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APPLICATIONS OF SODIUM IN ORGANIC SYNTHESES

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TABLE OF CONTENTS

CARBINOL SYNTHESIS

I Introduction

Page

II Results and Discussion

III Experimental

TABLE OF CONTENTS
(continued)

I INTRODUCTION

A. OBJECT OF THIS RESEARCH

Successful preparation of carbinols by reaction of organo-sodium compounds with carbonyls has been reported in several rather specialized cases (1,2,3,4). The reaction,

$$R\,Na + R'COR'' \longrightarrow RR'R''CONa$$

has not, however, been studied systematically to define its useful scope, limitations and merits relative to the analagous Grignard preparation. This study was undertaken in an effort to provide such a comparison.

In order to make the comparison meaningful, the effects of variation in reaction temperature, solvent and order of addition of the reactants were studied. The possibility of improving upon the results of earlier work by application of new techniques recently reported (5) for more effective utilization of sodium in organic reactions was also examined.

B. BACKGROUND

1. Limitations of the Grignard Reaction

Despite the wide applicability of the Grignard reaction in carbinol syntheses, there are some characteristic cases where it either fails or provides very poor yields. The most important interfering reactions are the following.

(a) Reduction. With branched carbonyl compounds or Grignard reagents the most prominent side reaction is reduction of the carbonyl. Thus , reaction of isopropyl magnesium bromide and diisopropyl ketone gave 65 per cent reduction to diisopropyl carbinol and no addition to triisopropyl carbinol (6).

Allen and Blatt have summarized this effect by observing that it is not possible to prepare secondary alcohols containing two tertiary groups or tertiary alcohols containing more than two branched chain groups by the Grignard reaction with present methods. (7).

(b) Enolization. Carbonyl compounds in which α-hydrogen atoms are particularly active react as enols producing the hydrocarbon from the Grignard reagent and the halomagnesium enolate from the carbonyl which is recovered unchanged on acidification. Acetomesitylene forms the enolate quantitatively (7).

(c) Carbonyl Condensation. With carbonyl compounds which contain an active α- hydrogen and which are not sufficiently hindered to prevent condensation, aldol or Claisen type condensation can intervene. Thus both the Grignard reagent and the primary reaction product, a halomagnesium alcoholate, are sufficiently basic to cause acetone to undergo the aldol condensation; reaction of acetone and isobutyl magnesium bromide gives only 40 per cent yield of dimethylisobutyl carbinol plus a variety of condensation products from the acetone (8).

(d) Rearrangement. No rearrangements occur in the action of aliphatic halides with magnesium, employing the term "aliphatic" in the general non-conjugated sense. Rearrangements may occur however, in the reactions of allylic Grignard reagents. The reaction of benzylmagnesium chloride, producing ortho and para substitution in some cases, has been studied extensively (9, 10, 31). The amount and type of rearranged product depends upon the particular carbonyl compound reacted with the benzyl Grignard reagent.

(e) Dehydrohalogenation. Whitmore has indicated that it is possible to prepare the Grignard reagent in nearly quantitative yield from the simpler alkyl halides of all types, but that the increasing tendency for olefin formation by dehydrohalogenation causes the yield to drop rapidly with tertiary halides higher than amyl (11).

2. Potential Limitations of Sodium Reaction.

(a) Wurtz Coupling. Aliphatic halides which do not dehydrohalogenate too readily can give fair yields of hydrocarbon by the Wurtz reaction with sodium. It has been demonstrated amply, however, that organo-sodium compounds can be prepared in excellent yield from a wide variety of halides by working in dilute solution at moderate temperature (5,12). The general rule that the Wurtz reaction occurs most readily with iodides and least readily with chlorides suggests that chlorides should be most effective in the carbinol synthesis. For that reason and because of availability, they were employed throughout this investigation.

(b) Reduction. The utility of the sodium reaction to supplement the Grignard reaction for preparation of highly branched alcohols with less reduction of the carbonyl reactant was indicated by two previous studies (1,2). Several alcohols were reported which had not previously been accessible due to failure of the Grignard reaction. Although the yields reported were generally poor, it appeared likely that they might be improved by developing optimum reaction conditions and by utilizing sodium dispersions.

(c) Enolization and Carbonyl Condensation. These side reactions arise from the organo-sodium intermediate reacting as a base with an α-hydrogen atom activated by the carbonyl group. They may therefore be looked upon as one type of metallation reaction. This limitation might be expected to be more severe in the sodium reaction than in the Grignard reaction because organo-sodium compounds are, in general, more reactive than organo-magnesium halides. In fact, it has been stated that the reactivity of the colored alkyl aryl sodium compounds, as triphenylmethyl sodium, is so high that acetone and ethyl acetate react with them as pure enols (13). That observation is too general, however, as the reaction of benzyl sodium with both acetone and ethyl acetate to the corresponding tertiary alcohols has been demonstrated in this research. Sufficient data has not been published previously to establish the actual severity of the limitation by the metallation reaction.

(d) Rearrangement. The reaction of allylic sodium compounds such as benzyl sodium with carbonyl compounds to give alcohols had not been reported previously so the possibility of obtaining a rearranged product had to be tested.

(e) Dehydrohalogenation. The tendency of metallic sodium to cause dehydrohalogenation of secondary and tertiary halides is known to be greater than that of magnesium. As with the metallation reaction, however, the extent of this limitation had not previously been defined.

(f) Bimolecular Reduction. Metallic sodium can produce acyloin condensation of esters and pinacol reduction of aldehydes and ketones. These reactions should be minimized, however, in the presence of the organo-sodium intermediate from the halide.

II RESULTS AND DISCUSSION

A. REACTION CONDITIONS FOR CARBINOL SYNTHESES

The effects of modifications in the reaction conditions and procedure were studied for the sodium promoted reaction of benzyl chloride with acetone. The reaction sought was that leading to the tertiary alcohol, benzyldimethyl carbinol:

$$PhCH_2Cl + 2Na + CH_3COCH_3 \longrightarrow PhCH_2C(CH_3)_2ONa + NaCl \quad .$$

At moderate reaction temperatures, the principal products obtained were the desired carbinol and toluene. The yields of dibenzyl from Wurtz coupling were relatively small in most cases. The problem was therefore to establish the conditions which favor most strongly the addition of benzyl sodium to acetone, as shown above, over the toluene producing metallation reaction:

$$PhCH_2Na + CH_3COCH_3 \longrightarrow PhCH_3 + [CH_3COCH_2]^{-}Na^{+} .$$

That work is summarized in Table I.

The general reaction procedure was to add a dilute solution of the benzyl chloride and acetone dropwise to a sodium dispersion of about 1 to 50 microns particle size, also quite dilute. After reaction was complete, the slight excess of sodium was quenched by dropwise addition of distilled water with strong external cooling. The products indicated in Table I were obtained by fractional distillation of the water insoluble portion of the reaction mixture. The carbinol fraction was found to contain a small amount of a carbonyl compound. Hydroxylamine hydrochloride titration (14) gave the amounts shown in Table I, calculated as benzyl acetone. The benzyl acetone was not separated from the benzyldimethyl carbinol because it was present in such small amounts. Their boiling points are very similar b.p. 103 -105°/ 10mm. and b.p. 110 -112°/ 12 mm. respectively (15, 16) and the fact that acetonyl sodium was known to be present , from the metallation reaction producing toluene, strongly suggests the formation of some benzyl acetone by reaction of the acetonyl sodium with more benzyl chloride. Carbon atom alkylation by reaction of alkyl halides with the sodium salts from metallation of aliphatic ketones has been reported previously (17).

As might be expected, the metallation reaction is increased by working with an excess of acetone (second reaction in butyl ether). The other reactions, employing equimolar amounts of halide and ketone, were therefore conducted with the halide addition 10 per cent ahead of the carbonyl addition throughout.

Because the metallation is essentially the reaction of a stronger acid with the salt of a weaker acid (18,19,12) and therefore ionic, it should be minimized in solvents of low dielectric constant. Accordingly, both benzene and isooctane were tested as reaction solvents (ϵ 2.282 and 1.959 at 20°C. respectively compared with butylether, ϵ 3.5 approx.). This improved the carbinol yield considerably. The Wurtz reaction was largely eliminated while the toluene from metallation increased, contrary to the reasoning which suggested the change.

The influence of the reaction temperature was considered next. Reducing the temperature from 50° to 5° C. increased the carbinol yield very slightly. The metallation reaction decreased and Wurtz coupling increased by about equal amounts. The initial reaction of benzyl chloride with the sodium was reasonably complete at both 50° and 5° as indicated by Volhard titration of the chloride ion in the aqueous washings from the reaction mixture. Further reducing the temperature to -25° completely stopped the reaction of the sodium with the benzyl chloride.

The possibility of taking advantage of the metallation reaction to produce benzyl acetone in significant yields was tested by carrying out the reaction with the acetone addition 10 per cent ahead of the benzyl chloride addition (Table I, third reaction in butyl ether). An excess of both benzyl chloride and acetone was employed to minimize the direct reaction of benzyl chloride and sodium. The proportion of benzyl acetone in the carbinol product increased appreciably, however, the benzyldimethyl carbinol remained the principal product. It was concluded that this does not offer a generally useful method of ketone synthesis.

Stepwise reaction was also considered, first forming the benzyl sodium, then adding the acetone separately in dilute solution. This method permits formation of the benzyl sodium at a temperature high enough to sustain the reaction and subsequent reaction with acetone at a much lower temperature.

Accordingly, the method was tested at 25°and at -40° (Table I). The carbinol yield was significantly lower in both cases; however,a slightly better yield was obtained at the lower temperature, confirming the relatively small temperature effect observed previously. No ketone was present in the carbinol product from these reactions. Since the halide was all reacted before the acetone addition was started, that result was expected and confirms the suggestion that the ketone arose from coupling of acetonyl sodium and benzyl chloride in the one-step reactions. The reaction mixture from the reaction at -40° was carbonated by pouring it on an excess of crushed dry ice at the end of the reaction with acetone, to trap any unreacted phenyl or benzyl sodium. No benzoic or phenylacetic acid was obtained. Carbonation of the product, sodium benzyldimethyl carbinolate, did not interfere with isolation of the carbinol as alkyl sodium carbonates are hydrolysed by water (20).

The yield of carbinol was reduced significantly by carrying out the reaction in two separate steps. Accordingly, simultaneous addition of the halide and the carbonyl reactants in a single dilute solution was retained as the simpler and more effective procedure. The simplicity of this method is a distinct advantage over the Grignard reaction when the two give comparable yields.

The benzyl sodium for the two-step reactions was prepared by metallation of toluene by phenyl sodium because that is the practical method, e.g. in the synthesis of phenylacetic acid (5), due to the lower cost of chlorobenzene and because Wurtz coupling occurs less readily with chlorobenzene than with benzyl chloride. The effectiveness of the benzyl sodium preparation was tested in a separate reaction by carbonating the benzyl sodium with crushed solid dry ice. The crude yield of phenylacetic acid was 88 per cent. Crystallization from water gave 80 per cent yield phenylacetic acid m. 75.5- 76.5°C.

While the two-step reaction resulted in some reduction in yield, the preparation of the benzyl sodium from chlorobenzene, sodium and toluene demonstrates a simplification which is much more often available with the sodium than with the Grignard reaction. That is the preparation of relatively complex organo-sodium intermediates by reaction of sodium with a simple, readily available halide followed by metallation of the more complex hydrocarbon. For example, fluorenyl sodium is readily prepared by metallation of fluorene with amyl or phenyl sodium. The preparations of fluorenyl carbinols which have been reported by the Grignard method have started with 9-bromfluorene which is not readily available.

It was concluded from these tests that the optimum results are obtained, in the synthesis of carbinols by the sodium promoted reaction of chlorides and carbonyl compounds, when working with equivalent amounts of the two organic reactants in dilute solution with a solvent of low dielectric constant. The reactants are added simultaneously to a dilute dispersion of sodium in the same solvent, with the halide addition about ten per cent ahead of the carbonyl addition. The lowest temperature which will maintain the reaction is employed. Under those conditions, benzyldimethyl carbinol was prepared in 42 per cent yield from benzyl chloride and acetone. Permanganate oxidation of the carbinol to benzoic acid indicated that only the normal product was obtained with no dimethyl-*o*-tolyl carbinol from rearrangement.

B. RELATIVE EFFECTIVENESS OF DIFFERENT CLASSES OF HALIDES AND CARBONYL COMPOUNDS

In order to define the useful scope of this method of carbinol synthesis, the reaction was conducted with a number of combinations of five different carbonyl compounds and five chlorides. The results are summarized in Tables II and III. Throughout most of the reactions the principal product obtained, other than the desired carbinol, was the parent hydrocarbon from the chloride, e.g. toluene from benzyl chloride, benzene from chlorobenzene and pentane from amyl chloride. This indicates that the principal interfering reaction is metallation of the active, acidic, α-hydrogen of the carbonyl reagent.

The order of increasing effectiveness of the reactants in Table III is in accord with the known relative α-hydrogen activity of the carbonyl types, aldehyde $>$ ketone $>$ ester. It also demonstrates that the tendency toward metallation is a function of the halide as well as the carbonyl compound. That is reasonable, as it should actually depend upon the difference in acidity of the two parent hydrocarbons; i.e. it should occur least with the halide whose parent hydrocarbon is the strongest acid and the carbonyl compound having the least reactive (acidic) hydrogen. That is precisely the relative order of effectiveness obtained with both the halides and carbonyls. Considering the parent hydrocarbons of the halides, the following metallation reactions would be normal, demonstrating the order of increasing acidity (12,18):

$$(CH_3)_3CNa + CH_3CH_2CH_3 \longrightarrow (CH_3)_3CH + CH_3CH_2CH_2Na$$
$$(CH_3)_2CHNa + CH_3(CH_2)_3CH_3 \longrightarrow (CH_3)_2CH_2 + CH_3(CH_2)_3CH_2Na$$
$$CH_3(CH_2)_3CH_2Na + C_6H_6 \longrightarrow CH_3(CH_2)_3CH_3 + C_6H_5Na$$
$$C_6H_5Na + C_6H_5CH_3 \longrightarrow C_6H_6 + C_6H_5CH_2Na\ .$$

Published reports of relative α-hydrogen activity of other carbonyl compounds and of relative acidity of various hydrocarbons should thus make possible extrapolation of this table to predict the probable results in other sodium promoted carbinol preparations. Such extrapolation should be valid so long as the metallation tendency may reasonably be expected to be the limiting factor rather than some other effect such as steric interference. The change to dehydrohalogenation as the limiting reaction with the branched aliphatic chlorides does not affect the order of increasing halide utility because those halides also are least effective on the basis of relative hydrocarbon acidity.

From the considerations outlined above, optimum reactants should be an ester such as methyl pivalate, having no α-hydrogen atoms, and a halide such as benzyl or benzhydril chloride. While triphenyl methyl chloride would be still less active toward metallation, the reaction of two molecules of triphenylmethyl sodium with the ester should be subject to strong steric retardation.

The 6 per cent yield of triisopropyl carbinol obtained in the reaction of isopropyl chloride with diisopropyl ketone essentially duplicates the results obtained by Bartlett and Schneider (2) employing sodium sand. This indicates that there is little advantage to the use of the dispersed form of sodium in those reactions where dehydrohalogenation of the chloride is an important limitation except that the reactions of dispersed sodium are generally much more readily controlled.

C. COMPARISON OF SODIUM PROMOTED SYNTHESIS WITH GRIGNARD REACTION

The carbinol yields which have been reported in the literature for Grignard reactions with the same halides and carbonyl compounds are summarized in Table IV. Comparison with the yields obtained in the sodium promoted reactions, Table III, leads to the following conclusions.

In those cases where the metallation reaction is minimized so that the sodium promoted reaction is most effective, the two methods give nearly comparable yields. The advantage then lies with the sodium reaction in consequence of the simplicity of the single step reaction plus the fact that it utilizes chlorides while the Grignard reaction frequently is most effective with bromides. The possibility of reacting a less expensive halide, or one which is more readily available, with sodium and metallating the hydrocarbon to form the required organo-sodium intermediate is an additional advantage of the sodium reaction in many cases. This might easily compensate for a somewhat lower yield in the sodium reaction in cases where preliminary synthesis of the particular bromide required would be necessary for the Grignard reaction.

The advantage of the sodium reaction in some cases where the Grignard reaction fails completely, e.g. in the synthesis of triisopropyl carbinol, which has been reported previously, is evident.

The relative effectiveness of the two methods with acetone clearly demonstrates that the Grignard reaction gives much higher yields with carbonyl compounds having very active and accessible α-hydrogen atoms. The fact that the arrangement of the table does not correspond to regularly increasing carbinol yields by the Grignard reaction indicates that the limiting factor here usually is not the tendency for metallation or enolization. That is particularly evident in the 60 per cent yield of the <u>tert</u>-butylethyl carbinol reported from <u>tert</u>-butyl magnesium bromide and propionaldehyde.

The two methods of carbinol synthesis are, therefore, supplementary. The sodium method is most effective in preparation of complex, highly branched carbinols. The Grignard method is most effective in the larger number of cases, i.e., in preparation of the less highly branched carbinols.

III EXPERIMENTAL

(A) BENZYL CHLORIDE AND ETHYL ACETATE

The procedure employed in the preparation of dibenzylmethyl carbinol from benzyl chloride and ethyl acetate is representative of the general method applied in the series of sodium promoted reactions of organic chlorides with carbonyl compounds.

A one-liter round-bottomed flask was equipped with a mercury-sealed stirrer, a dropping funnel, a thermometer extending into the reaction mixture, a nitrogen inlet and a reflux condenser vented through a cold trap and oil bubbler. The apparatus was purged with dry nitrogen. A few crystals of benzophenone to activate the sodium, 200 ml. dry isooctane and 50.6 g. 50 per cent dispersion of sodium in di-n-butyl ether (1.1 g. atom sodium) were added and the system was again purged with nitrogen.

Dropwise addition of a solution of 6.3 g. benzyl chloride (fractionated, b.p. 86°/33mm.) in 30 ml. isooctane was started at 24°. As there was no evolution of heat, the mixture was warmed to 30°. The addition was completed in one-half hour with no evidence of the reaction having started.

Dropwise addition of 57.0 g. benzyl chloride ($\frac{1}{2}$ g. mole total) and 19.8 g. ethyl acetate (fractionated, b.p. 76.4 - 76.9°) in 240 ml. isooctane was started at 22°. The mixture immediately began turning black and the reaction became mildly exothermic. The temperature was maintained between 22° and 32° by external cooling during the remainder of the addition over three and one-fourth hours. The mixture remained dark black and a moderate amount of heat was evolved throughout the reaction.

Finally, a solution of 2.2 g. ethyl acetate ($\frac{1}{4}$ g. mole total) in 30 ml. isooctane was added over one-half hour at 22° - 30° and the mixture was stirred one hour more at 24°. The unreacted sodium was then quenched by dropwise addition of 100 ml. distilled water (still under a nitrogen atmosphere). During the quenching, the reaction mixture was held at 6° - 20° with strong external cooling. It is important not to cool below 0° as the water then freezes as it is added and reacts violently with the dispersed sodium on warming.

Some hydrogen gas was evolved through the oil-bubbler during the quenching. The aqueous and oil layers were separated. The oil layer was washed with three portions of dilute sodium carbonate solution and dried over Drierite. Duplicate Volhard titrations of the chloride ion in aliquot portions of the combined aqueous layers indicated that the benzyl chloride had reacted completely.

The dry product solution was distilled from anhydrous potassium carbonate through a three-foot, helices-packed column (approximately 40 theoretical plates, Column A). A very small ethyl acetate forerun was obtained, followed by the isooctane and butyl ether. The residue of 46.4 g. was distilled from a Claisen flask with a slow stream of nitrogen. The flask was previously rinsed with ammonium hydroxide and dried to insure against acid-catalysed dehydration. The first portion, 8.1 g., boiled at 65.5° - 105° at $1\frac{1}{2}$ mm. and gave strong positive tests for unsaturation with bromine in carbon tetrachloride and with alkaline potassium permanganate solution. The second portion, 32.7 g., boiled at 107° - 135° at $1\frac{1}{4}$ mm.

and gave a very weak permanganate test for unsaturation. This left 5.6 g. dark brown residue. The first portion was a mixture of the desired dibenzylmethyl carbinol and the olefin resulting from partial dehydration during distillation; the second was principally carbinol with a small amount of olefin. The yield of crude carbinol was thus 72 per cent.

Part of the second fraction was refractionated through a three-foot glass column 5 mm. in diameter packed with a monel wire spiral (Column B). A small forerun containing unsaturated material was followed by a large center cut of constant refractive index, dibenzylmethyl carbinol, n_D^{25} 1.5665, analysis: calculated for $C_{16}H_{18}O$, C 84.91, H 8.02; found C 85.16, 85.41; H 8.20, 7.91. The isooctane fraction from the original distillation was washed with water to remove ethyl acetate and dried. The refractive index indicated the presence of 6.6 g. toluene corresponding to 14 per cent metallation reaction. The corresponding properties reported for dibenzylmethyl carbinol by Levy and Tabart are b.p. 197° - 198°/20mm., n_D^{18} 1.5735. (23)

(B) BENZYL CHLORIDE AND DIISOPROPYL KETONE

The procedure employed in the preparation of benzyldiisopropyl carbinol from benzyl chloride and diisopropyl ketone was essentially the same as that described in (A). The principal difference was the use of only $\frac{1}{4}$ g. mole of benzyl chloride because only one mole of halide is required per mole of ketone. Therefore, only 0.55 g. atom of sodium (25.4 g. 50 per cent dispersion) was required to provide the 10 per cent excess regularly employed.

The first 10 per cent of the benzyl chloride (3.2 g.) dissolved in 30 ml. isooctane was added over twenty minutes at 23° - 25° to the reaction mixture of dispersed sodium, activated with benzophenone, in isooctane. A solution of 28.5 g. benzyl chloride and 25.7 g. diisopropyl ketone (fractionated b.p. 45.0° - 45.5°/40mm.) in 240 ml. isooctane was added dropwise over three hours at 25° - 35°. The reaction mixture rapidly turned black and remained so throughout the addition and subsequent stirring. Finally, 2.9 g. diisopropyl ketone in 30 ml. isooctane was added over one-half hour and the mixture was stirred one hour more to insure complete reaction. The unreacted sodium was quenched with distilled water, as in (A).

After the oil layer was separated and washed, Volhard titration of the aqueous layers indicated that 97 per cent of the benzyl chloride had reacted.

The dried oil layer was fractionated from potassium carbonate through Column A. After the isooctane and most of the butyl ether had been removed, the residue, principally benzyldiisopropyl carbinol, was fractionated directly through column B. The following product fractions were obtained:

Sample	Weight, g.	n_D^{25}	Identity
(a)	3.51	1.5068	carbinol and butyl ether
(b)	9.32	1.5107	benzyldiisopropyl carbinol
(c)	9.40	1.5120	" "
(d)	9.01	1.5120	" "
(e)	1.24	1.5123	" "
residue	2.8	-	-

Analysis of (C): calculated for $C_{14}H_{22}O$, C 81.50, H 10.75; found C 81.72, 81.98; H 10.67, 10.64. Murat and Amouroux have reported b.p. 161° - 164°/35 mm., n_D 1.538 for benzyl-diisopropyl carbinol (24).

The still-head temperature was 99° - 105° at 1 - 2 mm. pressure throughout the carbinol distillation. However, evidence of superheating has been noted, even with the column wet, at very low pressures. The total yield of crude carbinol was 32.5 g. or 65 per cent. The refractive index of the isooctane fraction indicated the presence of 4.6 g. toluene or 20 per cent.

(C) BENZYL CHLORIDE AND DIISOBUTYL KETONE

The procedure employed in the preparation of benzyl diisobutyl carbinol from benzyl chloride and diisobutyl ketone was the same as that described in (B) for benzyl-diisopropyl carbinol except that ½ g. mole portions were used instead of ¼ g. mole because a lower yield was anticipated. Since the product carbinol had not been reported previously it was desirable to prepare enough to permit effective purification for characterization. The initial portion of 3.2 g. benzyl chloride in 30 ml. isooctane was added during one-half hour at 20° - 22° to 50.0 g. of 50 per cent dispersion of sodium (1.1 g. atom sodium) in butyl ether mixed with 300 ml. isooctane containing a few crystals of benzophenone activator. Following that, a solution of 60.1 g. benzyl chloride (½ g. mole total) and 67.5 g. diisobutyl ketone (fractionated b.p. 69.8° - 70.0°/24 mm.) in 540 ml. isooctane was added over six and one-half hours at 22° - 35°. Finally, 3.6 g. diisobutyl ketone (½ g. mole total) in 30 ml. isooctane was added over one-half hour and the reaction mixture was stirred for one hour more.

The reaction mixture was treated exactly as described in (A) and (B). The chloride titration indicated that the benzyl chloride had reacted completely.

In the product distillation, 15.8 g. toluene from metallation (35 per cent) was obtained in the isooctane; 37 per cent of the diisobutyl ketone was recovered unchanged, regenerated from the enolate formed by metallation. The higher boiling portion was fractionated through column B into the following portions:

sample	weight, g.	n_D^{25}	identity
(a)	4.63	1.4749	ketone and product carbinol
(b)	9.20	1.4957	benzyldiisobutyl carbinol
(c)	9.29	1.4963	
(d)	9.14	1.4953	
(e)	9.00	1.4952	
(f)	8.83	1.4950	
(g)	9.04	1.4943	
(h)	7.92	1.4938	
(i)	1.73	1.4926	
residue	2.4	-	

The still-head temperature ranged from 92° to 100° at ½ mm pressure. The still-pot temperature ranged from 135° to 190°. Analysis of (e): calculated for $C_{16}H_{26}O$ C 81.99 H 11.18; found C 82.28, 82.41; H 11.15, 11.25. The total yield of crude carbinol was 69 g. or 59 per cent. This product has not been reported previously.

D. BENZYL CHLORIDE AND ACETONE

A number of preparations were carried out with this pair of reactants to establish the optimum procedure for the synthesis. Because they produce an intermediate yield of carbinol (42 per cent) under optimum conditions, either an increase or decrease in yield is readily observable with changed reaction conditions. The results of this set of reactions is summarized in Table I. The following are typical examples of the principal modifications.

(1) Most Effective Procedure. The best yield of benzyldimethyl carbinol was obtained by conducting the synthesis as described in example (B) for benzyl chloride and diisopropyl ketone.

A total of 31.7 g. benzyl chloride and 14.5 g. acetone (C.P. acetone was employed without redistillation) were reacted ($\frac{1}{4}$ g. mole each). As before, 0.55 g. atom sodium was employed. In this case, the sodium was initially dispersed in xylene instead of in butyl ether, however the principal solvent for the reaction was again isooctane. The procedure during the reaction and the treatment of the reaction mixture was the same as that described in example (B) with the single exception that the reaction was carried out at $0^{\circ} - 10^{\circ}$. The chloride ion titration indicated that 98 percent of the benzyl chloride reacted.

The dried oil layer was distilled through column A. A total of 6.2 g. toluene from metallation (27 percent) was obtained in the isooctane fractions. Following the isooctane, toluene and xylene, 15.9 g. crude benzyldimethyl carbinol (42.5 per cent) was distilled, n_D^{25} 1.5082. Indications had been obtained previously that a small amount of benzylacetone is formed with the benzyldimethyl carbinol by reaction of benzyl chloride with acetonyl sodium formed by metallation. The carbonyl content of the crude benzyldimethyl-carbinol was determined by duplicate hydroxylamine hydrochloride titrations (14). This indicated that the crude product contained 1½ per cent benzylacetone. A portion of the crude carbinol was subsequently redistilled through column B. A small forerun with the odor of benzyl chloride was followed by a second small fraction b.p. 77°/5mm., n_D^{16} 1.5164. Finally, the principal fraction was collected, b.p. 84°-85°/5mm., n_D^{16} 1.5171; the constants reported in the literature are b.p. 104°-105°/17mm., n_D^{16} 1.5173-4 (21). The residue from the original distillation was 4.2 g. from which a small amount of crude dibenzyl was recovered.

A portion of the dimethylbenzyl carbinol was oxidized with alkaline potassium permanganate. The product was isolated by acidification, ether extraction and solution of the acid products in chloroform according to the procedure of Gilman and Kirby (22) in order to establish the presence or absence of phthalic acids. Only benzoic acid was isolated, demonstrating that only normal addition occurs in the reaction of benzyl sodium with acetone.

Similar reactions were carried out in various inert solvents and at different temperatures with the results indicated in Table I. These led to the conclusion that the desired reaction is favored by employing a solvent of minimum dielectric constant and the minimum temperature which will sustain the reaction between the chloride and the sodium. Within the range of 5° to 50° the temperature effect is quite small. It is usually desirable to conduct the reaction at room temperature to insure reasonably complete reaction since the ability of the sodium to sustain the reaction at lower temperatures was found to depend strongly on the activity or freshness of the dispersion.

(2) Acetone Addition Leading. In order to explore the possibility of capitolizing on the side reaction producing benzylacetone by Wurtz type reaction between acetonyl sodium and benzyl chloride, a reaction was run in essentially the same fashion as example (1) but with the addition of acetone 10 per cent ahead of the benzyl chloride. The reaction was run at 50°. in butyl ether. Only 0.28 g. atom sodium was employed with $\frac{1}{4}$ g. mole each of benzyl chloride and acetone in order to minimize the direct reaction of the sodium and the benzyl chloride. A solution of 1.5 g. acetone in 30ml. butyl ether was added during twenty minutes followed by a solution of 13.0 g. acetone and 28.5 g. benzyl chloride in 240 ml. butyl ether during one and one-half hours and finally by 3.2 g. benzyl chloride in 30 ml. butyl ether during fifteen minutes. The reaction mixture was quenched and the products were separated as in example (B). The chloride titration indicated that 52 per cent of the benzyl chloride reacted; reaction of the sodium was therefore essentially complete. The yield of crude benzyldimethyl carbinol was 8.93 g. Duplicate hydroxlamine hydrochloride titrations indicated that this product contained 26 per cent ketone as benzyl acetone. The yields were therefore 6 $\frac{1}{4}$ per cent benzylacetone and 17 3/4 per cent benzyldimethyl carbinol (12$\frac{1}{2}$ and 35$\frac{1}{2}$ per cent respectively based on benzyl chloride reacted). The proportion of benzylacetone in the product was thus increased signifi-

cantly, although the carbinol remained the principal product.

(3) Two Step Reaction. The effect of employing a procedure more closely paralleling the Grignard synthesis was studied by conducting the reaction in two steps. Benzyl sodium was first formed by metallation of toluene by phenyl sodium. A dilute solution of acetone was then added slowly to the benzyl sodium.

The equipment described in example (A) was purged with nitrogen; 25.4 g. 50 per cent dispersion of sodium in eicosane (0.55 g. atom) and 200 ml. dry toluene were introduced. A solution of 28.2 g. chlorobenzene, $\frac{1}{4}$ g. mole, (fractionated, b.p. 72.8°/109 mm.) in 100 ml. toluene was added dropwise during one hour at 17° - 27°. The reaction mixture turned jet black during the addition. It was heated to reflux for three hours. The color quickly changed from black to brown. A solution of 14.5 g. acetone ($\frac{1}{4}$ g. mole) in 100 ml. toluene was added dropwise during one hour at 20° - 30° and the mixture was stirred for one hour more. The brown color remained.

The reaction mixture was quenched and the products were separated as in example (A). The chloride titration indicated that 94 per cent of the chlorobenzene reacted. Fractional distillation of the oil layer through column A gave 9.9 g. crude benzyldimethyl carbinol (26.4 per cent yield) n_D^{25} 1.5126. Indications were obtained that up to 3 g. biphenyl (8 per cent yield) remained in the distillation residue. The following phenylacetic acid preparation was therefore carried out to establish the efficiency of this method of preparing benzyl sodium by metallation.

The same equipment was purged with nitrogen and charged with 200 ml. dry toluene, 25.4 g. 50 per cent dispersion sodium in eicosane (0.55 g. atom sodium) and a few crystals of benzophenone to activate the sodium. A solution of 28.2 g. chlorobenzene ($\frac{1}{4}$ g. mole) in 100 ml. toluene was added dropwise over one and one-fourth hours at 15° - 25°. The typical black color of phenyl sodium again developed. The mixture was stirred one-half hour at room temperature, then heated to reflux for three hours. It was then partially cooled and poured with stirring into a large excess of crushed dry-ice in 100 ml. toluene under a nitrogen atmosphere in a stainless steel beaker. After warming overnight to evaporate the excess dry-ice, the mixture was returned to the reaction flask and quenched at 5° to 20°, under nitrogen, with distilled water. The toluene and aqueous layers were separated and the toluene was washed with three portions of distilled water. The combined aqueous layers were filtered through sintered glass and made acid to Congo red with concentrated sulfuric acid. A heavy precipitate of tan, crystalline phenylacetic acid was removed, 27.0 g., m.p. 75.5°- 76.5°. Extraction of the acid water with three portions of ethyl ether gave an additional 3 g. of very impure phenylacetic acid. The total yield was therefore 80 to 88 per cent of theory. A yield that high in a one-fourth g. mole reaction verified the effectiveness of this method of preparing the benzyl sodium.

Synthesis of benzyldimethyl carbinol by addition of acetone to preformed benzyl sodium renders possible reaction with the acetone at a much lower temperature since the benzyl chloride-sodium reaction does not have to be maintained simultaneously. Accordingly, the preparation was repeated exactly as described above except that the solution of 14.5 g. acetone in 100 ml. toluene was added dropwise over one hour to the reaction mixture at -35° to -45°. In this case the yield of benzyldimethyl carbinol was 11.8 g. (31.5 per cent). This substantiated the earlier observations that the carbinol synthesis is favored by lowering the reaction temperature and that the effect is relatively small.

E. BENZYL CHLORIDE AND PROPIONALDEHYDE

The procedure described in example (B) was followed throughout in the preparation of benzylethyl carbinol from benzyl chloride and propionaldehyde. A total of 31.7 g. benzyl chloride and 14.5 g. propionaldehyde ($\frac{1}{4}$ g. mole each) were reacted with 0.55 g. atom of dispersed sodium. The chloride ion titration indicated that 99 per cent of the benzyl chloride reacted. The initial product distillation through column A gave 13.4 g. toluene from metallation (59 per cent) and 3.9 g. crude benzylethyl carbinol (16 per cent). This was not enough carbinol to permit fractional distillation. It was distilled from a Claisen flask into the following two portions:

(a) 1.0 g., b.p. 62.5°-70.5/0.6 mm., n_D^{16} 1.5143

(b) 0.6 g., b.p. 67.5°-75.5°/1 mm., n_D^{16} 1.5233

Analysis of (b): Calculated for $C_{10}H_{14}O$, C 79.95, H 9.39; found C 80.66, 80.72, H 8.83, 8.58. This carbinol was reported once previously (34). The properties reported were b.p. 124°-127°/15mm, n_D^{16} 1.4301. No analysis was given. Most aryl-substituted carbinols have been observed to have refractive indices greater than 1.5.

F. CHLOROBENZENE AND ETHYL ACETATE

Three attempts were made to prepare diphenylmethyl carbinol by reaction of chlorobenzene and ethyl acetate following the procedure described in example (A). In each case the dark color of phenyl sodium developed during the initial addition of chlorobenzene solution but the reaction stopped when the simultaneous addition of ethyl acetate and chlorobenzene began. It can be started again by warming the reaction mixture sufficiently; however, that was not useful because chlorobenzene undergoes the Wurtz-Fittig reaction to biphenyl very readily above 45°- 50°. Also, if much chlorobenzene has been added without reacting, the reaction is violent when it does "catch" and may exceed the capacity of the reflux condenser. This peculiarly sluggish behavior appears to be unique with this particular combination of reactants because ethyl acetate worked very well with benzyl chloride. No diphenylmethyl carbinol was isolated from any of the three reactions.

G. CHLOROBENZENE AND DIISOPROPYL KETONE

The procedure described in example (B) was followed throughout in the preparation of diisopropylphenyl carbinol from chlorobenzene and diisopropyl ketone. A total of 28.2 g. chlorobenzene and 28.6 g. diisopropyl ketone ($\frac{1}{4}$ g. mole each) were reacted with 0.55 g. atom of dispersed sodium at 39° - 44°. The chloride ion titration indicated that 86 per cent of the chlorobenzene reacted. The initial product distillation through column A gave 8.30 g. benzene from metallation (50 per cent of the chlorobenzene reacted), 36 per cent recovery of unchanged diisopropyl ketone, probably regenerated from the enolate formed by metallation, and 15.7 g. crude diisopropylphenyl carbinol (38 per cent). The crude carbinol was vacuum distilled from a Claisen flask. Three fractions were collected:

(a) 4.83 g., b.p. 75°-80°/0.4 mm., n_D^{20} 1.5114
(b) 6.26 g., b.p. 68°-74°/0.3 mm., n_D^{20} 1.5119
(c) 2.40 g., b.p. 73°5°-75°/0.3 mm., n_D^{20} 1.5612

Fractions (a) and (b) were combined and distilled through column B. The following fractions were collected:

(1) 1.6 g., b.p. 82°-85°/1.2 mm., n_D^{25} 1.5114
(2) 3.4 g., b.p. 74°-78°/0.5 mm., n_D^{25} 1.5109
(3) 3.9 g., b.p. 74°-76°/0.5 mm., n_D^{25} 1.5107

Stas has reported b.p. 118°-119°/11 mm., n_D^{20} 1.5239 (26). Fraction (2) gave negative tests for unsaturation and for carbonyl contamination. Analysis of fraction (2): calculated for $C_{13}H_{20}O$, C 81.20 H 10.48; found C 81.18, 80.96; H 10.44, 10.52.

H. CHLOROBENZENE AND PROPIONALDEHYDE

The procedure of example (B) was again followed in the preparation of ethylphenyl carbinol from chlorobenzene and propionaldehyde. A total of 28.2 g. chlorobenzene and 14.5 g. propionaldehyde ($\frac{1}{4}$ g. mole each) were reacted with 0.55 g. atom dispersed sodium at 50°. The chloride ion titration showed that 99 per cent of the chlorobenzene reacted. Distillation of the dried oil layer through column A gave

13.8 g. benzene from metallation (71 per cent) and 3.2 g. crude ethylphenyl carbinol (10 per cent). The carbinol was distilled under reduced pressure from a Claisen flask into two fractions:

(a) 0.58 g., b.p. 77°-78.5°/3 mm., n_D^{20} 1.5147

(b) 2.36 g., b.p. 52°-55°/0.8 mm., n_D^{20} 1.5183, n_D^{23} 1.5174

Reported properties for ethylphenyl carbinol are:

b.p. 93°/4 mm., n_D^{20} 1.5208 (35)

b.p. 76°/3mm., n_D^{23} 1.5210, p-nitrobenzoate m.p. 56.5° (36)

The yield of carbinol was too small to permit fractionation through column B. The identity of the product was established by preparing the p-nitrobenzoate by a procedure similar to that reported previously. (36) Fraction (b) was diluted with dry diethyl ether and reacted with metallic sodium. The unreacted sodium was removed and 2.0 g. solid p-nitrobenzoyl chloride was added to the solution of sodium carbinolate in ether. The reaction mixture stood at room temperature overnight. The precipitate was removed by filtration. The ether was evaporated and a new precipitate formed. It was removed by filtration and found to be p-nitrobenzoic acid. The viscous filtrate was allowed to stand for ten days. The ester crystallized from it very slowly. It was removed by filtration and purified by repeated washing with petroleum ether. The product ethylphenyl carbinol p-nitrobenzoate melted at 55-6°.

I. n-AMYL CHLORIDE AND ETHYL ACETATE

Diamylmethyl carbinol was prepared from n-amyl chloride and ethyl acetate by the procedure described in example (A).

The reaction of 53.3 g. n-amyl chloride, refractionated b.p. 105.8°-107.4°/745 mm., ($\frac{1}{2}$ g. mole) and 22.0 g. ethyl acetate ($\frac{1}{4}$ g. mole) with 1.1 g. atom of dispersed sodium was carried out at 9°-15°. The chloride titration indicated that 83 per cent of the amyl chloride reacted. Distillation of the oil layer through column A gave 22.6 g. pentane from metallation and 9.0 g. crude diamyl methyl carbinol (75 per cent and 23 per cent yield respectively based on amyl chloride reacted). An attempt to distil the carbinol from a Claisen flask at atmospheric pressure gave some distillate b.p. 211°-213°, n_D^{20} 1.4373. The refractive index of methylundecene obtained by dehydration of this carbinol has been reported to be n_D^{20} 1.4368 (28). The remainder of the carbinol was distilled under reduced pressure from the Claisen flask, b.p. 74°-83°/2 mm., n_D^{20} 1.4386. The physical properties previously reported for di-n-amylmethyl carbinol are b.p. 80°-83°/2mm., n_D^{20} 1.4392. (28)

J. n-AMYLCHLORIDE AND DIISOPROPYL KETONE

Amyldiisopropyl carbinol was prepared from n-amyl chloride and diisopropyl ketone by the procedure described in example (c) using $\frac{1}{2}$ g. mole each of chloride and ketone. The reaction of 53.3 g. n-amyl chloride and 57.1 g. diisopropyl ketone ($\frac{1}{2}$ g. mole each) with 1.1 g. atom of dispersed sodium was carried out at 25°-30°. The chloride ion titration indicated that 98 per cent of the amyl chloride reacted. Distillation of the dried oil layer through column A gave 23.8 g. pentane (66 per cent). The product distilling in the range where amyldiisopropyl carbinol was expected was 20.4 g. It gave strong positive tests for unsaturation and a weak carbonyl test. Careful distillation through column B failed to separate the carbinol product from the unsaturated material. Since the high yield of pentane and the relatively small amount of crude product (22 per cent yield as carbinol) indicate that this pair of reactants is in the group for which the Grignard reaction is much more effective, no further effort was made to separate the carbinol from the unsaturated product.

K. n-AMYL CHLORIDE AND DIISOBUTYL KETONE

Amyldiisobutyl carbinol was prepared from n-amyl chloride and diisobutyl ketone by the procedure described in example (B). The reaction of 26.7 g. n-amyl chloride and 35.6 diisobutyl ketone ($\frac{1}{4}$ g. mole each) with 0.55 g. atom of dispersed sodium was carried out at 22°-25°. The chloride ion titration indicated that 86 per cent of the amyl chloride reacted. Distillation of the oil layer through column A gave 9.8 g. pentane and 5.5 g. crude n-amyldiisobutyl carbinol (63 per cent and 12 per cent yield respectively based on amyl chloride reacted); 81 per cent of the diisobutyl ketone was recovered unchanged, regenerated from the enolate. The crude carbinol was distilled under reduced pressure from a Claisen flask. The entire sample boiled from 80° to 87° at $1\frac{1}{2}$ mm. The principal center cut gave b.p. 77.5°-78.5°/0.2 mm., n_D^{25} 1.4424, analysis: calculated for $C_{14}H_{30}O$, C 78.43, H 14.11; found C 78.61, 78.78; H 14.07, 13.90. This carbinol has not been reported previously.

L. ISOPROPYL CHLORIDE AND DIISOPROPYL KETONE

Triisopropyl carbinol was prepared from isopropyl chloride and diisopropyl ketone by the procedure described in example (B). The reaction of 19.6 g. isopropyl chloride (refractionated b.p. 35.1°/736 mm.) and 28.6 diisopropyl ketone (¼ g. mole each) with 0.55 g. atom sodium was carried out at 25°-34°. The chloride ion titration indicated that the isopropyl chloride reacted completely. The cold-trap retained 0.2 g. very low boiling liquid during the reaction. It gave only a very weak test for unsaturation with bromine in carbon tetrachloride. It was therefore principally propane from metallation with a little propene from dehydrohalogenation. Any propane remaining in solution in theoil layer was lost during the washing and drying operations. The yield of metallation product was therefore not established in this reaction. Distillation of the oil layer through column A gave 2.61 g. crude triisopropyl carbinol (6½ per cent yield). This was fractionated through column B into the following portions:

(1) 0.14 g., b.p. 94°-95°/30.5 mm., n_D^{20} 1.4445

(2) 0.38 g., b.p. 94°-95°/30.5 mm., n_D^{20} 1.4465

(3) 0.79 g., b.p. 94°-95°/30.5 mm., n_D^{20} 1.4479

(4) 0.40 g., b.p. 95°-97°/30.5 mm., n_D^{20} 1.4487

The properties previously reported for this carbinol are b.p. 84°-85°/30 mm., n_D^{20} 1.4478 (2) and n_D^{20} 1.4476-80 (37). The discrepancy in boiling point is probably due to the tendency of column B noted previously to give a boiling point elevation, superheating, even with the monel spiral packing thoroughly wetted. The 6½ per cent yield of crude triisopropyl carbinol obtained here, employing optimum reaction conditions, is essentially the same as the 7 per cent crude yield obtained by Bartlett and Schneider who carried out the reaction at reflux in isooctane employing sodium sand. This clearly demonstrates that the modified procedure for the carbinol preparation and the use of dispersed sodium will not provide any large general improvement in the yields reported in earlier work on this reaction when applied to the synthesis of highly branched carbinols.

M. ISOPROPYL CHLORIDE AND ETHYL ACETATE

The readtion of isopropyl chloride and ethyl acetate was carried out following the procedure described in example A at 30°-34°. The chloride ion titration indicated that 87 per cent of the isopropyl chloride reacted. No diisopropylmethyl carbinol was obtained.

N. ISOPROPYL CHLORIDE AND ACETONE

Isopropyl chloride and acetone were reacted by the prodedure described in example (B) at 30°-34°. The chloride ion titration indicated that 99 per cent of the isopropyl chloride reacted. No dimethylisopropyl carbinol was obtained.

O. t-BUTYL CHLORIDE AND ETHYL ACETATE

The reaction of tert-butyl chloride and ethyl acetate was carried out following the procedure of example (A). Cyclohexane was substituted for isooctane as reaction solvent to facilitate isolation of any tert-butylmethyl ketone formed. The reaction was run at reflux (82°) because it was found to be quite sluggish in an earlier run which gave only 4 per cent reaction of the tert-butyl chloride at 38°-45°. The chloride ion titration showed that 65.6 per cent of the tert-butyl chloride reacted in this case. The cold trap caught 16.0 g. of a liquid boiling at -10°to 0°C which gave a very strong positive test for unsaturation with bromine in carbon tetrachloride. This corresponds to 87 per cent yield of isobutylene from dehydrohalogenation plus isobutane from metallation based on the chloride reacted. No tert-butylmethyl ketone or di-tert-butylmethyl carbinol was obtained.

P. BENZYL CHLORIDE AND PARAFORMALDEHYDE

A solution of 63.3 g. benzyl chloride (½ g. mole) in 200 ml. toluene was added dropwise to 200 ml. toluene containing 33.0 g. paraformaldehyde (1.1 g. mole) and 63.6 g. 40 per cent dispersion of sodium in Nujol (1.1 g. atom sodium) at 25°-30°. No reaction of the benzyl chloride was obtained. The procedure was repeated with external heating to initiate reaction. The only product obtained was dibenzyl.

IV Summary

(A) An effective procedure has been developed for the preparation of carbinols by the simultaneous addition of an organic chloride and a carbonyl compound in dilute solution to a dilute dispersion of metallic sodium. The preparation is most effective when carried out in a solvent of minimum dielectric constant, such as isooctane, at the minimum temperature which will sustain the reaction.

(B) The alternative two-step procedure comprising addition of a dilute solution of the carbonyl compound to a dilute solution of the preformed organo-sodium intermediate was demonstrated to result in a reduced yield of carbinol. The loss in yield is not so great, however, as to preclude the use of this procedure in conjunction with a metallation reaction when that permits formation of a difficultly accessible organo-metallic intermediate from a readily available chloride.

(C) Synthesis of carbinols by the sodium promoted condensation of organic chlorides and carbonyl compounds was shown to be limited principally by metallation of active α-hydrogen atoms of the carbonyl reactant by the organo-sodium intermediate. The effectiveness of carbonyl compounds in this reaction increases with decreasing α-hydrogen activity. The effectiveness of chlorides increases with decreasing base strength of the organo-sodium intermediates which they produce.

(D) The relative utility of the sodium reaction and the Grignard reaction and the types of compounds with which each is most effective have been shown. The sodium reaction is most advantageous when the Grignard reaction is prevented by carbonyl reduction, when the metallation reaction with sodium eliminates the necessity of preliminary synthesis of a suitable halide, and when the two methods give comparable yields because of the simplicity of the sodium reaction. The Grignard reaction is most advantageous when metallation of the carbonyl reactant leads to a severe reduction in carbinol yield by the sodium synthesis.

(E) The procedure described under (A) for the sodium promoted synthesis of carbinols improves upon analagous sodium reactions reported previously in that simultaneous addition of the reactants is more convenient, gradual addition of the halide at a moderate temperature is safer and reaction at a moderate temperature minimizes loss in yield by Wurtz reaction with sensitive halides such as benzyl chloride. In the synthesis of highly branched carbinols this procedure does not effect the improvement in yield hoped for in comparison with reactions reported previously.

(F) Two carbinols were prepared which have not been reported previously. They are benzyldiisobutyl carbinol and _n_-amyldiisobutyl carbinol.

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TABLE I *BENZYLDIMETHYL CARBINOL SYNTHESIS*

Solvent	Reaction Temp., °C	Reactants Moles Chloride	Reactants Moles Acetone	% Chloride Reacted	Yield Benzyl-Dimethyl Carbinol	Yield Ketone (2)	Yield Toluene	Yield High Boiling Residue
$Ph-CH_2Cl + 2Na + CH_3COCH_3 \longrightarrow Ph-CH_2C(CH_3)_2ONa + NaCl$ (1)								
Butyl Ether	50°	¼	¼	100%	25%	4.4%	24%	31%
Butyl Ether (3)	50	¼	½	100	21	1.2	55	4
Butyl Ether (4)	50	¼	¼	52	35	12.0	22	33
Benzene	50	¼	½	93	39	-	42	5
Benzene	5	¼	¼	89	40	1.0	31	12
Isooctane	5	¼	¼	98	42	0.7	27	11 (5)
Isooctane	-25	¼	¼	No reaction				
$Ph-Cl + 2Na \longrightarrow PhNa \xrightarrow{PhCH_3} PhCH_2Na \xrightarrow{CH_3COCH_3} PhCH_2C(CH_3)_2ONa$								
Toluene	25°	¼	¼	94%	27%	0%	-	0% 13
Toluene (6)	-40	¼	¼	98	32	0	-	

(1) Benzyl chloride and acetone added simultaneously to 0.55 g. atom of dispersed sodium; benzyl chloride addition led acetone by 10 percent except as noted otherwise.

(2) Ketone product boiling with the benzyldimethyl carbinol, evidently benzyl acetone. Not isolated to prove identity.

(3) Benzyl chloride and acetone added together from the start.

(4) Acetone addition led benzyl chloride by 10 percent. Employed only 0.27 g. atom sodium.

(5) A small amount of crude dibenzyl was isolated from this residue. It was not isolated from the others although there were indications that it was present.

(6) The reaction mixture was carboxylated at the end of the reaction to trap any unreacted phenyl or benzyl sodium. Neither benzoic nor phenylacetic acid was obtained.

TABLE II REACTION PRODUCTS

Reactants	Carbinol Product	Yield at Crude Carbonol (1),%	Boiling Point, °C/mmHg	Refractive Index N_D^t	Other Characterization	Reference
Benzylchloride and ethyl acetate	Dibenzylmethyl carbinol	72	138-9/0.5-1.0 197-8/20	1.5665^{25} 1.5708^{18} 1.5735^{18}	d 1.0495 Theory C 84.91 H 8.02 Found C 85.16,85.41 H 8.20,7.91	- (23)
Benzyl chloride and diisopropyl ketone	Benzyldiisopropyl carbinol	65	99/1-105/2 161-4/35	1.5125^{25} 1.538-	d 1.0258 No analysis Theory C 81.50 H 10.75 Found C 81.98,81.72. H 10.67,10.64	- (24)
Benzyl chloride and diisobutyl ketone	Benzyldiisobutyl carbinol	59	103-5/1	1.4957^{25}	Theory C 81.99 H 11.18 Found C 82.28,82.41 H 11.25,11.15	-
Benzylchloride and acetone	Benzyldimethyl carbinol	42	83-5/4.5 104-5/17	1.5171^{16} 1.5174^{16}	- -	- (21)
Benzylchloride and propionaldehyde	Benzylethyl carbinol	16	68-75/1 124-7/15	1.5233^{16} 1.4301^{16}	Theory C 79.95 H 9.39 Found C 80.66,80.72 H 8.83,8.58	- (34)
Chlorobenzene and ethyl acetate	-	0 (2)	-	-	-	
Chlorobenzene and diisopropylketone	Diisopropylphenyl carbinol	38	74-76/0.5 118-119/11	1.5109^{25} 1.5140^{20} 1.5239^{20}	Theory C 81.20 H 10.48 Found C 81.18;80.96 H 10.44,10.52 80.8 10.7	- (26)
Chlorobenzene and propionaldehyde	Ethylphenyl carbinol	10	77-8.5/3,52-[illegible]/08 93/4 76/3	1.5178^{20} 1.5208^{20} 1.5210^{23}	- p-nitrobenzoate m. 55-56 p-nitrobenzoate m. 56.5	- (35) (36)
n-Amyl chloride and ethyl acetate	Diamylmethyl carbinol	23	78-83/1.5-2.0 80-3/2	1.4386^{20} 1.4392^{20}	dehydrated to olefin n_D^{20} 1.4373 dehydrated to olefin n_D^{20} 1.4368	- (28)
n-Amyl chloride and diisopropyl ketone	Amyldiisopropyl carbinol	low, carbinol was not isolated.				-
n-Amyl chloride and diisobutyl ketone	Amyldiisobutyl carbinol	12	77.5-8.5/0.[illegible]	1.4419^{25}	Theory C 78.43 H 14.11 Found C 78.61,78.78 H 14.07,13.90	-
Isopropyl chloride and diisopropyl ketone	Triisopropyl carbinol	6	94-5/30.5 84-5/30,105/50 106.6-8.0/5	1.4479^{20} 1.4478^{20} $1.4476\text{-}80^{20}$	- -	- (2) (37)
Isopropyl chloride and ethyl acetate	-	0				
Isopropyl chloride and acetone	-	0				
Tert-butyl chloride and ethyl acetate	-	0				
Benzyl chloride and paraformaldehyde	-	0 (3)				

(1) Carbinol yields based on chloride reacted.
(2) The ethyl acetate appeared to inhibit the reaction of chlorobenzene with sodium.
(3) The solid paraform aldehyde appeared to inhibit the reaction of benzyl chloride with sodium.

TABLE III

Yields of Carbinol (Addition Product) and Hydrocarbon (Metallation Product) in Sodium Promoted Condensations of Chlorides with Carbonyl Compounds

Chloride \ Carbonyl Compound →	$CH_3COOC_2H_5$	$\left(\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CH\right)_2CO$	$\left(\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CH\text{-}CH_2\right)_2CO$	$(CH_3)_2CO$	CH_3CH_2CHO
$C_6H_5CH_2Cl$	72% Carbinol 14% Toluene	65% Carbinol 20% Toluene	59% Carbinol 35% Toluene	42% Carbinol 27% Toluene	16% Carbinol 60% Toluene
C_6H_5Cl	No Carbinol (1) 74% Benzene	33% Carbinol 50% Benzene	-	-	10% Carbinol 71% Benzene
n-Amyl Cl	23% Carbinol 75% Pentane	Carbinol low 66% Pentane	12% Carbinol 63% Pentane	-	-
$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CH\text{-}Cl$ (2)	No Carbinol >12% C_3 Hydrocarbon	6% Carbinol >2% C_3Hydrocarbon	-	No Carbinol >7% C_3Hydrocarbon	-
$CH_3\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}Cl$	No Carbinol 87% C_4Hydrocarbon (3)	-	-	-	-

(1) The chlorobenzene-ethyl acetate pair gave a peculiarly sluggish reaction which failed to proceed smoothly in several attempts. Accordingly, this data is not consistent with the rest of the Table.

(2) Due to the low boiling point of propane, the "C_3hydrocarbon, " propane and possibly propene, was largely lost and accurate yields were not obtained.

(3) With tert-butyl chloride the hydrocarbon was mostly isobutylene from dehydrohalogenation and/or ketone reduction.

TABLE IV

Yields of Carbinol by Grignard Reaction of Halide-Carbonyl Pairs from the Literature (1)

Carbonyl Compound → Halide	$CH_3COOC_2H_5$	$\left(\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}\!>CH\right)_2CO$	$\left(\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}\!>CH-CH_2\right)_2CO$	$(CH_3)_2CO$	CH_3CH_2CHO
$C_6H_5CH_2X$	"ca 80% (23)	"low" (24)	-	70% (25)	-
C_6H_5X	75% (38)	57% (26)	-	61% (27)	-
n-Amyl X	75% (28)	60% with isoamyl (24)	-	63% (29)	-
$\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}\!>CH\ X$	-	0% (30,6)	0% (7)	40% (11, p. 138)	-
$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-X$	0% (32)	0% (7)	0% (7)	28% (33)	60% (33)

(1) Products for which yields are not given either have not been reported, have not been prepared by this combination of reactants or have been reported without yields.