

Aluminum Chloride Catalyzed Formation of Arylamides. A Novel Synthesis¹

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Several general methods for the aluminum chloride catalyzed synthesis of aromatic amides have been reported.² Gattermann allowed carbamyl chloride to react with aromatic compounds to give the corresponding amides. The major disadvantage of the Gattermann synthesis was the instability of carbamyl chloride. Hopff overcame this difficulty by using stable addition compounds of carbamyl chloride with aluminum chloride. Leuckart was also able to synthesize a variety of aromatic amides by the reaction of aryl isocyanates with hydrogen chloride followed by reaction of the resulting arylcarbamyl chloride with the appropriate aromatic compound. Carboxyamidation with cyanic acid or potassium cyanate and hydrogen chloride, in which unstable carbaminic chloride is formed *in situ*, has also been used for arylamide synthesis.

A plausible reaction course (Scheme I), which is an extension of the Hopff mechanism,² is proposed for the carboxyamidation of benzene. Urea reacts with aluminum chloride to produce a urea-aluminum chloride adduct (1). This intermediate is decomposed on heating to give carbaminic chloride (2) and an aluminum chloride salt (3). Carbaminic chloride then reacts with aluminum chloride to provide the reactive carbonium ion (4), which attacks the aromatic nucleus in the conventional manner to give benzamide (5). Several investigators have reported the presence of cyanuric acid in the thermal-decomposition products of urea.^{5,6} It is therefore not surprising that a carbaminic carbonium ion would be generated during the exothermic reaction of urea with anhydrous aluminum chloride.

The postulated intermediate (1) has not been reported in the literature and we have not attempted to characterize it. There was evidence of existence of ammonium aluminum chloride (3) because ammonia was evolved when the aqueous solutions of these salts were neutralized.

The arylamides (Table I) contained *ortho*- and *para*-orientating groups on the aromatic nucleus, but owing to the stronger *para*-orientating groups and to the

TABLE I
ARYLAMIDES

Amide	Mp, °C			% yield	Calcd, %				Found, %			
	Literature	Reference ^a	Found		C	H	N	X	C	H	N	X
Benzamide	130	IX, 195	128-129	6	69.40	5.83	11.56		69.62	6.06	11.26	
4-Chlorobenzamide	179	IX, 341	179-180	2	54.02	3.89	8.99	22.81	54.06	4.11	9.15	22.93
4-Fluorobenzamide	154.5	IX-I, 137	156-157	6	60.43	4.35	10.06	13.30	60.67	4.34	9.93	13.42
4-Hydroxybenzamide	162	X, 164	151-152	13	61.31	5.15	10.21		61.54	4.99	10.38	
4-Phenylbenzamide	222-223	IX, 672	229-230	27	79.16	5.62	7.10		79.00	5.53	7.19	
4-Methylbenzamide	159-160	IX, 486	157-158	4	71.09	6.71	10.36		71.10	6.62	10.08	
3-Chloro-4-methylbenzamide		<i>b</i>	162-163	14	56.63	4.75	8.26	20.93	56.58	4.64	8.07	20.64
3,4-Dimethylbenzamide	130-131	IX, 536	105-106	9	72.46	7.43	9.38		72.45	7.47	9.50	
2,4,6-Trimethylbenzamide	187-188	IX, 553	190-191	25	73.59	8.03	8.58		73.64	8.00	8.40	
4-Methoxybenzamide	166.5-167.5	X, 164	167-168	22	63.56	6.00	9.27		63.47	5.98	9.24	

^a "Beilstein's Handbuch," 4th ed, Julius Springer Verlag, Berlin 1926-1927. ^b Not found in the literature.

While a urea-aluminum chloride solvent system for the reaction of carbohydrates with aromatic compounds was being investigated, unexpected crystalline by-products were isolated. Purification and characterization of these compounds revealed that arylamides had been formed by a novel route that utilized urea as the carboxyamidating agent.

Addition of urea to anhydrous aluminum chloride results in an exothermic reaction, and in formation of a fluid system which has been used as a solvent-catalyst for various chemical reactions.^{3,4} We have synthesized 10 arylamides (Table I) by reaction between the appropriate aromatic compounds and this urea-aluminum chloride solution.

(1) Sponsored by the Nebraska Department of Agriculture and Economic Development.

(2) G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. 3, Part 2, Wiley-Interscience, New York, N. Y., 1964, p 1262.

(3) W. Braun, German Patent 878,647 (June 5, 1953); *Chem. Abstr.*, **50**, 4203a (1956).

(4) W. Braun, German Patent 1,085,514 (July 21, 1960); *Chem. Abstr.*, **55**, 16490i (1961).

low yields, only the *para*-substituted amides were isolated.

The melting point of 3,4-dimethylbenzamide (105-106°) differs significantly from the literature value (130-131°); however the elemental analysis of the amide (Table I) is in agreement with the empirical formula. The only other structural alternative would be 2,3-dimethylbenzamide,⁷ which has an even higher melting point (155-156°). In view of these data we hydrolyzed the low melting 3,4-dimethylbenzamide and identified the product as 3,4-dimethylbenzoic acid. Isolation of this acid verified that the assigned structure of 3,4-dimethylbenzamide was correct.

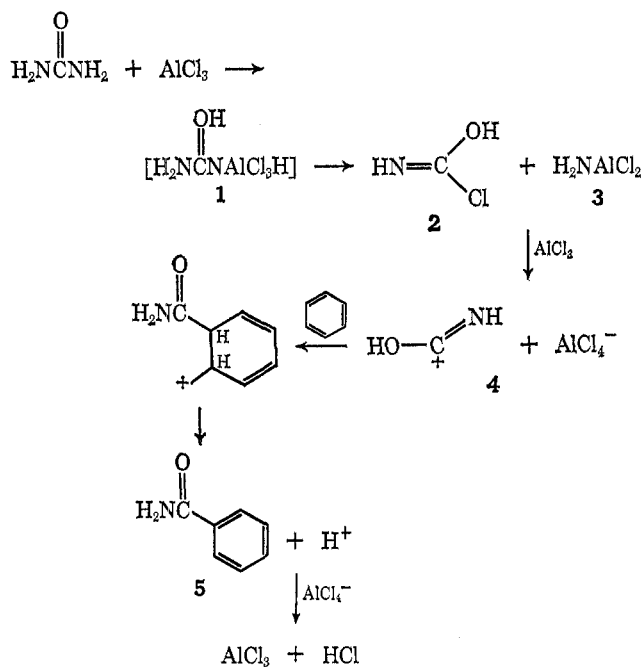
In the present investigation no attempts were made to maximize the yields of aromatic amides.

(5) N. I. Malkina and S. N. Kazarnovskii, *Zh. Prikl. Khim.*, **34**, 1583 (1961); *Chem. Abstr.*, **55**, 27362h (1961).

(6) L. J. Christmann, U. S. Patent 2,822,363 (Feb 4, 1958); *Chem. Abstr.*, **52**, 10223b (1958).

(7) T. Terakawa, H. Ouchi, H. Zenno, K. Nakanishi, and S. Umio, *J. Pharm. Soc. Jap.*, **74**, 312 (1954); *Chem. Abstr.*, **49**, 3078h (1955).

SCHEME I



Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. Melting points were uncorrected and obtained by using a Hoover capillary melting point apparatus.

Synthesis of Arylamides.—The general method for the preparation of these compounds was as follows. Urea, 24 g (0.40 mol), was carefully added to 113 g (0.85 mol) of anhydrous aluminum chloride. Care must be exercised during this addition because an exothermic reaction results. The temperature of the reaction was controlled by the rate of urea addition. However, the reaction temperature was usually kept in the range of 90–100°. After the addition of the urea was complete, the resulting mixture was cooled to 25° and 0.35 mol of the appropriate aromatic compound was added. The reactants were stirred for 2–18 hr at 50–70°, cooled, and slowly poured into 500 ml of ice water. Because substantial amounts of unchanged aluminum chloride are present in the reaction mixture, extreme care must be exercised while decomposing it in the ice water. Pentane (500 ml) was added, and the two phases filtered. Arylamides which are water- and pentane-insoluble remain as a solid on the filter paper. Water-soluble arylamides (e.g., 4-methylbenzamide) were ether extracted from the water phase. The ether extracts were dried over anhydrous calcium sulfate, the ether was evaporated, and the residues were recrystallized from benzene or water to give pure arylamides.

Properties of Arylamides.—The arylamides were characterized by their elemental analyses, infrared spectra, and comparisons of their respective melting points with literature values.

Table I summarizes the results of the elemental analyses and the comparative melting point data. The infrared spectra of the arylamides exhibited the following characteristic absorption bands: ir (Nujol) 3450–3320 cm^{-1} (free NH), 3210–3160 cm^{-1} (associated NH), 1660–1640 cm^{-1} (amide I band), 1620–1610 cm^{-1} (amide II band), and 1560 cm^{-1} (phenyl nucleus).

Hydrolysis of 3,4-Dimethylbenzamide.—A mixture of 200 mg (1.30 mmol) of 3,4-dimethylbenzamide, mp 105–106° (Table I), and 10 ml of 3 N NaOH was heated at reflux for 6 hr, cooled, and acidified with 4 ml of concentrated HCl to give 192 mg of crude acid, mp 152–156°. Sublimation of this material at 60° *in vacuo* afforded 163 mg (82%) of 3,4-dimethylbenzoic acid, mp 162–163°; ir spectrum was identical with that of 3,4-dimethylbenzoic acid.⁸

Anal. Calcd for $\text{C}_9\text{H}_{10}\text{O}_2$: C, 71.98; H, 6.71. Found: C, 72.48; H, 6.67.

Registry No.—Aluminum chloride, 7446-70-0; 3-chloro-4-methylbenzamide, 24377-95-5.

The Oxidation of 2,6-Disubstituted Phenols with Isoamyl Nitrite. A Simple Preparation of Diphenoquinones

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Phenol oxidation by alkyl nitrites has not been extensively studied. The reported oxidations have been concerned chiefly with 2,4,6-trisubstituted compounds.² In Bacon's survey of oxidants for 2,6-dimethylphenol, the reaction of isoamyl nitrite (60 mol) with phenol (1 mol) in water gave 2,2',6,6'-tetramethyl-4,4'-biphenol (20%) and 3,3',5,5'-tetramethyldiphenoquinone (37%).³ When the mole ratio was reduced to 7.5:1 in ethyl alcohol, the diphenoquinone (6%) was obtained along with the major product, *p*-nitroso-2,6-dimethylphenol (75%).

We have extended this oxidation to a convenient synthesis of certain diphenoquinones by oxidation of 2,6-disubstituted phenols with isoamyl nitrite in methylene chloride. The reaction is run for 18–24 hr at ambient temperature and the insoluble product is isolated by filtration. Table I gives the results for a number of phenols; yields are in the 50–65% range. When sterically hindering groups such as *t*-butyl or deactivating groups such as chlorine occupy the *ortho* positions, the yields are lower. The higher oxidation potential of 2,6-dichlorophenol completely inhibited its oxidation to the diphenoquinone whereas 2-chloro-6-phenylphenol gave a small yield of quinone. The yields were improved by using chloroform at reflux for 2.5 hr.

TABLE I

2,6-Disubstituted phenol	Diphenoquinone		Mol of oxidant/mol of phenol
	% yield of CH_2Cl_2	Mp, °C	
Dimethyl-	53 ^a	205.5–208 ^b	2.1
Diphenyl-	58	283–285 ^b	3.0
Methyl phenyl-	51	202–204 ^b	2.5
Dimethoxy-	65	288–290 ^b	2.5
Di- <i>t</i> -butyl-	16	242.5–244 ^b	3.3
Chloro phenyl-	10 ^c	287.5–288.5	3.0
Dichloro-			

^a 64% yield obtained in CHCl_3 . ^b The infrared spectrum was identical with that of the authentic material. ^c 21% yield obtained in CHCl_3 .

(1) Food and Drug Administration, Bureau of Drugs, Washington, D. C. 20204.

(2) (a) J. Thiele and H. Siewerde, *Ann.*, **311**, 363 (1900). (b) V. V. Ershov and G. A. Zlobina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2138 (1964).

(3) R. G. R. Bacon and A. R. Izzat, *J. Chem. Soc.*, 791 (1966).

(8) "Sadtler Standard Spectra," No. 24490, Microfilm Edition, Sadtler Research Laboratories, Inc., 1969.