

A Convenient General Method for the Preparation of Aldehydes and Ketones, III

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Five aldehydes and six ketones were synthesized by a new, mild, and general method. The method has been applied for the first time for the synthesis of ketones. The synthesis appears general for aldehydes and ketones.

IN TWO PREVIOUS publications (6, 7) a new and general procedure for the preparation of aldehydes was described. The method involved the cleavage of *p*-dimethylaminophenylcarbinols with diazotized sulfanilic acid.

This article reports the preparation of five additional aldehydes and six unsymmetrical ketones. The technique has been successfully used, for the first time, for the preparation of moderate quantities of ketones (0.1–0.3 mole) in high purity, Equation 1.

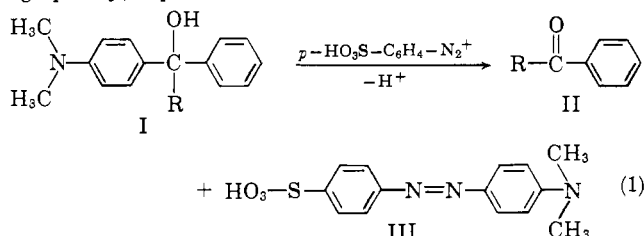


Table I lists the amino carbinols prepared from the corresponding Grignard reagent and *p*-dimethylaminobenzaldehyde (first five entries in Table I), and those prepared from *p*-dimethylaminobenzophenone (3), and the corresponding Grignard reagent (I, R = Alkyl).

The *p*-dimethylaminophenylcarbinols listed in Table I were all converted to the corresponding aldehydes and ketones by the cleavage reaction in yields of 50 to 75 per cent. One notable exception—namely, phenyl cyclohexyl ketone—was produced in only a 23 per cent yield; the low yield is believed due to a solubility problem with the amino carbinol. All carbonyl compounds were characterized by comparison with their previously reported physical properties (m.p. or b.p.) and by conversion to the 2,4-dinitrophenylhydrazones. The 2,4-dinitrophenylhydrazones of isocaprophenone and β -phenylpropiofenone were not previously characterized, and the pertinent data is listed in Table I (footnotes *c* and *d*).

Table I. *p*-Dimethylaminophenylcarbinols^a

$$\begin{array}{c} \text{O-H} \\ | \\ \text{R}'-\text{C}-\text{C}_6\text{H}_4-\text{N}(\text{CH}_3)_2(p) \\ | \\ \text{R} \end{array}$$

R	R'	Yield, o/o	M.P.	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
2-Naphthyl	H	78	81–83	82.31	6.85	5.06	82.38	6.82	5.15
Benzyl ^b	H
4-Diphenyl	H	51	149–150	83.17	6.93	4.62	83.12	6.92	4.56
2-Thienyl	H	78	77–79	66.95	6.44	6.01	67.04	6.43	6.15
2-Phenylvinyl	H	40	89–90	80.63	7.51	5.53	80.53	7.63	5.58
Phenyl	Isovaleryl ^c	66	81–83	80.81	9.09	4.71	80.81	9.05	4.66
Phenyl	2-Phenethyl ^d	84	98–100	83.38	7.55	4.23	82.99	7.48	4.38
Phenyl	Cyclohexyl	62	83–85	81.55	8.74	4.53	81.38	8.85	4.46
Phenyl	Methyl ^b
Phenyl	Benzyl ^b
Phenyl	Ethyl ^b

^aAll carbinols were recrystallized from benzene petroleum ether (30°–60°). All halides were commercial products. ^bCompounds previously reported and characterized (1, 2, 4, 5). ^c2,4-Dinitrophenylhydrazone, m.p. 176–178, from benzene-ethanol; Calcd.

C, 60.50; H, 5.88; N, 15.68; Found C, 60.43; H, 5.89; N, 15.75. ^d2,4-Dinitrophenylhydrazone, m.p. 176–179, from benzene-ethanol; Calcd. C, 64.62; H, 4.62; N, 14.35; Found C, 64.68; H, 4.68; N, 14.45.

PREPARATION OF ALDEHYDES AND KETONES

The experimental procedure for the preparation of aldehydes and ketones has been already described (7) except for the inclusion of the following: before extraction with ether, the reaction mixture was heated to 50° for one-half hour in order to expel dissolved nitrogen and decompose excess diazotizes sulfanilic acid. This operation facilitates the extraction procedure.

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3,4,5-Trimethoxymandelic Acid

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DURING THE INVESTIGATION of the metabolic fate of mescaline, it became necessary to prepare 3,4,5-trimethoxymandelic acid (III) tagged with C-14 in the carboxyl group. The synthesis of this compound is reported herein. No published information concerning this material is available.

Classical methods of hydrolysis of the cyanohydrin formed from 3,4,5-trimethoxybenzaldehyde and potassium cyanide failed to yield the desired product. Alkaline hydrolysis gave a good yield of 3,4,5-trimethoxybenzoic acid, while acid hydrolysis afforded a red, intractable material. The compound was successfully synthesized by acetylation of the cyanohydrin and hydrolysis of the cyanoester (3), and by forming the imino ether from the cyanohydrin and subsequent hydrolysis of the ethyl ester (1). In the preparation of the radioactive material, using C-14 labelled potassium cyanide to form the cyanohydrin, the former synthesis was employed.

Using the method of Rapoport (2), a portion of the radioactive 3,4,5-trimethoxymandelonitrile was converted to carboxyl labelled 3,4,5-trimethoxyphenylacetic acid.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,4,5-Trimethoxymandelonitrile (I) (2). A solution of 13.4 grams (0.13 mole) of sodium bisulfite in 50 ml. of water was added to 19.6 grams (0.1 mole) of 3,4,5-trimethoxybenzaldehyde in a beaker and the mixture stirred for 10 minutes, whereupon the contents solidified. Sufficient water was added to form a paste, the beaker placed in an ice bath, 150 ml. of ether added, and stirring continued for an additional 10 minutes. The lumps of addition product were broken up with a stirring rod, a cold solution of 11.7 grams (0.24 mole) of potassium cyanide in 30 ml. of water was added in one portion and the mixture stirred rapidly for one hour. An additional 20 ml. of ether and 1.4 grams of sodium bisulfite were added and stirring was continued for 30 minutes. After the ether layer was separated, the aqueous solution was extracted with two 25-ml.

portions of ether, the ether extracts were combined and washed with two 25-ml. portions of 20% sodium bisulfite solution and two 25-ml. portions of ice water. The ether solution was chilled in ice, dried with sodium sulfate and the solvent removed in vacuo to give 19 grams (90%) of (I), m.p. 99–100° [ref. (2), m.p. 99.6–100.8° C.] This material was used without further purification in subsequent syntheses.

α -Acetoxy-3,4,5-trimethoxyphenylacetone nitrile (II) (3). To 8 grams (0.036 mole) of (I), previously dried at 60° for 3 hours in a vacuum oven, was added a mixture of 8 ml. of dry pyridine and 20 ml. of acetic anhydride with cooling. The mixture was allowed to stand overnight. To the red solution was added 100 ml. of water and 100 ml. of ether. The separated aqueous layer was extracted with 25 ml. of ether, and the combined ethereal extracts were washed with two 25-ml. portions of water, two 25-ml. portions of 5% sodium bicarbonate solution, and finally with water. The ether solution was dried with sodium sulfate and filtered. The filtrate was shaken with 0.5 gram of activated charcoal, filtered, and the solvent removed under vacuum. Recrystallization of the residue from ethanol-water gave 7.2 gram (90%) of (II), m.p. 68°; b.p. 178–82° at 4 mm. of Hg pressure.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.85; H, 5.70. Found: C, 59.33; H, 5.60.

3,4,5-Trimethoxymandelic acid (III). Dry hydrogen chloride was bubbled through a solution of 5.6 grams (0.025 mole) of (II) in 50 ml. of anhydrous methanol for 30 minutes at 15°. The reaction vessel was protected with a silica gel drying tube. After standing at room temperature for two hours, the excess solvent was removed under water pump vacuum, 75 ml. of water added, the mixture stirred for two hours, 6 grams of sodium hydroxide pellets added, and stirring continued for one hour. Upon acidification with 6N hydrochloric acid and saturation with sodium chloride, the solution was extracted with five 25-ml. portions of ethyl acetate. The extract was dried with sodium sulfate and the solvent removed under vacuum. Recrystallization of the crystalline residue from chloroform-petroleum ether gave 5.0 grams of (III), m.p. 121–121.5°.

Anal. Calcd. for $C_{11}H_{13}O_6$: C, 54.54; H, 5.82; neutralization equivalent 242. Found: C, 54.23, 54.74; H, 5.85, 5.78; neutral. equiv. 245.

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