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Aldol Type Condensation of Ketones and Esters in the Presence of Diethylaminomagnesium Bromide and Related Compounds[1]

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RECEIVED JUNE 2, 1952

Aldol type condensation between various ketones and esters can be effected by means of diethylaminomagnesium bromide and some related aminomagnesium bromides as well as mesitylmagnesium bromide. When an equimolar mixture of benzophenone and *t*-butyl acetate was treated with an excess of diethylaminomagnesium bromide in ether, *t*-butyl β,β-diphenylhydracrylate was obtained in a 91% yield. Other combinations of ketones and esters gave inferior yields of the corresponding β-hydroxy esters.

Hauser and Puterbaugh[2] have recently recorded the aldol condensation of ketones and *t*-butyl acetate by means of metal amides. Similar observations have independently been made in our laboratory using diethylaminomagnesium bromide and some related compounds.

When a stoichiometric mixture of benzophenone and ethyl acetate was treated with equimolar diethylaminomagnesium bromide in ether, ethyl β,β-diphenylhydracrylate was obtained in a 24% yield, along with a considerable amount (50%) of unchanged benzophenone.

TABLE I

ALDOL CONDENSATION OF BENZOPHENONE WITH ACETATES IN THE PRESENCE OF DIETHYLAMINOMAGNESIUM BROMIDE[a]

Acetates CH_3COOR R	$(C_2H_5)_2NMgBr$ Mol. ratio	Yield,[b] %	M.p., °C.	Products $(C_6H_5)_2C(OH)CH_2COOR$ Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	2	40(80)	106.5[c]	$C_{16}H_{16}O_3$	74.98	75.01	6.29	6.47
CH_3CH_2	1	24(48)	86[d]	$C_{17}H_{18}O_3$	75.53	75.19	6.71	6.76
	2	46(68)						
	3	61.5						
$CH_3(CH_2)_2$	2	18(52)	52[c]	$C_{18}H_{20}O_3$	76.03	76.10	7.09	7.52
$(CH_3)_2CH$	2	67(86)	98[c]	$C_{18}H_{20}O_3$	76.03	75.72	7.09	7.08
$CH_3(CH_2)_3$	2	9(24)	66–67[c]	$C_{19}H_{22}O_3$	76.48	76.49	7.43	7.57
$(CH_3)_3C$[e]	2	91	92–93[c]	$C_{19}H_{22}O_3$	76.48	76.22	7.43	7.52
$(CH_3)_2CH(CH_2)_2$	2	4(11)	An oil[f]					
C_6H_5	2	0						

[a] In each case 0.1 mole of benzophenone and 0.1 mole of the acetates were used. [b] The yields parenthesized are based on the consumed benzophenone. [c] These compounds are new. [d] *Cf.* ref. 18. [e] *Cf.* ref. 19. [f] Since the product formed a yellowish oil, b.p. 210–215° at 8 mm., it was identified after saponification to be β,β-diphenylhydracrylic acid, m.p. and mixed m.p. 210–211°.

It is probable that this aldol type condensation proceeds by the generally accepted mechanism through the enolate anion of the acetate which adds to the carbonyl group of the ketone. Possible side reactions are the formation of N,N-diethylacetamide, the self-condensation of the enolate anion or the formation of β-keto ester,[3,4] and the addition of the condensation agent to the carbonyl group of the ketone[5] which may account for recovering the original ketone.

Improvements in the yield of the diphenylhydracrylate may, therefore, be attainable in the following ways. The use of an excess of the condensing agent will favor the formation of the ester anion. The choice of an acetate which is resistant to hydrolysis,[6] ammonolysis[7] and other anionoid replacements of the alkoxy group[8] may hinder the above-mentioned side reactions which involve the nucleophilic attack on the carbonyl carbon of the ester. Such expectations have been realized in our experiments, whose results are summarized in Table I.

Thus, the treatment of an equimolar mixture of benzophenone and ethyl acetate with an excess (3 moles) of the condensing agent raised the yield of ethyl β,β-diphenylhydracrylate to 61.5%. It is remarkable that the condensation of benzophenone and *t*-butyl acetate under similar conditions gave *t*-butyl β,β-diphenylhydracrylate in a nearly quantitative yield.

The use of condensing agents other than diethylaminomagnesium bromide has also been examined. When a mixture of benzophenone and *t*-butyl acetate was treated with mesitylmagnesium bromide, there was obtained *t*-butyl β,β-diphenylhydracrylate in a 41% yield. The similar condensation of benzophenone and isopropyl acetate was carried on in 62 and 84% yields, respectively, by means of dibenzylaminomagnesium bromide as well as of dicyclohexylaminomagnesium bromide,[9] but the latter two are less convenient for use than diethylaminomagnesium bromide, since the hydrolysis of

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[1] This research was supported by a Grant-in-Aid for Fundamental Scientific Research, Japanese Government Department of Education, 1950-1951.

[2] C. R. Hauser and W. H. Puterbaugh, THIS JOURNAL, **73**, 2972 (1951).

[3] C. R. Hauser and H. G. Walker, Jr., *ibid.*, **69**, 295 (1947).

[4] F. C. Frostick and C. R. Hauser, *ibid.*, **71**, 1350 (1949).

[5] V. V. Chelintsev and A. V. Pataraya, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 461 (1941).

[6] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 121, 211, 216.

[7] M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948). *Cf.* also C. R. Hauser, R. Levine and R. F. Kibler, *ibid.*, **68**, 26 (1946).

[8] J. K. Sneed and R. Levine, *ibid.*, **72**, 5219 (1950).

[9] K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1934).

TABLE II

ALDOL CONDENSATION OF KETONES AND VARIOUS ESTERS IN THE PRESENCE OF DIETHYLAMINOMAGNESIUM BROMIDE

Ketones	Esters	$(C_2H_5)_2$-NMgBr mole ratio	Products	M.p. or (b.p.), °C.	Yields,[a] %
Benzophenone	Ethyl butyrate	1	Ethyl β,β-diphenyl-α-ethylhydracrylate	M. 107[b]	13 (20)
Benzophenone	Methyl cyanoacetate	1	Methyl α-cyano-β-phenylcinnamate[c,d]	M. 111–111.7	17 (43)
Acetophenone	*t*-Butyl acetate	2	*t*-Butyl β-hydroxy-β-phenyl-*n*-butyrate	148–152 at 26 mm.	65 (78)
Acetophenone	Ethyl acetate	1	Ethyl β-hydroxy-β-phenyl-*n*-butyrate	133–137 at 26 mm.	16 (19)
α-Tetralone	Ethyl acetate	1	Ethyl 1-hydroxy-1,2,3,4-tetrahydronaphthyl-1-acetate	172–178 at 18 mm.	5 (10)[e]
o-Acetoxyacetophenone		2	4-Methylcoumarin	M. 81[f]	27
Methyl *o*-acetoxybenzoate		2	4-Hydroxycoumarin	M. 205–206[g]	8

[a] The yields parenthesized are based on the consumed ketones. [b] R. du Fazi (*Gazz. chim. ital.*, **45II**, 143 (1915)) reported the m.p. as 107–108°. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.67; H, 7.74. [c] *Anal.* Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98. Found: C, 77.92; H, 5.07. [d] This is an unknown compound, which gives upon saponification the corresponding acid, colorless needles, m.p. 200–201°. *Anal.* Calcd. for $C_{16}H_{11}O_2N$: C, 77.09; H, 4.45. Found: C, 77.42; H, 4.91. [e] The oily β-hydroxy ester was converted to the crystalline α-naphthylacetic acid according to the method of Bachmann (*cf.* ref. 15). The yield herein described is the over-all yield of the acid based on α-tetralone. The product melted at 130° and showed no depression of the m.p. when admixed with an authentic specimen of α-naphthylacetic acid. *Anal.* Calcd. for $C_{12}H_{10}O_2$: C, 77.41; H, 5.41. Found: C, 77.24; H, 5.58. [f] K. Fries and W. Volk (*Ann.*, **379**, 94 (1911)) gave the melting point as 82°. *Anal.* Calcd. for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.14; H, 5.41. [g] M. A. Stahman, C. F. Huebner and K. P. Link (*J. Biol. Chem.*, **138**, 522 (1941)) recorded the melting point as 210°. *Anal.* Calcd. for $C_9H_6O_3$: C, 66.67; H, 3.75. Found: C, 66.83; H, 3.85.

the reaction mixtures is accompanied by difficulties and the yields are not superior. On the other hand, isopropylmagnesium bromide and benzylaminomagnesium bromide failed to affect the aldol-type condensation. It should be added that Ivanov and his co-workers[10] have obtained β,β-disubstituted α-phenylhydracrylic acids upon treatment of ketones with α-halomagnesium derivatives of phenylacetic acid prepared from its salt and some Grignard reagents such as isopropylmagnesium and ethylmagnesium bromides.

It is well known that the condensation of acetophenone with ethyl acetate in the presence of basic reagents such as amides or alkoxides of alkali metals leads to a 1,3-diketone, benzoylacetone.[11] We have discovered that the use of diethylaminomagnesium bromide as a condensing agent in this reaction results in the formation of a product of aldol type, *i.e.*, ethyl β-hydroxy-β-phenyl-*n*-butyrate besides a small amount of benzoylacetone, the former product being converted to β-phenylcrotonic acid and identified.

When *t*-butyl acetate was used as an ester component in the presence of an excess of the condensing agent, there was obtained 78% yield of the corresponding *t*-butyl β-hydroxy-β-phenyl-*n*-butyrate. The formation of benzoylacetone was not observed in the latter reaction. Hauser and Puterbaugh[2] reported a 31% yield of *t*-butyl β-hydroxy-β-phenyl-*n*-butyrate in the same condensation using sodium amide and zinc chloride and 76% yield of the butyrate by means of lithium amide. It should be added that the action of equimolar diethylaminomagnesium bromide upon acetophenone alone afforded 1,3,5-triphenylbenzene[12] and dypnone[13] in 20 and 24% yields, respectively, 17% of acetophenone being recovered unchanged. Colonge[14] has obtained the ketol, β-hydroxy-β-phenylbutyrophenone with anilinomagnesium bromide.

Treatment of other combinations of carbonyl compounds and esters with diethylaminomagnesium bromide gave inferior results as shown in Table II. The action of the condensing agent upon a mixture of α-tetralone and ethyl acetate gave ethyl 1-hydroxy-1,2,3,4-tetrahydronaphthyl-1-acetate which was converted to α-naphthylacetic acid according to the method of Bachmann.[15] In this case the formation of 2-acetyl-1-tetralone, which might occur as a result of the Claisen ester condensation, was not detected. This aldol-type condensation could also be applied to the intramolecular cyclization of the compounds bearing both carbonyl and ester groups in the same molecule. Thus, 4-methylcoumarin and 4-hydroxycoumarin were obtained, respectively, from *o*-acetoxyacetophenone and methyl *o*-acetoxybenzoate, although the yields were unsatisfactory.

Hauser and Puterbaugh[2] reported that the condensation of benzaldehyde with *t*-butyl acetate in the presence of sodium amide and zinc chloride resulted in the formation of the desired *t*-butyl β-hydroxy-β-phenylpropionate in a 58% yield. In our experiment, however, benzaldehyde did not react with ethyl acetate in the presence of diethylaminomagnesium bromide. When *t*-butyl acetate was used in the place of the ethyl ester only a small amount (3%) of the β-hydroxy ester was obtained, which was converted to cinnamic acid and identified. In each case most of the original aldehyde was recovered unchanged. It is probable that the addition of diethylaminomagnesium bromide to the reactive carbonyl group of the aldehyde may be favored over the α-hydrogen reaction of ester with the condensing reagent and accordingly hydrolysis

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[10] (a) D. Ivanov and A. Spassov, *Bull. soc. chim.*, [4] **49**, 377 (1931); (b) D. Ivanov and N. I. Nicolloff, *ibid.*, [4] **51**, 1325 (1932).

[11] (a) C. Beyer and L. Claisen, *Ber.*, **20**, 2180 (1887); (b) L. Claisen, *ibid.*, **38**, 695 (1905).

[12] The hydrocarbon melted at 168°. C. Engler and H. E. Berthold (*ibid.*, **7**, 1123 (1874)) reported the melting point as 169–170°. *Anal.* Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 94.12; H, 5.77.

[13] The unsaturated ketone, b.p. 175–180° at 7 mm., was converted to the semicarbazone, m.p. 150–151°. A. Courtot (*Bull. soc. chim.*, [3] **35**, 356 (1906)) recorded the melting point as 151°.

[14] J. Colonge, *ibid.*, [5] **1**, 1101 (1934). *Cf.* also J. Colonge, *Compt. rend.*, **196**, 1414 (1933); J. Colonge and V. Grignard, *ibid.*, **194**, 929 (1932). They have described a mixed condensation between benzophenone and pinacolone.

[15] W. E. Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

of the addition complex regenerates the original aldehyde.

Experimental[16,17]

Condensation of Benzophenone with Esters in the Presence of Diethylaminomagnesium Bromide.—The preparation of ethyl β,β-diphenylhydracrylate is typical for all of the reactions in this series. To a Grignard reagent prepared from 33 g. (0.3 mole) of ethyl bromide, 7.3 g. (0.3 atom) of magnesium and 120 cc. of ether was added dropwise a solution of 22 g. (0.3 mole) of anhydrous diethylamine in 40 cc. of ether under stirring and cooling with ice, and the mixture was refluxed for about 30 minutes. A solution of 18.2 g. (0.1 mole) of benzophenone and 8.8 g. (0.1 mole) of purified ethyl acetate in 50 cc. of ether was then added dropwise to the above prepared reagent under vigorous stirring and cooling at −5°. After the addition was completed the temperature was raised gradually to that of boiling. Refluxing was continued for two hours and the reaction mixture was poured onto 150 g. of crushed ice acidified with 20 g. of concentrated sulfuric acid. The organic layer was separated and the aqueous phase was extracted with benzene. The combined organic layer was washed with water, saturated sodium bicarbonate solution and then with water, dried over anhydrous sodium sulfate and the solvent was evaporated. Distillation of the residue gave a fraction, b.p. 190–193° at 8 mm., which solidified immediately. After recrystallization from methanol colorless plates, m.p. 87°, were obtained. The recorded m.p. of ethyl β,β-diphenylhydracrylate[18] is 87°; yield 16.5 g. or 61.5%.

Saponification with methanolic potash, followed by recrystallization, yielded colorless plates, m.p. 210–211°, which showed no depression of the m.p. on admixture with an authentic sample of diphenylhydracrylic acid.

In some instances, *viz.*, when methyl, isopropyl and *t*-butyl acetate[19] were used, the evaporation residue crystallized immediately. The diphenylhydracrylates were filtered, recrystallized and analyzed. In Tables I and II are listed the yields and properties of β,β-diphenylhydracrylates and related compounds prepared in similar operations together with analyses.

Condensation of Acetophenone with Acetates.—A solution of 0.3 mole of diethylaminomagnesium bromide in 160 cc. of ether was cooled to −5° in an ice-salt mixture and mixture of 0.15 mole of acetophenone and 0.15 mole of *t*-butyl acetate in 40 cc. of toluene was added dropwise. The resulting mixture was stirred for 30 minutes at room temperature and for an additional four hours at 45° and allowed to stand overnight.

After treating the reaction product in the same way as above 23 g. of *t*-butyl β-hydroxy-β-phenylbutyrate, b.p. 148–152° at 26 mm., was obtained, about 3 g. of acetophenone being recovered from the fore-run. Treatment of the oily β-hydroxy ester with saturated copper acetate solution did not give the precipitates of the copper salt of benzoylacetone. Dehydration of *t*-butyl β-hydroxy-β-phenylbutyrate with a mixture of acetyl chloride and acetic anhydride followed by saponification, gave 8.5 g. of β-phenylcrotonic acid as colorless plates, m.p. 98°.[20] Over-all yield based on the acetophenone consumed is 42%.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.14; H, 6.18.

When a mixture of 0.15 mole of acetophenone and 0.15 mole of ethyl acetate was treated with 0.15 mole of diethylaminomagnesium bromide, 6.2 g. of an oil, b.p. 135–137° under 26 mm., was obtained, about 3.1 g. of acetophenone being recovered unchanged. The crude β-hydroxy ester was stirred with 150 cc. of saturated copper acetate solution for one hour and allowed to stand overnight. The precipitates were collected and recrystallized from benzene. Thus was obtained 1 g. of the copper salt of benzoylacetone, m.p. and mixed m.p. 190°.

The filtrate and the mother liquors were combined and the aqueous layer was extracted with benzene. The benzene solution was washed, dried and distilled to give a light-yellow oil, b.p. 135–137° at 23 mm., which weighed 4.9 g.

Condensation of Benzophenone with Isopropyl Acetate in the Presence of Other Aminomagnesium Bromides.—To an ethereal solution of ethylmagnesium bromide prepared from 14 g. (0.133 mole) of ethyl bromide and 3.2 g. (0.133 atom) of magnesium was added dropwise 26.3 g. (0.133 mole) of dibenzylamine in 30 cc. of ether at 0–5° and refluxed for 40 minutes. A solution of 14.4 g. (0.08 mole) of benzophenone and 9 g. (0.08 mole) of isopropyl acetate in 40 cc. of ether was added to the resulting reagent and after heating at 40–45° for 3.5 hours the contents of the flask were poured onto iced water containing 40 g. of concentrated hydrochloric acid and the precipitates collected by filtration were washed four times with 50 cc. of benzene and the mother liquor was extracted with the above benzene solution. When the solvent was distilled off after washing and drying, 10.5 g. of the crude isopropyl β,β-diphenylhydracrylate, m.p. 96–97°, was obtained which showed no depression of the mixed melting point with an authentic sample.

Similarly, with dicyclohexylaminomagnesium bromide the same condensation was carried out in 84% yield.

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(16) All melting points and boiling points are uncorrected.

(17) Our thanks are due to Mr. Akira Kuroda for assistance.

(18) H. Rupe and E. Buvolt, *Ber.*, **40**, 4537 (1907).

(19) *t*-Butyl acetate was prepared from *t*-butyl alcohol and acetic anhydride in the presence of a trace of hydrogen bromide. Unpublished result by K. Sisido, H. Nozaki and M. Matô. *Cf.* K. Sisido and H. Nozaki, THIS JOURNAL, **70**, 3326 (1948).

(20) Rupe and Buvolt (ref. 18) described the melting point as 98–99°