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Fluoride-promoted Epoxidation of α,β-Unsaturated Compounds[#]

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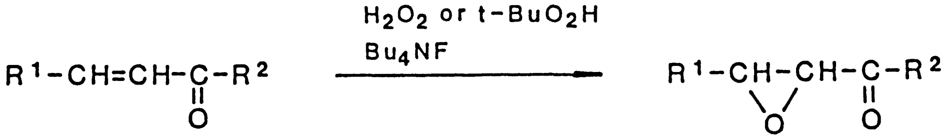
The epoxidation of α,β-unsaturated compounds using tetrabutylammonium fluoride is described. This method has been demonstrated to be directly applicable to base-sensitive substrates such as cinnamaldehyde and α-phenylcinnamonitrile.

The epoxidation of unsaturated carbonyl compounds and congeners with alkaline hydrogen peroxide[1)] or t-butyl hydroperoxide[2)] is one of the most important oxidation reactions in organic synthesis and has provided potentially useful synthetic intermediates suitable for the elaboration of complex organic molecules. One serious drawback to available methods is, however, that they are not applicable to base-sensitive substrates such as acrolein and cinnamaldehyde unless the pH of reaction media is strictly controlled at 8-8.5.[3)]

We have explored the epoxidation reaction without employing a strong base and pH control and now wish to report a new method using tetrabutylammonium fluoride (Bu_4NF). It is well-known that fluoride ion acts as a base under aprotic conditions[4)] and effects the conjugate addition of carbon nucleophiles[5)] or thiols[6)] to unsaturated compounds. We considered that fluoride ion should promote the conjugate addition of hydroperoxides to polarized carbon-carbon double bonds and this assumption was readily proven valid by experiment.



$$R^1\text{-CH=CH-}\underset{\overset{\|}{O}}{C}\text{-}R^2 \xrightarrow[Bu_4NF]{H_2O_2 \text{ or } t\text{-}BuO_2H} R^1\text{-}\underset{\diagdown O \diagup}{\text{CH-CH}}\text{-}\underset{\overset{\|}{O}}{C}\text{-}R^2$$

Thus when carvone (**1**) was treated with 30% hydrogen peroxide (1.5 equiv.) and Bu_4NF (1 equiv.) in dimethyl sulfoxide (DMSO) at room temperature for 6 h, the desired epoxide **2** was obtained in 82% yield (Table 1, entry 3). Some common fluorides (KF, CsF, and Bu_4NF) were examined to optimize the yield, and Bu_4NF was found to be best.[7)] In addition, the stoichiometric amount of the fluoride was required for completion. On the other hand, the use of t-butyl hydroperoxide as an oxidant gave a similar result (entry 3).

To illustrate the potential of this method, a number of reactions with a

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[#] Dedicated to Professor T. Mukaiyama on the occasion of his 60th birthday.

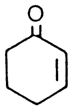
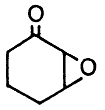
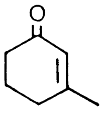
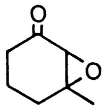
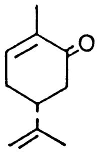
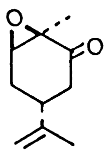
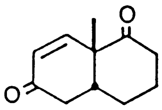
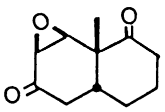
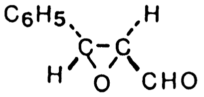
variety of unsaturated compounds were examined and the corresponding epoxides were obtained in good yields (Table 1). Table 1 demonstrates that hydrogen peroxide is superior to t-butyl hydroperoxide for the epoxidation of α,β-unsaturated ketones (entries 1-4, 6, and 7).

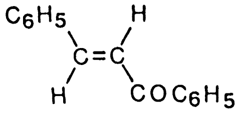
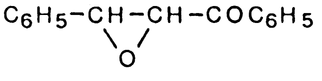
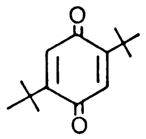
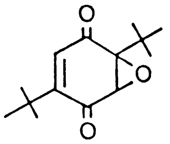
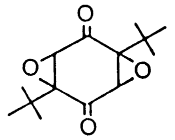
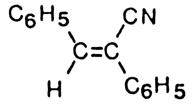
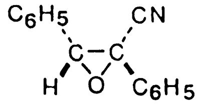
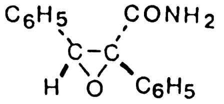
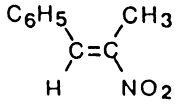
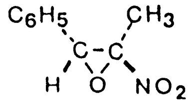
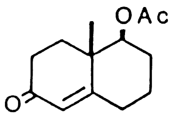
The major advantage of the present method lies in its direct application to highly sensitive substrates e.g. cinnamaldehyde[3b,3c] and α-phenylcinnamonitrile[8] (entries 5 and 8). Another important feature of the present method is that the epoxidation product of the unsaturated nitrile was changed depending upon an oxidant employed, i.e. this compound was efficiently epoxidized with t-butyl hydroperoxide to the corresponding epoxy nitrile, while the use of hydrogen peroxide gave epoxy amide in excellent yield (entry 8). Both yields were much higher than those obtained with available methods.[3b,3c,8]

Of interest is the observation that trans-chalcone produced cis-epoxide by the present method besides major trans-epoxide (entry 6) since it has been shown that both cis- and trans-chalcones gave exclusively trans-epoxide upon usual alkaline epoxidation.[9] On the other hand, sterically hindered enones such as isophorone[1a] and Δ^4-3-octalone 3 were inert under the present conditions (entry 10).

In all cases, fluoride-containing by-products were not isolated due to the poor nucleophilic character of fluoride ion.[10]

Table 1. Fluoride-promoted epoxidation of α,β-unsaturated compounds in DMSO at 17 °C

Entry	Substrate	Oxidant[a] (equiv.)	Bu$_4$NF equiv.	Time	Product(s)	Yield/%
1		H P (1.5)	1	20 min		60
2		H P (2)	1	7 h		61
3	 **1**	H P (1.5) B P (1.5)	1 1	6 h 3 h	 **2**	82 75
4		H P (1.5)	1	40 min	 [b]	93[c]
5	C_6H_5-CH=CH-CHO	B P (1.3)[d]	1[e]	1.5 h		80

6		H P (1.5) B P (1.5)	1 1	1.5 h 2 h	 $C_6H_5-CH-CH-COC_6H_5$	96[f] 58[g]
7		H P (1) B P (1)	1 1	15 min 20 min		85 61
		H P (2)	2	30 min		80[h]
8		B P (1.3)	1	3 h		94
		H P (1.5)	1	1 h		96
9		H P (1.5)	1	10 min		67[i]
10	 **3**	H P (1.5)	1	25 h		--[j]

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a) H P = 30% H_2O_2, B P = t-BuO_2H (anhydrous 3 M solution in toluene).

b) The stereochemistry of the product was assigned on the oxidant approach from the convex face.

c) Reaction temperature ; 3 °C.

d) The use of H_2O_2 resulted in lower yield of the product.

e) Six portions of 0.16 equiv. of Bu_4NF (1 equiv. in total) were added dropwise at intervals of 10 min.

f) A 94:6 mixture of trans- and cis-isomers. The ratio was determined by the isolation of each isomer and its comparison with the authentic specimen.

g) A 91:9 mixture of trans- and cis-isomers.

h) A 17:83 mixture of trans- and cis-isomers. The ratio was determined by 90MHz ^1H-NMR.

i) DMF was used as solvent.

j) Starting material was recovered unchanged.

The following experimental procedure is illustrative: A solution of Bu_4NF (1 M solution in THF, 1 mmol) was added dropwise to a mixture of carvone (**1**) (150 mg, 1 mmol) and 30% H_2O_2 (1.5 mmol) in DMSO (1 mL) at room temperature under argon and the mixture was stirred at the same temperature for 6 h. Water was added and product was extracted with ethyl acetate, and the extract was washed with half-saturated brine. Removal of the solvent left a residue which was purified by silica gel chromatography to give pure carvone epoxide (**2**) (136 mg, 82%).

The application of this oxidation reaction in other systems is currently under investigation.

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References

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