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

II. The Preparation of 3-Methyl- and 2,3-Dimethylalkanoic Acids

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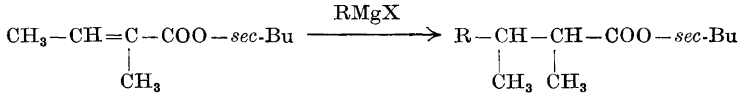
A previously published method for the preparation of 3-methyl-alkanoic acids from *sec*-butyl crotonate and Grignard reagents has been revised, improved and simplified. It has further been extended to *sec*-butyl tiglate, from which fair yields of 2,3-dimethylalkanoic acids are obtained.

In a recent publication [1] the addition of Grignard reagents to the double bond of *sec*-butyl crotonate as a way of preparing in high yields 3-methyl-substituted fatty acids was described. Certain other α,β-unsaturated esters were investigated, but only with cinnamic ester were reasonable yields obtained, whereas the reaction with tiglic and methacrylic esters failed. Of these, the reaction with tiglic esters would be of particular interest, on one hand since this ester is rather easily accessible, and on the other hand because of the difficulties reported [2] in obtaining 2,3-dimethyl-substituted fatty acids by other routes:



Since the publication of the first paper there have been difficulties in obtaining the high yield stated for the preparation of *sec*-butyl 3-methylheptanoate from *sec*-butyl crotonate and *n*-butylmagnesium bromide. This has prompted a reinvestigation of the reaction and of most of the work reported in the first paper. Although no explanation for the discrepancy has been found so far, a new procedure has been worked out, which gives almost as good a yield, and which is considerably simpler. Furthermore, by this procedure tiglic ester gives good to fair yields of *sec*-butyl esters of 2,3-dimethylalkanoic acids (Table 1).

In the first paper it was reported that the presence of cuprous chloride was essential to the success of the addition reaction, since it had been found that, under the conditions there described, the absence of this catalyst resulted in the formation of a high-boiling condensation-addition product. It has not been possible to verify this remarkable catalytic effect of cuprous chloride in promoting the simple 1,4-addition to the conjugated carbon-carbon double bound in competition with the condensation-addition process. On the contrary, carrying out the addition as described resulted in varying, but rather low yields (30—50 %), and with the formation of larger amounts of the high-boiling condensation compound. In numerous experiments with *sec*-butyl

Table 1.

sec-Butyl ester	Grignard reagent RMgBr	Product: *sec*-butyl ester	Yield %	Yield Ref. [1] %	Data
Crotonate	n-C_4H_9	3-methylheptanoic	67—80	84—86	Ref. [1]
»	CH_3	*iso*valeric	0	45	Ref. [1]
»	C_2H_5	3-methylvaleric	78	56	Ref. [1]
»	i-C_3H_7	3,4-dimethylvaleric	57	39	Ref. [1]
»	t-C_4H_9 [a]	3,4,4-trimethylvaleric	14	14	Ref. [1]
»	n-C_8H_{17}	3-methylhendecanoic	—	75	Ref. [1]
»	n-$C_{14}H_{29}$	3-methylheptadecanoic	—	86	Ref. [1]
»	C_6H_5	3-phenylbutyric	72	67	Ref. [1]
Tiglate	n-C_4H_9	2,3-dimethylheptanoic [b]	71	0	b. p. 109°/13 n_D^{25} 1.4257
»	i-C_3H_7	2,3,4-trimethylvaleric [c]	68 [d]	—	b. p. 90°/12 mm n_D^{20} 1.4262
»	n-C_5H_{11}	2,3-dimethyloctanoic [e]	47 [d]	—	b. p. 87°/1.5 mm n_D^{20} 1.4307
»	n-C_8H_{17}	2,3-dimethylhendecanoic	(55) [d,f]	—	b. p. 109—110°/1 mm
»	C_6H_5	2-methyl-3-phenyl-butyric [g]	53 [d]	—	b. p. 94—95°/1 mm n_D^{20} 1.4838
Methacrylate	n-C_4H_9	—	0	0	
Acrylate	n-C_4H_9	—	0	—	
β,β-Dimethyl-acrylate	n-C_4H_9	—	0	—	
Cinnamate	n-C_4H_9	3-phenylheptanoic	52	46	Ref. [1]

[a]) *tert*-Butylmagnesium chloride used. [b]) Calcd. for $C_{13}H_{26}O_2$ (214.34): C 72.84; H 12.23 Found: C 72.80; H 12.27. [c]) Calcd. for $C_{12}H_{24}O_2$ (200.31): C 71.95; H 12.08. Found: C 71.90 H 12.07. [d]) Reaction carried out in 0.1 mole scale. [e]) Calcd. for $C_{14}H_{28}O_2$ (228.36): C 73.63; H 12.36. Found: C 73.75; H 12.45. f) This product is not pure, probably contaminated with n-hexadecane; over-all yield of 2,3-dimethylhendecanoic acid, obtained by saponification (see experimental part), is 40 %. [g]) Calcd. for $C_{15}H_{22}O_2$ (234.33): C 76.88; H 9.46. Found: C 76.85; H 9.53.

crotonate and *n*-butylmagnesium bromide the conditions have been varied systematically (including the testing of different qualities of cuprous chloride and magnesium, and changes in the addition temperature, the addition time and the dilution of the ester), apparently without effect on the yield.

Eventually the use of a greater excess of Grignard reagent (at least 0.5 mole with 0.2 mole of ester) was found to result in an increase in the yield, and at the same time the use of cuprous chloride appeared to be of little effect. The procedure now worked out and described below gives about a 75 % yield for the reaction of crotonic ester with *n*-butylmagnesium bromide.

Using the new procedure, those other additions, which had previously been found to give low or no yields of simple 1,4-addition product, were repeated. These results, as well as those of some new addition reactions, are given in Table 1, which for comparison also includes the results previously reported using the cuprous chloride procedure.

The yields for crotonic ester with ethyl- and *iso*propylmagnesium bromides have increased, but methylmagnesium bromide — in contrast to the earlier findings with cuprous chloride — now gives an unseparable mixture of compounds. Similar results of reactions of methylmagnesium halides with α,β-unsaturated systems have been reported previously [3,1]. The yields with tiglic ester from *n*-butyl- and *iso*propylmagnesium bromides are quite good, whereas those from *n*-amyl-, *n*-octyl-, and phenylmagnesium bromides are somewhat lower. Methacrylic and acrylic esters give mostly polymerisation products, β,β-dimethylacrylic ester gives a mixture of unreacted ester and some unidentified low-boiling compound as well as some polymerisation product.

The high-boiling compounds obtained as by-products from the reactions with crotonic and tiglic esters were identified previously [1] and were not further investigated during the course of this work. They are considered to be di-*sec*-butyl α-(2-alkyl)-β-methylglutarates and di-*sec*-butyl α-(2-alkyl)-α, β, γ-trimethylglutarates, respectively, (2-alkyl = $R-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$), produced by addition of the Grignard reagents to the α,β-unsaturated dimerisation products, which are again formed by a Michael-type self-condensation of the original esters.

Further investigations of the reaction are in progress.

EXPERIMENTAL

Analyses are by Mr. Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen. Fractional distillations were through a simple 45 cm × 8 mm Podbielniak-type column with a tantalum wire spiral, heated jacket and a partial reflux head.

sec-Butyl esters were obtained by esterification of the corresponding acids in 75—85 % yield, according to the general procedure previously described [1] for crotonic, tiglic, methacrylic, and cinnamic esters. The yield for *sec*-butyl tiglate, b. p. 75°/16 mm, n_D^{25} 1.4339, has been raised to 75 % (Ref.[1] b. p. 86—87°/30 mm, n_D^{25} 1.4335, yield 60 %). New esters are: *sec*-butyl acrylate, b. p. 29°/18 mm, n_D^{20} 1.4268, and *sec*-butyl β,β-dimethylacrylate, b. p. 68—70°/13 mm, n_D^{20} 1.4379.

The corresponding acids were commercial products (Fluka AG., Buchs/SG, Switzerland), except for methacrylic [4] and tiglic [5] acids, which were prepared through the corresponding ketone cyanohydrins as described in the literature. It should be pointed out that it has been found essential for the success of the tiglic acid synthesis [5] that the temperature-controlled hydrolysis and elimination process between methyl ethyl ketone cyanohydrin and 100 % sulfuric acid be carried out under extremely vigorous stirring, since otherwise foaming and tar-formation takes place, resulting in low yields.

Additions of Grignard reagents to α,β-unsaturated esters. The solution of Grignard reagent was prepared (without use of iodine or other catalyst) in an 1 liter three-necked flask, provided with effective stirrer, from 12.5 g (0.52 g-atom) of magnesium turnings and 0.65 mole of halide dissolved in 150—200 ml of ether. The reaction is completed by boiling for 10—15 min, after which the Grignard solution is cooled for 15—20 min in an ice-water bath. Under effective stirring in the ice-bath, 0.20 mole of ester, dissolved in 200 ml of ether is now added dropwise from a graduated dropping funnel during a period of at least 1.5 h. When the addition is completed, stirring is continued in the ice-bath for additional 15 min, and for 1 h at room temperature. The reaction mixture is then worked up in the conventional way, as previously described [1].

The higher halides (octyl *etc.*) are dissolved in a somewhat greater quantity of ether in order to prevent crystallisation of the Grignard reagent during the cooling. Working up after reactions with phenylmagnesium bromide should include a washing of the ether extract with sodium hydroxide solution in order to remove phenol, which will otherwise make distillation troublesome and contaminate the product.

Saponification of sec-butyl esters may be carried out with ethanolic potassium hydroxide as previously described [1]. In this way (on a 0.05 mole scale) *2,3-dimethylheptanoic acid*, b. p. 89°/1 mm, n_D^{20} 1.4356, was obtained in 80 % yield; neutr.equiv. calcd. for $C_9H_{18}O_2$ 158.2, found 157. *2,3-Dimethylhendecanoic acid*, b. p. 131°/1 mm, n_D^{20} 1.4461, yield 73 % (*cf.* Table 1); calcd. for $C_{13}H_{26}O_2$ (214.34): C 72.84; H 12.23. Found C 72.85; H 12.20; neutr. equiv. 213.

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