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The Reaction of Superoxide with Cinnamyl Bromide: The Surprising Formation of an Ether and an Epoxy Acetal

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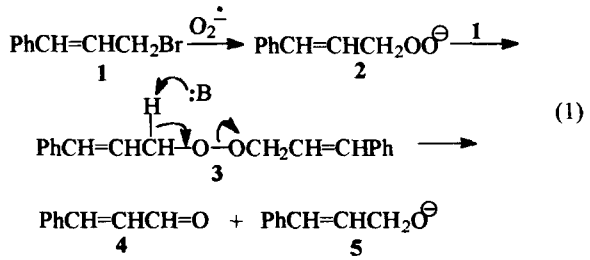
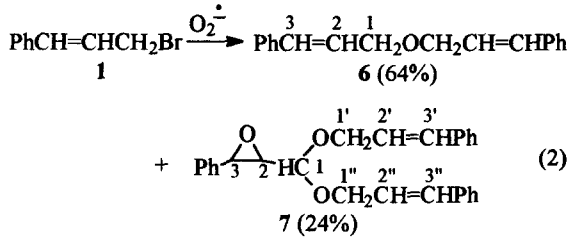
Abstract: The reaction of $O_2^{-\cdot}$ (KO_2/18-crown-6 in toluene) with cinnamyl bromide yielded neither the expected cinnamyl peroxide nor its Kornblum-DeLaMare fragmentation products, cinnamaldehyde (**4**) and cinnamyl alcohol. Instead we observed the novel formation of dicinnamyl ether and 2,3-epoxycinnamylaldehyde dicinnamyl acetal (88% yield). Benzyl bromide reacted with $O_2^{-\cdot}$ in the presence of **4** yielding dibenzyl ether and epoxycinnamaldehyde dibenzyl acetal. When the reaction was repeated with CH_3I, the corresponding epoxycinnamaldehyde dimethyl acetal was the major product.

Nucleophilic attack is one of the most common reactions of $O_2^{-\cdot}$ in inert aprotic media.[1] Thus, alkyl halides are reported to yield the corresponding hydroperoxides and/or peroxides.[1] In our attempt to discover highly sensitive tests for the various modes of superoxide action, we explored the reaction of superoxide anion radical (generated from KO_2/18-crown-6 polyether) with *trans*-cinnamyl bromide (**1**) in aprotic media (toluene). In light of the fact that S_N2 attack on allylic bromide **1** should be a very facile process, we hoped that the initially formed peroxy anion **2** would react further yielding the corresponding peroxide **3** (eq. 1). The latter would then easily undergo Kornblum-DeLaMare fragmentation[1d,2] to the highly conjugated and UV detectable cinnamaldehyde (**4**) and the corresponding cinnamyl alcohol (**5**, after protonation).



(1)

The superoxide reaction of **1** in toluene proved to be a rapid reaction, complete within 2 h. However, upon aqueous work-up, we obtained none of the expected products **4** and **5**; instead, we observed the surprising and unprecedented formation of the corresponding dicinnamyl ether (**6**) and the novel 2,3-epoxycinnamylaldehyde dicinnamyl acetal (**7**) in an overall yield of 88% (eq. 2).

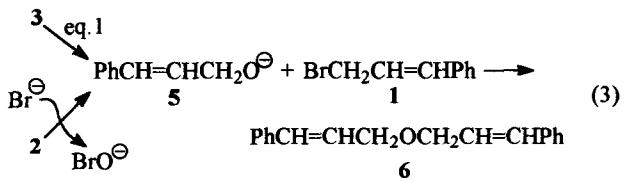


Dicinnamyl ether is known in the literature,[3] but no spectral data is supplied. Synthesis of the literature-described dicinnamyl ether[3] confirmed that both samples were indeed identical. Not surprisingly, the ^{1}H NMR of **6** is very similar to that of cinnamyl alcohol (Aldrich), though the C-1 methylene hydrogens of **6** resonate at 4.22 ppm, upfield from those of the alcohol, which appear at 4.33 ppm. The identification of **7** as the epoxy acetal of cinnamaldehyde was based on its spectral data which was in good agreement with that of 2,3-epoxycinnamyl-1,1-diacetate.[4] In addition, the vinylic absorptions were reminiscent of cinnamyl alcohol but substantially more complex because of the various diastereotopicity relationships.[5]

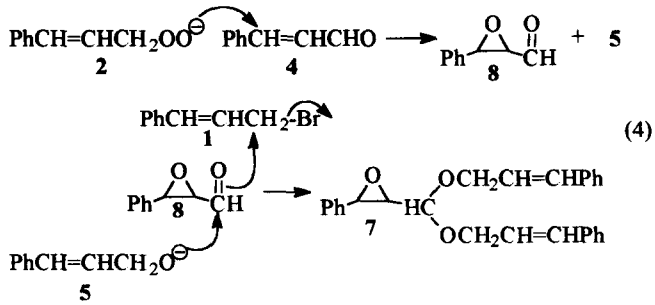
In order to verify that, indeed, no peroxides were present in the reaction mixture prior to work-up, we added an equivalent of either Ph_3P or $LiAlH_4$ upon the disappearance of the substrate; no influence on the products' identity or distribution was seen. In addition, cinnamyl ether is completely stable to the reaction conditions and, hence, can be ruled out as an intermediate in the formation of **7**.

Turning now to the question of mechanism, we assume that, as outlined in eq. 1, cinnamyl bromide (**1**) does in fact undergo facile reaction with $O_2^{-\cdot}$ yielding the cinnamyl peroxy anion **2** and dicinnamyl peroxide **3**. Moreover, the latter readily undergoes the expected Kornblum-DeLaMare fragmentation[1d,2] yielding cinnamaldehyde (**4**) and the corresponding cinnamyl alcoholate (**5**). We believe, however, that these primary products are not observed in the product mixture because they serve in turn as the substrates for the formation of ether **6** and acetal **7**.

If this assumption is correct, then the mechanism for the formation of dicinnamyl ether (**6**) seems relatively straight forward. It simply results from the coupling of cinnamyl alcoholate (**5**) with the starting bromide **1** (eq. 3). (Indeed, the literature procedure[3] for the synthesis of ether **6** involves the reaction of cinnamyl alkylsulfonate with sodium cinnamyl alcoholate, prepared from the alcohol and $NaNH_2$.) We should note, however, that Kornblum-DeLaMare fragmentation of peroxide **3** is not the only possible source of alcoholate **5**. Halide ions reduce peroxides to the corresponding alkoxides with the concomitant formation of hypohalite (eq 3).[6]



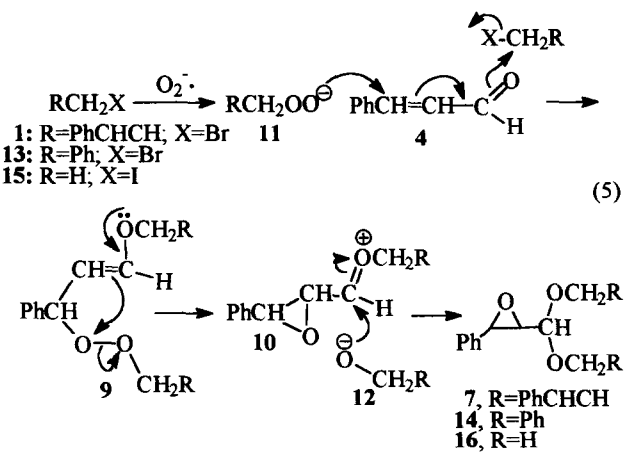
Regarding the formation of epoxyacetal **7**, one plausible mechanism (eq. 4) involves the epoxidation of cinnamaldehyde by peroxy anion **2**, a well precedented process.[7] Epoxide **8** may then undergo acetal formation by nucleophilic attack of alkoxide **5** at the carbonyl center of **8**, followed by alkylation of the resulting oxyanion.



(4)

This mechanism seems unlikely, however, in light of the fact that the reaction of sodium cinnamyl alcoholate **5** (prepared from cinnamyl alcohol and sodium metal or NaH[3] in toluene containing 18-crown-6) with 2,3-epoxycinnamaldehyde[7b] in the presence of cinnamyl bromide yielded only dicinnamyl ether and no acetal whatsoever. Nor were we able to find any literature record of acetal formation in the reaction of an aldehyde with an alkoxide and a bromide. While acetalization in basic media has been reported, it is limited to electron poor carbonyl groups which readily form stable hemi-acetals.[8] We are perforce led to consider other prospects.

Eq. 5 outlines one such possibility. This mechanism assumes that the fundamental requirement for combined epoxidation-acetal formation is the simultaneous presence of a reactive enone, an unhindered peroxide and a good alkylating agent. In the present system, all three are present since the first two - cinnamaldehyde (**4**) and cinnamyl peroxy anion (**2**; **11**, R=PhCHCH) - are generated *in situ* from the third, cinnamyl bromide (**1**), by the action of superoxide (see eq. 1). Normally, in the peroxy anion epoxidation of enones, the Michael attack of a peroxy anion on an α,β-unsaturated carbonyl results in initial β-peroxy enolate formation, which closes to the corresponding epoxy ketone.[7e] In the present system, however, the cinnamyl bromide (**1**) effects a facile O-alkylation of the peroxy enolate generating β-peroxy enol ether **9**. The latter could *then* collapse in a fashion analogous to peroxy enolates[7e] to oxonium epoxide **10**. Nucleophilic attack on the oxycarbonium ion of the latter by cinnamyl alkoxide **5** (**12**, R=PhCHCH) yields the observed epoxy acetal **7**.

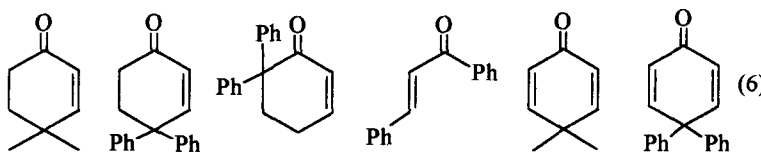


(5)

If this mechanism is correct, then a tandem epoxidation-acetal formation should also be observed when superoxide is allowed to react with other benzylic or primary halides in the presence of cinnamaldehyde. Like cinnamyl bromide, these halides would undergo facile S_N2 reactions and can, therefore, serve both as *in situ*

sources for peroxy anions and as alkylating reagents of the β-peroxy enolates formed. Indeed, when benzyl bromide (**13**; see eq. 5) was allowed to react with superoxide in the presence of cinnamaldehyde (**4**), two major products were obtained and identified as the commercially (Aldrich) available dibenzyl ether (formed as outlined in eq. 3) and the dibenzyl acetal of epoxycinnamaldehyde (**14**, formed as outlined in eq. 5). When the reaction was repeated with methyl iodide (**15**), epoxycinnamaldehyde dimethyl acetal (**16**) was the major product; dimethyl ether was not isolated - but this is undoubtedly due to its volatility at room temperature (bp -23 °C).

We were unsuccessful. however, in observing this superoxide mediated acetal formation-epoxidation process using other α,β-unsaturated carbonyl systems. Thus, the reaction of benzyl bromide (**13**) with superoxide in the presence of enones **17-22** (eq. 6) generated only dibenzyl ether, a small amount of benzyl alcohol and, in the case of **17-20** the previously reported superoxide products.[9] Cyclohexadienones **21** and **22** are inert to $O_2^{-\bullet}$; nevertheless, only unreacted starting dienone was observed. The absence of epoxy acetal presumably results from steric hindrance to Michael attack caused by the geminal substituents at carbon 4. The uniqueness of cinnamaldehyde as a suitable substrate for this tandem process would seem to result, then, from a combination of traits: its very slow oxidation by superoxide, on the one hand, and its unhampered facile Michael addition reaction with peroxy anions, on the other.



17 **18** **19** **20** **21** **22**

Experimental

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM 300 Fourier Transform spectrometer. In all cases, TMS served as the internal standard. High resolution mass spectra (HRMS) were performed by the Mass Spectroscopy Center at the Technion, Haifa. FTIR spectra were obtained on a Nicolet 60 SXB FTIR spectrometer while UV-visible spectra were taken on Varian DMS 100S spectrometer. Analytical thin layer chromatography (TLC) was performed using Merck silica gel microcards. Preparative TLC runs were carried out on Merck silica gel F_{254} precoated plates, and products were extracted from the silica by stirring overnight in a solution of 30% CH_3OH in $CHCl_3$. *Trans*-cinnamyl bromide (3-bromo-1-phenyl-1-propene, Fluka) was twice distilled under reduced pressure over K_2CO_3.[10] *Trans*-cinnamyl alcohol (Fluka) was distilled under reduced pressure and stored along with the bromide at -18 °C. *Trans*-cinnamaldehyde (Aldrich) was freshly distilled before use. Potassium superoxide (Callery, supplied as a fine powder in 1 kg cans) was transferred to 25 cc bottles in a glove bag under dry argon prior to use. 18-Crown-6 polyether (Aldrich) was recrystallized from acetonitrile[11] and stored along with the potassium superoxide in a desiccator. Analytical grade methyl iodide was stored at +5 °C under argon.

Reaction of Cinnamyl Bromide with Superoxide: Cinnamyl bromide [**1**; R_f (10% acetone in hexane) 0.44] (0.50 g, 2.5 mmol) was allowed to react with superoxide anion radical, generated in sodium dried toluene (75 mL) from KO_2 (0.73 g, 10 mmol), with 18-crown-6-polyether (1.35 g, 5 mmol). The reaction was followed by TLC (10% acetone in hexane) and, upon disappearance of the substrate (2h), was quenched with water and worked-up as usual.[9a] Products were then separated by preparative TLC (or on a silica column in the case of samples larger than 1 g) using 10% acetone in hexane. The upper (less polar) band was identified as the dicinnamyl ether (**6**); while the lower band was identified as the epoxy acetal **7**, in 4:1 molar ratio and a total

yield of 88%. Taking into account, however, that each mole of **6** consumes two moles of substrate, while three moles are incorporated into **7**, the relative yields of **6** and **7** are calculated to be 64% and 24%, respectively. Dicinnamyl ether (**6**) is known in the literature,[3] but the spectral data are lacking. A sample of the ether was prepared according to the literature procedure[3] and found to be identical with that isolated from the above $O_2^{-\cdot}$ reaction of **1**.

6: R_f (10% acetone in hexane) 0.33; ^{1}H NMR ($CDCl_3$) δ 7.45-7.23 (m, 10H, Ar-H), 6.65 (bd, $J_{2,3}$ = 16 Hz, 2H, H-3), 6.37 (dt, $J_{2,3}$ = 16 Hz, $J_{1,2}$ = 6 Hz, 2H, H-2), 4.22 (dd, $J_{1,2}$ = 6 Hz, $J_{1,3}$ = 1.5 Hz, 4H, H-1); ^{13}C NMR ($CDCl_3$) δ 136.75 (*ipso*), 132.53 (C-3), 128.52 (*m*), 127.65 (C-2), 126.49 (*o*), 126.07 (*p*), 70.71 (C-1); HRMS calcd ($C_{18}H_{18}O$, M^+) 250.1358, obsd 250.1355; MS (EI) m/z 250 (M^+, 1.82%), 133 (M-PhCH=CHCH$_2$, 2.28%), 117 (PhCH=CHCH$_2$, 100%), 103 (PhCH=CH, 10.89%).

7: R_f (10% acetone in hexane) 0.22; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 15H, Ar-H), 6.64 and 6.65 (each dt, $J_{2',3'} = J_{2'',3''}$ = 16 Hz, $J_{1',3'} = {}_{1'',3''}$ = 1.5 Hz, 2H, H-3' and H-3"), 6.33 and 6.30 (each dt, $J_{2',3'} = J_{2'',3''}$ = 16 Hz, $J_{1',2'} = J_{1'',2''}$ = 6 Hz, 2H, H-2' and H-2"), 4.78 (d, $J_{1,2}$ = 4 Hz, 1H, H-1), 4.45-4.34 (m, 4H, 4 diastereotopic H of H-1' and H-1"), 3.99 (d, $J_{2,3}$ = 2 Hz, 2H, H-3), 3.28 (dd, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 2 Hz, 2H, H-2); ^{13}C NMR ($CDCl_3$) δ 136.59, 136.54 and 136.41 (3C, ipso), 132.89 (C-3' and C-3"), 128.56, 128.36, 128.22, 127.79, 126.54, 125.81 and 125.41 (aromatic as well as C-2' and C-2" which presumably absorb together), 99.75 (C-1), 67.81 and 67.15 (C-1' and C-1"), 61.82 (C-3), 55.39 (C-2); UV ($CHCl_3$) λ_{max} = 253 nm; FTIR ($CHCl_3$) 1034 (s, CO) cm-1; HRMS calcd ($C_{27}H_{26}O_3$, M+) 398.1182, obsd 398.1880; MS (EI) m/z 398 (M+, 0.81%), 281 (M-PhCH=CHCH$_2$, 2.11%), 265 (M-PhCH=CHCH$_2$O, 0.41%), 133 (PhCH=CHCH$_2$O, 21.96%), 119 (PhCH(O)CH, 3.25%), 117 (PhCH=CHCH$_2$, 100%).

Reaction of Benzyl Bromide (13) and Cinnamaldehyde (4) with Superoxide: Benzyl bromide (**13**) (1.0 g, 5.8 mmol) and cinnamaldehyde (**4**) (0.38 g, 2.9 mmol) were allowed to react with superoxide anion radical, generated in sodium dried toluene (150 mL) from KO_2 (0.83 g, 11.7 mmol), with 18-crown-6-polyether (1.35 g, 5 mmol). The reaction was followed by TLC (10% acetone in hexane) and, upon disappearance of the substrate (3h), was quenched with water and worked-up as usual.[11] The yield of product was quantitative. Products were then separated by preparative TLC (or on a silica column in the case of samples larger than 1g) using 10% acetone in hexane. The upper (less polar) band was identified as the commercially available (Aldrich) dibenzyl ether; while the lower band was identified as the 2,3-epoxycinnamaldehyde dibenzyl acetal (**14**). The molar ratio of ether to acetal was 3:2. ^{1}H NMR of the crude reaction mixture revealed the presence of trace amounts of benzoic acid, benzaldehyde and cinnamic acid.

14: R_f (25% acetone in hexane) 0.38; ^{1}H NMR ($CDCl_3$) δ 7.39-7.20 (m, 15H, Ar-H), 4.76 (d, $J_{1,2}$ = 4 Hz, 1H, H-1), 4.69 and 4.67 (each ABq, J_{gem} = 12 Hz, 4H, 4 diastereotopic H of H-1' and H-1"), 3.91 (d, $J_{2,3}$ = 2 Hz, 2H, H-3), 3.28 (dd, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 2 Hz, 2H, H-2); ^{13}C NMR ($CDCl_3$) δ 137.61 and 137.54 (*ipso* benzyl) 136.34 (*ipso* cinnamyl), 128.45 (6C, all *meta*), 128.30 (*para* cinnamyl), 127.87 (2C, *para* benzyl), 127.79 (4C, *ortho* benzyl), 125.73 (2C, *ortho* cinnamyl), 99.67 (C-1), 69.04 and 68.34 (C-1' and C-1"), 61.83 (C-3), 55.32 (C-2); HRMS calcd ($C_{23}H_{22}O_3$, M^+) 346.1569, obsd 346.1585; calcd ($C_{16}H_{15}O_2$, M-PhCH$_2$O) 239.1072, obsd 239.1075; MS (EI) 346 (M^+, <0.2 %), 239 (M-PhCH$_2$O, 0.3%), 181 ($C_{14}H_{13}$, 16.76%), 132 (PhCH[O]CHCH, 6.98%), 91 (PhCH$_2$, 100%).

Reaction of Methyl Iodide (15) and Cinnamaldehyde (4) with Superoxide: The reaction was the same as described above for benzyl bromide (**13**), except that CH_3I (**15**) served as the halide component, the ratio of KO_2:crown:CH_3I:**4** was 16:8:8:1, and the reaction was allowed to proceed overnight. ^{1}H NMR of the crude reaction mixture revealed only the presence of unreacted **4** and trace amounts of cinnamic acid in addition to the main product 2,3-epoxycinnamaldehyde dimethyl acetal (**16**). The latter was isolated in a 75% yield (based on **4**) and purified by preparative TLC.

16: R_f(25% acetone in hexane) 0.30; ^{1}H NMR ($CDCl_3$) δ 7.38-7.25 (m, 5H, Ar-H), 4.45 (d, $J_{1,2}$ = 4 Hz, 1H, H-1), 3.92 (d, $J_{2,3}$ = 2 Hz, 2H, H-3), 3.43 (two overlapping s, separated by ca. 0.002 ppm, 6H, OCH_3), 3.28 (dd, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 2 Hz, 2H, H-2); ^{13}C NMR ($CDCl_3$) δ 138.35 (*ipso*), 128.46 (*meta*), 128.32 (*para*), 125.69 (*ortho*), 102.05 (C-1), 61.21 (C-3), 55.04 (C-2), 54.51 and 53.67 (acetal OCH_3); HRMS calcd ($C_{11}H_{14}O_3$, M^+) 194.0943, obsd 194.0940; calcd ($C_{10}H_{11}O_2$, M-OCH_3) 163.0759, obsd 163.0763; MS (EI) 194 (M^+, 0.39%), 163 (M-OCH_3, 10.58%), 131 (M-OCH_3-$HOCH_3$, 14.29%), 121 (M-$C_3H_5O_2$, 100%), 103 (PhCHCH, 84.77%).

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References and Footnotes

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5. The epoxide renders C-2 (and for that matter, C-3) chiral; as a result, the two acetal cinnamyl alkoxy groups are diastereotopic to one another. The situation is further complicated by the fact that the alkoxymethylene hydrogens on C-1' (and C-1") are themselves diastereotopic to each other. This is because exchanging one of the methylene hydrogens on C-1' for a deuterium now renders the C-1 acetal carbon chiral. For a complete discussion of this phenomenon, see: Günther, H. *NMR Spectroscopy*; Wiley: Chichester, 1980; pp. 197-205; see especially p. 201 and the related discussion of the ^{1}H NMR spectrum of acetaldehyde diethyl acetal (Fig. 6.7).
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