Reactions of Active Methylene Compounds. I. Alkylation of Cyclohexanone via Ethyl 2-Ketocyclohexylglyoxalate

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(Received February 19, 1957)

Alkylations of cyclohexanone derivatives are usually carried out by two methods, A and B shown in Chart I. The procedure of method A involves only one step employing sodium amide or potassium *t*-butoxide, and the ketone is alkylated at the α-carbon atom having less hydrogen according to the extended Saytzeff rule[1], but the product is contaminated with polyalkylated compounds. In the case of method B, the ketone is alkylated in the unsubstituted α-methylene group according to the Hofmann rule and the product is obtained in pure state, but the procedure involves many steps, namely, carbethoxylation (or formylation), alkylation, and hydrolytic decomposition.

A method of alkylation analogous to method B was reported by A. Kötz et al.[2] in 1912, in which substituted ethyl 2-ketocyclohexylglyoxalate was alkylated and the product was decomposed to alkylketone by alkaline hydrolysis. But this method has not often been used hitherto[1a,3].

Here, A. Kötz's method has been studied, and seems to be better than method B when the alkylation according to the Hofmann rule is desired. In this paper, some alkylations of cyclohexanone via ethyl 2-ketocyclohexylglyoxalate, which have not yet been reported, are described.

The sodio compound of ethyl 2-ketocyclohexylglyoxalate (I), prepared from cyclohexanone and ethyl oxalate in absolute ethanol without isolation, was refluxed with an alkylating reagent such as methyl iodide, benzyl bromide, ethyl bromoacetate, and 1-(diethylamino)-3-pentanone methyl iodide. (see Table).

As the alkylated product was obtained together with ethyl oxalate without hydrolysis, it seemed that the intermediate ethyl 1-alkyl-2-ketocyclohexylglyoxalate (II) was liable to cleave to alkylcyclohexanone and ethyl oxalate in ethanol. (see Chart II). In the case of methylation, 2-methylcyclohexanone (III) was purified by alkaline hydrolysis as it was contaminated by ethyl oxalate, and it seemed that the yield of ethyl 2-ketocyclohexylacetate (V) was lowered by secondary condensation of the product.

Experimental[4]

Preparation of 2-Methylcyclohexanone (III). (*a*) *From Cyclohexanone.*—A mixture of 19.6 g. of cyclohexanone and 29.2 g. of ethyl oxalate was slowly added with stirring below 10° to the sodium ethoxide solution (4.5 g. of sodium in 100 ml. of absolute ethanol) according to H.R. Snyder et al.'s method[5], and the mixture was allowed to stand overnight at room temperature. The was mixture heated at 70~80° for six hours with 40 g. of methyl iodide with stirring. After the solvent was evaporated, the cooled residue was diluted with water and extracted with ether. The ethereal solution was washed with water, fully dried on calcium chloride, and evaporated. By distillation of the residue, crude 2-methylcyclohexanone (III) was obtained in colorless oil boiling at 164~177° (mainly at 164~169°)[6]. Yield, 15 g. (68% of the theory from cyclohexanone). It was purified by hydrolysis with 30% aqueous sodium hydroxide, acidification, extraction with ether, drying on calcium chloride and distillation. From the aqueous mother solution of ether extraction, oxalic acid was obtained. The pure III was colorless oil boiling at 162~5°. Yield, 8.5 g. (40% of the theory from cyclohexanone), and gave semicarbazone, m.p. 189.5~190.5° (from ethanol).

Anal. of semicarbazone. Found: C, 56.87; H, 8.87; N, 24.82. Calcd. for $C_8H_{15}ON_3$: C, 56.87; H, 8.94; N, 24.83%.

The m.p. of semicarbazone showed no depression on admixture with an authentic sample, which was prepared in 30.5% yield from cyclohexanone by method B—a. Reported b.p. of III and m.p. of semicarbazone are 165° and 192° (prepared by method B—b)[7] respectively.

(*b*) *From Ethyl 2-Ketocyclohexylglyoxalate.*—

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1) a) R. Cornubert et al., *Bull. soc. chim.*, (4) **49**, 1229 (1931); b) H. M. E. Cardwell, *J. Chem. Soc.*, **1951**, 2442.

2) A. Kötz et al., *Ber.*, **45**, 3702 (1912); *J. pr. Chem.*, (ii) **88**, 257 (1913); ibid., **90**, 382 (1914).

3) O. Wallach, *Ann.*, **397**, 197 (1913); ibid., **414**, 219 (1916).

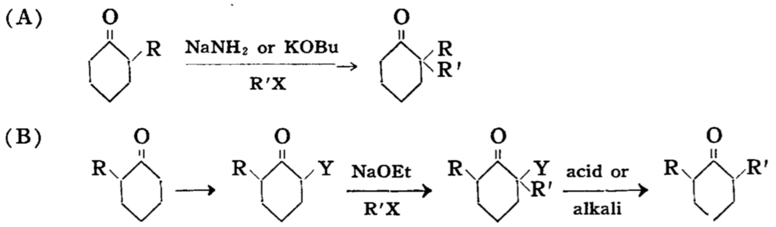
4) Melting and boiling points are uncorrected.

5) H. R. Snyder, L. A. Brookes and S. H. Shapiro, "Org. Synth." Coll. Vol., **II**, 531 (1943).

6) Almost pure III was obtained in 70% yield by distillation under diminished pressure (b. p. 84°/50mm.).

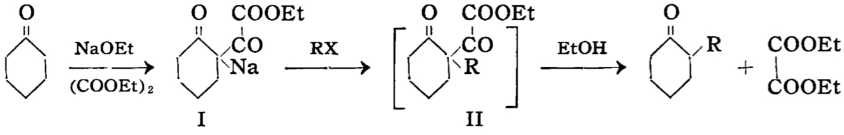
7) H. K. Sen and K. Mondal, *J. Indian Chem. Soc.*, **5**, 621 (1928).

Chart I

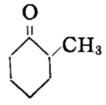


(a) Y=COOEt (b) Y=CHO

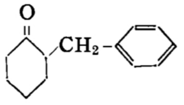
Chart II



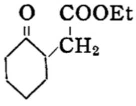
I II



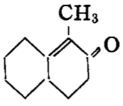
III



IV



V



VI

TABLE

Reagent	Reac. temp. (°C) & time (hr.)	Product	b.p. (°C/mm.)	m.p. (°C) of the deriv.[i]	Yield in %[ii]
MeI	70~80; 6	III	162~5	189.4~190.5 Se	40.
MeI	70~80; 6	III	159~161	189 Se	36.[iii]
MeI	method B—a	III	84/50	189 Se	30.5
PhCH$_2$Br	70~80; 7	IV	162~5/16[iv]	165~6 Se	60.
PhCH$_2$Cl	80~90; 8	IV	164~171/17	167~8 Se	37.2
BrCH$_2$COOEt	80~90; 6	V	131~142/17	194~5 Se	13.6
BrCH$_2$COOEt	method A	V	126~135/16	192~192.5 Se	43.
[v]	room tem.; 3 hr. then 80~90°; 2 hr.	VI	140~5/17	216 (dec.) Se 177 Dn	21.
[v]	method B—a	VI	136~140/15	213~4 (dec.) Se 175~7 Dn	16.8

i) Se and Dn mean semicarbazone and 2,4-dinitrophenylhydrazone, respectively.
ii) Yields were calculated from cyclohexanone.
iii) Ethyl 2-ketocyclohexylglyoxalate was isolated.
iv) M.p. was 28~31°.
v) 1-(diethylamino)-3-pentanone methyl iodide.

Ethyl 2-ketocyclohexylglyoxalate[5] (20 g.) was dropped into an absolute ethanol solution of sodium ethoxide (2.3 g. of sodium in 50 ml. of absolute ethanol) and the mixture was heated with 20 g. of methyl iodide at 70~80° for six hours, and treated as usual. Crude III distilled at 160~175° (mainly at 160~5°). Yield, 8.5 g. (75% of the theory). The pure III was obtained by purification in the same way as above, b.p. 159~161°. Yield, 6 g. (55%), and gave semicarbazone, m.p. 189° (from ethanol).

Preparation of 2-Benzylcyclohexanone (IV).—The sodio compound (I), prepared from 9.8 g. of cyclohexanone in the same way, was mixed with 17.1 g. of benzyl bromide, and the mixture was heated at 70~80° for seven hours. After the usual treatment, two fractions were obtained by vacuum distillation, that is fraction (i), b.p. 76~81°/17 mm. (10 g.), and fraction (ii), b.p. 162~177°/17 mm. (mainly 162~7°) (11.5 g.). As fraction i gave oxalic acid by alkaline hydrolysis, it seemed to consist mainly of diethyl oxalate, corresponding to about 60% of the amount initially used. By redistillation of fraction ii, 2-benzylcyclohexanone (IV) was obtained in colorless oil boiling at 162~5°/16 mm., and it crystallized afterwards, m.p. 28~31° (yield, 60% of the theory from cyclohexanone). It gave semicarbazone, m.p. 165~6° (from ethanol).

Anal. of semicarbazone. Found: C. 68.88; H. 7.84; N, 17.72. Calcd. for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81; N, 17.13%.

The m.p. of semicarbazone showed no depression on admixture with the authentic sample, prepared by method A[8]. Reported b.p. of IV and m.p. of semicarbazone are 165~6°/18 mm. and 166~7°[8] respectively. When the benzylation was carried out with benzyl chloride, instead of bromide, at 80~90° for eight hours, the yield was 37.2%.

Preparation of Ethyl 2-Ketocyclohexylacetate (V).—To the sodio compound (I) prepared from 9.8 g. of cyclohexanone, 16.7 g. of ethyl bromoacetate was added and the mixture was refluxed for six hours. After a similar treatment as described above, 10 g. (64% recovery) of ethyl oxalate, b.p. 81°/17 mm., and 2.5 g. (13.6% yield) of ethyl 2-ketocyclohexylacetate (V), b.p. 131~142°/17 mm. were obtained, and the latter gave semicarbazone, m.p. 194~5° (from ethanol).

Anal. of semicarbazone. Found: C, 54.83; H, 7.93; N, 17.44. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.93; N, 17.41%.

The m.p. of semicarbazone showed no depression on admixture with the authentic sample, prepared by method A as follows: to the sodio compound of cyclohexanone, prepared from 10 g. of cyclohexanone and 4 g. of sodium amide in absolute ether, 17 g. of ethyl bromoacetate was added and the mixture was refluxed for six hours. By the usual treatment, ethyl 2-ketocyclohexylacetate (V) was obtained in colorless oil, boiling at 126~135°/16 mm. (yield, 8 g. or 43%), and gave semicarbazone, m.p. 192~192.5°.

Anal. of semicarbazone. Found: C, 54.85; H, 7.89; N, 17.50. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.93; N, 17.41%.

Reported b.p. of V is 131~3°/9.8 mm. (25.4% yield from cyclohexanone by method B—a) and m.p. of semicarbazone is 191~3°[9].

Preparation of 2-Keto-1-methyl-2,3,4,5,6,-7,8,10-octahydronaphthalene (VI).—To the sodio compound (I) prepared from 9.8 g. of cyclohexanone, 1-(diethylamino)-3-pentanone methyl iodide (from 15.7 g. of amine and 14.2 g. of methyl iodide in 20 ml. of ethanol) was added and the mixture was allowed to stand at room temperature for three hours, and then refluxed for two hours. The solvent was evaporated, the residue was diluted with water, extracted with ether, the ethereal solution was washed with dilute hydrochloric acid and water, dried and evaporated. After the residue was refluxed with 50 ml. of 40% aqueous potassium hydroxide in 20 ml. of ethanol for fifteen hours, the resulting mixture was diluted with water, extracted with ether, the ethereal solution was washed with water, dried and evaporated. By the distillation of the residue, 3.4 g. (21% yield) of 2-keto-1-methyl-octahydronaphthalene (VI) was obtained in colorless oil boiling at 140~5°/17 mm. and gave 2,4-dinitrophenylhydrazone, m.p. 177° (from ethanol), and semicarbazone, m.p. 216° (decomp.) (from ethanol).

Anal. of 2,4-dinitrophenylhydrazone. Found: C, 59.37; H, 5.57; N, 15.39. Calcd. for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85; N, 16.29%. *Anal.* of semicarbazone. Found: C, 65.14; H, 8.38; N, 18.70. Calcd. for $C_{12}H_{19}ON_3$: C, 65.12; H, 8.65; N, 18.99%.

Their m.p. showed no depression on admixture with the authentic samples, prepared by method B—a according to the method of Robinson[10] as follows: to the sodio compound prepared from 7.4 g. of ethyl 2-ketocyclohexylcarboxylate and sodium ethoxide (from 2.3 g. of sodium) in absolute ethanol, 1-(diethylamino)-3-pentanone methyl iodide (from 6.8 g. of amine and 6.2 g. of methyl iodide) was added and the mixture was allowed to stand at room temperature for three hours and then refluxed for two hours. Then the product was cyclized and hydrolyzed into VI by refluxing with 40% aqueous potassium hydroxide in ethanol for fifteen hours. The product VI was colorless oil boiling at 136~140°/15 mm. (yield, 2 g. or 16.8% from cyclohexanone), and gave 2,4-dinitrophenylhydrazone, m.p. 175~7°, and semicarbazone, m.p. 213~4° (decomp.). Reported b.p. of VI is 125~7°/8 mm. (22% yield from cyclohexanone by the method described in footnote) and m.p. of semicarbazone is 212° (decomp.)[11].

The author wishes to express his hearty thanks to Professor K. Fukui for his helpful advice and encouragement, to Professor Y. Yukawa of Osaka University for his valuable discussion during the course of this work and to the members of Agricultural Department of Kyoto University for microanalyses.

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