Preparation of Ortho-Substituted Benzoic Acids by the Copper(II)-Catalyzed Reaction of Diphenyliodonium-2-carboxylate with Anilines and Other Nucleophiles

Robert A. Scherrer*[1] and Helga R. Beatty

Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan 48106

Received January 14, 1980

Diphenyliodonium-2-carboxylate (DPIC) reacts readily in copper ion catalyzed condensations with a variety of nucleophiles to give ortho-substituted substituted benzoic acids. These reactions occur at temperatures (80–100 °C) below those at which benzyne formation and other side reactions become important. The nature of the Cu(II) catalysis appears to be different from the more common Cu(I) catalysis of diaryliodonium reactions in that high specificity in the displacement reaction is retained. Products obtained directly from DPIC condensations include *N*-[2,6-dichloro-3-(dimethylsulfamoyl)phenyl]anthranilic acid (**5b**), *N*-methyl-*N*-phenylanthranilic acid (**5c**), *N*-mesyl-*N*-(2,3-dimethylphenyl)anthranilic acid (**5d**), *N*-(3-chloro-2-methylphenyl)-*N*-tosylanthranilic acid (**5e**), and *o*-(2,3-dimethylphenoxy)benzoic acid (**5f**). Compound **5d** has been cyclized to *N*-(2,3-dimethylphenyl)-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**6**).

We wish to describe details of our work on nucleophilic displacement reactions of diphenyliodonium-2-carboxylate (DPIC). We find DPIC is an excellent reagent for the preparation of ortho-substituted benzoic acids under mild conditions. This reaction is very unusual for a diaryliodonium salt in two respects. First, it is highly specific for nucleophilic attack on the carboxylate-bearing ring. Second, this selective reaction is copper(II) catalyzed, whereas Ar_2I^+ reactions are usually catalyzed by copper(I) and in a way which reduces selectivity (via reduction to the radical species $Ar_2I\cdot$).[2-4]

DPIC is known primarily for its usefulness as a precursor to benzyne[5-9] (Scheme I, path A). While the decomposition is reported to be catalyzed by $CuSO_4$, AgOAc, and iodine,[6] catalysts are usually not used to generate benzyne. At temperatures in the range of 130–150 °C the predominant decomposition course is to phenyl *o*-iodobenzoate[7] (Scheme I, path B), presumably occurring by an intramolecular displacement by the carboxylate ion on the adjacent ring. This work describes a third reaction course which is available at temperatures below 130 °C (generally 80–100 °C; Scheme I, path C). The nucleophilic displacement reactions illustrated in path C cover reactants with a range of nucleophilicity and steric hindrance. The products obtained are characteristically tar free. Brief descriptions of the reaction of DPIC with anilines have appeared.[10-12]

Results and Discussion

Reaction with Anilines. 2,3-Dimethylaniline reacts slowly with DPIC in 2-propanol at reflux (80 °C) to give a 2.5% yield of *N*-(2,3-dimethylphenyl)anthranilic acid (**5a**) after 3 h (Table I, expt 1). The addition of 3.6 mol % of cupric acetate, however, has a very beneficial effect, increasing the yield of anthranilic acid to 76% in the same reaction time (and to 90% after 15 h). The advantage of the DPIC method becomes most apparent with hindered weakly basic anilines. *N*-[2,6-Dichloro-3-(dimethylsulfamoyl)phenyl]anthranilic acid (**5b**) was obtained from a DPIC reaction in 2-propanol in 38% yield (56% based on unrecovered aniline; 48 h).

A wide variety of solvents can be used, ranging from water to 1,2-dichloroethane to excess arylamine (Table I). An exception is CCl_4 which leads to *o*-chlorobenzoic acid, presumably from HCl produced by reaction of solvent with arylamine. This reaction of DPIC with anilines is in marked contrast to the (uncatalyzed) reaction of aniline with diphenyliodonium bromide.[13] With 2 equiv of aniline in water at reflux for 3 h the products were bromobenzene (79%) and only a trace of diphenylamine; with 10 equiv of aniline at reflux in water for 24 h a 27% yield was obtained; in neat aniline at 130–140 °C for 1.5 h the yield of diphenylamine was 18%.

Reaction with *N*-Methylaniline. *N*-Methyl-*N*-phenylanthranilic acid can be prepared directly by the reaction of DPIC with *N*-methylaniline. A 44% yield was obtained after 24 h reaction in 2-propanol. This product otherwise has been obtained by *N*-methylation.[14] Prior unsuccessful attempts to react *N*-methylaniline with *o*-chlorobenzoic acid[15] and 5-nitro-2-chlorobenzoic acid[16] are recorded.

Reaction with Sulfonanilides. Sulfonamides of *N*-arylanthranilic acids are difficult to obtain by direct sulfonylation.[17] DPIC reacts with the sodium salts of sulfonanilides at 80 °C in dimethoxyethane (with cupric acetate). The *N*-mesyl derivative **5d** was obtained in 57% yield (24-h reaction time). Subsequent to the completion of this work, **5d**[18] and *N*-tosyl-*N*-(2,3-dimethylphenyl)-anthranilic acid[19] have been reported in the patent literature. They were prepared by heating a mixture of sulfonanilide, *o*-chlorobenzoic acid, $CuBr_2$, and K_2CO_3 in xylene for 24 h. Beringer et al.[13] phenylated toluenesulfonamide and benzenesulfonanilide in 45 and 56% yields with diphenyliodonium bromide in ethanol.

(1) Present address: Riker Laboratories, 3M Center, St. Paul, MN 55144.
(2) M. C. Caserio, D. L. Glusker, and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 336 (1959).
(3) F. M. Beringer and R. A. Falk, *J. Chem. Soc.*, 4442 (1964).
(4) F. M. Beringer and P. Bodlaender, *J. Org. Chem.*, **34**, 1981 (1969).
(5) E. Le Goff, *J. Am. Chem. Soc.*, **84**, 3786 (1962).
(6) F. M. Beringer and S. J. Huang, *J. Org. Chem.*, **29**, 445 (1964).
(7) F. M. Beringer and S. J. Huang, *J. Org. Chem.*, **29**, 1637 (1964).
(8) J. B. S. Bonilha, N. Petragnani, and V. G. Toscano, *Chem. Ber.*, 111, 2510 (1978).
(9) L. F. Fieser and M. J. Haddadin in "Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 1037.
(10) R. A. Scherrer, The Netherlands Patent 6 507 783; *Chem. Abstr.*, **64**, 19501c (1966).
(11) E. F. Elslager and N. F. Haley, *J. Heterocycl. Chem.*, **9**, 1109 (1972).
(12) R. A. Scherrer in "Antiinflammatory Agents", Vol. I, R. A. Scherrer and M. W. Whitehouse, Eds., Academic Press, New York, 1974, pp 60–4.
(13) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Am. Chem. Soc.*, **75**, 2708 (1953).
(14) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **17**, 860 (1952).
(15) K. Gleu and S. Nitzsche, *J. Prakt. Chem.*, **153**, 200 (1939).
(16) K. Lehmstedt and H. Hundertmark, *Chem. Ber.*, **64**, 2386 (1931).
(17) Unpublished work from this laboratory.
(18) M. Takenaka, Japanese Kokai 74 43 942; *Chem. Abstr.*, **82**, 97848 (1975).
(19) S. Komura, K. Nakamura, and M. Takenaka, Japanese Kokai 74 43 943; *Chem. Abstr.*, **81**, 120226 (1974).

0022-3263/80/1945-2127$01.00/0

Scheme I

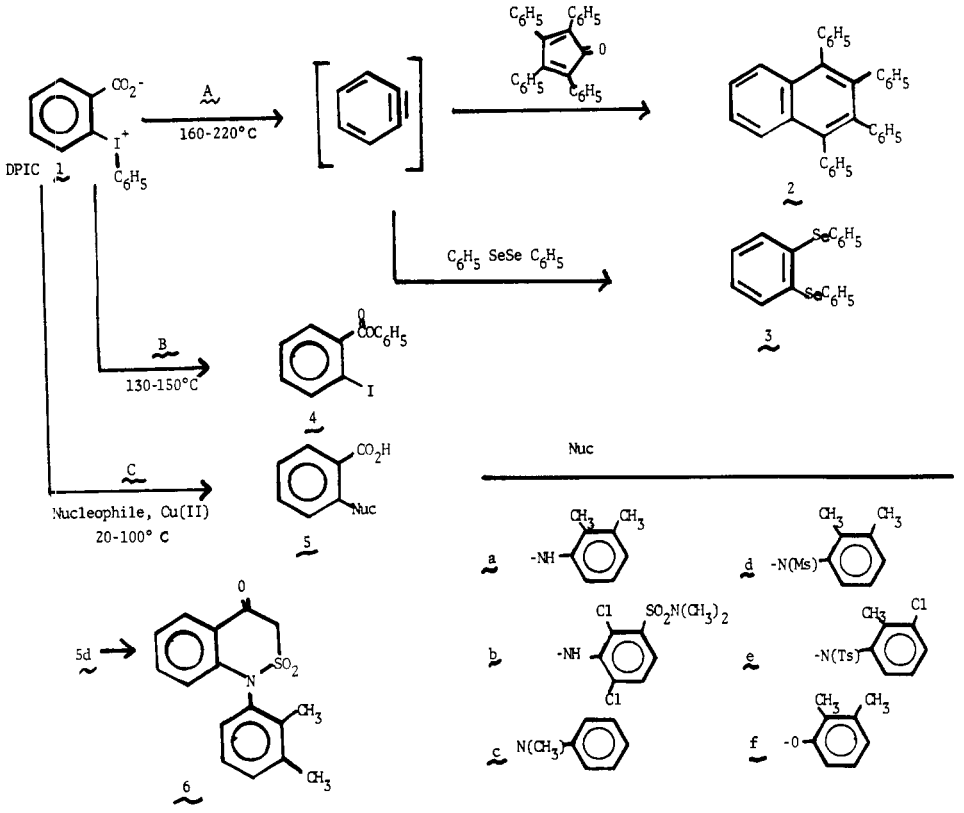


Table I. Exploratory Condensations of DPIC with 2,3-Dimethylaniline

expt	comments	molar ratio $ArNH_2$/ DPIC	solvent[a]	time, h	temp, °C	catalyst[b]	yield of anthranilic acid, % crude	adj[c]
1		1.4	$(CH_3)_2CHOH$	3	80	none	2.7	2.5
2		1.4	$(CH_3)_2CHOH$	3	80	$Cu(OAc)_2$	85	76
3		1.2	$(CH_3)_2CHOH$	15	80	$Cu(OAc)_2$	97	90
4	aniline	1.2	$(CH_3)_2CHOH$	1	80	$Cu(OAc)_2$	68	66
5	2',4',6'-$(CH_3)_3$DPIC	0.8	$(CH_3)_2CHOH$	1	80	$Cu(OAc)_2$	65	58
6		0.8	$(CH_3)_2CHOH$	1	80	$Cu(OAc)_2$	53	50
7	+1 molar equiv of K_2CO_3	1.4	$(CH_3)_2CHOH$	3	80	$Cu(OAc)_2$ + cuproin	31	26
8	+1 molar equiv of K_2CO_3	1.4	$(CH_3)_2CHOH$	3	80	$Cu(OAc)_2$	75	67
9		1.2	$(CH_3)_2CHOH$	3	80	Cu_2Cl_2[d]	86	80
10		1.2	$CH_3CON(CH_3)_2$	5	100	$Cu(OAc)_2$	100	87
11		16	none	66	22	$Cu(OAc)_2$	29	26
12		1.2	CCl_4	15	77	$Cu(OAc)_2$	0[e]	
13		1.2	misc[f]	15-20	reflux	$Cu(OAc)_2$	*f*	*f*

[a] Four milliliters per gram of DPIC. [b] Twenty milligrams per gram of DPIC; 3.6 mol %. [c] Calculated from the UV absorption at 279 and 350 nm. [d] 3.6 mol %; freshly prepared, but from the color of the mixture cupric ion was obviously present. [e] *o*-Chlorobenzoic acid, 69%. [f] The following yields were obtained (solvent, % adj yield): 1,2-dimethoxyethane, 80%; water, 80%; 1,2-dichloroethane (6 mL/g), 69%.

As an aside, the mesyl derivative **5d** can be readily cyclized to *N*-(2,3-dimethylphenyl)-1*H*-2,1-benzothiazin-4-(3*H*)-one 2,2-dioxide (**6**) by treatment of the methyl ester with sodium hydride. *N*-aryl derivatives have not previously been described, but *N*-alkyl derivatives have been obtained by a similar cyclization[20] and by a polyphosphoric acid cyclization of carbethoxy-[21] and carboxymethanesulfonanilides.[22]

Reaction with Phenoxide Ion. Beringer and Gindler[23] studied the reaction of diphenyliodonium nitrate with phenoxide ion. They found that this reaction is not copper catalyzed. A general synthetic procedure for diaryl ethers involves reaction of Ar_2I^+ with phenoxide in water at 100 °C for 5 h.[24] We obtained a 42% yield of 2-(2,3-dimethylphenoxy)benzoic acid (**5f**) from the reaction of 2',4',6'-Me_3DPIC with 1 equiv of phenoxide in excess phenol at 80–90 °C for 5 h. The common route to this class of compounds, the copper-catalyzed reaction of an *o*-halobenzoate with a phenol salt, requires bringing two anions to close proximity in the transition state. Examples of the fairly vigorous conditions required are heating the molten salts briefly at 190 °C or for 13 h in nitrobenzene

(20) J. G. Lombardino, *J. Heterocycl. Chem.*, **9**, 315 (1972).
(21) S. Rossi and G. Pagani, *Ann. Chim. (Rome)*, **56**, 741 (1966).
(22) B. Loev, U.S. Patent 3 303 191; *Chem. Abstr.*, **66**, 65489 (1967).
(23) F. M. Berlinger and E. M. Gindler, *J. Am. Chem. Soc.*, **77**, 3203 (1955).
(24) J. R. Crowder, E. E. Glover, M. F. Grundon, and H. X. Kaempfen, *J. Chem. Soc.*, 4578 (1963).

Scheme II

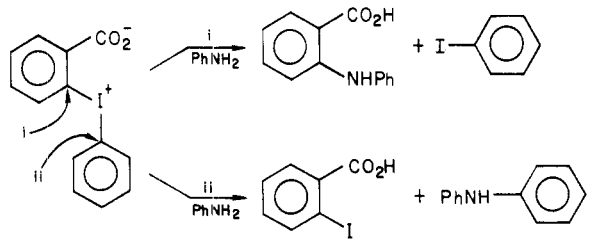


Table II. Ratio of Products from Pyrolysis of Diaryliodonium Bromides[a,b]

$Ar—I^+—Ar'$ Br^-

Ar	ArBr/Ar'Br	Ar	ArBr/Ar'Br
4-CH_3	0.5:1	2,4,6-$(CH_3)_3$	24:1
2-CH_3	6.7:1		

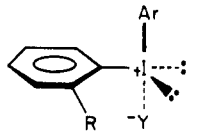
[a] Reference 28. [b] Ar' is unsubstituted.

at 165 °C.[25] Anderson and Connelly[26] recently described an improved procedure in which a sodium phenoxide is heated with sodium *o*-chlorobenzoate and 1 equiv of sodium iodide (no copper) in excess phenol at 170 °C for 7 h. It is said to be of particular advantage for the absence of tars, which is also a feature of the DPIC reaction.

Specificity of the Reaction. The remarkable product specificity in the direction of cleavage of this unsymmetrical iodonium compound was examined more closely by looking at the products from the reaction with aniline. In 1 h at 80 °C (Table I, expt 4), the products consisted of 66% *N*-phenylanthranilic acid and 2.2% diphenylamine. A separate control experiment showed that no detectable diphenylamine was formed from decarboxylation of the anthranilic acid or coupling of iodobenzene with aniline under the reaction conditions. The ratio of reaction by path i to that by path ii (Scheme II) is therefore about 30:1.

While cupric acetate catalyzes a very specific nucleophilic reaction with DPIC, it is not obvious why the ring bearing the carboxylate ion should be the one attacked. Carboxylate has a σ value[27] which is zero (para) to −0.1 (meta) and would surely be even more negative in the ortho position. Yamata et al.[28] determined that for (4-carboxyphenyl)-*p*-tolyliodonium bromide (acid form), the ratio of uncatalyzed bromide ion attack on the carboxylic acid ring (σ = 0.73) to the tolyl ring (σ = −0.07) was 6.5:1 and 12.3:1 in the melt and in DMF, respectively. These appear to be fairly clearly nucleophilic displacement reactions from the more recent work of Lancer and Wiegand.[29] These values contrast with the approximate 30:1 ratio found for the Cu(II)-catalyzed reaction of aniline with DPIC.

Another factor that affects the specificity of nucleophilic reactions with unsymmetrical diaryliodonium ions is ortho substitution on the aryl ring (Table II). Lancer and Wiegand[29] found that attack on the hindered ring is favored even though the reaction still appears to be a nucleophilic displacement reaction. They propose that in the trigonal-bipyramidal structure of Ar_2I^+ (7), steric factors may favor the ortho-substituted ring being in an equatorial position which puts it closer to the counterion Y. This may



7

be even more likely if R is also the counterion (CO_2^-). Simple steric factors do not seem to be the explanation for the specificity of the DPIC reactions since 2',4',6'-trimethyldiphenyliodonium-2-carboxylate reacts with 2,3-dimethylaniline with about the same specificity (based on product yield) as does DPIC (Table I, expt 5 and 6).

Copper Catalysis. The copper catalysis has several unusual aspects. First, the copper ion catalysis that is associated with the reaction of simple diaryliodonium salts with nucleophiles is Cu(I) catalysis even when the added species is Cu(II).[2,3] Evidence includes kinetic studies, inhibition of reactions by cuproin, and the markedly reduced rates of reaction with Cu(II) in an acid and O_2 environment where conversion to the Cu(I) species is retarded.[2] Cu(I) exerts its catalytic effect by promoting homolytic dissociation of simple diaryliodonium salts at the expense of any S_NAr pathway.[4] For example, Beringer and Falk[3] have found that an aqueous solution of 4-nitrodiphenyliodonium tosylate reacts with sulfite ion in the absence of catalyst to give more than 10 times as much 4-nitrobenzenesulfonate as benzenesulfonate. With 0.1 mol of cupric sulfate/mol of iodonium salt, the ratio is reduced to 1.9:1 and with 0.9 mol of cupric sulfate to 0.5:1. For some nucleophiles (alkoxides[30] and cyanide[31]) an uncatalyzed radical chain reaction predominates. Addition of 1,1-diphenylethylene as a radical scavenger in these cases allows the nucleophilic reaction to become important.[30,31]

In contrast to the above examples, the nucleophilic reactions of DPIC are Cu(II) catalyzed, and high specificity is retained. Cuproin does not prevent the reaction of DPIC with 2,3-dimethylaniline, although the rate is reduced, possibly due to weak Cu(II) complex formation (Table I, expt 8). With fresh Cu_2Cl_2 the nucleophilic reaction still occurred (Table I, expt 9), but cupric ion was obviously present from the color of the mixture.

Experimental Section

The yields of **5a–f** are not optimized. They represent single experiments run to illustrate a range of possibilities for the use of DPIC. In all cases anhydrous DPIC was used. Melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Infrared spectra were obtained on a Beckman IR-7 or IR-9 spectrophotometer and the ultraviolet spectra on a Cary Model 11 spectrophotometer. The NMR spectra were determined in deuteriochloroform by using a Varian A-60 spectrometer. Gas–liquid phase chromatography was done on a Model 810 F&M chromatograph. The DPIC reactions were routinely run under nitrogen.

Diphenyliodonium-2-carboxylate (1, DPIC). Potassium persulfate (42.0 g, 0.156 mol) was added at 10 °C over 40 min to a solution of *o*-iodobenzoic acid (20.0 g, 0.0807 mol) in 80 mL of concentrated sulfuric acid, and the mixture was kept at that temperature for an additional 20 min. Benzene (75 mL) was added, and the mixture was stirred for 3 h at 25 °C and then poured onto ice. A small amount of 2-carboxydiphenyliodonium bisulfate was collected. The addition of 40 g of potassium iodide in a minimum of water precipitated the iodonium iodide. The salts were combined and stirred with 200 mL of 5 N sodium hydroxide, and the DPIC was collected and washed with water. Recrystallization from ca. 350 mL of water gave 20.1 g (77%) of

(25) N. C. Yang, P. Kumler, and S. S. Yang, *J. Org. Chem.*, **37**, 4022 (1972).
(26) E. L. Anderson and G. A. Connelly (SmithKline Corp.), U.S. Patent 4 094 900 (1978).
(27) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(28) Y. Yamada and M. Okawara, *Bull. Chem. Soc. Jpn.*, **45**, 1860 (1972).
(29) K. M. Lancer and G. H. Wiegand, *J. Org. Chem.*, **41**, 3360 (1976).
(30) J. J. Lubinkowski, J. W. Knapczyk, J. L. Calderon, L. R. Petit, and W. E. McEwen, *J. Org. Chem.*, **40**, 3010 (1975).
(31) J. J. Lubinkowski, M. Gomez, J. L. Calderon, and W. E. McEwen, *J. Org. Chem.*, **43**, 2432 (1978).

DPIC as coarse prisms (not hydrated), mp 223–225 °C dec (lit. mp 205 °C,[6] 215–216 °C,[9] 220.5–221 °C;[5] hydrate, mp 220 °C,[6] 220–222 °C,[9] all with decomposition). Our preferred procedure for obtaining anhydrous DPIC is to concentrate a methylene chloride–methanol solution to dryness under vacuum. The water content can be easily determined from the IR in the 3400 cm^{-1} region.

Anal. Calcd for $C_{13}H_9IO_2$: C, 48.17; H, 2.80; I, 39.16. Found: C, 48.09; H, 2.98; I, 38.97.

2′,4′,6′-Trimethyldiphenyliodonium-2-carboxylate. *o*-Iodobenzoic acid (20.0 g) was oxidized with potassium persulfate as in the preparation of DPIC, and mesitylene (16.7 mL, 0.12 mol) was added at 0 °C. The mixture was stirred at 0–6 °C for 1.5 h, poured onto ice, and made alkaline with concentrated sodium hydroxide. Extraction with chloroform, washing, drying, and concentrating gave a paste which on trituration with ether–pentane afforded 25.0 g (85%) of 2′,4′,6′-Me_3DPIC, mp 224–225 °C dec (lit.[3] mp 213–214 °C). This was used directly. A sample obtained from chloroform–methanol and then methanol had a melting point of 227–229 °C dec.

Anal. Calcd for $C_{16}H_{15}IO_2$: C, 52.47; H, 4.13. Found: C, 52.14; H, 4.07.

Exploratory Condensations (Table I, Expt 3). A solution of 2.0 g (6.18 mmol) of DPIC, 0.90 g (7.4 mmol) of 2,3-dimethylaniline, and 40 mg of cupric acetate in 8 mL of 2-propanol was heated under reflux for 15 h. The mixture was concentrated and taken up in dilute sodium hydroxide. After an ether extraction and filtration of the aqueous phase, the filtrate was added slowly to acid to give 1.45 g (97%) of **5a**, mp 220–222 °C dec. Comparison of the ultraviolet spectrum with that of analytical material indicated the crude **5a** to be 93% pure. The analytical material had a melting point of 229–230 °C dec and ultraviolet absorptions at λ_{max} 279 and 350 nm (ϵ 8480 and 7020) in methanol 0.01 N in HCl.

Water as Solvent. A mixture of 2.00 g (6.17 mmol) of DPIC, 0.89 g (7.35 mmol) of 2,3-dimethylaniline, and 40 mg of cupric acetate in 8 mL of water was stirred under reflux for 15 h. Dilute sodium hydroxide was added, and iodobenzene and unreacted aniline were extracted with ether. Filtration and acidification of the alkaline solution gave 1.28 g (86%) of **5a**, mp 221–225 °C dec.

Ethylene Chloride as Solvent. A solution of 1.00 g of DPIC, 0.75 g of 2,3-dimethylaniline, and 0.02 g of cupric acetate in 6 mL of ethylene chloride was heated under reflux for 20 h. Product began to precipitate from the solution by the second hour. The mixture was filtered and the product washed with cold carbon tetrachloride to give 0.56 g (75%) of **5a** as off-white needles, mp 227–229 °C dec.

***N*-Phenylanthranilic Acid and Diphenylamine (Expt 4).** A solution of DPIC (3.00 g, 9.25 mmol), aniline (1.03 g, 11.1 mmol), and cupric acetate (0.06 g) in 18 mL of 2-propanol was heated under reflux for 1 h. The crude *N*-phenylanthranilic acid (1.34 g, 68%) had a melting point of 180–182 °C and was 97% pure by the ultraviolet spectrum. Analytical material had a melting point of 183–184 °C and λ_{max} 350 and 284 nm (ϵ 7150 and 14 100) in methanol 0.01 N in HCl.

The ether extract of the basified reaction concentrate was washed with 0.1 N hydrochloric acid (to remove some of the aniline but not diphenylamine) and then sodium chloride solution, dried, and concentrated. GLC indicated 2.6% by weight of the iodobenzene–diphenylamine components to be diphenylamine (calculated from chromatography of an authentic mixture). Assuming a 68% yield of iodobenzene, this corresponds to a 2.2% yield of diphenylamine.

A control experiment was run in which a mixture of *N*-phenylanthranilic acid (1.00 g), aniline (0.50 g), *p*-iodotoluene (1.00 g), and cupric acetate (0.06 g) in 18 mL of 2-propanol was heated 1.5 h under reflux. GLC of the neutral fraction showed no diphenylamine or 4-methyldiphenylamine.

***N*-[2,6-Dichloro-3-(dimethylsulfamoyl)phenyl]anthranilic Acid (5b).** A mixture of 3-amino-2,4-dichloro-N^1,N^1-dimethylbenzenesulfonamide (18.2 g, 0.067 mol), DPIC (26.3 g, 0.081 mol), and cupric acetate (0.55 g) in 75 mL of 2-propanol was heated under reflux for 48 h. The mixture was concentrated, diluted with 1 N sodium hydroxide, and extracted with methylene chloride. (The sodium salt of **5b** had an appreciable solubility in the methylene chloride phase.) The neutral fraction yielded 5.9 g of starting sulfonamide. Acidification of the filtered aqueous solution gave 17.2 g of **5b**, mp 207–212 °C. Recrystallization from aqueous ethanol gave 10.0 g (38%; 56% based on unrecovered arylamine) of **5b**, mp 217.5–219.5 °C.

Anal. Calcd for $C_{15}H_{14}Cl_2N_2O_4S$: C, 46.28; H, 3.63; Cl, 18.22; N, 7.19; S, 8.23. Found: C, 46.55; H, 3.78; Cl, 18.14; N, 7.03; S, 8.39.

The 3-amino-2,4-dichloro-N^1,N^1-dimethylbenzenesulfonamide was obtained in a series of steps from 4′-bromo-2′,6′-dichloroacetanilide. Nitration, reduction of the nitro group, and reductive dehalogenation gave 3′-amino-2′,6′-dichloroacetanilide. The 3′-amino group was diazotized, replaced by sulfonyl chloride and converted to the dimethylsulfonamide.

A solution of 4′-bromo-2′,6′-dichloroacetanilide[32] (62.8 g, 0.22 mol) in 390 mL of concentrated sulfuric acid was treated at room temperature with 15.5 g (0.22 mol) of nitric acid (specific gravity 1.5) in 55 mL of sulfuric acid. After 1 h the solution was poured onto ice, and the solid was collected and recrystallized from ethanol to give 53.5 g of 4′-bromo-2′,6′-dichloro-3′-nitroacetanilide, mp 190–195 °C (analytical material, mp 198–199 °C). This acetanilide (53.4 g, 0.163 mol) was reduced catalytically with Raney nickel (2 g) in methanol to the 3′-amino derivative (crude, mp 194–197 °C) and then with 20% Pd/C (2 g) in ethanol containing sodium acetate (14 g, 0.17 mol) to 3′-amino-2′,6′-dichloroacetanilide: 30.1 g; mp 217.5–221 °C. An analytical sample had a melting point of 222–224 °C (ethanol).

Anal. Calcd for $C_8H_8Cl_2NO$: C, 43.86; H, 3.68; N, 12.79. Found: C, 43.77; H, 3.76; N, 12.71.

A suspension of 3′-amino-2′,6′-dichloroacetanilide (15.0 g, 0.068 mol) in 70 mL of concentrated hydrochloric acid was treated at 2–4 °C with 4.96 g (0.072 mol) of sodium nitrite in water. After 30 min the mixture was poured into a cooled solution of sulfur dioxide (30 g) in 70 mL of acetic acid to which a saturated solution of cupric chloride dihydrate (3.3 g) in water had been added. When nitrogen evolution had ceased (ca. 1 h), dilution with ice and water precipitated 3-acetamido-2,4-dichlorobenzenesulfonyl chloride. The acid chloride was collected (a sample had a melting point of 161–163 °C dec) and added in portions to 100 g of anhydrous dimethylamine. Partial evaporation of the solvent and dilution with water gave 11.0 g of 3-acetamido-2,4-dichloro-*N*,*N*-dimethylbenzenesulfonamide, mp 186–189 °C. An analytical sample from ethanol had a melting point of 186–187 °C.

Anal. Calcd for $C_{10}H_{12}Cl_2N_2O_3S$: C, 38.59; H, 3.89; Cl, 22.79; N, 9.00; S, 10.30. Found: C, 38.79; H, 3.80; Cl, 22.87; N, 9.01; S, 10.43.

A suspension of the above amide (18.0 g, 0.058 mol) in 72 mL of 6 N hydrochloric acid and 36 mL of ethanol was heated under reflux for 4 h. The resulting solution was concentrated to remove ethanol and extracted (from acid) with methylene chloride. From the methylene chloride solution there was obtained 15.0 g of 3-amino-2,4-dichloro-N^1,N^1-dimethylbenzenesulfonamide as an oil which crystallized on standing; mp ca. 55–58 °C. An analytical sample from aqueous methanol had a melting point of 60.5–61.5 °C.

Anal. Calcd for $C_8H_{10}Cl_2N_2O_2S$: C, 35.70; H, 3.75; Cl, 26.34; N, 10.41; S, 11.91. Found: C, 35.86; H, 3.78; Cl, 26.51; N, 10.45; S, 12.09.

***N*-Methyl-*N*-phenylanthranilic Acid (5c).** A solution of DPIC (32.4 g, 0.10 mol), *N*-methylaniline (12.8 g, 0.12 mol), and cupric acetate (0.6 g) in 100 mL of 2-propanol was heated under reflux for 24 h. The 2-propanol was removed under reduced pressure and the mixture diluted with sodium hydroxide solution and ether. The aqueous phase was heated to remove ether and then added to dilute hydrochloric acid containing a small amount of ethanol to give *N*-methyl-*N*-phenylanthranilic acid: 17.4 g; mp 82–98 °C. Two recrystallizations from aqueous ethanol gave 10.0 g (44%) of **5c**, mp 103–104 °C (lit.[14] mp 104–104.5 °C).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 73.86; H, 5.81; N, 6.13.

***N*-Methanesulfonyl-*N*-(2,3-dimethylphenyl)anthranilic Acid (5d).** 2′,3′-Dimethylmethanesulfonanilide (40.0 g, 0.201 mol; mp 82.5–86 °C) was added to a suspension of 9.65 g (0.201 mol)

(32) W. W. Reed and K. J. P. Orton, *J. Chem. Soc.*, 91, 1543 (1907).

of 50% sodium hydride (dispersed in mineral oil) in 200 mL of 1,2-dimethoxyethane. When hydrogen evolution was complete, 71.6 g (0.221 mol) of DPIC and 1.5 g of cupric acetate were added, and the mixture was heated for 24 h under reflux. It was diluted with water, made alkaline with sodium hydroxide, and filtered through Super-cel, and the filtrate was acidified to give **5d**. The product was taken up in ether, extracted into a sodium bicarbonate solution, liberated with acid, and again taken up in ether. After the ether washing, drying, and concentrating, there was obtained 51.2 g (80%) of a viscous oil which solidified, mp 104–130 °C. Recrystallizations of a 3.0-g portion from benzene gave 2.4 g (57% overall) of **5d** with 0.5 mol of benzene of crystallization: mp 103–106 °C, with gas evolution and resolidifying and melting at 134–136 °C; IR (KBr) 1700, 1730 (sh) cm^{-1}; IR ($CHCl_3$) 1705 (s), 1740 (m) cm^{-1}; NMR δ 3.13 (SO_2CH_3), 11.23 (CO_2H), spectrum integrated as expected; pK_a' = 6.2 (67% DMF).

Anal. Calcd for $C_{16}H_{17}NO_4S \cdot {}^1/_2C_6H_6$: C, 63.66; H, 5.63; N, 3.91; S, 8.95. Found: C, 64.04; H, 5.53; N, 4.12; S, 8.69.

An analytical sample of the starting 2′,3′-dimethylmethanesulfonanilide had a melting point of 85.5–87.5 °C (aqueous ethanol).

Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.57; N, 7.03. Found: C, 54.57; H, 6.47; N, 6.96.

1-(2,3-Dimethylphenyl)-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-Dioxide (6). The methyl ester of **5d** was obtained by treatment of 3.4 g (0.0106 mol) of **5d** in 15 mL of dimethylformamide with 2.9 g of potassium carbonate and 7.5 g of methyl iodide for 2 h at 60 °C. The crude ester (3.2 g, a pale yellow oil, infrared absorption at 1730 cm^{-1} in $CHCl_3$) was heated in 10 mL of dimethylacetamide containing 0.92 g (0.019 mol) of 50% sodium hydride for 2 h at 60 °C. Dilution of the solution with water and acidification gave a sticky solid which after recrystallization from ethanol afforded 0.8 g of **6**: mp 163–164.5 °C; infrared absorption (KBr) at 1697 cm^{-1} (s) and, probably indicative of some enolic contribution, a broad absorption centered at 3550 cm^{-1}; ultraviolet absorption at λ_{max} (CH_3OH) 335, 258, and 224 nm (ϵ 3920, 7770, and 24 750); λ_{max} (CH_3OH + KOH) 299 and 240 nm (ϵ 7900 and 10 200); pK_a' = 8.8 (67% DMF).

Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.72; H, 4.95; N, 4.65; S, 10.85.

***N*-(*p*-Toluenesulfonyl)-*N*-(3-chloro-2-methylphenyl)anthranilic Acid (5e).** 3′-Chloro-2′-methyl-*p*-toluenesulfonanilide[33] (16.5 g, 0.056 mol) was added to 1 equiv of sodium hydride (2.68 g of a 50% dispersion in mineral oil) in 225 mL of 1,2-dimethoxyethane. DPIC (18.15 g, 0.056 mol) and cupric acetate (0.36 g) were added, and the mixture was heated 6 h under reflux. (The reaction could probably have been run longer to advantage.) The mixture was made alkaline with dilute sodium hydroxide, filtered through Super-cel, and acidified. By extraction with ether, an oil (31.2 g) was obtained which on dilution with carbon tetrachloride afforded 9.2 g of a solid, mp 112–181 °C. Extraction with sodium bicarbonate left 2.9 g of DPIC undissolved. On acidification, there was obtained 6.3 g (27%) of **5e**, mp 189–196 °C. Recrystallizations from aqueous ethanol gave 4.0 g (17%) of **5e**: mp 197–199 °C dec; infrared absorption (KBr) at 1700 cm^{-1} with a shoulder at 1730 cm^{-1}. There were no maxima above 220 nm in the ultraviolet spectrum in methanol with or without added potassium hydroxide.

Anal. Calcd for $C_{21}H_{18}ClNO_4S$: C, 60.65; H, 4.36; Cl, 8.52; N, 3.37; S, 7.71. Found: C, 60.48; H, 4.06; Cl, 8.66; N, 3.38; S, 7.79.

***o*-(2,3-Dimethylphenoxy)benzoic Acid (5f).** A solution of sodium methoxide (1.5 g, 0.028 mol) in 2,3-dimethylphenol (13.3 g, 0.11 mol) was heated under reduced pressure to remove methanol and then heated with 10.0 g (0.0273 mol) of 2′,4′,6′-Me_3DPIC and 0.20 g of cupric acetate at 80–90 °C for 5 h. The mixture was made alkaline with dilute sodium hydroxide solution, filtered through Super-cel, and then acidified, and excess phenol was removed by steam distillation. The solid remaining (4.9 g, mp 155–173 °C) was recrystallized from aqueous ethanol and from benzene to give 2.8 g (42.3%) of **5f** as yellow prisms, mp 178–180 °C.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.45; H, 5.95.

Acknowledgment. We wish to thank Dr. J. M. Vandenbelt and his staff for the spectral data and Mr. C. E. Childs and his staff for the analytical and gas chromatographic results. We are indebted to Messrs. H. D. Troutman and D. R. Johnson for the preparation of intermediates and to Mr. W. Pearlman for the catalytic hydrogenations.

Registry No. **1**, 1488-42-2; **5a**, 61-68-7; **5b**, 10311-56-5; **5b** Na salt, 73323-81-6; **5c**, 73323-82-7; **5d**, 55109-69-8; **5d** methyl ester, 73323-83-8; **5e**, 73323-84-9; **5f**, 73323-85-0; **6**, 73323-86-1; *o*-iodobenzoic acid, 88-67-5; benzene, 71-43-2; 2′,4′,6′-trimethyldiphenyliodonium-2-carboxylate, 5619-68-1; mesitylene, 108-67-8; 2,3-dimethylaniline, 87-59-2; cupric acetate, 142-71-2; aniline, 62-53-3; *N*-phenylanthranilic acid, 91-40-7; 3-amino-2,4-dichloro-*N*,*N*-dimethylbenzenesulfonamide, 13055-37-3; 4′-bromo-2′,6′-dichloroacetanilide, 13953-09-8; 4′-bromo-2′,6′-dichloro-3′-nitroacetanilide, 13953-10-1; 4′-bromo-2′,6′-dichloro-3′-aminoacetanilide, 73323-87-2; 3′-amino-2′,6′-dichloroacetanilide, 10311-36-1; 3-acetamido-2,4-dichlorobenzenesulfonyl chloride, 73323-88-3; 3-acetamido-2,4-dichloro-*N*,*N*-dimethylbenzenesulfonamide, 73323-89-4; *N*-methylaniline, 100-61-8; 2′,3′-dimethylmethanesulfonanilide, 53915-33-6; 3′-chloro-2′-methyl-*p*-toluenesulfonanilide, 7230-50-4; $CuCl_2$, 7447-39-4.

(33) G. T. Morgan and T. Glover, *J. Chem. Soc.*, **125**, 1597 (1924).