Use of Substituted α-Diazoacetophenones for the Preparation of Derivatives of Sulfonic Acids, *N*-Benzoylated Aminocarboxylic and Aminosulfonic Acids, *N*-Benzoylated Aminophenols, and a *N*-Benzoylated Amino Thiol[1]

THOMAS SUMNER, LAWRENCE E. BALL, AND JOHN PLATNER

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The catalytic decomposition of α-diazoacetophenones in the presence of carboxylic acids yields esters of the acids in good yield.[2] This paper reports the extension of this reaction to sulfonic, aminosulfonic, and aminocarboxylic acids and also to amino phenols and an amino thiol.

The overall reaction is:

$$R{-}COCHN_2 + H^+ + A^- \xrightarrow{CuCl_2} R{-}COCH_2A + N_2$$

This reaction affords a rapid and convenient method for the conversion of many acids to their phenacyl esters. These compounds are usually crystalline, are easily purified, and have convenient melting points. They have long been widely used as derivatives for the identification of acids, but their preparation has frequently involved the use of disagreeable reagents.

Simple sulfonic acids react smoothly to give esters in good yield (Table I).

TABLE I

ESTERS[a] PREPARED BY THE REACTION OF *p*-BROMO-α-DIAZOACETOPHENONE WITH SULFONIC ACIDS

Acid	% Br Theory	% Br Found	M.P. of Esters (°C.)[3]
Methanesulfonic	27.27	27.09	118–119
Ethanesulfonic	26.01	25.83	87–88
Benzenesulfonic	22.50	22.77	110–111
p-Toluenesulfonic	21.64	21.60	127.5–129
2,5-Xylenesulfonic	20.85	20.62	114
m-Nitrobenzenesulfonic	19.60	19.78	125–126
p-Nitrobenzenesulfonic	19.60	19.82	173–174
2-Nitrobromobenzene-4-sulfonic	33.36	33.29	127
Thymolsulfonic	18.78	18.80	171–172
2-Chloro-5-nitrobenzenesulfonic	26.54	26.30	191–192
D-Camphorsulfonic	18.34	18.70	113–115
m-Benzenedisulfonic	25.70	24.70	68–69

[a] These esters were purified by method A.

The reaction of α-diazoacetophenones with aminosulfonic and aminocarboxylic acids fails to produce esters, probably because of the inner salt structures of these compounds which do not dissociate to produce the H^+ ion necessary for the reaction. Mixtures of the aminosulfonic acids and hydrochloric acid were also unsuccessful, the α-diazoacetophenones reacting preferentially with the mineral acid, producing α-chloroacetophenones. However, conversion of the amino group to its benzoyl derivative destroys the inner salt and permits the acid group to react to produce the desired esters (Table II).

TABLE II

ESTERS PREPARED BY THE REACTION OF *p*-NITRO-α-DIAZOACETOPHENONE WITH THE *N*-BENZOYLATED DERIVATIVES OF AMINOCARBOXYLIC ACIDS AND AMINOSULFONIC ACIDS

Acid	Purification Method	% N_2 Theory	% N_2 Found	M.P. of Esters (°C.)[3]
Glycine	B or C	8.13	8.12	134–134.5
p-Aminobenzoic	B or C	7.25	7.22	222–223
2-Aminoethyl hydrogen sulfate	D	6.86	6.83	135–136
p-Aminobenzenesulfonic	D	6.36	6.33	129–130
8-Amino-2-naphthalene sulfonic	D	5.71	5.70	128

The same substitution also allows the acid group of amino phenols and thiols to react to produce the respective ethers or thioethers.

The esters, ethers, and thioethers listed in Tables I, II, and III are believed to be new compounds.

TABLE III

ETHERS AND A THIOETHER PREPARED BY THE REACTION OF *p*-NITRO-α-DIAZOACETOPHENONE WITH THE *N*-BENZOYLATED DERIVATIVES OF AMINO PHENOLS AND AN AMINO THIOL

Phenol or Thiol	Purification Method	% N_2 Theory	% N_2 Found	M.P. of Ethers (°C.)[3]
p-Aminophenol	B	7.45	7.41	207–208
o-Aminophenol	B	7.45	7.40	183–184
m-Aminophenol	B	7.45	7.42	153–154
5-Amino-2-naphthol	B	6.57	6.64	204–205
o-Aminobenzenethiol	B	7.14	7.38	110–111

EXPERIMENTAL

p-Nitro-α-diazoacetophenone. A solution of 10 g. (0.05 mol.) of *p*-nitrobenzoyl chloride in ether is slowly added to a diazomethane solution prepared from 43 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Eastman Kodak Co. 7066). The diazomethane must be present in more than an excess of 2:1 at all times during the reaction, as the HCl produced in the primary step will react with the diazo-compound to form the ω-chloro derivative unless it is removed by reaction with excess diazomethane. The product is isolated as lemon yellow prisms from the ether solution by evaporation and cooling; m.p. 109–110°. Other diazoacetophenones are prepared in the same manner using the appropriately substituted benzoyl chloride.

N-benzoyl derivatives of amino acids, amino phenols, and an amino thiol. The *N*-benzoyl derivatives were prepared by

(1) Based upon the theses presented by Lawrence E. Ball (1958) and John Platner (1954) to The University of Akron in partial fulfillment of the requirements for the degree of Master of Science.

(2) J. L. E. Erickson, J. M. Dechary, and M. R. Kesling, *J. Am. Chem. Soc.*, **73**, 5301 (1951).

(3) All melting points are uncorrected.

the reaction of the amino compounds with benzoyl chloride in pyridine solutions in the conventional manner.

Phenacyl esters and ethers. The sulfonic acids or substituted amino acids, amino phenols and amino thiols were placed in solution with equimolar quantities of the substituted α-diazo acetophenone in commercial dioxane. No appreciable reaction occurred until a trace (5 mg.) of anhydrous cupric chloride was added. The reaction mixture was then heated to 60–70° for 15 to 20 min. The reaction product was separated and purified by one of the following four methods:

Method A. The reaction mixture is poured slowly into 500 ml. of ice cold water containing 5–10 ml. of 10% K_2CO_3 solution. The ester precipitates and may be collected and recrystallized from alcohol.

Method B. The reaction mixture is heated to boiling and water is slowly added until the solution becomes permanently turbid. The solution is then cooled and the ester or ether crystallizes and may be recrystallized from alcohol.

Method C. Water is added as in method B and the mixture is shaken with an equal volume of chloroform. The chloroform layer is then washed first with 2% K_2CO_3 solution and then with distilled water, and then is dried over anhydrous calcium chloride. The chloroform solution is then concentrated and slowly cooled to −50° by the use of an acetone–dry ice bath. The ester crystallizes, may be rapidly filtered and then may be recrystallized from alcohol.

Method D. The anhydrous chloroform solution of the ester as obtained in method C is evaporated to dryness at low temperature under reduced pressure. The resulting material is recrystallized from alcohol with decolorizing charcoal added.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF AKRON
AKRON 4, OHIO

Preparation and Degradation of 3α-Hydroxycholanic Acid[1]

SHALOM SAREL[2] AND YEHUDA YANUKA

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For another research program, a convenient method was desired for the preparation of 3α-hydroxynorcholanic acid on large scale and in high yield. Since the Barbier-Wieland degradation of 3α-hydroxycholanic acid has been described by several authors,[3,4] this degradation was undertaken.

The first step was the conversion of cholic acid into 3α-hydroxycholanic acid. This conversion was accomplished in 95% over-all yield by the modified Wolf-Kishner reduction[5] of the intermediate, methyl 3α - succinoxy - 7,12 - diketocholanate. The yield reported here could be obtained only when the modified procedure for alkali-sensitive carbonyls was adopted. Otherwise, the yields did not exceed 40%, and the purification of the reduction product was rather tedious. It appears that, unlike the monoketocholanic acids which are smoothly reduced by the ordinary Huang-Minlon modification,[5,6] the above mentioned diketocholanic acid derivative is sensitive to alkali.

The next step was the conversion of methyl 3-hydroxycholanate (I) into 3α-acetoxy-24,24-diphenylchol-23-ene (II). This conversion was accomplished in 90% yield by the known procedures.[3,4] The oxidation step of II with chromic acid in glacial acetic acid was found to be largely dependent upon reaction temperature. The highest yield (65%) of 3α-acetoxynorcholanic acid (III) was attained only when this oxidation was performed at 40–45°. Above and below this narrow temperature range, it was observed that the yield of III tended to decrease rather markedly.

The success of the ruthenium oxide–catalyzed oxidation of olefinic bonds with periodate[7] prompted the investigation of this new method for the oxidation of II into III. The present note describes the results of the use of ruthenium oxide as catalyst for the oxidation step involved in the Barbier-Wieland degradation of I.

The new method has proved to be successful with II. This involved the use of aqueous acetone (80–85%), 5 mole % of ruthenium tetroxide, and 140 mole % of solid sodium metaperiodate at 15–25°. II was readily oxidized to III and benzophenone in 78–83% yield. The over-all yield of 3α-hydroxynorcholanic acid from cholic acid was more than 70%. Osmium tetroxide,[8] used in place of ruthenium tetroxide, was found to be completely ineffective.

EXPERIMENTAL[9]

Preparation of 3α-hydroxycholanic acid. Methyl cholate (106 g.) was first converted into methyl 3α-succinoxy-7,12-diketocholanate (not isolated) by the procedure previously described,[10] and then it was mixed with 85% hydrazine hydrate (500 ml.) and ethylene glycol (1000 ml.) and the mixture was heated for 1 hr. at 100°. The resulting clear solution was cooled and then potassium hydroxide pellets (200 g.) were added portionwise through the condenser during 30 min. at room temperature. The condenser was then removed and the reaction mixture was slowly heated allowing the temperature to rise to about 200°. After re-

(1) Presented before the 21st meeting of the Israel Chemical Society, Jerusalem, 1957 [*Bull. Res. Council Israel*, 6A, 286 (1957)].

(2) Formerly Shalom Israelashvili.

(3) W. M. Hoehn and H. L. Mason, *J. Am. Chem. Soc.*, **62**, 569 (1940).

(4) C. Meystre and K. Miescher, *Helv. Chim. Acta*, **29**, 33 (1946).

(5) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(6) I. G. Anderson, G. A. D. Haselwood, H. S. Wiggins, and I. D. P. Wooton, *Nature*, **169**, 621 (1952).

(7) R. Pappo and A. Becker, *Bull. Res. Council Israel*, **5A**, 300 (1956); for more fully documented accounts of the use of this catalyst, see L. M. Berkowitz and P. N. Rylader, *J. Am. Chem. Soc.*, **80**, 6682 (1958).

(8) R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(9) All m.p.s are uncorrected. Optical rotations were determined with a Zeiss polarimeter with circular scale 0.01°. Infrared spectra were taken with a Baird double beam recording spectrophotometer, Model B.

(10) H. Heusser and H. Wuthier, *Helv. Chim. Acta*, **30**, 2165 (1947).