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Ortho selectivity in S_NAr substitutions of 2,4-dihaloaromatic compounds. Reactions with piperidine

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ABSTRACT

A broad survey of aromatic compounds with halogens positioned both *ortho* and *para* to activating groups was studied in S_NAr reactions with piperidine. Regioselectivities varied with the substituent group and the polarity of the solvent. Many activating groups exhibited an overall bias toward *ortho*-substitution, and this led in nonpolar solvents to very high *ortho* selectivity. More polar solvents uniformly shifted the product ratio toward *para* substitution. Evidence is presented that argues for coordination via hydrogen bonding as a driver of much of the *ortho* selectivity observed. The data presented show ample evidence of the generality and synthetic utility of the *ortho*-directing ability of several common activating groups for this reaction type.

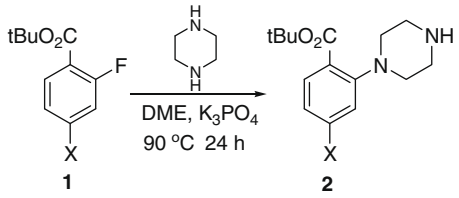
In the course of our drug discovery work, we recently targeted a 4-amino-substituted-2-fluorobenzoate. We first tried a Buchwald–Hartwig coupling of piperazine with the 4-bromo-2-fluoroester **1a**, but found that under the reaction conditions, simple S_NAr displacement of the fluorine was much faster, and **2a** was formed in near-quantitative yield. Assuming that the corresponding 2,4-difluorobenzoate would result in predominant reaction at the 4-position, we ran **1b** under identical conditions, minus the palladium catalyst. However, these conditions again provided a nearly quantitative yield of the *ortho*-product **2b**, with only a trace amount of the product resulting from reaction at the 4-fluorine.

We were unaware of other examples of such high *ortho*-selectivity in similar substrates. Upon examination of the literature, we found no examples of esters directing S_NAr reactions preferentially *ortho*, though a few related reactions had been studied. Over 50 years ago, Bunnett and co-workers reported on the *ortho*-directing ability of nitro[1] and carboxylate[2] groups in S_NAr reactions with piperidine. In the former case, they also noted a solvent effect on the observed regioselectivity, with more polar solvents increasing the relative amount of *para*-derived product. They also argued that the preponderance of *ortho* product likely arose from more favorable electrostatic interactions between the incoming nucleophile and the directing group, rather than hydrogen bonding.

Other cases of amines adding with high regioselectivity to 2,4-dihaloaromatic or closely related compounds are exceedingly rare; in fact, we were only able to find a few unequivocal examples concerning nitrobenzenes in the patent literature. Among S_NAr reactions in general, several other examples of high *ortho*/*para* ratios exist, but they exclusively concern anionic nucleophiles.[3,4] Many of these involve pentafluoroaromatic substrates, and are largely confined to the Russian literature.[5] There seems, then, to be a gap in the understanding of both the regioselective outcomes of this reaction and of the drivers of these outcomes.

We wanted to determine the extent of the generality of the extreme *ortho* selectivity of reactions exemplified by the one shown in Figure 1. As there seemed to be no systematic study of the effects of directing groups on the selectivity profile of amine reactions with 2,4-difluoroaromatic compounds, we decided to look at the behavior of several substrates in reactions with piperidine.

The collected data from these reactions are shown in Table 1. In most cases, reaction sets for a given substrate were run at a temperature that allowed complete or nearly complete reaction over



1a, 2a X = Br, reaction w/Pd cat.
1b, 2b X = F, reaction w/o Pd cat.

Figure 1.

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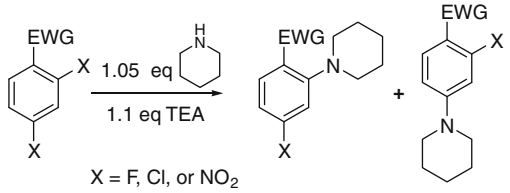
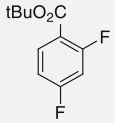
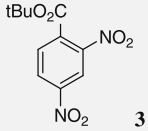
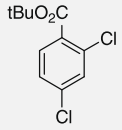
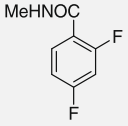
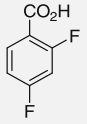
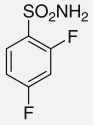
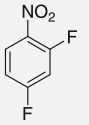
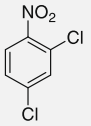
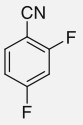
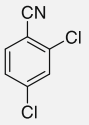
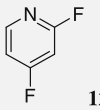
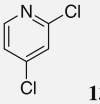
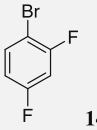
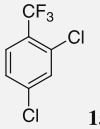
Table 1
Reaction of piperidine with 2,4-disubstituted aromatic compounds



Substrate	Solvent	Temp Time	Product ratio 2- / 4-substitution[a]	Yield[b]
 **1b**	toluene	80°C 24 h	>98 : 2	67%[c]
	dioxane		97 : 3	90%
	DME		95 : 5	94%
	MeCN		89 : 11	90%
	EtOH		86 : 14	93%
	DMSO		42 : 58	92%
	DMF		36 : 64	93%
 **3**	DME	80°C 24 h	87 : 13	50%[c]
	DMSO		41 : 59	95%
 **4**	diglyme	125°C 24 h	98 : 2	30%[c]
	DMSO		58 : 42	82%[c]
 **5**	dioxane	80°C 24 h	98 : 2	90%
	MeCN		82 : 18	91%
	DMSO		55 : 45	91%
 **6**	dioxane	90°C 24 h	97 : 3	80%[c]
	DMSO		40 : 60	77%
 **7**	dioxane	80°C 24 h	96 : 4	92%
	DMSO		32 : 68	93%

Substrate	Solvent	Temp Time	Product ratio 2- / 4-substitution[a]	Yield[b]
 **8**	dioxane	80°C 24 h	97 : 3	90%
	MeCN		91 : 9	92%
	EtOH		86 : 14	96%
	DMSO		70 : 30	92%
 **9**	dioxane	80°C 24 h	>98 : 2	67%[c]
	EtOH		92 : 8	70%[c]
	DMSO		85 : 15	93%
 **10**	dioxane	80°C 24 h	42 : 58	96%
	DME		22 : 78	91%
	DMSO		15 : 85	90%
 **11**	dioxane	105°C 72 h	38 : 62	64%[c]
	DMSO		16 : 84	82%
 **12**	THF	0°C 24 h	8 : 92	95%
	DMF		3 : 97	93%
 **13**	dioxane	100°C 24 h	47 : 53	57%[c]
	DMSO		14 : 86	83%[c]
 **14**	diglyme	125°C 24 h	69 : 31	14%[c]
	DMSO		51 : 49	91%
 **15**	diglyme	140°C 24 h	13 : 87	20%[c]
	DMSO		5 : 95	65%[c]

[a]Ratios determined by NMR integration of crude product.
[b]Yields are of crude product mixture unless noted.
[c]Yield estimated by NMR integration of crude product mixture containing unreacted starting material

the allotted time for the least polar solvent used, unless boiling point considerations intervened. Reactions were profiled by NMR spectra of the crude product mixture. Product mixtures were remarkably clean in all cases; there was virtually no presence of bis-substitution products or unknown side products. In cases where reactions did not go to completion, yields are estimated based on the amount of starting material in the crude product mixture, as determined by NMR integration.

The collected reactions of the original ester **1b** show a clear relationship between solvent polarity and regioselectivity, with increasing solvent polarity progressively favoring *para* reaction. In particular, dipolar aprotic solvents with high polarizability, for example, DMF and DMSO, favored *para* substitution much more than other solvents.[6] Similar reaction sets run with other substrates show the same effect, though this is superimposed on the individual regiochemical preferences of the substrates. There is no correlation between these regiochemical preferences and the Hammett values σ or $\sigma-$.[7] However, it is clear that those substrates which display a strong preference for *ortho*-substitution in nonpolar solvents (**1b**, **3**–**9**) all possess functionalities that can coordinate to the incoming amine, biasing it toward *ortho* attack via a hydrogen bond. Substrates unable to form an attractive interaction with

the incoming nucleophile (**10**–**15**) almost always provide predominantly *para*-substituted products. In addition, the spread of product ratios over a full span of solvent polarities is correspondingly greater for those substrates that may be expected to provide energetic stabilization to the *ortho* transition state.

Additionally, reactions in less polar solvents proceeded more slowly, as expected. Qualitatively, overall reaction rates seemed to increase in polar solvents by an amount roughly commensurate with a rate increase of the *para*-oriented reaction, in keeping with the observations of Bunnett and others. Solvent effects on rates of reactions involving ionic transition states from uncharged substrates are well understood, and are commonly explained as being driven primarily by an increase in the entropy of activation with increasing solvent polarity, leading to faster reactions in polar solvents.[1,2,8] This is due to more effective solvation of the ionic transition state compared to the neutral substrate and nucleophile. In the cases of substrates such as **1b** and **3**–**9**, interactions with the directing group can be thought of as internal, 'built-in' solvation for the *ortho* transition state. This interaction thus provides a basis for excellent *ortho* selectivity in nonpolar solvents, and also reduces the capacity for stabilization by polar solvents, so upon increasing the solvent polarity, the rate of *ortho* reaction changes very little, while the rate of reaction at the *para* center undergoes a large increase.

For compounds such as **14** and **15**, there is still a small shift in regioselectivity toward the *para* product in polar solvents, which can be rationalized as coming from a small steric effect on solvation, or on small differences in charge separation in the *ortho* and *para* transition states. This is again accompanied by a rate increase for reaction in polar solvents. The other non-pyridyl compounds in Table 1 will bear more of the transition state negative charge on their electron-withdrawing substituents, leading to greater charge separation and a larger potential for transition state stabilization by polar solvents, which, together with internal stabilization of the *ortho* transition state, generates the larger ranges of regioselectivities seen for these compounds.

A comparison of F and Cl as leaving groups (**1b** vs **4**, **8** vs **9**, **10** vs **11**, **12** vs **13**), indicates that Cl tends to favor *ortho*-substitution relative to F, albeit by a small amount. In particular, the near 1:1 ratio of *ortho* to *para* products for **13** in dioxane is surprising, given the general *para* preference of pyridines. A possible explanation for this relates to the superior capacity of fluorine substituents to both increase the susceptibility of the adjacent carbon center toward nucleophilic attack and to stabilize the negative charge on the ring of the intermediate structure. This should result in an earlier transition state for difluoro compounds relative to their dichloro counterparts, and a consequent reduction in the attractive interaction between directing group and nucleophile in the transition state. If possible, then, when *ortho* selectivity is required, employment of chloride precursors may be warranted if the elevated temperatures necessary for reaction are acceptable.

The question of whether *ortho*-substitution is favored through electrostatic interactions or through actual coordination via a hydrogen bond is still not entirely clear. Bunnett argued for the former, citing a paper disclosing a lack of an isotope effect in the reaction of *N*-deuteropiperidine with *o*- and *p*-chloronitrobenzenes.[9] However, this seems an odd result, since there should be a small positive secondary isotope effect regardless of mechanism. If, in addition, a hydrogen bond was present in the transition state, the primary isotope effect relating to the weakening of the N–H(D) bond should be small and positive, while any effect relating to the forming NO_2–H(D) hydrogen bond would be expected to be small and negative. It may be that the individual or combined isotope effects were too small to be measured, but a rate ratio of 1.0 does not seem to argue forcefully for an absence of hydrogen bonding in the rate-determining step.

The data for the cyano compounds **10** and **11** seem particularly instructive in this regard. The electron-rich nitrile functionality is capable of an electrostatic interaction with the incipient positive charge on the incoming amine, but is incapable of hydrogen bonding in the transition state, and **10** and **11** show less of an *ortho*-bias in nonpolar solvents than those capable of hydrogen bonding; in fact their selectivities are instead comparable to the pyridine **13** or the bromide **14**. On the other hand, if one imagines that the activating group is required to be still nearer to the incoming piperidine in order to provide meaningful electrostatic stabilization, then it is difficult to imagine why the two groups would fail to form a hydrogen bond, given their close proximity and the consequent extremely low entropic barrier to doing so. Thus it seems reasonable to speak of hydrogen bonding as being operative in these reactions. Finally, we note that it is unclear as to whether a hydrogen bonding event takes place before or during the C(2)–N bond forming process.

Finally, for S_NAr additions of anionic nucleophiles, it is generally accepted that coordination is operative for many directing groups. Coordination has been implicated in *ortho*-substitutions of anions to aromatic compounds, though much of this work has been performed on perfluoroarenes.[5] Pentafluoropyridine appears to add metal salts to the 2-position via coordination in nonpolar solvents; addition of a crown ether or changing to a polar solvent results in 4-substitution.[10] Di-[4] and pentafluorobenzoic[11] acids are known to react regioselectively with alkoxides or hydroxide at the *ortho* position, even in polar solvents.

The natural tendency to choose polar solvents in which to run S_NAr reactions has no doubt served to at least partially obscure the *ortho*-directing ability of some activating substituents, which may also help to maintain the common assumption among organic chemists that the *para* position is normally favored over an *ortho* position when a competition between the two is possible. This in turn is probably based mostly on the correct view that reactions of pyridines (such as **12** and **13**) proceed preferentially at the *para* position.[12] In addition, quite a bit of work has been reported on the regioselectivity of pentafluoropyridine[13] and other pentafluoroaromatic compounds,[5,14] which overwhelmingly give *para* substitution in the absence of coordination.

It is hoped that the foregoing discussion provides sufficient rationalization of the observed product data. We also expect that the data provided should provide guidance as to both the manner of regioselectivity to be expected in S_NAr reactions of amines, and the ability to choose conditions to maximize the desired regiochemical product for reactions of this type.

Acknowledgments

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Supplementary data

Supplementary data (representative procedures and NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.087.

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