Conjugate Addition of Grignard Reagents to

α,β-Unsaturated Esters

XVI. Reactions with sec-Butyl Cinnamate

S. ROSENDAL JENSEN, A.-M. KRISTIANSEN, and (the late) J. MUNCH-PETERSEN

Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Previously reported low yields of conjugate addition products from the reaction between sec-butyl cinnamate and butylmagnesium bromide are shown to be caused by impurities in the standard grade magnesium employed. Triply sublimed magnesium affords excellent yields.

A major part of the by-products formed in the low yield reactions is shown to consist of diastereomeric esters of meso- and racemic 3,4-diphenyladipic acid, the latter accompanied by a Dieckmann cyclisation product.

Addition of various metal chlorides to the reactions performed with purified magnesium results in suppression of conjugate addition products. Thus, addition of one mole per cent of ferric chloride yields an ester mixture which, after saponification, affords an 80 % yield of the mixed, diastereomeric 3,4-diphenyladipic acids.

As reported in previous communications from this laboratory,[1-4,22] yields are moderate to low (30 — 35 %) when diastereomeric sec-butyl 3-phenyl-heptanoates (2), are formed by conjugate addition of butylmagnesium bromide to sec-butyl cinnamate.* Addition of cuprous chloride raised the yield to about 50 %.

(1) (2) (3)

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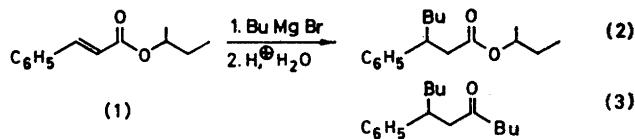
* Throughout the present paper sec-butyl refers to the racemic alkyl.

A suspicion that impurities in the magnesium employed were partly responsible for the extensive side-reactions,[5-7] caused us to repeat the reactions with triply sublimed magnesium. The results are presented in Table 1. In fact, purified magnesium gives a much better yield than the standard grade metal. In the cuprous chloride catalyzed reaction, the yield is not much better, but the formation of ketone (3) is totally suppressed.

Table 1. Yields of conjugate addition products from the reaction of butylmagnesium bromide with *sec*-butyl cinnamate.

Mg-quality used to prepare BuMgBr	Uncatalysed reaction			CuCl-catalysed reaction		
	Expt. No.	(2) [b] %	(3) [b] %	Expt. No.	(2) [b] %	(3) [b] %
III [a]	1	28	5	3	50	*ca.* 2
I [a]	2	83	6	4	64	0

[a] The numbers refer to the analysed samples described in an earlier paper.[5] III is a commercial grade of Grignard magnesium (Fluka), containing 295 ppm Fe and 695 ppm Mn. I contains *ca.* 10 ppm Fe and <10 ppm Mn. Thanks are due to Dow Chemical International Inc. for the generous gift of this high-grade magnesium.
[b] Formula number.

From the non-distillable residue from experiment No. 1 (*cf.* Table 1), two crystalline ester fractions were obtained, designated "4a" and "5", and yielding *meso* [9] (6a) and *racemic* [9] (6b) 3,4-diphenyladipic acid, respectively, on alkaline hydrolysis. Hydrolysis of "5" with hydrobromic acid in acetic acid afforded the known [13] *trans*-3,4-diphenylcyclopentanone (7). Hence, "4a"
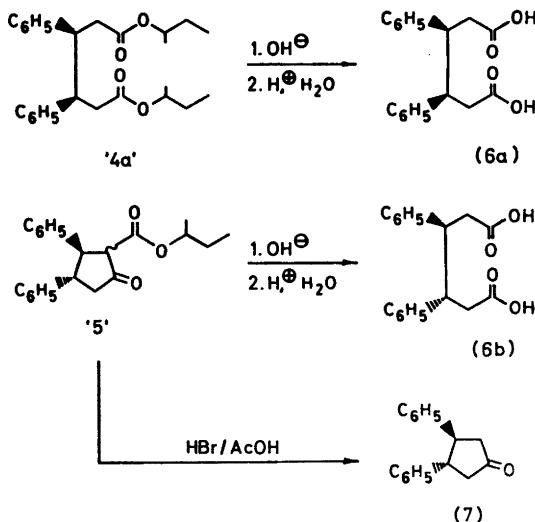
and "5" represent mixtures, of unknown compositions, of diastereomeric *sec*-butyl esters with the structure shown in the annexed formula scheme.*

The ester "4b" derived from the racemic acid (6b) was demonstrated to be present in the mother liquors (see Experimental), but was not isolated.

Though the formation of reductive dimerisation products from α,β-unsaturated esters under the influence of Grignard reagents seems unprecedented, several cases are on record of the production of diphenyladipates,[8-12] or Dieckmann cyclization products hereof,[13-15] from cinnamic esters with other reagents such as aluminium amalgam [8-12] or sodium in ether.[13-15] Kharash and Sayles [16] demonstrated that the reaction of benzalacetophenone (8) with excess methylmagnesium bromide, proceeding to the expected conjugate addition product (9), took an entirely different course in the presence of cobaltous chloride (2 mole %), yielding the diastereomeric ketones (10) in high yield. Ferric, cuprous, and manganous chlorides were far less efficient in this respect. In
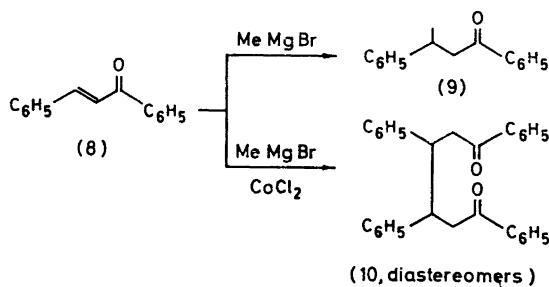
order to rationalise the catalytic effects Kharash and Fields [17] have proposed a chain mechanism. The overall reaction is shown below for the present case.
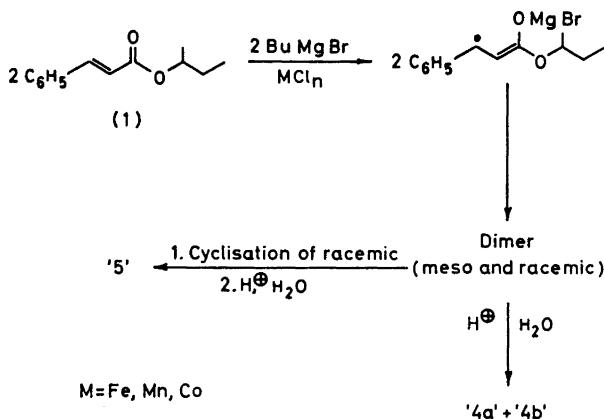
* Theoretically, "4a" consists of a mixture of one racemic modification and two *meso*-forms; "5" of four *racemic* modifications. Only in the case of "5" has a homogeneous ester been isolated (see Experimental).

With a view to studying the possible effects of impurities in the standard grade magnesium employed,* a known amount of metal chloride was added to the butylmagnesium bromide solution, prepared from triply sublimed magnesium, prior to the cinnamate. The results are presented in Table 2.

Table 2. Product compositions from the reaction of butylmagnesium bromide with *sec*-butyl cinnamate catalysed by various metal salts.

Mg sample	Catalyst	Conjugate add.prod. (2)+(3), %	Reductive dimerisation.			
			Total, %	Approx. product ratio; %		
				"4a"	"4b"	"5"
III	none	35	65	15	35	50
I	none	89	*ca.* 5			
I	FeCl$_3$ (0.1 %)	64	30	15	35	50
I	FeCl$_3$ (1 %) ^{a}	0	91	20	35	45
I	MnCl$_2$ (1 %)	13	83	15	25	60
I	CoCl$_2$ (1 %) ^{b}	22	54	15	40	40

^{a} An experiment in which the reaction mixture was stirred overnight before hydrolysis gave the same result.

^{b} In this experiment was produced 21 % of hydrocinnamic ester, found in trace amounts only in the other experiments.

Analyses of the reaction mixture were conducted as described in Experimental. It is evident that addition of these salts dramatically influence the course of the reaction. In the present case, addition of 1 mole % of ferric chloride results in virtually quantitative formation of reductive dimerisation products. Cobaltous chloride, in the present series, has a far less dramatic effect than ferric chloride in this respect, but causes some reduction to hydrocinnamic ester.** We have no explanation for these observations. The ferric chloride catalysed reaction between butylmagnesium bromide and *sec*-butyl cinnamate can conveniently be employed for the production, in about 80 % yield, of a mixture of *meso-* and racemic 3,4-diphenyladipic acid.

It was noted above that only esters derived from the racemic acid undergo partial cyclization. Accepting the most stable conformers presented by Curtis and Dayasi [18] it appears reasonable that the racemic series cyclizes readily, due to the proximity of the groups involved.

* Impurities, apart from manganese (695 ppm) and iron (295 ppm), did not exceed 75 ppm; see foot-note in Table 1.

** Reduction of the double bond in α,β-unsaturated esters is only observed in a few instances and only in cases of dicarboxylic acid esters. Known cases comprise alkylidenemalonic and cyanoacetic esters,[19] with and without CuCl-catalysis, citraconic and mesaconic esters,[19] with CuCl-catalysis. Finally, *t*-butyl esters of α-isopropyl- and α-*t*-butylmaleic acid,[20] give the α-alkylsuccinates (24 and 38 %, respectively) on reaction with a Grignard reagent, prepared from triply sublimed magnesium and without addition of catalyst.

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; chemical shift values are given in ppm on the δ-scale. Boiling points and melting points are uncorrected.

The Grignard reagent was prepared in the usual way [21] with slight modifications; thus, only 1.05 equiv. of butyl bromide was used (relative to magnesium). Consequently, boiling was continued for 2−3 h until all magnesium had dissolved.

sec-Butyl cinnamate (1) was prepared by the standard method,[21] b.p. 110°/1.2 mm; $n_D^{20} = 1.5410$.

Conjugate additions. Reactions were performed in the following way: The Grignard reagent (0.25 mole) from the appropriate magnesium sample was prepared in 100 ml of ether and cooled to 0°. The ester (0.1 mole), dissolved in 100 ml of ether, was added with stirring and cooling during 1 h. Stirring was continued for another hour at room temperature, whereupon the reaction mixture was poured onto a mixture of ice and excess hydrochloric acid and taken up into ether. After drying (Na_2SO_4), the ether was evaporated *in vacuo* and the product distilled. Gas chromatographic analysis (4 mm i.d. × 1 m, silicone gum E 301 on Celite 445) was used to determine the composition of the distillate. From experiment No. 4 (Table 1) *sec*-butyl 3-phenylheptanoate (2) of unknown stereochemical composition was obtained, b.p. 130°/1.6 mm; $n_D^{20} = 1.4795$. Reported:[1] b.p. 115°/0.8 mm; $n_D^{20} = 1.4792$.

Saponification of the distillate from experiment No. 1 (Table 1), followed by distillation of the neutral part, gave *3-phenyl-undecan-5-one* (3), b.p. 105°/0.3 mm; $n_D^{22} = 1.4908$. (Found: C 82.62; H 10.68. Calc. for $C_{17}H_{26}O$: C 82.87; H 10.64). Distillation of the acid fraction afforded *3-phenylheptanoic acid*, b.p. 118°/0.3 mm; $n_D^{22} = 1.5042$. (Found: C 75.85; H 8.76. Calc. for $C_{13}H_{18}O_2$: C 75.69; H 8.80).

Isolation of the products from reductive dimerization. From the distillation residue, diastereomeric mixtures of *di-sec-butyl* meso-*3,4-diphenyladipate* ("4a") and *sec-butyl* trans-*3,4-diphenylcyclopentanone-2-carboxylate* ("5") could be isolated in yields of about 10 and 15 %, respectively, by fractional crystallization from chloroform with increasing amounts of acetone.

The first fraction (m.p. 135−140°), from pure chloroform, consisted essentially of "4a" (NMR). Three additional recrystallizations from chloroform raised the melting point to 145−155°. (Found: C 76.05; H 8.43. Calc. for $C_{26}H_{34}O_4$: C 76.06; H 8.34). NMR-spectrum: 7.28 ppm (broad singlet, Ar−H), 4.55 ppm (*m*, O−CH), 3.30 ppm (*m*, Ar−CH), 2.40 ppm (*m*, CH_2−COO), and a complex group of signals at 0.5−1.5 ppm arising from the *sec*-butoxy groups. Alkaline hydrolysis of "4a" with excess ethanolic potassium hydroxide gave meso-*3,4-diphenyladipic acid* (6a), m.p. 270−271°; reported [9] 270−271°. Dimethyl ester, m.p. 175−176°; reported [9] 175°.

The subsequent fractions were mixtures of "4a" and "5", crystallizing on addition of increasing amounts of acetone. When no more material crystallized, the solvent was evaporated, and the residue crystallized from ethanol to give a crop of "5". Two additional recrystallizations from ethanol gave a product with m.p. 125−126°. Elemental analysis was consistently too low in carbon, and further recrystallizations from ethanol did not improve this result.[*] The NMR-spectrum revealed absorptions from more than one type of *sec*-butoxy group, which might be due to either impurities or diastereomers. Ten recrystallizations from ether accompanied by substantial losses gave a homogeneous compound, m.p. 132.5−133.5°. (Found: C 77.95; H 6.92. Calc. for $C_{22}H_{24}O_3$: C 78.54; H 7.19). NMR-spectrum: 7.20 ppm (broad singlet, Ar-H), 4.90 ppm (*m*, O−CH), complex signals 3.1−4.2 ppm (benzylic CH and CH α to carbonyl), 2.5−3.1 ppm (*m*, CH_2−CO), and 0.5−1.7 ppm (CH_2 and CH_3 in the *sec*-butoxy group). The homogeneous compound exhibited a doublet centered at 1.11 ppm arising from the protons at C_1 in the *sec*-butoxy group, while the original mixture (m.p. 125−126°) displayed two doublets centered at 1.11 and 1.22 ppm and of approximately equal intensities. The 2,4-dinitrophenylhydrazone was prepared, m.p. 147°. (Found: C 64.75; H 6.07; N 11.05. Calc. for $C_{28}H_{28}N_4O_6$: C 65.10; H 5.45; N 11.85). Alkaline hydrolysis gave (6b), m.p. 182−184°; reported [9]

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[*] Totton *et al.*[14] report a melting point of 111−112° for a similar preparation, unfortunately though, without analysis.

185—186°. Dimethyl ester, m.p. 74—75°; reported[9] 73—74°. Acid hydrolysis with 48 % hydrobromic acid in glacial acetic acid gave *trans*-3,4-diphenylcyclopentanone (7), m.p. 178°; reported[13] 177°. Oxime, m.p. 118°; reported[13] 117—118°.

The NMR-spectra of the dimethyl esters of (6a) and (6b) are very different. In the former the aromatic protons give rise to a broad singlet at 7.35 ppm, while the corresponding signals from the latter appear as a complex multiplet at 6.80—7.35 ppm, due to magnetic anisotropy, caused by the closely positioned phenyl groups.[18]

Examination by NMR of the mother liquors from the crystallization of "4a" and "5", reveal the presence of "4b" in the mixture. In addition to residual absorptions of the aromatic protons from "4a" and "5", signals quite similar to those of the methyl ester of (6b) were present. Attempts to isolate the product were unsuccessful.

Catalysis with metal halides. After preparation of the Grignard reagent as before (0.25 mole), the specified (Table 2) amounts of $FeCl_3$, $CoCl_2$ or $MnCl_2$ were added to the warm, clear reagent, producing black-brown solutions or dispersions. The mixtures were then stirred at room temperature for 15 min ($FeCl_3$ and $CoCl_2$), or for 1 h at the boiling point ($MnCl_2$), whereupon they were cooled in an ice bath for 15 min. Addition of the ester (0.10 mole) and work-up procedure were as described for the uncatalyzed reactions. The reaction products were distilled to isolate conjugate addition products ((2) and (3), see Table 2). The residues from the distillations were analyzed in the following way: An aliquot of the residue was saponified with excess KOH in ethanol whereby "4a" was converted to (6a), and "4b" as well as "5" into (6b). Acid hydrolysis of another aliquot converted "4a" and "4b" into (6a) and (6b), respectively, but "5" into the ketone (7), which was discarded. Esterification with diazomethane of the two hydrolyzed fractions yielded mixtures of dimethyl esters in different proportions; they were analyzed by NMR technique.* From the two different proportions, the original compositions of the residue could be calculated (see Table 2).

Saponification. One half of a residue (0.05 equiv.) was saponified with KOH (0.11 mole) in ethanol (50 ml) under reflux for 3 h. The solvent was removed *in vacuo*, and the residue was dissolved in water and extracted with 3×5 ml of ether to remove neutral components. The aqueous solution was acidified with conc. hydrochloric acid and extracted again with 3×50 ml of ether. The organic phase was dried (Na_2SO_4) and taken to dryness. The sum total of (2), (3), and the present solid acid residue, amounted to 90—100 % of the theoretical.

Conversion to the methyl esters. The acid mixtures were converted into methyl esters by diazomethane in the usual way. About 70 mg of the ester mixtures were employed for recording the NMR-spectra. The relative amounts of the dimethyl esters of (6a) and (6b) were determined by measuring peak heights of the respective methoxy absorption signals.

Acid hydrolysis. The other halves of the residues were dissolved in 50 ml of glacial acetic acid. 15 ml of 48 % hydrobromic acid was added, and the mixtures boiled for 24 h. Acetic acid was removed *in vacuo*, and the residue dissolved in excess KOH solution. From here on work-up, methylation, and measurements were performed as described above.

Preparation of 3,4-diphenyladipic acids. To 0.25 mole of Grignard solution, prepared from commercial magnesium, is added 0.8 g (5 mmole) of $FeCl_3$; the solution is boiled under stirring for 15 min. Stirring is continued with ice cooling for an additional period of 15 min, and 40.8 g (0.2 mole) of *sec*-butyl cinnamate in 100 ml of ether is added in the course of 1 h. Stirring is continued for another hour at room temperature. The resulting dark red-brown solution (sometimes two phases) is then added to a stirred mixture of 100 ml of ether, 50 ml of hydrochloric acid, and 300 g of ice. The phases are separated — regardless of the suspended solid material in the organic phase — and the aqueous phase extracted with 2×100 ml of chloroform. The combined organic solutions are dried (Na_2SO_4) and the solvents removed in *vacuo*. The residue is dissolved in ethanol (100 ml), NaOH (25 g) is added, and the mixture refluxed for 3 h. Ethanol is then removed *in vacuo*, and the residue dissolved in water which is extracted with ether, and the ether

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* The dimethyl esters of (6a) and (6b) absorb at 3.40 and 3.58 ppm, respectively. Preliminary experiments with known mixtures of the dimethyl esters ((6a):(6b)=1:4 and 1:5) showed good agreement (better than 3 % accuracy) between the ratio of the peak heights and the proportions of the esters.

discarded. The resulting aqueous solution is acidified with hydrochloric acid and the organic compounds taken up into ether, which is dried as before; the ether is removed *in vacuo*. The solid residue amounts to 28 g (94 %).

For crystallization, the product is dissolved in a mixture of 150 ml of benzene and 15 ml of ethanol. Cooling overnight in the refrigerator gives 15.5 g of colourless crystals melting over a wide range (170—230°). The mother liquors are concentrated almost to dryness and redissolved in as little benzene as possible. Addition of ligroin (b.p. 60—80°) and cooling gives an additional crop of crystals (9.5 g), m.p. 170—180°. Total yield 24 g (80 %).

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