[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Friedel–Crafts Reaction with *o*-Nitrophenol and Acyl Halides[1]

BY FRANCES C. BROWN

According to the present conception of the Friedel–Crafts reaction, a positive alkyl or acyl ion attacks the aromatic hydrocarbon at that position where the center of electron density is greatest. When the electron density of the hydrocarbon is decreased by the presence of meta-directing substituents, reaction takes place less readily or fails completely. Nitrobenzene is so inert that it may be used as a solvent for other more reactive aromatic hydrocarbons. The presence of an ortho-para-directing substituent in nitrobenzene should increase the electron density sufficiently to give appreciable yields of the product of the Friedel–Crafts reaction. A systematic investigation of the reaction of such compounds with various acyl halides seems desirable.[2]

Stockhausen and Gattermann[3] acylated *o*-nitroanisole and *o*-nitrophenetole dissolved in carbon bisulfide. With *o*-nitroanisole, they obtained a 9% yield of 3-nitro-4-methoxyacetophenone and a smaller amount of 3-nitro-4-hydroxyacetophenone. When this work was repeated using nitrobenzene instead of carbon bisulfide and keeping the reaction mixture at a temperature of 75–80° for one and one-half hours, the yields of 3-nitro-4-methoxyacetophenone and of 3-nitro-4-hydroxyacetophenone were increased to 13 and 44%, respectively. Behaghel and Ratz[4] repeated the same experiment, using nitrobenzene as the solvent and a reaction temperature of 0°, and obtained a 36% yield of 3-nitro-4-methoxyacetophenone with slight amounts of the hydroxy ketone.[5] It is evident that at the higher temperature cleavage of the ether linkage takes place to a greater extent.

Since the conditions used in the preliminary experiment gave a favorable yield of 3-nitro-4-hydroxyacetophenone, the reaction was tried with 0.2 mole of *o*-nitrophenol, 0.3 mole of acetyl chloride, 0.55 mole of aluminum chloride, and nitrobenzene as solvent. A 47% yield of the crude ketone was obtained and 46% of the nitrophenol was recovered. The melting point of the purified product was 132–132.5° as compared with 130.5° reported by Stockhausen and Gattermann.[3] The same compound was obtained by the nitration of *p*-hydroxyacetophenone by Pope (m. p. 135°)[6] and by Edkins and Linnell (m. p. 129.5°).[7] In spite of the fact that Edkins and Linnell report that they were unable to obtain ketone derivatives of this compound, no difficulty was encountered in the preparation of the phenylhydrazone or the 2,4-dinitrophenylhydrazone.

In a series of reactions the same general procedure was followed and the reaction of *o*-nitrophenol with propionyl chloride, *n*-butyryl chloride, *n*-valeryl chloride and *n*-caproyl chloride was investigated. Reaction occurred in all cases, and the corresponding 3-nitro-4-hydroxyphenyl ketone was obtained. A similar procedure was used with *p*-nitrodiphenyl and benzoyl chloride and resulted in a 43% yield of 4-nitro-4'-benzoyldiphenyl, m. p. 158.2–159.8°.[8] The per cent. yield of the crude reaction product, the per cent. of *o*-nitrophenol recovered, the solvent used in recrystallization, the melting point of the purified ketone, and the analytical results are assembled in Table I.

Table II gives the melting point and analytical results of the 2,4-dinitrophenylhydrazone of each ketone reported in Table I.

The pharmacological properties of the ketones reported in Table I were investigated by Dr. Henry Kohn of the Duke Medical School. He found that the first member of the series is mildly bacteriostatic, and that there is a progressive decrease in bacteriostatic power with the increase in the length of the carbon chain.

As the Fries shift is closely related to the Friedel–Crafts reaction, the effect of aluminum chloride on *o*-nitrophenyl acetate was studied. This reaction was attempted by Lindemann and Romanoff.[9] They state that a mixture of *o*-nitrophenyl acetate and aluminum chloride decomposes when heated to about 60° with the formation of a bad smelling gas and considerable darkening of the contents of the flask. They obtained no ketone. In the present attempt to bring about a Fries shift with *o*-nitrophenyl acetate, the same conditions were used which were successful in the preparation of 3-nitro-4-hydroxyacetophenone from *o*-nitrophenol by the Friedel–Crafts reaction. *o*-Nitrophenyl acetate, dissolved in nitrobenzene, was added to a solution of aluminum chloride in nitrobenzene and the reaction mixture heated on the water-bath. When the

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(1) Presented before the meeting of the Organic Division of the American Chemical Society in Buffalo, September, 1942.

(2) Borsche and Barthenheier, *Ann.*, **553**, 250 (1942), have investigated the Friedel–Crafts reaction with aromatic hydrocarbons containing the methoxyl group in addition to meta-directing groups and have acylated the following compounds: *o*-nitroanisole, *o*-methoxyacetophenone, methyl *o*-methoxybenzoate and *o*-methoxybenzonitrile.

(3) Stockhausen and Gattermann, *Ber.*, **25**, 3521 (1892).

(4) Behaghel and Ratz, *ibid.*, **72**, 1266 (1939).

(5) In this connection it is interesting that Gilman, Parker, Bailie and Brown, THIS JOURNAL, **61**, 2840 (1939), report that when nitrobenzene is used as the solvent, 3-nitrodibenzofuran will give a 93.5% yield of 2-acetyl-7-nitrodibenzofuran, but that no reaction occurs when carbon bisulfide is the solvent.

(6) Pope, *Proc. Chem. Soc.*, **28**, 331 (1912).

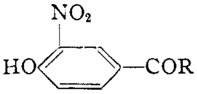
(7) Edkins and Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 90 (1936).

(8) Hey and Jackson, *J. Chem. Soc.*, 805 (1936), obtained the same product, m. p. 154–156°, by the nitration of *p*-benzoyldiphenyl.

(9) Lindemann and Romanoff, *J. prakt. Chem.*, **122**, 227 (1929).

TABLE I

3-NITRO-4-HYDROXYPHENYL KETONES

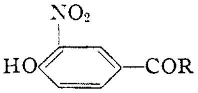


R group	Yield, %	o-Nitrophenol recov., %	Recrystn. solvent	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	47	46	Ethyl alcohol	132–132.5	7.7	7.8
C_2H_5[a]	41	23	Ligroin (70–90°)	65.4–66.2	7.2	6.9
(n-C_3H_7)	43	36	Ligroin (70–90°)	47.6–48.2	6.7	6.8
(n-C_4H_9)	34	27	Ligroin (70–90°) Pet. ether (30–60°)(1:1 mixture)	27.4–28.2	6.3	6.1
(n-C_5H_{11})	26	14	Pet. ether (30–60°)	37.2–37.6	5.9	6.0

[a] This compound has been prepared by Edkins and Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 215 (1936), by the nitration of *p*-hydroxypropiophenone, m. p. 66°.

TABLE II

2,4-DINITROPHENYLHYDRAZONES OF



R group	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	244–244.5	19.4	19.1
C_2H_5	219.6–220	18.7	18.7
(n-C_3H_7)	192.4–192.8	18.0	17.7
(n-C_4H_9)	167.8–168.4	17.4	17.2
(n-C_5H_{11})	162.6–163.2	16.8	16.7

product was worked up, both *o*-nitrophenol and 3-nitro-4-hydroxyacetophenone were obtained in 43 and 33% yields, respectively. Evidently the use of nitrobenzene as a solvent moderates the reaction sufficiently to permit fair yields of the phenol and of the ketone.

Experimental

3-Nitro-4-hydroxyacetophenone.—To a well-stirred mixture of 74 g. of aluminum chloride in 100 ml. of nitrobenzene was added a solution of 28 g. of *o*-nitrophenol, 24 g. of acetyl chloride and 75 ml. of nitrobenzene. After the addition was complete, the solution was stirred at 55–60° for two and one-half hours and overnight at room temperature. Hydrolysis was accomplished by pouring onto a mixture of 500 g. of ice and 100 ml. of concentrated hydrochloric acid. The acid solution was steam distilled to remove nitrobenzene and unreacted *o*-nitrophenol. The ether extract of the residue was extracted with 3% sodium hydroxide solution. Upon acidification of the basic solution with hydrochloric acid, 17.1 g. of 3-nitro-4-hydroxy acetophenone was obtained. Recrystallization from alcohol gave a product melting at 132–132.5°.. When the nitrobenzene solution was extracted with 3% sodium hydroxide and the alkaline solution acidified, 13 g. of *o*-nitrophenol, m. p. 41–43, was obtained.

3-Nitro-4-hydroxyacetophenone Phenylhydrazone.—A mixture of 1 g. of the ketone, 1.2 g. of phenylhydrazine hydrochloride, 1.5 g. of sodium acetate and 20 ml. of water was heated on a water-bath for ten minutes, filtered hot, washed with water, and produced 1.6 g. of crude product. This was recrystallized twice from a solution of three parts acetone, two parts ethyl alcohol and one part water. Red needles, m. p. 195–196, were obtained.

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: N, 15.5. Found: N, 15.7.[10]

3-Nitro-4-hydroxyacetophenone 2,4-Dinitrophenylhydrazone.—This was prepared by the method of Brady.[11] The dinitrophenylhydrazone separated immediately, and was recrystallized from acetic acid. The melting point and analytical data are given in Table II.

The other ketones and their derivatives were prepared in a similar manner. Detailed information is given in Tables I and II.

Fries Shift of *o*-Nitrophenyl Acetate.—*o*-Nitrophenyl acetate was prepared by the method of Lindemann and Romanoff.[9] After extracting with ice cold sodium hydroxide solution, it was washed with ice and water, and recrystallized from ligroin, m. p. 38–39°. In the rearrangement experiment, 18.1 g. (0.1 mole) *o*-nitrophenyl acetate, dissolved in nitrobenzene, was added to a well-stirred solution of 60 g. (0.45 mole) of aluminum chloride in nitrobenzene. After the addition was complete, the solution was heated to 95° for one and one-half hours. Twenty-four hours later, the product was hydrolyzed and worked up in the same manner as the Friedel–Crafts reaction product. The yield of the crude *o*-nitrophenol was 6 g. (43%) and of the crude 3-nitro-4-hydroxyacetophenone, 6 g. (33%). On purification, 3.9 g. of *o*-nitrophenol, m. p. 43–45°, and 4.75 g. of 3-nitro-4-hydroxyacetophenone, m. p. 130–131.2°, were obtained.

Summary

The Friedel–Crafts reaction of *o*-nitrophenol and acyl halides proceeds smoothly in nitrobenzene and produces the corresponding ketones in fair yields.

o-Nitrophenyl acetate, dissolved in nitrobenzene, undergoes the Fries shift and produces *o*-nitrophenol and 3-nitro-4-hydroxyacetophenone.

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(10) Analysis by Saul Gottlieb. All other analyses are by William Saschek.

(11) As described in Campbell, "Qualitative Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1939, p. 87.