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

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ABSTRACT

The nucleophilic addition of organic anions to aromatic compounds with halogens positioned both *ortho* and *para* to activating groups was studied in a variety of solvents. Substrates showed strong preferences for *ortho* substitution in most cases. Evidence is presented for activating group-dependent coordination, which contributes to very high *ortho*-selectivity in nonpolar solvents. This also drives the overall reaction rate in these solvents, and is of close to the same magnitude of rate increase derived from polar solvents. *para*-Products are maximized by using crown ethers in protic solvents. Solvent effects overall are very different from corresponding reactions with amine nucleophiles due primarily to the different charges present in the transition states, and to solvation of the nucleophile.

We recently reported on a study of regioselectivity in S_NAr additions of amines to activated 2,4-dihaloaromatic compounds.[1] We found that this extremely underutilized reaction displayed strong *ortho*-selectivity under most conditions, and that this was almost certainly driven by a coordination effect. Additionally, the choice of solvent had a large bearing on regioselectivity, with highly polarizable solvents such as DMF and DMSO shifting the product distribution toward the *para* product. Parallel to this work, we began to look at the regioselectivity of alkoxides and other anionic nucleophiles with the same substrates.

Similar to the situation with regard to amine nucleophiles, examples of S_NAr additions of alkoxides or other organic anions to activated 2,4-dihaloaromatic compounds are surprisingly difficult to find in the literature.[2–6] Additionally, for the majority of examples it is not clear what selectivity was observed, and most reports concern additionally substituted ring systems, usually perfluoroaromatic compounds,[7] which are known to display different regioselectivities.[8] Additionally, there is almost nothing in the way of studies comparing solvents or activating groups. For these reasons we sought a broader understanding of this reaction.

In the course of our work, it quickly became apparent that, unsurprisingly, anions do not add as cleanly to the various dihaloarenes as do amines. In the latter case, just over 1 equiv of nucleophile assured complete reaction without generating any impurity due to bis-addition. However, because of the lesser degree of ring deactivation resulting from the substitution of a single alkoxide, conditions necessary to completely consume starting material often resulted in significant amounts of bis-addition product along with the usual regioisomeric product mixture. For this reason, we chose to first look at the reactions of methyl 2,4-difluorobenzoate (**1**) with exactly 1 equiv of alkali metal methoxides in a variety of solvents (Table 1).

In keeping with recent results of alkoxide S_NAr additions,[2] our data show extraordinary *ortho*-selectivity for this reaction when run in either dioxane or toluene. Additionally, the reaction rate in dioxane, while slower than in DMSO, was surprisingly fast, and much faster than the reactions run in methanol. This stands in sharp contrast to the set of reactions we recently described using piperidine as the nucleophile.[1] In that study, rates consistently varied in the order dioxane < alcohol < DMSO. This was a result of *ortho* reaction rates remaining roughly constant while *para* rates increased dramatically with solvent polarizability, in line with expectations.[9] It has long been known that S_NAr rates are faster in dipolar aprotic solvents such as DMSO than in alcoholic solvents.[10] However, nonpolar solvents were for obvious reasons not usually included in these studies. Moreover, the conclusions reached were based on studies of reactants with one possible site of attack; thus the issue of competing coordination-assisted reaction rates did not normally enter into an assessment of rates. The data here does not offer anything approximating a quantitative assessment of relative rates; nevertheless it is clear from both Tables 1 and 2 given below that *overall* reaction rates for alkoxide nucleophiles with these substrates increase in the order alcohol < dioxane < DMSO.

Interestingly, *para* substitution is favored more by using methanol as a solvent than by using DMSO. This again differs from the results found with piperidine as a nucleophile,[1] but here the transition state, nucleophile, and leaving group are all anionic, whereas with amine nucleophiles a zwitterionic transition state derives from uncharged reactants. For both reaction types highly polarizable solvents are most effective at stabilizing the transition states.

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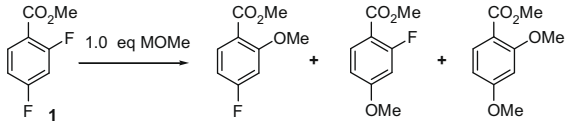
Table 1
Solvent dependence of rate and regioselectivity for the reaction of **1** with alkali metal methoxides



Reagent	Solvent	Temp/time	Products[a] (% of recovered material)			
			SM	*ortho*-subst	*para*-subst	Bis-subst
NaOMe	Toluene	90 °C 24 h	12	85	3	—
	Dioxane	rt 24 h	9	91	—	—
	Dioxane	90 °C 24 h	5	95	—	—
	Dioxane[b]	90 °C 24 h	17	61	18	4
	MeOH	rt 24 h	89	3	8	—
	MeOH	60 °C 24 h	18	25	55	2
	MeOH[b]	rt 24 h	78	2	20	—
	MeOH[b]	60 °C 24 h	3	8	87	2
	DMSO	rt 5 h	9	48	32	11
	DMSO[b]	rt 24 h	19	29	44	8
LiOMe	Dioxane	90 °C 24 h	26	74	—	—
	MeOH	70 °C 24 h	6	32	58	4
	DMSO	90 °C 24 h	9	57	29	5
KOMe	Dioxane	90 °C 24 h	9	91	2	—
	MeOH	70 °C 24 h	13	20	65	2
	DMSO	90 °C 24 h	31	20	32	17

[a] Determined by NMR integration of crude product.
[b] Reaction carried out with 2 equiv of 18-crown-6.

In this case, though, the additional factor of the solvation of reactant alkoxides increases dramatically in the order dioxane < DMSO < methanol.[10] This reactant stabilization provides a basis for the slower reaction rate in methanol. Additionally, it results in weaker coordination to the directing group, which further specifically retards the *ortho* reaction rate, increasing the relative amount of *para* product.

Thus, as coordination of primary or secondary amines occurs via the amine hydrogen atom and is not destroyed by polar solvents, the amine hydrogen will coordinate with the available directing groups regardless of solvent, and *para* reaction only outcompetes the coordination-assisted *ortho* reaction by virtue of a polar solvent-assisted rate increase. However, with alkoxides or other anionic nucleophiles, the 'carrier' of coordination is the counterion, and protic solvents can effectively outcompete directing groups for solvation of the cation. Thus alcohol solvents provide the most *para* product by reducing the *ortho* reaction rate, and thereby also the overall reaction rate.

The *ortho* selectivity in dioxane can be eroded to some extent by the use of 18-crown-6, indicative of the crown ether binding the Na^+ counterion and consequently reducing the importance of the directing effect of transition state coordination by the ester group. This is again commensurate with an overall rate decrease. Additionally, combining 18-crown-6 with polar solvents further increases the relative amount of *para* product, indicating that DMSO or even methanol alone does not maximally stabilize the Na^+ cation. Finally, there appears to be a hint of a counterion effect on the product distribution, with the amount of *para* product increasing in the order $Li^+ < Na^+ < K^+$, as would be expected from relative solvation energies. Unfortunately, additional experiments (data not shown) indicate that K^+ counterions also tend to promote the production of bis-substitution products, reducing the attractiveness of this counterion. The lithium salt, on the other hand, suffered from solubility limitations in dioxane, contributing to a slower rate of reaction.

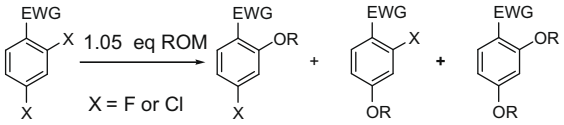
With the Table 1 results in hand, we extended the study to include other activating groups and nucleophiles; these results are contained in Table 2. Again, we sought to identify trends and conditions that would maximize individual regioisomeric products, so reactions were for the most part run with 1.05 equiv of nucleophile. As *para* products are more difficult to obtain in high yield, we increased the amount of nucleophile in some cases in an attempt to drive the reactions to completion without producing a large amount of bis-substitution product.

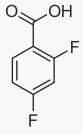
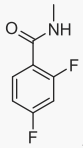
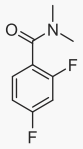
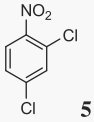
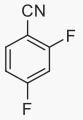
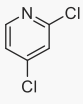
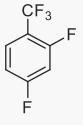
The data show that *ortho* products are in general simple to obtain in good yield regardless of the nature of the nucleophile, as long as the directing group is capable of coordination. Overall, the dominance of *ortho* product for a given nucleophile and solvent, particularly dioxane, correlates well with the hydrogen-bond acceptor strength of the directing group.[11] The fully deprotonated **2** produces only a trace of *para* product under all conditions studied. Using NaOEt fails to give any product in ethanol either with or without added crown ether. The more soluble bidentate $Mg(OEt)_2$ does produce *ortho* product in ethanol, so even in alcoholic solvent, *para* product is difficult to access.

The amides **3** and **4** and nitro **5** all display excellent *ortho*-selectivity in dioxane; **5** does not react cleanly with alkoxides in dioxane due to competing reduction.[12] Even the benzonitrile **6**, which is unable to maintain coordination with the attacking nucleophile as it attacks the *ortho* carbon atom, provides only a small amount of *para* product in dioxane. Only the pyridine **7** shows a lack of *ortho*-selectivity in dioxane. As in our earlier report, compound **8**, the dichloro version of **7**, provides much more *ortho* product than its difluoro counterpart in dioxane,[1] though this preference once again disappears in ethanol or dipolar aprotic solvents. The difference between the two substrates may be due to reduced electron density in the nitrogen lone pair in **7** due to inductive effects of the fluorine atoms.

It is difficult to find additional examples of activating groups that are incapable of coordinating metal ions. It is known that halogens direct aromatic metallation *ortho*,[13] and recent work has shown that halogens effectively *ortho*-direct S_NAr alkoxide substitutions.[2] We thus chose to look at the trifluoromethyl group. Entries 40–43 show that the trifluoromethyl group of **9** provides relatively poor *ortho*-selectivity in dioxane, as is expected when the activating group affords little stabilization of the *ortho* transition state. Compound **9** also displays a more typical dioxane ≈ alcohol ≪ DMSO rate progression. Nevertheless, there is

Table 2
Reactions of anionic nucleophiles with 2,4-disubstituted aromatic compounds



Substrate	Nucleophile	Entry	Solvent	Conditions	Products[a] (% of recovered material)			
					SM	*ortho*-subst	*para*-subst	Bis-subst
 **2**	NaOEt	1	Dioxane[b]	100 °C 48 h	70	30	—	—
		2	DMSO[b]	80 °C 18 h	—	99	1	—
	$Mg(OEt)_2$	3	EtOH	80 °C 18 h	49	51	—	—
		4	DMSO	100 °C 18 h	20	80	—	—
 **3**	NaOPh	5	Dioxane	100 °C 24 h	11	89	—	—
		6	DMSO	100 °C 24 h	17	83	—	—
	NaSPh	7	Dioxane	50 °C 72 h	7	90	3	—
		8	*n*-PrOH	100 °C 72 h	—	70	26	4
		9	DMSO	50 °C 72 h	12	69	—	19
 **4**	NaOEt	10	Dioxane	80 °C 20 h	2	97	1	—
		11	EtOH	80 °C 48 h	25	16	59	—
		12	EtOH[c,d]	80 °C 48 h	4	—	96	—
		13	DMSO	80 °C 4 h	6	20	73	1
		14	HMPA	80 °C 4 h	2	22	74	2
 **5**	NaOEt	15	EtOH	75 °C 18 h	1	69	21	9
		16	EtOH[c,d]	75 °C 18 h	—	33	55	12
		17	DMSO	50 °C 18 h	1	75	20	4
	NaOPh	18	Dioxane	100 °C 48 h	37	63	—	—
		19	DMSO	100 °C 48 h	28	50	18	4
		20	DMSO[c,d]	120 °C 24 h	12	54	23	11
		21	HMPA	100 °C 24 h	7	57	29	7
	NaSPh	22	Dioxane	rt 2 h	—	82	18	—
		23	EtOH	50 °C 24 h	21	49	12	18
		24	DMSO	rt 24 h	30	37	15	18
 **6**	NaOEt	25	Dioxane	rt 24 h	9	85	6	—
		26	EtOH	rt 24 h	5	35	60	—
		27	EtOH[c,d]	rt 24 h	—	27	69	4
		28	DMSO	rt 5 h	6	53	36	5
		29	HMPA	rt 5 h	5	32	56	7
	NaOPh	30	Dioxane	95 °C 18 h	7	90	2	1
		31	DMSO	95 °C 18 h	2	53	30	15
		32	DMSO[c,d]	95 °C 18 h	6	52	32	10
		33	HMPA	80 °C 18 h	4	45	45	6
 **7**	NaOEt	34	THF	0 °C 18 h	—	28[e]	72	—
		35	EtOH	0 °C 18 h	—	—	100	—
		36	DMF	0 °C 18 h	—	9	91	—
 **8**	NaOEt	37	Dioxane	70 °C 18 h	67	31	2	—
		38	EtOH	70 °C 18 h	8	—	92	—
		39	DMSO	70 °C 18 h	5	5	90	—
 **9**[f]	NaOEt	40	Dioxane	80 °C 48 h	—	64	32	4
		41	Dioxane[c]	80 °C 48 h	—	39	58	3
		42	EtOH	80 °C 48 h	—	8	90	2
		43	DMSO	rt 6 h	—	28	72	—

[a]Determined by NMR integration of crude product.
[b]Reaction carried out with 2.0 equiv of nucleophile.
[c]Reaction carried out with 2.0 equiv of 18-crown-6.
[d]Reaction carried out with 1.2 equiv of nucleophile.
[e]Product isolated as pyridone.
[f]Reactions followed by LC–MS, substrate evaporates on workup.

still a broad range of product ratios, and entry 41, which adds crown ether to dioxane, indicates that coordination may still play a small role in the weak *ortho*-selectivity seen.[14]

Overall, reactions with NaOEt produce results similar to those in Table 1, with ethanol producing the most *para* product, and 18-crown-6 further improving the product ratio. Addition of crown ether to DMSO also shifted ratios toward *para* products, as in Table 1, but the result was again inferior to that produced when the alcohol/18-crown-6 combination was employed (data not shown). The still more polarizable aprotic solvent HMPA (entries 14 and 29) produces results similar to those with ethanol alone. While the qualitative shift in product ratios upon changing solvent is entirely consistent and predictable, the degree of the shift varies between substrates in a manner that does not accord with the degree of hydrogen bonding capacity, and the maximally *para*-favoring product ratios probably reflect additional factors such as the relative electrophilicity of the relevant ring carbon atoms, secondary solvent interactions with the directing groups, and the polarizability and solvent stabilization of the anionic intermediate structures. Thus, **4**, which has a relatively strong directing group, provides a surprising amount of *para* product in ethanol both with and without added crown ether, while the weaker *ortho*-directing **5** and **6** evince a smaller shift toward *para* products.

For a given substrate, the bias toward *ortho* products decreases in the order $RO^- > ArO^- > ArS^-$. The increasing nucleophilicity of these anions should dampen the regiochemical preferences asserted by the directing groups, and the strongly increasing polarizability across this set makes them progressively less well solvated by alcohols relative to DMSO. While NaOPh in protic solvents unfortunately produces mixtures of phenoxide and alkoxide addition products (data not shown), comparisons of NaSPh additions in alcohol and DMSO (entries 8, 9, 23 and 24) show similar product ratios; thus the relative advantage of protic solvents is greatly reduced if not completely eliminated for this nucleophile. Still, both phenoxides and thiophenoxides produce much more *para* product in DMSO than in dioxane.

As the pairs of entries 19, 20, 31, and 32 show, the addition of 18-crown-6 to DMSO does not dramatically shift the product ratio toward more *para* product for phenoxide additions, indicating that for this anion, DMSO alone may be close to optimally effective in disrupting transition state coordination. Nevertheless, an alternate strategy for maximizing *para* product is to use the more powerful aprotic solvent HMPA; entry 33 shows a meaningful improvement in the yield of *para* product. The fact that crown ether does not improve the yield of *para* product for the **6**/phenoxide combination, while HMPA does, probably indicates that factors other than transition state coordination are being affected. HMPA is known to be particularly effective at stabilizing S_NAr intermediate ions; differential stabilization of *ortho* and *para* intermediates or transition states may be responsible for the additional shift toward *para* products. We note that in entry 21, HMPA fails to produce the same effect for the **5**/phenoxide combination.

Finally, the reduced deactivating power of phenoxides and thiophenoxides makes it particularly important to closely follow their reactions when multiple reaction sites are present in order to minimize the production of bis-addition products. We also note in passing that for all three of the nucleophile types in this work, we employed phase-transfer conditions[4,5] in an attempt to find other conditions that would provide better *para* selectivity, and these tended to give product ratios intermediate to those found in dioxane and DMSO.

In summary, when coordination to a directing group is possible, a variety of anionic nucleophiles prefer *ortho* products more strongly than amine nucleophiles,[1] and it is for this broad substrate type a simple matter to achieve high regioselectivities and yields if one is targeting *ortho* products. In line with recently reported results,[2] we also found that an excess of alkoxide in dioxane did not result in bis-substitution products and produced outstanding *ortho* regioselectivities. In addition, phenoxide and even thiophenoxide additions produced excellent results under these conditions. The difficulty is in achieving good yields and regioselectivities for *para* products. Normally, when the nucleophile is a simple alkoxide, reactions are run in the corresponding alcohol. While we have shown here that this is the best choice, we have also shown that addition of a crown ether can further improve product ratios. Alcohol solvents are also amenable to thiol additions, but for these, as well as for both alkoxides whose conjugate alcohols cannot be employed as solvent, and other anionic nucleophiles, dipolar aprotic solvents such as DMSO, or better still, even more powerful solvents in this class such as HMPA should be used. In spite of this change, the yields and product ratios are not likely to be as satisfactory as when one desires *ortho* product. It is hoped that the data and analysis presented provide an expectation of the regioselectivity to be encountered in these reactions, and sufficient background to allow one to choose conditions to maximize the amount of the desired regiochemical product.

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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.2010.03.124.

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