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1,3-Addition of *t*-Butylmagnesium Chloride to Ethyl Cinnamate: an Unprecedented Course of Reaction

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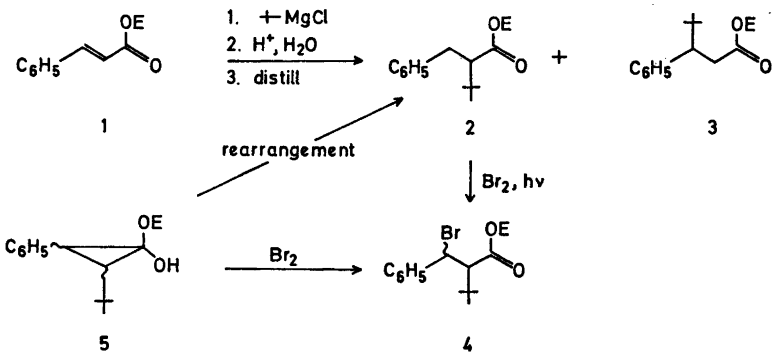
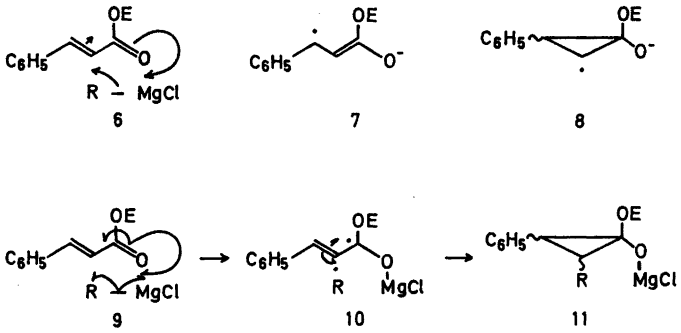
The distilled reaction mixture, resulting from addition of *t*-butylmagnesium chloride to ethyl cinnamate, contains, in addition to ethyl 3-*t*-butylhydrocinnamate (the expected 1,4-addition product) a considerable proportion of the isomeric 2-*t*-butylhydrocinnamate. A cyclopropanone hemiketal is suggested as the initial reaction product undergoing thermal rearrangement to the α-substituted ester. The reaction seems without precedent in addition reactions of the present type.

Alkyl cinnamates undergo unexceptional reactions (1,2- and 1,4-addition, dimerisation) with primary alkylmagnesium halides [1] whereas non-identifiable products,[2] or, after saponification, a low yield of β-*t*-butylhydrocinnamic acid,[3] constitute the only reported outcome of the reaction with *t*-butylmagnesium chloride. In contrast to the ester, cinnamic acid undergoes 1,4-addition with the tertiary reagent under similar conditions.[4,5]

In the present work, the distilled ester fraction, resulting from addition of *t*-butylmagnesium chloride to ethyl cinnamate in ether solution, was found to consist of a 2:3 mixture of ethyl 2-*t*-butylhydrocinnamate *2* and ethyl 3-*t*-butylhydrocinnamate *3* (total yield 70 %), as apparent from ^{1}H NMR spectra and from the selective removal of the latter ester on controlled alkaline hydrolysis, followed by conversion of the former into 2-*t*-butylhydrocinnamic acid [6] on prolonged alkali treatment. Magnesium purity, so important for the course of reaction in similar additions,[1] was of no decisive significance in the present case.

^{1}H NMR-Inspection of the original reaction mixture, after protonation but prior to distillation, reveals the presence of only small amounts of *2*. Singlets, positioned close to that arising from the *t*-butyl group of *2* and apparently converted into the latter upon distillation, may be attributed to dimeric, or polymeric species, but may arise also from one or more of the four cyclopropanone hemiketal racemates, collectively represented as *5*. Though still unproven, the intermediacy of *5* in the production of *2* is consonant with the finding that simple bromina-





tion of the non-distilled reaction mixture yields one of the diastereoisomeric 2-*t*-butyl-3-bromohydrocinnamic esters *4* in crystalline form.[6,7] Significantly, ethyl 2-*t*-butylhydrocinnamate *2* is virtually unsusceptible to bromination under these conditions. Subjected to photobromination, however, it readily affords a product mixture from which a bromoester *4*, identical with that prepared above, may be crystallized.

The ability of tertiary Grignard reagents to react by way of radical species, formed either by single electron transfer [8,9] or by induced homolysis,[10] may be reflected in the product composition of the present reaction, so different from that of similar reactions involving primary Grignard reagents.[1] A concerted mechanism, as indicated in *6*, is therefore hardly likely. A single electron transfer mechanism may be invoked to explain the formation of the *β*-*t*-butyl adduct *via* the radical *7*, but the production of *11* by a similar single electron transfer would involve the supposedly far less stable species *8*. For these reasons, the α-alkylation is rather believed to involve attack of a *t*-butyl radical, formed by induced homolysis of the Grignard reagent as formulated by *9*. The *t*-butyl radical may subsequently attack the α-carbon of an other ethyl cinnamate molecule (chain reaction), or react directly with the α (or *β*) carbon of the ketyl as shown in *10*. The main driving force in the initial step of this reaction sequence is believed to be the remarkably low C – Mg bond energy of *t*-butylmagnesium chloride [10] paired with the high energy of the O – Mg bond in the adduct.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on a Varian A-60 instrument using approx. 25 % solutions in $CDCl_3$. Chemical shift values are given in ppm on the *δ*-scale. Boiling points and melting points are uncorrected.

Ethyl 2- and 3-t-butylhydrocinnamate. (*2* and *3*) Ethyl cinnamate (20 mmol) was added at once with stirring to 60 mmol of *t*-butylmagnesium chloride [11] in ether (100 ml) at 5 °C. The cooling bath was removed and the temperature rose to 22 °C within 15 min. The suspension was poured into ice, acidified, and the aqueous phase was extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$) and distilled to give a yellow oil (3.24 g, 80 – 112 °C/0.5 mmHg). NMR analyses revealed it to be a mixture of ethyl cinnamate (0.28 g), ethyl 2-*t*-butylhydrocinnamate (1.19 g), and ethyl 3-*t*-butylhydrocinnamate (1.80 g). The yields and product composition were practically unaltered by using triply sublimed magnesium. NMR data for the two *t*-butylated esters were obtained from a mixture of the two esters and from the α-butylated ester *2*, isolated below; *δ*-values for the isomer *3* are given in parentheses: *t*-butyl 1.06 (0.87); methyl 0.99 (0.94); ABC system between 2.23 and 3.18; methylene 3.96 (3.91); phenyl 7.21.

2- and 3-t-Butylhydrocinnamic acid. The above procedure may be modified for larger scale synthesis and for preparation of the acids: the Grignard reagent (410 ml, 1.48 M by acid titration) was cooled to −8 °C and the ester (35.2 g) added rapidly with stirring. The cooling bath was removed after 2 min and the temperature rose to 25 °C within 10 min. After a total of 20 min, the mixture was worked up as above to give a mixture of the esters (32.9 g, containing less than 3 % of ethyl cinnamate). Reflux of the esters in a mixture of water (10 ml), ethanol (33 ml), and NaOH (5.7 g) for 1 h followed by addition of water, extraction with $CHCl_3$, and distillation gave crude ethyl 2-*t*-butylhydrocinnamate (12.43 g, 80 – 87 °C/0.5 mmHg. Saponi-

fication of the latter ester in methanolic sodium hydroxide (10 g in 40 ml) for 17 days gave crude 2-*t*-butylhydrocinnamic acid (5.2 g from petroleum ether, m.p. 68 – 70 °C). Recrystallization from a mixture of water (10 ml), acetic acid (10 ml), and ethanol (7 ml) gave colourless crystals, m.p. 69 – 71 °C; reported:[5] 70 °C.

The aqueous phase from the extraction of ethyl 2-*t*-butylhydrocinnamate (above) was acidified and extracted with $CHCl_3$ to give 16.1 g of crude acid. Recrystallization from a mixture of ethanol (18 ml), acetic acid (16 ml), and water (32 ml) gave 14.5 g of 3-*t*-butylhydrocinnamic acid, m.p. 113 – 115 °C; reported [4] 115 – 116 °C.

Ethyl 2-t-butyl-3-bromohydrocinnamate 4. Bromine (0.7 ml) was added to ethyl 2-*t*-butylhydrocinnamate (2.32 g crude, above) in CCl_4 (10 ml). No reaction took place in the dark. Two hours in the sun (evolution of HBr) and distillation gave crude ethyl 2-*t*-butyl-3-bromohydrocinnamate (2.66 g, 80 – 112 °C/0.5 mmHg). NMR analysis disclosed a 4 to 1 content of two similar, most likely diastereoisomeric compounds. Trituration with petroleum ether gave crystals (1.17 g) and an oil (1.48 g, isomer ratio *ca* 2:1). Recrystallization from ethanol (5 ml) gave colourless crystals (746 mg, m.p. 48 – 49 °C). The product was recrystallized from ethanol for analysis (Found: C 57.70; H 6.76; Br 25.46. Calc. for $C_{15}H_{21}BrO_2$: C 57.52; H 6.76; Br 25.51). NMR: δ 0.78 (*t*-butyl); 1.35 (methyl, triplet); 3.32 (C^{α} H, doublet, $J = 12.0$ Hz); 4.30 (methylene, quartet); 5.43 (C^{β} H; doublet, $J = 12.0$ Hz); *ca.* 7.45 (multiplet, phenyl). NMR on the crude product showed also a singlet at δ 1.35 and two doublets (δ 3.27 and 5.21, $J = 11$ Hz).

The same bromoester was also obtained from the adduct above (from 20 mmol ethyl cinnamate and 60 mmol of the Grignard reagent). The suspension was cooled to −50 °C and poured into excess ice with vigorous swirling. Acidification with hydrochloric acid, immediate bromination (20 mmol of Br_2 in 10 ml of CCl_4), and thorough shaking for about 1 min gave two phases. The aqueous phase was set aside (see below). The organic phase was washed with cold, aqueous ammonia, dried and distilled. A fraction (720 mg, 100 – 120 °C/0.4 mmHg) contained approximately equal amounts of ethyl 3-*t*-butylhydrocinnamate and the bromoester (the same isomer as isolated above, according to NMR). Less than 10 % of ethyl 2-*t*-butylhydrocinnamate was present. Crystallization as above gave crystals, m.p. 47 – 49 °C.

The bromination was modified as follows: Bromine (20 mmol) in CCl_4 (10 ml) was added to a mixture of ethyl 2-*t*-butylhydrocinnamate (2.34 g), ether (100 ml), ice and the aqueous phase (from the bromination, above). The suspension was stirred thoroughly for 15 min and worked up as above. The distillate contained less than 1.5 % of ethyl 3-bromo-2-*t*-butylhydrocinnamate (integration of the two relevant resonances from *t*-butyl groups).

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