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Practical synthesis of aromatic ethers by S_NAr of fluorobenzenes with alkoxides

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Abstract—Aromatic fluorines have been substituted by alkoxides in a variety of activated and unactivated aromatic systems.

The aromatic nucleophilic substitution of fluorine[1] by a variety of nucleophiles has been amply studied when the benzene ring has electron-withdrawing substituents, mainly nitro-, cyano-, keto-, sulphonyl-, sulphinyl-, polyhalogenated and ester-substituted benzenes.[2] This reaction usually requires polar aprotic solvents such as DMF, DMSO or HMPA and temperatures ranging from <0 °C to 100 °C depending on the activation of the ring toward the nucleophilic substitution.

On the other hand, the S_NAr of fluorine with alkoxides in non-activated or deactivated aromatic rings has been scarcely used[3] probably due to the belief that a strongly activating substituent or very harsh conditions are required for this reaction to take place or to provide the desired compounds in good yields. Some examples have been reported in which the addition of additives, like phase transfer catalysts[4] or transition metals[5] or the use of microwaves[6] provides the desired alkyl phenyl ethers in good yields.

As part of our investigations we required a variety of alkyl phenyl ethers in bulk quantities. Considering that many substituted fluorobenzenes could be purchased, a very straight forward method for this synthesis could be the direct nucleophilic substitution of fluorine by the corresponding alkoxides. We decided to study the feasibility of this reaction for our needs. To our surprise, the scope of this reaction was broader than what we had expected.

We started the study by reacting 3,5-difluorobenzene with the sodium anion of benzyl alcohol in NMP[7] in a sealed tube at 100 °C. The substitution of one fluorine by NaOBn was complete after 2 h, with a 86% isolated yield and no side products observed. These conditions were then used for the synthesis of other ethers. The results are collected in Table 1.

As can be observed from entries 1–6, a single halogen or CF_3 is a good activating agent for this reaction, providing the desired derivatives in a very good yield (86–97% isolated yield). Even a fluorobenzene with one activating substituent in *ortho*-position such as CF_3 and one deactivating substituent in *para*-position provides the product in a 98% yield (entry 7). The use of 2 equiv of alkoxide is not necessary when the aromatic ring has activating substituents, since 1.1 equiv of nucleophile for entries 3, 5 and 6 provided the corresponding ethers with comparable reaction times and yields.

As fluorine is a better leaving group for the S_NAr reaction than bromine or iodine, no displacement of these other halogens was observed in any case.

The substitution of fluorine in non-activated systems, like methyl-substituted or unsubstituted fluorobenzene (entries 8 and 9) also provide the corresponding benzyloxy derivatives in a good yield under standard conditions.

The reaction of deactivated methoxy benzene (entries 10–12) also provided the desired resorcinols in a moderate to good yield for *ortho*- and *meta*-substituted derivatives (48% and 81% yield, respectively)[8] and in low

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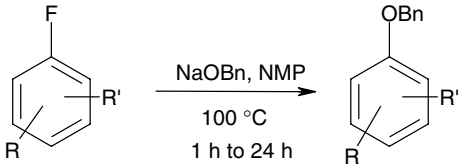
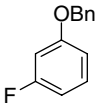
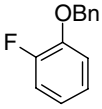
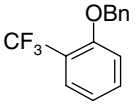
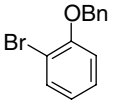
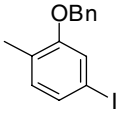
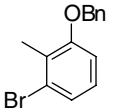
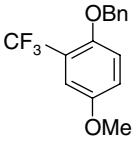
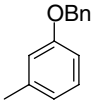
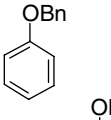
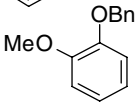
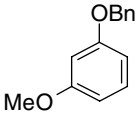
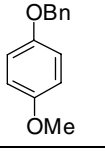
Table 1. S_NAr reaction of NaOBn[a] with fluorobenzenes



Entry	Yield (%)[b]	Time (h)	Product[c]
1	86	1	
2	97	1	
3	95	1	
4	95	1	
5	92	2	
6	94	2	
7	98	1	
8	77[d]	15	
9	75	2	
10	48[d]	24	
11	81[d]	24	
12	12	24	

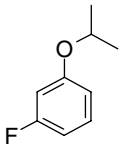
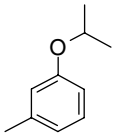
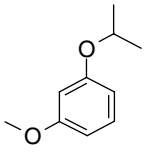
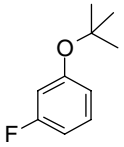
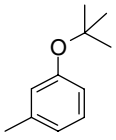
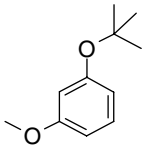
[a] Two equivalents.
[b] Isolated yield.
[c] All new compounds have been isolated in pure form and characterized by ^1H, ^{13}C and MS.
[d] Addition of 2 more equiv of NaOBn after 2 h.

yield for the *para*-substituted compound (12% yield).[9] With these non-activated systems (entries 8, 10–12) the reaction does not go to completion unless 2 more equivalents of alkoxide are added.

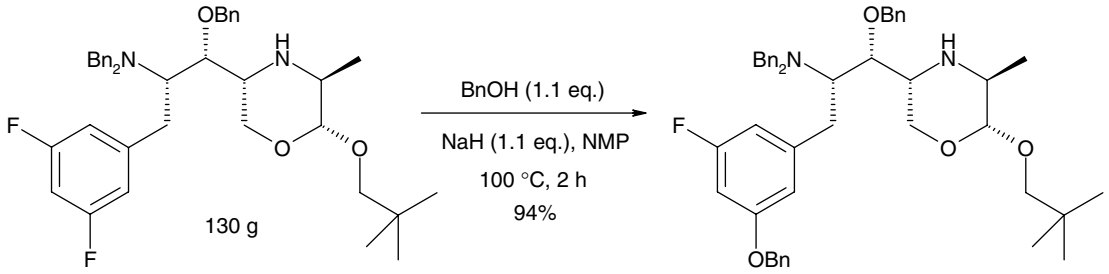
In order to determine the scope of this reaction to the use of alcohols other than primary, we chose one activated, one non-activated and one deactivated fluorobenzene for the nucleophilic substitution by the anions of *i*-PrOH and *t*-BuOH.[10] The results of this study are collected in Table 2. While the secondary alkoxide provides the desired compounds in moderate to good yields depending on the activation of the aromatic system, the substitution by the anion of the tertiary alcohol is unpractical under these conditions.

To prove the suitability of these conditions for bulk quantities, they were applied to the nucleophilic substitution of a fluorine in a more functionalized system at

Table 2. S_NAr reaction of secondary and tertiary alkoxides[a] with fluorobenzenes

Entry	Yield (%)[b]	Time (h)	Product[c]
1	90	2	
2	50	24	
3	30[d]	24	
4	60 (11)[e]	2	
5	12[d]	24	
6	7[d]	24	

[a] Two equivalents.
[b] Isolated yield.
[c] All new compounds have been isolated in pure form and characterized by ^1H, ^{13}C and MS.
[d] Addition of 2 more equiv of NaOR after 2 h.
[e] In parenthesis isolated yield due to partial decomposition.



Scheme 1. Application of the S_NAr to bulk quantities.

130 g scale.[11] The substitution compound was obtained cleanly in a 94% isolated yield (Scheme 1).

In summary, we show the broad scope of the nucleophilic substitution of aromatic fluorine by primary and secondary alkoxides in NMP, a simple and high yielding reaction suitable for bulk scale.

Experimental: A 1 M solution of sodium benzyloxide in *N*-methylpyrrolidone was prepared by adding benzyl alcohol (1 equiv) to a suspension of NaH (1 equiv) in NMP and stirring the mixture for 10 min. This freshly prepared solution (2 equiv) was added to a 0.2 M solution of the fluorobenzene (1 equiv) in NMP. The reaction was heated at 100 °C and was monitored by LCMS until complete consumption of the starting material. Water and ethyl acetate were added, the aqueous layer was separated and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed eluting with hexane/EtOAc mixtures.

Acknowledgements

We thank Dr. Howard Broughton for his helpful discussion on the reactivity of anisoles.

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