

Carbanion-Induced Decompositions of β,γ -Unsaturated Peroxides Containing Electron-Deficient Double Bonds

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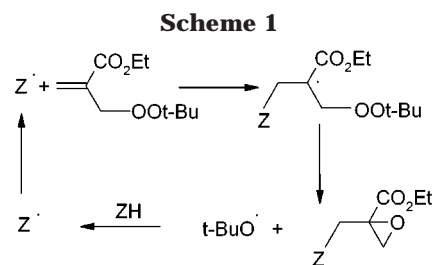
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The treatment of a β,γ -unsaturated peroxide, containing an electron-deficient double bond, by a carbanion Z^- led to the transformation of the compound by a process involving the addition of the carbanion to the double bond, followed by an S_Ni reaction on the peroxidic bond, with the liberation of an alkoxylate anion. When the carbanion was regenerated by proton abstraction from a ZH substrate by this oxyanion, the anionically induced decomposition occurred using catalytic amounts of sodium ethoxylate to initiate it. When this abstraction was not efficient, stoichiometric amounts of carbanion were necessary to decompose the unsaturated peroxide. These induced decompositions are a good source of epoxides, which were the end reaction products. However, in some cases, this heterocycle could give secondary reactions as a result of the attack of the liberated 1,1-dimethylethoxylate on it. The importance of these reactions depended upon the nature of the precursor of carbanion ZH.

Free radical chemistry, based on the induced decomposition of unsaturated peroxy derivatives, has been developed in our group.¹ In particular, the free radical decomposition of unsaturated "acrylic" peroxides was used to synthesize glycidic esters² (Scheme 1). The mechanism involves the addition of a carbon-centered radical, obtained by abstraction of a hydrogen atom from the solvent ZH by 1,1-dimethylethoxyl radicals, to the carbon-carbon double bond of the peroxide. However, this method has limitations because it requires, first, a selective hydrogen abstraction from the substrate and, second, an efficient addition of the produced radical to the unsaturation. This has been pointed out for reactions involving diethyl malonate for which a very poor selectivity of the hydrogen abstraction was observed. Two main radicals were generated in the reactions of 1,1-dimethylethoxyl or methyl radicals with the diester.³ A selective and general production of the required adding carbon centered radicals was developed by replacing ZH by ZBr or ZI and operating in the presence of tributyltin hydride or hexabutyliditin,⁴ for 1,1-dimethylethyl 2-ethoxycarbonylprop-2-enyl peroxide **1a**, or by using an "acrylic" peroxyketal of acetone.⁵ However, the existence of an efficient addition is limited to the case of nucleophilic radicals for the peroxidic derivatives containing electron-poor double bonds, as a result of the polar effects involved in these reactions.⁶ Indeed, electrophilic radicals, as for



example diethoxycarbonylmethyl, do not add significantly to such a class of unsaturations.

This situation prompted us to envisage the replacement of the free radical induced decomposition by the anionic equivalent. Indeed, considering the existence of an umpolung effect on changing from the radical (electrophilic) to the anion (nucleophilic),⁷ the results reported by Michael and other workers following his approach⁸ for the addition of carbanions to electron-poor double bonds, and the existence of a S_Ni reaction onto a peroxidic bond,⁹ we envisaged the use of the reaction depicted in Scheme 2 to complement the free radical methodology. In a preliminary communication,¹⁰ we proved the validity of this approach. This paper reports evidence of the general character of this reaction now involving carbanions instead of oxygen¹¹ or nitrogen anions¹² by the study of the influence of (i) the nature of the electron-withdrawing substituent A on the double bond in the 1,1-dimethylethyl

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Scheme 2

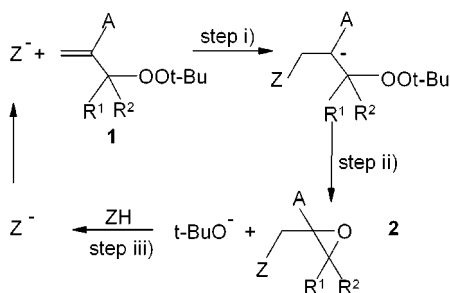


Table 1

	A	R ¹	R ²	Z	2 yield (%) ^a
a ^b	CO ₂ Et	H	H	CH(CO ₂ Et) ₂	60
b ^b	COMe	H	H	CH(CO ₂ Et) ₂	63
c ^b	CN	H	H	CH(CO ₂ Et) ₂	61
d ^b	CO ₂ Et	Me	H	CH(CO ₂ Et) ₂	58
e ^b	CO ₂ Et	Me	Me	CH(CO ₂ Et) ₂	22
f ^c	CO ₂ Et	H	H	Me ₂ CCO ₂ Me	74
g ^c	CO ₂ Et	H	H	C ₄ H ₉ CHCO ₂ Me	20
h ^c	CO ₂ Et	H	H	Me ₂ CCN	10
i ^b	CO ₂ Et	H	H	MeC(CO ₂ Et) ₂	78
j ^b	CO ₂ Et	H	H	MeC(O)CHCO ₂ Et	67
k ^b	CO ₂ Et	H	H	NCCO ₂ Et	
l ^b	CO ₂ Et	H	H	MeC(O)CHC(O)Me	

^a Relative to **1**. ^b Catalytic sodium ethoxide method. ^c Stoichiometric LDA method.

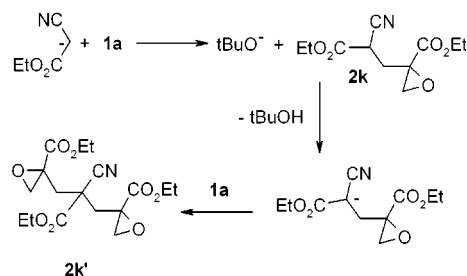
2-substituted prop-2-enyl peroxides, (ii) the presence of methyl substituents on the allylic carbon, and (iii) the nature of the attacking carbanion.

In the preliminary report,¹⁰ the anionically induced decomposition of 1,1-dimethylethyl 2-ethoxycarbonyl-prop-2-enyl peroxide **1a** (A = CO₂Et) was identified in the addition of sodium ethoxide to a tetrahydrofuran solution of **1a** and diethyl malonate to produce the epoxide **2a** in a yield of 60%. To analyze the influence of the structural characteristics of the unsaturated peroxidic derivatives several peroxides were reacted under the same conditions.

First, to test the influence of the nature of the electron-withdrawing substituent present on the double bond, two other peroxides **1b** (A = COMe) and **1c** (A = CN), previously prepared,¹¹ were treated under the same conditions. The expected epoxides **2b** and **2c** were isolated with yields of about 60%, showing that the carbanion, arising from diethyl malonate, added as efficiently to the double bonds of peroxides **1b** and **1c** as to that of **1a** (Table 1).

The anionically induced decomposition of the unsaturated peroxide **1** occurred through a three-step mechanism (Scheme 2): (i) addition of the carbanion to the double bond, (ii) intramolecular nucleophilic substitution, and (iii) regeneration of the carbanion by proton abstraction from the malonate by the 1,1-dimethylethoxy anion. The presence of substituents on the allylic carbon of the peroxide could influence steps (i) and (ii) by affecting the rates of addition of the carbanion onto the double bond of the unsaturated peroxide and of intramolecular nucleophilic substitution. This prompted us to study the treatment of peroxides **1d** and **1e** with the carbanion generated from diethyl malonate under the same conditions as for **1a**. In the standard conditions of reaction, each peroxide led to the formation of the expected epoxides **2d** and **2e** but in very different yields (Table 1), indicating that if the presence of one methyl in the

Scheme 3



allylic position does not affect significantly the reaction, a second one drastically decreases its efficiency. No peroxyepoxide was obtained from treatment of the same peroxides by peroxyates.¹¹

After the analysis of the influence of the structural parameters of the allylic peroxide, the effect of the nature of the carbanion upon the formation of epoxide was approached by the study of two families of precursors, compounds having one or two single electron withdrawing groups on the carbon bearing the proton, elimination of which generates the carbanion. The relative acidities¹³ of the 1,1-dimethylethanol, the conjugate acid of the 1,1-dimethylethoxy anion, and of the monoesters and mononitrile indicated that there was no possible regeneration of Z⁻ [absence of step (iii)]. Thus, the anion would have to be produced by the preliminary action of a stronger base such as lithium diisopropylamide (LDA) on the ester or the nitrile. This was realized for methyl 2-methylpropionate, methyl hexanoate, and 2-methylpropionitrile. The reactions led to a single product, epoxide **2f**, for the first ester with a yield of 74%, but it was totally different in the other cases, which led to numerous byproducts besides the expected epoxides, respectively **2g** and **2h**, isolated with poorer yields (Table 1).

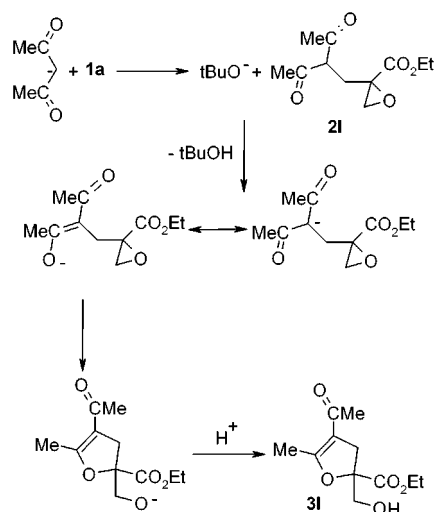
In the case of the various precursors having two electron withdrawing groups on the carbon bearing the proton to be eliminated, 1,1-dimethylethoxy anion is sufficiently basic to abstract this proton. Thus, they were reacted with peroxide **1a** under the standard conditions used for diethyl malonate. The expected epoxides **2i** and **2j** were obtained, in the reactions involving diethyl 2-methylmalonate and ethyl acetylacrylate, respectively, with fair yields (Table 1). However, the reactions performed with ethyl cyanoacetate gave a main reaction product but not the one expected from the mechanism (Scheme 2). The NMR analyses of this product indicated the formation of glycidic ester **2k'** with a yield of 66% relative to the peroxide. The formation of this compound corresponds to the alkylation of the expected epoxide **2k** via the induced decomposition of **1a** by the anion arising from **2k**. Such an observation of dialkylation of cyanoacetic derivatives has previously been mentioned.¹⁴ However, this is apparently the first case in which there is no monoalkyl derivative present in the reaction mixture. This difference could be attributed to a very fast reaction occurring in the cage between the epoxyanoester **2k** and the 1,1-dimethylethoxy anion generated at the same time (Scheme 3).

The observation of a diepoxide with ethyl cyanoacetate prompted us to investigate the possible existence of

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Scheme 4



similar reactions in the cases of diethyl malonate and of ethyl acetoacetate. The treatment of the glycidic esters obtained in these reactions, **2a** and **2j**, respectively, with the peroxide **1a** and sodium ethoxide led to the corresponding diepoxides **2a'** and **2j'** with yields of about 55%. GC analysis of the reaction mixtures obtained from the reactions of **1a** with diethyl malonate and ethyl acetylacetate also indicated the presence of the diepoxides produced in yields of 5–10%.

When acetylacetone was used as the anion precursor, the reaction product was the five-membered cyclic ether **3l**, isolated with a yield of 70%, instead of epoxide **2l**. Consideration of the existence of a possible reaction between the latter, formed in the anionic induced decomposition of **1a**, and 1,1-dimethylethoxyate led us to propose the mechanism outlined in Scheme 4 to account for the generation of the cyclic ether **3l**.

In conclusion, this research demonstrates the synthetic potential of carbanionically induced decompositions of unsaturated peroxides having electron-deficient double bonds. This process is a good complement to the free radical chain homologous reaction as a result of the existence of an umpolung effect on changing a radical (electrophilic) to the corresponding anion (nucleophilic). However, some limitations were identified when:

(i) allylic hydrogens were replaced by methyl substituents, whereupon a decrease of the efficiency of the induced decomposition was obtained;

(ii) the attacking carbanion arises from ethyl cyanoacetate, formation of the product of dialkylation occurred, or from acetylacetone, generation of a cyclic ether super-vened;

(iii) 1,1-dimethylethoxyate is not sufficiently basic to regenerate the carbanion in initiating the induced decomposition. In this case the carbanion has to be produced in the first step by the reaction of the ester or the nitrile with a stronger base, LDA. The reaction seems to be less useful because the epoxide **2** was only obtained in good yield with methyl 2-methylpropionate and in low yields with methyl hexanoate and with methylpropionitrile.

Experimental Section

Carbanions Arising from Compounds Containing *gem* Electron-Withdrawing Groups (Representative Catalytic Sodium Ethoxide Method). To a three-necked flask containing 10 mL of THF and 1 mmol of absolute ethanol was added 1 mmol of sodium hydride in small portions with stirring. After 15 min, 10 mmol of the carbanion precursor was added at 0 °C. Thirty minutes later, 10 mmol of the unsaturated peroxide (**1a**,² **1b**,¹¹ **1c**,¹¹ **1d**,² **1e**.²) was added dropwise at –10 °C, taking care that the temperature did not reach 0 °C in the course of the addition. The mixture was left for 12 h at room temperature. After evaporation of the solvent under reduced pressure and addition of 50 mL of diethyl ether, the organic phase was washed with brine and then dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the reaction product was purified by column chromatography over silica or by distillation.

The same procedure was used to prepare dialkylation products of diethyl malonate and ethyl acetylacetate, but using 5 mmol of carbanion precursor for 10 mmol of peroxide **1a**.

Carbanions Arising from Compounds Containing One Electron Withdrawing Group (Representative Stoichiometric LDA Method). To a three-necked flask containing 10 mL of THF and 5.5 mmol of diisopropylamine was added *n*-BuLi (5.5 mmol) with stirring at –78 °C. After 30 min, 10 mmol of the carbanion precursor was added dropwise to this solution. Thirty minutes later, this solution was added dropwise to a solution of 5 mmol of **1a** in 10 mL of anhydrous THF at –78 °C. Fifteen minutes after the end of the addition, the cooling bath was removed and the reaction mixture was allowed to reach room temperature. After evaporation of the solvent under reduced pressure and addition of 20 mL of diethyl ether and 5 mL of water; the organic phase was washed with brine and then dried over anhydrous magnesium sulfate. The solvent was evaporated, and the reaction product was purified by column chromatography over silica or by distillation.

Supporting Information Available: General procedure and characterization data for **2a–2h**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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