[CONTRIBUTION FROM ROHM AND HAAS CO.]

The Preparation of Cinnamaldehydes by the Formylation of Styrenes

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The reaction of styrenes with dimethylformamide in the presence of phosphorus oxychloride has been found to yield cinnamaldehydes.

Dimethylformamide, in the presence of phosphorus oxychloride, has been employed to effect the formylation of a number of reactive carbocyclic and heterocyclic compounds. 3-Formylindole has been obtained from indole,[1,2] 2-pyrrolecarboxaldehyde[2-4] from pyrrole, N-methyl-2-pyrrolecarboxaldehyde[4,5] from N-methylpyrrole, 2-thenaldehyde[6] from thiophene and *p*-dimethylaminobenzaldehyde from dimethylaniline.[7]

TABLE I

PREPARATION OF CINNAMALDEHYDES, Ar—C(R)=C(R')—CHO

I, phenylhydrazone; II, semicarbazone; III, oxime

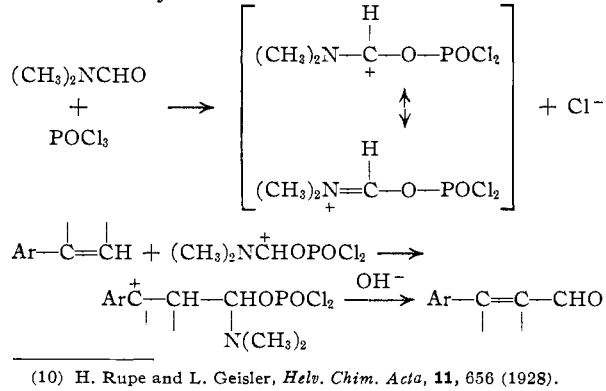
Ar	R	R'	B.p. °C.	Mm.	$n^{25}D$	Yield, % Method A	Yield, % Method B	Derivative	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Phenyl	H	H	84–87	2.0	1.6165	41	38			81.80	81.15	6.10	6.12		
								I	166–168[a]	81.05	81.27	6.35	6.53	12.63	12.54
p-Tolyl	H	H	76–80	0.5			46			82.16	82.41	6.89	7.05		
								II	209–211[b]	65.00	65.26	6.44	6.88	20.68	20.96
Phenyl	CH_3	H	79–84	0.1	1.5861	52	37			82.16	82.22	6.89	7.14		
								I	136–139	81.32	81.23	6.82	6.91	11.86	11.94
								II	201–202[c]	65.00	65.08	6.44	6.50	20.68	20.92
								III	66–68	74.50	75.54	6.88	6.83	8.69	8.60
p-Tolyl	CH_3	H	80–90	0.25	1.5950	62				82.46	82.59	7.55	7.49		
								I	124–125	81.56	81.60	7.25	7.28	11.19	11.13
								II	205–207	66.34	66.45	6.96	6.84	19.34	19.27
p-Isopropylphenyl	CH_3	H	100–114	1.0	1.5700		34			82.93	83.05	8.57	8.61		
								II	198–200	68.54	68.72	7.81	7.68	17.13	17.42
p-Anisyl	H	CH_3	106–109	0.1	1.6290	68	54			74.97	75.11	6.86	7.10		
								I	161–165	76.66	75.95	6.81	6.90	10.52	10.30
3,4-Methylenedioxyphenyl	H	CH_3	110–130	0.1		27				69.44	69.98	5.30	5.48		
								II	230–233	58.29	58.16	5.29	5.30	17.00	17.15
								III	124–126[d]	64.38	64.71	5.40	5.40	6.82	6.81

[a] A mixture with the phenylhydrazone of an authentic sample of cinnamaldehyde showed no depression in m.p. [b] M. Scholtz and A. Wiedmann, *Ber.*, **36**, 851 (1903), reported m.p. 210°. [c] Reference 12 reported m.p. 201–202°. [d] M. T. Bogert and G. Powell, *Am. Perfumer*, **25**, 617 (1930), reported m.p. 124–125°.

The reaction of styrene with N-methylformanilide has been reported[8] to give cinnamaldehyde.

While cinnamaldehyde and α-substituted cinnamaldehydes may be prepared readily by conventional methods, the β-substituted cinnamaldehydes are more difficult to prepare. β-Methylcinnamaldehyde, for example, has been prepared by Arens and Van Dorp[9] by the condensation of acetophenone with hydroxymaleic anhydride followed by decarboxylation, and also by the condensation of acetophenone with organometallic derivatives of ethoxyacetylene followed by partial hydrogenation and hydrolysis. The Rupe rearrangement of methylphenylethynylcarbinol which had been reported[10] to give β-methylcinnamaldehyde has been shown[11] to give phenylbutenone. Royals and Covington[12] have recently prepared β-methylcinnamaldehyde by the lithium aluminum hydride reduction of ethyl β-methylcinnamate followed by the oxidation of the resulting alcohol with activated manganese dioxide.

We have found that a variety of α- and β-substituted styrenes react with dimethylformamide in the presence of phosphorus oxychloride to give cinnamaldehydes.



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The reaction has been carried out in the presence of excess dimethylformamide or ethylene dichloride as solvents. Styrene, *p*-methylstyrene, α-methylstyrene, *p*,α-dimethylstyrene, *p*-isopropyl-α-methylstyrene, anethole and isosafrole have been employed to give cinnamaldehyde, *p*-methylcinnamaldehyde, β-methylcinnamaldehyde, *p*,β-dimethylcinnamaldehyde, *p*-isopropyl-β-methylcinnamaldehyde, *p*-methoxy-α-methylcinnamaldehyde and α-piperonylidenepropionaldehyde, respectively.

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Experimental

Method A. Formylation Using Excess Dimethylformamide.—Seventy-seven grams (0.5 mole) of phosphorus oxychloride was added dropwise with stirring and cooling to 146 g. (2 moles) of dimethylformamide while the temperature was kept below 20°. One-half mole of the olefin was then added. The mixture was heated slowly to 55°. An exothermic reaction took place and cooling was necessary to maintain the temperature at 55–60°. After the exotherm had ceased, the mixture was heated and kept at 75–80° for 1 hr. The mixture was cooled in an ice-bath and a solution of 278 g. (2.75 moles) of anhydrous sodium acetate in 700 ml. of water was added to the mixture slowly at first and then rapidly with stirring and cooling. The mixture was heated to 70–75° for 15 minutes and cooled. The aldehyde was extracted with ether, washed with water, dried over anhydrous magnesium sulfate and distilled.

Method B. Formylation Using Ethylene Dichloride as Solvent.—The procedure of Silverstein, Ryskiewicz, *et al.*,[4] for the formylation of pyrrole was utilized for the formylation of olefins. To 40 g. (0.55 mole) of dimethylformamide, cooled to 5°, was added 84.5 g. (0.55 mole) of phosphorus oxychloride; 125 ml. of ethylene dichloride was then added and the mixture was stirred for 15 minutes while it was cooled to 5°. One-half mole of the olefinic compound dissolved in 125 ml. of ethylene dichloride was added dropwise with stirring over the course of 40 minutes. The mixture was then refluxed for 15 minutes and cooled to room temperature. A solution of 278 g. (2.75 moles) of anhydrous sodium acetate in 600 ml. of water was added to the mixture slowly at first and then rapidly with stirring and cooling. The mixture was refluxed for 15 minutes, cooled and extracted with ether. The upper (organic) layer was separated, washed with water, dried over anhydrous magnesium sulfate and distilled.

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[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Iodinated 3,5-Diaminobenzoic Acid Derivatives[1]

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Thirty-two di- and triiodo-3,5-diaminobenzoic acid derivatives have been prepared and evaluated for use as urographic contrast media. Among this group of compounds 3,5-diacetamido-2,4,6-triiodobenzoic acid is noteworthy as a urographic agent. Investigations into the structures of the diiodo-3,5-diaminobenzoic acid derivatives are reported. Iodination of 3-acylamino-5-aminobenzoic acids was found to be a two-step process wherein the introduction of the third iodine was found to be dependent on the acidity of the media. Directions are given for the preparation of aqueous solutions of potassium iododichloride and some of the advantages of this reagent over iodine chloride are indicated.

As part of a continuing program related to the development of new and useful radiopaques, we have prepared a number of iodinated 3,5-diaminobenzoic acid derivatives and within this group of compounds several have been found which possess the requisite properties for use in urography.

A number of iodinated benzoic and monoaminobenzoic acid derivatives have been prepared in past and investigated for use as radiopaques. The culmination of these various efforts with regard to urography was achieved by Wallingford[2] who prepared 3-acetamido-2,4,6-triiodobenzoic acid and found that it fulfilled in large measure the requirements for visualizing the kidneys. No results, however, had been published previous to the initiation of this present work on the investigation and use of iodinated 3,5-diaminobenzoic acid derivatives as radiopaque agents. In 1896 Lütgens[3] iodinated 3,5-diaminobenzoic acid, isolating 3,5-diamino-2,4,6-triiodobenzoic acid. This compound is, however, much too unstable to be employed as a radiopaque. Subsequent to the start of our investigation Langecker, Harwart and Junkmann[4] reported on the physical and physiological properties of one of the compounds included in this study, 3,5-diacetamido-2,4,6-triiodobenzoic acid.

Two different approaches were employed for the preparation of the iodinated compounds. One of these, used for the preparation of the diiodo and triiodo unsymmetrical diamides (III and V), involved introduction of one of the N-acyl variants prior to iodination. The second procedure was for the preparation of the triiodo symmetrical diamides (VIII), and here the N-acyl groups were introduced following iodination. In connection with the first method, initial attempts to iodinate 3-acylamino-5-aminobenzoic acid (I) in dilute hydrochloric acid media with iodine chloride gave only the diiodo derivative II. Extending the time of reaction and the increasing of the amount of iodine chloride or substitution of acetic acid for the hydrochloric acid were to no avail in isolating the 3-acylamino-5-amino-2,4,6-triiodobenzoic acids (IV). Heating the reaction mixture for any length of time resulted in amide hydrolysis and isolation of 3,5-diamino-2,4,6-triiodobenzoic acid.[5] Successful introduction of the third iodine atom was found to be dependent on reducing the acidity of the reaction media. When an aqueous solution of an alkali or amine salt of 3-

(1) Presented in part at the 126th meeting of the American Chemical Society, New York, September, 1954, Abstracts, p. 11-N.

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(3) J. Lütgens, *Ber.*, **29**, 2836 (1896).

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(5) Iodination of 3-amino-5-formamidobenzoic acid, even under the most gentle conditions, gave only the hydrolysis product, 3,5-diamino-2,4,6-triiodobenzoic acid.