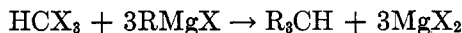


THE BODROUX-TSCHITSCHIBABIN, AND THE BOUVEAULT ALDEHYDE SYNTHESSES

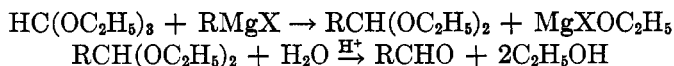
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Bodroux (2), who prepared triaryl methanes by action of Grignard reagents upon chloroform or bromoform, found that the yield was usually quite low and never better than 25%.



Hoping to improve the yields, he substituted ethylorthoformate for the haloform, but in this case no triaryl methanes resulted; only aldehydes were formed.



Tschitschibabin (3), independently and at about the same time, discovered the same reaction. He discovered that if the orthoformic ester was first added to the ethereal solution of the Grignard reagent, and then most of the solvent removed by distillation, a point was reached at which a vigorous reaction ensued. Much heat was evolved and the reaction product was a viscous oil which gave the acetal on treatment with acidified water. The acetal could be obtained pure by fractionation and from it the aldehyde could be obtained. Tschitschibabin and Jelgasin (4) discovered somewhat later that the reaction was not confined to one of the ethoxyl groups of the ester, although Bodroux (5) found that replacement of the first ethoxyl group was a slow reaction and that yields (of benzaldehyde) were improved by refluxing the mixture after addition of the orthoformic ester.

Wood and Comley (6) also found that poor yields of aldehydes were obtained unless, after adding the orthoformic ester, most of the ether was removed and the residue was heated.

Bert (7) prepared an extensive series of aldehydes using chlorides of the type $\text{Ar}(\text{CH}_2)_n\text{Cl}$, and a number of other investigators have prepared aldehydes by means of the orthoformate synthesis (8).

As the yields of aldehydes obtained by different investigators using this method have varied widely, it appeared that the reaction was greatly affected by relatively slight differences in procedure. In order to evaluate

these, a study was undertaken which had as its object the determination of the optimum conditions for preparation of a simple aromatic aldehyde, benzaldehyde, and the application of these conditions to the preparation of a few other aromatic aldehydes. In general, the Grignard reagents (0.2 moles) were prepared in ether in the usual way. After formation of the reagent, enough ether was added to bring the total amount up to 4.5 moles per mole of halogen compound. The orthoformic ester was then mixed with an equal volume of ether and slowly added to the Grignard solution, after which the mixture was processed. Four variants in the conditions were examined: 1. the length of time the reagents were allowed to stand after mixing; 2. the duration of the period of refluxing, after the ether was removed; 3. the relative amount of orthoformic ester used; 4. the effect of the nature of the solvent. In addition, the isolation and purification of the aldehyde itself was investigated.

Three experiments were made in which the time of standing was varied. After three hours, 10.7 g. (21.5%) of benzaldehyde bisulfite compound was obtained; after six and one-half hours, 37 g. (81%), and after fifteen hours, 40.2 g. (89.2%). Using a fifteen-hour period of standing, the ether was then boiled off and the residue was heated on the steam-bath. After fifteen minutes of heating, the yield of bisulfite compound was 40.2 g. (89.2%) and after sixty minutes the yield was 34.5 g. (75.6%). These results showed that heating after removal of the ether offered no advantages and might even be disadvantageous if the time of heating were prolonged.

Using a fifteen hour period of standing, then removing the ether and heating the residue for fifteen minutes, the effect of varying the amount of orthoformic ester was determined. The results showed that there was a slight increase in the yield (89.2% to 95.0%) of benzaldehyde when a 100% excess of the halogen compound was used. However, this advantage is more than offset when the halogen compound is a costly one.

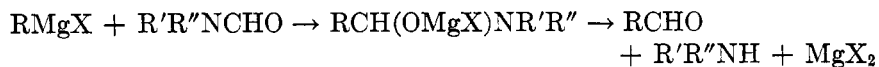
In determining the effect of the solvent, the Grignard reagent (0.2 moles) was prepared in the usual way, then dry toluene (50 cc.) was added. The ether was distilled off and when the temperature reached 90°, orthoformic ester (0.2 moles) was added. The reaction-mixture was decomposed by boiling for fifteen minutes with 5 *N* sulfuric acid and the aldehyde was then isolated. The results showed that this procedure is not advantageous, but rather the reverse. Thus, when the reaction product was decomposed immediately after mixing the reagents, the yield of aldehyde bisulfite compound was 29.6%; when the mixture was heated for fifteen hours, the yield was 65.8%.

Blank experiments showed that the yield of bisulfite compound from benzaldehyde was from 85-90%. Decomposition of the bisulfite com-

pound with dilute sulfuric acid, followed by steam distillation, ether extraction of the distillate and fractionation of the aldehyde gave yields of aldehyde of about 80%. When the bisulfite compound was decomposed by dilute sodium hydroxide, the yield of aldehyde was only 55–60%.

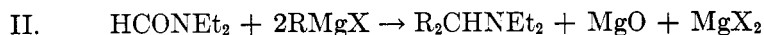
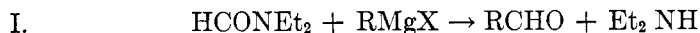
It thus appeared that the maximum yield of benzaldehyde, weighed as the bisulfite compound, was around 90% and that this high yield could be obtained by observing the following conditions: 1. The reaction-mixture should be allowed to stand for fifteen hours after mixing the reagents; 2. The ether should be removed and the residue heated for not longer than fifteen minutes on the steam-bath; 3. Equimolecular quantities of the Grignard reagent and orthoformic ester should be used. Using these conditions, *o*-, *m*- and *p*-bromotoluenes were converted to the toluic aldehydes *via* the Grignard reagents in yields of 51.7, 56.2, and 50.4% respectively.

Bouveault, in 1903, prepared a series of aldehydes by means of the reaction between Grignard reagents and disubstituted formamides (9):



The unsubstituted formamide cannot be used, and Bouveault used dimethyl-, diethyl-, and piperidyl- formamides as well as methyl- and ethyl-formanilides. Bouveault did not give exact yields of his products, but stated that the yields were "generally good, although poor in some instances." Houben and Doescher (10) have also used this synthesis.

The Bouveault synthesis is complicated by the fact that bases, as well as hydrocarbons are also formed, a fact noted by Bouveault himself (11), by Viguier (12), and by Maxim and Mavrodineanu (13). Maxim (14) found that diethylformamide could react with Grignard reagents in two ways:



Ethylmagnesium bromide and ethylmagnesium iodide reacted entirely according to reaction II, while isobutylmagnesium bromide reacted about equally according to both equations. Using three moles of RMgX per mole of amide, Maxim obtained good yields of tertiary amines in all the cases he investigated. Using equimolecular amounts of amide and Grignard reagent, the aldehyde was the chief product when methyl- or ethyl- formanilide or diphenylformamide were employed, the latter giving only the aldehyde. But when diethylformamide or piperidylformamide were used, more amine than aldehyde was formed. The amount of

aldehyde increased as the molecular weight of R in RMgX increased, but in all cases large amounts of the amide were recovered. Phenylmagnesium bromide behaved in a rather specific manner, giving considerable amounts of tetraphenylethylene when its reaction product with piperidylformamide, dimethylformamide, or diethylformamide was decomposed by dilute sulfuric acid, while decomposition by ammonium chloride gave the tertiary amine $(\text{C}_6\text{H}_5)_2\text{CHNR}_2$. Methylformanilide and diphenylformamide re-

TABLE I
REACTION BETWEEN PHENYLMAGNESIUM BROMIDE AND METHYLFORMANILIDE

HALIDE, MOLES	METHYLFORMANILIDE, MOLES	BISULFITE COMPOUND, G.	YIELD, %
0.2	0.2	27.0	59
0.2	0.2	5	11 ^a
0.2	0.37	30.5	67 ^b
0.2	0.37	30.5	67 ^c

^a Ether boiled off, 50 cc. toluene added and reaction conducted at 90°.

^b Excess formanilide added to the Grignard solution in ether.

^c Grignard solution slowly added to the formanilide in ether.

TABLE II
YIELDS OF ALDEHYDES FROM GRIGNARD REAGENTS AND METHYLFORMANILIDE

HALOGEN COMPOUND, MOLES	PRODUCT, G.	YIELD, %	YIELD OF GRIGNARD REAGENT, %	YIELD OF PRODUCT BASED UPON RMgX , %.
<i>o</i> -Bromotoluene..... 0.2	11 ^a	50	—	—
<i>m</i> -Bromotoluene..... 0.2	8 ^b	33	—	—
<i>p</i> -Bromotoluene..... 0.2	9 ^c	37	—	—
Bromohydroquinone dimethyl ether. 0.1	5 ^d	22	52	43
Bromohydroquinone dimethyl ether. 0.1	3.9 ^d	17	52	33
Bromomesitylene..... 0.144	6.0 ^e	18.8	—	—

^a Aldehyde; 100% excess methylformanilide used.

^b Aldehyde; 25% excess methylformanilide used.

^c Aldehyde.

^d Aldehyde semicarbazone; 38% of hydroquinone dimethyl ether obtained.

^e Aldehyde semicarbazone; 40% of mesitylene obtained.

acted with phenylmagnesium bromide to give benzaldehyde and benzhydrol exclusively.

Although the Bouveault reaction appeared to be a very complex reaction leading to a variety of products, the reaction between methylformanilide and several Grignard reagents was investigated to determine the best conditions for the formation of aldehydes. In the initial experiments, phenylmagnesium bromide was used. The reaction was conducted in

ether alone, in toluene after boiling off the ether, and by adding excess formanilide to the Grignard reagent in ether as well as by the inverse procedure. The results are given in Table I.

It thus appeared that the reaction produced chiefly benzaldehyde, although the yields were inferior to those obtained when ethylorthoformate was used. The reaction was then applied to several aromatic Grignard reagents, adding the methylformanilide to the Grignard solution in ether. Equimolecular quantities of reagents were used except as noted. The results are given in Table II.

Thus of the two syntheses, one using ethylorthoformate, and the other using methylformanilide, the former is superior for the preparation of aldehydes from aromatic halogen compounds.

EXPERIMENTAL PART

The apparatus consisted of a 1-liter 3-necked flask, fitted with a dropping-funnel, mechanical stirrer, and condenser. All openings to the air were protected by calcium chloride guard tubes. Magnesium turnings, which had been washed with ether and dried in a desiccator, were placed in the flask, the apparatus was assembled and heated on the steam-bath while a current of dry air was passed through. After the flask had cooled, ether (10 cc.) and a crystal of iodine were introduced. The halogen compound was mixed with an equal volume of ether and about 10 cc. of this solution was dropped onto the magnesium. After the reaction started, enough ether was added to the solution of the halogen compound to bring the total up to 4.5 moles per mole of halogen compound. This solution was then added, with vigorous stirring, at the rate of about two drops per second. After the addition was complete, the mixture was refluxed and stirred for fifteen minutes longer. Then, with stirring, the orthoformic ester, dissolved in an equal volume of ether, was added at the rate of about two drops per second. No apparent reaction occurred. After the addition of the reagent was complete, the reaction-mixture was processed as described under the several headings above. The reaction-mixture was decomposed by addition of ice and 5*N* sulfuric acid and refluxed for a few minutes to decompose the acetal. If the ether had been distilled off, the cooled mixture was extracted with ether three times (50 cc. each time); otherwise, the ether layer was merely separated. The combined ethereal solutions (volume about 150 cc.) were shaken vigorously with saturated sodium bisulfite solution (50 cc.) and filtered. The filtrate was shaken with fresh bisulfite solution and again filtered. The combined solids were washed with cold alcohol (50 cc.), then with ether (50 cc.), and spread in the air to dry. After fifteen minutes, the material was weighed.

In the experiments using methylformanilide, the Grignard reagent was formed as above and then made up to a volume of 300 cc. with ether. The methylformanilide was slowly added with stirring. A heavy white precipitate formed at once; this gradually darkened. After standing overnight, the reaction-mixture was decomposed with 5 *N* sulfuric acid and the aldehyde was removed by ether extraction. The aldehyde in the ether was converted into the bisulfite compound as described above, or the ether was evaporated and the residue treated with semicarbazide in the usual way.

Methylaniline formed in the reaction was recovered by making the aqueous solutions alkaline and extracting with ether.

SUMMARY

1. This paper reports the effect of changing various conditions in the Bodroux-Tschitschibabin synthesis of aldehydes. The optimum conditions for conversion of bromobenzene to benzaldehyde *via* the Grignard reagent have been investigated.

2. A similar investigation of the Bouveault aldehyde synthesis has been made.

3. The synthesis of aldehydes from Grignard reagents using ethylorthoformate is superior to that using methylformanilide.

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