Catalytic Epoxidation of Alkenes with Hexafluoroacetone/Hydrogen Peroxide: 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane

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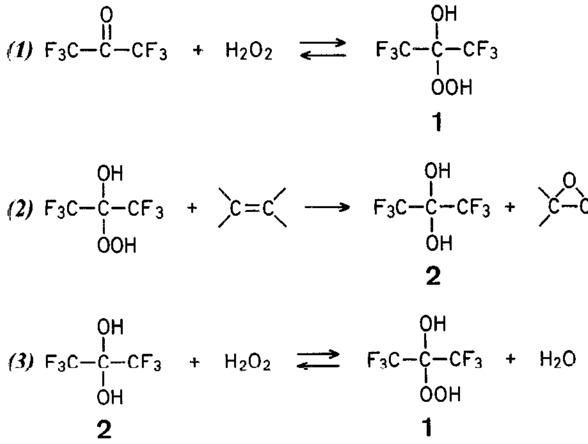
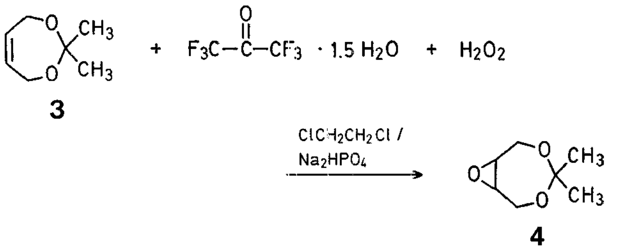
The combination of anhydrous hexafluoroacetone with hydrogen peroxide produces 2-hydroperoxyhexafluoro-2-propanol (**1**), a useful reagent for the epoxidation of alkenes[2], the conversion of aldehydes to carboxylic acids[3], and the oxidation of amines and sulfides to their corresponding oxides[4]. We now report experimental details of a catalytic epoxidation process which provides an attractive alternative to large-scale operations with expensive oxidants such as *m*-chloroperoxybenzoic acid. The by-product of oxidation with **1**, hexafluoroacetone hydrate (**2**), readily undergoes exchange with 90% hydrogen peroxide at the reflux temperature of 1,2-dichloroethane and thereby implements a simple catalytic cycle.

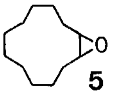


The oxidation is performed in the presence of disodium hydrogen phosphate which serves a dual role both as a buffer against the acidic hydrate **2** (pK_A 6.76)[5] and as a dehydrating agent to drive the equilibrium in equation *(3)* above.

The title epoxide **4** is acid-labile and has been prepared previously from dioxepin **3** using *m*-chloroperoxybenzoic acid[6]. It represents a key starting material in many synthetic approaches to the macrocyclic antitumor agent maytansine[6,7,8].



Other alkenes which are successfully epoxidized by this procedure include cyclododecene (to give **5**) and 1-dodecene (to give **6**).



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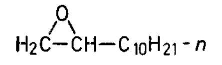

$H_2C(-O-)CH-C_{10}H_{21}$-*n*

6

4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (4):

A 500 ml, 3-necked, round-bottomed flask is equipped with a 1 m Graham condenser, overhead mechanical stirrer, and a jointed, 2-way stopcock. All joints are lightly greased. A Dry Ice condenser is mounted on top of the Graham condenser and positive pressure is maintained during the course of the reaction by the use of two nitrogen-filled balloons attached by a Claisen tube to the outlet of the Dry Ice condenser. The temperature of the condenser water is lowered by passing it through a 10 foot copper coil immersed in a bucket of ice. The flask is charged with 2,2-dimethyl-4,7-dihydro-1,3-dioxepin[6] (**3**; 25.6 g, 0.20 mol), 1,2-dichloroethane (100 ml), finely ground, anhydrous disodium hydrogen phosphate [14.2 g, 0.10 mol; from Mallinckrodt; the solid must be ground in a mortar and then dried for 12 h in a vacuum oven (140 °C/0.2 torr) before use; otherwise, considerable clumping is observed which obstructs efficient stirring and results in lowered yields], and hexafluoroacetone sesquihydrate (1.93 g, 0.010 mol). [When using the sesquihydrate obtained from Aldrich, we observe considerable variation in the yield of epoxide depending on the batch of catalyst employed. More reproducible and reliable results are obtained with sesquihydrate which is freshly made from anhydrous hexafluoroacetone. Alternatively, we find it equally convenient to introduce the catalyst directly in its active form, 2-hydroperoxyhexafluoro-2-propanol (**1**), prepared from the reaction[2] of anhydrous hexafluoroacetone with 90% hydrogen peroxide in 1,2-dichloroethane.] The condenser is filled with a Dry Ice/2-propanol slurry [use of a water-cooled condenser is insufficient since it permits free hexafluoroacetone to escape during the catalyst turnover] and the heterogeneous reaction mixture is brought to reflux with vigorous stirring. A 5 ml glass syringe fitted with a flexible 6 cm Teflon needle is used to add dropwise 90% hydrogen peroxide (11.0 ml, 0.405 mol) through the two-way stopcock which is immediately closed after the addition and fitted with a septum seal.

The progress of the reaction is monitored by removing aliquots with a syringe through the stopcock for G.L.C. analysis (conditions: 6 ft column of 10% SE-30 on 60/80 mesh acid-washed Chromosorb W at 90 °C). After 8 h of reflux, the epoxidation is ~80% complete. No more Dry Ice is added to the condenser and the reac-

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tion is allowed to continue overnight (~24 h total). The reaction mixture is allowed to cool to room temperature and the liquid is decanted into a 250 ml flask. The solid buffer is pulverized in a mortar and washed with dichloromethane (2 × 25 ml). The organic layers are combined and dried with anhydrous potassium carbonate. At this time, a negative peroxide test (acidified starch / potassium iodide paper) of the organic layer is obtained. After filtration, the solvent is removed by distillation at atmospheric pressure through a 9 cm Vigreaux column. Vacuum distillation of the residue (considerable product decomposition is observed if the oil bath temperature is permitted to exceed 110 °C) gives a forerun of unreacted alkene; yield: 0.4 g; b.p. 50–60 °C/0.2 torr, followed by the product; yield: 23.9 g (83%); b.p. 60–62 °C/2 torr.

13-Oxabicyclo[10.1.0]tridecane (5):
Prepared similarly from cyclododecene (1.66 g, 0.01 mol); yield: 1.67 g (92%); b.p. 80–85 °C/1 torr.

1-*n*-Decyloxirane (6):
Prepared similarly from 1-dodecene (1.68 g, 0.01 mol); yield: 1.58 g (94%); b.p. 105 °C/1 torr.

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