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Alternating addition of carbon-centered radicals to unsaturated systems. Novel homolytic aromatic substitutions.

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Abstract. A novel type of homolytic aromatic substitution is reported; it is based on the addition of alkyl radicals to maleic anhydride and on the subsequent attack of the electrophilic radical adduct to nucleophilic aromatics. Copyright © 1996 Elsevier Science Ltd

The alternating effect in free-radical copolymerization has been one of the first significant examples of polar effects in free-radical reactions[1]. Several years ago we[2] have taken advantage of the same effect for synthetic purposes, by generating alkyl radicals in the presence of a pair of monomers (an electrophilic alkene and a nucleophilic conjugated diene or styrene derivative) and metal salt redox system (eqs.1-3)

$$R\cdot + CH_2{=}CHX \longrightarrow \underset{\mathbf{1}}{R\text{-}CH_2\text{-}\dot{C}HX} \qquad (1)$$

$$R\text{-}CH_2\text{-}\dot{C}HX + CH_2{=}CH\text{-}CH{=}CH_2 \longrightarrow \underset{\mathbf{2}}{\left[R\text{-}CH_2\text{-}CHX\text{-}CH_2\text{-}CH \overset{\text{- - -}}{—} CH \overset{\text{- - -}}{—} CH_2\right]^{\bullet}} \qquad (2)$$

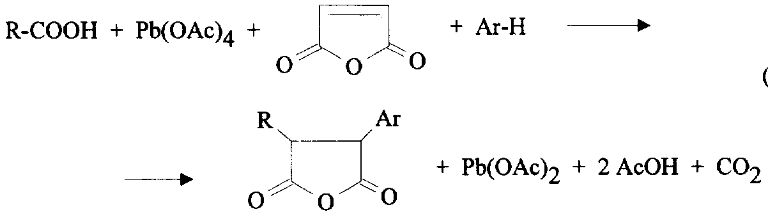
$$\left[R\text{-}CH_2\text{-}CHX\text{-}CH_2\text{-}CH \overset{\text{- - -}}{—} CH \overset{\text{- - -}}{—} CH_2\right]^{\bullet} \longrightarrow \text{Products} \qquad (3)$$

The synthetic success was related to polar and enthalpic effects so that the initial alkyl radical (R$^{\cdot}$) adds with good selectivity to the electrophilic monomer (eq.1); the radical adduct **2**, being electrophilic for the proximity of the polar substituent, selectively adds to the diene or styrene (eq.2). The allyl (**2**) or benzyl radicals are less reactive towards alkenes than are alkyl radicals, for enthalpic reasons[3] and they are selectively oxidized to the reaction products (eq.3)

We report for the first time how this general concept can be applied to homolytic aromatic substitutions. Alkyl radicals, not bearing an electron-withdrawing group directly bonded to the radical center, can show nucleophilic character. Aryl radicals can also exhibit nucleophilic character, even if it is much less marked compared to alkyl radicals; one must always consider that the polar effect, being kinetic in nature, is not an intrinsic property of a free-radical, but it depends on the particular type of reaction involved[4].

As the electrophilic alkene, we have chosen maleic anhydride because, as a cheap industrial intermediate, it can be suitable for industrial developments; besides, it has no tendency to homopolymerization.

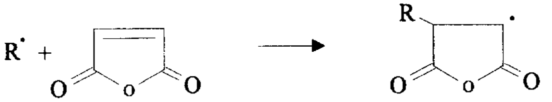
A general procedure involves oxidative decarboxylation of carboxylic acids by $Pb(OAc)_4$ in the presence of maleic anhydride and a nucleophilic aromatic compound. The stoichiometry of the reaction is shown by eq.4:



(4)

$$Pb(OAc)_4 + 2\,RCOOH \rightleftarrows Pb(OAc)_2(OCOR)_2 + 2\,AcOH \quad (5)$$

$$Pb(OAc)_2(OCOR)_2 \longrightarrow Pb(OAc)_2 + 2\,R^{\bullet} + 2\,CO_2 \quad (6)$$



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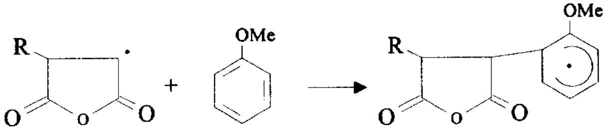

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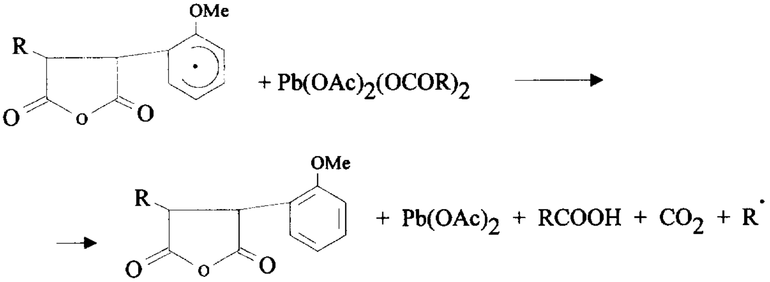


(9)

The reaction is a radical chain process, conceptually similar to the one described by eqs. 1-3; it involves initiation (eq.6) and propagation steps (eqs. 7-9), depending on the ligand exchange equilibrium of eq.5.

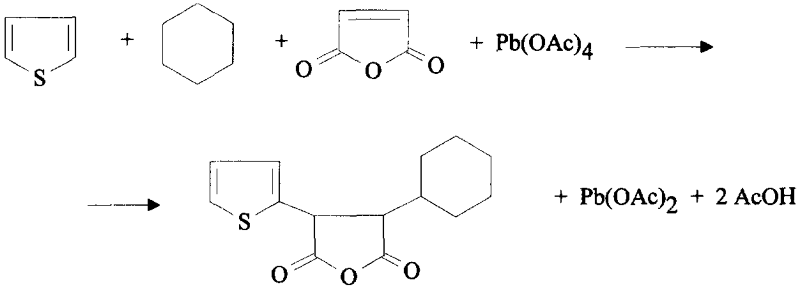
Since initiation (eq.6) is rather slow, a relatively high kinetic length and good synthetic results are obtained with nucleophilic aromatics, such as anisole or thiophene (fast reaction of the electrophilic radical, eq. 8). The reaction is completely selective for the position 2 on thiophene, and attack onto the ortho position of anisole is largely prevailing. Basically any carboxylic acid without electron-withdrawing substituents in α-position are suitable, as shown by the results reported in the Table.

A variation of this procedure is shown by eq.10.

Table - Homolytic aromatic substitution according to eq.4 (Procedure A) and eq.10 (Procedure B)*

Aromatic substrate	Alkyl radical	Procedure[a]	Orientation	Yields (%)[b]
Anisole	t-Bu$^{\cdot}$	A	42.6 (o); 7.2 (m+p)	49.8
Anisole	i-Pr$^{\cdot}$	A	53.2 (o); 9.3 (m+p)	62.5
Anisole	$C_6H_{11}^{\cdot}$	A	52.6 (o); 8.9 (m+p)	61.5
4-Me-anisole	i-Pr$^{\cdot}$	A	25.3 (2)	25.3
Thiophene	t-Bu$^{\cdot}$	A	2	62.0
Thiophene	i-Pr$^{\cdot}$	A	2	70.0
Thiophene	$C_6H_{11}^{\cdot}$	A	2	88.1
Thiophene	Ph-CH$_2^{\cdot}$	A	2	75.0
Thiophene	m-Cl-benzyl	A	2	45.5
2-Et-Thiophene[c]	$C_6H_{11}^{\cdot}$	A	5	31.2
Thiophene[d]	$C_6H_{11}^{\cdot}$	B	2	75.2
Thiophene[e]	dioxanyl	B	2	12.0

a) Procedure A: 5 mmol of carboxylic acid, 15 mmol of thiophene (or 40 mmol of anisole), 5 mmol of Pb(OAc)$_4$ and 10 mmol of maleic anhydride in 15 mL of benzene were refluxed for 2 hrs. The reaction products were analyzed by GC-MS and NMR. Procedure B: 5 mmol of t-BuOH, 10 mmol of maleic anhydride, 15 mmol of thiophene, 5 mmol of Pb(OAc)$_4$ in 20 mL of cyclohexane or dioxane and 10 mL of benzene were refluxed for 2 hrs. b) based on Pb(OAc)$_4$ c) Procedure A with 5 mmol of thiophene; d) **3** is formed in 9% yield; e) dioxane as solvent without benzene; **4** is formed in 23% yield.



(10)

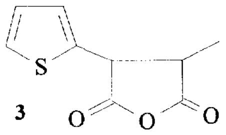
The reaction, in this case, takes place in the presence of t-BuOH, which is oxidized to t-BuO$^{\cdot}$ by Pb(OAc)$_4$ (eq.11). Hydrogen abstraction from cyclohexane (eq.12) leads to cyclohexyl radical, which reacts with maleic anhydride and thiophene in a way similar to reactions 7-9.

$$\text{t-BuOH} + \text{Pb(OAc)}_4 \longrightarrow \text{t-BuO}^{\bullet} + \text{Pb(OAc)}_3 + \text{AcOH} \qquad (11)$$

$$\text{t-BuO}^{\bullet} + \text{C}_6\text{H}_{12} \xrightarrow{k} \text{t-BuOH} + \text{C}_6\text{H}_{11}^{\bullet} \qquad (12)$$

$$k = 1.6 \times 10^6\ \text{M}^{-1}\,\text{s}^{-1} \text{ at } 300\ \text{K}$$

Compounds **3** and **4** are significant byproducts; they arise from the addition of methyl radical to maleic anhydride.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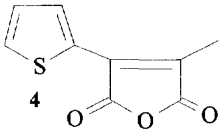
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Methyl radical is generated by b-scission of t-BuO$^{\bullet}$ radical and by oxidative decarboxylation of the acetate group.

Two stereoisomers are always formed, according to eqs. 4 and 10, their ratio depending on the bulk of the alkyl radical. The reaction is highly stereoselective with tertiary alkyl radicals, while a poor selectivity is observed with methyl radical.

References

1. Walling, C. *Free Radicals in Solution*, John Wiley, New York:1957, p.132.
2. Minisci, F.; Caronna, T.; Cecere, M.; Galli, R.; Malatesta, V. *Tetrahedron Lett.* **1968**, 5609; Minisci, F.; Zammori, P.; Bernardi, R.; Cecere, M.; Galli, R.; Malatesta, V. *Tetrahedron.* **1970**, *26*, 4153; Citterio, A.; Minisci, F.; Arnoldi, A. *J.Org.Chem..* **1979**, *44*, 2674; Citterio, A.; Minisci, F.; Serravalle, M. *J.Chem.Res.(S).* **1981**, 198; Minisci, F., in *Fundamental Research in Homogeneous Catalysis*, Graziani, M., ed.; Plenum Press: New York (1984), P. 173.
3. Heberger, K.; Walbiner, M.; Fischer, H. *Angew.Chem. Int.Ed.Eng.* **1992**, *31*, 635.
4. Minisci, F.; *Substituent Effects in Free Radical Chemistry*, Viehe, H.G., Ed.; Reidel Publ. Co.: Dordrecht (1986), p.391.

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