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Conjugate Additions of Grignard Reagents to alpha, beta-Unsaturated Esters

XIII. Additions to *cis,trans*-Isomeric But-2-enoic and 2-Methylbut-2-enoic Esters

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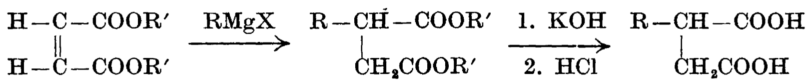
In reactions with butylmagnesium bromide isocrotonic and angelic esters give lower yields of conjugate addition products than do crotonic and tiglic ester, respectively. Stereochemical interpretations of this result are considered.

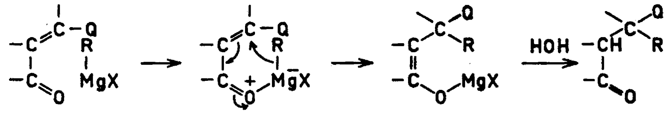
In previous communications[1,2] the reaction of Grignard reagents with esters of *cis, trans*-isomeric ethylene-1,2-dicarboxylic acids, such as maleic and fumaric esters and citraconic and mesaconic esters, were described. The present paper reports some results encountered by the addition of butylmagnesium bromide to *sec*-butyl esters of isocrotonic and crotonic acids as well as of angelic (*cis*-2-methylbut-2-enoic) and tiglic (*trans*-2-methylbut-2-enoic) acids.

Among the *cis,trans*-isomeric *di*carboxylic esters the *cis* compounds gave considerably higher yields of simple conjugate addition products than did the *trans* compounds. This difference in reactivity was particularly pronounced in the case of maleic and fumaric esters (*cf.* below). In fact, the reaction of maleic esters with a number of Grignard reagents may be utilized as a practical route for the preparation of alkylsuccinic acids[2]:



$$\begin{array}{l} \mathrm{H-C-COOR'} \\ \quad \| \\ \mathrm{H-C-COOR'} \end{array} \xrightarrow{\mathrm{RMgX}} \begin{array}{l} \mathrm{R-CH-COOR'} \\ \qquad | \\ \qquad \mathrm{CH_2COOR'} \end{array} \xrightarrow[\mathrm{2.\ HCl}]{\mathrm{1.\ KOH}} \begin{array}{l} \mathrm{R-CH-COOH} \\ \qquad | \\ \qquad \mathrm{CH_2COOH} \end{array}$$

Considering the commonly accepted mechanism for the conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds, involving a cyclic synchronous electron shift within a six-membered ring[3]:



(1)

the presence of a large group Q in the *cis* position relative to that carbonyl group, with which the Grignard reagent forms a coordinative bond, should obviously constitute a hindrance to the reaction. The higher reactivity of the *cis* compounds towards conjugate addition was therefore unexpected; on the other hand, it may be explained on the basis of the preclusion of coplanarity between the carbon-carbon double bond and *both* carbonyl groups in a *cis* compound, such as maleic ester. This missing coplanarity not only renders the double bond more reactive in general, but more specifically it annihilates the internal symmetry of the ethylenic bond, in that this bond always may be coplanar — and therefore enter into conjugation — with one, *but only with one* carbonyl group at a time. Thus, the polarity and therefore the reactivity towards conjugate addition of nucleophilic reagents is enhanced.

In the present study it has been found that, in contrast to the results obtained with maleic and fumaric esters, the *cis*-isomers of crotonic and α-methylcrotonic esters give considerably lower yields of conjugate addition product than do the *trans*-isomers (Tables 1 and 2). This result is, however, exactly what would be expected from the above-mentioned considerations concerning the steric implications of the cyclic mechanism (eqn. 1).

Furthermore, also the coplanarity between the carbon-carbon double bond and the carbonyl group will be sterically hindered by a methyl group in the *cis* position (isocrotonic and angelic esters). This steric effect on coplanarity, on the other hand, is quite different from the just above discussed effect encountered in the case of maleic ester. A carboxylic ester group is — considered as a substituent group Q, such as in the case of maleic ester — sterically much less demanding than a methyl group. The carboxyl group is in itself planar, and as the substituent Q (eqn. 1) it does not, therefore, hinder coplanarity between the double bond and the other carbonyl group, if it is rotated to a plane approximately vertical to the plane of the double bond. Therefore, the conjugate addition to the double bond (involving conjugation with the other carbonyl group) is not hindered if the substituent Q is a carboxylic ester group. On the other hand, if Q, as in isocrotonic and angelic esters, is a methyl group, it will to a considerable degree hinder coplanarity; thus other reaction types competing with the conjugate addition may be favoured. The steric coplanarity effect considered above to be operative in maleic ester, favouring the conjugate addition, was just the prevention of the coplanarity with *one* of the two carbonyl groups, such as to enhance the dissymmetry of the double bond, produced by the conjugation with the other carbonyl group.

The same substituent effect of the methyl group as that observed in the case of isocrotonic and angelic esters, was met with in mesaconic (methylfumaric) ester.[1] By the conjugate addition of butylmagnesium bromide the total yield of simple conjugate addition product was smaller (42—55 %) than that obtained from citraconic (methylmaleic) ester (62—70 %). Furthermore, whereas the α-methyl-α-butylsuccinic ester is produced in the larger amount

Table 1. Yields and compositions of low-boiling conjugate addition products obtained by reactions of *sec*-butyl esters of *cis*-,*trans*-isomeric but-2-enoic and 2-methylbut-2-enoic acids with butylmagnesium bromide.

Ester	Catalyst	Total conj. add. prod. %	Saturated ester (1,4-add.)		Saturated ketone (1,2 + 1,4-add.)	
			%	% of total**	%	% of total**
Crotonic	none	75	73	97 (98)	2	3 (2)
	CuCl	85	82	96 (98)	3	4 (2)
Isocrotonic *	none	40	32	80 (83)	8	20 (17)
	CuCl	54	51	94 (95)	3	6 (5)
Tiglic	none	72–76	57–60	79 (80)	15–16	21 (20)
	CuCl	58–61	44–46	76 (77)	14–15	24 (23)
Angelic *	none	44	22	50 (52)	22	50 (48)
	CuCl	37	20	54 (56)	17	46 (44)

* The percentages given for the yields from the *cis* compounds are corrected in consideration of the amount of the *trans*-isomer present in the *cis*-product used (*cf.* experimental part).

** The percentages given in parentheses in the two last columns are percentages by weight of compounds.

from both isomeric esters, the percentage of α-methyl-α′-butylsuccinic ester in the product from mesaconic ester was larger (30 %) than in the product from citraconic ester (10 %) *. The *polarity effect* of the methyl group could be made responsible for the predominant formation of the α,α-compound from both isomeric esters. On the other hand, the lower total yield, as well as the formation of the α,α′-compound to a larger degree from mesaconic ester than from citraconic ester may be explained by the *steric effects* exerted by the methyl group. The above-mentioned coplanarity effect as well as the direct steric hindrance from the methyl group would be expected to favour the formation of the α,α′-compound, this orientation for the addition being opposed by the polarity effect of the methyl group.

By the reactions of the unsaturated esters with butylmagnesium bromide now described two types of compounds were obtained (besides higher-boiling products):** a saturated ester, as the result of simple conjugate addition

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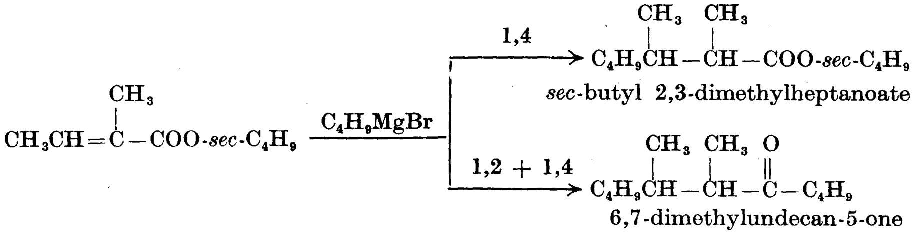
* It has recently been found by one of us (Aa. J.) that the previously reported much more drastic difference in composition between the products from citraconic and mesaconic esters, *viz.* α,α/α,α′ equal to 9/1 in the case of citraconic ester and 3/7 in the case of mesaconic ester, is incorrect. The latter ratio should be 7/3. This correction will be communicated shortly.

** It should be noted that by the addition process one or more carbon atoms become asymmetric. Thus, from tiglic and angelic esters mixtures of diastereomers might be expected. We have made no investigation yet of this problem. Until now no evidence of the presence of more than one stereoisomer has been obtained, and the configuration has not been determined. The high-boiling by-products from the additions, on the other hand, appear to be mixtures of racemates (*cf.* the following paper [8]).

(1,4-addition) and a saturated ketone, resulting from one addition to the ester carbonyl group (1,2-addition), followed by conjugate addition (to the α,β-unsaturated ketone primarily formed), thus from tiglic and angelic esters:*



Similarly, from the crotonic esters 3-methylheptanoic ester and 7-methylundecan-5-one, respectively, are obtained. The composition and identity of the mixtures of reaction products have been determined by means of gas chromatography and infra-red spectroscopy.

The lower reactivity of the *cis*-esters as compared to the *trans*-esters towards conjugate addition manifests itself in two ways by the results (Table 1): The total yields of conjugate addition products were smaller, and the ratios of saturated ketones (1,2 + 1,4-addition products) to saturated esters (pure 1,4-addition) were higher.

The fact, that as much as 20 % of the conjugate addition product obtained from tiglic ester is actually saturated ketone, was previously overlooked; the entire amount of constant boiling distillate obtained by earlier investigations [4] has — on the basis of elementary analyses — been considered to be ester. On the other hand, the high content of ketone now explains the fact, that the yield of free acid obtained by the saponification of the ester was only 70 % in the case of the addition product from tiglic ester, whereas more than 90 % yield of acid was secured from the corresponding reaction with crotonic ester. The conjugate addition product from *sec*-butyl crotonate and butylmagnesium bromide contains only about 2 % saturated ketone (7-methylundecan-5-one).

The presence of copper(I) chloride has previously been found to be favourable to the formation of simple conjugate addition product from crotonic ester, whereas the opposite effect was observed in the case of tiglic ester[5]. Both of these effects of copper(I) chloride have now been encountered also in the reactions of the *cis*-isomers of these two unsaturated esters. Although the yield from the catalyzed reaction with isocrotonic ester is moderate and lower than that from the uncatalyzed reaction with *trans*-crotonic ester, the yield is nevertheless considerably higher than in the uncatalyzed reaction with isocrotonic ester. Conversely, the low yield obtained from angelic ester, when the reaction is uncatalyzed, is even more decreased by the presence of copper(I) chloride.

This rather surprising contrast between the "positive" copper(I) chloride effect with the crotonic esters and the "negative" effect with the α-methylcrotonic esters is not easily understood.

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* In a later set of experiments with angelic ester (*cf.* experimental part and Table 2) some unknown compound was obtained from the uncatalyzed reaction, probably resulting from 1,2-addition.

Other effects of copper(I) chloride, previously described, such as the promotion of the reduction of methylmaleic and methylfumaric esters,[1] the change of the orientation of addition to sorbic ester from 1,4- to 1,6-addition,[6] and the change in stereoselectivity by the conjugate addition of phenylmagnesium bromide to optically active menthyl crotonate, recently reported by Inouye and Walborsky,[7] add support to the assumption of the formation of a regular complex between the copper(I) compound (probably the copper(I) alkyl [1,6]) and the unsaturated ester. This being the case, the negative copper(I) chloride effect in the case of the α-methylcrotonic esters might be ascribed to the overcrowding around the α-carbon atom, constituting a steric hindrance to the cyclic mechanism (1). Since, however, the effect is a catalytic one, this interpretation implies that the copper(I) compound be continuously transferred from once reacted to unreacted tiglic ester, which is slowly being added to the Grignard reagent.

It should be noted, however, that although copper(I) chloride changes the total yields of conjugate addition products, it does not to any significant degree alter the ratios of saturated ketone to saturated ester [(1,2 + 1,4)/1,4] in the mixtures of addition products (*cf.*, however, Table 2).

EXPERIMENTAL

Microanalysis are by Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen.

The fractional distillation columns, the infra-red spectrophotometer and the gas-chromatograph were either those previously used [6] or those mentioned in the following paper[8]. Boiling points are uncorrected.

sec-*Butyl crotonate* was obtained as previously described.[9,10]

sec-*Butyl isocrotonate* was prepared by the catalytic hydrogenation of *sec*-butyl tetrolate [11] as outlined by Paal and Schiedewitz [12] for the preparation of isocrotonic acid from tetrolic acid. The catalyst used was 1 % palladium on barium sulfate, prepared as described for the 5 % palladium catalyst in *Organic Syntheses*.[13] The catalyst (42 g) was suspended in butan-2-ol (800 ml), and hydrogen was passed through the suspension in order to sweep out the air from the system. *sec*-Butyl tetrolate [11] (84.3 g, 0.6 mole) was added in one portion, and hydrogen was passed through the reaction mixture, the temperature being kept at about 30°. After 4 ½ h the calculated amount of hydrogen had been consumed. The catalyst was filtered off and the solvent was distilled through a 100 cm Widmer column at slightly reduced pressure (100—150 mm). By fractional distillation of the residue 64.2 g (75 %) of *sec*-butyl isocrotonate was obtained, b.p. 75°/35 mm. This product contained 91 % isocrotonic and 9 % crotonic ester. By refractionation through the Widmer-type column described by Clauson-Kaas and Limborg [14] was obtained 48.2 g, b.p. 100—105°/130 mm, n_D^{20} 1.4269 and 10.8 g, b.p. 105°/130 mm, n_D^{20} 1.4286. The first of these fractions contained 95 % of isocrotonic ester and 5 % of crotonic ester. (Found: C 67.70; H 10.55. Calc. for $C_8H_{14}O_2$ (142.19): C 67.57; H 9.93). This fraction was used for the additions. The second fraction contained 86 % isocrotonic and 14 % crotonic ester.

sec-*Butyl tiglate*, b.p. 84.5°/27 mm, n_D^{25} 1.4332, was prepared as previously described [9,10] by the esterification of tiglic acid[15].

sec-*Butyl angelate* was synthesized from tiglic acid [15] essentially as outlined by Kupchan and Afonso[16]. Tiglic acid was transformed into 3-bromoangelic acid essentially as described by Buckles and Mock[15]. The yields in the elimination of hydrogen bromide from α,β-dibromo-α-methylbutyric acid were consistently lower (40—46 %) than those reported [15,16] (64 %). 3-Bromoangelic acid, on treatment with thionyl chloride, gave an 87 % yield of 3-bromoangeloyl chloride, b.p. 60—65°/10 mm. From this and 2-butanol, by boiling under reflux for 2 h, *sec*-butyl 3-bromoangelate, b.p. 95—96°/12 mm, n_D^{20} 1.4743, was obtained in 91—94 % yield (Found: C 46.50; H 6.68. Calc. for $C_9H_{15}O_2Br$

(235.13): C 45.97; H 6.43). The bromo ester was reduced with hydrogen in the presence of a 10 % palladium-on-carbon catalyst[16]. This was prepared from palladium chloride (4 g) and purified active carbon (Merck, Darmstadt, *p.a.*, 21.6 g) as described in *Organic Syntheses*,[13] and activated with 10 % potassium hydroxide solution. The catalyst was not isolated in dry state because of its high activity, which made it ignite on drying. The moist catalyst was added to a mixture of triethylamine (335 ml, 2.4 mole) and butan-2-ol (800 ml), and hydrogen was passed through the mixture in order to sweep out the air from the system. The β-bromoangelic ester (181 g, 0.77 mole) was added, and hydrogen passed in until the calculated amount had been consumed (about 5 h). The process was exothermic, and cooling was applied during the first period. The yield of crude *sec*-butyl angelate, b.p. 59–67°/10 mm was 89.6 g (75 %). (Found: C 68.60; H 10.33, Calc. for $C_9H_{16}O_2$ (156.22): C 69.12; 10.32). This product was obtained as 3 fractions of which the last one (4.8 g) to a degree of 65 % was *sec*-butyl tiglate, and therefore was not further used. In total the product had the following composition: *sec*-butyl angleate, 71 %, *sec*-butyl tiglate 27 %, and *sec*-butyl α-methylbutyrate 2 %. The first two fractions were redistilled at 11 mm through the Widmer-type column described by Clauson-Kaas and Limborg [14] to give the following fractions (given: percentages of α-methylbutyric, angelic, and tiglic esters, resp.): forerun, 0.6 g; fraction 1, 5.6 g, b.p. 52–59°, n_D^{20} 1.4283 (7, 84, 9); fraction 2, 32.9 g, b.p. 59–60°, n_D^{20} 1.4305 (4, 87, 9); fraction 3, 26.2 g, b.p. 60–62°, n_D^{20} 1.4330 (trace, 77, 23); fraction 4, 14.2 g, b.p. 62–67°, n_D^{20} 1.4344 (0, 36, 64); fraction 5, 2.0 g, b.p. 67–75°, n_D^{20} 1.4358 (0, 2, 98). Thus, by repeated fractionations separation of angelic and tiglic esters could indeed be accomplished. For the addition reactions fraction 2, containing 87 % of angelic ester, was used. The percentages given in Tables 1 and 2 for the yields obtained from angelic ester are corrected in consideration of the amount of tiglic ester present in the angelic ester used.

Additions were carried out, on a 0.1 mole scale, non-catalyzed [4,10] and copper(I) chloride catalyzed,[5] as previously described. The addition time for the ester was 60 min. The period of stirring at room temperature was 60 min with the *cis*- and *trans*-crotonic esters and 90 min with angelic and tiglic esters. The amount of copper(I) chloride used for a catalyzed reaction was approximately 0.6 g added in 6 portions.

Whereas the reactions with crotonic, isocrotonic, and tiglic esters gave clear-cut, completely reproducible results, the angelic ester experiments need further comment. The results given in Table 1 are those of the first experiment (performed by T.K.-L.). Later two more additions have been carried out (by V.B.) giving, in particular for the uncatalyzed reaction, results which differed somewhat from those of the first run (Table 2). Considerably larger amounts of unreacted angelic ester were found, and in the uncatalyzed reaction the conjugate addition product contained a rather large quantity of

Table 2. Products and yields from two sets of reactions between 0.1 mole = 15.5 g of *sec*-butyl angelate and 0.25 mole of butylmagnesium bromide. Percentage yields (but not gram values) given are corrected in consideration of the tiglic ester content in the angelic ester used (*cf.* experimental part).

Product found	Uncatalyzed reaction				CuCl-catalyzed reaction			
	set 1		set 2		set 1		set 2	
	g	%	g	%	g	%	g	%
Recovered ester	≥2.3	≥13	≥3.9	≥24	≥3.8	≥24	≥6.0	≥40
2,3-Dimethylheptanoic ester (1,4-addition)	5.2	22	5.0	21	4.7	20	3.7	15
6,7-Dimethylundecan-5-one (1,2 + 1,4-addition)	4.1	22	1.1	5	3.3	17	2.2	10
Unknown substance	0.0		3.1		0.0		0.0	
Residue	4.9		2.5		5.0		2.9	

an unknown substance. This was not isolated in a pure state. Its infra-red spectrum showed no other absorption bands than those of saturated hydrocarbons. The amount corresponds roughly to the difference between the amounts of saturated ketone found in the first and in the later experiments, a fact which suggests that the compound is some kind of product resulting from further reaction of the ketone (*i.e.* 1,2-addition). This type of substance, which actually consists of two compounds (according to gas chromatography) was present, but only as traces, also in the products from the other esters. This discrepancy in detail between the two sets of reactions with angelic ester does not, however, alter the fundamental results of the investigation.

Authentic samples required for the infra-red and gas-chromatographic investigations

sec-*Butyl 3-methylheptanoate* was available from previous work[4,5,10].

7-Methylundecan-5-one was obtained in 62 % yield by the reaction between 3-methylheptanoyl chloride [6] and the butylcadmium reagent, essentially as described by Cason.[17] The product had the b.p. 103–105°/9 mm and n_D^{20} 1.4310 (Found: C 77.50; H 12.93. Calc. for $C_{12}H_{24}O$ (184.31): C 78.19; H 13.13).

sec-*Butyl* 2,3-*dimethylheptanoate*. An analytical sample, b.p. 109°/13 mm, n_D^{25} 1.4257, obtained during previous work [4] by repeated redistillations, was found, by gas-chromatographic analysis, to consist of 94 % ester and 6 % ketone (*cf.* Table 1). A pure ester sample was obtained by esterification of the acid, which was prepared by saponification of the crude ester (*cf.* below). This product, b.p. 106°/15 mm, which was 100 % pure, showed the refractive index n_D^{25} 1.4244.

6,7-*Dimethylundecan*-5-*one*, b.p. 116°/11 mm, n_D^{20} 1.4400, was obtained directly by saponification of the reaction products from the additions (Found: C 78.70; H 13.25. Calc. for $C_{13}H_{26}O$ (198.34): C 78.72; H 13.21).

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