (1 :1 :1) at 0° for 20 min. The crude product, obtained by addition of water and extraction, was treated with triphenylphosphine in ether (to reduce a small amount of 15-hydroperoxide which accompanied the desired inverted alcohol), then with ethyl chloroformate and lithium hydroxide in 1 :1 H_2O--DME (0°, 2 hr) (to relactonize any hydroxy acid formed by lactone hydrolysis--vide infra), and finally with potassium carbonate (1.0 equiv) in methanol at 25° for 30 min to afford in ca. 75% yield the desired 15-S-dihydroxy lactone III as an oil, $[\alpha]^{25}D$ -7.48° (c = 2.1 in $CHCl_3$), after chromatography.[8] Many attempts to accomplish such an inversion using derivatives of I such as II or the corresponding trichloroacetate with nucleophiles such as $R_4N^+ R'CO_2^-$ in a variety of solvents had been made previously in this laboratory without success.[9]

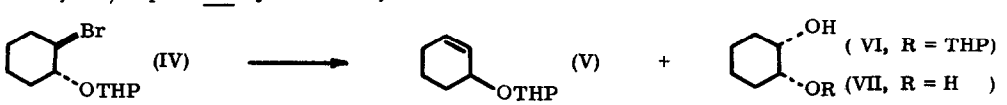
The p-toluenesulfonate of trans-4-t-butylcyclohexanol was converted into pure cis-4-t-butylcyclohexanol in 95% yield by reaction with KO_2 (4 equiv) in the presence of 18-crown-6 (4 equiv) in DMSO--DME (1 :1) at 25° for 4 hr, and similarly, the methanesulfonate of cis-4-t-butylcyclohexanol was transformed into pure trans-4-t-butylcyclohexanol in 96% yield.

The p-toluenesulfonate of cholesterol[10] was converted to 3-epi-cholesterol,[11,12] mp 140-141°, in 56% yield by 4 equiv of KO_2 and 3 equiv of 18-crown-6 in DMSO--DME (1 :1) at 25° in 4 hr. No cholesterol or 6-hydroxy-3,5-cyclocholestane were observed in the reaction product, although some cholestadiene was formed by concurrent elimination. The absence of 3,5-cyclo steroid alcohols is noteworthy.[13]

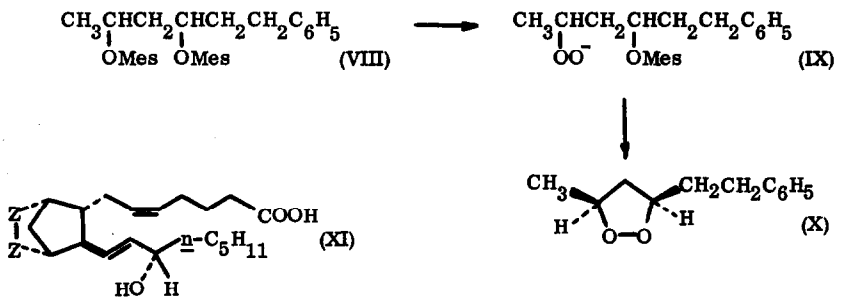
Elimination can be an important pathway of reaction with the KO_2 reagent in certain cases. Thus, trans-1,2-dibromocyclohexane reacts with 8 equiv of KO_2 in the presence of 18-crown-6 in ether at 25° to form 2-cyclohexenol in quantitative yield:



This remarkable and potentially valuable reaction probably proceeds by way of displacement to form cis-2-bromoperoxide and subsequent elimination. t-Butyl bromide reacts with KO_2 to give simultaneously the products from displacement (t-BuOH) and elimination (isobutylene). Similarly the bromo ether IV affords a mixture of V (67%) and VI (29%). The stereochemistry of VI was verified by hydrolysis (aqueous methanolic HCl, 25°) to pure cis-cyclohexan-1,2-diol.



The reaction of KO_2 with the dimesylate VIII[14] was studied in the hope that superoxide displacement and subsequent electron transfer would generate a peroxy mesylate (e.g., IX) which could cyclize to the peroxide X. Such a process could be of value in the synthesis of the biologically important prostaglandin endoperoxides such as PGH_2 (XI, Z-Z = O-O).[15] In fact, treatment of VIII with KO_2 (4 equiv) and 18-crown-6 (5 equiv) in dimethyl sulfoxide at 25° for 3 min afforded the desired cyclic peroxide X[16] in ca. 35% yield. The use of KO_2 for the synthesis of PGH_2 is now under study using the requisite 9β,11β-dimesyloxy prostanoic acid, which has previously been prepared in these laboratories and utilized for the synthesis of the biologically potent PGH_2 mimic XI, Z-Z = N=N.[17]



One especially interesting mechanistic point concerns the formation of alkoxide or alcohol from hydroperoxide, the intermediacy of which could reasonably be expected according to the scheme: $RHal + K^+O_2^{-\bullet} \longrightarrow ROO\bullet + K^+Hal^- \xrightarrow{O_2^{-\bullet}} ROO^- + O_2$. It is noteworthy in this regard that potassium t-butylhydroperoxide is converted to potassium t-butoxide under the conditions used in the KO_2 displacements described above.[18-20]

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2. A. U. Khan, Science, 168, 476 (1970).
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4. See G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, J. Org. Chem., 39, 2445 (1974); also available from Aldrich Chemical Co.
5. All yields refer to isolated pure product; yields determined analytically were substantially higher.
6. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, J. Amer. Chem. Soc., 92, 397 (1970).
7. This and the following reactions were carried out with rigorous exclusion of moisture (dry argon atmosphere).

8. Variable but small amounts (10% or less) of the 15-R-diastereomer of III were also obtained. The identity of III with authentic material[6] was confirmed by spectroscopic and chromatographic comparison.

9. Unpublished work of Drs. W. Huber, T. K. Schaaf, and S. Terashima (1969-1972). Under all conditions used a complex mixture of products (elimination, allylic rearrangement, inversion and retention of configuration) resulted.

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11. L. Ruzicka and M. W. Goldberg, Helv. Chim. Acta, 19, 1407 (1936).

12. An authentic sample was prepared stereospecifically and in high yield by reduction of Δ^5-cholesten-3-one (from Jones oxidation of cholesterol) using lithium tri-s-butylborohydride in ether at -78°; cf., Y. Houminer, J. Org. Chem., 40, 1361 (1975).

13. See R. Aneja, A. P. Davies, and J. A. Knaggs, Tetrahedron Lett., 1033 (1975), for a typical result using conventional methods.

14. P. M. Jacobs and A. H. Soloway, J. Org. Chem., 39, 3427 (1974). A mixture of the 2 diastereomeric mesylates (ratio 3 : 2 with that corresponding to the less polar diol predominating) was used.

15. See M. Hamberg, J. Svensson, and B. Samuelsson, Proc. Nat. Acad. Sci. U. S. A., 71, 3824 (1974).

16. The cis structure X is assigned to the cyclic peroxide, since reduction by stannous chloride in ethanol affords only one of the diastereomeric forms of 6-phenylhexan-2, 4-diol, the less polar isomer, and that which reacts more rapidly with acetone to form a ketal than does the other diol.

17. E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. Samuelsson, Proc. Nat. Acad. Sci. U. S. A., in press.

18. For a brief summary of the literature on the formation of alkoxides from alkyl hydroperoxide anions, see "Organic Peroxides," D. Swern, ed., Wiley-Interscience, New York, Vol II, p 77.

19. Interesting new reactions of dissolved KO_2 other than substitution and elimination processes described herein have been observed and will be reported in due course. These include, for example, ester or lactone → acid, ketone → α-diketone. See also A. LeBerre and Y. Berguer, Bull. Soc. Chim. France, 2363, 2368 (1966).

20. This study was assisted financially by a grant from the National Science Foundation.