[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

The Decarboxylative Acylation of Arylacetic Acids

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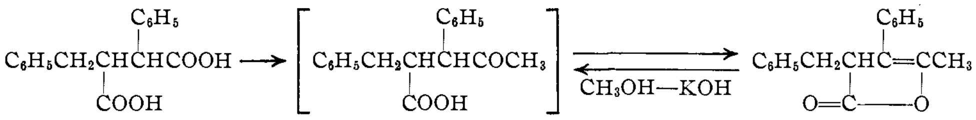
The several examples in the literature of the conversion of arylacetic acids to ketones by means of acetic anhydride have been correlated and it has been shown that this reaction, stripped to its fundamentals, is another instance of the familiar base-catalyzed condensation of carbonyl compounds. In this instance, acid anhydride molecules function as both the addendum and the acceptor and there is presented for the reaction a mechanism, involving a quasi-six-membered ring, which not only satisfactorily accommodates all the known facts but also serves to demonstrate the manner in which carbon dioxide evolution acts as the driving force for the reaction.

It was reported by Dakin and West,[1] although neither experimental details nor yields were given, that phenylacetic acid on being heated with pyridine and acetic anhydride was converted into phenylacetone.

Some experimental details of this rather unusual reaction were supplied by Stoermer and Stroh,[2] who, unaware of the earlier work of Dakin and West, used sodium acetate as the base instead of pyridine, and obtained a very good yield of phenylacetone from acetic anhydride, phenylacetic acid and the base. Another example of the reaction was also given by them, its unexpected occurrence having been their reason for trying the reaction on the more simple phenylacetic acid: each of two stereoisomers of α-phenyl-α′-benzylsuccinic acid on being boiled with acetic anhydride and sodium acetate gave α-benzyl-β-phenyl-β,γ-angelica lactone, opened by methanolic potassium hydroxide to the α-benzyl-β-phenyllevulinic acid which must have been its precursor. Since this starting material was both a phenylacetic and a hydrocinnamic acid they tried the reaction on both of these, finding that the latter failed to undergo the reaction. We have verified this finding, obtaining as our sole reaction product a nearly quantitative yield of hydrocinnamic anhydride.



$$C_6H_5CH_2\underset{COOH}{CH}\overset{C_6H_5}{C}HCOOH \longrightarrow \left[C_6H_5CH_2\underset{COOH}{CH}\overset{C_6H_5}{C}HCOCH_3\right] \underset{CH_3OH-KOH}{\overset{}{\rightleftarrows}} C_6H_5CH_2CH\overset{C_6H_5}{C}{=}CCH_3 \; (O{=}C\text{——}O)$$

The same preparation of phenylacetone by heating phenylacetic acid and acetic anhydride, this time with potassium acetate as the base, was again reported by Hurd and Thomas,[3] in a correction of an earlier paper.[4] These authors, who did not refer to the earlier work,[1,2] had previously reported that phenylacetic anhydride gave good yields of dibenzyl ketone by distillation at reduced pressure, the experimental section of their paper stating that equal quantities of phenylacetic acid and acetic anhydride were refluxed two hours, distilled to 200°, and then distilled under vacuum to give about a 50% yield of dibenzyl ketone, and that the presence of a small amount of sodium acetate did not influence the yield; and they suggested that the unidentified product obtained, together with phenylacetic anhydride, by Bakunin and Fisceman[5] when the reaction product of acetic anhydride and sodium phenylacetate was vacuum distilled was likewise dibenzyl ketone, since it had the correct composition and melting point for that substance. After learning that their earlier experimental details did not permit reproduction Hurd and Thomas reported that potassium acetate was a helpful ingredient in the reaction mixture of phenylacetic acid and acetic anhydride from which they now described the isolation of both phenylacetone and dibenzyl ketone. The reactions which they believed to occur were represented by the equations

$$C_6H_5CH_2COOH + (CH_3CO)_2O \longrightarrow C_6H_5CH_2COOCOCH_3 + CH_3COOH$$
$$C_6H_5CH_2COOCOCH_3 \longrightarrow C_6H_5CH_2COCH_3 + CO_2$$
$$C_6H_5CH_2COOCOCH_3 \longrightarrow (C_6H_5CH_2CO)_2O + (CH_3CO)_2O$$
$$(C_6H_5CH_2CO)_2O \longrightarrow C_6H_5CH_2COCH_2C_6H_5 + CO_2$$

Apparently not cognizant of the work of Hurd, Breslow and Hauser[6] described, in their admirable work on the elucidation of the mechanism of the Perkin reaction, the isolation, in addition to a small amount of phenylcinnamic acid, of dibenzyl ketone after sodium phenylacetate and acetic anhydride had been heated four hours, then benzaldehyde added and the mixture heated another eight hours. They thought that "this product undoubtedly resulted from self-condensation of the phenylacetic anhydride (formed by the anhydride–salt exchange), followed by decarboxylation. This reaction must have occurred during the preliminary heating of the anhydride–salt mixture, since, as pointed out above, when the preliminary heating is omitted and benzaldehyde heated directly with the anhydride and salt a high yield of phenylcinnamic acid is obtained."

The explanation of Hurd and Thomas of the course of the reaction was subscribed to, without comment, by Magidson and Garkusha[7] who studied the effect of variation (1) of the ratio of phenylacetic acid, acetic anhydride and sodium acetate and (2) of the reaction time on the yield of phenylacetone, their best procedure having been used by King and McMillan[8] who likewise obtained dibenzyl ketone from the reaction, as well as phenylacetone.

The reaction was recently used by Burger and Walter[9] for the synthesis of 3-pyridylacetone from

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(1) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91 (1928).

(2) R. Stoermer and H. Stroh, *Ber.*, **68**, 2112 (1935).

(3) C. D. Hurd and C. L. Thomas, THIS JOURNAL, **58**, 1240 (1936).

(4) C. D. Hurd, R. Christ and C. L. Thomas, *ibid.*, **55**, 2589 (1933).

(5) M. Bakunin and G. Fisceman, *Gazz. chim. ital.*, **46**, I, 77 (1916).

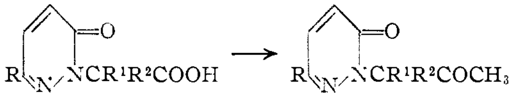
(6) D. S. Breslow and C. R. Hauser, THIS JOURNAL, **61**, 786 (1939).

(7) O. U. Magidson and G. A. Garkusha, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 339 (1941).

(8) J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 525 (1946).

(9) A. Burger and C. R. Walter, *ibid.*, **72**, 1988 (1950).

3-pyridylacetic acid, acetic anhydride and sodium acetate, and its most recent application has been by us[10] in the conversion of the 2-(3-pyridazonyl)-acetic acids I, II and III to the ketones V, VI and VII, respectively, by means of acetic anhydride and pyridine; IV did not undergo the reaction.



I, $R = R^1 = R^2 = H$
II, $R = CH_3, R^1 = R^2 = H$
III, $R = R^1 = CH_3, R^2 = H$
IV, $R = R^1 = R^2 = CH_3$
V, $R = R^1 = R^2 = H$
VI, $R = CH_3, R^1 = R^2 = H$
VII, $R = R^1 = CH_3, R^2 = H$

The necessity of the presence of a base for this reaction to proceed seemed obvious to us, inasmuch as the heating of an acid with acetic anhydride either alone or with an acid catalyst is a standard preparative procedure for higher acid anhydrides[11,12,13] and no decarboxylative acylation has been recorded as having occurred under such conditions. In other words, this reaction is a base-catalyzed condensation reaction. We tested our supposition of the essential equivalence of organic and inorganic bases in the reaction by substituting pyridine for sodium acetate in the reaction of acetic anhydride with phenylacetic acid, from which we had previously[8] obtained a 50% yield of phenylacetone and a 20% yield of dibenzyl ketone. With pyridine we obtained a 56% yield of phenylacetone and a 24% yield of dibenzyl ketone. Although this was the reaction first reported by Dakin and West they mentioned only the isolation of phenylacetone and omitted all experimental details. Thus, our results, together with those of Hurd on the use of potassium acetate, adequately demonstrated the correctness of our supposition.

The essentiality of an α-hydrogen atom in the arylacetic acid for the reaction to take place was indicated by the failure to react of the pyridazonyl acid IV, while the sufficiency of a single α-hydrogen atom was established by the success of the reaction with α-phenyl-α'-benzylsuccinic acid[2] and with the pyridazonyl acid III. Other factors were shown to operate in the reaction by the failure of both α-phenylpropionic (hydratropic) acid and diphenylacetic acid to yield any ketone; each of these substances furnished only the corresponding acid anhydrides with acetic anhydride in the presence of either pyridine or sodium acetate.

Critical consideration of all of the thus far known facts concerning this reaction led us to the development of an hypothesis concerning its mechanism. In any anhydrous mixture of a carboxylic acid RCOOH and a carboxylic anhydride $(R'CO)_2O$ there will be set up the equilibria

$$\begin{tikzcd}[column sep=small]
\mathrm{2RCOOH} + \underset{\mathrm{A}}{\mathrm{(R'CO)_2O}} \arrow[rr, shift left] \arrow[dr, shift left] & & \underset{\mathrm{B}}{\mathrm{(RCO)_2O}} + \mathrm{2R'COOH} \arrow[ll, shift left] \arrow[dl, shift left] \\
& \underset{\mathrm{C}}{\mathrm{RCOOCOR'}} + \mathrm{RCOOH} + \mathrm{R'COOH} \arrow[ul, shift left] \arrow[ur, shift left] &
\end{tikzcd}$$

the position of the equilibrium being determined by the nature of R and R',[11-14] provided none of the components are removed from the reaction sphere. Kalnin[15] effectively demonstrated, and Breslow and Hauser verified, that in base-catalyzed condensation reactions an acid anhydride will serve as the addendum in preference to an acid salt (and by the same token to a free acid). Also, as Baker and co-workers[16] have pointed out, since the bridge oxygen cannot effectively neutralize the cationoid character of both carbonyl groups simultaneously a carbonyl group in an anhydride can develop much stronger cationoid properties than can that in a free acid, as required by the fact that an acid anhydride functions effectively as an electrophilic reagent.[17] One is thus led to the inescapable conclusion that in a mixture of arylacetic acid and acetic anhydride undergoing a base-catalyzed condensation reaction both the addendum and the acceptor will be acid anhydrides.

In the case of phenylacetic acid and acetic anhydride the three anhydrides A, B and C ($R = C_6H_5CH_2$, $R' = CH_3$) are the possible reactants. It can be considered established[18] that a benzyl group in an acid anhydride has an appreciably greater tendency to become anionic than does a methyl group similarly situated, so that the acceptor molecule may be either B or C with the result that the condensation product will always contain a benzyl group as one part of the ketone, and, because either part of any of the three anhydrides may be the addendum, the other moiety of the ketone may be either benzyl or methyl. The only function of the base is to cause carbanion formation in the acceptor molecule. As a check on our conclusion that only the anhydrides actually take part in this condensation reaction phenylacetic anhydride and acetic anhydride were heated in the presence of pyridine and of sodium acetate to give, in each case, both phenylacetone and dibenzyl ketone. Another test experiment, showing the reaction not to be unique with acetic anhydride, was run using a mixture of phenylacetic anhydride and propionic anhydride in the presence of pyridine; the expected and obtained products were benzyl ethyl ketone and dibenzyl ketone.

Having conclusively demonstrated that it is the anhydride which serves as both addendum and acceptor in this reaction, and that the $C_6H_5CH_2CO$– portion of the anhydride may fulfil both functions (*e.g.*, in the formation of dibenzyl ketone in the several reactions just discussed), it seemed to us that if phenylacetic anhydride alone were heated with a basic catalyst it should yield dibenzyl ketone; this anticipation was realized, using either pyridine or sodium acetate as the basic catalyst; with the latter catalyst there was also obtained a small amount of phenylacetone derived from the acetic anhydride generated by the catalyst. We have

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[10] J. A. King and F. H. McMillan, unpublished data.

[11] C. Liebermann, *Ber.*, **21**, 3372 (1888).

[12] R. Robinson and J. Shinoda, *J. Chem. Soc.*, **127**, 1973 (1925).

[13] J. W. Fisher, British Patent 570,271, June 29, 1945.

[14] H. Sokol (to Heyden Chem. Corp.), U. S. Patent 2,423,569, July 8, 1947.

[15] P. Kalnin, *Helv. Chim. Acta*, **11**, 977 (1928).

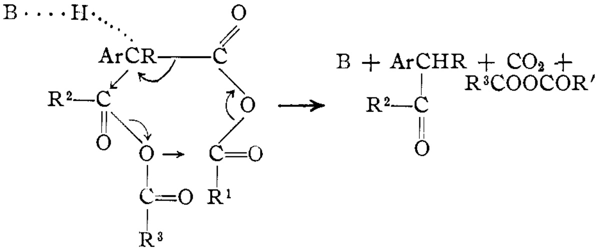
[16] W. Baker, W. D. Ollis and V. D. Poole, *J. Chem. Soc.*, 1542 (1950).

[17] A. R. Emery and V. Gold, *ibid.*, 1443 (1950).

[18] For a summary of some of the evidence see ref. 6. The obvious explanation resides in the greater resonance stabilization of $[C_6H_5CHCOOacyl]^-$ over $[CH_2COOacyl]^-$.

further demonstrated the general effectiveness of bases of various types, open-chain as well as cyclic, in catalyzing the reaction by successfully carrying out the conversion of phenylacetic anhydride to dibenzyl ketone while using as the catalyst isoquinoline, 2,4,6-collidine, tri-*n*-butylamine and β-picoline. In the absence of a catalyst phenylacetic anhydride is completely stable and can be distilled at atmospheric pressure without change. We have likewise demonstrated the general applicability of the reaction to arylacetic acids by successfully applying it to *o*-chlorophenylacetic anhydride, *m*-methoxyphenylacetic anhydride and α-naphthylacetic anhydride, with pyridine as the catalyst, obtaining 1,3-di-(*o*-chlorophenyl)-2-propanone, 1,3-di-(*m*-methoxyphenyl)-2-propanone and 1,3-di-(α-naphthyl)-2-propanone, respectively.

With the establishment that this reaction is a base-catalyzed condensation reaction of two acid anhydride molecules, we believe that the detailed mechanism of the generalized reaction can best be represented as involving a quasi-six-membered ring, in the following manner



The identities and possibilities of Ar, R, R¹, R² and R³ are obvious and need not be discussed *in extenso*. The merit of this concept of the mechanism of the transformation lies in the fact that it not only explains the facts but also appears to us to be the only one which satisfactorily delineates the driving force of the reaction, namely, carbon dioxide evolution.

With the scope of the reaction appreciated and a reasonable mechanism for it at hand, it is now possible to more critically examine some of the earlier reports of its usage.[19] Hurd's conclusion that the unidentified product obtained, together with phenylacetic anhydride, by Bakunin and Fisceman, from acetic anhydride and sodium phenylacetate was dibenzyl ketone is undoubtedly correct; the acid anhydride–salt exchange reaction was shown by Michael and Hartman[20] to be rapid at 100° and recent radioactive studies by Ruben, Allen and Nahinsky[21] have shown that it is surprisingly rapid even at room temperature; and Bakunin's isolation of phenylacetic anhydride, together with our demonstration of the conversion of phenylacetic anhydride to dibenzyl ketone by sodium acetate, constitute strong circumstantial evidence for Hurd's conclusion. Although there is no doubt whatsoever that at more elevated temperatures acid anhydrides undergo pyrolysis our demonstration of the thermal stability of phenylacetic anhydride on distillation at atmospheric pressure together with the other experiments herein reported appear to us to render void the conclusions of Hurd and Thomas relevant to the course of the phenylacetic acid–acetic anhydride reaction. On the other hand, our experiments show that Breslow and Hauser were correct in their supposition, concerning their own work, that dibenzyl ketone was formed by the self-condensation of phenylacetic anhydride. The several experiments, both in this paper and in others,[2,10] on the use of α-substituted arylacetic acids can also now be more fully understood. The -I effect of the methyl group in hydratropic acid apparently sufficiently counter-balances the electron attraction of the phenyl group to prevent initiation of the reaction by the basic catalyst whose function it is to render the α-carbon atom anionoid by proton attraction, while the more powerful electron attraction of the 2-(3-pyridazonyl) group over that of the phenyl group allows III to undergo the reaction. In α-phenyl-α′-benzylsuccinic acid, considered as phenylacetic acid containing a benzylcarboxymethyl group as an α-substituent, the strong electron-attraction of the substituent carboxyl group is probably partially relayed through the adjacent carbon atom to the phenylacetic α-carbon to such an extent that the reaction is actually facilitated. On a solely electronic basis similar facilitation should have been encountered in diphenylacetic acid, but here the large bulk of the second electron-attracting group (phenyl) presents a steric barrier to the reaction.

Experimental[22,23]

Action of Acetic Anhydride and Pyridine on Phenylacetic Acid.—A mixture of phenylacetic acid (13.6 g., 0.10 mole),

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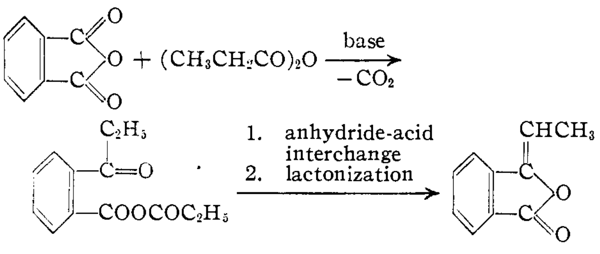
(19) We consider it possible that the condensation of phthalic anhydride with propionic anhydride in the presence of potassium propionate, as described by D. T. Mowry, E. L. Ringwald and M. Renoll, THIS JOURNAL, **71**, 120 (1949), to give ultimately 3-ethylidenephthalide may proceed in its initial stage *via* a cyclic decarboxylative acylation of the type herein proposed, *i.e.*



That all such reactions cannot proceed exclusively by this route is indicated, as summarized in ref. 3 of the quoted paper, by the isolation of phthalylacetic acid when acetic anhydride and potassium acetate are heated with phthalic anhydride for only a few minutes. Analogous results were obtained by D. B. Limaye, and V. M. Bhave, *J. Univ. Bombay*, **2**, Pt. 2, 82 (1933) (*C. A.*, **28**, 6128 (1934)) in the condensation of β-arylglutaconic anhydrides with acetic anhydride in the presence of sodium acetate to give both β-arylglutaconylacetic acids and β-aryl-γ-acetovinylacetic (or crotonic ?) acids, of which the latter may well be formed as indicated herein.

Added in Proof.—Additional examples of this general anhydride condensation reaction were provided in Paper No. 67 by G. G. Smith presented before the Divison of Organic Chemistry at the Boston session of the 119th ACS meeting, April 4, 1951. Phenylacetic acid was treated with acetic, propionic and butyric anhydrides in the presence of pyridine to give the expected 1-phenyl-2-alkanones and their enol acylates, and *p*-nitrophenylacetic and *o*-chlorophenylacetic acids were both converted to the expected acetones by acetic anhydride and pyridine.

(20) A. Michael and R. N. Hartman, *Ber.*, **34**, 918 (1901).

(21) S. Ruben, M. B. Allen and P. Nahinsky, THIS JOURNAL, **64**, 3050 (1942).

(22) Melting points and boiling points are uncorrected.

(23) Microanalyses were carried out in these laboratories under the supervision of Dr. F. A. Buhler.

acetic anhydride (50 cc.) and pyridine (50 cc.) was refluxed six hours, during the first part of which time carbon dioxide evolution was vigorous. After removal of the solvent the residue was taken up in benzene and shaken out with 10% sodium hydroxide. Removal of the benzene left 12 g. of non-acidic material which on fractional distillation was separated into 7.5 g. (56% yield) phenylacetone, b.p. 30–64° (0.1 mm.), phenylhydrazone, m.p. 82–84° (reported,[3] m.p. 84.5–85°); an intermediate cut; and 2.5 g. (24% yield) *sym*-diphenylacetone, b.p. 112–125° (0.1 mm.), oxime, m.p. 120–122° (reported,[8] m.p. 119–122°).

Action of Acetic Anhydride and Base on α-Phenylpropionic, β-Phenylpropionic and Diphenylacetic Acids. Anhydride Formation.—In each case a mixture of 0.10 mole of the acid and 50 or 100 cc. of acetic anhydride and an equal volume of pyridine was refluxed from 2 to 3 hours with no detectable evolution of carbon dioxide. After removal of excess reagents under vacuum the residue was either fractionally distilled or crystallized (diphenylacetic) to give the acid anhydride. α-Phenylpropionic anhydride, b.p. 121–127° (0.15 mm.).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; neut. equiv., 141. Found: C, 76.69; H, 6.63; neut. equiv., 138.

β-Phenylpropionic anhydride, b.p. 135–145° (0.05 mm.); reported,[12] 216–217° (14 mm.); identified by hydrolysis to the acid, m.p. and mixed m.p. 47–48.5°. Diphenylacetic anhydride, m.p. 93.5–95°, reported,[4] m.p. 98°; derivative with aniline, diphenylacetanilide, m.p. 177–179°; reported,[24] 180°. Replacement of pyridine by sodium acetate (0.10 mole) had no influence on the course of the reactions.

Preparation of Acid Anhydrides.—The most convenient procedure for obtaining a pure product was to drop one molar equivalent of acid chloride into a stirred suspension of one molar equivalent of vacuum-dried sodium salt of the acid in about ten volumes of benzene and then stir the mixture three hours after the exothermic addition was complete; after filtration the filtrate was concentrated and the acid anhydride recrystallized.

m-Methoxyphenylacetic anhydride (83% yield) melted at 41–41.5°.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.79; H, 5.77. Found: C, 68.72; H, 5.90.

α-Naphthylacetic anhydride (79% yield) melted at 116–117°.

Anal. Calcd. for $C_{24}H_{18}O_3$: C, 81.33; H, 5.12. Found: C, 81.56; H, 5.40.

Reactions with Phenylacetic Anhydride.—A mixture of phenylacetic anhydride (25.4 g., 0.10 mole), acetic anhydride (100 cc.) and pyridine (100 cc.) was refluxed for 130 minutes, during which time about 1600 cc. (*not* N.T.P.) of carbon dioxide was evolved. Excess reagents were removed by distillation under vacuum, the cooled residue was decomposed with 150 cc. of 10% sodium hydroxide, and the resultant mixture was extracted with two 125-cc. portions of ether. The dried ethereal extract of the neutral products was fractionally distilled to give 9.3 g. (33% yield) of phenylacetone, b.p. 84–95° (5 mm.) and 5.4 g. (26% yield) of *sym*-diphenylacetone, b.p. 160–168° (5 mm.). The use of sodium acetate instead of pyridine gave 22% phenylacetone and 45% *sym*-diphenylacetone.

Pyridine alone with phenylacetic anhydride gave a 30% yield of *sym*-diphenylacetone while sodium acetate alone gave a 4% yield of phenylacetone and a 10% yield of *sym*-diphenylacetone.

In the following tabulated experiments a mixture of phenylacetic anhydride (12.7 g., 0.05 mole) and the base (50 cc.) was heated at 130–140° for 2.5 hours and then cooled and diluted with benzene (100 cc.). The benzene solution was washed twice with 100-cc. portions of 1:1 hydrochloric acid, once with water, once with 10% aqueous sodium hydroxide and then dried over potassium carbonate. Fractional vacuum distillation of the benzene solution furnished *sym*-diphenylacetone identified in each case by formation of its oxime. The results are given in the following table. In the case of tri-*n*-butylamine the temperature was raised to 180° since no carbon dioxide evolution was noted, and the higher reaction temperature may account for the increased yield of ketone.

Base	Cc. of CO_2	*sym*-Diphenylacetone g.	%	B.p., °C.	Mm.	Oxime, m.p., °C
Isoquinoline	30	0.2	4	80–85	0.04–0.05	117–119
2,4,6-Collidine	150	1.3	25	100–110	.12–0.5	119–120
β-Picoline	70	0.7	13	96–97	.10	122–124
Tri-*n*-butylamine	(none)	5.3	(quant.)	106–116	.15	117–119.5

Phenylacetic anhydride was obtained in 87% yield, m.p. 68–71° (reported,[25] 72.5°).

o-Chlorophenylacetic anhydride (77% yield) melted, after recrystallization from petroleum ether containing a little benzene, at 71–73°.

Anal. Calcd. for $C_{16}H_{12}Cl_2O_3$: C, 59.46; H, 3.74. Found: C, 59.75; H, 3.99.

Thionyl chloride (125 cc.) was added dropwise to vigorously stirred commercial *m*-methoxyphenylacetic acid (33.2 g., 0.20 mole), after which the mixture was refluxed (drying tube) for 2.5 hours. Fractional vacuum distillation of the reaction mixture furnished 25 g. (68% yield) of product, b.p. 91–93° (0.6 mm.). A sample of the *m*-methoxyphenylacetyl chloride for analysis was redistilled, b.p. 80–84° (0.3–0.4 mm.); redistilled again, b.p. 44–47° (0.02 mm.).

Action of Pyridine on a Mixture of Phenylacetic Anhydride and Propionic Anhydride.—A mixture of phenylacetic anhydride (12.7 g., 0.05 mole), propionic anhydride (50 cc.) and pyridine (50 cc.) was refluxed three and one-quarter hours, during which 920 cc. of carbon dioxide was evolved. Materials volatile on the steam-bath under water-pump vacuum were removed and the residue was partitioned between benzene (200 cc.) and 10% aqueous sodium hydroxide (200 cc.). Fractional vacuum distillation of the dried benzene layer gave 3.3 g. (22% yield) of benzyl ethyl ketone, b.p. 50–52° (0.1 mm.), and 3.7 g. (35% yield) of *sym*-diphenylacetone, b.p. 105–117° (0.1 mm.). The benzyl ethyl ketone was identified by conversion to its semicarbazone, m.p. 148–149° after two recrystallizations from alcohol; reported,[26] m.p. 148°.

$ArCH_2COCH_2Ar$

Ar or deriv.	Yield, %	B.p., °C.	Mm.	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
o-ClC_6H_4	43	150–151	0.02	100.5–101	$C_{15}H_{12}Cl_2O$	64.53	4.33	64.74	4.53
Semicarbazone				153–155	$C_{16}H_{15}Cl_2N_3O$	N, 12.50		N, 12.44	
m-$CH_3OC_6H_4$	12	154–158	.2		$C_{17}H_{18}O_3$	75.53	6.71	75.74	6.93
Semicarbazone				136–136.5	$C_{18}H_{21}N_3O_3$	N, 12.84		N, 13.12	
α-$C_{10}H_7$	19	190–200	.1	108–109	$C_{23}H_{18}O$	89.00	5.84	88.86	6.09
Semicarbazone				143–144	$C_{24}H_{21}N_3O$	N, 11.44		N, 11.50	

Anal. Calcd. for $C_9H_9ClO_2$: C, 58.55; H, 4.91. Found: C, 58.70; H, 5.17.

Preparation of *sym*-Diarylacetones.—In each case a mixture of 0.05 mole of acid anhydride and 50 cc. of pyridine was refluxed until appreciable carbon dioxide evolution ceased

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(24) H. Staudinger, *Ber.*, **38**, 1735 (1905).

(25) R. Anschütz and W. Berns, *ibid.*, **20**, 1389 (1887).

(26) P. Jacobson and H. Jost, *Ann.*, **400**, 195 (1913).

(one to ten hours) then the pyridine was stripped from the mixture under vacuum. The residue was partitioned between 100 cc. each of benzene and 10% aqueous potassium hydroxide and the dried benzene layer was fractionally distilled to give the substituted acetone.

We wish to acknowledge the technical assistance of Messrs. Charles Anderson and Kenneth Hutton.

NEW YORK 11, N. Y. RECEIVED MARCH 28, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

A Study of the Interaction of Certain Unsaturated Grignard Reagents and Nitriles[1,2]

BY HENRY R. HENZE, GEORGE L. SUTHERLAND AND GAYLE D. EDWARDS

Previously, the Grignard reagent prepared from allyl bromide had been shown to react "abnormally" (in the ratio of 2:1) with nitriles to form carbinamines rather than ketones. In this investigation, the Grignard reagent prepared from methallyl chloride, although used in large excess, reacted with ethoxyacetonitrile to form a mixture of products. As a result of reaction in a 2:1 ratio, some of the expected carbinamine was obtained (10% yield); however, most of the reactants interacted in 1:1 ratio to form a mixture of two isomeric ketones (60% yield); finally, about 5% of a dienol, structurally analogous to the carbinamine, was isolated from the reaction mixture. Similarly, lower homologs of both the carbinamine and the isomeric unsaturated ketones resulted from interaction of methoxyacetonitrile and the methallylmagnesium chloride. Since the activity of benzyl chloride is thought to approach that of an allyl halide, the former was converted into a Grignard reagent and the latter allowed to react with ethoxyacetonitrile; however, no evidence of carbinamine formation was found. The initial attempt to methylate a tertiary carbinamine by the Wallach modification of the Leuckart reaction was successful.

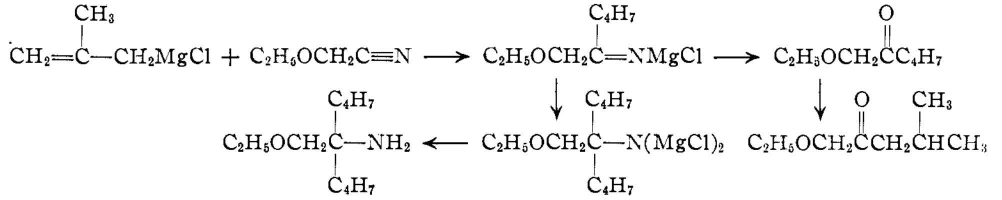
For some time past, there has been conducted in this Laboratory an intensive study of the preparation of substituted ketones of the alkoxy-, aryloxy- and halogenoalkoxyalkyl (or aryl) types. These ketones, for the most part, have been synthesized by means of a modification, by Béhal and Sommelet,[3] of the Grignard reaction. In this case the Grignard reagent adds to the nitrile in an equimolecular ratio. Upon hydrolysis of the adduct, either a stable ketimine or, in sequence, a ketone was obtained

$$\mathrm{RMgX} + \mathrm{R'C{\equiv}N} \longrightarrow \mathrm{RR'C{=}N{-}MgX} \longrightarrow \mathrm{RR'C{=}NH} \longrightarrow \mathrm{RR'C{=}O}$$

Allen and Henze[4] attempted to prepare allyl ethoxymethyl ketone from interaction of equivalent quantities (1:1) of α-ethoxyacetonitrile and allylmagnesium bromide. However, the Grignard reagent added to the nitrile in 2:1 molecular ratio, and the sole product isolated from hydrolysis of the adduct was neither a ketimine nor a ketone, but a primary amine, namely, diallylethoxymethylcarbinamine $(CH_2CH{=}CH_2)_2(C_2H_5OCH_2)C\text{-}NH_2$. Since a nitrile is considered to be the least active[5] of the common functional groups to which Grignard reagents add, this "abnormal" behavior has been attributed to the greater reactivity of allylmagnesium bromide over the alkylmagnesium halides. Such greater activity was demonstrated also by the ability of allylmagnesium bromide to react by addition to the adducts formed by interaction of an excess of alkylmagnesium halides to a nitrile. Hydrolysis of these (second) addition products yielded tertiary carbinamines[4] of the type $RR'(CH_2CH{=}CH_2)C\text{-}NH_2$.

Tamele, *et al.*,[6] have reported the preparation of β-methallylmagnesium chloride in a 90 mole per cent. yield, as determined by titration and by measurement of the isobutylene produced on hydrolysis of the reagent.[7]

It has now been found that when methallylmagnesium chloride in excess was allowed to react with ethoxyacetonitrile, ketonic material as well as carbinamine was obtained as hydrolysis products



$$\begin{array}{l} CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CH_2MgCl + C_2H_5OCH_2C{\equiv}N \longrightarrow C_2H_5OCH_2\overset{C_4H_7}{\overset{|}{C}}{=}NMgCl \longrightarrow C_2H_5OCH_2\overset{O}{\overset{\|}{C}}C_4H_7 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\downarrow \qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \\ C_2H_5OCH_2\underset{C_4H_7}{\underset{|}{\overset{C_4H_7}{\overset{|}{C}}}}{-}NH_2 \longleftarrow C_2H_5OCH_2\underset{C_4H_7}{\underset{|}{\overset{C_4H_7}{\overset{|}{C}}}}{-}N(MgCl)_2 \quad C_2H_5OCH_2\overset{O}{\overset{\|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}HCH_3 \end{array}$$

The ketonic material could be hydrogenated and converted into the known ethoxymethyl isobutyl ketone. Ozonolysis of the ketonic material yielded a mixture of formaldehyde, acetone, ethoxyacetone, ethoxypyruvic acid and acetic acid. Therefore, the ketonic material was a mixture of two isomers; however, it was chiefly 1-ethoxy-4-methyl-3-penten-2-one. The unsaturated carbinamine readily underwent catalytic hydrogenation to form 1-(ethoxymethyl)-3-methyl-1-(2-methylpropyl)-1-butylamine.

Methoxyacetonitrile reacted with methallylmagnesium chloride in a wholly analogous manner to yield the methoxymethylcarbinamine [1-(meth-

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[1] From a portion of the Ph.D. dissertation of George Leslie Sutherland, June, 1950.

[2] From the M.A. thesis of Gayle Dameron Edwards, August, 1948.

[3] A. Béhal and M. Sommelet, *Compt. rend.*, **138**, 89 (1904).

[4] B. B. Allen and H. R. Henze, THIS JOURNAL, **61**, 1790 (1939).

[5] C. E. Entemann, Jr., and J. R. Johnson, *ibid.*, **55**, 2900 (1933).

[6] M. W. Tamele, C. J. Ott, K. E. Marple and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

[7] In order to prove that methallylmagnesium chloride was typical in its reactions, it was converted through reaction with acetaldehyde and subsequent hydrolysis of the adduct into the secondary alcohol (4-methyl-4-penten-3-ol) in 65% yield. The Barbier synthesis also was successfully applied using acetone, methallyl chloride and magnesium.