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An Ortho-Directing Effect in the Nucleophilic Aromatic Substitution Reactions of Primary and Secondary 2,4-Dichloro- and 2,3,4-Trichlorobenzamides with Ethanethiolate

Geoffrey K. Cooper [a] , Don R. Baker [a] & Larry B. Barden [a]
[a] Western Research Center, Zeneca Agricultural Products , Richmond, California, 94804
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AN *ORTHO*-DIRECTING EFFECT IN THE NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF PRIMARY AND SECONDARY 2,4-DICHLORO- AND 2,3,4-TRICHLOROBENZAMIDES WITH ETHANETHIOLATE

Geoffrey K. Cooper,* Don R. Baker, and Larry B. Barden

Western Research Center, Zeneca Agricultural Products,
Richmond, California, 94804

Abstract: The reactions of the primary amide and several secondary amides of 2,4-dichloro- and 2,3,4-trichlorobenzoic acid with potassium ethanethiolate in DMF were observed to proceed with a remarkable degree of *ortho*-regioselectivity. This effect was found to be absent using related tertiary amides as substrates.

Few synthetically useful methods exist for regioselective nucleophilic *ortho*-substitution of polyhalo aromatic systems.[1] An *ortho*-directing effect was observed in the reaction of 2,4-dichloronitrobenzene with amine nucleophiles and in the reaction of 2,4-dichlorobenzoate anions with amines, but not with methoxide.[2] An *ortho*-directing effect was also noted in the copper-catalyzed Ullman coupling of benzoates with aryl halides.[3] *Ortho*-displacement reactions of 2,4-dichloro-N-pivaloylaniline and 2,4-dichloro-N-acetylaniline with

*Author to whom correspondence should be addressed.

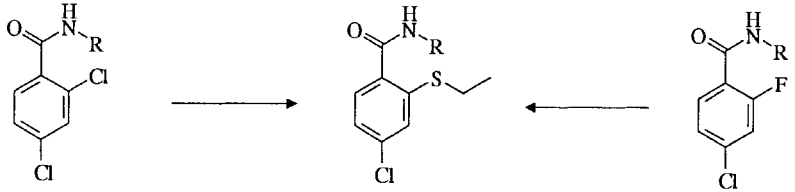
potassium phenylthiolate in NMP have been described.[4] An analogous effect in the displacement of nitro groups in dinitroalkylbenzenes has been reported.[5] A recent report discusses the *ortho*-selectivity of substitution of 2,4-difluoroacetophenone with a thiolate nucleophile.[6]

As part of a study aimed at devising methods for the industrial preparation of 1,2,4- and 1,2,3,4-substituted benzene derivatives useful as herbicides, we examined the reactions of various derivatives of 2,3,4-trichlorobenzoic acid with potassium ethanethiolate in DMF (Table). Among other derivatives, the primary amide and several secondary amides of this carboxylic acid were prepared by standard methods and were allowed to react with the sulfur nucleophile. It was noted that the products of these reactions were much cleaner than the products resulting from reactions of tertiary amides of the same acid. Chromatographic (GC) and spectroscopic (NMR, MS) analysis revealed that in the case of the primary amide and of secondary amides such as the isobutylamide, mono-substitution had occured in one specific sense with very little formation of isomers, whereas reaction of tertiary amides such as the di-isobutylamide or the methyl isobutylamide resulted in two isomeric products being formed in approximately equal quantities at a lower reaction rate.

We were unable to unambiguously identify the single products formed in the reactions of the secondary amides of 2,3,4-trichlorobenzoic acid by spectroscopic means, so we resorted to a model system (Scheme 1). Reactions of some of the same secondary amides of 2,4-dichlorobenzoic acid including

the isobutylamide **1** also yielded a single isomer **2**, whereas tertiary amides again gave a mixture of products. The amides of 4-chloro-2-fluorobenzoic acid and 2-chloro-4-fluorobenzoic acid were then prepared and allowed to react with ethanethiolate. Products were then analyzed by GC-MS. The reaction product of isobutyl 4-chloro-2-fluorobenzamide **3** was found to be identical with the product **2** resulting from reaction of isobutyl 2,4-dichlorobenzamide, whereas in the case of isobutyl 2-chloro-4-fluorobenzamide neither of the two products formed (isobutyl 2-ethylthio-4-fluorobenzamide and isobutyl 2-chloro-4-ethylthiobenzamide) could be correlated with the product from isobutyl 2,4-dichlorobenzamide. This confirmed that *ortho*-substitution had occurred in this case. The formation of two products in the reaction of isobutyl 2-chloro-4-

Scheme 1: Reactions of 2,4-Dihalobenzamides



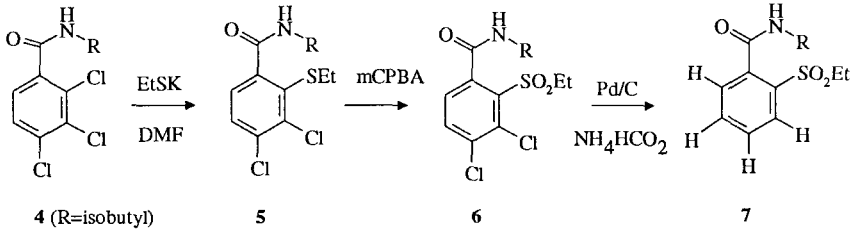
1 (R=isobutyl) **2** **3**

fluorobenzamide was attributed to the greater nucleofugacity of fluoride relative to chloride in nucleophilic aromatic substitution, which enhanced the otherwise disfavored *para*-substitution reaction.[1]

Attention was then turned to devising a conclusive structure proof of the reaction product resulting from reaction of a secondary 2,3,4-

trichlorobenzamide (Scheme 2). Treatment of isobutyl 2,3,4-trichlorobenzamide **4** with ethanethiolate yielded a single dichloro-monoethylthiobenzamide **5**, which was oxidized with *m*-chloroperbenzoic acid to the corresponding ethyl sulfone **6**. Reductive removal of the chloro-groups with ammonium formate in methanol over palladium on carbon catalyst gave a single ethylsulfonylbenzamide **7**.[7] Proton NMR analysis of this material clearly showed the compound to be substituted with hydrogen atoms on the ring in a 1,2,3,4-relationship, proving that the original substitution reaction had also occured at the *ortho* position. This is consistent with the result from the isobutyl 2,4-dichlorobenzamide reaction.

Scheme 2: *Ortho*-Substitution of N-Isobutyl 2,3,4-Trichlorobenzamide

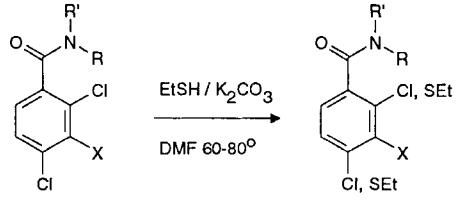


4 (R=isobutyl) **5** **6** **7**

Experimental

Typical Reaction Procedure: The starting amide (1 equivalent) was dissolved in DMF to give a concentration of about 0.2 M, then anhydrous potassium carbonate (2 equivalents) plus ethanethiol (1.75 equivalents) were added. The reaction mixture was heated to 60°C and the reaction followed by GC (DB5 15 m capillary column, 100-280°C, 20°C/min rise, 15 psi He head

Table: Reactions of 2,4-Dichloro and 2,3,4-Trichlorobenzamides with Ethanethiolate



R	R'	X	PRODUCTS (%)
H	H	Cl	100 mono
Me	H	Cl	82 mono; 17 bis
Me	Me	Cl	38, 43 mono; 3 bis
i-Butyl	H	Cl	100 mono
i-Butyl	*i*-Butyl	Cl	90 SM; 3, 4 mono
Benzyl	H	Cl	99 mono
Benzyl	Me	Cl	66 SM; 18,16 mono
Phenethyl	H	Cl	3 SM; 92 mono
Phenethyl	Me	Cl	54, 42 mono
H	H	H	100 mono*
i-Butyl	H	H	100 mono
i-Butyl	*i*-Butyl	H	76 SM; 7, 14 mono

Key: SM=starting material, mono=monosubstitution product, isomer unidentified, (two numbers signifies isomeric mix, isomers not further identified), bis=bis-substitution product.
*Nucleophile was potassium methanethiolate

pressure). It was noted that secondary amides reacted faster than tertiary amides. The reaction of the secondary amides was generally complete within a few hours at 60°, whereas tertiary amide reactions generally required heating at 80° for several more hours. The reaction was worked up by adding sufficient

1N HCl to neutralize the K_2CO_3, extracting the mix with ether several times, backwashing the ether with water to remove DMF, then drying over $MgSO_4$ and removing the solvent on a rotary evaporator. Products were analyzed by GC, GC/MS, and $^1H/^{13}C$ NMR.

Structure Proof:

The isobutylamide of ethylthiodichlorobenzoate **5** (6.5 mmol, 2.00 g) was treated with *m*-chloroperbenzoic acid (19.6 mmol, 3.40 g) in dichloromethane (100 mL) at room temperature, the reaction mixture washed with aqueous sodium bisulfite and sodium bicarbonate, dried ($MgSO_4$) and the solvent removed on a rotary evaporator. Spectroscopic evidence supported the product being the ethylsulfone **6**or a positional isomer. (Proton NMR: 7.70, 1H, d, 9 Hz (aryl); 7.29, 1H, d, 9 Hz (aryl); 6.07, 1H, t(br), 6 Hz (NH); 3.51, 2H, q, 6 Hz (ethyl); 3.23, 2H, dd, 6Hz, 6 Hz (isobutyl); 1.93, 1H, m (isobutyl); 1.41, 3H, t, 8 Hz (ethyl); 0.98, 6H, d, 9 Hz (isobutyl). Carbon NMR: 167.47 (C=O); 140.67, 136.67, 134.69, 133.19, 127.67 (aryl); 50.29, 47.87 (methylenes); 28.15 (methine); 20.24, 6.10 (methyls). For determination of which isomer had been formed in the initial displacement reaction, the following derivatization and spectroscopic analysis was carried out.

A sample of the sulfone **6** (3.40 mmol, 1.15 g) was dissolved in methanol (50 mL) and ammonium formate (17.1 mmol, 1.08 g) added, followed by 10% palladium on carbon (1 g). The mixture was stirred overnight at room temperature, filtered, the filter cake washed with methanol, and the solvent removed from the filtrate on a rotary evaporator. The residue was triturated

with ether, filtered and the solvent removed. Mass spectrometry showed the loss of both chlorine atoms but no reduction of the sulfonyl or amide groups (m/z 269), substantiating structure **7**. Proton NMR analysis (d_6-DMSO) at 400 MHz clearly showed all four ring protons with *ortho* couplings, two doublets and two triplets with *meta* coupling fine structure. Aromatic region (δ, #H, mult, J): 7.92, 1H, dd, 8 Hz, 1 Hz; 7.78, 1H, td, 8 Hz, 1 Hz; 7.68, 1H, td, 8 Hz, 1 Hz; 7.53, 1H, dd, 8 Hz, 1 Hz. Other resonances: 8.60, 1H, t, (NH); 3.55, 2H, q, (ethyl); 3.1, 2H, dd, (isobutyl); 1.85, 1H, m (isobutyl); 1.10, 3H, t, (ethyl); 0.95, 6H, d, (isobutyl).

Discussion

The striking difference in reactivity between the less reactive tertiary amides and the faster-reacting primary and secondary amides suggests that the tertiary amides are less activating for nucleophilic displacement. This effect can possibly be attributed to unfavorable steric interactions in the cases of the more hindered tertiary amides inhibiting full planarization of the carbonyl with the aromatic π-system, reducing stabilization of the intermediate anionic Meisenheimer complex formed by addition of the anionic nucleophile to the aromatic ring. The cause of the *ortho*-regioselectivity observed in the primary and secondary amides cannot be due solely to an enhanced Meisenheimer complex stabilization, as the *para*-adduct should be stabilized to about the same degree due to resonance. An additional effect that may be operative in determining the preference for *ortho* attack may be the interaction of the incoming anionic nucleophile and the amide nitrogen atom bearing a partial

positive charge though an attractive electrostatic interaction. This steering effect could provide a lower energy pathway for the approach of the thiolate to the π-cloud of the ring. Whatever the factor determining the *ortho* over *para* selectivity observed, it must be of sufficient strength to overcome the apparent steric disfavorment of *ortho* attack.

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