[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Behavior of 3,6-Dimethylphthalic Anhydride in Friedel–Crafts and Grignard Condensations

BY MELVIN S. NEWMAN AND BRADLEY T. LORD[1]

While preparing certain compounds required in another investigation[2] we obtained some results which were not at all what we expected. Because of their bearing on the mechanisms of the Grignard and Friedel–Crafts reactions, we are reporting these results separately.

The Grignard Reaction.—Many believe that the first step in the reaction of Grignard reagents with esters or acid halides consists in addition to the carbonyl group.[3] An alternate mechanism supposes a metathetical reaction involving the carbon–oxygen single bond in esters and the carbon–halogen bond in acid halides.[4]

As an outgrowth of many studies of the reactions of Grignard reagents with substituted phthalic anhydride types, we have become interested in this same choice of mechanisms as applied to anhydrides. In previous work it was found that when Grignard reagents reacted with unsymmetrical phthalic anhydride types, substituents ortho to one of the carboxyl functions cut down reaction at this group.[5] A more careful study of the reaction of phenylmagnesium bromide on 3-methylphthalic anhydride[6] showed that the ratio of products of reaction at the carboxyl in the unhindered position (position 1) to products of reaction at the hindered carboxyl (position 2) was about 3. This ratio is lower than one would expect on the assumption that condensation takes place exclusively by addition to the carbonyl groups.

Because of the hindrance to both carbonyl groups in 3,6-dimethylphthalic anhydride it was expected that reaction with the Grignard reagent would take place with difficulty if at all. However, this anhydride reacted smoothly with phenylmagnesium bromide to give the expected 3,6-dimethyl-2-benzoylbenzoic acid in 81% yield. Successful condensations also took place with 2,4-dimethyl- and 2,4,6-trimethylphenylmagnesium bromides (see Table I). These condensations provide evidence that Grignard reagents may react with anhydrides by a metathetical mechanism involving the carbon–oxygen single bond. The successful competition of the metathetical reaction with the addition reaction is probably responsible for the above-mentioned low ratio in the case of 3-methylphthalic anhydride and similar anhydrides.

The Friedel–Crafts Reaction.—Little or nothing is known about the effect of steric hindrance on the ease of reaction of acylating agents in the Friedel–Crafts reaction. Several 3-substituted phthalic anhydrides have been condensed with aromatic derivatives but in most cases the separation and identification of the isomeric keto-acids were not carried out carefully enough for valid conclusions to be drawn.[7] Frequently a preference for condensation at the 2-position was noted.

In previous work with benzene and 3-methylphthalic anhydride, we determined that condensation at the 1- and 2-positions took place to almost the same extent.[6] Consequently we expected that 3,6-dimethylphthalic anhydride would condense readily with benzene. However, after refluxing for five hours, 78% of the anhydride was recovered with the production of only 12% of keto acid. Heating in *sym*-tetrachloroethane solution at 100° for eight hours was required for complete disappearance of anhydride yet only 57% of keto-acid was obtained. No obvious explanation of the contrasting behaviors of 3-methyl- and 3,6-dimethylphthalic anhydrides is apparent. However, with the more reactive *m*-xylene 3,6-dimethylphthalic anhydride condensed readily. The condensations of 3,6-dimethylphthalic anhydride with benzene, *m*-xylene, and mesitylene are summarized in Table I.

The keto-acids resulting from condensations with benzene and *m*-xylene were reasonably pure as first isolated. The acid fractions from reaction with mesitylene, however, had wide melting ranges. Although this suggested that rearrangement of the methyl groups might have taken place, the mesitylene recovered was pure. In order to establish the structure of 3,6-dimethyl-2-(2,4,6-trimethylbenzoyl)-benzoic acid, it was decarboxylated to 2,4,6,2′,5′-pentamethylbenzophenone. This new ketone, synthesized by condensing 2,5-dimethylbenzoyl chloride with mesitylene, proved identical with the decarboxylation product.

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(1) Part of the material in this paper is contained in the Ph.D. thesis of B. T. L., The Ohio State University, August, 1943.

(2) Newman and Lord, THIS JOURNAL, **66**, 731 (1944).

(3) Part of the evidence supporting this view is well summarized in Gilman, "Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 501 ff.

(4) Evidence for the metathetical mechanism is provided by the reaction of hindered acid chlorides with Grignard reagents; see Fuson, *et al.*, THIS JOURNAL, **59**, 1508 (1937); **60**, 2063, 2269 (1938).

(5) For examples see Newman, *et al.*, *ibid.*, **58**, 2376 (1936); **59**, 1003 (1937); **60**, 586, 1368 (1938); **61**, 244 (1939); and **63**, 2109 (1941).

(6) Newman and McCleary, *ibid.*, **63**, 1542 (1941).

(7) Lawrance, *ibid.*, **42**, 1874 (1920); Stephens, *ibid.*, **43**, 1950 (1921); Knesebeck and Ullmann, *Ber.*, **55**, 306 (1922); Simonsen and Rau, *J. Chem. Soc.*, **119**, 1339 (1921); Bistrzycki and de Schepper, *Ber.*, **31**, 2790 (1898); Graebe and Leonhardt, *Ann.*, 290, 217 (1896); Eder and Widmer, *Helv. Chim. Acta*, **6**, 419 (1923); Mitter, *et al.*, *J. Ind. Chem. Soc.*, **7**, 619 (1930); **8**, 685 (1931); Graves and Adams, THIS JOURNAL, **45**, 2439 (1923); Waldmann, *J. prakt. Chem.*, [2] **127**, 195 (1930); **131**, 71 (1931); Mayer and Stark, *Ber.*, **64**, 2003 (1931); and Hayashi, *et al.*, *Bull. Chem. Soc., Japan*, **11**, 184 (1936).

TABLE I

REACTIONS OF 3,6-DIMETHYLPHTHALIC ANHYDRIDE

Reactants	Conditions	% rec. anhyd.	Acid yield, %	M. p. (uncor.), °C.
C_6H_5MgBr	Reflux 1 hr. in C_6H_6	..	81	180–182
m-$CH_3)_2C_6H_3MgBr$	Reflux 1 hr. in C_6H_6	31	56	162–165
2,4,6-$CH_3)_3C_6H_2MgBr$	Reflux 2 hr. in ether	33	27	174–175
2,4,6-$CH_3)_3C_6H_2MgBr$	Reflux 1 hr. in C_6H_6	22	44	174–176
Benzene–$AlCl_3$	Reflux 5 hr. in C_6H_6	78	5	182–183
Benzene–$AlCl_3$	Stir 2 days, reflux 5 hr. in C_6H_6	63	28	179–182
Benzene–$AlCl_3$	Stir 2 days, reflux 11 hr. in C_6H_6	43	34	178–183
Benzene–$AlCl_3$	8 hr. at 100° in *sym*-$C_2H_2Cl_4$	..	57	180–183
m-Xylene–$AlCl_3$	Reflux 3.5 hours in C_6H_6	8	72	150–155
m-Xylene–$AlCl_3$	Reflux 12 hours in C_6H_6	..	80	146–156
m-Xylene–$AlCl_3$	Heated to 48° in *m*-xylene during 11 hr.	..	96	161–165
Mesitylene–$AlCl_3$	Heated to 60° during 15 hr. in mesitylene	34	34	125–150
	Heated to 68° during 11 hours in mesitylene	24	23	143–157

The 3,6-dimethylphthalic anhydride used was prepared by the dehydration in 90% sulfuric acid of the adduct of dimethylfuran and maleic anhydride.[8]

Experimental[9]

3,6-Dimethylphthalic Anhydride.—To a well-stirred suspension of 49 g. (0.5 mole) of freshly distilled maleic anhydride in 50 cc. of dry ether was added slowly 48 g. (0.5 mole) of 2,5-dimethylfuran.[10] After stirring for four and one-half hours at room temperature, during which the maleic anhydride dissolved and crystals of adduct began to separate, the mixture was cooled in an ice–salt-bath for one hour. The liquid was drawn off through a filter stick using cheesecloth and the air-dried pinkish crystals, m. p. 59–63°, weighed 82.7 g. (85%).[8] The neutral equivalent of this crude product was 96.6 (calcd. 97.1). Dehydration was best accomplished by slowly adding 81.6 g. (0.42 mole) of the above powdered adduct to 800 cc. of 90% sulfuric acid at −6 to 0°. The solution was agitated for one-half hour at 0° and the temperature then allowed to rise to 10°. After pouring on 2 kg. of ice the light brown precipitate was collected, washed with ice water, and dissolved in 600 cc. of water containing 30 g. of sodium hydroxide. Upon addition of 50 cc. of glacial acetic acid 5.3 g., m. p. 132–134°, of crude 2,5-dimethylbenzoic acid was obtained. From the filtrate 38.4 g. (52%) of crude 3,6-dimethylphthalic anhydride, m.p. 139–142°, was obtained by strongly acidifying with hydrochloric acid. On crystallization from benzene 21.8 g. (29%) of pure anhydride, m. p. 142–143°, and 12.0 g. (16%) of anhydride, m. p. 140–142°, were obtained. Some reagents found unsuitable for dehydration included dry hydrogen chloride and phosphorus pentoxide in benzene, sodium sulfate, acetyl chloride, and acetic anhydride. Although it is reported that[11] the addition of hydrochloric acid to a solution of the sodium salt of 3,6-dimethylphthalic acid precipitated the free acid, we were unable to confirm this fact. In our hands, such treatment precipitated white plates which melted without any evidence of dehydration at 142–143° and showed no depression when mixed with authentic anhydride, m. p. 142–143°. Samples of supposed acid, precipitated at 0° and dried over calcium chloride at room temperature or recrystallized from ether by cooling with dry-ice showed the correct neutralization equivalent (88) and carbon–hydrogen values[b] (C, 67.9, 67.8; H, 4.3, 4.5) for the anhydride.

Grignard Reactions.—One molar equivalent of the appropriate Grignard reagent in ether was added to a stirred benzene solution of the anhydride. The mixture was heated until the ether was removed and then refluxed for the indicated time (see Table I). An ether–benzene solution of the hydrolyzed reaction products was shaken with carbonate. The keto-acid was liberated with acetic acid and crystallized once from a suitable solvent. The unreacted anhydride was recovered after strong acidification with mineral acid. The original ether–benzene extract contained varying amounts of phthalide-like material not further examined.

Friedel–Crafts Reactions.—A slight excess of anhydrous aluminum chloride (Calco Standard) was added to a suspension of the anhydride in the reacting hydrocarbon, with or without added solvent. The reaction mixture was stirred for varying times before warming produced moderate or copious evolution of hydrogen chloride. Heating and stirring were then increased as dictated by gas evolution. When this slowed considerably the mixture was poured on ice and the products isolated as described under Grignard reactions.

2-Benzoyl-3,6-dimethylbenzoic Acid.—This acid was recrystallized from benzene and finally from alcohol for analysis to a constant melting point of 182.6–183.2° cor. It formed dense colorless plates.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.5; H, 5.6. Found[a]: C, 75.9, 75.6; H, 5.7, 5.7.

2-(2,4-Dimethylbenzoyl)-3,6-dimethylbenzoic Acid.—This acid, m. p. 165.2–165.8° cor., was crystallized from benzene for analysis.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found[b]: C, 76.5, 76.4; H, 6.7, 6.5.

2-(2,4,6-Trimethylbenzoyl)-3,6-dimethylbenzoic Acid.—This acid separated from benzene as transparent prisms which became opaque on drying to constant weight, evidently losing benzene of crystallization. The pure crystals melted at 174.8–175.6° cor.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8. Found[b]: C, 76.9, 76.9; H, 6.9, 6.9.

2,2′,4,5′,6-Pentamethylbenzophenone (by Decarboxylation).—A mixture of 0.78 g. of the above acid and 0.06 g. of its copper salt was heated at 192–195° for one hour. On vacuum distillation and crystallization from ether by cooling in dry-ice 0.28 g. of white needles, m. p. 74–78°, was obtained. Recrystallization from alcohol yielded the pure ketone, m. p. 77.0–78.0° cor.

By Friedel–Crafts Reaction.—To a cold solution of 8.6 g. of pure mesitylene and 6.5 g. of pure 2,5-dimethylbenzoyl chloride in 50 cc. of carbon bisulfide was added in portions 5.7 g. of aluminum chloride. Immediate gas evolution was followed by the appearance of a bright orange complex. After stirring at room temperature for twenty-five minutes

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(8) Diels and Alder, *Ber.*, **62**, 554 (1929).

(9) All melting points, except those corrected, were taken with the same thermometer which was calibrated within one degree of a standard thermometer. All benzene used in condensations was sulfur-free. Analyses marked *a* by J. E. Varner and *b* by Jean Anderson.

(10) The authors thank Professor C. E. Boord for gifts of purified dimethylfuran and *m*-xylene by the American Petroleum Institute Project at the Ohio State University.

(11) Freund and Fleischer, *Ann.*, **411**, 14 (1916).

and refluxing for one hour, the reaction mixture was poured on ice. Vacuum distillation yielded 9.0 g. (90%) of a pale green liquid, b. p. 147–148° at 3 mm., m. p. 76–78°. A sample recrystallized from alcohol for analysis melted at 77.0–78.0° cor. A mixed melting point with the decarboxylation product was not depressed.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found[b]: C, 85.7, 85.6; H, 7.9, 8.0.

Summary

Evidence is provided that when Grignard reagents react with phthalic anhydride types, the mechanism involves reaction both by addition to the carbonyl group and metathetical reaction by cleavage of the carbon–oxygen single bond. A series of reactions of 3,6-dimethylphthalic anhydride with Grignard reagents and with aromatic hydrocarbons is described.

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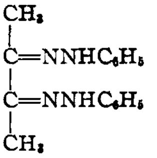
The Action of Copper Sulfate on Phenylosazones of the Sugars. Phenyl-D-glucosotriazole

BY RAYMOND M. HANN AND C. S. HUDSON

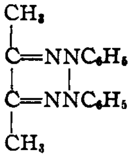
In a previous communication[1] it was shown that the phenylhydrazides of the aldonic acids of the sugar group are readily decomposed in hot aqueous copper sulfate solution with the production of nitrogen, benzene and the free sugar acid; the reaction appears to proceed quantitatively, as is evident from the fact that upon removal of the inorganic materials and concentration of the solution, a nearly theoretical yield of lactone of the acid is obtained. It seemed of interest to test the action of copper sulfate solutions on the phenylosazones of the sugars. They are known to reduce Fehling solution but no record has been found of a test with copper sulfate under acid conditions.

In the initial experiments a suspension of pulverized phenyl-D-glucosazone (5.0 g.) in 600 cc. of an aqueous solution containing two molecular equivalents (7.0 g.) of copper sulfate pentahydrate was boiled under reflux,[2] most of the osazone dissolved in one hour and as the reaction progressed the precipitation of a small amount of copper or cuprous oxide was noted and the color of the solution changed from blue to green. At the end of a second hour only traces of undissolved osazone remained; the mixture was filtered hot and from the filtrate, while still warm, glistening needle crystals separated. They were filtered from the cooled solution and a second crop was obtained by concentration of the mother liquor to 100 cc.; the total yield of product, which proved to be nearly pure though its color was tan from adsorbed dye, was 2–3 g. It was obtained as colorless pure asbestos-like crystals by recrystallizing once or twice from one hundred parts of boiling water and filtering through a bed of decolorizing carbon in a steam-heated Buchner funnel. The substance melts sharply at 195–196° without decomposition and the cooled melt crystallizes; the compound is very stable. It is not sufficiently soluble in water at ordinary temperatures to permit observation of its rotation, but in pyridine its specific rotation $[\alpha]^{20}\text{D}$ was $-81.6°$ (c, 0.8). The crystals are anhydrous and their analysis showed 54.44% carbon, 5.71% hydrogen and 15.78% nitrogen (Dumas), values which lead to the formula $C_{12}H_{15}O_4N_3$.

It will be observed that the empirical formula of the substance differs from that of phenyl-D-glucosazone by the elements of aniline, as though the reaction might be $C_{18}H_{22}O_4N_4 = C_{12}H_{15}O_4N_3 + C_6H_5NH_2$. Aniline was indeed detected in the mother liquor by removing the copper as sulfide, making the solution alkaline, extracting it with ether and converting the oily residue from the evaporation of the ether extract to acetanilide (yield, 20%). The evidence led to the possibility that the substance might belong to the class of osotriazoles of v. Pechmann,[3] which are very stable substances. In the case of diacetyl diphenylhydrazone (I), he showed that it was converted by oxidation with potassium dichromate in dilute acetic acid to an osotetrazone (II), which with stronger acidity (HCl) gave a 20% yield of the osotriazole (III). The latter reaction is evidently complex; much tar was produced and aniline was detected.



(I)



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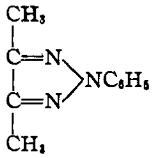
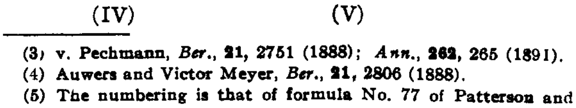


(III)

A direct conversion of an osazone type of compound to the corresponding osotriazole was reported by Auwers and Victor Meyer,[4] who heated benzil diphenylhydrazone (IV) in alcohol solution at 200° and obtained 2,4,5-triphenylosotriazole (V) and aniline.



(IV) (V)

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[1] Hann and Hudson, THIS JOURNAL, 56, 957 (1934).

[2] The osazone is difficult to wet and foaming during the first half hour was troublesome; in later experiments this was much reduced by the addition of a few cc. of *n*-butyl alcohol. It was also found that the reaction proceeds equally well but somewhat slower on the steam-bath; the best solvent that has been found so far is acidified 40% isopropyl alcohol at its boiling point, as is described further on.

[3] v. Pechmann, *Ber.*, 21, 2751 (1888); *Ann.*, 262, 265 (1891).

[4] Auwers and Victor Meyer, *Ber.*, 21, 2806 (1888).

[5] The numbering is that of formula No. 77 of Patterson and Capell's "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940. The name osotriazole, introduced by v. Pechmann, implies the 2,1,3-triazole that is related to osazones.