The Reaction of Carbon Monoxide with Organometallic Compounds*. VI. Synthesis of Symmetrical Ketones by the Reaction of Carbon Monoxide with Organolithium Compounds

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In the last previous paper[1] of this series, the present authors reported that carbon monoxide reacted with an organolithium compound in an ether solution at $-10°C$, producing various products. The formation of these products could be interpreted in terms of an ionic reaction mechanism from the results of the reaction of carbon monoxide with organomagnesium halides[2].

The reaction of an organolithium compound with carbon monoxide occurs violently, so it seems desirable to control the reaction on applying this reaction to a synthetic method.

In this regard, we have undertaken a study of the reaction of carbon monoxide with phenyllithium in an ether solution at $-70°C$.

Phenyllithium[3] was prepared from bromobenzene and metallic lithium in anhydrous ether, and then dry, pure carbon monoxide was bubbled into the solution at $-70°C$.

The above reaction gave benzophenone in a 55% yield, instead of the benzoin which was expected on the basis of the previous results[2,3].

The symmetrical ketones were prepared by various methods. For example, Marvel[4] prepared benzophenone from benzene and carbon tetrachloride in the presence of aluminum chloride, but this method was not used for preparing other ketones. Sommelet[5] obtained 4,4'-ditolyl ketone from p-toluic acid chloride and toluene in a poor yield.

Furthermore, the preparations of di-n-butyl ketone[6], di-n-amyl ketone[7] and diisopropyl ketone[8] by earlier methods are not satisfactory in yield and involve complicated starting materials.

We have found that the new method is simple and can be extended to similar reactions in good yields.

The symmetrical ketones prepared by this new method are as follows: benzophenone (55%), 4,4'-ditolyl ketone (50%), di-n-amyl ketone (28%), di-n-butyl ketone (40%) and diisopropyl ketone (30%).

Results and Discussion

The results of the synthesis of various ketones according to our new method are summarized in Table I.

Although the mechanism of this reaction is still open to question, two probable reaction paths may be considered.

In the first, the carbon monoxide adducts (A), mentioned in previous papers, react with organic halides (Wurz-Fitting type reaction) to produce ketones (Eq. 1).

$$R-\underset{\underset{O}{\|}}{C}-Li + R-X \longrightarrow R-\underset{\underset{O}{\|}}{C}-R + LiX \qquad (1)$$
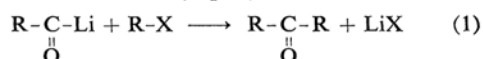
In the second, carbon monoxide attacks organolithium compounds and abstracts lithium as lithium carbonyl, producing ketone (Eq. 2). The stoichiometric equation is shown as follows:

$$2R-Li + 3CO \longrightarrow R-\underset{\underset{O}{\|}}{C}-R + 2LiCO \qquad (2)$$
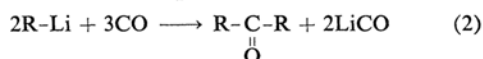
The reaction path of Eq. 1 may be considered to be improbable for the following reasons: 1) The carbonation of organolithium compounds by solid carbon dioxide gave acids in good yields, and the number of organic halides was found to be very small[9]. 2) The yields of ketones in this reaction are parallel with those of organolithium compounds (C_6H_5-Li 97.5%[10], $p-CH_3C_6H_4-Li$ 95.6%[10], $n-Bu-Li$ 85%[11], $n-Am-Li$ 85%[11], $iso-Pr-Li$ 75%[11]) and, in the case of phenyllithium, the further addition of equimol bromobenzene did not increase the yield of benzophenone. 3) The Wurz-Fittig type reaction would not be expected at such a low temperature.

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Table I

Starting material	Solvent	Temp., °C	Ketone	Yield*, %
Bromobenzene	Ether	−70	Benzophenone	55
p-Tolyl bromide	Ether	−70	4,4'-Ditolyl ketone	50
n-Amyl chloride	Ether and petroleum ether	−70	Di-n-amyl ketone	28
n-Butyl chloride	Ether	−70	Di-n-butyl ketone	40
Isopropyl chloride	Petroleum ether	−70	Diisopropyl ketone	30

* The calculations of yields are based on the number of the organic halides used.

The above consideration indicates that the unreacted organic halides do not react with (A) in Eq. 1.

If the reaction path of Eq. 1 is improbable for the above reasons, the ketones must be formed by the reaction path of Eq. 2.

Although there is no experimental evidence for the formation of lithium carbonyl in these reaction systems, several workers have reported that ionized alkali metals react easily with carbon monoxide, producing alkali metal carbonyls.

For example, Liebig[12] obtained potassium carbonyl by passing carbon monoxide over heated potassium, and Joannis[13] more easily prepared alkali metal compound corresponding to the formulas, KCO and NaCO, by the action of carbon monoxide on alkali metals in a liquid ammonia solution.

Pearson[14] also prepared the carbonyls of lithium, rubidium and calcium by passing carbon monoxide into the solution of the metals in liquid ammonia at −60°C.

Although there are various opinions about the behavior of alkali metals in a liquid ammonia solution, it is generally believed that the metals exist in a positively charged state[15].

The above facts seem to suggest that carbon monoxide can react more easily with an ionized alkali metal than with an alkali metal itself.

As the carbon-lithium bond in an organolithium compound has a 43% ionic character, it seems probable that the nucleophilic attack of carbon monoxide on positively charged lithium gives lithium carbonyl and ketone.

Furthermore, the authors carried out the reaction of iron pentacarbonyl with phenyllithium in an ether solution at −70°C. It is improbable to suppose the formation of lithium carbonyl by the reaction of iron pentacarbonyl with the organolithium compound, because the carbon monoxide in iron pentacarbonyl is coordinated to the iron atom and has not the ability to abstract lithium as lithium carbonyl.

For the above reasons, benzophenone was not obtained in this reaction; benzoin (25%) was the main product, the formation of which was explained by an ionic reaction mechanism, as has already been discussed.

Experimental

Materials.—*Bromobenzene.*—Commercial bromobenzene was purified by fractional distillation; b. p. 150°C, n_D^{15} 1.5625. *p*-Bromotoluene was prepared by the Sandmeyer reaction of *p*-toluidine[16]; b. p. 185°C, m. p. 25~26°C.

n-Amyl chloride was prepared from *n*-amyl alcohol by reaction with thionyl chloride[17]; b. p. 106°C, n_D^{20} 1.4122.

n-Butyl Chloride.—Commercial *n*-butyl chloride was purified by fractional distillation; b. p. 78°C, n_D^{20} 1.4022.

Isopropyl Chloride.—Commercial isopropyl chloride was purified by fractional distillation; b. p. 36°C.

Carbon monoxide was prepared by the reaction of formic acid with concentrated sulfuric acid, was washed with a 10% sodium hydroxide solution, and dried with calcium chloride and phosphorus pentoxide.

Synthesis of Symmetrical Ketones. — *Benzophenone.*—Into a 500 ml. four-necked flask equipped with a mechanical stirrer, a low temperature thermometer, a reflux condenser protected from moisture, a gas bubbler and a dropping funnel, were placed 50 ml. of anhydrous ether (dried over sodium) and, after sweeping the apparatus with dry oxygen-free nitrogen, 4.9 g. (0.7 g. atom) of lithium in the form of small pieces of thin coil. A solution of 47.1 g. (0.3 mol.) of bromobenzene in 200 ml. of anhydrous ether stirred in from the dropping funnel over a period of 2 hr., while the internal temperature was maintained at 35°C. After the addition was completed, the stirring was continued for a further 2 hr., after which the reaction mixture was cooled to −70°C with a dry ice-methanol bath kept at −78°C.

Dry pure carbon monoxide was next introduced from the gas bubbler at a rate of 0.5 l/min. for 2 hr.

The reaction mixture was then decomposed with 50 ml. of 95% ethanol and further with 100 ml. of 4 N hydrochloric acid. The separated organic layer was treated with three succesive 100 ml. portions of saturated aqueous potassium carbonate and then with three succesive 100 ml. portions of 5% aqueous sodium hydroxide and divided into (1) the organic layer, (2) potassium carbonate solution and (3)

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sodium hydroxide solution. The organic layer containing neutral compounds was washed with water and dried over anhydrous sodium sulfate. The brownish residual oil obtained after removal of the solvent was distilled under reduced pressure to give the following fractions: (1) b. p. 70~120°C/4 mmHg 3.5 g., (2) b. p. 120~125°C/4 mmHg 15 g., (3) b. p. 130~140°C/2 mmHg 2.4 g., (4) b. p. 190~210°C/2 mmHg 3.3 g. and a dark orange residue.

Fraction 1 was assumed to be mainly diphenyl and was identified by mixed melting point measurement.

Fraction 2 was identified as benzophenone by mixed melting point measurement of its 2,4-dinitrophenylhydrazone (m. p. 236°C, recrystallized from ethyl acetate) or its semicarbazone (m. p. 165°C, recrystallized from ligroin and benzene) (theoretical yield: 55%).

Fraction 3 was recrystallized from benzene and ligroin to give colorless crystals, m. p. 87~88°C, while fraction 4 gave white crystals by recrystallization from benzene, m. p. 201~202°C. The structures of the above two compounds have not yet been determined.

The acidic and phenolic compounds which were involved in the potassium carbonate solution and the sodium hydroxide solution respectively were confirmed to be the same as those of a previous report[1].

4,4'-Ditolyl Ketone.—The procedure employed here was identical to that described above. The ether solution of *p*-tolyllithium was prepared by using 34.2 g. (0.2 mol.) of *p*-bromotoluene, 3.5 g. (0.5 g. atom) of lithium and 250 ml. of anhydrous ether, and the introduction of carbon monoxide into the solution was carried out at −70°C. The organic layer, separated after the decomposition of the reaction mixture, was divided into a neutral part, an acidic part and a phenolic part by means of the above-mentioned method. The neutral part was distilled under reduced pressure to give the following fractions: (1) b. p. 115~140°C/9 mmHg 1.8 g., (2) b. p. 175~185°C/9 mmHg 10.4 g., (3) b. p. 180~215°C/1 mmHg 4.6 g. and a dark, brownish residue. Fraction 1 was identified as 4,4'-ditolyl by its mixed melting point measurement (m. p. 121°C, recrystallized from ethanol).

Found: C, 92.36; H, 7.67. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74%.

Fraction 2 was recrystallized from ethanol to give 4,4'-ditolyl ketone as colorless prisms, m. p. 95~95.5°C (theoretical yield: 50%).

Found: C, 86.03; H. 6.71. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71%.

Fraction 3 solidified on standing and was recrystallized from ligroin to give yellow crystals, m. p. 109~110°C, the structure of which has not yet been determined.

Found: C, 84.02; H, 6.30%.

The acidic and phenolic parts were not examined.

Di-n-butyl Ketone.—Dry pure carbon monoxide was introduced into an ether solution, cooled to −70°C, of *n*-butyllithium prepared from 27.75 g. (0.3 mol.) of *n*-butyl chloride, 4.9 g. (0.7 g. atom) of lithium and 300 ml. of anhydrous ether at the rate of 0.5 l./min. for 2 hr. The reaction mixture was decomposed immediately and divided into a neutral part and an acidic part. The neutral part was distilled under reduced pressure to give the following fractions: (1) b. p. 105~115°C/50 mmHg 9.3 g. and (2) b. p. 147~150°C/35 mmHg 2.2 g.

The infrared absorption spectra measurement showed the presence of a carbonyl group in fraction 1 and that the semicarbazone of fraction 1 had an identical melting point with that of di-*n*-butyl ketone (m. p. 90°C, recrystallized from ligroin).

Found: C, 60.38; H, 10.59. Calcd. for $C_{10}H_{21}ON_3$: C, 60.26, H, 10.62%.

The results of gas chromatographic analysis showed that fraction 1 was mainly di-*n*-butyl ketone and that about 10% of impurities was included. (Column-SiDC 550 2 m.; column temperature, 167°C; carrier gas, H_2; gas pressure, 0.3 kg./cm²; retension time of di-*n*-butyl ketone, 14~15 min.) (theoretical yield: 40%). Pure di-*n*-butyl ketone was obtained by purification of fraction 1 using preparative gas chromatography (column-SiDC 550; column temperature, 170°C; carrier gas, N_2; gas pressure, 1 kg./cm²). B. p. 111~112°C/70 mmHg, n_D^{15} 1.4210.

Found: C, 75.60; H, 12.86. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.76%.

Fraction 2 and the acidic part were not examined.

Di-n-amyl Ketone.—Carbon monoxide was introduced at −70°C, into an ether solution of *n*-amyllithium prepared by using 32 g. (0.3 mol.) of *n*-amyl chloride, 4.9 g. (0.7 g. atom) of lithium, 150 ml. of ether and 150 ml. of petroleum ether (b. p. 40~50°C). The distillation of the neutral part, obtained from the reaction mixture, under reduced pressure gave the following fractions: (1) b. p. 100~120°C/37 mmHg 2 g., (2) b. p. 123~133°C/37 mmHg 7.5 g., and high boiling fractions. Fraction 2 was purified by preparative gas chromatography. (Column-SiDC; column temperature, 160°C; carrier gas, N_2; gas pressure, 1 kg./cm²). The colorless liquid, thus obtained 6.9 g., was confirmed to be di-*n*-amyl ketone. B. p. 110~111°C/19 mmHg, n_D^{15} 1.4301.

Found: C, 77.50; H, 12.97, Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02%.

Diisopropyl Ketone.—Carbon monoxide was introduced at −70°C into a solution of isopropyllithium prepared from 23.7 g. (0.3 mol.) of isopropyl chloride, 4.9 g. (0.7 g. atom) of lithium and 200 ml. of petroleum ether. The distillation of the neutral part, obtained from the reaction mixture, gave 5 g. of an oily product, boiling at 120~127°C/760 mmHg. This was identified as diisopropyl ketone from the results of infrared absorption spectra measurement and a mixed melting point test of its semicarbazone (m. p. 144~145°C, recrystallized from ligroin and benzene) (theoretical yield: 30%).

Found: C, 56.37; H, 9.93. Calcd. for $C_8H_{17}ON_3$: C, 56.11; H, 10.01%.

The other high boiling products were not identified.

The Reaction of Iron Pentacarbonyl with Phenyllithium. — To an ether solution of phenyllithium, prepared from 31.4 g. (0.2 mol.) of bromobenzene, 3.5 g. (0.5 g. atom) of lithium and 250 ml.

of anhydrous ether, was added 9.4 g. (0.048 mol.) of iron pentacarbonyl in 100 ml. of anhydrous ether at $-70°C$ over a period of 30 min. The reaction mixture was decomposed with ethanol and dilute hydrochloric acid, and the organic layer was divided into neutral, acidic and phenolic parts. The distillation of the neutral part under reduced pressure gave the following fractions: (1) b. p. $80\sim100°C/2$ mmHg 2.9 g., (2) b. p. $144\sim147°C/$ 3mmHg 5.2 g., (3) b. p. $150\sim170°C/3$ mmHg 0.9 g. and a dark brownish residue.

Fraction 1 was identified as diphenyl. Fraction 2 solidified on standing and was recrystallized from ethanol to give white crystals, m. p. $132\sim133°C$, which were identified as benzoin by a mixed melting point test (yield: 25%).

Found: C, 79.14; H, 5.61. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70%.

Fraction 3 was recrystallized from ethanol to give triphenylmethane, m. p. 93°C (yield: 5.6%).

Found: C, 93.34; H, 6.66. Calcd. for $C_{19}H_{16}$: C, 93.40; H, 6.60%.

Summary

The reaction of carbon monoxide with an organolithium compound at $-70°C$ yielded symmetrical ketones.

Benzophenone (55%), 4, 4'-ditolyl ketone (50%), di-n-butyl ketone (40%), di-n-amyl ketone (28%) and diisopropyl ketone (30%) were prepared by this new method.

A reaction path for the formation of ketones was discussed.

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