sium amide, which was prepared from potassium (0.4 mole, 15.6 g.) and 350–400 ml. of anhydrous liquid ammonia. The resulting blood-red mixture was stirred for 2 hr. and then *n*-butyl bromide (0.2 mole, 27.4 g.), diluted with an equal volume of anhydrous ether, was added over a 20-min. period. After the halide was added, the mixture was stirred for an additional hour and then the reaction was quenched by the addition of solid ammonium chloride (0.41 mole, 22.0 g.). The mixture was then processed as described previously for the acylation of 3-picoline[11] to give 1.8 g. of *n*-butyl bromide, 15.5 g. of recovered 3-picoline, b.p. 135–143°, and 21.5 g. (72%) of 3-*n*-amylpyridine, b.p. 110–112° at 20 mm.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Conjugate Additions of Grignard Reagents to α,β-Unsaturated Esters

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Received August 17, 1956

The reactions of *sec*-butyl esters of certain α,β-unsaturated acids with Grignard reagents have been studied. In the presence of catalytic amounts of cuprous chloride, Grignard reagents from a number of primary bromides (as well as bromobenzene) add in high yields to the double bond of *sec*-butyl crotonate. This provides a practical route to 3-methylalkanoic acids. The Grignard reagents from isopropyl bromide and *tert*-butyl chloride give lower yields under the same conditions. When no catalyst is used the yield is low, and a higher-boiling condensation-addition product is formed. Condensation products are the only isolated compounds from the cuprous chloride catalyzed reaction with *sec*-butyl methacrylate and tiglate. With *sec*-butyl cinnamate a fair yield of 3-phenylheptanoic ester is obtained with *n*-butylmagnesium bromide, while methylmagnesium bromide gives 4-phenylpentanone-2 as a result of both 1,2- and 1,4-addition. When ferric chloride is used as a catalyst very little 1,4-addition takes place and a dimer of the crotonic ester is formed in varying yields.

The addition of Grignard reagents to carbon-carbon double bonds conjugated with polar double bonds has been the subject of many investigations. Although the 1,4- addition products are generally obtained in moderate to good yields from α,β-unsaturated esters which carry strongly electron-withdrawing groups such as carbalkoxy and cyano groups at the α-carbon,[2–6,23] the yields with other α,β-unsaturated esters have varied widely. Kohler and Heritage[7] have reported that ethyl cinnamate gives exclusively 1,2- addition (dimethylcinnamylcarbinol) with methylmagnesium iodide, but predominantly 1,4- addition (ethyl β,β-diphenylpropionate) with phenylmagnesium bromide. They also found that with increasing size of the alcohol moiety in the cinnamic ester, the rate of 1,4- to 1,2-addition of phenylmagnesium bromide increased, and Hauser *et al.*[8] have reported that with *tert*-butyl cinnamate only the 1,4- addition product is formed. Ethyl α-methylcinnamate[9] and ethyl α-methyl-β-phenylcinnamate[10] give predominantly 1,2- addition with phenylmagnesium bromide, while ethyl α-phenylcinnamate gives exclusively 1,4-addition.[11] Methylmagnesium halides appear to give 1,2-addition in all cases except with the alkylidenemalonic and -cyanoacetic esters. Ethyl crotonate is likewise reported[12] to give crotyldimethylcarbinol with methylmagnesium bromide. It is reported[13] that the Grignard reagent from 2-bromothiophene with ethyl crotonate gives 1,3-di-(2-thenyl)butanone-1 as a result of both 1,2- and 1,4- addition, and the reaction between ethyl methacrylate and methylmagnesium iodide is likewise reported[14] to give both 1,2- and 1,4- addition.

Recently Wotiz *et al.*[15] reported 1,4- addition in up to 40% yield of ethyl-, *tert*-butyl- and phenylmagnesium halides to free crotonic and cinnamic acids. Although we have been able to verify the result reported for the addition of phenylmagnesium bromide to crotonic acid, we have obtained only a low yield (10% or less) of 3-methylheptanoic acid from *n*-butylmagnesium bromide and crotonic acid; large amounts of unidentified nonacidic and high-boiling acidic products are produced.

Since it may be considered established [*e.g.* in

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[2] Kohler and Reimer, *Am. Chem. J.*, **33**, 333 (1905) [*Chem. Zentr.*, I, 1389 (1905)]; Kohler, *Am. Chem. J.*, **34**, 132 (1905) [*Chem. Zentr.*, II, 1021 (1905)].

[3] Alexander, McCollum, and Paul, *J. Am. Chem. Soc.*, **72**, 4791 (1950).

[4] Wideqvist, *Arkiv Kemi, Mineral. Geol.*, **B 23**, No. 4 (1946); *Arkiv Kemi*, **2**, 321 (1950).

[5] Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).

[6] Bush and Beauchamp, *J. Am. Chem. Soc.*, **75**, 2949 (1953); van Heyningen, *J. Am. Chem. Soc.*, **76**, 2241 (1954).

[7] Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905) [*Chem. Zentr.*, I, 521 (1905)].

[8] Hauser, Yost and Ringler, *J. Org. Chem.*, **14**, 261 (1949).

[9] Kohler, *Am. Chem. J.*, **36**, 529 (1906) [*Chem. Zentr.*, I, 559 (1907)].

[10] Bergmann and Weiss, *Ann.*, **480**, 64 (1930).

[11] Kohler and Heritage, *Am. Chem. J.*, **33**, 153 (1905) [*Chem. Zentr.*, I, 824 (1905)].

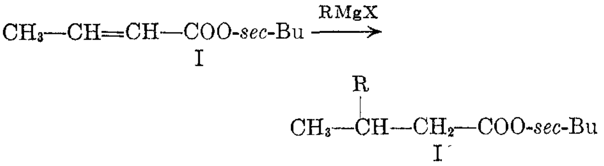
[12] Keersblick, *Bull. soc. chim. Belg.*, **38**, 205 (1929) [*Chem. Zentr.*, II, 2036 (1929)].

[13] Hirao, *J. Pharm. Soc. Japan*, **73**, 1024 (1953) [*Chem. Abstr.*, **48**, 10724a (1954)].

[14] Blaise and Courtot, *Compt. rend.*, **140**, 370 (1905) [*Chem. Zentr.*, I, 726 (1905)]; cf. also ref. 9.

[15] Wotiz, Matthews, and Greenfield, *J. Am. Chem. Soc.*, **75**, 6342 (1953); cf. Wotiz and Matthews, *J. Am. Chem. Soc.*, **74**, 2559 (1952).

ref. (7)] that large groups at the carbonyl carbon decrease the extent to which 1,2- addition (to the carbonyl group) takes place, it was thought worth while to investigate the addition of Grignard reagents to *sec*-butyl esters of α,β-unsaturated acids as a way of preparing 3-substituted fatty acids, *e.g.*:



$$\underset{\text{I}}{CH_3—CH{=}CH—COO\text{-}sec\text{-}Bu} \xrightarrow{\text{RMgX}} \underset{\text{I}'}{CH_3—\overset{\overset{\text{R}}{|}}{C}H—CH_2—COO\text{-}sec\text{-}Bu}$$

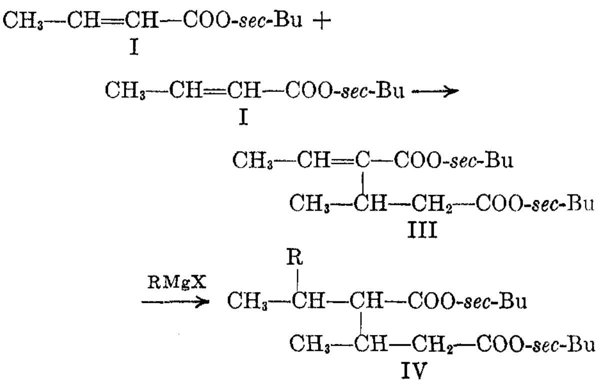
Although such acids could be prepared by malonic ester syntheses, *e.g.* 3-methylheptanoic acid[16,17] and 3-methylstearic acid[18] from the corresponding secondary halides, these halides are often difficult to obtain entirely free of isomers[19] and, unless the corresponding alcohol is commercially available, the route *via* the malonic acid would consist of many steps. Another pathway for 3-methyl-substituted fatty acids is the electrolysis[20] of the mixture of β-methylglutaric acid mono-methyl ester and a fatty acid, but the yields are rather low and the procedure laborious.

In the reaction between *sec*-butyl crotonate and *n*-butylmagnesium bromide, the 1,4- addition product (II) was obtained in only 25% yield. A rather large quantity of a higher-boiling substance (described below) was formed.

Attention was drawn to the report by Kharasch and Tawny,[21] that the presence of catalytic amounts of cuprous chloride changes the direction of addition of methylmagnesium bromide to isophorone from predominantly 1,2- to almost exclusively 1,4- addition. This effect of cuprous halides on the addition of methyl magnesium halides to cyclic 2-en-1-ones has more recently been reported also by other workers.[22] Cuprous chloride has also been found effective in promoting addition in competition with reduction at the carbon-carbon double bond of alkylidenemalonic and -cyanoacetic esters.[23] Finally, Cook and Percival[24] have reported the cuprous chloride catalyzed formation of hexamethylacetone (that is addition to the carbonyl group) instead of reduction product from trimethylacetyl chloride and *tert*-butylmagnesium chloride.

It has now been found that, in the reaction between *n*-butylmagnesium bromide and *sec*-butyl crotonate, the presence of one mole per cent of cuprous chloride results in an increase in the yield of 1,4- addition product (II) from 25 to 60%, a yield which could be further improved to 85% by increasing the ratio of Grignard reagent.

The higher-boiling product mentioned above is only found in minor amounts when cuprous chloride is present. This compound, however, is not a 1,2- addition product, and such a product has never been obtained with *sec*-butyl crotonate, not even in the reaction with methylmagnesium bromide. The higher-boiling products are believed to be α,β-dialkylglutaric esters (IV)[25] formed by dimerization of the crotonic ester[26,27] by a Michael condensation, followed by a 1,4- addition of the Grignard reagent:



$$\underset{\text{I}}{CH_3—CH{=}CH—COO\text{-}sec\text{-}Bu} + \underset{\text{I}}{CH_3—CH{=}CH—COO\text{-}sec\text{-}Bu} \longrightarrow \underset{\text{III}}{\begin{array}{l} CH_3—CH{=}C—COO\text{-}sec\text{-}Bu \\ \quad\quad\quad\quad | \\ \quad CH_3—CH—CH_2—COO\text{-}sec\text{-}Bu \end{array}} \xrightarrow{\text{RMgX}} \underset{\text{IV}}{\begin{array}{l} \quad\quad\quad R \\ \quad\quad\quad | \\ CH_3—CH—CH—COO\text{-}sec\text{-}Bu \\ \quad\quad\quad\quad\quad | \\ \quad CH_3—CH—CH_2—COO\text{-}sec\text{-}Bu \end{array}}$$

The structure (III) shown above for the dimer is given by Pechman[26] and by Hurd and Kelso[27] for the corresponding ethyl ester. The product (IV) was first thought to be formed by a Michael condensation between the 1,4-addition product (II) and unreacted crotonic ester (I), but an attempt to prepare IV from these reactants, using sodium *sec*-butoxide as the condensing agent, failed; the 1,4-addition product (II) was recovered and the crotonic ester (I) was converted to its dimer (III). Products of type IV are reported in the literature, *e.g.* by Hauser *et al.*[8] from the reaction between *tert*-butyl cinnamate and diethylaminomagnesium bro-

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(16) Linstead, Shephard, Weedon, and Lunt, *J. Chem. Soc.*, 1538 (1953).

(17) Levene and Marker, *J. Biol. Chem.*, **91**, 77 (1931).

(18) Kuhn, Köhler, and Köhler, *Zeit. Physiol. Chem.*, **242**, 182 (1936).

(19) Cason and Mills, *J. Am. Chem. Soc.*, **73**, 1354 (1951).

(20) Ställberg-Stenhagen, *Arkiv Kemi*, **2**, 95 (1950).

(21) Kharasch and Tawny, *J. Am. Chem. Soc.*, **63**, 2308 (1941).

(22) Birch and Robinson, *J. Chem. Soc.*, 501 (1943); Büchi, Jeger and Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948); Stoll and Commarmont, *Helv. Chim. Acta*, **31**, 554 (1948).

(23) Hook and Robinson, *J. Chem. Soc.*, 152 (1944); Brändström and Forsblad, *Arkiv Kemi*, **6**, 561 (1953).

(24) Cook and Percival, *J. Am. Chem. Soc.*, **71**, 4141 (1949).

(25) The products give the correct elementary analyses, but give by alkaline hydrolyses (in methanolic potassium hydroxide for up to 48 hr.) equivalent weights equal to the molecular weights. This latter fact is probably due to the high degree of steric hindrance. The product from *sec*-butyl tiglate and *n*-butylmagnesium bromide is not hydrolyzed at all in alcoholic potassium hydroxide. By more vigorous saponification of the product from *sec*-butyl crotonate and *n*-butylmagnesium bromide, and treatment of the acid with acetyl chloride, a product was obtained which gave the correct analysis for α-(2-hexyl)-β-methylglutaric anhydride.

(26) von Pechmann, *Ber.*, **33**, 3323 (1900).

(27) Hurd and Kelso, *J. Am. Chem. Soc.*, **62**, 2187 (1940).

mide, and by Kohler and Peterson[28] and Wittig *et al.*[29] from the reaction between benzalacetophenone and a number of arylmetallic compounds.

In the case of the noncatalyzed reaction between *sec*-butyl crotonate and 1.2 equivalents of *n*-butylmagnesium bromide, the product IV was obtained in 44% yield but when cuprous chloride was present in only about 25% yield. Since the formation of IV is believed to be the result of initial reaction of crotonic ester with itself, it should be suppressed by increasing the excess of Grignard reagent. It was found that, in the cases of *n*-butyl- and *n*-octylmagnesium bromides, an increase in the amount of Grignard reagent from 1.2 to 1.5 equivalents (as measured by the amount of magnesium, in relation to which an excess of bromide was used), did indeed result in an increase in the yield of 1,4-addition product (II) from 60% to 85%, while the yield of by-product dropped to practically zero. A further increase to 2 equivalents did not result in increased yield in these cases. In the case of *n*-tetradecylmagnesium bromide an increase from 1.2 to 2.0 equivalents of Grignard reagent, similarly, resulted in an increase in the yield of 1,4- addition product (II) from 10% to 86%. It was also found that the ratio of higher-boiling product (IV) is increased if more concentrated solution of crotonic ester and a shorter time of ester addition are used.

The results are shown in Table I, while the names of the products and their properties are given in Table II.

It has been suggested[30] that the effect of cuprous halides should be due to a facilitation of the addition to the carbon-carbon double bond, which has been labilized by complex formation with the metallic halide. This theory is consistent with the fact that cuprous chloride not only facilitates 1,4- addition in preference to 1,2- addition, but also favors addition to the carbon-carbon double bond in situations when 1,2- addition (to the carbonyl group) is hindered, but then some other reaction, such as reduction of the double bond,[22] competes with the addition process. In the case here reported, the increased reactivity of the double bond should make the ester react more rapidly; as the Grignard reagent is in large excess during the entire, very slow addition of the ester, the increased reactivity of the double bond makes the ester more likely to react with a molecule of Grignard reagent than with another ester molecule. This is consistent with the great sensitivity of the yield to any excess of crotonic ester; the increase in yield with the increase in the excess of Grignard reagent; and the decrease in yield with the increase of the concentration of crotonic ester solution as well as of the rate of addition of the crotonic ester.

The role of cuprous chloride in effecting ketone synthesis (addition) rather than reduction in the reaction between trimethylacetyl chloride and *tert*-butylmagnesium chloride, for which earlier a free-radical mechanism was suggested,[24] is now also thought[31,32] to be one of a Lewis acid, in this case forming a complex with the acid chloride. However, as the effect does not always increase with increasing Lewis acid strength, other factors must be involved. It was found that ferric chloride was superior to cuprous chloride, also to aluminum chloride in effecting ketone synthesis in certain cases,[31] but in other cases[32] that cuprous, ferric, and manganous chlorides had the same effects superior to those of aluminum chloride, boron trifluoride, and others.

In the reaction here considered the presence of ferric chloride resulted in formation of a mixture of compounds, among which only a dimerization product (different from the crotonic ester dimer obtained under the influence of basic reagents) of the crotonic ester was isolated. The results are the same when the addition procedure is that used with cuprous chloride or when the Grignard reagent is added to the crotonic ester containing the ferric chloride. It should, however, be pointed out that these metallic halides may react with or promote coupling reactions of the Grignard reagent.[33,34] In the reaction here under consideration, this type of reaction must be avoided, since the effect of the catalyst is thereby eliminated. This is accomplished by cooling of the Grignard reagent before adding the cuprous chloride. In the case of ferric chloride a vigorous reaction took place when the catalyst was added to the Grignard reagent, even when this had been precooled in an ice-salt mixture to about $-20°$. This reaction of ferric chloride with a Grignard solution is mentioned by Kharasch and Tawny,[21] but apparently not considered as being of any significance.

It was further found that the presence of cuprous chloride does not change the reaction between free crotonic acid and *n*-butylmagnesium bromide to give any simple 1,4-addition product; only high-boiling acidic products are obtained.

Finally the reaction of *sec*-butyl crotonate with di-*n*-butylcadmium was tried. Riegel, Siegel, and Lilienfeld[35] state that the yields of 1,4- addition to alkylidenemalonic esters were somewhat higher with α-naphthylmethylcadmium reagent than with the corresponding Grignard compound. In the re-

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[28] Kohler and Peterson, *J. Am. Chem. Soc.*, **55**, 1073 (1933).

[29] Wittig, Meyer and Lange, *Ann.*, **571**, 167 (1951).

[30] Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 221.

[31] Percival, Wagner and Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

[32] Morrison and Wishman, *J. Am. Chem. Soc.*, **76**, 1059 (1954).

[33] Gilman and Lichtenwalter, *J. Am. Chem. Soc.*, **61**, 957 (1939).

[34] Kharasch and Fields, *J. Am. Chem. Soc.*, **63**, 2316 (1941).

[35] Riegel, Siegel, and Lilienfeld, *J. Am. Chem. Soc.*, **68**, 984 (1946).

TABLE I—RESULTS OF REACTIONS OF α,β-UNSATURATED ACID DERIVATIVES WITH GRIGNARD REAGENTS

α,β-Unsaturated Acid		RMgX				Products %		
Derivative	Moles	R	Mg g.-atoms	RX moles	Catalyst, 1 Mole %	II 1,4- add.	IV cond. + 1,4- add.	Other products; comments
Crotonic acid	0.5	n-C_4H_9	1.24	1.24	None	10		High-boiling acidic and unidentified nonacidic products
	0.25	n-C_4H_9	0.62	0.62	CuCl	0		
	0.25	C_6H_5	0.62	0.62	None	40		Not identified crystalline nonacidic product
sec-Butyl crotonate	0.20	n-C_4H_9	0.24	0.24	None	25	44	
	0.20	n-C_4H_9	0.24	0.30	CuCl	59.3	24.5	
	0.30	n-C_4H_9	0.36	0.40	None	21.4	44	
	0.20	n-C_4H_9	0.30	0.35	CuCl	85	0	
	0.50	n-C_4H_9	0.75	0.93	CuCl	47	31	Ester dissolved in only 240 ml. of ether and added during only 1.5 hr.
	0.40	n-C_4H_9	0.60	0.75	CuCl	84	0	25-cm. Vigreux column used for distillation of ester; with Podbielniak column the yield is 86%
	0.20	n-C_4H_9	0.30	0.35	$FeCl_3$	3		Dimerization product of crotonic ester in 12% yield.[a] Cooling of Grignard reagent in ice water for 5 min. before adding catalyst
	0.20	n-C_4H_9	0.30	0.35	$FeCl_3$	3		Dimerization product of crotonic ester in 44% yield.[a] Cooling of Grignard reagent in ice water for 15 min. before adding catalyst
	0.20	n-C_4H_9	0.30	0.37	$FeCl_3$	0		Dimerization product of crotonic ester in 20% yield.[a] Cooling of Grignard reagent in ice salt for 15 min. before adding catalyst
	0.20	n-C_4H_9	0.40	0.50	$FeCl_3$	5		Dimerization product of crotonic ester in 28% yield.[a] Filtered Grignard reagent added to ester solution containing suspended catalyst, while cooling in ice water
	0.3	CH_3	0.45	0.69	CuCl	44.5	35	Cooling in ice salt of Grignard reagent before adding catalyst
	0.2	C_2H_5	0.30	0.37	CuCl	0	47	Cooling of Grignard reagent in ice water only, before adding catalyst
	0.2	C_2H_5	0.30	0.37	CuCl	56	22	Cooling of Grignard reagent in ice salt before adding catalyst
	0.2	*iso*-C_3H_7	0.30	0.37	CuCl	39		High-boiling, resinous residue. Isopropyl bromide, *tert*-butyl chloride used
	0.2	*tert.*-C_4H_9	0.30	0.38	CuCl	14		
	0.3	n-C_8H_{17}	0.36	0.40	CuCl	56	40	n-Octane, n-octanol, n-hexadecane. Higher-boiling product contaminated with n-hexadecane
	0.2	n-C_8H_{17}	0.30	0.35	CuCl	75	16	
	0.2	n-C_8H_{17}	0.40	0.50	CuCl	70	17	
	0.1	n-$C_{14}H_{29}$	0.12	0.13	CuCl	25	(40–50)	n-Tetradecane, 1-tetradecanol, n-octacosane. Higher-boiling product not pure
	0.1	n-$C_{14}H_{29}$	0.12	0.14	CuCl	12	(60)	
	0.1	n-$C_{14}H_{29}$	0.20	0.25	CuCl	86	0	
	0.2	C_6H_5	0.30	0.35	CuCl	67		Ether solution of ester should be washed with sodium hydroxide to remove phenol. Product contaminated with small amounts of biphenyl. Saponification as described for 3-methylheptanoic acid gives pure acid in 90% yield
	0.2	C_6H_5	0.30	0.35	CuCl	67		
Methyl crotonate	0.2	n-C_4H_9	0.30	0.37	CuCl	4.4		Self-condensation product of 1,4-addition product: Methyl 2-(2′-hexyl)-3-keto-5-methylnonanoate obtained in 66% yield
sec-Butyl methacrylate	0.2	n-C_4H_9	0.30	0.40	CuCl	0	30	Small amounts of unidentified solid passed over with first part of distillate. In the first experiment the ester contained 0.1% hydroquinone; in the two latter pure ester was used
	0.2	n-C_4H_9	0.30	0.35	CuCl	0	41	
	0.2	n-C_4H_9	0.60	0.75	CuCl	0	52	
sec-Butyl tiglate	0.2	n-C_4H_9	0.24	0.30	CuCl	0	25	Mixture of unidentified low- and high-boiling products
sec-Butyl cinnamate	0.1	n-C_4H_9	0.15	0.20	CuCl	0	0	Grignard solution not cooled before adding catalyst. Unreacted ester and high-boiling residue obtained
	0.1	n-C_4H_9	0.15	0.20	CuCl	46	0	High-boiling residue
	0.2	CH_3	0.3	0.7	CuCl			4-Phenylpentanone-2 (1,2 and 1,4-addition) in 40% yield. 20% unreacted ester recovered. Residue

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[a] Calcd. for $C_{16}H_{28}O_4$ (284.4): C, 67.57, H, 9.92. Found C, 67.43; H, 9.92. Sap. equiv. found 281. I.R. spectrum shows one very sharp carbonyl band at 5.80 μ (1725 cm^{-1}), but no absorption in the 6.0–6.20 μ region (conjug. C=C).

TABLE II—PRODUCTS ISOLATED FROM REACTIONS OF GRIGNARD REAGENTS WITH α,β-UNSATURATED ESTERS

α,β-Unsaturated Ester	RMgX	Products
sec-Butyl crotonate	*n*-C_4H_9MgBr (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylheptanoate, b.p. 110–111°/19 mm., 116–116.5°/25 mm., 102–103°/13.5 mm., 71°/2 mm., n_D^{25} 1.4190. Calcd. for $C_{12}H_{24}O_2$ (200.3) C, 71.95; H, 12.08. Found C, 71.59; H, 11.77. Sap. equiv. found 200. 2. (Cond. + 1,4- add.): di-*sec*-butyl α-(2-hexyl)-β-methylglutarate, b.p. 136°/0.8 mm., 140–141°/1.2 mm., 143–145°/1.5 mm., n_D^{25} 1.4400. Calcd. for $C_{20}H_{38}O_4$ (342.5) C, 70.13; H, 11.18. Found C, 70.50; H, 10.88. Sap. equiv. found 342.
sec-Butyl crotonate	*n*-C_4H_9MgBr ($FeCl_3$)	Dimer of *sec*-butyl crotonate, b.p. 99°/0.3 mm., n_D^{25} 1.4322. Calcd. for $C_{16}H_{28}O_4$ (284.4) C, 67.57; H, 9.92. Found C, 67.43; H, 9.91. Sap. equiv. found 281.
sec-Butyl crotonate	CH_3MgBr (CuCl)	1. (1,4- add.): *sec*-butyl isovalerate, b.p. 100°/98 mm. (rep. 163–164°/752 mm.,[a] n_D^{25} 1.4075. Calcd. for $C_9H_{18}O_2$ (158.2) C, 68.31; H, 11.46. Found C, 68.50; H, 11.49. Sap. equiv. found 157. 2. (Cond. + 1,4- add.): di-*sec*-butyl α-isopropyl-β-methylglutarate, b.p. 124°/2 mm., n_D^{25} 1.4341. Calcd. for $C_{17}H_{32}O_4$ (300.4) C, 67.96; H, 10.74. Found C, 68.06; H, 10.52. Sap. equiv. found 302.
sec-Butyl crotonate crotonate	C_2H_5MgBr (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylvalerate, b.p. 79–81°/19 mm., n_D^{25} 1.4103. Calcd. for $C_{10}H_{20}O_2$ (172.3) C, 69.72; H, 11.70. Found C, 69.94; H, 11.58. Sap. equiv., found 174. 2. (Cond. + 1,4- add.): di-*sec*-butyl α-*sec*-butyl-β-methylglutarate, b.p. 130°/1.4 mm., n_D^{25} 1.4367. Calcd. for $C_{18}H_{34}O_4$ (314.5) C, 68.75; H, 10.90. Found C, 68.84; H, 10.73. Sap. equiv. found 312.5.
sec-Butyl crotonate	*iso*-C_3H_7MgBr (CuCl)	(1,4- add.): *sec*-butyl 3,4-dimethylvalerate, b.p. 93°/20 mm., n_D^{25} 1.4173. Calcd. for $C_{11}H_{22}O_2$ (186.3) C, 70.91; H, 11.91. Found C, 71.18; H, 11.90. Sap. equiv. found 186.0.
sec-Butyl crotonate	*tert*-C_4H_9MgCl (CuCl)	(1,4- add.): *sec*-butyl 3,4,4-trimethylvalerate, b.p. 95°/12 mm., n_D^{25} 1.4231. Calcd. for $C_{12}H_{24}O_2$ (200.3) C, 71.95; H, 12.08. Found C, 71.89; H, 12.18. Sap. equiv. found 202.2.
sec-Butyl crotonate	*n*-$C_8H_{17}MgBr$ (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylhendecanoate, b.p. 115°/1.5 mm., n_D^{25} 1.4305. Calcd. for $C_{16}H_{32}O_2$ (256.4) C, 74.94; H, 12.58. Found C, 75.13; H, 12.43. Sap. equiv. found 260. 2. (Cond. + 1,4- add.): di-*sec*-butyl α-(2-decyl)-β-methylglutarate, b.p. 186°/1.5 mm., n_D^{25} 1.4447. Calcd. for $C_{24}H_{46}O_4$ (398.6) C, 72.31; H, 11.63. Found C, 72.47; H, 11.46. Sap. equiv. found 420.
sec-Butyl crotonate	*n*-$C_{14}H_{29}MgBr$ (CuCl)	1. (1,4- add.): *sec*-butyl 3-methylheptadecanoate, b.p. 196°/3.5 mm., n_D^{25} 1.4405. Calcd. for $C_{22}H_{44}O_2$ (340.6) C, 77.58; H, 13.02. Found C, 77.61; H, 13.01. Sap. equiv. found 338. 2. (Cond. + 1,4-add.): di-*sec*-butyl α-(2-hexadecyl)-β-methylglutarate, b.p. 225°/1.7 mm., n_D^{25} 1.4498. Calcd. for $C_{30}H_{58}O_4$ (482.7) C, 74.63; H, 12.11. Found C, 74.57; H, 11.94. Sap. equiv. found 486.
sec-Butyl crotonate	C_6H_5MgBr (CuCl)	1a. (1,4- add.): *sec*-butyl 3-phenylbutyrate, b.p. 105.5°/2 mm., n_D^{25} 1.4811. Calcd. for $C_{14}H_{20}O_2$ (220.3) C, 76.32; H, 9.15. Found C, 76.53; H, 8.99. Sap. equiv. found 220.9. 1b. (Saponification of 1a): 3-phenylbutyric acid, b.p. 104.5–105°/0.5 mm. (rep.[b] 112–113°/2 mm.), n_D^{25} 1.5147, m. p. 35–36° (rep. 35–36°). Calcd. for $C_{10}H_{12}O_2$ (164.2) C, 73.14; H, 7.37. Found C, 73.37; H, 7.46. Neut. equiv. found 164.4.
Methyl crotonate	*n*-C_4H_9MgBr (CuCl)	1. (1,4- add.): methyl 3-methylheptanoate, b.p. 70°/13.5 mm. (rep.[c] 90.2°/30 mm.), n_D^{25} 1.4144. Calcd. for $C_9H_{18}O_2$ (158.2) C, 68.31; H, 11.46. Found C, 68.33; H, 11.43. Sap. equiv. found 159.2. 2a. (Self-condensation of 1): methyl 2-(2′-hexyl)-3-keto-5-methylnonanoate, b.p. 135°/2.5 mm., n_D^{25} 1.4419. Calcd. for $C_{17}H_{33}O_3$ (284.4) C, 71.79; H, 11.34. Found C, 72.03; H, 11.02. Sap. equiv. found 277. 2b. (Saponification and decarboxylation of 2a): 5,9-dimethyltridecanone-7, b.p. 93.5°/1 mm., n_D^{25} 1.4354. Calcd. for $C_{15}H_{30}O$ (226.4) C, 79.57; H, 13.36. Found C, 79.74; H, 13.53.
sec-Butyl methacrylate	*n*-C_4H_9MgBr (CuCl)	(Cond. + 1,4- add.): di-*sec*-butyl α-*n*-amyl-α,γ-dimethylglutarate, b.p. 142°/1.7 mm., n_D^{27} 1.4371. Calcd. for $C_{20}H_{38}O_4$ (342.5) C, 70.13; H, 11.18. Found C, 70.19; H, 11.13. Sap. equiv. found 344.
sec-Butyl tiglate	*n*-C_4H_9MgBr	(Cond. + 1,4- add.): di-*sec*-butyl α-(2-hexyl)-α,β,γ-trimethylglutarate, b.p. 158°/1.5 mm., n_D^{25} 1.4520. Calcd. for $C_{22}H_{42}O_4$ (370.6) C, 71.30; H, 11.43. Found C, 71.58; H, 11.36. Sap. equiv. found 4800 (!).
sec-Butyl cinnamate	*n*-C_4H_9MgBr (CuCl)	(1,4- add.): *sec*-butyl 3-phenylheptanoate, b.p. 115°/0.8 mm., n_D^{25} 1.4792. Calcd. for $C_{17}H_{26}O_2$ (262.4) C, 77.81; H, 9.99. Found C, 77.99; H, 10.00. Sap. equiv. found 262.6.
sec-Butyl cinnamate	CH_3MgBr (CuCl)	(1,2- + 1,4- add.): 4-phenylpentanone-2, b.p. 88.5°/1.7 mm., n_D^{25} 1.5102 (rep. b.p. 113–115°/13 mm., n_D^{20} 1.5124[d]; b.p. 109°/11 mm., n_D^{15} 1.5090[e]). Intensive rhubarb-like odor. I.R. spectrum shows strong carbonyl-band. Calcd. for $C_{11}H_{14}O$ (162.2) C, 81.44; H, 8.70. Found C, 81.46; H, 8.87. Sap. equiv. found 2500.

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[a] Norris and Green, *Am. Chem. J.*, **26**, 311 (1901) [*Chem. Zentr.*, II, 1113 (1901)]. [b] Reference (14). [c] Reference (19). [d] Nenitzescu and Gavat, *Ann.*, **519**, 260 (1935); (*e*) Cologne and Pichat, *Bull. soc. chim.*, 177 (1949).

action here reported very little, if any, 1,4- addition took place when the cadmium reagent was used. Even after heating under reflux in ether-benzene solution, the crotonic ester was recovered.

It should be noted that, in the presence of cuprous chloride, *n*-butylmagnesium bromide also adds only to the carbon-carbon double bond of methyl crotonate. However, in this case only traces of the simple 1,4- addition product (corresponding to II) are obtained; this initial product apparently self-condenses to the corresponding acetoacetic ester [methyl α,γ-di-(2-hexyl)acetoacetate]. This compound (obtained in 67% yield), on saponification, spontaneously decarboxylates into the corresponding ketone in 75% yield.

It is further remarkable that even methylmagnesium bromide does not add to the carbonyl group of *sec*-butyl crotonate when cuprous chloride is present; however, in the cases of methyl- and ethylmagnesium bromides, the proportion of simple 1,4- addition product (II) to condensation addition product (IV) is somewhat smaller than in the cases of the larger primary Grignard reagents. The explanation for this should probably be sought in the above-mentioned possibility of competitive reaction of the cuprous chloride with the Grignard reagent before the crotonic ester is added, to which reaction the Grignard solutions from methyl and ethyl bromide were considerably more sensitive than the higher Grignard reagents.

Isopropylmagnesium bromide and *tert*-butylmagnesium chloride give only rather poor yields (39% and 14%, respectively) of the simple 1,4- addition products (II), and large amounts of resinous material are formed. Secondary and tertiary Grignard reagents have been reported to give poor yields also in the reaction with alkylidenecyanoacetic esters.[3,5]

The introduction of a methyl group in the α-position of an α,β-unsaturated ester (*e.g.*, methacrylic and tiglic esters) results in the exclusive formation of the condensation addition product (IV), even in the presence of a large excess of Grignard reagent. The yields, however, are rather small.

To *sec*-butyl cinnamate, *n*-butylmagnesium bromide adds 1,4- to give a fair yield of *sec*-butyl 3-phenylheptanoate, but methyl-magnesium bromide adds at both 1,2- and 1,4- positions to give a 40% yield of 4-phenylpentanone-2; the yield of this product could probably be improved by using a greater excess of Grignard reagent, since a considerable amount of unreacted *sec*-butyl cinnamate was recovered.

The usual by-products are formed from the Grignard reagents, RMgX: the hydrocarbons RH and R—R, and traces of the hydroxyl compounds ROH. As mentioned in Table I, these products sometimes contaminate the main products, but mostly they can be separated.

EXPERIMENTAL[36]

Preparation of sec-butyl esters (Table III). A mixture of 258 g. (3 moles) of crotonic acid (Eastman, pract.), 370 g. (5 moles) of 2-butanol in which were dissolved 6–7 ml. of concentrated sulfuric acid, and 300 ml. of thiophene-free benzene was heated under reflux overnight, as water (65 ml.) was removed from the reaction mixture by means of a Wideqvist water separator.[38] The cooled reaction mixture was diluted with 200 ml. of ether, then washed with sodium bicarbonate solution and with water, and finally dried over anhydrous sodium sulfate. After distillation of the solvents the ester was fractionated through a 25-cm. Vigreux column.

TABLE III

sec-BUTYL ESTERS

					Analyses						
					Calcd.				Found		
sec-Butyl	B.p. °C./mm.	n_D^{25}	Moles	Yield, %	for	C	H	S.E.	C	H	S.E.
Crotonate	74–75/30 83–84/45	1.4261	1–3	85–90	$C_8H_{14}O_2$	67.57	9.92	142.2	67.56	9.87	142.6
Methacrylate	59–62/34	1.4161	2	85	$C_8H_{14}O_2$	67.57	9.92	142.2	67.64	10.12	143.2
Tiglate	84.5/27	1.4332	0.5	60	$C_9H_{16}O_2$			156.6			156.0
Cinnamate	122/2	1.5382	1	92	$C_{13}H_{16}O_2$	76.43	7.90	204.3	76.31	7.92	204

The other esters were prepared similarly. The methacrylic ester was stabilized with 1% hydroquinone during the preparation and with 0.1% hydroquinone for storage after distillation. Glacial methacrylic acid was purchased from Monomer-Polymer, Inc., Leominster, Mass. Tiglic acid was prepared as described in the literature.[39]

Reactions of α,β-unsaturated esters with Grignard reagents (Tables I and II). Reaction of *sec*-butyl crotonate with *n*-butylmagnesium bromide is illustrative. A solution of *n*-butylmagnesium bromide was prepared from 7.2 g. (0.3 g.-atom) of magnesium turnings and 50 g. (0.37 mole) of *n*-butyl bromide in 120 ml. of ether. This solution was cooled for about 10 min. in ice water, after which 0.3 g. (1 mole %)

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(36) All melting and boiling points are uncorrected; pressures above 5 mm. were measured with a Zimmerli gage, those below 5 mm. with a tilting McLeod gage. Unless otherwise specified, all distillations were through a 45-cm. Podbielniak-type column with simple tantalum wire spiral, heated jacket, and partial reflux head.[37] Microanalyses were by the Microanalytical Division, Department of Chemistry and Chemical Engineering, University of California, Berkeley. Infrared spectra were recorded on a Baird double-beam spectrophotometer.

(37) Cason and Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, New York, 1950, p. 237 ff.

(38) Wideqvist, *Acta Chem. Scand.*, **3**, 303 (1949).

(39) Buckles and Mock, *J. Org. Chem.*, **15**, 680 (1950).

of cuprous chloride[40] was added in one portion. While stirring in the ice bath, a solution of 28.4 g. (0.2 mole) of *sec*-butyl crotonate in 125 ml. of ether was added dropwise during 1–1.5 hr. (*With runs on a larger scale, it was found necessary to increase the amount of ether as solvent, as well as the addition time, proportionally, in order to obtain the maximum yield.*) After the addition of the ester had been completed, the reaction mixture was stirred in the ice bath for an additional 10–15 min. and then at room temperature for 1–1.5 hr. It was then poured, under vigorous shaking or swirling, onto ice to which 35 ml. of concentrated hydrochloric acid and 50 ml. of ether had beeen added. The two clear layers were separated and the water layer was extracted with ether. Then the combined ether layers were washed with sodium bicarbonate solution and with water, and dried over anhydrous sodium sulfate. The ether was distilled and the residue fractionated. The products obtained are given in Tables I and II; in the last column of Table I is given certain additional experimental information.

Saponification of sec-butyl 3-methylheptanoate. This ester (40 g., 0.2 mole) was saponified by heating under reflux in a solution of potassium hydroxide (35 g., 0.6 mole) in 95% ethanol (250 ml.) for 6–8 hr., after which time about half of the alcohol was distilled. The corresponding amount of water was added, and the distillation repeated in order to remove any volatile compounds. After pouring into water, acidifying, and extracting with ether, distillation produced 3-methylheptanoic acid in 94% yield, b.p. 116.5–117°/10 mm., n^{25}_{D} 1.4242 [lit. 121°/15 mm., n^{16}_{D} 1.4276[16]].

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18; neut. equiv., 144.2. Found: C, 66.64; H, 11.05; neut. equiv., 144.4.

The amide, crystallized from heptane, melted at 81.5–82°.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 67.16; H, 11.88; N, 9.62.

Attempted preparation of product IV. A mixture of 14.2 g. (0.1 mole) of *sec*-butyl crotonate and 20 g. (0.1 mole) of *sec*-butyl 3-methylheptanoate, dissolved in 100 ml. of ether, was added to a stirred suspension of sodium *sec*-butoxide in 100 ml. of ether, prepared from 1.2 g. (0.05 g.-atom) of sodium and 7.4 g. (0.1 mole) of 2-butanol. The mixture was stirred at room temperature for 9 hr., then for 3 hr. under reflux, after which it was worked up in the conventional way. Fractionation gave 17.5 g. (87%) of recovered *sec*-butyl 3-methylheptanoate, b.p. 98–99°/10 mm., n^{25}_{D} 1.4191, and 9.3 g. (65%) of the dimer of *sec*-butyl crotonate (III), b.p. 120–121°/1.5 mm., n^{25}_{D} 1.4443.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92; sap. equiv., 142.2. Found: C, 67.70; H, 10.09; sap. equiv., 253.

The infrared spectrum showed two carbonyl bands at 5.78 μ (1730 cm.$^{-1}$), 5.86 μ (1708 cm.$^{-1}$) and one conjugated carbon-carbon double bond band at 6.10 μ (1640 cm.$^{-1}$). These data show that this compound is different from the isomeric dimer obtained in the attempted ferric chloride catalyzed 1,4- addition of *n*-butylmagnesium bromide to *sec*-butyl crotonate.

Preparation of the anhydride corresponding to product IV from sec-butyl crotonate and n-butylmagnesium bromide [*α-(2-hexyl)-β-methylglutaric anhydride*]. A 10-g. (0.03-mole) sample of IV was saponified under reflux with a solution of 12 g. (0.2 mole) of potassium hydroxide in 95 ml. of ethylene glycol for 72 hr. After dilution with water, washing with ether and boiling to expel volatile compounds, the solution was acidified and the acid extracted with ether. After removal of the ether, the crude liquid acid (7.6 g.) was heated under reflux with acetyl chloride (20 ml.) for 4 hr. The excess of acetyl chloride was removed and the residue distilled to give 3 g. of a colorless oil, b.p. 116°/0.5 mm., n^{25}_{D} 1.4635.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50; sap. equiv., 106.2. Found: C, 68.00; H, 9.41; sap. equiv. 107.3.

Acknowledgments. The author wants to express his gratitude to Prof. James Cason for valuable advice and discussion during the course of this research.

The author is further indebted to the Technical University of Denmark and to Danmark-Amerika Fondet for financial support, to the United States Educational Foundation for a Fulbright Travel Grant, and to the University of California at Berkeley for providing excellent working conditions.

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[40] Cuprous chloride was prepared by heating under reflux with copper-metal a solution of commercial cuprous chloride in hydrochloric acid, isolation of the cuprous chloride in the conventional way, drying and storing *in vacuo* over phosphorus pentoxide and sodium hydroxide, applying dry nitrogen whenever the vacuum was released.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Some Reactions Effected by Means of Bromomagnesium *t*-Alkoxides[1]

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Received August 27, 1956

It has been found that tribenzoylmethane results in about 10% yield when methyl ketones are caused to react with benzoyl chloride in the presence of bromomagnesium *t*-alkoxides. Bromomagnesium *t*-butoxide has been shown to be effective in bringing about some carbonyl condensations with methyl ketones.

In an attempt to prepare benzoates directly by the action of benzoyl chloride on the reaction mixtures obtained from methyl ketones and Grignard reagents, it was observed[3] that a small amount of a high-melting aromatic compound was formed in several cases. In the present investigation this material has been shown to be tribenzoylmethane.

A detailed study of the reaction product obtained from the treatment of the complex from *n*-dodecylmagnesium bromide and methyl *n*-hexyl ketone with benzoyl chloride afforded 7–18% of tribenzoylmethane, an olefin which might have been produced by the dehydration of methyl-*n*-hexyl-*n*-

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[1] Presented, in part, at the 128th Meeting of the AMERICAN CHEMICAL SOCIETY, Minneapolis, Minn., Sept. 11-16, 1955.

[2] Abstracted from the Ph.D. thesis of J. L. Guthrie, 1956.

[3] These experiments were carried out by G. R. Collins.