# Intramolecular homolytic displacements. Part 29:† induced decompositions of 4,5-ethylenic peroxyketals

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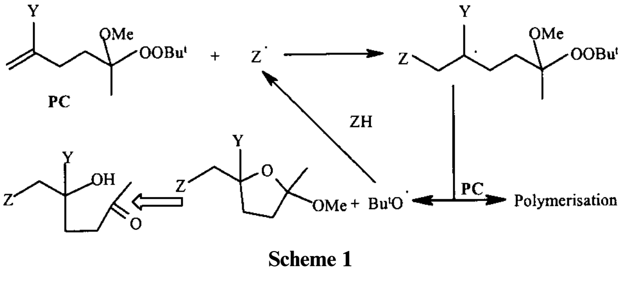
Thermolysis of a free radical initiator in solutions of hydrogen donor solvents such as cyclohexane, 1,4-dioxane and methyl isobutyrate, generated radicals by hydrogen abstraction of the solvent that were capable of adding to the unsaturated bond of 4,5-ethylenic peroxyketals. The adduct radical obtained led to 2-alkoxytetrahydrofuran by an $S_Hi$ on the O–O bond.

During the past years, we have been studying the induced decomposition of unsaturated peroxy derivatives for applications in synthesis[1,2] and in polymer chemistry.[3] In a previous paper,[4] it was shown that the nature of the reaction products, obtained in the induced decompositions of 4,5-ethylenic peroxyketals, was dependant on the unsaturation type. In particular, for the "methacrylic derivatives" the nature of the substituent Y [Y = C(O)NEt$_2$ or CO$_2$Et] plays an important role in the formation of a tetrahydrofuran or a homopolymer of the unsaturated peroxyketal. The addition of a free radical Z$^\cdot$ onto the double bond generates an adduct radical (Scheme 1) that reacts by intramolecular substitution on the O–O bond to produce the heterocycle or adds to the double bond of another molecule of peroxyketal, leading to a homopolymer of the latter. The work described in this paper completes the study of the influence of the substituent Y of the double bond of the peroxyketal **PC** upon the formation of the 2-methoxytetrahydrofuran. Indeed, such heterocycles appear as precursors of γ-hydroxyketones (Scheme 1).

## Results and discussion

### Synthesis of 4,5-ethylenic peroxyketals

If hex-5-en-2-one is commercially available, the other unsaturated ketones, precursors of the peroxyketals **PC**, could be prepared according to a method derived from that of Boatman and Hauser.[5] 2-Acetylhex-5-en-2-one was produced by the auto-condensation of methyl vinyl ketone.[6] The peroxyketals prepared are reported in Table 1.

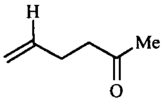
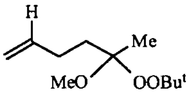
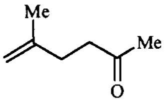
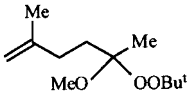
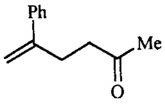
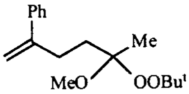
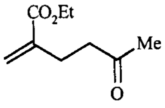
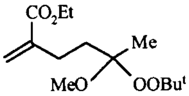
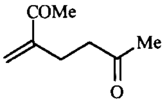
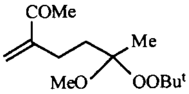
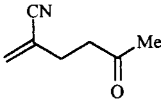
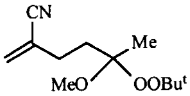
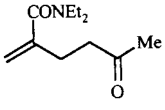
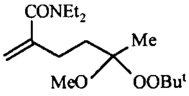


**Scheme 1**

### Thermal stability of 4,5-ethylenic peroxyketals

The objective of this work being the preparation of tetrahydrofurans *via* the induced decomposition of unsaturated peroxyketals, it appears desirable to perform this reaction under conditions in which the peroxyketals are thermally stable. Indeed, under such conditions the peroxyketal would decompose by the induced process and not by the homolysis of the O–O bond. To have a good knowledge of the stability of these peroxides, the rate constants of their homolysis were determined using DSC.[7] From these results, activation parameters were calculated and an upper limit of the percentage of

**Table 1** Peroxyketals PC

| Ketone | | Peroxyketal | Yield (%)[a] |
|---|---|---|---|
|  | **PC$_1$** |  | 40 |
|  | **PC$_2$** |  | 46 |
|  | **PC$_3$** |  | 63 |
|  | **PC$_4$** |  | 57 |
|  | **PC$_5$** |  | 52 |
|  | **PC$_6$** |  | 38 |
|  | **PC$_7$** |  | 50 |

[a] Yield of the isolated compound relative to the starting ketone.

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† For part 28 see ref. 4. Electronic supplementary information (ESI) available: full details of the syntheses and characterisation of the products. See http://www.rsc.org/suppdata/nj/a909434b/

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Table 2 Activation parameters of the homolysis of the O–O bond of unsaturated peroxyketals

| | $E_a$ [a] | ln $Z$ | ln $k_{110\,°C}$ | $\Delta G^{\neq}_{110\,°C}$ [a] | $T_{\mathrm{stardec}}$ |
|---|---|---|---|---|---|
| **$PC_1$** | 135.4 (±2.5) | 33 (±0.7) | −9.49 | 124.9 (±0.2) | 94 |
| **$PC_2$** | 137.9 (±2.5) | 33.7 (±0.7) | −9.56 | 125.2 (±0.2) | 99 |
| **$PC_3$** | 127.1 (±1.7) | 30.8 (±0.5) | −9.09 | 123.6 (±0.5) | 94 |
| **$PC_4$** | 123.3 (±2.9) | 29.5 (±0.9) | −9.19 | 124.0 (±0.2) | 103 |
| **$PC_6$** | 115.4 (±1.7) | 26.9 (±0.5) | −9.01 | 124.4 (±0.3) | 98 |
| **$PC_7$** | 121.2 (±2.9) | 28.8 (±0.8) | −9.23 | 124.1 (±0.3) | 99 |

[a] $E_a$ et $\Delta G^{\neq}$ in kJ mol$^{-1}$

peroxyketal decomposed by homolysis only could be estimated (Tables 2 and 3).

Taking into account the errors on the values of $\Delta G^{\neq}$ one can conclude that the various peroxyketals have similar stabilities. Comparison with the $\Delta G^{\neq}$ of 2-methoxy-2-(1,1-dimethylethylperoxy)hexane (124.4 kJ mol$^{-1}$)[8] shows no significant influence of the presence of the double bond in the molecule on the homolysis of the peroxidic bond of the peroxyketal. The activation parameters of the homolysis of the O–O bond of peroxyketal **$PC_5$** could not be determined from the DSC study, as a result of the occurrence of other reactions.[9] However, in order to situate its thermal stability relative to that of other peroxyketals, the temperatures of the starting decomposition, measured on the thermograms, were compared. For all these peroxyketals, values in the range 94–103 °C (Table 2) indicate similar stabilities.

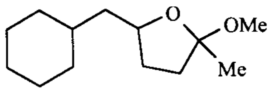
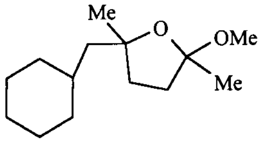
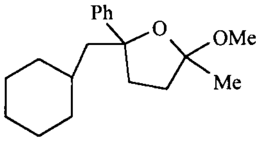
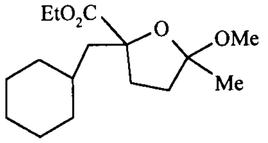
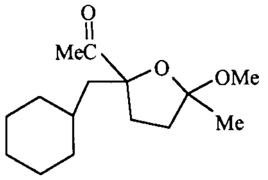
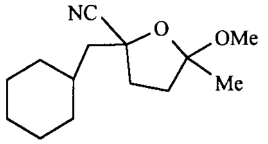
## Induced decomposition of 4,5-ethylenic peroxyketals

**Free radical addition of cyclohexane.** Taking into account the relative amounts of spontaneous decomposition at 110 °C for these compounds (Table 3) and the inefficiency of the initiation by the system triethylborane–dioxygen at room temperature, the free radical reactions were performed at 80 °C using dilauroyl peroxide as initiator, with the following molar ratios: cyclohexane–peroxyketal–peroxide = 20 : 1 : 0.2. However, under these reaction conditions peroxyketals **$PC_1$** (Y = H), **$PC_2$** (Y = Me) and **$PC_7$** (Y = CONEt$_2$) were not totally consumed. Thus the reactions were rerun at 110 °C with 1,1-dimethylethyl peracetate as initiator. Tetrahydrofurans were isolated with yields in the range of 32–50% (Table 4). Only peroxyketal **$PC_7$** did not yield a tetrahydrofuran, as mentioned previously,[4] but a homopolymer. The heterocycles issued from **$PC_1$** and **$PC_2$** were produced with modest yields. The necessity to operate at 110 °C, because of a short free radical chain reaction for the induced decomposition, was responsible for the consumption of the unsaturated peroxyketal *via* its unproductive spontaneous decomposition (Table 3). For the peroxyketals containing an activated double bond, **$PC_3$**(Y = Ph), **$PC_4$** (Y = CO$_2$Et), **$PC_5$** (Y = COMe) et **$PC_6$** (Y = CN), the yields of formation of the heterocycle were similar. As observed for the 2,3-ethylenic peroxides,[10] it is not only the rate of addition of the cyclohexyl radical to the double bond that determines the yield of the tetrahydrofuran. As shown in the analysis of the residues, such yields must be attributed to an S$_H$i reaction that is slower than the addition of the adduct radical to another molecule of peroxyketal, to produce a homopolymer of the unsaturated peroxyketal.

Table 3 Percentage of spontaneous decomposition of peroxyketals at 80 and 110 °C

| | $k_{80\,°C}$ $10^{-6}$ s$^{-1}$ | Spont. dec.$_{80\,°C}$ % | $k_{110\,°C}$ $10^{-6}$ s$^{-1}$ | Spont. dec.$_{110\,°C}$ % |
|---|---|---|---|---|
| **$PC_1$** | 2 | 8 | 75 | 96 |
| **$PC_2$** | 1.8 | 7 | 69 | 95 |
| **$PC_3$** | 3.9 | 15 | 114 | 99 |
| **$PC_4$** | 3.7 | 15 | 101 | 99 |
| **$PC_6$** | 2.9 | 12 | 81 | 97 |
| **$PC_7$** | 3.9 | 16 | 98 | 99 |

Table 4 Heterocycles produced in the free radical addition of cyclohexane to unsaturated peroxyketals

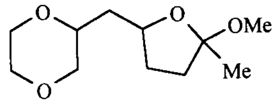
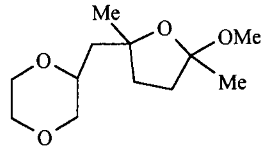
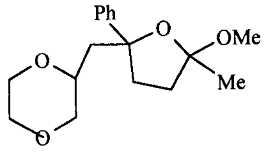
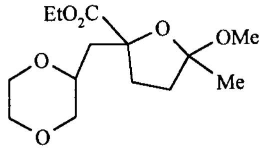
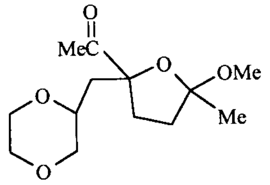
| PC | Tetrahydrofurans | | Yield (%)[a] |
|---|---|---|---|
| **$PC_1$**[b] | **$HC_1$** |  | 37 |
| **$PC_2$**[b] | **$HC_2$** |  | 32 |
| **$PC_3$**[c] | **$HC_3$** |  | 44 |
| **$PC_4$**[c] | **$HC_4$** |  | 50 |
| **$PC_5$**[c] | **$HC_5$** |  | 40 |
| **$PC_6$**[c] | **$HC_6$** |  | 44 |

[a] Isolated product yield relative to peroxyketal. [b] Reaction at 110 °C. [c] Reaction at 80 °C.

**Free radical addition of other hydrogen donor solvents.** The free radical addition of other substrates to unsaturated peroxyketals **PC** was performed in order to see if the results given with cyclohexane could be generalized. The reaction conditions were those previously used: donor solvent–peroxyketal–initiator = 20 : 1 : 0.2; initiation for **$PC_1$** and **$PC_2$** with 1,1-dimethylethyl peracetate at 110 °C and for **$PC_3$**, **$PC_4$**, **$PC_5$** and **$PC_6$** with dilauroyl peroxide at 80 °C.

The reactions performed with 1,4-dioxane yielded tetrahydrofurans with yields in the range of 27–55% (Table 5) with

**Table 5** Heterocycles produced in the free radical addition of 1,4-dioxane to unsaturated peroxyketals

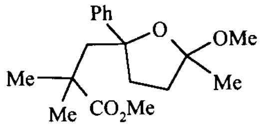
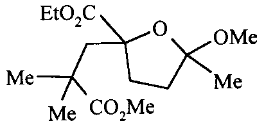
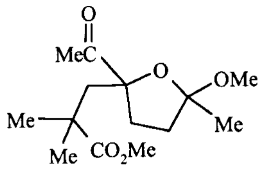
| PC | Tetrahydrofurans | | Yield (%)[a] |
|---|---|---|---|
| **PC$_1$**[b] | **HD$_1$** |  | 54 |
| **PC$_2$**[b] | **HD$_2$** |  | 27 |
| **PC$_3$**[c] | **HD$_3$** |  | 55 |
| **PC$_4$**[c] | **HD$_4$** |  | 43 |
| **PC$_5$**[c] | **HD$_5$** |  | 35 |

[a] Isolated product yield relative to peroxyketal. [b] Reaction at 110 °C. [c] Reaction at 80 °C.

the exception of **PC$_6$**. Indeed, the separation of the corresponding heterocycle from the high boiling point products (certainly oligomers of **PC$_6$**) was not possible. Except for **PC$_1$** and **PC$_3$**, one can identify a slight decrease of the tetrahydrofuran yield relative to the corresponding reaction performed with cyclohexane. In the case of **PC$_2$**, this result could, *a priori*, be attributed to the 1,4-dioxan-2-yl radical addition, which would be slower than that of the cyclohexyl radical to the double bond, according to the relative nucleophilicities of such radicals. However, concerning peroxyketals **PC$_1$** and **PC$_3$**, one cannot imagine that polar effects, occurring in the addition of the 1,4-dioxan-2-yl radical, could account for the increase in the yield of the formation of the heterocycle. Indeed, the replacement of cyclohexane by dioxane would *disfavour* the generation of the tetrahydrofuran. Concerning the peroxyketals **PC$_4$** and **PC$_5$**, a similar contradiction was identified. All these observations confirm that the free radical addition to the double bond cannot be the single reaction to be considered to account for the formation of the cyclic ether produced in the induced decomposition of unsaturated peroxy derivatives.

For the reactions performed in solutions of methyl isobutyrate, in many cases no tetrahydrofuran was formed, as for the reactions of **PC$_1$** and **PC$_2$** at 110 °C. A dimer of the radical $^{\bullet}C(Me)_2CO_2Me$ was obtained, indicating the low tendancy of this radical to add to the unsaturation of these peroxyketals. These compounds seemed to be consumed essentially *via* their spontaneous decomposition. **PC$_6$** led to a mixture of compounds with high boiling points from which it was very difficult to separate the produced tetrahydrofuran. The other peroxyketals gave the expected heterocycles with yields of 32–38% (Table 6).

**Table 6** Heterocycles produced in the free radical addition of methyl isobutyrate to unsaturated peroxyketals

| PC | Tetrahydrofurans | | Yield (%)[a] |
|---|---|---|---|
| **PC$_3$**[b] | **HB$_3$** |  | 32 |
| **PC$_4$**[b] | **HB$_4$** |  | 38 |
| **PC$_5$**[b] | **HB$_5$** |  | 33 |

[a] Isolated product yield relative to peroxyketal. [b] Reaction at 110 °C.

These results show that, considering the numerous free radical reactions in competition, it is very difficult to forecast the more efficient ones and then to estimate the efficiency of the induced decomposition of an unsaturated peroxyketal to produce tetrahydrofurans. It is important to underline that for the peroxyketals bearing an unactivated double bond, such as **PC$_1$** and **PC$_2$**, it is necessary to operate under conditions in which spontaneous decomposition occurs in order to consume totally the peroxy derivative, which makes predicting the outcome more hazardous.

## Conclusion

The decomposition of free radical initiators in a solution of a 4,5-ethylenic peroxyketal in the presence of a hydrogen donor solvent generally provokes the total consumption of this peroxy derivative. This is due to the addition of a radical produced by the solvent to the unsaturation to form an adduct radical, generating either a tetrahydrofuran by an intramolecular substitution on the O–O bond or ultimately a homopolymer of the peroxyketal by addition to another molecule of peroxyketal. If the free radical addition of a hydrogen donor solvent to a 4,5-ethylenic peroxyketal cannot be considered, under the conditions used, as a general way to synthesise 5-membered oxygenated heterocycles, it can allow, in certain cases, the easy preparation of 2-alkoxytetrahydrofurans, precursors of γ-hydroxyketones. However, an optimisation of the reaction conditions, in order to favour the $S_Hi$ at the expenses of the homopolymerisation of the unsaturated peroxyketal, would improve the process.

## Experimental

$^1H$ NMR spectra were recorded in $CDCl_3$ with $Si(CH_3)_4$ as an internal standard using Hitachi–Perkin–Elmer R24B (60 MHz) and Brucker AC 250 spectrometers; the $^{13}C$ NMR spectra were recorded on the Bruker AC250 (62.9 MHz) spectrometer. They are reported by δ values and coupling constants (*J*, Hz). Microanalysis of compounds was realised by the CNRS at Vernaison. GC studies were performed with a Varian 3400 coupled with a Spectra Physic Chromjet Integrator. The capillary column used was a DB5 (5% Ph, 30 m in length, 0.25 mm I.D. and with a stationary phase film thickness of 0.25 μm); the gas carrier was nitrogen (0.5 bar flow rate).

Thermolysis study of the peroxy derivatives was performed with a Perkin–Elmer DSC 7. Thermograms were treated following ref. 9.

Thin layer chromatography was realised using silica gel coated on plastic sheets (Schleicher and Schuell F1500/LS254, 0.25 mm) and alumina coated aluminium sheets (Merck $60F_{254}$ neutral). SDS 200–400 mesh silica gel and Aldrich 150 mesh neutral alumina gel were used for preparative chromatography.

1,1-Dimethylethyl hydroperoxide was purchased from Fluka (as a mixture with bis-1,1-dimethylethyl peroxide). Elimination under vacuum of the peroxide yielded the hydroperoxide used for the synthesis of the peroxyketals. Iodometric titration of the hydroperoxide was realised according to Silbert and Swern.[11] Other starting materials were provided by Aldrich and Acros.

### Synthesis of 4,5-unsaturated peroxyketals

The unsaturated ketones were prepared according to the method of Boatman and Hauser.[5] Ethyl 2-methylene-5-oxohexanoate and *N*,*N*-diethyl-2-methylene-5-oxohexanamide were prepared according to ref. 4 and 3-methyleneheptane-2,6-dione according to ref. 6.

Peroxyketals were prepared from the ketone without isolating the ketal according to the procedure previously described.[4]

### Thermal stability of 4,5-unsaturated peroxyketals

In order to determine the rate constants of the homolysis of the O–O bond of peroxyketals at different temperatures and, from them, the activation parameters ($E_a$ and ln $Z$) of this reaction, the thermolysis of these peroxy derivatives in a mixture of triphenylmethane–diphenylmethane was performed in a DSC 7.[7] The rate constants are presented in Tables 7 and 8 given as supplementary material.

### Induced decompositions of 4,5-unsaturated peroxyketals

A mixture of 10 mmol of peroxy derivative, 2 mmol of free radical initiator and 200 mmol of hydrogen donor solvent (cyclohexane, 1,4-dioxane or methyl isobutyrate) were heated in a pyrex tube for 12 h (lauroyl peroxide: 80 °C, 1,1-dimethylethyl peracetate:[13] 110 °C). The solvent was then removed with a rotavapor. When lauroyl peroxide was employed, pentane was added to the residue and extracted 3 times with acetonitrile. After elimination of the acetonitrile, the heterocycle was purified by chromatography on an alumina column deactivated with 6% water.

The conditions of preparation and separation of the compounds and their characterisation are given in the supplementary material.

## Acknowledgements

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