[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Condensation of Ketones by Aluminum *t*-Butoxide to Compounds of the Mesityl Oxide Type

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In attempting to determine the relative oxidation potentials of ketones, Cox observed that acetophenone in the presence of aluminum *t*-butoxide was converted to dypnone[2]

$$2PhCOCH_3 \longrightarrow PhC(CH_3){=}CHCOPh + H_2O$$

This suggested a method whereby unsaturated ketones of the mesityl oxide type[3] could be made from various ketones.

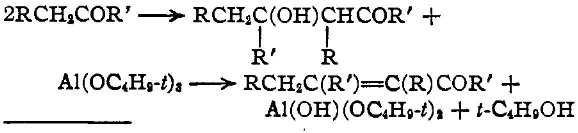
Reagents which have been used on ketones to yield mesityl oxide type condensation products include sodium ethoxide,[4] hydrogen halides,[5] aluminum halides,[6] calcium hydride,[7] calcium carbide,[8] diethyl zinc,[9] a mixture of zinc chloride and acetyl chloride,[10] sulfuric acid,[11] potassium hydroxide,[12] phosphorus pentachloride,[13] triphenylaluminum,[6] sodium,[14] and alumina.[15] Bromomagnesium amines,[16] bromomagnesium alkoxides,[17] and barium hydroxide[18] have been used to prepare ketols which upon distillation with iodine or oxalic acid yield the mesityl oxide type compounds. Under certain conditions, in the preparation of methyl ketones by means of dimethyl zinc and the corresponding acid chloride, the condensation product of the ketone is formed.[19] The action of aniline and aniline zinc chloride on ketones in some cases forms an anil which upon hydrolysis yields the condensation product of the ketone.[20] Ekeley and Howe,[21] Kunze,[22] Abbott, Kon and Satchell,[4] Kon and Leton,[23] and Colonge[5] have made comparative studies of various reagents.

Aluminum *t*-butoxide differs from most of the reagents referred to above in that it not only brings about the aldol condensation, but absorbs the water formed in the next step without the liberation of a strong acid or base. The use of the alkoxide makes it possible to carry out both the condensation and the dehydration in an inert anhydrous solvent.

Sixteen representative ketones have been subjected to the condensing action of aluminum *t*-butoxide, particular attention being given at first to the effect of experimental conditions upon the condensation of acetophenone. Representative results are given in Table I.

The temperature required for the condensation varies from 60 to 140°. Aluminum *t*-butoxide in solution slowly decomposes above 115°, in accord with the observation made by Tischtschenko long ago for the solid alkoxide.[24] The boiling point of xylene is apparently the highest temperature that may be used satisfactorily for the condensation. The reaction of the lower molecular weight ketones may begin at their boiling points and the temperature of reaction can only be raised after a considerable portion of the ketone has been condensed. Since *t*-butyl alcohol is formed during the condensation it must be distilled out of the reaction mixture if the temperature of the latter is to be raised much above 80°.

Since three moles of water are required for the complete hydrolysis of one mole of aluminum *t*-butoxide, it would appear that six moles of the ketone might be used for each mole of the alkoxide. However, experience showed that the yields of dimer were poor if there was less than one mole of the alkoxide for three moles of the ketone. In practice one mole of the alkoxide was used for two moles of ketone as indicated in the formulation given below:



$$2RCH_2COR' \longrightarrow RCH_2\underset{R'}{\underset{|}{C}}(OH)\underset{R}{\underset{|}{C}}HCOR' + Al(OC_4H_9\text{-}t)_3 \longrightarrow RCH_2C(R'){=}C(R)COR' + Al(OH)(OC_4H_9\text{-}t)_2 + t\text{-}C_4H_9OH$$

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[1] Research assistant on funds allotted by the Wisconsin Alumni Research Foundation.

[2] Adkins and Cox, THIS JOURNAL, **60**, 1151 (1938).

[3] For the sake of convenience in the discussion and tabulation of data these "mesityl oxide type condensation products," such as dypnone, will be referred to as dimers of the various ketones.

[4] Abbott, Kon and Satchell, *J. Chem. Soc.*, 2514 (1928).

[5] Colonge, *Bull. soc. chim.*, [4] **49**, 426 (1931).

[6] Calloway and Green, THIS JOURNAL, **59**, 809 (1937).

[7] Porlezza and Gatti, *Gazz. chim. ital.*, **56**, 265 (1926).

[8] Taboury and Godchot, *Compt. rend.*, **169**, 64 (1919).

[9] Henrich and Wirth, *Monatsh.*, **25**, 431 (1904).

[10] Descude, *Ann. chim. phys.*, [7] **29**, 496 (1903).

[11] Kipping, *J. Chem. Soc.*, **65**, 495 (1894).

[12] Wallach and Behnke, *Ann.*, **369**, 99 (1909).

[13] Taylor, *J. Chem. Soc.*, 308 (1937).

[14] Schramm, *Ber.*, **16**, 1581 (1883).

[15] Petrov, *Bull. soc. chim.*, [4] **43**, 1272 (1928).

[16] Colonge, *ibid.*, [5] **1**, 1101 (1934); [5] **2**, 57 (1935).

[17] Grignard and Fluchaire, *Ann. chim.*, [10] **9**, 32 (1928).

[18] Kyriakides, THIS JOURNAL, **36**, 534 (1914).

[19] Pawlow, *Ann.*, **188**, 138 (1877).

[20] Reddelien and Meyn, *Ber.*, **53**, 345 (1920).

[21] Ekeley and Howe, THIS JOURNAL, **45**, 1917 (1923).

[22] Kunze, *Ber.*, **59**, 2085 (1926).

[23] Kon and Leton, *J. Chem. Soc.*, 2496 (1931).

[24] Tischtschenko, *J. Russ. Phys.-Chem. Soc.*, **31**, 784 (1899); *Chem. Centr.*, [1] **71**, 585 (1900).

TABLE I

CONDENSATION OF KETONES

Moles of ketone		Ratio[a]	Temp.,[b] °C.	Time, hr.		Yield of products, g.	%
0.33	MeCOPh	1-1.2-450 A	80-82	50	Ketone	19.0	
					Dimer	15.8	43
.33	MeCOPh	1-1.2-450 D	100-90	24	Ketone	3.2	
					Dimer	28.5	77
.33	MeCOPh	1-1.2-450 T	108-95	24	Ketone	4.1	
					Dimer	28.2	76
.33	MeCOPh	1-0.5-300 T	110-95	24	Ketone	5.8	
					Dimer	29.6	80
1.00	MeCOPh	1-0.55-400 X	133-137	2	Ketone	6.1	
					Dimer	91.5	82
1.00	Me$_2$CO	1-0.5-100 B	65-80	8	Dimer	18.3	37
					Phorone	9.0	19
0.70	MeCOEt	1-0.5-50 B	82-84	24	Dimer	31.2	72
1.00	MeCOEt	1-0.167 N	82-88	8[c]	Dimer	30.2	49
1.00	MeCOi-Pr	1-0.5-400 X	117-120	13[c]	Ketone	2.5	
					Dimer	37.8	49
0.50	MeCOn-Bu	1-0.5-400 X	125-130	1.7[c]	Dimer	33.4	73
.50	MeCOi-Bu	1-0.5-300 X	125-130	3[c]	Dimer	32.0	70
.50	MeCOt-Bu	1-0.5-400 X	120-125	15[c]	Ketone	23.3	
					Dimer	4.6	10
.45	MeCOneo-Am	1-0.5-400 X	132-136	4[c]	Dimer	17.6	36
.50	Cyclohexanone	1-0.5-400 X	117-120	0.8	Dimer	34.6	78
.20	α-Hydrindone	1-0.5-400 X	125-130	0.4	Dimer	11.9	48
.33	EtCOPh	1-0.5-450 X	140-146	5.5[c]	Ketone	32.8	
					Dimer	9.0	22
.33	Et$_2$CO	1-0.5-400 X	120-125	12[c]	Ketone	11.3	
					Dimer	5.3	21
.50	*n*-Pr$_2$CO	1-0.5-400 X	128-133	8[c]	Dimer	0	0
.50	*i*-Pr$_2$CO	1-0.5 N	128-100	24	Ketone	47.7	
					Dimer	0	0
.50	*i*-Bu$_2$CO	1-0.5-400 X	130-140	10[c]	Ketone	43.4	
					Dimer	0	0
.15	Phorone	1-1-700 T	110-95	24	Ketone	4.9	
					Dimer (?)	4.3	21

[a] The figures in this column express the proportions of the ketone, alkoxide and solvent. The first two are given in moles and the latter in ml. The type of solvent is indicated by B for benzene, A for *t*-butyl alcohol, D for dioxane, T for toluene, X for xylene and N where no solvent was used. [b] If the *t*-butyl alcohol was not removed as the reaction proceeded, the temperature of the reaction mixture decreased, while in other preparations the temperature rose as the ketone condensed and the alcohol distilled out of the mixture. [c] In these cases the reaction mixture solidified before the expiration of the time interval indicated.

Excessive dilution of the reaction mixture with benzene, toluene, dioxane or *t*-butyl alcohol decreases the rate of condensation. In fact other work in this Laboratory has shown[25] that in a 0.05 *M* solution even the very reactive ketones, such as acetone and acetophenone, do not undergo any detectable condensation at 60° after several hours in a solution 0.07 *M* with respect to the alkoxide. However, the use of toluene or xylene as a solvent offers in some cases advantages where condensations are made on a larger scale and for preparative purposes. In those cases where the boiling point of the ketone makes it feasible, it has proven advantageous to distil out the *t*-butyl alcohol as it was formed and thus make it possible to complete the condensation at a higher temperature and shorter time than would otherwise be possible. The time of reaction required for the optimum yields varied from a half hour to two days, depending upon the ketone and the conditions of reaction.

The relation between the structure of the ketones and the yields of dimer may be summarized as follows. Acetone underwent condensation readily to mesityl oxide, but the reaction proceeded further to give phorone and compounds of even higher molecular weight. The optimum yield of dimer from the methyl ketones, where the

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(25) Baker and Adkins, THIS JOURNAL, 62, 3305 (1940).

second radical was ethyl, *n*-butyl, *i*-butyl or phenyl amounted to 70 to 80%. The branched chain methyl ketones, where the second radical was *i*-propyl, neopentyl or *t*-butyl, gave yields of 49, 36 and 10%, respectively. However, the low yield from pinacolone was accompanied by a high recovery of the original ketone so that the yield based upon the ketone reacting was about 20%. Apparently the methyl group in vinylogous position to the carbonyl in phorone reacted and gave a dimer b. p. 104–110° (1 mm.) in 21% yield, but the condensation proceeded to give higher molecular weight compounds.

The cyclic ketones, cyclohexanone and α-hydrindone, condensed well and gave yields comparable to those of the more reactive methyl ketones. The other ketones which carried no methyl groups condensed very poorly if at all. Two other ketones not carrying methyl groups, *i. e.*, diethyl and ethyl phenyl ketone, gave fair yields (21%) of dimer, which would be raised to 34 and 81%, respectively, if allowance is made for the original ketone recovered. However, three other such ketones, *i. e.*, di-*n*-propyl, di-iso-propyl and di-iso-butyl, gave no dimer.

In view of the inactivity of the ketones not containing methyl groups (except the cyclic ketones), it seems safe to assume that the condensation of the methyl ketones involves reaction of the methyl group. This would be in accord with the studies made by Abbott, Kon and Satchell.[4] The position of the double bond in the dimers is not certain. The names assigned have been given on the assumption that the products were α,β-unsaturated ketones like mesityl oxide. However, the work of Kon and his associates indicates that the β,γ-isomer would also be present to a limited extent in the product of such condensations as are here under consideration.[4,23,26]

It is impossible to make any precise comparison of the method developed in this investigation with those previously described, because of the incompleteness of many of the papers as to yield and purity of products. However, aluminum *t*-butoxide has given yields at least as good and in most cases distinctly superior to those obtained with other reagents. The amounts of products boiling above the dimer were negligible except in the case of acetone and phorone, so that there was almost no loss of ketone except those incidental to the mechanical operations.

Experimental Part

Aluminum *t*-butoxide was prepared by a modification of the method described earlier.[2] The exact procedure will be given in a forthcoming volume of "Organic Syntheses." The general procedure used in the condensation of the ketones was as follows, where the solvent was xylene and the alcohol was to be distilled out as it was formed by hydrolysis of the alkoxide.

In a round-bottomed, three-necked flask, fitted with a thermometer, an efficient mechanical stirrer and a (35 cm.) Vigreux column fitted to a condenser and receiver protected with a drying tube, were placed the ketone, aluminum *t*-butoxide and dry xylene. The contents of the flask were heated with stirring in an oil-bath to the desired reaction temperature. The rate of heating was adjusted so that none of the ketone reached the top of the column. If the ketone was sufficiently high boiling, *t*-butyl alcohol was allowed to distil through the column. In several cases the reaction mixture set to a gel after a time. Heating beyond this stage probably did not materially increase the yield of dimer.

After the reaction had proceeded for the desired length of time, the mixture was cooled to 100° and 3 moles of water per mole of alkoxide plus a 10% excess was cautiously added in small portions with continued stirring. Vigorous refluxing resulted and the mixture set to a gel. With gentle tapping of the flask and the addition of the remainder of the water, the stiff mass broke up and vigorous boiling took place. The reaction mixture was refluxed in the oil-bath for another fifteen minutes to complete the hydrolysis of the alkoxide.

After cooling, the reaction mixture was centrifuged in 250 ml. bottles and the upper liquid layer decanted. A total of approximately 1 liter of undried ether was used per 0.5 mole of original alkoxide to rinse out the reaction flask, balance the centrifuge bottles and to extract the aluminum hydroxide four times. The extraction consisted of working up the aluminum hydroxide and added ether to a smooth paste with a spatula. The aluminum hydroxide was again centrifuged out and the ether layer poured off. This was repeated three more times. It is essential that this extraction be carried out carefully and thoroughly to get the maximum recovery of organic material. The ether, *t*-butyl alcohol and the water were conveniently removed through a Widmer column from an oil-bath and the xylene, b. p. 57–60° (45 mm.), under reduced pressure at the water pump. The exact procedure at this stage depended upon the boiling point of the ketone and whether an attempt was to be made to recover it. The dimer was distilled through a modified Widmer column under reduced pressure. The Widmer and modified Widmer columns were of types previously described[27] and were fitted with helices of 15 cm. length with 16 or 6 turns, respectively.

The procedure when no solvent or *t*-butyl alcohol, benzene, dioxane, or toluene was used, was identical with that described above except that a reflux condenser protected with a drying tube was used in place of the Vigreux column.

In most of the preparations the residue after the distillation of the dimer was 1 to 3 g. Acetone, cyclohexanone.

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(26) Kon and Nutland, *J. Chem. Soc.*, 3101 (1926).

(27) Smith and Adkins, THIS JOURNAL, **60**, 657 (1938).

TABLE II

PHYSICAL PROPERTIES AND ANALYSES OF DIMERS

Dimer	B. p., °C. (mm.)	d^{25}_4	n^{25}_D	M_D Calcd.	M_D Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Dypnone	138–140 (1)	1.0868	1.6273	69.03	68.96	...	...	...	...
2,4,8-Trimethyl-4,6-nonenone	86–90 (8)	0.8334	1.4509	57.16	58.79	79.06	79.11	12.16	12.28
3-Methyl-3,5-heptenone	82–86 (42)	.8539	1.4488	38.69	39.56	...	...	...	...
2,3,6-Trimethyl-3,5-heptenone	100–104 (45)	.8472	1.4510	47.92	48.94	77.87	77.75	11.76	11.81
5-Methyl-5,7-undecenone	99–104 (8)	.8468	1.4548	57.16	58.29	79.06	78.96	12.16	12.29
2,2,3,6,8-Pentamethyl-3,5-heptenone	74–76 (8)	.8414	1.4529	57.16	58.16	79.06	78.88	12.16	12.08
2,2,4,8,8-Pentamethyl-4,6-nonenone	102–106 (8)	.8383	1.4587	66.40	68.45	79.93	79.80	12.46	12.45
2-Cyclohexylidene-1-cyclohexanone	123–126 (8)	.9964	1.5084	52.76	53.29	...	...	...	...
α-Anhydro-bis-hydrindone	M. p. 142–144	....	....	...	...	...	...	...	...
α-Methyl-β-ethylchalcone	135–140 (1)	1.0433	1.5827	77.67	80.15	86.40	86.18	7.25	7.50
4-Methyl-3-ethyl-3,5-heptenone	101–104 (44)	0.8552	1.4484	47.92	48.24	77.87	77.82	11.76	12.05

phorone and methyl ethyl, methyl isopropyl and di-isobutyl ketones gave about 5 g. of residue, while there was 9 g. of substance boiling above dypnone when it was prepared in xylene at 133–137°. Triphenylbenzene, m. p. 173–174°, was isolated from this residue in 1% yield based upon acetophenone. The hydrocarbon was identified by a mixed melting point with an authentic sample.[28]

Since the dimer of α-hydrindone[29] is a rather high melting, insoluble compound, the general procedure, described above, was modified in that hot benzene was used instead of ether to extract the dimer from the aluminum hydroxide. The alcohol, benzene and most of the xylene was then distilled. Yellow crystals of the dimer formed in the cold and were removed. The remaining xylene was then removed and the product crystallized several times from 95% alcohol. A pure product was obtained by refluxing the product with insufficient alcohol to dissolve the crystals, filtering them off and allowing crystals to form in the alcohol solution.

The dimers of methyl isobutyl, methyl isopropyl, methyl *n*-butyl, methyl neopentyl, and diethyl ketones were quantitatively hydrogenated at 150° over copper chromite and shown to absorb two moles of hydrogen per mole of dimer. Solid derivatives of four of the dimers were prepared: two oximes of dypnone, m. p. 134–135° and 78–79°[9]; semicarbazones of 3-methyl-3,5-heptenone, m. p. 113–114°,[30] of 2-cyclohexylidene-1-cyclohexanone, m. p. 192–193°,[31] and of 4-methyl-3-ethyl-3,5-heptenone, m. p. 106–108°.[23]

The sample of dimer obtained from propiophenone was not pure. The molecular refraction found was higher than the calculated value, the product and the saturated ketone produced from it by hydrogenation followed by oxidation were liquids. Both of these ketones have been described as solids, m. p. 75°[32] and 60.5°,[33] respectively.

Summary

Various ketones have been condensed to unsaturated ketones of the mesityl oxide type through the use of aluminum *t*-butoxide. The methyl ketones in which the second radical was a phenyl or *n*-alkyl group condensed to give yields of 70 to 80%. Methyl ketones with a branched chain in which the second radical was isopropyl, neopentyl, *t*-butyl or *i*-butyl condensed in yields of 20 to 70%. Except for cyclohexanone and α-hydrindone, ketones without a methyl group condensed in poor yields or not at all. Propiophenone and diethyl ketone gave 20% yields but di-*n*-propyl, di-*i*-propyl and di-*i*-butyl underwent no reaction. Acetone and phorone condensed readily but the reaction went beyond the stage of the "dimer."[3] The yields obtained through the use of aluminum *t*-butoxide appear to be equal and in most cases superior to those obtained through the use of any other condensing agent. Several condensations not hitherto attained with any reagent have been brought about by the use of aluminum *t*-butoxide.

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[28] Engler and Heine, *Ber.*, **6**, 638 (1873).

[29] Kipping, *J. Chem. Soc.*, **65**, 495 (1894).

[30] Bodroux and Taboury, *Compt. rend.*, **149**, 422 (1909).

[31] Braun and Ritter, *Ber.*, **55**, 3798 (1922).

[32] Grignard and Colonge, *Compt. rend.*, **190**, 1349 (1930).

[33] Reynolds, *Am. Chem. J.*, **44**, 318 (1910).