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SYNTHESIS OF 2,6-DISUBSTITUTED AND 2,3,6-TRISUBSTITUTED ANILINES

R. Garth Pews,* James E. Hunter, and Richard M. Wehmeyer

Central Research Laboratory, The Dow Chemical Company, Midland, MI 48674, U S.A.

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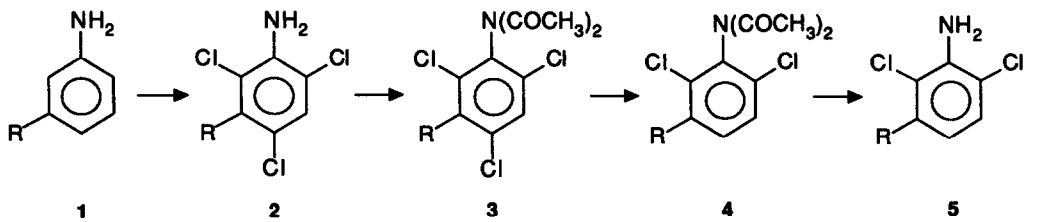
Abstract: A number of 2,6-disubstituted and 2,3,6-trisubstituted anilines have been prepared via the selective *para* dehalogenation of the corresponding anilines. Modification of the substituents on the amino nitrogen demonstrates that the selectivity is derived from steric rather than electronic effects. The effects of the choice of formate hydrogen donor, Pd catalyst, solvent, and temperature upon the efficiency and selectivity of the dehalogenation are discussed.

We have previously reported[1] the synthesis of 2,6-disubstituted and 2,3,6-trisubstituted anilines by the selective reduction of a *para* halogen of the diacetanilide derivatives utilizing a palladium on carbon catalyst and formic acid salts as the *in situ* hydrogen donor. The four-step approach involved halogenation, amine protection, reduction and deprotection as illustrated in Scheme 1. The initial report demonstrated that 2,6-dichloroaniline and 2,6-dichloro-3-



1 **2** **3** **4** **5**

Scheme 1

methylaniline could be prepared in high yields by reduction of the corresponding diacetanilides. In contrast, no selectivity was observed for the reduction of either the acetanilide or unprotected aniline. With the recent interest in synthetic methodology for the introduction of *ortho* substituents in aromatic compounds,[2,3] and the need for 2,6-disubstituted anilines and 2,3,6-trisubstituted anilines for the synthesis of agricultural chemicals,[4] we have explored the synthetic utility of the reduction. We now report these results as well as studies on the modification of the substituents on the amino nitrogen that indicate that the selectivity is derived from steric rather than from electronic effects. In addition, the effects of the choice of formate hydrogen donor, Pd catalyst, solvent, and temperature upon the efficiency and selectivity of the dehalogenation are discussed.

Results and Discussion

Chloroanilines were generally prepared by first protecting the amine moiety of commercially available *ortho*- and *meta*-substituted anilines as the HCl salt followed by treatment with chlorine.[5] This method usually works well if the uptake of chlorine is strictly monitored. Excess chlorine yields intractable tars. Alternatively, the anilines may be chlorinated in acetic acid either as the free aniline or acetanilide. The bromoanilines were synthesized in high yields

by treatment of the *ortho*- and *meta*-substituted anilines with bromine in acetic acid. Anilines were converted to the corresponding diacetanilides with excess acetic anhydride and catalytic methanesulfonic acid. Modification of the aniline moiety for studies on the steric and electronic effects were carried out with conventional chemistries as described in the experimental.

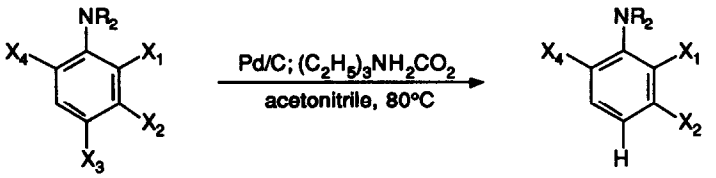
Scope of *Para* Dehalogenation Reaction

A number of 2,6- and 2,3,6-trisubstituted diacetanilides were prepared and reduced with Pd/C and a formate donor. The results, which are summarized in Table 1, are not optimized. Yield data was obtained on runs using excess formate and essentially complete conversion of substrate to reduced material. When the reactions were assayed at 50-60% conversion, the GC analyses (area %) indicated that the *para* selectivity was 80-90% This high selectivity of the reaction is further supported by more extensive studies (see Table 2, 31a-c). These experiments provide a better indication of the *para* selectivity of the reaction. Initial studies were carried out with sodium formate. However, the poor solubility of the salt in acetonitrile resulted in long reaction times. Ammonium formate was found to be the more reactive of the two hydrogen transfer agents, but it was difficult to obtain and keep dry. Thus, in order to maximize the rate of reduction and minimize the rate of hydrolysis of the diacetanilides, the reactions were conducted with triethylammonium formate in acetonitrile. Poisoning of the catalyst, presumably due to halide poisoning, could be avoided by heating the substrates with a base (e.g. sodium acetate) prior to the addition of the catalyst. In this manner, five to ten molar percent of 5-10% Pd/C was satisfactory. To facilitate purification and analysis, the diacetanilides were usually converted to the acetanilide by partial hydrolysis with aqueous methanol-sodium methoxide at ambient temperature. Structural assignments were based on ^{1}H NMR as well as MS and IR data One proton in the aromatic region of the ^{1}H NMR had a coupling constant of 7.4 Hz or greater than with the other two aromatic protons. This is only consistent with an acetanilide containing three contiguous protons on the aromatic ring. As noted in the earlier communication, the diacetanilides of 2,4,6-trichloroaniline and 3-methyl-2,4,6-trichloroaniline are readily *para* dehalogenated with high selectivity. The introduction of 2-CF_3 (**10**), 2-OCH_3 (**12**), 2-Br (**14**), 2-$COOCH_3$ (**18**), 2-CH_3 (**20**), 2-F (**22**), and 3-OCH_3 (**26** and **28**) all provided consistent *para* dehalogenations. It is of interest to note that in the case of the 2-fluoro-4,6-dibromoaniline that the dipropionanilide gave selectivity similar to the corresponding diacetanilide. With the trichloro-3-methoxy-diacetanilides, two equivalents of formate gave selectivities to the 2-halo-3-methoxyanilines. With one equivalent, selective monodehalogeneration is observed. The *para* selectivity for the 3-methoxyaniline derivatives was established by hydrolysis of the crude diacetanilide mixture to anilines followed by reductive diazotization with t-butyl nitrate in methanol. The isolated dibromoanisole gave spectral data identical to 2,4-dibromoanisole.

Reduction of N,N-Disubstituted Anilines. Effect of Nitrogen Substitution on the Reduction.

The selective *para* dehalogenation of diacetanilides as summarized in Table 1 provides a novel synthetic route to 2,6- and 2,3,6-trisubstituted anilines. Since difunctionality of the aniline nitrogen is required to achieve selectivity, it was of interest to determine what effect modification of the nitrogen substituents would have on the selectivity and whether such modification would provide data to indicate if the selectivity were controlled by either electronic or steric effects. A number of N,N-disubstituted derivatives of 2,4,6-trichloroaniline were prepared and reduced with Pd/C and a formate source. The results are summarized in Table 2. Nitrogen substituents include acetyl, methanesulfonyl,

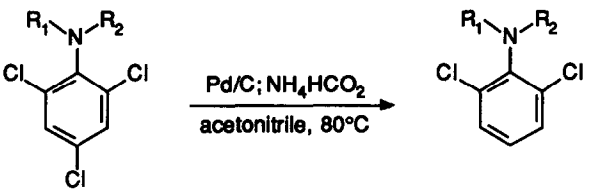
Table 1. Reduction of Diacetanilides



	Substrate					Product			
	X_1	X_2	X_3	X_4		X_1	X_2	X_4	Yield
6	Cl	H	Cl	Cl	**7**	Cl	H	Cl	80[1]
8	Cl	CH_3	Cl	Cl	**9**	Cl	CH_3	Cl	90[1,2]
10	CF_3	H	Cl	Cl	**11**	CF_3	H	Cl	61[3]
12	OCH_3	H	Cl	Cl	**13**	OCH_3	H	Cl	57[3]
14	Br	H	Br	Cl	**15**	Br	H	Cl	49[3]
16	OCH_3	H	Br	Br	**17**	OCH_3	H	Br	20[3]
18	CO_2CH_3	H	Cl	Cl	**19**	CO_2CH_3	H	Cl	74
20	CH_3	H	Br	Br	**21**	CH_3	H	Br	57[3]
22	F	H	Br	Br	**23**	F	H	Br	61
24	F	H	Br	Br	**25**	F	H	Br	64[4]
26	Cl	OCH_3	Cl	Cl	**27**	Cl	OCH_3	H	49[3]
28	Br	OCH_3	Br	Br	**29**	Br	OCH_3	H	55[3]
28	Br	OCH_3	Br	Br	**30**	Br	OCH_3	Br	60[3]

1. Isolated as the aniline by hydrolysis of the diacetanilide
2. Sodium formate utilized in place of triethylammonium formate
3. Isolated as the acetanilide
4. R = $COCH_2CH_3$

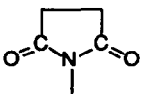
Table 2. Reduction of N,N-Disubstituted Anilines



31 **32**

a $R_1 = R_2 = COCH_3$

b $R_1 = R_2 = SO_2CH_3$

c $R_1R_2N =$ 

d $R_1 = COCH_3$; $R_2 = COOCH_3$

e $R_1 = SO_2C_6H_5$; $R_2 = COCH_3$

f $R_1 = SO_2C_6H_5$; $R_2 = CH_3$

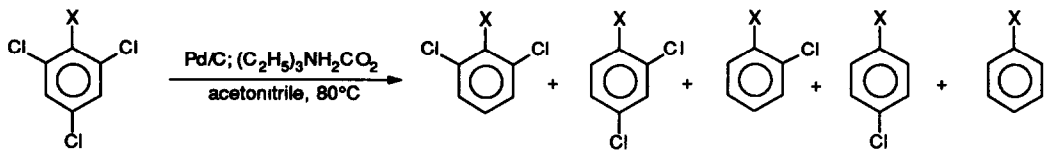
g $R_1 = R_2 = CH_3$

	Mol Ratio (Formate:Substrate)	g Catalyst (% Pd/C)	Time	Conversion	Selectivity
31a	Na (2.0)	0.22 (5)	24	100	78[1]
31b	NH_4 (2.0)	1.06 (10)	2	100	83 (60)[2]
31c	NH_4 (1.4)	0.19 (5)	2	85	90 (50)[2]
31d[5]	NH_4 (1.6)	0.50 (10)	24	79	50[3]
31e	NH_4 (1 0)	0.11 (10)	16	77	42[3]
31f	NH_4 (1.1)	0.11 (10)	7	100	76 (45)[2]
31g[5]	NH_4 (1.1)	0.01 (10)	1 5	27	63[4]

1. 10% "dimer"; triethylammonium formate gives 87% selectivity
2. Isolated yield
3. 20-25% deacetylation of 2,6-isomer
4. By-product is overreduction
5. Solvent was 2-propanol at room temperature

methyl, succinyl, carbomethoxy, and phenylsulfonyl. All are electron withdrawing with the exception of the methyl moiety and will show good selectivity. Noteworthy is the N,N-dimethyl derivative which gave 63% *para* selectivity at 27% conversion. The by-product was essentially overreduction of the initially formed N,N-dimethyl-2,6-dichloroaniline. This result indicates that the reduction is sterically controlled rather than electronic in nature. Further support for the steric control is obtained from the results of reduction of 2,4,6-trichloroanisole where the OCH_3 moiety is a *para*-R substituent and 2,4,6-trichlorobenzonitrile where the -CN moiety is a *para* +R substituent for selective dehalogenation. The results are summarized in Table 3 along with data for the previously reported 2,4,6-trichloroaniline. The present results show that initial selectivity favors the *para* dehalogenation, but overreduction is the controlling factor in determining the final product ratio. Hence, steric effects rather than electronic are the dominant factor in controlling the reaction.

Table 3. Dehalogenation of 2,4,6-Trichlorosubstituted Benzenes



33a 33b 33c 33d 33e 33f

		Product%					
33a	Conversion	33a	33b	33c	33d	33e	33f
$X = NH_2$	86	14	3	8	3	0	72
$X = OCH_3$	71	29	25	5	12	0	29
X-CN	75	25	40	7	26	1	1

Summary

The results of the study have provided an understanding of the scope of the dehalogenation of diacetanilides as well as some insight into the steric factors that control selectivity. During the course of these studies, it became apparent that the amount of Pd catalyst used in the reaction is critical, as the reaction is often "poisoned" during the course of the reaction. Added bases such as sodium acetate decrease catalyst degradation. Palladium on activated carbon was found to be the most effective catalyst for the reaction. Palladium acetate (or its triphenylphosphine complex) showed little or no catalyst activity. Nickel powder showed no reactivity toward the halogenated aniline derivatives, even when the metal was activated using high-density ultrasound. The amount of formate salt must be carefully controlled as overreduction appears to be the principal side reaction. The selectivity of the hydrodehalogenation appears to be quite good, however, when one equivalent of the formate salt is utilized.

Preformed triethylammonium formate solution does not appear to offer any distinct advantages to the reagent formed *in situ*. The reductions are rapid compared to ammonium and sodium formate and, therefore, the amount of H-donor, rather than reaction time, dictates the extent of reduction (or overreduction). In addition to overreduction, the coupling of the diacetanilide derivatives to give symmetrical 4,4'-biaryl products has been observed. Reflux temperatures and less active H-donors (such as sodium formate) typically provided the highest yields of biaryl product. The nature of the biaryl coupling is not well understood at this time.

The choice of solvent may have beneficial effects in some of the reduction reactions. Initial studies utilized acetonitrile almost exclusively. More recently, 2-propanol has been found to be an excellent solvent for the reductions. Furthermore, the combination of excess sodium formate as the H-donor and 2-propanol as the solvent offers a very convenient alternative to reactions employing triethylammonium formate. The reductions using excess formate in 2-propanol proceeded at a reasonable rate even at room temperature, and the reduction could be monitored and stopped before overreduction occurred.

From a more practical point, the value of the reaction would be significantly increased if H_2 could be substituted as the H-donor. Preliminary experiments with H_2 and Pd/C at atmospheric pressure did not reduce 2,4,6-trichlorodiacetanilide. However, when reduced under pressure (50 psi) in 2-propanol at 60°C, selective *para* dechlorination was observed. At 50% conversion, the ratio of 2,6- to 2,4-dichloroaniline was 43 with minimal overreduction Further work continues in this area.

Experimental

General Procedures. All solvents and reagents were obtained from commercial suppliers without further purification except as noted. Dry acetonitrile was obtained by distillation from CaH_2 under an N_2 atmosphere. Ammonium formate was dried by sublimation. ^1H NMR spectra were recorded on either a Varian XL-300 or Varian EM-360. Chemical shifts were reported in ppm downfield from an internal tetramethylsilane standard with $CDCl_3$ as the solvent unless otherwise stated. Infrared spectra were obtained on a Perkin-Elmer 683 spectrophotometer as a chloroform solution unless otherwise noted. Low resolution electron impact mass spectra were obtained on a Hewlett-Packard 5995 GC-MC. Melting points given are uncorrected, and the temperature given for Kugelrohr distillations are those of the hot air bath and not necessarily an accurate measure of boiling points.

Triethylammonium Formate. To 46.2 ml (0.331 mol) of triethylamine in 150 ml of toluene, 11.4 ml (0.290 mol) of 95% formic acid was added in a dropwise fashion under an N_2 atmosphere. After 2 h of stirring at ambient temperature, the toluene was removed by distillation leaving 23.2 g (55%) of triethylammonium formate as a light yellow oil. The oil was diluted to 158 ml with dry acetonitrile giving a 1 M solution in triethylammonium formate.

General Procedure for Chlorination of Anilines.[5] Dry HCl was bubbled through a solution of aniline (0.200 mol) in 500 ml of CCl_4 and 5 ml of ethanol for 10-15 min. The salt solution was then cooled in an ice bath and treated with Cl_2 gas until the reaction was determined to be complete by gas chromatographic analysis (approximately 10% excess Cl_2). The reaction mixture was then poured into ice cold methanol, was taken up in H_2O, and extracted three times with dichloromethane. The combined organic phases were dried (Na_2SO_4), reduced *in vacuo*, and purified by Kugelrohr distillation.

General Procedure for Bromination of Anilines. Aniline (0.200 mol) was diluted in 200 ml of glacial acetic acid, cooled in an ice bath, and under an N_2 atmosphere was treated in a dropwise fashion with bromine

(approximately 10% excess). The mixture was warmed to ambient temperature and stirred until the reaction was determined to be complete by gas chromatographic analysis (1-4 h). The crude reaction mixture was taken up in dichloromethane, washed with water and brine, dried (Na_2SO_4), reduced *in vacuo*, and purified by Kugelrohr distillation.

General Procedure for Preparation of Diacetanilides. The diacetanilides were prepared as described below for 2,4,6-trichlorodiacetanilide. The products were purified by either distillation or recrystallization or both.

General Procedure for Reduction of N,N-Disubstituted Anilines. The N,N-disubstituted anilines were reduced as described below for the preparation of 2,6-dichlorodiacetanilide. The products were purified by either distillation or recrystallization or both. In some examples, the product was isolated as the acetanilide. The latter was obtained by stirring at room temperature the crude reaction production of the reduction in a solution prepared from equal volumes of methanol and 10% NaOH.

2,4,6-Trichlorodiacetanilide (6). A solution of 2,4,6-trichloroaniline (10.08 g, 51.30 mmol) in acetic anhydride (52.09 g, 510.3 mmol, 48.1 ml) and methanesulfonic acid (0 295 g, 3 07 mmol) was heated at reflux until the reaction was complete. The solution was diluted with dichloromethane (50 ml) and washed twice with pH 7.0 phosphate buffer (50 ml each). The organic layer was then washed with brine and dried over sodium sulfate. The solvent and most of the remaining excess acetic anhydride were removed by rotoevaporation. The residual acetic anhydride and other volatiles were removed by Kugelrohr distillation (60°C/4 torr). The product was distilled at 120-125°C/2.3 mm, giving 2,4,6-trichlorodiacetanilide (13.82 g, 96% yield) as a white solid. The product was recrystallized from ethyl acetate-hexane to give white crystals; mp 81-83°C, lit[6] 81-82°C; ^{1}H NMR δ 7.49 (s, 2 H, arom), 2.30 (s, 6 H); MS (70 ev) *m/z:* 279 (M^+, calcd for $C_{10}H_8Cl_3N_2O_2^{\cdot}$ 279).

2,6-Dichlorodiacetanilide (7). 2,4,6-Trichlorodiacetanilide (5 61 g, 0 02 mol) was dissolved in acetonitrile (100 ml). Anhydrous sodium formate (2.72 g, 0 04 mol) was added to the solution along with 2 mol % Pd/C catalyst (5 60 mg of 5% Pd/C). The solution was refluxed under N_2 for 24 h. GC analysis indicated 100% conversion of starting material and 91% (area) of product The catalyst was filtered from the hot solution; after cooling, the filtrate yielded 0.4 g of insoluble material, mp 261-262°C. Evaporation of the filtrate and recrystallation of the residue from ethyl acetate-hexane gave 1.60 g (65%) of product; mp 59-62°C; ^{1}H NMR δ 2.35 (s, 2 H, CH_3CO), 7.45 (m, 1 H, arom). Anal calcd for $C_{10}H_9Cl_2NO_2$: C, 48.81; H, 3.69; N, 5.72. Found: C, 48.54; H, 3 51; N, 5.62 The product was hydrolyzed by refluxing in glacial acetic acid (25 ml) containing concentrated HCl (10 ml) for 1 h The product, isolated by removing the solvent and aqueous acid on a Büchi evaporator, had IR, NMR and MS identical to that of 2,6-dichloroaniline The insoluble material of mp 261-262°C was identified as diacetanilide of 3,5,5',5'-tetrachloro-4,4-diaminobiphenyl; ^{1}H NMR (acetone d-6) δ 2.35 (s, 3 H, CH_3CO), 7.55 (s, 1 H, arom); MS (70 ev) *m/z:* 488 (M^+, calcd for $C_{20}H_{16}Cl_4N_2O_4$: 488). Anal calcd for $C_{20}H_{16}Cl_4N_2O_4^{\cdot}$ C, 49 01; H, 3.29; N, 5.71. Found. C, 48.91; H, 3 35; N, 5.45.

2,4,6-Trichloro-3-methyldiacetanilide (8). Recrystallized from ethyl acetate-hexane; mp 79-81°C; ^{1}H NMR δ 2 35 (s, 6 H, CH_3CO), 2.55 (s, 3 H, CH_3), 7.60 (s, 1 H, arom); MS (70 ev) *m/z:* 293 (M^+, calcd for $C_{11}H_{10}Cl_3NO_2^{\cdot}$ 293). Anal calcd for for $C_{11}H_{10}Cl_3NO_2$: C, 44.85; H, 3.42, N, 4 76. Found· C, 44.66; H, 3 33; N, 4.72

2,6-Dichloro-3-methyldiacetanilide (9). Isolated as a viscous oil; ^{1}H NMR δ 2.30 (s, 6 H, CH_3CO), 2.40 (s, 3 H, CH), 7.35 (m, 2 H, arom); MS (70 ev) *m/z:* 259 (M^+, calcd for $C_{11}H_{11}Cl_2NO_2$: 259) Hydrolysis in aqueous HCl-

acetic acid gave a 90% yield of 2,3-dichloro-3-methylaniline. Calcd for $C_{11}H_{11}Cl_2NO_2$: C, 50.79; H, 4.26; N, 5.38. Found: C, 50.54; H, 4.13; N, 5.48.

2,4-Dichloro-6-trifluoromethyldiacetanilide (10). Distilled Kugelrohr; bp 145°C (2.5 mm); ^{1}H NMR δ 2.29 (s, 6 H, CH_3CO), 7.715 (d, J = 2.1 Hz, 1, H, arom), 7.715 (d, J = 2.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 313 (M^+, calcd for $C_{11}H_8F_3Cl_2NO_2$: 313). Anal calcd for $C_{11}H_8F_3Cl_2NO_2$: C, 42.06; H, 2.57; N, 4.46. Found: C, 42.31; H, 2.67; N, 4.16.

2-Chloro-6-trifluoromethylacetanilide (11). Recrystallized from ethanol; mp 166°C (lit[7] 165-166°C); ^{1}H NMR δ 2.23 (s, 3H, $COCH_3$), 6.98 (br, s, NH), 7.37 (t, J = 7.9 Hz, 1 H, arom), 7.60 (d, J = 7.9 Hz, 1 H), 7.67 (d, J = 8.0 Hz, 1 H, arom); MS (70 ev) *m/z*: 237 (M^+, calcd for $C_9H_7F_3ClNO$: 237).

2,4-Dichloro-6-methoxydiacetanilide (12). Recrystallized from ethyl acetate; mp 104-106°C; ^{1}H NMR δ 2.19 (s, 6 H, $COCH_3$), 3.83 (s, 3 H, OCH_3), 6.918 (d, J = 2.1 Hz, 1 H, arom), 7.142 (d, J = 2.1 Hz, 1 H, arom); MS (70 ev) *m/z*: 275 (M^+, calcd for $C_{11}H_{11}Cl_2NO_3$: 275). Anal calcd for $C_{11}H_{11}Cl_2NO_3$: C, 47.85; H, 4.02; N, 5.07. Found: C, 48.00; H, 3.71; N, 5.22.

2-Chloro-6-methoxyacetanilide (13). Recrystallized from ethanol; mp 146.5-147.5°C (lit[8] 147-148°C); ^{1}H NMR δ 2.16 (s, 3 H, $COCH_3$), 3.83 (s, 3 H, OCH_3), 6.83 (d, J = 8.1 Hz, 1 H, arom), 6.95 (br, s, 1 H, NH), 7.03 (d, J = 8.1 Hz, 1 H, arom), 7.17 (d, J = 8.1 Hz, 1 H, arom), 6.95 (br, s, 1 H, NH), 7.03 (d, J = 8.1 Hz, 1 H, arom), 7.17 (d, J = 8.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 199 (M^+, calcd for $C_9H_{10}ClNO_2$: 199).

2,4-Dibromo-6-chlorodiacetanilide (14). Recrystallized from ethyl acetate-hexane; mp 85-86°C; ^{1}H NMR δ 2.31 (s, 6 H, $COCH_3$), 7.673 (d, J = 2.1 Hz, 1 H, arom), 7.792 (d, J = 2.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 367 (M^+, calcd for $C_{10}H_8Br_2ClNO_2$: 367). Anal calcd for $C_{10}H_8Br_2ClNO_2$: C, 32.51; H, 2.18; N, 3.79. Found: C, 32.35; H, 2 06; N, 3.82.

2-Bromo-6-chloroacetanilide (15). Purified by Kugelrohr distillation; mp 186-189°C; ^{1}H NMR δ 2.24 (s, 3 H, $COCH_3$), 6.99 (br, s, 1 H, NH), 7.10 (dd, J = 8.1, 7.4 Hz, 1 H, arom), 7.41 (d, J = 8 1 Hz, 1 H, arom), 7.54 (d, J = 7.4 Hz, 1 H, arom); MS (70 ev) *m/z:* 247 (M^+, calcd for $C_8H_7BrClNO$: 247). Anal calcd for $C_8H_7BrClNO$: C, 38 67; H, 2.84; N, 5.64. Found: C, 39.30; H, 2.81; N, 5.53.

2,4-Dibromo-6-methoxydiacetanilide (16). Distilled bp 160°C (2.0 mm); mp 96-99°C; ^{1}H NMR δ 2.26 (s, 6 H, $COCH_3$), 3.82 (s, 3 H, OCH_3), 7.084 (d, J = 2.1 Hz, 1 H, arom), 7.584 (d, J = 2.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 363 (M^+, calcd for $C_{11}H_{11}Br_2NO_3$: 363). Anal calcd for $C_{11}H_{11}Br_2NO_3$: C, 36.2, H, 3.04; N. 3.84. Found: C, 36.00; H, 2.88; N, 3.79.

2-Bromo-6-methoxyacetanilide (17). Recrystallized from ethanol; mp 158°C; ^{1}H NMR δ 2.29 (br, s, $COCH_3$), 3.84 (s, 3 H, OCH_3), 6.78 (br, s, 1 H, arom), 6.89 (d, J = 8 1 Hz, 1 H, arom), 7.13 (t, J = 8.1 Hz, 1 H, arom), 7.25 (d, J = 8 1 Hz, 1 H, arom); MS (70 ev) *m/z:* 243: (M^+, calcd for $C_9H_{10}BrNO_2$: 243). Anal calcd for $C_9H_{10}BrNO_2$: C, 44.29; H, 4.13; N, 5 74. Found: C, 44.35; H, 3.89; N, 5.28.

2,4-Dichloro-6-carbomethoxydiacetanilide (18). Distilled; bp 130-135°C (0.9 mm), mp 122-125°C; ^{1}H NMR ($CDCl_3$) δ 2.278 (s, 6 H, $COCH_3$), 3.876 (s, 3 H, $COOCH_3$), 7.736 (d, J = 2.1 Hz, 1 H, arom), 7.9839 (d, J = 2.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 303 (M^+, calcd for $C_{12}H_{11}Cl_2NO_4$: 303). Anal calcd for $C_{12}H_{11}Cl_2NO_4$. C, 47.39; H, 3.65; N, 4.61. Found: C, 47.18; H, 3.50; N, 4.77.

2-Chloro-6-carbomethoxydiacetanilide (19). Distillation on a Kugelrohr; bp 130-135°C (1.4 mm) to give **19** as a viscous oil. ^{1}H NMR δ 2.28 (s, 6 H, $COCH_3$), 3.87 (s, 3 H, OCH_3), 7.47 (t, J = 8.0 Hz, 1 H, arom), 7.72 (dd, J =

8.1, 1.5 Hz, 1 H, arom), 8.00 (dd, J = 7.9, 1.5 Hz, 1 H, arom); MS (70 Ev) *m/z:* 269 (M^+, calcd for $C_{12}H_{12}ClNO_4$: 269) Anal calcd for $C_{12}H_{12}ClNO_4$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.27; H, 4.29; N, 5.02.

2,4-Dibromo-6-methoxydiacetanilide (20). Distilled on Kugelrohr; mp 86-88°C; ^1H NMR δ 2.191 (s, 3 H, CH_3), 2.271 (s, 6 H, $COCH_3$), 7.442 (s, 1 H, arom), 7.70 (s, 1 H, arom); MS (70 ev) *m/z:* 347 (M^+, calcd for $C_{11}H_{11}Br_2NO_2$: 347). Anal calcd for $C_{11}H_{11}Br_2NO_2$: C, 37.85; H, 3.18; N, 4.01. Found: C, 37.72; H, 3.01; N, 3.70

2-Bromo-6-methylacetanilide (21). Recrystallized from ethanol; mp 164-166°C (lit[9] 166°C); ^1H NMR (d_6-DMSO) δ 2.03 (s, 3 H, CH_3), 2.17 (s, 3 H, $COCH_3$), 7 10 (t, J = 7.5 Hz, 1 H, arom), 7.25 (d, J = 7.5 Hz, 1 H, arom), 7 47 (d, J = 7.5 hz, 1 H, arom), 9.50 (br, s, 1 H, NH); MS (70 ev) *m/z:* 227 (M^+, calcd for $C_9H_{10}BrNO$: 227).

2,6-Dibromo-6-fluorodiacetanilide (22). Distilled on Kugelrohr; bp 180°C (3 mm); mp 58-60°C; ^1H NMR δ 2.31 (s, 6 H, $COCH_3$), 7.396 (dd, 1 H, arom), 7.688 (s, 1 H, arom); MS (70 ev) *m/z:* 351 (M^+, calcd for $C_{10}H_8Br_2FNO_2$: 351). Anal calcd for $C_{10}H_8Br_2FNO_2$: C, 34.03; H, 2.28; N, 3.97. Found. C, 33.80; H, 1.92; N, 3.90.

2-Bromo-6-fluoroacetanilide (23). Distilled on Kugelrohr, colorless oil (120, 2.0 mm); ^1H NMR δ 2.23 (s, 6 H, $COCH_3$), 7.17 (dt, J = 8.1, 1.3 Hz, 1 H, arom), 7.30 (dt, J = 5.7, 8.1 Hz, 1 H, arom), 7.48 (dt, J = 1.3, 8.5 Hz, 1 H, arom); MS (70 ev) *m/z:* 273 (M^+, calcd for $C_{10}H_9BrFNO_2$: 273). Anal calcd for $C_{10}H_9BrFNO_2$: C, 43.82; H, 3 31; N, 5.11. Found: C, 43.97; H, 3.18, N, 4.62.

2,4-Dibromo-6-fluorodipropionylanilide (24). Distilled on Kugelrohr; bp 140°C (2 mm), mp 68-71°C; ^1H NMR δ 1.14 (t, J = 7.5 Hz, 6 H, CH_3), 2.59 (q, J = 7.5 Hz, 4 H, CH_2), 7.38 (dd, J = 8.4, 2.1 Hz, 1 H, arom), 7.68 (t, J = 2.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 379 (M^+, calcd for $C_{12}H_{12}Br_{12}FNO_2$: 379). Anal calcd for $C_{12}H_{12}Br_{12}FNO_2$: C, 37.83; H, 3.17; N, 3.68. Found: C, 37.72; H, 3.07; N, 3.53.

2-Bromo-6-fluorodipropionylanilide (25). Distilled on Kugelrohr, colorless oil; bp 130°C (2.6 mm), mp 68-70°C; ^1H NMR δ 1.14 (t, J = 7.3 Hz, 6 H, CH_3), 2.60 (q, J = 7.3 Hz, 4 H, CH_2), 7.17 (dt, J = 8.1, 1.3 Hz, 1 H, arom), 7.30 (dt, J = 5.7, 8.1 Hz, 1 H, arom), 7.48 (dt, J = 1.3, 8.5 Hz, 1 H, arom); MS (70 ev) *m/z:* 301 (M^+, calcd for $C_{12}H_{13}BrFNO_2$: 301). Anal calcd for $C_{12}H_{13}BrFNO_2$: C, 47.70, H, 4.34; N, 4.64 Found· C, 47.55; H, 4.18; N, 4.78.

2,4,6-Trichloro-3-methoxydiacetanilide (26). Distilled on Kugelrohr, viscous liquid; bp 150°C (3 mm), mp 68-70°C; ^1H NMR δ 2.23 (s, 6 H, $COCH_3$), 3.93 (s, 3 H, OCH_3), 7.54 (s, 1 H, arom); MS (70 ev) *m/z:* 309 (M^+, calcd for $C_{11}H_{10}Cl_3NO_3$: 309) Anal calcd for $C_{11}H_{10}Cl_3NO_3$: C, 42.54; H, 3.25; N, 4.51. Found: C, 42.20; H, 3.01; N, 4.28.

2-Chloro-3-methoxyacetanilide (27). Distilled on Kugelrohr and recrystallized from ethanol; mp 106-107.5°C; ^1H NMR δ 2.23 (s, 3H, $COCH_3$), 3.89 (s, 3 H, OCH_3), 6.70 (d, J = 8.1 Hz, 1 H, arom), 7.21 (t, J = 8.1 Hz, 1 H, arom), 7.70 (br, s, 1 H, arom), 7.99 (d, J = 8.1 Hz, 1 H, arom); MS (70 ev) *m/z:* 199 (M^+, calcd for $C_9H_{10}ClNO_2$: 199). Anal calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 53.86; H, 4.97; N, 7.41.

2,4,6-Tribromo-3-methoxydiacetanilide (28). Distilled on Kugelrohr, bp 165°C (2 mm), mp 86-88°C; ^1H NMR δ 2.23 (s, 6 H, $COCH_3$), 3.93 (s, 3 H, OCH_3), 7.54 (s, 1 H, arom); MS (70 ev) *m/z:* 441 (M^+, calcd for $C_{11}H_{10}Br_3NO_3$: 441). Anal calcd for $C_{11}H_{10}Br_3NO_3$: C, 29.76; H, 2.27; N, 3.16. Found: C, 29.70; H, 2.03; N, 2.99.

2-Bromo-3-methoxyacetanilide (29). Recrystallized from ethanol; mp 123-124.5°C; ^1H NMR δ 2.23 (s, 3H, $COCH_3$), 3.89 (s, 3 H, OCH_3), 6.67 (d, J = 8.4 Hz, 1 H, arom), 7.26 (t, J = 8.4 Hz, 1 H, arom), 7.72 (br, s, 1H, NH), 7.98 (d, J = 8.4 Hz, 1 H, arom); MS (70 ev) *m/z:* 243 (M^+, calcd for $C_9H_{10}BrNO_2$: 243). Anal calcd for $C_9H_{10}BrNO_2$: C, 44.29; H, 4.13; N, 4.34. Found: C, 43.87; H, 3.92; N, 4.06.

2,6-Dibromo-3-methoxyacetanilide (30). Recrystallized from chloroform; mp 178.5-179°C (lit[10] 150.5°C); ^{1}H NMR δ 2.22 (s, 3 H, $COCH_3$), 3.88 (s, 3 H, OCH_3), 6.74 (d, J = 8.9 Hz, 1 H, arom), 7.15 (br, s, 1 H, arom), 7.51 (d, J = 8.9 Hz, 1 H, arom); MS (70 ev) *m/z:* 321 (M^+, calcd for $C_9H_9Br_2NO_2$: 321). Anal calcd for $C_9H_9Br_2NO_2$: C, 33.47; H, 2.81; N, 4.34. Found: C, 33.23; H, 2.69; N, 4.33.

2,4,6-Trichlorophenyldimethanesulfonylanilide (31b). 2,4,6-Trichloroaniline (19.5 g, 0.10 mol) was dissolved in toluene (250 ml) in a 500 ml round-bottom flask Triethylamine (36 ml, 0.25 mol) and methanesulfonyl chloride (25.2 g. 0.22 mol) were added slowly to the aniline solution. The flask was fitted with a condenser and the mixture stirred for 2 h at room temperature, then heated for 1 hr at 80°C. The product was isolated by extraction and recrystallized from toluene-hexane to give 7.0 g (77%) of product, mp 167-170°C; ^{1}H NMR δ 3.57 (s, 3 H, CH_3SO_2), 7.50 (s, 1 H, arom); MS (70 ev) *m/z:* 351 (M^+, calcd for $C_8H_8Cl_3NS_2O_4$: 351). Anal calcd for $C_8H_8Cl_3NS_2O_4$: C, 27.25; H, 2.29; N, 3.97. Found: C, 27.19; H, 2.06; N, 3.87.

2,6-Dichlorophenyldimethanesulfonylanilide (32b). Prepared from 2,6-dichloroaniline as described for **31b**. Recrystallized from ethyl acetate; mp 171-172°C; ^{1}H NMR δ 3.57 (s, 6 H, CH_3SO_2), 7.46 (m, 3 H, arom); MS (70 ev) *m/z:* 285 (M^+, calcd for $C_8H_9Cl_2NS_2O_4^{\cdot}$ 285). Anal calcd for $C_8H_9Cl_2NS_2O_4$. C, 30 30; H, 2.84; N, 4.42. Found: C, 30.18; H, 2.70; N, 4.27.

N-2,4,6-Trichlorophenylsuccinimide (31c). 2,4,6-Trichloroaniline (19.6 g, 0.1 mol) was dissolved in a 500 ml round-bottom flask equipped with a magnetic stirrer and water condenser. Pyridine (19.77 g, 0.25 mol) and succinyl cloride (15.5 g. 0.1 mol) was added and the reaction stirred for 2 h at room temperature. GC analysis indicated product formation. The reaction was refluxed for an additional 1 h during which time a considerable amount of black, insoluble material was formed. The solution was poured into water and the product and unreacted aniline isolated by extraction. After drying over $MgSO_4$ and solvent removal on a Büchi evaporator, the unreacted aniline was removed on a Kugelrohr. The residue was recrystallized from ethyl acetate to give 3.50 g (13%) of product; mp 163-165°C; ^{1}H NMR δ 2.93 (s, 4 H, $-CH_2CH_2-$), δ 7.54 (s, 2 H, arom); MS (70 ev) *m/z:* 277 (M^+, calcd for $C_{10}H_6Cl_3NO_2$: 277). Anal calcd for $C_{10}H_6Cl_3NO_2$: C, 43.12; H, 2.17; N, 5.03. Found. C, 43.28; H, 2.08; N, 4.94.

N-2,6-Dichlorophenylsuccinimide (32c). Prepared as described for **31c**. Recrystallized from dichloromethane-hexane; mp 143-146°C; ^{1}H NMR δ 3,00 (s, 4 H, $-CH_2CH_2$), 7.47 (m, 3 H, arom); MS (70 ev) *m/z:* 243 (M^+, calcd for $C_{10}H_7Cl_2NO_2^{\cdot}$ 243). Anal calcd for $C_{10}H_7Cl_2NO_2$: C, 49.21; H, 2.89; N, 5.74. Found: C, 49.15; N, 2.88; H, 5.69.

N-Carbomethoxy-2,4,6-trichloroacetanilide (31d). 2,4,6-Trichloroacetanilide (7.11 g, 0.03 mol) was dissolved in tetrahydrofuran (50 ml) in a 250 ml 3-neck round-bottom flask equipped with condenser, thermometer, magnetic stirrer, and dropping funnel. Triethylamine (5 ml) in tetrahydrofuran (50 ml) was added dropwise to the acetanilide solution, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured onto water and the product isolated by extraction with ethyl acetate. After drying over $MgSO_4$, the solvent was evaporated on a Büchi evaporator and the residue recrystallized from dichloromethane-hexane to give 6.0 g (68%) of product; mp 132-134°C; ^{1}H NMR δ 2.67 (s, 3 H, CH_3CO), 3.73 (s, 3 H, OCH_3), 7.43 (s, 2 H, arom); MS (70 ev) *m/z:* 295 (M^+, calcd for $C_{10}H_8Cl_3NO_3$: 295). Anal calcd for $C_{10}H_8Cl_3NO_3$: C, 40.50; H, 2.72; N, 4.72. Found: C, 40 46; H, 2.57; N, 4.67.

N-Carbomethoxy-2,6-dichloroacetanilide (32d). Prepared as described for **31d**. Recrystallized from hexane-dichloromethane; mp 110-112°C; ^{1}H NMR δ 2.69 (s, 3 H, CH_3CO), 3.74 (s, 3 H, OCH_3), 7.26, 7.38 (d, t, 3 H,

arom); MS (70 ev) *m/z:* 261 (M^+, calcd for $C_{10}H_9Cl_2NO_3$: C, 45.83; H, 3.46; N, 5.34; Found: C, 45.59; H, 3.22; N, 5.24.

N-Acetyl-N-2,4,6-trichlorophenylbenzenesulfonamide (31e). 2,4,6-Trichloroaniline (39.2 g, 0.2 mol) and benzenesulfonyl chloride (52.8 g. 0.3 mol) was heated in the melt at 150°C for 8 h. After cooling, the reaction mixture was dissolved in ethyl acetate and washed with water. After drying over $MgSO_4$, the solvent was removed on a Büchi evaporator, and the residue recrystallized from CCl_4 to give 30 g (46%) of product; mp 151-152°C; ^1H NMR δ 6.50 (sb, 1 H, NH), 7.32 (s, 2 H, arom), 7.32-8.05 (m, 5 H, C_6H_5); MS (70 ev) *m/z:* 335 (M^+, calcd for $C_{12}H_8Cl_3NO_2S$: 335). N-(2,4,6-Trichlorophenyl)benzenesulfonamide (6.75 g, 0.02 mol) was dissolved in tetrahydrofuran (50 ml) in a 100 ml 3-neck round-bottom flask, and triethylamine (5 ml, excess) was added. Acetyl chloride (2 ml, excess) was added dropwise to the triethylamine-sulfonamide solution and the reaction mixture stirred at room temperature for 15 min. The reaction mixture was poured onto water and the product isolated by extraction with ethyl acetate. After drying over $MgSO_4$, the solvent was evaporated on a Büchi evaporator and the residue recrystallized from CCl_4 to give 6.1 g (81%) product; mp 185-188°C; ^1H NMR δ 1.92 (s, 3 H, CH_3CO), 7.60 (s, 2, $C_6H_2Cl_3$), 7.25-8.35 (m, 5, C_6H_5); MS (70 ev) *m/z:* 334 (M^+, calcd for $C_{14}H_{10}Cl_3NO_3S$: 377; and M^+, calcd for M^+-43 $(CH_3CO)^·$ 334). Anal calcd for $C_{14}H_{10}Cl_3NO_3S$: C, 44.41; H, 2.66; N, 3.70. Found: C, 44.17; H, 2.56; N, 3.58.

N-Acetyl-N-2,6-trichlorophenylbenzenesulfonamide (32e). N-2,6-Dichlorophenylbenzenesulfonamide was prepared from 2,6-dichloroaniline and benzenesulfonyl chloride as described for the corresponding 2,4,6-trichloroaniline. The product, after recrystallization from CCl_4, had mp 154-156°C. N-2,6-Dichlorophenylbenzenesulfonamide (7.0 g, 0.023 mol) was converted to the N-acetyl derivative as described for the trichloro derivative. The product, after recrystallization from ethyl acetate-hexane, had mp 198-200°C. ^1H NMR δ 1.86 (s, 3 H, CH_3CO), 7.30-7.80 and 8.15-8.45 (m, 8 H, arom); MS (70 ev) *m/z:* 301 (M^+, calcd for $C_{14}H_{11}Cl_2NO_3S^·$ 343, and M^+, calcd for M^+-43 (CH_3CO): 301). Anal calcd for $C_{14}H_{11}Cl_2NO_3S$: C, 48.85; H, 3.22; N, 4.07. Found: C, 48.43; H, 3.12; N, 3.96.

N-Methyl-2,4,6-trichlorophenylbenzenesulfonamide (31f). N-2,4,6-Trichlorophenylbenzenesulfonamide (6.70 g, 0.02 mol) and methyl chloroformate (2.5 ml, excess) were dissolved in tetrahydrofuran and triethylamine (5 ml, excess) added dropwise at room temperature. The reaction was stirred at room temeprature 15 min and then poured onto water. The product was isolated by extraction with ethyl acetate. After drying over $MgSO_4$, the solvent was removed on a Büchi evaporator and the residue recrystallized from dichoromethane-hexane to give 5.1 g (73%) product; mp 120-122°C; ^1H NMR δ 3.17 (s, 3 H, CH_3N-), 7.00-8.15 (m, 7 H, arom); MS (70 ev) *m/z:* 349 (M^+, calcd for $C_{13}H_{10}Cl_3NO_2S$. 349). Anal calcd for $C_{13}H_{10}Cl_3NO_2S$: C, 44 53; H, 2 87; N, 3.99. Found C, 44.78, H, 2.70; N, 3.85.

N-Methyl-2,6-dichlorophenylbenzenesulfonamide (32f). N-2,6-Dichlorophenylbenzenesulfonamide (7.0 g. 0 023 mol) was converted to the N-methyl derivative with methyl chloroformate as described for the 2,4,6-trichloro derivative. The product, after recrystallization from ethyl acetate-hexane, had mp 106-108°C. ^1H NMR δ 3.20 (s, 3 H, CH_3N-), 6.90-8.20 (m, 8 H, arom); MS (70 ev) *m/z:* 315 (M^+, calcd for $C_{13}H_{11}Cl_2NO_2S$: 315) Anal calcd for $C_{13}H_{11}Cl_2NO_2S^·$ C, 49.52, H, 2.86; N, 4 44 Found: C, 49.30; H, 3.12; N, 3.96.

N,N-Dimethyl-2,4,6-trichloroaniline (31g). 2,4,6-Trichloroaniline (19.6 g, 0.1 mol), toluene (100 ml), dimethyl sulfate (0.4 mol, 38 ml), and anhydrous potassium carbonate (13 8 g. 0 1 mol) were added to a 250 ml round-bottom flask and the mixture refluxed overnight. The contents were diluted with ethyl acetate, the organic

layer washed with dilute aqueous sodium by hydroxide, dried over $MgSO_4$, and the solvent removed on a Büchi evaporator. The residue was distilled on a Nester-Faust spinning band column to give 12.0 g of product; bp 112-114°C (20 mm), lit[11] 128-138°C (20 mm); ^1H NMR δ 2.90 (s, 3 H, $N(CH_3)_2$), 7.40 (s, 2 H, arom); MS (70 ev) *m/z:* 223 (M^+, calcd for $C_8H_8Cl_3N$: 223).

N,N-Dimethyl-2,6-dichloroaniline (32g). N,N-Dimethyl-2,6-dichloroaniline was prepared from 2,6-dichloroaniline as described for the trichloro derivative. The product distilled at 94-95°C (8 mm). ^1H NMR δ 2.90 (s, 2 H, $-N(CH_3)_2$), 6.60-7.35 (m, 1 H, arom); MS (70 ev) *m/z:* 189 (M^+, calcd for $C_8H_9Cl_2N$: 189). Anal calcd for $C_8H_9Cl_2N$: C, 50.55; H, 4.77; N, 7.37. Found: C, 50.08; H, 4.61; N, 7.82.

Reduction of 2,4,6-trichlorodiacetanilide (6) with H_2 and Pd/C. 2,4,6-Trichlorodiacetanilide (2.79 g), 50 ml of 2-propanol, 5 ml of pyridine, and 106 mg of 10% Pd/C were charged into a 200 ml Hastelloy C pressure reactor. The reactor was sealed, purged of air, and pressurized to 50 psig with hydrogen. The mixture was stirred overnight at 60°C at which point the reactor pressure had been reduced to 0 psig. The catalyst was removed by filtration, and the filtrate was treated with 2 g of 5N NaOH to hydrolyze the product to a mixture of anilines which had the following composition: 2,4,6-trichloroaniline (49%), 2,4-dichloroaniline (1%), 2,6-dichloroaniline (43%), 2-chloroaniline (2%), and aniline (1%).

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