TABLE II

REACTION OF ETHYLENE FLUOROBROMIDE WITH POTASSIUM IODIDE IN METHANOL AT 40°

$[FCH_2CH_2Br]_0 = 0.0931$

Time, sec.	$[KI]_t$	$k \times 10^6$, mole^{-1} sec.$^{-1}$ l.
0	0.0501	
85,380	.0477	6.24
202,620	.0456	5.19
367,260	.0420	5.42
606,840	.0378	5.38
966,400	.0330	5.21
		5.49 ± 0.30

action is relatively slow the concentration thus determined was taken as the initial concentration and from concentrations determined similarly at later times, rate constants were calculated from the integrated form of the second-order rate equation. Data from one of the runs are listed in Table II. In the other run the rate constant was $5.74 \pm 0.06 \times 10^{-6}$ sec.$^{-1}$ mole^{-1} l. All of the points taken gave an average value of 5.60 ± 0.27. No observable amount of iodine was formed in either run.

Acknowledgment.—The authors would like to express their appreciation to the National Science Foundation for their grant in support of this investigation.

ATLANTA, GEORGIA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Polyphosphoric Acid as a Reagent in Organic Chemistry. VII. Acylation[1]

BY H. R. SNYDER AND C. T. ELSTON[2]

RECEIVED AUGUST 9, 1954

The synthesis of ketones by intermolecular acylation with carboxylic acids in the presence of polyphosphoric acid is examined further. Thiophene and phenol are acetylated at 75°, in good yields, but less reactive compounds like benzene and toluene react with aliphatic acids only under conditions vigorous enough to cause self-condensation of the resulting ketones. Fully aromatic ketones are more stable to polyphosphoric acid; toluene and benzoic acid react at 160° to give *p*-methylbenzophenone in 70% yield. Phenyl acetate undergoes the Fries rearrangement in polyphosphoric acid, giving *p*-hydroxyacetophenone in about the same yield as can be obtained by the direct acetylation of phenol. Phenyl benzoate is more stable to polyphosphoric acid; the yield of *p*-hydroxybenzophenone obtained from it is less than that from the direct acylation of phenol. Other observations on the acylation of aromatic compounds are reported.

In a preliminary study[3] of the acylation of reactive aromatic hydrocarbons under the influence of polyphosphoric acid it was found that although mesitylene and durene reacted with aliphatic acids, the ketones formed were, for the most part, unstable in the reaction mixture under the conditions employed. In an extension of this work it now has been found that highly reactive compounds such as thiophene and phenol undergo acetylation at a temperature (75°) at which the resulting methyl or methylene ketones are fairly stable. Thus, *p*-hydroxyacetophenone and 2-acetylthiophene can be prepared in yields of 67 and 70%, respectively. Less reactive compounds such as benzene and toluene do not undergo acylation at an appreciable rate at this temperature, and higher temperatures bring about self-condensation of the ketones. Acylation with aromatic acids is not restricted in this way since the aromatic ketones produced are stable in polyphosphoric acid at 160°. Benzoic acid can be used to acylate toluene in a yield of 70%. However, electron-withdrawing substituents on the ring render an aromatic acid ineffective in acylations. For example, *p*-nitrobenzoic acid and phenol do not react even at 160°. *o*-Nitrobenzoic acid similarly fails to yield the expected ketone. The lack of reactivity of such compounds in acylation of carbon is paralleled to some extent in the data observed on the Lossen rearrangement[4] and the formation of amides.[5]

The use of unsaturated acids in acylation reactions also appears to be limited in its scope. Anisole is readily acylated by cinnamic acid giving a 50% yield of benzal-*p*-methoxyacetophenone. However, reaction of cinnamic acid with benzene is effected only at high temperatures and the product is so badly contaminated that it has not been possible to effect its purification. It is quite interesting that cinnamic acid reacts with anisole at the carbonyl carbon in the presence of polyphosphoric acid; both sulfuric acid and aluminum chloride catalyze the conjugate addition of aromatic compounds to cinnamic acid.

The formation of *p*-hydroxyacetophenone as the sole product from the acetylation of phenol suggested that the use of polyphosphoric acid might provide a convenient general method for the preparation of *p*-acylphenols. The yield of *p*-hydroxyacetophenone (69%) is about equal to that which can be obtained by the Fries rearrangement of phenyl acetate.[6] Unfortunately, an experiment with phenol and caproic acid gave only a 35% yield of *p*-caproylphenol, along with an 18% yield of phenyl caproate. The benzoylation of phenol was somewhat more attractive, *p*-benzoylphenol being obtained in 51% yield, along with a substantial amount (15%) of *p*-benzoylphenyl benzoate and a trace of phenyl benzoate. More vigorous conditions did not improve the yield of the ketone.

The acylation of substituted phenols led to divergent results. *p*-Cresol reacted with benzoic acid to give *p*-cresyl benzoate rather than the expected *o*-hydroxyketone. Acylation *ortho* to a hydroxyl group does occur in polyphosphoric acid, however.

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[1] For the preceding paper in this series, see THIS JOURNAL, **76**, 3039 (1954). P. D. Gardner [*ibid.*, **76**, 4550 (1954)] also has reported intermolecular acylations affected by polyphosphoric acid.

[2] Visking Corporation Fellow, 1953–1954.

[3] H. R. Snyder and R. W. Roeske, THIS JOURNAL, **74**, 5820 (1952).

[4] H. R. Snyder, C. T. Elston and D. B. Kellom, *ibid.*, **75**, 2014 (1953).

[5] H. R. Snyder and C. T. Elston, *ibid.*, **76**, 3039 (1954).

[6] A. H. Blatt in R. Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 342.

m-Cresol reacted with propionic and caproic acids to give low yields of both the *ortho* and *para* isomers. Fries rearrangement of *m*-cresyl caproate leads exclusively to the *ortho* isomer.[6] Resorcinol and acetic acid gave resacetophenone in a rather low yield (40%).

Phenyl esters can be prepared in high yields by employing a large excess of phenol and an amount of polyphosphoric acid equal to the combined weight of the phenol and the carboxylic acid. This result was reported by Bader and Kontowicz[7] before our investigation was complete. The authors made no reference to carbon acylation. However, if an increased amount of polyphosphoric acid is employed, rearrangement of the acylphenol occurs readily. Phenyl acetate gives *p*-hydroxyacetophenone in the same yield as that obtained from acetic acid and phenol. Phenyl benzoate, on the other hand, is much more stable in polyphosphoric acid and although a low yield of *p*-hydroxybenzophenone was obtained, most of the phenyl benzoate was recovered unchanged. Unexpectedly, no *p*-benzoylphenyl benzoate could be isolated from the reaction mixture. It thus seems unlikely that esterification is a preliminary step in the acylation reaction.

The ring positions of aromatic amides and amines, with the exception of diphenylamine, have proved to be unreactive toward carboxylic acids in the presence of polyphosphoric acid. Diphenylamine and benzoic acid reacted to give a crystalline compound corresponding in elementary analysis to a dibenzoyldiphenylamine. The infrared absorption spectrum indicates that the benzoyl groups are in the *para* positions.

Experimental[8]

***p*-Hydroxyacetophenone. (a) From Phenol and Acetic Acid.**—A solution of 6 g. (0.0638 mole) of phenol and 3.9 g. (0.0650 mole) of glacial acetic acid in 90 g. of polyphosphoric acid[9] was stirred at 70–75° for 1.5 hours. The color changed from water-white to an orange-red in approximately one-half hour and then gradually darkened to a red-brown. Addition of ice-water precipitated a fluffy, brown solid. The mixture was extracted with three 60-ml. volumes of ether. The combined ether extract was washed with three 25-ml. portions of 10% sodium hydroxide solution, dried over magnesium sulfate and then evaporated to dryness under reduced pressure. There was no residue. The sodium hydroxide was acidified with hydrochloric acid and the liberated phenol was extracted with ether. The ether was dried over magnesium sulfate and then evaporated to yield 5.8 g. (67%) of a brown solid, melting point 105–108°. One recrystallization from benzene gave colorless crystals, melting at 109°.

Reactions carried out at higher temperatures gave only ether-insoluble oils.

(b) From Phenyl Acetate.—A mixture of 6.8 g. of phenyl acetate and 75 g. of polyphosphoric acid was treated in the same manner as that outlined in (a). The crude product melted in the range 103–106° and weighed 4.7 g. (69%).

Similar results were obtained when a mixture of phenyl acetate and polyphosphoric acid was stirred vigorously for 15 minutes and then allowed to stand at room temperature for one week.

Reaction of Phenol and Benzoic Acid.—A mixture of 5.2 g. (0.0426 mole) of benzoic acid and 4.0 g. (0.0426 mole) of phenol was stirred with 95 g. of polyphosphoric acid at 75° for three hours. Addition of ice-water precipitated a pasty, orange solid. The mixture was extracted with three 80-ml. portions of ether. The combined ether extract was then washed with three 20-ml. portions of 10% sodium hydroxide solution. Evaporation of the ether layer gave 2.0 g. of a white solid, melting point 80–100°. Recrystallization from ethanol gave colorless crystals, melting at 112–114°. (The reported m.p. of *p*-benzoylphenyl benzoate is 112.5°.)[10] Neutralization of the sodium hydroxide wash precipitated 4.3 g. (51%) of an orange solid, melting point 130–132°. Recrystallization from nitromethane gave pale yellow crystals, melting at 134–135° (lit.[10] 134°).

An analogous reaction carried out at 75° for 20 hours gave a 46% yield of *p*-hydroxybenzophenone and a 15% yield of a neutral solid, melting point 60–95°. Recrystallization of this material from ethanol failed to effect separation into its components.

A stirred solution of 10.0 g. (0.106 mole) of phenol and 20.0 g. (0.164 mole) of benzoic acid in 80 g. of polyphosphoric acid was heated to 160° in the course of 20 minutes and then held at that temperature for an additional ten minutes. The orange solid, which precipitated upon addition of ice-water, was filtered off and then leached with sodium hydroxide solution. The residual white solid weighed 7.7 g. and melted in the range 105–110°. Recrystallization from ethanol gave 6.3 g. of colorless crystals, melting at 113–114°. The basic extract was treated with carbon dioxide, precipitating a pale orange colored oil which gradually solidified upon standing. It weighed 3.0 g. and melted at 132–133°.

Reaction of *m*-Cresol and *n*-Caproic Acid.—A solution of 5.0 g. (0.0463 mole) of *m*-cresol and 5.4 g. (0.0465 mole) of *n*-caproic acid in 82 g. of polyphosphoric acid was stirred at 80° for one hour. The hydrolyzed mixture was extracted with three 80-ml. portions of ether and the combined extract was washed with 15% sodium carbonate solution. Distillation of the dried extract gave 2.1 g. (22%) of *o*-caproyl-*m*-cresol, boiling point 101° (0.4 mm.). The phenylhydrazone melted at 94° (lit.[11] 93°). The residue from the distillation solidified upon cooling and after chromatography on alumina and recrystallization from cyclohexane gave 0.6 g. (6.3%) of colorless crystals, melting point 77–77.5°. The compound is assumed to be the *para* isomer.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.71; H, 8.79. Found: C, 75.52; H, 8.60.

2-Acetylthiophene.—A solution of 10 g. (0.119 mole) of thiophene and 14.3 g. (0.238 mole) of acetic acid in 100 g. of polyphosphoric acid was stirred at 75° for three hours. After hydrolysis, the liquid product was extracted with ether. The ether extract was dried over magnesium sulfate and then distilled through a Holtzmann column. Only one fraction was obtained, b.p. 55–56° (0.7 mm.), n^{20}_D 1.5660 (lit.[12] n^{20}_D 1.5662). The yield was 10.5 g. (70%).

4-Methylbenzophenone.—A mixture of 10 g. (0.109 mole) of toluene, 23 g. (0.188 mole) of benzoic acid and 75 g. of polyphosphoric acid was placed in a three-necked flask fitted with a stirrer, reflux condenser and calcium chloride tube. The two-phase liquid system was vigorously stirred at 160–165° for three hours. Hydrolysis yielded an oil which after washing with sodium hydroxide solution distilled completely in the range 114–116° (0.4 mm.). The distillate solidified upon cooling, giving 15.0 g. (70%) of crystalline 4-methylbenzophenone, melting point 59°.

Benzal-*p*-methoxyacetophenone.—A solution of 5.0 g. (0.0338 mole) of cinnamic acid and 3.6 g. (0.0338 mole) of anisole in 90 g. of polyphosphoric acid was stirred at 100° for 15 minutes and then at 125° for ten minutes more. Hydrolysis gave an orange paste which solidified upon standing overnight. The solid was filtered off, digested with dilute sodium hydroxide and then refiltered. Recrystallization of this material from ethanol–water gave 4.0 g. (50%) of colorless crystals, melting point 106–107° (lit.[13] 106–107°).

Reaction of Benzoic Acid and Diphenylamine.—A mixture of 30 g. (0.178 mole) of diphenylamine and 65 g. (0.533 mole) of benzoic acid in 390 g. of polyphosphoric acid was heated, with stirring, to 160° in the course of 25 minutes

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[7] A. R. Bader and A. D. Kontowicz, THIS JOURNAL, **75**, 5419 (1953).

[8] The authors are indebted to Mrs. Lucy Chang, Mrs. Esther Fett and Mr. Joseph Nemeth for the microanalyses.

[9] The authors are indebted to the Victor Chemical Works, Chicago, Illinois, for generous supplies of polyphosphoric acid.

[10] O. Doebner, *Ann.*, **210**, 251 (1881).

[11] C. Coulthard, J. Marshall and F. Pyman, *J. Chem. Soc.*, 288 (1930).

[12] A. Kosak and H. Hartough, *Org. Syntheses*, **28**, 1 (1948).

[13] F. Stockhausen and L. Gattermann, *Ber.*, **25**, 3536 (1892).

and then held at this temperature for 15 minutes more. A dark red color developed during the reaction. Hydrolysis yielded a greenish-brown, sticky solid. It was washed well with water and then digested with 300 ml. of 10% sodium hydroxide solution. The insoluble residue was filtered, washed with water and air-dried. Further purification was effected by digesting the dry solid with 100 ml. of hot ethanol, filtering and then washing with another 100 ml. of hot ethanol. Recrystallization of the solid from dimethylformamide gave, as a first fraction, 8.6 g. of a yellow crystalline solid, m.p. 241–243°. Reworking of the mother liquor yielded an additional 1.5 g. of yellow crystals of the same melting point, and 9.0 g. of very impure mixture (m.p. 130–235°). This mixture could not be further separated into its components. The total yield of product, m.p. 241–243°, was 10.1 g. (15%). Recrystallization from dimethylformamide raised the melting point to 244°.

Anal. Calcd. for $C_{26}H_{19}NO_2$: C, 82.73; H, 5.07; N, 3.71. Found: C, 82.79; H, 4.91; N, 3.61.

Infrared absorption maxima: 3305, 1652, 1640, 1610, 1600, 1582, 1505, 1339, 1285, 840, 740 and 696 cm.$^{-1}$.

The amine (m.p. 244°) reacted with acetic anhydride to give an amide, melting point 142°.

Anal. Calcd. for $C_{28}H_{21}NO_3$: C, 80.17; H, 5.05; N, 3.34. Found: C, 80.41; H, 5.31; N, 3.35.

In the presence of hydroxylamine a mixture of solid oximes was obtained, which resisted attempts at purification.

p-Toluic acid and diphenylamine react in an analogous manner, giving yellow crystals, melting point 206°.

Anal. Calcd. for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 82.79; H, 5.47; N, 3.47.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Action of Lithium Aluminum Hydride and Phenyllithium on Phenylated Chalcones[1]

BY ROBERT E. LUTZ AND EVERETT H. RINKER, JR.

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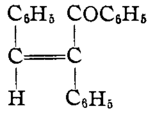
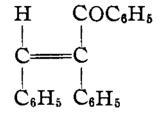
Aluminum isopropoxide in normal fashion reduces the carbonyl of *trans*- but not of *cis*-α-phenylchalcone; lithium aluminum hydride reduces the carbonyls of both, and also the carbonyl of α,β-diphenylchalcone. Phenyllithium adds 48% 1,2 and 33% 1,4 to the *trans* isomer but chiefly 1,4 to the *cis;* and it adds only 1,2 to the carbonyl of α,β-diphenylchalcone. These results are shown to fit a consistent pattern.

The configurations and conformations of the *cis*- and *trans*-α-phenylchalcones (I and II) have been demonstrated.[2] In certain nucleophilic 1,4-additions it has been shown that the *trans* isomer has the more effectively conjugated α,β-unsaturated ketone system. In the *cis* isomer the *cis*-stilbene is the more planar and more effectively conjugated system and the benzoyl group is forced out of the plane of conjugation; the carbonyl, while freer from the influence of conjugation with the ethylene double bond, is at the same time more seriously shielded sterically than in the *trans* isomer because it is boxed in by both the α- and β-phenyls. Examples of favored attack on the α,β-unsaturated ketone system of the *trans* isomer are addition of hydrogen chloride, base-catalyzed addition of desoxybenzoin and addition of methoxide ion; an example of hindrance at the carbonyl group is the failure of the *cis* compound to give a phenylhydrazone.[2] It is of particular interest in this connection that phenyl- and ethylmagnesium bromides add predominantly 1,4 to both *cis* and *trans* isomers,[3] and the present investigation was undertaken to confirm and to extend the work in this field.



$$\begin{array}{ccc} C_6H_5 & & COC_6H_5 \\ | & & | \\ C & = & C \\ | & & | \\ H & & C_6H_5 \end{array}$$

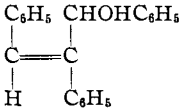
I *cis* (m.p. 89°)



$$\begin{array}{ccc} H & & COC_6H_5 \\ | & & | \\ C & = & C \\ | & & | \\ C_6H_5 & & C_6H_5 \end{array}$$

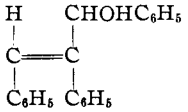
II *trans* (m.p. 101°)

Aluminum isopropoxide reduction of *trans*-α-phenylchalcone (II) (a repetition of an earlier experiment[4]) gave the corresponding alcohol IV in almost quantitative yield. The structure assigned to the product was confirmed by its stilbene-like ultraviolet absorption at 260 mμ, by its infrared hydroxyl band at 2.86 μ, and by the absence of either ultraviolet or infrared bands typical of the benzoyl or carbonyl groups. Chromic acid oxidized the alcohol to the *trans*-α-phenylchalcone (II), but this fact does not demonstrate retention of configuration during these transformations because the *cis*-alcohol III (to be described below) is oxidized similarly to the same *trans*-ketone II.



$$\begin{array}{ccc} C_6H_5 & & CHOHC_6H_5 \\ | & & | \\ C & = & C \\ | & & | \\ H & & C_6H_5 \end{array}$$

III *cis* (m.p. 101°)
(a *trans*-stilbene)



$$\begin{array}{ccc} H & & CHOHC_6H_5 \\ | & & | \\ C & = & C \\ | & & | \\ C_6H_5 & & C_6H_5 \end{array}$$

IV *trans* (m.p. 93°)
(a *cis*-stilbene)

cis-α-Phenylchalcone (I) was recovered unchanged under reducing conditions comparable to those employed successfully to reduce the *trans* isomer.

These results are consistent with expectations based on the carbonyl-specificity of the reagent, and on the high degree of steric hindrance at the carbonyl in the *cis* compound[5] which would be expected adversely to affect its reducibility.

Lithium aluminum hydride reduction of *trans*-α-phenylchalcone (II) also gives the corresponding 1,2-reduction product IV in excellent yield. This result is of a special interest because, unlike aluminum isopropoxide, lithium aluminum hydride does on occasion react 1,4 with an α,β-unsaturated ketone in which the carbonyl group is sterically hindered as it is in vinyl mesityl ketones.[6]

As was anticipated this reagent, which is much

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[1] This work was supported by a research grant from the Office of Ordnance Research.

[2] W. B. Black and R. E. Lutz, THIS JOURNAL, **75**, 5990 (1953); *cf.* also references cited therein.

[3] E. P. Kohler, *Am. Chem. J.*, **36**, 177, 511 (1906).

[4] (a) F. Bergmann, *J. Org. Chem.*, **6**, 443 (1941); (b) F. Bergmann, D. Shapiro and H. E. Eschinazi, THIS JOURNAL, **64**, 559 (1942).

[5] *Cf.* "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 187.

[6] *Cf.* R. E. Lutz and D. F. Hinkley, THIS JOURNAL, **72**, 4091 (1950).