A Novel Synthesis of 2,6-Disubstituted and 2,3,6-Trisubstituted Anilines

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Abstract: 2,6-Disubstituted and 2,3,6-trisubstituted anilines have been synthesized by a four-step approach involving the selective reduction of a para halogen of the diacetanilide derivatives utilizing a palladium-oncarbon catalyst and formic acid salts as the *in situ* hydrogen donor.

Synthetic methodology for the introduction of ortho substituents into aromatic compounds is of considerable interest. Recently, Eaton and Martin¹ reported on the synthesis of 2,6-disubstituted benzamides by use of the reagent lithium tetramethylpiperidine (LiTMP/mercuric chloride). Adachi and Sugasawa have described an exclusive ortho cyanation and alkylthiocarbonylation of anilines via an anilinochloroborane.² We now report a novel synthesis of 2,6-disubstituted and 2,3,6-trisubstituted anilines that involves a selective reduction of the para halogen of corresponding diacetanlides. 2,6-Disubstituted anilines and 2,3,6-trisubstituted anilines are valuable intermediates for the synthesis of agricultural chemicals, specifically, sulfonamide herbicides of the structure (1).³ Since the direct electrophilic aromatic halogenation of anilines provides little or no selectivity for halogenation at



(1)

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carbons ortho versus para to the amino group, the selective dehalogenation at the 4-position of a polyhalogenated aniline would provide a useful method for preparing the desired anilines. 2,6-Dichloro-3-methylaniline is presently manufactured from the acetanilide of m-toluidine in a multistep process involving an intermediate aminosulfonamide.⁴ We now describe this selective reduction via catalytic transfer hydrogenation of the diacetanilide derivatives using a Pd/C catalyst and formic acid salts as the *in situ* hydrogen donor.⁵



The diacetanilides are readily prepared from the aniline and acetic anhydride with a catalytic amount of methanesulfonic acid.⁶ After reduction, the aniline is recovered by hydrolysis of the diacetanilide.⁷ Preliminary results are summarized in Table 1. Initial experiments on selective para halogen reduction were carried out with 2,4,6-trichloroaniline (**7a**) in order to eliminate, if possible, the protection-deprotection of the amino moiety. As illustrated in Table 1, 2,4-dichloroaniline, (**9a**), is the principal product of mono reduction. Further reduction to aniline proceeds rapidly. A similar reduction pattern was found for 2,4,6-trichloroacetanilide, (**7b**). However, when 2,4,6-trichlorodiacetanilide, (**7c**), was reduced either with or without added sodium acetate buffer, the selectivity of reduction of the para halogen was remarkable. Triethylammonium formate, prepared either separately or *in situ*, sodium formate and ammonium formate were examined, with the latter being the least selective. Comparable results were obtained with the 3-methyl derivative, 2,4,6-trichloro-3-methylaniline, (**7d**). With sodium formate and acetonitrile as solvent, a 90% yield of the desired 2,6-dichloro-3-methylaniline was obtained.

Table 1. Selective Para Chlorine Reduction of Substituted Diacetanilides.

R	¹ _N R ²		R ¹ _N	.R ²	R¹	N ^{-R2}			P R		2		R¹、,	R2
CI		HCO2 Pd/C		+ R ³ +		Í) 	+ ³	Ô	_CI + 	Ø	`R³	+		
	(7)		(8)		(ČI (9)		(10)		Ċ (11)			(:	(2)
<u>\$</u> 1	ubstrate (mol)	"H" Source	<u>e (mol)</u>	Equiv 10% PdC	Solvent (ml)	Temp ℃	Time <u>Hr</u>	Additive	Conversion	(8)	<u>P</u> (9)	roduci (10)	<u>%</u> (11)	(12)
(7a)	R ₁ =R ₂ =R ₃ = (0.01)	H NH4 NH4 NH4 Na	(0.011) (0.011) (0.011) (0.028)	0.05 0.01 0.01 0.01	A (20) B (20) B (20) C (20)	80 80 RT RT 65	2.0 1.0 0.5 1.0 2.0	- 	42 60 22 33 16	15 9 15 12 15	27 21 41 34 58	7 5 7 8 	>1 - - -	50 65 37 46 27
(7b)	R ₁ =R ₃ =H; R ₂ =COCH ₃ (0.01)	NH4 NH4	(0.011) (0.011)	0.01 0.05	B (20) B (20)	80 80	2.0 2.0	_	65 47	7 17	22 24	6 6	3 1	62 52
(7c)	R ₁ =R ₂ =COC R ₃ =H (0.011)	°H3; C2H5)3NH	(0.011)	0.02 ^b	A (20)	80	3.75	NaOAc (0.015)	80	97		3	-	-
	(0.007)	C2H5)3N HCOOH	(0.011) (0.008)	0.05	A (20)	80	2.0	-	86	84		16	-	-
	(0.011)	C2H5)3N HCOOH	(0.014) (0.013)	0.02	A (20)	25	2.0	-	85	96		4	NJ.L	
	(0.0054)	С2H5)3N НСООН	(0.0055) (0.011)	0.05°	A (20)	80	2.0	NaOH (0.0054)	98	87		7	-	-
	(0.0054)	Na	(0.0054)	0.05 ^d	A (20)	80	3.5	NaOAc (0.0054)	82	94		6	-	
	(0.0054)	Na	(0.007)	0.05	B (25)	80	1.5	-	97	82		16	-	
	(0.005)	NH4	(0.0055)	0.05	B (20)	80	1.5	-	70	76	2	7		18
(7d)	R ₁ =R ₂ =COC R ₃ =CH ₃ (0.005) (0.005) (0.02)	H3; NH4 NH4 Na	(0.0055) (0.0055) (0.04)	0.05 0.05 0.05	A (20) B (20) A (75)	80 80 80	2.0 2.0 72		40 75 100	54 76 90 ^e	8 2 	24 11 _	14 10 -	

A = Acetonitrile; B = 2-Propanol; C = Methanol a Small amounts of the dimeric product are formed in some reductions, e.g., 1-7% b Additive NaOAc (0.015 mol) c Additive NaOA((0.0054 mol)) d Additive NaOAc (0.0054 mol) e Isolated as aniline

Research is in progress to determine the electronic and steric effects of the substituents on the

amino nitrogen as well as the general utility of the reaction with regard to other aryl substituents.

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- 6. A solution of the haloaniline and acetic anhydride (excess) was heated to reflux in the presence of a catalytic amount of methanesulfonic acid until the reaction was determined to be complete by gas chromatographic analysis (4-12 hr). The diacetanilide was isolated by extraction and purified by either Kugelrohr distillation or recrystallization.
- 7. For analysis of the mixture of diacetanilides obtained from the Pd/C formate reduction, the diacetanilides were hydrolyzed to the corresponding anilines by either refluxing overnight in a solution of acetic acid-concentrated HCl (50:50) or by refluxing in aqueous NaOH (20%) until the hydrolysis was complete (4-6 hr) and isolating the anilines by extraction.

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