

INVESTIGATION OF THE REACTION OF ORGANOLITHIUM  
REAGENTS WITH NITRILES HAVING  $\alpha$ -HYDROGEN\*GENE SUMRELL<sup>1</sup>*Received October 19, 1953*<sup>2</sup>

Hauser and Humphlett (1) have reported that two competing reactions occur when a Grignard reagent is allowed to react with a nitrile having hydrogen in the  $\alpha$ -position; namely, (A) normal addition yielding a ketimine which, on hydrolysis, yields a ketone; or, (B) reaction of the Grignard reagent with an  $\alpha$ -hydrogen to give a metallated intermediate,  $(RCHCN)MgX$ , which can add to a second molecule of nitrile giving a dimer. On carbonation of this intermediate, a carboxylic acid,  $RCH(COOH)CN$ , results. Ziegler and Ohlinger (2) report alkylation of such metallated complexes at the  $\alpha$ -position on treatment with alkyl halides.

In the reaction between Grignard reagents and nitriles (1), the aromatic reagents in general were found to react more with the nitrile group, giving good yields of ketones (over 80%), whereas aliphatic Grignard reagents gave much smaller yields of ketones and larger amounts of dimers and higher polymers. Allen and Henze (3) have reported that the allyl Grignard reagent adds to the CN group of nitriles having  $\alpha$ -hydrogen with no reaction with the  $\alpha$ -hydrogen being observed.

Gilman and associates (see reference 4) have determined by competitive experiments that the order of decreasing rate of addition of various Grignard reagents with benzonitrile is as follows: Mesityl, allyl, *p*-tolyl, phenyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, phenylethynyl. It will be noted that those Grignard reagents giving the better yields of ketones with aliphatic nitriles are found early in this series, whereas the aliphatic Grignard reagents which give poorer yields of ketones and more metallation with aliphatic nitriles are also found to react more slowly with benzonitrile, with which metallation cannot occur. It is also known (see 4) that aliphatic Grignard reagents have a greater tendency to metallate than do aromatic ones. Thus, the observation of Hauser and Humphlett (1) that aliphatic Grignard reagents in general tend to react more with the  $\alpha$ -hydrogen and less with the CN group than aromatic Grignard reagents seems to result both from a greater tendency of the aliphatic reagents to metallate and a slower rate of addition to CN than is the case with the aromatic reagents.

Swain (4) reports that phenyllithium reacts at least one hundred times as fast with benzonitrile as does phenylmagnesium bromide. This report suggests

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<sup>1</sup> Present address, Research Laboratory, J. T. Baker Chemical Co., Phillipsburg, New Jersey.

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TABLE I  
YIELDS OF KETONES FROM NITRILES AND LITHIUM REAGENTS

NITRILE	R in RLi	KETONE	B.P., °C. (660 mm.)	YIELD, %	YIELD FROM GRIGNARD REAGENT (1)
Capro-	Methyl	2-Heptanone	145-146	60	40
Capro-	Phenyl	Caprophenone	258-260	87	89
Aceto-	Phenyl	Acetophenone	193-195.5	36	37
Aceto-	Amyl	2-Heptanone	145-146	25	14

the possibility that aliphatic organolithium reagents may give better yields of ketones with nitriles having  $\alpha$ -hydrogen than the corresponding Grignard reagents, since they also undoubtedly react more rapidly with the CN group. Some experimental results are given in Table I, with the yields of ketones reported by Hauser and Humphlett from the corresponding Grignard reagents also being given for comparison. Of considerable interest is the yield of 60% of 2-heptanone from the reaction of capronitrile and methylolithium, as compared to 40% yield with the Grignard reagent. Amyllithium and acetonitrile gave a 25% yield of 2-heptanone, as compared to 14% for amyilmagnesium bromide. Within experimental error, phenyllithium and phenylmagnesium bromide gave the same yields of ketones with capronitrile and acetonitrile.

#### EXPERIMENTAL

Unless otherwise indicated, all distillations were through a 60-cm. Podbielniak type column with heated jacket and head, similar to that described by Cason and Rapoport (5), and were at atmospheric pressure (approximately 660 mm.). Boiling points are uncorrected. Liquid reagents were purified by fractional distillation, the material used being taken over a boiling range of 2° or less.

*The lithium reagents.* Phenyllithium was made from bromobenzene and lithium as previously described (6) in 90% yield. Methylolithium was made from the iodide and amyllithium from the bromide as described by Gilman and associates (7), except that the reaction mixture was cooled in an ice-bath instead of Dry Ice-acetone. The yield of amyllithium was approximately 60% and that of methylolithium 75% by this method.

The lithium was obtained from the Metalloy Corporation in the form of ribbon. The grease coating was removed by wiping with a Kleenex tissue, then with Kleenex wet with kerosene. The ribbon was cut in lengths of about eight inches and most of the adhering kerosene was removed carefully with a tissue just prior to cutting the ribbon into small pieces in a flow of dry nitrogen as described by Rapoport and Williams (8). The thin coat of kerosene left adhering to the lithium did not interfere with the reactions and helped prevent corrosion of the metal while it was being handled.

*The reaction with nitriles.* The reaction of the nitriles with lithium reagents were carried out in a manner similar to that described (1) for the Grignard reagents, except that the reflux time was shorter or, in most cases, omitted, with cooling in an ice-bath instead.

The reaction of capronitrile with methylolithium is illustrative of a typical run. The reaction was carried out in a nitrogen atmosphere in a one-liter three-necked, round-bottomed flask equipped through ground joints with a mercury-sealed stirrer, dropping-funnel, and a reflux condenser. To the flask was added 200 ml. of dry diethyl ether, then, with the dropping-funnel removed and a stream of nitrogen flowing out of the opening, 5.55 g. (0.8 mole) of lithium ribbon was cut into small pieces with scissors and allowed to drop into the

flask. The reaction flask was cooled in ice and 52.1 g. (0.367 mole) of methyl iodide dissolved in 100 ml. of dry ether was added dropwise over a period of one hour. Stirring with cooling was continued for 30 minutes, then 24.4 g. (0.25 mole) of capronitrile dissolved in 125 ml. of dry ether was added dropwise during a period of 15 minutes. Stirring was continued with cooling in an ice-bath for two hours. The reaction mixture was then hydrolyzed, while still cooled by an ice-bath and stirred, by the cautious addition of 50 g. of chipped ice, followed by the dropwise addition of 200 ml. of ice-cold 6 *N* sulfuric acid. The two phase mixture was refluxed for 2½ hours, then separated and the ether phase was washed with saturated sodium chloride solution until neutral, and dried over sodium sulfate. Further heating of the aqueous phase yielded no additional ketone.

The ether was flash distilled and the residue was fractionated yielding 17.1 g. (60%) of 2-heptanone distilling at 145–146° (660 mm.),  $n_D^{20}$  1.4043 [literature (9), b.p. 150.5° (760 mm.),  $n_D^{25}$  1.4073]. There was 3.65 g. of viscous brown residue which was not further investigated.

On a similar run with amyllithium and acetonitrile, with a reflux period of 2½ hours, the yield of 2-heptanone was 21%. When the reaction was allowed to go for 80 minutes in an ice-bath the yield of ketone was 25%; when allowed to go 20 minutes in an ice-bath it was 17%; when allowed to stand overnight at room temperature it was 10%.

On a run using 0.25 mole of acetonitrile and a 10% excess of phenyllithium and a reflux period of two hours, the yield of acetophenone was 10.8 g. (36%) of b.p. 193–195.5° (660 mm.),  $n_D^{28}$  1.5300 [literature (10), b.p. 202° (760 mm.),  $n_D^{20}$  1.5342].

When 0.25 mole of capronitrile and a 10% excess of phenyllithium were allowed to react for 1½ hours in an ice-bath, the yield of caprophenone of b.p. 258–260° (660 mm.) was 37.4 g. (87%), with 4 g. of viscous brown residue remaining. A cut taken at 260° had  $n_D^{28}$  1.5082. [literature (11), b.p. 265° (760 mm.)].

#### SUMMARY

Lithium reagents react more readily with nitriles than do Grignard reagents. Methylithium and capronitrile were found to give a 60% yield of 2-heptanone, as compared with 40% for the Grignard reagent. Amyllithium and acetonitrile gave a 25% yield of 2-heptanone, as compared with 14% for the Grignard reagent.

PORTALES, NEW MEXICO

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