NOTES

Interaction of Organolithium Compounds and Salts of Carboxylic Acids

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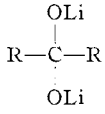
The reaction between alkyl or aryl lithium compounds and certain carboxylic acids or their lithium salts gives good yields of ketones and little or none of the tertiary alcohols.[2,3] The analogous reactions of the corresponding esters or acyl halides lead primarily to the tertiary carbinols. This difference in behavior has been attributed to the formation in the former reactions of a dilithium salt which resists further substitution or loss of lithium oxide.



The literature of this reaction has been reviewed recently.[3] In most instances, the formation of a solid precipitate prior to hydrolysis is described.

We have isolated and analyzed this intermediate from the reaction of excess phenyllithium and lithium benzoate. The compound is a fine white solid insoluble in ether or pentane. It is hydrolyzed to benzophenone and lithium hydroxide when exposed to air but is stable even at 100° in an atmosphere of nitrogen. The formula $(C_6H_5)_2C(OLi)_2$ is in agreement with its quantitative hydrolysis to benzophenone and lithium hydroxide as well as the gravimetric determination of lithium as the sulfate.

Reactions of the salt with methyl iodide, ethyl bromide, dimethyl sulfate or benzyl chloride gave benzophenone even when hydrolysis of the reaction mixture with water was omitted. Thus, the replacement of one atom of lithium by an alkyl group gave an unstable salt which lost alkoxide ion before a second substitution occurred to produce a ketal. The reaction with benzyl chloride also produced

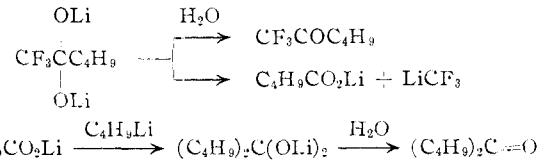
$$(C_6H_5)_2C(OLi)_2 + RX \longrightarrow (C_6H_5)_2C(OLi)(OR) + LiX \quad (1)$$

$$(C_6H_5)_2C(OLi)(OR) \longrightarrow (C_6H_5)_2C{=}O + ROLi \quad (2)$$

benzaldehyde, dibenzyl ether and stilbene. These products are best explained by reactions 1 and 2 followed by a Williamson reaction between benzyl chloride and lithium benzylate to give dibenzyl ether. This ether is oxidized to benzaldehyde in the presence of air.[4] The formation of stilbene can be ascribed to the rearrangement of this ether in basic media to benzylphenylcarbinol[5] followed by dehydration.

Cyclic ketal derivatives could not be prepared from the dilithium salt and ethylene bromide or oxalyl chloride. The intermediate from the reaction of the latter compound by equation 1 would be $(C_6H_5)_2C(OLi)OCOCOCl$. The reaction at room temperature gave only carbon monoxide, carbon dioxide and benzophenone.

It has been proposed that the stability of the dilithium salt is related directly to the electron-attracting ability of the groups attached to the carbon atom carrying the two oxygen atoms. Therefore, it was hoped that the readily available trifluoroacetic acid could be utilized in the preparation of alkyl trifluoromethyl ketones. This hope was partially realized by the preparation of *n*-butyl trifluoromethyl ketone in 61% yield from lithium trifluoroacetate and *n*-butyllithium. Di-*n*-butyl ketone and *n*-valeric acid were identified in the higher-boiling material from the preparation. All three products probably have a common origin in the adduct. Similar by-products from the reaction of phenyllithium and lithium trifluoroacetate have been described recently.[6]



Experimental

All reactions were carried out in a static nitrogen atmosphere.

Lithium Compounds.—Phenyllithium was prepared from bromobenzene and lithium wire by a modification of an earlier procedure.[2] Lithium benzoate and lithium trifluoroacetate were made from lithium carbonate and the corresponding acids in aqueous solution. The latter salt has not been reported.

Anal. Calcd. for $C_2O_2F_3Li$: Li, 5.79. Found: Li, 5.77, 5.75.

Reaction of Phenyllithium and Lithium Benzoate.—To 0.43 mole of phenyllithium in 550 ml. of ether was added all at once 36 g., 0.26 mole, of lithium benzoate. The white solid was well dispersed by a high-speed air stirrer. The stirred mixture was refluxed for 48 hours during which time the character of the precipitate changed markedly. At this point an additional 0.40 mole of phenyllithium was added. Stirring and refluxing were continued for 42 hours. The filtrate was separated through a sintered glass filter stick and the precipitate washed by shaking with five successive 150-ml. portions of dry ether. The solid was dried at 1 mm. pressure to a very fine light yellow powder. Dry nitrogen was allowed to enter the flask and a sample was removed for analysis. At this point the solid contained 4.9% by weight of lithium bromide and gave upon hydrolysis 96% of the calculated amount of lithium hydroxide. The entire washing and drying process was repeated to give 56 g., 100%, of cream-colored product.

Anal. Calcd. for $C_{13}H_{10}O_2Li_2$: Li, 6.55. Found: Li, 6.51, 6.51.

Initially, an excess of lithium benzoate was employed following the procedure of Gilman and Van Ess.[2] The adduct in this case contained 4.84% lithium, a value which

(1) To whom inquiries regarding this article should be sent.

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corresponds closely to the formula $(C_6H_5)_2C(OLi)_2\cdot(C_2H_5)_2O$. However, later experiments in which excess lithium benzoate was used, as well as experiments in which equivalent quantities were employed, gave adducts in which the lithium content varied from 3.8 to 5.7%. No ether could be isolated when a 10-g. sample of the adduct was hydrolyzed. These adducts then were shown to be contaminated with lithium benzoate by total lithium analysis as lithium sulfate and by acid hydrolysis to benzoic acid and benzophenone in quantities indicated by the analysis. Only when an excess of phenyllithium was used could an adduct be obtained for which the lithium content determined by titration agreed with that determined as the sulfate.

The adduct is insoluble in ether or pentane. It is stable over long periods of time in nitrogen atmosphere but is rapidly hydrolyzed to benzophenone when exposed to air. When the dry salt was heated in a sealed tube for 12 hours at 100°, a negligible quantity of benzophenone was isolated by ether extraction.

Reactions of Halides with the Dilithium Salt.—A mixture of 10.3 g., 0.049 mole, of the adduct, 25.8 g., 0.2 mole, of distilled benzyl chloride and 0.8 g. of triethylamine catalyst were heated under nitrogen with stirring. Because no noticeable change occurred at 100°, the temperature was raised to 145° for 45 minutes and finally to 180°. At this point the mixture was a viscous semi-solid. No water was added. The mass was cooled, extracted with dry pentane and filtered. Fractionation of the pentane through an 18-plate column gave 15.9 g. of recovered benzyl chloride, b.p. 63° at 15 mm., $n^{20}D$ 1.5390, and 11.1 g. of liquid product, b.p. 79–174° at 15 mm. Refractionation of the latter liquid at 1–2 mm. gave eight fractions, $n^{20}D$ 1.5800–1.5890. This material consisted of four compounds which were separated by chromatography on alumina columns. Obtained were: benzophenone, m.p. 48–49°; 2,4-dinitrophenylhydrazone, m.p. 239°[8]; benzaldehyde, 2,4-dinitrophenylhydrazone m.p. and mixed m.p. 235–236.5°[9]; stilbene, m.p. 123–124°, dibromo derivative m.p. 235–236.5°[10]; dibenzyl ether, infrared spectral peaks at 3.33, 3.55, 6.25, 6.30, 6.68, 7.37, 8.08, 8.30, 9.02, 9.11, 9.32, 9.73, 12.70, 13.17, 13.41, 13.65 and 14.37; autoxidation to benzaldehyde after seven days.[4] The mixture contained about 35% of benzophenone as shown by a quantitative precipitation of its 2,4-dinitrophenylhydrazone.[11] No dibenzyl ketal of benzophenone, b.p. 305° at 40 mm., m.p. 103–105°, could be detected.

Similar reactions were carried out in which the adduct was treated with ethyl bromide, methyl iodide, dimethyl sulfate, ethylene bromide and oxalyl chloride. In each case benzophenone was the only compound isolated in more than trace amounts. Ketals could not be detected even when questionable fractions were subjected to hydrolysis and a search made for the corresponding alcohols. The reaction with oxalyl chloride occurred at room temperature with evolution of carbon dioxide and carbon monoxide.

***n*-Butyl Trifluoromethyl Ketone.**—To 64.2 g., 0.54 mole, of lithium trifluoroacetate suspended in 100 ml. of dry ether at 5° was added a solution of 0.54 mole of *n*-butyllithium[12] in 320 ml. of ether. The mixture became very viscous but returned to a more fluid state when heated. After 11 hours of stirring and refluxing, the complex was decomposed by the addition of 150 ml. of cold concentrated hydrochloric acid. This addition was made rapidly with stirring over a period of five minutes. Fractionation through a 12-plate column gave 50.3 g., 61%, of *n*-butyl trifluoromethyl ketone, b.p. 29–32° at 65 mm., and 7.7 g. of material, b.p. 69.5° at 8.5 mm., from which the amide of *n*-valeric acid, m.p. 114–116°,[13] the *p*-phenylphenacyl ester of this acid, m.p. 68°,[14] and the semicarbazone of di-*n*-butyl ketone, m.p. 89–90°,[15] were prepared. Refractionation of a portion of the main product gave *n*-butyl trifluoromethyl ketone, b.p. 90° at 740 mm., $n^{20}D$ 1.3410.

Anal. Calcd. for $C_6H_9OF_3$: C, 46.75; H, 5.84. Found: C, 47.15; H, 5.93.

The ketone was cleaved readily by warming with 10% sodium hydroxide solution. A gas was liberated and valeric acid was identified in the residual solution as the amide, m.p. 114–115°.[13]

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Use of the Carboxylic Cation Exchange Resin IRC-50 in the Purification of Thyrotropic Hormone (TSH)

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Use of the carboxylic cation exchange resin IRC-50 for the purification of thyrotropic hormone (TSH) was first reported by Heideman.[2] More recently other workers reported that this resin irreversibly adsorbs TSH and have developed a multistep method for obtaining a TSH preparation comparable in specific activity to that described below.[3]

Attempts to repeat the experiments described by Heideman were unsuccessful in that TSH activity was not adsorbed. It was found that the adsorbent should first be equilibrated at paired values of *p*H and ionic strength in order to establish conditions under which TSH activity may be selectively adsorbed. The range investigated comprises *p*H values from 7.0 to 8.0 and corresponding ionic strengths below 0.05 (0.02 to 0.0025 *M*). The protein is dissolved in the same buffer used to equilibrate the resin.

The following procedure is one that has been found satisfactory in using IRC-50 for purifying TSH from beef anterior pituitaries. The resin is prepared in a manner described for XE-64 by Hirs, *et al.*,[4] except that the final equilibration is with 0.01 *M* sodium phosphate buffer at *p*H 7.6 (ionic strength approx. 0.027). A water extract of acetone powder of beef anterior pituitaries[5] containing approximately 0.05 U.S.P. unit per mg. protein (dry weight) was used at a level of 1 U.S.P. unit per 20 ml. of packed resin in a column 30 × 0.9 cm. The column was operated at a rate of approximately 0.5 ml./minute when using a solution containing 1 mg./ml. of protein (dry weight). Following adsorption of TSH activity, the column was washed free of unadsorbed protein with the equilibrating buffer prior to elution with 1 *M* sodium chloride (other cations can be used).

The product obtained represented approximately 5% of the original protein (calculated from ultraviolet absorption) and was found to contain 1.0 to 2.0 U.S.P. units of TSH activity per mg. The assay used employed the uptake of radioactive iodine

(1) Aided by a Fellowship from the National Foundation for Infantile Paralysis.

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(5) Acetone powder of anterior pituitaries was kindly supplied us by Armour and Company through the courtesy of Dr. Sanford Steelman.