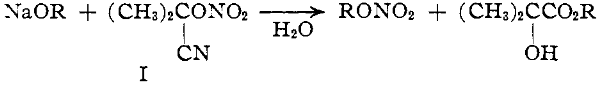
Alkaline Nitration. III. The Reaction of Acetone Cyanohydrin Nitrate with Metal Alkoxides[1]

By William D. Emmons and Jeremiah P. Freeman

Received April 25, 1955

In view of the unique reactivity of acetone cyanohydrin nitrate (I) as an alkaline nitrating agent,[2] its reaction with metal alkoxides has been investigated as a synthetic route to nitrate esters. This study was initiated when it was found that the nitration of active methylene compounds with acetone cyanohydrin nitrate could not be accomplished with sodium ethoxide as a catalyst since this base rapidly destroyed the nitrate ester. It now has been found that this reaction proceeds with the production of two compounds, *i.e.*, the desired nitrate ester and the corresponding ester of α-hydroxyisobutyric acid. The reactions were carried out in tetrahydrofuran employing a molar excess of alkoxide. The alkoxide was prepared from the appropriate alcohol and sodium hydride. Table I summarizes the experimental results.



$$\mathrm{NaOR} + \underset{\mathrm{CN}}{\underset{|}{(\mathrm{CH_3})_2\mathrm{CONO_2}}} \xrightarrow[\mathrm{H_2O}]{\mathrm{H^+}} \mathrm{RONO_2} + \underset{\mathrm{OH}}{\underset{|}{(\mathrm{CH_3})_2\mathrm{CCO_2R}}}$$

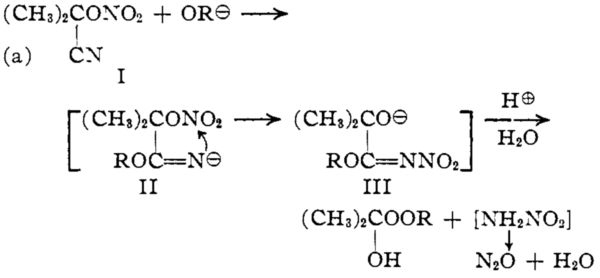
I

Table I

Reaction of Alcohols with Acetone Cyanohydrin Nitrate

Alcohol	Ester yield,[a] % Nitrate	Ester yield,[a] % α-Hydroxy-isobutyric
n-Amyl	20	33
n-Hexyl	22	33
n-Octyl	26	36

[a] Based on acetone cyanohydrin nitrate.



$$\text{(a)}\quad \underset{\mathrm{I}}{\underset{\mathrm{CN}}{\underset{|}{(\mathrm{CH_3})_2\mathrm{CONO_2}}}} + \mathrm{OR}^{\ominus} \longrightarrow \left[\underset{\mathrm{II}}{\underset{\mathrm{ROC{=}N^{\ominus}}}{\underset{|}{(\mathrm{CH_3})_2\mathrm{CONO_2}}}} \longrightarrow \underset{\mathrm{III}}{\underset{\mathrm{ROC{=}NNO_2}}{\underset{|}{(\mathrm{CH_3})_2\mathrm{CO}^{\ominus}}}}\right] \xrightarrow[\mathrm{H_2O}]{\mathrm{H}^{\oplus}} \underset{\mathrm{OH}}{\underset{|}{(\mathrm{CH_3})_2\mathrm{COOR}}} + \underset{\mathrm{N_2O + H_2O}}{\underset{\downarrow}{[\mathrm{NH_2NO_2}]}}$$

The formation of an α-hydroxy ester as the predominant product of this reaction was surprising. Attack of the alkoxide ion at the nitrile group might be expected to lead to an α-nitrato ester as it is highly unlikely that the negatively charged intermediate II could undergo further attack by alkoxide at the nitro group. For instance, it can be observed qualitatively that acetone cyanohydrin nitrate reacts much more rapidly with alkoxide ions than does ethyl α-nitratoisobutyrate, the uncharged oxygen analog of intermediate II. This difference in reactivity is in line with the proposed general mechanism[2] of nitrations with acetone cyanohydrin nitrate which attributes its unique reactivity to the concerted fragmentation of the cyanohydrin leaving group. It is suggested that the denitration step may be an intramolecular one initiated by the strongly nucleophilic imide ion (equation a). Subsequent hydrolysis of intermediate III would produce the α-hydroxy ester with loss of the elements of nitramide. Since nitramide is known to decompose to nitrous oxide and water, the gaseous products of the hydrolysis were examined in an infrared spectrometer. Nitrous oxide was identified by the presence of the characteristic doublet at 4.5–4.6 μ. This suggested mechanism is similar to that recently proposed for the hydrolytic rearrangement of another acetone cyanohydrin ester, α-cyanoisopropyl mesitoate.[3] In connection with this study the alkaline hydrolysis of acetone cyanohydrin nitrate also was examined and was found to yield predominantly α-hydroxyisobutyric acid. The ratio of attack at nitrile to attack at the nitro group was approximately 3:1.

These reactions constitute the first in which attack at the nitrile group of acetone cyanohydrin nitrate has been observed. Apparently the alkoxide ion is a less discriminating species than are amines or highly resonance-stabilized anions and the nitrile group activated by the α-nitrato group is sufficiently electrophilic to react with this reagent. This lack of discrimination becomes intelligible in terms of Hammond's recent postulate.[4] Since alkoxide ion is a more powerful nucleophile (a higher energy species) than either amines or active methylene anions, the transition state for this reaction is looser and is closer to reactants than to products. In this situation acetone cyanohydrin nitrate's unique structural features[2] (its ability to undergo concerted fragmentation) become less important and the reagent fails to discriminate between the nitrile and nitro groups.

Experimental[5]

Reaction of Sodium Alkoxides with Acetone Cyanohydrin Nitrate. Sodium *n*-Amylate.—A solution of 17.6 g. (0.2 mole) of *n*-amyl alcohol in 100 ml. of tetrahydrofuran was added slowly to a slurry of 5.0 g. (0.21 mole) of sodium hydride in 100 ml. of tetrahydrofuran. The resulting mixture was heated under reflux for one hour and then cooled to room temperature. A solution of 13.0 g. (0.1 mole) of acetone cyanohydrin nitrate[2] in 50 ml. of tetrahydrofuran was added slowly. Following this addition the reaction mixture was heated under reflux for two hours. At the end of this period it was poured onto ice. The mixture was acidified with hydrochloric acid and exhaustively extracted with ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was distilled, two fractions being taken. The first fraction, b.p. 52–65° (20 mm.) consisted of a mixture of *n*-amylnitrate and unreacted amyl alcohol. It was found that these two materials are most effectively separated by slurrying the mixture with silica[6] in methylene chloride following by filtration. Ten grams of silica and 25 ml. of methylene chloride were used per gram of the mixture. The alcohol was preferentially adsorbed and the nitrate ester was washed through; yield of **_n_-amyl nitrate**, 2.6 g. (20%).

The second fraction, b.p. 86–87° (9 mm.), consisted of **_n_-amyl α-hydroxyisobutyrate**, yield 5.8 g. (33%). Redistillation yielded an analytical sample, b.p. 76° (2.6 mm.), $n^{20}\mathrm{D}$ 1.4208.

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[1] This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

[2] W. D. Emmons and J. P. Freeman, This Journal, **77**, 4387 (1955).

[3] J. P. Freeman and G. B. Lucas, *ibid.*, **77**, 2334 (1955).

[4] G. S. Hammond, *ibid.*, **77**, 334 (1955).

[5] We are indebted to Miss Annie Smelley for the microcombustion data and to Dr. Keith S. McCallum for infrared interpretations.

[6] G. Frederick Smith Chemical Company, Columbus, Ohio.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.94; H, 10.41. Found: C, 62.55; H, 11.09.

Sodium *n*-Hexylate.—The same general procedure was followed. From 20.4 g. (0.2 mole) of *n*-hexyl alcohol, 5.0 g. (0.21 mole) of sodium hydride and 13.0 g. (0.1 mole) of acetone cyanohydrin nitrate there was obtained, after following the same purification procedure outlined above, 3.3 g. (22%) of ***n*-hexyl nitrate**, b.p. 68–70° (13 mm.), $n^{25}D$ 1.4176 [lit.[7] b.p. 46° (1 mm.), $n^{25}D$ 1.4180], and 6.3 g. (33%) of ***n*-hexyl α-hydroxyisobutyrate**, b.p. 78° (0.3 mm.), $n^{20}D$ 1.4248.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.61; H, 11.31.

Sodium *n*-Octylate.—Following the general procedure described, from 26.0 g. (0.2 mole) of *n*-octyl alcohol, 5.0 g. (0.21 mole) of sodium hydride and 13.0 g. (0.1 mole) of acetone cyanohydrin nitrate there was obtained, after purification, 5.2 g. (26%) of ***n*-octyl nitrate**, b.p. 55–56° (0.3 mm.), $n^{20}D$ 1.4280 [lit.[8] b.p. 110–112° (20 mm.)], and 7.8 g. (36%) ***n*-octyl α-hydroxyisobutyrate**, b.p. 62–64° (0.05 mm.), $n^{20}D$ 1.4310.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.62; H, 11.18. Found: C, 66.07; H, 10.87.

Alkaline Hydrolysis of Acetone Cyanohydrin Nitrate.—A solution of 13.0 g. (0.1 mole) of acetone cyanohydrin nitrate in 25 ml. of ethanol was added slowly to a solution of 11.2 g. (0.2 mole) of potassium hydroxide dissolved in 100 ml. of ethanol. The reaction was noticeably exothermic. The mixture was heated under reflux for two hours and then poured on ice. The water solution was extracted with ether to remove any unreacted nitrate ester (only a trace was found), then acidified with dilute sulfuric acid and subjected to continuous ether extraction for 18 hours. Upon drying the extracts and evaporating the ether, 7.2 g. (69%) of α-hydroxyisobutyric acid, m.p. 79–82°, was obtained. Its infrared spectrum was identical to that of an authentic sample.

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[7] L. M. Soffer, E. W. Parrotta and J. DiDomenico, THIS JOURNAL, **74**, 5301 (1952).

[8] L. Bouveault and C. Wahl, *Bull. soc. chim. France*, [3] **29**, 957 (1903).

ROHM AND HAAS COMPANY
REDSTONE ARSENAL RESEARCH DIVISION
HUNTSVILLE, ALABAMA

Phosphorus Acids in Organic Systems. II. "Polyphosphoric Acid" as a Catalyst in the Fries Rearrangement

BY PETE D. GARDNER

RECEIVED MARCH 2, 1955

In the course of a study of the "polyphosphoric acid" (PPA) catalyzed acylation reaction, certain anomalies were noted in the case of phenols and their esters[1] which are accountable for in terms of a Fries-type of rearrangement. The Experimental section of the present report describes these results only in so far as they supplement a more recent paper.[2]

Phenyl acetate, for example, gave 35–50% yields of 4-hydroxyacetophenone when treated with PPA at moderate temperatures. Phenyl benzoate under similar conditions afforded a mixture of 4-hydroxybenzophenone and its benzoate. Resorcyl diacetate was converted to 4,6-diacetylresorcinol. In no case was the yield of rearranged product sufficiently high to recommend the method over the classical aluminum chloride catalyzed reaction. The reaction is of interest, however, in that (a) in the case of phenyl benzoate the phenolic ketone was accompanied by its benzoate and (b) exclusively *para* rearrangement products were observed.[3] Some of these observations are consistent with the finding that phosphorus pentoxide in nitrobenzene is effective in the rearrangement[4] with resultant formation of keto esters. These authors also report *para* rearrangement.

When phenyl acetate was allowed to react with benzoic acid, in the catalyst as a medium, the major product was 4-acetylphenylbenzoate accompanied by some of the expected product, 4-benzoylphenyl acetate. This suggests that phenyl acetate is not receptive to attack by benzoyl ion under these conditions and that the observed ratio of products probably represents the result of competitive attack of the phenol moiety by acetyl and benzoyl ions. The acetylation of phenyl benzoate proceeded normally to give a poor yield of 4-acetylphenyl benzoate as the only isolable product. Acetylation of phenyl acetate (or phenol) afforded fair yields of 4-acetylphenyl acetate.

The aluminum chloride catalyzed reaction generally favors 4-substitution at low temperatures and 2-substitution at high temperatures, the 4-substituted product undergoing further rearrangement to the 2-isomer when the temperature is raised.[5] A reasonable explanation of this has been proposed.[6] To determine whether such a relationship exists in the PPA-catalyzed reaction one run (phenyl acetate) was made at 27° for 24 hours. Most of the starting material was recovered along with a very small amount of the 4-isomer. Temperatures higher than 100° did not permit the isolation of any of the 2-isomer but markedly increased the amount of resin formed. Further, to determine whether the 2-isomer might serve as an intermediate in one path to the 4-isomer, a sample of 2-hydroxyacetophenone was treated with the reagent. From a series of experiments of varying times and temperatures, only starting material and ether-insoluble resins could be isolated. The rate of resinification of this substance appeared to be much faster than that of rearrangement of phenyl acetate. Since some resinification occurs in all of these rearrangements, it can be concluded only that the 4-isomer is the more stable one in PPA and none of it is formed *via* the 2-isomer.

Experimental

Rearrangement of Phenyl Acetate.—Under conditions essentially the same as those reported by Snyder and Elston[2] 50% yields of 4-hydroxyacetophenone were obtained. A temperature of 90° for 1.5 hr. reduced the yield to 35%. A mixture of 28.0 g. of phenyl acetate and 250 g. of PPA was allowed to stand at 27° for 24 hr., decomposed with ice and water and the product separated by extraction with ether. Distillation of the liquid thus obtained through a 10-in. helices-packed column afforded 11.5 g. of starting material, b.p. 97–100° (20 mm.), 1.2 g. of intermediate fraction and 3.5 g. of 4-hydroxyacetophenone, b.p. 170–194° (20 mm.), m.p. and mixture m.p. 107–109°. The intermediate fraction yielded only phenyl acetate and 4-hydroxyacetophenone upon separation with aqueous base.

4-Acetylphenyl Acetate. (a) From Phenol.—A solution of 47.0 g. of phenol and 60.0 g. of acetic anhydride in 450 g.

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[1] P. D. Gardner, THIS JOURNAL, **76**, 4550 (1954).

[2] H. R. Snyder and C. T. Elston, *ibid.*, **77**, 364 (1955).

[3] One example[2] of *ortho* rearrangement has been reported.

[4] A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 79 (1943).

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

[6] G. W. Wheland, "Advanced Organic Chemistry," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 565.