[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

1,6-Addition of *n*-Butyllithium to Hindered Diaryl Ketones[1]

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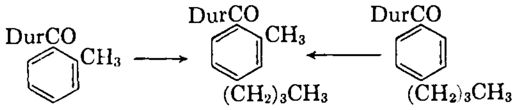
1,6-Addition of *n*-butyllithium has been realized with duryl *o*-tolyl ketone. The product, duryl 2-methyl-4-*n*-butylphenyl keone, has been synthesized also by the condensation of the methyl Grignard reagent with duryl 4-*n*-butylphenyl ketone. Duryl phenyl ketone under similar conditions yielded a mixture of the products of 2- and 4-butylation. Butylation of mesityl α-naphthyl ketone was effected also.

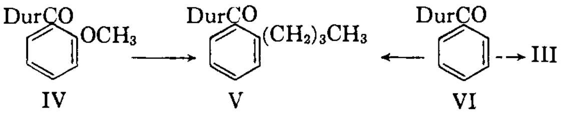
In a study of the selective side chain metalation of duryl *o*-tolyl ketone (I) by the action of *n*-butyllithium, the position taken by the lithium atom was established by addition of carbon dioxide to the reaction mixture and isolation of the corresponding carboxylic acid.[3] From the neutral fraction it has now been possible to isolate a butylation product which has proved to be, surprisingly, the *p*-isomer, duryl 2-methyl-4-*n*-butylphenyl ketone (II). Its structure, indicated by the elemental analysis and infrared spectrum, was confirmed by an independent synthesis.



I II III

This synthesis was facilitated by an extension of the study to duryl phenyl ketone, the object being to determine whether the methyl group in the *o*-tolyl ketone I had an influence on the position taken by the butyl group. With duryl phenyl ketone (VI), butylation was found to occur predominantly at the *p*-position to give duryl 4-*n*-butylphenyl ketone (III). This ketone, made also by condensation of 4-*n*-butylbenzoyl chloride with durene, reacted with the methyl Grignard reagent to give duryl 2-methyl-4-*n*-butylphenyl ketone (II). The structure of this butylated derivative of the *o*-tolyl ketone I was thereby confirmed.

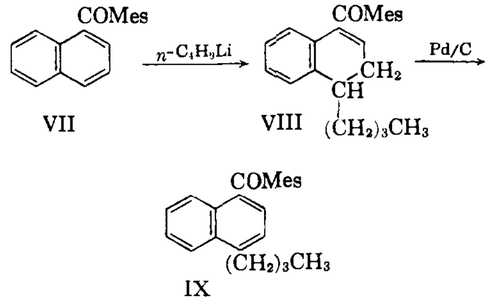
Duryl 2-*n*-butylphenyl ketone (V), the other product of the condensation of duryl phenyl ketone (VI) with *n*-butyllithium, was identified by comparison with a sample made by the action of the *n*-butyl Grignard reagent on duryl *o*-methoxyphenyl ketone (IV).



IV V VI

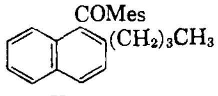
The condensation of *n*-butyllithium with mesityl α-naphthyl ketone (VII) was studied also. A dihydro product, presumed to have structure VIII, was obtained; it underwent dehydrogenation with palladium-on-charcoal to give the corresponding, fully aromatic ketone, IX.

Structures VIII and IX are consistent with the analytical data. 1-Mesitoyl-2-*n*-butylnaphthalene



VII VIII IX

(X), the other product that might have been expected, is known and differs from the product actually obtained. The assignment of structure IX is, thus, strongly supported.



X

Nuclear attack of aryl ketones by organolithium compounds had been observed previously only with aryllithium reagents; also, attack was always in the 1,2- or 1,4-manner.[4] The preferential attack by *n*-butyllithium in the 1,6-manner parallels the behavior of certain Grignard reagents such as those from *sec*- and *t*-butyl halides.[5] On the other hand, the Grignard reagent from *n*-butyl bromide fails to condense with duryl phenyl ketone. These results indicate that *n*-butyllithium is more reactive and less selective than its magnesium analog. Apparently, this is the first example of 1,6-addition to any system by lithium reagents.

Experimental[6]

Reaction of Duryl *o*-Tolyl Ketone with *n*-Butyllithium.—A solution of 0.02 mole of *n*-butyllithium in 50 ml. of anhydrous ether was added, with stirring over a period of 15 min., to a solution of 5.1 g. (0.02 mole) of duryl *o*-tolyl ketone in 60 ml. of anhydrous ether. The temperature was maintained at −5° for 3.5 hr., after which the reaction mixture was hydrolyzed with ice-cold, dilute hydrochloric acid. The organic layer was washed with water and dried over anhydrous sodium sulfate. Concentration of the dried ether solution afforded an orange-colored oil which was chromatographed over alumina. A white solid (2.5 g., 40%) was obtained which, after several recrystallizations from ethanol, was in the form of colorless plates, m.p. 64–64.5°. The infrared spectrum[7] has bands assignable to a conjugated hindered ketone group (1667 cm.$^{-1}$), a duryl group (872 cm.$^{-1}$), 1,2,4-trisubstituted phenyl (805 cm.$^{-1}$) and aliphatic hydrogen (2840 and 2920 cm.$^{-1}$).

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(2) U. S. Rubber Co. Fellow, 1957–1958.

(3) R. C. Fuson, W. C. Hammann and P. R. Jones, THIS JOURNAL, **79**, 928 (1957).

(4) R. C. Fuson, G. P. Speranza and R. Gaertner, *J. Org. Chem.*, **15**, 1155 (1950).

(5) R. C. Fuson and R. Tull, THIS JOURNAL, **71**, 2543 (1949).

(6) All melting points are corrected.

(7) The infrared spectra were recorded by Mr. James Brader, Mr. Brian Cloonan, Mrs. Louise Griffing, Mr. Paul McMahon and Miss Mary DeMott.

Anal.[8] Calcd. for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.68; H, 9.18.

Reaction of Duryl Phenyl Ketone with *n*-Butyllithium.—Duryl phenyl ketone (4.6 g., 0.02 mole) and *n*-butyllithium (0.02 mole) were allowed to react under the conditions just described. The product was an oil which could not be induced to crystallize from methanol, ethanol or low-boiling petroleum ether. The infrared spectrum of this material showed virtually no aromatic substitution or aromatic hydrogen bands, with the exception of those attributable to the duryl group. The oil rapidly decolorized aqueous potassium permanganate and bromine in carbon tetrachloride.

A solution of the oil in 15 ml. of pure *m*-xylene was heated under reflux for 3.5 hr. with 5.24 g. (0.021 mole) of chloranil. The cooled reaction mixture was filtered to remove the hydroquinone and any chloranil and extracted several times with 4% potassium hydroxide. Removal of solvent left 6.7 g. of a dark oil which was chromatographed over alumina. The polarity of the eluting solvent was changed by a gradual transition from pure cyclohexane to pure ether. Two pure crystalline compounds were isolated. The yield of one of these, m.p. 70–70.5°, was 23% (1.34 g.). The infrared spectrum has bands which may be assigned to *p*-disubstituted phenyl (825 cm.$^{-1}$), a duryl group (875 cm.$^{-1}$) and a conjugated hindered ketone group (1675 cm.$^{-1}$).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.88; H, 9.23.

The yield of the other compound, m.p. 96.5–97°, was 10% (0.57 g.). The infrared spectrum has bands corresponding to *o*-disubstituted phenyl (755 cm.$^{-1}$), a duryl group (875 cm.$^{-1}$) and a conjugated hindered ketone function (1675 cm.$^{-1}$).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.78; H, 8.60.

Subsequent attempts to dehydrogenate the dihydro oils with 10 and 30% palladium-on-charcoal met with failure. Efforts to isolate and characterize the dihydro products also failed.

Duryl phenyl ketone did not react with the *n*-butyl Grignard reagent; starting material was recovered to the extent of 72%.

Reaction of Mesityl α-Naphthyl Ketone with *n*-Butyllithium.—A solution of 0.019 mole of *n*-butyllithium in 50 ml. of anhydrous ether was added, over a period of 20 min., to a solution of 5.21 g. (0.019 mole) of mesityl α-naphthyl ketone in 250 ml. of anhydrous ether. The contents of the flask were maintained at −40°, under a nitrogen blanket, during the addition and for 1 hr. thereafter. The temperature was allowed to rise slowly to 10° and, after 30 min. at this temperature, the reaction mixture was hydrolyzed and worked up in the usual way. The residual, dark red oil deposited, from ethanol, 0.41 g. of white crystals melting at 201–205°. Recrystallization of this product from the same solvent raised the melting point to 208–209°. The infrared spectrum is considerably different from that of the original ketone; a large increase in the amount of aliphatic hydrogen, loss of the characteristic 780 and 910 cm.$^{-1}$ naphthalene bands and an appreciable decrease in the amount of aromatic hydrogen are noticeable. The product also decolorized an aqueous potassium permanganate solution.

Anal. Calcd. for $C_{24}H_{28}O$: C, 86.70; H, 8.49. Found: C, 86.39; H, 8.35.

The compound just described (0.20 g.), mixed with 0.05 g. of 10% palladium–charcoal, was heated at 300° for 2 hr. The cooled mixture was extracted with hot methanol to remove the organic material from the catalyst, and the extracts were concentrated. The residual, dark oil was chromatographed over 8 g. of alumina. The product isolated was a pale yellow compound (4.6 mg.) melting at 73–78°. Its infrared spectrum suggested that it was an aromatic butylation product. A mixture melting point test and a comparison of infrared spectra showed that the compound was not 1-mesitoyl-2-*n*-butylnaphthalene.[9]

4-*n*-Butylbenzoic Acid.—Freshly ground magnesium (6.1 g., 0.25 g. at.), 20 ml. of anhydrous ether and several drops of 4-bromo-*n*-butylbenzene[10] were mixed under nitrogen. Once the reaction had started, a solution of 53 g. (0.25 mole) of the bromide in 150 ml. of anhydrous ether was added at a rate such that the mixture continued to boil. After completion of the addition, the solution was maintained under reflux for 20 hr. by heating. The Grignard reagent was poured into a slurry of solid carbon dioxide and anhydrous ether and, after most of the carbon dioxide had disappeared, was acidified with dilute hydrochloric acid. The organic layer was extracted with 5% sodium hydroxide. Acidification of the basic extracts produced 23 g. (52%) of crude 4-*n*-butylbenzoic acid melting at 96–99°. One recrystallization of the acid from ethanol raised the melting point to 99–101° (reported[11] melting points are 101° and 102–103°). The infrared spectrum has absorption maxima which can be assigned to *p*-disubstituted phenyl (850 cm.$^{-1}$), the oxygen–hydrogen bond of an aromatic carboxylic acid (2540, 2660 and 2900 cm.$^{-1}$) and the carbonyl group of such an acid (1685 cm.$^{-1}$).

Duryl 4-*n*-Butylphenyl Ketone.—In a flask containing the acid chloride, prepared by the action of thionyl chloride on 23 g. (0.13 mole) of 4-*n*-butylbenzoic acid, was placed a solution of 17.5 g. (0.13 mole) of durene in 100 ml. of carbon disulfide. The mixture was cooled to −5° in a salt-ice-bath, and 17.3 g. (0.13 mole) of aluminum chloride was added slowly, the temperature being kept below 0°. The reaction mixture was stirred for 4 hr. and hydrolyzed with dilute, ice-cold hydrochloric acid. The organic layer was washed, dried and concentrated. The residual oil was dissolved in ethanol and treated with decolorizing charcoal. When cooled, the solution deposited 25.4 g. (91%) of duryl 4-*n*-butylphenyl ketone in the form of colorless crystals, m.p. 69–70°. The infrared spectrum of this material was nearly superimposable on that obtained from the compound isolated in the reaction of duryl phenyl ketone with *n*-butyllithium. A mixture melting point of these two materials shows no depression.

Duryl 2-Methyl-4-*n*-butylphenyl Ketone.—To the Grignard reagent prepared from 9.8 g. (0.068 mole) of methyl iodide and 1.6 g. (0.068 g. at.) of magnesium in 30 ml. of anisole was added a solution of 5.0 g. (0.017 mole) of duryl 4-*n*-butylphenyl ketone in 30 ml. of anisole. The reaction mixture, under nitrogen, was heated at reflux with stirring for 4 hr. To the cooled mixture was added 20 ml. of ice-cold, 3 *N* hydrochloric acid, and stirring was continued under nitrogen for 18 hr. After being washed, the organic layer was dried and concentrated. Chromatographic separation over alumina gave 0.4 g. of duryl 2-methyl-4-*n*-butylphenyl ketone which, after recrystallization from ethanol, was in the form of colorless plates, m.p. 63–64°.

A mixture melting point test with a sample of the compound obtained by the addition of *n*-butyllithium to duryl *o*-tolyl ketone showed no depression. The infrared spectra of the two samples are nearly identical.

Duryl 2-*n*-Butylphenyl Ketone.—A solution of 1.44 g. (0.005 mole) of duryl 2-methoxyphenyl ketone in 50 ml. of anhydrous ether was added to the Grignard reagent prepared from 0.126 g. (0.005 g. at.) of magnesium and 0.712 g. (0.005 mole) of *n*-butyl bromide in 40 ml. of anhydrous ether. During the 15 min. required for the addition, and for 4 hr. thereafter, the mixture was heated under reflux. Stirring was discontinued and, after hydrolysis and the usual work-up, a solution of the organic portion in ethanol deposited 0.30 g. of white crystals, m.p. 248–253°. This material was shown to be 2,2′-diduroylbiphenyl. The remainder of the organic material could not be induced to crystallize and was subjected to chromatography over alumina. In addition to starting material (0.32 g., 22%) was obtained 0.11 g. of duryl 2-*n*-butylphenyl ketone; after recrystallization from ethanol, it melted at 96–97°. The infrared spectrum of this product was almost identical with that of the material obtained by the condensation of *n*-butyllithium with duryl phenyl ketone. The melting point of a mixture of these two materials was not depressed.

All attempts to displace the methoxyl group with *n*-butyllithium resulted in failure.

URBANA, ILL.

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(8) The microanalyses were performed by Mr. Joseph Nemeth, Miss Claire Higham and Mrs. Frederick Ju.

(9) R. C. Fuson and S. B. Speck, THIS JOURNAL, **64**, 2446 (1942).

(10) J. W. Copenhaver, M. F. Roy and C. S. Marvel, *ibid.*, **57**, 1311 (1935).

(11) A. Zakir and H. Fachim, *J. Chem. Soc.*, 307 (1942).