[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

THE INFLUENCE OF STRUCTURE ON THE REACTIONS OF GRIGNARD REAGENTS WITH NITRILES HAVING α-HYDROGEN[1]

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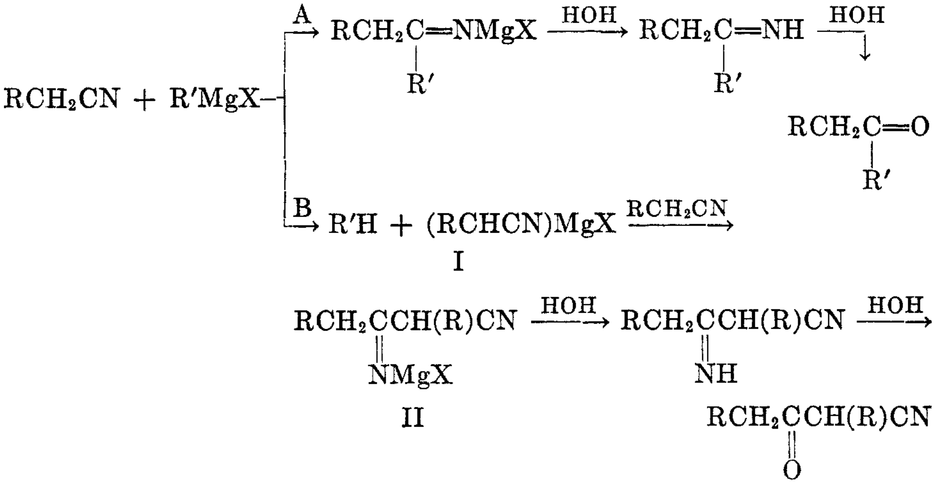
The reaction of nitriles having α-hydrogen with Grignard reagents may involve course A or B:[3]



$$\mathrm{RCH_2CN + R'MgX} \xrightarrow{A} \underset{\mathrm{R'}}{\mathrm{RCH_2C{=}NMgX}} \xrightarrow{\mathrm{HOH}} \underset{\mathrm{R'}}{\mathrm{RCH_2C{=}NH}} \xrightarrow{\mathrm{HOH}} \underset{\mathrm{R'}}{\mathrm{RCH_2C{=}O}}$$

$$\mathrm{RCH_2CN + R'MgX} \xrightarrow{B} \mathrm{R'H} + \underset{\mathrm{I}}{\mathrm{(RCHCN)MgX}} \xrightarrow{\mathrm{RCH_2CN}} \underset{\mathrm{II}}{\underset{\mathrm{NMgX}}{\mathrm{RCH_2CCH(R)CN}}} \xrightarrow{\mathrm{HOH}} \underset{\mathrm{NH}}{\mathrm{RCH_2CCH(R)CN}} \xrightarrow{\mathrm{HOH}} \underset{\mathrm{O}}{\mathrm{RCH_2CCH(R)CN}}$$

Course B, which is initiated by reaction of the Grignard reagent with the α-hydrogen of the nitrile, may be extended to form trimers. Thus, I may condense with the nitrile group of II to form III which cyclizes leading to an aromatic trimer (IV), and II may condense with unchanged nitrile to form V which cyclizes to another aromatic trimer (VI). Trimer IV ($R = C_6H_5$) has been isolated in 35% yield from the reaction mixture of phenylacetonitrile and phenylmagnesium bromide (1) and trimer VI ($R = CH_3$) in 10% yield, from propionitrile and ethylmagnesium bromide (2).

In the presence of a large excess of Grignard reagent the magnesium derivative (I) appears to be capable of adding a molecule of the reagent to form the dimagnesium derivative (VII) which on hydrolysis would produce the ketone. This would account for the observation of Shriner and Turner (3) that, with acetonitrile and phenylmagnesium bromide, the yield of acetophenone is in-

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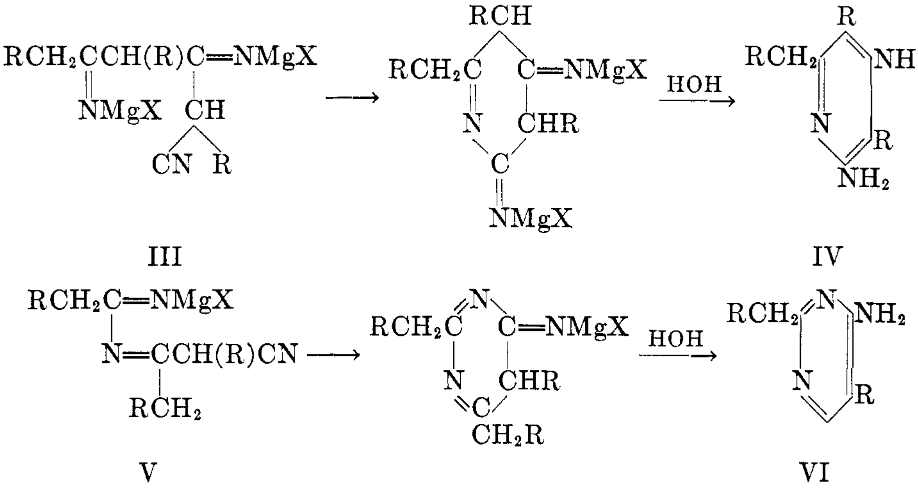
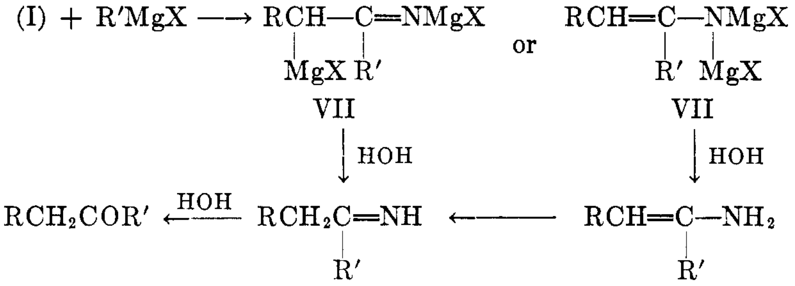
[2] Eli Lilly Fellow, 1949–1950.

[3] It seems probable that the magnesium of the Grignard reagent first coordinates with the nitrogen of the nitrile and that the two courses of reaction (A and B) take place within the resulting coordination complex. For a discussion of the analogous reactions with esters see Hauser, Saperstein, and Shivers, *J. Am. Chem. Soc.*, **70**, 606 (1948).

creased considerably by the use of a large (300%) excess of the reagent. Similarly we have found that the yields of ketone are increased somewhat (7–14%) in the reactions of propionitrile or capronitrile with methylmagnesium iodide and of phenylacetonitrile with phenylmagnesium bromide by employing a 300% excess of the reagent. However, with propionitrile or higher aliphatic nitriles and phenylmagnesium bromide, a large excess of the reagent is not required to produce maximum yields of ketones (4).





$$(I) + R'MgX \longrightarrow \underset{\text{VII}}{RCH(MgX)\text{—}C(R')\text{=}NMgX} \quad \text{or} \quad \underset{\text{VII}}{RCH\text{=}C(R')\text{—}NMgX}$$

$$\downarrow HOH \qquad\qquad \downarrow HOH$$

$$RCH_2COR' \xleftarrow{HOH} RCH_2C(R')\text{=}NH \longleftarrow RCH\text{=}C(R')\text{—}NH_2$$

The main purpose of the present investigation has been to determine the influence of structure of both the nitrile and the Grignard reagent on the relative extent of courses A and B. Relatively simple nitriles were treated with a 10% excess of the Grignard reagent, and the acidified reaction mixture was heated to hydrolyze the ketimine to the ketone and the β-imino nitrile to the β-keto nitrile. The yields of these products are given in Table I. For comparison, two of our earlier results, those from propionitrile and capronitrile with phenylmagnesium bromide (4), are included in the table. Also in this table are given the yields of residue calculated as the trimer which earlier workers have reported to be the main constituent (1, 2, 5). The 10% excess of Grignard reagent was employed in order to minimize somewhat the formation of trimers. A larger excess was usually avoided in order to be reasonably certain that the ketone would be formed practically entirely by course A and not appreciably by course B in the manner described above. Under the conditions employed, the yields of ketone may be considered a rough measure of the relative extent of course A and the combined yields of β-keto nitrile and the residue (calculated as the trimer), a rough measure of the relative extent of course B. Although the total yields given in Table I may be regarded as satisfactory in most cases, certain of them were only fair, especially when the products were water-soluble. Earlier workers have similarly reported (1, 6) only fair total yields in such reactions employing various proportions of reactants.

It can be seen from Table I that, with a particular Grignard reagent, the yields of ketone increase, and the combined yields of β-keto nitrile and residue (calculated as trimer) decrease as the R group of the nitrile, RCH_2CN, is varied in the order: phenyl, hydrogen, alkyl. For example, with *n*-amylmagnesium bromide, the yields of ketone were 0%, 14%, and 61% whereas the combined yields of β-keto nitrile and residue were 82%, 49%, and 5% when R of the nitrile was phenyl, hydrogen, and methyl, respectively. Since this is the order of decreasing activation of the α-hydrogen, the relative extent of course A appears to increase and that of course B to decrease as the relative reactivities of the α-hydrogen are decreased. In agreement with this, cyanocyclopropane in which the α-hydrogen may be considered to be deactivated by two alkyl groups has previously been reported to react with a slight excess of ethylmagnesium bromide to form predominantly (70%) the corresponding ketone (1). However, alkyl groups appear not only to deactivate the α-hydrogen but also to deactivate (presumably to a smaller degree) the nitrile group, since we have found that diethylacetonitrile failed to react appreciably with ethylmagnesium bromide in refluxing ethyl ether even after eleven hours.

With a particular nitrile, phenylmagnesium bromide and apparently most aromatic Grignard reagents[4] react relatively more with the nitrile group (course A) and relatively less with the α-hydrogen (course B) than alkylmagnesium halides. For example, with phenylacetonitrile, phenylmagnesium bromide gave a 33% yield of ketone and a 51% combined yield of β-keto nitrile and residue whereas *n*-amylmagnesium bromide gave no ketone and an 82% combined yield of β-keto nitrile and residue. In general, increasing the size or complexity of the Grignard reagent appears to favor the α-hydrogen reaction. Thus with phenylacetonitrile, phenylmagnesium bromide gave a 33% yield of ketone whereas the more sterically hindered mesitylmagnesium bromide gave no ketone. Apparently only α-hydrogen reaction products were formed with the hindered Grignard reagent. With propionitrile, *n*-amylmagnesium bromide gave a much better yield of ketone and a lower yield of α-hydrogen products than the more complex *tert*-butylmagnesium chloride although the total yield of products with the latter Grignard reagent was only 25%.[5]

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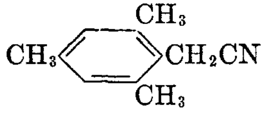
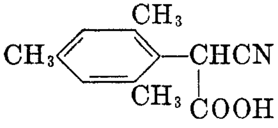
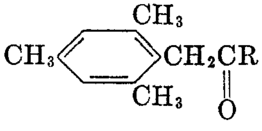
[4] Various arylmagnesium halides have been found to react with the nitrile group of γ-diethylaminobutyronitrile to give good yields of ketones [Humphlett, Weiss, and Hauser, *J. Am. Chem. Soc.*, **70**, 4020 (1948)] whereas we have been unable to obtain an appreciable amount of ketone from the reaction of methylmagnesium iodide with this nitrile.

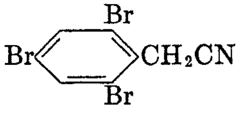
[5] Since reduction of the nitrile group by a β-hydrogen of the Grignard reagent to form an aldimine magnesium derivative (RCH=NMgX) seemed possible, we carried out the reaction of capronitrile with *tert*-butylmagnesium chloride, and attempted to isolate the cor-

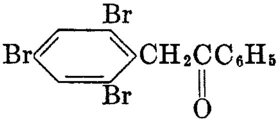
With the hindered phenylacetonitriles, mesitylacetonitrile (VIII) and 2,4,6-tribromophenylacetonitrile (XI) which undergo self-condensation only sluggishly, the extent of the α-hydrogen reaction (course B) was determined conveniently by carbonation of the magnesium derivative (I) and isolation of the corresponding carboxylic acid (such as IX). As usual the extent of course B was determined by the yield of ketone (X and XII).


VIII


IX


X


XI


XII

Mesitylacetonitrile gave with phenylmagnesium bromide apparently only the corresponding ketone (X, R = C_6H_5) and, with methylmagnesium iodide, a 63% yield of the corresponding ketone (X, R = CH_3) and a 27% yield of the acid (IX).[6] 2,4,6-Tribromophenylacetonitrile gave with phenylmagnesium bromide a 42% yield of the corresponding ketone (XII) and none of the corresponding acid, 46% of the nitrile being recovered. The tribromo nitrile failed to react with methylmagnesium iodide even after eight hours of refluxing.

The predominant formation of the ketone with these *ortho*-substituted phenylacetonitriles is in contrast to the main formation of α-hydrogen reaction products obtained in the analogous reaction with phenylacetonitrile itself (see Table I). The decrease in the rate of reaction at the α-hydrogen in the *ortho*-substituted nitriles relative to the rate at the nitrile group appears to be due to a steric factor.

Similarly to phenylmagnesium bromide, mesitylmagnesium bromide gave with mesitylacetonitrile (after a relatively long reflux period) none of the acid (IX). Reaction occured apparently only at the nitrile group to form the ketimine (obtained as its hydrochloride), although this product was not identified. However, with *tert*-butylmagnesium chloride, mesitylacetonitrile gave (after a rela-

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responding aldehyde which would have been readily formed from the aldimine. However, after decomposition of the reaction mixture, no aldehyde could be isolated as its sodium bisulfite derivative.

[6] In a preliminary experiment by Miss Passie Saperstein in this laboratory, the ether solution of mesitylacetonitrile (0.055 mole) and methylmagnesium bromide (0.075 mole) was refluxed for two days. There was isolated a 30% yield of the ketone [m.p. 56–59°; reported m.p. 56–60° (17)] and, after recrystallization from ethanol a 20% yield of the self-condensation product of the nitrile. The latter product melts at 183–184°.

Anal. Calc'd for $C_{22}H_{25}NO$: C, 82.76; H, 8.00.

Found: C, 82.76; H, 8.17.

TABLE I

YIELDS OF PRODUCTS FROM NITRILES WITH 10% EXCESS OF GRIGNARD REAGENTS

NITRILE	R in RMgBr	KETONE	B.P., °C.	MM.	YIELD, %	β-KETONITRILE	B.P., °C.	MM.	YIELD, %	RESIDUE, % TRIMER?
Phenylaceto	Phenyl	Phenyl benzyl	M.P. 55		33	α-Phenylacetylphenylaceto	197–202	2	15	36
Aceto	Phenyl	Acetophenone	200–205	atm.	37					*ca.* 50
Propio	Phenyl	Propiophenone	105–106	17	83					
Capro	Phenyl	Caprophenone	137–138	13	89					
Phenylaceto	*n*-Amyl					α-Phenylacetylphenylaceto	197–202	2	51	31
Aceto	*n*-Amyl	Methyl *n*-amyl	140–150	atm.	14					49
Propio	*n*-Amyl	Ethyl *n*-amyl	164–172	atm.	61					*ca.* 5
Phenylaceto	Methyl[a]	Methyl benzyl	86–87	6	8	α-Phenylacetylphenylaceto	197–202	2	71	
Propio	Methyl[a]	Methyl ethyl	77–78	atm.	21	α-Propionylpropio	190–194	atm.	28	
Capro	Methyl[a]	Methyl *n*-amyl	140–150	atm.	40	Caproylcapro[c]			>20	
Phenylaceto	*tert*-Butyl[b]					α-Phenylacetylphenylaceto	197–202	2	80	
Propio	*tert*-Butyl[b]	Ethyl *tert*-butyl	120–125	atm.	5	α-Propionylpropio	190–194	atm.	20	
Phenylaceto	Ethyl					α-Phenylacetylphenylaceto	197–202	2	51[d]	36
Phenylaceto	Isopropyl					α-Phenylacetylphenylaceto	197–202	2	64[e]	*ca.* 15
Phenylaceto	*n*-Butyl					α-Phenylacetylphenylaceto	197–202	2	23[f]	46
Phenylaceto	Mesityl					α-Phenylacetylphenylaceto	197–202	2	45	43

[a] Methylmagnesium iodide. [b] tert-Butylmagnesium chloride. [c] This product was not obtained sufficiently pure for analysis; it boiled at 224–228° at 22 mm. [d] Phenylacetonitrile (10%) was recovered. [e] Phenylacetonitrile (9%) was recovered. [f] Phenylacetonitrile (24%) was recovered.

tively long reflux period) a 37% yield of the acid (IX) and none of the ketone, 48% of the nitrile being recovered. Under similar conditions, 2,4,6-tribromophenylacetonitrile failed to react with *tert*-butylmagnesium chloride, 83% of the nitrile being recovered.

Thus, although the hindered aromatic Grignard reagent, mesitylmagnesium bromide, reacts only at the nitrile group, the hindered aliphatic Grignard reagent reacts apparently only at the α-hydrogen. This is in line with the observation made above that, in general, aliphatic Grignard reagents react relatively more at the α-hydrogen and relatively less at the nitrile group than aromatic Grignard reagents. It may seem rather remarkable that *tert*-butylmagnesium chloride reacts only at the α-hydrogen of mesitylacetonitrile, but it is to be noted that this Grignard reagent also reacts only at the α-hydrogen of phenylacetonitrile (see Table I).

It should be mentioned that Hellerman (7) has observed the predominant formation of the corresponding ketone with β,β,β-triphenylpropionitrile and aromatic or aliphatic Grignard reagents.

EXPERIMENTAL[7]

*Mesitylacetonitrile.*This nitrile (m.p. 78–80°) was prepared as described in Organic Syntheses (8) from α^2-chloroisodurene (b.p. 126–128° at 21 mm.) which was obtained conveniently in 80% yield from mesitylene and chloromethyl ether (9).

2,4,6-*Tribromophenylacetonitrile.* 2,4,6-Tribromotoluene (10) (100 g., 0.305 mole) was brominated in the side chain by the dropwise addition of 56 g. (0.35 mole) of bromine beneath the surface of the molten mass at 200–220° over a period of five hours as indicated by Asinger (11). The reaction mixture was cooled to 75°, taken up with carbon tetrachloride, diluted with ether, and washed with a saturated solution of sodium bicarbonate. The ether phase was dried over Drierite, filtered, and the solvent removed. The residue was distilled *in vacuo* through a 15-cm. Vigreux column yielding 104 g. (84%) of 2,4,6-tribromobenzyl bromide, b.p. 154–158° at 1 mm. and 174–178° at 6 mm.; reported b.p. 202° at 18 mm. (11).

To 55 g. (0.135 mole) of 2,4,6-tribromobenzyl bromide dissolved in one liter of 95% ethanol was added 10.5 g. (0.162 mole) of potassium cyanide dissolved in a minimum of water, and the resulting clear solution was gently refluxed for five hours. The reaction mixture was diluted with water, cooled, and the precipitated nitrile filtered. The product was recrystallized from ethanol yielding 38 g. (79%) of 2,4,6-tribromophenylacetonitrile, m.p. 126°.

Anal. Calc'd for $C_8H_4Br_3N$: N, 3.95; Br, 67.75.
Found: N, 3.81; Br, 67.46.

Henraut (12) reported that this nitrile, prepared from 2,4,6-tribromobenzyl chloride in 25% yield, melted at 138–139°.

Grignard reagents. Most of these reagents were prepared in a concentration of approximately 2 *N* in yields of 90–95% as determined by titration (13).

Mesitylmagnesium bromide was obtained in 80% yield according to the procedure described in Organic Syntheses (14) in which the yield (55–61%) of only the carbonation product was reported.

tert-Butylmagnesium chloride was obtained in 83% yield by the Organic Syntheses method (15) except that the addition period was increased to 15 hours using a drying tube filled with a mixture of calcium chloride and soda-lime.

Reaction of unhindered nitriles and Grignard reagents. In a three-necked, round-bottomed

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[7] Melting points and boiling points are uncorrected. Microanalyses are by the Microchemical Laboratory of the University of Pittsburgh.

flask equipped through ground-glass joints with a mercury-sealed stirrer, dropping-funnel, and a reflux condenser (having a drying tube) was placed the ether solution of the Grignard reagent. To the stirred refluxing solution of the reagent was added an ether solution of the nitrile over twenty minutes. Stirring and refluxing were continued 4–6 hours. The cooled mixture was decomposed by the cautious addition of dilute hydrochloric acid and the ether removed on the steam-bath. After heating for one hour longer to insure hydrolysis of the ketimine, the ketone was extracted four times with ether. The solvent was distilled from the dried, combined ether solutions and the residue fractionated through a 15-cm. Vigreux column or recrystallized from ethanol.

The results are summarized in Table I. All of the ketones listed in this table were identified by means of suitable derivatives. The β-keto nitrile, α-phenylacetylphenylacetonitrile, was identified by its oxime, m.p. 107°; the reported melting point is 107–108° (16). Although reported by earlier workers (2) we have been unable to prepare the oxime or semicarbazone of α-propionylpropionitrile.

Reaction of mesitylacetonitrile with Grignard reagents. To 60 ml. of an ether solution of 0.083 mole of methylmagnesium iodide was added 10 g. (0.055 mole) of mesitylacetonitrile dissolved in 100 ml. of anhydrous ether, followed by stirring and refluxing for eight hours. A ten-fold excess of finely powdered Dry Ice was added with vigorous stirring. After coming to room temperature, the mixture was decomposed by a dropwise addition of dilute hydrochloric acid and stirred vigorously until a clear solution of two layers resulted. The ether phase was separated and the remaining aqueous phase extracted with ether. The combined ether phases were extracted with 10% sodium hydroxide. The ether solution was dried over Drierite, the solvent distilled, and the residue fractionated *in vacuo* through a 15-cm. Vigreux column yielding 6.0 g. (63%) of mesitylacetone, b.p. 104–107° at 2 mm. The semicarbazone melted at 204°; reported m.p. 204° (17).

The sodium hydroxide extract was cooled, acidified with concentrated hydrochloric acid, and the liberated mesitylcyanoacetic acid extracted with ether. The combined ether portions were washed with water, dried over Drierite and the solvent distilled leaving a clear, viscous oil. After washing with water and ligroin (b.p. 60–90°), the oil solidified on standing 2–3 hours. One recrystallization from ligroin (b.p. 60–90°) yielded 3.0 g. (27%) of of crude mesitylcyanoacetic acid, m.p. 145–148° dec. Further recrystallization from a mixture of benzene and petroleum ether (b.p. 30–60°) gave the pure acid, m.p. 149–150° dec.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44; N, 6.88; Neut. equiv., 203.
Found: C, 71.15; H, 6.03; N, 6.89; Neut. equiv., 203.

In a similar manner, 8.0 g. (0.05 mole) of mesitylacetonitrile in 75 ml. of ether was added to 75 ml. of an ether solution of 0.075 mole of *tert*-butylmagnesium chloride. The mixture was refluxed for 25 hours under nitrogen, employing a nitrogen safety trap (18). The mixture was carbonated, and the ether solution extracted with dilute sodium hydroxide. From the alkaline phase there was obtained 3.8 g. (37%) of mesitylcyanoacetic acid, m.p. 150°, and from the ether phase, mesitylacetonitrile (40%), m.p. 78–80° after recrystallization from ethanol-water.

Similarly, mesitylacetonitrile (6.4 g., 0.04 mole) in 50 ml. of ether was reacted with 100 ml. of an ether solution of 0.08 mole of phenylmagnesium bromide, the mixture being refluxed for six hours. Omitting the carbonation, the solution was poured onto a mixture of 100 g. of ice and 50 ml. of concentrated hydrochloric acid. Distillation of the ether phase yielded a small amount of mesitylacetophenone and no nitrile. On standing, the aqueous phase yielded a precipitate of mesitylacetophenone (9.3 g., 97%) obtained by the hydrolysis of the water-soluble ketimine hydrochloride. After recrystallization from ethanol-water, the ketone was obtained in a total yield of 78% as white crystals, m.p. 159–160° and at 162° after further recrystallization.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.67; H, 7.61.
Found: C, 86.06; H, 7.90.

Reaction of 2,4,6-tribromophenylacetonitrile with phenylmagnesium bromide. To 60 ml. of an ether solution of 0.028 mole of phenylmagnesium bromide was added 6 g. (0.017 mole) of 2,4,6-tribromophenylacetonitrile (m.p. 126°) in 160 ml. of ether. The solution was stirred and refluxed for eight hours forming after the first few minutes a yellow precipitate. The reaction mixture was carbonated. After treating with acid, the two phases were separated. On standing the aqueous phase, containing the water-soluble ketimine hydrochloride gave, after recrystallization from ethanol, 3.2 g. (42%) of white crystals of 2,4,6-tribromophenylacetophenone, m.p. 147–148°.

Anal. Calc'd for $C_{14}H_9Br_3O$: C, 38.83, H, 2.09; Br, 55.37.
Found: C, 38.97; H, 2.10; Br, 55.27.

From the ether phase, which was extracted with alkali, there was recovered on fractionation 2.8 g. (46%) of crude 2,4,6-tribromophenylacetonitrile which, after one recrystallization from ethanol, melted at 126°. Acidification of the alkali extract yielded no carboxylic acid.

SUMMARY

A study has been made of the influence of structure of nitriles having α-hydrogen and of Grignard reagents on the relative extent of reaction at the α-hydrogen and at the nitrile group of the nitrile.

In general, reaction at the α-hydrogen decreases and that at the nitrile group increases as the nitrile is varied in the order: phenylacetonitrile, acetonitrile, propionitrile or higher aliphatic nitriles. Phenylmagnesium bromide reacts at the α-hydrogen of nitriles relatively less and at the nitrile group relatively more than aliphatic Grignard reagents.

Hindrance in the Grignard reagent, as with mesitylmagnesium bromide or *tert*-butylmagnesium chloride, favors reaction at the α-hydrogen whereas hindrance in the nitrile, as with mesitylacetonitrile or 2,4,6-tribromophenylacetonitrile, favors reaction at the nitrile group.

Cyclic products reported in the literature are accounted for on the basis of reaction at the α-hydrogen followed by reaction at nitrile groups.

The synthesis of several new compounds and improvements in the synthesis of certain known compounds are reported.

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