Pergamon

Tetrahedron Letters, Vol. 35, No. 22, pp. 3759-3762, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0612-2

New Free-Radical Syntheses under Gif-Barton Oxidation Conditions

Francesco Minisci,* Francesca Fontana, Silvia Araneo, Francesco Recupero

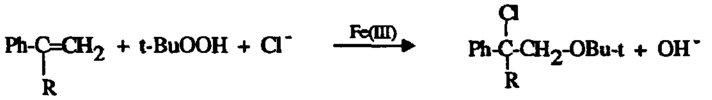
Dipartimento di Chimica del Politecnico, via Mancinelli, 7, I-20131 Milano, Italy

Abstract New free-radical syntheses were developed under Gif-Barton conditions by trapping t-BuO· radicals with electron-rich alkenes (vinyl ether, styrene, α-methylstyrene) and acetaldehyde.

Recently, the halogenation of alkenes and alkanes under Gif[1] conditions has been the subject of different interpretations. We[1] explain this halogenation by a ligand transfer from Fe(III) halides to alkyl radicals, while Barton and coworkers[2] suggest a more complex mechanism involving organo-iron (V) intermediates.

Our results[1] indicated that not only alkyl radicals, but also t-BuO· radicals were formed from t-BuOOH; this was proved by trapping methyl radicals deriving from β-scission; however, this evidence was not conclusive owing to the small amount (1% based on t-BuOOH) of the trapped methyl radical and the solvent dependence[3] of the β-scission reaction.

In the present paper we report new synthetically interesting reactions, providing strong evidence that t-BuO· radicals are reaction intermediates under Gif conditions: these electrophilic radicals are trapped by electron-rich alkenes, such as vinyl ether, styrene, α-methylstyrene. Styrene and α-methylstyrene react with t-BuOOH and Cl⁻ to give cloroethers **1** and **2** following eq.1. The results are reported in Table 1.



$$\text{Ph-}\underset{\text{R}}{\text{C}}\text{=CH}_2 + \text{t-BuOOH} + \text{Cl}^- \xrightarrow{\text{Fe(III)}} \text{Ph-}\overset{\text{Cl}}{\underset{\text{R}}{\text{C}}}\text{-CH}_2\text{-OBu-t} + \text{OH}^- \qquad (1)$$

1 R=H
2 R=Me

In the reaction with α-methylstyrene, product **2** undergoes partial dehydrochlorination under the reaction conditions, leading to alkenes *cis*- (**3**) and *trans*- (**4**) Ph-C(Me)=CH-OBu-t and Ph-C(=CH$_2$)-CH$_2$-OBu-t (**5**); similar results were obtained with Fe(II) and LiCl in aqueous acetonitrile solution. Clearly, the redox chain of eqs.2-4 occurs in both cases.

$$\text{t-BuOOH} + \text{Fe(II)} \longrightarrow \text{t-BuO}\cdot + \text{Fe(III)} + \text{OH}^- \qquad (2)$$

$$\text{t-BuO}\cdot + \text{CH}_2\text{=CH-Ph} \longrightarrow \text{t-BuO-CH}_2\text{-}\dot{\text{C}}\text{H-Ph} \qquad (3)$$

$$\text{t-BuO-CH}_2\text{-}\dot{\text{C}}\text{H-Ph} + \text{Cl-Fe(III)} \longrightarrow \text{t-BuO-CH}_2\text{-}\underset{\text{Cl}}{\text{C}}\text{H-Ph} + \text{Fe(II)} \qquad (4)$$

Under Gif conditions the chain is likely to be initiated by the relatively slow reaction of eq.5.

$$\text{t-BuOOH} + \text{Fe(III)} \longrightarrow \text{t-BuO}\cdot + \text{Fe(IV)=O} + \text{H}^+ \qquad (5)$$

Gif conditions can be even more effective than the classical Fenton chemistry (Table 1), because the very low stationary concentration of Fe(II) salt minimizes the main, fast competitive reaction of t-BuO· (eq.6).

$$\text{t-BuO}^{\cdot} + \text{Fe(II)} + \text{H}^{+} \longrightarrow \text{t-BuOH} + \text{Fe(III)} \qquad (6)$$

In the presence of cyclohexane under the same conditions chlorocyclohexane (**6**) was formed according to the Barton report[2]; if styrene and α-methylstyrene are added to the reaction mixture, the formation of **1** and **2** competes with that of **6**, the ratios between these three products being strictly dependent on the cyclohexane:alkene ratios and in good agreement with previous[4] studies on the absolute and relative reactivity of t-BuO· towards hydrogen abstraction from cyclohexane and addition to styrene (Table 1).

Table 1. Reactions of cyclohexane, styrene and α-methylstyrene under Gif conditions in the presence of Cl^-

Alkene (mmol)	Cyclohexane (mmol)	**1** (%)	**2** (%)	**3** (%)	**4** (%)	**5** (%)	**6** (%)	Yields[d] (%)
-	5[a]	-	-	-	-	-	60.2	60.2
Styrene (5)	-	63.6	-	-	-	-	-	63.6
Styrene (2.5)[a]	5	25.0	-	-	-	-	53.0	78.0
Styrene (2.5)[a]	2.5	42.0	-	-	-	-	32.0	74.0
Styrene (5)	2.5	50.6	-	-	-	-	21.6	72.2
Styrene (5)[b]	-	58.4	-	-	-	-	-	58.4
α-Methylstyrene (5)[a]	-	-	34.0	9.1	28.0	13.6	-	84.7
α-Methylstyrene (5)[c]	-	-	68.0	1.6	4.6	2.1	-	76.3
α-Methylstyrene (5)[a]	2.5	-	5.5	7.2	20.8	10.3	29.8	73.6

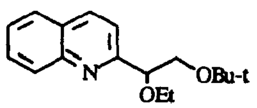
a) Barton conditions: 3 mmol pyridine, 0.3 mmol acetic acid, 0.5 mmol $Fe(NO_3)_3 . 9 H_2O$, 2 mmol LiCl cyclohexane and alkene, as reported in the Table, 1 mmol t-BuOOH, 60°C. 18h.
b) 10 mL MeCN, 10 mL H_2O, 5 mmol styrene, 1 mmol t-BuOOH, 2 mmol LiCl, 1 mmol $FeSO_4$, 20°C, 15 min.
c) as in a) at 20°C.
d) based on t-BuOOH

This is a strong evidence that cyclohexyl radical is formed by hydrogen abstraction from cyclohexane by t-BuO· (eq.7) while **6** derives from chlorine transfer from Fe(III)-Cl to cyclohexyl radical (eq.8).

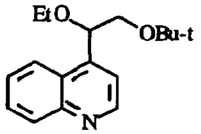
$$C_6H_{12} + \text{t-BuO}^{\cdot} \longrightarrow C_6H_{11}^{\cdot} + \text{t-BuOH} \qquad (7)$$

$$C_6H_{11}^{\cdot} + \text{Fe(III)-Cl} \longrightarrow C_6H_{11}Cl + \text{Fe(II)} \qquad (8)$$

When ethyl vinyl ether was made to react under Gif conditions in the presence of quinoline and in the absence of halide ions, compounds **7** and **8** were formed, but the prevailing products were α (**9**) and γ (**10**) acetylquinolines (Table 2).



7



8

These results are easily explained by a partial hydrolysis of the vinyl ether to acetaldehyde, so that t-BuO· can either add to the double bond of vinyl ether, leading to the formation of **7** and **8**, or abstract a hydrogen atom from acetaldehyde, thus forming products **9** and **10**. This is confirmed by the fact that at lower temperature the amounts of **7** and **8** increase; besides, by using acetaldehyde instead of vinyl ether under Gif conditions only products **9** and **10** are formed, while if vinyl ether is reacted with Fe(II) salt under conditions in which it cannot be hydrolyzed, the greatly prevailing products are again **7** and **8**. (Table 2). The ratios between **7** and **8** can be strongly affected by the reaction medium, as it has been previously shown for the α-tetrahydrofuranyl radical[5].

Table 2. Reactions of ethylvinylether and acetaldehyde under Gif conditions in the presence of quinoline.

T (°C)	Substrate	7 (mmol)	8 (mmol)	9 (mmol)	10 (mmol)	Yields (%)^c
60^a	ethyl vinyl ether	0.008	0.012	0.17	0.12	31.0
20^a	ethyl vinyl ether	0.035	0.017	0.163	0.043	25.8
20^b	ethyl vinyl ether	0.062	0.355	-	-	49.7
60^a	acetaldehyde	-	-	0.370	0.287	65.7

a) 1.5 mL pyridine, 1.5 mL quinoline, 0.3 mL AcOH, 1 mmol t-BuOOH, 0.5 mmol Fe(NO$_3$)$_3$. 9 H$_2$O, 5 mmol vinyl ether or acetaldehyde, 18h.

b) 10 mL MeCN, 10 mL H$_2$O, 1 mmol quinoline, 1 mmol CF$_3$COOH, 5 mmol ethyl vinyl ether, 1 mmol FeSO$_4$, 1 mmol t-BuOOH, 30 min; 0.04 mmol of quinoline 2,4-disubstituted by EtO-CH-CH$_2$- OBu-t is also formed.

c) based on t-BuOOH

The formation of **7** and **8** represents a new simple type of radical functionalization of heteroaromatic bases, in which once again the polar effect is dominant: the electrophilic t-BuO· radical selectively adds to the electron-rich alkene, thus forming a nucleophilic radical adduct, which selectively attacks the heterocyclic ring.

As concerns the general features of the Gif chemistry, we think that three redox chains can be envisaged (Schemes 1, 2 and 3; S = Substrate)

$$\mathrm{Fe(II) + ROOH \longrightarrow Fe(III) + OH^- + RO\cdot \xrightarrow{S} S\cdot} \tag{9}$$

$$\mathrm{S\cdot + Fe(III) \longrightarrow Products + Fe(II)} \tag{10}$$

Scheme 1

$$\mathrm{Fe(III) + ROOH \longrightarrow H^+ + Fe(IV){=}O + RO\cdot \xrightarrow{S} S} \tag{11}$$

$$\mathrm{S\cdot + Fe(IV){=}O \longrightarrow Products + Fe(III)} \tag{12}$$

Scheme 2

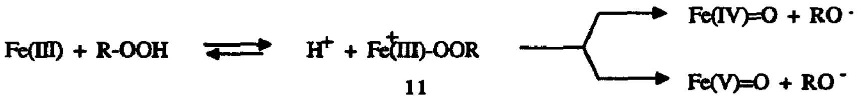
$$\mathrm{Fe(III) + ROOH \longrightarrow ROH + Fe(V){=}O \xrightarrow{S} S\text{-}Fe(V){=}O} \tag{13}$$

$$\mathrm{S\text{-}Fe(V){=}O \longrightarrow Products + Fe(III)} \tag{14}$$

Scheme 3

An overall qualitative kinetic evaluation clearly indicates that when reaction 10 is fast, as in the ligand transfer oxidation of alkyl radicals (eqs. 4 and 8), Scheme 1 must be by far prevailing because the possible, not yet well defined, reactions 11 and 13 would be in any case much slower than the fast reaction 9, and there is strong evidence that free radicals, initiating the chain of Scheme 1, are formed under Gif conditions.

Investigations are in progress in order to better understand the possibility of Schemes 2 and 3 when reaction 10 cannot take place, as reactions 11 and 13 could arise from the same intermediate 11 by homolysis or heterolysis of the O-O bond (eq.15).



$$\mathrm{Fe(III)} + \mathrm{R\text{-}OOH} \rightleftharpoons \mathrm{H^+} + \underset{11}{\overset{+}{\mathrm{Fe}}\mathrm{(III)\text{-}OOR}} \longrightarrow \begin{cases} \mathrm{Fe(IV){=}O} + \mathrm{RO\cdot} \\ \mathrm{Fe(V){=}O} + \mathrm{RO^-} \end{cases} \qquad (15)$$

References.

1. Minisci, F.; Fontana, F. *Tetrahedron Lett.*, in press
2. Barton, D.H.R.; Hill, D.R., *Tetrahedron Lett.*, in press; (b) Barton, D.H.R.; Bévière, S.D.; Chavasiri, W.; Doller, D.; Hu, B. *Tetrahedron Lett.* **1993**, *34* 1871; (c) Barton, D.H.R.; Bévière, S.D.;*Tetrahedron Lett.* **1993**, *34* 5689.
3. Walling, C.; Wagner, P.J. *J.Am.Chem.Soc.* **1964**, *86*, 3368.
4. Howard, J.A.; Scaiano, J.C. *Landolt-Bornstein* vol.13,**1984**; p. 19; (b) Encina, M.V.; Rivera, M.; Lissi, E.A.; *J.Polymer Sci. Chem.Ed.*, **1978**, *16*, 1709; (c) Walling, C; Thaler, W. *J.Am.Chem.Soc.***1961**, *83*, 3877.
5. Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J.Org.Chem.* **1987**, *52*, 730.
6. Minisci, F.; Fontana, F.;.Vismara, E. *Heterocycles* **1989**, *28*, 489.

(*Received in UK* 8 *February* 1994; *revised* 17 *March* 1994; *accepted* 24 *March* 1994)