Conjugate Addition of Grignard Reagents to α,β-Unsaturated Esters. XVII.* Additions to Some α-Phenylsubstituted Esters

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The addition of butylmagnesium bromide to *sec*-butyl esters of phenylmaleic, α-phenylacrylic, α-phenylcrotonic, and β,β-dimethyl-α-phenylacrylic acids has been investigated. The phenylmaleic ester gives conjugate addition in 70 % yield accompanied by some reduction of the double bond. The conjugate addition product is predominantly the α,α,'-di-substituted succinic ester. Presence of copper(I) chloride favours reduction over conjugate addition. The α-phenylacrylic ester gives only 11 % conjugate addition, the main product being Michael addition products. With α-phenylcrotonic ester the conjugate addition product has been obtained in 90 % yield, while β,β-dimethyl-α-phenylacrylic ester did not react even by boiling the reaction mixture.

In a previous communication [1] the reaction of butylmagnesium bromide with *sec*-butyl cinnamate was studied. Presently we wish to report the reactions of some other phenyl substituted esters with the same Grignard reagent (prepared from commercial Grignard magnesium).

From di-*sec*-butyl phenylmaleinate *** (I) three products have been recognized and identified (by GLC), namely the two possible conjugate addition products (II) and (III), and a product (IV) in which the double bond is reduced (see Table 1). Products of this type were expected from the results found with citraconic ester [2] (I), $R = CH_3$, although the ratio (85:15) of the two isomeric addition products (II) and (III) is different from that obtained from citraconic

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* No. XVI in this series, see Ref. 1.

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*** Due to the presence of two or more chiral centers in the molecules (I)− (IV), (VI) (VIII), and (XI) the products obtained are probably mixtures of diastereomers, which could not be separated by GLC.

Table 1. Yields obtained from the reactions of butylmagnesium bromide with *sec*-butyl esters of some phenyl substituted α,β-unsaturated acids.

sec-Butyl ester of acid	CuCl added	Conjugate addition product, %	Other products %
Phenylmaleic (I)	No	58 (II) [a] 10 (III) [a]	20 (IV) (reduction)
	Yes	42 (II) [a] 7 (III) [a]	31 (IV) (reduction)
α-Phenylacrylic (V)	No Yes	11 (VI) 12 (VI)	*ca.* 80 (IX) Michael add. *ca.* 75 (IX) Michael add.
α-Phenylcrotonic (VII)	No Yes	90 (VIII) 75 (VIII)	
β,β-Dimethyl-α-phenylacrylic (IX)	No Yes	No reaction	

[a] Ratio (II)/(III): 85:15

ester.* The predominant isomer, obtained from phenylmaleic ester (I), is α-butyl-α'-phenylsuccinic ester (II), the alkyl group of the Grignard reagent having entered preferentially at the unsubstituted carbon of the double bond.
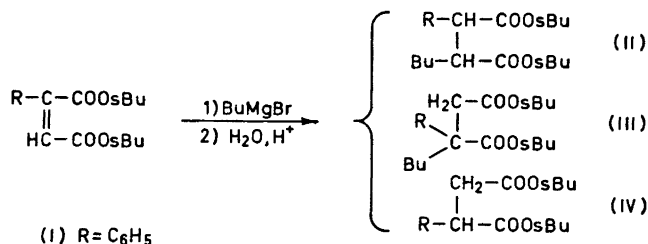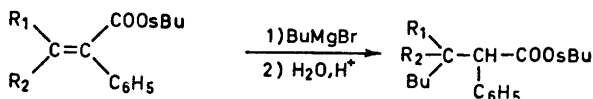

This is the opposite result of that found with citraconic ester. However, as in the latter case, the addition of copper(I) chloride gives rise to an increased proportion of the reduced product (IV).
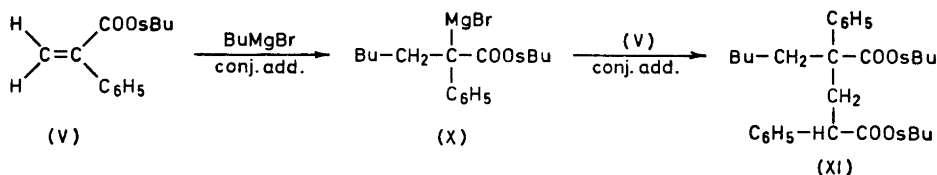
In the series of α-phenylacrylic esters (V), (VII), and (IX), with increasing methyl substitution in the β-position, only α-phenylcrotonic ester (VII) gives a good yield (90 %, see Table 1) of the conjugate addition product.

α-Phenylacrylic ester (V) yields only 11 % of conjugate addition product, the main component from the reaction being a Michael addition product, the trisubstituted glutaric ester (XI). This ester is probably derived from an initial conjugate addition of the Grignard reagent to one mole of (V), followed

* Later, more refined investigations[3] have shown, that the percentages given in the published paper[2] are incorrect due to the presence of diastereomeric products. The ratio between (II) and (III) for R=CH$_3$ seems to be as high as 45:55.

$$\underset{(V)\ R_1=R_2=H}{\underset{R_2}{\overset{R_1}{>}}C=C\underset{C_6H_5}{\overset{COOsBu}{<}}} \xrightarrow[\text{2) }H_2O,H^+]{\text{1) BuMgBr}} \underset{Bu}{\overset{R_1}{\underset{R_2-}{>}}}C-\underset{C_6H_5}{\overset{|}{CH}}-COOsBu$$

(V) $R_1 = R_2 = H$ (VI) $R_1 = R_2 = H$

(VII) $R_1 = H$; $R_2 = CH_3$ (VIII) $R_1 = H$; $R_2 = CH_3$

(IX) $R_1 = R_2 = CH_3$

by another conjugate addition of this adduct (X) to a new mole of (V) (see Scheme). This is completely analogous to the reactions of acrylic,[3] crotonic,[4] and tiglic [4] esters.

$$\underset{(V)}{\underset{H}{\overset{H}{>}}C=C\underset{C_6H_5}{\overset{COOsBu}{<}}} \xrightarrow[\text{conj. add.}]{\text{BuMgBr}} \underset{(X)}{Bu-CH_2-\underset{C_6H_5}{\overset{MgBr}{\underset{|}{C}}}-COOsBu} \xrightarrow[\text{conj. add.}]{(V)} \underset{(XI)}{\underset{C_6H_5-HC-COOsBu}{Bu-CH_2-\overset{C_6H_5}{\underset{CH_2}{\overset{|}{C}}}-COOsBu}}$$

The β,β-dimethyl substituted ester (IX) does not react at all even under forced conditions, such as boiling the reaction mixture.

These trends are presumably best explained by steric effects. Thus, the β-unsubstituted ester (V) shows very little hindrance towards addition of either the Grignard reagent or of the primary adduct (X). When one methyl group is present in the β-position the addition of the Grignard reagent proceeds smoothly, but further reaction to (XI) is hindered. Finally, two methyl groups in the β-position renders conjugate addition of either type impossible.

EXPERIMENTAL

Microanalyses were performed by Mr. Preben Hansen, Chemical Laboratory II, The University of Copenhagen; NMR-spectra were recorded on a Varian A-60 instrument in deuteriochloroform (δ-values). For gaschromatographic analyses was used a Perkin-Elmer 116E fractometer fitted with a 4 mm i.d. × 1 m column (20 % silicone gum E 301 on Celite 445), unless otherwise stated. Boiling points and melting points are uncorrected.

The Grignard reagent was prepared from a commercial grade magnesium * in the usual way [5] in the stated amounts, and the additions were carried out as previously described.[1] In the copper(I) chloride catalysed additions, the catalyst was added in seven 0.1 g portions during the addition of the ester.[2]

Preparation of di-sec-butyl phenylmaleinate (I). Phenylmaleic anhydride was prepared from phenylsuccinic anhydride [7,8] according to Miller *et al.*[9] The ester (I) was obtained by esterification of the anhydride in the usual way; [5] the conversion was incomplete, but on distillation the unreacted anhydride was separated as a lower boiling fraction, and phenylmaleic ester (conversion 28 %) was obtained, b.p. $149-150°/0.6$ mm, $n_D^{24} = 1.5158$. The purity was checked by GLC and analysis. (Found: C 70.85; H 7.77. Calc. for $C_{18}H_{24}O_4$: C 71.02; H 7.95.) NMR-spectrum: $0.8-2.0$ ppm (16 H, complex group of signals arising

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* An analysis is given in Ref. 6 (Mg sample II).

from the *sec*-butoxy groups), 5.05 (*m*, 2H, O−CH), 6.29 ppm (*s*, 1 H, vinylic CH) and 7.42 ppm (*m*, 5 H, aromatic CH).

Additions to di-sec-butyl phenylmaleinate. The additions were carried out using 0.05 mol of ester and 0.13 mol of butylmagnesium bromide in 100 ml of ether. The distilled reaction mixtures − containing the three products (II), (III), and (IV) − were analysed by GLC (4 mm i.d. × 2 m, 25 % Apiezon grease M on Celite 445) by comparison with authentic compounds prepared as described below. The compositions of the mixtures were calculated on the assumption that the proportions of the peak areas in the chromatograms were equivalent to the mol proportions.

The authentic compounds (II), (III), and (IV) were prepared by alkylation of the appropriate α-phenyl-substituted ester with an α-bromo-substituted ester, essentially according to the general procedure described by Hauser and Chambers [10] using potassium amide in liquid ammonia.

Di-sec-butyl α-butyl α'-phenylsuccinate (II) was obtained in 80 % yield from *sec*-butyl phenylacetate (b.p. 106°/4 mm; $n_D^{20}=1.4870$) * and *sec*-butyl α-bromohexanoate (b.p. 69°/0.9 mm; $n_D^{22.5}=1.4475$). (Found: C 47.86; H 7.75. Calc. for $C_{10}H_{19}O_2Br$: C 47.81; H 7.61.)* These esters were obtained in about 80 % yield from the corresponding acids by the standard method.[5] Data for (II): b.p. 152−155°/1. 1 mm; $n_D^{20}=1.4753$. (Found: C 72.85; H 9.34. Calc. for $C_{22}H_{34}O_4$: C 72.89; H 9.45.)

Di-sec-butyl α-butyl-α-phenylsuccinate (III) was obtained in a rather low yield (28 %) from *sec*-butyl bromoacetate [1] and *sec*-butyl 2-phenylhexanoate (b.p. 110−111°/1.5 mm; $n_D^{24.5}=1.4772$). (Found: C 77.22; H 9.74. Calc. for $C_{16}H_{24}O_2$: C 77.37; H 9.74.) The latter ester was in turn obtained by the alkylation of *sec*-butyl phenylacetate with butyl bromide. Data for (III): b.p. 155°/0.8 mm, $n_D^{23}=1.4788$. (Found: C 72.70; H 9.40. Calc. for $C_{22}H_{34}O_4$: C 72.89; H 9.45).

Di-sec-butyl phenylsuccinate (IV) was obtained analogously from *sec*-butyl phenylacetate and *sec*-butyl bromoacetate, yield 66 %. Data: b.p. 157−158°/3 mm; $n_D^{23}=1.4770$. (Found: C 70.70; H 8.60. Calc. for $C_{18}H_{26}O_4$: C 70.56; H 8.55.)

Preparation of sec-butyl α-phenylacrylate (V). Esterification of atropic acid with butan-2-ol by the standard method [5] was unsuccessful as the acid was recovered unchanged after work-up.** However, it could be prepared essentially according to the method given by Schinz and Hinder.[12] Thus, *sec*-butyl phenylacetate was condensed with di-*sec*-butyl oxalate,*** using potassium *sec*-butanolate as base, giving 65 % yield of crude di-*sec*-butyl oxaloyl-phenylacetate. Treatment of this ester with formaldehyde and potassium carbonate gave the desired ester (V) in 40 % yield. B.p. 85.5°/0.7 mm; $n_D^{22}=1.5083$. (Found: C 76.62; H 7.80. Calc. for $C_{13}H_{16}O_2$: C 76.44; H 7.90.) NMR-spectrum: 0.96 ppm, 1.28 ppm and 1.59 ppm (*t*, *d*, and *m*, corresponding to the 4-CH₃, 1-CH₃ and 3-CH₂ protons of the *sec*-butoxy group, respectively), 5.03 ppm (*m*, O-CH), 5.88 ppm and 6.33 ppm (*d* and *d*, vinylic protons (*J*=1.4 cps)) and lastly 7.40 ppm (*m*, aromatic protons).

Additions to sec-butyl-α-phenylacrylate (V) were carried out with 0.05 mol of ester and 0.13 mol of Grignard reagent in 100 ml of ether, both non-catalysed and copper(I) chloride catalysed. The conjugate addition product, *sec-butyl 2-phenylhexanoate* (VI), had b.p. 120°/1.8 mm; $n_D^{24}=1.4791$. (Found: C 77.80; H 9.96. Calc. for $C_{17}H_{26}O_2$: C 77.82; H 9.99.) The residue from the fractionation was not distillable up to 220°/1 mm (bath temperature). An NMR-spectrum of this residue indicated that it was largely the Michael addition product (expected NMR-integrals for aromatic CH, alkoxy CH and aliphatic CH$_x$, 10:2:28; found: 10:2:30). The residue was not subjected to further analysis.

Preparation of sec-butyl-α-phenylcrotonate (VII). This ester was obtained from α-phenyl-*trans*-crotonic acid [15] by the standard esterification method.[5] B.p. 90.5°/1 mm; $n_D^{20}=1.5090$. (Found: C 77.00; H 8.45. Calc. for $C_{14}H_{16}O_2$: C 77.03; H 8.31.) NMR-spectrum: 0.9 ppm, 1.22 ppm, and 1.5 ppm (*t*, *d* and *m*, corresponding to the 4-CH₃, 1-CH₃, and 3-CH₂ protons from the *sec*-butoxy group, respectively), 1.74 ppm (*d*, allylic CH₃ (*J*=7 cps)), 4.97 ppm (*m*, O−CH) and 7.0−7.7 ppm (*m*, aromatic and vinylic CH).

⌐ * The NMR-spectrum was in agreement with the expected structure.

** The ester has later been prepared by the esterification of atropic acid in 35 % yield using boron trifluoride etherate as catalyst.[14]

*** Prepared by the standard procedure.[5] B.p. 110°/15 mm; $n_D^{26}=1.4150$. (Found: C 59.55; H 9.06. Calc. for $C_{10}H_{18}O_4$: C 59.38; H 8.97.) Reported:[13] b.p. 221−222.5°/774.4 mm; $n_D^{16}=1.4206$.

Additions to sec-*butyl* α-*phenylcrotonate* (VII) were carried out with 0.1 mol of ester and 0.25 mol of Grignard reagent in 100 ml of ether, both non-catalysed and copper(I) chloride catalysed. The conjugate addition product sec-*butyl 2-phenyl-3-methylheptanoate* (VIII) boiled at 112°/1 mm; $n_D^{25} = 1.4787$. (Found: C 78.45; H 10.10. Calc. for $C_{18}H_{28}O_2$: C 78.21; H 10.21.)

Preparation of sec-*butyl* β,β-*dimethyl*-α-*phenylacrylate* (IX). 3-Hydroxy-2-phenyl-isovaleric acid was prepared according to the method of Ivanoff and Spassoff [16] from acetone (14.5 g) and sodium phenylacetate (39.5 g). The crude product, after work-up, was poured into conc. sulfuric acid (40 ml), and after 1 h, water (200 ml) was added. The mixture was then refluxed for 1 h. After cooling, the crystals were collected and re-crystallised from ethanol giving 19 g (43 %), m.p. 148 − 150°.

The corresponding acid chloride was prepared by treatment with thionyl chloride in benzene and distillation giving 9.8 g (47 %) of an oil, b.p. 115 − 118°/12 mm; $n_D^{22} = 1.5520$. Reaction of the chloride with butan-2-ol (10 ml) in benzene (30 ml) under reflux gave, after work-up, 10.3 g of (X), b.p. 101 − 102°/1.1 mm; $n_D^{23} = 1.5050$. (Found: C 57.60; H 8.40. Calc. for $C_{15}H_{20}O_2$: C 77.55; H 8.68.)

Attempts to react (X) with butylmagnesium bromide were unsuccessful whether catalysed with copper (I) chloride or non-catalysed; not even boiling of the ether solution under reflux for 4 h gave any reaction and the ester was recovered in 90 % yield by distillation.

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