

application of the method of Fieser and Newman. An alternate method was found impractical because of the difficulty of reducing 2-(α -naphthoyl)-1-naphthoic acid. The hydro-

carbon is being tested for carcinogenic activity.

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Studies on Lignin and Related Compounds. XXXVIII. The Effect of Solvents in the Grignard Analysis for Active Hydrogen and Carbonyl

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It was the purpose of this investigation to ascertain the effect of using solvents such as dioxane and pyridine in the analysis for active hydrogen and carbonyl³ using Grignard reagent. This became necessary because of the present extended application of the Grignard machine to the study of lignins, which are, for the most part, not sufficiently soluble in other solvents to ensure complete reaction.

Even with these, the reactions of compounds containing a variety of reactive groups are often incomplete. The results show that pyridine is much more satisfactory than dioxane. Thus, cellulose acetate in dioxane reacts with less than half the amount of Grignard reagent required by theory, and pentaacetylglucose with less than one-third, although in pyridine the latter consumes two-thirds of the theoretical amount. While it is not surprising that low carbonyl values should be obtained with these polyacetyl compounds, the discrepancies may not be owing entirely to incomplete reaction. This reservation is suggested by the anomalous behavior of catechol diacetate. While the latter reacts normally and completely in xylene, active hydrogen and a lower carbonyl value are found when pyridine is used. This same effect is found accentuated in dioxane. The source of this active hydrogen is being investigated. Regardless of this abnormal behavior it is certain that a compound such as glucose does not react completely with methyl iodide Grignard reagent in dioxane although a close approximation (4.6 active hydrogen per mole) to the theoretical value is obtained in pyridine and in quinoline (4.2 active hydrogen per mole).

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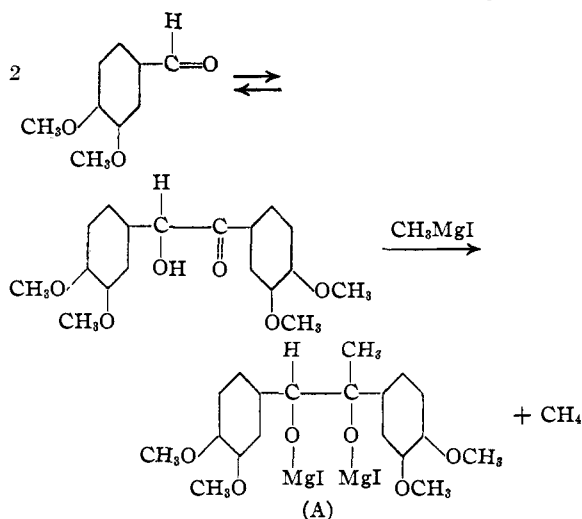
(3) Kohler, Fuson and Stone, *THIS JOURNAL*, **49**, 3181 (1927); Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930).

The carbonyl group in carboxylic acids is also not indicated quantitatively by the Grignard reagent in dioxane. Benzoic acid consumes only half of the theoretical amount required for formation of the ketone, and cinnamic acid none at all. In pyridine, on the other hand, benzoic acid reacts normally (1 active hydrogen, one addition) while cinnamic acid consumes 0.8 mole of RMgX. In xylene, however, the reaction seems to go beyond the ketone stage (1.23 moles per mole).

From these results it can be said that dioxane is an unsatisfactory solvent for the Grignard analysis except in cases where reasonably predictable incompleteness of reaction can, by comparison with complete reaction, be employed to give an insight into structure. It has been used in this way with lignins to differentiate reactive carbonyl groups from the inert carboxylic acids.

Grignard analyses of vanillin types at first seemed to indicate that reaction was incomplete in dioxane and in isoamyl ether only because of precipitation of the magnesium phenoxide. Similar results were obtained with isovanillin, although analysis of each of these compounds in pyridine indicated one active hydrogen and one carbonyl. The isovanillin likewise reacted normally in xylene. In confirmation of the incomplete reaction in dioxane, 63% of the vanillin was recovered from the reaction product in this solvent. In agreement with these results, the hydroxyl group of 3-methoxy-4-hydroxyacetophenone reacted completely with the methyl iodide Grignard reagent in dioxane, but the ketone group did not react at all. In xylene both active hydrogen and carbonyl reacted, while the value for active hydrogen found in pyridine was augmented as a result of a slight amount of enolization. When veratraldehyde was used to substantiate these results it was found that it reacted normally (one carbonyl) in xylene

while in pyridine and dioxane a decrease in carbonyl was *compensated by presence of active hydrogen*. The gas representing this active hydrogen was proved to be methane. It is improbable that this gas could arise from fission of a methoxyl linkage, since veratrole, pyrogallol trimethyl ether, and isoeugenol methyl ether are unaffected by similar treatment. Although the product (A) indicated in the following hypothesis has not yet been isolated, it is reasonable to assume that the veratraldehyde undergoes a benzoin condensation, the resulting product from which then reacts with the Grignard reagent.



Condensation reactions accompanying Grignard reactions have been observed before.⁴

The effect of substituent groups upon degree of enolization has been studied by means of the Grignard reagent,^{5,6} and has been termed "the enolizing action of methylmagnesium iodide."

In the present investigation, effect of solvent has been shown to change the course of reaction. Thus, acetophenone, which exhibits no enol form in xylene⁵ and about 12% enol in isoamyl ether,³ was found to be 78% enolized in either pyridine or dioxane. With diphenylacetophenone, the results of Kohler⁶ were confirmed in isoamyl ether, and in pyridine this likewise acts as if it were chiefly in the keto form. In dioxane 48% of active hydrogen expected from Biltz⁷ triphenylvinyl alcohol is obtained. The unexpected variability of the data thus far presented shows the behavior of these solvents does not alone affect

(4) Conant and Blatt, *THIS JOURNAL*, **51**, 1227 (1929); Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

(5) Smith and Guss, *ibid.*, **59**, 804 (1937).

(6) Kohler, *Am. Chem. J.*, **36**, 177 (1906).

(7) Biltz, *Ann.*, **296**, 242 (1897); *Ber.*, **32**, 650 (1899).

the Grignard reagent but rather the compounds analyzed. Abundant evidence has been provided⁸ that a compound can be defined correctly only in relation to its environment. Specifically it has been shown⁹ that pyridine has an enolizing effect on the substances analyzed by the Zerewitinoff method. It would seem preferable, therefore, to consider the degree of enolization not only as a result of relative speeds of competing reactions (addition and reaction with active hydrogen), but also as related to the compound itself because of electronic equilibria within it, which can be redistributed according to the solvent-environment. For this reason it is considered that the term "enolizing effect of methylmagnesium iodide" is misleading, implying as it does that methylmagnesium iodide alone induces enolization.

Similar abnormalities were observed when certain benzoin types were examined. In both dioxane and pyridine the ketone linkage in benzoin methyl ether reacted completely, showing that this group was not unreactive in these solvents. When benzoin itself (which gives quantitative results in isoamyl ether and is commonly used as a standard in the Grignard analysis) was analyzed, in dioxane 35%, in pyridine 25%, was shown to be in the ene-diol form. This was confirmed by a 23% recovery (as the 2,4-dinitrophenylhydrazine) of benzoin from the reaction in dioxane. The benzoin esters are even more completely enolized in these solvents. Thus benzoin formate is 86% and benzoin acetate 42% enolized in dioxane; the latter however is 58% enolized in pyridine, but neither shows an appreciable enolization in xylene. It should be noted that the formate radical in both benzoin formate and phenylethyl formate reacts incompletely with methyl iodide Grignard reagent in dioxane, although reaction with the latter ester is quite as normal in pyridine as in xylene.

Experimental

The Grignard machine was altered only by inclining the reaction flask at an angle of 15° from the vertical so that solution of the reaction mixture could be effected by turning the flask on the ground joint during the analysis. A condenser at the gas outlet is advantageous with volatile solvents such as dioxane and pyridine, although a strong air blast at this position is nearly as effective in retaining solvent. The solvent dioxane was purified by distillation

(8) Ingold, *J. Chem. Soc.*, 1120 (1933); *Chem. Rev.*, **15**, 225 (1934).

(9) Ishikawa and Kojima, *Sci. Rep. Tokyo Bunrika Daigaku*, Sect. A, **1**, 289 (1930-1934); *Chem. Zentr.*, **105**, I, 2411 (1934); Clutterbuck, Raistrick and Reuter, *Biochem. J.*, **29**, 300 (1935).

TABLE I

| Substance | GRIGNARD ANALYSES | | | | | | | |
|--|-------------------|------------------------|-----------------|------------------------|-----------------|------------------------|-----------------|------------------------|
| | In isoamyl ether | | In xylene | | In dioxane | | In pyridine | |
| | Act. H /mole | RMgX added /mole | Act. H /mole | RMgX added /mole | Act. H /mole | RMgX added /mole | Act. H /mole | RMgX added /mole |
| Cellulose acetate (2.6 acetyl groups) | | | | | 1.62 | 2.50 | | |
| Glucose pentaacetate | | | | | 1.9 | 3.0 | 1.6 | 6.0 |
| Catechol diacetate | | | 0.06 | 3.77 | 0.73 | 1.47 | 0.24 | 3.49 |
| Glucose | | | | | 1.1 | 0.1 | 4.58 | 0.36 |
| Benzoic acid | | | | | 1.06 | .5 | 1.18 | 1.11 |
| Cinnamic acid | | | 1.08 | 1.23 | 0.98 | .03 | 1.15 | 0.78 |
| Vanillin | 0.65 | 0.33 | | | .99 | .21 | 0.99 | .96 |
| Isovanillin | | | 0.89 | 0.56 | .92 | .19 | 1.02 | .87 |
| Veratraldehyde | .05 | .18 | .03 | .93 | .44 | .60 | 0.36 | .66 |
| Veratrole | .01 | .00 | | | | | .00 | .00 |
| Pyrogallol trimethyl ether | | | .03 | .00 | .03 | .00 | .03 | .00 |
| Isoeugenol methyl ether | | | | | .06 | .0 | .04 | .00 |
| Acetophenone | .12 | .85 | .03 | .96 | .78 | .14 | .78 | .22 |
| ω -Diphenylacetophenone | .02 | 1.08 | | | .48 | .60 | .11 | .96 |
| 3-Methoxy-4-hydroxyacetophenone | | | .97 | .78 | .91 | .05 | 1.25 | .73 |
| Benzoin methyl ether | | | | | .13 | .95 | 0.07 | .97 |
| Benzoin | 1.04 | 0.95 | | | 1.35 | .58 | 1.25 | .75 |
| Benzoin formate | | | .05 | 2.98 | 0.86 | 1.55 | | |
| Benzoin acetate | | | .10 | 2.99 | .42 | 1.27 | 0.58 | 2.17 |
| β -Phenylethyl formate | | | .04 | 1.89 | .51 | 0.91 | .08 | 1.83 |
| Methyl 2,3,4,6-tetramethyl β -glucopyranoside | | | | | .09 | .0 | .18 | 0.0 |
| Methyl 2,3,4,6-tetramethyl α -glucopyranoside | | | .24 | 0.09 | .35 | .07 | .33 | .11 |
| 4-Hydroxymethyl-1,3 dioxolane | | | | | 1.06 | .01 | 1.09 | .03 |

from sodium-benzophenone, the xylene from sodium and the pyridine by drying over barium oxide for several weeks. The correction factors for these three solvents were 1.4–2.0, 0.0–0.2, 1.5–2.0 cc. of gas, respectively. These blanks, determined for five-minute heating periods were unchanged by twenty minutes of heating in dioxane and xylene, but the blank for pyridine increased to 2.5–3.0.

All of the substances used in this investigation were prepared or purified according to conventional methods. In experiments recorded as being carried out in isoamyl ether the substances were actually treated in the dry state with the isoamyl ether solution of Grignard reagent.

Preparation of Benzoin Formate.—A solution of 2.36 g. (0.01 mole) of benzoin in 40 cc. of 95% formic acid was boiled under reflux for sixteen hours, after which the solvent was distilled off at 20 mm. pressure. The residue was dissolved in 5 cc. of hot formic acid; upon cooling the solution was filtered from 0.72 g. of unchanged benzoin. The filtrate was evaporated again to dryness at 20 mm. pressure and the residue washed with ether leaving more unchanged benzoin behind. The evaporated ether solution (residue m. p. 67–68°) was twice crystallized from petroleum ether (b. p. 60–70°); m. p. 73–74°.

Anal. Calcd. for $C_{15}H_{12}O_3$; C, 74.9; H, 5.04; OCOH, 18.8. Found: C, 74.6; H, 5.22; OCOH, 19.0.

Recovery of Benzoin.—After analysis of 0.119 g. of benzoin in the Grignard machine using solvent dioxane, the solution was processed in the usual manner to give an

ether solution from which 0.051 g. of benzoin 2,4-dinitrophenylhydrazone was obtained after two crystallizations from ethyl acetate,¹⁰ m. p. 231–232°. This 23% yield is lower than the value of 35% required by the Grignard analysis, but the yield of hydrazone prepared from pure benzoin is 87% of theoretical, mixed melting point unchanged.

Recovery of Vanillin.—The reaction mixture resulting from analysis of 0.103 g. of vanillin in dioxane was acidified with acetic acid, and recovered as the *m*-nitrobenzoylhydrazone, m. p. 207–210°,¹¹ wt. 0.103 g. or 63%.

Analysis of Gas Obtained from Veratraldehyde.—Combustion of 11.2 cc. of the evolved gas yielded 10.4 cc. of carbon dioxide, demonstrating that this gas was methane.

Summary

1. It has been demonstrated that pyridine as a solvent for quantitative determination of active hydrogen and carbonyl in the Grignard analysis gives more uniform results than dioxane.

2. Comparison of the analytical data shows that the solvent apparently affects the behavior of the substance analyzed.

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(10) Allen, *THIS JOURNAL*, **52**, 2055 (1930).

(11) Tomlinson and Hibbert, *ibid.*, **58**, 345 (1936).