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Free Radicals in the Reaction of *tert*-Butylmagnesium Chloride with Ethyl Cinnamate

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The mechanism of the formation of the abnormal 1,3-addition product ethyl 2-*tert*-butyl-3-phenylpropanoate (*19*) in the reaction of ethyl cinnamate with *tert*-butylmagnesium chloride involves addition of a free *tert*-butyl radical to neutral ethyl cinnamate at C-2 followed by electron transfer reactions. The initial bifunctional adduct *10* cyclizes to diastereomeric cyclopropanone hemiketal salts *11*. Several reactions of this intermediate are described, including the base catalyzed rearrangement to the final ester *19*.

Ethyl cinnamate and *tert*-butylmagnesium chloride react to yield a mixture of the 1,4-addition product (ethyl 3-*tert*-butylhydrocinnamate (*8*)) and the abnormal 1,3-addition product (ethyl 2-*tert*-butylhydrocinnamate (*19*)).[1] Since this type of reaction was unprecedented, it was found interest to get insight into the reaction mechanism and to study the properties of the cyclopropanone hemiketal previously suggested as an intermediate.[1]

The formation of a 1,3-adduct would be expected to start with the addition of a free *tert*-butyl radical to C-2 of ethyl cinnamate producing the stable benzylic radical *9*. Kharasch and Sage [2] showed that the trichloromethyl radical adds in this way to ethyl cinnamate. It might be argued that trichloromethyl is an electrophilic radical and that *tert*-butyl radicals, being nucleophilic, would behave differently.[3] During the present work, however, it was found that when *tert*-butyl radicals were generated by heating 4-*tert*-butyl-1,4-dihydrobenzophenone [4] in the presence of either cinnamic acid or ethyl cinnamate, 1,3- and 1,4-addition products were produced in a ratio of 10:1. Similar results were obtained when the *tert*-butyl radicals were generated by heating of tri-*tert*-butylcarbinol.[5]

In order to test whether free radicals are in fact responsible for the observed 1,3-addition of *tert*-butylmagnesium chloride to ethyl cinnamate, two experiments were carried out which differed only by the presence in the second experiment of 2.2 mol of the radical scavenger α-methylstyrene per mol of ester. The yields of the reaction products were estimated by GLC using an internal standard. Whereas the yield of 1,4-addition product was unchanged (38 %) in the presence of methylstyrene, the yield of 1,3-addition product decreased from 27 % to 8 %. Eleven percent of the missing 19 % were accounted for by the hydrocarbons *13* and *14* formed by addition of *tert*-butyl radicals to methylstyrene, reaction *a*, Scheme 2. The formation of 1,3-addition product was totally suppressed when methylstyrene was present in large excess (0.3 M) over ethyl cinnamate (0.003 M).

Two conclusions may be drawn from the results obtained: (1) free *tert*-butyl radicals are produced in the title reaction and (2) 1,3-addition is the result of an addition of free *tert*-butyl radicals to some species in the reaction mixture.

The following mechanism is suggested (Scheme 1): the production of *tert*-butyl radicals is initiated by single electron transfer (SET) from the Grignard reagent *1* to the ester *2* in analogy with the SET mechanisms which have been observed in the reactions of *tert*-butylmagnesium chloride with substrates like

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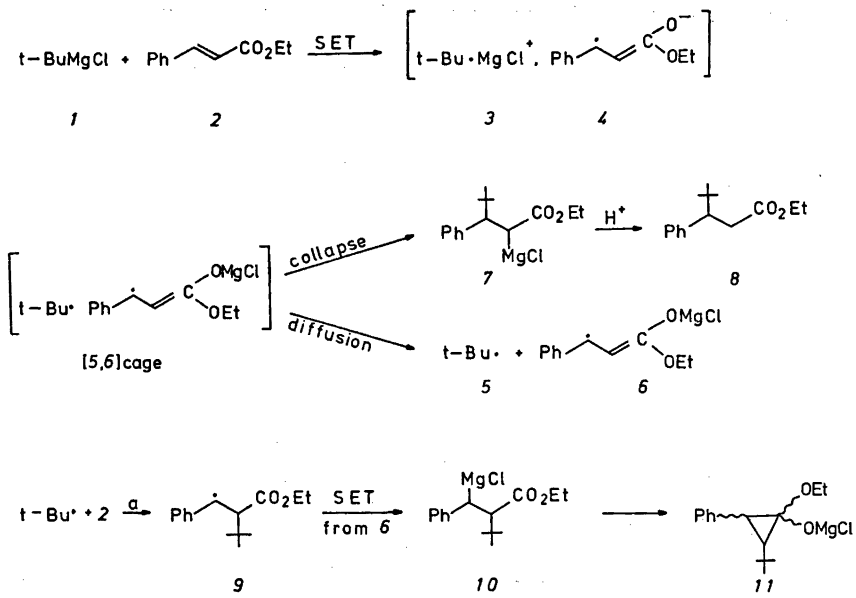
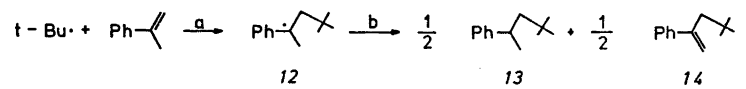


Scheme 1.

benzophenone[4] and di-*tert*-butyl peroxide.[5] The electron transfer converts the cinnamic ester into a radical anion *4* and the Grignard reagent into a radical cation *3*. Both are formed within a cage and may rearrange to $[5,6]_{cage}$. The latter may either collapse to give the "normal" 1,4-adduct *7* or give the radicals *5* and *6* by diffusion.* The free *tert*-butyl radical may react with radical scavengers, reaction *a* in Scheme 1 or *a* in Scheme 2. α-Methylstyrene thus competes with ethyl cinnamate in the reaction with *tert*-butyl radicals. In the absence of methylstyrene, ethyl cinnamate will be the radical acceptor, resulting in the formation of *9* (reaction *a*). An SET from the radical anion *6* to *9* and association with $MgCl^+$ affords the bifunctional ester-Grignard reagent *10*, which subsequently undergoes cyclization to form the cyclopropanone hemiketal salt *11*. The source of the electron in the latter SET is suggested to be *6* rather than the Grignard reagent *1*, as no tendency to chain reactions was observed.

Only about 70 % of the starting materials are accounted for as distillable 1,3- and 1,4-addition products. A by-product found in amounts of 2–5 %, was the ketone resulting from 1,2- + 1,4-addition of *tert*-butylmagnesium chloride to ethyl cinnamate. The distillation residue was separated into various fractions by TLC. None of these were identified, but it was observed that they, when injected into the gas chromatograph, produced peaks corresponding to ethyl cinnamate and the 1,3- and 1,4-addition products. This was taken as evidence of fission at injector temperature of products formed by addition of *7* and *10* to ethyl cinnamate.

NMR analysis of the high boiling fraction revealed *tert*-butyl signals at δ 1.3, which indicate the presence of ring-alkylated products also observed by Degrand and Lund.[8] Mass



Scheme 2.

* Relevant discussions of SET-formation of free radicals and the possibility of a stepwise development from the paired and caged, magnesium bound radical cation to the totally free, diffused *tert*-butyl radical, are given by Nugent *et al.*[6] and by Ashby and Bowers.[7]

spectroscopy gave evidence for the presence of doubly alkylated products as also observed by the authors mentioned.

The ratio of 1,3- to 1,4-addition product was typically 1:5 when the Grignard reagent was in large excess and the ratio varied very little whether the reaction was run at −80 or 100 °C. When only a small excess of Grignard reagent was used, and when the reagents were relatively concentrated (see Experimental) the ratio increased to about 1:1. The reason for this is unknown, but it seems reasonable that the cage effect which prevents diffusion of *tert*-butyl radicals is less efficient when the ester concentration is high.

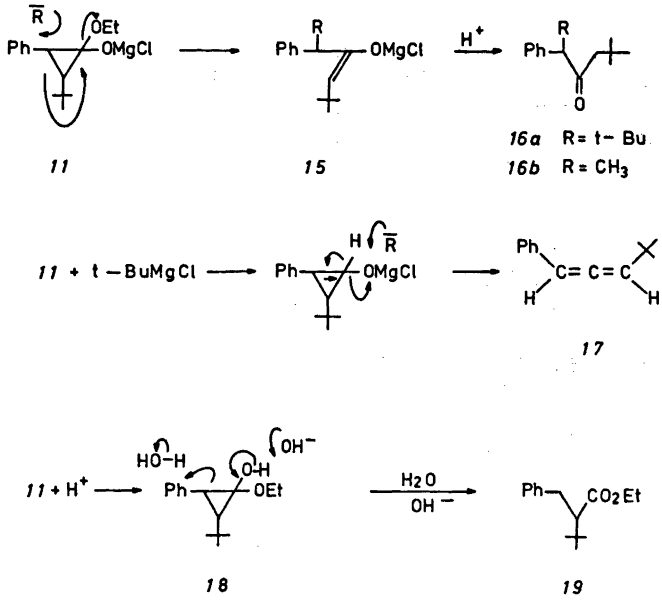
The structure of the cyclopropanone hemiketal was deduced from several pieces of evidence although all attempts at isolating it in the pure state failed. If the reaction mixture A was worked up with care (see Experimental) NMR analysis of the crude product showed several groups of peaks which disappeared when the solution was shaken with dilute base. The vanishing peaks were identified as the spectra of two isomers of *18*. Since the peaks representing ethyl α-*tert*-butylhydrocinnamate increased correspondingly, the reaction observed must be the base-catalysed rearrangement of *18* to *19*.[10]

The hemiketal *18* was silylated to give a 1:3 mixture of two isomers. The coupling constant of the ring protons (8 Hz) suggests *trans* configuration in both.[9]

Further evidence for the structure *18* was obtained from various reactions performed on the hemiketal magnesium salt *11*. When *11* was treated with excess *tert*-butylmagnesium chloride (or dimethylmagnesium, see Experimental) two products were formed, Scheme 3. Of these the ketones *16a* and *16b* seem to be formed by anionic attack of the alkyl of a Grignard reagent at the benzylic carbon of *11*, which by the indicated shifts of electrons produces the enolates *15* of the ketones.

The allene *17* may arise from *11* by reduction and subsequent deprotonation by *tert*-butylmagnesium chloride.

The kinetics of the reaction was studied by UV spectroscopy using pseudo first-order conditions with a large excess of Grignard reagent. The mixture of the ester and the Grignard reagent assumes an intense reddish-brown color which is believed to be the color of the ethyl cinnamate radical anion magnesium salt *6*. The absorption at 450 nm disappears as the reaction proceeds showing constant half lives (~40 s at 22 °C for [*t*-BuMgCl] = 0.5 M). The absorption of the reaction mixture at



Scheme 3.

345 nm increases during the reaction due to intense absorption by the products. The half lives calculated on this basis were closely the same. At ester concentrations as high as 0.1 M the rates were higher than expected ($\tau = 16$ s for 0.5 M Grignard reagent). The reason for this is believed to be changes in fast pre-equilibria between Grignard reagent and substrate. The half life of the ester at 100 °C was found by means of a flow stream arrangement to be ~ 1 s and at −80 °C it was 100 h. This corresponds to $E_A = 42.3$ kJ mol^{-1} and $\Delta S^{\ddagger} = -138$ J K^{-1} mol^{-1}. For comparison the activation parameters for the reaction of *tert*-butylmagnesium chloride with benzophenone are $E_A = 16.7$ kJ mol^{-1} and $\Delta S^{\ddagger} = -138$ J K^{-1} mol^{-1}.[4]

EXPERIMENTAL

Mass spectra were recorded on a VG Micromass 7070F instrument; IP 70 eV. ^{1}H NMR were recorded on a Varian 360 instrument at 60 MHz or on a Bruker HX-270 instrument at 270 MHz, and ^{13}C NMR on a Bruker WH-90 at 22.93 MHz with a broad band noise ^{1}H decoupling. Long relaxation times are indicated by a superscript a. Ethyl cinnamate (Rohm and Hass) was distilled *in vacuo*. *tert*-Butylmagnesium chloride was prepared from reagent grade magnesium and *tert*-butyl chloride (Fluka *puriss.*) using ether distilled from lithium aluminium hydride.

Addition of ethyl cinnamate to tert-*butylmagnesium chloride: reaction mixture A.* To *tert*-butylmagnesium chloride (40 mmol, *ca.* 1 M in ether) cooled to 0 °C was added at once ethyl cinnamate (20 mmol) with stirring. The solution turned dark red brown. After 15 min at room temperature the color had faded and a precipitate had formed. This reaction mixture A was metastable. For normal work-up the mixture was poured onto ice and acidified with dilute hydrochloric acid. The organic layer was washed with water, with 1.0 M NaOH, and dried with K_2CO_3. To determine yields and product distribution 10.53 mol % of tetradecane was added to the ethyl cinnamate and the crude product was analyzed by GLC using the tetradecane as an internal standard.

Diastereomers of 2-tert-*butyl-1-ethoxy-3-phenylcyclopropanol (18).* A crude mixture of the isomeric hemiketals, contaminated mainly by ethyl 3-*tert*-butyl-3-phenylpropanoate, was obtained by diluting reaction mixture A (above) with ether (200 ml, *ca.* −50 °C). The solution was cooled below −50 °C, poured onto a mixture of ice (*ca.* 200 g) and hydrochloric acid (20 ml conc.), the organic layer washed with water, dried (Na_2SO_4), and the solvent removed at room temperature *in vacuo*. The ketals dissolved in carbon tetrachloride rearranged immediately to ethyl 2-*tert*-butyl-3-phenylpropanoate (*19*) by the action of aqueous sodium hydroxide. ^{1}H NMR (270 MHz, CCl_4, C_6D_6) data for two of the four possible racemates of *18* were obtained from spectra of the crude product before and after the rearrangement. The ratio was *ca.* 3:2; δ of the minor component in parenthesis: 1.05 [1.06] (*tert*-butyl), 1.38 [1.34] (d, J 8 Hz), 2.17 [2.18] (d, J 8 Hz), 1.19 [1.15] (t, J 8 Hz), 3.40−3.65 (m, apparently four quartets). Double resonance experiments correlate the resonances near 1.2 ppm with those of the multiplet (ethoxy group) and correlate the two doublets (methines of the ring). Resonances of the hydroxyl and the phenyl groups were not identified.

Diastereomers of 2-tert-*butyl-1-ethoxy-3-phenyl-1-trimethylsilyloxycyclopropane* were obtained by adding trimethylchlorosilane (1 ml) and pyridine (1 ml) to a solution of the hemiketals (above) in carbon tetrachloride (10 ml) at room temperature. The reaction was apparently rapid. Filtration of salts, distillation (80−112 °C/1 mmHg) and chromatography (TLC, 5 % ether in light petroleum, R_F *ca.* 0.7) gave a mixture of the two cyclopropanes (ratio *ca.* 1 to 3) and *ca.* 8 % of ketone *16a*. MS [*m/e* (% rel.int.)]: 291 (0.5, M−CH_3), 261 (0.3, M−OEt), 249 (23, M−C_4H_7) 131 [100, 249−Et−O−Si$(CH_3)_3$], 103 (8, 131−CO), 73 (35, $(CH_3)_3$Si), 57 (12); *m** 249 → 131, obs. 68.8, calc. 68.9, *m** 131 → 103, obs. 81.0, calc. 81,0. ^{1}H NMR (90 MHz, CCl_4, $DCCl_3$ 1:1; δ of the minor component is given in parenthesis) δ 0.12 [0.18] (trimethylsilyl), 1.06 [1.04] (*tert*-butyl), 1.21 (t, J 7.2 Hz), 1.32 [1.14] (both d, J 8.0 Hz) 2.04 [2.13] (both d, J 8.0 Hz), 3.57 and 3.83 (4 quartets, calc. as AB part of ABX_3 system: $J_{AB} = -9.4$ Hz, $J_{AX} = J_{BX} = 7.2$ Hz), 7.14 (phenyl).

Reactions of magnesium 2-*tert*-butyl-1-ethoxy-3-phenylcyclopropanolate *(11): 4,4-dimethyl-1-phenyl-1,2-pentadiene* 17 and *3-phenyl-2,2,6,6-tetramethyl-4-heptanone* (16a). The reaction mixture A (above) and *tert*-butylmagnesium chloride (40 mmol) was heated to 80 °C in an ampoule for 1 h. After normal work-up as described, an aliquot part of the distillate was chromatographed by TLC (silica gel, light petroleum). Allene *17*, R_F 0.8, was isolated, yield 1.5 %. The sample was slightly impure. Found: C 89.32; H 9.30. Calc. for $C_{13}H_{16}$: C 90.68; H 9.37. MS [*m/e* (% rel.int.)]: 172 (54, M), 157 (33, M−CH_3), 116 (79, M−C_4H_8), 115 (55, M−C_4H_9), 57 (100, C_4H_9). ^{1}H NMR (60 MHz, CCl_4): 1.12 (9 H, s), 5.55 (1 H, d, J 6.4) 6.16 (1 H, d, J 6.4 Hz), 7.22 (5 H, s). ^{13}C NMR ($CDCl_3$): δ 96.2 (C1), 202.4[a] (C2), 106.8 (C3), 30.2 and 32.6[a] (*tert*-butyl), 126.4, 128.5 and 135.2[a] (aromatic); J (C1, H1) = J(C3,H3) 162 Hz. The C3 doublet was highly splitted (J *ca.* 5 Hz) in the ^{1}H undecoupled

spectrum. In the presence of atmospheric oxygen, approximately 1 mol of oxygen was taken up by the allene. Anal., found: C 77.29; H 8.37. Calc. for $C_{13}H_{16}O_3$: C 76.44; H 7.90. Ketone *16a* was isolated from the same chromatogram, R_f 0.4, yield 1 %. Anal. $C_{17}H_{26}O$: C,H MS [*m/e* (% rel.int.)]: 246 (1, M), 190 (67, $[M-C_4H_8]$), 147 (30, $[M-C_4H_9CH_2CO]$), 99 (100). ^1H NMR (270 MHz, $CDCl_3$): δ 0.93 (9 H, s), 0.97 (9 H, s), 2.21 (1 H, d, *J* 16 Hz), 2.26 (1 H, d, *J* 16 Hz), 3.54 (1 H, s), 7.27 (5 H, s). IR (KBr): 1710 cm^{-1} (s).

Reaction of mixture A (above) with excess dimethylmagnesium for 24 h at 20 °C gave, besides the compounds characterized above, 5,5-dimethyl-2-phenyl-3-hexanone (*16 b*). MS [*m/e* (% rel.int.)]: 204 (4, M), 148 (1, $M-C_4H_8$), 147 (1, $M-C_4H_9$), 105 (39, $M-C_4H_9CH_2CO$), 99 (81, $C_4H_9CH_2C{=}O^+$), 57 (100, $C_4H_9^+$). ^1H NMR (60 MHz, $CDCl_3$): 0.97 (9 H, s), 1.37 (3 H, d, *J* 7 Hz), 2.22 and 2.32 (AB-system, *J* 15 Hz), 3.73 (1 H, q, *J* 7 Hz), 7.28 (5 H, s). IR (KBr): 1710(s) cm^{-1}.

Radical tert-*butylation of ethyl cinnamate and cinnamic acid.* Ethyl cinnamate (28 mmol) was heated on the steam bath for 3 h with *tert*-butyldihydrobenzophenone prepared as described [4] from *tert*-butylmagnesium chloride and benzophenone (100 mmol). GLC analysis of the products indicated a 10:1 content of 1,3- to 1,4-adducts. After saponification of unreacted ethyl cinnamate and distillation, a fraction containing 1.3 g of the 2-alkylated product *19* was isolated. A similar experiment with tri-*tert*-butylcarbinol [5] conducted at 200 °C (ampoule) for 15 min again showed a 10:1 production of the two isomers (GLC). Alkylation of cinnamic acid (10 mmol) with the dihydrobenzophenone (above) gave mainly (NMR) the 2-alkylated hydrocinnamic acid. Chromatography and recrystallization gave the acid, m.p. 69 – 71 °C, lit. 69 – 71 °C.[1]

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