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

Application of the Ritter Reaction to Mesityl Oxide and Chalcone

PAUL J. SCHEUER, HENYLSON C. BOTELHO,[1] AND CRELLIN PAULING

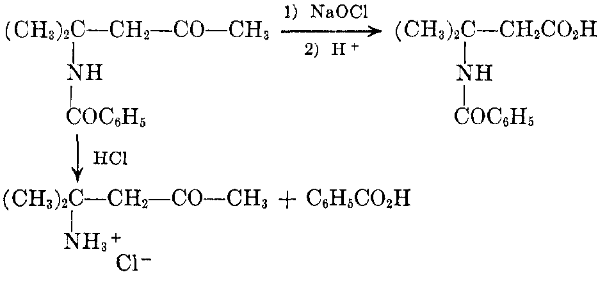
Received November 30, 1956

The acid-catalyzed addition of nitriles to mesityl oxide yields the expected 4-methyl-4-amido-2-pentanones. Chalcone as the olefin component gives rise to only small amounts of the expected adducts in addition to an anomalous product with acetonitrile. The significance of these results is discussed briefly.

An attractive first synthetic step toward the otherwise rather inaccessible 4-oxoperhydroöxindole system seemed to be the acid-catalyzed addition of α-chloroacetonitrile to 2-cyclohexenone according to the general method developed by Ritter.[2] This elegant reaction has since been extended to a variety of systems such as long-chain fatty acids with nitriles[3] or with hydrogen cyanide,[4] olefins with cyanogen chloride,[5,6] haloölefins with nitriles[7,8] and camphene with hydrogen cyanide.[9] Ritter and Hartzel[2d] had successfully utilized several α,β-unsaturated carbonyl compounds such as β,β-dimethylacrylic acid and ethyl cinnamate as the olefin components. However, the results with these systems were less conclusive than with simple olefins as *e.g.*, methyl crotonate or maleic acid failed to react. Furthermore, no report had appeared in the literature of an extension of the Ritter reaction to α,β-unsaturated *ketones* although the Ritter patent[2h] mentions the applicability of the reaction to mesityl oxide. It was therefore felt desirable to study the reaction with some model α,β-unsaturated ketones before proceeding to the cyclohexenone case. This paper deals with the results of these model investigations.

From the standpoint of ready availability and relative dissimilarity mesityl oxide and chalcone were chosen as the model olefin components. Each was reacted with benzonitrile and acetonitrile.

The addition of benzonitrile to mesityl oxide led to the expected 4-methyl-4-benzamido-2-pentanone in yields averaging 50%. The careful experimental directions of Roe and Swern,[3] who in their work with olefinic fatty acids employed an excess of nitrile, were followed initially. But in this case it was found that equimolar quantities of olefin and nitrile led to a more easily purified product. The analytical results and the infrared data (2.91 μ, imine; 5.85 μ, carbonyl; 6.01 μ, amide) were consistent with the structure of the expected adduct. Since this compound had not been reported previously, its structure was confirmed by the following degradative scheme.



$$\underset{\substack{|\\NH\\|\\COC_6H_5}}{(CH_3)_2C}\text{—}CH_2\text{—}CO\text{—}CH_3 \xrightarrow[2)\ H^+]{1)\ NaOCl} \underset{\substack{|\\NH\\|\\COC_6H_5}}{(CH_3)_2C}\text{—}CH_2CO_2H$$

$$\downarrow \text{HCl}$$

$$\underset{\substack{|\\NH_3^+\\Cl^-}}{(CH_3)_2C}\text{—}CH_2\text{—}CO\text{—}CH_3 + C_6H_5CO_2H$$

The haloform reaction led to β-benzamidoisovaleric acid in 80% yield. The acid was characterized by analytical data, neutral equivalent and comparison of the melting point and that of its anilide with those reported for this acid by Baker and Ollis.[10]

The acid hydrolysis of 4-methyl-4-benzamido-2-pentanone furnished benzoic acid identified by direct comparison, but no diacetone amine or any of its salts. In fact, ammonium chloride was the only other hydrolysis product isolated. This, however, is not too surprising in view of the known decomposition of diacetone amine into ammonia and mesityl oxide,[11] which may have been followed by a reverse aldol reaction leading to acetone. Yet no acetone could be detected at the end of the 30-hr. hydrolysis or after making the solution, from which benzoic acid had been removed, alkaline.

If the acid hydrolysis of this *N-tertiary* benzamide had followed the mechanism suggested for such

---

(1) In part from the M. S. Thesis of H. C. Botelho, June 1956.

(2) (a) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948); (b) J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048, (1948); (c) F. R. Benson with J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949); (d) L. W. Hartzel with J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949); (e) R. M. Lusskin with J. J. Ritter, *J. Am. Chem. Soc.*, **72**, 5577 (1950); (f) H. Plaut with J. J. Ritter, *J. Am. Chem. Soc.*, **73**, 4076 (1951); (g) J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.*, **74**, 763 (1952); (h) J. J. Ritter, U. S. Patent **2,573,673** (Oct. 30, 1951).

(3) E. T. Roe and D. Swern, *J. Am. Chem. Soc.*, **75**, 5479 (1953).

(4) E. T. Roe and D. Swern, *J. Am. Chem. Soc.*, **77**, 5408 (1955).

(5) F. M. Cowen, *J. Org. Chem.*, **20**, 287 (1955).

(6) E. M. Smolin, *J. Org. Chem.*, **20**, 295 (1955).

(7) Ch. Malen and J. R. Boissier, *Bull. soc. chim. France*, 923 (1956).

(8) R. Maugé, Ch. Malen, and J. R. Boissier, *Bull. soc. chim. France*, 926 (1956).

(9) G. A. Stein, M. Sletzinger, H. Arnold, D. Reinhold, W. Gaines, and K. Pfister, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

(10) W. Baker and W. D. Ollis, *J. Chem. Soc.*, 345 (1949).

(11) E. H. Rodd, ed., *Chemistry of Carbon Compounds*, Elsevier, New York, 1951, Vol. I, pp. 532–5.

substances by Ritter and Minieri,[2a] the primary products should have been benzamide and mesityl oxide. The amide would be expected to react further to yield benzoic acid and the failure to isolate the olefinic ketone can be rationalized by the previous argument. In spite of this failure there seems to be sufficient evidence to consider the structure of the adduct established beyond doubt.

Acetonitrile could also be added to mesityl oxide to yield the exceedingly hygroscopic 4-methyl-4-acetamido-2-pentanone. The yields of this reaction were only about 20% due to some extent to the difficulty of isolating and handling the water-soluble hygroscopic adduct. Its structure was inferred from analytical and infrared data and by analogy with the benzamido compound.

Chalcone proved to be a far less satisfactory olefin component for the Ritter reaction. Benzonitrile did not add at all below 55°. Above that temperature, formation of large amounts of benzamide and tars could not be avoided even when acetic acid was used as a diluent or when phosphoric acid was substituted for sulfuric acid. Small amounts of 3-benzamido-3-phenylpropiophenone could be isolated by extraction of the solid mixture with cyclohexane or by fractional crystallization from ethyl acetate. Analytical and infrared data served to characterize the compound.

Acetonitrile under a wide variety of conditions yielded only small amounts of the expected 3-acetamido-3-phenylpropiophenone, which was characterized by physical methods and by analogy with the mesityl oxide case. This reaction, however, furnished a major crystalline substance which was neutral, contained nitrogen and *sulfur* and formed a crystalline semicarbazone. The outstanding bands in the infrared spectrum of this compound (5.90 μ, benzoyl; 6.00 μ, amide; 7.38 and 8.53 μ, sulfone) point to the possibility that under the conditions of the reaction (4 hr. at 70–80°) sulfonation followed by intramolecular cyclodehydration might have occurred. A reasonable structure for this product might thus be 2-(1′-acetamido-2′-benzoyl)ethylbenzenesulfonic acid sultam. The combustion data agree with a dihydrate of a substance of this composition and an infrared band at 2.85 μ in the spectrum of the mulled solid also indicates a hydrated compound. However, no chemical structure proof has been carried out as yet.[12]

One point emerges readily if one attempts to rationalize these results. Mesityl oxide in contrast to chalcone can provide a favorable tertiary carbonium ion *beta* to the carbonyl to allow attack by the nitrile nitrogen. This would tend to facilitate normal addition at a temperature at which side reactions are negligible. At the higher temperature which is needed for the chalcone reaction polymerization, or at least dimerization,[13] seems to take precedence over attack on the somewhat less favorable secondary carbonium ion. It would be desirable to test this hypothesis by carrying out the reaction with *e.g.* β-methylchalcone. However, it should be noted that Hartzel and Ritter[2d] obtained a 26% yield of the normal adduct from ethyl cinnamate and only 9% from ethyl β-hydroxy-β-methyl-γ-phenylbutyrate, which is structurally equivalent to a compound with a tertiary *beta*-carbon atom. An attempt to answer the further question of the isolation of the sulfur-containing compound from the acetonitrile but not from the benzonitrile reaction should be deferred until the anomalous product has been fully characterized. It may be pointed out, though, that acetonitrile has been proposed as a good solvent in sulfonation reactions.[14]

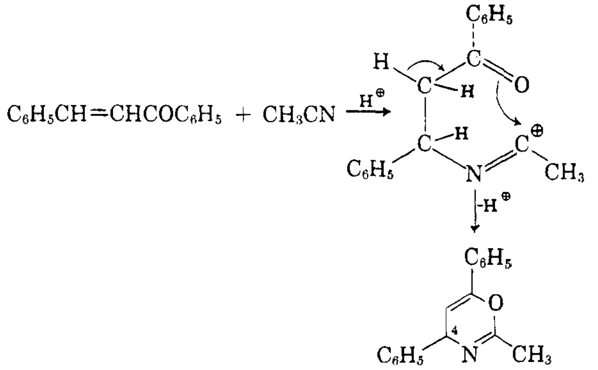
EXPERIMENTAL[15]

4-Methyl-4-benzamido-2-pentanone. To a solution of 19.6 g. (0.2 mole) of mesityl oxide and 22.0 g. (0.21 mole) of benzonitrile[16] was added 20 ml. of concentrated sulfuric acid. The temperature was kept below 30° by means of an ice bath. After addition was complete the reaction mixture was warmed to 50° and was kept at this temperature for 1 hr. The dark viscous liquid was poured into 300 ml. of ice cold water. The resulting solid was filtered and washed with 10% potassium carbonate solution, then with water. Yield, 20–24 g. (45–55%), m.p. 98–100°. Recrystallization from cyclohexene and dilute ethanol furnished white needles, m.p. 100–101°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.34; H, 7.73; N, 5.29, 5.40.

---

[12] We are indebted to Dr. J. J. Ritter who, on the basis of unpublished results from his laboratory, pointed out that the anomalous chalcone-acetonitrile adduct might have arisen through cyclization to an oxazine:



Subsequent sulfonation of the 4-phenyl group would lead to a sulfonic acid of empirical composition identical with that of the suggested sultam. The infrared data and the formation of the semicarbazone could equally well be interpreted on the basis of the oxazine. However, the neutral character of our product would require further cyclization of the oxazinesulfonic acid with concomitant loss of the elements of water.

[13] *cf.* H. Wieland, *Ber.* **37,** 1147 (1904).

[14] D. S. Henderson and A. N. Sachanen, U.S. Patent 2,448,370 (Aug. 31, 1948).

[15] (a) All melting points and boiling points are uncorrected. (b) Microanalyses by Drs. Weiler & Strauss, Oxford, England.

[16] A generous gift of benzonitrile from the Tennessee Products and Chemical Corp. is gratefully acknowledged.

2,4-Dinitrophenylhydrazone prepared by Johnson's[17] method and recrystallized from methanol; yellow needles, m.p. 204–205°.

Anal. Calcd. for $C_{19}H_{21}N_5O_5$: C, 57.13; H, 5.30; N, 17.5. Found: C, 57.10; H, 5.20; N, 18.2.

β-Benzamidoisovaleric acid. The haloform reaction with 4-methyl-4-benzamido-2-pentanone was carried out according to *Organic Syntheses.*[18] The resulting acid was recrystallized from water and from dilute ethanol, m.p. 144–146°. (Reported,[10] 141°.).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83: N, 6.32; Neut. equiv., 221. Found: C, 64.55, 64.53; H, 6.89, 6.75; N, 6.15; Neut. equiv. 222 ± 4 (3 determinations in nonaqueous medium[19]).

The anilide of this acid was recrystallized from water and dilute ethanol. White needles, m.p. 172–173°. (Reported,[10] 170°.)

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 73.47, 73.45; H, 6.80, 6.81; N, 9.25.

Hydrolysis of 4-methyl-4-benzamido-2-pentanone. Four g. of the amide was refluxed for 30 hr. with 50 ml. of 12*N* hydrochloric acid. Cooling led directly to the theoretical amount of benzoic acid, as determined by melting point and mixed melting point. The filtrate failed to react with 2,4-dinitrophenylhydrazine reagent. Upon evaporation to dryness it yielded a residue identified as ammonium chloride.

4-Methyl-4-acetamido-2-pentanone. To a solution of 30.0 g. (0.30 mole) of mesityl oxide and 41.0 g. (1.0 mole) of acetonitrile was added dropwise 60 ml. of concentrated sulfuric acid. The temperature was kept below 30° by external cooling. The mixture was then warmed to 70–80° and kept at that temperature for 2 hr. The viscous mixture was poured into 400 ml. of crushed ice and water and stirred vigorously. It was then neutralized with 20% sodium hydroxide solution and extracted with twelve 50-ml. portions of chloroform. The solvent was removed after drying over magnesium sulfate and the residue distilled *in vacuo.* The fraction boiling 140–146°/28 mm. (12.1 g., 25%) was collected and redistilled. The product, b.p. 145–146°/28 mm. crystallized in a vacuum desiccator and was recrystallized from cyclohexane, m.p. 47.5° in an evacuated capillary.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.84; H, 9.50; N, 7.80.

Yellow *2,4-dinitrophenylhydrazone* recrystallized from ethanol, m.p. 194–195°.

Anal. Calcd. for $C_{14}H_{19}N_5O_5$: C, 49.84; H, 5.68; N, 20.8. Found: C, 50.03; H, 5.56; N, 19.8.

3-Benzamido-3-phenylpropiophenone. A solution of 20.8 g. (0.1 mole) of chalcone[20] in 31.2 g. (0.3 mole) benzonitrile was added over 12 min. to 10.4 g. (0.1 mole) of benzonitrile in 33 ml. of concentrated sulfuric acid. The temperature was kept below 80° during the addition and the mixture was stirred for another hour at 70–80°. It was then poured into 400 ml. of crushed ice and water. After standing for 2 hr. the yellow crystalline material was filtered off. Repeated recrystallizations from ethanol and ethyl acetate removed chalcone and benzamide thus leading to a white crystalline solid, m.p. 158–159°.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.88; H, 5.62; N, 4.10.

The orange-yellow *2,4-dinitrophenylhydrazone* was recrystallized from 95% acetone, m.p. 238–239°.

Anal. Calcd. for $C_{28}H_{23}N_5O_5$: C, 66.00; H, 4.55; N, 13.8. Found: C, 65.22; H, 4.81; N, 13.90.

Reaction of chalcone and acetonitrile. To a solution of 20.8 g. (0.1 mole) of chalcone and 16.4 g. (0.4 mole) of acetonitrile was added 34 ml. of concentrated sulfuric acid while the temperature was kept below 30°. The mixture was then heated to 70–80° for 4 hr. and poured into 300 ml. of ice water. The solids which precipitated immediately were filtered and washed with small portions of chloroform to remove the yellow chalcone. Recrystallization from isopropyl alcohol and dilute ethanol led to a white solid, m.p. 221° (dec.). The substance was neutral and contained nitrogen and sulfur.

Anal. Calcd. for $C_{17}H_{15}NO_4S\cdot 2H_2O$: C, 55.89; H, 5.24; S, 8.77. Found: C, 56.31; H, 5.70; S, 8.70.

The substance formed a colorless semicarbazone which melted at 251–252° after recrystallization from methanol and isopropyl alcohol.

By recrystallizing the chloroform-washed material from dimethylformamide, followed by repeated recrystallizations from water and from dilute ethanol, an analytical sample of the normal adduct, 3-acetamido-3-phenylpropiophenone, m.p. 104–105°, could be obtained.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.41; H, 6.69; N, 4.97.

It formed a yellow *2,4-dinitrophenylhydrazone,* m.p. 211°, after recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{21}N_5O_5$: C, 61.74; H, 4.73; N, 15.6. Found: C, 61.53; H, 4.48; N, 15.2.

Acknowledgment. It is a pleasure to acknowledge the assistance of Dr. C. Djerassi and Dr. R. H. Eastman with the determination of most of the infrared spectra and, particularly, the generous financial support of this work by a grant from Research Corporation.

HONOLULU 14, HAWAII

---

[17] G. D. Johnson, *J. Am. Chem. Soc.,* **73,** 5888 (1951).

[18] *Org. Syntheses,* Coll. Vol 2, 428 (1943).

[19] J. S. Fritz, *Acid-Base Titrations in Non-Aqueous Solvents,* The G. Frederick Smith Chemical Co., Columbus, O., 1952, pp. 28–29.

[20] *Org. Syntheses,* Coll. Vol. 1, 2nd Edition, 78 (1941).